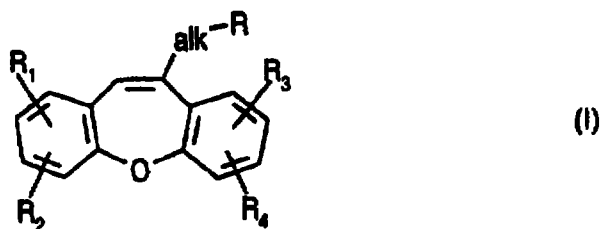


Anti-neurodegeneratively effective 10-aminoalipharyl-dibenz[b,f]oxepine salts

The invention relates to the use of acid addition salts of 10-aminoalipharyl-dibenz[b,f]oxepines of formula I



wherein alk signifies a divalent, aliphatic radical,

R represents an amino group, either unsubstituted or mono- or di-substituted by monovalent aliphatic and/or araliphatic radicals, or disubstituted by divalent aliphatic, araliphatic or heteroarylaliphatic radicals, and

R₁, R₂, R₃ and R₄, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl,

with organic carboxylic acids, as anti-neurodegenerative active ingredients for medicaments, or for the preparation thereof, as well as new acid addition salts of compounds of formula I with organic carboxylic acids as such, processes for their production and pharmaceutical preparations containing them.

New acid addition salts of compounds of formula I are for example acid addition salts of 10-aminoalipharyl-dibenz[b,f]oxepines of formula I, in which

a1) R is different from methylamino, dimethylamino, N'-methylpiperazino and N'-(2-hydroxyethyl)-piperazino, or at least one of radicals R₁, R₂ and R₄ is different from hydrogen or R₃ is different from hydrogen and 8-methoxy, or R is different from dimethylamino and diethylamino or at least one of radicals R₁, R₂ and R₄ is different from hydrogen or R₃ is different from 8-chloro, or R is different from pyrrolidino or at least one of radicals R₁, R₂ and R₄ is different from hydrogen, if alk respectively signifies methylene,

b1) R is different from methylamino or at least one of radicals R₁, R₂ and R₄ is different from hydrogen or R₃ is different from 6-methyl, or R is different from diethylamino, at least one of radicals R₁, R₂ and R₄ is different from hydrogen or R₃ is different from 7-methyl or at least one of radicals R₂, R₃ and R₄ is different from hydrogen or R₁ is different from 3-methyl, if alk is ethylene,

- c1) R is different from methylamino and dimethylamino or at least one of radicals R₁, R₂, R₃ and R₄ is different from hydrogen, if alk signifies ethylidene, and
- d1) R is different from dimethylamino or at least one of radicals R₂ and R₄ is different from hydrogen or R₁ is different from hydrogen, 3-chloro and 3-trifluoromethyl, or R₃ is different from hydrogen, 8-chloro and 8-trifluoromethyl, or R is different from diethylamino or at least one of radicals R₁, R₂, R₃ and R₄ is different from hydrogen, or R is different from piperidino, R₂, R₃ and R₄ from hydrogen, or R₁ is different from 1-bromo or R₁, R₂ and R₄ from hydrogen and R₃ from 9-bromo, if alk signifies propylene, in each case with the exception of the hydrogenoxalate of N-(Dibenzo[b,f]oxepin-10-ylmethyl-N-methyl-N-prop-2-ynyl-amine, preferably those, wherein
- a2) alk is different from methylene and ethylidene, if R signifies amino, lower alkylamino, di-lower-alkylamino or nitrogen-bonded alkyleneamino, oxaalkyleneamino, azaalkyleneamino, N'-lower-alkyl-azaalkyleneamino, N'-hydroxyalkyl-azaalkyleneamino or N'-alkanoyloxyalkyl-azaalkyleneamino radical with 5 to 7 ring members, and R₁, R₂, R₃ and R₄ signify hydrogen, lower alkyl, lower alkoxy, bromine or chlorine, and
- b2) alk is different from ethylene, 1,2- and 1,3-propylene, 1,2-, 1,3- and 1,4-butylene and 1,3-(2-methyl)propylene, if R signifies di-lower-alkylamino, pyrrolidino, piperidino, N-lower-alkylpiperidinyl, piperazino, N'-methylpiperazine, N'-formylpiperazino, N'-(2-hydroxyethyl)piperazino, N'-(2-acetoxyethyl)piperazino or N'-[2-(2-hydroxyethoxy)ethyl]-piperazino radical, R₁ and R₃ signify hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl and R₂ and R₄ signify hydrogen, and
- c2) alk is different from ethylene, if R is methylamino, R₁ and R₃ signify hydrogen, hydroxy, lower alkyl or lower alkoxy and R₂ and R₄ signify hydrogen.

Monovalent aliphatic radicals are for example lower alkyl, lower alkenyl or lower alkynyl groups that are unsubstituted or substituted by optionally esterified or amidated carboxy, cyano, optionally etherified or esterified hydroxy or by optionally aliphatically substituted amino, such as lower alkyl, carboxy-lower-alkyl, lower-alkoxycarbonyl-lower-alkyl, carbamoyl-lower-alkyl, cyano-lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, lower-alkanoyloxy-lower-alkyl, lower-alkylamino-lower-alkyl, di-lower-alkylamino-lower-alkyl, lower-alkyleneamino-lower-alkyl, lower-alkenyl, hydroxy-lower-alkenyl, lower-alkoxy-lower-alkenyl, lower-alkanoyloxy-lower-alkenyl, di-lower-alkylamino-lower-alkenyl, lower-alkynyl, hydroxy-lower-alkynyl, lower-alkoxy-lower-alkynyl, lower-alkanoyloxy-lower-alkynyl or di-lower-alkylamino-lower-alkynyl.

Araliphatic radicals are for example phenyl-lower-alkyl radicals that are unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl and/or in the lower alkyl moiety by optionally esterified carboxy.

Amino groups mono- or di-substituted by monovalent aliphatic or araliphatic radicals are thus for example lower alkylamino; phenyl-lower-alkylamino, phenyl(carboxy-lower-alkyl)amino, phenyl(lower-alkoxycarbonyl-lower-alkyl)amino or phenyl-lower-alkyl-lower-alkylamino radicals that are unsubstituted or substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl; hydroxy-lower-alkylamino, carboxy-lower-alkylamino, lower-alkoxycarbonyl-loweralkylamino, carbamoyl-lower-alkylamino, cyano-lower-alkylamino, lower-alkoxy-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, lower-alkyleneamino-lower-alkylamino, lower-alkenylamino, hydroxy-lower-alkenylamino, lower-alkoxy-lower-alkenylamino, lower-alkanoyloxy-lower-alkenylamino, di-lower-alkylamino-lower-alkenylamino, lower-alkinylamino, hydroxy-lower-alkinylamino, lower-alkoxy-lower-alkinylamino, lower-alkanoyloxy-lower-alkinylamino, di-lower-alkylamino-lower-alkinylamino, di-lower-alkylamino, di(hydroxy-lower-alkyl)amino, hydroxy-lower-alkyl-lower-alkylamino, di(lower-alkoxy-lower-alkyl)amino, lower-alkoxy-lower-alkyl-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkanoyloxy-lower-alkyl-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkyl-lower-alkylamino, di-lower-alkenylamino, lower-alkenyl-lower-alkylamino, hydroxy-lower-alkenyl-lower-alkylamino, di(lower-alkoxy-lower-alkenyl)amino, lower-alkoxy-lower-alkenyl-lower-alkylamino, lower-alkanoyloxy-lower-alkenyl-lower-alkylamino, di-lower-alkylamino-lower-alkenyl-lower-alkylamino, lower-alkinyl-lower-alkylamino, lower-alkoxy-lower-alkinyl-lower-alkylamino, lower-alkanoyloxy-lower-alkinyl-lower-alkylamino or di-lower-alkylamino-lower-alkinyl-lower-alkylamino.

Divalent aliphatic radicals alk are for example lower-alkylidene radicals, as a constituent of an amino group di-substituted by a divalent aliphatic radical, lower-alkylene, lower-alkenylene or lower-alkadienylene radicals either unsubstituted or substituted by optionally esterified or amidated carboxy or cyano; aza-lower-alkylene or oxa- or thia-lower-alkylene radicals either unsubstituted or substituted by lower alkyl, lower alkanoyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, or by phenyl which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl; such as 3- or 4-aza-lower-alkylene either

unsubstituted or N'-substituted by lower alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, phenyl, halogen-phenyl or lower-alkoxyphenyl or lower-alkanoyl; 3- or 4-oxa-lower-alkylene or optionally S-oxidised 3- or 4-thia-lower-alkylene.

