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Description

Substituted heterocyclic carboxamides, their preparation and their use as pharmaceuticals

The invention relates to substituted heterocyclic carboxamides, to their preparation and to their use as inhibitors of prolyl-4-hydroxylase, and to their use as pharmaceuticals for treating fibrotic diseases.

Compounds which inhibit the enzymes proline hydroxylase and lysine hydroxylase bring about a very selective inhibition of collagen biosynthesis by their influence on the collagen-specific hydroxylation reactions. In the course of these reactions, protein-bound proline or lysine is hydroxylated by the enzymes proline hydroxylase or lysine hydroxylase, respectively. If this reaction is prevented by inhibitors, there then arises a non-functional, subhydroxylated collagen molecule which can only be secreted by the cells into the extracellular space in small quantities. Furthermore, the subhydroxylated collagen cannot be incorporated into the collagen matrix and is very readily degraded proteolytically. These effects result in a diminution of the overall quantity of collagen which is deposited extracellularly.

Inhibitors of prolyl hydroxylase are therefore suitable substances for use in the therapy of diseases in which the deposition of collagens makes a substantial contribution to the clinical picture. These diseases include, inter alia, fibroses of the lung, liver and skin (scleroderma and cicatrizations following burns, injuries and surgical intervention) and also atherosclerosis.

It is known that the enzyme proline hydroxylase is efficiently inhibited by pyridine-2,4-dicarboxylic acid and pyridine-2,5-dicarboxylic acid (K. Majamaa et al.,

Eur. J. Biochem. 138 (1984) 239-245). However, these compounds are only active as inhibitors in cell culture at very high concentrations (Tschank, G. et al., Biochem. J. 238 (1987) 625 to 633).

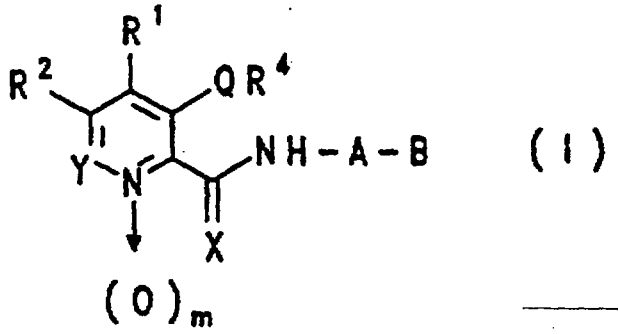
Prodrugs of pyridine-2,4(5)-dicarboxylates are also known. These are described in the relatively old German Applications P 42 33 124.2, P 42 38 506.7 and P 42 09 424.0.

N-Oxalylglycines which are inhibitors of prolyl-4-hydroxylase are disclosed in J. Med. Chem. 1992, 35, 2652 to 2658 (Cunliffe et al.), and EP-A-0 457 163 (Baader et al.).

Hydroxyisoquinolinecarboxylic acid glycylamides and hydroxycinnolinecarboxylic acid glycylamides are disclosed in Biochem. Soc. Trans. 1991, 19, 812 to 815 (Franklin et al.). 3-Benzyloxypyridine-2-carboxylic acid (L-threonyl)amide and 3-benzyloxypyridine-2-carboxylic acid ((Fmoc-Phg)-L-threonyl)amide hydrochloride are disclosed in Liebigs Ann. Chem. 1986, 1 to 20, Kessler et al.

It has now been found, surprisingly, that heterocyclic carboxamides having an ether substituent, a thioether substituent or an amino substituent in the ortho position to the amide function have a strong inhibitory action on prolyl-4-hydroxylase.

The compounds according to the invention conform to the formula I



(I)

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in which

Q is O, S, NR' or a bond,

X is O or S,

Y is C-R^3 or,

if R^1 and R^2 form a cycle,

Y is N or CR^3,

m is 0 or 1,

A is (C_1-C_4)-alkylene, which is optionally substituted by one or two substituents from the group halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, $-O-[CH_2]_x-C_fH_{(2f+1-g)}Hal_g$, preferably (C_1-C_8)-fluoroalkoxy, (C_1-C_8)-fluoroalkenyloxy, (C_1-C_8)-fluoroalkynyloxy, $-OCF_2Cl$ or $-O-CF_2-CHFCl$, (C_1-C_6)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, anilino, N-methylanilino, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl or N,N-di-(C_1-C_4)-alkylsulfamoyl, or

by a substituted (C_6-C_{12})-aryloxy, (C_7-C_{11})-aralkyloxy, (C_6-C_{12})-aryl or (C_7-C_{11})-aralkyl radical which carries in the aryl moiety 1, 2, 3, 4 or 5 identical or different substituents from the group halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, $-O-[CH_2]_x-C_fH_{(2f+1-g)}Hal_g$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, (C_1-C_6)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl or N,N-di-(C_1-C_4)-alkylsulfamoyl, or

by the substituents R^5 of the α-carbon atom of an α-amino acid, it being possible to use the natural

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L-amino acids and their D-isomers;

B is an acid grouping from the group $-CO_2H$, -CONHCOR"', -CONHSOR'", $CONHSO_2R"'$, $-NHSO_2CF_3$, tetrazolyl, imidazolyl or 3-hydroxyisoxazolyl, where R"' is aryl, heteroaryl, (C_3-C_7)-cycloalkyl or (C_1-C_4)-alkyl, optionally monosubstituted by (C_6-C_{12})-aryl, heteroaryl, OH, SH, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, (C_1-C_4)-thioalkyl, (C_1-C_4)-sulfinyl, (C_1-C_4)-sulfonyl, CF_3, Cl, Br, F, I, NO_2, -COOH, (C_2-C_5)-alkoxycarbonyl, NH_2, mono-$(C_1-C_4$-alkyl)-amino, di-$(C_1-C_4$-alkyl)-amino or (C_1-C_4)-perfluoroalkyl,

R^1, R^2 and R^3 are identical or different and are hydrogen, hydroxyl, halogen, cyano, trifluoromethyl, nitro, carboxyl, (C_1-C_{20})-alkyl, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyloxy-(C_1-C_2)-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl-(C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkoxy, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_7-C_{16})-aralkenyl, (C_7-C_{16})-aralkynyl, (C_2-C_{20})-alkenyl, (C_2-C_{20})-alkynyl, (C_1-C_{20})-alkoxy, (C_2-C_{20})-alkenyloxy, (C_2-C_{20})-alkynyloxy, retinyloxy, (C_1-C_{20})-alkoxy-(C_1-C_{12})-alkyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxy, (C_1-C_{16})-hydroxyalkyl, (C_6-C_{16})-aryloxy-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_7-C_{12})-aralkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_2-C_{20})-alkenyloxy-(C_1-C_6)-alkyl, (C_2-C_{20})-alkynyloxy-(C_1-C_6)-alkyl, retinyloxy-(C_1-C_6)-alkyl, $-O-[CH_2-]_x-C_zH_{(2z+1-g)}F_g$, $-OCF_2Cl$, $-OCF_2-CHFCl$,

(C_1-C_{20})-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl,

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(C_6-C_{12})-arylcarbonyl, (C_7-C_{16})-aralkylcarbonyl, cinnamoyl, (C_2-C_{20})-alkenylcarbonyl, (C_2-C_{20})-alkynylcarbonyl,

(C_1-C_{20})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{20})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_2-C_{20})-alkynyloxycarbonyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxycarbonyl, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxycarbonyl,

(C_1-C_{12})-alkylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_7-C_{16})-aralkylcarbonyloxy, cinnamoyloxy, (C_2-C_{12})-alkenylcarbonyloxy, (C_2-C_{12})-alkynylcarbonyloxy,

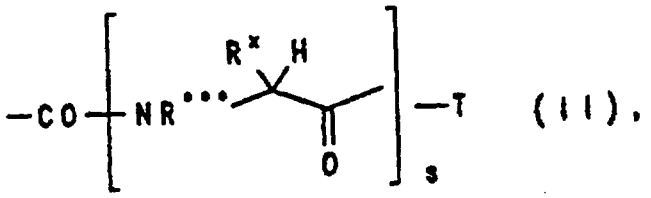
(C_1-C_{12})-alkoxycarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{16})-aralkyloxycarbonyloxy, (C_3-C_8)-cycloalkoxycarbonyloxy, (C_2-C_{12})-alkenyloxycarbonyloxy, (C_2-C_{12})-alkynyloxycarbonyloxy,

carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-dicyclo-(C_3-C_8)-alkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-$((C_3-C_8)$-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-$((C_3-C_8)$-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N-$((C_1-C_{18})$-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-$((C_6-C_{16})$-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-$((C_7-C_{16})$-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-$((C_1-C_{10})$-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-$((C_6-C_{12})$-

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aryloxy(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, or $CON(CH_2)_h$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7,

a carbamoyl radical of the formula II



(II),

in which

R^x is the substituent of an α-amino acid to which the L- and D-amino acids belong,

s is 1, 2, 3, 4 or 5, and

T is OH, OR or NR^*R^{**}, where

R^*, R^{**} and R^{***} are identical or different and are hydrogen, (C_6-C_{12})-aryl, (C_7-C_{11})-aralkyl, (C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyl, (+)-dehydroabietyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkyl, (C_1-C_{10})-alkanoyl, optionally substituted (C_7-C_{16})-aralkanoyl or optionally substituted (C_6-C_{12})-aroyl, or

R^* and R^{**} together are $-[CH_2]_h$, in which a CH_2 group can be replaced by O, S, SO, SO_2, N-acylamino, N-(C_1-C_{10})-alkoxycarbonylimino, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7,

carbamoyloxy, N-(C_1-C_{12})-alkylcarbamoyloxy, N,N-di-(C_1-C_{12})-alkylcarbamoyloxy, N-(C_3-C_8)-cycloalkylcarbamoyloxy, N-(C_6-C_{12})-arylcarbamoyloxy,

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N-(C_7-C_{16})-aralkylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyloxy, N-((C_1-C_{10})-alkyl)carbamoyloxy, N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)-carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy,

amino, (C_1-C_{12})-alkylamino, di-(C_1-C_{12})-alkylamino, (C_3-C_8)-cycloalkylamino, (C_3-C_{12})-alkenylamino, (C_3-C_{12})-alkynylamino, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_1-C_{12})-alkoxyamino, (C_1-C_{12})-alkoxy-N-(C_1-C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino, (C_3-C_8)-cycloalkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{16})-aralkanoylamino, (C_1-C_{12})-alkanoyl-N-(C_1-C_{10})-alkylamino, (C_3-C_8)-cycloalkanoyl-N-(C_1-C_{10})-alkylamino, (C_6-C_{12})-aroyl-N-(C_1-C_{10})-alkylamino, (C_7-C_{11})-aralkanoyl-N-(C_1-C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkanoylamino-(C_1-C_8)-alkyl, (C_6-C_{12})-aroylamino-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkanoylamino-(C_1-C_8)-alkyl, amino-(C_1-C_{10})-alkyl, N-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, N,N-di(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, (C_3-C_8)-cycloalkylamino-(C_1-C_{10})-alkyl, (C_1-C_{20})-alkylmercapto, (C_1-C_{20})-alkylsulfinyl, (C_1-C_{20})-alkylsulfonyl, (C_6-C_{12})-arylmercapto, (C_6-C_{12})-arylsulfinyl, (C_6-C_{12})-arylsulfonyl, (C_7-C_{16})-aralkylmercapto, (C_7-C_{16})-aralkylsulfinyl, (C_7-C_{16})-aralkylsulfonyl, (C_1-C_{12})-alkylmercapto-(C_1-C_6)-alkyl, (C_1-C_{12})-alkylsulfinyl-(C_1-C_6)-alkyl, (C_1-C_{12})-alkylsulfonyl-(C_1-C_6)-alkyl, (C_6-C_{12})-arylmercapto-(C_1-C_6)-alkyl, (C_6-C_{12})-arylsulfinyl-(C_1-C_6)-alkyl, (C_6-C_{12})-arylsulfonyl-(C_1-C_6)-alkyl, (C_7-C_{16})-aralkylmercapto-(C_1-C_6)-alkyl,

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(C_7-C_{16})-aralkylsulfinyl-(C_1-C_6)-alkyl, (C_7-C_{16})-aralkylsulfonyl-(C_1-C_6)-alkyl,

sulfamoyl, N-(C_1-C_{10})-alkylsulfamoyl, N,N-di-(C_1-C_{10})-alkylsulfamoyl, (C_3-C_8)-cycloalkylsulfamoyl,
N-(C_6-C_{12})-arylsulfamoyl,
N-(C_7-C_{16})-aralkylsulfamoyl,
N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylsulfamoyl,
N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylsulfamoyl,
(C_1-C_{10})-alkylsulfonamido,
N-$((C_1-C_{10})$-alkyl$)$-(C_1-C_{10})-alkylsulfonamido, (C_7-C_{16})-aralkylsulfonamido or N-$((C_1-C_{10})$-alkyl-(C_7-C_{16})-aralkylsulfonamido,
where the radicals which contain an aryl radical can, for their part, be substituted on the aryl by from 1 to 5 identical or different radicals from the group:
hydroxyl, halogen, cyano, trifluoromethyl, nitro, carboxyl, (C_1-C_{16})-alkyl, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl-(C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkoxy, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_2-C_{16})-alkenyl, (C_2-C_{12})-alkynyl, (C_1-C_{16})-alkoxy, (C_1-C_{16})-alkenyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxy, (C_1-C_8)-hydroxyalkyl, (C_6-C_{16})-aryloxy-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_7-C_{12})-aralkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, $-O-[CH_2-]_x-C_zH_{(2z+1-g)}F_g$, $-OCF_2Cl$, $OCF_2-CHFCl$,

(C_1-C_{12})-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl,

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(C_6-C_{12})-arylcarbonyl, (C_7-C_{16})-aralkylcarbonyl,

(C_1-C_{12})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{12})-alkenyloxycarbonyl, (C_2-C_{12})-alkynyloxycarbonyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxycarbonyl, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxycarbonyl,

(C_1-C_{12})-alkylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_7-C_{16})-aralkylcarbonyloxy, cinnamoyloxy, (C_2-C_{12})-alkenylcarbonyloxy, (C_2-C_{12})-alkynylcarbonyloxy,

(C_1-C_{12})-alkoxycarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{16})-aralkyloxycarbonyloxy, (C_3-C_8)-cycloalkoxycarbonyloxy, (C_2-C_{12})-alkenyloxycarbonyloxy, (C_2-C_{12})-alkynyloxycarbonyloxy,

carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-dicyclo-(C_3-C_8)-alkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-$((C_3-C_8)$-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-$((C_3-C_8)$-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N-$((C_1-C_{16})$-alkoxy-(C_1-C_{10})-alkyl)-carbamoyl, N-$((C_6-C_{16})$-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-$((C_7-C_{16})$-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl,
N-(C_1-C_{10})-alkyl-N-$((C_1-C_{10})$-alkoxy-(C_1-C_{10})-alkyl)-carbamoyl, N-(C_1-C_{10})-alkyl-N-$((C_6-C_{12})$-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-$((C_7-C_{16})$-

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aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, $CON(CH_2)_h$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7,

carbamoyloxy, N-(C_1-C_{12})-alkylcarbamoyloxy, N,N-di-(C_1-C_{12})-alkylcarbamoyloxy, N-(C_3-C_8)-cycloalkylcarbamoyloxy, N-(C_6-C_{16})-arylcarbamoyloxy, N-(C_7-C_{16})-aralkylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyloxy, N-((C_1-C_{10})-alkyl)carbamoyloxy, N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy,

amino, (C_1-C_{12})-alkylamino, di-(C_1-C_{12})-alkylamino, (C_3-C_8)-cycloalkylamino, (C_3-C_{12})-alkenylamino, (C_3-C_{12})-alkynylamino, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_1-C_{12})-alkoxyamino, (C_1-C_{12})-alkoxy-N-(C_1-C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino, (C_3-C_8)-cycloalkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{16})-aralkanoylamino, (C_1-C_{12})-alkanoyl-N-(C_1-C_{10})-alkylamino, (C_3-C_8)-cycloalkanoyl-N-(C_1-C_{10})-alkylamino, (C_6-C_{12})-aroyl-N-(C_1-C_{10})-alkylamino, (C_7-C_{11})-aralkanoyl-N-(C_1-C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkanoylamino-(C_1-C_8)-alkyl, (C_6-C_{12})-aroylamino-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkanoylamino-(C_1-C_8)-alkyl, amino-(C_1-C_{10})-alkyl, N-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, N,N-di-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl,

(C_3-C_8)-cycloalkylamino-(C_1-C_{10})-alkyl,

(C_1-C_{12})-alkylmercapto, (C_1-C_{12})-alkylsulfinyl, (C_1-C_{12})-alkylsulfonyl, (C_6-C_{16})-arylmercapto, (C_6-C_{16})-arylsulfinyl, (C_6-C_{16})-arylsulfonyl, (C_7-C_{16})-aralkylmercapto, (C_7-C_{16})-aralkylsulfinyl or (C_7-C_{16})-aralkylsulfonyl,

R^1 and R^2 or R^2 and R^3 form a chain $[CH_2]_o$ in which one or two CH_2 groups of the chain, which is saturated or unsaturated by a C=C double bond, are optionally replaced by O, S, SO, SO_2 or NR', and o is 3, 4 or 5, and

R' is hydrogen, (C_6-C_{12})-aryl, (C_1-C_8)-alkyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkyl, (C_1-C_{10})-alkanoyl, optionally substituted (C_7-C_{16})-aralkanoyl or optionally substituted (C_6-C_{12})-aroyl, where

the radicals R^1 and R^2 or R^2 and R^3, together with the pyridine or pyridazine carrying them, preferably form a 5, 6, 7, 8-tetrahydroisoquinoline ring, a 5, 6, 7, 8-tetrahydroquinoline ring or a 5, 6, 7, 8-tetrahydrocinnoline ring,
or
R^1 and R^2 or R^2 and R^3 form a carbocyclic or a heterocyclic, 5- or 6-membered aromatic ring, where

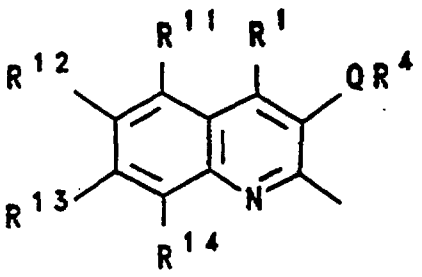
the radicals R^1 and R^2 or R^2 and R^3, together with the pyridine or pyridazine carrying them, preferably form the following optionally substituted heterocyclic ring systems:

Thienopyridines,
Furanopyridines,
Pyridopyridines,
Pyrimidinopyridines,
Imidazopyridines,

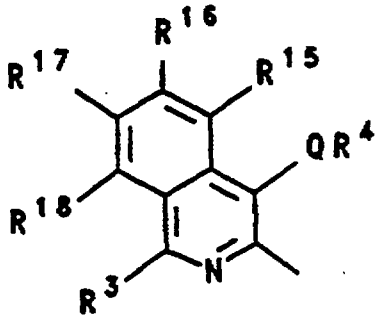
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Thiazolopyridines,
Oxazolopyridines,
Quinoline, isoquinoline and
Cinnoline,

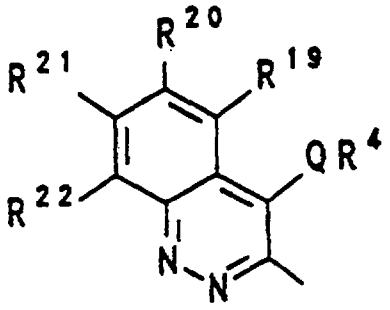
where quinoline, isoquinoline or cinnoline preferably satisfy the formulae 1a, 1b and 1c



1a



1b



1c

and the substituents R^{11} to R^{22}, in each case independently of each other, have the meaning of R^1, R^2 and R^3,

R^4 is, if Q is a bond, halogen, nitrile or trifluoromethyl, or, if Q is O, S or NR', a branched or unbranched (C_1-C_{20})-alkyl radical, an unsubstituted, saturated fluoroalkyl radical of the formula $[CH_2]_x$-$C_fH_{(2f+1-g)}F_g$, a (C_6-C_{16})-aryl radical, a (C_7-C_{16})-aralkyl radical, a heteroaryl radical or a heteroaralkyl radical,

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where these radicals are substituted by one or more radicals from the group
hydroxyl, halogen, cyano, trifluoromethyl, nitro, carboxyl, (C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl-(C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkoxy, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_2-C_{12})-alkenyl, (C_2-C_{12})-alkynyl, (C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxy, (C_1-C_8)-hydroxyalkyl, (C_6-C_{16})-aryloxy-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_7-C_{12})-aralkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, $-O-[CH_2-]_x-C_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-OCF_2-CHFCl$,

(C_1-C_{12})-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, (C_6-C_{12})-arylcarbonyl, (C_7-C_{16})-aralkylcarbonyl, cinnamoyl, (C_2-C_{12})-alkenylcarbonyl, (C_2-C_{12})-aklynylcarbonyl,

(C_1-C_{12})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy-carbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxy-carbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{12})-alkenyl-oxycarbonyl, (C_2-C_{12})-alkynyloxycarbonyl, (C_6-C_{12})-aryl-oxy-(C_1-C_6)-alkoxycarbonyl, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)cycloalkoxy-(C_1-C_6)-alkoxycarbonyl,

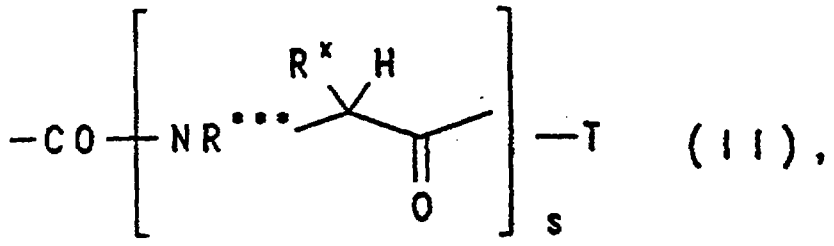
(C_1-C_{12})-alkylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_7-C_{16})-aralkylcarbonyloxy, cinnamoyloxy, (C_2-C_{12})-alkenylcarbonyloxy, (C_2-C_{12})-alkynylcarbonyloxy,

(C_1-C_{12})-alkoxycarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy-

carbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{16})-aralkyloxycarbonyloxy, (C_3-C_8)-cycloalkoxycarbonyloxy, (C_2-C_{12})-alkenyloxycarbonyloxy, (C_2-C_{12})-alkynyloxycarbonyloxy,

carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-dicyclo-(C_3-C_8)-alkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-((C$_3$-C$_8$)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-((C$_3$-C$_8$)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N((C$_1$-C$_{10}$)-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C$_6$-C$_{16}$)-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C$_7$-C$_{16}$)-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C$_1$-C$_{10}$)-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C$_6$-C$_{12}$)-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N(C$_1$-C$_{10}$)-alkyl-N-((C$_7$-C$_{16}$)-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, $CON(CH_2)_h$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7, or by

a carbamoyl radical of the formula II



(II),

in which

R^x is the substituent of an α-amino acid to which the L- and D-amino acids belong,

s is 1, 2, 3, 4 or 5, and

T is OH, OR or NR^*R^{**}, where

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R^*, R^{**}, and R^{***} are identical or different and are hydrogen, (C_6-C_{12})-aryl, (C_7-C_{11})-aralkyl, (C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyl, (+)-dehydroabietyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkyl, (C_1-C_{10})-alkanoyl, optionally substituted (C_7-C_{16})-aralkanoyl or optionally substituted (C_6-C_{12})-aroyl, or

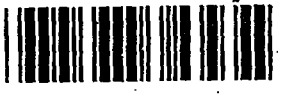
R^* and R^{**} together are $-[CH_2]_h$, in which a CH_2 group can be replaced by O, S, SO, SO_2, N-acylamino, N-(C_1-C_{10})-alkoxycarbonylimino, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7, or by

carbamoyloxy, N-(C_1-C_{12})-alkylcarbamoyloxy, N,N-di-(C_1-C_{12})-alkylcarbamoyloxy, N-(C_3-C_8)-cycloalkylcarbamoyloxy, N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_7-C_{16})-aralkylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyloxy, N-$((C_1-C_{10})$-alkyl)carbamoyloxy, N-$((C_6-C_{12})$-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-$((C_7-C_{16})$-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-$((C_1-C_{10})$-alkoxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-$((C_6-C_{12})$-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-$((C_7-C_{16})$-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy,

amino, (C_1-C_{12})-alkylamino, di-(C_1-C_{12})-alkylamino, (C_3-C_8)-cycloalkylamino, (C_3-C_{12})-alkenylamino, (C_3-C_{12})-alkynylamino, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_1-C_{12})-alkoxyamino, (C_1-C_{12})-alkoxy-N-(C_1-C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino, (C_3-C_8)-cycloalkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{16})-aralkanoylamino, (C_1-C_{12})-alkanoyl-N-(C_1-C_{10})-alkylamino, (C_3-C_8)-cycloalkanoyl-N-(C_1-C_{10})-alkylamino, (C_6-C_{12})-aroyl-N-(C_1-C_{10})-alkylamino, (C_7-C_{11})-aralkanoyl-N-(C_1-C_{10})-alkylamino,

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(C_1-C_{12})-alkanoylamino-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkanoylamino-(C_1-C_8)-alkyl, (C_6-C_{12})-aroylamino-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkanoylamino-(C_1-C_8)-alkyl, amino-(C_1-C_{10})-alkyl, N-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, N,N-di(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, (C_3-C_8)-cycloalkylamino-(C_1-C_{10})-alkyl,

(C_1-C_{12})-alkylmercapto, (C_1-C_{12})-alkylsulfinyl, (C_1-C_{12})-alkylsulfonyl, (C_6-C_{12})-arylmercapto, (C_6-C_2)-arylsulfinyl, (C_6-C_{12})-arylsulfonyl, (C_7-C_{16})-aralkylmercapto, (C_7-C_{16})-aralkylsulfinyl, (C_7-C_{16})-aralkylsulfonyl,

sulfamoyl, N-(C_1-C_{10})-alkylsulfamoyl, N,N-di-(C_1-C_{10})-alkylsulfamoyl, (C_3-C_8)-cycloalkylsulfamoyl,
N-(C_6-C_{12})-arylsulfamoyl,
N-(C_7-C_{16})-aralkylsulfamoyl,
N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylsulfamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylsulfamoyl,
(C_1-C_{10})-alkylsulfonamido,
N-$((C_1-C_{10})$-alkyl$)$-(C_1-C_{10})-alkylsulfonamido, (C_7-C_{16})-aralkylsulfonamido or N-$((C_1-C_{10})$-alkyl-(C_7-C_{16})-aralkyl-sulfonamido, where the radicals which contain an aryl radical can, for their part, be substituted on the aryl by from 1 to 5 identical or different radicals from the group:
hydroxyl, halogen, cyano, trifluoromethyl, nitro, carboxyl, (C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkoyloxy-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl-(C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkoxy, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_2-C_{12})-alkenyl, (C_2-C_{12})-alkynyl, (C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxy,

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(C_1-C_8)-hydroxyalkyl, (C_6-C_{16})-aryloxy-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_7-C_{12})-aralkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, -O-$[CH_2-]_x$-$C_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-OCF_2-CHFCl$,

(C_1-C_{12})-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, (C_6-C_{12})-arylcarbonyl, (C_7-C_{16})-aralkylcarbonyl,

(C_1-C_{12})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{12})-alkenyloxycarbonyl, (C_2-C_{12})-alkynyloxycarbonyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxycarbonyl, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxycarbonyl, (C_1-C_{12})-alkylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_7-C_{16})-aralkylcarbonyloxy, cinnamoyloxy, (C_2-C_{12})-alkenylcarbonyloxy, (C_2-C_{12})-alkynylcarbonyloxy,

(C_1-C_{12})-alkoxycarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{16})-aralkyloxycarbonyloxy, (C_3-C_8)-cycloalkoxycarbonyloxy, (C_2-C_{12})-alkenyloxycarbonyloxy, (C_2-C_{12})-alkynyloxycarbonyloxy,

carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-di-cyclo-(C_3-C_8)-alkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-$((C_3-C_8)$-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-$((C_3-C_8)$-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N-$((C_1-C_{10})$-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-$((C_6-C_{16})$-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-$((C_7-C_{16})$-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-$((C_1-C_{10})$-alkoxy-

(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, $CON(CH_2)_h$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7,

carbamoyloxy, N-(C_1-C_{12})-alkylcarbamoyloxy, N,N-di-(C_1-C_{12})-alkylcarbamoyloxy, N-(C_3-C_8)-cycloalkylcarbamoyloxy, N-(C_6-C_{16})-arylcarbamoyloxy, N-(C_7-C_{16})-aralkylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyloxy, N-((C_1-C_{10})-alkyl)carbamoyloxy, N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy,

amino, (C_1-C_{12})-alkylamino, di-(C_1-C_{12})-alkylamino, (C_3-C_8)-cycloalkylamino, (C_3-C_{12})-alkenylamino, (C_3-C_{12})-alkynylamino, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_1-C_{12})-alkoxyamino, (C_1-C_{12})-alkoxy-N-(C_1-C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino, (C_3-C_8)-cycloalkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{16})-aralkanoylamino, (C_1-C_{12})-alkanoyl-N-(C_1-C_{10})-alkylamino, (C_3-C_8)-cycloalkanoyl-N-(C_1-C_{10})-alkylamino, (C_6-C_{12})-aroyl-N-(C_1-C_{10})-alkylamino, (C_7-C_{11})-aralkanoyl-N-(C_1-C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkanoylamino-(C_1-C_8)-alkyl, (C_6-C_{12})-aroylamino-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkanoylamino-(C_1-C_8)-alkyl, amino-(C_1-C_{10})-alkyl, N-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, N,N-di-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, (C_3-C_8)-cycloalkylamino-(C_1-C_{10})-alkyl,

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(C_1-C_{12})-alkylmercapto, (C_1-C_{12})-alkylsulfinyl, (C_1-C_{12})-alkylsulfonyl, (C_6-C_{16})-arylmercapto, (C_6-C_{16})-arylsulfinyl, (C_6-C_{16})-arylsulfonyl, (C_7-C_{16})-aralkylmercapto, (C_7-C_{16})-aralkylsulfinyl or (C_7-C_{16})-aralkylsulfonyl, and

R^4 is R", provided that Q has the meaning of NR', where R' and R" are identical or different and are hydrogen, (C_6-C_{12})-aryl, (C_7-C_{11})-aralkyl, (C_1-C_8)-alkyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkyl, (C_1-C_{10})-alkanoyl, optionally substituted (C_7-C_{16})-aralkanoyl or optionally substituted (C_6-C_{12})-aroyl, or

R' and R" together are -$[CH_2]$h, in which a CH_2 group can be replaced by O, S, N-acylimino or N-(C_1-C_{10})-alkoxycarbonylimino, and

f is 1 to 8,
g is 0 or 1 to (2f+1),
x is 0 to 3,
h is 3 to 7,

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including the physiologically active salts,
with 3-benzyloxypyridine-2-carboxylic acid (L-threonyl)-amide and 3-benzyloxypyridine-2-carboxylic acid ((Fmoc-Phg)L-threonyl)amide hydrochloride being excepted.

In general, aryl is understood to mean carbocyclic and heterocyclic aromatic ring systems. In particular, it is understood to include phenyl-substituted, biphenyl-substituted, naphthyl-substituted or unsubstituted 5- and 6-membered heteroaromatic rings having 1, 2 or 3 nitrogen and/or oxygen and/or sulfur atoms, such as derivatives of pyridyl, pyridazyl, pyrimidyl, pyrazyl, imidazolyl, triazolyl, thienyl, oxazolyl and thiazolyl, and their benzo-fused derivatives.

The invention also embraces salts of the compounds of the formula I.

The formation of salts with basic reagents can take place once, twice or three times on the acidic groups of the compounds of the formula I (i.e. radicals B, R^1, R^2, R^3 and R^4), in particular on the radicals B, R^2 and/or R^4.

Examples of reagents being used are alcoholates, hydroxides, carbonates, hydrogen carbonates, hydrogen phosphates, organometallic compounds of the alkali and alkaline earth elements, the elements of the third and fourth main groups of the periodic system, and the elements of the transition metals,

amines, optionally substituted 1 to 3 times by (C_1-C_8)-hydroxyalkyl, (C_1-C_4)-alkoxy-(C_1-C_8)-alkyl, phenyl, benzyl or (C_1-C_8)-alkyl, which can be substituted 1 to 3 times by hydroxyl or (C_1-C_4)-alkoxy, for example tromethane (Tris buffer), 2-aminoethanol, 3-aminopropanol, hydroxylamine, dimethylhydroxylamine, 2-methoxyethylamine, 3-ethoxypropylamine, and
basic amino acids and amino derivatives, such as amino acid esters, histidine, arginine and lysine, and their derivatives, and also

pharmaceuticals which contain a basic group, such as, for example, ®Amiloride, ®Verapamil and beta blockers.

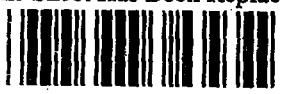
The invention also relates to the compounds according to formula I, plus 3-benzyloxypyridine-2-carboxylic acid (L-threonyl)amide and 3-benzyloxypyridine-2-carboxylic acid ((Fmoc-Phg)L-threonyl)amide hydrochloride for use as pharmaceuticals.

Compounds of the formula I are of great interest, in which

Q is O, S, NR' or a bond,
X is O,
Y is CR^3 or,
if R^1 and R^2 form a cycle,
Y is N or CR^3,

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m is 0 or 1.

Compounds of the formula I are very important, in which
Q is O, NR' or a bond,
X is O.

Compounds of the formula I are also very important in which Q is S and X is O.

Compounds of the formula I are of particular importance in which
Q is O, NR' or a bond,
X is O,
Y is CR^3 or, if R^1 and R^2 form a cycle, N or CR^3,
m is 0 or 1,

A is (C_1-C_3)-alkylene which is optionally substituted once by halogen, cyano, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy or $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$, or

A is $-CHR^5-$, where R^5 is one of the substituents of the α-carbon atom of an α-amino acid, in particular of a natural L-amino acid and of its D-isomer,

B is CO_2H,

R^2 is hydrogen, (C_1-C_{20})-alkyl, (C_2-C_{20})-alkenyl, (C_2-C_{20})-alkynyl, (C_1-C_{20})-alkoxy, (C_2-C_{20})-alkenyloxy, (C_2-C_{20})-alkynyloxy, retinyloxy, (C_1-C_{20})-alkoxy-(C_1-C_3)-alkyl, (C_2-C_{20})-alkenyloxy-(C_1-C_3)-alkyl, retinyloxy-(C_1-C_3)-alkyl, (C_2-C_{20})-alkynyloxy-(C_1-C_3)-alkyl, halogen, cyano, trifluoromethyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_{20})-alkanoyl, (C_7-C_{16})-aralkanoyl, (C_6-C_{12})-aroyl, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$, $NR'R''$, (C_1-C_{10})-alkylmercapto, (C_1-C_{10})-alkylsulfinyl, (C_1-C_{10})-alkylsulfonyl, (C_6-C_{12})-arylmercapto, (C_6-C_{12})-arylsulfinyl, (C_6-C_{12})-arylsulfonyl, (C_7-C_{12})-aralkylmercapto,

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(C_7-C_{12})-aralkylsulfinyl, (C_7-C_{12})-aralkylsulfonyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, carboxyl, (C_1-C_{20})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{20})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_2-C_{20})-alkynyloxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxycarbonyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxycarbonyl, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxycarbonyl,

carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-dicyclo(C_3-C_8)-alkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-$((C_3-C_8)$-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N-$((C_1-C_{12})$-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-$((C_6-C_{16})$-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-$((C_7-C_{16})$-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-$((C_1-C_{10})$-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-$((C_6-C_{12})$-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-$((C_7-C_{16})$-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, $CON(CH_2)_h$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7,

where aryl is substituted in the manner as defined for R^1 and R^3,

R^1 and R^3 are identical or different and are hydrogen, halogen, (C_1-C_{12})-alkyl, (C_1-C_{12})-alkoxy, -O-$[CH_2]_x$-C_f-

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$H_{(2f+1-g)}Hal_g$, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkyl, (C_1-C_8)-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_8)-alkoxy-(C_2-C_6)-alkyl, (C_7-C_{11})-aralkyloxy, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyloxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkoxy, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl-(C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, NR^YR^Z, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl or (C_1-C_8)-alkylsulfonyl, (C_6-C_{12})-arylmercapto, (C_6-C_{12})-arylsulfinyl, (C_6-C_{12})-arylsulfonyl, (C_7-C_{12})-aralkylmercapto, (C_7-C_{11})-aralkylsulfinyl, (C_7-C_{11})-aralkylsulfonyl, substituted (C_6-C_{12})-aryloxy-(C_1-C_6)-alkyl, (C_7-C_{11})-aralkoxy-(C_1-C_6)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_7-C_{11})-aralkyloxy-(C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{11})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy or (C_7-C_{11})-aralkoxy-(C_1-C_6)-alkoxy, where an aromatic radical carries by 1, 2, 3, 4 or 5 identical or different substituents from the group hydrogen, halogen, cyano, nitro, trifluoromethyl, (C_1-C_{16})-alkyl, (C_1-C_{16})-alkenyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_{16})-alkoxy, (C_1-C_{16})-alkenyloxy, -O-$[CH_2]_x$-$C_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, -O-CF_2-CHFCl, (C_1-C_6)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkylcarbamoyl, phenyl, benzyl, phenoxy, benzyloxy, NR^YR^Z, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl or N,N-di-(C_1-C_4)-alkylsulfamoyl, or optionally carries up to 3 of the abovementioned identical or different substituents, and two adjacent carbon atoms of the aralkyloxy radical together carry a chain-$[CH_2]$ and/or -CH=CH-CH=CH-, where a CH_2 group of the chain is optionally replaced by O, S, SO, SO_2 or NR',

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R^1 and R^2 or R^2 and R^3 form a chain $[CH_2]_o$, where o is 3, 4 or 5, or

form, together with the pyridine or pyridazine carrying them, a cinnoline ring, a quinoline ring or an isoquinoline ring,

R^4 is, if Q is a bond, fluorine, chlorine or bromine, or, if Q is O or NR', a branched or unbranched (C_1-C_{20})-alkyl radical, which can contain up to 3 C-C multiple bonds, an unsubstituted saturated fluoroalkyl radical of the formula $[CH_2]_x$-$C_fH_{(2f+1-g)}F_g$, a (C_6-C_{16})-aryl radical or a (C_7-C_{16})-aralkyl radical, which can contain up to 2 C-C multiple bonds in the alkyl chain, or an heteroaryl radical or an heteroaryl alkyl radical, where these radicals are substituted by one or more radicals from the group hydroxyl, fluorine, chlorine, cyano, trifluoromethyl, carboxyl, (C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl-(C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxy-(C_1-C_8)-alkoxy, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_2-C_{12})-alkenyl, (C_2-C_{12})-alkynyl, (C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxy, (C_1-C_8)-hydroxyalkyl, -O-$[CH_2]_x$-$C_fH_{(2f+1-g)}F_g$,

(C_1-C_{12})-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, (C_6-C_{12})-arylcarbonyl, (C_7-C_{16})-aralkylcarbonyl,

(C_1-C_{12})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{12})-alkenyloxycarbonyl, (C_2-C_{12})-alkynyloxycarbonyl,

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(C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl,

(C_1-C_{12})-alkylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_7-C_{16})-aralkylcarbonyloxy, carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-dicyclo-(C_3-C_8)-alkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-$((C_3-C_8)$-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-$((C_3-C_8)$-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N-$((C_1-C_{10})$-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-$((C_6-C_{16})$-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-$((C_7-C_{16})$-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, $CON(CH_2)_h$ in which a CH_2 group can be replaced by O, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino or N-(C_7-C_{16})-aralkylimino, and h is from 3 to 6,

where the radicals which contain an aryl radical can, for their part, be substituted on the aryl by from 1 to 5 identical or different radicals from the group:

hydroxyl, fluorine, chlorine, cyano, trifluoromethyl, carboxyl, (C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyl, (C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkoxy, (C_1-C_{12})-alkoxycarbonyl,

N-(C_1-C_6)-alkylcarbamoyl, N,N-di-(C_1-C_6)-alkylcarbamoyl or N-(C_3-C_8)-cycloalkylcarbamoyl, and

R^4 is R^*, provided Q has the meaning of NR', where R' and R^* are identical or different and are hydrogen, (C_1-C_8)-alkyl, or (C_7-C_{11})-aralkyl which is optionally

substituted once by fluorine, chlorine or (C_1-C_4)-alkoxy,

R^Y and R^Z are identical or different and are hydrogen, (C_6-C_{12})-aryl, (C_1-C_{10})-alkyl, (C_3-C_{10})-cycloalkyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkyl, (C_1-C_{10})-alkanoyl, optionally substituted (C_7-C_{16})-aralkanoyl or optionally substituted (C_6-C_{12})-aroyl, or

R^Y and R^Z together are $-[CH_2]_{h-}$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_4)-alkanoylimino or N-(C_1-C_4)-alkoxycarbonylimino, and

f is 1 to 8,
g is 0 or 1 to (2f + 1),
h is 3 to 6,
x is 0 to 3, and
n is 3 or 4.

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Compounds of the formula I are preferred in which

Q is O, NR' or a bond,
X is O,
Y is CR^3 or, if R^1 and R^2 form a cycle, N or CR^3,
m is 0,

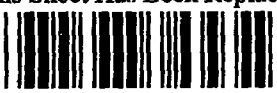
A is (C_1-C_3)-alkylene which is optionally substituted once by halogen, cyano, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy or $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$ or

A is $-CHR^5-$, where R^5 is one of the substituents of the α-carbon atom of an α-amino acid, in particular of a natural L-amino acid and of its D-isomer,

B is CO_2H

R^2 is hydrogen, (C_1-C_{20})-alkyl, (C_2-C_{20})-alkenyl, (C_2-C_{20})-alkenyloxy, (C_2-C_{20})-alkynyloxy, retinyloxy,

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(C_1-C_{20})-alkoxy-(C_1-C_3)-alkyl, (C_1-C_{20})-alkoxy-(C_1-C_3)-alkyl, (C_2-C_{20})-alkenyloxy-(C_1-C_3)-alkyl, retinyloxy-(C_1-C_3)-alkyl, (C_2-C_{20})-alkynyloxy-(C_1-C_3)-alkyl, (C_1-C_{20})-alkoxy, halogen, cyano, trifluoromethyl, (C_1-C_{16})-hydroxyalkyl, (C_1-C_{20})-alkanoyl, (C_7-C_{12})-aralkanoyl, (C_6-C_{12})-aroyl, $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$, $NR'R''$, (C_1-C_{10})-alkylmercapto, (C_1-C_{10})-alkylsulfinyl, (C_1-C_{10})-alkylsulfonyl, (C_6-C_{12})-arylmercapto, (C_6-C_{12})-arylsulfinyl, (C_6-C_{12})-arylsulfonyl, $(C_7-C_{12}$aralkylmercapto, (C_7-C_{12})-aralkylsulfinyl, (C_7-C_{12})-aralkylsulfonyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, carboxyl, (C_1-C_{20})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{20})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_2-C_{20})-alkynyloxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxycarbonyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxycarbonyl, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-dicyclo(C_3-C_8)-alkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-$((C_3-C_8)$-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{12})-aralkylcarbamoyl, N-$((C_1-C_{12})$-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-$((C_6-C_{16})$-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-$((C_7-C_{16})$-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-$((C_1-C_{10})$-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-$((C_6-C_{12})$-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-$((C_7-C_{16})$-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, or $CON(CH_2)_h$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino,

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N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 6,

where aryl is substituted in the manner as defined for R^1 and R^3,

R^1 and R^3 are identical or different and are hydrogen, halogen, (C_1-C_{12})-alkyl, (C_1-C_{12})-alkoxy, -O-[CH_2]$_x$-$C_fH_{(2f+1-g)}Hal_g$, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkyl, (C_1-C_8)-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_8)-alkoxy-(C_2-C_6)-alkyl, (C_7-C_{11})-aralkyloxy, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyloxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkoxy, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl-(C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, NR^YR^Z, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl or (C_1-C_8)-alkylsulfonyl, (C_6-C_{12})-arylmercapto, (C_6-C_{12})-arylsulfinyl, (C_6-C_{12})-arylsulfonyl, (C_7-C_{12})-aralkylmercapto, (C_7-C_{11})-aralkylsulfinyl, (C_7-C_{11})-aralkylsulfonyl, substituted (C_6-C_{12})-aryloxy-(C_1-C_6)-alkyl, (C_7-C_{11})-aralkoxy-(C_1-C_6)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_7-C_{11})-aralkyloxy-(C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{11})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy or (C_7-C_{11})-aralkoxy-(C_1-C_6)-alkoxy, where an aromatic radical carries by 1, 2, 3, 4 or 5 identical or different substituents from the group hydrogen, halogen, cyano, nitro, trifluoromethyl, (C_1-C_{12})-alkyl, (C_1-C_{12})-alkenyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_{12})-alkoxy, (C_1-C_{12})-alkenyloxy, -O-[CH_2]$_x$-$C_fH_{(2f+1-g)}F_g$, -OCF_2Cl, -O-CF_2-CHFCl, (C_1-C_6)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy,

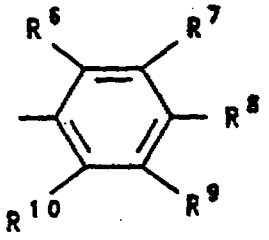
(C_3-C_8)-cycloalkylcarbamoyl, phenyl, benzyl, phenoxy, benzyloxy, NR^YR^Z, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl or N,N-di-(C_1-C_4)-alkylsulfamoyl, or optionally carries up to 3 of the abovementioned identical or different substituents, and two adjacent carbon atoms of the aralkyloxy radical together carry a chain -$[CH_2-]$ and/or -CH=CH-CH=CH-, where a CH_2 group of the chain is optionally replaced by O, S, SO, SO_2 or NR^Y,

R^1 and R^2 or R^2 and R^3 can form a chain $[CH_2]_o$, where o is 3, 4 or 5, and

R^4, provided Q is a bond, is chlorine or, if Q is O or NR', is a branched or unbranched (C_1-C_{10})-alkyl radical, which can contain one or two C-C multiple bonds, or an unsubstituted fluoroalkyl radical of the formula -$[CH_2]_x-C_fH_{(2f+1-g)}F_g$ or (C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_1-C_6)-alkoxy-(C_1-C_4)-alkoxy-(C_1-C_4)-alkyl or a radical of the formula Z,

$$-[CH_2]_v-[O]_w-[CH_2]_t-E \qquad (Z)$$

where E is a substituted phenyl radical of the formula F



(F),

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or a (C_3-C_8)-cycloalkyl radical, where

v is 0, 1, 2, 3, 4, 5 or 6, w is 0 or 1, and t is 0, 1, 2 or 3, with the restriction that v is not equal to 0 if w is 1, and R^6, R^7, R^8, R^9 and R^{10} are identical or different and are hydrogen, halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-alkyl,

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(C_3-C_8)-cycloalkyl, (C_1-C_6)-alkoxy, $-O-[CH_2-]_x-C_zH_{(2z+1-g)}F_g$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, (C_1-C_6)-alkylmercapto, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy-(C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_8)-alkoxycarbonyl, carbamoyl, N-(C_1-C_8)-alkylcarbamoyl, N,N-di-(C_1-C_8)-alkylcarbamoyl, (C_7-C_{11})-aralkylcarbamoyl which is optionally substituted by fluorine, chlorine, bromine, trifluoromethyl or (C_1-C_6)-alkoxy, N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, phenyl, benzyl, phenoxy, benzyloxy, NR^YR^Z, such as amino, anilino, N-methylanilino, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_8)-alkylsulfamoyl or N,N-di-(C_1-C_8)-alkylsulfamoyl, or two adjacent substituents together are a chain $-[CH_2-]_n-CH=CH-CH=CH-$, where a CH_2 group of the chain is optionally replaced by O, S, SO, SO_2 or NR^Y, and where a heteroaryl radical can carry 1, 2 or 3 substituents, and a cycloalkyl radical one substituent, from the above group, and

R^4 is R^*, provided Q has the meaning of NR', where

R' is hydrogen or methyl, and

R^* is benzyl, and

if R^1 and/or R^3 have the meaning of (C_6-C_{12})-aryloxy, (C_7-C_{11})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy, (C_7-C_{11})-aralkoxy-(C_1-C_6)-alkoxy or a corresponding radical containing terminal cycloalkyl groups, this radical is preferably then a radical of the formula D

(D), or

if R^1 and/or R^3 have the meaning of (C_7-C_{11})-aralkyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkyl, (C_7-C_{11})-aralkoxy-(C_1-C_6)-alkyl or a corresponding radical containing terminal cycloalkyl groups, this radical is preferably then a radical of the formula Z,

R^Y and R^Z are identical or different and are hydrogen, (C_6-C_{12})-aryl, (C_1-C_{10})-alkyl, (C_3-C_{10})-cycloalkyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkyl, (C_1-C_{10})-alkanoyl, optionally substituted (C_7-C_{16})-aralkanoyl or optionally substituted (C_6-C_{12})-aroyl, or

R^Y and R^Z are together $-[CH_2]_{h}-$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_4)-alkanoylimino or N-(C_1-C_4)-alkoxycarbonylimino, and

f is 1 to 8,
g is 0 or 1 to (2f+1),
h is 3 to 6,
x is 0 to 3, and
n is 3 or 4.

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Compounds of the formula I are particularly preferred in which

Q is O,
X is O,
Y is CR^3 and, additionally, N if R^1 and R^2 form a cycle,
m is 0,
A is $-CHR^5-$, where R^5 is the substituent of the α-carbon atom of an α-amino acid, in particular of a natural L-amino acid or its D-isomer,

B is CO_2H,

R^2 is hydrogen, bromine, chlorine, cyano, (C_1-C_{18})-alkyl, (C_1-C_8)-alkoxy, (C_1-C_{18})-alkoxymethyl, (C_2-C_{18})-alkenyloxymethyl, (C_2-C_{18})-alkynyloxymethyl, carbamoyl, N-(C_1-C_{10})-alkylcarbamoyl, N-$((C_1-C_{12})$-alkoxy-(C_1-C_4)-alkyl)carbamoyl, N,N-di-(C_1-C_8)-alkylcarbamoyl, N(C_3-C_8)-cycloalkylcarbamoyl, N-(C_6-C_{12})-phenylcarbamoyl, N-(C_7-C_{12})-phenylalkylcarbamoyl, N-(C_1-C_6)-alkyl-N-(C_6-C_{12})phenylcarbamoyl, N-(C_1-C_6)-alkyl-N-(C_7-C_{12})-phenylalkylcarbamoyl,

N-((C_1-C_6)-alkoxy-(C_1-C_6)-alkyl)carbamoyl, carboxyl, (C_1-C_{20})-alkoxycarbonyl, (C_2-C_{20})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxycarbonyl, phenyl-(C_1-C_6)-alkoxycarbonyl, phenoxy-(C_1-C_6)-alkoxycarbonyl or benzyloxy-(C_1-C_6)-alkoxycarbonyl, where a phenyl radical is substituted in the manner as defined for R^1 and R^3, and one of the radicals

R^1 or R^3 is hydrogen and the other a radical from the group hydrogen, fluorine, chlorine, (C_1-C_8)-alkyl, (C_1-C_{10})-alkoxy, (C_5-C_6)-cycloalkyl, (C_5-C_6)-cycloalkyl-(C_1-C_6)-alkyl, (C_5-C_6)-cycloalkyloxy, (C_5-C_6)-cycloalkyl-(C_1-C_6)-alkoxy, (C_5-C_6)-cycloalkyloxy-(C_1-C_6)-alkyl, (C_5-C_6)-cycloalkyloxy-(C_1-C_6)-alkoxy, (C_5-C_6)-cycloalkyl-(C_1-C_4)-alkyl-(C_1-C_4)-alkoxy, (C_5-C_6)-cycloalkyl-(C_1-C_4)-alkoxy-(C_1-C_2)-alkyl, (C_5-C_6)-cycloalkoxy-(C_1-C_4)-alkoxy-(C_1-C_2)-alkyl, $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$, ($C_1$-$C_6$)-alkoxy-($C_1$-$C_6$)-alkyl, ($C_1$-$C_6$)-alkoxy-($C_1$-$C_6$)-alkoxy, ($C_1$-$C_6$)-alkoxy-($C_1$-$C_4$)-alkoxy-($C_1$-$C_2$)-alkyl, substituted ($C_6$-$C_{12}$)-phenoxy, ($C_7$-$C_{11}$)-phenylalkyloxy, ($C_6$-$C_{12}$)-phenoxy-($C_1$-$C_6$)-alkoxy or ($C_7$-$C_{11}$)-phenylalkoxy-($C_1$-$C_6$)-alkoxy, phenoxy-($C_1$-$C_4$)-alkyl, ($C_7$-$C_{11}$)-phenylalkyloxy-($C_1$-$C_4$)-alkyl, phenoxy-($C_1$-$C_4$)-alkoxy-($C_1$-$C_2$)-alkyl or ($C_7$-$C_{11}$)-phenylalkyloxy-($C_1$-$C_4$)-alkoxy-($C_1$-$C_2$)-alkyl, where an aromatic radical is substituted by 1, 2 or 3 identical or different substituents from the group fluorine, chlorine, cyano, trifluoromethyl, (C_1-C_{12})-alkyl, (C_2-C_{12})-alkenyl, (C_2-C_{12})-alkenyloxy or (C_1-C_{12})-alkoxy,

R^1 and R^2, with the pyridine carrying them, form a 5, 6, 7, 8-tetrahydroisoquinoline ring,

R^4 is a branched or unbranched (C_1-C_{10})-alkyl radical, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl or a radical of the formula Z,

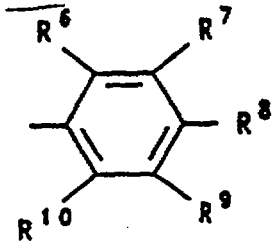
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$$-[CH_2]_v-[O]_w-[CH_2]_t-E \qquad (Z)$$

where E is a substituted phenyl radical of the formula F



(F),

or a (C_3-C_8)-cycloalkyl radical, where v is 0, 1, 2 or 3, w is 0, and t can be 0 or 1, and in which R^6, R^7, R^8, R^9 and R^{10} are identical or different and are hydrogen, fluorine, chlorine, cyano, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$, N-$(C_1-C_8)$-alkylcarbamoyl, N,N-di-$(C_1-C_6)$-alkylcarbamoyl, N-$(C_3-C_6)$-cycloalkylcarbamoyl, N-(+)-dehydroabietylaminocarbonyl, or (C_7-C_{11})-phenylalkylcarbamoyl, which is optionally substituted by fluorine, chlorine, trifluoromethyl or (C_1-C_6)-alkoxy, or where R^6 and R^7 or R^7 and R^8, together with the phenyl ring carying them, form naphthalene derivatives.

If R^1 or R^3 has the meaning of (C_6-C_{12})-phenoxy, (C_7-C_{11})-phenylalkyloxy, (C_6-C_{12})-phenoxy-(C_1-C_6)-alkoxy, (C_7-C_{11})-phenylalkoxy-(C_1-C_6)-alkoxy, (C_5-C_6)-cycloalkyloxy-(C_1-C_6)-alkoxy, (C_5-C_6)-cycloalkoxy-(C_1-C_6)-alkoxy or (C_5-C_6)-cycloalkyl-(C_1-C_4)-alkyl-(C_1-C_4)-alkoxy, this radical is then, especially, a radical of the formula D

OZ (D), or

if R^1 or R^3 has the meaning of phenyl, phenoxy-(C_1-C_6)-alkyl, (C_7-C_{11})-phenylalkyl (C_7-C_{11})-phenylalkyloxy-(C_1-C_4)-alkyl, (C_5-C_6)-cycloalkyl, (C_5-C_6)-cycloalkyl-(C_1-C_6)-alkyl, (C_5-C_6)-cycloalkoxy-(C_1-C_4)-alkyl, (C_5-C_6)-cycloalkyl-(C_1-C_4)-alkoxy-(C_1-C_2)-alkyl or (C_5-C_6)-cycloalkoxy-

(C_1-C_4)-alkoxy-(C_1-C_2)-alkyl, this radical is then, especially, a radical of the formula Z in which, in both cases,

v is 1, 2, 3 or 4, w is 0 and t is 0, or
v is 1, 2, 3 or 4, w is 1 and t is 0, or
v is 1, 2, 3 or 4, w is 1, t is 1, and
f is 1 to 4,
g is 0 or 1 to (2f+1),
x is 0 or 1.

Compounds of the formula I are very particularly preferred in which

Q is O,
X is O,
Y is CR^3,
m is 0,
A is a $-CH_2-$ group which can be substituted by a methyl group,
B is $-CO_2H$,
R^2 is hydrogen, (C_1-C_8)-alkoxy, (C_1-C_{16})-alkoxymethyl, (C_2-C_{16})-alkenyloxymethyl, retinyloxymethyl, N-(C_1-C_{10})-alkylcarbamoyl, N-(((C_1-C_{12})-alkoxy-(C_1-C_3)-alkyl)carbamoyl, N,N-di-(C_1-C_8)-alkylcarbamoyl, N-(C_5-C_6)-cycloalkylcarbamoyl, N-phenylcarbamoyl, N-phenyl-(C_1-C_4)-alkylcarbamoyl, carboxyl, (C_1-C_{16})-alkoxycarbonyl, (C_2-C_{16})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_5-C_6)-cycloalkoxycarbonyl, (C_5-C_6)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl or phenyl-(C_1-C_6)-alkoxycarbonyl, where a phenyl radical is substituted in the manner as defined for R^1 and R^3, and one of the radicals

R^1 or R^3 is hydrogen and the other radical is a radical from the group hydrogen, (C_1-C_{10})-alkoxy, (C_5-C_6)-cycloalkyloxy, (C_5-C_6)-cycloalkyl-(C_1-C_2)-alkoxy, $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$, (C_1-C_4)-alkoxy-(C_1-C_4)-alkoxy, substituted (C_6-C_{12})-phenoxy, (C_7-C_{11})-phenylalkyloxy, (C_6-C_{12})-phenoxy-(C_1-C_4)-alkoxy or (C_7-C_{11})-phenyl-

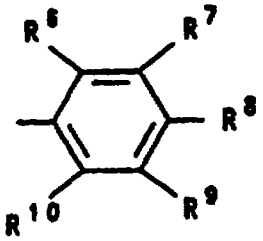
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alkoxy-(C_1-C_4)-alkoxy, where an aromatic radical is substituted by 1, 2 or 3 identical or different substituents from the group fluorine, chlorine, cyano, trifluoromethyl, (C_1-C_{10})-alkyl, (C_1-C_{10})-alkoxy or (C_1-C_{10})-alkenyloxy, and

R^4 is a branched or unbranched (C_1-C_8)-alkyl radical or a radical of the formula Z,

$$-[CH_2]_v-[O]_w-[CH_2]_t-E \qquad (Z)$$

where E is a substituted phenyl radical of the formula F



(F),

or a (C_3-C_8)-cycloalkyl radical, where
v is 0, 1, 2 or 3, w is 0, and t can be 0 or 1, and in which R^6, R^7, R^8, R^9 and R^{10} are identical or different and are hydrogen, fluorine, chlorine, cyano, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$, N-($C_1$-$C_8$)-alkylcarbamoyl, N,N-di-(C_1-C_6)-alkylcarbamoyl, N-(C_3-C_6)-cycloalkylcarbamoyl, N-(+)-dehydroabietylaminocarbonyl substituted benzyl radical, and f is 1 to 4, g is 0 or 1 to (2f+1) and x is 0 or 1.

