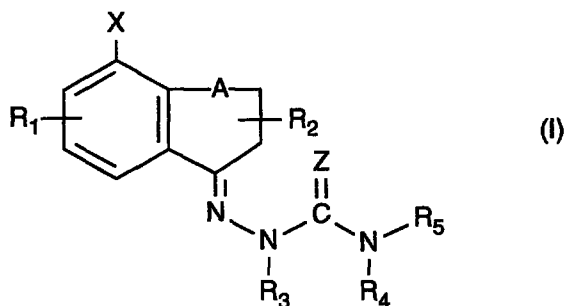


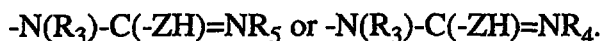
The invention relates to compounds of formula I



wherein A is a direct bond or $-(CH_2)_n-$, wherein n is 1, 2 or 3; X is a radical $-C(=Y)-NR_6R_7$; Y is NR_8 , O or S; Z is NR_9 , O or S; R_1 and R_2 are each independently of the other hydrogen or one or more substituents selected from lower alkyl, trifluoromethyl, C_3-C_8 cycloalkyl that is unsubstituted or lower alkyl-substituted, aryl-lower alkyl, hydroxy, lower alkoxy, aryl-lower alkoxy, aryloxy, lower alkanoyloxy, halogen, amino, N-lower alkylamino, N,N-di-lower alkylamino, lower alkanoylamino, nitro, lower alkanoyl, aryl-carbonyl, carboxy, lower alkoxy-carbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, N-arylcarbamoyl, cyano, mercapto, lower alkylthio, lower alkyl-sulfonyl, sulfamoyl, N-lower alkylsulfamoyl and N,N-di-lower alkylsulfamoyl; the radicals R_3 , R_4 , R_6 , R_8 and R_9 are each independently of the others hydrogen or lower alkyl; and R_5 and R_7 are each independently of the other hydrogen, lower alkyl, hydroxy, lower alkoxy, lower alkanoyloxy, unsubstituted amino, di-lower alkylamino, C_4-C_7 -alkyleneamino or oxa-, thia- or aza- C_4-C_7 -alkyleneamino; tautomers thereof, or salts thereof; aryl being phenyl or naphthyl each of which is unsubstituted or substituted by one or more substituents selected from lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, nitro, amino, halogen, trifluoromethyl, carboxy, lower alkoxy-carbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, cyano, lower alkanoyl, aryl-carbonyl, lower alkylsulfonyl, sulfamoyl, N-lower alkylsulfamoyl and N,N-di-lower alkyl-sulfamoyl; and the term "lower" or "-lower" indicating a radical having up to and including a maximum of 7 carbon atoms.

Tautomers may occur, for example, when Z is NR_9 and R_3 and/or R_4 and/or R_5 are hydrogen:

The corresponding guanyl radical, represented by $-N(R_3)-C(=Z)-NR_4R_5$ in formula I, can then, for example, also be in the tautomeric form $-N=C(-ZH)-NR_4R_5$,



A further example: when Y is NR_8 and R_6 and/or R_7 is hydrogen, then the corresponding amidine structure, defined as $X = -C(=Y)-NR_6R_7$ in formula I, may also be in the tautomeric form $-C(-YH)=NR_7$ or $-C(-YH)=NR_6$. The existence of those and similar tautomers is familiar to the person skilled in the art. All those tautomers are covered by the general formula I.

In the case where A is a group $-(CH_2)_n-$ and R_2 is other than hydrogen, the substituent(s) corresponding to the radical R_2 can also be linked to the carbon atoms of the group $-(CH_2)_n-$.

R_2 is, for example, hydrogen or from one to four substituents other than hydrogen, especially hydrogen or one or two substituents other than hydrogen and more especially hydrogen or one substituent other than hydrogen.

R_1 is, for example, hydrogen or from one to three substituents other than hydrogen and especially hydrogen or one or two substituents other than hydrogen.

The general terms used hereinabove and hereinbelow preferably have the following meanings in the context of this Application:

The term "lower" denotes a radical having up to and including 7 and especially up to and including 4 carbon atoms.

Lower alkyl is, for example, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl or n-heptyl, preferably ethyl and especially methyl.

Aryl is phenyl or naphthyl, such as 1- or 2-naphthyl. The phenyl and naphthyl radicals can be unsubstituted or substituted, especially as indicated below for phenyl. Aryl is preferably phenyl that is unsubstituted or substituted by one or more, especially one or two, substituents from the group consisting of lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, nitro, amino, halogen, trifluoromethyl, carboxy, lower alkoxy carbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, cyano, lower alkanoyl, arylcarbonyl, lower alkylsulfonyl, sulfamoyl, N-lower alkylsulfamoyl and N,N-di-lower alkylsulfamoyl. Aryl is especially phenyl that is unsubstituted or substituted by

lower alkyl, lower alkoxy, hydroxy, halogen or by trifluoromethyl, and is more especially phenyl.

Arylcarbonyl is, for example, benzoyl that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen or by trifluoromethyl, and is especially benzoyl.

Aryl-lower alkyl is, for example, phenyl-lower alkyl and especially benzyl.

Halogen is especially chlorine and bromine, but may also be fluorine or iodine.

Lower alkanoyl is, for example, formyl, acetyl, propionyl or pivaloyl.

Cycloalkyl is C_3 - C_8 - and especially C_5 - C_6 -cycloalkyl, which is intended to indicate that it contains from 3 to 8 and 5 or 6 ring carbon atoms, respectively. It may, however, also be substituted by lower alkyl.

Lower alkoxy, lower alkanoyloxy, lower alkylamino, di-lower alkylamino, C_4 - C_7 alkylene-amino, especially C_4 - C_5 alkyleneamino, for example piperidino, or oxa-, thia- or aza-lower alkyleneamino, for example morpholino, thiomorpholino, piperazino or 4-lower alkyl-piperazino, may be represented by R_5 and/or R_7 .

Salts of compounds according to the invention are especially pharmaceutically acceptable, non-toxic salts. For example, compounds of formula I having basic groups may form acid addition salts, for example with inorganic acids, such as hydrochloric acid, sulfuric acid or phosphoric acid, or with suitable organic carboxylic or sulfonic acids, for example acetic acid, fumaric acid or methanesulfonic acid, or, for example, with amino acids, such as arginine or lysine. When several basic groups are present, mono- or poly-salts may be formed. Compounds of formula I having an acidic group, for example carboxy, and a basic group, for example amino, may be, for example, in the form of internal salts, that is to say in zwitterionic form, or part of the molecule may be in the form of an internal salt and another part may be in the form of a normal salt.

For the purposes of isolation or purification it is also possible to use pharmaceutically unacceptable salts, for example picrates or perchlorates. Only the pharmaceutically acceptable, non-toxic salts are used therapeutically and these are therefore preferred.

Depending upon the structural configuration, the compounds of the present invention may be in the form of mixtures of isomers or in the form of pure isomers. For example, when R_2 is a substituent other than hydrogen, the corresponding compounds of formula I may be in the form of racemates or pure enantiomers.

The compounds according to the invention have valuable, especially pharmacologically acceptable, properties. In particular, they have a strong, specific inhibitory action on the enzyme S-adenosylmethionine decarboxylase (SAMDC). SAMDC as a key enzyme plays an important part in the polyamine synthesis that takes place in virtually all cells of mammals, including humans. The polyamine concentration in the cell is regulated by SAMDC. Inhibition of the SAMDC enzyme results in a reduction in the polyamine concentration. Since a reduction in the polyamine concentration effects inhibition of cell growth, it is possible by administering SAMDC-inhibiting substances to inhibit the growth of both eukaryotic and prokaryotic cells and even to kill cells or to inhibit the onset of cell differentiation.

The inhibition of the SAMDC enzyme can be demonstrated, for example, using the method of H.G. Williams-Ashmann and A. Schenone, *Biochem. Biophys. Res. Commun.* **46**, 288 (1972). The compounds of the invention have IC_{50} values of a minimum of approximately 0.005 μM .

A further advantage of the compounds according to the invention lies in the fact that in comparison with their strong inhibitory action on SAMDC their inhibitory action on diamine oxidase is only slight and they are well tolerated. According to J. Jaenne and D.R. Morris, *Biochem. J.* **218**, 974 (1984), the inhibition of diamine oxidase is disadvantageous since it can result in an accumulation of putrescine and indirect SAMDC activation.