Amino groups disubstituted by divalent aliphatic radicals are for example respectively 3- to 8-membered lower-alkylene-amino, lower-alkenyleneamino or lower-alkadienyleneamino either unsubstituted or substituted by optionally esterified or amidated carboxy, such as carboxy, lower-alkoxycarbonyl or carbamoyl, or by cyano; 3- or 4-aza-lower-alkyleneamino either unsubstituted or N'-substituted by lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, by phenyl which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl, or by lower-alkanoyl; 3- or 4-oxa-lower-alkyleneamino or optionally S-oxidised 3- or 4-thia-lower-alkyleneamino, such as in particular pyrrolidino, pyrrolino (2,5-dihydropyrrol-1-yl), pyrrolo (pyrrol-1-yl), piperidino, di-lower-alkylpiperidino, carboxypiperidino, lower-alkoxy-carbonylpiperidino, carbamoylpiperidino, cyanopiperidino, tetrahydropyridino, such as 1,2,5,6-tetrahydropyridino or 1,2,3,4-tetrahydropyridino, dihydropyridino, such as 1,2-dihydropyridino, hexamethyleneimino, heptamethyleneimino, piperazino, N'-phenyl-, N'-chlorophenyl- or N'-lower-alkoxyphenyl-piperazino, N'-lower-alkylpiperazino, N'-hydroxy-lower-alkylpiperazino, N'-lower-alkoxy-lower-alkylpiperazino, N'-loweralkanoylpiperazino, morpholino, thiomorpholino, S-oxothiomorpholino or S,S-dioxothiomorpholino.

Divalent araliphatic radicals are for example phenyl-lower-alkylene, phenyl(cyano)-lower-alkylene, phenyl-lower-alkyl-lower-alkylene, N'-phenylaza-lower-alkylene or N'-phenyl-lower-alkylaza-lower-alkylene radicals either unsubstituted or substituted in the phenyl moiety by lower-alkyl, lower-alkoxy, halogen and/or trifluoromethyl.

Amino groups substituted by divalent araliphatic radicals are for example respectively 3- to 8-membered phenyl-lower-alkyleneamino, N'-phenylaza-lower-alkylene or N'-phenyl-lower-alkylaza-loweralkyleneamino radicals either unsubstituted or substituted in the phenyl moiety by lower-alkyl, lower-alkoxy, halogen and/or trifluoromethyl, such as phenylpiperidino optionally substituted as indicated, such as 4-phenylpiperidino, phenyl(cyano)piperidino such as 4-cyano-4-phenylpiperidino, phenyl-lower-alkylpiperidino such as benzylpiperidino, N'-phenylpiperazino or N'-phenyl-lower-alkylpiperazino such as N'-benzylpiperazino.

Amino groups disubstituted by divalent heteroarylaliphatic radicals are for example N'-heteroaryla-lower-alkyleneamino groups in which heteroaryl signifies pyridyl, pyrimidinyl or triazinyl bonded for example by means of a C-atom, such as N'-pyridyl-, N'-pyrimidinyl- or N'-triazinylpiperazino.

Above and below, the lower radicals and compounds are understood to be for example those which have up to and including 7, preferably up to and including 4 carbon atoms (C-atoms).

Di(hydroxy-lower-alkyl)amino is for example N,N-di(hydroxy-C₂-C₄-alkyl)amino, such as N,N-di(2-hydroxyethyl)amino or N,N-di(3-hydroxypropyl)amino.

Di(lower-alkoxy-lower-alkenyl)amino is for example N,N-di(C₁-C₄-alkoxy-C₂-C₄-alkenyl)amino, such as N,N-di(4-methoxy-but-2-enyl)amino.

Di(lower-alkoxy-lower-alkyl)amino is for example N,N-di(C₁-C₄-alkoxy-C₁-C₄-alkyl)amino, such as N,N-di(2-methoxyethyl)amino, N,N-di(2-ethoxyethyl)amino or N,N-di(3-methoxypropyl)amino.

Di-lower-alkenylamino is for example N,N-di-C₂-C₄-alkenylamino, such as N,N-diallylamino or N-methallyl-N-allylamino.

Di-lower-alkylamino is for example N,N-di-C₁-C₄-alkylamino, such as dimethylamino, diethylamino, ethylmethylamino, dipropylamino, methylpropylamino, ethylpropylamino, dibutylamino or butylmethylamino.

Di-lower-alkylamino-lower-alkenyl-lower-alkylamino is for example N-(di-C₁-C₄-alkylamino-C₂-C₄-alkenyl)-N-C₁-C₄-alkylamino, such as N-(4-dimethylaminobut-2-enyl)-N-methylamino.

Di-lower-alkylamino-lower-alkenylamino is for example N-(di-C₁-C₄-alkylamino-C₂-C₄-alkenyl)amino, such as N-(4-dimethylaminobut-2-enyl)amino.

Di-lower-alkylamino-lower-alkynylamino is for example N-(di-C₁-C₄-alkylamino-C₂-C₄-alkynyl)-amino, such as N-(4-dimethylaminobut-2-ynyl)amino.

Di-lower-alkylamino-lower-alkyl-lower-alkylamino is for example N-(di-C₁-C₄-alkylamino-C₂-C₄-alkyl)-N-C₁-C₄-alkylamino, such as N-(2-dimethylaminoethyl)-N-methylamino, N-(2-dimethylaminoethyl)-N-ethylamino, N-(3-dimethylaminopropyl)-N-methylamino or N-(4-dimethylaminobutyl)-N-methylamino.

Di-lower-alkylamino-lower-alkylamino is for example N-(di-C₁-C₄-alkylamino-C₂-C₄-alkyl)-amino, such as N-(2-dimethylaminoethyl)amino, N-(2-dimethylaminoethyl)amino, N-(3-dimethylaminopropyl)amino or N-(4-dimethylaminobutyl)amino.

Halogen is for example halogen with an atomic number of up to and including 35, such as chlorine or bromine.

Hydroxy-lower-alkenyl-lower-alkylamino is for example N-(hydroxy-C₂-C₄-alkenyl)-N-(C₁-C₄-alkylamino, such as N-(4-hydroxybut-2-enyl)-N-methylamino.

Hydroxy-lower-alkenylamino is for example hydroxy-C₂-C₄-alkenylamino, such as 4-hydroxybut-2-enylamino.

Hydroxy-lower-alkynylamino is for example hydroxy-C₂-C₄-alkynylamino, such as 4-hydroxybut-2-ynylamino.

Hydroxy-lower-alkyl-lower-alkylamino is for example N-(hydroxy-C₂-C₄-alkyl)-N-C₁-C₄-alkylamino, such as N-(2-hydroxyethyl)-N-methylamino, N-(3-hydroxypropyl)-N-methylamino or N-(4-hydroxybutyl)-N-methylamino.

Hydroxy-lower-alkylamino is for example hydroxy-C₂-C₄-alkylamino, such as 2-hydroxyethylamino, 3-hydroxypropylamino or 4-hydroxybutylamino.

N'-hydroxy-lower-alkylpiperazino is for example N'-(hydroxy-C₁-C₄-alkyl)piperazino, such as N'-(2-hydroxyethyl)piperazino or N'-(3-hydroxypropyl)piperazino.

N'-lower-alkanoylpiperazino is for example N'-C₁-C₇-alkanoylpiperazino, such as N'-acetyl-piperazino.

N'-lower-alkoxy-lower-alkylpiperazino is for example N'-(C₁-C₄-alkoxy-C₁-C₄-alkyl)piperazino, such as N'-(2-methoxyethyl)piperazino or N'-(3-methoxypropyl)piperazino.

N'-lower-alkylpiperazino is for example N'-C₁-C₄-alkylpiperazino, such as N'-methylpiperazino, N'-ethylpiperazino, N'-propylpiperazino or N'-butylpiperazino.

Lower-alkanoyloxy-lower-alkenyl-lower-alkylamino is for example N-(C₁-C₇-alkanoyloxy-C₂-C₄-alkenyl)-N-(C₁-C₄-alkyl)-amino, such as N-(4-acetoxybut-2-enyl)-N-methylamino.

Lower-alkanoyloxy-lower-alkenylamino is for example N-(C₁-C₇-alkanoyloxy-C₂-C₄-alkenyl)-amino, such as N-(4-acetoxybut-2-enyl)amino.

Lower-alkanoyloxy-lower-alkinyl-lower-alkylamino is for example N-(C₁-C₇-alkanoyloxy-C₂-C₄-alkinyl)-N-(C₁-C₄-alkyl)amino, such as N-(4-acetoxybut-2-ynyl)-N-methylamino.

Lower-alkanoyloxy-lower-alkinylamino is for example N-(C₁-C₇-alkanoyloxy-C₂-C₄-alkinyl)-amino, such as N-(4-acetoxybut-2-ynyl)amino.

Lower-alkanoyloxy-lower-alkyl-lower-alkylamino is for example N-(C₁-C₇-alkanoyloxy-C₂-C₄-alkyl)-N-(C₁-C₄-alkyl)amino, such as N-(2-acetoxyethyl)-N-methylamino, N-(2-acetoxyethyl)-N-ethylamino, N-(3-acetoxypropyl)-N-methylamino or N-(4-acetoxybutyl)-N-methylamino.

Lower-alkanoyloxy-lower-alkylamino is for example N-(C₁-C₇-alkanoyloxy-C₂-C₄-alkyl)amino, such as N-(2-acetoxyethyl)amino, N-(3-acetoxypropyl)amino or N-(4-acetoxybutyl)amino.

Lower-alkenyl-lower-alkylamino is for example N-(C₂-C₇-alkenyl)-N-(C₂-C₇-alkyl)-amino, especially N-(C₂-C₄-alkenyl)-N-(C₁-C₄-alkyl)-amino, such as N-vinyl-N-methylamino-N-allyl-N-methylamino, N-allyl-N-ethylamino, N-but-2-enyl-N-methylamino or N-but-3-enyl-N-methylamino.