Compounds of the formula I are particularly preferred in which

Q is O,
X is O,
Y is CR^3,
m is 0,
B is $-CO_2H$,
A is a $-CH_2$-group,

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R^1 is hydrogen, (C_1-C_6)-alkoxy or $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$,

R^2 is hydrogen, N-(C_1-C_{10})-alkylcarbamoyl, N-$((C_1-C_{12})$-alkoxy-(C_1-C_3)-alkyl)carbamoyl, N,N-di-(C_1-C_8)-alkylcarbamoyl, N-(C_5-C_6)-cycloalkylcarbamoyl, N-phenylcarbamoyl, N-phenyl-(C_1-C_4)-alkylcarbamoyl, carboxyl, (C_1-C_{16})-alkoxycarbonyl, (C_2-C_{16})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_5-C_6)-cycloalkoxycarbonyl, (C_5-C_6)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl or phenyl-(C_1-C_6)-alkoxycarbonyl, where a phenyl radical is substituted by 1 or 2 identical or different substituents from the group fluorine, chlorine, cyano, trifluoromethyl, (C_1-C_{10})-alkyl, (C_1-C_{10})-alkenyloxy or (C_1-C_{10})-alkoxy, and

R^3 is hydrogen, (C_1-C_5)-alkoxy or (C_5-C_6)-cycloalkyl-(C_1-C_2)-alkoxy, where one of the substituents R^1 and R^3 is hydrogen,

R^4 is a branched or unbranched (C_1-C_6)-alkyl radical, or a 2-phenylethyl radical, or a benzyl radical substituted by 1 or 2 radicals from the group fluorine, chlorine, cyano, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$, N-$(C_1-C_8)$-alkylcarbamoyl, N,N-di-$(C_1-C_6)$-alkylcarbamoyl, N-$(C_3-C_6)$-cycloalkylcarbamoyl or N-(+)-dehydroabietylaminocarbonyl, and f is 1 to 4, g is 0 or 1 to (2f+1) and x is 1.

Compounds of the formula I are preferred to the highest degree in which

Q is O,

X is O,

Y is CR^3,

m is 0,

A is a $-CH_2-$group,

B is $-CO_2H$,

R^1 is hydrogen,

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R^2 is hydrogen, N-(C_1-C_{10})-alkylcarbamoyl, N-((C_1-C_{12})-alkoxy-(C_1-C_3)-alkyl)carbamoyl, N-cyclohexylcarbamoyl, N-phenylcarbamoyl, N-(phenyl-(C_1-C_2)-alkyl)-carbamoyl, where, in the last two cases, the phenyl radical can carry a fluorine substituent, (C_1-C_{10})-alkyl substituent or (C_1-C_{10})-alkoxy substituent, carboxyl, (C_1-C_{16})-alkoxycarbonyl, (C_2-C_{16})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_5-C_6)-cycloalkoxycarbonyl or benzyloxycarbonyl,

R^3 is hydrogen, (C_1-C_6)-alkoxy or 2-(cyclohexyl)ethyloxy, where one of the substituents R^2 and R^3 is hydrogen,

R^4 is a branched or unbranched (C_1-C_4)-alkyl radical or a benzyl radical which is substituted once by fluorine, chlorine, trifluoromethyl, (C_1-C_4)-alkyl or (C_1-C_3)-alkoxy.

Compounds of the formula I are also preferred to the highest degree in which

Q is S,

X is O,

Y is CR^3,

m is 0,

A is a $-CH_2-$ group,

B is $-CO_2H$,

R^1 is hydrogen,

R^2 is hydrogen, N-(C_1-C_{10})-alkylcarbamoyl, N-((C_1-C_{12})-alkoxy-(C_1-C_3)-alkyl)carbamoyl, N-cyclohexylcarbamoyl, N-phenylcarbamoyl, N-(phenyl-(C_1-C_2)alkyl)-carbamoyl, where, in the last two cases, the phenyl radical can carry a fluorine substituent, (C_1-C_{10})-alkyl substituent or (C_1-C_{10})-alkoxy substituent, carboxyl, (C_1-C_{16})-alkoxycarbonyl, (C_2-C_{16})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_5-C_6)-cycloalkoxycarbonyl or benzyloxycarbonyl,

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R^3 is hydrogen, (C_1-C_6)-alkoxy or 2-(cyclohexyl)-ethyloxy, where one of the substituents R^2 and R^3 is hydrogen, and

R^4 is a branched or unbranched (C_1-C_4)-alkyl radical or a benzyl radical which is substituted once by fluorine, chlorine, trifluoromethyl, (C_1-C_4)-alkyl or (C_1-C_3)-alkoxy.

The compounds of the formula I are also preferred to the highest degree in which

Q is S,
X is O,
Y is CR^3,
m is 0,
A is a $-CH_2-$group,
B is $-CO_2H$,
R^1 is hydrogen,
R^2 is carboxyl or (C_1-C_{16})-alkoxycarbonyl,
R^3 is hydrogen, and
R^4 is a branched or unbranched (C_1-C_4)-alkyl radical.

The compound of the formula I is also preferred to the highest degree in which

Q is O,
X is O,
Y is CR^3, where R^3 is hydrogen,
m is 0,
A is a $-CH_2-$group,
B is $-CO_2H-$,
R^1 and R^2, together with the pyridine carrying them, form an isoquinoline ring having an unsubstituted benzo moiety, and
R^4 is methyl.

The compound of the formula I is also preferred to the highest degree in which

Q is O,

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X is O,
Y is CR^3,
m is 0,
A is a $-CH_2-$group,
B is $-CO_2H$,
R^1 is hydrogen,
R^2 and R^3, together with the pyridine carrying them, form a quinoline ring having an unsubstituted benzo moiety, and
R^4 is methyl.

The invention also embraces prodrugs for the compounds of the formula (I), which prodrugs bring about an inhibition of collagen biosynthesis in vivo by liberating compounds of the formula I or their salts.

Finally, the invention also embraces prodrugs which, by liberating compounds of the formula I or their salts, bring about an inhibitory effect in vivo on prolyl-4-hydroxylase.

Prodrug groupings are chemical groups which, in vivo,

- are converted into the carboxylate group of the compounds of the formula I, and/or
- can be cleaved from the amide N atom, and/or
- can be converted into a pyridine ring.

Those prodrug groups which are suitable are known to the person skilled in the art.

The following prodrug groupings receive particular mention:
for the carboxylate group, ester groups, amide groups, hydroxymethyl groups and aldehyde groups, and their derivatives; for the pyridine N atom, N-oxides and N-alkyl derivatives; and for the pyridine ring, 1,4-dihydropyridine derivatives or tetrahydropyridine derivatives.

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The invention relates to the use of compounds of the formula I, and also the physiologically tolerated salts, for inhibiting collagen biosynthesis.

The invention relates to the use of compounds of the formula I, and also the physiologically tolerated salts, for inhibiting prolyl-4-hydroxylase.

The invention also relates to the use of compounds of the formula I, and also the physiologically tolerated salts, for producing a pharmaceutical against fibrotic diseases.

The invention also relates to the use of compounds of the formula I, and also the physiologically tolerated salts, for producing a pharmaceutical against fibrotic diseases of the liver, the lung and the skin.

Finally, the invention relates to the compounds of the formula I for use as pharmaceuticals.

The invention relates, in particular, to the compounds of the formula I for use as fibrosuppressive agents.

The invention also relates to a process for preparing compounds of the formula I.

The compounds of the formula I, in which A is a substituted alkylene moiety, B is CO_2H, Y is CR^3 and m is 0 or 1, are prepared by

i1.) Reacting pyridine-2-carboxylic acids of the formula II (R^{23} is H) with the amino esters of the formula III to form the amide esters of the formula IV, or

i2.) Reacting pyridine-2-carboxylic esters of the formula II (R^{23} is lower alkyl), under the conditions of aminolysis, to form the compounds of the formula IV; and

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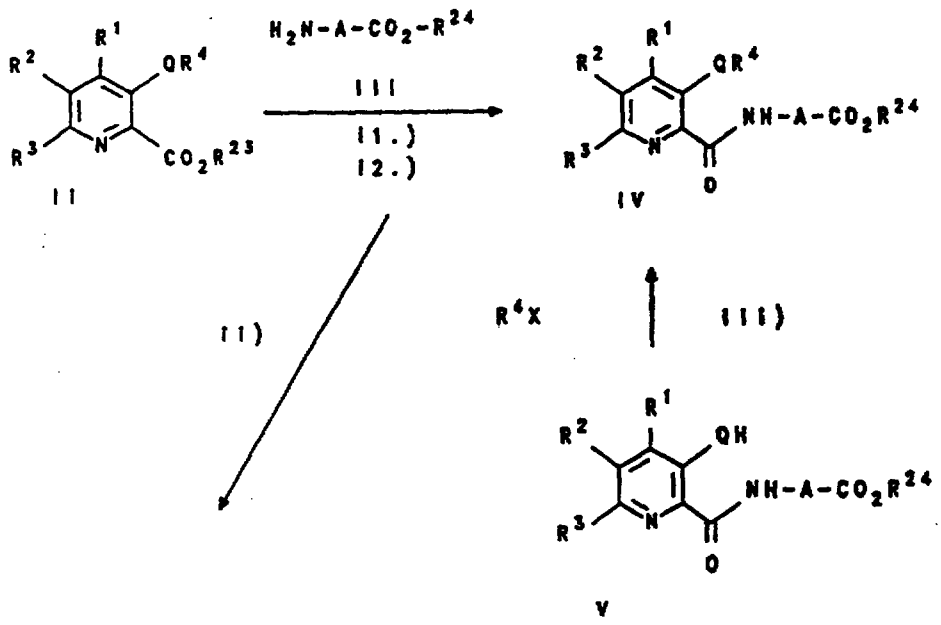


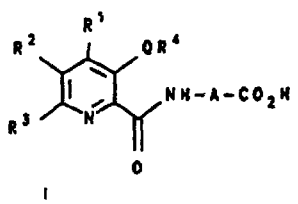
ii) liberating the compounds of the formula I from their esters of the formula IV; with, where appropriate,

iii) the compounds of the formula IV being prepared by alkylation of compounds of the formula V with R^4X, and, where appropriate,

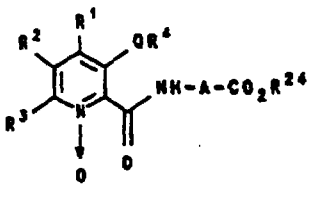
iv) the compounds of the Formula IV being converted, provided Q is O or NR', into their pyridine N-oxides IV' (R^{24} is (C_1-C_{16})-alkyl or benzyl) and the latter being hydrolyzed to form the pyridine N-oxides of the formula I' (R^{24} is H).

Scheme 1





I



IV': R^{24} = (C_1-C_{16})-alkyl, benzyl

I': R^{24} = H

R^{23} is H or (C_1-C_{16})-alkyl,

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R^{24} is H, (C_1-C_{16})-alkyl or benzyl,
X is a leaving group, in particular halogen, OSO_2Me or OSO_2phenyl

The methods of carboxyl activation and the condensation reactions known from peptide chemistry are suitable processes for the amide formation (reaction i1).

The substances which are known to the person skilled in the art, such as thionyl chloride, oxalyl chloride, pivaloyl chloride, chloroformate derivatives, or N,N'-carbonyldiimidazole, can be used as reagents for the carboxylic acid activation. The activated derivatives of the compounds of the formula II are prepared in situ and then reacted with the amide derivatives of the formula III.

An example of a suitable condensing agent is the combination of N,N'-dicyclohexylcarbodiimide/N-hydroxy-1H-benzotriazole and N-ethylmorpholine.

Suitable solvents are dichloromethane, tetrachloromethane, butyl acetate, ethyl acetate, toluene, tetrahydrofuran, dimethoxyethane, 1,4-dioxane, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, nitromethane and/or pyridine.

The compounds of the formula I, in which R^1 and R^3 are hydrogen and R^2 is a carboxyl substituent, a carbamoyl substituent or an ester substituent, were prepared as outlined in schemes 1, 2 and 3.

Scheme 2 illustrates the preparation of the compounds of the formula II in which R^2 is a carboxylic acid substituent, or its derivative, and R^1 and R^3 are hydrogen.

The 3-substituted 5-carboxypyridine-2-carboxylic esters of the formula XI and their isomers of the formula XII

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are prepared from the pyridine-2,5-dicarboxylic diesters of the formula VII.

The oxidation of the pyridine-2,5-dicarboxylates of the formula VII is described in J. Chem. Soc. Perkin Trans. 2, 1978, 34-38 and in J. Org. Chem. 25 (1960) 565 to 568 (M.L. Peterson).

The halogenation (chlorination) of the pyridine N-oxides of the formula VIII with thionyl chloride and the reaction of the 3-chloropyridine-2,5-dicarboxylic diester (Formula IX) with alcoholates (Q is O or S) can be carried out in analogy with the process described in the patent specification CH 658 651 (LONZA), where M is a singly charged or doubly charged metal ion, preferably from the first or second main group of the periodic system.

In analogy with the known literature (CA: vol. 68, 1968, 68 840 h), the monoesters of the formula XII are prepared, under hydrolysis conditions, from the substituted pyridine-2,5-dicarboxylic diesters of the formula Xb.

Selective hydrolysis using Cu(II) salts, J. Delarge in Pharmaceutica Acta Helvetiae 44, 637-643, 1969, represents another process for preparing the compounds of the formula XII from the diesters of the formula Xb.

The compounds of the formula XII thus obtained are reacted with the amino esters of the formula III to form the compounds of the formula IV (Scheme 2).

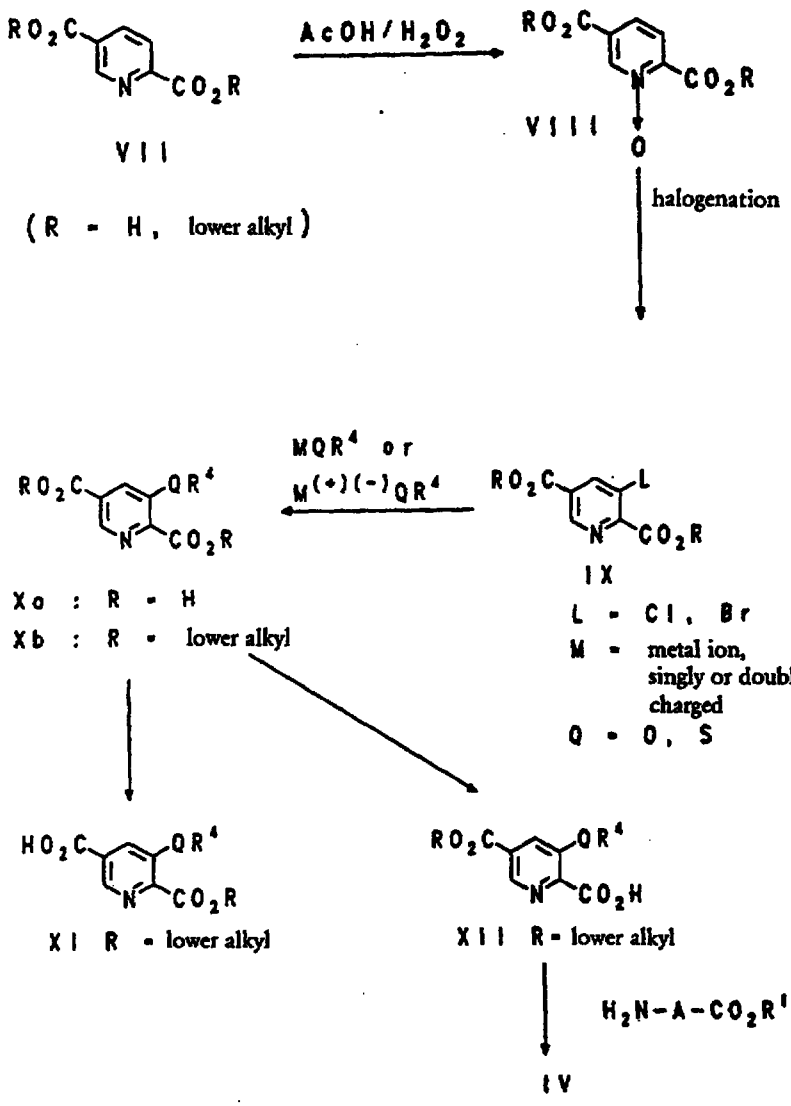
The pyridine-2-carboxylic ester-5-carboxylates of the formula XI can be prepared, under esterification conditions, from substituted pyridine-2,5-dicarboxylic acids of the formula Xa (see CA: vol. 68, 1968, 68840 h). Suitable conditions are, for example, esterification with methanol in the presence of sulfuric acid, it being necessary to choose the reaction time so that complete

esterification to form the diester product only takes place to a secondary extent, or so that the diester products can be separated off as by-products.

The compounds of the formula XI are converted with amines or alcohols into the 5-carboxylic acid derivatives of the formula XIV (Scheme 3).

These are then hydrolysed to form the compounds of the formula II (R^{23} is H), which compounds are subsequently reacted in analogy with Scheme 1.

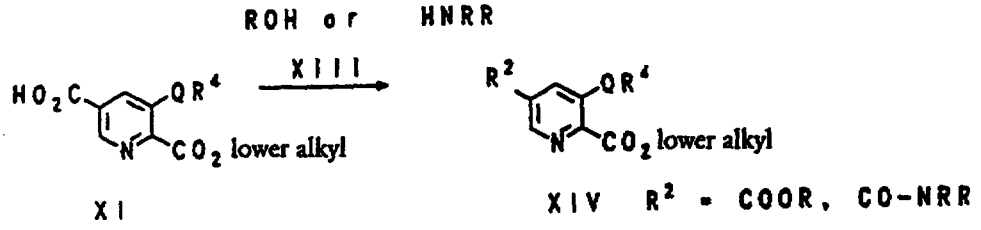
Scheme 2



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Scheme 3

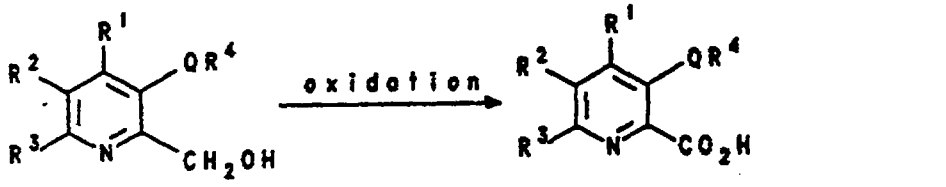


XI

XIV R^2 = COOR, CO-NRR

The 2-hydroxymethylpyridines of the formula VIa, which are disclosed in EP-A-0 304 732, EP-A-0 321 385 and EP-A-0 208 452, can be used as intermediates for preparing derivatives (R^1) which are substituted in the 4 position.

Scheme 4



VI II (R^{11} = H)

VIa / IIa : OR^4 = OMe (Me = methyl)

VIb / IIb : OR^4 = OBn (Bn = benzyl)

The 3-O-benzyl derivatives of the formula VIb were also obtained in an analogous manner, as described in those documents.

The compounds of the formulae VIa and VIb were reacted with an oxidizing agent, preferably with $KMnO_4$ in aqueous alkaline medium, to form the pyridine-2-carboxylic acid derivatives of the formula II (cf. Scheme 4).

The preparation of substituted pyridine-2-carboxylic acids is, for example, disclosed in DE-A-353 046, and for 3-(3-chlorophenoxy)pyridine-2-carboxylic acid and 3-(3-methylphenoxy)pyridine-2-carboxylic acid in J. Med. Chem. 1975, 18, pp. 1-8, Villani et al.; for

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3,5-diethoxypyridine-2-carboxylic acid in J. Med. Chem. 1974, 17, pp. 172-181, French et al.; and for 3-methylthiopyridine-2-carboxylic acid and 3-benzylthiopyridine-2-carboxylic acid in J. Med. Chem. 1974, 17, pp. 1065-1071, Blank et al.; and for 3-methoxypyridine-2,5-dicarboxylic acid in CH-PS 658 651.

The compounds of the formula I are inhibitors of prolyl-4-hydroxylase. The inhibition of this enzyme was determined as described by Kaule and Günzler in Annal. Biochem. 184, 219 to 297 (1990).

The novel compounds of the formula I possess valuable pharmacological properties and exhibit, in particular, antifibrotic activity.

The antifibrotic effect can, for example, be determined using the model of carbon tetrachloride-induced hepatic fibrosis. For this, rats are treated twice a week with CCl_4 (1 ml/kg) - dissolved in olive oil. The substance under test is administered daily, where appropriate even twice a day, per os, or intraperitoneally - dissolved in a suitable tolerated solvent. The extent of the hepatic fibrosis is determined by histology, and the proportion of collagen in the liver is analyzed by means of determining hydroxyproline - as described in Kivirikko et al. (Anal. Biochem. 19, 249 f. (1967)). The fibrogenic activity can be measured by the radioimmunological determination of collagen fragments and procollagen peptides in the serum. In this model, the novel compounds are active at a concentration of from 1 to 100 mg/kg.

The fibrogenic activity can be measured by radioimmunological determination of the N-terminal propeptide of collagen type III or of the N-terminal or C-terminal crosslinking domain of collagen type IV (7s collagen or type IV collagen NC_1) in the serum.

For this purpose, measurements were made of the

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concentrations of hydroxyproline, procollagen III peptide, 7s collagen and type IV collagen NC in the liver of

a) untreated rats (control)

b) rats which were administered carbon tetrachloride (CCl_4 control)

c) rats which were first administered CCl_4 and then a novel compound

(this test method is described by Rouiller, C., Experimental toxic injury of the liver; in The Liver, C. Rouiller, vol. 2, 5. 335 to 476, New York, Academic Press, 1964).

The novel compounds can also be demonstrated to be active in the following systems.

Inhibition of hepatic prolyl-4-hydroxylase in vivo:

This model is used to demonstrate the acute inhibition of prolyl-4-hydroxylase in vivo. For this, rats of both sexes (healthy or with induced hepatic fibrosis) are administered (intraperitoneally, intravenously or per os) the substance under test or the corresponding vehicle and, after this, are given ^{14}C-L-proline (250 µCi/kg of bodyweight), which is administered intraperitoneally. There then follows a second intraperitoneal administration of ^{14}C-L-proline (250 µCi/kg of bodyweight). Finally, the animals are exsanguinated under pentobarbital anesthesia and the livers removed. The hepatic collagen was purified by digestion with pepsin and fractional ammonium sulfate precipitation in conformity with published protocols (Ref. 1 and 2). The purified liver collagen was hydrolyzed and the content of ^{14}C-hydroxyproline and ^{14}C-proline was determined by means of amino acid analysis using ion exchange chromatography. Inhibition of prolyl-4-hydroxylase is shown by a decrease in the quotient ^{14}C-hydroxyproline/[^{14}C-hydroxyproline+^{14}C-proline]. 2,2'-Dipyridyl is used as the reference substance. (1: Chojkier, M. 1986, Hepatocyte

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collagen production in vivo in normal rats, J. Clin. Invest. 78: 333-339 and 2: Ogata I., et al. 1991, Minor contribution of hepatocytes to collagen production in normal and early fibrotic livers, Hepatology 14: 361-367).

Inhibition of prolyl-4-hydroxylase in cell cultures:

The following cell types are used for testing inhibitors of prolyl-4-hydroxylase in cell cultures:
Normal human skin fibroblasts, (NHDF), rat liver epithelial cells, (ref. 1) and primary fat storing cells from rat liver (ref. 2). For this, the cells are cultivated in the presence of inhibitors. At the same time, the collagen which is newly synthesized during this period is metabolically labelled with 4-^{3}H-L-proline and ^{14}C-proline. The influence of the test substances on the degree of hydroxylation of the collagen is then determined in accordance with the method of Chojkier et al (ref. 3). 2,2'-Dipyridyl is employed as the reference substance. (1.: Schrode, W., Mecke, D., Gebhard, R. 1990, Induction of glutamine synthetase in periportal hepatocytes by co-cultivation with a liver epithelial cell line, Eur. J. Cell. Biol. 53: 35-41; 2. Blomhoff, R., Berg T. 1990, Isolation and cultivation of rat liver stellate cells, Methods Enzymol. 190: 59-71; and 3.: Chojkier, M. Peterkofsky, B. Bateman, J. 1980, A new method for determining the extent of proline hydroxylation by measuring changes in the ration of [4-^{3}H]:[^{14}C] proline in collagenase digests, Anal. Biochem. 108: 385-393).

The compounds of the formula I may be used as medicaments in the form of pharmaceutical preparations, which contain the compounds, where appropriate together with tolerated pharmaceutical excipients. The compounds can be used as medicines, for example in the form of pharmaceutical preparations which contain these compounds in a mixture together with a pharmaceutical, organic or inorganic

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excipient which is suitable for enteral, percutaneous or parenteral administration, such as, for example, water, gum arabic, gelatin, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkylene glycols, vaseline, etc.

For this purpose, they can be administered orally in doses of from 0.1 to 25 mg/kg/day, preferably of from 1 to 5 mg/kg/day, or parenterally in doses of from 0.01 to 5 mg/kg/day, preferably of from 0.01 to 2.5 mg/kg/day, in particular of from 0.5 to 1.0 mg/kg/day. The dosage can also be increased in severe cases. In many cases, however, smaller doses are also sufficient. These data refer to an adult of about 75 kg in weight.

The novel compounds of the formula I are designated substituted heterocyclic carboxylic acid glycylamides, preferably pyridine-2-carboxylic acid glycylamides, in the examples described below.
This mode of designation is understood to mean substituted N-carboxymethylpyridine-2-carboxamides.
Another option is to classify them as substituted N-(pyridyl-2-carbonyl)glycines.

Example 1
3-Methoxy-4-(2,2,2-trifluoroethyloxy)pyridine-2-carboxylic acid glycylamide

a) 2-Methyl-3-methoxy-4-chloropyridine N-oxide

11.2 g (80.5 mmol) of 3-methoxy-2-methyl-4(1H)-pyridone were heated under reflux for 10 hours in 100 ml of phosphorus oxychloride. Subsequently, the mixture was concentrated and 30 ml of toluene were added to each 2 ml volume; concentration then took place once again and the residue was taken up in 150 ml of water, with the pH of the mixture then being adjusted to 11 with K_2CO_3; this mixture was then extracted with dichloromethane and the organic phase was washed with water, dried and freed from

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solvent.

8 g of the product were obtained, under standard conditions, from the pale brown oil (9 g) using m-chloroperbenzoic acid in dichloromethane, m.p. 88 to 89°C (from petroleum ether).

b) 2-Methyl-3-methoxy-4-(2,2,2-trifluoroethoxy)pyridine N-oxide

6.7 g of potassium tert-butoxide were added in portions, at -20°C, while stirring and under a nitrogen atmosphere, to 20 ml of trifluoroethanol. After the mixture had been warmed to 0°C, 5.2 g (30 mmol) of 2-methyl-3-methoxy-4-chloropyridine N-oxide were added in portions. The mixture was heated under reflux for 3 hours, and then cooled down to room temperature; a further 3.45 g of potassium tert-butoxide were then added and the mixture was heated under reflux for 2 hours. After it had cooled down, 40 ml of water were added to the reaction mixture, which was then extracted with dichloromethane; the extract was then dried over $MgSO_4$ and freed from solvent in vacuo. The resulting oily product was subjected to further reaction.

c) 3-Methoxy-4-(2,2,2-trifluoroethoxy)-2-hydroxymethylpyridine

8 g (33.8 mmol) of the above compound were dissolved in 16 ml of glacial acetic acid, and 24 ml of acetic anhydride were added, at 80°C and while stirring, to this mixture. The reaction mixture was heated at 110°C for 2 hours and then cooled down to 80°C; 40 ml of methanol were then added to it dropwise. Subsequently, the mixture was concentrated in vacuo, and the oily residue added to 75 ml of 2N methanolic NaOH, with this mixture being stirred for 30 minutes. Following treatment with active charcoal, and filtration, the mixture was concentrated in vacuo and 50 ml of water were added to the residue, after

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which extraction took place with dichloromethane; the extract was dried ($MgSO_4$) and concentrated, and the residue was treated with diisopropyl ether. 3.9 g of the product were obtained in the form of colorless crystals, m.p. 107 to 108°C.

d) 3-Methoxy-4-(2,2,2-trifluoroethyloxy)pyridine-2-carboxylic acid

0.8 g (3.3 mmol) of the above alcohol was dissolved in a solution composed of 0.3 g of potassium hydroxide and 25 ml of water, and 1.6 g of potassium permanganate were added in portions at 100°C and while stirring. After decolorization, the manganese dioxide which had formed was filtered off with suction from the hot mixture and washed twice with hot water; the filtrate was concentrated in vacuo to 1/3 of the volume, adjusted to pH 1 with conc. aqueous hydrochloric acid, and concentrated in vacuo; the residue was treated with anhydrous ethanol and the undissolved material was filtered off. 0.73 g of product, m.p. 157°, was obtained from the filtrate.

e) 3-Methoxy-4-(2,2,2-trifluoroethyloxy)pyridine-2-carboxylic acid (glycyl ethyl ester) amide

0.58 g (2.3 mmol) of the above carboxylic acid was suspended in 100 ml of anhydrous tetrahydrofuran, after which 322 mg (2.3 mmol) of glycine ethyl ester hydrochloride, 0.64 ml (5 mmol) of N-ethylmorpholine, 350 mg (2.6 mmol) of 1-hydroxy-1H-benzotriazole and 537 mg (2.6 mmol) of N,N'-dicyclohexylcarbodiimide were added at 20°C and while stirring, and the mixture was then stirred at 20°C for 48 hours. Undissolved material was then filtered off and the filtrate was concentrated in vacuo; the residue was taken up in ethyl acetate and undissolved material was filtered off; the filtrate was stirred together with 100 ml of a saturated, aqueous solution of Na bicarbonate, and the organic phase was dried and concentrated in vacuo; the residue was

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crystallized using diisopropyl ether. 0.45 g of the colorless crystalline product were obtained, m.p. 80 to 82°C.

f) 0.4 g (1.2 mmol) of the above ester was added to 50 ml of a 1.5 N methanolic solution of sodium hydroxide, and this mixture was stirred at 20°C for 30 minutes. It was then concentrated in vacuo and the residue was taken up in 50 ml of water; this mixture was adjusted to pH 1 with comp. aqueous hydrochloric acid and the small amount of undissolved material was filtered off; the filtrate was concentrated in vacuo and the residue was treated with 50 ml of anhydrous ethanol; this mixture was filtered and the filtrate was concentrated and brought to crystallization using diethyl ether. 0.32 g of the title compound was obtained, m.p. 163 to 165°C (with gas evolution).

Example 2

4-Chloro-3-methoxypyridine-2-carboxylic acid glycylamide

a) 4-Chloro-2-hydroxymethyl-3-methoxypyridine

30 g (173 mmol) of 4-chloro-3-methoxy-2-methylpyridine N-oxide (cf. Example 1a) were dissolved in 100 ml of glacial acetic acid, after which 150 ml of acetic anhydride were added dropwise, at 80°C and while stirring, and the mixture was then stirred at 110°C for 2 hours. The mixture was then cooled down to 80°C and 200 ml of methanol were added dropwise; the mixture was then heated to boiling for 15 minutes and, after having been cooled down, concentrated in vacuo; the residue was taken up in methanol and this mixture was allowed to flow into 300 ml of a 1.5 N methanolic solution of sodium hydroxide, with this mixture then being stirred at 20°C for 30 minutes and concentrated in vacuo; the residue was taken up in water, and this mixture extracted three times with dichloromethane, with the organic phase being dried and concentrated; the residue was crystallized using

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petroleum ether. 23 g of product were obtained, m.p. 64 to 66°C.

b) 4-Chloro-3-methoxypyridine-2-carboxylic acid

8.65 g (50 mmol) of the above alcohol were dissolved in a mixture composed of 0.8 g of potassium hydroxide and 60 ml of water, after which potassium permanganate was added in portions, at 60°C and while stirring, until no more discoloration could be seen (12 g, 75 mmol). After 1 hour at 60°C, the manganese dioxide was filtered off with suction and then washed with hot water; the filtrate was concentrated in vacuo to 200 ml and adjusted, while cooling, to pH 1 with aqueous conc. HCl. After grinding, the product crystallizes out in association with cooling. Additional product can be obtained from the mother liquor by treatment with petroleum ether. Total quantity, 4.2 g, m.p. 116 to 117°C (with gas evolution).

c) 4-Chloro-3-methoxypyridine-2-carboxylic acid (glycyl ethyl ester) amide

4.7 g (25 mmol) of the above carboxylic acid were suspended in 200 ml of anhydrous dichloromethane, and after that 3.5 g (25 mmol) of glycine ethyl ester hydrochloride, 6.4 ml (50 mmol) of N-ethylmorpholine, 3.8 g (28 mmol) of 1-hydroxy-1H-benzotriazole and 5.15 g (25 mmol) of N,N'-dicyclohexylcarbodiimide were added sequentially, at 20°C and while stirring, and the mixture was then stirred at 20°C for 20 hours. Undissolved material was then filtered off and the organic phase was shaken with a saturated, aqueous solution of sodium carbonate, dried and concentrated in vacuo; the residue (6 g of oil) was chromatographed on silica gel using ethyl acetate and 5.4 g of oily product were obtained.

d) The title compound was obtained by hydrolyzing the above ethyl ester. For this, 0.7 g (2.6 mmol) of this

ester was dissolved in 50 ml of methanol/water (3:1), and after that 170 mg (7 mmol) of lithium hydroxide were added at 20°C and while stirring. After 30 minutes, the mixture was concentrated in vacuo; the residue was brought to pH 1 with conc. aqueous hydrochloric acid and this mixture was concentrated in vacuo; the residue was treated twice with anhydrous ethanol and the ethanolic phase was concentrated; the residue was treated with hot ethyl acetate and the amorphous residue was dried on an oil pump. 0.31 g of the title compound was obtained.

Example 3
4-Butyloxy-3-methoxypyridine-2-carboxylic acid glycylamide
M.p. 137 to 139°C (with gas evolution, from tetrahydrofuran)

Examples 4 to 16 were prepared in an analogous manner:

Example 4
3,4-Dimethoxypyridine-2-carboxylic acid glycylamide

Example 5
3-Ethyloxy-4-(3-methoxybenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 6
4-Hexyloxy-3-methoxypyridine-2-carboxylic acid glycylamide

Example 7
3-Methoxy-4-(3-methyl-1-butyloxy)pyridine-2-carboxylic acid glycylamide

Example 8
4-(4-Fluorobenzyloxy)-3-methoxypyridine-2-carboxylic acid glycylamide

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Example 9

3-Methoxy-4-(4-trifluoromethylbenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 10

3-Methoxy-4-(2,2,3,3,3-pentafluoropropyloxy)pyridine-2-carboxylic acid glycylamide

Example 11

4-(2,2,3,3,4,4,4-Heptafluorobutyloxy)-3-methoxypyridine-2-carboxylic acid glycylamide

Example 12

4-(3-Methoxybenzyloxy)-3-methoxypyridine-2-carboxylic acid glycylamide

Example 13

3-Ethyloxy-4-(2,2,2-trifluoroethyloxy)pyridine-2-carboxylic acid glycylamide

Example 14

4-Butyloxy-3-ethyloxypyridine-2-carboxylic acid glycylamide

Example 15

3-Methoxy-4-((phenoxyethyl)oxy)pyridine-2-carboxylic acid glycylamide

Example 16

3-Ethyloxy-4-benzyloxypyridine-2-carboxylic acid glycylamide

Example 17

3,6-Dimethoxypyridine-2-carboxylic acid glycylamide

a) 3,6-Dimethoxy-2-methylpyridine N-oxide

1.15 g (50 mmol) of sodium were dissolved in 100 ml of anhydrous methanol, and after that 7.4 g (40 mmol) of

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3-methoxy-2-methyl-6-nitropyridine N-oxide were added at 20°C and while stirring. The mixture was then heated to reflux for 3 hours and, after having been cooled down, concentrated in vacuo; the residue was taken up in water and this mixture was extracted with dichloromethane; the organic phase was dried and concentrated and the residue was crystallized using diisopropyl ether. 7 g of product were obtained, m.p. 63 to 65°C.

b) 3,6-Dimethoxy-2-hydroxymethylpyridine

7 g (41.4 mmol) of the above compound were reacted with glacial acetic acid/acetic anhydride in analogy with Example 1c) and the resulting acetate was hydrolyzed using 1.5 N methanolic sodium hydroxide solution. 5.6 g were obtained of oily product which was subjected to further reaction under c).

c) 3,6-Dimethoxypyridine-2-carboxylic acid

5.6 g (33 mmol) of the above compound and 2.4 g of potassium hydroxide were dissolved in 150 ml of water, and after that 15 g (100 mmol) of potassium permanganate were added in portions at 60°C and while stirring. The manganese dioxide which had formed was then filtered off with suction and washed twice with hot water; the combined water phase was concentrated to 100 ml, adjusted to pH 1 with conc. aqueous hydrochloric acid while being cooled with ice, and concentrated in vacuo; the residue was treated with ethyl acetate and ethanol, and undissolved material was filtered off from this mixture, with the filtrate being concentrated in vacuo. The residue was crystallized using diethyl ether. 4 g of product were obtained, m.p. 131-132°C (with gas evolution).

d) 3,6-Dimethoxypyridine-2-carboxylic acid (glycyl ethyl ester) amide

2.2 g (12 mmol) of the above carboxylic acid were

suspended in 300 ml of anhydrous dichloromethane, and after that 1.68 g (12 mmol) of glycine ethyl ester hydrochloride, 3.25 ml (25 mmol) of N-ethylmorpholine, 1.62 g (12 mmol) of 1-hydroxy-1H-benzotriazole and 5.2 g (12 mmol) of N-cyclohexyl-N'-(2-morpholinoethyl)carbodiimide methyl-p-toluenesulfonate were added, while stirring, and the mixture was then stirred at 20°C for 20 hours. The small amount of undissolved material was then filtered off and the filtrate was shaken once with water and then with a saturated, aqueous solution of Na bicarbonate; the organic phase was dried and concentrated in vacuo and the residue was crystallized using diisopropyl ether. 2 g of product were obtained, m.p. 93 to 95°C.

e) The title compound was obtained by hydrolyzing 0.6 g (2.24 mmol) of the above ethyl ester at 20°C using 120 mg of lithium hydroxide in 60 ml of methanol/water (3:1). After concentration had taken place in vacuo, the residue was acidified and extracted, at 20°C, with tetrahydrofuran; the filtrate was concentrated in vacuo and the yellow, resinous residue was crystallized using diethyl ether. 0.14 g were obtained of the title compound, m.p. 130°C (decomposition), which is strongly hygroscopic. The residue from the inspissated reaction mixture was then extracted three times with 50 ml of hot acetone on each occasion and the inspissation residue was crystallized using diethyl ether. A further 0.35 g of the title compound was obtained, m.p. 155°C (decomposition).

Example 18

3,5-Diethoxypyridine-2-carboxylic acid glycylamide

Example 19

3-Methoxy-6-(3-methyl-1-butyloxy)pyridine-2-carboxylic acid glycylamide

M.p.: 105 to 107°C (from aqueous hydrochloric acid, pH 3 to 4)

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Example 20

3-Benzyloxy-4-(3-ethyloxypropyloxy)pyridine-2-carboxylic acid glycylamide

M.p. 118-120°C (from acetone)

According to ^{1}H NMR, the product contains approximately 15 % of the 3-hydroxy derivative.

Example 21

3-Benzyloxy-4-hexyloxypyridine-2-carboxylic acid glycylamide

M.p. 130 to 132°C (from aqueous hydrochloric acid)

Example 22

6-(2-Butoxyethyloxy)-3-methoxypyridine-2-carboxylic acid glycylamide

Example 23

6-(2-Cyclohexyl)ethyl)oxy-3-methoxypyridine-2-carboxylic acid glycylamide

M.p. from 70°C (sintering from 50°C, from aqueous hydrochloric acid, pH 3)

Example 24

3-Ethyloxy-6-methylpyridine-2-carboxylic acid glycylamide

Example 25

6-Benzyloxy-3-methoxypyridine-2-carboxylic acid glycylamide

Example 26

3-Benzyloxypyridine-2-carboxylic acid glycylamide

M.p. 142-144°C

Example 27.1

3-Methoxypyridine-2-carboxylic acid glycylamide

amorphous substance, prepared by hydrolyzing the 3-methoxypyridine-2-carboxlic acid (glycyl ethyl ester) amide, m.p. 141 to 142°C (with gas evolution, from

diethyl ether).

This ethyl ester was obtained by catalytic hydrogenation of 4-chloro-3-methoxypyridine-2-carboxylic acid (glycyl ethyl ester) amide (see Example 2c), which was obtained from 4-chloro-3-methoxypyridine-2-carboxylic acid (m.p. 119 to 120°C, from 4-chloro-3-methoxy-2-methylpyridine N-oxide by reaction with acetic anhydride/glacial acetic acid and subsequent oxidation of the 2-hydroxymethyl-pyridine derivative) (see Example 2a, b) and glycine ethyl ester hydrochloride.

Example 27.2
3-Methoxypyridine-2-carboxylic acid glycylamide hydrochloride

a) 4-Chloro-3-methoxypyridine-2-carboxylic acid (glycyl benzyl ester) amide

The product was obtained, in analogy with Example 90a), from 4-chloro-3-methoxypyridine-2-carboxylic acid (cf. Example 2b), glycine benzyl ester tosylate, N-ethylmorpholine, 1-hydroxy-1H-benzotriazole and CMC, m.p. 57-58°C.

b) The title compound was obtained by hydrogenating the above product in methanol/tetrahydrofuran (1:1) using Pd on charcoal (10 %) in a hydrogenation vessel. After removing the catalyst, and freeing from the solvent, the product was crystallized using acetone, m.p. 168°C (with foaming).

Example 28
3-Ethoxypyridine-2-carboxylic acid glycylamide

Example 29
3-Propyloxypyridine-2-carboxylic acid glycylamide

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Example 30

3-Butyloxypyridine-2-carboxylic acid glycylamide

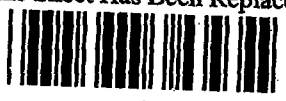
a) 3-n-Butyloxypyridine-2-carboxylic acid

6 g (150 mmol) of NaH (60 %, in mineral oil) were added in portions, at 20°C and while stirring, to 9.8 g (70 mmol) of 3-hydroxypyridine-2-carboxylic acid in 150 ml of N,N-dimethylacetamide. After 30 minutes, 15 ml (140 mmol) of butyl bromide were added dropwise and the mixture was heated at between 95°C and 125°C for 2.5 hours. After having been cooled down, the mixture was concentrated in vacuo, treated with an aqueous solution of Na bicarbonate and extracted with dichloromethane; after drying, the residue was purified by chromatography on silica gel using ethyl acetate.

The 13 g of oily product thus obtained were introduced into 250 ml of a 1.5 N methanolic solution of sodium hydroxide, and the mixture was then stirred at 20°C for 30 minutes and concentrated in vacuo; the residue was taken up in 200 ml of water and this mixture was extracted with dichloromethane and the aqueous phase was adjusted to pH 1 with conc. aqueous hydrochloric acid; concentration took place in vacuo and the residue was treated with ethyl acetate and then with anhydrous ethanol. The resulting solutions were concentrated and the residue was crystallized using acetone. 9.3 g were obtained of product (m.p. 93-95°C) which, according to ^{1}H NMR, still contained approximately 20 % of 3-hydroxy-pyridine-2-carboxylic acid.

b) 2.8 g (20 mmol) of glycine ethyl ester hydrochloride, 5.2 ml (40 mmol) of N-ethylmorpholine, 2.7 g (20 mmol) of 1-hydroxy-1H-benzotriazole and 3.0 ml (20 mmol) of N,N'-diisopropylcarbodiimide were added, at 20°C and while stirring, to 4 g (20 mmol) of the above product in 200 ml of anhydrous tetrahydrofuran and 100 ml of anhydrous acetonitrile, and the mixture was then stirred at 20°C for 20 hours.

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After working up (treatment with Na bicarbonate solution, removal of precipitated diisopropylurea), 3.5 g of oily product, which still contained N,N'-diisopropylurea, were obtained following chromatography on silica gel (ethyl acetate/n-heptane 1:1; then pure ethyl acetate).
This mixture was introduced, at 20°C and while stirring, into 150 ml of a 1.5 N methanolic solution of sodium hydroxide and the total mixture was stirred for 30 minutes.
This latter mixture was then concentrated in vacuo and the residue was taken up in water; this mixture was in turn extracted with 200 ml of dichloromethane and the aqueous phase was brought to pH 1 using conc. aqueous HCl and concentrated in vacuo; the residue was treated with anhydrous ethanol and then with N,N-dimethylformamide, with each extract being filtered to remove undissolved material and then concentrated and each of the residues being crystallized using ethyl acetate. 1.65 g of the title compound were obtained from the ethanol phase (slightly contaminated according to ^{1}H NMR, m.p. 170°C with gas evolution) and a further 0.63 g from the dimethylformamide phase (m.p. 182°C, with gas evolution).

Example 31
3-(4-Chlorobenzyloxy)pyridine-2-carboxylic acid glycylamide

a) 4-Chlorobenzyl 3-(4-chlorobenzyloxy)pyridine-2-carboxylate

8.4 g (60 mmol) of 3-hydroxypyridine-2-carboxylic acid were alkylated (3 hours, 110°C) with 5.2 g (approximately 130 mmol, 60 %) of sodium hydride and 19.3 g (120 mmol) of 4-chlorobenzyl chloride in N,N-dimethylacetamide in analogy with Example 30a). After concentration in vacuo and extraction with Na bicarbonate solution, the residue was purified on silica gel using heptane/ethyl acetate (1:1), and 14.8 g of the product were crystallized from appropriate fractions using diisopropyl ether, m.p. 92 to

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94°C.

b) 3-(4-Chlorobenzyloxy)pyridine-2-carboxylic acid

9.7 g (25 mmol) of the above ester were hydrolyzed with 200 ml of a 1.5 N methanolic solution of sodium hydroxide (24 h, 20°C). After working up (concentration, taking up of the residue in water, extraction with dichloromethane and acidification), 6.5 g of product were obtained, m.p. 144°C (from water, decomposition).

c) 3-(4-Chlorobenzyloxy)pyridine-2-carboxylic (glycyl ethyl ester) amide

3.2 g (12 mmol) of the above pyridine-2-carboxylic acid were reacted, in analogy with example 17d), with 1.7 g (12 mmol) of glycine ethyl ester hydrochloride, 1.62 g (12 mmol) of 1-hydroxy-(1H)-benzotriazole, 3.3 ml (25 mmol) of N-ethylmorpholine and 5.2 g (12 mmol) of N-cyclohexyl-N'-(2-morpholinoethyl)carbodiimide methyl-p-toluenesulfonate. After working up, 3.0 g of the product were crystallized using diisopropyl ether, m.p. 106 to 108°C.

d) The title compound was obtained by hydrolyzing the above ethyl ester. 120 mg (5 mmol) of lithium hydroxide were added to 0.9 g (2.5 mmol) of the ethyl ester in 60 ml of methanol/water (3:1), and the mixture was stirred at 20°C for 1 hour. It was then concentrated in vacuo and the resulting aqueous phase was adjusted to pH 3; the resulting precipitate was filtered off with suction, washed with water and dried in vacuo. 0.52 g of the title compound was obtained, m.p. 155 to 157°C.

Example 32

3-(3-Methoxybenzyloxy)pyridine-2-carboxylic acid glycyl-amide

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a) 3-Methoxybenzyl 3-(3-methoxybenzyloxy)pyridine-2-carboxylate

In analogy with Example 38a), 10 g of the product were obtained as a colorless oil, which was subjected to further reaction, from 8.4 g (60 mmol) of 3-hydroxy-pyridine-2-carboxylic acid and 3-methoxybenzyl chloride following chromatography on silica gel.

b) 3-(3-Methoxybenzyloxy)pyridine-2-carboxylic acid

10 g of the above ester were hydrolyzed in 300 ml of a 1.5 N methanolic solution of sodium hydroxide. 7.5 g of product were obtained, m.p. 147°C (decomposition, from aqueous hydrochloric acid)

c) 3-(3-Methoxybenzyloxy)pyridine-2-carboxylic acid (glycyl ethyl ester) amide

3.2 g (12 mmol) of the above carboxylic acid were reacted in analogy with Example 31c). 3.6 g of oily crude product were isolated which, according to the ^{1}H NMR spectrum, still contained N-ethylmorpholine. The pure substance, m.p. 135 to 137°C (from diisopropyl ether/ethyl acetate) was obtained from this crude product.

d) 2.1 g (6 mmol) of the above product were hydrolyzed using 0.4 g of NaOH in 60 ml of methanol. Following acidification to pH 3, 1.6 g of the title compound were obtained as a colorless crystalline substance, m.p. 89 to 91°C (from aqueous hydrochloric acid).

Example 33

3-(2-Phenylethyloxy)pyridine-2-carboxylic acid glycyl-amide sodium salt

a) 3-(2-Phenylethyloxy)pyridine-2-carboxylic acid

In analogy with Example 30a), 8.4 g (60 mmol) of

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3-hydroxypyridine-2-carboxylic acid were alkylated with NaH/2-phenylethyl bromide in N,N-dimethylacetamide. The 10 g of oily product obtained after purification by column chromatography were hydrolyzed with methanolic sodium hydroxide solution in analogy with Example 30a). 3 g of product were obtained (m.p. 145°C (with foaming, from acetone)) which, according to the ^{1}H NMR spectrum, contained approximately 25 % of 3-hydroxypicolinic acid.

b) 3-((2-Phenylethyl)oxy)pyridine-2-carboxylic acid (glycyl ethyl ester) amide

2.9 g of the above compound were reacted, in analogy with Example 30b), with glycine ethyl ester hydrochloride, N-ethylmorpholine, 1-hydroxy-1H-benzotriazole and N,N-dicyclohexylcarbodiimide. After working up, the crude product was chromatographed on silica gel using ethyl acetate. 3-Hydroxypyridine-2-carboxylic acid (glycyl ethyl ester) amide was initially eluted as a by-product and crystallized from appropriate fractions using petroleum ether; 1.1 g (m.p. 86 to 88°C, strong fluorescence in UV light). The product was then crystallized from appropriate fractions using diisopropyl ether, and 1.7 g of the product were obtained, m.p. 73-75°C.

c) The title compound was obtained by hydrolyzing 0.99 g (3 mmol) of the above ethyl ester using 100 ml of a 1N methanolic solution of sodium hydroxide. After the mixture had been stirred at 20°C for 1 hour, it was concentrated and the residue was dissolved in a little water; this latter mixture was extracted with dichloromethane and the aqueous phase was acidified, while being cooled with ice, to pH 1 using conc. aqueous hydrochloric acid and then concentrated in vacuo; the residue was extracted twice with tetrahydrofuran and the extracts were concentrated; the residue was dissolved in a little water/tetrahydrofuran (1:1), and 252 mg (3 mmol) of sodium bicarbonate were added to this solution. This mixture was concentrated to dryness and the residue was

crystallized using anhydrous ethanol. 0.38 g of the title compound was obtained as sodium salt, m.p. > 300°C.

Example 34
3-(4-Trifluoromethylbenzyloxy)pyridine-2-carboxylic acid glycylamide
M.p. 161 to 163°C (from aqueous hydrochloric acid, pH 3)

Example 35
3-(4-(2-Propyl)benzyloxy)pyridine-2-carboxylic acid glycylamide sodium salt
M.p. 108°C (with decomp., from diisopropyl ether)

Example 36
3-(4-Fluorobenzyloxy)pyridine-2-carboxylic acid glycylamide
M.p.: 135 to 138°C (from aqueous hydrochloric acid, pH 3 to 4)

Example 37
3-(4-(2-(4-Methoxyphenyl)ethylamino)carbonyl)benzyloxy)-pyridine-2-carboxylic acid glycylamide
M.p. 168-170°C (from dichloromethane)

The following example nos. 38-64 were prepared in an analogous manner:

Example 38
3-(2,4-Dichlorobenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 39
3-(3-Fluorobenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 40
3-(3-Chlorobenzyloxy)pyridine-2-carboxylic acid glycylamide

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Example 41
3-(3,4-Dichlorobenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 42
3-(3-Trifluoromethylbenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 43
3-(4-Trifluoromethoxybenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 44
3-(3-Ethoxybenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 45
3-(4-Cyanobenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 46
3-((2-Pyridylmethyl)oxy)pyridine-2-carboxylic acid glycylamide hydrochloride

Example 47
3-((3-Pyridylmethyl)oxy)pyridine-2-carboxylic acid glycylamide hydrochloride

Example 48
3-((4-Pyridylmethyl)oxy)pyridine-2-carboxylic acid glycylamide hydrochloride

Example 49
3-((2-Thienylmethyl)oxy)pyridine-2-carboxylic acid glycylamide

Example 50
3-(3,5-Dimethoxybenzyloxy)pyridine-2-carboxylic acid glycylamide

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Example 51
3-Cyclohexyloxypyridine-2-carboxylic acid glycylamide

Example 52
3-(3-Phenylpropyloxy)pyridine-2-carboxylic acid glycylamide

Example 53
3-(4-Phenylbutyloxy)pyridine-2-carboxylic acid glycylamide

Example 54
3-(((4-Methoxy-2-pyridyl)methyl)oxy)pyridine-2-carboxylic acid glycylamide

Example 55
3-(((4-Ethoxy-2-pyridyl)methyl)oxy)pyridine-2-carboxylic acid glycylamide

Example 56
3-Methylthiopyridine-2-carboxylic acid glycylamide

Example 57
3-Benzylthiopyridine-2-carboxylic acid glycylamide

Example 58
3-(3-Chlorophenoxy)pyridine-2-carboxylic acid glycylamide

Example 59
3-(3-Methoxyphenoxy)pyridine-2-carboxylic acid glycylamide

Example 60
3-Phenoxypyridine-2-carboxylic acid glycylamide

Example 61
3-Butyloxypyridine-2-carboxylic acid L-alanylamide

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Example 62
3-Butyloxypyridine-2-carboxylic acid D-alanylamide

Example 63
3-Benzyloxypyridine-2-carboxylic acid β-alanylamide

Example 64
3-(3-Methylbutyloxy)pyridine-2-carboxylic acid L-leucylamide

Example 65
4-Methoxyisoquinoline-3-carboxylic acid glycylamide

a) Methyl 1,2-dihydro-4-hydroxy-1-oxoisoquinoline-3-carboxylate, was prepared as described (M. Suzuki et al., Synthesis 1978, 461).

b) Methyl 1,2-dihydro-4-methoxy-1-oxoisoquinoline-3-carboxylate, from a) using (trimethylsilyl)-diazomethane in methanol/acetonitrile, m.p. 177 to 179°C (ethyl acetate/heptane).

c) Methyl 1-chloro-4-methoxyisoquinoline-3-carboxylate, from b) using phosphorus oxychloride, m.p. 108°C (ethyl acetate).

d) Methyl 4-methoxyisoquinoline-3-carboxylate, from c) using hydrogen/Pd/C, m.p. 129°C (from methyl tert-butyl ether).

e) 4-Methoxyisoquinoline-3-carboxylic acid, from d) by hydrolysis, m.p. 185-189°C (from aqueous hydrochloric acid).

f) 4-Methoxyisoquinoline-3-carboxylic acid (glycyl methyl ester) amide, from e) using glycine methyl ester hydrochloride, DCC, HOBT, THF and NEM, oily substance (crude product).

g) The title compound was obtained by hydrolyzing the above methyl ester, m.p. 147°C (from aqueous hydrochloric acid)

Examples 66 to 76 were obtained in an analogous manner from the corresponding isoquinoline-3-carboxylic acids or the 5,6,7,8-tetrahydro derivatives, respectively:

Example 66
4-Ethoxyisoquinoline-3-carboxylic acid glycylamide

Example 67
4-Propyloxyisoquinoline-3-carboxylic acid glycylamide

Example 68
4-(3-Methylbutyloxy)isoquinoline-3-carboxylic acid glycylamide

Example 69
4-Methoxy-5,6,7,8-tetrahydroisoquinoline-3-carboxylic acid glycylamide

Example 70
4-(3-Methylbutyloxy)-5,6,7,8-tetrahydroisoquinoline-3-carboxylic acid glycylamide

Example 71
4-Ethoxy-5,6,7,8-tetrahydroisoquinoline-3-carboxylic acid glycylamide

Example 72
4-Benzyloxy-5,6,7,8-tetrahydroisoquinoline-3-carboxylic acid glycylamide

Example 73
4-Benzyloxyisoquinoline-3-carboxylic acid glycylamide

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Example 74
4-(3-Methoxybenzyloxy)-5,6,7,8-tetrahydroisoquinoline-3-carboxylic acid glycylamide

Example 75
7-Bromo-4-methoxyisoquinoline-3-carboxylic acid glycylamide

Example 76
7-Methoxy-4-methoxyisoquinoline-3-carboxylic acid glycylamide

Example 77
3-Methoxy-6-((3-methylbutyloxy)methyl)pyridine-2-carboxylic acid glycylamide

Example 78
3-Methoxy-6-((cyclohexyloxy)methyl)pyridine-2-carboxylic acid glycylamide

Example 79
3-Methoxy-6-benzyloxymethylpyridine-2-carboxylic acid glycylamide

Examples 80 to 91 were prepared in accordance with the processes described in Schemes 1, 2 and 3.

Example 80
5-Carboxy-3-methoxypyridine-2-carboxylic acid glycylamide

270 mg of the title compound from Example 81 were hydrolyzed at 20°C using 50 ml of 1N methanolic NaOH. After 30 minutes, the mixture was concentrated in vacuo and the residue was dissolved in 50 ml of water; this solution was extracted with diethyl ether and the aqueous phase was adjusted to pH 1 with conc. aqueous hydrochloric acid and then concentrated in vacuo; the water was removed azeotropically from the residue using ethyl

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acetate and the residue was then treated with ethanol and this mixture was concentrated; the residue was crystallized using diethyl ether. 230 mg were obtained of the title compound, m.p. 173°C (with gas evolution, sintering at 170°C), which, according to the ^{1}H NMR spectrum, still contains approximately 20 % of an impurity.

The title compound was also obtained by hydrolyzing 0.45 g of 5-((-1-butyloxy)carbonyl)-3-methoxypyridine-2-carboxylic acid N-(((1-butyloxy)carbonyl)methyl)amide, m.p. 80-81°C (from petroleum ether), using 50 ml of 1.5 N methanolic NaOH. 0.23 g was obtained of the title compound, m.p. 198-200°C (from an ethanolic phase whose residue, following concentration, was crystallized using diethyl ether). According to the ^{1}H NMR spectrum and MS, the substance contains approximately 5-10 % of its ethyl ester.