The compounds of formula I are therefore, for example, useful for the treatment of benign and malignant tumours. They can bring about the regression of tumours and also prevent the spread of tumour cells and the growth of micrometastases. Furthermore, they can be used, for example, for the treatment of protozoa infections, for example trypanosomiasis, malaria, or pulmonary inflammation caused by Pneumocystis carinii.

As selective SAMDC-inhibitors, the compounds of formula I can be used alone or alternatively in combination with other pharmacologically active substances. Possible combinations are, for example, a combination with (a) inhibitors of other enzymes of the poly-

amine biosynthesis, for example ornithine decarboxylase inhibitors, (b) inhibitors of protein kinase C, (c) inhibitors of tyrosine protein kinase, (d) cytokines, (e) negative growth regulators, (f) aromatase inhibitors, (g) anti-oestrogens or (h) classic cytostatic active ingredients.

The invention relates preferably to compounds of formula I wherein A is a direct bond or $-(CH_2)_n-$, wherein n is 1 or 2; X is a radical $-C(=Y)-NR_6R_7$; Y is NR_8 , O or S; Z is NR_9 , O or S; R_1 and R_2 are each independently of the other hydrogen or one or two substituents from the group consisting of lower alkyl, trifluoromethyl, cycloalkyl, aryl-lower alkyl, hydroxy, lower alkoxy, aryl-lower alkoxy, aryloxy, lower alkanoyloxy, halogen, amino, N-lower alkylamino, N,N-di-lower alkylamino, lower alkanoylamino, nitro, lower alkanoyl, arylcarbonyl, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkyl-carbamoyl, N,N-di-lower alkylcarbamoyl, N-arylcarbamoyl, cyano, mercapto, lower alkylthio, lower alkylsulfonyl, sulfamoyl, N-lower alkylsulfamoyl and N,N-di-lower alkyl-sulfamoyl, aryl being phenyl that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen or by trifluoromethyl; the radicals R_3 , R_4 , R_6 , R_8 and R_9 are each independently of the others hydrogen or lower alkyl; and R_5 and R_7 are each independently of the other hydrogen, lower alkyl, hydroxy, lower alkoxy, lower alkanoyl-oxy, amino, lower alkylamino, di-lower alkylamino, lower alkyleneamino or oxa-, thia- or aza-lower alkyleneamino; tautomers thereof, and salts thereof.

Preference is given especially to compounds of formula I wherein A is a direct bond or $-(CH_2)_n-$, wherein n is 1 or 2; X is a radical $-C(=Y)-NR_6R_7$; Y is NH, O or S; Z is NH, O or S; R_1 and R_2 are each independently of the other hydrogen or one or two substituents from the group consisting of lower alkyl, trifluoromethyl, phenyl-lower alkyl, hydroxy, lower alkoxy and halogen; the radicals R_3 , R_4 and R_6 are hydrogen; and R_5 and R_7 are each independently of the other hydrogen, lower alkyl, hydroxy or amino; tautomers thereof, and salts thereof.

Preference is given more especially to compounds of formula I wherein A is a direct bond or $-CH_2-$; X is a radical $-C(=Y)-NR_6R_7$; Y is NH or S; Z is NH; R_1 is hydrogen or one or two substituents from the group consisting of lower alkyl, hydroxy, lower alkoxy and halogen; R_2 is hydrogen or lower alkyl; the radicals R_3 , R_4 and R_6 are hydrogen; and R_5 and R_7 are each independently of the other hydrogen, lower alkyl or hydroxy; tautomers thereof, and pharmaceutically acceptable salts thereof.

Very special preference is given to compounds of formula I wherein A is a direct bond, X is a radical $-C(=NH)-NH_2$; Z is NH; R_1 is hydrogen or one or two substituents from the group consisting of lower alkyl, hydroxy and lower alkoxy; the radicals R_2 , R_3 and R_4 are hydrogen; and R_5 is hydrogen or hydroxy; tautomers thereof, and pharmaceutically acceptable salts thereof.

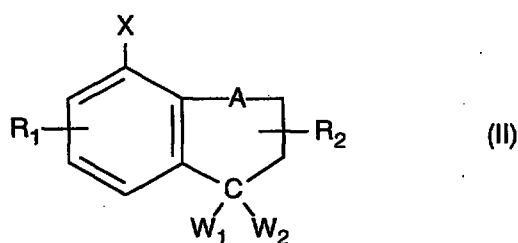
Special mention should be made of each of the following sub-groups of a group of compounds of formula I:

(a) compounds of formula I wherein A is a direct bond; (b) compounds of formula I wherein X is a radical $-C(=NH)-NH_2$; (c) compounds of formula I wherein Z is NH, R_4 is hydrogen and R_5 is hydrogen or hydroxy; and (d) compounds of formula I wherein R_1 and R_2 are hydrogen.

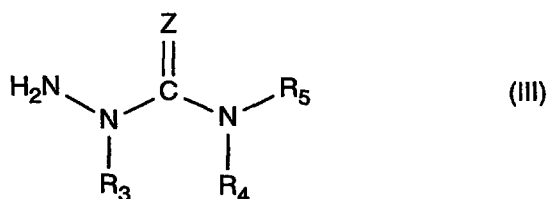
The invention relates especially to the specific compounds described in the Examples and salts thereof.

The compounds of formula I can be prepared in a manner known per se, for example by

(a) condensing a compound of formula II

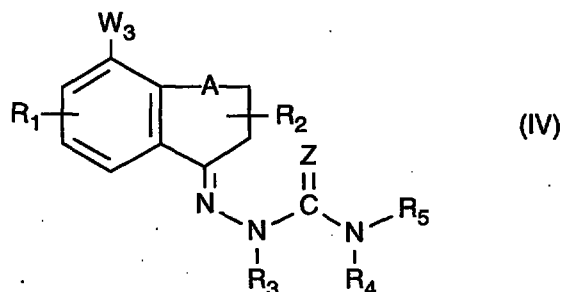


wherein the group CW_1W_2 is carbonyl, functionally modified carbonyl or protected carbonyl and A, X, R_1 and R_2 are as defined for formula I, with an amine of formula III



wherein Z, R₃, R₄ and R₅ are as defined for formula I, or

(b) in a compound of formula IV



wherein W₃ is a radical that can be converted into a group X in formula I and A, Z, R₁, R₂, R₃, R₄ and R₅ are as defined for formula I, converting the radical W₃ into the group X; and, if desired, converting a resulting compound of formula I into a different compound of formula I and/or, if desired, converting a resulting salt into the free compound or into a different salt and/or, if desired, converting a resulting free compound of formula I having salt-forming properties into a salt.

In the following, more detailed description of processes a)-b), the symbols A, X, Y, Z and R₁-R₉ are each as defined for formula I, unless otherwise indicated.

Process (a):

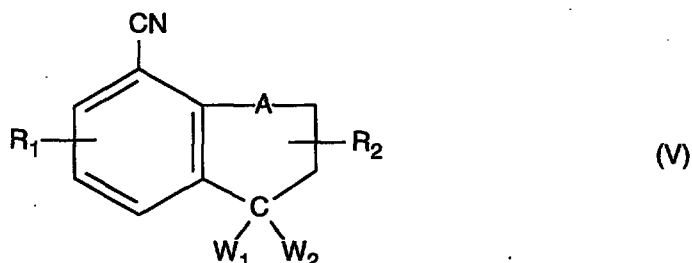
Examples of functionally modified or protected carbonyl CW₁W₂ that may be mentioned are: di-lower alkoxymethyl, C₁-C₂alkylenedioxyethyl, dihalomethyl, di-lower alkylthiomethyl or C₁-C₂alkylenedithiomethyl.

The group CW₁W₂ in compounds of formula II is preferably in the form of free carbonyl.

The condensation reaction according to process (a) is carried out under conditions known *per se* for the formation of hydrazones. It is preferably acid-catalysed. In compounds of formula II, suitable protected carbonyl groups CW₁W₂ are those which are converted into free carbonyl under the conditions of the condensation.

For the preparation of compounds of formula I wherein R₅ is amino it is advisable to use the compound of formula III in excess.