Lower-alkenylamino is for example N-(C₂-C₇-alkenyl)amino, especially N-(C₂-C₄-alkenyl)-amino, such as vinylamino, allylamino, but-2-enylamino or N-but-3-enylamino, especially allylamino.

Lower-alkynyl-lower-alkylamino is for example N-(C₂-C₄-alkynyl)-N-(C₁-C₄-alkyl)-amino, such as N-propargyl-N-methylamino, N-but-2-ynyl-N-methylamino or N-but-3-ynyl-N-methylamino.

Lower-alkynylamino is for example N-(C₂-C₇-alkynyl)amino, especially N-(C₂-C₄-alkynyl)amino, such as propargylamino, but-2-ynylamino or N-but-3-ynylamino, especially propargylamino.

Lower-alkoxy is for example C₁-C₇-alkoxy, preferably C₁-C₄-alkoxy, such as methoxy, ethoxy, propyloxy, isopropyloxy or butyloxy, but may also be isobutyloxy, secondary butyloxy, tertiary butyloxy or a C₅-C₇-alkoxy group, such as a pentyloxy, hexyloxy or heptyloxy group.

Lower-alkoxy-lower-alkenyl-lower-alkylamino is for example N-(C₁-C₄-alkoxy-C₂-C₄-alkenyl)-N-N-(C₁-C₄-alkyl)-amino, such as N-(4-methoxybut-2-enyl)-N-(methylamino, N-(4-methoxybut-2-enyl)-N-ethylamino or N-(4-ethoxybut-2-enyl)-N-methylamino.

Lower-alkoxy-lower-alkenylamino is for example N-(C₁-C₄-alkoxy-C₂-C₄-alkenyl)amino, such as N-(4-methoxybut-2-enyl)amino or N-(4-ethoxybut-2-enyl)amino.

Lower-alkoxy-lower-alkynyl-lower-alkylamino is for example N-(C₁-C₄-alkoxy-C₂-C₄-alkynyl)-N-(C₁-C₄-alkyl)amino, such as N-(4-methoxybut-2-ynyl)-N-methylamino, N-(4-methoxybut-2-ynyl)-N-ethylamino or N-(4-ethoxybut-2-ynyl)-N-methylamino.

Lower-alkoxy-lower-alkynylamino is for example N-(C₁-C₄-alkoxy-C₂-C₄-alkynyl)amino, such as N-(4-methoxybut-2-ynyl)amino, N-(4-ethoxybut-2-ynyl)amino or N-(4-propyloxybut-2-ynyl)-amino.

Lower-alkoxy-lower-alkylamino is for example C₁-C₄-alkoxy-C₂-C₄-alkylamino, such as 2-methoxyethylamino, 2-ethoxyethylamino, 2-propyloxyethylamino, 3-methoxypropylamino,

3-ethoxypropylamino, 4-methoxybutylamino, 2-isopropoxyethylamino or 2-butyloxyethylamino.

Lower-alkoxy-lower-alkyl-lower-alkylamino is for example N-(C₁-C₄-alkoxy-C₂-C₄-alkyl)-N-(C₁-C₄-alkyl)-amino, such as N-(2-methoxyethyl)-N-methylamino, N-(2-ethoxyethyl)-N-methylamino, N-(2-propyloxyethyl)-N-methylamino, N-(3-methoxypropyl)-N-methylamino, N-(3-ethoxypropyl)-N-methylamino or N-(4-methoxybutyl)-N-methylamino.

Lower alkyl is for example C₁-C₇-alkyl, preferably C₁-C₄-alkyl, such as methyl, ethyl, propyl, isopropyl or butyl, but it may also be isobutyl, secondary butyl, tertiary butyl or a C₅-C₇-alkyl group, such as a pentyl, hexyl or heptyl group.

Lower alkylamino is for example C₁-C₇-alkylamino, preferably C₁-C₄-alkylamino, such as methylamino, ethylamino, propylamino, isopropylamino or butylamino, but may also be isobutylamino, secondary butylamino, tertiary butylamino or a C₅-C₇-alkylamino group, such as a pentylamino, hexylamino or heptylamino group, and it is in particular methylamino or propylamino.

Lower-alkylamino-lower-alkylamino is for example N-(C₁-C₄-alkylamino,-C₂-C₄-alkyl)amino, such as N-(2-methylaminoethyl)amino, N-(1-methylaminoethyl)amino, N-(3-methylaminopropyl)amino, N-(4-methylaminobutyl)amino, N-(2-ethylaminoethyl)amino, N-(1-ethylaminoethyl)amino, N-(3-ethylaminopropyl)amino or N-(4-ethylaminobutyl)amino.

Lower-alkyleneamino-lower-alkylamino is for example 3- to 8-membered alkyleneamino-C₂-C₄-alkylamino, such as 2-pyrrolidinoethylamino, 2-piperidinoethylamino, 2-dimethylpiperidinoethylamino, 2-hexamethyleneiminoethylamino, 3-pyrrolidinopropylamino, 3-piperidinopropylamino, 3-dimethylpiperidinopropylamino or 3-hexamethyleneiminopropylamino.

Lower alkylidene is for example C₁-C₄-alkylidene, such as methylene or ethylidene.

Phenyl(carboxy-lower-alkyl)amino is for example 1-carboxy- ω -phenyl-C₂-C₄-alkylamino, such as 1-carboxy-2-phenylethyl or 1-carboxy-3-phenylpropyl.

Phenyl(lower-alkoxycarbonyl-lower-alkyl)amino is for example 1-C₁-C₄-alkoxycarbonyl- ω -phenyl-C₂-C₄-alkylamino, such as 1-methoxycarbonyl-2-phenylethyl, 1-ethoxycarbonyl-2-phenylethyl, 1-methoxycarbonyl-3-phenylpropyl or 1-ethoxycarbonyl-3-phenylpropyl.

Phenyl-lower-alkyl-lower-alkylamino is for example N-(phenyl-C₁-C₄-alkyl)-N-(C₁-C₄-alkyl)-amino, such as N-benzyl-N-methylamino, N-(2-phenylethyl)-N-methylamino or N-(4-phenylbutyl)-N-methylamino.

Phenyl-lower-alkylamino is for example phenyl-C₁-C₄-alkylamino, such as benzylamino, 1- or 2-phenylethylamino, 3-phenylpropylamino or 4-phenylbutylamino.

Phenyl-lower-alkyl-lower-alkyleneamino is for example phenyl-C₁-C₄-alkyl-pyrrolidino either unsubstituted or substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl, such as 2- or 3-benzylpyrrolidino; phenyl-C₁-C₄-alkylpiperidino such as 2-, 3- or 4-benzylpiperidino, furthermore phenyl-C₁-C₄-alkylhexahydroazepino such as 2-, 3- or 4-benzylhexahydroazepino, phenyl-C₁-C₄-alkylaziridino such as 2-benzylaziridino or phenyl-C₁-C₄-alkylazetidino such as 2- or 3-benzylazetidino.

N-phenyl-lower-alkylaza-lower-alkyleneamino is for example N'-phenyl-C₁-C₄-alkyl-imidazolidino either unsubstituted or substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl, such as N'-benzylimidazolidino, phenyl-C₁-C₄-alkylpiperazino such as N'-benzylpiperazino, or phenyl-C₁-C₄-alkylhexahydro-1,3-diazepino such as N'-benzylhexahydro-1,3-diazepino, furthermore phenyl-C₁-C₄-alkyl-1,3-diazetidino such as N'-benzyl-1,3-diazetidino, or phenyl-C₁-C₄-alkylpyridazino such as N'-benzylpyridazino.

Acid addition salts of compounds of formula I with organic carboxylic acids are for example pharmaceutically employable acid addition salts with pharmaceutically applicable, optionally hydroxylated lower alkanic acids, e.g. acetic acid, propionic acid, pivalic acid, glycolic acid, pyroacemic acid, lactic acid or gluconic acid, optionally hydroxylated, aminated and/or oxo-substituted lower alkane-dicarboxylic acids, e.g. oxalic acid, malonic acid, succinic acid, glutamic acid, aspartic acid, tartaric acid or malic acid, optionally hydroxylated and/or oxo-substituted lower-alkane-tricarboxylic acids, e.g. citric acid or aconitic acid, optionally hydroxylated and/or oxo-substituted lower-alkene-dicarboxylic acids, e.g. fumaric acid,

maleic acid or itaconic acid, optionally hydroxylated and/or oxo-substituted lower-alkyne-dicarboxylic acids, e.g. acetylene-dicarboxylic acid, furthermore with aromatic, hetero-aromatic or araliphatic carboxylic acids, such as benzoic acid, salicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid or nicotinic acid.

Parts of the compounds of formula I, which have been proposed for use according to the invention, are already known. In GB Patent No. 1.080.979, compounds of formula I, wherein alk is methylene or ethylidene and R is amino, methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, dimethylamino, diethylamino, dipropylamino, pyrrolidino, piperidino, hexahydroazepino, morpholino, N'-methylpiperazino, N'-(2-hydroxyethyl)piperazino, N'-(2-acetoxyethyl)piperazino, N'-(2-pivaloxyloxyethyl)piperazino or N'-methylhomopiperazino, and R₁, R₂, R₃ and R₄ signify hydrogen, lower alkyl, lower alkoxy and/or halogen, have been proposed as adrenolytic and centrally depressant, such as sedative and narcosis-potentiating active ingredients of medicaments.