The isomeric 2-carboxy-3-methoxypyridine-5-carboxylic acid glycylamide was obtained in an analogous manner, m.p. from 65°C (sintering from 45°C, with foaming, from diethyl ether, hygroscopic).

Example 81
5-Methoxycarbonyl-3-methoxypyridine-2-carboxylic acid glycylamide

a) 5-Methoxycarbonylpyridine-2-carboxylic acid 1-oxide

12 g (60 mmol) of dimethyl pyridine-2,5-dicarboxylate were suspended in 30 ml of glacial acetic acid, and after that 13 ml of hydrogen peroxide (35 %) were added at 20°C and while stirring. The mixture was then heated to 100°C (internal temperature), while stirring, with a clear solution being formed at 50°C. After the mixture had been stirred at 100°C for 90 minutes, it was allowed to cool down to 20°C and the crystalline precipitate was filtered off with suction and washed with water; After drying, 7.5 g of product were obtained, m.p. 160°C (decomp.).

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b) Dimethyl 3-chloropyridine-2,5-dicarboxylate

17 ml of thionyl chloride, 35 ml of anhydrous chloroform and 1.5 ml of N,N-dimethylformamide were heated to 60°C, while stirring, and 7.5 g of the above product were then added in portions at this temperature. The mixture was then stirred at 60°C for a further 60 minutes, and, after cooling, the solvent and excess reagent were distilled off in vacuo; dichloromethane was added to the residue, and the N,N-dimethylformamide x HCl complex was filtered off with suction and washed with dichloromethane. Approximately 15 ml of triethylamine and 10 ml of methanol were added, while cooling, to the mother liquor and the mixture was stirred for 30 minutes. After concentrating by evaporation in vacuo, the residue was dissolved in 50 ml of water and this mixture was then extracted 3 x with dichloromethane; the organic phase was dried and concentrated, and the residue was chromatographed on silica gel using n-heptane and n-heptane:ethyl acetate (3:1). 5.3 g of product were crystallized, using petroleum ether, from appropriate fractions, m.p. 36 to 38°C.

c) 3-Methoxypyridine-2,5-dicarboxylic acid

53 g (0.231 mol) of the above diester were dissolved in 500 ml of methanol, and after that 150 ml (0.81 mol) of sodium methoxide solution (30 % in methanol) were added, at 20°C and while stirring, whereupon the temperature rose to 30°C. The mixture was heated under reflux for 4.5 hours, 300 ml of water were added at 20°C, and the mixture was then stirred at 35°C for 30 minutes. The excess methanol was distilled off in vacuo and the aqueous phase was adjusted to pH 2, while cooling, with half-concentrated aqueous hydrochloric acid; the colorless crystalline product was filtered off with suction and dried. 49 g were obtained, m.p. 185°C (gas evolution); 255°C (decomp.).

d) Dimethyl 3-methoxypyridine-2,5-dicarboxylate, cf. Example 90a)

e) 5-Methoxycarbonyl-3-methoxypyridine-2-carboxylic acid

The compound was obtained, as a mixture with the isomeric monomethyl ester (cf. Example 90a)), from 3.4 g (15 mmol) of the above diester by hydrolysis with a dilute solution of methanolic sodium hydroxide (0.54 g of NaOH (13.5 mmol)). 1.8 g of monoester mixture, m.p. 152°C, were obtained in addition to 0.8 g of unreacted diester.

f) 5-Methoxycarbonyl-3-methoxypyridine-2-carboxylic acid (glycyl benzyl ester) amide

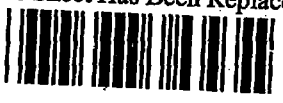
1.8 g of the above mixture were condensed, in analogy with Example 90b), with 2.9 g (8.6 mmol) of glycine benzyl ester tosylate in the presence of N-ethylmorpholine, 1-hydroxy-1H-benzotriazole and CMC. After working up, 2.3 g of oily mixture were chromatographed on silica gel using dichloromethane (in the presence of up to 2 % methanol). 0.82 g of product was obtained, m.p. 108°C. 0.6 g of the oily isomer was also isolated.

g) The title compound was obtained by dissolving 650 mg of the above benzyl ester in 100 ml of tetrahydrofuran/methanol (1:1) and hydrogenating it using Pd/C in a hydrogenation vessel. Once the catalyst had been filtered off with suction, the filtrate was concentrated and the residue was crystallized using diethyl ether. 380 mg were obtained of a colorless crystalline product, m.p. 158 to 160°C.

Example 82

5-(3-Pentyloxy)carbonyl-3-methoxypyridine-2-carboxylic acid glycylamide

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Example 83

5-Cyclohexyloxycarbonyl-3-methoxypyridine-2-carboxylic acid glycylamide

Example 84

5-(n-Butylaminocarbonyl)-3-methoxypyridine-2-carboxylic acid glycylamide

Example 85

5-(2-Methyl-2-butylaminocarbonyl)-3-methoxypyridine-2-carboxylic acid glycylamide

Example 86

5-(Cyclohexylaminocarbonyl)-3-methoxypyridine-2-carboxylic acid glycylamide

a) 5-(Cyclohexylaminocarbonyl)-3-methoxypyridine-2-carboxylic acid

The product was obtained, in analogy with Example 90b), from 5-carboxy-3-methoxypyridine-2-carboxylic acid and cyclohexylamine,
m.p. 155°C (sintering at 80°C, from aqueous hydrochloric acid).

b) 5-(Cyclohexylaminocarbonyl)-3-methoxypyridine-2-carboxylic acid (glycyl ethyl ester) amide

The product was obtained, in analogy with Example 90c), from the above compound, m.p. 187 to 188°C (from diethyl ether)

c) The colorless crystalline title compound was obtained by hydrolyzing the above compound in analogy with Example 90c),
m.p. 110°C (with foaming, a deep-black coloration at 240°C).

Example 87

5-(Cyclohexylaminocarbonyl)-3-ethyloxypyridine-2-carboxylic acid glycylamide

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Example 88

5-((2-Phenylethyl)aminocarbonyl)-3-methoxypyridine-2-carboxylic acid glycylamide

Example 89

5-((+)-Dehydroabietylaminocarbonyl)-3-methoxypyridine-2-carboxylic acid glycylamide

a) 5-((+)-Dehydroabietylaminocarbonyl)-3-methoxypyridine-2-carboxylic acid

The resinous product was obtained, in analogy with Example 90a), from 5-carboxy-3-methoxypyridine-2-carboxylic acid and (+)-dehydroabietylamine.

b) 5-((+)-Dehydroabietylaminocarbonyl)-3-methoxypyridine-2-carboxylic acid (glycyl ethyl ester) amide

The product was obtained in analogy with Example 90c), from the above compound, m.p. from 150°C with foaming, sintering at 120°C, from diethyl ether).

c) The title compound was obtained by hydrolyzing the above compound in analogy with Example 90 d), m.p. 215°C (sintering at 150°C, from aqueous hydrochloric acid).

Example 90

5-((2-(4-Fluorophenyl)ethyl)aminocarbonyl)-3-methoxypyridine-2-carboxylic acid glycylamide

a) Methyl 5-carboxy-3-methoxypyridine-2-carboxylate

10 g (50.7 mmol) of the 3-methoxypyridine-2,5-dicarboxylic acid (Example 81c) were suspended in 150 ml of anhydrous methanol, and after that 2 ml of concentrated sulfuric acid were added and the mixture was heated under reflux for 3 hours. Half of the methanol was then distilled off in vacuo and the residue was introduced

into 400 ml of ice water; the crystalline residue was filtered off with suction and washed with water; the residue was dissolved in 150 ml of a saturated, aqueous solution of Na bicarbonate and this mixture was extracted twice with 80 ml of dichloromethane on each occasion; the bicarbonate phase was adjusted to pH 1, while cooling, with half-concentrated aqueous hydrochloric acid and the precipitated product was filtered off with suction and dried. 5 g of colorless, crystalline substance were obtained, m.p. 196 to 197°C. 1.7 g of dimethyl ester, m.p. 53 to 55°C (from petroleum ether), were obtained from the dichloromethane phase.

b) 5-(((2-(4-Fluorophenyl)ethyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid

3.2 g of methyl 5-carboxy-3-methoxypyridine-2-carboxylate were suspended in 300 ml of anhydrous dichloromethane, and after that 2.0 ml (15 mmol) of 2-(4-fluorophenyl)-ethylamine, 1.95 ml (15 mmol) of N-ethylmorpholine, 2.2 g (16.5 mmol) of 1-hydroxy-1H-benzotriazole and 6.35 g (15 mmol) of N-cyclohexyl-N'-(2-morpholinoethyl)carbodiimide methyl-p-toluenesulfonate (CMC) were added sequentially, at 20°C and while stirring, and the mixture was stirred for 24 hours. The undissolved material was then filtered off and the organic phase was extracted, in each case 3 x, with an aqueous solution of Na bicarbonate, with 1N aqueous hydrochloric acid and with water, and the organic phase was dried and concentrated. 3.7 g were obtained of methyl ester, m.p. 168 to 169°C, which was introduced into 150 ml of 1.5N methanolic NaOH. After 30 minutes, the mixture was concentrated and dissolved in 100 ml of water, and this mixture was adjusted to pH 1 with conc. aqueous hydrochloric acid; the crystalline precipitate was filtered off with suction, washed with water and dried. 3.4 g of product were obtained, m.p. 110°C (with foaming, sintering at 75°C).

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c) 5-(((2-(4-Fluorophenyl)ethyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid (glycyl ethyl ester) amide

In analogy with Example 90a), 3.2 g (10 mmol) of the above compound were reacted with 1.4 g (10 mmol) of glycine ethyl ester hydrochloride, N-ethylmorpholine, 1-hydroxy-1H-benzotriazole and CMC. Following analogous working up, 2.8 g of the colorless crystalline product were crystallized using diisopropyl ether, m.p. 170 to 171°C.

d) The title compound was obtained by hydrolysing 1.0 g of the above glycine ethyl ester, at 20°C, in 1.5N methanolic NaOH. 0.95 g of product, m.p. 206°C (with foaming) crystallizes from aqueous medium at pH 3.

Example 91
5-((2-(4-Methoxyphenyl)ethyl)aminocarbonyl)-3-ethyloxy-pyridine-2-carboxylic acid glycylamide

Examples 92 to 105 were obtained from the correspondingly substituted pyridine-2-carboxylic acid derivatives of the formula II and glycine ethyl ester hydrochloride and with subsequent hydrolysis of the glycine ethyl ester compounds.

Example 92
5-Chloro-3-ethyloxypyridine-2-carboxylic acid glycyl-amide

Example 93
5-Chloro-3-methyloxypyridine-2-carboxylic acid glycyl-amide

Example 94
5-Cyclohexyloxymethyl-3-methoxypyridine-2-carboxylic acid glycylamide

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Example 95
5-(3-Methylbutyl)oxymethyl-3-methoxypyridine-2-carboxylic acid glycylamide

Example 96
5-Benzyloxymethyl-3-ethyloxypyridine-2-carboxylic acid glycylamide

Example 97
3-((Cyclohexyl)methyloxy)pyridine-2-carboxylic acid glycylamide

Example 98
3-((2-Cyclohexyl)ethyloxy)pyridine-2-carboxylic acid glycylamide

Example 99
3-((3-Cyclohexyl)propyloxy)pyridine-2-carboxylic acid glycylamide

Example 100
3-(3-Methylbutyloxy)pyridine-2-carboxylic acid glycylamide

Example 101
3-Hexyloxypyridine-2-carboxylic acid glycylamide

Example 102
3-(4-Ethylbenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 103
3-(4-Propylbenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 104
3-(4-Butylbenzyloxy)pyridine-2-carboxylic acid glycylamide

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Example 105
3-(4-tert-Butylbenzyloxy)pyridine-2-carboxylic acid glycylamide

Examples 106 to 188 were prepared in analogy with Examples 80 to 91.

Example 106
5-Methoxycarbonyl-3-(2-methyl-1-propyloxy)pyridine-2-carboxylic acid glycylamide

a) 3-(2-Methyl-1-propyloxy)pyridine-2,5-dicarboxylic acid

In analogy with Example 81c), 3.5 g (146 mmol) of sodium were dissolved in 350 ml of 2-methyl-1-propanol (isobutyl alcohol), and after that 13.7 g (55 mmol) of 3-chloropyridine-2-carboxylic acid ethyl ester 5-carboxylic acid methyl ester (prepared in analogy with Example 81b)) were added at 20°C and while stirring. The mixture was then stirred at 80°C for 90 minutes and, after cooling, concentrated in vacuo; the residue was taken up in 200 ml of 1 N methanolic NaOH and this mixture was stirred at 20°C. After 15 minutes, the solution became cloudy. Water was added until a clear solution was obtained and this was stirred for 1 hour and then concentrated in vacuo; the aqueous solution was acidified with aqueous hydrochloric acid and the crystalline product was filtered off with suction, washed and dried, and 10.6 g of dicarboxylic acid were obtained, m.p. 192°C (decomp.).

b) Dimethyl 3-(2-methyl-1-propyloxy)pyridine-2,5-dicarboxylate

The oily product was obtained from the above dicarboxylic acid under esterification conditions (methanol/sulfuric acid) and after working up (washing with water and extracting with ethyl acetate).

c) 5-Methoxycarbonyl-3-(2-methyl-1-propyloxy)pyridine-2-carboxylic acid (glycyl benzyl ester) amide

0.48 g (12 mmol) of NaOH, dissolved in 50 ml of methanol, was added to 3.2 g (12 mmol) of the above diester in 25 ml of methanol, and the mixture was stirred at 65°C for 90 minutes. The mixture was then acidified, while being cooled, with dilute aqueous hydrochloric acid and freed from methanol in vacuo. 2.5 g (10 mmol) of the monoester mixture thus obtained were stirred, in analogy with Example 90b), in 250 ml of dichloromethane, at 20°C for 24 hours, together with 3.4 g (10 mmol) of glycine benzyl ester tosylate, 1.4 g (10 mmol) of 1-hydroxy-(1H)-benzotriazole, 2.6 ml (20 mmol) of N-ethylmorpholine and 4.3 g (10 mmol) of CMC.
The undissolved material was then filtered off with suction and the filtrate was extracted with an aqueous solution of Na bicarbonate, with dilute hydrochloric acid and with water; the organic phase was dried and concentrated and the residue was chromatographed on silica gel using n-heptane/ethyl acetate (1:1). 0.8 g of colorless product was obtained from appropriate fractions, m.p. 103 to 105°C. 1.1 g of the isomeric resinous product were also obtained.

d) The title compound was obtained by dissolving 0.7 g of the above compound in 100 ml of tetrahydrofuran/methanol (1:1) and hydrogenating it for 2 hours using Pd on charcoal (10 %) in a hydrogenation vessel. The catalyst was then filtered off with suction and the filtrate was concentrated; the residue was crystallized using diisopropylether and 0.45 g was obtained of the title compound,
m.p. approximately 70°C (with foaming).

The isomeric compound was obtained in an analogous manner, m.p. approximately 60°C (with foaming, from diisopropyl ether).

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Example 107
5-Ethoxycarbonyl-3-(2-methyl-1-propyloxy)pyridine-2-carboxylic acid glycylamide

Example 108
5-Methoxycarbonyl-3-(3-methyl-1-butyloxy)pyridine-2-carboxylic acid glycylamide

Example 109
5-Ethoxycarbonyl-3-ethoxypyridine-2-carboxylic acid glycylamide

Example 110
5-Ethoxycarbonyl-3-(1-propyloxy)pyridine-2-carboxylic acid glycylamide

Example 111
5-Ethoxycarbonyl-3-(2-propyloxy)pyridine-2-carboxylic acid glycylamide

Example 112
3-Benzyloxy-5-ethoxycarbonylpyridine-2-carboxylic acid glycylamide

Example 113
3-(4-Chlorobenzyloxy)-5-ethoxycarbonylpyridine-2-carboxylic acid glycylamide

Example 114
5-Ethoxycarbonyl-3-(4-fluorobenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 115
5-Ethoxycarbonyl-3-(4-(trifluoromethyl)-benzyloxy)pyridine-2-carboxylic acid glycylamide

Example 116
5-Ethoxycarbonyl-3-(4-(trifluoromethoxy)benzyloxy)-pyridine-2-carboxylic acid glycylamide

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Example 117
5-Ethoxycarbonyl-3-(4-(2-propyl)benzyloxy)pyridine-2-carboxylic acid glycylamide

Example 118
3-(4-Ethoxybenzyloxy)-5-ethoxycarbonylpyridine-2-carboxylic acid glycylamide

Example 119
5-Ethoxycarbonyl-3-(3,4-dimethoxybenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 120
5-Ethoxycarbonyl-3-(2-(4-fluorophenyl)ethyloxy)pyridine-2-carboxylic acid glycylamide

Example 121
5-Ethoxycarbonyl-3-(2,2,2-trifluoroethyloxy)pyridine-2-carboxylic acid glycylamide

Example 122
3-Cyclohexyloxy-5-ethoxycarbonylpyridine-2-carboxylic acid glycylamide

Example 123
5-Ethoxycarbonyl-3-(naphthyl-2-methyloxy)pyridine-2-carboxylic acid glycylamide

Example 124
5-Ethoxycarbonyl-3-(naphthyl-1-methyloxy)pyridine-2-carboxylic acid glycylamide

Example 125
5-Carboxy-3-(2-methyl-1-propyloxy)pyridine-2-carboxylic acid glycylamide

The title compound was obtained by hydrolyzing 0.3 g of the title compound from Example 106, at 20°C, in 50 ml of a 1N methanolic solution of sodium hydroxide. After 1 hour, the mixture was concentrated in vacuo and

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extracted with diethyl ether; the aqueous phase was acidified, while being cooled, with aqueous hydrochloric acid; the aqueous phase was concentrated and then freed from water azeotropically using ethyl acetate and the residue was treated with acetone; the solution was concentrated and the residue was crystallized using petroleum ether. 0.27 g of product was obtained, m.p. 80°C (with foaming).

Example 126

5-Carboxy-3-(3-methyl-1-butyloxy)pyridine-2-carboxylic acid glycylamide

Example 127

5-Carboxy-3-ethoxypyridine-2-carboxylic acid glycylamide

Example 128

5-Carboxy-3-propyloxypyridine-2-carboxylic acid glycylamide

Example 129

5-Carboxy-3-(2-propyloxy)pyridine-2-carboxylic acid glycylamide

Example 130

3-Benzyloxy-5-carboxypyridine-2-carboxylic acid glycylamide

Example 131

5-Carboxy-3-(4-chlorobenzyloxy)-2-carboxylic acid glycylamide

Example 132

5-Carboxy-3-(4-fluorobenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 133

5-Carboxy-3-((4-trifluoromethyl)benzyloxy)pyridine-2-carboxylic acid glycylamide

Example 134
5-Carboxy-3-((4-trifluoromethoxy)benzyloxy)pyridine-2-carboxylic acid glycylamide

Example 135
5-Carboxy-3-(4-(2-propyl)benzyloxy)pyridine-2-carboxylic acid glycylamide

Example 136
5-Carboxy-3-(4-ethoxybenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 137
5-Carboxy-3-(3,4-dimethoxybenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 138
5-Carboxy-3-(2-(4-fluorophenyl)ethyloxy)pyridine-2-carboxylic acid glycylamide

Example 139
5-Carboxy-3-(2,2,2-trifluoroethyloxy)pyridine-2-carboxylic acid gylcylamide

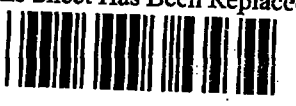
Example 140
5-Carboxy-3-cyclohexyloxypyridine-2-carboxylic acid glycylamide

Example 141
5-Carboxy-3-(naphthyl-2-methyloxy)pyridine-2-carboxylic acid glycylamide

Example 142
5-Carboxy-3-(naphthyl-1-methyloxy)pyridine-2-carboxylic acid glycylamide

Example 143
5-(3-Pentyloxy)carbonyl-3-(2-methyl-1-propyloxy)pyridine-2-carboxylic acid glycylamide

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Example 144
5-(3-Pentyloxy)carbonyl-3-(3-methyl-1-butyloxy)pyridine-2-carboxylic acid glycylamide

Example 145
3-Ethoxypyridine-5-(3-pentyloxy)carbonyl-2-carboxylic acid glycylamide

Example 146
5-(3-Pentyloxy)carbonyl-3-propyloxypyridine-2-carboxylic acid glycylamide

Example 147
5-(3-Pentyloxy)carbonyl-3-(2-propyloxy)pyridine-2-carboxylic acid glycylamide

Example 148
3-Benzyloxy-5-(3-pentyloxy)carbonylpyridine-2-carboxylic acid glycylamide

Example 149
3-(4-Chlorobenzyloxy)-5-(3-pentyloxy)carbonylpyridine-2-carboxylic acid glycylamide

Example 150
3-(4-Fluorobenzyloxy)-5-(3-pentyloxy)carbonylpyridine-2-carboxylic acid glycylamide

Example 151
5-(3-Pentyloxy)carbonyl-3-((4-trifluoromethyl)benzyloxy)-pyridine-2-carboxylic acid glycylamide

Example 152
5-(3-Pentyloxy)carbonyl-3-((4-trifluoromethoxy)benzyloxy)pyridine-2-carboxylic acid glycylamide

Example 153
5-(3-Pentyloxy)carbonyl-3-(4-(2-propyl)benzyloxy)-pyridine-2-carboxylic acid glycylamide

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Example 154
3-(4-Ethoxybenzyloxy)-5-(3-pentyloxy)carbonylpyridine-2-carboxylic acid glycylamide

Example 155
3-(3,4-Dimethoxybenzyloxy)-5-(3-pentyloxy)carbonyl-pyridine-2-carboxylic acid glycylamide

Example 156
3-(2-(4-Fluorophenyl)ethyloxy)-5-(3-pentyloxy)carbonyl-pyridine-2-carboxylic acid glycylamide

Example 157
5-(3-Pentyloxy)carbonyl-3-(2,2,2-trifluoroethyloxy)-pyridine-2-carboxylic acid glycylamide

Example 158
3-Cyclohexyloxy-5-(3-pentyloxy)carbonylpyridine-2-carboxylic acid glycylamide

Example 159
3-(Naphthyl-2-methyloxy)-5-(3-pentyloxy)carbonylpyridine-2-carboxylic acid glycylamide

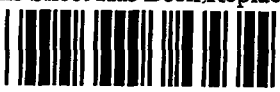
Example 160
3-(Naphthyl-1-methyloxy)-5-(3-pentyloxy)carbonylpyridine-2-carboxylic acid glycylamide

Example 161
5-(4-Heptyloxy)carbonyl-3-(2-methyl-1-propyloxy)pyridine-2-carboxylic acid glycylamide

Example 162
5-(4-Heptyloxy)carbonyl-3-ethoxypyridine-2-carboxylic acid glycylamide

Example 163
3-Benzyloxy-5-(4-heptyloxy)carbonylpyridine-2-carboxylic acid glycylamide

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Example 164
3-(4-Chlorobenzyloxy)-5-(4-heptyloxy)carbonylpyridine-2-carboxylic acid glycylamide

Example 165
3-(4-Fluorobenzyloxy)-5-(4-heptyloxy)pyridine-2-carboxylic acid glycylamide

Example 166
5-(4-Heptyloxy)carbonyl-3-(4-(2-propyl)benzyloxy)-pyridine-2-carboxylic acid glycylamide

Example 167
3-(2-Methyl-1-propyloxy)-5-(5-nonyloxy)carbonylpyridine-2-carboxylic acid glycylamide

Example 168
3-Benzyloxy-5-(5-nonyloxy)carbonyl)pyridine-2-carboxylic acid glycylamide

Example 169
3-(4-Fluorobenzyloxy)-5-(5-nonyloxy)carbonylpyridine-2-carboxylic acid glycylamide

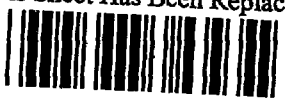
Example 170
5-(5-Nonyloxy)carbonyl-3-(4-(2-propyl)benzyloxy)pyridine-2-carboxylic acid glycylamide

Example 171
5-Geranyloxycarbonyl-3-ethoxypyridine-2-carboxylic acid glycylamide

Example 172
3-Benzyloxy-5-(geranyloxycarbonyl)pyridine-2-carboxylic acid glycylamide

Example 173
3-(4-Chlorobenzyloxy)-5-(geranyloxycarbonyl)pyridine-2-carboxylic acid glycylamide

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Example 174

3-(4-Fluorobenzyloxy)-5-(geranyloxycarbonyl)pyridine-2-carboxylic acid glycylamide

Example 175

5-Geranyloxycarbonyl-3-(2-propyloxy)pyridine-2-carboxylic acid glycylamide

Example 176

5-Farnesyloxycarbonyl-3-(2-propyloxy)pyridine-2-carboxylic acid glycylamide

Example 177

3-Benzyloxy-5-(farnesyloxycarbonyl)pyridine-2-carboxylic acid glycylamide

Example 178

5-Farnesyloxycarbonyl-3-(4-fluorobenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 179

5-Farnesyloxycarbonyl-3-ethoxypyridine-2-carboxylic acid glycylamide

Example 180

3-Methoxy-5-(retinyloxycarbonyl)pyridine-2-carboxylic acid glycylamide

Example 181

3-Ethoxy-5-(retinyloxycarbonyl)pyridine-2-carboxylic acid glycylamide

Example 182

3-(2-Propyloxy)-5-(retinyloxycarbonyl)pyridine-2-carboxylic acid glycylamide

Example 183
3-Benzyloxy-5-(retinyloxycarbonyl)pyridine-2-carboxylic acid glycylamide

Example 184
3-(4-Fluorobenzyloxy)-5-(retinyloxycarbonyl)pyridine-2-carboxylic acid glycylamide

Example 185
3-(3-Methoxybenzyloxy)-5-(retinyloxycarbonyl)pyridine-2-carboxylic acid glycylamide

Example 186
5-Benzyloxycarbonyl-3-(4-(2-propyloxy)benzyloxy)pyridine-2-carboxylic acid glycylamide

Example 187
5-Benzyloxycarbonyl-3-(4-fluorobenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 188
5-Butyloxycarbonyl-3-benzyloxypyridine-2-carboxylic acid glycylamide

Example 189
5-(((4-Ethoxyphenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid glycylamide, analogously to Example 191

Example 190
5-(((4-Ethoxyphenyl)amino)carbonyl)-3-benzyloxypyridine-2-carboxylic acid glycylamide

Example 191
5-(((4-(1-Butyloxy)phenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid glycylamide

a) Methyl 5-(((4-(1-butyloxy)phenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylate

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3.2 g (15 mmol) of methyl 5-carboxy-3-methoxypyridine-2-carboxylate (cf. Example 90a)) were reacted, in analogy with Example 90b), with 2.5 g (15 mmol) of 4-n-butoxyaniline and the reagents described in that example. 3.9 g of product were crystallized using diethyl ether (m.p. 138 to 141°C.

b) 5-(((4-(1-Butyloxy)phenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid

3.2 g of the above ester were hydrolyzed at 20°C using 100 ml of 1.5 N methanolic sodium hydroxide solution. 2.7 g of product were obtained from aqueous hydrochloric acid, m.p. 128 to 130°C, sintering from 120°C.

c) 5-(((4-(1-Butyloxy)phenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid N-((ethoxycarbonyl)-methyl) amide

2.7 g (7.8 mmol) of the above pyridine-2-carboxylic acid were stirred in 500 ml of anhydrous dichloromethane, at 20°C for 24 h, together with 1.1 g (7.8 mmol) of glycine ethyl ester hydrochloride, 3.0 ml (23.4 mmol) of N-ethylmorpholine, 1.2 g (8.6 mmol) of 1-hydroxy-1H-benzotriazole and 3.3 g (7.8 mmol) of CMC.

The undissolved material was then filtered off and the organic phase was extracted sequentially with 200 ml each of water, aqueous Na bicarbonate solution, 1N aqueous hydrochloric acid and water, dried over Mg sulfate and concentrated in vacuo; the residue was crystallized using diethyl ether. 2.4 g of product were obtained, m.p. 193-195°C.

d) The title compound was obtained by hydrolyzing 1.0 g of the above glycine ester, at 20°C, in 100 ml of a 1.5 N methanolic solution of sodium hydroxide. After 30 min, the mixture was concentrated in vacuo and the residue was dissolved in water; this solution was extracted with

diethyl ether and the aqueous solution adjusted to pH 3 using aqueous hydrochloric acid. When the solution was cooled with ice, 390 mg of the title compound crystallized, m.p. 230°C, sintering at 193°C.

Example 192
5-(((4-(1-Butyloxy)phenyl)amino)carbonyl)-3-(4-fluorobenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 193
5-(((4-(1-Butyloxy)phenyl)amino)carbonyl)-3-benzyloxypyridine-3-carboxylic acid glycylamide

Example 194
3-(2-Methyl-1-propyloxy)pyridine-2,5-dicarboxylic acid diglycylamide
M.p. 103-105°C (from ethyl acetate)

Example 195
5-(Di-N,N-ethylaminocarbonyl)-3-ethoxypyridine-2-carboxylic acid glycylamide, amorphous substance, prepared in analogy with Example 223 using N,N-diethylamine.

Example 196
5-(N-Benzyl-N-methylaminocarbonyl)-3-methoxypyridine-2-carboxylic acid glycylamide

Example 197
5-Farnesyloxycarbonyl-3-methoxypyridine-2-carboxylic acid glycylamide

Example 198
5-Geranyloxycarbonyl-3-methoxypyridine-2-carboxylic acid glycylamide

Example 199
5-(Farnesyloxymethyl)-3-methoxypyridine-2-carboxylic acid glycylamide

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Example 200
5-(Geranyloxymethyl)-3-methoxypyridine-2-carboxylic acid glycylamide

Example 201
5-Retinyloxymethyl-3-methoxypyridine-2-carboxylic acid glycylamide

Example 202
5-Retinyloxymethyl-3-ethyloxypyridine-2-carboxylic acid glycylamide

Example 203
N-(Carboxymethyl)-4-methoxycinnoline-3-carboxamide

Examples 204 to 209 were prepared in analogy with Example 191:

Example 204
5-(((4-(1-Hexyloxy)phenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

a) Methyl 5-(((4-(1-hexyloxy)phenyl)amino)carbonyl)-3-methoxy-2-carboxylate was prepared from methyl 5-carboxy-3-methoxypyridine-2-carboxylate and 4-hexyloxyaniline, m.p. 118-119°C (from diethyl ether).

b) 5-(((4-(1-Hexyloxy)phenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid, 160-162°C, sintering at 148°C (from aqueous hydrochloric acid/tetrahydrofuran)

c) 5-(((4-(1-Hexyloxy)phenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid N-((ethoxycarbonyl)-methyl)amide was obtained, in analogy with Example 191c), from 4.2 g of the above compound. 4.0 g of product were crystallized using ethyl acetate, m.p. 157-159°C.

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d) The title compound was obtained by hydrolyzing 1.2 g of the above ester, at 20°C, using 100 ml of a 1.5N methanolic solution of sodium hydroxide. Following concentration in vacuo, acidification to pH 1 took place in water/tetrahydrofuran using aqueous hydrochloric acid; the mixture was concentrated in vacuo and the residue was crystallized using acetone. 840 mg of product were obtained, m.p. 193-195°C.

Example 205

5-(((4-(1-Decyloxy)phenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 206

5-(((4-(1-Decyl)phenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

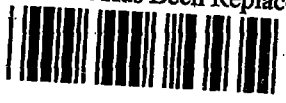
a) 5-(((4-(1-Decyl)phenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid N-((ethoxycarbonyl)-methyl)amide was prepared from 5-(((4-n-decylphenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid (m.p. 160°C (decomp.); from aqueous hydrochloric acid/THF) and glycine ethyl ester hydrochloride, m.p. 155-157°C (from diisopropyl ether).

b) The title compound was obtained by hydrolyzing 1.5 g of the above ester in 200 ml of a 1 N methanolic solution of sodium hydroxide. 1.4 g of product, m.p. 195°C (decomp.), were isolated from aqueous hydrochloric acid/tetrahydrofuran.

Example 207

5-(((4-Geranyloxyphenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

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Example 208
5-(((4-(1-Octyloxy)phenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 209
5-(((3-(1-Octyloxy)propyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 210
5-((1-Butoxy)methyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 211
5-((1-Hexyloxy)methyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 212
5-((1-Octyloxy)methyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 213
5-((1-Hex-3-enyloxy)methyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 214
5-((1-Decyloxy)methyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 215
5-((1-Dodecyloxy)methyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 216
5-((1-Hexadecyloxy)methyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 217
3-(4-(((+)-Dehydroabietylamino)carbonyl)benzyloxy)pyridine-2-carboxylic acid N-(carboxymethyl)amide

a) 4-(((+)-Dehydroabietylamino)carbonyl)chloromethylbenzene was obtained from 4-chloromethylbenzoic acid and (+)-dehydroabietylamine, m.p. 170-172°C (from ethyl acetate/heptane (1:1)).

b) 3-(4-(((+)-Dehydroabietylamino)carbonyl)benzyloxy)-pyridine-2-carboxylic acid N-((ethyloxycarbonyl)-methyl)amide, m.p. approximately 80°C (amorphous substance, from ethyl acetate).

c) The title compound was obtained by hydrolyzing the above ester, m.p. 125°C (with foaming, from diisopropyl ether).

Example 218

3-Methoxyquinoline-2-carboxylic acid N-(carboxymethyl)-amide

a) 2-Acetyl-3-hydroxyquinoline, known from D.W. Bayne et al., J. Chem. Soc. Chem. Comm. 1975, 782 (M.p. 106°C from aqueous hydrochloric acid).

b) 2-Acetyl-3-methoxyquinoline, from a) using potassium carbonate/methyl iodide in acetone, oily crude product.

c) 3-Methoxyquinoline-2-carboxylic acid, from b) using potassium hypochlorite in water/dioxane, m.p. 123°C (from methyl tert-butyl ether).

d) 3-Methoxyquinoline-2-carboxylic acid N-((methoxy-carbonyl)methyl)amide, from c) using DCC, HOBT, THF, NEM and glycine methyl ester hydrochloride.

e) The title compound was obtained by hydrolyzing the above ester, m.p. 106°C (from ethyl acetate).

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Example 219

5-(((4-(1-Butyloxy)phenyl)amino)carbonyl)-3-chloropyridine-2-carboxylic acid N-(carboxymethyl)amide

a) Methyl 5-carboxy-3-chloropyridine-2-carboxylate was prepared in analogy with Example 90a), m.p. 182-184°C (from aqueous hydrochloric acid).

b) Methyl 5-(((1-butyloxy)phenyl)amino)carbonyl)-3-chloropyridine-2-carboxylate was obtained from the above compound using oxalyl chloride and 4-(1-butyloxy)aniline, m.p. 121-123°C (from diethyl ether).

c) 5-(((4-(1-Butyloxy)phenyl)amino)carbonyl)-3-chloropyridine-2-carboxylic acid by hydrolyzing the product from b), m.p. 163-164°C (from aqueous hydrochloric acid).

d) 5-(((4-(1-Butyloxy)phenyl)amino)carbonyl)-3-chloropyridine-2-carboxylic acid N-((ethyloxycarbonyl)-methyl)amide was obtained, in analogy with Example 90b), from the above substance by condensation (N-ethylmorpholine, 1-hydroxy-1H-benzotriazole and CMC) with glycine ethyl ester hydrochloride, m.p. 177-179°C (from ethanol).

e) The title compound was obtained by hydrolyzing the above ester, m.p. 190°C (with decomposition, from aqueous hydrochloric acid).

Example 220

3-(N-Benzyl-N-methylamino)-5-(((4-(1-butyloxy)phenyl)-amino)carbonyl)pyridine-2-carboxylic acid N-(carboxy-methyl)amide

0.5 g (1.23 mmol) of the title compound from Example 219 was stirred in 10 ml of N-benzyl-N-methylamine, firstly at 100-110°C for 2 h and then at 130°C for a further 2 h. After the mixture had been cooled down, it was introduced

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into 100 ml of 1N hydrochloric acid and the half-crystalline precipitate was taken up in dichloromethane; the undissolved material was filtered off and the residue was crystallized; 0.2 g of the title compound, m.p. 155-157°C.

Example 221

3-(N-Benzylamino)-5-(((4-(1-butyloxy)phenyl)amino)carbonyl)pyridine-2-carboxylic acid N-(carboxymethyl)amide

0.5 g (1.23 mmol) of the title compound from Example 219 was stirred in 10 ml of benzylamine, firstly at 120°C for 2 h and then at 135°C for 1.5 h. After the mixture had been cooled down, it was acidified and the precipitated resin was dissolved in dichloromethane; this solution was dried and concentrated and the residue was chromatographed on silica gel using ethyl acetate (with the addition of up to 20 % methanol). 0.1 g of the title compound was crystallized from appropriate fractions using diisopropyl ether, m.p. 185-190°C.

Example 222

3-(4-Chlorobenzyloxy)pyridine-2-carboxylic acid N-(carboxymethyl)amide 1-oxide

a) 3-(4-Chlorobenzyloxy)pyridine-2-carboxylic acid N-((ethyloxy)methyl)amide 1-oxide

0.7 g (2 mmol) of the compound from Example 31c) was dissolved in dichloromethane and reacted with 1.41 g of 3-chloroperbenzoic acid. After the mixture had been stirred at 20°C for 1 h, ammonia was passed in until there was no further precipitation; the precipitate was filtered off and the filtrate was concentrated and the oily residue crystallized using diethyl ether, m.p. 70-72°C.

b) 0.18 g of the title compound, m.p. 206-208°C

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(sintering at 200°C, from aqueous hydrochloric acid) was obtained by hydrolyzing 0.3 g of the above compound.

Example 223

5-(((3-(1-Butyloxy)propyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

a) Methyl 5-(((3-(1-butyloxy)propyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid

1.7 ml of oxalyl chloride (20 mmol), and also 2 drops of N,N-dimethylformamide, dissolved in tetrahydrofuran, were added dropwise, at 10°C and while stirring, to 2.1 g (10 mmol) of methyl 5-carboxy-3-methoxypyridine-2-carboxylate in 100 ml of anhydrous tetrahydrofuran and the reaction mixture was stirred at 10°C for 30 min and at 20°C for 1 h. It was then concentrated and the residue was dissolved in dichloromethane; 6.8 ml (50 mmol) of triethylamine, and then 1.3 g (1.5 ml, 10 mmol) of 3-butoxypropylamine, dissolved in dichloromethane, were added, at 0°C, to this solution.
After 30 min, the mixture was allowed to warm to room temperature and was extracted with water, a solution of Na bicarbonate and aqueous 1N HCl; the organic phase was dried and concentrated and the residue was crystallized using diethylether/petroleum ether (3:1). 2.3 g of product were obtained, m.p. 51-53°C.

b) 5-(((3-(1-Butyloxy)propyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid N-((benzyloxycarbonyl)-methyl)amide

The above substance was hydrolyzed by standard procedures, and 1.5 g (5 mmol) of the amorphous 5-(((3-(1-butyloxy)propyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid, which was dried on an oil pump, was reacted with glycine benzyl ester tosylate,

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N-ethylmorpholine, 1-hydroxy-1H-benzotriazole and CMC (as described). 1.42 g of the product were crystallized using acetone, m.p. 97-99°C.

c) 1.3 g of the above benzyl ester were hydrogenated in 100 ml of tetrahydrofuran/methanol (1:1) using Pd/C (10 %) in a hydrogenation vessel. 0.8 g of the title compound was crystallized using diethyl ether, m.p. 155-157°C.

Example 224

5-(((3-(1-Lauryloxy)propyl)amino)carbonyl)-3-methoxy-pyridine-2-carboxylic acid N-(carboxymethyl)amide

a) 5-(((3-Lauryloxypropyl)amino)carbonyl)-3-methoxy-pyridine-2-carboxylic acid N-((benzyloxycarbonyl)-methyl)amide was obtained, in analogy with Example 223, using 3-lauryloxypropylamine, m.p. from 109-111°C (from diisopropyl ether).

b) 1.3 g of the above benzyl ester were hydrogenated as described under 223c). 0.9 g of the title compound were obtained from petroleum ether, m.p. from 120°C.

Example 225

5-(((2-Methoxyethyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

The title compound was prepared in analogy with Example 223 using 2-methoxyethylamine.

a) 5-(((2-Methoxyethyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid, m.p. 160-161°C (with gas evolution, from ethyl acetate)

b) 5-(((2-Methoxyethyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid N-((benzyloxycarbonyl)-methyl)amide was crystallized using diisopropyl ether, m.p. 129-131°C.

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c) The title compound was obtained, as above, from the benzyl ester, m.p. 186-188°C (from diethyl ether).

Example 226

N-(3-Benzyloxypyridyl-2-carbonyl)alanine racemate,
M.p. 186-187°C (from pentane/ethyl acetate)

Example 227

N-(3-Benzyloxypyridyl-2-carbonyl)-L-phenylalanine,
M.p. 100-101°C (from pentane/ethyl acetate).

Example 228

5-((1-Butyloxy)carbonyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide trifluoroacetate

a) Di-(1-butyl) 3-methoxypyridine-2,5-dicarboxylate

5.0 g of dimethyl 3-methoxypyridine-2,5-dicarboxylate (cf. Example 90a)) were dissolved in 100 ml of 1-butanol, and after that 1.5 ml of conc. sulfuric were added and the mixture was heated to boiling for 2 h, with a part of the solvent being distilled off. After the mixture had been cooled, it was concentrated in vacuo and the residue was taken up in dichloromethane; this solution was extracted with a saturated, aqueous solution of Na bicarbonate and the organic phase was dried and concentrated. 6 g of oily crude product.

b) Bis[5-((1-butyloxy)carbonyl)-3-methoxypyridine-2-carboxylic acid]-Cu(II) complex

6 g (20 mmol) of the above product were added, dissolved in 10 ml of methanol, to a solution of 4.8 g (20 mmol) of Cu(II) nitrate × 3 H_2O in 100 ml of methanol, and the mixture was heated to boiling for 4 h. It was then cooled down to 0-5°C and the crystalline precipitate was filtered off with suction and washed with diethyl ether. 4.2 g of blue-green, crystalline product were obtained, m.p. 267°C (with decomposition).

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c) 5-((1-Butyloxy)carbonyl)-3-methoxypyridine-2-carboxylic acid

4 g of the above Cu complex were suspended in 75 ml of 1,4-dioxane. H_2S gas was passed in, while the mixture was being stirred, for 30 min, and the sediment (CuS) which had precipitated out was filtered off with suction through kieselguhr and then washed with 1,4-dioxane (continued introduction of H_2S did not lead to any further precipitation); the filtrate was concentrated in vacuo. The residue was crystallized using petroleum ether, m.p. 96-98°C.

d) 5-((1-Butyloxy)carbonyl)-3-methoxypyridine-2-carboxylic acid N-((tert-butyloxycarbonyl)-methyl)amide

0.76 g (3 mmol) of the above pyridinecarboxylic acid was condensed with 0.52 g (3 mmol) of glycine tert-butyl ester hydrochloride, 1.2 ml (9 mmol) of N-ethylmorpholine, 0.45 g (3.3 mmol) of 1-hydroxy-(1H)-benzotriazole and 1.3 g (3 mmol) of CMC. 0.8 g of product was obtained, m.p. 50-52°C (from petroleum ether).

e) The title compound was obtained by adding 2.7 ml of trifluoroacetic acid, at 20°C, to 0.4 g of the above tert-butyl ester in dichloromethane. After 20 h, the mixture was concentrated in vacuo and 0.2 g was obtained of the colorless, crystalline, strongly hygroscopic product, which, on being filtered off with suction, deliquesced on the suction filter.

Example 229

5-Ethyloxycarbonyl-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 230

3-Methoxy-5-((1-propyloxy)carbonyl)pyridine-2-carboxylic acid N-(carboxymethyl)amide

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Example 231
5-((1-Hexyloxy)carbonyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 232
3-Methoxy-5-((1-pentyloxy)carbonyl)pyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 233
5-((1-Heptyloxy)carbonyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 234
3-Methoxy-5-((1-octyloxy)carbonyl)pyridine-2-carboxylic acid N-(carboxymethyl)amide

Examples 235-238 were prepared in an analogous manner to Example 228 proceeding from 3-(2-propyloxy)pyridine-2,5-dicarboxylic acid or the corresponding dialkyl esters.

Example 235
5-Ethyloxycarbonyl-3-(2-propyloxy)pyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 236
5-((1-Butyloxy)carbonyl)-3-(2-propyloxy)pyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 237
5-((1-Hexyloxy)carbonyl)-3-(2-propyloxy)pyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 238
5-((-1-Octyloxy)carbonyl)-3-(2-propyloxy)pyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 239
5-Carboxy-3-(methylthio)pyridine-2-carboxylic acid N-(carboxymethyl)amide disodium salt

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a) 3-(Methylthio)pyridine-2,5-dicarboxylic acid

4.6 g (12 mmol) of dibenzyl 3-chloropyridine-2,5-dicarboxylate were dissolved, at 20°C and while stirring, in 30 ml of dimethyl sulfoxide, and after that 5.0 g (70 mmol) of sodium thiomethoxide were added, in association with which the temperature rose to 80°C. The reaction mixture was heated at 140°C for 1 h and then cooled down; water was added and the oily layer was separated off; conc. hydrochloric acid (pH 1) was added to the aqueous DMSO phase and the precipitated product was filtered off with suction. 2.8 g were obtained of a yellow crystalline product, m.p. 223°C (with decomposition).

b) Dimethyl 3-(methylthio)pyridine-2,5-dicarboxylate

50 ml of 1,4-dioxane, 40 ml of tetrahydrofuran and 0.5 ml of conc. sulfuric acid were added to 2.8 g of the above compound in 150 ml of methanol, and the mixture was heated to reflux for 2 h, during which time a solution was formed. After the solution had been cooled down, it was concentrated in vacuo and 100 ml of an aqueous solution of Na bicarbonate were added to the residue; the latter mixture was extracted with dichloromethane and the organic phase was dried and concentrated. 1.4 g were obtained of the yellow, crystalline product, m.p. 103-105°C.

c) 5-Methoxycarbonyl-3-(methylthio)pyridine-2-carboxylic acid-Cu(II) complex

1.3 g of the above dimethyl 3-methylthiopyridine-2,5-dicarboxylate were reacted in analogy with Example 228b). 1.3 g of greenish/crystalline product were obtained, m.p. > 330°C.

d) 5-Methoxy-3-(methylthio)pyridine-2-carboxylic acid

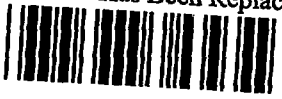
1.3 g of the above compound were reacted in analogy with Example 228c), 0.72 g of product, m.p. 183-185°C.

e) 5-Methoxycarbonyl-3-(methylthio)pyridine-2-carboxylic acid N-((1-butyloxy)carbonyl)methyl)amide

The compound was obtained by condensing 0.68 g (3 mmol) of the above pyridinecarboxylic acid with 0.91 g (3 mmol) of glycine 1-butyl ester tosylate (1-hydroxy-1H-benzotriazole, N-ethylmorpholine and CMC). 0.55 g of pale yellow product was obtained, m.p. 47-49°C (from petroleum ether).

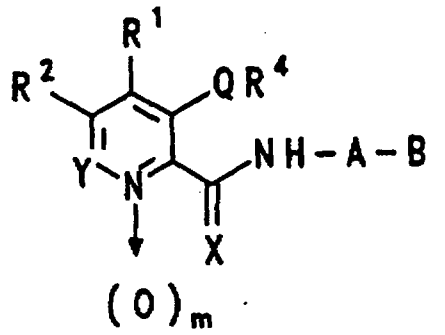
f) The title compound was obtained by hydrolysing 0.45 g (1.3 mmol) of the above ester using 50 ml of 1 N methanolic NaOH. The clear yellow solution became cloudy after 30 min. After 2 h, the precipitate was filtered off with suction, washed twice with methanol and dried in vacuo. 0.32 g of the title compound was obtained, m.p. 345°C (decomp.).

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Patent claims:

1. A compound of the formula I



(I),

in which

Q is O, S, NR' or a bond,

X is O or S,

Y is C-R^3 or,

if R^1 and R^2 form a cycle,

Y is N or CR^3,

m is 0 or 1,

A is (C_1-C_4)-alkylene, which is optionally substituted by one or two substituents from the group halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, $-O-[CH_2]_x-C_zH_{(2z+1-g)}Hal_g$, preferably (C_1-C_8)-fluoroalkoxy, (C_1-C_8)-fluoroalkenyloxy, (C_1-C_8)-fluoroalkynyloxy, $-OCF_2Cl$ or $-O-CF_2-CHFCl$, (C_1-C_6)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, anilino, N-methylanilino, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl or N,N-di-(C_1-C_4)-alkylsulfamoyl, or

by a substituted (C_6-C_{12})-aryloxy, (C_7-C_{11})-aralkyloxy, (C_6-C_{12})-aryl or (C_7-C_{11})-aralkyl radical which carries in the aryl moiety 1, 2, 3, 4 or 5 identical or different substituents from the

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group halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, $-O-[CH_2]_x-C_zH_{(2z+1-g)}Hal_g$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, (C_1-C_6)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl or N,N-di-(C_1-C_4)-alkylsulfamoyl, or

by the substituents R^5 of the α-carbon atom of an α-amino acid, it being possible to use the natural L-amino acids and their D-isomers;

B is an acid grouping from the group $-CO_2H$, -CONHCOR"', -CONHSOR'", $CONHSO_2R"'$, $-NHSO_2CF_3$, tetrazolyl, imidazolyl or 3-hydroxyisoxazolyl, where R"' is aryl, heteroaryl, (C_3-C_7)-cycloalkyl or (C_1-C_4)-aklyl, optionally monosubstituted by (C_6-C_{12})-aryl, heteroaryl, OH, SH, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, (C_1-C_4)-thioalkyl, (C_1-C_4)-sulfinyl, (C_1-C_4)-sulfonyl, CF_3, Cl, Br, F, I, NO_2, -COOH, (C_2-C_5)-alkoxycarbonyl, NH_2, mono-(C_1-C_4)-alkyl)-amino, di-$(C_1-C_4$-alkyl)-amino or (C_1-C_4)-perfluoroalkyl,

R^1, R^2 and R^3 are identical or different and are hydrogen, hydroxyl, halogen, cyano, trifluoromethyl, nitro, carboxyl, (C_1-C_{20})-alkyl, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl-(C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkoxy, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_7-C_{16})-aralkenyl, (C_7-C_{16})-aralkynyl, (C_2-C_{20})-alkenyl,

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(C_2-C_{20})-alkynyl, (C_1-C_{20})-alkoxy, (C_2-C_{20})-alkenyloxy, (C_2-C_{20})-alkynyloxy, retinyloxy, (C_1-C_{20})-alkoxy-(C_1-C_{12})-alkyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxy, (C_1-C_{16})-hydroxyalkyl, (C_6-C_{16})-aryloxy-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_7-C_{12})-aralkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_2-C_{20})-alkenyloxy-(C_1-C_6)-alkyl, (C_2-C_{20})-alkynyloxy-(C_1-C_6)-alkyl, retinyloxy-(C_1-C_6)-alkyl, $-O-[CH_2-]_x-C_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-OCF_2-CHFCl$,

(C_1-C_{20})-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, (C_6-C_{12})-arylcarbonyl, (C_7-C_{16})-aralkylcarbonyl, cinnamoyl, (C_2-C_{20})-alkenylcarbonyl, (C_2-C_{20})-alkynylcarbonyl,

(C_1-C_{20})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{20})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_2-C_{20})-alkynyloxycarbonyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxycarbonyl, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxycarbonyl,

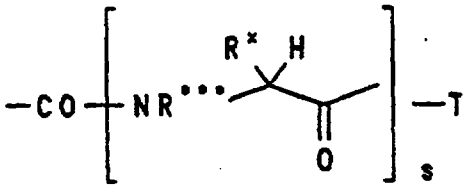
(C_1-C_{12})-alkylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_7-C_{16})-aralkylcarbonyloxy, cinnamoyloxy, (C_2-C_{12})-alkenylcarbonyloxy, (C_2-C_{12})-alkynylcarbonyloxy,

(C_1-C_{12})-alkoxycarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{16})-aralkyloxycarbonyloxy, (C_3-C_8)-cycloalkoxycarbonyloxy, (C_2-C_{12})-alkenyloxycarbonyloxy, (C_2-C_{12})-alkynyloxycarbonyloxy,

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carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-dicyclo-(C_3-C_8)-alkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N-((C_1-C_{18})-alkoxy-(C_1-C_{10})alkyl)carbamoyl, N-((C_6-C_{16})-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, or $CON(CH_2)_h$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7,

a carbamoyl radical of the formula II



(II),

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in which

R^x is the substituent of an α-amino acid to which the L- and D-amino acids belong,

s is 1, 2, 3, 4 or 5, and

T is OH, OR or NR^*R^{**}, where

R^*, R^{**} and R^{***} are identical or different and are hydrogen, (C_6-C_{12})-aryl, (C_7-C_{11})-aralkyl,

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(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyl, (+)-dehydroabietyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkyl, (C_1-C_{10})-alkanoyl, optionally substituted (C_7-C_{16})-aralkanoyl or optionally substituted (C_6-C_{12})-aroyl, or

R^* and R^{**} together are $-[CH_2]_h$, in which a CH_2 group can be replaced by O, S, SO, SO_2, N-acylamino, N-(C_1-C_{10})-alkoxycarbonylimino, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7,

carbamoyloxy, N-(C_1-C_{12})-alkylcarbamoyloxy, N,N-di-(C_1-C_{12})-alkylcarbamoyloxy, N-(C_3-C_8)-cycloalkylcarbamoyloxy, N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_7-C_{16})-aralkylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyloxy, N-$((C_1-C_{10})$-alkyl)carbamoyloxy, N-$((C_6-C_{12})$-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-$((C_7-C_{16})$-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-$((C_1-C_{10})$-alkoxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-$((C_6-C_{12})$-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-$((C_7-C_{16})$-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy,

amino, (C_1-C_{12})-alkylamino, di-(C_1-C_{12})-alkylamino, (C_3-C_8)-cycloalkylamino, (C_3-C_{12})-alkenylamino, (C_3-C_{12})-alkynylamino, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_1-C_{12})-alkoxyamino, (C_1-C_{12})-alkoxy-N-(C_1-C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino, (C_3-C_8)-cycloalkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{16})-aralkanoylamino, $(C_1-$

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C_{12})-alkanoyl-N-(C_1-C_{10})-alkylamino, (C_3-C_8)-cycloalkanoyl-N-(C_1-C_{10})-alkylamino, (C_6-C_{12})-aroyl-N-(C_1-C_{10})-alkylamino, (C_7-C_{11})-aralkanoyl-N-(C_1-C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkanoylamino-(C_1-C_8)-alkyl, (C_6-C_{12})-aroylamino-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkanoylamino-(C_1-C_8)-alkyl, amino-(C_1-C_{10})-alkyl, N-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, N,N-di(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, (C_3-C_8)-cycloalkylamino-(C_1-C_{10})-alkyl, (C_1-C_{20})-alkylmercapto, (C_1-C_{20})-alkylsulfinyl, (C_1-C_{20})-alkylsulfonyl, (C_6-C_{12})-arylmercapto, (C_6-C_{12})-arylsulfinyl, (C_6-C_{12})-arylsulfonyl, (C_7-C_{16})-aralkylmercapto, (C_7-C_{16})-aralkylsulfinyl, (C_7-C_{16})-aralkylsulfonyl, (C_1-C_{12})-alkylmercapto-(C_1-C_6)-alkyl, (C_1-C_{12})-alkylsulfinyl-(C_1-C_6)-alkyl, (C_1-C_{12})-alkylsulfonyl-(C_1-C_6)-alkyl, (C_6-C_{12})-arylmercapto-(C_1-C_6)-alkyl, (C_6-C_{12})-arylsulfinyl-(C_1-C_6)-alkyl, (C_6-C_{12})-arylsulfonyl-(C_1-C_6)-alkyl, (C_7-C_{16})-aralkylmercapto-(C_1-C_6)-alkyl, (C_7-C_{16})-aralkylsulfinyl-(C_1-C_6)-alkyl, (C_7-C_{16})-aralkylsulfonyl-(C_1-C_6)-alkyl,

sulfamoyl, N-(C_1-C_{10})-alkylsulfamoyl, N,N-di-(C_1-C_{10})-alkylsulfamoyl, (C_3-C_8)-cycloalkylsulfamoyl,
N-(C_6-C_{12})-arylsulfamoyl,
N-(C_7-C_{16})-aralkylsulfamoyl,
N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylsulfamoyl,
N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylsulfamoyl,
(C_1-C_{10})-alkylsulfonamido,
N-((C_1-C_{10})-alkyl)-(C_1-C_{10})-alkylsulfonamido, (C_7-C_{16})-aralkylsulfonamido or N-((C_1-C_{10})-alkyl-(C_7-C_{16})-aralkylsulfonamido,
where the radicals which contain an aryl radical can, for their part, be substituted on the aryl by from 1 to 5 identical or different radicals from the group:
hydroxyl, halogen, cyano, trifluoromethyl, nitro,

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carboxyl, (C_1-C_{16})-alkyl, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl-(C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkoxy, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_2-C_{16})-alkenyl, (C_2-C_{12})-alkynyl, (C_1-C_{16})-alkoxy, (C_1-C_{16})-alkenyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxy, (C_1-C_8)-hydroxyalkyl, (C_6-C_{16})-aryloxy-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_7-C_{12})-aralkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-OCF_2-CHFCl$,

(C_1-C_{12})-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, (C_6-C_{12})-arylcarbonyl, (C_7-C_{16})-aralkylcarbonyl,

(C_1-C_{12})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{12})-alkenyloxycarbonyl, (C_2-C_{12})-alkynyloxycarbonyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxycarbonyl, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxycarbonyl,

(C_1-C_{12})-alkylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_7-C_{16})-aralkylcarbonyloxy, cinnamoyloxy, (C_2-C_{12})-alkenylcarbonyloxy, (C_2-C_{12})-alkynylcarbonyloxy,

(C_1-C_{12})-alkoxycarbonyloxy, (C_1-C_{12})-alkoxy-

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(C_1-C_{12})-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{16})-aralkyloxycarbonyloxy, (C_3-C_8)-cycloalkoxycarbonyloxy, (C_2-C_{12})-alkenyloxycarbonyloxy, (C_2-C_{12})-alkynyloxycarbonyloxy,

carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-dicyclo-(C_3-C_8)-alkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-$((C_3-C_8)$-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-$((C_3-C_8)$-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N-$((C_1-C_{16})$-alkoxy-(C_1-C_{10})-alkyl)-carbamoyl, N-$((C_6-C_{16})$-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-$((C_7-C_{16})$-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-$((C_1-C_{10})$-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-$((C_6-C_{12})$-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-$((C_7-C_{16})$-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, $CON(CH_2)_h$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7,

carbamoyloxy, N-(C_1-C_{12})-alkylcarbamoyloxy, N,N-di-(C_1-C_{12})-alkylcarbamoyloxy, N-(C_3-C_8)-cycloalkylcarbamoyloxy, N-(C_6-C_{16})-arylcarbamoyloxy, N-(C_7-C_{16})-aralkylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyloxy, N-$((C_1-C_{10})$-alkyl)carbamoyloxy, N-$((C_6-C_{12})$-aryloxy-(C_1-C_{10})-alkyl)-carbamoyloxy, N-$((C_7-C_{16})$-aralkyloxy-(C_1-C_{10})-alkyl)-