The intermediates of formula II wherein Y in the radical X is NH are obtained, for example, by first converting a compound of formula V



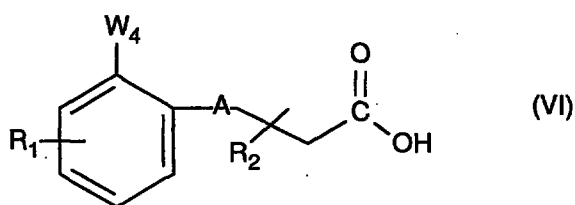
by treatment with hydrogen sulfide into the corresponding thiocarboxamide $[-C(=S)-NH_2]$. The latter can also be obtained by a different method starting from the analogous carboxamide $[-C(=O)-NH_2]$, for example by reaction with the Lawesson reagent [2,4-bis-(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane]. The thiocarboxamides are S-alkylated, for example with lower alkyl iodide or tri-lower alkylxonium tetrafluoroborate, and thus converted into imino-lower alkylthio ester hydroiodides $[-C(=NH)-S-alkyl \cdot HI]$ or tetrafluoroborates, respectively, which can readily be converted by reaction with ammonia or amines of the formula NHR_6R_7 into the desired carboximide amides of formula II [see S. Patai (Ed.), The Chemistry of amidines and imidates, Wiley, London etc. 1975, p 303-304].

The preparation of the carboxamides of formula II from the cyano compounds of formula V proceeds analogously to the preparation of carboxamides of formula I from cyano compounds of formula IV described below under process (b) and is described in detail there.

In a further possible method of preparing compounds of formula II, a compound of formula V, wherein the group CW_1W_2 is as defined for formula II, is treated, for example, with ethanol and hydrochloric acid in, for example, chloroform or diethyl ether, to form the corresponding iminoethyl ester hydrochloride which can be converted, for example by reaction with ammonia or a primary or secondary amine of the formula NHR_6R_7 and, for example, methanol, into the desired carboximide amide of formula II. In some cases, however, this method may not work as a result of sterical hindrance by the groups A and R_1 .

The starting compounds of formula V are known per se or are prepared analogously to the known compounds.

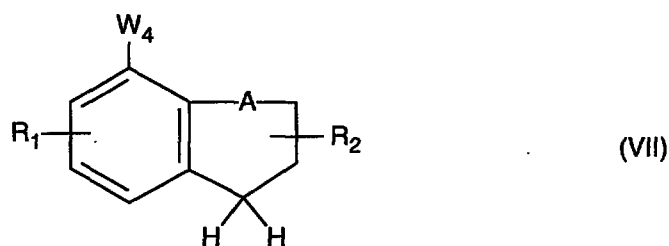
The compounds of formula V can be prepared, for example, by intramolecular Friedel-Crafts acylation of ω -phenyl-lower alkanolic acids of formula VI



wherein W_4 is cyano or a cyano precursor, or acid derivatives thereof, for example acid chlorides or acid anhydrides. In the case of free acids, the catalyst used may be, for example, polyphosphoric acid, and in the case of acid chlorides or anhydrides the catalyst may be, for example, $AlCl_3$.

In this reaction it is preferable to use compounds of formula VI wherein W_4 is not cyano but a cyano precursor, for example halogen, especially bromine, or protected amino, for example acetylamino. After the cyclisation step, the cyano precursors can then be converted into cyano in a manner known per se, for example in the case of bromine by reaction with copper(I) cyanide or in the case of acetylamino by removal of the acetyl protecting group, diazotisation and reaction with copper(I) cyanide.

Compounds of formula V wherein the group CW_1W_2 is carbonyl can also be prepared, for example, by oxidation, for example with chromium trioxide (CrO_3), from the corresponding non-carbonyl compounds of formula VII



wherein W_4 is cyano or a cyano precursor as defined above. If a cyano precursor is used, it should again be converted into cyano after the oxidation is complete, for example as

indicated above.

In a further possible method of preparing the compounds of formula V wherein the group CW_1W_2 is carbonyl, compounds of formula II wherein X is hydrogen are used as starting materials and the cyano group is introduced, for example, by using a reaction sequence analogous to that in US Patent 3 956 363, Example 10, which consists of nitration, reduction of the nitro group to amino, diazotisation and reaction with copper(I) cyanide (Sandmeyer reaction).

The preparation of aminoguanidines, aminoureas and aminothiureas of formula III is known per se. Amino(thio)ureas [$\hat{=}$ semi(thio)carbazides] are prepared, for example, in an analogous manner to corresponding simple (thio-)ureas. For example, instead of an amine the corresponding hydrazine of the formula H_2N-NHR_3 is used and is reacted, for example, with an isocyanate of the formula $R_4N=C=O$ or $R_5N=C=O$, an isothiocyanate of the formula $R_4N=C=S$ or $R_5N=C=S$, a carbamoyl chloride of the formula $R_4R_5N-COCl$ or a thiocarbamoyl chloride of the formula $R_4R_5N-CSCl$. Furthermore, it is also possible, for example, to react a hydrazine of the formula H_2N-NHR_3 with an acylisothiocyanate, for example acetylisothiocyanate, followed by acid hydrolysis.

Aminoguanidines of formula III wherein Z is NR_9 and R_3 , R_4 , R_5 and R_9 are as defined for formula I, are known per se and can be prepared, for example, from corresponding aminothiureas of formula III by converting the latter by alkylation, for example with an alkyl tosylate or halide, into the corresponding S-alkylisothiuronium salts which are then reacted with an amine of the formula NHR_4R_5 .

Process (b):

In the intermediates of formula IV, W_3 is, for example, free or functionally modified carboxy, especially halocarbonyl, cyano, imino-lower alkoxy carbonyl or imino-lower alkylthiocarbonyl.

For the preparation of amidines of formula I ($Y \hat{=} NR_8$) the group W_3 in a compound of formula IV can be, for example: an acid addition salt of an imino-lower alkyl ester ($\hat{=}$ imino-lower alkyl ether) or imino-lower alkylthio ester, for example $-C(=NH)-OC_2H_5 \cdot HCl$ or $-C(=NH)-SC_2H_5 \cdot HI$, or cyano.

The reaction of an imino-lower alkyl ester of formula IV (in salt form) with ammonia or

primary or secondary amines results in the unsubstituted or mono- or di-substituted amidines of formula I. Cyano compounds of formula IV can be converted, for example by reaction with an alkali metal amide, for example KNH_2 , or by reaction with a primary or secondary (di-)lower alkylammonium halide, for example $^{\oplus}\text{NH}_3\text{CH}_3 \text{Cl}^{\ominus}$, into an unsubstituted or mono- or di-substituted amidine of formula I.

For the preparation of carbamoyl compounds of formula I ($\text{Y}=\text{O}$) the group W_3 in a compound of formula IV may be, for example: carboxy, halocarbonyl (for example $-\text{COCl}$), lower alkoxy carbonyl or cyano. The formation of unsubstituted or mono- or di-substituted carbamoyl compounds of formula I from corresponding intermediates of formula IV wherein W_3 is carboxy, halocarbonyl or lower alkoxy carbonyl, by reaction with ammonia or primary or secondary amines is known per se. Intermediates of formula IV wherein W_3 is cyano can be converted, for example by partial hydrolysis, in the manner of a Graf-Ritter reaction, or by way of carboxylic acid ester imide salts, into unsubstituted or mono- or di-substituted carbamoyl compounds of formula I. The conditions for the hydrolysis of the cyano intermediates can be so chosen that the reaction is interrupted at the amide stage. Especially suitable for this purpose is hydrolysis with acids, for example with 80 % sulfuric acid (with heating), polyphosphoric acid (at 110-150°C), hydrogen bromide/glacial acetic acid (at room temperature, in the presence of formic acid or without a further solvent) or HCl gas in ethereal solution followed by the addition of water or aqueous hydrochloric acid, or reaction with boron halides.

Using the Graf-Ritter reaction it is also possible to prepare N-substituted amides from nitriles of formula IV. For this purpose the nitriles are reacted in the presence of a strong acid, especially 85-90 % sulfuric acid, or alternatively polyphosphoric acid, formic acid, boron trifluoride or other Lewis acids, but not aluminium chloride, with compounds capable of forming carbenium ions in the acidic medium, that is to say, for example, with olefins, such as propylene, or alcohols, such as ethanol.

The carboxylic acid ester imides are obtained, for example, by acid-catalysed addition of alcohols to the nitriles of formula IV. The amides are obtained from the ester imides in the manner of a Pinner cleavage by thermal decomposition of the ester imide salts at temperatures above approximately 80°C.