The invention is based on the surprising discovery that compounds of formula I, when administered to newly-born rats in an experimental setup according to Ansari et al., J. Neuroscience 13, 4042-4053 (1993) at doses of approximately 0.1 mg/kg s.c. and less, have a marked protective effect of the facial motor neurones from apoptotic cytolysis, and when administered to fully-developed rats in an experimental setup according to Golowitz and Paterson, Soc. Neurosc. Abstr. 20, 246, 113.2 (1994) at 0.275 mg/kg s.c. and less over 4 days, have a marked protective effect of hippocampal pyramidal cells from cytolysis by administering kainic acid.

Similarly, compounds of formula I protect mesencephalic, dopaminergic neurones in culture at approximately 10⁻⁸ molar concentrations, from apoptotic cytolysis induced by MPP⁺.

Furthermore, when compounds of formula I are administered to mice at 0.14 mg/kg p.o. and less over 20 days, they show a marked protective effect on tyrosin-hydroxylase-positive, nigral neurones from cytolysis by administering MPTP.

Accordingly, the compounds of formula I and their pharmaceutically employable salts, over and above their already-known adrenolytic and centrally depressant applicability, are eminently suitable for the prophylactic or therapeutic treatment of neurodegenerative

disorders, especially those in which apoptotic cytolysis plays a role, such as cerebral ischaemia, Alzheimer's disease, Huntington's and Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, types of glaucoma, retina degeneration, especially retinitis pigmentosa, as well as general or diabetic peripheral neuropathy.

The invention relates primarily to the use of acid addition salts of compounds of formula I, wherein

alk signifies lower alkylidene,

R represents amino, lower-alkylamino; phenyl-lower-alkylamino, phenyl(carboxy-lower-alkyl)amino, phenyl(lower-alkoxycarbonyl-lower-alkyl)amino or phenyl-lower-alkyl-lower-alkylamino radicals either unsubstituted or substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl; hydroxy-lower-alkylamino, carboxy-lower-alkylamino, lower-alkoxy-carbonyl-lower-alkylamino, carbamoyl-lower-alkylamino, cyano-lower-alkylamino, lower-alkoxy-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, lower-alkyleneamino-lower-alkylamino, lower-alkenylamino, hydroxy-lower-alkenylamino, lower-alkoxy-lower-alkenylamino, lower-alkanoyloxy-lower-alkenylamino, di-lower-alkylamino-lower-alkenylamino, lower-alkinylamino, hydroxy-lower-alkinylamino, lower-alkoxy-lower-alkinylamino, lower-alkanoyloxy-lower-alkinylamino, di-lower-alkylamino-lower-alkinylamino, di-lower-alkylamino, di(hydroxy-lower-alkyl)amino, hydroxy-lower-alkyl-lower-alkylamino, di(lower-alkoxy-lower-alkyl)amino, lower-alkoxy-lower-alkyl-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkanoyloxy-lower-alkyl-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkyl-lower-alkylamino, di-lower-alkenylamino, lower-alkenyl-lower-alkylamino, hydroxy-lower-alkenyl-lower-alkylamino, di(lower-alkoxy-lower-alkenyl)amino, lower-alkoxy-lower-alkenyl-lower-alkylamino, lower-alkanoyloxy-lower-alkenyl-lower-alkylamino, di-lower-alkylamino-lower-alkenyl-lower-alkylamino, lower-alkinyl-lower-alkylamino, lower-alkoxy-lower-alkinyl-lower-alkylamino, lower-alkanoyloxy-lower-alkinyl-lower-alkylamino, di-lower-alkylamino-lower-alkinyl-lower-alkylamino; respectively 3- to 8-membered lower-alkyleneamino, lower-alkenyleneamino or lower-alkadienylene-amino either unsubstituted or substituted by carboxy, lower-alkoxycarbonyl or carbamoyl or cyano; cyano(phenyl)lower-alkylene-amino either unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl; 3- or 4-aza-lower-alkylene-amino either unsubstituted or N-substituted by lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, pyridinyl, pyrimidinyl, triazinyl or lower-alkanoyl; 3- or 4-oxa-lower-

alkylene-amino, optionally S-oxidised 3- or 4-thia-lower-alkylene-amino; or a N'-phenylaza-lower-alkylene-amino or N'-benzylaza-lower-alkylene-amino radical either unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl, and

R₁, R₂, R₃ and R₄, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl,

with pharmaceutically applicable, optionally hydroxylated lower alkanic acids, e.g. acetic acid, propionic acid, pivalic acid, glycolic acid, pyroacetic acid, lactic acid or gluconic acid, optionally hydroxylated, aminated and/or oxo-substituted lower alkane-dicarboxylic acids, e.g. oxalic acid, malonic acid, succinic acid, glutamic acid, aspartic acid, tartaric acid or malic acid, optionally hydroxylated and/or oxo-substituted lower-alkane-tricarboxylic acids, e.g. citric acid or aconitic acid, optionally hydroxylated and/or oxo-substituted lower-alkene-dicarboxylic acids, e.g. fumaric acid, maleic acid or itaconic acid, optionally hydroxylated and/or oxo-substituted lower-alkyne-dicarboxylic acids, e.g. acetylenedicarboxylic acid, furthermore with aromatic, hetero-aromatic or araliphatic carboxylic acids, such as benzoic acid, salicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid or nicotinic acid,

as anti-neurodegenerative active ingredients for medicaments, or for the production thereof, as well as acid addition salts of new compounds of formula I as such, as defined above, preferably those in which alk signifies methylene or ethylidene and R is different from amino, methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, dimethylamino, diethylamino, dipropylamino, pyrrolidino, piperidino, hexahydro-azepino, morpholino, N'-methylpiperazino, N'-(2-hydroxyethyl)piperazino, N'-(2-acetoxyethyl)piperazino, N'-(2-pivaloyloxyethyl)piperazino and N'-methyl-homopiperazino, if R₁ and R₃ signify hydrogen, lower alkyl, lower alkoxy or halogen and R₂ and R₄ signify hydrogen,

with the above-mentioned acids, as well as processes for the production thereof.

The invention relates primarily, for example, to the use of acid addition salts of compounds of formula I, wherein

alk signifies methylene or ethylidene,

R represents amino, lower-alkylamino; phenyl-lower-alkylamino, phenyl(carboxy-lower-alkyl)amino, phenyl(lower-alkoxycarbonyl-lower-alkyl)amino or phenyl-lower-alkyl-lower-alkylamino radicals either unsubstituted or substituted by lower alkyl, lower alkoxy, halogen

and/or trifluoromethyl; hydroxy-lower-alkylamino, lower-alkoxy-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, lower-alkylene-amino-lower-alkylamino, lower-alkenylamino, hydroxy-lower-alkenylamino, lower-alkoxy-lower-alkenylamino, lower-alkanoyloxy-lower-alkenylamino, di-lower-alkylamino-lower-alkenylamino, lower-alkinylamino, hydroxy-lower-alkinylamino, lower-alkoxy-lower-alkinylamino, lower-alkanoyloxy-lower-alkinylamino, di-lower-alkylamino-lower-alkinylamino, di-lower-alkylamino, di(hydroxy-lower-alkyl)amino, hydroxy-lower-alkyl-lower-alkylamino, di(lower-alkoxy-lower-alkyl)amino, lower-alkoxy-lower-alkyl-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkanoyloxy-lower-alkyl-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkyl-lower-alkylamino, di-lower-alkenylamino, lower-alkenyl-lower-alkylamino, hydroxy-lower-alkenyl-lower-alkylamino, di(lower-alkoxy-lower-alkenyl)amino, lower-alkoxy-lower-alkenyl-lower-alkylamino, lower-alkanoyloxy-lower-alkenyl-lower-alkylamino, di-lower-alkylamino-lower-alkenyl-lower-alkylamino, lower-alkinyl-lower-alkylamino, lower-alkoxy-lower-alkinyl-lower-alkylamino, lower-alkanoyloxy-lower-alkinyl-lower-alkylamino, di-lower-alkylamino-lower-alkinyl-lower-alkylamino, 3- to 8-membered lower-alkylene-amino; 3- or 4-aza-lower-alkylene-amino either unsubstituted or N-substituted by lower alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl or lower-alkanoyl; 3- or 4-oxa-lower-alkylene-amino or optionally S-oxidised 3- or 4-thia-lower-alkyleneamino, and

R₁, R₂, R₃ and R₄, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl,

with pharmaceutically applicable, optionally hydroxylated lower alkanolic acids, e.g.

acetic acid, glycolic acid, propionic acid, lactic acid or pivalic acid, optionally hydroxylated

and/or oxo-substituted lower-alkane-dicarboxylic acids, e.g. oxalic acid, succinic acid,

fumaric acid, maleic acid, tartaric acid, citric acid, pyroacemic acid or malic acid, furthermore with aromatic, heteroaromatic or araliphatic carboxylic acids, such as benzoic acid, nicotinic acid or mandelic acid,

as anti-neurodegenerative active ingredients for medicaments, or for the production thereof,

as well as acid addition salts of new compounds of formula I as such, as defined above,

preferably those in which R is different from amino, methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, dimethylamino, diethylamino, dipropylamino,

pyrrolidino, piperidino, hexahydro-azepino, morpholino, N'-methylpiperazino, N'-(2-hydroxyethyl)piperazino, N'-(2-acetoxyethyl)piperazino, N'-(2-pivaloyloxyethyl)piperazino

and N'-methyl-homopiperazino, if R₁ and R₃ signify hydrogen, lower alkyl, lower alkoxy or halogen and R₂ and R₄ signify hydrogen, with the above-mentioned acids, as well as processes for the production thereof.