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carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy,

amino, (C_1-C_{12})-alkylamino, di-(C_1-C_{12})-alkylamino, (C_3-C_8)-cycloalkylamino, (C_3-C_{12})-alkenylamino, (C_3-C_{12})-alkynylamino, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_1-C_{12})-alkoxyamino, (C_1-C_{12})-alkoxy-N-(C_1-C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino, (C_3-C_8)-cycloalkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{16})-aralkanoylamino, (C_1-C_{12})-alkanoyl-N-(C_1-C_{10})-alkylamino, (C_3-C_8)-cycloalkanoyl-N-(C_1-C_{10})-alkylamino, (C_6-C_{12})-aroyl-N-(C_1-C_{10})-alkylamino, (C_7-C_{11})-aralkanoyl-N-(C_1-C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkanoylamino-(C_1-C_8)-alkyl, (C_6-C_{12})-aroylamino-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkanoylamino-(C_1-C_8)-alkyl, amino-(C_1-C_{10})-alkyl, N-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, N,N-di-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, (C_3-C_8)-cycloalkylamino-(C_1-C_{10})-alkyl,

(C_1-C_{12})-alkylmercapto, (C_1-C_{12})-alkylsulfinyl, (C_1-C_{12})-alkylsulfonyl, (C_6-C_{16})-arylmercapto, (C_6-C_{16})-arylsulfinyl, (C_6-C_{16})-arylsulfonyl, (C_7-C_{16})-aralkylmercapto, (C_7-C_{16})-aralkylsulfinyl or (C_7-C_{16})-aralkylsulfonyl,

R^1 and R^2 or R^2 and R^3 form a chain $[CH_2]_o$ in which one or two CH_2 groups of the chain, which is saturated or unsaturated by a C=C double bond, are optionally replaced by O, S, SO, SO_2 or NR', and o is 3, 4 or 5, and

* C L M S *

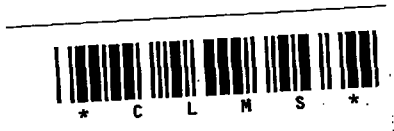
R' is hydrogen, (C_6-C_{12})-aryl, (C_1-C_8)-alkyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkyl, (C_1-C_{10})-alkanoyl, optionally substituted (C_7-C_{16})-aralkanoyl or optionally substituted (C_6-C_{12})-aroyl, where

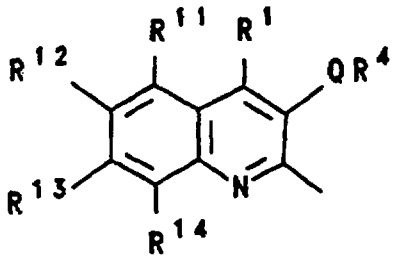
the radicals R^1 and R^2 or R^2 and R^3, together with the pyridine or pyridazine carrying them, preferably form a 5, 6, 7, 8-tetrahydroisoquinoline ring, a 5, 6, 7, 8-tetrahydroquinoline ring or a 5, 6, 7, 8-tetrahydrocinnoline ring,
or
R^1 and R^2 or R^2 and R^3 form a carbocyclic or a heterocyclic, 5- or 6-membered aromatic ring, where

the radicals R^1 and R^2 or R^2 and R^3, together with the pyridine or pyridazine carrying them, preferably form the following optionally substituted heterocyclic ring systems:

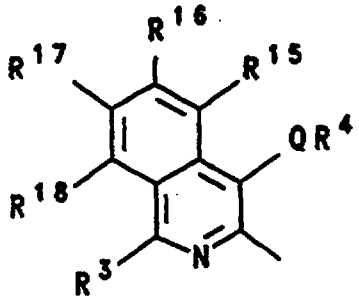
Thienopyridines,
Furanopyridines,
Pyridopyridines,
Pyrimidinopyridines,
Imidazopyridines,
Thiazolopyridines,
Oxazolopyridines,
Quinoline, isoquinoline and
Cinnoline,
where quinoline, isoquinoline or cinnoline preferably satisfy the formulae 1a, 1b and 1c

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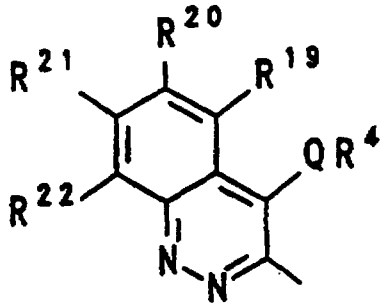




1a



1b



1c

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and the substituents R^{11} to R^{22}, in each case independently of each other, have the meaning of R^1, R^2 and R^3,

R^4 is, if Q is a bond, halogen, nitrile or trifluoromethyl, or, if Q is O, S or NR', a branched or unbranched (C_1-C_{20})-alkyl radical, an unsubstituted, saturated fluoroalkyl radical of the formula $[CH_2]_x$-$C_zH_{(2z+1-g)}F_g$, a (C_6-C_{16})-aryl radical, a (C_7-C_{16})-aralkyl radical, a heteroaryl radical or a heteroaralkyl radical,

where these radicals are substituted by one or more radicals from the group
hydroxyl, halogen, cyano, trifluoromethyl, nitro, carboxyl, (C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyl,

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(C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl-(C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkoxy, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_2-C_{12})-alkenyl, (C_2-C_{12})-alkynyl, (C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxy, (C_1-C_8)-hydroxyalkyl, (C_6-C_{16})-aryloxy-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_7-C_{12})-aralkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-OCF_2-CHFCl$,

(C_1-C_{12})-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, (C_6-C_{12})-arylcarbonyl, (C_7-C_{16})-aralkylcarbonyl, cinnamoyl, (C_2-C_{12})-alkenylcarbonyl, (C_2-C_{12})-alkynylcarbonyl,

(C_1-C_{12})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{12})-alkenyloxycarbonyl, (C_2-C_{12})-alkynyloxycarbonyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxycarbonyl, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxycarbonyl,

(C_1-C_{12})-alkylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_7-C_{16})-aralkylcarbonyloxy, cinnamoyloxy, (C_2-C_{12})-alkenylcarbonyloxy, (C_2-C_{12})-alkynylcarbonyloxy,

(C_1-C_{12})-alkoxycarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-

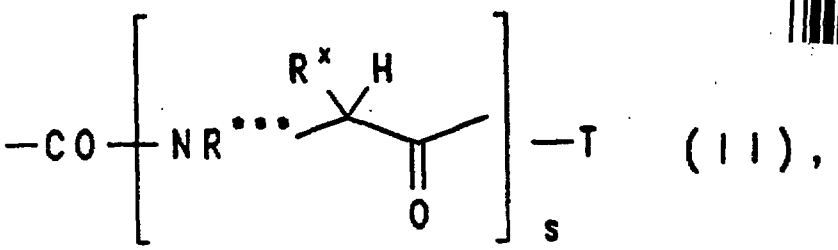
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alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{16})-aralkyloxycarbonyloxy, (C_3-C_8)-cycloalkoxycarbonyloxy, (C_2-C_{12})-alkenyloxycarbonyloxy, (C_2-C_{12})-alkynyloxycarbonyloxy,

carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-dicyclo-(C_3-C_8)-alkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C_6-C_{16})-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, $CON(CH_2)_h$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7, or by

a carbamoyl radical of the formula II

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(II),

in which

R^x is the substituent of an α-amino acid to which the L- and D-amino acids belong,

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s is 1, 2, 3, 4 or 5, and

T is OH, OR or NR^*R^{**}, where

R^*, R^{**}, and R^{***} are identical or different and are hydrogen, (C_6-C_{12})-aryl, (C_7-C_{11})-aralkyl, (C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyl, (+)-dehydroabietyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkyl, (C_1-C_{10})-alkanoyl, optionally substituted (C_7-C_{16})-aralkanoyl or optionally substituted (C_6-C_{12})-aroyl, or

R^* and R^{**} together are $-[CH_2]_h-$, in which a CH_2 group can be replaced by O, S, SO, SO_2, N-acylamino, N-(C_1-C_{10})-alkoxycarbonylimino, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7, or by

carbamoyloxy, N-(C_1-C_{12})-alkylcarbamoyloxy, N,N-di-(C_1-C_{12})-alkylcarbamoyloxy, N-(C_3-C_8)-cycloalkyl-carbamoyloxy, N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_7-C_{16})-aralkylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkyl-carbamoyloxy, N-$((C_1-C_{10})$-alkyl)carbamoyloxy, N-$((C_6-C_{12})$-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-$((C_7-C_{16})$-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-$((C_1-C_{10})$-alkoxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-$((C_6-C_{12})$-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-$((C_7-C_{16})$-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy,

amino, (C_1-C_{12})-alkylamino, di-(C_1-C_{12})-alkylamino, (C_3-C_8)-cycloalkylamino, (C_3-C_{12})-alkenylamino, (C_3-C_{12})-alkynylamino, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_1-C_{12})-alkoxyamino, (C_1-C_{12})-alkoxy-N-(C_1-C_{10})-alkylamino,

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(C_1-C_{12})-alkanoylamino, (C_3-C_8)-cycloalkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{16})-aralkanoylamino, (C_1-C_{12})-alkanoyl-N-(C_1-C_{10})-alkylamino, (C_3-C_8)-cycloalkanoyl-N-(C_1-C_{10})-alkylamino, (C_6-C_{12})-aroyl-N-(C_1-C_{10})-alkylamino, (C_7-C_{11})-aralkanoyl-N-(C_1-C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkanoylamino-(C_1-C_8)-alkyl, (C_6-C_{12})-aroylamino-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkanoylamino-(C_1-C_8)-alkyl, amino-(C_1-C_{10})-alkyl, N-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, N,N-di(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, (C_3-C_8)-cycloalkylamino-(C_1-C_{10})-alkyl,

(C_1-C_{12})-alkylmercapto, (C_1-C_{12})-alkylsulfinyl, (C_1-C_{12})-alkylsulfonyl, (C_6-C_{12})-arylmercapto, (C_6-C_2)-arylsulfinyl, (C_6-C_{12})-arylsulfonyl, (C_7-C_{16})-aralkylmercapto, (C_7-C_{16})-aralkylsulfinyl, (C_7-C_{16})-aralkylsulfonyl,

sulfamoyl, N-(C_1-C_{10})-alkylsulfamoyl, N,N-di-(C_1-C_{10})-alkylsulfamoyl, (C_3-C_8)-cycloalkylsulfamoyl,
N-(C_6-C_{12})-arylsulfamoyl,
N-(C_7-C_{16})-aralkylsulfamoyl,
N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylsulfamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylsulfamoyl,
(C_1-C_{10})-alkylsulfonamido,
N-$((C_1-C_{10})$-alkyl)-(C_1-C_{10})-alkylsulfonamido, (C_7-C_{16})-aralkylsulfonamido or N-(C_1-C_{10})-alkyl-(C_7-C_{16})-aralkylsulfonamido, where the radicals which contain an aryl radical can, for their part, be substituted on the aryl by from 1 to 5 identical or different radicals from the group:
hydroxyl, halogen, cyano, trifluoromethyl, nitro, carboxyl, (C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl-(C_1-C_6)-

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alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkoxy, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_2-C_{12})-alkenyl, (C_2-C_{12})-alkynyl, (C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxy, (C_1-C_8)-hydroxyalkyl, (C_6-C_{16})-aryloxy-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_7-C_{12})-aralkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, $-O-[CH_2-]_x-C_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-OCF_2-CHFCl$,

(C_1-C_{12})-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, (C_6-C_{12})-arylcarbonyl, (C_7-C_{16})-aralkylcarbonyl,

(C_1-C_{12})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{12})-alkenyloxycarbonyl, (C_2-C_{12})-alkynyloxycarbonyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxycarbonyl, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxycarbonyl,
(C_1-C_{12})-alkylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_7-C_{16})-aralkylcarbonyloxy, cinnamoyloxy, (C_2-C_{12})-alkenylcarbonyloxy, (C_2-C_{12})-alkynylcarbonyloxy,

(C_1-C_{12})-alkoxycarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{16})-aralkyloxycarbonyloxy, (C_3-C_8)-cycloalkoxycarbonyloxy, (C_2-C_{12})-alkenyloxycarbonyloxy, (C_2-C_{12})-alkynyloxycarbonyloxy,

carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-

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dicyclo-(C_3-C_8)-alkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)-carbamoyl, N-((C_6-C_{16})-aryloxy-(C_1-C_{10})-alkyl)-carbamoyl, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, $CON(CH_2)_h$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7,

carbamoyloxy, N-(C_1-C_{12})-alkylcarbamoyloxy, N,N-di-(C_1-C_{12})-alkylcarbamoyloxy, N-(C_3-C_8)-cycloalkylcarbamoyloxy, N-(C_6-C_{16})-arylcarbamoyloxy, N-(C_7-C_{16})-aralkylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyloxy, N-((C_1-C_{10})-alkyl)carbamoyloxy, N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)-carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy,

amino, (C_1-C_{12})-alkylamino, di-(C_1-C_{12})-alkylamino, (C_3-C_8)-cycloalkylamino, (C_3-C_{12})-alkenylamino, (C_3-C_{12})-alkynylamino, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_1-C_{12})-alkoxyamino, (C_1-C_{12})-alkoxy-N-(C_1-

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C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino, (C_3-C_8)-cycloalkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{16})-aralkanoylamino, (C_1-C_{12})-alkanoyl-N-(C_1-C_{10})-alkylamino, (C_3-C_8)-cycloalkanoyl-N-(C_1-C_{10})-alkylamino, (C_6-C_{12})-aroyl-N-(C_1-C_{10})-alkylamino, (C_7-C_{11})-aralkanoyl-N-(C_1-C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkanoylamino-(C_1-C_8)-alkyl, (C_6-C_{12})-aroylamino-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkanoylamino-(C_1-C_8)-alkyl, amino-(C_1-C_{10})-alkyl, N-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, N,N-di-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, (C_3-C_8)-cycloalkylamino-(C_1-C_{10})-alkyl,

(C_1-C_{12})-alkylmercapto, (C_1-C_{12})-alkylsulfinyl, (C_1-C_{12})-alkylsulfonyl, (C_6-C_{16})-arylmercapto, (C_6-C_{16})-arylsulfinyl, (C_6-C_{16})-arylsulfonyl, (C_7-C_{16})-aralkylmercapto, (C_7-C_{16})-aralkylsulfinyl or (C_7-C_{16})-aralkylsulfonyl, and

R^4 is R", provided that Q has the meaning of NR', where R' and R" are identical or different and are hydrogen, (C_6-C_{12})-aryl, (C_7-C_{11})-aralkyl, (C_1-C_8)-alkyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkyl, (C_1-C_{10})-alkanoyl, optionally substituted (C_7-C_{16})-aralkanoyl or optionally substituted (C_6-C_{12})-aroyl, or

R' and R" together are -$[CH_2]_h$-, in which a CH_2 group can be replaced by O, S, N-acylimino or N-(C_1-C_{10})-alkoxycarbonylimino, and

f is 1 to 8,
g is 0 or 1 to (2f+1),
x is 0 to 3,
h is 3 to 7,

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including the physiologically active salts, with 3-benzyloxypyridine-2-carboxylic acid (L-threonyl)amide and 3-benzyloxypyridine-2-carboxylic acid ((Fmoc-Phg)L-threonyl)amide hydrochloride being excepted.

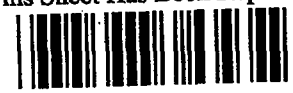
2. A compound of the formula I as claimed in claim 1, in which
Q is O, S, NR' or a bond,
X is O,
Y is CR^3, or,
if R^1 and R^2 form a cycle,
Y is N or CR^3,
m is 0 or 1.

3. A compound of the formula I as claimed in claims 1 and 2,
in which
Q is O, NR' or a bond, and
X is O.

4. A compound of the formula I as claimed in claims 1 and 2, in which
Q is S, and
X is O, and
m is 0 or 1.

5. A compound of the formula I as claimed in claims 1, 2 and 4, in which
Q is S,
X is O, and
m is 0.

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6. A compound of the formula I as claimed in claims 1 to 3, in which
Q is O, NR' or a bond,
X is O,
Y is CR^3 or, if R^1 and R^2 form a cycle, N or CR^3,
m is 0 or 1,



A is (C_1-C_3)-alkylene which is optionally substituted once by halogen, cyano, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy or $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$, or

A is $-CHR^5-$, where R^5 is one of the substituents of the α-carbon atom of an α-amino acid, in particular of a natural L-amino acid and of its D-isomer,

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B is CO_2H,

R^2 is hydrogen, (C_1-C_{20})-alkyl, (C_2-C_{20})-alkenyl, (C_2-C_{20})-alkynyl, (C_1-C_{20})-alkoxy, (C_2-C_{20})-alkenyloxy, (C_2-C_{20})-alkynyloxy, retinyloxy, (C_1-C_{20})-alkoxy-(C_1-C_3)-alkyl, (C_2-C_{20})-alkenyloxy-(C_1-C_3)-alkyl, retinyloxy-(C_1-C_3)-alkyl, (C_2-C_{20})-alkynyloxy-(C_1-C_3)-alkyl, halogen, cyano, trifluoromethyl, (C_1-C_8)-hydroxyalkyl, (C_1-C_{20})-alkanoyl, (C_7-C_{16})-aralkanoyl, (C_6-C_{12})-aroyl, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$, $NR'R''$, (C_1-C_{10})-alkylmercapto, (C_1-C_{10})-alkylsulfinyl, (C_1-C_{10})-alkylsulfonyl, (C_6-C_{12})-arylmercapto, (C_6-C_{12})-arylsulfinyl, (C_6-C_{12})-arylsulfonyl, (C_7-C_{12})-aralkylmercapto, (C_7-C_{12})-aralkylsulfinyl, (C_7-C_{12})-aralkylsulfonyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, carboxyl, (C_1-C_{20})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{20})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_2-C_{20})-alkynyloxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxycarbonyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxycarbonyl, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxycarbonyl,

carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-dicyclo(C_3-C_8)-alkylcarbamoyl,



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N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N-((C_1-C_{12})-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C_6-C_{16})-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, $CON(CH_2)_h$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7,

where aryl is substituted in the manner as defined for R^1 and R^3,

R^1 and R^3 are identical or different and are hydrogen, halogen, (C_1-C_{12})-alkyl, (C_1-C_{12})-alkoxy, -O-$[CH_2]_x$-$C_zH_{(2z+1-g)}Hal_g$, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkyl, (C_1-C_8)-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_8)-alkoxy-(C_2-C_6)-alkyl, (C_7-C_{11})-aralkyloxy, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyloxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkoxy, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl-(C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, NR^YR^Z, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl or (C_1-C_8)-alkylsulfonyl, (C_6-C_{12})-arylmercapto,

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$(C_6$-$C_{12})$-arylsulfinyl, $(C_6$-$C_{12})$-arylsulfonyl, $(C_7$-$C_{12})$-aralkylmercapto, $(C_7$-$C_{11})$-aralkylsulfinyl, $(C_7$-$C_{11})$-aralkylsulfonyl, substituted $(C_6$-$C_{12})$-aryloxy-$(C_1$-$C_6)$-alkyl, $(C_7$-$C_{11})$-aralkoxy-$(C_1$-$C_6)$-alkyl, $(C_6$-$C_{12})$-aryloxy-$(C_1$-$C_6)$-alkoxy-$(C_1$-$C_6)$-alkyl, $(C_7$-$C_{11})$-aralkyloxy-$(C_1$-$C_6)$-alkoxy-$(C_1$-$C_6)$-alkyl, $(C_6$-$C_{12})$-aryloxy, $(C_7$-$C_{11})$-aralkyloxy, $(C_6$-$C_{12})$-aryloxy-$(C_1$-$C_6)$-alkoxy or $(C_7$-$C_{11})$-aralkoxy-$(C_1$-$C_6)$-alkoxy, where an aromatic radical carries 1, 2, 3, 4 or 5 identical or different substituents from the group hydrogen, halogen, cyano, nitro, trifluoromethyl, $(C_1$-$C_{16})$-alkyl, $(C_1$-$C_{16})$-alkenyl, $(C_1$-$C_6)$-hydroxyalkyl, $(C_1$-$C_{16})$-alkoxy, $(C_1$-$C_{16})$-alkenyloxy, $-O-[CH_2]_x-C_zH_{(2z+1-g)}F_g$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, $(C_1$-$C_6)$-alkylmercapto, $(C_1$-$C_6)$-alkylsulfinyl, $(C_1$-$C_6)$-alkylsulfonyl, $(C_1$-$C_6)$-alkylcarbonyl, $(C_1$-$C_6)$-alkoxycarbonyl, carbamoyl, N-$(C_1$-$C_4)$-alkylcarbamoyl, N,N-di-$(C_1$-$C_4)$-alkylcarbamoyl, $(C_1$-$C_6)$-alkylcarbonyloxy, $(C_3$-$C_8)$-cycloalkylcarbamoyl, phenyl, benzyl, phenoxy, benzyloxy, NR^YR^Z, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-$(C_1$-$C_4)$-alkylsulfamoyl or N,N-di-$(C_1$-$C_4)$-alkylsulfamoyl, or optionally carries up to 3 of the abovementioned identical or different substituents, and two adjacent carbon atoms of the aralkyloxy radical together carry a chain $-[CH_2-]$ and/or $-CH=CH-CH=CH-$, where a CH_2 group of the chain is optionally replaced by O, S, SO, SO_2 or NR',

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R^1 and R^2 or R^2 and R^3 form a chain $[CH_2]_o$, where o is 3, 4 or 5, or

form, together with the pyridine or pyridazine carrying them, a cinnoline ring, a quinoline ring or an isoquinoline ring,

R^4 is, if Q is a bond, fluorine, chlorine or bromine, or, if Q is O or NR', a branched or

* C L M S *

unbranched (C_1-C_{20})-alkyl radical, which can contain up to 3 C-C multiple bonds, an unsubstituted saturated fluoroalkyl radical of the formula $[CH_2]_x$-$C_fH_{(2f+1-g)}F_g$, a (C_6-C_{16})-aryl radical or a (C_7-C_{16})-aralkyl radical, which can contain up to 2 C-C multiple bonds in the alkyl chain, or a heteroaryl radical or a heteroaryl alkyl radical, where these radicals are substituted by one or more radicals from the group hydroxyl, fluorine, chlorine, cyano, trifluoromethyl, carboxyl, (C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkocy, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl-(C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkoxy, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_2-C_{12})-alkenyl, (C_2-C_{12})-alkynyl, (C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxy, (C_1-C_8)-hydroxyalkyl, -O-[CH_2-]$_x$-$C_fH_{(2f+1-g)}F_g$,

(C_1-C_{12})-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, (C_6-C_{12})-arylcarbonyl, (C_7-C_{16})-aralkylcarbonyl,

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(C_1-C_{12})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{12})-alkenyloxycarbonyl, (C_2-C_{12})-alkynyloxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl,

(C_1-C_{12})-alkylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_7-C_{16})-aralkylcarbonyloxy,
carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkyl-

* C L M S *

carbamoyl, N,N-dicyclo-(C_3-C_8)-alkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C_6-C_{16})-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, $CON(CH_2)_h$ in which a CH_2 group can be replaced by O, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino or N-(C_7-C_{16})-aralkylimino, and h is from 3 to 6,

where the radicals which contain an aryl radical can, for their part, be substituted on the aryl by from 1 to 5 identical or different radicals from the group:

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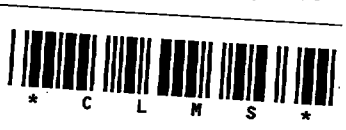


hydroxyl, fluorine, chlorine, cyano, trifluoromethyl, carboxyl, (C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyl, (C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkoxy, (C_1-C_{12})-alkoxycarbonyl,

N-(C_1-C_6)-alkylcarbamoyl, N,N-di-(C_1-C_6)-alkylcarbamoyl or N-(C_3-C_8)-cycloalkylcarbamoyl, and

R^4 is R^*, provided Q has the meaning of NR', where R' and R^* are identical or different and are hydrogen, (C_1-C_8)-alkyl, or (C_7-C_{11})-aralkyl which is optionally substituted once by fluorine, chlorine or (C_1-C_4)-alkoxy,

R^Y and R^Z are identical or different and are hydrogen, (C_6-C_{12})-aryl, (C_1-C_{10})-alkyl, (C_3-C_{10})-



cycloalkyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkyl, (C_1-C_{10})-alkanoyl, optionally substituted (C_7-C_{16})-aralkanoyl or optionally substituted (C_6-C_{12})-aroyl, or

R^Y and R^Z together are $-[CH_2]_{h-}$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_4)-alkanoylimino or N-(C_1-C_4)-alkoxycarbonylimino, and

f is 1 to 8,
g is 0 or 1 to (2f + 1),
h is 3 to 6,
x is 0 to 3, and
n is 3 or 4, including the physiologically active salts, with 3-benzyloxypyridine-2-carboxylic acid (L-threonyl)amide and 3-benzyloxypyridine-2-carboxylic acid ((Fmoc-Phg)L-threonyl)amide hydrochloride being excepted.

7. A compound of the formula I as claimed in claims 1 to 3 and 6, in which

Q is O, NR′ or a bond,
X is O,
Y is CR^3 or, if R^1 and R^2 form a cycle, N or CR^3,
m is 0,
A is (C_1-C_3)-alkylene which is optionally substituted once by halogen, cyano, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy or $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$ or

A is $-CHR^5-$, where R^5 is one of the substituents of the α-carbon atom of an α-amino acid, in particular of a natural L-amino acid and of its D-isomer,

B is CO_2H,

R^2 is hydrogen, (C_1-C_{20})-alkyl, (C_2-C_{20})-alkenyl,

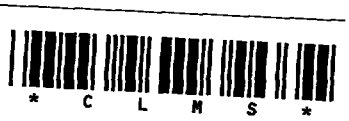
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(C_2-C_{20})-alkenyloxy, (C_2-C_{20})-alkynyloxy, retinyloxy, (C_1-C_{20})-alkoxy-(C_1-C_3)-alkyl, (C_1-C_{20})-alkoxy-(C_1-C_3)-alkyl, (C_2-C_{20})-alkenyloxy-(C_1-C_3)-alkyl, retinyloxy-(C_1-C_3)-alkyl, (C_2-C_{20})-alkynyloxy-(C_1-C_3)-alkyl, (C_1-C_{20})-alkoxy, halogen, cyano, trifluoromethyl, (C_1-C_{16})-hydroxyalkyl, (C_1-C_{20})-alkanoyl, (C_7-C_{12})-aralkanoyl, (C_6-C_{12})-aroyl, $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$, $NR'R''$, (C_1-C_{10})-alkylmercapto, (C_1-C_{10})-alkylsulfinyl, (C_1-C_{10})-alkylsulfonyl, (C_6-C_{12})-arylmercapto, (C_6-C_{12})-arylsulfinyl), (C_6-C_{12})-arylsulfonyl, (C_7-C_{12})-aralkylmercapto, (C_7-C_{12})-aralkylsulfinyl, (C_7-C_{12})-aralkylsulfonyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, carboxyl, (C_1-C_{20})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{20})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_2-C_{20})-alkynyloxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxycarbonyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxycarbonyl, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-dicyclo-(C_3-C_8)-alkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-$((C_3-C_8)$-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{12})-aralkylcarbamoyl, N-$((C_1-C_{12})$-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-$((C_6-C_{16})$-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-$((C_7-C_{16})$-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-$((C_1-C_{10})$-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-$((C_6-C_{12})$-aryloxy-(C_1-C_{10})-

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alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, or $CON(CH_2)_h$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 6,

where aryl is substituted in the manner as defined for R^1 and R^3,

R^1 and R^3 are identical or different and are hydrogen, halogen, (C_1-C_{12})-alkyl, (C_1-C_{12})-alkoxy, $-O-[CH_2]_x-C_fH_{(2f+1-g)}Hal_g$, ($C_1$-$C_{12}$)-alkoxy-($C_1$-$C_{12}$)-alkyl, ($C_1$-$C_8$)-alkoxy-($C_1$-$C_{12}$)-alkoxy, ($C_1$-$C_{12}$)-alkoxy-($C_1$-$C_8$)-alkoxy-($C_2$-$C_6$)-alkyl, ($C_7$-$C_{11}$)-aralkyloxy, ($C_3$-$C_8$)-cycloalkyl, ($C_3$-$C_8$)-cycloalkyl-($C_1$-$C_8$)-alkyl, ($C_3$-$C_8$)-cycloalkyloxy, ($C_3$-$C_8$)-cycloalkyl-($C_1$-$C_8$)-alkoxy, ($C_3$-$C_8$)-cycloalkyloxy-($C_1$-$C_8$)-alkyl, ($C_3$-$C_8$)-cycloalkyloxy-($C_1$-$C_8$)-alkoxy, ($C_3$-$C_8$)-cycloalkyl-($C_1$-$C_6$)-alkyl-($C_1$-$C_6$)-alkoxy, ($C_3$-$C_8$)-cycloalkyl-($C_1$-$C_6$)-alkoxy-($C_1$-$C_6$)-alkyl, ($C_3$-$C_8$)-cycloalkoxy-($C_1$-$C_6$)-alkoxy-($C_1$-$C_6$)-alkyl, NR^YR^Z, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl or (C_1-C_8)-alkylsulfonyl, (C_6-C_{12})-arylmercapto, (C_6-C_{12})-arylsulfinyl, (C_6-C_{12})-arylsulfonyl, (C_7-C_{12})-aralkylmercapto, (C_7-C_{11})-aralkylsulfinyl, (C_7-C_{11})-aralkylsulfonyl, substituted (C_6-C_{12})-aryloxy-(C_1-C_6)-alkyl, (C_7-C_{11})-aralkoxy-(C_1-C_6)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_7-C_{11})-aralkyloxy-(C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{11})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy or (C_7-C_{11})-aralkoxy-(C_1-C_6)-alkoxy, where an aromatic radical carries by 1, 2, 3, 4 or 5 identical or different substituents from the group hydrogen, halogen, cyano, nitro, trifluoromethyl, (C_1-C_{12})-alkyl, (C_1-C_{12})-alkenyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_{12})-alkoxy, (C_1-C_{12})-alkenyloxy,

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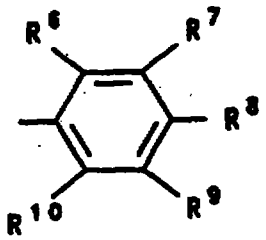
$-O-[CH_2]_xC_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, (C_1-C_6)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkylcarbamoyl, phenyl, benzyl, phenoxy, benzyloxy, NR^YR^Z, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl or N,N-di-(C_1-C_4)-alkylsulfamoyl, or optionally carries up to 3 of the abovementioned identical or different substituents, and two adjacent carbon atoms of the aralkyloxy radical together carry a chain $-[CH_2-]$ and/or $-CH=CH-CH=CH-$, where a CH_2 group of the chain is optionally replaced by O, S, SO, SO_2 or NR^Y,

R^1 and R^2 or R^2 and R^3 can form a chain $[CH_2]_o$, where o is 3, 4 or 5, and

R^4 is, provided Q is a bond, chlorine or, if Q is O or NR', is a branched or unbranched (C_1-C_{10})-alkyl radical, which can contain one or two C-C multiple bonds, or an unsubstituted fluoroalkyl radical of the formula $-[CH_2]_x-C_fH_{(2f+1-g)}F_g$ or (C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_1-C_6)-alkoxy-(C_1-C_4)-alkoxy-(C_1-C_4)-alkyl or a radical of the formula Z,

$$-[CH_2]_V-[O]_W-[CH_2]_t-E \qquad (Z)$$

where E is a substituted phenyl radical of the formula F



(F),

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or a (C_3-C_8)-cycloalkyl radical, where

v is 0, 1, 2, 3, 4, 5 or 6, w is 0 or 1, and t is 0, 1, 2 or 3, with the restriction that v is not equal to 0 if w is 1, and R^6, R^7, R^8, R^9 and R^{10} are identical or different and are hydrogen, halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyl, (C_1-C_6)-alkoxy, $-O-[CH_2-]_x-C_fH_{(2f+1-g)}F_g$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, (C_1-C_6)-alkylmercapto, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy-(C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_8)-alkoxycarbonyl, carbamoyl, N-(C_1-C_8)-alkylcarbamoyl, N,N-di-(C_1-C_8)-alkylcarbamoyl, (C_7-C_{11})-aralkylcarbamoyl which is optionally substituted by fluorine, chlorine, bromine, trifluoromethyl or (C_1-C_6)-alkoxy, N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, phenyl, benzyl, phenoxy, benzyloxy, NR^yR^z, such as amino, anilino, N-methylanilino, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_8)-alkylsulfamoyl or N,N-di-(C_1-C_8)-alkylsulfamoyl, or two adjacent substituents together are a chain $-[CH_2-]_n$ or $-CH=CH-CH=CH-$, where a CH_2 group of the chain is optionally replaced by O, S, SO, SO_2 or NR^y, and where a heteroaryl radical can carry 1, 2 or 3 substituents, and a cycloalkyl radical one substituent, from the above group, and

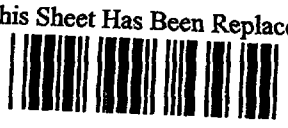
R^4 is R^*, provided Q has the meaning of NR', where

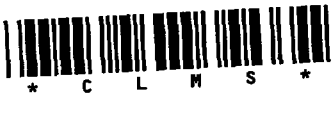
R' is hydrogen or methyl, and

R^* is benzyl, and

if R^1 and/or R^3 have the meaning of (C_6-C_{12})-aryloxy, (C_7-C_{11})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy, (C_7-C_{11})-aralkoxy-(C_1-C_6)-alkoxy or a corresponding radical containing terminal cycloalkyl groups, this

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radical is preferably then a radical of the formula D

$$OZ \quad (D), \text{ or}$$

if R^1 and/or R^3 have the meaning of (C_7-C_{11})-aralkyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkyl, (C_7-C_{11})-aralkoxy-(C_1-C_6)-alkyl or a corresponding radical containing terminal cycloalkyl groups, this radical is preferably then a radical of the formula Z,

R^Y and R^Z are identical or different and are hydrogen, (C_6-C_{12})-aryl, (C_1-C_{10})-alkyl, (C_3-C_{10})-cycloalkyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkyl, (C_1-C_{10})-alkanoyl, optionally substituted (C_7-C_{16})-aralkanoyl or optionally substituted (C_6-C_{12})-aroyl, or

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R^Y and R^Z are together $-[CH_2]_{h}-$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_4)-alkanoylimino or N-(C_1-C_4)-alkoxycarbonylimino, and

f is 1 to 8,
g is 0 or 1 to (2f+1),
h 3 to 6,
x is 0 to 3, and
n is 3 or 4,

including the physiologically active salts, with 3-benzyloxypyridine-2-carboxylic acid (L-threonyl)amide and 3-benzyloxypyridine-2-carboxylic acid ((Fmoc-Phg)L-threonyl)amide hydrochloride being excepted.

* C L M S *

8. A compound of the formula I as claimed in claims 1 to 5, in which

Q is O,
X is O,
Y is CR^3 and, additionally, N if R^1 and R^2 form a

cycle,

m is 0,

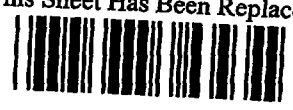
A is $-CHR^5-$, where R^5 is the substituent of the α-carbon atom of an α-amino acid, in particular of a natural L-amino acid or its D-isomer,

B is CO_2H,

R^2 is hydrogen, bromine, chlorine, cyano, (C_1-C_{18})-alkyl, (C_1-C_8)-alkoxy, (C_1-C_{18})-alkoxymethyl, (C_2-C_{18})-alkenyloxymethyl, (C_2-C_{18})-alkynyloxymethyl, carbamoyl, N-(C_1-C_{10})-alkylcarbamoyl, N-$((C_1-C_{12})$-alkoxy-(C_1-C_4)-alkyl)carbamoyl, N,N-di-(C_1-C_8)-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_6-C_{12})-phenylcarbamoyl, N-(C_7-C_{12})-phenylalkylcarbamoyl, N-(C_1-C_6)-alkyl-N-(C_6-C_{12})phenylcarbamoyl, N-(C_1-C_6)-alkyl-N-(C_7-C_{12})-phenylalkylcarbamoyl, N-$((C_1-C_6)$-alkoxy-(C_1-C_6)-alkyl)carbamoyl, carboxyl, (C_1-C_{20})-alkoxycarbonyl, (C_2-C_{20})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxycarbonyl, phenyl-(C_1-C_6)-alkoxycarbonyl, phenoxy-(C_1-C_6)-alkoxycarbonyl or benzyloxy-(C_1-C_6)-alkoxycarbonyl, where a phenyl radical is substituted in the manner as defined for R^1 and R^3, and one of the radicals

R^1 or R^3 is hydrogen and the other a radical from the group hydrogen, fluorine, chlorine, (C_1-C_8)-alkyl, (C_1-C_{10})-alkoxy, (C_5-C_6)-cycloalkyl, (C_5-C_6)-cycloalkyl-(C_1-C_6)-alkyl, (C_5-C_6)-cycloalkyloxy, (C_5-C_6)-cycloalkyl-(C_1-C_6)-alkoxy, (C_5-C_6)-cycloalkyloxy-(C_1-C_6)-alkyl, (C_5-C_6)-cycloalkyloxy-(C_1-C_6)-alkoxy, (C_5-C_6)-cycloalkyl-(C_1-C_4)-alkyl-(C_1-C_4)-alkoxy, (C_5-C_6)-cycloalkyl-(C_1-C_4)-alkoxy-(C_1-C_2)-alkyl, (C_5-C_6)-cycloalkoxy-(C_1-C_4)-alkoxy-(C_1-C_2)-alkyl, $-O-[CH_2]_x-C_tH_{(2t+1-s)}F_s$, (C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_1-C_6)-alkoxy-(C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy-(C_1-C_4)-alkoxy-(C_1-C_2)-

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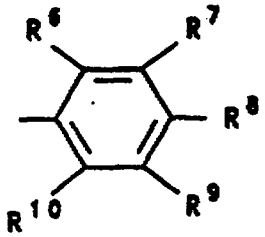
alkyl, substituted (C_6-C_{12})-phenoxy, (C_7-C_{11})-phenylalkyloxy, (C_6-C_{12})-phenoxy-(C_1-C_6)-alkoxy or (C_7-C_{11})-phenylalkoxy-(C_1-C_6)-alkoxy, phenoxy-(C_1-C_4)-alkyl, (C_7-C_{11})-phenylalkyloxy-(C_1-C_4)-alkyl, phenoxy-(C_1-C_4)-alkoxy-(C_1-C_2)-alkyl or (C_7-C_{11})-phenylalkyloxy-(C_1-C_4)-alkoxy-(C_1-C_2)-alkyl, where an aromatic radical is substituted by 1, 2 or 3 identical or different substitutents from the group fluorine, chlorine, cyano, trifluoromethyl, (C_1-C_{12})-alkyl, (C_2-C_{12})-alkenyl, (C_2-C_{12})-alkenyloxy or (C_1-C_{12})-alkoxy,

R^1 and R^2, with the pyridine carrying them, form a 5, 6, 7, 8-tetrahydroisoquinoline ring,

R^4 is a branched or unbranched (C_1-C_{10})-alkyl radical, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl or a radical of the formula Z,

$$-[CH_2]_v-[O]_w-[CH_2]_t-E \qquad (Z)$$

where E is a substituted phenyl radical of the formula F



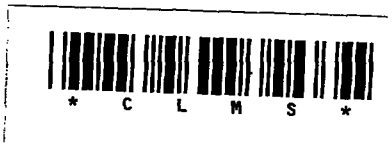
(F),

or a (C_3-C_8)-cycloalkyl radical, where v is 0, 1, 2 or 3, w is 0, and t can be 0 or 1, and in which R^6, R^7, R^8, R^9 and R^{10} are identical or different and are hydrogen, fluorine, chlorine, cyano, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, $-O-[CH_2-]_x-C_zH_{(2z+1-g)}F_g$, N-$(C_1-C_8)$-alkylcarbamoyl, N,N-di-$(C_1-C_6)$-alkylcarbamoyl, N-$(C_3-C_6)$-cycloalkylcarbamoyl, N-(+)-dehydroabietylaminocarbonyl, or (C_7-C_{11})-phenylalkylcarbamoyl, which

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is optionally substituted by fluorine, chlorine, trifluoromethyl and (C_1-C_6)-alkoxy, or where R^6 and R^7 or R^7 and R^8, together with the phenyl ring carrying them, form naphthalene derivatives, or

if R^1 or R^3 has the meaning of (C_6-C_{12})-phenoxy, (C_7-C_{11})-phenylalkyloxy, (C_6-C_{12})-phenoxy-(C_1-C_6)-alkoxy, (C_7-C_{11})-phenylalkoxy-(C_1-C_6)-alkoxy, (C_5-C_6)-cycloalkyloxy, (C_5-C_6)-cycloalkyl-(C_1-C_6)-alkoxy, (C_5-C_6)-cycloalkoxy-(C_1-C_6)-alkoxy or (C_5-C_6)-cycloalkyl-(C_1-C_4)-alkyl-(C_1-C_4)-alkoxy, this radical is then, especially, a radical of the formula D



OZ (D), or

if R^1 or R^3 has the meaning of phenyl, phenoxy-(C_1-C_6)-alkyl, (C_7-C_{11})-phenylalkyl, (C_7-C_{11})-phenylalkyloxy-(C_1-C_4)-alkyl, (C_5-C_6)-cycloalkyl, (C_5-C_6)-cycloalkyl-(C_1-C_6)-alkyl, (C_5-C_6)-cycloalkoxy-(C_1-C_4)-alkyl, (C_5-C_6)-cycloalkyl-(C_1-C_4)-alkoxy-(C_1-C_2)-alkyl or (C_5-C_6)-cycloalkoxy-(C_1-C_4)-alkoxy-(C_1-C_2)-alkyl, this radical is then, especially, a radical of the formula Z in which, in both cases,

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v is 1, 2, 3 or 4, w is 0 and t is 0, or
v is 1, 2, 3 or 4, w is 1 and t is 0, or
v is 1, 2, 3 or 4, w is 1, t is 1, and
f is 1 to 4,
g is 0 or 1 to (2f+1),
x is 0 or 1
including the physiologically active salts, with 3-benzyloxypyridine-2-carboxylic acid (L-threonyl)amide and 3-benzyloxypyridine-2-carboxylic acid ((Fmoc-Phg)L-threonyl)amide hydrochloride being excepted.

9. A compound of the formula I as claimed in claims 1

to 6, in which

Q is O,

X is O,

Y is CR^3,

m is 0,

A is a $-CH_2-$ group which can be substituted by a methyl group,

B is CO_2H,

R^2 is hydrogen, (C_1-C_8)-alkoxy, (C_1-C_{16})-alkoxymethyl, (C_2-C_{16})-alkenyloxymethyl, retinyloxymethyl, N-(C_1-C_{10})-alkylcarbamoyl, N-$((C_1-C_{12})$-alkoxy-(C_1-C_3)-alkyl)carbamoyl, N,N-di-(C_1-C_8)-alkylcarbamoyl, N-(C_5-C_6)-cycloalkylcarbamoyl, N-phenylcarbamoyl, N-phenyl-(C_1-C_4)-alkylcarbamoyl, carboxy, (C_1-C_{16})-alkoxycarbonyl, (C_2-C_{16})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_5-C_6)-cycloalkoxycarbonyl, (C_5-C_6)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl or phenyl-(C_1-C_6)-alkoxycarbonyl, where a phenyl radical is substituted in a manner as defined for R^1 and R^3, and one of the radicals

R^1 or R^3 is hydrogen and the other radical is a radical from the group hydrogen, (C_1-C_{10})-alkoxy, (C_5-C_6)-cycloalkyloxy, (C_5-C_6)-cycloalkyl-(C_1-C_2)-alkoxy, $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$, (C_1-C_4)-alkoxy-(C_1-C_4)-alkoxy, substituted (C_6-C_{12})-phenoxy, (C_7-C_{11})-phenylalkyloxy, (C_6-C_{12})-phenoxy-(C_1-C_4)-alkoxy or (C_7-C_{11})-phenylalkoxy-(C_1-C_4)-alkoxy, where an aromatic radical is substituted by 1, 2 or 3 identical or different substituents from the group fluorine, chlorine, cyano, trifluoromethyl, (C_1-C_{10})-alkyl, (C_1-C_{10})-alkoxy or (C_1-C_{10})-alkenyloxy, and

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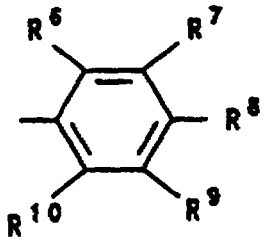


R^4 is a branched or unbranched (C_1-C_8)-alkyl radical or a radical of the formula Z,

$$-[CH_2]_v-[O]_w-[CH_2]_t-E \qquad (Z),$$



where E is a substituted phenyl radical of the formula F



(F),

or a (C_3-C_8)-cycloalkyl radical, where
v is 0, 1, 2 or 3, w is 0, and t can be 0 or 1,
and in which R^6, R^7, R^8, R^9 and R^{10} are identical or different and are hydrogen, fluorine, chlorine, cyano, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$, N-$(C_1-C_8)$-alkylcarbamoyl, N,N-di-$(C_1-C_6)$-alkylcarbamoyl, N-$(C_3-C_6)$-cycloalkylcarbamoyl, N-(+)-dehydroabietylaminocarbonyl substituted benzyl radical, and f is 1 to 4, g is 0 or 1 to (2f+1) and x is 0 or 1 including the physiologically active salts.

10. A compound of the formula I as claimed in claims 1 to 3 and 6 to 9, in which

Q is O,
X is O,
Y is CR^3,
m is 0,
A is a $-CH_2$ group,
B is CO_2H,

R^1 is hydrogen, (C_1-C_6)-alkoxy or $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$,
R^2 is hydrogen, N-(C_1-C_{10})-alkylcarbamoyl, N-((C_1-C_{12})-alkoxy-(C_1-C_3)-alkyl)carbamoyl, N,N-di-(C_1-C_8)-alkylcarbamoyl,N-(C_5-C_6)-cycloalkylcarbamoyl, N-phenylcarbamoyl, N-phenyl-(C_1-C_2)-alkylcarbamoyl, carboxyl, (C_1-C_{16})-alkoxycarbonyl,

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(C_2-C_{16})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_5-C_6)-cycloalkoxycarbonyl, (C_5-C_6)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl or phenyl-(C_1-C_6)-alkoxycarbonyl, where a phenyl radical is substituted by 1 or 2 identical or different substituents from the group fluorine, chlorine, cyano, trifluoromethyl, (C_1-C_{10})-alkyl, (C_1-C_{10})-alkoxy or (C_1-C_{10})-alkenyloxy, and

R^3 is hydrogen, (C_1-C_5)-alkoxy or (C_5-C_6)-cycloalkyl-(C_1-C_2)-alkoxy, where one of the substituents R^1 and R^3 is hydrogen,

R^4 is a branched or unbranched (C_1-C_6)-alkyl radical, or a 2-phenylethyl radical, or a benzyl radical substituted by 1 or 2 radicals from the group fluorine, chlorine, cyano, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, $-O-[CH_2-]_x-C_fH_{(2f+1-g)}F_g$, N-$(C_1-C_8)$-alkylcarbamoyl, N,N-di-$(C_1-C_6)$-alkylcarbamoyl, N-$(C_3-C_6)$-cycloalkylcarbamoyl or N-(+)-dehydroabietylaminocarbonyl, and f is 1 to 4, g is 0 or 1 to (2f+1) and x is 1, including the physiologically active salts.

11. Compounds of the formula I as claimed in claims 1 to 3 and 6 to 10, in which

Q is O,

X is O,

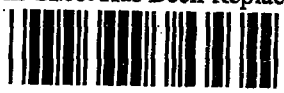
Y is CR^3,

m is 0,

A is a $-CH_2-$group,

B is CO_2H,

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R^1 is hydrogen,

R^2 is hydrogen, N-(C_1-C_{10})-alkylcarbamoyl, N-$((C_1-C_{12})$-alkoxy-(C_1-C_3)-alkyl)carbamoyl, N-cyclo-



hexylcarbamoyl, N-phenylcarbamoyl, N-(phenyl-(C_1-C_2)-alkyl)carbamoyl, where, in the last two cases, the phenyl radical can carry a fluorine substituent, a (C_1-C_{10})-alkyl substituent or a (C_1-C_{10})-alkoxy substituent, carboxyl, (C_1-C_{16})-alkoxycarbonyl, (C_2-C_{16})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_5-C_6)-cycloalkoxycarbonyl or benzyloxycarbonyl,

R^3 is hydrogen, (C_1-C_6)-alkoxy or 2-(cyclohexyl)-ethyloxy, where one of the substituents R^2 and R^3 is hydrogen,

R^4 is a branched or unbranched (C_1-C_4)-alkyl radical or a benzyl radical which is substituted once by fluorine, chlorine, trifluoromethyl, (C_1-C_4)-alkyl or (C_1-C_3)-alkoxy, including the physiologically active salts.

12. A compound of the formula I as claimed in claims 1 to 3 and 6, in which

Q is O

X is O,

Y is CR^3,

where R^3 is hydrogen,

m is 0,



A is a $-CH_2$ group,

B is $-CO_2H$, and

R^1 and R^2, together with the pyridine carrying them, form an isoquinoline ring having an unsubstituted benzo moiety, and

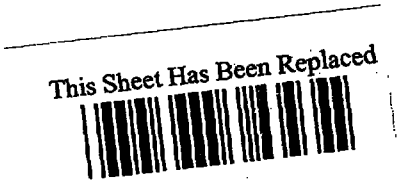
R^4 is methyl.

13. A compound of formula I as claimed in claims 1 to 3 and 6, in which

Q is O,

X is O

Y is CR^3,



m is 0,

A is a $-CH_2$ group,

B is $-CO_2H$,

R^1 is hydrogen, and

R^2 and R^3, together with the pyridine carrying them, form a quinoline ring having an unsubstituted benzo moiety, and

R^4 is methyl.

14. A compound of the formula I as claimed in claims 1, 2, 4 and 5, in which

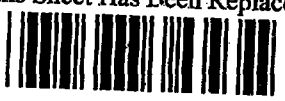
Q is S,

X is O,

Y is CR^3,

m is 0,

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A is a $-CH_2$ group,

B is $-CO_2H$,

R^1 is hydrogen,

R^2 is hydrogen, N-(C_1-C_{10})-alkylcarbamoyl, N-((C_1-C_{12})-alkoxy-(C_1-C_3)alkyl)carbamoyl, N-cyclohexylcarbamoyl, N-phenylcarbamoyl, N-(phenyl-(C_1-C_2)alkyl)carbamoyl, where, in the last two cases, the phenyl radical can carry a fluorine substituent, (C_1-C_{10})-alkyl substituent or (C_1-C_{10})-alkoxy substituent, carboxyl, (C_1-C_{16})-alkoxycarbonyl, (C_2-C_{16})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_5-C_6)-cycloalkoxycarbonyl or benzyloxycarbonyl,

R^3 is hydrogen, (C_1-C_6)-alkoxy or 2-(cyclohexyl)-ethyloxy, where one of the substituents R^2 and R^3 is hydrogen, and

R^4 is a branched or unbranched (C_1-C_4)-alkyl radical or a benzyl radical which is substituted once by fluorine, chlorine, trifluoromethyl, (C_1-C_4)-alkyl or (C_1-C_3)-alkoxy.



15. A compound of the formula I as claimed in claims 1, 2, 4, 5 and 14, in which

Q is S,
X is O,
Y is CR^3,
m is 0,
A is a $-CH_2$ group,
B is $-CO_2H$,
R^1 is hydrogen,
R^2 is carboxyl or (C_1-C_{16})-alkoxycarbonyl,
R^3 is hydrogen, and
R^4 is an unbranched or branched (C_1-C_4)-alkyl radical.

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16. A compound of the formula I as claimed in claims 1 to 15, plus 3-benzyloxypyridine-2-carboxylic acid L-threonylamide and 3-benzyloxypyridine-2-carboxylic acid ((Fmoc-Phg)-L-threonyl)amide for use as pharmaceuticals.

17. A compound as claimed in claims 1 to 16 to be used for inhibiting collagen biosynthesis.

18. A compound as claimed in claims 1 to 16 as an inhibitor of prolyl hydroxylase.

19. A compound as claimed in claims 1 to 16 for use as a fibrosuppressive agent.

20. A compound as claimed in claims 1 to 16 for preparing a pharmaceutical against fibrotic diseases.

21. A compound as claimed in claims 1 to 16 for preparing a pharmaceutical against fibrotic diseases of the liver.

22. A compound as claimed in claims 1 to 16 for preparing a pharmaceutical against fibrotic diseases of the lung.

* C L M S *

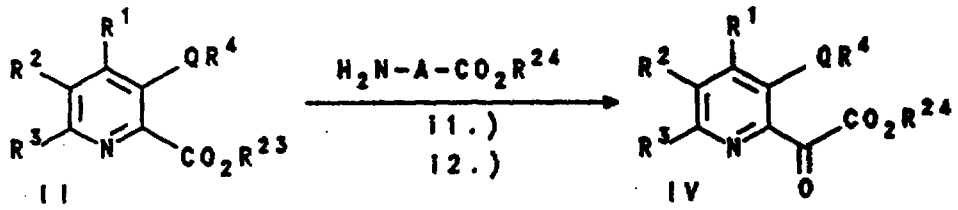
23. A compound as claimed in claims 1 to 16 for preparing a pharmaceutical against fibrotic diseases of the skin.

24. A process for preparing compounds according to formula I as claimed in claims 1 to 15, in which formula A is a substituted alkylene moiety, B is CO_2H, Y is CR^3 and m is 0 or 1, by

i1.) reacting pyridine-2-carboxylic acids of the formula II (R^{23} is H) with the amino esters of the formula III (R^{24} is (C_1-C_{16})-alkyl or benzyl) to form the amide esters of the formula IV, or

i2.) reacting pyridine-2-carboxylic esters of the formula II (R^{23} is lower alkyl), under the conditions of aminolysis, to form the compounds of the formula IV;
and

III



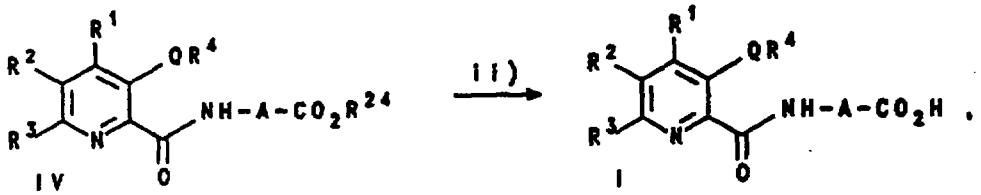
II IV

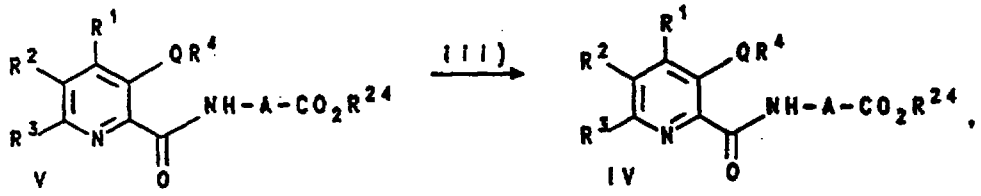
ii) liberating the compounds of the formula I from their esters of the formula IV;
with, where appropriate,

iii) the compounds of the formula IV (R^4 is alkyl) being prepared by alkylation of compounds of the formula V (R^4 is H) with R^4X,

* C L M S *

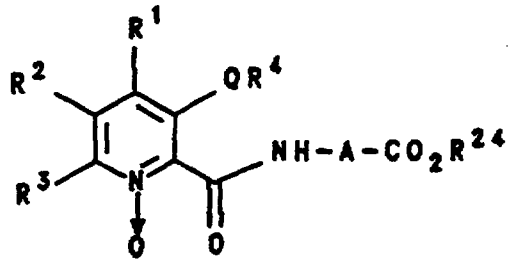
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where X is a leaving group, in particular halogen, OSO_2Me or OSO_2 phenyl, and, where appropriate,

iv) the compounds of the formula IV, provided Q is O, S or NR', being converted into their pyridine N-oxides (IV')



IV'

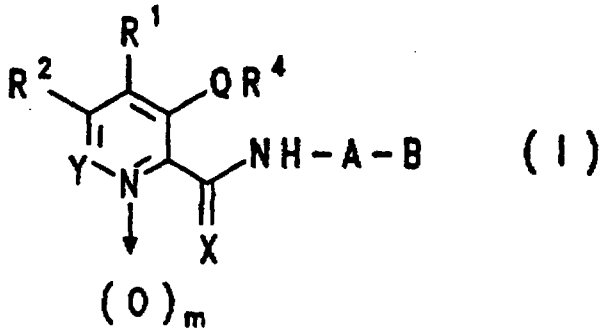
and, where appropriate, the latter being hydrolysed to form the compounds of the formula I' (R^{24} is H).

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Abstract of the disclosure

Substituted heterocyclic carboxamides, their preparation and their use as pharmaceuticals

The invention relates to compounds of the formula I,



(I)

to a process for their preparation and to their use as pharmaceuticals. The compounds are employed, in particular, for inhibiting collagen biosynthesis and as inhibitors of prolyl hydroxylase and as fibrosuppressive agents.

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REPLACEMENT
27 FEB 1997

REPLACEMENT SHEETS SG
☒ Description : paged 1 to paged 104
☒ Claim(s) : paged 105 to paged 145
☐ Drawing(s) : paged — to paged —
☒ Abstract : paged 146 to paged 146
DATE OF RECEIPT 27/02/97

Description

Substituted heterocyclic carboxamides, their preparation and their use as pharmaceuticals

The invention relates to substituted heterocyclic carboxamides, to their preparation and to their use as inhibitors of prolyl-4-hydroxylase, and to their use as pharmaceuticals for treating fibrotic diseases.

Compounds which inhibit the enzymes proline hydroxylase and lysine hydroxylase bring about a very selective inhibition of collagen biosynthesis by their influence on the collagen-specific hydroxylation reactions. In the course of these reactions, protein-bound proline or lysine is hydroxylated by the enzymes proline hydroxylase or lysine hydroxylase, respectively. If this reaction is prevented by inhibitors, there then arises a non-functional, subhydroxylated collagen molecule which can only be secreted by the cells into the extracellular space in small quantities. Furthermore, the subhydroxylated collagen cannot be incorporated into the collagen matrix and is very readily degraded proteolytically. These effects result in a diminution of the overall quantity of collagen which is deposited extracellularly.

Inhibitors of prolyl hydroxylase are therefore suitable substances for use in the therapy of diseases in which the deposition of collagens makes a substantial contribution to the clinical picture. These diseases include, inter alia, fibroses of the lung, liver and skin (scleroderma and cicatrizations following burns, injuries and surgical intervention) and also atherosclerosis.