Compounds of formula IV wherein W_3 is cyano can be prepared, for example, by reacting

a compound of formula V with a compound of formula III in accordance with process a). From compounds of formula IV wherein W_3 is cyano it is possible to prepare, in a manner known per se or as described above, the other compounds of formula IV wherein W_3 is free carboxy or carboxy functionally modified in some other way.

Compounds of formula I can be converted into different compounds of formula I.

For example, compounds of formula I wherein X is a radical $-C(=S)-NH_2$ can be converted by S-alkylation, for example with tri-lower alkyloxonium tetrafluoroborate, and subsequent reaction with ammonia or an amine of the formula NHR_6R_7 , or especially a corresponding ammonium salt thereof, into compounds of formula I wherein X is a radical $-C(=NH)-NR_6R_7$.

Compounds of formula I wherein X is an N-hydroxyamidino radical $-C(=NR_8)-NHOH$ can be converted, for example by reaction with iron pentacarbonyl $[Fe(CO)_5]$, into other compounds of formula I wherein X is an analogous amidino radical $-C(=NR_8)-NH_2$ (see, for example, J. Chem. Soc. Chem. Commun. 1975, 761).

Free compounds of formula I obtainable in accordance with the process having salt-forming properties can be converted into their salts in a manner known per se; compounds having basic properties can be converted into their salts, for example, by treatment with acids or suitable derivatives thereof, and compounds having acidic properties can be converted into their salts, for example, by treatment with bases or suitable derivatives thereof.

As a result of the close relationship between the compounds of formula I in free form and in the form of salts, hereinabove and hereinbelow any reference to the free compounds or their salts is to be understood as including the corresponding salts or free compounds, respectively, as appropriate and expedient.

The compounds, including their salts, can also be obtained in the form of hydrates, or their crystals may include, for example, the solvent used for crystallisation.

Mixtures of isomers obtainable in accordance with the invention can be separated into the individual isomers in a manner known per se; racemates can be separated, for example, by the formation of salts with optically pure salt-forming reagents and separation of the dia-

stereoisomeric mixture so obtainable, for example by fractional crystallisation.

The above-mentioned reactions can be carried out under reaction conditions known per se, in the absence or, usually, in the presence of solvents or diluents, preferably those solvents or diluents which are inert towards the reagents used and are solvents therefor, in the absence or presence of catalysts, condensation agents or neutralising agents, and, depending upon the nature of the reaction and/or the reactants, at reduced, normal or elevated temperature, for example in a temperature range of from approximately -70°C to approximately 190°C, preferably from approximately -20°C to approximately 150°C, for example at the boiling point of the solvent used, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under a nitrogen atmosphere.

In the process of the present invention it is preferable to use those starting materials which result in the compounds described at the beginning as being especially valuable.

It is also possible to use those forms of the process in which a compound obtainable as intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example a salt thereof.

The present invention relates also to pharmaceutical compositions that comprise one of the pharmacologically active compounds of formula I as active ingredient. Compositions for enteral, especially oral, and for parenteral administration are especially preferred. The compositions comprise the active ingredient on its own or, preferably, together with a pharmaceutically acceptable carrier. The dosage of the active ingredient depends upon the disease to be treated and upon the species, its age, weight and individual condition, and also upon the mode of administration.

The pharmaceutical compositions comprise from approximately 0.1 % to approximately 95 % active ingredient, dosage forms in single dose form preferably comprising from approximately 1 % to approximately 90 % active ingredient and dosage forms that are not in single dose form preferably comprising from approximately 0.1 % to approximately 20 % active ingredient. Unit dose forms, such as dragées, tablets or capsules, comprise from approximately 1 mg to approximately 500 mg of active ingredient.

The pharmaceutical compositions of this invention are prepared in a manner known per se, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes. For example, pharmaceutical compositions for oral use can be obtained by combining the active ingredient with one or more solid carriers, optionally granulating a resulting mixture, and, if desired, processing the mixture or granules, if necessary with the addition of additional excipients, to form tablets or dragée cores.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tri-calcium phosphate or calcium hydrogen phosphate, also binders, such as starches, for example corn, wheat, rice or potato starch, methylcellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, cross-linked polyvinylpyrrolidone, alginic acid or a salt thereof, such as sodium alginate.

Additional excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol, or derivatives thereof.

Dragée cores can be provided with suitable, optionally enteric, coatings, there being used inter alia concentrated sugar solutions which may contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures, or, for the production of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate. Colourings or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

Orally administrable pharmaceutical compositions also include dry-filled capsules consisting of gelatin, and also soft, sealed capsules consisting of gelatin and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, such as corn starch, binders and/or glidants, such as talc or magnesium stearate, and optionally stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquid excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols, to which stabilisers may also be added.

Other oral dosage forms are, for example, syrups prepared in customary manner which comprise the active ingredient, for example, in suspended form and in a concentration of about 0.1 % to 10 %, preferably about 1 %, or in a similar concentration that provides a suitable single dose, for example, when administered in measures of 5 or 10 ml. Also suitable are, for example, powdered or liquid concentrates for the preparation of shakes, for example in milk. Such concentrates may also be packaged in single dose quantities.

Suitable rectally administrable pharmaceutical compositions are, for example, suppositories that consist of a combination of the active ingredient and a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols.

For parenteral administration there are especially suitable aqueous solutions of an active ingredient in water-soluble form, for example in the form of a water-soluble salt, or aqueous injection suspensions that contain viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, if desired, stabilisers. The active ingredient, optionally together with excipients, can also be in the form of a lyophilisate and can be made into a solution prior to parenteral administration by the addition of suitable solvents.

Solutions such as are used, for example, for parenteral administration can also be used as infusion solutions.

The invention relates also to the compounds of formula I for use in a therapeutic method, especially in the treatment of the above-mentioned pathological conditions. The compounds of this invention can be administered prophylactically or therapeutically, preferably in the form of pharmaceutical compositions. In the case of an individual having a body weight of about 70 kg the daily dose administered is from approximately 1 mg to approximately 1000 mg, preferably approximately from 25 to 100 mg in the case of oral administration and approximately from 2 to 50 mg in the case of parenteral administration, of a compound of the present invention.

The following Examples illustrate the present invention; temperatures are given in degrees Celsius. The following abbreviations are used: DMF = N,N-dimethylformamide; ether = diethyl ether; THF = tetrahydrofuran; MS (FAB) = mass spectrum ("Fast Atom

Bombardment").

Example 1: 4-Amidino-1-indanone-2'-amidinohydrazone dihydrochloride

A solution of 3.8 g (27.9 mmol) of aminoguanidine hydrogen carbonate in 200 ml of water and 14.7 ml of 2N hydrochloric acid is heated to 60° and, with stirring, a solution of 5.85 g (27.8 mmol) of 4-amidino-1-indanone hydrochloride in 200 ml of methanol is added thereto within a period of 30 minutes. The reaction mixture is boiled at reflux for 24 hours and, after cooling, concentrated to dryness by evaporation. The residue is suspended in 50 ml of ethanol, filtered, washed with ethanol and ether and dried, yielding the title compound containing 1 mol of water of crystallisation, m.p. >330°;

MS(FAB): (M+H)⁺=231; ¹H-NMR (D₂O): δ=8.08 (d,1H); 7.75 (d,1H); 7.58 (t,1H); 3.35 (m,2H); 2.96 (m,2H).

The starting compounds are prepared as follows:

(a) 4-Thiocarbamoyl-1-indanone

A solution of 12.1 g (77 mmol) of 4-cyano-1-indanone [Coll. Czechoslov. Chem. Commun. **43**, 3227 (1978)] in 220 ml of pyridine and 10.6 ml (77 mmol) of triethylamine is saturated with hydrogen sulfide for 3 hours at 40° and then stirred for a further 16 hours at the same temperature. After cooling, the reaction mixture is concentrated to dryness by evaporation and then 300 ml of water are added to the residue. The yellow product that crystallises out is filtered off with suction, washed with water, dried and recrystallised from ethyl acetate, yielding starting compound (a), m.p. 197° (decomp.).

b) 4-Amidino-1-indanone hydrochloride

10.8 g (54 mmol) of triethyloxonium tetrafluoroborate are added at room temperature under argon to a solution of 9.8 g (51.3 mmol) of 4-thiocarbamoyl-1-indanone in 500 ml of absolute methylene chloride. After 16 hours a mixture of 4.2 g of potassium carbonate and 4.2 ml of water is added to the reaction solution. The mixture is then stirred briefly and filtered, and the filtrate is washed with water. The organic phase is dried over magnesium sulfate, filtered and concentrated by evaporation. The resulting crude ethylthioimino ether is dissolved in 160 ml of absolute ethanol; 3.3 g (60 mmol) of ammonium chloride are added and the mixture is heated at reflux for 20 hours. After cooling, the reaction mixture is concentrated to dryness by evaporation. Starting compound (b) is purified by chromatography on 1000 ml of Amberlite[®] ER-180 resin (water as eluant) and recrystallised from ethanol/ether, m.p. 215-218° (decomp.).