The invention relates in particular to the use of acid addition salts of compounds of formula I wherein

alk signifies lower alkylidene,

R represents amino, lower-alkylamino, cyano-lower-alkylamino; a phenyl-lower-alkylamino, phenyl(carboxy-lower-alkyl)amino, phenyl(lower-alkoxycarbonyl-lower-alkyl)amino or phenyl-lower-alkyl-lower-alkylamino radical either unsubstituted or substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl; lower-alkinylamino, di-lower-alkylamino, 3- to 8-membered lower-alkylene-amino or cyano(phenyl)lower-alkylene-amino, 3- to 8-membered lower-alkenylene-amino; 3- or 4-aza-lower-alkylene-amino either unsubstituted or N-substituted by lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl or lower-alkanoyl; 3- or 4-oxa-lower-alkylene-amino, optionally S-oxidised 3- or 4-thia-lower-alkylene-amino or a respectively 3- to 8-membered N'-pyrimidinylaza-lower-alkylene-amino radical; a phenyl-lower-alkylene, phenyl(cyano)lower-alkylene, N'-phenylaza-lower-alkylene-amino or N'-benzylaza-lower-alkylene-amino radical either unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl, and

R₁, R₂, R₃ and R₄, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl,

with pharmaceutically applicable, optionally hydroxylated lower alkanolic acids, e.g. acetic acid, propionic acid, pivalic acid, glycolic acid, pyroacemic acid, lactic acid or gluconic acid, optionally hydroxylated, aminated and/or oxo-substituted lower-alkane-dicarboxylic acids, e.g. oxalic acid, malonic acid, succinic acid, glutamic acid, aspartic acid, tartaric acid or malic acid, optionally hydroxylated and/or oxo-substituted lower-alkane-tricarboxylic acids, e.g. citric acid or aconitic acid, optionally hydroxylated and/or oxo-substituted lower-alkene-dicarboxylic acids, e.g. fumaric acid, maleic acid or itaconic acid, optionally hydroxylated and/or oxo-substituted lower-alkyne-dicarboxylic acids, e.g. acetylene-dicarboxylic acid, furthermore, with aromatic, heteroaromatic or araliphatic carboxylic acids, such as benzoic acid, salicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid or nicotinic acid,

as anti-neurodegenerative active ingredients for medicaments, or for the preparation thereof, as well as acid addition salts of new compounds of formula I as such, as defined

above, preferably those in which alk signifies methylene or ethylidene and R is different from amino, methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, dimethylamino, diethylamino, dipropylamino, pyrrolidino, piperidino, hexahydroazepino, morpholino, N'-methylpiperazino, N'-(2-hydroxyethyl)piperazino, N'-(2-acetoxyethyl)piperazino, N'-(2-pivaloyloxyethyl)piperazino and N'-methyl-homopiperazino, if R₁ and R₃ signify hydrogen, lower alkyl, lower alkoxy or halogen and R₂ and R₄ signify hydrogen,

with the above-mentioned acids, as well as processes for the production thereof.

The invention relates in particular to the use of acid addition salts of compounds of formula I, wherein

alk signifies methylene,

R represents C₁-C₄-alkylamino, such as methylamino, ethylamino, propylamino or butylamino, cyano-C₁-C₄-alkylamino, such as cyanomethylamino; a phenyl-C₁-C₄-alkylamino, phenyl-C₁-C₄-alkyl-C₁-C₄-alkylamino, phenyl-(1-carboxy-C₁-C₄-alkyl)amino or phenyl-(1-C₁-C₄-alkoxycarbonyl-C₁-C₄-alkylamino radical either unsubstituted or substituted by C₁-C₄-alkyl such as methyl, C₁-C₄-alkoxy such as methoxy, halogen with an atomic number up to and including 35 such as chlorine or bromine, and/or by trifluoromethyl; such as benzylamino, phenethylamino, N-benzyl-N-methylamino, 2-phenyl-1-carboxyethylamino, 2-phenyl-1-ethoxycarbonylethylamino or N-benzyl-N-methylamino, C₂-C₇-alkenylamino such as allylamino, methallylamino or but-2-enylamino, C₂-C₇-alkinylamino such as propargylamino or but-2-ynylamino, N-C₂-C₇-alkenyl-N-C₁-C₄-alkylamino such as N-allyl-N-methylamino, N-allyl-N-ethylamino, N-methallyl-N-methylamino or N-but-2-enyl-N-methylamino, N-C₂-C₇-alkinyl-N-C₁-C₄-alkylamino such as N-propargyl-N-methylamino, N-propargyl-N-ethylamino or N-but-2-ynyl-N-methylamino, di-C₁-C₄-alkylamino such as dimethylamino, diethylamino, N-methyl-N-propylamino or N-butyl-N-methylamino, pyrrolidino, piperidino, 1,2,3,6-tetrahydropyridino; 4-cyano-4-phenylpiperidino either unsubstituted or substituted by C₁-C₄-alkyl such as methyl, C₁-C₄-alkoxy such as methoxy, halogen with an atomic number up to and including 35 such as chlorine or bromine, and/or by trifluoromethyl; such as 4-cyano-4-phenylpiperidino, morpholino, piperazino, N'-C₁-C₄-alkylpiperazino such as N'-methylpiperazino, N'-(hydroxy-C₂-C₄-alkyl)piperazino such as N'-(2-hydroxyethyl)piperazino, N'-pyrimidinylpiperazino; or a N'-phenylpiperazino or N'-phenyl-C₁-C₄-alkylpiperazino radical either unsubstituted or substituted by C₁-C₄-alkyl such as methyl, C₁-C₄-alkoxy such as methoxy, halogen with an atomic number up to and including

35 such as chlorine or bromine, and/or by trifluoromethyl; such as N'-phenylpiperazino, N'-(4-chlorophenyl)piperazino, N'-(4-methoxyphenyl)piperazino or N'-benzylpiperazino, and R₁, R₂, R₃ and R₄, independently of one another, denote hydrogen, C₁-C₄-alkyl such as methyl, C₁-C₄-alkoxy such as methoxy, halogen with an atomic number up to and including 35 such as chlorine or bromine or trifluoromethyl,

with pharmaceutically applicable, optionally hydroxylated C₁-C₇-alkanoic acids, e.g. acetic acid, propionic acid, pivalic acid, glycolic acid, pyroacemic acid, lactic acid or gluconic acid, optionally hydroxylated, aminated and/or oxo-substituted C₂-C₇-alkane-dicarboxylic acids, e.g. oxalic acid, malonic acid, succinic acid, glutamic acid, aspartic acid, tartaric acid or malic acid, optionally hydroxylated and/or oxo-substituted C₄-C₇-alkane-tricarboxylic acids, e.g. citric acid or aconitic acid, optionally hydroxylated and/or oxo-substituted C₄-C₇-alkene-dicarboxylic acids, e.g. fumaric acid, maleic acid or itaconic acid, optionally hydroxylated and/or oxo-substituted C₄-C₇-alkyne-dicarboxylic acids, e.g. acetylene-dicarboxylic acid, furthermore with benzoic acid, salicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid or nicotinic acid,

as anti-neurodegenerative active ingredients for medicaments, or for the production thereof, as well as acid addition salts of new compounds of formula I as such, as defined above, preferably those in which R is different from amino, methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, dimethylamino, diethylamino, dipropylamino, pyrrolidino, piperidino, hexahydroazepino, morpholino, N'-methylpiperazino, N'-(2-hydroxyethyl)piperazino, N'-(2-acetoxyethyl)piperazino, N'-(2-pivaloyloxyethyl)piperazino and N'-methyl-homopiperazino, if R₁ and R₃ signify hydrogen, lower alkyl, lower alkoxy or halogen, and R₂ and R₄ signify hydrogen,

with the above-mentioned acids, as well as processes for the production thereof.