It is known that the enzyme proline hydroxylase is efficiently inhibited by pyridine-2,4-dicarboxylic acid and pyridine-2,5-dicarboxylic acid (K. Majamaa et al.,

Eur. J. Biochem. 138 (1984) 239-245). However, these compounds are only active as inhibitors in cell culture at very high concentrations (Tschank, G. et al., Biochem. J. 238 (1987) 625 to 633).

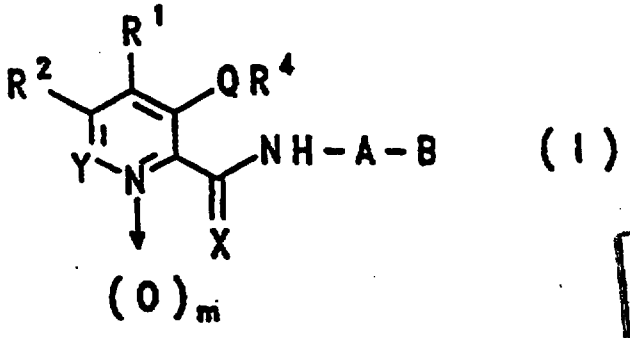
Prodrugs of pyridine-2,4(5)-dicarboxylates are also known. These are described in the relatively old German Applications P 42 33 124.2, P 42 38 506.7 and P 42 09 424.0.

N-Oxalylglycines which are inhibitors of prolyl-4-hydroxylase are disclosed in J. Med. Chem. 1992, 35, 2652 to 2658 (Cunliffe et al.), and EP-A-0 457 163 (Baader et al.).

Hydroxyisoquinolinecarboxylic acid glycylamides and hydroxycinnolinecarboxylic acid glycylamides are disclosed in Biochem. Soc. Trans. 1991, 19, 812 to 815 (Franklin et al.). 3-Benzyloxypyridine-2-carboxylic acid (L-threonyl)amide and 3-benzyloxypyridine-2-carboxylic acid ((Fmoc-Phg)-L-threonyl)amide hydrochloride are disclosed in Liebigs Ann. Chem. 1986, 1 to 20, Kessler et al.

It has now been found, surprisingly, that heterocyclic carboxamides having an ether substituent, a thioether substituent or an amino substituent in the ortho position to the amide function have a strong inhibitory action on prolyl-4-hydroxylase.

The compounds according to the invention conform to the formula I



(I)

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in which

Q is O, S, NR' or a bond,

X is O or S,

Y is C-R^1 or,

if R^1 and R^2 form a cycle,

Y is N or CR^3,

m is 0 or 1,

A is (C_1-C_4)-alkylene, which is optionally substituted by one or two substituents from the group halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, -O-$[CH_2]_x$-$C_zH_{(2z+1-g)}Hal_g$, preferably (C_1-C_8)-fluoroalkoxy, (C_1-C_8)-fluoroalkenyloxy, (C_2-C_8)-fluoroalkynyloxy, -OCF_2Cl or -O-CF_2-CHFCl, (C_1-C_6)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, anilino, N-methylanilino, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl or N,N-di-(C_1-C_4)-alkylsulfamoyl, or

by a substituted (C_6-C_{12})-aryloxy, (C_7-C_{11})-aralkyloxy, (C_6-C_{12})-aryl or (C_7-C_{11})-aralkyl radical which carries in the aryl moiety 1, 2, 3, 4 or 5 identical or different substituents from the group halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, -O-$[CH_2]_x$-$C_zH_{(2z+1-g)}Hal_g$, -OCF_2Cl, -O-CF_2-CHFCl, (C_1-C_6)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl or N,N-di-(C_1-C_4)-alkylsulfamoyl, or

by the substituents R^5 of the α-carbon atom of an α-amino acid, it being possible to use the natural

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L-amino acids and their D-isomers;

B is an acid grouping from the group $-CO_2H$, $-CONHCOR''$, $-CONHSOR''$, $CONHSO_2R''$, $-NHSO_2CF_3$, tetrazolyl, imidazolyl or 3-hydroxyisoxazolyl, where R'' is aryl, heteroaryl, (C_3-C_7)-cycloalkyl or (C_1-C_4)-alkyl, optionally monosubstituted by (C_6-C_{12})-aryl, heteroaryl, OH, SH, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, (C_1-C_4)-thioalkyl, (C_1-C_4)-sulfinyl, (C_1-C_4)-sulfonyl, CF_3, Cl, Br, F, I, NO_2, -COOH, (C_2-C_5)-alkoxycarbonyl, NH_2, mono-$(C_1-C_4$-alkyl)-amino, di-$(C_1-C_4$-alkyl)-amino or (C_1-C_4)-perfluoroalkyl,

R^1, R^2 and R^3 are identical or different and are hydrogen, hydroxyl, halogen, cyano, trifluoromethyl, nitro, carboxyl, (C_1-C_{20})-alkyl, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyloxy-(C_1-C_2)-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl-(C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkoxy, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_7-C_{16})-aralkenyl, (C_7-C_{16})-aralkynyl, (C_2-C_{20})-alkenyl, (C_2-C_{20})-alkynyl, (C_1-C_{20})-alkoxy, (C_2-C_{20})-alkenyloxy, (C_2-C_{20})-alkynyloxy, retinyloxy, (C_1-C_{20})-alkoxy-(C_1-C_{12})-alkyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxy, (C_1-C_{16})-hydroxyalkyl, (C_6-C_{16})-aryloxy-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_7-C_{12})-aralkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_2-C_{20})-alkenyloxy-(C_1-C_6)-alkyl, (C_2-C_{20})-alkynyloxy-(C_1-C_6)-alkyl, retinyloxy-(C_1-C_6)-alkyl, $-O-[CH_2-]_x-C_zH_{(2z+1-y)}F_y$, $-OCF_2Cl$, $-OCF_2-CHFCl$,

(C_1-C_{20})-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl,

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(C_6-C_{12})-arylcarbonyl, (C_7-C_{16})-aralkylcarbonyl, cinnamoyl, (C_2-C_{20})-alkenylcarbonyl, (C_2-C_{20})-alkynylcarbonyl,

(C_1-C_{20})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{20})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_2-C_{20})-alkynyloxycarbonyl, (C_6-C_{12})-aryloxy-(C_2-C_6)-alkoxycarbonyl, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxycarbonyl,

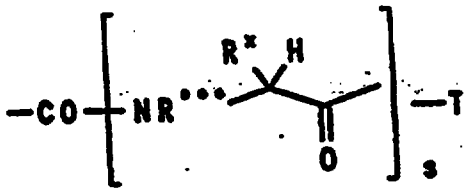
(C_1-C_{12})-alkylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_7-C_{16})-aralkylcarbonyloxy, cinnamoyloxy, (C_2-C_{12})-alkenylcarbonyloxy, (C_2-C_{12})-alkynylcarbonyloxy,

(C_1-C_{12})-alkoxycarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{16})-aralkyloxycarbonyloxy, (C_3-C_8)-cycloalkoxycarbonyloxy, (C_2-C_{12})-alkenyloxycarbonyloxy, (C_2-C_{12})-alkynyloxycarbonyloxy,

carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-dicyclo-(C_3-C_8)-alkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N-((C_1-C_{18})-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C_6-C_{16})-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-

aryloxy(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, or $CON(CH_2)_h$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7,

a carbamoyl radical of the formula II



(II),

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in which

R^x is the substituent of an α-amino acid to which the L- and D-amino acids belong,

s is 1, 2, 3, 4 or 5, and

T is OH, OR or NR^*R^{**}, where

R^*, R^{**} and R^{***} are identical or different and are hydrogen, (C_6-C_{12})-aryl, (C_7-C_{11})-aralkyl, (C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyl, (+)-dehydroabietyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkyl, (C_1-C_{10})-alkanoyl, optionally substituted (C_7-C_{16})-aralkanoyl or optionally substituted (C_6-C_{12})-aroyl, or

R^* and R^{**} together are $-[CH_2]_h-$, in which a CH_2 group can be replaced by O, S, SO, SO_2, N-acylamino, N-(C_1-C_{10})-alkoxycarbonylimino, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7,

carbamoyloxy, N-(C_1-C_{12})-alkylcarbamoyloxy, N,N-di-(C_1-C_{12})-alkylcarbamoyloxy, N-(C_3-C_8)-cycloalkylcarbamoyloxy, N-(C_6-C_{12})-arylcarbamoyloxy,

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N-(C_7-C_{16})-aralkylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyloxy, N-((C_1-C_{10})-alkyl)carbamoyloxy, N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)-carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy,

amino, (C_1-C_{12})-alkylamino, di-(C_1-C_{12})-alkylamino, (C_3-C_8)-cycloalkylamino, (C_3-C_{12})-alkenylamino, (C_3-C_{12})-alkynylamino, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_1-C_{12})-alkoxyamino, (C_1-C_{12})-alkoxy-N-(C_1-C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino, (C_3-C_8)-cycloalkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{16})-aralkanoylamino, (C_1-C_{12})-alkanoyl-N-(C_1-C_{10})-alkylamino, (C_3-C_8)-cycloalkanoyl-N-(C_1-C_{10})-alkylamino, (C_6-C_{12})-aroyl-N-(C_1-C_{10})-alkylamino, (C_7-C_{11})-aralkanoyl-N-(C_1-C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkanoylamino-(C_1-C_8)-alkyl, (C_6-C_{12})-aroylamino-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkanoylamino-(C_1-C_8)-alkyl, amino-(C_1-C_{10})-alkyl, N-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, N,N-di(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, (C_3-C_8)-cycloalkylamino-(C_1-C_{10})-alkyl, (C_1-C_{20})-alkylmercapto, (C_1-C_{20})-alkylsulfinyl, (C_1-C_{20})-alkylsulfonyl, (C_6-C_{12})-arylmercapto, (C_6-C_{12})-arylsulfinyl, (C_6-C_{12})-arylsulfonyl, (C_7-C_{16})-aralkylmercapto, (C_7-C_{16})-aralkylsulfinyl, (C_7-C_{16})-aralkylsulfonyl, (C_1-C_{12})-alkylmercapto-(C_1-C_6)-alkyl, (C_1-C_{12})-alkylsulfinyl-(C_1-C_6)-alkyl, (C_1-C_{12})-alkylsulfonyl-(C_1-C_6)-alkyl, (C_6-C_{12})-arylmercapto-(C_1-C_6)-alkyl, (C_6-C_{12})-arylsulfinyl-(C_1-C_6)-alkyl, (C_6-C_{12})-arylsulfonyl-(C_1-C_6)-alkyl, (C_7-C_{16})-aralkylmercapto-(C_1-C_6)-alkyl,

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(C_7-C_{16})-aralkylsulfinyl-(C_1-C_6)-alkyl, (C_7-C_{16})-aralkylsulfonyl-(C_1-C_6)-alkyl,

sulfamoyl, N-(C_1-C_{10})-alkylsulfamoyl, N,N-di-(C_1-C_{10})-alkylsulfamoyl, (C_3-C_8)-cycloalkylsulfamoyl, N-(C_6-C_{12})-arylsulfamoyl, N-(C_7-C_{16})-aralkylsulfamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylsulfamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylsulfamoyl, (C_1-C_{10})-alkylsulfonamido, N-$((C_1-C_{10})$-alkyl$)$-(C_1-C_{10})-alkylsulfonamido, (C_7-C_{16})-aralkylsulfonamido or N-$((C_1-C_{10})$-alkyl-(C_7-C_{16})-aralkylsulfonamido, where the radicals which contain an aryl radical can, for their part, be substituted on the aryl by from 1 to 5 identical or different radicals from the group: hydroxyl, halogen, cyano, trifluoromethyl, nitro, carboxyl, (C_1-C_{16})-alkyl, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl-(C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxy-(C_1-C_6)-alkoxy, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_2-C_{16})-alkenyl, (C_2-C_{12})-alkynyl, (C_1-C_{16})-alkoxy, (C_1-C_{16})-alkenyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxy, (C_1-C_8)-hydroxyalkyl, (C_6-C_{16})-aryloxy-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_7-C_{12})-aralkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, $-O-[CH_2-]_x-C_zH_{(2z+1-g)}F_g$, $-OCF_2Cl$, $OCF_2-CHFCl$,

(C_1-C_{12})-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl,

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(C_6-C_{12})-arylcarbonyl, (C_7-C_{16})-aralkylcarbonyl,

(C_1-C_{12})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{12})-alkenyloxycarbonyl, (C_2-C_{12})-alkynyloxycarbonyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxycarbonyl, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxycarbonyl,

(C_1-C_{12})-alkylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_7-C_{16})-aralkylcarbonyloxy, cinnamoyloxy, (C_2-C_{12})-alkenylcarbonyloxy, (C_2-C_{12})-alkynylcarbonyloxy,

(C_1-C_{12})-alkoxycarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{16})-aralkyloxycarbonyloxy, (C_3-C_8)-cycloalkoxycarbonyloxy, (C_2-C_{12})-alkenyloxycarbonyloxy, (C_2-C_{12})-alkynyloxycarbonyloxy,

carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-dicyclo-(C_3-C_8)-alkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N-((C_1-C_{16})-alkoxy-(C_1-C_{10})-alkyl)-carbamoyl, N-((C_6-C_{16})-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl,
N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)-carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-

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aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, $CON(CH_2)_h$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7,

carbamoyloxy, N-(C_1-C_{12})-alkylcarbamoyloxy, N,N-di-(C_1-C_{12})-alkylcarbamoyloxy, N-(C_3-C_8)-cycloalkyl-carbamoyloxy, N-(C_6-C_{16})-arylcarbamoyloxy, N-(C_7-C_{16})-aralkylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyloxy, N-((C_1-C_{10})-alkyl)carbamoyloxy, N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy,

amino, (C_1-C_{12})-alkylamino, di-(C_1-C_{12})-alkylamino, (C_3-C_8)-cycloalkylamino, (C_3-C_{12})-alkenylamino, (C_3-C_{12})-alkynylamino, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_1-C_{12})-alkoxyamino, (C_1-C_{12})-alkoxy-N-(C_1-C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino, (C_3-C_8)-cycloalkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{16})-aralkanoylamino, (C_1-C_{12})-alkanoyl-N-(C_1-C_{10})-alkylamino, (C_3-C_8)-cycloalkanoyl-N-(C_1-C_{10})-alkylamino, (C_6-C_{12})-aroyl-N-(C_1-C_{10})-alkylamino, (C_7-C_{11})-aralkanoyl-N-(C_1-C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkanoylamino-(C_1-C_8)-alkyl, (C_6-C_{12})-aroylamino-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkanoylamino-(C_1-C_8)-alkyl, amino-(C_1-C_{10})-alkyl, N-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, N,N-di-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl,

(C_3-C_8)-cycloalkylamino-(C_1-C_{10})-alkyl,

(C_1-C_{12})-alkylmercapto, (C_1-C_{12})-alkylsulfinyl, (C_1-C_{12})-alkylsulfonyl, (C_6-C_{16})-arylmercapto, (C_6-C_{16})-arylsulfinyl, (C_6-C_{16})-arylsulfonyl, (C_7-C_{16})-aralkylmercapto, (C_7-C_{16})-aralkylsulfinyl or (C_7-C_{16})-aralkylsulfonyl,

R^1 and R^2 or R^2 and R^3 form a chain $[CH_2]_o$ in which one or two CH_2 groups of the chain, which is saturated or unsaturated by a C=C double bond, are optionally replaced by O, S, SO, SO_2 or NR', and o is 3, 4 or 5, and

R' is hydrogen, (C_6-C_{12})-aryl, (C_1-C_8)-alkyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkyl, (C_1-C_{10})-alkanoyl, optionally substituted (C_7-C_{16})-aralkanoyl or optionally substituted (C_6-C_{12})-aroyl, where

the radicals R^1 and R^2 or R^2 and R^3, together with the pyridine or pyridazine carrying them, preferably form a 5, 6, 7, 8-tetrahydroisoquinoline ring, a 5, 6, 7, 8-tetrahydroquinoline ring or a 5, 6, 7, 8-tetrahydrocinnoline ring,

or

R^1 and R^2 or R^2 and R^3 form a carbocyclic or a heterocyclic, 5- or 6-membered aromatic ring, where

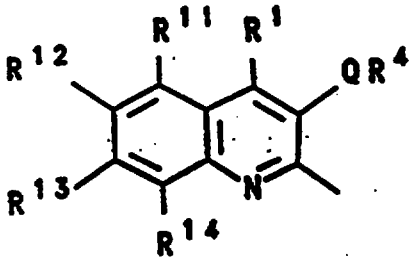
the radicals R^1 and R^2 or R^2 and R^3, together with the pyridine or pyridazine carrying them, preferably form the following optionally substituted heterocyclic ring systems:

Thienopyridines,
Furanopyridines,
Pyridopyridines,
Pyrimidinopyridines,
Imidazopyridines,

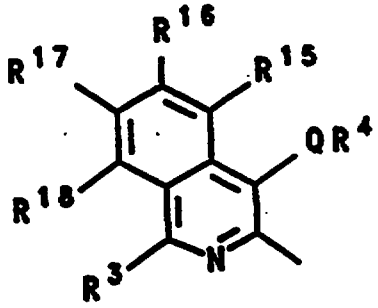
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Thiazolopyridines,
Oxazolopyridines,
Quinoline, isoquinoline and
Cinnoline,

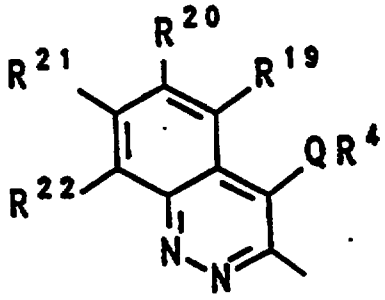
where quinoline, isoquinoline or cinnoline preferably satisfy the formulae 1a, 1b and 1c



1a



1b



1c

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and the substituents R^{11} to R^{22}, in each case independently of each other, have the meaning of R^1, R^2 and R^3,

R^4 is, if Q is a bond, halogen, nitrile or trifluoromethyl, or, if Q is O, S or NR', a branched or unbranched (C_1-C_{20})-alkyl radical, an unsubstituted, saturated fluoroalkyl radical of the formula $[CH_2]_x$-$C_zH_{(2z+1-g)}F_g$, a (C_6-C_{16})-aryl radical, a (C_7-C_{16})-aralkyl radical, a heteroaryl radical or a heteroaralkyl radical,

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where these radicals are substituted by one or more radicals from the group hydroxyl, halogen, cyano, trifluoromethyl, nitro, carboxyl, (C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl-(C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkoxy, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_2-C_{12})-alkenyl, (C_2-C_{12})-alkynyl, (C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxy, (C_1-C_8)-hydroxyalkyl, (C_6-C_{16})-aryloxy-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_7-C_{12})-aralkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, $-O-[CH_2-]_z-C_zH_{(2z+1-g)}F_g$, $-OCF_2Cl$, $-OCF_2-CHFCl$,

(C_1-C_{12})-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, (C_6-C_{12})-arylcarbonyl, (C_7-C_{16})-aralkylcarbonyl, cinnamoyl, (C_2-C_{12})-alkenylcarbonyl, (C_2-C_{12})-aklynylcarbonyl,

(C_1-C_{12})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy-carbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxy-carbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{12})-alkenyl-oxycarbonyl, (C_2-C_{12})-alkynyloxycarbonyl, (C_6-C_{12})-aryl-oxy-(C_1-C_6)-alkoxycarbonyl, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)cycloalkoxy-(C_1-C_6)-alkoxycarbonyl,

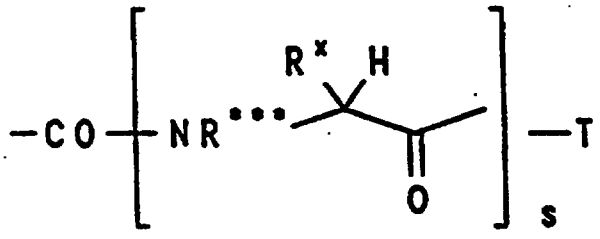
(C_1-C_{12})-alkylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_7-C_{16})-aralkylcarbonyloxy, cinnamoyloxy, (C_2-C_{12})-alkenylcarbonyloxy, (C_2-C_{12})-alkynylcarbonyloxy,

(C_1-C_{12})-alkoxycarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy-

carbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{16})-aralkyloxycarbonyloxy, (C_3-C_8)-cycloalkoxycarbonyloxy, (C_2-C_{12})-alkenyloxycarbonyloxy, (C_2-C_{12})-alkynyloxycarbonyloxy,

carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-di-cyclo-(C_3-C_8)-alkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-((C$_3$-C$_8$)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-((C$_3$-C$_8$)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N((C$_1$-C$_{10}$)-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C$_6$-C$_{16}$)-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C$_7$-C$_{16}$)-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C$_1$-C$_{10}$)-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C$_6$-C$_{12}$)-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N(C$_1$-C$_{10}$)-alkyl-N-((C$_7$-C$_{16}$)-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, $CON(CH_2)_h$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C$_3$-C$_8$)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7, or by

a carbamoyl radical of the formula II



(II),

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in which

R^x is the substituent of an α-amino acid to which the L- and D-amino acids belong,

s is 1, 2, 3, 4 or 5, and

T is OH, OR or NR^*R^{**}, where

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R^*, R^{**}, and R^{***} are identical or different and are hydrogen, (C_6-C_{12})-aryl, (C_7-C_{11})-aralkyl, (C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyl, (+)-dehydroabietyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkyl, (C_1-C_{10})-alkanoyl, optionally substituted (C_7-C_{16})-aralkanoyl or optionally substituted (C_6-C_{12})-aroyl, or

R^* and R^{**} together are $-[CH_2]_h-$, in which a CH_2 group can be replaced by O, S, SO, SO_2, N-acylamino, N-(C_1-C_{10})-alkoxycarbonylimino, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_2-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7, or by

carbamoyloxy, N-(C_1-C_{12})-alkylcarbamoyloxy, N,N-di-(C_1-C_{12})-alkylcarbamoyloxy, N-(C_3-C_8)-cycloalkylcarbamoyloxy, N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_7-C_{16})-aralkylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyloxy, N-$((C_1-C_{10})$-alkyl)carbamoyloxy, N-$((C_6-C_{12})$-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-$((C_7-C_{16})$-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-$((C_1-C_{10})$-alkoxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-$((C_6-C_{12})$-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-$((C_7-C_{16})$-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy,

amino, (C_1-C_{12})-alkylamino, di-(C_1-C_{12})-alkylamino, (C_3-C_8)-cycloalkylamino, (C_3-C_{12})-alkenylamino, (C_3-C_{12})-alkynylamino, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_1-C_{12})-alkoxyamino, (C_1-C_{12})-alkoxy-N-(C_1-C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino, (C_3-C_8)-cycloalkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{16})-aralkanoylamino, (C_1-C_{12})-alkanoyl-N-(C_1-C_{10})-alkylamino, (C_3-C_8)-cycloalkanoyl-N-(C_1-C_{10})-alkylamino, (C_6-C_{12})-aroyl-N-(C_1-C_{10})-alkylamino, (C_7-C_{11})-aralkanoyl-N-(C_1-C_{10})-alkylamino,

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(C_1-C_{12})-alkanoylamino-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkanoylamino-(C_1-C_8)-alkyl, (C_6-C_{12})-aroylamino-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkanoylamino-(C_1-C_8)-alkyl, amino-(C_1-C_{10})-alkyl, N-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, N,N-di(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, (C_3-C_8)-cycloalkylamino-(C_1-C_{10})-alkyl,

(C_1-C_{12})-alkylmercapto, (C_1-C_{12})-alkylsulfinyl, (C_1-C_{12})-alkylsulfonyl, (C_6-C_{12})-arylmercapto, (C_6-C_2)-arylsulfinyl, (C_6-C_{12})-arylsulfonyl, (C_7-C_{16})-aralkylmercapto, (C_7-C_{16})-aralkylsulfinyl, (C_7-C_{16})-aralkylsulfonyl,

sulfamoyl, N-(C_1-C_{10})-alkylsulfamoyl, N,N-di-(C_1-C_{10})-alkylsulfamoyl, (C_3-C_8)-cycloalkylsulfamoyl,
N-(C_6-C_{12})-arylsulfamoyl,
N-(C_7-C_{16})-aralkylsulfamoyl,
N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylsulfamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylsulfamoyl,
(C_1-C_{10})-alkylsulfonamido,
N-$((C_1-C_{10})$-alkyl$)$-(C_1-C_{10})-alkylsulfonamido, (C_7-C_{16})-aralkylsulfonamido or N-$((C_1-C_{10})$-alkyl-(C_7-C_{16})-aralkyl-sulfonamido, where the radicals which contain an aryl radical can, for their part, be substituted on the aryl by from 1 to 5 identical or different radicals from the group:
hydroxyl, halogen, cyano, trifluoromethyl, nitro, carboxyl, (C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkoyloxy-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl-(C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkoxy, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_2-C_{12})-alkenyl, (C_2-C_{12})-alkynyl, (C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxy,

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(C_1-C_8)-hydroxyalkyl, (C_6-C_{16})-aryloxy-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_7-C_{12})-aralkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, $-O-[CH_2-]_x-C_zH_{(2z+1-g)}F_g$, $-OCF_2Cl$, $-OCF_2-CHFCl$,

(C_1-C_{12})-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, (C_6-C_{12})-arylcarbonyl, (C_7-C_{16})-aralkylcarbonyl,

(C_1-C_{12})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{12})-alkenyloxycarbonyl, (C_2-C_{12})-alkynyloxycarbonyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxycarbonyl, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxycarbonyl, (C_1-C_{12})-alkylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_7-C_{16})-aralkylcarbonyloxy, cinnamoyloxy, (C_2-C_{12})-alkenylcarbonyloxy, (C_2-C_{12})-alkynylcarbonyloxy,

(C_1-C_{12})-alkoxycarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{16})-aralkyloxycarbonyloxy, (C_3-C_8)-cycloalkoxycarbonyloxy, (C_2-C_{12})-alkenyloxycarbonyloxy, (C_2-C_{12})-alkynyloxycarbonyloxy,

carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-di-cyclo-(C_3-C_8)-alkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-$((C_3-C_8)$-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-$((C_3-C_8)$-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N-$((C_1-C_{10})$-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-$((C_6-C_{16})$-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-$((C_7-C_{16})$-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-$((C_1-C_{10})$-alkoxy-

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(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, $CON(CH_2)_h$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7,

carbamoyloxy, N-(C_1-C_{12})-alkylcarbamoyloxy, N,N-di-(C_1-C_{12})-alkylcarbamoyloxy, N-(C_3-C_8)-cycloalkylcarbamoyloxy, N-(C_6-C_{16})-arylcarbamoyloxy, N-(C_7-C_{16})-aralkylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyloxy, N-((C_1-C_{10})-alkyl)carbamoyloxy, N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy,

amino, (C_1-C_{12})-alkylamino, di-(C_1-C_{12})-alkylamino, (C_3-C_8)-cycloalkylamino, (C_3-C_{12})-alkenylamino, (C_3-C_{12})-alkynylamino, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_1-C_{12})-alkoxyamino, (C_1-C_{12})-alkoxy-N-(C_1-C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino, (C_3-C_8)-cycloalkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{16})-aralkanoylamino, (C_1-C_{12})-alkanoyl-N-(C_1-C_{10})-alkylamino, (C_3-C_8)-cycloalkanoyl-N-(C_1-C_{10})-alkylamino, (C_6-C_{12})-aroyl-N-(C_1-C_{10})-alkylamino, (C_7-C_{11})-aralkanoyl-N-(C_1-C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkanoylamino-(C_1-C_8)-alkyl, (C_6-C_{12})-aroylamino-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkanoylamino-(C_1-C_8)-alkyl, amino-(C_1-C_{10})-alkyl, N-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, N,N-di-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, (C_3-C_8)-cycloalkylamino-(C_1-C_{10})-alkyl,

(C_1-C_{12})-alkylmercapto, (C_1-C_{12})-alkylsulfinyl, (C_1-C_{12})-alkylsulfonyl, (C_6-C_{16})-arylmercapto, (C_6-C_{16})-arylsulfinyl, (C_6-C_{16})-arylsulfonyl, (C_7-C_{16})-aralkylmercapto, (C_7-C_{16})-aralkylsulfinyl or (C_7-C_{16})-aralkylsulfonyl, and

R^4 is R", provided that Q has the meaning of NR', where R' and R" are identical or different and are hydrogen, (C_6-C_{12})-aryl, (C_7-C_{11})-aralkyl, (C_1-C_8)-alkyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkyl, (C_1-C_{10})-alkanoyl, optionally substituted (C_7-C_{16})-aralkanoyl or optionally substituted (C_6-C_{12})-aroyl, or

R' and R" together are $-[CH_2]h$, in which a CH_2 group can be replaced by O, S, N-acylimino or N-(C_1-C_{10})-alkoxycarbonylimino, and

f is 1 to 8,
g is 0 or 1 to (2f+1),
x is 0 to 3,
h is 3 to 7,

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including the physiologically active salts, with 3-benzyloxypyridine-2-carboxylic acid (L-threonyl)-amide and 3-benzyloxypyridine-2-carboxylic acid ((Fmoc-Phg)L-threonyl)amide hydrochloride being excepted.

In general, aryl is understood to mean carbocyclic and heterocyclic aromatic ring systems. In particular, it is understood to include phenyl-substituted, biphenyl-substituted, naphthyl-substituted or unsubstituted 5- and 6-membered heteroaromatic rings having 1, 2 or 3 nitrogen and/or oxygen and/or sulfur atoms, such as derivatives of pyridyl, pyridazyl, pyrimidyl, pyrazyl, imidazolyl, triazolyl, thienyl, oxazolyl and thiazolyl, and their benzo-fused derivatives.

The invention also embraces salts of the compounds of the formula I.

The formation of salts with basic reagents can take place once, twice or three times on the acidic groups of the compounds of the formula I (i.e. radicals B, R^1, R^2, R^3 and R^4), in particular on the radicals B, R^2 and/or R^4.

Examples of reagents being used are alcoholates, hydroxides, carbonates, hydrogen carbonates, hydrogen phosphates, organometallic compounds of the alkali and alkaline earth elements, the elements of the third and fourth main groups of the periodic system, and the elements of the transition metals,

amines, optionally substituted 1 to 3 times by (C_1-C_8)-hydroxyalkyl, (C_1-C_4)-alkoxy-(C_1-C_8)-alkyl, phenyl, benzyl or (C_1-C_8)-alkyl, which can be substituted 1 to 3 times by hydroxyl or (C_1-C_4)-alkoxy, for example tromethane (Tris buffer), 2-aminoethanol, 3-aminopropanol, hydroxylamine, dimethylhydroxylamine, 2-methoxyethylamine, 3-ethoxypropylamine, and
basic amino acids and amino derivatives, such as amino acid esters, histidine, arginine and lysine, and their derivatives, and also

pharmaceuticals which contain a basic group, such as, for example, ®Amiloride, ®Verapamil and beta blockers.

The invention also relates to the compounds according to formula I, plus 3-benzyloxypyridine-2-carboxylic acid (L-threonyl)amide and 3-benzyloxypyridine-2-carboxylic acid ((Fmoc-Phg)L-threonyl)amide hydrochloride for use as pharmaceuticals.

Compounds of the formula I are of great interest, in which

Q is O, S, NR′ or a bond,
X is O,
Y is CR^3 or,
if R^1 and R^2 form a cycle,
Y is N or CR^3,

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m is 0 or 1.

Compounds of the formula I are very important, in which
Q is O, NR' or a bond,
X is O.

Compounds of the formula I are also very important in which Q is S and X is O.

Compounds of the formula I are of particular importance in which
Q is O, NR' or a bond,
X is O,
Y is CR^3 or, if R^1 and R^2 form a cycle, N or CR^3,
m is 0 or 1,

A is (C_1-C_3)-alkylene which is optionally substituted once by halogen, cyano, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy or $-O-[CH_2]_x-C_zH_{(2z+1-g)}F_g$, or

A is $-CHR^5-$, where R^5 is one of the substituents of the α-carbon atom of an α-amino acid, in particular of a natural L-amino acid and of its D-isomer,

B is CO_2H,

R^2 is hydrogen, (C_1-C_{20})-alkyl, (C_2-C_{20})-alkenyl, (C_2-C_{20})-alkynyl, (C_1-C_{20})-alkoxy, (C_2-C_{20})-alkenyloxy, (C_2-C_{20})-alkynyloxy, retinyloxy, (C_1-C_{20})-alkoxy-(C_1-C_3)-alkyl, (C_2-C_{20})-alkenyloxy-(C_1-C_3)-alkyl, retinyloxy-(C_1-C_3)-alkyl, (C_2-C_{20})-alkynyloxy-(C_1-C_3)-alkyl, halogen, cyano, trifluoromethyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_{20})-alkanoyl, (C_7-C_{16})-aralkanoyl, (C_6-C_{12})-aroyl, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, $-O-[CH_2]_x-C_zH_{(2z+1-g)}F_g$, $NR'R''$, (C_1-C_{10})-alkylmercapto, (C_1-C_{10})-alkylsulfinyl, (C_1-C_{10})-alkylsulfonyl, (C_6-C_{12})-arylmercapto, (C_6-C_{12})-arylsulfinyl, (C_6-C_{12})-arylsulfonyl, (C_7-C_{12})-aralkylmercapto,

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(C_7-C_{12})-aralkylsulfinyl, (C_7-C_{12})-aralkylsulfonyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, carboxyl, (C_1-C_{20})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{20})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_2-C_{20})-alkynyloxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxycarbonyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxycarbonyl, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxycarbonyl,

carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-dicyclo(C_3-C_8)-alkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-$((C_3-C_8)$-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N-$((C_1-C_{12})$-alkoxy-(C_2-C_{10})-alkyl)carbamoyl, N-$((C_6-C_{16})$-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-$((C_7-C_{16})$-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-$((C_1-C_{10})$-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-$((C_6-C_{12})$-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-$((C_7-C_{16})$-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, $CON(CH_2)_h$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7,

where aryl is substituted in the manner as defined for R^1 and R^3,

R^1 and R^3 are identical or different and are hydrogen, halogen, (C_1-C_{12})-alkyl, (C_1-C_{12})-alkoxy, -O-$[CH_2]_x$-C_z-

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$H_{(2z+1-g)}Hal_g$, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkyl, (C_1-C_8)-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_8)-alkoxy-(C_2-C_6)-alkyl, (C_7-C_{11})-aralkyloxy, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyloxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkoxy, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl-(C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, NR^yR^z, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl or (C_1-C_8)-alkylsulfonyl, (C_6-C_{12})-arylmercapto, (C_6-C_{12})-arylsulfinyl, (C_6-C_{12})-arylsulfonyl, (C_7-C_{12})-aralkylmercapto, (C_7-C_{11})-aralkylsulfinyl, (C_7-C_{11})-aralkylsulfonyl, substituted (C_6-C_{12})-aryloxy-(C_1-C_6)-alkyl, (C_7-C_{11})-aralkoxy-(C_1-C_6)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_7-C_{11})-aralkyloxy-(C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{11})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy or (C_7-C_{11})-aralkoxy-(C_1-C_6)-alkoxy, where an aromatic radical carries by 1, 2, 3, 4 or 5 identical or different substituents from the group hydrogen, halogen, cyano, nitro, trifluoromethyl, (C_1-C_{16})-alkyl, (C_1-C_{16})-alkenyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_{16})-alkoxy, (C_1-C_{16})-alkenyloxy, $-O-[CH_2]_x-C_zH_{(2z+1-g)}F_g$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, (C_1-C_6)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkylcarbamoyl, phenyl, benzyl, phenoxy, benzyloxy, NR^yR^z, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl or N,N-di-(C_1-C_4)-alkylsulfamoyl, or optionally carries up to 3 of the abovementioned identical or different substituents, and two adjacent carbon atoms of the aralkyloxy radical together carry a chain-$[CH_2]$ and/or $-CH=CH-CH=CH-$, where a CH_2 group of the chain is optionally replaced by O, S, SO, SO_2 or NR',

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R^1 and R^2 or R^2 and R^3 form a chain $[CH_2]_o$, where o is 3, 4 or 5, or

form, together with the pyridine or pyridazine carrying them, a cinnoline ring, a quinoline ring or an isoquinoline ring,

R^4 is, if Q is a bond, fluorine, chlorine or bromine, or, if Q is O or NR', a branched or unbranched (C_1-C_{20})-alkyl radical, which can contain up to 3 C-C multiple bonds, an unsubstituted saturated fluoroalkyl radical of the formula $[CH_2]_x$-$C_zH_{(2z+1-g)}F_g$, a (C_6-C_{16})-aryl radical or a (C_7-C_{16})-aralkyl radical, which can contain up to 2 C-C multiple bonds in the alkyl chain, or an heteroaryl radical or an heteroaryl alkyl radical, where these radicals are substituted by one or more radicals from the group hydroxyl, fluorine, chlorine, cyano, trifluoromethyl, carboxyl, (C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl-(C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkoxy, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_2-C_{12})-alkenyl, (C_2-C_{12})-alkynyl, (C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxy, (C_1-C_8)-hydroxyalkyl, -O-$[CH_2]_x$-$C_zH_{(2z+1-g)}F_g$,

(C_1-C_{12})-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, (C_6-C_{12})-arylcarbonyl, (C_7-C_{16})-aralkylcarbonyl,

(C_1-C_{12})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{12})-alkenyloxycarbonyl, (C_2-C_{12})-alkynyloxycarbonyl,

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(C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl,

(C_1-C_{12})-alkylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_7-C_{16})-aralkylcarbonyloxy, carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-dicyclo-(C_3-C_8)-alkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C_6-C_{16})-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, $CON(CH_2)_h$ in which a CH_2 group can be replaced by O, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino or N-(C_7-C_{16})-aralkylimino, and h is from 3 to 6,

where the radicals which contain an aryl radical can, for their part, be substituted on the aryl by from 1 to 5 identical or different radicals from the group:

hydroxyl, fluorine, chlorine, cyano, trifluoromethyl, carboxyl, (C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyl, (C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkoxy, (C_1-C_{12})-alkoxycarbonyl,

N-(C_1-C_6)-alkylcarbamoyl, N,N-di-(C_1-C_6)-alkylcarbamoyl or N-(C_3-C_8)-cycloalkylcarbamoyl, and

R^4 is R^*, provided Q has the meaning of NR', where R' and R^* are identical or different and are hydrogen, (C_1-C_8)-alkyl, or (C_7-C_{11})-aralkyl which is optionally

substituted once by fluorine, chlorine or (C_1-C_4)-alkoxy,

R^Y and R^Z are identical or different and are hydrogen, (C_6-C_{12})-aryl, (C_1-C_{10})-alkyl, (C_3-C_{10})-cycloalkyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkyl, (C_1-C_{10})-alkanoyl, optionally substituted (C_7-C_{16})-aralkanoyl or optionally substituted (C_6-C_{12})-aroyl, or

R^Y and R^Z together are $-[CH_2]_h-$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_4)-alkanoylimino or N-(C_1-C_4)-alkoxycarbonylimino, and

f is 1 to 8,
g is 0 or 1 to (2f + 1),
h is 3 to 6,
x is 0 to 3, and
n is 3 or 4.

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Compounds of the formula I are preferred in which

Q is O, NR' or a bond,
X is O,
Y is CR^3 or, if R^1 and R^2 form a cycle, N or CR^3,
m is 0,

A is (C_1-C_3)-alkylene which is optionally substituted once by halogen, cyano, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy or $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$ or

A is $-CHR^5-$, where R^5 is one of the substituents of the α-carbon atom of an α-amino acid, in particular of a natural L-amino acid and of its D-isomer,

B is CO_2H

R^2 is hydrogen, (C_1-C_{20})-alkyl, (C_2-C_{20})-alkenyl, (C_2-C_{20})-alkenyloxy, (C_2-C_{20})-alkynyloxy, retinyloxy,

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(C_1-C_{20})-alkoxy-(C_1-C_3)-alkyl, (C_1-C_{20})-alkoxy-(C_1-C_3)-alkyl, (C_2-C_{20})-alkenyloxy-(C_1-C_3)-alkyl, retinyloxy-(C_1-C_3)-alkyl, (C_2-C_{20})-alkynyloxy-(C_1-C_3)-alkyl, (C_1-C_{20})-alkoxy, halogen, cyano, trifluoromethyl, (C_1-C_{16})-hydroxyalkyl, (C_1-C_{20})-alkanoyl, (C_7-C_{12})-aralkanoyl, (C_6-C_{12})-aroyl, $-O-[CH_2]_x-C_yH_{(2y+1-z)}F_z$, $NR'R''$, (C_1-C_{10})-alkylmercapto, (C_1-C_{10})-alkylsulfinyl, (C_1-C_{10})-alkylsulfonyl, (C_6-C_{12})-arylmercapto, (C_6-C_{12})-arylsulfinyl, (C_6-C_{12})-arylsulfonyl, $(C_7-C_{12}$aralkylmercapto, (C_7-C_{12})-aralkylsulfinyl, (C_7-C_{12})-aralkylsulfonyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, carboxyl, (C_1-C_{20})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{20})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_2-C_{20})-alkynyloxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxycarbonyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxycarbonyl, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-dicyclo(C_3-C_8)-alkylcarbamoyl, N-(C_2-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-$((C_3-C_8)$-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{12})-aralkylcarbamoyl, N-$((C_1-C_{12})$-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-$((C_6-C_{16})$-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-$((C_7-C_{16})$-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-$((C_1-C_{10})$-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-$((C_6-C_{12})$-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-$((C_7-C_{16})$-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, or $CON(CH_2)_h$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_6)-alkylimino, N-(C_3-C_8)-cycloalkylimino,

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N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 6,

where aryl is substituted in the manner as defined for R^1 and R^3,

R^1 and R^3 are identical or different and are hydrogen, halogen, (C_1-C_{12})-alkyl, (C_1-C_{12})-alkoxy, -O-$[CH_2]_x$-$C_zH_{(2z+1-g)}Hal_g$, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkyl, (C_1-C_8)-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_8)-alkoxy-(C_2-C_6)-alkyl, (C_7-C_{11})-aralkyloxy, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyloxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkoxy, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl-(C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, NR^YR^Z, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl or (C_1-C_8)-alkylsulfonyl, (C_6-C_{12})-arylmercapto, (C_6-C_{12})-arylsulfinyl, (C_6-C_{12})-arylsulfonyl, (C_7-C_{12})-aralkylmercapto, (C_7-C_{11})-aralkylsulfinyl, (C_7-C_{11})-aralkylsulfonyl, substituted (C_6-C_{12})-aryloxy-(C_1-C_6)-alkyl, (C_7-C_{11})-aralkoxy-(C_1-C_6)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_7-C_{11})-aralkyloxy-(C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{11})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy or (C_7-C_{11})-aralkoxy-(C_1-C_6)-alkoxy, where an aromatic radical carries by 1, 2, 3, 4 or 5 identical or different substituents from the group hydrogen, halogen, cyano, nitro, trifluoromethyl, (C_1-C_{12})-alkyl, (C_1-C_{12})-alkenyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_{12})-alkoxy, (C_1-C_{12})-alkenyloxy, -O-$[CH_2]_x$-$C_zH_{(2z+1-g)}F_g$, -OCF_2Cl, -O-CF_2-CHFCl, (C_1-C_6)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy,

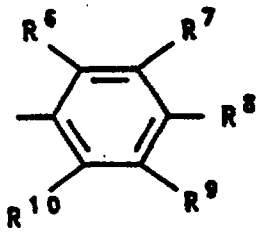
(C_3-C_8)-cycloalkylcarbamoyl, phenyl, benzyl, phenoxy, benzyloxy, NR^2R^2, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl or N,N-di-(C_1-C_4)-alkylsulfamoyl, or optionally carries up to 3 of the abovementioned identical or different substituents, and two adjacent carbon atoms of the aralkyloxy radical together carry a chain $-[CH_2-]$ and/or $-CH=CH-CH=CH-$, where a CH_2 group of the chain is optionally replaced by O, S, SO, SO_2 or NR^y,

R^1 and R^2 or R^2 and R^3 can form a chain $[CH_2]_o$, where o is 3, 4 or 5, and

R^4 , provided Q is a bond, is chlorine or, if Q is O or NR', is a branched or unbranched (C_1-C_{10})-alkyl radical, which can contain one or two C-C multiple bonds, or an unsubstituted fluoroalkyl radical of the formula $-[CH_2]_x-C_fH_{(2f+1-g)}F_g$ or (C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_1-C_6)-alkoxy-(C_1-C_4)-alkoxy-(C_1-C_4)-alkyl or a radical of the formula Z,

$$-[CH_2]_v-[O]_w-[CH_2]_t-E \qquad (Z)$$

where E is a substituted phenyl radical of the formula F



(F),

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or a (C_3-C_8)-cycloalkyl radical, where

v is 0, 1, 2, 3, 4, 5 or 6, w is 0 or 1, and t is 0, 1, 2 or 3, with the restriction that v is not equal to 0 if w is 1, and R^6, R^7, R^8, R^9 and R^{10} are identical or different and are hydrogen, halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-alkyl,

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(C_3-C_8)-cycloalkyl, (C_1-C_6)-alkoxy, $-O-[CH_2]_x-C_zH_{(2z+1-g)}F_g$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, (C_1-C_6)-alkylmercapto, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy-(C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_8)-alkoxycarbonyl, carbamoyl, N-(C_1-C_6)-alkylcarbamoyl, N,N-di-(C_1-C_6)-alkylcarbamoyl, (C_7-C_{11})-aralkylcarbamoyl which is optionally substituted by fluorine, chlorine, bromine, trifluoromethyl or (C_1-C_6)-alkoxy, N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, phenyl, benzyl, phenoxy, benzyloxy, NR^yR^z, such as amino, anilino, N-methylanilino, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_6)-alkylsulfamoyl or N,N-di-(C_1-C_6)-alkylsulfamoyl, or two adjacent substituents together are a chain $-[CH_2]_n-CH=CH-CH=CH-$, where a CH_2 group of the chain is optionally replaced by O, S, SO, SO_2 or NR^y, and where a heteroaryl radical can carry 1, 2 or 3 substituents, and a cycloalkyl radical one substituent, from the above group, and

R^4 is R^*, provided Q has the meaning of NR', where

R' is hydrogen or methyl, and

R^* is benzyl, and

if R^1 and/or R^3 have the meaning of (C_6-C_{12})-aryloxy, (C_7-C_{11})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy, (C_7-C_{11})-aralkoxy-(C_1-C_6)-alkoxy or a corresponding radical containing terminal cycloalkyl groups, this radical is preferably then a radical of the formula D

OZ (D), or

if R^1 and/or R^3 have the meaning of (C_7-C_{11})-aralkyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkyl, (C_7-C_{11})-aralkoxy-(C_1-C_6)-alkyl or a corresponding radical containing terminal cycloalkyl groups, this radical is preferably then a radical of the formula Z,

R^y and R^z are identical or different and are hydrogen, (C_6-C_{12})-aryl, (C_1-C_{10})-alkyl, (C_3-C_{10})-cycloalkyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkyl, (C_1-C_{10})-alkanoyl, optionally substituted (C_7-C_{16})-aralkanoyl or optionally substituted (C_6-C_{12})-aroyl, or

R^y and R^z are together $-[CH_2]_h-$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_4)-alkanoylimino or N-(C_1-C_4)-alkoxycarbonylimino, and

f is 1 to 8,
g is 0 or 1 to (2f+1),
h is 3 to 6,
x is 0 to 3, and
n is 3 or 4.

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Compounds of the formula I are particularly preferred in which

Q is O,
X is O,
Y is CR^3 and, additionally, N if R^1 and R^2 form a cycle,
m is 0,
A is $-CHR^5-$, where R^5 is the substituent of the α-carbon atom of an α-amino acid, in particular of a natural L-amino acid or its D-isomer,

B is CO_2H,

R^2 is hydrogen, bromine, chlorine, cyano, (C_1-C_{10})-alkyl, (C_1-C_8)-alkoxy, (C_1-C_{10})-alkoxymethyl, (C_2-C_{10})-alkenyloxymethyl, (C_2-C_{10})-alkynyloxymethyl, carbamoyl, N-(C_1-C_{10})-alkylcarbamoyl, N-$((C_1-C_{12})$-alkoxy-(C_1-C_4)-alkyl)carbamoyl, N,N-di-(C_1-C_8)-alkylcarbamoyl, N(C_3-C_8)-cycloalkylcarbamoyl, N-(C_6-C_{12})-phenylcarbamoyl, N-(C_7-C_{12})-phenylalkylcarbamoyl, N-(C_1-C_6)-alkyl-N-(C_6-C_{12})phenylcarbamoyl, N-(C_1-C_6)-alkyl-N-(C_7-C_{12})-phenylalkylcarbamoyl,

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N-((C$_1$-C$_6$)-alkoxy-(C$_1$-C$_6$)-alkyl)carbamoyl, carboxyl, (C$_1$-C$_{20}$)-alkoxycarbonyl, (C$_2$-C$_{20}$)-alkenyloxycarbonyl, retinyloxycarbonyl, (C$_3$-C$_8$)-cycloalkoxycarbonyl, (C$_3$-C$_8$)-cycloalkyl-(C$_1$-C$_6$)-alkoxycarbonyl, (C$_3$-C$_8$)-cycloalkoxy-(C$_1$-C$_6$)-alkoxycarbonyl, phenyl-(C$_1$-C$_6$)-alkoxycarbonyl, phenoxy-(C$_1$-C$_6$)-alkoxycarbonyl or benzyloxy-(C$_1$-C$_6$)-alkoxycarbonyl, where a phenyl radical is substituted in the manner as defined for R^1 and R^3, and one of the radicals

R^1 or R^3 is hydrogen and the other a radical from the group hydrogen, fluorine, chlorine, (C$_1$-C$_6$)-alkyl, (C$_1$-C$_{10}$)-alkoxy, (C$_3$-C$_6$)-cycloalkyl, (C$_3$-C$_6$)-cycloalkyl-(C$_1$-C$_6$)-alkyl, (C$_3$-C$_6$)-cycloalkyloxy, (C$_3$-C$_6$)-cycloalkyl-(C$_1$-C$_6$)-alkoxy, (C$_3$-C$_6$)-cycloalkyloxy-(C$_1$-C$_6$)-alkyl, (C$_3$-C$_6$)-cycloalkyloxy-(C$_1$-C$_6$)-alkoxy, (C$_3$-C$_6$)-cycloalkyl-(C$_1$-C$_4$)-alkyl-(C$_1$-C$_4$)-alkoxy, (C$_3$-C$_6$)-cycloalkyl-(C$_1$-C$_4$)-alkoxy-(C$_1$-C$_2$)-alkyl, (C$_3$-C$_6$)-cycloalkoxy-(C$_1$-C$_4$)-alkoxy-(C$_1$-C$_2$)-alkyl, -O-[CH$_2$]$_x$-C$_z$H$_{(2z+1-y)}$F$_y$, (C$_1$-C$_6$)-alkoxy-(C$_1$-C$_6$)-alkyl, (C$_1$-C$_6$)-alkoxy-(C$_1$-C$_6$)-alkoxy, (C$_1$-C$_6$)-alkoxy-(C$_1$-C$_4$)-alkoxy-(C$_1$-C$_2$)-alkyl, substituted (C$_6$-C$_{12}$)-phenoxy, (C$_7$-C$_{11}$)-phenylalkyloxy, (C$_6$-C$_{12}$)-phenoxy-(C$_1$-C$_6$)-alkoxy or (C$_7$-C$_{11}$)-phenylalkoxy-(C$_1$-C$_6$)-alkoxy, phenoxy-(C$_1$-C$_4$)-alkyl, (C$_7$-C$_{11}$)-phenylalkyloxy-(C$_1$-C$_4$)-alkyl, phenoxy-(C$_1$-C$_4$)-alkoxy-(C$_1$-C$_2$)-alkyl or (C$_7$-C$_{11}$)-phenylalkyloxy-(C$_1$-C$_4$)-alkoxy-(C$_1$-C$_2$)-alkyl, where an aromatic radical is substituted by 1, 2 or 3 identical or different substituents from the group fluorine, chlorine, cyano, trifluoromethyl, (C$_1$-C$_{12}$)-alkyl, (C$_2$-C$_{12}$)-alkenyl, (C$_2$-C$_{12}$)-alkenyloxy or (C$_1$-C$_{12}$)-alkoxy,

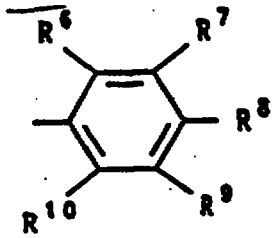
R^1 and R^2, with the pyridine carrying them, form a 5, 6, 7, 8-tetrahydroisoquinoline ring,

R^4 is a branched or unbranched (C$_1$-C$_{10}$)-alkyl radical, (C$_1$-C$_4$)-alkoxy-(C$_1$-C$_4$)-alkyl or a radical of the formula Z,

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$$-[CH_2]_v-[O]_w-[CH_2]_t-E \qquad (Z)$$

where E is a substituted phenyl radical of the formula F



(F),

or a (C_3-C_8)-cycloalkyl radical, where v is 0, 1, 2 or 3, w is 0, and t can be 0 or 1, and in which R^6, R^7, R^8, R^9 and R^{10} are identical or different and are hydrogen, fluorine, chlorine, cyano, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, $-O-[CH_2]_x-C_zH_{(2z+1-g)}F_g$, N-$(C_1-C_8)$-alkylcarbamoyl, N,N-di-$(C_1-C_6)$-alkylcarbamoyl, N-$(C_3-C_6)$-cycloalkylcarbamoyl, N-(+)-dehydroabietylaminocarbonyl, or (C_7-C_{11})-phenylalkylcarbamoyl, which is optionally substituted by fluorine, chlorine, trifluoromethyl or (C_1-C_6)-alkoxy, or where R^6 and R^7 or R^7 and R^8, together with the phenyl ring carying them, form naphthalene derivatives.

If R^1 or R^3 has the meaning of (C_6-C_{12})-phenoxy, (C_7-C_{11})-phenylalkyloxy, (C_6-C_{12})-phenoxy-(C_1-C_6)-alkoxy, (C_7-C_{11})-phenylalkoxy-(C_1-C_6)-alkoxy, (C_5-C_6)-cycloalkyloxy-(C_1-C_6)-alkoxy, (C_5-C_6)-cycloalkoxy-(C_1-C_6)-alkoxy or (C_5-C_6)-cycloalkyl-(C_1-C_4)-alkyl-(C_1-C_4)-alkoxy, this radical is then, especially, a radical of the formula D

OZ (D), or

if R^1 or R^3 has the meaning of phenyl, phenoxy-(C_1-C_6)-alkyl, (C_7-C_{11})-phenylalkyl (C_7-C_{11})-phenylalkyloxy-(C_1-C_4)-alkyl, (C_5-C_6)-cycloalkyl, (C_5-C_6)-cycloalkyl-(C_1-C_6)-alkyl, (C_5-C_6)-cycloalkoxy-(C_1-C_4)-alkyl, (C_5-C_6)-cycloalkyl-(C_1-C_4)-alkoxy-(C_1-C_2)-alkyl or (C_5-C_6)-cycloalkoxy-

(C_1-C_4)-alkoxy-(C_1-C_2)-alkyl, this radical is then, especially, a radical of the formula Z in which, in both cases,

v is 1, 2, 3 or 4, w is 0 and t is 0, or
v is 1, 2, 3 or 4, w is 1 and t is 0, or
v is 1, 2, 3 or 4, w is 1, t is 1, and
f is 1 to 4,
g is 0 or 1 to (2f+1),
x is 0 or 1.

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Compounds of the formula I are very particularly preferred in which

Q is O,
X is O,
Y is CR^3,
m is 0,
A is a $-CH_2-$ group which can be substituted by a methyl group,
B is $-CO_2H$,
R^2 is hydrogen, (C_1-C_8)-alkoxy, (C_1-C_{16})-alkoxymethyl, (C_2-C_{16})-alkenyloxymethyl, retinyloxymethyl, N-(C_1-C_{10})-alkylcarbamoyl, N-(((C_1-C_{12})-alkoxy-(C_1-C_3)-alkyl)carbamoyl, N,N-di-(C_1-C_8)-alkylcarbamoyl, N-(C_5-C_6)-cycloalkylcarbamoyl, N-phenylcarbamoyl, N-phenyl-(C_1-C_4)-alkylcarbamoyl, carboxyl, (C_1-C_{16})-alkoxycarbonyl, (C_2-C_{16})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_5-C_6)-cycloalkoxycarbonyl, (C_5-C_6)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl or phenyl-(C_1-C_6)-alkoxycarbonyl, where a phenyl radical is substituted in the manner as defined for R^1 and R^3, and one of the radicals

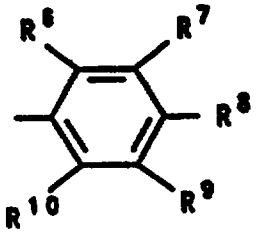
R^1 or R^3 is hydrogen and the other radical is a radical from the group hydrogen, (C_1-C_{16})-alkoxy, (C_5-C_6)-cycloalkyloxy, (C_5-C_6)-cycloalkyl-(C_1-C_2)-alkoxy, $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$, (C_1-C_4)-alkoxy-(C_1-C_4)-alkoxy, substituted (C_6-C_{12})-phenoxy, (C_7-C_{11})-phenylalkyloxy, (C_6-C_{12})-phenoxy-(C_1-C_4)-alkoxy or (C_7-C_{11})-phenyl-

alkoxy-(C_1-C_4)-alkoxy, where an aromatic radical is substituted by 1, 2 or 3 identical or different substituents from the group fluorine, chlorine, cyano, trifluoromethyl, (C_1-C_{10})-alkyl, (C_1-C_{10})-alkoxy or (C_1-C_{10})-alkenyloxy, and

R^4 is a branched or unbranched (C_1-C_8)-alkyl radical or a radical of the formula Z,

$$-[CH_2]_v-[O]_w-[CH_2]_t-E \qquad (Z)$$

where E is a substituted phenyl radical of the formula F



(F),

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or a (C_3-C_8)-cycloalkyl radical, where v is 0, 1, 2 or 3, w is 0, and t can be 0 or 1, and in which R^6, R^7, R^8, R^9 and R^{10} are identical or different and are hydrogen, fluorine, chlorine, cyano, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$, N-($C_1$-$C_8$)-alkylcarbamoyl, N,N-di-(C_1-C_6)-alkylcarbamoyl, N-(C_3-C_6)-cycloalkylcarbamoyl, N-(+)-dehydroabietylaminocarbonyl substituted benzyl radical, and f is 1 to 4, g is 0 or 1 to (2f+1) and x is 0 or 1.