Example 2: 4-Amidino-1-indanone-2'-(N-hydroxyamidino)-hydrazone dihydrochloride

A solution of 394 mg (1.5 mmol) of 1-amino-3-hydroxyguanidine-4-toluenesulfonate in 6 ml of water and 0.75 ml (1.5 mmol) of 2N hydrochloric acid is added to a solution of 316 mg (1.5 mmol) of 4-amidino-1-indanone hydrochloride (Example 1b) in 7 ml of methanol, and the mixture is heated at reflux for 2 hours and stirred at room temperature for 16 hours. The reaction mixture is concentrated by evaporation and the residue is purified by chromatography (Pharmacia column SR-28-100) on silica gel OPTI-UP C₁₂ (water as eluant, 5 ml fractions, throughflow rate 27.5 ml/h). The contents of fractions 58-78 are combined and concentrated by evaporation, and the residue is crystallised from ethanol, yielding the title compound in the form of wax-like crystals,

MS (FAB): (M+H)⁺ = 247; ¹H-NMR (D₂O): δ =8.06 (d,1H); 7.73 (d,1H); 7.58 (t,1H); 3.36 (m,2H); 2.98 (m,2H).

Example 3: 5-Amidino-1-tetralone-2'-amidinohydrazone dihydrochloride

0.675 g (3 mmol) of 5-amidino-1-tetralone hydrochloride is added to a solution of 0.41 g (3 mmol) of aminoguanidine hydrogen carbonate in 31.5 ml of 0.1N hydrochloric acid and the mixture is heated at reflux for 72 hours. After cooling, the mixture is concentrated to dryness by evaporation and the title compound is recrystallised from methanol/ether, m.p. >250°; MS (FAB): (M+H)⁺ = 245; ¹H-NMR (DMSO-d₆): δ =11.3 (s, 1H); 9.5 (m,4H); 8.65 (d,1H); 7.92 (m,3H); 7.52 (d,1H); 7.46 (t,1H); 2.7-2.85 (m,4H); 1.9 (m,4H).

The starting compounds are prepared as follows:

(a) 5-Cyano-1-tetralone

0.41 g (4.5 mmol) of copper(I) cyanide is added to a solution of 1.0 g (4.4 mmol) of 5-bromo-1-tetralone [J. Org. Chem. **49**, 4226 (1984)] in 1.3 ml of DMF and stirred for 6 hours at 160°. The reaction mixture is then cooled to 80° and a solution of 1.6 g of iron(III) chloride hexahydrate in 2.5 ml of water and 0.44 ml of concentrated hydrochloric acid is added. The reaction mixture is stirred for 45 minutes, cooled, diluted with water and extracted with toluene. The organic phase is washed with water, dried over magnesium sulfate, filtered and concentrated by evaporation, yielding starting compound (a) in the form of yellowish-orange crystals. IR (CH₂Cl₂): 2220, 1690 cm⁻¹; ¹H-NMR (CDCl₃): δ = 8.26 (q,1H); 7.81 (q,1H); 7.43 (t,1H); 3.21 (t,2H); 2.72 (t,2H); 2.23 (m,2H).

(b) 5-Thiocarbamoyl-1-tetralone

Analogously to Example 1a, 10.6 g (62 mmol) of 5-cyano-1-tetralone in 200 ml of pyridine and 8.6 ml of triethylamine are treated with hydrogen sulfide and worked up, yielding starting compound (b) in the form of yellow crystals, m.p. 200-205°.

(c) 5-Amidino-1-tetralone hydrochloride

Analogously to Example 1b, 8.6 g (42 mmol) of 5-thiocarbamoyl-1-tetralone are treated with 8.8 g (44 mmol) of triethyloxonium tetrafluoroborate and 2.6 g (49 mmol) of ammonium chloride, yielding starting compound (c) in the form of slightly pink crystals, MS (FAB): $(M+H)^+ = 189$.

Example 4: 4-Thiocarbamoyl-1-indanone-2'-amidinohydrazone hydrochloride

1.36 g (10 mmol) of aminoguanidine hydrogen carbonate and 10 ml of 2N hydrochloric acid are added to a solution of 1.9 g (10 mmol) of 4-thiocarbamoyl-1-indanone (Example 1a) in 50 ml of ethanol and the mixture is heated at reflux for 24 hours. After cooling, the reaction mixture is concentrated to dryness by evaporation, yielding the title compound.

Example 5: 4-Amidino-1-indanone-2'-amidinohydrazone dihydrochloride

Analogously to Example 1b, 4-thiocarbamoyl-1-indanone-2'-amidinohydrazone hydrochloride (Example 4) is reacted with triethyloxonium tetrafluoroborate and ammonium chloride, yielding the title compound, m.p. >330°; MS (FAB): $(M+H)^+ = 231$; $^1\text{H-NMR}$ (D_2O): $\delta=8.08$ (d,1H); 7.75 (d,1H); 7.58 (t,1H); 3.35 (m,2H); 2.96 (m,2H).

Example 6: 4-Amidino-1-indanone-2'-amidinohydrazone dihydrochloride

1.2 ml of a 1N sodium methoxide solution in methanol are added to a solution of 0.26 g (1 mmol) of 4-cyano-1-indanone-2'-amidinohydrazone hydrochloride in 5 ml of absolute methanol and the mixture is heated at reflux for 16 hours. After cooling, 0.16 g (3 mmol) of solid ammonium chloride is added to the reaction mixture which is then stirred for 1 hour at 60°. The reaction mixture is then concentrated by evaporation and the residue is crystallised from dilute ethanol, yielding the title compound, m.p. >330°.

The starting compound is prepared as follows:

(a) 4-Cyano-1-indanone-2'-amidinohydrazone hydrochloride

Analogously to Example 1, 314 mg (2 mmol) of 4-cyano-1-indanone are dissolved in

20 ml of methanol; a solution of 272 mg (2 mmol) of aminoguanidine hydrogen carbonate in 9 ml of water and 1 ml of 2N hydrochloric acid is added and the mixture is stirred at reflux for 4 days. After cooling, the reaction mixture is concentrated to dryness by evaporation and the residue is crystallised from water, yielding starting compound (a), m.p. >230°; ¹H-NMR (DMSO-d₆/D₂O): δ=8.16 (d,1H); 7.9 (d,1H); 7.55 (t,1H); 3.28 (m,2H); 2.9 (m,2H); IR(Nujol): 2190 cm⁻¹ (CN).

Example 7: 4-(N-Hydroxyamidino)-1-indanone-2'-amidinohydrazone dihydrochloride

0.2 g (3 mmol) of hydroxylamine hydrochloride is suspended in 1 ml of absolute ethanol, and 2 ml of a 1N sodium ethoxide solution in ethanol are added. This mixture is stirred for 1 hour and filtered. A solution of 0.26 g (1 mmol) of 4-cyano-1-indanone-2'-amidinohydrazone hydrochloride (Example 6a) in 2 ml of water is added to the filtrate, and the mixture is heated at reflux for 6 hours. After cooling, the reaction mixture is concentrated by evaporation and the title compound is crystallised from water, m.p. >250°; ¹H-NMR (DMSO-d₆ + D₂O): δ = 8.12 (m,1H); 7.55 (m,2H); 3.22 (m,2H); 2.83 (m,2H).

Example 8: 4-Amidino-2-methyl-1-indanone-2'-amidinohydrazone dihydrochloride

Analogously to Example 1, the title compound is prepared from 4-cyano-2-methyl-1-indanone (see US Patent 3 956 363).

Example 9: 5-Amidino-6-methoxy-1-tetralone-2'-amidinohydrazone dihydrochloride

Analogously to Example 1, the title compound is prepared from 5-cyano-6-methoxy-1-tetralone [Chem. Pharm. Bull. 31, 2329 (1983)].

Example 10: 4-Amidino-6-methyl-1-indanone-2'-amidinohydrazone dihydrochloride

Analogously to Example 3, the title compound is prepared from 4-bromo-6-methyl-1-indanone (Bull. Soc. Chim. France 1964, 3103).