The invention preferably relates to the use of acid addition salts of compounds of formula I, wherein

alk is methylene,

R represents C₁-C₄-alkylamino, such as methylamino, ethylamino, propylamino or butylamino; a phenyl-C₁-C₄-alkylamino, phenyl-C₁-C₄-alkyl-C₁-C₄-alkylamino, phenyl-(1-carboxy-C₁-C₄-alkyl)amino or phenyl-(1-C₁-C₄-alkoxycarbonyl-C₁-C₄-alkylamino radical either unsubstituted or substituted by C₁-C₄-alkyl such as methyl, C₁-C₄-alkoxy such as methoxy, halogen with an atomic number up to and including 35 such as chlorine or bromine, and/or by trifluoromethyl; such as benzylamino, phenethylamino, N-benzyl-N-methylamino, 2-

phenyl-1-carboxyethylamino, 2-phenyl-1-ethoxycarbonyl ethylamino or N-benzyl-N-methylamino, C₂-C₇-alkenylamino such as allylamino, methallylamino or but-2-enylamino, C₂-C₇-alkinylamino such as propargylamino or but-2-ynylamino, N-C₂-C₇-alkenyl-N-C₁-C₄-alkylamino such as N-allyl-N-methylamino, N-allyl-N-ethylamino, N-methallyl-N-methylamino or N-but-2-enyl-N-methylamino, N-C₂-C₇-alkinyl-N-C₁-C₄-alkylamino such as N-propargyl-N-methylamino, N-propargyl-N-ethylamino or N-but-2-ynyl-N-methylamino, di-C₁-C₄-alkylamino such as dimethylamino, diethylamino, N-methyl-N-propylamino or N-butyl-N-methylamino, pyrrolidino, piperidino, morpholino, piperazino, N'-C₁-C₄-alkylpiperazino such as N'-methylpiperazino, N'-(hydroxy-C₂-C₄-alkyl)piperazino such as N'-(2-hydroxyethyl)piperazino, and

R₁, R₂, R₃ and R₄, independently of one another, denote hydrogen, C₁-C₄-alkyl such as methyl, C₁-C₄-alkoxy such as methoxy, halogen with an atomic number up to and including 35 such as chlorine or bromine, or trifluoromethyl, with acetic acid, propionic acid, pivalic acid, glycolic acid, pyroacetic acid, lactic acid, oxalic acid, succinic acid, tartaric acid or malic acid, citric acid, fumaric acid, maleic acid, furthermore with benzoic acid, mandelic acid or nicotinic acid, as anti-neurodegenerative active ingredients for medicaments, or for the preparation thereof, as well as acid addition salts of new compounds of formula I as such, as defined above, preferably those in which R is different from amino, methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, dimethylamino, diethylamino, dipropylamino, pyrrolidino, piperidino, hexahydroazepino, morpholino, N'-methylpiperazino, N'-(2-hydroxyethyl)piperazino, N'-(2-acetoxyethyl)piperazino, N'-(2-pivaloyloxyethyl)piperazino and N'-methyl-homopiperazino, if R₁ and R₃ signify hydrogen, lower alkyl, lower alkoxy or halogen and R₂ and R₄ signify hydrogen, with the above-mentioned acids, as well as processes for the production thereof.

The invention preferably relates to acid addition salts of compounds of formula I, wherein alk is methylene,

R represents C₂-C₇-alkenylamino such as allylamino, methallylamino or but-2-enylamino, C₂-C₇-alkinylamino such as propargylamino or but-2-ynylamino, N-C₂-C₇-alkenyl-N-C₁-C₄-alkylamino such as N-allyl-N-methylamino, N-allyl-N-ethylamino, N-methallyl-N-methylamino or N-but-2-enyl-N-methylamino, N-C₂-C₇-alkinyl-N-C₁-C₄-alkylamino such as N-propargyl-N-methylamino, N-propargyl-N-ethylamino or N-but-2-ynyl-N-methylamino; or phenyl-C₁-C₄-alkylamino either unsubstituted or substituted by C₁-C₄-alkyl such as methyl, C₁-C₄-alkoxy

such as methoxy, halogen with an atomic number up to and including 35 such as chlorine or bromine, and/or by trifluoromethyl; such as benzylamino or phenethylamino, and R_1 , R_2 , R_3 and R_4 , independently of one another, denote hydrogen, C_1 - C_4 -alkyl such as methyl, C_1 - C_4 -alkoxy such as methoxy, halogen with an atomic number up to and including 35 such as chlorine or bromine or trifluoromethyl, with pharmaceutically applicable, optionally hydroxylated C_1 - C_7 -alkanoic acids, e.g. acetic acid, propionic acid, pivalic acid, glycolic acid, pyroacemic acid, lactic acid or gluconic acid, optionally hydroxylated, aminated and/or oxo-substituted C_2 - C_7 -alkane-dicarboxylic acids, e.g. oxalic acid, malonic acid, succinic acid, glutamic acid, aspartic acid, tartaric acid or malic acid, optionally hydroxylated and/or oxo-substituted C_4 - C_7 -alkane-tricarboxylic acids, e.g. citric acid or aconitic acid, optionally hydroxylated and/or oxo-substituted C_4 - C_7 -alkene-dicarboxylic acids, e.g. fumaric acid, maleic acid or itaconic acid, optionally hydroxylated and/or oxo-substituted C_4 - C_7 -alkyne-dicarboxylic acids, e.g. acetylene-dicarboxylic acid, furthermore with benzoic acid, salicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid or nicotinic acid, processes for the production thereof and their use as anti-neurodegenerative active ingredients for medicaments, or for the production thereof.

The invention relates primarily to acid addition salts of compounds of formula I, wherein alk is methylene,

R represents C_2 - C_7 -alkenylamino such as allylamino, methallylamino or but-2-enylamino, C_2 - C_7 -alkinylamino such as propargylamino or but-2-ynylamino, N- C_2 - C_7 -alkenyl-N- C_1 - C_4 -alkylamino such as N-allyl-N-methylamino, N-allyl-N-ethylamino, N-methallyl-N-methylamino or N-but-2-enyl-N-methylamino, N- C_2 - C_7 -alkinyl-N- C_1 - C_4 -alkylamino such as N-propargyl-N-methylamino, N-propargyl-N-ethylamino or N-but-2-ynyl-N-methylamino and

R_1 , R_2 , R_3 and R_4 signify hydrogen, C_1 - C_4 -alkyl such as methyl, C_1 - C_4 -alkoxy such as methoxy, halogen with an atomic number up to and including 35 such as chlorine or bromine, and/or trifluoromethyl,

with pharmaceutically applicable, optionally hydroxylated C_1 - C_7 -alkanoic acids, e.g. acetic acid, propionic acid, pivalic acid, glycolic acid, pyroacemic acid, lactic acid or gluconic acid, optionally hydroxylated, aminated and/or oxo-substituted C_2 - C_7 -alkane-dicarboxylic acids, e.g. oxalic acid, malonic acid, succinic acid, glutamic acid, aspartic acid, tartaric acid or malic acid, optionally hydroxylated and/or oxo-substituted C_4 - C_7 -alkane-tricarboxylic acids, e.g. citric acid or aconitic acid, optionally hydroxylated and/or oxo-substituted C_4 - C_7 -alkene-

dicarboxylic acids, e.g. fumaric acid, maleic acid or itaconic acid, optionally hydroxylated and/or oxo-substituted C₄-C₇-alkyne-dicarboxylic acids, e.g. acetylene-dicarboxylic acid, furthermore with benzoic acid, salicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid or nicotinic acid, processes for the production thereof and the use thereof.

The invention most preferably relates to acid addition salts of compounds of formula I, wherein

alk is methylene,

R represents C₂-C₇-alkenylamino such as allylamino, methallylamino or but-2-enylamino, C₂-C₇-alkynylamino such as propargylamino or but-2-ynylamino, N-C₂-C₇-alkenyl-N-C₁-C₄-alkylamino such as N-allyl-N-methylamino, N-allyl-N-ethylamino, N-methallyl-N-methylamino or N-but-2-enyl-N-methylamino, or N-C₂-C₇-alkynyl-N-C₁-C₄-alkylamino such as N-propargyl-N-methylamino, N-propargyl-N-ethylamino or N-but-2-ynyl-N-methylamino and

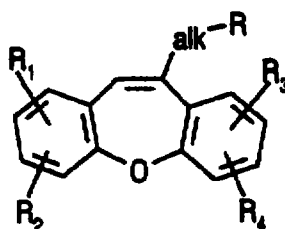
R₁ and R₃, independently of one another, signify hydrogen, C₁-C₄-alkyl, C₁-C₄-alkoxy, halogen or trifluoromethyl and

R₂, R₄ signify hydrogen,

with glycolic acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, tartaric acid, citric acid, pyroacemic acid, malic acid, benzoic acid, nicotinic acid or mandelic acid, processes for their production and their use.

The invention relates particularly to the acid addition salts of compounds of formula I named in the examples.

The process for the production of acid addition salts of compounds of formula I is characterised in that a compound of formula I

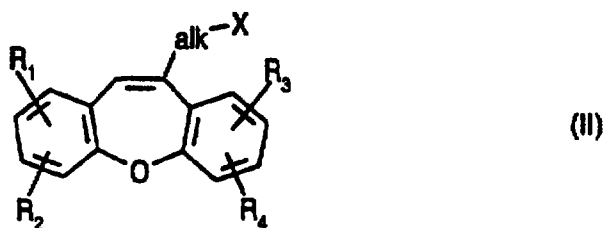


(I)

in free form is reacted with at least the quantity of an organic carboxylic acid that is required for salt formation, and the desired salt is isolated.