Compounds of the formula I are particularly preferred in which

Q is O,
X is O,
Y is CR^3,
m is 0,
B is $-CO_2H$,
A is a $-CH_2$-group,

R^1 is hydrogen, (C_1-C_6)-alkoxy or $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$,

R^2 is hydrogen, N-(C_1-C_{10})-alkylcarbamoyl, N-$((C_1-C_{12})$-alkoxy-(C_1-C_3)-alkyl)carbamoyl, N,N-di-(C_1-C_8)-alkylcarbamoyl, N-(C_5-C_6)-cycloalkylcarbamoyl, N-phenylcarbamoyl, N-phenyl-(C_1-C_4)-alkylcarbamoyl, carboxyl, (C_1-C_{16})-alkoxycarbonyl, (C_2-C_{16})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_5-C_6)-cycloalkoxycarbonyl, (C_5-C_6)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl or phenyl-(C_1-C_6)-alkoxycarbonyl, where a phenyl radical is substituted by 1 or 2 identical or different substituents from the group fluorine, chlorine, cyano, trifluoromethyl, (C_1-C_{10})-alkyl, (C_1-C_{10})-alkenyloxy or (C_1-C_{10})-alkoxy, and

R^3 is hydrogen, (C_1-C_5)-alkoxy or (C_5-C_6)-cycloalkyl-(C_1-C_2)-alkoxy, where one of the substituents R^1 and R^3 is hydrogen,

R^4 is a branched or unbranched (C_1-C_6)-alkyl radical, or a 2-phenylethyl radical, or a benzyl radical substituted by 1 or 2 radicals from the group fluorine, chlorine, cyano, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$, N-$(C_1-C_6)$-alkylcarbamoyl, N,N-di-$(C_1-C_6)$-alkylcarbamoyl, N-$(C_3-C_6)$-cycloalkylcarbamoyl or N-(+)-dehydroabietylaminocarbonyl, and f is 1 to 4, g is 0 or 1 to (2f+1) and x is 1.

Compounds of the formula I are preferred to the highest degree in which

Q is O,

X is O,

Y is CR^3,

m is 0,

A is a $-CH_2-$group,

B is $-CO_2H$,

R^1 is hydrogen,

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R^2 is hydrogen, N-(C_1-C_{10})-alkylcarbamoyl, N-((C_1-C_{12})-alkoxy-(C_1-C_3)-alkyl)carbamoyl, N-cyclohexylcarbamoyl, N-phenylcarbamoyl, N-(phenyl-(C_1-C_2)-alkyl)-carbamoyl, where, in the last two cases, the phenyl radical can carry a fluorine substituent, (C_1-C_{10})-alkyl substituent or (C_1-C_{10})-alkoxy substituent, carboxyl, (C_1-C_{16})-alkoxycarbonyl, (C_2-C_{16})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_5-C_6)-cycloalkoxycarbonyl or benzyloxycarbonyl,

R^3 is hydrogen, (C_1-C_6)-alkoxy or 2-(cyclohexyl)ethyloxy, where one of the substituents R^2 and R^3 is hydrogen,

R^4 is a branched or unbranched (C_1-C_4)-alkyl radical or a benzyl radical which is substituted once by fluorine, chlorine, trifluoromethyl, (C_1-C_4)-alkyl or (C_1-C_3)-alkoxy.

Compounds of the formula I are also preferred to the highest degree in which

Q is S,

X is O,

Y is CR^3,

m is 0,

A is a $-CH_2-$ group,

B is $-CO_2H$,

R^1 is hydrogen,

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R^2 is hydrogen, N-(C_1-C_{10})-alkylcarbamoyl, N-((C_1-C_{12})-alkoxy-(C_1-C_3)-alkyl)carbamoyl, N-cyclohexylcarbamoyl, N-phenylcarbamoyl, N-(phenyl-(C_1-C_2)alkyl)-carbamoyl, where, in the last two cases, the phenyl radical can carry a fluorine substituent, (C_1-C_{10})-alkyl substituent or (C_1-C_{10})-alkoxy substituent, carboxyl, (C_1-C_{16})-alkoxycarbonyl, (C_2-C_{16})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_5-C_6)-cycloalkoxycarbonyl or benzyloxycarbonyl,

R^3 is hydrogen, (C_1-C_6)-alkoxy or 2-(cyclohexyl)-ethyloxy, where one of the substituents R^2 and R^3 is hydrogen, and

R^4 is a branched or unbranched (C_1-C_6)-alkyl radical or a benzyl radical which is substituted once by fluorine, chlorine, trifluoromethyl, (C_1-C_4)-alkyl or (C_1-C_3)-alkoxy.

The compounds of the formula I are also preferred to the highest degree in which

Q is S,
X is O,
Y is CR^3,
m is 0,
A is a $-CH_2-$group,
B is $-CO_2H$,
R^1 is hydrogen,
R^2 is carboxyl or (C_1-C_{16})-alkoxycarbonyl,
R^3 is hydrogen, and
R^4 is a branched or unbranched (C_1-C_4)-alkyl radical.

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The compound of the formula I is also preferred to the highest degree in which

Q is O,
X is O,
Y is CR^3, where R^3 is hydrogen,
m is 0,
A is a $-CH_2-$group,
B is $-CO_2H-$,
R^1 and R^2, together with the pyridine carrying them, form an isoquinoline ring having an unsubstituted benzo moiety, and
R^4 is methyl.

The compound of the formula I is also preferred to the highest degree in which

Q is O,

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X is O,
Y is CR^3,
m is 0,
A is a $-CH_2-$group,
B is $-CO_2H$,
R^1 is hydrogen,
R^2 and R^3, together with the pyridine carrying them, form a quinoline ring having an unsubstituted benzo moiety, and
R^4 is methyl.

The invention also embraces prodrugs for the compounds of the formula (I), which prodrugs bring about an inhibition of collagen biosynthesis in vivo by liberating compounds of the formula I or their salts.

Finally, the invention also embraces prodrugs which, by liberating compounds of the formula I or their salts, bring about an inhibitory effect in vivo on prolyl-4-hydroxylase.

Prodrug groupings are chemical groups which, in vivo,

- are converted into the carboxylate group of the compounds of the formula I, and/or
- can be cleaved from the amide N atom, and/or
- can be converted into a pyridine ring.

Those prodrug groups which are suitable are known to the person skilled in the art.

The following prodrug groupings receive particular mention:
for the carboxylate group, ester groups, amide groups, hydroxymethyl groups and aldehyde groups, and their derivatives; for the pyridine N atom, N-oxides and N-alkyl derivatives; and for the pyridine ring, 1,4-dihydropyridine derivatives or tetrahydropyridine derivatives.

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The invention relates to the use of compounds of the formula I, and also the physiologically tolerated salts, for inhibiting collagen biosynthesis.

The invention relates to the use of compounds of the formula I, and also the physiologically tolerated salts, for inhibiting prolyl-4-hydroxylase.

The invention also relates to the use of compounds of the formula I, and also the physiologically tolerated salts, for producing a pharmaceutical against fibrotic diseases.

The invention also relates to the use of compounds of the formula I, and also the physiologically tolerated salts, for producing a pharmaceutical against fibrotic diseases of the liver, the lung and the skin.

Finally, the invention relates to the compounds of the formula I for use as pharmaceuticals.

The invention relates, in particular, to the compounds of the formula I for use as fibrosuppressive agents.

The invention also relates to a process for preparing compounds of the formula I.

The compounds of the formula I, in which A is a substituted alkylene moiety, B is CO_2H, Y is CR^3 and m is 0 or 1, are prepared by

i1.) Reacting pyridine-2-carboxylic acids of the formula II (R^{23} is H) with the amino esters of the formula III to form the amide esters of the formula IV, or

i2.) Reacting pyridine-2-carboxylic esters of the formula II (R^{23} is lower alkyl), under the conditions of aminolysis, to form the compounds of the formula IV; and

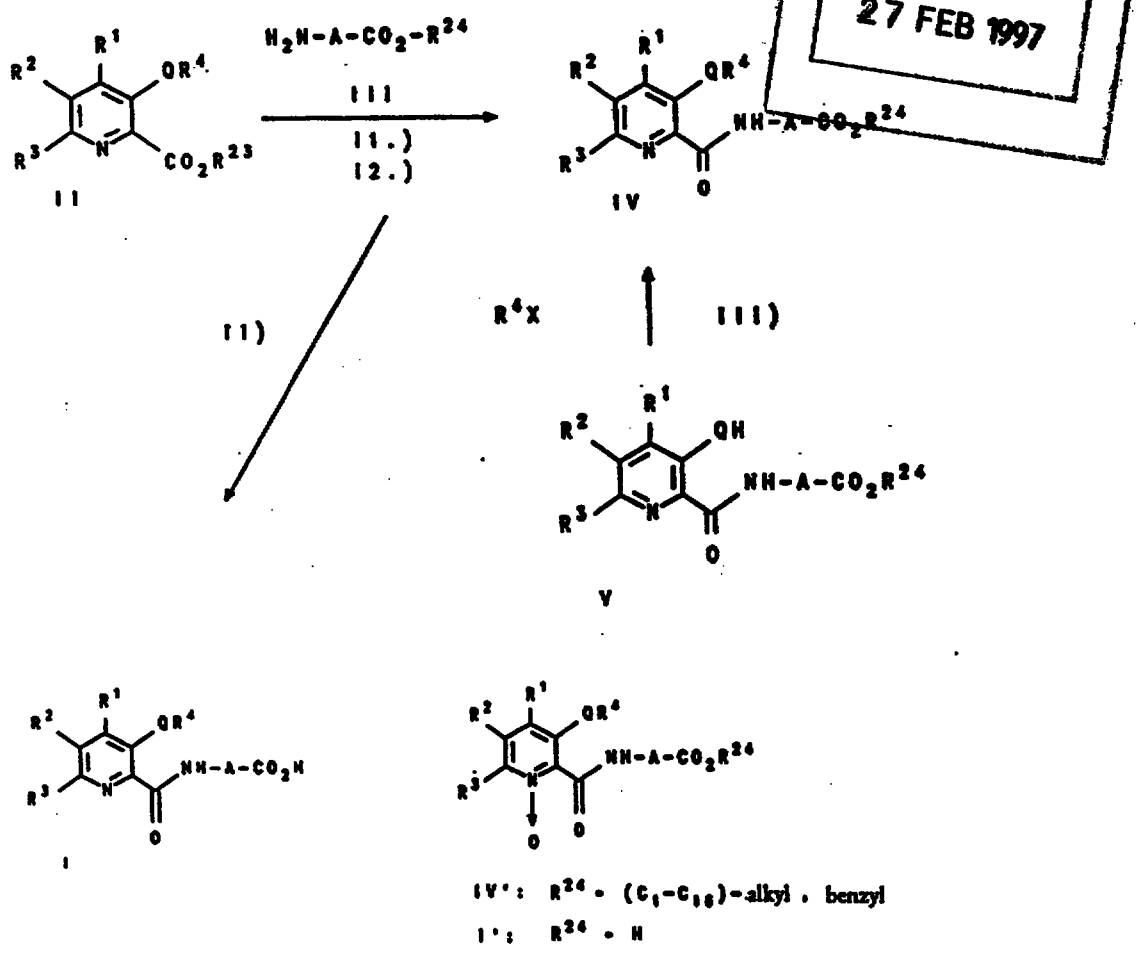
ii) liberating the compounds of the formula I from their esters of the formula IV; with, where appropriate,

iii) the compounds of the formula IV being prepared by alkylation of compounds of the formula V with R^4X, and, where appropriate,

iv) the compounds of the Formula IV being converted, provided Q is O or NR', into their pyridine N-oxides IV' (R^{24} is (C_1-C_{16})-alkyl or benzyl) and the latter being hydrolyzed to form the pyridine N-oxides of the formula I' (R^{24} is H).

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Scheme 1



R^{23} is H or (C_1-C_{16})-alkyl,

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R^{24} is H, (C_1-C_{16})-alkyl or benzyl,
X is a leaving group, in particular halogen, OSO_2Me or OSO_2phenyl

The methods of carboxyl activation and the condensation reactions known from peptide chemistry are suitable processes for the amide formation (reaction i1).

The substances which are known to the person skilled in the art, such as thionyl chloride, oxalyl chloride, pivaloyl chloride, chloroformate derivatives, or N,N'-carbonyldiimidazole, can be used as reagents for the carboxylic acid activation. The activated derivatives of the compounds of the formula II are prepared in situ and then reacted with the amide derivatives of the formula III.

An example of a suitable condensing agent is the combination of N,N'-dicyclohexylcarbodiimide/N-hydroxy-1H-benzotriazole and N-ethylmorpholine.

Suitable solvents are dichloromethane, tetrachloromethane, butyl acetate, ethyl acetate, toluene, tetrahydrofuran, dimethoxyethane, 1,4-dioxane, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, nitromethane and/or pyridine.

The compounds of the formula I, in which R^1 and R^3 are hydrogen and R^2 is a carboxyl substituent, a carbamoyl substituent or an ester substituent, were prepared as outlined in schemes 1, 2 and 3.

Scheme 2 illustrates the preparation of the compounds of the formula II in which R^2 is a carboxylic acid substituent, or its derivative, and R^1 and R^3 are hydrogen.

The 3-substituted 5-carboxypyridine-2-carboxylic esters of the formula XI and their isomers of the formula XII

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are prepared from the pyridine-2,5-dicarboxylic diesters of the formula VII.

The oxidation of the pyridine-2,5-dicarboxylates of the formula VII is described in J. Chem. Soc. Perkin Trans. 2, 1978, 34-38 and in J. Org. Chem. 25 (1960) 565 to 568 (M.L. Peterson).

The halogenation (chlorination) of the pyridine N-oxides of the formula VIII with thionyl chloride and the reaction of the 3-chloropyridine-2,5-dicarboxylic diester (Formula IX) with alcoholates (Q is O or S) can be carried out in analogy with the process described in the patent specification CH 658 651 (LONZA), where M is a singly charged or doubly charged metal ion, preferably from the first or second main group of the periodic system.

In analogy with the known literature (CA: vol. 68, 1968, 68 840 h), the monoesters of the formula XII are prepared, under hydrolysis conditions, from the substituted pyridine-2,5-dicarboxylic diesters of the formula Xb.

Selective hydrolysis using Cu(II) salts, J. Delarge in Pharmaceutica Acta Helvetiae 44, 637-643, 1969, represents another process for preparing the compounds of the formula XII from the diesters of the formula Xb.

The compounds of the formula XII thus obtained are reacted with the amino esters of the formula III to form the compounds of the formula IV (Scheme 2).

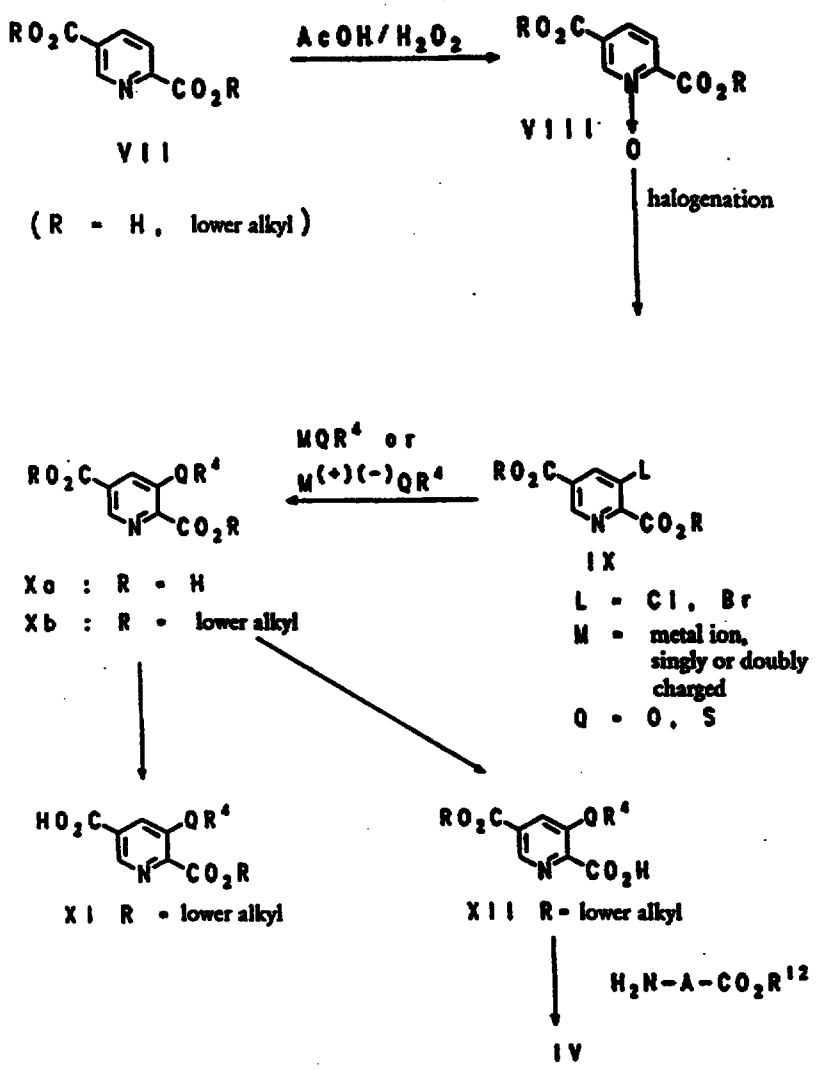
The pyridine-2-carboxylic ester-5-carboxylates of the formula XI can be prepared, under esterification conditions, from substituted pyridine-2,5-dicarboxylic acids of the formula Xa (see CA: vol. 68, 1968, 68840 h). Suitable conditions are, for example, esterification with methanol in the presence of sulfuric acid, it being necessary to choose the reaction time so that complete

esterification to form the diester product only takes place to a secondary extent, or so that the diester products can be separated off as by-products.

The compounds of the formula XI are converted with amines or alcohols into the 5-carboxylic acid derivatives of the formula XIV (Scheme 3).

These are then hydrolysed to form the compounds of the formula II (R^{23} is H), which compounds are subsequently reacted in analogy with Scheme 1.

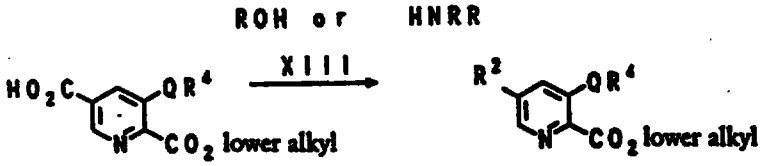
Scheme 2



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Scheme 3



XI XIV R^2 = COOR, CO-NRR

The 2-hydroxymethylpyridines of the formula VIa, which are disclosed in EP-A-0 304 732, EP-A-0 321 385 and EP-A-0 208 452, can be used as intermediates for preparing derivatives (R^1) which are substituted in the 4 position.

Scheme 4



VI II (R^{11} = H)

VIa / IIa : QR^4 = OMe (Me = methyl)

VIb / IIb : QR^4 = OBn (Bn = benzyl)

The 3-O-benzyl derivatives of the formula VIb were also obtained in an analogous manner, as described in those documents.

The compounds of the formulae VIa and VIb were reacted with an oxidizing agent, preferably with $KMnO_4$ in aqueous alkaline medium, to form the pyridine-2-carboxylic acid derivatives of the formula II (cf. Scheme 4).

The preparation of substituted pyridine-2-carboxylic acids is, for example, disclosed in DE-A-353 046, and for 3-(3-chlorophenoxy)pyridine-2-carboxylic acid and 3-(3-methylphenoxy)pyridine-2-carboxylic acid in J. Med. Chem. 1975, 18, pp. 1-8, Villani et al.; for

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3,5-diethoxypyridine-2-carboxylic acid in J. Med. Chem. 1974, 17, pp. 172-181, French et al.; and for 3-methylthiopyridine-2-carboxylic acid and 3-benzylthiopyridine-2-carboxylic acid in J. Med. Chem. 1974, 17, pp. 1065-1071, Blank et al.; and for 3-methoxypyridine-2,5-dicarboxylic acid in CH-PS 658 651.

The compounds of the formula I are inhibitors of prolyl-4-hydroxylase. The inhibition of this enzyme was determined as described by Kaule and Günzler in Annal. Biochem. 184, 219 to 297 (1990).

The novel compounds of the formula I possess valuable pharmacological properties and exhibit, in particular, antifibrotic activity.

The antifibrotic effect can, for example, be determined using the model of carbon tetrachloride-induced hepatic fibrosis. For this, rats are treated twice a week with CCl_4 (1 ml/kg) - dissolved in olive oil. The substance under test is administered daily, where appropriate even twice a day, per os, or intraperitoneally - dissolved in a suitable tolerated solvent. The extent of the hepatic fibrosis is determined by histology, and the proportion of collagen in the liver is analyzed by means of determining hydroxyproline - as described in Kivirikko et al. (Anal. Biochem. 19, 249 f. (1967)). The fibrogenic activity can be measured by the radioimmunological determination of collagen fragments and procollagen peptides in the serum. In this model, the novel compounds are active at a concentration of from 1 to 100 mg/kg.

The fibrogenic activity can be measured by radioimmunological determination of the N-terminal propeptide of collagen type III or of the N-terminal or C-terminal crosslinking domain of collagen type IV (7s collagen or type IV collagen NC_1) in the serum.

For this purpose, measurements were made of the

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concentrations of hydroxyproline, procollagen III peptide, 7s collagen and type IV collagen NC in the liver of

a) untreated rats (control)

b) rats which were administered carbon tetrachloride (CCl_4 control)

c) rats which were first administered CCl_4 and then a novel compound

(this test method is described by Rouiller, C., Experimental toxic injury of the liver; in The Liver, C. Rouiller, vol. 2, 5. 335 to 476, New York, Academic Press, 1964).

The novel compounds can also be demonstrated to be active in the following systems.

Inhibition of hepatic prolyl-4-hydroxylase in vivo:

This model is used to demonstrate the acute inhibition of prolyl-4-hydroxylase in vivo. For this, rats of both sexes (healthy or with induced hepatic fibrosis) are administered (intraperitoneally, intravenously or per os) the substance under test or the corresponding vehicle and, after this, are given ^{14}C-L-proline (250 µCi/kg of bodyweight), which is administered intraperitoneally. There then follows a second intraperitoneal administration of ^{14}C-L-proline (250 µCi/kg of bodyweight). Finally, the animals are exsanguinated under pentobarbital anesthesia and the livers removed. The hepatic collagen was purified by digestion with pepsin and fractional ammonium sulfate precipitation in conformity with published protocols (Ref. 1 and 2). The purified liver collagen was hydrolyzed and the content of ^{14}C-hydroxyproline and ^{14}C-proline was determined by means of amino acid analysis using ion exchange chromatography. Inhibition of prolyl-4-hydroxylase is shown by a decrease in the quotient ^{14}C-hydroxyproline/[^{14}C-hydroxyproline+^{14}C-proline]. 2,2'-Dipyridyl is used as the reference substance. (1: Chojkier, M. 1986, Hepatocyte

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collagen production in vivo in normal rats, J. Clin. Invest. 78: 333-339 and 2: Ogata I., et al. 1991, Minor contribution of hepatocytes to collagen production in normal and early fibrotic livers, Hepatology 14: 361-367).

Inhibition of prolyl-4-hydroxylase in cell cultures:

The following cell types are used for testing inhibitors of prolyl-4-hydroxylase in cell cultures:
Normal human skin fibroblasts, (NHDF), rat liver epithelial cells, (ref. 1) and primary fat storing cells from rat liver (ref. 2). For this, the cells are cultivated in the presence of inhibitors. At the same time, the collagen which is newly synthesized during this period is metabolically labelled with 4-^{3}H-L-proline and ^{14}C-proline. The influence of the test substances on the degree of hydroxylation of the collagen is then determined in accordance with the method of Chojkier et al (ref. 3). 2,2'-Dipyridyl is employed as the reference substance. (1.: Schrode, W., Mecke, D., Gebhard, R. 1990, Induction of glutamine synthetase in periportal hepatocytes by co-cultivation with a liver epithelial cell line, Eur. J. Cell. Biol. 53: 35-41; 2. Blomhoff, R., Berg T. 1990, Isolation and cultivation of rat liver stellate cells, Methods Enzymol. 190: 59-71; and 3.: Chojkier, M. Peterkofsky, B. Bateman, J. 1980, A new method for determining the extent of proline hydroxylation by measuring changes in the ration of [4-^{3}H]:[^{14}C] proline in collagenase digests, Anal. Biochem. 108: 385-393).

The compounds of the formula I may be used as medicaments in the form of pharmaceutical preparations, which contain the compounds, where appropriate together with tolerated pharmaceutical excipients. The compounds can be used as medicines, for example in the form of pharmaceutical preparations which contain these compounds in a mixture together with a pharmaceutical, organic or inorganic

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excipient which is suitable for enteral, percutaneous or parenteral administration, such as, for example, water, gum arabic, gelatin, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkylene glycols, vaseline, etc.

For this purpose, they can be administered orally in doses of from 0.1 to 25 mg/kg/day, preferably of from 1 to 5 mg/kg/day, or parenterally in doses of from 0.01 to 5 mg/kg/day, preferably of from 0.01 to 2.5 mg/kg/day, in particular of from 0.5 to 1.0 mg/kg/day. The dosage can also be increased in severe cases. In many cases, however, smaller doses are also sufficient. These data refer to an adult of about 75 kg in weight.

The novel compounds of the formula I are designated substituted heterocyclic carboxylic acid glycylamides, preferably pyridine-2-carboxylic acid glycylamides, in the examples described below.
This mode of designation is understood to mean substituted N-carboxymethylpyridine-2-carboxamides.
Another option is to classify them as substituted N-(pyridyl-2-carbonyl)glycines.

Example 1
3-Methoxy-4-(2,2,2-trifluoroethyloxy)pyridine-2-carboxylic acid glycylamide

a) 2-Methyl-3-methoxy-4-chloropyridine N-oxide

11.2 g (80.5 mmol) of 3-methoxy-2-methyl-4(1H)-pyridone were heated under reflux for 10 hours in 100 ml of phosphorus oxychloride. Subsequently, the mixture was concentrated and 30 ml of toluene were added to each 2 ml volume; concentration then took place once again and the residue was taken up in 150 ml of water, with the pH of the mixture then being adjusted to 11 with K_2CO_3; this mixture was then extracted with dichloromethane and the organic phase was washed with water, dried and freed from

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solvent.

8 g of the product were obtained, under standard conditions, from the pale brown oil (9 g) using m-chloroperbenzoic acid in dichloromethane, m.p. 88 to 89°C (from petroleum ether).

b) 2-Methyl-3-methoxy-4-(2,2,2-trifluoroethoxy)pyridine N-oxide

6.7 g of potassium tert-butoxide were added in portions, at -20°C, while stirring and under a nitrogen atmosphere, to 20 ml of trifluoroethanol. After the mixture had been warmed to 0°C, 5.2 g (30 mmol) of 2-methyl-3-methoxy-4-chloropyridine N-oxide were added in portions. The mixture was heated under reflux for 3 hours, and then cooled down to room temperature; a further 3.45 g of potassium tert-butoxide were then added and the mixture was heated under reflux for 2 hours. After it had cooled down, 40 ml of water were added to the reaction mixture, which was then extracted with dichloromethane; the extract was then dried over $MgSO_4$ and freed from solvent in vacuo. The resulting oily product was subjected to further reaction.

c) 3-Methoxy-4-(2,2,2-trifluoroethoxy)-2-hydroxymethylpyridine

8 g (33.8 mmol) of the above compound were dissolved in 16 ml of glacial acetic acid, and 24 ml of acetic anhydride were added, at 80°C and while stirring, to this mixture. The reaction mixture was heated at 110°C for 2 hours and then cooled down to 80°C; 40 ml of methanol were then added to it dropwise. Subsequently, the mixture was concentrated in vacuo, and the oily residue added to 75 ml of 2N methanolic NaOH, with this mixture being stirred for 30 minutes. Following treatment with active charcoal, and filtration, the mixture was concentrated in vacuo and 50 ml of water were added to the residue, after

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which extraction took place with dichloromethane; the extract was dried ($MgSO_4$) and concentrated, and the residue was treated with diisopropyl ether. 3.9 g of the product were obtained in the form of colorless crystals, m.p. 107 to 108°C.

d) 3-Methoxy-4-(2,2,2-trifluoroethyloxy)pyridine-2-carboxylic acid

0.8 g (3.3 mmol) of the above alcohol was dissolved in a solution composed of 0.3 g of potassium hydroxide and 25 ml of water, and 1.6 g of potassium permanganate were added in portions at 100°C and while stirring. After decolorization, the manganese dioxide which had formed was filtered off with suction from the hot mixture and washed twice with hot water; the filtrate was concentrated in vacuo to 1/3 of the volume, adjusted to pH 1 with conc. aqueous hydrochloric acid, and concentrated in vacuo; the residue was treated with anhydrous ethanol and the undissolved material was filtered off. 0.73 g of product, m.p. 157°, was obtained from the filtrate.

e) 3-Methoxy-4-(2,2,2-trifluoroethyloxy)pyridine-2-carboxylic acid (glycyl ethyl ester) amide

0.58 g (2.3 mmol) of the above carboxylic acid was suspended in 100 ml of anhydrous tetrahydrofuran, after which 322 mg (2.3 mmol) of glycine ethyl ester hydrochloride, 0.64 ml (5 mmol) of N-ethylmorpholine, 350 mg (2.6 mmol) of 1-hydroxy-1H-benzotriazole and 537 mg (2.6 mmol) of N,N'-dicyclohexylcarbodiimide were added at 20°C and while stirring, and the mixture was then stirred at 20°C for 48 hours. Undissolved material was then filtered off and the filtrate was concentrated in vacuo; the residue was taken up in ethyl acetate and undissolved material was filtered off; the filtrate was stirred together with 100 ml of a saturated, aqueous solution of Na bicarbonate, and the organic phase was dried and concentrated in vacuo; the residue was

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crystallized using diisopropyl ether. 0.45 g of the colorless crystalline product were obtained, m.p. 80 to 82°C.

f) 0.4 g (1.2 mmol) of the above ester was added to 50 ml of a 1.5 N methanolic solution of sodium hydroxide, and this mixture was stirred at 20°C for 30 minutes. It was then concentrated in vacuo and the residue was taken up in 50 ml of water; this mixture was adjusted to pH 1 with comp. aqueous hydrochloric acid and the small amount of undissolved material was filtered off; the filtrate was concentrated in vacuo and the residue was treated with 50 ml of anhydrous ethanol; this mixture was filtered and the filtrate was concentrated and brought to crystallization using diethyl ether. 0.32 g of the title compound was obtained, m.p. 163 to 165°C (with gas evolution).

Example 2
4-Chloro-3-methoxypyridine-2-carboxylic acid glycylamide

a) 4-Chloro-2-hydroxymethyl-3-methoxypyridine

30 g (173 mmol) of 4-chloro-3-methoxy-2-methylpyridine N-oxide (cf. Example 1a) were dissolved in 100 ml of glacial acetic acid, after which 150 ml of acetic anhydride were added dropwise, at 80°C and while stirring, and the mixture was then stirred at 110°C for 2 hours. The mixture was then cooled down to 80°C and 200 ml of methanol were added dropwise; the mixture was then heated to boiling for 15 minutes and, after having been cooled down, concentrated in vacuo; the residue was taken up in methanol and this mixture was allowed to flow into 300 ml of a 1.5 N methanolic solution of sodium hydroxide, with this mixture then being stirred at 20°C for 30 minutes and concentrated in vacuo; the residue was taken up in water, and this mixture extracted three times with dichloromethane, with the organic phase being dried and concentrated; the residue was crystallized using

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petroleum ether. 23 g of product were obtained, m.p. 64 to 66°C.

b) 4-Chloro-3-methoxypyridine-2-carboxylic acid

8.65 g (50 mmol) of the above alcohol were dissolved in a mixture composed of 0.8 g of potassium hydroxide and 60 ml of water, after which potassium permanganate was added in portions, at 60°C and while stirring, until no more discoloration could be seen (12 g, 75 mmol). After 1 hour at 60°C, the manganese dioxide was filtered off with suction and then washed with hot water; the filtrate was concentrated in vacuo to 200 ml and adjusted, while cooling, to pH 1 with aqueous conc. HCl. After grinding, the product crystallizes out in association with cooling. Additional product can be obtained from the mother liquor by treatment with petroleum ether. Total quantity, 4.2 g, m.p. 116 to 117°C (with gas evolution).

c) 4-Chloro-3-methoxypyridine-2-carboxylic acid (glycyl ethyl ester) amide

4.7 g (25 mmol) of the above carboxylic acid were suspended in 200 ml of anhydrous dichloromethane, and after that 3.5 g (25 mmol) of glycine ethyl ester hydrochloride, 6.4 ml (50 mmol) of N-ethylmorpholine, 3.8 g (28 mmol) of 1-hydroxy-1H-benzotriazole and 5.15 g (25 mmol) of N,N'-dicyclohexylcarbodiimide were added sequentially, at 20°C and while stirring, and the mixture was then stirred at 20°C for 20 hours. Undissolved material was then filtered off and the organic phase was shaken with a saturated, aqueous solution of sodium carbonate, dried and concentrated in vacuo; the residue (6 g of oil) was chromatographed on silica gel using ethyl acetate and 5.4 g of oily product were obtained.

d) The title compound was obtained by hydrolyzing the above ethyl ester. For this, 0.7 g (2.6 mmol) of this

ester was dissolved in 50 ml of methanol/water (3:1), and after that 170 mg (7 mmol) of lithium hydroxide were added at 20°C and while stirring. After 30 minutes, the mixture was concentrated in vacuo; the residue was brought to pH 1 with conc. aqueous hydrochloric acid and this mixture was concentrated in vacuo; the residue was treated twice with anhydrous ethanol and the ethanolic phase was concentrated; the residue was treated with hot ethyl acetate and the amorphous residue was dried on an oil pump. 0.31 g of the title compound was obtained.

Example 3
4-Butyloxy-3-methoxypyridine-2-carboxylic acid glycylamide
M.p. 137 to 139°C (with gas evolution, from tetrahydrofuran)

Examples 4 to 16 were prepared in an analogous manner:

Example 4
3,4-Dimethoxypyridine-2-carboxylic acid glycylamide

Example 5
?-Ethyloxy-4-(3-methoxybenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 6
4-Hexyloxy-3-methoxypyridine-2-carboxylic acid glycylamide

Example 7
3-Methoxy-4-(3-methyl-1-butyloxy)pyridine-2-carboxylic acid glycylamide

Example 8
4-(4-Fluorobenzyloxy)-3-methoxypyridine-2-carboxylic acid glycylamide

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Example 9
3-Methoxy-4-(4-trifluoromethylbenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 10
3-Methoxy-4-(2,2,3,3,3-pentafluoropropyloxy)pyridine-2-carboxylic acid glycylamide

Example 11
4-(2,2,3,3,4,4,4-Heptafluorobutyloxy)-3-methoxypyridine-2-carboxylic acid glycylamide

Example 12
4-(3-Methoxybenzyloxy)-3-methoxypyridine-2-carboxylic acid glycylamide

Example 13
3-Ethyloxy-4-(2,2,2-trifluoroethyloxy)pyridine-2-carboxylic acid glycylamide

Example 14
4-Butyloxy-3-ethyloxypyridine-2-carboxylic acid glycylamide

Example 15
3-Methoxy-4-((phenoxyethyl)oxy)pyridine-2-carboxylic acid glycylamide

Example 16
3-Ethyloxy-4-benzyloxypyridine-2-carboxylic acid glycylamide

Example 17
3,6-Dimethoxypyridine-2-carboxylic acid glycylamide

a) 3,6-Dimethoxy-2-methylpyridine N-oxide

1.15 g (50 mmol) of sodium were dissolved in 100 ml of anhydrous methanol, and after that 7.4 g (40 mmol) of

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3-methoxy-2-methyl-6-nitropyridine N-oxide were added at 20°C and while stirring. The mixture was then heated to reflux for 3 hours and, after having been cooled down, concentrated in vacuo; the residue was taken up in water and this mixture was extracted with dichloromethane; the organic phase was dried and concentrated and the residue was crystallized using diisopropyl ether. 7 g of product were obtained, m.p. 63 to 65°C.

b) 3,6-Dimethoxy-2-hydroxymethylpyridine

7 g (41.4 mmol) of the above compound were reacted with glacial acetic acid/acetic anhydride in analogy with Example 1c) and the resulting acetate was hydrolyzed using 1.5 N methanolic sodium hydroxide solution. 5.6 g were obtained of oily product which was subjected to further reaction under c).

c) 3,6-Dimethoxypyridine-2-carboxylic acid

5.6 g (33 mmol) of the above compound and 2.4 g of potassium hydroxide were dissolved in 150 ml of water, and after that 15 g (100 mmol) of potassium permanganate were added in portions at 60°C and while stirring. The manganese dioxide which had formed was then filtered off with suction and washed twice with hot water; the combined water phase was concentrated to 100 ml, adjusted to pH 1 with conc. aqueous hydrochloric acid while being cooled with ice, and concentrated in vacuo; the residue was treated with ethyl acetate and ethanol, and undissolved material was filtered off from this mixture, with the filtrate being concentrated in vacuo. The residue was crystallized using diethyl ether. 4 g of product were obtained, m.p. 131-132°C (with gas evolution).

d) 3,6-Dimethoxypyridine-2-carboxylic acid (glycyl ethyl ester) amide

2.2 g (12 mmol) of the above carboxylic acid were

suspended in 300 ml of anhydrous dichloromethane, and after that 1.68 g (12 mmol) of glycine ethyl ester hydrochloride, 3.25 ml (25 mmol) of N-ethylmorpholine, 1.62 g (12 mmol) of 1-hydroxy-1H-benzotriazole and 5.2 g (12 mmol) of N-cyclohexyl-N'-(2-morpholinoethyl)carbodiimide methyl-p-toluenesulfonate were added, while stirring, and the mixture was then stirred at 20°C for 20 hours. The small amount of undissolved material was then filtered off and the filtrate was shaken once with water and then with a saturated, aqueous solution of Na bicarbonate; the organic phase was dried and concentrated in vacuo and the residue was crystallized using diisopropyl ether. 2 g of product were obtained, m.p. 93 to 95°C.

e) The title compound was obtained by hydrolyzing 0.6 g (2.24 mmol) of the above ethyl ester at 20°C using 120 mg of lithium hydroxide in 60 ml of methanol/water (3:1). After concentration had taken place in vacuo, the residue was acidified and extracted, at 20°C, with tetrahydrofuran; the filtrate was concentrated in vacuo and the yellow, resinous residue was crystallized using diethyl ether. 0.14 g were obtained of the title compound, m.p. 130°C (decomposition), which is strongly hygroscopic. The residue from the inspissated reaction mixture was then extracted three times with 50 ml of hot acetone on each occasion and the inspissation residue was crystallized using diethyl ether. A further 0.35 g of the title compound was obtained, m.p. 155°C (decomposition).

Example 18

3,5-Diethoxypyridine-2-carboxylic acid glycylamide

Example 19

3-Methoxy-6-(3-methyl-1-butyloxy)pyridine-2-carboxylic acid glycylamide

M.p.: 105 to 107°C (from aqueous hydrochloric acid, pH 3 to 4)

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Example 20
3-Benzyloxy-4-(3-ethyloxypropyloxy)pyridine-2-carboxylic acid glycylamide
M.p. 118-120°C (from acetone)
According to ^{1}H NMR, the product contains approximately 15 % of the 3-hydroxy derivative.

Example 21
3-Benzyloxy-4-hexyloxypyridine-2-carboxylic acid glycylamide
M.p. 130 to 132°C (from aqueous hydrochloric acid)

Example 22
6-(2-Butoxyethyloxy)-3-methoxypyridine-2-carboxylic acid glycylamide

Example 23
6-(2-Cyclohexyl)ethyl)oxy-3-methoxypyridine-2-carboxylic acid glycylamide
M.p. from 70°C (sintering from 50°C, from aqueous hydrochloric acid, pH 3)

Example 24
3-Ethyloxy-6-methylpyridine-2-carboxylic acid glycylamide

Example 25
6-Benzyloxy-3-methoxypyridine-2-carboxylic acid glycylamide

Example 26
3-Benzyloxypyridine-2-carboxylic acid glycylamide
M.p. 142-144°C

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Example 27.1
3-Methoxypyridine-2-carboxylic acid glycylamide
amorphous substance, prepared by hydrolyzing the 3-methoxypyridine-2-carboxlic acid (glycyl ethyl ester) amide, m.p. 141 to 142°C (with gas evolution, from

diethyl ether).

This ethyl ester was obtained by catalytic hydrogenation of 4-chloro-3-methoxypyridine-2-carboxylic acid (glycyl ethyl ester) amide (see Example 2c), which was obtained from 4-chloro-3-methoxypyridine-2-carboxylic acid (m.p. 119 to 120°C, from 4-chloro-3-methoxy-2-methylpyridine N-oxide by reaction with acetic anhydride/glacial acetic acid and subsequent oxidation of the 2-hydroxymethyl-pyridine derivative) (see Example 2a, b) and glycine ethyl ester hydrochloride.

Example 27.2
3-Methoxypyridine-2-carboxylic acid glycylamide hydrochloride

a) 4-Chloro-3-methoxypyridine-2-carboxylic acid (glycyl benzyl ester) amide

The product was obtained, in analogy with Example 90a), from 4-chloro-3-methoxypyridine-2-carboxylic acid (cf. Example 2b), glycine benzyl ester tosylate, N-ethylmorpholine, 1-hydroxy-1H-benzotriazole and CMC, m.p. 57-58°C.

b) The title compound was obtained by hydrogenating the above product in methanol/tetrahydrofuran (1:1) using Pd on charcoal (10 %) in a hydrogenation vessel. After removing the catalyst, and freeing from the solvent, the product was crystallized using acetone, m.p. 168°C (with foaming).

Example 28
3-Ethoxypyridine-2-carboxylic acid glycylamide

Example 29
3-Propyloxypyridine-2-carboxylic acid glycylamide

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Example 30

3-Butyloxypyridine-2-carboxylic acid glycylamide

a) 3-n-Butyloxypyridine-2-carboxylic acid

6 g (150 mmol) of NaH (60 %, in mineral oil) were added in portions, at 20°C and while stirring, to 9.8 g (70 mmol) of 3-hydroxypyridine-2-carboxylic acid in 150 ml of N,N-dimethylacetamide. After 30 minutes, 15 ml (140 mmol) of butyl bromide were added dropwise and the mixture was heated at between 95°C and 125°C for 2.5 hours. After having been cooled down, the mixture was concentrated in vacuo, treated with an aqueous solution of Na bicarbonate and extracted with dichloromethane; after drying, the residue was purified by chromatography on silica gel using ethyl acetate.

The 13 g of oily product thus obtained were introduced into 250 ml of a 1.5 N methanolic solution of sodium hydroxide, and the mixture was then stirred at 20°C for 30 minutes and concentrated in vacuo; the residue was taken up in 200 ml of water and this mixture was extracted with dichloromethane and the aqueous phase was adjusted to pH 1 with conc. aqueous hydrochloric acid; concentration took place in vacuo and the residue was treated with ethyl acetate and then with anhydrous ethanol. The resulting solutions were concentrated and the residue was crystallized using acetone. 9.3 g were obtained of product (m.p. 93-95°C) which, according to ^{1}H NMR, still contained approximately 20 % of 3-hydroxy-pyridine-2-carboxylic acid.

b) 2.8 g (20 mmol) of glycine ethyl ester hydrochloride, 5.2 ml (40 mmol) of N-ethylmorpholine, 2.7 g (20 mmol) of 1-hydroxy-1H-benzotriazole and 3.0 ml (20 mmol) of N,N'-diisopropylcarbodiimide were added, at 20°C and while stirring, to 4 g (20 mmol) of the above product in 200 ml of anhydrous tetrahydrofuran and 100 ml of anhydrous acetonitrile, and the mixture was then stirred at 20°C for 20 hours.

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After working up (treatment with Na bicarbonate solution, removal of precipitated diisopropylurea), 3.5 g of oily product, which still contained N,N'-diisopropylurea, were obtained following chromatography on silica gel (ethyl acetate/n-heptane 1:1; then pure ethyl acetate).
This mixture was introduced, at 20°C and while stirring, into 150 ml of a 1.5 N methanolic solution of sodium hydroxide and the total mixture was stirred for 30 minutes.
This latter mixture was then concentrated in vacuo and the residue was taken up in water; this mixture was in turn extracted with 200 ml of dichloromethane and the aqueous phase was brought to pH 1 using conc. aqueous HCl and concentrated in vacuo; the residue was treated with anhydrous ethanol and then with N,N-dimethylformamide, with each extract being filtered to remove undissolved material and then concentrated and each of the residues being crystallized using ethyl acetate. 1.65 g of the title compound were obtained from the ethanol phase (slightly contaminated according to ^{1}H NMR, m.p. 170°C with gas evolution) and a further 0.63 g from the dimethylformamide phase (m.p. 182°C, with gas evolution).

Example 31
3-(4-Chlorobenzyloxy)pyridine-2-carboxylic acid glycylamide

a) 4-Chlorobenzyl 3-(4-chlorobenzyloxy)pyridine-2-carboxylate

8.4 g (60 mmol) of 3-hydroxypyridine-2-carboxylic acid were alkylated (3 hours, 110°C) with 5.2 g (approximately 130 mmol, 60 %) of sodium hydride and 19.3 g (120 mmol) of 4-chlorobenzyl chloride in N,N-dimethylacetamide in analogy with Example 30a). After concentration in vacuo and extraction with Na bicarbonate solution, the residue was purified on silica gel using heptane/ethyl acetate (1:1), and 14.8 g of the product were crystallized from appropriate fractions using diisopropyl ether, m.p. 92 to

94°C.

b) 3-(4-Chlorobenzyloxy)pyridine-2-carboxylic acid

9.7 g (25 mmol) of the above ester were hydrolyzed with 200 ml of a 1.5 N methanolic solution of sodium hydroxide (24 h, 20°C). After working up (concentration, taking up of the residue in water, extraction with dichloromethane and acidification), 6.5 g of product were obtained, m.p. 144°C (from water, decomposition).

c) 3-(4-Chlorobenzyloxy)pyridine-2-carboxylic (glycyl ethyl ester) amide

3.2 g (12 mmol) of the above pyridine-2-carboxylic acid were reacted, in analogy with example 17d), with 1.7 g (12 mmol) of glycine ethyl ester hydrochloride, 1.62 g (12 mmol) of 1-hydroxy-(1H)-benzotriazole, 3.3 ml (25 mmol) of N-ethylmorpholine and 5.2 g (12 mmol) of N-cyclohexyl-N'-(2-morpholinoethyl)carbodiimide methyl-p-toluenesulfonate. After working up, 3.0 g of the product were crystallized using diisopropyl ether, m.p. 106 to 108°C.

d) The title compound was obtained by hydrolyzing the above ethyl ester. 120 mg (5 mmol) of lithium hydroxide were added to 0.9 g (2.5 mmol) of the ethyl ester in 60 ml of methanol/water (3:1), and the mixture was stirred at 20°C for 1 hour. It was then concentrated in vacuo and the resulting aqueous phase was adjusted to pH 3; the resulting precipitate was filtered off with suction, washed with water and dried in vacuo. 0.52 g of the title compound was obtained, m.p. 155 to 157°C.

Example 32

3-(3-Methoxybenzyloxy)pyridine-2-carboxylic acid glycyl-amide

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a) 3-Methoxybenzyl 3-(3-methoxybenzyloxy)pyridine-2-carboxylate

In analogy with Example 38a), 10 g of the product were obtained as a colorless oil, which was subjected to further reaction, from 8.4 g (60 mmol) of 3-hydroxy-pyridine-2-carboxylic acid and 3-methoxybenzyl chloride following chromatography on silica gel.

b) 3-(3-Methoxybenzyloxy)pyridine-2-carboxylic acid

10 g of the above ester were hydrolyzed in 300 ml of a 1.5 N methanolic solution of sodium hydroxide. 7.5 g of product were obtained, m.p. 147°C (decomposition, from aqueous hydrochloric acid)

c) 3-(3-Methoxybenzyloxy)pyridine-2-carboxylic acid (glycyl ethyl ester) amide

3.2 g (12 mmol) of the above carboxylic acid were reacted in analogy with Example 31c). 3.6 g of oily crude product were isolated which, according to the ^{1}H NMR spectrum, still contained N-ethylmorpholine. The pure substance, m.p. 135 to 137°C (from diisopropyl ether/ethyl acetate) was obtained from this crude product.

d) 2.1 g (6 mmol) of the above product were hydrolyzed using 0.4 g of NaOH in 60 ml of methanol. Following acidification to pH 3, 1.6 g of the title compound were obtained as a colorless crystalline substance, m.p. 89 to 91°C (from aqueous hydrochloric acid).

Example 33

3-(2-Phenylethyloxy)pyridine-2-carboxylic acid glycyl-amide sodium salt

a) 3-(2-Phenylethyloxy)pyridine-2-carboxylic acid

In analogy with Example 30a), 8.4 g (60 mmol) of

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3-hydroxypyridine-2-carboxylic acid were alkylated with NaH/2-phenylethyl bromide in N,N-dimethylacetamide. The 10 g of oily product obtained after purification by column chromatography were hydrolyzed with methanolic sodium hydroxide solution in analogy with Example 30a). 3 g of product were obtained (m.p. 145°C (with foaming, from acetone)) which, according to the ^{1}H NMR spectrum, contained approximately 25 % of 3-hydroxypicolinic acid.

b) 3-((2-Phenylethyl)oxy)pyridine-2-carboxylic acid (glycyl ethyl ester) amide

2.9 g of the above compound were reacted, in analogy with Example 30b), with glycine ethyl ester hydrochloride, N-ethylmorpholine, 1-hydroxy-1H-benzotriazole and N,N-dicyclohexylcarbodiimide. After working up, the crude product was chromatographed on silica gel using ethyl acetate. 3-Hydroxypyridine-2-carboxylic acid (glycyl ethyl ester) amide was initially eluted as a by-product and crystallized from appropriate fractions using petroleum ether; 1.1 g (m.p. 86 to 88°C, strong fluorescence in UV light). The product was then crystallized from appropriate fractions using diisopropyl ether, and 1.7 g of the product were obtained, m.p. 73-75°C.

c) The title compound was obtained by hydrolyzing 0.99 g (3 mmol) of the above ethyl ester using 100 ml of a 1N methanolic solution of sodium hydroxide. After the mixture had been stirred at 20°C for 1 hour, it was concentrated and the residue was dissolved in a little water; this latter mixture was extracted with dichloromethane and the aqueous phase was acidified, while being cooled with ice, to pH 1 using conc. aqueous hydrochloric acid and then concentrated in vacuo; the residue was extracted twice with tetrahydrofuran and the extracts were concentrated; the residue was dissolved in a little water/tetrahydrofuran (1:1), and 252 mg (3 mmol) of sodium bicarbonate were added to this solution. This mixture was concentrated to dryness and the residue was

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crystallized using anhydrous ethanol. 0.38 g of the title compound was obtained as sodium salt, m.p. > 300°C.

Example 34
3-(4-Trifluoromethylbenzyloxy)pyridine-2-carboxylic acid glycylamide
M.p. 161 to 163°C (from aqueous hydrochloric acid, pH 3)

Example 35
3-(4-(2-Propyl)benzyloxy)pyridine-2-carboxylic acid glycylamide sodium salt
M.p. 108°C (with decomp., from diisopropyl ether)

Example 36
3-(4-Fluorobenzyloxy)pyridine-2-carboxylic acid glycylamide
M.p.: 135 to 138°C (from aqueous hydrochloric acid, pH 3 to 4)

Example 37
3-(4-(2-(4-Methoxyphenyl)ethylamino)carbonyl)benzyloxy)-pyridine-2-carboxylic acid glycylamide
M.p. 168-170°C (from dichloromethane)

The following example nos. 38-64 were prepared in an analogous manner:

Example 38
3-(2,4-Dichlorobenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 39
3-(3-Fluorobenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 40
3-(3-Chlorobenzyloxy)pyridine-2-carboxylic acid glycylamide

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Example 41
3-(3,4-Dichlorobenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 42
3-(3-Trifluoromethylbenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 43
3-(4-Trifluoromethoxybenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 44
3-(3-Ethoxybenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 45
3-(4-Cyanobenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 46
3-((2-Pyridylmethyl)oxy)pyridine-2-carboxylic acid glycylamide hydrochloride

Example 47
3-((3-Pyridylmethyl)oxy)pyridine-2-carboxylic acid glycylamide hydrochloride

Example 48
3-((4-Pyridylmethyl)oxy)pyridine-2-carboxylic acid glycylamide hydrochloride

Example 49
3-((2-Thienylmethyl)oxy)pyridine-2-carboxylic acid glycylamide

Example 50
3-(3,5-Dimethoxybenzyloxy)pyridine-2-carboxylic acid glycylamide

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Example 51
3-Cyclohexyloxypyridine-2-carboxylic acid glycylamide

Example 52
3-(3-Phenylpropyloxy)pyridine-2-carboxylic acid glycylamide

Example 53
3-(4-Phenylbutyloxy)pyridine-2-carboxylic acid glycylamide

Example 54
3-(((4-Methoxy-2-pyridyl)methyl)oxy)pyridine-2-carboxylic acid glycylamide

Example 55
3-(((4-Ethoxy-2-pyridyl)methyl)oxy)pyridine-2-carboxylic acid glycylamide

Example 56
3-Methylthiopyridine-2-carboxylic acid glycylamide

Example 57
3-Benzylthiopyridine-2-carboxylic acid glycylamide

Example 58
3-(3-Chlorophenoxy)pyridine-2-carboxylic acid glycylamide

Example 59
3-(3-Methoxyphenoxy)pyridine-2-carboxylic acid glycylamide

Example 60
3-Phenoxypyridine-2-carboxylic acid glycylamide

Example 61
3-Butyloxypyridine-2-carboxylic acid L-alanylamide

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Example 62
3-Butyloxypyridine-2-carboxylic acid D-alanylamide

Example 63
3-Benzyloxypyridine-2-carboxylic acid β-alanylamide

Example 64
3-(3-Methylbutyloxy)pyridine-2-carboxylic acid L-leucylamide

Example 65
4-Methoxyisoquinoline-3-carboxylic acid glycylamide

a) Methyl 1,2-dihydro-4-hydroxy-1-oxoisoquinoline-3-carboxylate, was prepared as described (M. Suzuki et al., Synthesis 1978, 461).

b) Methyl 1,2-dihydro-4-methoxy-1-oxoisoquinoline-3-carboxylate, from a) using (trimethylsilyl)-diazomethane in methanol/acetonitrile, m.p. 177 to 179°C (ethyl acetate/heptane).

c) Methyl 1-chloro-4-methoxyisoquinoline-3-carboxylate, from b) using phosphorus oxychloride, m.p. 108°C (ethyl acetate).

d) Methyl 4-methoxyisoquinoline-3-carboxylate, from c) using hydrogen/Pd/C, m.p. 129°C (from methyl tert-butyl ether).

e) 4-Methoxyisoquinoline-3-carboxylic acid, from d) by hydrolysis, m.p. 185-189°C (from aqueous hydrochloric acid).

f) 4-Methoxyisoquinoline-3-carboxylic acid (glycyl methyl ester) amide, from e) using glycine methyl ester hydrochloride, DCC, HOBT, THF and NEM, oily substance (crude product).

g) The title compound was obtained by hydrolyzing the above methyl ester, m.p. 147°C (from aqueous hydrochloric acid)

Examples 66 to 76 were obtained in an analogous manner from the corresponding isoquinoline-3-carboxylic acids or the 5,6,7,8-tetrahydro derivatives, respectively:

Example 66
4-Ethoxyisoquinoline-3-carboxylic acid glycylamide

Example 67
4-Propyloxyisoquinoline-3-carboxylic acid glycylamide

Example 68
4-(3-Methylbutyloxy)isoquinoline-3-carboxylic acid glycylamide

Example 69
4-Methoxy-5,6,7,8-tetrahydroisoquinoline-3-carboxylic acid glycylamide

Example 70
4-(3-Methylbutyloxy)-5,6,7,8-tetrahydroisoquinoline-3-carboxylic acid glycylamide

Example 71
4-Ethoxy-5,6,7,8-tetrahydroisoquinoline-3-carboxylic acid glycylamide

Example 72
4-Benzyloxy-5,6,7,8-tetrahydroisoquinoline-3-carboxylic acid glycylamide

Example 73
4-Benzyloxyisoquinoline-3-carboxylic acid glycylamide

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Example 74
4-(3-Methoxybenzyloxy)-5,6,7,8-tetrahydroisoquinoline-3-carboxylic acid glycylamide

Example 75
7-Bromo-4-methoxyisoquinoline-3-carboxylic acid glycylamide

Example 76
7-Methoxy-4-methoxyisoquinoline-3-carboxylic acid glycylamide

Example 77
3-Methoxy-6-((3-methylbutyloxy)methyl)pyridine-2-carboxylic acid glycylamide

Example 78
3-Methoxy-6-((cyclohexyloxy)methyl)pyridine-2-carboxylic acid glycylamide

Example 79
3-Methoxy-6-benzyloxymethylpyridine-2-carboxylic acid glycylamide

Examples 80 to 91 were prepared in accordance with the processes described in Schemes 1, 2 and 3.

Example 80
5-Carboxy-3-methoxypyridine-2-carboxylic acid glycylamide

270 mg of the title compound from Example 81 were hydrolyzed at 20°C using 50 ml of 1N methanolic NaOH. After 30 minutes, the mixture was concentrated in vacuo and the residue was dissolved in 50 ml of water; this solution was extracted with diethyl ether and the aqueous phase was adjusted to pH 1 with conc. aqueous hydrochloric acid and then concentrated in vacuo; the water was removed azeotropically from the residue using ethyl

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acetate and the residue was then treated with ethanol and this mixture was concentrated; the residue was crystallized using diethyl ether. 230 mg were obtained of the title compound, m.p. 173°C (with gas evolution, sintering at 170°C), which, according to the ^{1}H NMR spectrum, still contains approximately 20 % of an impurity.

The title compound was also obtained by hydrolyzing 0.45 g of 5-((-1-butyloxy)carbonyl)-3-methoxypyridine-2-carboxylic acid N-(((1-butyloxy)carbonyl)methyl)amide, m.p. 80-81°C (from petroleum ether), using 50 ml of 1.5 N methanolic NaOH. 0.23 g was obtained of the title compound, m.p. 198-200°C (from an ethanolic phase whose residue, following concentration, was crystallized using diethyl ether). According to the ^{1}H NMR spectrum and MS, the substance contains approximately 5-10 % of its ethyl ester.

The isomeric 2-carboxy-3-methoxypyridine-5-carboxylic acid glycylamide was obtained in an analogous manner, m.p. from 65°C (sintering from 45°C, with foaming, from diethyl ether, hygroscopic).

Example 81
5-Methoxycarbonyl-3-methoxypyridine-2-carboxylic acid glycylamide

a) 5-Methoxycarbonylpyridine-2-carboxylic acid 1-oxide

12 g (60 mmol) of dimethyl pyridine-2,5-dicarboxylate were suspended in 30 ml of glacial acetic acid, and after that 13 ml of hydrogen peroxide (35 %) were added at 20°C and while stirring. The mixture was then heated to 100°C (internal temperature), while stirring, with a clear solution being formed at 50°C. After the mixture had been stirred at 100°C for 90 minutes, it was allowed to cool down to 20°C and the crystalline precipitate was filtered off with suction and washed with water; After drying, 7.5 g of product were obtained, m.p. 160°C (decomp.).