Example 11: 4-Amidino-6-methoxy-7-methyl-1-indanone-2'-amidinohydrazone dihydrochloride

Analogously to Example 3, the title compound is prepared from 4-bromo-6-methoxy-7-methyl-1-indanone (J. Chem. Soc. Perkin Trans. 1 1974, 1911).

Example 12: 4-Amidino-6,7-dimethyl-1-indanone-2'-amidinohydrazone dihydrochloride

Analogously to Example 3, the title compound is prepared from 4-bromo-6,7-dimethyl-1-indanone [J. Het. Chem. 24, 677 (1987)].

Example 13: 4-Amidino-7-hydroxy-3-methyl-1-indanone-2'-amidinohydrazone dihydrochloride

Analogously to Example 3, the title compound is prepared from 4-bromo-7-hydroxy-3-methyl-1-indanone [Indian J. Chem. Sect. B 24B, 1061 (1985)].

Example 14: 4-(Methylamidino)-1-indanone-2'-amidinohydrazone dihydrochloride

Analogously to Example 1b, 4-thiocarbamoyl-1-indanone-2'-amidinohydrazone hydrochloride (Example 4) is reacted with triethyloxonium tetrafluoroborate and methylammonium chloride, yielding the title compound.

Example 15: 4-Amidino-1-indanone-2'-amidinohydrazone dihydrochloride

9.45 g (44.9 mmol) of 4-amidino-1-indanone hydrochloride (see Example 1b) are added to a solution of 6.12 g (45 mmol) of aminoguanidine hydrogen carbonate in 100 ml of water and 46 ml of 1N hydrochloric acid and the mixture is stirred for 24 hours at 24°. The product that crystallises out is filtered off with suction, washed with a small amount of water and recrystallised from 300 ml of water, yielding the title compound containing 1 mol of water of crystallisation, m.p. >330°; MS (FAB): (M + H)⁺ = 231; ¹H-NMR (D₂O): δ = 8.08 (d,1H); 7.75 (d,1H); 7.58 (t,1H); 3.35 (m,2H); 2.96 (m,2H).

Example 16: 4-Amidino-2-methyl-1-indanone-2'-amidinohydrazone dihydrochloride

A solution of 1.0 g (5.0 mmol) of 4-amidino-2-methyl-1-indanone hydrochloride and 0.68 g (5.0 mmol) of aminoguanidine hydrogen carbonate in 10 ml of 0.5N hydrochloric acid is stirred for 120 hours at 25°. The product that crystallises out is filtered off with suction, washed with a small amount of water and dried, yielding the title compound, m.p. >250°; MS (FAB): (M + H)⁺ = 245; ¹H-NMR (D₂O): δ = 7.95 (d,1H); 7.66 (d,1H); 7.48 (t,1H); 3.45 (m,2H); 2.85 (d,1H); 1.12 (d,3H).

The starting compounds are prepared as follows:

(a) 4-Thiocarbamoyl-2-methyl-1-indanone

Analogously to Example 1a, 11.1 g (65 mmol) of 4-cyano-2-methyl-1-indanone [see US Patent 3 956 363] in 200 ml of pyridine and 9.7 ml of triethylamine are treated with hydrogen sulfide and worked up, yielding starting compound (a) in the form of yellow crystals, m.p. 195-198° (decomp.); ¹H-NMR (DMSO-d₆): δ = 9.61 (s,1H); 7.71 (m,2H); 7.48 (m,1H); 3.48 (m,1H); 2.81 (m,2H); 1.23 (s,3H); 1.19 (s,3H).

(b) 4-Amidino-2-methyl-1-indanone hydrochloride

Analogously to Example 1b, 10.2 g (50 mmol) of starting compound (a) are treated with 11.0 g (55 mmol) of triethyloxonium tetrafluoroborate and 3.2 g (60 mmol) of ammonium chloride, yielding starting compound (b) in the form of pink crystals. It is immediately reacted further.

Example 17: 4-Amidino-6,7-dimethyl-1-indanone-2'-amidinohydrazone dihydrochloride

Analogously to Example 1, the title compound is prepared from 4-amidino-6,7-dimethyl-1-indanone hydrochloride, m.p. $>240^{\circ}\text{C}$; MS (FAB): $(\text{M}+\text{H})^{\oplus} = 259$;

$^1\text{H-NMR}$ (D_2O): $\delta = 7.43$ (s,1H); 3.12 (m,2H); 2.75 (m,2H); 2.43 (s,3H); 2.24 (s,3H).

The starting compounds are prepared as follows:

(a) 4-Cyano-6,7-dimethyl-1-indanone

A mixture of 17.8 g (74.5 mmol) of 4-bromo-6,7-dimethyl-1-indanone [J. Het. Chem. **24**, 677 (1987)] and 7.3 g (82 mmol) of copper(I) cyanide in 18 ml of DMF is stirred for 6 hours at 170° . The reaction mixture is then cooled to 100° and 200 ml of toluene and a solution of 31.2 g of iron(III) chloride hexahydrate in 47 ml of water and 8.2 ml of concentrated hydrochloric acid are added in succession thereto. The reaction mixture is stirred for 20 minutes at 70° , cooled and diluted with toluene and water. The organic phase is separated off, washed with water, a semi-saturated sodium hydrogen carbonate solution and again with water, dried and concentrated by evaporation. The residue is crystallised from ethyl acetate and ether and corresponds to starting compound (a). Beige crystals having a melting point of $160\text{-}163^{\circ}$ are obtained; IR (CH_2Cl_2): $2220, 1710\text{ cm}^{-1}$.

(b) 4-Thiocarbamoyl-6,7-dimethyl-1-indanone

Analogously to Example 1a, 10 g (54.1 mmol) of starting compound (a) in 200 ml of pyridine and 7.5 ml of triethylamine are treated with hydrogen sulfide and worked up, yielding starting compound (b) in the form of yellow crystals, m.p. $207\text{-}208^{\circ}$;

$^1\text{H-NMR}$ (DMSO-d_6): $\delta = 10.03$ (s,1H); 9.49 (s,1H); 7.49 (s,1H); 3.12 (m,2H); 2.61 (m,2H); 2.54 (s,3H); 2.29 (s,3H).

(c) 4-Amidino-6,7-dimethyl-1-indanone hydrochloride

Analogously to Example 1b, 4.4 g (20 mmol) of starting compound (b) are treated with 4.26 g (21 mmol) of triethyloxonium tetrafluoroborate and 1.2 g (24 mmol) of ammonium

chloride, yielding starting compound (c) in the form of beige crystals.

Example 18: 4-Amidino-6,7-dimethoxy-1-indanone-2'-amidinohydrazone dihydrochloride

0.73 g (2.7 mmol) of 4-amidino-6,7-dimethoxy-1-indanone hydrochloride is added to a solution of 0.4 g (3 mmol) of aminoguanidine hydrogen carbonate in 6 ml of 0.5N hydrochloric acid and the mixture is stirred for 24 hours at 50°. After cooling, the product that has crystallised out is filtered with suction, washed with a small amount of water and dried, yielding the title compound, m.p. >220°; MS (FAB): (M + H)⁺ = 291; ¹H-NMR (D₂O): δ = 7.45 (s,1H); 3.97 (s,6H); 3.27 (m,2H); 2.98 (m,2H).

The starting compounds are prepared as follows:

(a) 4-Cyano-6,7-dimethoxy-1-indanone

A mixture of 6.57 g (24.2 mmol) of 4-bromo-6,7-dimethoxy-1-indanone [Can. J. Chem. 57, 1603 (1979)] and 2.5 g (28 mmol) of copper(I) cyanide in 7 ml of DMF is stirred for 5.75 hours at 170°. The reaction mixture is then cooled to 100° and then 70 ml of toluene and a solution of 9.7 g (36 mmol) of iron(III) chloride hexahydrate in 15.6 ml of water and 3.5 ml of concentrated hydrochloric acid are added in succession thereto. The reaction mixture is then stirred for 30 minutes at 80°, cooled and diluted with toluene and water. The organic phase is separated off, washed with water, a semi-saturated sodium hydrogen carbonate solution and again with water, dried and concentrated by evaporation. The residue is distilled at 150-160°/0.1 mbar in a bulb tube still and corresponds to starting compound (a), m.p. 150°; IR (CH₂Cl₂): 2220, 1710 cm⁻¹; ¹H-NMR (CDCl₃): δ = 7.33 (s,1H); 4.12 (s,3H); 3.90 (s,3H); 3.19 (m,2H); 2.76 (m,2H).