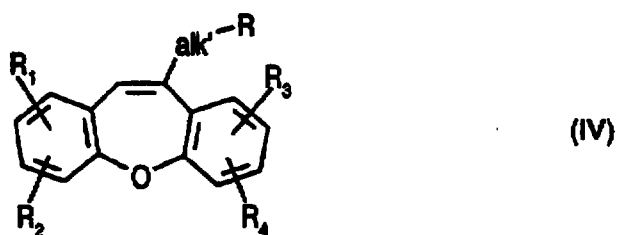
The reaction of compounds of formula I with organic carboxylic acids is carried out in a conventional manner, for example in an organic solvent which is preferably miscible with water, especially in a lower alkanol such as methanol, ethanol, propanol or isopropanol, or in a cycloaliphatic ether which is miscible with water, such as dioxane, if necessary whilst heating, for example in a temperature range of ca. 50°C to ca. 110°C, with the usual working up.

Compounds of formula I in free form which serve as starting materials for the above are obtained for example whereby a) a compound of formula II



wherein one of radicals X and Y signifies reactive, esterified hydroxy, and the other signifies optionally intermediately protected amino, and R, R₁, R₂, R₃ and R₄ have the above significances, and the optionally intermediately introduced amino protecting group is cleaved again, or

b) in a compound of formula IV



wherein alk' signifies a lower alkylidene group which is substituted by oxo or by optionally esterified hydroxy, the group alk' is reduced to the corresponding alk group by replacing the oxygen function, a salt which is obtainable according to the process is converted into the free compound, and if desired, a compound which is obtainable according to the process is respectively transformed into another compound of formula I.

Reactive, esterified hydroxy in the starting materials of formula II or III according to process variant a) is for example hydroxy which is esterified with a hydrohalic acid or an organic sulphonic acid, such as halogen, e.g. chlorine, bromine or iodine, benzene-sulphonyloxy optionally substituted by lower alkyl, halogen and/or nitro, such as benzene-sulphonyloxy, p-bromobenzene-sulphonyloxy or p-toluene-sulphonyloxy, or lower-alkane-sulphonyloxy such as methane-sulphonyloxy.

The reaction of compounds of formulae II and III is effected in conventional manner, for example in the presence of a basic condensation agent, such as a tertiary or sterically hindered binary organic nitrogen base, such as a tri-lower-alkylamine or sterically hindered di-lower-alkylamine, such as triethylamine or diisopropylamine, or a hetero-aromatic base such as pyridine or dimethylaminopyridine, advantageously in an organic solvent such as toluene, and if necessary with cooling or heating, e.g. in a temperature range of ca. 0°C to ca. 80°C.

The amino protecting groups which may be considered are those which are usual for the intermediate protection of primary amino groups, especially solvolytically cleavable amino protecting groups. These are for example acyl groups derived from a carboxylic acid or a semi-ester of carbonic acid, such as optionally halogenated lower alkanoyl, for example lower alkanoyl such as formyl, acetyl or pivaloyl, polyhalogen-lower-alkanoyl such as trifluoroacetyl, lower-alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, isopropylloxycarbonyl, or tertiary-butyloxycarbonyl, or optionally substituted phenyl-lower-alkoxycarbonyl such as benzyloxycarbonyl, furthermore silyl groups such as tri-lower-alkylsilyl, e.g. trimethylsilyl.

Cleavage of these amino protecting groups is effected in conventional manner, for example by treatment with a solvolysis agent, such as with water in the presence of an acid, e.g. an

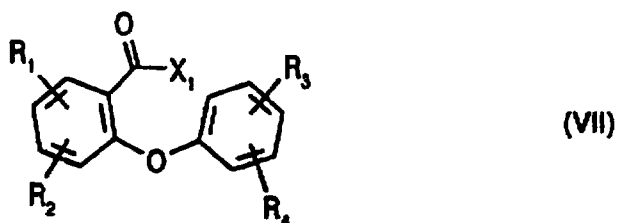
aqueous mineral acid such as hydrohalic acid, or an alkali metal hydroxide such as caustic soda or caustic potash solution, especially for cleaving a sulphonic acid such as methane-sulphonic acid in a halogenated hydrocarbon such as dichloromethane, or in particular for cleaving formyl, an appropriate silyl compound such as a tri-lower-alkylsilyl halide, such as trimethylsilyl bromide, or a disilazane such as hexamethyldisilazane.

The starting materials of formulae II and III are known or may be produced analogously to the method of forming known compounds of formulae II and III.

Thus, compounds of formula II, wherein alk signifies methylene and X signifies reactive hydroxy, are obtained for example whereby compounds of formula V and VI

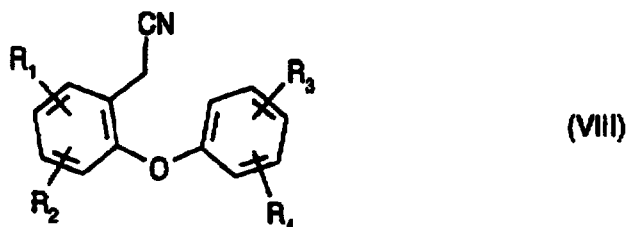


wherein X signifies halogen and X_2 signifies hydrogen or hydroxy, are condensed with one another in conventional manner, whereby the process is preferably effected in a temperature range of ca. 100°C to ca. 180°C, and when starting with compounds of formula V in which X_2 signifies hydroxy and X_1 signifies for example chlorine, the process is preferably effected in the presence of copper/copper-I-iodide, and when starting with compounds of formula V in which X_2 signifies hydrogen and X_1 signifies for example fluorine, the process is preferably effected in the presence of potassium carbonate in dimethylacetamide, then in the compounds of formula VII thus obtained

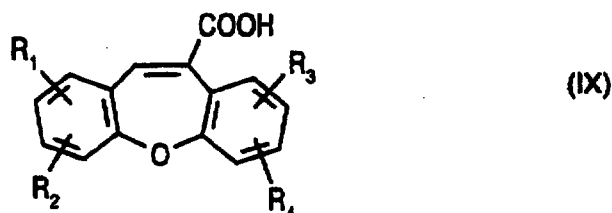


the group $-\text{C}(=\text{P})-\text{X}_1$ is reduced to hydroxymethyl in conventional manner, for example by treatment with a di- light metal hydride, such as lithium aluminium hydride in tetrahydrofuran, the hydroxymethyl group is converted to methyl halide in conventional manner, for example by heating with a hydrohalic acid, especially hydrobromic acid, the halogen atom is

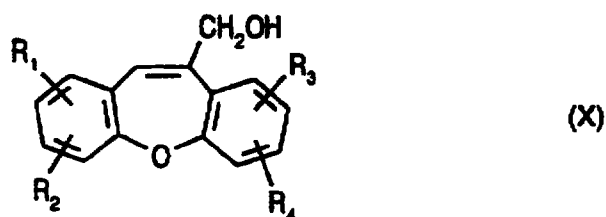
replaced by cyano in conventional manner, for example by treatment with an alkali metal cyanide, such as sodium cyanide in ethanol, and the compound of formula VIII thus obtained



is reacted with an oxalic acid di-lower-alkylester, e.g. diethyl oxalate, in conventional manner, for example in the presence of an alkali metal alkanolate such as sodium methanolate, worked up to form an acid, then in the compound of formula IX thus obtained



the carboxy group is reduced to hydroxymethyl in conventional manner, for example by treatment with a halogen-formic acid ester such as isobutyl chloroformate, in the presence of a nitrogen base such as N-methylmorpholine, preferably in an ethereal solvent such as dimethoxymethane, and subsequently with a di-light metal hydride such as sodium borohydride in water, and the compound of formula X thus obtained



is treated with an agent which introduces the group X, such as a hydrohalic acid or a sulphonyl halide such as methane sulphonyl chloride.

Higher homologues of compounds of formula II, wherein alk signifies ethylene, propylene etc., or ethylidene, propylidene etc., may be obtained for example whereby at the stage of

the acid IX either chain lengthening is carried out in conventional manner or the carboxy group is converted into the desired 1-oxoalkyl group in conventional manner.

Compounds of formula II, wherein X signifies optionally protected amino, may be obtained in conventional manner, for example from the reactive esters of the formula II in which X denotes reactively esterified hydroxy, obtained as above, by reaction with ammonia in conventional manner, for example, treatment with a saturated solution of ammonia in methanol, and if desired, subsequent introduction of the amino protecting group.

In the starting materials of formula IV according to process variant b), esterified hydroxy is for example esterified hydroxy that is derived from a carboxylic acid or a semi-ester of carbonic acid, such as optionally halogenated lower alkanoyloxy, for example lower alkanoyloxy such as formyloxy, acetyloxy or pivaloyloxy, lower alkoxycarbonyloxy such as methoxycarbonyloxy, ethoxycarbonyloxy, isopropylloxycarbonyloxy or tertiary butylloxycarbonyloxy, or optionally substituted phenyl-lower-alkoxycarbonyloxy such as benzyloxycarbonyloxy.

Reduction of compounds of formula IV is effected in conventional manner, for example by treatment with a di- light metal hydride such as lithium aluminium hydride in tetrahydrofuran.

Starting materials of formula IV, wherein alk' signifies ω -oxo-lower-alkyl bonded to the group R in ω -position, may be obtained for example from the corresponding acids of formula IX or the homologues thereof, by reacting them with an amine of formula III, wherein Y signifies optionally intermediately protected amino, in conventional manner, for example by treatment with an acid-halogenating agent such as oxalyl chloride in the presence of dimethylformamide. From these, the corresponding compounds of formula IV, in which alk' is lower alkylidene substituted by optionally esterified hydroxy, may be obtained by means of partial reduction and, if desired, esterification. Starting compounds of formula IV, wherein alk' signifies (ω -1)-oxo-lower-alkyl bonded to the group R in ω -position, may be obtained for example from the corresponding methyl ketones by means of halogenation, for example by means of N-bromo- or N-chloro-succinimide, and subsequently reacting with an amine of formula III, wherein Y signifies optionally intermediately protected amino.