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b) Dimethyl 3-chloropyridine-2,5-dicarboxylate

17 ml of thionyl chloride, 35 ml of anhydrous chloroform and 1.5 ml of N,N-dimethylformamide were heated to 60°C, while stirring, and 7.5 g of the above product were then added in portions at this temperature. The mixture was then stirred at 60°C for a further 60 minutes, and, after cooling, the solvent and excess reagent were distilled off in vacuo; dichloromethane was added to the residue, and the N,N-dimethylformamide x HCl complex was filtered off with suction and washed with dichloromethane. Approximately 15 ml of triethylamine and 10 ml of methanol were added, while cooling, to the mother liquor and the mixture was stirred for 30 minutes. After concentrating by evaporation in vacuo, the residue was dissolved in 50 ml of water and this mixture was then extracted 3 x with dichloromethane; the organic phase was dried and concentrated, and the residue was chromatographed on silica gel using n-heptane and n-heptane:ethyl acetate (3:1). 5.3 g of product were crystallized, using petroleum ether, from appropriate fractions, m.p. 36 to 38°C.

c) 3-Methoxypyridine-2,5-dicarboxylic acid

53 g (0.231 mol) of the above diester were dissolved in 500 ml of methanol, and after that 150 ml (0.81 mol) of sodium methoxide solution (30 % in methanol) were added, at 20°C and while stirring, whereupon the temperature rose to 30°C. The mixture was heated under reflux for 4.5 hours, 300 ml of water were added at 20°C, and the mixture was then stirred at 35°C for 30 minutes. The excess methanol was distilled off in vacuo and the aqueous phase was adjusted to pH 2, while cooling, with half-concentrated aqueous hydrochloric acid; the colorless crystalline product was filtered off with suction and dried. 49 g were obtained, m.p. 185°C (gas evolution); 255°C (decomp.).

d) Dimethyl 3-methoxypyridine-2,5-dicarboxylate, cf. Example 90a)

e) 5-Methoxycarbonyl-3-methoxypyridine-2-carboxylic acid

The compound was obtained, as a mixture with the isomeric monomethyl ester (cf. Example 90a)), from 3.4 g (15 mmol) of the above diester by hydrolysis with a dilute solution of methanolic sodium hydroxide (0.54 g of NaOH (13.5 mmol)). 1.8 g of monoester mixture, m.p. 152°C, were obtained in addition to 0.8 g of unreacted diester.

f) 5-Methoxycarbonyl-3-methoxypyridine-2-carboxylic acid (glycyl benzyl ester) amide

1.8 g of the above mixture were condensed, in analogy with Example 90b), with 2.9 g (8.6 mmol) of glycine benzyl ester tosylate in the presence of N-ethylmorpholine, 1-hydroxy-1H-benzotriazole and CMC. After working up, 2.3 g of oily mixture were chromatographed on silica gel using dichloromethane (in the presence of up to 2 % methanol). 0.82 g of product was obtained, m.p. 108°C. 0.6 g of the oily isomer was also isolated.

g) The title compound was obtained by dissolving 650 mg of the above benzyl ester in 100 ml of tetrahydrofuran/methanol (1:1) and hydrogenating it using Pd/C in a hydrogenation vessel. Once the catalyst had been filtered off with suction, the filtrate was concentrated and the residue was crystallized using diethyl ether. 380 mg were obtained of a colorless crystalline product, m.p. 158 to 160°C.

Example 82

5-(3-Pentyloxy)carbonyl-3-methoxypyridine-2-carboxylic acid glycylamide

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Example 83
5-Cyclohexyloxycarbonyl-3-methoxypyridine-2-carboxylic acid glycylamide

Example 84
5-(n-Butylaminocarbonyl)-3-methoxypyridine-2-carboxylic acid glycylamide

Example 85
5-(2-Methyl-2-butylaminocarbonyl)-3-methoxypyridine-2-carboxylic acid glycylamide

Example 86
5-(Cyclohexylaminocarbonyl)-3-methoxypyridine-2-carboxylic acid glycylamide

a) 5-(Cyclohexylaminocarbonyl)-3-methoxypyridine-2-carboxylic acid

The product was obtained, in analogy with Example 90b), from 5-carboxy-3-methoxypyridine-2-carboxylic acid and cyclohexylamine,
m.p. 155°C (sintering at 80°C, from aqueous hydrochloric acid).

b) 5-(Cyclohexylaminocarbonyl)-3-methoxypyridine-2-carboxylic acid (glycyl ethyl ester) amide

The product was obtained, in analogy with Example 90c), from the above compound, m.p. 187 to 188°C (from diethyl ether)

c) The colorless crystalline title compound was obtained by hydrolyzing the above compound in analogy with Example 90c),
m.p. 110°C (with foaming, a deep-black coloration at 240°C).

Example 87
5-(Cyclohexylaminocarbonyl)-3-ethyloxypyridine-2-carboxylic acid glycylamide

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Example 88

5-((2-Phenylethyl)aminocarbonyl)-3-methoxypyridine-2-carboxylic acid glycylamide

Example 89

5-((+)-Dehydroabietylaminocarbonyl)-3-methoxypyridine-2-carboxylic acid glycylamide

a) 5-((+)-Dehydroabietylaminocarbonyl)-3-methoxypyridine-2-carboxylic acid

The resinous product was obtained, in analogy with Example 90a), from 5-carboxy-3-methoxypyridine-2-carboxylic acid and (+)-dehydroabietylamine.

b) 5-((+)-Dehydroabietylaminocarbonyl)-3-methoxypyridine-2-carboxylic acid (glycyl ethyl ester) amide

The product was obtained in analogy with Example 90c), from the above compound, m.p. from 150°C with foaming, sintering at 120°C, from diethyl ether).

c) The title compound was obtained by hydrolyzing the above compound in analogy with Example 90 d), m.p. 215°C (sintering at 150°C, from aqueous hydrochloric acid).

Example 90

5-((2-(4-Fluorophenyl)ethyl)aminocarbonyl)-3-methoxypyridine-2-carboxylic acid glycylamide

a) Methyl 5-carboxy-3-methoxypyridine-2-carboxylate

10 g (50.7 mmol) of the 3-methoxypyridine-2,5-dicarboxylic acid (Example 81c) were suspended in 150 ml of anhydrous methanol, and after that 2 ml of concentrated sulfuric acid were added and the mixture was heated under reflux for 3 hours. Half of the methanol was then distilled off in vacuo and the residue was introduced

into 400 ml of ice water; the crystalline residue was filtered off with suction and washed with water; the residue was dissolved in 150 ml of a saturated, aqueous solution of Na bicarbonate and this mixture was extracted twice with 80 ml of dichloromethane on each occasion; the bicarbonate phase was adjusted to pH 1, while cooling, with half-concentrated aqueous hydrochloric acid and the precipitated product was filtered off with suction and dried. 5 g of colorless, crystalline substance were obtained, m.p. 196 to 197°C. 1.7 g of dimethyl ester, m.p. 53 to 55°C (from petroleum ether), were obtained from the dichloromethane phase.

b) 5-({(2-(4-Fluorophenyl)ethyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid

3.2 g of methyl 5-carboxy-3-methoxypyridine-2-carboxylate were suspended in 300 ml of anhydrous dichloromethane, and after that 2.0 ml (15 mmol) of 2-(4-fluorophenyl)-ethylamine, 1.95 ml (15 mmol) of N-ethylmorpholine, 2.2 g (16.5 mmol) of 1-hydroxy-1H-benzotriazole and 6.35 g (15 mmol) of N-cyclohexyl-N'-(2-morpholinoethyl)carbodiimide methyl-p-toluenesulfonate (CMC) were added sequentially, at 20°C and while stirring, and the mixture was stirred for 24 hours. The undissolved material was then filtered off and the organic phase was extracted, in each case 3 x, with an aqueous solution of Na bicarbonate, with 1N aqueous hydrochloric acid and with water, and the organic phase was dried and concentrated. 3.7 g were obtained of methyl ester, m.p. 168 to 169°C, which was introduced into 150 ml of 1.5N methanolic NaOH. After 30 minutes, the mixture was concentrated and dissolved in 100 ml of water, and this mixture was adjusted to pH 1 with conc. aqueous hydrochloric acid; the crystalline precipitate was filtered off with suction, washed with water and dried. 3.4 g of product were obtained, m.p. 110°C (with foaming, sintering at 75°C).

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c) 5-(((2-(4-Fluorophenyl)ethyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid (glycyl ethyl ester) amide

In analogy with Example 90a), 3.2 g (10 mmol) of the above compound were reacted with 1.4 g (10 mmol) of glycine ethyl ester hydrochloride, N-ethylmorpholine, 1-hydroxy-1H-benzotriazole and CMC. Following analogous working up, 2.8 g of the colorless crystalline product were crystallized using diisopropyl ether, m.p. 170 to 171°C.

d) The title compound was obtained by hydrolysing 1.0 g of the above glycine ethyl ester, at 20°C, in 1.5N methanolic NaOH. 0.95 g of product, m.p. 206°C (with foaming) crystallizes from aqueous medium at pH 3.

Example 91
5-((2-(4-Methoxyphenyl)ethyl)aminocarbonyl)-3-ethyloxy-pyridine-2-carboxylic acid glycylamide

Examples 92 to 105 were obtained from the correspondingly substituted pyridine-2-carboxylic acid derivatives of the formula II and glycine ethyl ester hydrochloride and with subsequent hydrolysis of the glycine ethyl ester compounds.

Example 92
5-Chloro-3-ethyloxypyridine-2-carboxylic acid glycylamide

Example 93
5-Chloro-3-methyloxypyridine-2-carboxylic acid glycylamide

Example 94
5-Cyclohexyloxymethyl-3-methoxypyridine-2-carboxylic acid glycylamide

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Example 95
5-(3-Methylbutyl)oxymethyl-3-methoxypyridine-2-carboxylic acid glycylamide

Example 96
5-Benzyloxymethyl-3-ethyloxypyridine-2-carboxylic acid glycylamide

Example 97
3-((Cyclohexyl)methyloxy)pyridine-2-carboxylic acid glycylamide

Example 98
3-((2-Cyclohexyl)ethyloxy)pyridine-2-carboxylic acid glycylamide

Example 99
3-((3-Cyclohexyl)propyloxy)pyridine-2-carboxylic acid glycylamide

Example 100
3-(3-Methylbutyloxy)pyridine-2-carboxylic acid glycylamide

Example 101
3-Hexyloxypyridine-2-carboxylic acid glycylamide

Example 102
3-(4-Ethylbenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 103
3-(4-Propylbenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 104
3-(4-Butylbenzyloxy)pyridine-2-carboxylic acid glycylamide

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Example 105
3-(4-tert-Butylbenzyloxy)pyridine-2-carboxylic acid glycylamide

Examples 106 to 188 were prepared in analogy with Examples 80 to 91.

Example 106
5-Methoxycarbonyl-3-(2-methyl-1-propyloxy)pyridine-2-carboxylic acid glycylamide

a) 3-(2-Methyl-1-propyloxy)pyridine-2,5-dicarboxylic acid

In analogy with Example 81c), 3.5 g (146 mmol) of sodium were dissolved in 350 ml of 2-methyl-1-propanol (isobutyl alcohol), and after that 13.7 g (55 mmol) of 3-chloropyridine-2-carboxylic acid ethyl ester 5-carboxylic acid methyl ester (prepared in analogy with Example 81b)) were added at 20°C and while stirring. The mixture was then stirred at 80°C for 90 minutes and, after cooling, concentrated in vacuo; the residue was taken up in 200 ml of 1 N methanolic NaOH and this mixture was stirred at 20°C. After 15 minutes, the solution became cloudy. Water was added until a clear solution was obtained and this was stirred for 1 hour and then concentrated in vacuo; the aqueous solution was acidified with aqueous hydrochloric acid and the crystalline product was filtered off with suction, washed and dried, and 10.6 g of dicarboxylic acid were obtained, m.p. 192°C (decomp.).

b) Dimethyl 3-(2-methyl-1-propyloxy)pyridine-2,5-dicarboxylate

The oily product was obtained from the above dicarboxylic acid under esterification conditions (methanol/sulfuric acid) and after working up (washing with water and extracting with ethyl acetate).

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c) 5-Methoxycarbonyl-3-(2-methyl-1-propyloxy)pyridine-2-carboxylic acid (glycyl benzyl ester) amide

0.48 g (12 mmol) of NaOH, dissolved in 50 ml of methanol, was added to 3.2 g (12 mmol) of the above diester in 25 ml of methanol, and the mixture was stirred at 65°C for 90 minutes. The mixture was then acidified, while being cooled, with dilute aqueous hydrochloric acid and freed from methanol in vacuo. 2.5 g (10 mmol) of the monoester mixture thus obtained were stirred, in analogy with Example 90b), in 250 ml of dichloromethane, at 20°C for 24 hours, together with 3.4 g (10 mmol) of glycine benzyl ester tosylate, 1.4 g (10 mmol) of 1-hydroxy-(1H)-benzotriazole, 2.6 ml (20 mmol) of N-ethylmorpholine and 4.3 g (10 mmol) of CMC.
The undissolved material was then filtered off with suction and the filtrate was extracted with an aqueous solution of Na bicarbonate, with dilute hydrochloric acid and with water; the organic phase was dried and concentrated and the residue was chromatographed on silica gel using n-heptane/ethyl acetate (1:1). 0.8 g of colorless product was obtained from appropriate fractions, m.p. 103 to 105°C. 1.1 g of the isomeric resinous product were also obtained.

d) The title compound was obtained by dissolving 0.7 g of the above compound in 100 ml of tetrahydrofuran/methanol (1:1) and hydrogenating it for 2 hours using Pd on charcoal (10 %) in a hydrogenation vessel. The catalyst was then filtered off with suction and the filtrate was concentrated; the residue was crystallized using diisopropylether and 0.45 g was obtained of the title compound,
m.p. approximately 70°C (with foaming).

The isomeric compound was obtained in an analogous manner, m.p. approximately 60°C (with foaming, from diisopropyl ether).

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Example 107
5-Ethoxycarbonyl-3-(2-methyl-1-propyloxy)pyridine-2-carboxylic acid glycylamide

Example 108
5-Methoxycarbonyl-3-(3-methyl-1-butyloxy)pyridine-2-carboxylic acid glycylamide

Example 109
5-Ethoxycarbonyl-3-ethoxypyridine-2-carboxylic acid glycylamide

Example 110
5-Ethoxycarbonyl-3-(1-propyloxy)pyridine-2-carboxylic acid glycylamide

Example 111
5-Ethoxycarbonyl-3-(2-propyloxy)pyridine-2-carboxylic acid glycylamide

Example 112
3-Benzyloxy-5-ethoxycarbonylpyridine-2-carboxylic acid glycylamide

Example 113
3-(4-Chlorobenzyloxy)-5-ethoxycarbonylpyridine-2-carboxylic acid glycylamide

Example 114
5-Ethoxycarbonyl-3-(4-fluorobenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 115
5-Ethoxycarbonyl-3-(4-(trifluoromethyl)-benzyloxy)pyridine-2-carboxylic acid glycylamide

Example 116
5-Ethoxycarbonyl-3-(4-(trifluoromethoxy)benzyloxy)-pyridine-2-carboxylic acid glycylamide

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Example 117
5-Ethoxycarbonyl-3-(4-(2-propyl)benzyloxy)pyridine-2-carboxylic acid glycylamide

Example 118
3-(4-Ethoxybenzyloxy)-5-ethoxycarbonylpyridine-2-carboxylic acid glycylamide

Example 119
5-Ethoxycarbonyl-3-(3,4-dimethoxybenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 120
5-Ethoxycarbonyl-3-(2-(4-fluorophenyl)ethyloxy)pyridine-2-carboxylic acid glycylamide

Example 121
5-Ethoxycarbonyl-3-(2,2,2-trifluoroethyloxy)pyridine-2-carboxylic acid glycylamide

Example 122
3-Cyclohexyloxy-5-ethoxycarbonylpyridine-2-carboxylic acid glycylamide

Example 123
5-Ethoxycarbonyl-3-(naphthyl-2-methyloxy)pyridine-2-carboxylic acid glycylamide

Example 124
5-Ethoxycarbonyl-3-(naphthyl-1-methyloxy)pyridine-2-carboxylic acid glycylamide

Example 125
5-Carboxy-3-(2-methyl-1-propyloxy)pyridine-2-carboxylic acid glycylamide

The title compound was obtained by hydrolyzing 0.3 g of the title compound from Example 106, at 20°C, in 50 ml of a 1N methanolic solution of sodium hydroxide. After 1 hour, the mixture was concentrated in vacuo and

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extracted with diethyl ether; the aqueous phase was acidified, while being cooled, with aqueous hydrochloric acid; the aqueous phase was concentrated and then freed from water azeotropically using ethyl acetate and the residue was treated with acetone; the solution was concentrated and the residue was crystallized using petroleum ether. 0.27 g of product was obtained, m.p. 80°C (with foaming).

Example 126
5-Carboxy-3-(3-methyl-1-butyloxy)pyridine-2-carboxylic acid glycylamide

Example 127
5-Carboxy-3-ethoxypyridine-2-carboxylic acid glycylamide

Example 128
5-Carboxy-3-propyloxypyridine-2-carboxylic acid glycylamide

Example 129
5-Carboxy-3-(2-propyloxy)pyridine-2-carboxylic acid glycylamide

Example 130
3-Benzyloxy-5-carboxypyridine-2-carboxylic acid glycylamide

Example 131
5-Carboxy-3-(4-chlorobenzyloxy)-2-carboxylic acid glycylamide

Example 132
5-Carboxy-3-(4-fluorobenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 133
5-Carboxy-3-((4-trifluoromethyl)benzyloxy)pyridine-2-carboxylic acid glycylamide

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Example 134
5-Carboxy-3-((4-trifluoromethoxy)benzyloxy)pyridine-2-carboxylic acid glycylamide

Example 135
5-Carboxy-3-(4-(2-propyl)benzyloxy)pyridine-2-carboxylic acid glycylamide

Example 136
5-Carboxy-3-(4-ethoxybenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 137
5-Carboxy-3-(3,4-dimethoxybenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 138
5-Carboxy-3-(2-(4-fluorophenyl)ethyloxy)pyridine-2-carboxylic acid glycylamide

Example 139
5-Carboxy-3-(2,2,2-trifluoroethyloxy)pyridine-2-carboxylic acid gylcylamide

Example 140
5-Carboxy-3-cyclohexyloxypyridine-2-carboxylic acid glycylamide

Example 141
5-Carboxy-3-(naphthyl-2-methyloxy)pyridine-2-carboxylic acid glycylamide

Example 142
5-Carboxy-3-(naphthyl-1-methyloxy)pyridine-2-carboxylic acid glycylamide

Example 143
5-(3-Pentyloxy)carbonyl-3-(2-methyl-1-propyloxy)pyridine-2-carboxylic acid glycylamide

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Example 144
5-(3-Pentyloxy)carbonyl-3-(3-methyl-1-butyloxy)pyridine-2-carboxylic acid glycylamide

Example 145
3-Ethoxypyridine-5-(3-pentyloxy)carbonyl-2-carboxylic acid glycylamide

Example 146
5-(3-Pentyloxy)carbonyl-3-propyloxypyridine-2-carboxylic acid glycylamide

Example 147
5-(3-Pentyloxy)carbonyl-3-(2-propyloxy)pyridine-2-carboxylic acid glycylamide

Example 148
3-Benzyloxy-5-(3-pentyloxy)carbonylpyridine-2-carboxylic acid glycylamide

Example 149
3-(4-Chlorobenzyloxy)-5-(3-pentyloxy)carbonylpyridine-2-carboxylic acid glycylamide

Example 150
3-(4-Fluorobenzyloxy)-5-(3-pentyloxy)carbonylpyridine-2-carboxylic acid glycylamide

Example 151
5-(3-Pentyloxy)carbonyl-3-((4-trifluoromethyl)benzyloxy)-pyridine-2-carboxylic acid glycylamide

Example 152
5-(3-Pentyloxy)carbonyl-3-((4-trifluoromethoxy)benzyloxy)pyridine-2-carboxylic acid glycylamide

Example 153
5-(3-Pentyloxy)carbonyl-3-(4-(2-propyl)benzyloxy)-pyridine-2-carboxylic acid glycylamide

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Example 154
3-(4-Ethoxybenzyloxy)-5-(3-pentyloxy)carbonylpyridine-2-carboxylic acid glycylamide

Example 155
3-(3,4-Dimethoxybenzyloxy)-5-(3-pentyloxy)carbonyl-pyridine-2-carboxylic acid glycylamide

Example 156
3-(2-(4-Fluorophenyl)ethyloxy)-5-(3-pentyloxy)carbonyl-pyridine-2-carboxylic acid glycylamide

Example 157
5-(3-Pentyloxy)carbonyl-3-(2,2,2-trifluoroethyloxy)-pyridine-2-carboxylic acid glycylamide

Example 158
3-Cyclohexyloxy-5-(3-pentyloxy)carbonylpyridine-2-carboxylic acid glycylamide

Example 159
3-(Naphthyl-2-methyloxy)-5-(3-pentyloxy)carbonylpyridine-2-carboxylic acid glycylamide

Example 160
3-(Naphthyl-1-methyloxy)-5-(3-pentyloxy)carbonylpyridine-2-carboxylic acid glycylamide

Example 161
5-(4-Heptyloxy)carbonyl-3-(2-methyl-1-propyloxy)pyridine-2-carboxylic acid glycylamide

Example 162
5-(4-Heptyloxy)carbonyl-3-ethoxypyridine-2-carboxylic acid glycylamide

Example 163
3-Benzyloxy-5-(4-heptyloxy)carbonylpyridine-2-carboxylic acid glycylamide

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Example 164
3-(4-Chlorobenzyloxy)-5-(4-heptyloxy)carbonylpyridine-2-carboxylic acid glycylamide

Example 165
3-(4-Fluorobenzyloxy)-5-(4-heptyloxy)pyridine-2-carboxylic acid glycylamide

Example 166
5-(4-Heptyloxy)carbonyl-3-(4-(2-propyl)benzyloxy)-pyridine-2-carboxylic acid glycylamide

Example 167
3-(2-Methyl-1-propyloxy)-5-(5-nonyloxy)carbonylpyridine-2-carboxylic acid glycylamide

Example 168
3-Benzyloxy-5-(5-nonyloxy)carbonyl)pyridine-2-carboxylic acid glycylamide

Example 169
3-(4-Fluorobenzyloxy)-5-(5-nonyloxy)carbonylpyridine-2-carboxylic acid glycylamide

Example 170
5-(5-Nonyloxy)carbonyl-3-(4-(2-propyl)benzyloxy)pyridine-2-carboxylic acid glycylamide

Example 171
5-Geranyloxycarbonyl-3-ethoxypyridine-2-carboxylic acid glycylamide

Example 172
3-Benzyloxy-5-(geranyloxycarbonyl)pyridine-2-carboxylic acid glycylamide

Example 173
3-(4-Chlorobenzyloxy)-5-(geranyloxycarbonyl)pyridine-2-carboxylic acid glycylamide

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Example 174
3-(4-Fluorobenzyloxy)-5-(geranyloxycarbonyl)pyridine-2-carboxylic acid glycylamide

Example 175
5-Geranyloxycarbonyl-3-(2-propyloxy)pyridine-2-carboxylic acid glycylamide

Example 176
5-Farnesyloxycarbonyl-3-(2-propyloxy)pyridine-2-carboxylic acid glycylamide

Example 177
3-Benzyloxy-5-(farnesyloxycarbonyl)pyridine-2-carboxylic acid glycylamide

Example 178

5-Farnesyloxycarbonyl-3-(4-fluorobenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 179
5-Farnesyloxycarbonyl-3-ethoxypyridine-2-carboxylic acid glycylamide

Example 180
3-Methoxy-5-(retinyloxycarbonyl)pyridine-2-carboxylic acid glycylamide

Example 181
3-Ethoxy-5-(retinyloxycarbonyl)pyridine-2-carboxylic acid glycylamide

Example 182
3-(2-Propyloxy)-5-(retinyloxycarbonyl)pyridine-2-carboxylic acid glycylamide

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Example 183
3-Benzyloxy-5-(retinyloxycarbonyl)pyridine-2-carboxylic acid glycylamide

Example 184
3-(4-Fluorobenzyloxy)-5-(retinyloxycarbonyl)pyridine-2-carboxylic acid glycylamide

Example 185
3-(3-Methoxybenzyloxy)-5-(retinyloxycarbonyl)pyridine-2-carboxylic acid glycylamide

Example 186
5-Benzyloxycarbonyl-3-(4-(2-propyloxy)benzyloxy)pyridine-2-carboxylic acid glycylamide

Example 187
5-Benzyloxycarbonyl-3-(4-fluorobenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 188
5-Butyloxycarbonyl-3-benzyloxypyridine-2-carboxylic acid glycylamide

Example 189
5-(((4-Ethoxyphenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid glycylamide, analogously to Example 191

Example 190
5-(((4-Ethoxyphenyl)amino)carbonyl)-3-benzyloxypyridine-2-carboxylic acid glycylamide

Example 191
5-(((4-(1-Butyloxy)phenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid glycylamide

a) Methyl 5-(((4-(1-butyloxy)phenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylate

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3.2 g (15 mmol) of methyl 5-carboxy-3-methoxypyridine-2-carboxylate (cf. Example 90a)) were reacted, in analogy with Example 90b), with 2.5 g (15 mmol) of 4-n-butoxyaniline and the reagents described in that example. 3.9 g of product were crystallized using diethyl ether (m.p. 138 to 141°C.

b) 5-(((4-(1-Butyloxy)phenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid

3.2 g of the above ester were hydrolyzed at 20°C using 100 ml of 1.5 N methanolic sodium hydroxide solution. 2.7 g of product were obtained from aqueous hydrochloric acid, m.p. 128 to 130°C, sintering from 120°C.

c) 5-(((4-(1-Butyloxy)phenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid N-((ethoxycarbonyl)-methyl) amide

2.7 g (7.8 mmol) of the above pyridine-2-carboxylic acid were stirred in 500 ml of anhydrous dichloromethane, at 20°C for 24 h, together with 1.1 g (7.8 mmol) of glycine ethyl ester hydrochloride, 3.0 ml (23.4 mmol) of N-ethylmorpholine, 1.2 g (8.6 mmol) of 1-hydroxy-1H-benzotriazole and 3.3 g (7.8 mmol) of CMC.

The undissolved material was then filtered off and the organic phase was extracted sequentially with 200 ml each of water, aqueous Na bicarbonate solution, 1N aqueous hydrochloric acid and water, dried over Mg sulfate and concentrated in vacuo; the residue was crystallized using diethyl ether. 2.4 g of product were obtained, m.p. 193-195°C.

d) The title compound was obtained by hydrolyzing 1.0 g of the above glycine ester, at 20°C, in 100 ml of a 1.5 N methanolic solution of sodium hydroxide. After 30 min, the mixture was concentrated in vacuo and the residue was dissolved in water; this solution was extracted with

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diethyl ether and the aqueous solution adjusted to pH 3 using aqueous hydrochloric acid. When the solution was cooled with ice, 390 mg of the title compound crystallized, m.p. 230°C, sintering at 193°C.

Example 192
5-(((4-(1-Butyloxy)phenyl)amino)carbonyl)-3-(4-fluorobenzyloxy)pyridine-2-carboxylic acid glycylamide

Example 193
5-(((4-(1-Butyloxy)phenyl)amino)carbonyl)-3-benzyloxypyridine-3-carboxylic acid glycylamide

Example 194
3-(2-Methyl-1-propyloxy)pyridine-2,5-dicarboxylic acid diglycylamide
M.p. 103-105°C (from ethyl acetate)

Example 195
5-(Di-N,N-ethylaminocarbonyl)-3-ethoxypyridine-2-carboxylic acid glycylamide, amorphous substance, prepared in analogy with Example 223 using N,N-diethylamine.

Example 196
5-(N-Benzyl-N-methylaminocarbonyl)-3-methoxypyridine-2-carboxylic acid glycylamide

Example 197
5-Farnesyloxycarbonyl-3-methoxypyridine-2-carboxylic acid glycylamide

Example 198
5-Geranyloxycarbonyl-3-methoxypyridine-2-carboxylic acid glycylamide

Example 199
5-(Farnesyloxymethyl)-3-methoxypyridine-2-carboxylic acid glycylamide

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Example 200
5-(Geranyloxymethyl)-3-methoxypyridine-2-carboxylic acid glycylamide

Example 201
5-Retinyloxymethyl-3-methoxypyridine-2-carboxylic acid glycylamide

Example 202
5-Retinyloxymethyl-3-ethyloxypyridine-2-carboxylic acid glycylamide

Example 203
N-(Carboxymethyl)-4-methoxycinnoline-3-carboxamide

Examples 204 to 209 were prepared in analogy with Example 191:

Example 204
5-(((4-(1-Hexyloxy)phenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

a) Methyl 5-(((4-(1-hexyloxy)phenyl)amino)carbonyl)-3-methoxy-2-carboxylate was prepared from methyl 5-carboxy-3-methoxypyridine-2-carboxylate and 4-hexyloxyaniline, m.p. 118-119°C (from diethyl ether).

b) 5-(((4-(1-Hexyloxy)phenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid, 160-162°C, sintering at 148°C (from aqueous hydrochloric acid/tetrahydrofuran)

c) 5-(((4-(1-Hexyloxy)phenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid N-((ethoxycarbonyl)-methyl)amide was obtained, in analogy with Example 191c), from 4.2 g of the above compound. 4.0 g of product were crystallized using ethyl acetate, m.p. 157-159°C.

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d) The title compound was obtained by hydrolyzing 1.2 g of the above ester, at 20°C, using 100 ml of a 1.5N methanolic solution of sodium hydroxide. Following concentration in vacuo, acidification to pH 1 took place in water/tetrahydrofuran using aqueous hydrochloric acid; the mixture was concentrated in vacuo and the residue was crystallized using acetone. 840 mg of product were obtained, m.p. 193-195°C.

Example 205

5-(((4-(1-Decyloxy)phenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 206

5-(((4-(1-Decyl)phenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

a) 5-(((4-(1-Decyl)phenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid N-((ethoxycarbonyl)-methyl)amide was prepared from 5-(((4-n-decylphenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid (m.p. 160°C (decomp.); from aqueous hydrochloric acid/THF) and glycine ethyl ester hydrochloride, m.p. 155-157°C (from diisopropyl ether).

b) The title compound was obtained by hydrolyzing 1.5 g of the above ester in 200 ml of a 1 N methanolic solution of sodium hydroxide. 1.4 g of product, m.p. 195°C (decomp.), were isolated from aqueous hydrochloric acid/tetrahydrofuran.

Example 207

5-(((4-Geranyloxyphenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

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Example 208
5-(((4-(1-Octyloxy)phenyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 209
5-(((3-(1-Octyloxy)propyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 210
5-((1-Butoxy)methyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 211
5-((1-Hexyloxy)methyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 212
5-((1-Octyloxy)methyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 213
5-((1-Hex-3-enyloxy)methyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 214
5-((1-Decyloxy)methyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 215
5-((1-Dodecyloxy)methyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 216
5-((1-Hexadecyloxy)methyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 217
3-(4-(((+)-Dehydroabietylamino)carbonyl)benzyloxy)pyridine-2-carboxylic acid N-(carboxymethyl)amide

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a) 4-(((+)-Dehydroabietylamino)carbonyl)chloromethylbenzene was obtained from 4-chloromethylbenzoic acid and (+)-dehydroabietylamine, m.p. 170-172°C (from ethyl acetate/heptane (1:1)).

b) 3-(4-(((+)-Dehydroabietylamino)carbonyl)benzyloxy)-pyridine-2-carboxylic acid N-((ethyloxycarbonyl)-methyl)amide, m.p. approximately 80°C (amorphous substance, from ethyl acetate).

c) The title compound was obtained by hydrolyzing the above ester, m.p. 125°C (with foaming, from diisopropyl ether).

Example 218

3-Methoxyquinoline-2-carboxylic acid N-(carboxymethyl)-amide

a) 2-Acetyl-3-hydroxyquinoline, known from D.W. Bayne et al., J. Chem. Soc. Chem. Comm. 1975, 782 (M.p. 106°C from aqueous hydrochloric acid).

b) 2-Acetyl-3-methoxyquinoline, from a) using potassium carbonate/methyl iodide in acetone, oily crude product.

c) 3-Methoxyquinoline-2-carboxylic acid, from b) using potassium hypochlorite in water/dioxane, m.p. 123°C (from methyl tert-butyl ether).

d) 3-Methoxyquinoline-2-carboxylic acid N-((methoxycarbonyl)methyl)amide, from c) using DCC, HOBT, THF, NEM and glycine methyl ester hydrochloride.

e) The title compound was obtained by hydrolyzing the above ester, m.p. 106°C (from ethyl acetate).

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Example 219

5-(((4-(1-Butyloxy)phenyl)amino)carbonyl)-3-chloropyridine-2-carboxylic acid N-(carboxymethyl)amide

a) Methyl 5-carboxy-3-chloropyridine-2-carboxylate was prepared in analogy with Example 90a), m.p. 182-184°C (from aqueous hydrochloric acid).

b) Methyl 5-(((1-butyloxy)phenyl)amino)carbonyl)-3-chloropyridine-2-carboxylate was obtained from the above compound using oxalyl chloride and 4-(1-butyloxy)aniline, m.p. 121-123°C (from diethyl ether).

c) 5-(((4-(1-Butyloxy)phenyl)amino)carbonyl)-3-chloropyridine-2-carboxylic acid by hydrolyzing the product from b), m.p. 163-164°C (from aqueous hydrochloric acid).

d) 5-(((4-(1-Butyloxy)phenyl)amino)carbonyl)-3-chloropyridine-2-carboxylic acid N-((ethyloxycarbonyl)-methyl)amide was obtained, in analogy with Example 90b), from the above substance by condensation (N-ethylmorpholine, 1-hydroxy-1H-benzotriazole and CMC) with glycine ethyl ester hydrochloride, m.p. 177-179°C (from ethanol).

e) The title compound was obtained by hydrolyzing the above ester, m.p. 190°C (with decomposition, from aqueous hydrochloric acid).

Example 220

3-(N-Benzyl-N-methylamino)-5-(((4-(1-butyloxy)phenyl)-amino)carbonyl)pyridine-2-carboxylic acid N-(carboxy-methyl)amide

0.5 g (1.23 mmol) of the title compound from Example 219 was stirred in 10 ml of N-benzyl-N-methylamine, firstly at 100-110°C for 2 h and then at 130°C for a further 2 h. After the mixture had been cooled down, it was introduced

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into 100 ml of 1N hydrochloric acid and the half-crystalline precipitate was taken up in dichloromethane; the undissolved material was filtered off and the residue was crystallized; 0.2 g of the title compound, m.p. 155-157°C.

Example 221

3-(N-Benzylamino)-5-(((4-(1-butyloxy)phenyl)amino)carbonyl)pyridine-2-carboxylic acid N-(carboxymethyl)amide

0.5 g (1.23 mmol) of the title compound from Example 219 was stirred in 10 ml of benzylamine, firstly at 120°C for 2 h and then at 135°C for 1.5 h. After the mixture had been cooled down, it was acidified and the precipitated resin was dissolved in dichloromethane; this solution was dried and concentrated and the residue was chromatographed on silica gel using ethyl acetate (with the addition of up to 20 % methanol). 0.1 g of the title compound was crystallized from appropriate fractions using diisopropyl ether, m.p. 185-190°C.

Example 222

3-(4-Chlorobenzyloxy)pyridine-2-carboxylic acid N-(carboxymethyl)amide 1-oxide

a) 3-(4-Chlorobenzyloxy)pyridine-2-carboxylic acid N-((ethyloxy)methyl)amide 1-oxide

0.7 g (2 mmol) of the compound from Example 31c) was dissolved in dichloromethane and reacted with 1.41 g of 3-chloroperbenzoic acid. After the mixture had been stirred at 20°C for 1 h, ammonia was passed in until there was no further precipitation; the precipitate was filtered off and the filtrate was concentrated and the oily residue crystallized using diethyl ether, m.p. 70-72°C.

b) 0.18 g of the title compound, m.p. 206-208°C

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(sintering at 200°C, from aqueous hydrochloric acid) was obtained by hydrolyzing 0.3 g of the above compound.

Example 223

5-(((3-(1-Butyloxy)propyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

a) Methyl 5-(((3-(1-butyloxy)propyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid

1.7 ml of oxalyl chloride (20 mmol), and also 2 drops of N,N-dimethylformamide, dissolved in tetrahydrofuran, were added dropwise, at 10°C and while stirring, to 2.1 g (10 mmol) of methyl 5-carboxy-3-methoxypyridine-2-carboxylate in 100 ml of anhydrous tetrahydrofuran and the reaction mixture was stirred at 10°C for 30 min and at 20°C for 1 h. It was then concentrated and the residue was dissolved in dichloromethane; 6.8 ml (50 mmol) of triethylamine, and then 1.3 g (1.5 ml, 10 mmol) of 3-butoxypropylamine, dissolved in dichloromethane, were added, at 0°C, to this solution.
After 30 min, the mixture was allowed to warm to room temperature and was extracted with water, a solution of Na bicarbonate and aqueous 1N HCl; the organic phase was dried and concentrated and the residue was crystallized using diethylether/petroleum ether (3:1). 2.3 g of product were obtained, m.p. 51-53°C.

b) 5-(((3-(1-Butyloxy)propyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid N-((benzyloxycarbonyl)methyl)amide

The above substance was hydrolyzed by standard procedures, and 1.5 g (5 mmol) of the amorphous 5-(((3-(1-butyloxy)propyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid, which was dried on an oil pump, was reacted with glycine benzyl ester tosylate,

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N-ethylmorpholine, 1-hydroxy-1H-benzotriazole and CMC (as described). 1.42 g of the product were crystallized using acetone, m.p. 97-99°C.

c) 1.3 g of the above benzyl ester were hydrogenated in 100 ml of tetrahydrofuran/methanol (1:1) using Pd/C (10 %) in a hydrogenation vessel. 0.8 g of the title compound was crystallized using diethyl ether, m.p. 155-157°C.

Example 224

5-(((3-(1-Lauryloxy)propyl)amino)carbonyl)-3-methoxy-pyridine-2-carboxylic acid N-(carboxymethyl)amide

a) 5-(((3-Lauryloxypropyl)amino)carbonyl)-3-methoxy-pyridine-2-carboxylic acid N-((benzyloxycarbonyl)-methyl)amide was obtained, in analogy with Example 223, using 3-lauryloxypropylamine, m.p. from 109-111°C (from diisopropyl ether).

b) 1.3 g of the above benzyl ester were hydrogenated as described under 223c). 0.9 g of the title compound were obtained from petroleum ether, m.p. from 120°C.

Example 225

5-(((2-Methoxyethyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

The title compound was prepared in analogy with Example 223 using 2-methoxyethylamine.

a) 5-(((2-Methoxyethyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid, m.p. 160-161°C (with gas evolution, from ethyl acetate)

b) 5-(((2-Methoxyethyl)amino)carbonyl)-3-methoxypyridine-2-carboxylic acid N-((benzyloxycarbonyl)-methyl)amide was crystallized using diisopropyl ether, m.p. 129-131°C.

c) The title compound was obtained, as above, from the benzyl ester, m.p. 186-188°C (from diethyl ether).

Example 226

N-(3-Benzyloxypyridyl-2-carbonyl)alanine racemate, M.p. 186-187°C (from pentane/ethyl acetate)

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Example 227

N-(3-Benzyloxypyridyl-2-carbonyl)-L-phenylalanine, M.p. 100-101°C (from pentane/ethyl acetate).

Example 228

5-((1-Butyloxy)carbonyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide trifluoroacetate

a) Di-(1-butyl) 3-methoxypyridine-2,5-dicarboxylate

5.0 g of dimethyl 3-methoxypyridine-2,5-dicarboxylate (cf. Example 90a)) were dissolved in 100 ml of 1-butanol, and after that 1.5 ml of conc. sulfuric were added and the mixture was heated to boiling for 2 h, with a part of the solvent being distilled off. After the mixture had been cooled, it was concentrated in vacuo and the residue was taken up in dichloromethane; this solution was extracted with a saturated, aqueous solution of Na bicarbonate and the organic phase was dried and concentrated. 6 g of oily crude product.

b) Bis[5-((1-butyloxy)carbonyl)-3-methoxypyridine-2-carboxylic acid]-Cu(II) complex

6 g (20 mmol) of the above product were added, dissolved in 10 ml of methanol, to a solution of 4.8 g (20 mmol) of Cu(II) nitrate x 3 H_2O in 100 ml of methanol, and the mixture was heated to boiling for 4 h. It was then cooled down to 0-5°C and the crystalline precipitate was filtered off with suction and washed with diethyl ether. 4.2 g of blue-green, crystalline product were obtained, m.p. 267°C (with decomposition).

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c) 5-((1-Butyloxy)carbonyl)-3-methoxypyridine-2-carboxylic acid

4 g of the above Cu complex were suspended in 75 ml of 1,4-dioxane. H_2S gas was passed in, while the mixture was being stirred, for 30 min, and the sediment (CuS) which had precipitated out was filtered off with suction through kieselguhr and then washed with 1,4-dioxane (continued introduction of H_2S did not lead to any further precipitation); the filtrate was concentrated in vacuo. The residue was crystallized using petroleum ether, m.p. 96-98°C.

d) 5-((1-Butyloxy)carbonyl)-3-methoxypyridine-2-carboxylic acid N-((tert-butyloxycarbonyl)-methyl)amide

0.76 g (3 mmol) of the above pyridinecarboxylic acid was condensed with 0.52 g (3 mmol) of glycine tert-butyl ester hydrochloride, 1.2 ml (9 mmol) of N-ethylmorpholine, 0.45 g (3.3 mmol) of 1-hydroxy-(1H)-benzotriazole and 1.3 g (3 mmol) of CMC. 0.8 g of product was obtained, m.p. 50-52°C (from petroleum ether).

e) The title compound was obtained by adding 2.7 ml of trifluoroacetic acid, at 20°C, to 0.4 g of the above tert-butyl ester in dichloromethane. After 20 h, the mixture was concentrated in vacuo and 0.2 g was obtained of the colorless, crystalline, strongly hygroscopic product, which, on being filtered off with suction, deliquesced on the suction filter.

Example 229

5-Ethyloxycarbonyl-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 230

3-Methoxy-5-((1-propyloxy)carbonyl)pyridine-2-carboxylic acid N-(carboxymethyl)amide

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Example 231
5-((1-Hexyloxy)carbonyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 232
3-Methoxy-5-((1-pentyloxy)carbonyl)pyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 233
5-((1-Heptyloxy)carbonyl)-3-methoxypyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 234
3-Methoxy-5-((1-octyloxy)carbonyl)pyridine-2-carboxylic acid N-(carboxymethyl)amide

Examples 235-238 were prepared in an analogous manner to Example 228 proceeding from 3-(2-propyloxy)pyridine-2,5-dicarboxylic acid or the corresponding dialkyl esters.

Example 235
5-Ethyloxycarbonyl-3-(2-propyloxy)pyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 236
5-((1-Butyloxy)carbonyl)-3-(2-propyloxy)pyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 237
5-((1-Hexyloxy)carbonyl)-3-(2-propyloxy)pyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 238
5-((-1-Octyloxy)carbonyl)-3-(2-propyloxy)pyridine-2-carboxylic acid N-(carboxymethyl)amide

Example 239
5-Carboxy-3-(methylthio)pyridine-2-carboxylic acid N-(carboxymethyl)amide disodium salt

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a) 3-(Methylthio)pyridine-2,5-dicarboxylic acid

4.6 g (12 mmol) of dibenzyl 3-chloropyridine-2,5-dicarboxylate were dissolved, at 20°C and while stirring, in 30 ml of dimethyl sulfoxide, and after that 5.0 g (70 mmol) of sodium thiomethoxide were added, in association with which the temperature rose to 80°C. The reaction mixture was heated at 140°C for 1 h and then cooled down; water was added and the oily layer was separated off; conc. hydrochloric acid (pH 1) was added to the aqueous DMSO phase and the precipitated product was filtered off with suction. 2.8 g were obtained of a yellow crystalline product, m.p. 223°C (with decomposition).

b) Dimethyl 3-(methylthio)pyridine-2,5-dicarboxylate

50 ml of 1,4-dioxane, 40 ml of tetrahydrofuran and 0.5 ml of conc. sulfuric acid were added to 2.8 g of the above compound in 150 ml of methanol, and the mixture was heated to reflux for 2 h, during which time a solution was formed. After the solution had been cooled down, it was concentrated in vacuo and 100 ml of an aqueous solution of Na bicarbonate were added to the residue; the latter mixture was extracted with dichloromethane and the organic phase was dried and concentrated. 1.4 g were obtained of the yellow, crystalline product, m.p. 103-105°C.

c) 5-Methoxycarbonyl-3-(methylthio)pyridine-2-carboxylic acid-Cu(II) complex

1.3 g of the above dimethyl 3-methylthiopyridine-2,5-dicarboxylate were reacted in analogy with Example 228b). 1.3 g of greenish/crystalline product were obtained, m.p. > 330°C.

d) 5-Methoxy-3-(methylthio)pyridine-2-carboxylic acid

1.3 g of the above compound were reacted in analogy with Example 228c), 0.72 g of product, m.p. 183-185°C.

e) 5-Methoxycarbonyl-3-(methylthio)pyridine-2-carboxylic acid N-((1-butyloxy)carbonyl)methyl)amide

The compound was obtained by condensing 0.68 g (3 mmol) of the above pyridinecarboxylic acid with 0.91 g (3 mmol) of glycine 1-butyl ester tosylate (1-hydroxy-1H-benzotriazole, N-ethylmorpholine and CMC). 0.55 g of pale yellow product was obtained, m.p. 47-49°C (from petroleum ether).

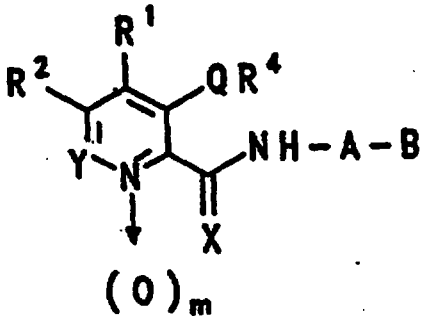
f) The title compound was obtained by hydrolysing 0.45 g (1.3 mmol) of the above ester using 50 ml of 1 N methanolic NaOH. The clear yellow solution became cloudy after 30 min. After 2 h, the precipitate was filtered off with suction, washed twice with methanol and dried in vacuo. 0.32 g of the title compound was obtained, m.p. 345°C (decomp.).

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* C L M S *

Patent claims:

1. A compound of the formula I



(I),

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in which

Q is O, S, NR′ or a bond,

X is O or S,

Y is C-R^3 or,
if R^1 and R^2 form a cycle,
Y is N or CR^3,

m is 0 or 1,

A is (C_1-C_4)-alkylene, which is optionally substituted by one or two substituents from the group halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy, $-O-[CH_2]_x-C_zH_{(2z+1-g)}Hal_g$, preferably ($C_1$-$C_6$)-fluoroalkoxy, ($C_1$-$C_6$)-fluoroalkenyloxy, ($C_1$-$C_6$)-fluoroalkynyloxy, $-OCF_2Cl$ or $-O-CF_2-CHFCl$, (C_1-C_6)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_6)-cycloalkyl, phenyl, benzyl, phenoxy, benzyloxy, anilino, N-methylanilino, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl or N,N-di-(C_1-C_4)-alkylsulfamoyl, or
by a substituted (C_6-C_{12})-aryloxy, (C_7-C_{11})-aralkyloxy, (C_6-C_{12})-aryl or (C_7-C_{11})-aralkyl radical which carries in the aryl moiety 1, 2, 3, 4 or 5 identical or different substituents from the

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group halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, $-O-[CH_2]_x-C_gH_{(2g+1-s)}Hal_s$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, (C_1-C_6)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl or N,N-di-(C_1-C_6)-alkylsulfamoyl, or

by the substituents R^5 of the α-carbon atom of an α-amino acid, it being possible to use the natural L-amino acids and their D-isomers;

B is an acid grouping from the group $-CO_2H$, $-CONHCOR''$, $-CONHSOR''$, $CONHSO_2R''$, $-NHSO_2CF_3$, tetrazolyl, imidazolyl or 3-hydroxyisoxazolyl, where R'' is aryl, heteroaryl, (C_3-C_7)-cycloalkyl or (C_1-C_4)-aklyl, optionally monosubstituted by (C_6-C_{12})-aryl, heteroaryl, OH, SH, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, (C_1-C_4)-thioalkyl, (C_1-C_4)-sulfinyl, (C_1-C_4)-sulfonyl, CF_3, Cl, Br, F, I, NO_2, -COOH, (C_2-C_5)-alkoxycarbonyl, NH_2, mono-(C_1-C_4)-alkyl)-amino, di-$(C_1-C_4$-alkyl)-amino or (C_1-C_4)-perfluoroalkyl,

R^1, R^2 and R^3 are identical or different and are hydrogen, hydroxyl, halogen, cyano, trifluoromethyl, nitro, carboxyl, (C_1-C_{20})-alkyl, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl-(C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyloxy-(C_2-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkoxy, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_7-C_{16})-aralkenyl, (C_7-C_{16})-aralkynyl, (C_2-C_{20})-alkenyl,

(C_2-C_{20})-alkynyl, (C_1-C_{20})-alkoxy, (C_2-C_{20})-alkenyloxy, (C_2-C_{20})-alkynyloxy, retinyloxy, (C_1-C_{20})-alkoxy-(C_1-C_{12})-alkyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxy, (C_1-C_{16})-hydroxyalkyl, (C_6-C_{16})-aryloxy-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_7-C_{12})-aralkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_2-C_{20})-alkenyloxy-(C_1-C_6)-alkyl, (C_2-C_{20})-alkynyloxy-(C_1-C_6)-alkyl, retinyloxy-(C_1-C_6)-alkyl, $-O-[CH_2-]_x-C_zH_{(2z+1-g)}F_g$, $-OCF_2Cl$, $-OCF_2-CHFCl$,

(C_1-C_{20})-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, (C_6-C_{12})-arylcarbonyl, (C_7-C_{16})-aralkylcarbonyl, cinnamoyl, (C_2-C_{20})-alkenylcarbonyl, (C_2-C_{20})-alkynylcarbonyl,

(C_1-C_{20})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{20})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_2-C_{20})-alkynyloxycarbonyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxycarbonyl, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxycarbonyl,

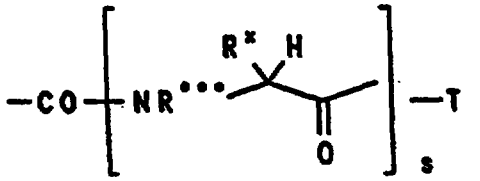
(C_1-C_{12})-alkylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_7-C_{16})-aralkylcarbonyloxy, cinnamoyloxy, (C_2-C_{12})-alkenylcarbonyloxy, (C_2-C_{12})-alkynylcarbonyloxy,

(C_1-C_{12})-alkoxycarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{16})-aralkyloxycarbonyloxy, (C_3-C_8)-cycloalkoxycarbonyloxy, (C_2-C_{12})-alkenyloxycarbonyloxy, (C_2-C_{12})-alkynyloxycarbonyloxy,

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carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-dicyclo-(C_3-C_8)-alkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N-((C_2-C_{10})-alkoxy-(C_1-C_{10})alkyl)carbamoyl, N-((C_6-C_{16})-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, or $CON(CH_2)_h$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7,

a carbamoyl radical of the formula II



(II),

in which

R^x is the substituent of an α-amino acid to which the L- and D-amino acids belong,

s is 1, 2, 3, 4 or 5, and

T is OH, OR or NR^*R^{**}, where

R^*, R^{**} and R^{***} are identical or different and are hydrogen, (C_6-C_{12})-aryl, (C_7-C_{11})-aralkyl,

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(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyl, (+)-dehydroabietyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkyl, (C_1-C_{10})-alkanoyl, optionally substituted (C_7-C_{16})-aralkanoyl or optionally substituted (C_6-C_{12})-aroyl, or

R^* and R^{**} together are $-[CH_2]_h-$, in which a CH_2 group can be replaced by O, S, SO, SO_2, N-acylamino, N-(C_1-C_{10})-alkoxycarbonylimino, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7,

carbamoyloxy, N-(C_1-C_{12})-alkylcarbamoyloxy, N,N-di-(C_1-C_{12})-alkylcarbamoyloxy, N-(C_3-C_8)-cycloalkylcarbamoyloxy, N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_7-C_{16})-aralkylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyloxy, N-(((C_1-C_{10})-alkyl)carbamoyloxy, N-(((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-(((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-(((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-(((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy,

amino, (C_1-C_{12})-alkylamino, di-(C_1-C_{12})-alkylamino, (C_3-C_8)-cycloalkylamino, (C_3-C_{12})-alkenylamino, (C_3-C_{12})-alkynylamino, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_1-C_{12})-alkoxyamino, (C_1-C_{12})-alkoxy-N-(C_1-C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino, (C_3-C_8)-cycloalkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{16})-aralkanoylamino, $(C_1-$

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C_{12})-alkanoyl-N-(C_1-C_{10})-alkylamino, (C_3-C_8)-cycloalkanoyl-N-(C_1-C_{10})-alkylamino, (C_6-C_{12})-aroyl-N-(C_1-C_{10})-alkylamino, (C_7-C_{11})-aralkanoyl-N-(C_1-C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkanoylamino-(C_1-C_8)-alkyl, (C_6-C_{12})-aroylamino-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkanoylamino-(C_1-C_8)-alkyl, amino-(C_1-C_{10})-alkyl, N-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, N,N-di(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, (C_3-C_8)-cycloalkylamino-(C_1-C_{10})-alkyl, (C_1-C_{20})-alkylmercapto, (C_1-C_{20})-alkylsulfinyl, (C_1-C_{20})-alkylsulfonyl, (C_6-C_{12})-arylmercapto, (C_6-C_{12})-arylsulfinyl, (C_6-C_{12})-arylsulfonyl, (C_7-C_{16})-aralkylmercapto, (C_7-C_{16})-aralkylsulfinyl, (C_7-C_{16})-aralkylsulfonyl, (C_1-C_{12})-alkylmercapto-(C_1-C_6)-alkyl, (C_1-C_{12})-alkylsulfinyl-(C_1-C_6)-alkyl, (C_1-C_{12})-alkylsulfonyl-(C_1-C_6)-alkyl, (C_6-C_{12})-arylmercapto-(C_1-C_6)-alkyl, (C_6-C_{12})-arylsulfinyl-(C_1-C_6)-alkyl, (C_6-C_{12})-arylsulfonyl-(C_1-C_6)-alkyl, (C_7-C_{16})-aralkylmercapto-(C_1-C_6)-alkyl, (C_7-C_{16})-aralkylsulfinyl-(C_1-C_6)-alkyl, (C_7-C_{16})-aralkylsulfonyl-(C_1-C_6)-alkyl,

sulfamoyl, N-(C_1-C_{10})-alkylsulfamoyl, N,N-di-(C_1-C_{10})-alkylsulfamoyl, (C_3-C_8)-cycloalkylsulfamoyl,
N-(C_6-C_{12})-arylsulfamoyl,
N-(C_7-C_{16})-aralkylsulfamoyl,
N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylsulfamoyl,
N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylsulfamoyl,
(C_1-C_{10})-alkylsulfonamido,
N-((C_1-C_{10})-alkyl)-(C_1-C_{10})-alkylsulfonamido, (C_7-C_{16})-aralkylsulfonamido or N-((C_1-C_{10})-alkyl-(C_7-C_{16})-aralkylsulfonamido,
where the radicals which contain an aryl radical can, for their part, be substituted on the aryl by from 1 to 5 identical or different radicals from the group:
hydroxyl, halogen, cyano, trifluoromethyl, nitro,

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carboxyl, (C_1-C_{16})-alkyl, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl-(C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkoxy, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_2-C_{16})-alkenyl, (C_2-C_{12})-alkynyl, (C_1-C_{16})-alkoxy, (C_1-C_{16})-alkenyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxy, (C_1-C_8)-hydroxyalkyl, (C_6-C_{16})-aryloxy-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_7-C_{12})-aralkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, $-O-[CH_2]_x-C_zH_{(2z+1-g)}F_g$, $-OCF_2Cl$, $-OCF_2-CHFCl$,

(C_1-C_{12})-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, (C_6-C_{12})-arylcarbonyl, (C_7-C_{16})-aralkylcarbonyl,

(C_1-C_{12})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{12})-alkenyloxycarbonyl, (C_2-C_{12})-alkynyloxycarbonyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxycarbonyl, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxycarbonyl,

(C_1-C_{12})-alkylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_7-C_{16})-aralkylcarbonyloxy, cinnamoyloxy, (C_2-C_{12})-alkenylcarbonyloxy, (C_2-C_{12})-alkynylcarbonyloxy,

(C_1-C_{12})-alkoxycarbonyloxy, (C_1-C_{12})-alkoxy-

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(C_1-C_{12})-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{16})-aralkyloxycarbonyloxy, (C_3-C_8)-cycloalkoxycarbonyloxy, (C_2-C_{12})-alkenyloxycarbonyloxy, (C_2-C_{12})-alkynyloxycarbonyloxy,

carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-dicyclo-(C_3-C_8)-alkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N-((C_1-C_{16})-alkoxy-(C_1-C_{10})-alkyl)-carbamoyl, N-((C_6-C_{16})-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, $CON(CH_2)_h$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7,

carbamoyloxy, N-(C_1-C_{12})-alkylcarbamoyloxy, N,N-di-(C_1-C_{12})-alkylcarbamoyloxy, N-(C_3-C_8)-cycloalkylcarbamoyloxy, N-(C_6-C_{16})-arylcarbamoyloxy, N-(C_7-C_{16})-aralkylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyloxy, N-((C_1-C_{10})-alkyl)carbamoyloxy, N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)-carbamoyloxy, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)-

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carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy,

amino, (C_1-C_{12})-alkylamino, di-(C_1-C_{12})-alkylamino, (C_3-C_8)-cycloalkylamino, (C_3-C_{12})-alkenylamino, (C_3-C_{12})-alkynylamino, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_1-C_{12})-alkoxyamino, (C_1-C_{12})-alkoxy-N-(C_1-C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino, (C_3-C_8)-cycloalkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{16})-aralkanoylamino, (C_1-C_{12})-alkanoyl-N-(C_1-C_{10})-alkylamino, (C_3-C_8)-cycloalkanoyl-N-(C_1-C_{10})-alkylamino, (C_6-C_{12})-aroyl-N-(C_1-C_{10})-alkylamino, (C_7-C_{11})-aralkanoyl-N-(C_1-C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkanoylamino-(C_1-C_8)-alkyl, (C_6-C_{12})-aroylamino-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkanoylamino-(C_1-C_8)-alkyl, amino-(C_1-C_{10})-alkyl, N-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, N,N-di-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, (C_3-C_8)-cycloalkylamino-(C_1-C_{10})-alkyl,

(C_1-C_{12})-alkylmercapto, (C_1-C_{12})-alkylsulfinyl, (C_1-C_{12})-alkylsulfonyl, (C_6-C_{16})-arylmercapto, (C_6-C_{16})-arylsulfinyl, (C_6-C_{16})-arylsulfonyl, (C_7-C_{16})-aralkylmercapto, (C_7-C_{16})-aralkylsulfinyl or (C_7-C_{16})-aralkylsulfonyl,