(b) 4-Thiocarbamoyl-6,7-dimethoxy-1-indanone

Analogously to Example 1a, 3.7 g (17 mmol) of starting compound (a) in 100 ml of pyridine and 2.4 ml of triethylamine are treated with hydrogen sulfide and worked up, yielding starting compound (b) in the form of bright yellow crystals, m.p. 196-199°; ¹H-NMR (DMSO-d₆): δ = 10.06 (s,1H); 9.50 (s,1H); 7.41 (s,1H); 3.84 (s,6H); 3.13 (m,2H); 2.63 (m,2H).

(c) 4-Amidino-6,7-dimethoxy-1-indanone hydrochloride

Analogously to Example 1b, 3.3 g (13 mmol) of starting compound (b) are treated with 2.8 g (14 mmol) of triethyloxonium tetrafluoroborate and 0.8 g (15 mmol) of ammonium chloride, yielding starting compound (c) in the form of beige crystals, m.p. 188° (with

decomp.); $^1\text{H-NMR}$ (DMSO- d_6): δ = 9.4 (s,3H); 7.63 (s,1H); 3.92 (s,3H); 3.89 (s,3H); 3.18 (m,2H); 2.68 (m,2H).

Example 19: 4-Amidino-3-methyl-1-indanone-2'-amidinohydrazone dihydrochloride

300 mg (2.3 mmol) of aminoguanidine hydrogen carbonate in 4 ml of 0.5N hydrochloric acid are added to a solution of 300 mg (1.3 mmol) of 4-amidino-3-methyl-1-indanone hydrochloride in 6 ml of water and the mixture is stirred for 24 hours at 80°. The reaction mixture is cooled and concentrated by evaporation and the residue is purified by chromatography on 180 ml of Amberlite® ER-180 resin with water as eluant. The title compound is recrystallised from methanol/ether, m.p. >250°; R_f = 0.18 (silica gel, methylene chloride/methanol/conc. ammonia 5:3:1); MS (FAB): $(M + H)^+ = 245$; $^1\text{H-NMR}$ (D_2O): δ = 7.97 (d,1H); 7.64 (d,1H); 7.49 (t,1H); 3.86 (m,1H); 3.17 (q,1H); 2.49 (d,1H); 1.24 (d,3H).

The starting compounds are prepared as follows:

(a) 4-Cyano-3-methyl-1-indanone

A mixture of 2.6 g (11.5 mmol) of 4-bromo-3-methyl-1-indanone [J. Org. Chem. 22, 1019 (1957)] and 1.14 g (12.7 mmol) of copper(I) cyanide in 2.5 ml of DMF is stirred for 6 hours at 170°. The reaction mixture is then cooled to 100°, and 50 ml of toluene and a solution of 4.5 g (16.5 mmol) of iron(III) chloride hexahydrate in 7 ml of water and 1.7 ml of concentrated hydrochloric acid are added in succession thereto. The reaction mixture is stirred for 20 minutes at 70°, cooled and diluted with toluene and water. The organic phase is separated off, washed with water, a semi-saturated sodium hydrogen carbonate solution and again with water, dried and concentrated by evaporation. The residue is distilled at 100-120°/0.05 mbar in a bulb tube still and corresponds to starting compound (a), m.p. 109-111°; IR (CH_2Cl_2): 2220, 1710 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3): δ = 7.92 (m,2H); 7.52 (t,1H); 3.73 (m,1H); 3.03 (q,1H); 2.40 (q,1H); 1.55 (d,3H).

(b) 4-Thiocarbamoyl-3-methyl-1-indanone

Analogously to Example 1a, 1.45 g (8.47 mmol) of starting compound (a) in 25 ml of pyridine and 1.2 ml of triethylamine are treated with hydrogen sulfide and worked up, yielding starting compound (b) in the form of pale yellow crystals, m.p. 198-200°; $^1\text{H-NMR}$ (DMSO- d_6): δ = 9.78 (s,1H); 7.65 (m,2H); 7.46 (m,1H); 3.98 (m,1H); 2.95 (q,1H); 2.26 (q,1H); 1.25 (d,3H).

(c) 4-Amidino-3-methyl-1-indanone hydrochloride

Analogously to Example 1b, 0.96 g (4.68 mmol) of starting compound (b) is treated with 1.0 g (4.93 mmol) of triethyloxonium tetrafluoroborate and 0.3 g (6 mmol) of ammonium chloride, yielding starting compound (c) in the form of beige crystals,

¹H-NMR (DMSO-d₆): δ = 9.59 (s, 4H); 7.65 (m, 2H); 7.46 (m, 1H); 3.98 (m, 1H); 2.95 (q, 1H); 2.26 (q, 1H); 1.25 (d, 3H).

Example 20: 4-Amidino-1-indanone-2'-amidinohydrazone dihydrochloride

A mixture of 0.32 g (1 mmol) of 4-(N-hydroxyamidino)-1-indanone-2'-amidinohydrazone dihydrochloride (Example 7), 0.36 ml (2 mmol) of triethylamine and 0.2 g (1 mmol) of iron pentacarbonyl in 10 ml of absolute THF is boiled at reflux for 16 hours. The reaction mixture is then concentrated by evaporation and the residue is crystallised from dilute hydrochloric acid, yielding the title compound, m.p. >330°.

Example 21: 4-Amidino-2-ethyl-1-indanone-2'-amidinohydrazone dihydrochloride

3-(2-Bromophenyl)-2-ethylpropionic acid (German Patent 2 733 868) is cyclised with polyphosphoric acid at elevated temperature to form the corresponding 1-indanone and converted into the title compound analogously to Example 3.

Example 22: 4-Amidino-2-n-butyl-1-indanone-2'-amidinohydrazone dihydrochloride

3-(2-Bromophenyl)-2-n-butylpropionic acid (German Patent 2 733 868) is cyclised with polyphosphoric acid at elevated temperature to form the corresponding 1-indanone and converted into the title compound analogously to Example 3.

Example 23: Capsules comprising 0.25 g of active ingredient, for example one of the compounds of Examples 1 to 22, can be prepared as follows:

Composition (for 5000 capsules)

active ingredient	1250 g
talc	180 g
wheat starch	120 g
magnesium stearate	80 g
lactose	20 g

The pulverulent substances are forced through a sieve of 0.6 mm mesh size and mixed together. 0.33 g portions of the mixture are introduced into gelatin capsules using a

capsule-filling machine.

Example 24: 10 000 tablets are prepared, each tablet comprising 5 mg of active ingredient, for example one of the compounds prepared according to Examples 1 to 22:

Composition

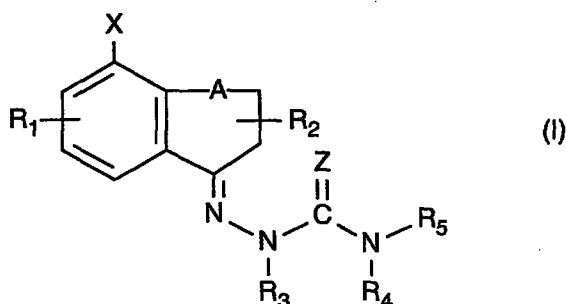
active ingredient	50.00 g
lactose	2535.00 g
corn starch	125.00 g
polyethylene glycol 6000	150.00 g
magnesium stearate	40.00 g
purified water	quantum satis

Procedure All the pulverulent constituents are passed through a sieve of 0.6 mm mesh size. Then the active ingredient, the lactose, the magnesium stearate and half of the starch are mixed together in a suitable mixer. The other half of the starch is suspended in 65 ml of water and the resulting suspension is added to a boiling solution of the polyethylene glycol in 260 ml of water. The resulting paste is added to the powder mixture and granulated, if necessary with the addition of more water. The granules are dried overnight at 35°C, forced through a sieve of 1.2 mm mesh size and compressed to form tablets having a breaking notch.