R^1 and R^2 or R^2 and R^3 form a chain $[CH_2]_o$ in which one or two CH_2 groups of the chain, which is saturated or unsaturated by a C=C double bond, are optionally replaced by O, S, SO, SO_2 or NR', and o is 3, 4 or 5, and

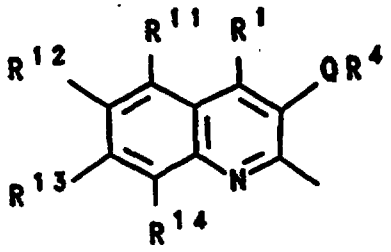
R' is hydrogen, (C_6-C_{12})-aryl, (C_1-C_8)-alkyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkyl, (C_1-C_{10})-alkanoyl, optionally substituted (C_7-C_{16})-aralkanoyl or optionally substituted (C_6-C_{12})-aroyl, where

the radicals R^1 and R^2 or R^2 and R^3, together with the pyridine or pyridazine carrying them, preferably form a 5, 6, 7, 8-tetrahydroisoquinoline ring, a 5, 6, 7, 8-tetrahydroquinoline ring or a 5, 6, 7, 8-tetrahydrocinnoline ring,
or
R^1 and R^2 or R^2 and R^3 form a carbocyclic or a heterocyclic, 5- or 6-membered aromatic ring, where

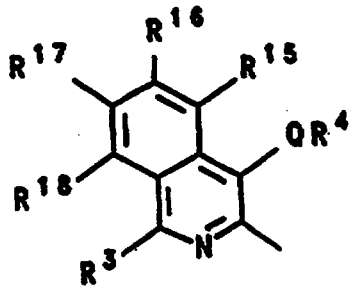
the radicals R^1 and R^2 or R^2 and R^3, together with the pyridine or pyridazine carrying them, preferably form the following optionally substituted heterocyclic ring systems:

Thienopyridines,
Furanopyridines,
Pyridopyridines,
Pyrimidinopyridines,
Imidazopyridines,
Thiazolopyridines,
Oxazolopyridines,
Quinoline, isoquinoline and
Cinnoline,
where quinoline, isoquinoline or cinnoline preferably satisfy the formulae 1a, 1b and 1c

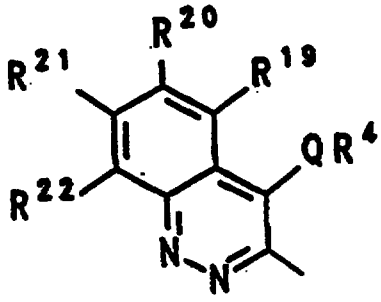
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1a



1b



1c

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and the substituents R^{11} to R^{22}, in each case independently of each other, have the meaning of R^1, R^2 and R^3,

R^4 is, if Q is a bond, halogen, nitrile or trifluoromethyl, or, if Q is O, S or NR', a branched or unbranched (C_1-C_{20})-alkyl radical, an unsubstituted, saturated fluoroalkyl radical of the formula $[CH_2]_x-C_zH_{(2z+1-g)}F_g$, a (C_6-C_{16})-aryl radical, a (C_7-C_{16})-aralkyl radical, a heteroaryl radical or a heteroaralkyl radical,

where these radicals are substituted by one or more radicals from the group
hydroxyl, halogen, cyano, trifluoromethyl, nitro, carboxyl, (C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyl,

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(C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl-(C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkoxy, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_2-C_{12})-alkenyl, (C_2-C_{12})-alkynyl, (C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxy, (C_1-C_8)-hydroxyalkyl, (C_6-C_{16})-aryloxy-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_7-C_{12})-aralkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, $-O-[CH_2-]_x-C_zH_{(2z+1-g)}F_g$, $-OCF_2Cl$, $-OCF_2-CHFCl$,

(C_1-C_{12})-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, (C_6-C_{12})-arylcarbonyl, (C_7-C_{16})-aralkylcarbonyl, cinnamoyl, (C_2-C_{12})-alkenylcarbonyl, (C_2-C_{12})-alkynylcarbonyl,

(C_1-C_{12})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{12})-alkenyloxycarbonyl, (C_2-C_{12})-alkynyloxycarbonyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxycarbonyl, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxycarbonyl,

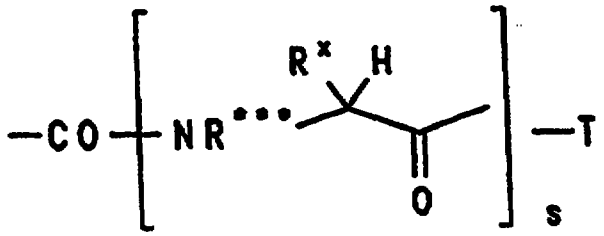
(C_1-C_{12})-alkylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_7-C_{16})-aralkylcarbonyloxy, cinnamoyloxy, (C_2-C_{12})-alkenylcarbonyloxy, (C_2-C_{12})-alkynylcarbonyloxy,

(C_1-C_{12})-alkoxycarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-

alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{16})-aralkyloxycarbonyloxy, (C_3-C_8)-cycloalkoxycarbonyloxy, (C_2-C_{12})-alkenyloxycarbonyloxy, (C_2-C_{12})-alkynyloxycarbonyloxy,

carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-dicyclo-(C_3-C_8)-alkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C_6-C_{16})-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, $CON(CH_2)_h$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7, or by

a carbamoyl radical of the formula II



(II),

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in which

R^x is the substituent of an α-amino acid to which the L- and D-amino acids belong,

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s is 1, 2, 3, 4 or 5, and
T is OH, OR or NR^*R^{**}, where

R^*, R^{**}, and R^{***} are identical or different and are hydrogen, (C_6-C_{12})-aryl, (C_7-C_{11})-aralkyl, (C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyl, (+)-dehydroabietyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkyl, (C_1-C_{10})-alkanoyl, optionally substituted (C_7-C_{16})-aralkanoyl or optionally substituted (C_6-C_{12})-aroyl, or

R^* and R^{**} together are $-[CH_2]_h-$, in which a CH_2 group can be replaced by O, S, SO, SO_2, N-acylamino, N-(C_1-C_{10})-alkoxycarbonylimino, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7, or by

carbamoyloxy, N-(C_1-C_{12})-alkylcarbamoyloxy, N,N-di-(C_1-C_{12})-alkylcarbamoyloxy, N-(C_3-C_8)-cycloalkyl-carbamoyloxy, N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_7-C_{16})-aralkylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkyl-carbamoyloxy, N-$((C_1-C_{10})$-alkyl)carbamoyloxy, N-$((C_6-C_{12})$-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-$((C_7-C_{16})$-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-$((C_1-C_{10})$-alkoxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-$((C_6-C_{12})$-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-$((C_7-C_{16})$-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy,

amino, (C_1-C_{12})-alkylamino, di-(C_1-C_{12})-alkylamino, (C_3-C_8)-cycloalkylamino, (C_3-C_{12})-alkenylamino, (C_3-C_{12})-alkynylamino, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_1-C_{12})-alkoxyamino, (C_1-C_{12})-alkoxy-N-(C_1-C_{10})-alkylamino,

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(C_1-C_{12})-alkanoylamino, (C_3-C_8)-cycloalkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{16})-aralkanoylamino, (C_1-C_{12})-alkanoyl-N-(C_1-C_{10})-alkylamino, (C_3-C_8)-cycloalkanoyl-N-(C_1-C_{10})-alkylamino, (C_6-C_{12})-aroyl-N-(C_1-C_{10})-alkylamino, (C_7-C_{11})-aralkanoyl-N-(C_1-C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkanoylamino-(C_1-C_8)-alkyl, (C_6-C_{12})-aroylamino-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkanoylamino-(C_1-C_8)-alkyl, amino-(C_1-C_{10})-alkyl, N-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, N,N-di(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, (C_3-C_8)-cycloalkylamino-(C_1-C_{10})-alkyl,

(C_1-C_{12})-alkylmercapto, (C_1-C_{12})-alkylsulfinyl, (C_1-C_{12})-alkylsulfonyl, (C_6-C_{12})-arylmercapto, (C_6-C_2)-arylsulfinyl, (C_6-C_{12})-arylsulfonyl, (C_7-C_{16})-aralkylmercapto, (C_7-C_{16})-aralkylsulfinyl, (C_7-C_{16})-aralkylsulfonyl,

sulfamoyl, N-(C_1-C_{10})-alkylsulfamoyl, N,N-di-(C_1-C_{10})-alkylsulfamoyl, (C_3-C_8)-cycloalkylsulfamoyl,
N-(C_6-C_{12})-arylsulfamoyl,
N-(C_7-C_{16})-aralkylsulfamoyl,
N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylsulfamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylsulfamoyl,
(C_1-C_{10})-alkylsulfonamido,
N-$((C_1-C_{10})$-alkyl$)-(C_1-C_{10})$-alkylsulfonamido, (C_7-C_{16})-aralkylsulfonamido or N-(C_1-C_{10})-alkyl-(C_7-C_{16})-aralkylsulfonamido, where the radicals which contain an aryl radical can, for their part, be substituted on the aryl by from 1 to 5 identical or different radicals from the group:
hydroxyl, halogen, cyano, trifluoromethyl, nitro, carboxyl, (C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl-(C_1-C_8)-

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alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkoxy, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_2-C_{12})-alkenyl, (C_2-C_{12})-alkynyl, (C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxy, (C_1-C_8)-hydroxyalkyl, (C_6-C_{16})-aryloxy-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, (C_7-C_{12})-aralkyloxy-(C_1-C_8)-alkoxy-(C_1-C_6)-alkyl, $-O-[CH_2-]_z-C_vH_{(2v+1-g)}F_g$, $-OCF_2Cl$, $-OCF_2-CHFCl$,

(C_1-C_{12})-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, (C_6-C_{12})-arylcarbonyl, (C_7-C_{16})-aralkylcarbonyl,

(C_1-C_{12})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{12})-alkenyloxycarbonyl, (C_2-C_{12})-alkynyloxycarbonyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxycarbonyl, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxycarbonyl,

(C_1-C_{12})-alkylcarbonyloxy, (C_3-C_8)-cycloalkyl-carbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_7-C_{16})-aralkylcarbonyloxy, cinnamoyloxy, (C_2-C_{12})-alkenylcarbonyloxy, (C_2-C_{12})-alkynylcarbonyloxy,

(C_1-C_{12})-alkoxycarbonyloxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyloxy, (C_6-C_{12})-aryloxycarbonyloxy, (C_7-C_{16})-aralkyloxycarbonyloxy, (C_3-C_8)-cycloalkoxy-carbonyloxy, (C_2-C_{12})-alkenyloxycarbonyloxy, (C_2-C_{12})-alkynyloxycarbonyloxy,

carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-

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dicyclo-(C_3-C_8)-alkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)-carbamoyl, N-((C_6-C_{16})-aryloxy-(C_1-C_{10})-alkyl)-carbamoyl, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, $CON(CH_2)_h$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_6)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7,

carbamoyloxy, N-(C_1-C_{12})-alkylcarbamoyloxy, N,N-di-(C_1-C_{12})-alkylcarbamoyloxy, N-(C_3-C_8)-cycloalkylcarbamoyloxy, N-(C_6-C_{16})-arylcarbamoyloxy, N-(C_7-C_{16})-aralkylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_6-C_{12})-arylcarbamoyloxy, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyloxy, N-((C_1-C_{10})-alkyl)carbamoyloxy, N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)-carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyloxy, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyloxy,

amino, (C_1-C_{12})-alkylamino, di-(C_1-C_{12})-alkylamino, (C_3-C_8)-cycloalkylamino, (C_3-C_{12})-alkenylamino, (C_3-C_{12})-alkynylamino, N-(C_6-C_{12})-arylamino, N-(C_7-C_{11})-aralkylamino, N-alkyl-aralkylamino, N-alkyl-arylamino, (C_1-C_{12})-alkoxyamino, (C_1-C_{12})-alkoxy-N-(C_1-

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C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino, (C_3-C_8)-cycloalkanoylamino, (C_6-C_{12})-aroylamino, (C_7-C_{16})-aralkanoylamino, (C_1-C_{12})-alkanoyl-N-(C_1-C_{10})-alkylamino, (C_3-C_8)-cycloalkanoyl-N-(C_1-C_{10})-alkylamino, (C_6-C_{12})-aroyl-N-(C_1-C_{10})-alkylamino, (C_7-C_{11})-aralkanoyl-N-(C_1-C_{10})-alkylamino,

(C_1-C_{12})-alkanoylamino-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkanoylamino-(C_1-C_8)-alkyl, (C_6-C_{12})-aroylamino-(C_1-C_8)-alkyl, (C_7-C_{16})-aralkanoylamino-(C_1-C_8)-alkyl, amino-(C_1-C_{10})-alkyl, N-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, N,N-di-(C_1-C_{10})-alkylamino-(C_1-C_{10})-alkyl, (C_3-C_8)-cycloalkylamino-(C_1-C_{10})-alkyl,

(C_1-C_{12})-alkylmercapto, (C_1-C_{12})-alkylsulfinyl, (C_1-C_{12})-alkylsulfonyl, (C_6-C_{16})-arylmercapto, (C_6-C_{16})-arylsulfinyl, (C_6-C_{16})-arylsulfonyl, (C_7-C_{16})-aralkylmercapto, (C_7-C_{16})-aralkylsulfinyl or (C_7-C_{16})-aralkylsulfonyl, and

R^4 is $R^{''}$, provided that Q has the meaning of NR', where R' and $R^{''}$ are identical or different and are hydrogen, (C_6-C_{12})-aryl, (C_7-C_{12})-aralkyl, (C_1-C_8)-alkyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkyl, (C_1-C_{10})-alkanoyl, optionally substituted (C_7-C_{16})-aralkanoyl or optionally substituted (C_6-C_{12})-aroyl, or

R' and $R^{''}$ together are $-[CH_2]_h-$, in which a CH_2 group can be replaced by O, S, N-acylimino or N-(C_1-C_{10})-alkoxycarbonylimino, and

f is 1 to 8,
g is 0 or 1 to (2f+1),
x is 0 to 3,
h is 3 to 7,

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including the physiologically active salts, with 3-benzyloxypyridine-2-carboxylic acid (L-threonyl)amide and 3-benzyloxypyridine-2-carboxylic acid ((Fmoc-Phg)L-threonyl)amide hydrochloride being excepted.

2. A compound of the formula I as claimed in claim 1, in which
Q is O, S, NR' or a bond,
X is O,
Y is CR^3, or,
if R^1 and R^2 form a cycle,
Y is N or CR^3,
m is 0 or 1.

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3. A compound of the formula I as claimed in claims 1 and 2,
in which
Q is O, NR' or a bond, and
X is O.

4. A compound of the formula I as claimed in claims 1 and 2, in which
Q is S, and
X is O, and
m is 0 or 1.

5. A compound of the formula I as claimed in claims 1, 2 and 4, in which
Q is S,
X is O, and
m is 0.

6. A compound of the formula I as claimed in claims 1 to 3, in which
Q is O, NR' or a bond,
X is O,
Y is CR^3 or, if R^1 and R^2 form a cycle, N or CR^3,
m is 0 or 1,

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A is (C_1-C_3)-alkylene which is optionally substituted once by halogen, cyano, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy or $-O-[CH_2]_x-C_zH_{(2z+1-g)}F_g$, or

A is $-CHR^3-$, where R^3 is one of the substituents of the α-carbon atom of an α-amino acid, in particular of a natural L-amino acid and of its D-isomer,

B is CO_2H,

R^2 is hydrogen, (C_1-C_{20})-alkyl, (C_2-C_{20})-alkenyl, (C_2-C_{20})-alkynyl, (C_1-C_{20})-alkoxy, (C_2-C_{20})-alkenyloxy, (C_2-C_{20})-alkynyloxy, retinyloxy, (C_1-C_{20})-alkoxy-(C_1-C_3)-alkyl, (C_2-C_{20})-alkenyloxy-(C_1-C_3)-alkyl, retinyloxy-(C_1-C_3)-alkyl, (C_2-C_{20})-alkynyloxy-(C_1-C_3)-alkyl, halogen, cyano, trifluoromethyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_{20})-alkanoyl, (C_7-C_{16})-aralkanoyl, (C_6-C_{12})-aroyl, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, $-O-[CH_2]_x-C_zH_{(2z+1-g)}F_g$, $NR'R''$, (C_1-C_{20})-alkylmercapto, (C_1-C_{20})-alkylsulfinyl, (C_1-C_{20})-alkylsulfonyl, (C_6-C_{12})-arylmercapto, (C_6-C_{12})-arylsulfinyl, (C_6-C_{12})-arylsulfonyl, (C_7-C_{12})-aralkylmercapto, (C_7-C_{12})-aralkylsulfinyl, (C_7-C_{12})-aralkylsulfonyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, carboxyl, (C_1-C_{20})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{20})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_2-C_{20})-alkynyloxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxycarbonyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxycarbonyl, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxycarbonyl,

carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-dicyclo(C_3-C_8)-alkylcarbamoyl,

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N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N-((C_1-C_{12})-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C_6-C_{16})-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, $CON(CH_2)_h$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 7,

where aryl is substituted in the manner as defined for R^1 and R^3,

R^1 and R^2 are identical or different and are hydrogen, halogen, (C_1-C_{12})-alkyl, (C_1-C_{12})-alkoxy, -O-$[CH_2]_x$-$C_cH_{(2c+1-g)}Hal_g$, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkyl, (C_1-C_8)-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_8)-alkoxy-(C_2-C_6)-alkyl, (C_7-C_{11})-aralkyloxy, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyloxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkoxy, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_8)-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl-(C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, NR^yR^z, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl or (C_1-C_8)-alkylsulfonyl, (C_6-C_{12})-arylmercapto,

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$(C_6$-$C_{12})$-arylsulfinyl, $(C_6$-$C_{12})$-arylsulfonyl, $(C_7$-$C_{12})$-aralkylmercapto, $(C_7$-$C_{11})$-aralkylsulfinyl, $(C_7$-$C_{11})$-aralkylsulfonyl, substituted $(C_6$-$C_{12})$-aryloxy-$(C_1$-$C_6)$-alkyl, $(C_7$-$C_{11})$-aralkoxy-$(C_1$-$C_6)$-alkyl, $(C_6$-$C_{12})$-aryloxy-$(C_1$-$C_6)$-alkoxy-$(C_1$-$C_6)$-alkyl, $(C_7$-$C_{11})$-aralkyloxy-$(C_1$-$C_6)$-alkoxy-$(C_1$-$C_6)$-alkyl, $(C_6$-$C_{12})$-aryloxy, $(C_7$-$C_{11})$-aralkyloxy, $(C_6$-$C_{12})$-aryloxy-$(C_1$-$C_6)$-alkoxy or $(C_7$-$C_{11})$-aralkoxy-$(C_1$-$C_6)$-alkoxy, where an aromatic radical carries 1, 2, 3, 4 or 5 identical or different substituents from the group hydrogen, halogen, cyano, nitro, trifluoromethyl, $(C_1$-$C_{16})$-alkyl, $(C_1$-$C_{16})$-alkenyl, $(C_1$-$C_6)$-hydroxyalkyl, $(C_1$-$C_{16})$-alkoxy, $(C_1$-$C_{16})$-alkenyloxy, $-O-[CH_2]_x-C_zH_{(2z+1-g)}F_g$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, $(C_1$-$C_6)$-alkylmercapto, $(C_1$-$C_6)$-alkylsulfinyl, $(C_1$-$C_6)$-alkylsulfonyl, $(C_1$-$C_6)$-alkylcarbonyl, $(C_1$-$C_6)$-alkoxycarbonyl, carbamoyl, N-$(C_1$-$C_4)$-alkylcarbamoyl, N,N-di-$(C_1$-$C_4)$-alkylcarbamoyl, $(C_1$-$C_6)$-alkylcarbonyloxy, $(C_3$-$C_8)$-cycloalkylcarbamoyl, phenyl, benzyl, phenoxy, benzyloxy, NR^YR^Z, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-$(C_1$-$C_4)$-alkylsulfamoyl or N,N-di-$(C_1$-$C_4)$-alkylsulfamoyl, or optionally carries up to 3 of the abovementioned identical or different substituents, and two adjacent carbon atoms of the aralkyloxy radical together carry a chain $-[CH_2-]$ and/or $-CH=CH-CH=CH-$, where a CH_2 group of the chain is optionally replaced by O, S, SO, SO_2 or NR',

R^1 and R^2 or R^2 and R^3 form a chain $[CH_2]_o$, where o is 3, 4 or 5, or

form, together with the pyridine or pyridazine carrying them, a cinnoline ring, a quinoline ring or an isoquinoline ring,

R^4 is, if Q is a bond, fluorine, chlorine or bromine, or, if Q is O or NR', a branched or

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unbranched (C_1-C_{20})-alkyl radical, which can contain up to 3 C-C multiple bonds, an unsubstituted saturated fluoroalkyl radical of the formula $[CH_2]_x$-$C_zH_{(2z+1-y)}F_y$, a (C_6-C_{16})-aryl radical or a (C_7-C_{16})-aralkyl radical, which can contain up to 2 C-C multiple bonds in the alkyl chain, or a heteroaryl radical or a heteroaryl alkyl radical, where these radicals are substituted by one or more radicals from the group hydroxyl, fluorine, chlorine, cyano, trifluoromethyl, carboxyl, (C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyloxy-(C_1-C_{12})-alkoxy, (C_3-C_8)-cycloalkyl-(C_1-C_8)-alkyl-(C_1-C_6)-alkoxy, (C_3-C_8)-cycloalkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkoxy, (C_6-C_{12})-aryl, (C_7-C_{16})-aralkyl, (C_2-C_{12})-alkenyl, (C_2-C_{12})-alkynyl, (C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxy, (C_1-C_{12})-alkoxy-(C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxy, (C_1-C_8)-hydroxyalkyl, -O-$[CH_2]_x$-$C_zH_{(2z+1-y)}F_y$,

(C_1-C_{12})-alkylcarbonyl, (C_3-C_8)-cycloalkylcarbonyl, (C_6-C_{12})-arylcarbonyl, (C_7-C_{16})-aralkylcarbonyl,

(C_1-C_{12})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{12})-alkenyloxycarbonyl, (C_2-C_{12})-alkynyloxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl,

(C_1-C_{12})-alkylcarbonyloxy, (C_3-C_8)-cycloalkylcarbonyloxy, (C_6-C_{12})-arylcarbonyloxy, (C_7-C_{16})-aralkylcarbonyloxy,
carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkyl-

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carbamoyl, N,N-dicyclo-(C_3-C_8)-alkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{16})-aralkylcarbamoyl, N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C_6-C_{16})-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, $CON(CH_2)_h$ in which a CH_2 group can be replaced by O, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino or N-(C_7-C_{16})-aralkylimino, and h is from 3 to 6,

where the radicals which contain an aryl radical can, for their part, be substituted on the aryl by from 1 to 5 identical or different radicals from the group:

hydroxyl, fluorine, chlorine, cyano, trifluoromethyl, carboxyl, (C_1-C_{12})-alkyl, (C_3-C_8)-cycloalkyl, (C_1-C_8)-alkoxy, (C_3-C_8)-cycloalkoxy, (C_1-C_{12})-alkoxycarbonyl,

N-(C_1-C_6)-alkylcarbamoyl, N,N-di-(C_1-C_6)-alkylcarbamoyl or N-(C_3-C_8)-cycloalkylcarbamoyl, and

R^4 is R^*, provided Q has the meaning of NR', where R' and R^* are identical or different and are hydrogen, (C_1-C_8)-alkyl, or (C_7-C_{11})-aralkyl which is optionally substituted once by fluorine, chlorine or (C_1-C_4)-alkoxy,

R^Y and R^Z are identical or different and are hydrogen, (C_6-C_{12})-aryl, (C_1-C_{10})-alkyl, (C_3-C_{10})-

cycloalkyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkyl, (C_1-C_{10})-alkanoyl, optionally substituted (C_7-C_{16})-aralkanoyl or optionally substituted (C_6-C_{12})-aroyl, or

R^1 and R^2 together are $-[CH_2]_h-$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_4)-alkanoylimino or N-(C_1-C_4)-alkoxycarbonylimino, and

f is 1 to 8,
g is 0 or 1 to (2f + 1),
h is 3 to 6,
x is 0 to 3, and
n is 3 or 4, including the physiologically active salts, with 3-benzyloxypyridine-2-carboxylic acid (L-threonyl)amide and 3-benzyloxypyridine-2-carboxylic acid ((Fmoc-Phg)L-threonyl)amide hydrochloride being excepted.

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7. A compound of the formula I as claimed in claims 1 to 3 and 6, in which

Q is O, NR′ or a bond,
X is O,
Y is CR^3 or, if R^1 and R^2 form a cycle, N or CR^3,
m is 0,
A is (C_1-C_3)-alkylene which is optionally substituted once by halogen, cyano, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy or $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$ or

A is $-CHR^5-$, where R^5 is one of the substituents of the α-carbon atom of an α-amino acid, in particular of a natural L-amino acid and of its D-isomer,

B is CO_2H,

R^2 is hydrogen, (C_1-C_{20})-alkyl, (C_2-C_{20})-alkenyl,

(C_2-C_{20})-alkenyloxy, (C_2-C_{20})-alkynyloxy, retinyloxy, (C_1-C_{20})-alkoxy-(C_1-C_3)-alkyl, (C_1-C_{20})-alkoxy-(C_1-C_3)-alkyl, (C_2-C_{20})-alkenyloxy-(C_1-C_3)-alkyl, retinyloxy-(C_1-C_3)-alkyl, (C_2-C_{20})-alkynyloxy-(C_1-C_3)-alkyl, (C_1-C_{20})-alkoxy, halogen, cyano, trifluoromethyl, (C_1-C_{16})-hydroxyalkyl, (C_1-C_{20})-alkanoyl, (C_7-C_{12})-aralkanoyl, (C_6-C_{12})-aroyl, $-O-[CH_2]_x-C_yH_{(2y+1-g)}F_g$, $NR'R''$, (C_1-C_{10})-alkylmercapto, (C_1-C_{10})-alkylsulfinyl, (C_1-C_{10})-alkylsulfonyl, (C_6-C_{12})-arylmercapto, (C_6-C_{12})-arylsulfinyl), (C_6-C_{12})-arylsulfonyl, (C_7-C_{12})-aralkylmercapto, (C_7-C_{12})-aralkylsulfinyl, (C_7-C_{12})-aralkylsulfonyl, (C_6-C_{12})-aryloxy, (C_7-C_{16})-aralkyloxy, carboxyl, (C_1-C_{20})-alkoxycarbonyl, (C_1-C_{12})-alkoxy-(C_1-C_{12})-alkoxycarbonyl, (C_6-C_{12})-aryloxycarbonyl, (C_7-C_{16})-aralkoxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_2-C_{20})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_2-C_{20})-alkynyloxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxycarbonyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxycarbonyl, (C_7-C_{16})-aralkoxy-(C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_{12})-alkylcarbamoyl, N,N-di-(C_1-C_{12})-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N,N-dicyclo-(C_3-C_8)-alkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(C_1-C_6)-alkyl-N-((C_3-C_8)-cycloalkyl-(C_1-C_6)-alkyl)carbamoyl, N-(+)-dehydroabietylcarbamoyl, N-(C_1-C_6)-alkyl-N-(+)-dehydroabietylcarbamoyl, N-(C_6-C_{12})-arylcarbamoyl, N-(C_7-C_{16})-aralkylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_6-C_{16})-arylcarbamoyl, N-(C_1-C_{10})-alkyl-N-(C_7-C_{12})-aralkylcarbamoyl, N-((C_1-C_{12})-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C_6-C_{16})-aryloxy-(C_1-C_{10})-alkyl)carbamoyl, N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_1-C_{10})-alkoxy-(C_1-C_{10})-alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_6-C_{12})-aryloxy-(C_1-C_{10})-

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alkyl)carbamoyl, N-(C_1-C_{10})-alkyl-N-((C_7-C_{16})-aralkyloxy-(C_1-C_{10})-alkyl)carbamoyl, or $CON(CH_2)_h$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_8)-alkylimino, N-(C_3-C_8)-cycloalkylimino, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylimino, N-(C_6-C_{12})-arylimino, N-(C_7-C_{16})-aralkylimino or N-(C_1-C_4)-alkoxy-(C_1-C_6)-alkylimino, and h is from 3 to 6,

where aryl is substituted in the manner as defined for R^1 and R^3,

R^1 and R^3 are identical or different and are hydrogen, halogen, (C_1-C_{12})-alkyl, (C_1-C_{12})-alkoxy, $-O-[CH_2]_x-C_zH_{(2z+1-g)}Hal_g$, ($C_1$-$C_{12}$)-alkoxy-($C_1$-$C_{12}$)-alkyl, ($C_1$-$C_8$)-alkoxy-($C_1$-$C_{12}$)-alkoxy, ($C_1$-$C_{12}$)-alkoxy-($C_1$-$C_8$)-alkoxy-($C_2$-$C_6$)-alkyl, ($C_7$-$C_{11}$)-aralkyloxy, ($C_3$-$C_8$)-cycloalkyl, ($C_3$-$C_8$)-cycloalkyl-($C_1$-$C_8$)-alkyl, ($C_3$-$C_8$)-cycloalkyloxy, ($C_3$-$C_8$)-cycloalkyl-($C_1$-$C_8$)-alkoxy, ($C_3$-$C_8$)-cycloalkyloxy-($C_1$-$C_8$)-alkyl, ($C_3$-$C_8$)-cycloalkyloxy-($C_1$-$C_8$)-alkoxy, ($C_3$-$C_8$)-cycloalkyl-($C_1$-$C_6$)-alkyl-($C_1$-$C_6$)-alkoxy, ($C_3$-$C_8$)-cycloalkyl-($C_1$-$C_6$)-alkoxy-($C_1$-$C_6$)-alkyl, ($C_3$-$C_8$)-cycloalkoxy-($C_1$-$C_6$)-alkoxy-($C_1$-$C_6$)-alkyl, NR^2R^2, (C_1-C_8)-alkylmercapto, (C_1-C_8)-alkylsulfinyl or (C_1-C_8)-alkylsulfonyl, (C_6-C_{12})-arylmercapto, (C_6-C_{12})-arylsulfinyl, (C_6-C_{12})-arylsulfonyl, (C_7-C_{12})-aralkylmercapto, (C_7-C_{11})-aralkylsulfinyl, (C_7-C_{11})-aralkylsulfonyl, substituted (C_6-C_{12})-aryloxy-(C_1-C_6)-alkyl, (C_7-C_{11})-aralkoxy-(C_1-C_6)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_7-C_{11})-aralkyloxy-(C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_6-C_{12})-aryloxy, (C_7-C_{11})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy or (C_7-C_{11})-aralkoxy-(C_1-C_6)-alkoxy, where an aromatic radical carries by 1, 2, 3, 4 or 5 identical or different substituents from the group hydrogen, halogen, cyano, nitro, trifluoromethyl, (C_1-C_{12})-alkyl, (C_1-C_{12})-alkenyl, (C_1-C_6)-hydroxyalkyl, (C_1-C_{12})-alkoxy, (C_1-C_{12})-alkenyloxy,

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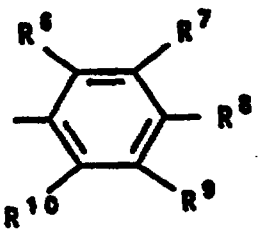
$-O-[CH_2]_xC_zH_{(2z+1-g)}F_g$, $-OCF_2Cl$, $-O-CF_2-CHFCl$, (C_1-C_6)-alkylmercapto, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_4)-alkylcarbamoyl, N,N-di-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, (C_3-C_8)-cycloalkylcarbamoyl, phenyl, benzyl, phenoxy, benzyloxy, NR^yR^z, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_4)-alkylsulfamoyl or N,N-di-(C_1-C_4)-alkylsulfamoyl, or optionally carries up to 3 of the abovementioned identical or different substituents, and two adjacent carbon atoms of the aralkyloxy radical together carry a chain $-[CH_2-]$ and/or $-CH=CH-CH=CH-$, where a CH_2 group of the chain is optionally replaced by O, S, SO, SO_2 or NR^y,

R^1 and R^2 or R^2 and R^3 can form a chain $[CH_2]_o$, where o is 3, 4 or 5, and

R^4 is, provided Q is a bond, chlorine or, if Q is O or NR', is a branched or unbranched (C_1-C_{10})-alkyl radical, which can contain one or two C-C multiple bonds, or an unsubstituted fluoroalkyl radical of the formula $-[CH_2]_x-C_zH_{(2z+1-g)}F_g$ or (C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_1-C_6)-alkoxy-(C_1-C_4)-alkoxy-(C_1-C_4)-alkyl or a radical of the formula Z,

$$-[CH_2]_v-[O]_w-[CH_2]_t-E \qquad (Z)$$

where E is a substituted phenyl radical of the formula F



(F),

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or a (C_3-C_8)-cycloalkyl radical, where

v is 0, 1, 2, 3, 4, 5 or 6, w is 0 or 1, and t is 0, 1, 2 or 3, with the restriction that v is not equal to 0 if w is 1, and R^6, R^7, R^8, R^9 and R^{10} are identical or different and are hydrogen, halogen, cyano, nitro, trifluoromethyl, (C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyl, (C_1-C_6)-alkoxy, -O-[CH_2-]$_x$-$C_yH_{(2y+1-z)}F_z$, -OCF_2Cl, -O-CF_2-CHFCl, (C_1-C_6)-alkylmercapto, (C_1-C_6)-hydroxyalkyl, (C_1-C_6)-alkoxy-(C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_1-C_6)-alkylsulfinyl, (C_1-C_6)-alkylsulfonyl, (C_1-C_6)-alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, N-(C_1-C_8)-alkylcarbamoyl, N,N-di-(C_1-C_8)-alkylcarbamoyl, (C_7-C_{11})-aralkylcarbamoyl which is optionally substituted by fluorine, chlorine, bromine, trifluoromethyl or (C_1-C_6)-alkoxy, N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkylcarbamoyl, (C_1-C_6)-alkylcarbonyloxy, phenyl, benzyl, phenoxy, benzyloxy, NR^yR^z, such as amino, anilino, N-methylanilino, phenylmercapto, phenylsulfonyl, phenylsulfinyl, sulfamoyl, N-(C_1-C_8)-alkylsulfamoyl or N,N-di-(C_1-C_8)-alkylsulfamoyl, or two adjacent substituents together are a chain -[CH_2-]$_n$ or -CH=CH-CH=CH-, where a CH_2 group of the chain is optionally replaced by O, S, SO, SO_2 or NR^y, and where a heteroaryl radical can carry 1, 2 or 3 substituents, and a cycloalkyl radical one substituent, from the above group, and

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R^4 is R^*, provided Q has the meaning of NR', where
R' is hydrogen or methyl, and
R^* is benzyl, and

if R^1 and/or R^3 have the meaning of (C_6-C_{12})-aryloxy, (C_7-C_{11})-aralkyloxy, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkoxy, (C_7-C_{11})-aralkoxy-(C_1-C_6)-alkoxy or a corresponding radical containing terminal cycloalkyl groups, this

radical is preferably then a radical of the formula D

OZ (D), or

if R^1 and/or R^3 have the meaning of (C_7-C_{11})-aralkyl, (C_6-C_{12})-aryloxy-(C_1-C_6)-alkyl, (C_7-C_{11})-aralkoxy-(C_1-C_6)-alkyl or a corresponding radical containing terminal cycloalkyl groups, this radical is preferably then a radical of the formula Z,

R^Y and R^Z are identical or different and are hydrogen, (C_6-C_{12})-aryl, (C_1-C_{10})-alkyl, (C_3-C_{10})-cycloalkyl, (C_1-C_8)-alkoxy-(C_1-C_8)-alkyl, (C_7-C_{12})-aralkoxy-(C_1-C_8)-alkyl, (C_6-C_{12})-aryloxy-(C_1-C_8)-alkyl, (C_1-C_{10})-alkanoyl, optionally substituted (C_7-C_{16})-aralkanoyl or optionally substituted (C_6-C_{12})-aroyl, or

R^Y and R^Z are together $-[CH_2]_h-$, in which a CH_2 group can be replaced by O, S, N-(C_1-C_4)-alkanoylimino or N-(C_1-C_4)-alkoxycarbonylimino, and

f is 1 to 8,
g is 0 or 1 to (2f+1),
h 3 to 6,
x is 0 to 3, and
n is 3 or 4,

including the physiologically active salts, with 3-benzyloxypyridine-2-carboxylic acid (L-threonyl)amide and 3-benzyloxypyridine-2-carboxylic acid ((Fmoc-Phg)L-threonyl)amide hydrochloride being excepted.

8. A compound of the formula I as claimed in claims 1 to 5, in which
Q is O,
X is O,
Y is CR^3 and, additionally, N if R^1 and R^2 form a

* C L M S *

cycle,

m is 0,

A is $-CHR^5-$, where R^5 is the substituent of the α-carbon atom of an α-amino acid, in particular of a natural L-amino acid or its D-isomer,

B is CO_2H,

R^2 is hydrogen, bromine, chlorine, cyano, (C_1-C_{18})-alkyl, (C_1-C_8)-alkoxy, (C_1-C_{18})-alkoxymethyl, (C_2-C_{18})-alkenyloxymethyl, (C_2-C_{18})-alkynyloxymethyl, carbamoyl, N-(C_1-C_{10})-alkylcarbamoyl, N-$((C_1-C_{12})$-alkoxy-(C_1-C_4)-alkyl)carbamoyl, N,N-di-(C_1-C_8)-alkylcarbamoyl, N-(C_3-C_8)-cycloalkylcarbamoyl, N-(C_6-C_{12})-phenylcarbamoyl, N-(C_7-C_{12})-phenylalkylcarbamoyl, N-(C_1-C_6)-alkyl-N-(C_6-C_{12})phenylcarbamoyl, N-(C_1-C_6)-alkyl-N-(C_7-C_{12})-phenylalkylcarbamoyl, N-$((C_1-C_6)$-alkoxy-(C_1-C_6)-alkyl)carbamoyl, carboxyl, (C_1-C_{20})-alkoxycarbonyl, (C_2-C_{20})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_3-C_8)-cycloalkoxycarbonyl, (C_3-C_8)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl, (C_3-C_8)-cycloalkoxy-(C_1-C_6)-alkoxycarbonyl, phenyl-(C_1-C_6)-alkoxycarbonyl, phenoxy-(C_1-C_6)-alkoxycarbonyl or benzyloxy-(C_1-C_6)-alkoxycarbonyl, where a phenyl radical is substituted in the manner as defined for R^1 and R^3, and one of the radicals

R^1 or R^3 is hydrogen and the other a radical from the group hydrogen, fluorine, chlorine, (C_1-C_8)-alkyl, (C_1-C_{10})-alkoxy, (C_5-C_6)-cycloalkyl, (C_5-C_6)-cycloalkyl-(C_1-C_6)-alkyl, (C_5-C_6)-cycloalkyloxy, (C_5-C_6)-cycloalkyl-(C_1-C_6)-alkoxy, (C_5-C_6)-cycloalkyloxy-(C_1-C_6)-alkyl, (C_5-C_6)-cycloalkyloxy-(C_1-C_6)-alkoxy, (C_5-C_6)-cycloalkyl-(C_1-C_4)-alkyl-(C_1-C_4)-alkoxy, (C_5-C_6)-cycloalkyl-(C_1-C_4)-alkoxy-(C_1-C_2)-alkyl, (C_5-C_6)-cycloalkoxy-(C_1-C_4)-alkoxy-(C_1-C_2)-alkyl, $-O-[CH_2]_z-C_zH_{(2z+1-g)}F_g$, (C_1-C_6)-alkoxy-(C_1-C_6)-alkyl, (C_1-C_6)-alkoxy-(C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy-(C_1-C_4)-alkoxy-(C_1-C_2)-

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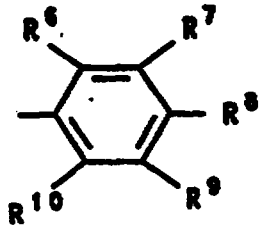
alkyl, substituted (C_6-C_{12})-phenoxy, (C_7-C_{11})-phenylalkyloxy, (C_6-C_{12})-phenoxy-(C_1-C_6)-alkoxy or (C_7-C_{11})-phenylalkoxy-(C_1-C_6)-alkoxy, phenoxy-(C_1-C_4)-alkyl, (C_7-C_{11})-phenylalkyloxy-(C_1-C_4)-alkyl, phenoxy-(C_1-C_4)-alkoxy-(C_1-C_2)-alkyl or (C_7-C_{11})-phenylalkyloxy-(C_1-C_4)-alkoxy-(C_1-C_2)-alkyl, where an aromatic radical is substituted by 1, 2 or 3 identical or different substitutents from the group fluorine, chlorine, cyano, trifluoromethyl, (C_1-C_{12})-alkyl, (C_2-C_{12})-alkenyl, (C_2-C_{12})-alkenyloxy or (C_1-C_{12})-alkoxy,

R^1 and R^2, with the pyridine carrying them, form a 5, 6, 7, 8-tetrahydroisoquinoline ring,

R^4 is a branched or unbranched (C_1-C_{10})-alkyl radical, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl or a radical of the formula Z,

$$-[CH_2]_v-[O]_w-[CH_2]_t-E \qquad (Z)$$

where E is a substituted phenyl radical of the formula F



(F),

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or a (C_3-C_8)-cycloalkyl radical, where v is 0, 1, 2 or 3, w is 0, and t can be 0 or 1, and in which R^6, R^7, R^8, R^9 and R^{10} are identical or different and are hydrogen, fluorine, chlorine, cyano, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, $-O-[CH_2-]_x-C_zH_{(2z+1-g)}F_g$, N-$(C_1-C_8)$-alkylcarbamoyl, N,N-di-$(C_1-C_6)$-alkylcarbamoyl, N-$(C_3-C_6)$-cycloalkylcarbamoyl, N-(+)-dehydroabietylaminocarbonyl, or (C_7-C_{11})-phenylalkylcarbamoyl, which

is optionally substituted by fluorine, chlorine, trifluoromethyl and (C_1-C_6)-alkoxy, or where R^6 and R^7 or R^7 and R^8, together with the phenyl ring carrying them, form naphthalene derivatives, or

if R^1 or R^3 has the meaning of (C_6-C_{12})-phenoxy, (C_7-C_{11})-phenylalkyloxy, (C_6-C_{12})-phenoxy-(C_1-C_6)-alkoxy, (C_7-C_{11})-phenylalkoxy-(C_1-C_6)-alkoxy, (C_5-C_6)-cycloalkyloxy, (C_5-C_6)-cycloalkyl-(C_1-C_6)-alkoxy, (C_5-C_6)-cycloalkoxy-(C_1-C_6)-alkoxy or (C_5-C_6)-cycloalkyl-(C_1-C_4)-alkyl-(C_1-C_4)-alkoxy, this radical is then, especially, a radical of the formula D

OZ (D), or

if R^1 or R^3 has the meaning of phenyl, phenoxy-(C_1-C_6)-alkyl, (C_7-C_{11})-phenylalkyl, (C_7-C_{11})-phenylalkyloxy-(C_1-C_4)-alkyl, (C_5-C_6)-cycloalkyl, (C_5-C_6)-cycloalkyl-(C_1-C_6)-alkyl, (C_5-C_6)-cycloalkoxy-(C_1-C_4)-alkyl, (C_5-C_6)-cycloalkyl-(C_1-C_4)-alkoxy-(C_1-C_2)-alkyl or (C_5-C_6)-cycloalkoxy-(C_1-C_4)-alkoxy-(C_1-C_2)-alkyl, this radical is then, especially, a radical of the formula Z in which, in both cases,

v is 1, 2, 3 or 4, w is 0 and t is 0, or
v is 1, 2, 3 or 4, w is 1 and t is 0, or
v is 1, 2, 3 or 4, w is 1, t is 1, and
f is 1 to 4,
g is 0 or 1 to (2f+1),
x is 0 or 1

including the physiologically active salts, with 3-benzyloxypyridine-2-carboxylic acid (L-threonyl)amide and 3-benzyloxypyridine-2-carboxylic acid ((Fmoc-Phg)L-threonyl)amide hydrochloride being excepted.

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9. A compound of the formula I as claimed in claims 1

* C L M S *

to 6, in which

Q is O,

X is O,

Y is CR^3,

m is 0,

A is a $-CH_2-$ group which can be substituted by a methyl group,

B is CO_2H,

R^2 is hydrogen, (C_1-C_8)-alkoxy, (C_1-C_{16})-alkoxymethyl, (C_2-C_{16})-alkenyloxymethyl, retinyloxymethyl, N-(C_1-C_{10})-alkylcarbamoyl, N-((C_1-C_{12})-alkoxy-(C_1-C_3)-alkyl)carbamoyl, N,N-di-(C_1-C_6)-alkylcarbamoyl, N-(C_3-C_6)-cycloalkylcarbamoyl, N-phenylcarbamoyl, N-phenyl-(C_1-C_4)-alkylcarbamoyl, carboxy, (C_1-C_{16})-alkoxycarbonyl, (C_2-C_{16})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_3-C_6)-cycloalkoxycarbonyl, (C_3-C_6)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl or phenyl-(C_1-C_6)-alkoxycarbonyl, where a phenyl radical is substituted in a manner as defined for R^1 and R^3, and one of the radicals

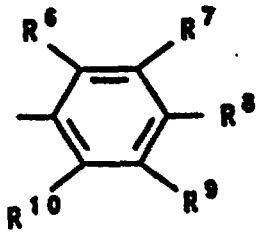
R^1 or R^3 is hydrogen and the other radical is a radical from the group hydrogen, (C_1-C_{10})-alkoxy, (C_3-C_6)-cycloalkyloxy, (C_3-C_6)-cycloalkyl-(C_1-C_2)-alkoxy, $-O-[CH_2]_x-C_zH_{(2z+1-y)}F_y$, (C_1-C_4)-alkoxy-(C_1-C_4)-alkoxy, substituted (C_6-C_{12})-phenoxy, (C_7-C_{11})-phenylalkyloxy, (C_6-C_{12})-phenoxy-(C_1-C_4)-alkoxy or (C_7-C_{11})-phenylalkoxy-(C_1-C_4)-alkoxy, where an aromatic radical is substituted by 1, 2 or 3 identical or different substituents from the group fluorine, chlorine, cyano, trifluoromethyl, (C_1-C_{10})-alkyl, (C_1-C_{10})-alkoxy or (C_1-C_{10})-alkenyloxy, and

R^4 is a branched or unbranched (C_1-C_8)-alkyl radical or a radical of the formula Z,

$$-[CH_2]_v-[O]_w-[CH_2]_t-E \qquad (Z),$$

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where E is a substituted phenyl radical of the formula F



(F),

or a (C_3-C_8)-cycloalkyl radical, where v is 0, 1, 2 or 3, w is 0, and t can be 0 or 1, and in which R^6, R^7, R^8, R^9 and R^{10} are identical or different and are hydrogen, fluorine, chlorine, cyano, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$, N-$(C_1-C_8)$-alkylcarbamoyl, N,N-di-$(C_1-C_6)$-alkylcarbamoyl, N-$(C_3-C_6)$-cycloalkylcarbamoyl, N-(+)-dehydroabietylaminocarbonyl substituted benzyl radical, and f is 1 to 4, g is 0 or 1 to (2f+1) and x is 0 or 1 including the physiologically active salts.

10. A compound of the formula I as claimed in claims 1 to 3 and 6 to 9, in which

Q is O,
X is O,
Y is CR^3,
m is 0,
A is a $-CH_2$ group,
B is CO_2H,

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R^1 is hydrogen, (C_1-C_6)-alkoxy or $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$,

R^2 is hydrogen, N-(C_1-C_{10})-alkylcarbamoyl, N-$((C_1-C_{12})$-alkoxy-(C_1-C_3)-alkyl)carbamoyl, N,N-di-(C_1-C_8)-alkylcarbamoyl, N-(C_3-C_6)-cycloalkylcarbamoyl, N-phenylcarbamoyl, N-phenyl-(C_1-C_2)-alkylcarbamoyl, carboxyl, (C_1-C_{16})-alkoxycarbonyl,

(C_2-C_{16})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_3-C_6)-cycloalkoxycarbonyl, (C_3-C_6)-cycloalkyl-(C_1-C_6)-alkoxycarbonyl or phenyl-(C_1-C_6)-alkoxycarbonyl, where a phenyl radical is substituted by 1 or 2 identical or different substituents from the group fluorine, chlorine, cyano, trifluoromethyl, (C_1-C_{10})-alkyl, (C_1-C_{10})-alkoxy or (C_1-C_{10})-alkenyloxy, and

R^3 is hydrogen, (C_1-C_5)-alkoxy or (C_3-C_6)-cycloalkyl-(C_1-C_2)-alkoxy, where one of the substituents R^1 and R^3 is hydrogen,

R^4 is a branched or unbranched (C_1-C_6)-alkyl radical, or a 2-phenylethyl radical, or a benzyl radical substituted by 1 or 2 radicals from the group fluorine, chlorine, cyano, trifluoromethyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, $-O-[CH_2]_x-C_fH_{(2f+1-g)}F_g$, N-$(C_1-C_5)$-alkylcarbamoyl, N,N-di-$(C_1-C_6)$-alkylcarbamoyl, N-$(C_3-C_6)$-cycloalkylcarbamoyl or N-(+)-dehydroabietylaminocarbonyl, and f is 1 to 4, g is 0 or 1 to (2f+1) and x is 1, including the physiologically active salts.

11. Compounds of the formula I as claimed in claims 1 to 3 and 6 to 10, in which

Q is O,

X is O,

Y is CR^3,

m is 0,

A is a $-CH_2-$group,

B is CO_2H,

R^1 is hydrogen,

R^2 is hydrogen, N-(C_1-C_{10})-alkylcarbamoyl, N-$((C_1-C_{12})$-alkoxy-(C_1-C_3)-alkyl)carbamoyl, N-cyclo-

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hexylcarbamoyl, N-phenylcarbamoyl, N-(phenyl-(C_1-C_2)-alkyl)carbamoyl, where, in the last two cases, the phenyl radical can carry a fluorine substituent, a (C_1-C_{10})-alkyl substituent or a (C_1-C_{10})-alkoxy substituent, carboxyl, (C_1-C_{16})-alkoxycarbonyl, (C_2-C_{16})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_5-C_6)-cycloalkoxycarbonyl or benzyloxycarbonyl,

R^3 is hydrogen, (C_1-C_6)-alkoxy or 2-(cyclohexyl)-ethyloxy, where one of the substituents R^2 and R^3 is hydrogen,

R^4 is a branched or unbranched (C_1-C_4)-alkyl radical or a benzyl radical which is substituted once by fluorine, chlorine, trifluoromethyl, (C_1-C_4)-alkyl or (C_1-C_3)-alkoxy, including the physiologically active salts.

12. A compound of the formula I as claimed in claims 1 to 3 and 6, in which
Q is O
X is O,
Y is CR^3,
where R^3 is hydrogen,
m is 0,

A is a $-CH_2$ group,
B is $-CO_2H$, and
R^1 and R^2, together with the pyridine carrying them, form an isoquinoline ring having an unsubstituted benzo moiety, and
R^4 is methyl.

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13. A compound of formula I as claimed in claims 1 to 3 and 6, in which
Q is O,
X is O
Y is CR^3,

* C L M S *

m is 0,
A is a $-CH_2$ group,
B is $-CO_2H$,
R^1 is hydrogen, and
R^2 and R^3, together with the pyridine carrying them, form a quinoline ring having an unsubstituted benzo moiety, and
R^4 is methyl.

14. A compound of the formula I as claimed in claims 1, 2, 4 and 5, in which
Q is S,
X is O,
Y is CR^3,
m is 0,

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A is a $-CH_2$ group,
B is $-CO_2H$,
R^1 is hydrogen,

R^2 is hydrogen, N-(C_1-C_{10})-alkylcarbamoyl, N-((C_1-C_{12})-alkoxy-(C_1-C_3)alkyl)carbamoyl, N-cyclohexylcarbamoyl, N-phenylcarbamoyl, N-(phenyl-(C_1-C_2)alkyl)carbamoyl, where, in the last two cases, the phenyl radical can carry a fluorine substituent, (C_1-C_{10})-alkyl substituent or (C_1-C_{10})-alkoxy substituent, carboxyl, (C_1-C_{16})-alkoxycarbonyl, (C_2-C_{16})-alkenyloxycarbonyl, retinyloxycarbonyl, (C_5-C_6)-cycloalkoxycarbonyl or benzyloxycarbonyl,

R^3 is hydrogen, (C_1-C_6)-alkoxy or 2-(cyclohexyl)-ethyloxy, where one of the substituents R^2 and R^3 is hydrogen, and

R^4 is a branched or unbranched (C_1-C_4)-alkyl radical or a benzyl radical which is substituted once by fluorine, chlorine, trifluoromethyl, (C_1-C_4)-alkyl or (C_1-C_3)-alkoxy.

* C L M S *

15. A compound of the formula I as claimed in claims 1, 2, 4, 5 and 14, in which
Q is S,
X is O,
Y is CR^3,
m is 0,
A is a $-CH_2$ group,
B is $-CO_2H$,
R^1 is hydrogen,
R^2 is carboxyl or (C_1-C_{16})-alkoxycarbonyl,
R^3 is hydrogen, and
R^4 is an unbranched or branched (C_1-C_4)-alkyl radical.

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16. A compound of the formula I as claimed in claims 1 to 15, plus 3-benzyloxypyridine-2-carboxylic acid L-threonylamide and 3-benzyloxypyridine-2-carboxylic acid ((Fmoc-Phg)-L-threonyl)amide for use as pharmaceuticals.

17. A compound as claimed in claims 1 to 16 to be used for inhibiting collagen biosynthesis.

18. A compound as claimed in claims 1 to 16 as an inhibitor of prolyl hydroxylase.

19. A compound as claimed in claims 1 to 16 for use as a fibrosuppressive agent.

20. A compound as claimed in claims 1 to 16 for preparing a pharmaceutical against fibrotic diseases.

21. A compound as claimed in claims 1 to 16 for preparing a pharmaceutical against fibrotic diseases of the liver.

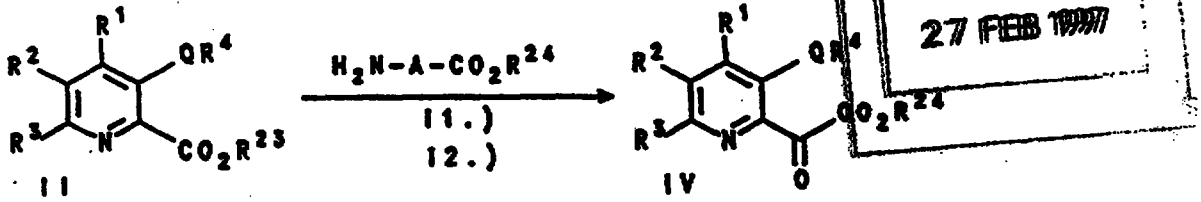
22. A compound as claimed in claims 1 to 16 for preparing a pharmaceutical against fibrotic diseases of the lung.

23. A compound as claimed in claims 1 to 16 for preparing a pharmaceutical against fibrotic diseases of the skin.

24. A process for preparing compounds according to formula I as claimed in claims 1 to 15, in which formula A is a substituted alkylene moiety, B is CO_2H, Y is CR^3 and m is 0 or 1, by

i1.) reacting pyridine-2-carboxylic acids of the formula II (R^{23} is H) with the amino esters of the formula III (R^{24} is (C_1-C_{16})-alkyl or benzyl) to form the amide esters of the formula IV, or

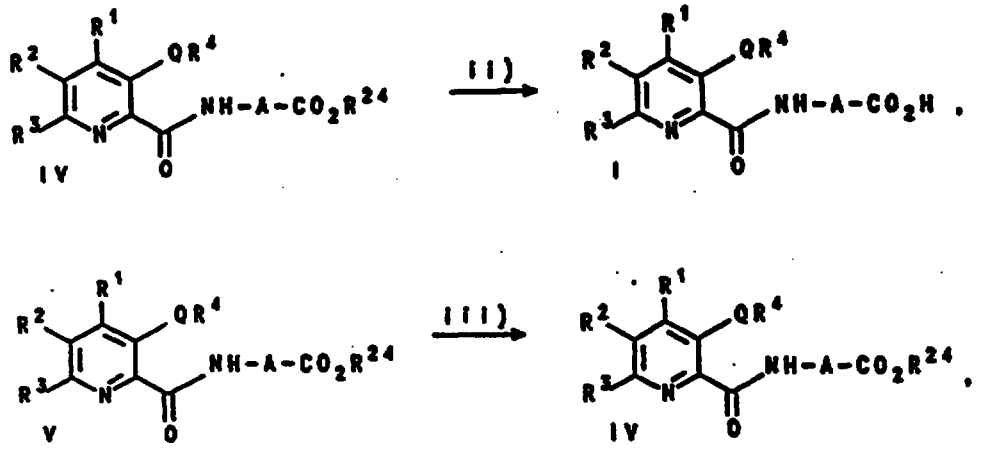
i2.) reacting pyridine-2-carboxylic esters of the formula II (R^{23} is lower alkyl), under the conditions of aminolysis, to form the compounds of the formula IV;
and



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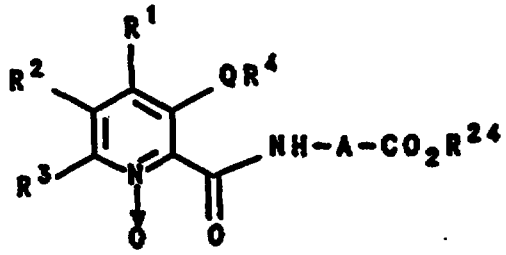
ii) liberating the compounds of the formula I from their esters of the formula IV;
with, where appropriate,

iii) the compounds of the formula IV (R^4 is alkyl) being prepared by alkylation of compounds of the formula V (R^4 is H) with R^4X,



where X is a leaving group, in particular halogen, OSO_2Me or OSO_2 phenyl, and, where appropriate,

iv) the compounds of the formula IV, provided Q is O, S or NR', being converted into their pyridine N-oxides (IV')



IV'

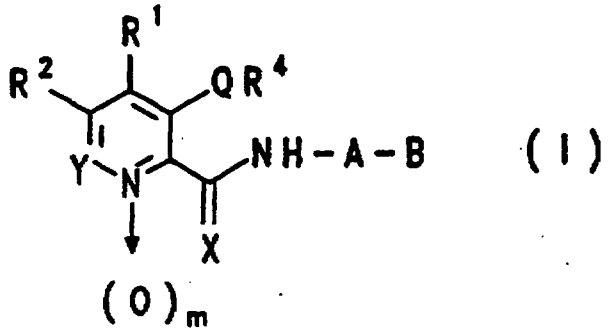
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and, where appropriate, the latter being hydrolysed to form the compounds of the formula I' (R^{24} is H).

Abstract of the disclosure

Substituted heterocyclic carboxamides, their preparation and their use as pharmaceuticals

The invention relates to compounds of the formula I,



(I)

to a process for their preparation and to their use as pharmaceuticals. The compounds are employed, in particular, for inhibiting collagen biosynthesis and as inhibitors of prolyl hydroxylase and as fibrosuppressive agents.

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