Patent claims for Contracting States AT, BE, CH, DE, DK, GB, FR, IT, LI, LU, NL and SE:

1. A compound of formula I



wherein A is a direct bond or $-(CH_2)_n-$, wherein n is 1, 2 or 3; X is a radical $-C(=Y)-NR_6R_7$; Y is NR_8 , O or S; Z is NR_9 , O or S; R_1 and R_2 are each independently of the other hydrogen or one or more substituents selected from lower alkyl, trifluoromethyl, C_3-C_8 cycloalkyl that is unsubstituted or lower alkyl-substituted, aryl-lower alkyl, hydroxy, lower alkoxy, aryl-lower alkoxy, aryloxy, lower alkanoyloxy, halogen, amino, N-lower alkylamino, N,N-di-lower alkylamino, lower alkanoylamino, nitro, lower alkanoyl, aryl-carbonyl, carboxy, lower alkoxy carbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, N-arylcarbamoyl, cyano, mercapto, lower alkylthio, lower alkyl-sulfonyl, sulfamoyl, N-lower alkylsulfamoyl and N,N-di-lower alkylsulfamoyl; the radicals R_3 , R_4 , R_6 , R_8 and R_9 are each independently of the others hydrogen or lower alkyl; and R_5 and R_7 are each independently of the other hydrogen, lower alkyl, hydroxy, lower alkoxy, lower alkanoyloxy, unsubstituted amino, di-lower alkylamino, C_4-C_7 -alkyleneamino or oxa-, thia- or aza- C_4-C_7 -alkyleneamino; a tautomer thereof, or a salt thereof; aryl being phenyl or naphthyl each of which is unsubstituted or substituted by one or more substituents selected from lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, nitro, amino, halogen, trifluoromethyl, carboxy, lower alkoxy carbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, cyano, lower alkanoyl, aryl-carbonyl, lower alkylsulfonyl, sulfamoyl, N-lower alkylsulfamoyl and N,N-di-lower alkyl-sulfamoyl; and the term "lower" or "-lower" indicating a radical having up to and including a maximum of 7 carbon atoms.

2. A compound of formula I according to claim 1 wherein A is a direct bond or $-(CH_2)_n-$, wherein n is 1 or 2; X is a radical $-C(=Y)-NR_6R_7$; Y is NR_8 , O or S; Z is NR_9 , O or S;



R_1 and R_2 are each independently of the other hydrogen or one or two substituents from the group consisting of lower alkyl, trifluoromethyl, cycloalkyl, aryl-lower alkyl, hydroxy, lower alkoxy, aryl-lower alkoxy, aryloxy, lower alkanoyloxy, halogen, amino, N-lower alkylamino, N,N-di-lower alkylamino, lower alkanoylamino, nitro, lower alkanoyl, aryl-carbonyl, carboxy, lower alkoxy-carbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, N-arylcarbamoyl, cyano, mercapto, lower alkylthio, lower alkyl-sulfonyl, sulfamoyl, N-lower alkylsulfamoyl and N,N-di-lower alkylsulfamoyl, aryl being phenyl that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen or by trifluoromethyl; the radicals R_3 , R_4 , R_6 , R_8 and R_9 are each independently of the others hydrogen or lower alkyl; and R_5 and R_7 are each independently of the other hydrogen, lower alkyl, hydroxy, lower alkoxy, lower alkanoyloxy, amino, lower alkyl-amino, di-lower alkylamino, C_4 - C_7 alkyleneamino or oxa-, thia- or aza- C_4 - C_7 alkylene-amino; a tautomer thereof, or a salt thereof; the term "lower" or "-lower" indicating a radical having up to and including a maximum of 7 carbon atoms.

3. A compound of formula I according to claim 1 wherein A is a direct bond or $-(CH_2)_n$, wherein n is 1 or 2; X is a radical $-C(=Y)-NR_6R_7$; Y is NH, O or S; Z is NH, O or S; R_1 and R_2 are each independently of the other hydrogen or one or two substituents from the group consisting of lower alkyl, trifluoromethyl, phenyl-lower alkyl, hydroxy, lower alkoxy and halogen; the radicals R_3 , R_4 and R_6 are hydrogen; and R_5 and R_7 are each independently of the other hydrogen, lower alkyl, hydroxy or amino; a tautomer thereof, or a salt thereof; the term "lower" or "-lower" indicating a radical having up to and including a maximum of 7 carbon atoms.

4. A compound of formula I according to claim 1 wherein A is a direct bond or $-CH_2-$; X is a radical $-C(=Y)-NR_6R_7$; Y is NH or S; Z is NH; R_1 is hydrogen or one or two substituents from the group consisting of lower alkyl, hydroxy, lower alkoxy and halogen; R_2 is hydrogen or lower alkyl; the radicals R_3 , R_4 and R_6 are hydrogen; and R_5 and R_7 are each independently of the other hydrogen, lower alkyl or hydroxy; a tautomer thereof, or a pharmaceutically acceptable salt thereof; the term "lower" or "-lower" indicating a radical having up to and including a maximum of 7 carbon atoms.

5. A compound of formula I according to claim 1 wherein A is a direct bond, X is a radical $-C(=NH)-NH_2$; Z is NH; R_1 is hydrogen or one or two substituents from the group consisting of lower alkyl, hydroxy and lower alkoxy; the radicals R_2 , R_3 and R_4 are hydrogen; and R_5 is hydrogen or hydroxy; a tautomer thereof, or a pharmaceutically



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acceptable salt thereof; the term "lower" or "-lower" indicating a radical having up to and including a maximum of 7 carbon atoms.

6. 4-Amidino-1-indanone-2'-amidinohydrazone according to claim 1 or a pharmaceutically acceptable salt thereof.

7. 4-Amidino-1-indanone-2'-(N-hydroxyamidino)-hydrazone according to claim 1 or a pharmaceutically acceptable salt thereof.

8. 5-Amidino-1-tetralone-2'-amidinohydrazone according to claim 1 or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition comprising a compound according to any one of claims 1 to 8 and at least one pharmaceutically acceptable carrier.

10. A compound according to any one of claims 1 to 8 for use in a method for the therapeutic treatment of the animal or human body.

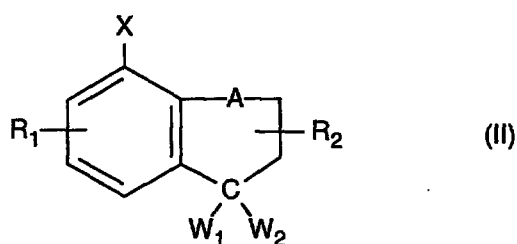
11. A compound according to any one of claims 1 to 8 for use in the treatment of diseases responsive to inhibition of the enzyme S-adenosylmethionine decarboxylase.

12. The use of a compound according to any one of claims 1 to 8 for the manufacture of pharmaceutical compositions.

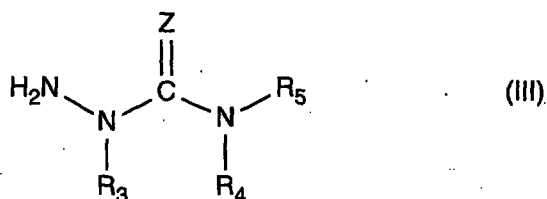
13. The use of a compound according to any one of claims 1 to 8 for the manufacture of pharmaceutical compositions for the treatment of diseases responsive to inhibition of the enzyme S-adenosylmethionine decarboxylase.

14. A process for the preparation of a compound of formula I according to claim 1, which process comprises

(a) condensing a compound of formula II

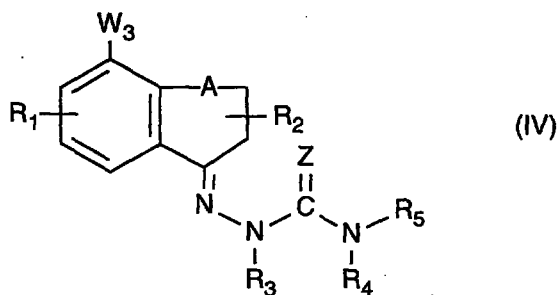


wherein the group CW_1W_2 is carbonyl, functionally modified carbonyl or protected carbonyl and A, X, R_1 and R_2 are as defined for formula I, with an amine of formula III



wherein Z, R_3 , R_4 and R_5 are as defined for formula I, or

(b) in a compound of formula IV



wherein W_3 is a radical that can be converted into a group X in formula I and A, Z, R_1 , R_2 , R_3 , R_4 and R_5 are as defined for formula I, converting the radical W_3 into the group X; and, if desired, converting a resulting compound of formula I into a different compound of formula I and/or, if desired, converting a resulting salt into the free compound or into a different salt and/or, if desired, converting a resulting free compound of formula I having salt-forming properties into a salt.