Compounds that are obtainable according to this process may be converted in conventional manner into other compounds of formula I.

In compounds of formula I, wherein R signifies unsubstituted amino, the amino group may be substituted in conventional manner by one or two identical or different monovalent aliphatic or araliphatic radicals or one divalent aliphatic radical. Similarly, in compounds of formula I, wherein R signifies amino which is substituted by a monovalent aliphatic or araliphatic radical, a further monovalent aliphatic or araliphatic radical may also be introduced.

The salts obtained may be converted in a manner known *per se* into the free compounds, e.g. by treatment with a base, such as an alkali metal hydroxide, a metal carbonate or hydrogen carbonate, or another salt-forming base mentioned initially, or with an acid such as a mineral acid, e.g. hydrochloric acid, or another salt-forming acid mentioned initially.

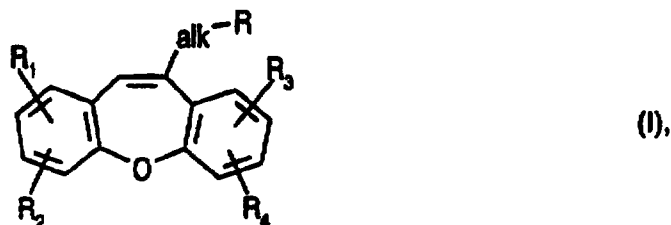
The acid addition salts of compounds of formula I may also be obtained in the form of hydrates, or may include the solvent used for crystallisation.

New starting materials that were developed especially for production of the compounds according to the invention, in particular the choice of starting materials leading to the compounds of formula I identified initially as the preferred compounds, the processes for their production and their use as intermediate products, similarly form an object of the invention.

This especially concerns compounds of formula I, wherein R signifies an amino group which is mono-substituted by optionally esterified or amidated carboxy-lower-alkyl, cyano-lower-alkyl or by a phenyl-lower-alkyl radical which in the phenyl moiety is unsubstituted or is substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl and in the lower-alkyl moiety is substituted by optionally esterified carboxy; or an amino group which is di-substituted by lower-alkylene, lower-alkenylene or lower-alkadienylene radicals either unsubstituted or substituted by optionally esterified or amidated carboxy or cyano, or by phenyl-lower-alkylene, phenyl(cyano)-lower-alkylene, phenyl-lower-alkyl-lower-alkylene, N'-phenylaza-lower-alkylene or N'-phenyl-lower-alkylaza-lower-alkylene radicals either

unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl; in free form.

As a further preferred object, the invention accordingly relates to compounds of formula



wherein alk is lower alkylidene,

R signifies an amino group mono-substituted by cyano-lower-alkyl or by a phenyl-lower-alkyl radical, either unsubstituted in the phenyl moiety or substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl and in the lower-alkyl moiety by optionally esterified carboxy; or an amino group disubstituted by lower-alkylene, lower-alkenylene or lower-alkadienylene radicals or by phenyl-lower-alkylene, cyano(phenyl)lower-alkylene, phenyl-lower-alkyl-lower-alkylene, N'-phenylaza-lower-alkylene or N'-phenyl-lower-alkylaza-lower-alkylene radicals, either unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl, and

R₁, R₂, R₃ and R₄, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl, in free form.

The invention preferably relates to compounds of formula I, wherein alk is lower alkylidene,

R represents cyano-lower-alkylamino, 3- to 8-membered lower-alkyleneamino, 3- to 8-membered lower-alkadienyleneamino, 3- to 8-membered pyrimidinylaza-lower-alkylene-amino; a 3- to 8-membered phenyl(carboxy-lower-alkyl)amino, phenyl(lower-alkoxycarbonyl-lower-alkyl)amino, cyano(phenyl)lower-alkylamino, N'-phenylaza-lower-alkyleneamino or N'-benzylaza-lower-alkyleneamino radical either unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl; or 1,2,3,6-tetrahydropyridino, and

R₁, R₂, R₃ and R₄, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl,

in free form, processes for their production, pharmaceutical preparations containing them and their use as active ingredients for medicaments.

The invention relates in particular to compounds of formula I, wherein alk is methylene,

R represents cyano-C₁-C₄-alkylamino such as cyanomethylamino; a phenyl-(1-carboxy-C₁-C₄-alkyl)amino or phenyl-(1-C₁-C₄-alkoxycarbonyl-C₁-C₄-alkylamino radical either unsubstituted or substituted by C₁-C₄-alkyl such as methyl, C₁-C₄-alkoxy such as methoxy, halogen with an atomic number up to and including 35, such as chlorine or bromine, and/or trifluoromethyl, such as 2-phenyl-1-carboxyethylamino or 2-phenyl-1-ethoxycarbonylethylamino; phenyl-C₁-C₄-alkylpyrrolidino either unsubstituted or substituted by C₁-C₄-alkyl such as methyl, C₁-C₄-alkoxy such as methoxy, halogen with an atomic number up to and including 35, such as chlorine or bromine, and/or trifluoromethyl, such as benzylpyrrolidino; 4-cyano-4-phenyl-piperidino or phenyl-C₁-C₄-alkylpiperidino either unsubstituted or substituted by C₁-C₄-alkyl such as methyl, C₁-C₄-alkoxy such as methoxy, halogen with an atomic number up to and including 35, such as chlorine or bromine, and/or trifluoromethyl, such as benzylpiperidino, 1,2,3,6-tetrahydropyridino, N'-pyrimidinylpiperazino; or phenylpiperazino or phenyl-C₁-C₄-alkylpiperazino either unsubstituted or substituted by C₁-C₄-alkyl such as methyl, C₁-C₄-alkoxy such as methoxy, halogen with an atomic number up to and including 35, such as chlorine or bromine, and/or trifluoromethyl, such as N'-benzylpiperazino, and

R₁, R₂, R₃ and R₄, independently of one another, denote hydrogen, C₁-C₄-alkyl such as methyl, C₁-C₄-alkoxy such as methoxy, halogen with an atomic number up to and including 35, such as chlorine or bromine, or trifluoromethyl,

in free form, processes for their production, pharmaceutical preparations containing them and their use as active ingredients for medicaments.

The invention relates primarily to compounds of formula I, wherein alk is methylene,

R represents a phenyl-(1-C₁-C₄-alkoxycarbonyl-C₁-C₄-alkylamino radical such as 2-phenyl-1-ethoxycarbonylethylamino, either unsubstituted or substituted by C₁-C₄-alkyl such as methyl, C₁-C₄-alkoxy such as methoxy, halogen with an atomic number up to and including 35, such as chlorine or bromine, and/or trifluoromethyl, and

R_1 , R_2 , R_3 and R_4 , independently of one another, denote hydrogen, C_1 - C_4 -alkyl such as methyl, C_1 - C_4 -alkoxy such as methoxy, halogen with an atomic number up to and including 35, such as chlorine or bromine, or trifluoromethyl, in free form, processes for their production, pharmaceutical preparations containing them and their use as active ingredients for medicaments.

In particular, the invention relates to

2-[(dibenzo[b,f]oxepin-10-ylmethyl)-amino]-3-phenyl-propionic acid ethyl ester;

1-(dibenzo[b,f]oxepin-10-ylmethyl)-1,2,3,6-tetrahydro-pyridine;

1-(dibenzo[b,f]oxepin-10-ylmethyl)-4-phenylpiperidine-4-carbonitrile;

1-(dibenzo[b,f]oxepin-10-ylmethyl)-4-(4-chlorophenyl)-piperazine;

(dibenzo[b,f]oxepin-10-ylmethylamino)acetonitrile;

1-(dibenzo[b,f]oxepin-10-ylmethyl)-4-(4-methoxyphenyl)-piperazine;

2-[4-(dibenzo[b,f]oxepin-10-ylmethyl)-piperazin-1-yl]-pyrimidine

and/or

1-benzyl-4-dibenzo[b,f]oxepin-10-ylmethyl-piperazine,

processes for their production, pharmaceutical preparations containing them and their use as active ingredients for medicaments.

As further preferred objects of the invention, the invention relates to pharmaceutical preparations, which contain the salts of compounds of formula I according to the invention with organic carboxylic acids, or new compounds of formula I or pharmaceutically applicable salts thereof as active ingredients, as well as processes for the production thereof.

The pharmaceutical preparations according to the invention are intended for enteral, such as oral, also rectal, and parenteral administration to warm-blooded animals, whereby the pharmacological active ingredient contained therein is on its own or together with a pharmaceutically applicable carrier material. The daily dosage of the active ingredient depends on the age and individual condition as well as on the method of application.

The new pharmaceutical preparations contain e.g. from ca. 10% to ca. 80%, preferably from ca. 20% to ca. 60%, of the active ingredient. Pharmaceutical preparations according to the invention for enteral or parenteral administration are e.g. those in single dose form, such as dragées, tablets, capsules or suppositories, furthermore ampoules. These are produced in

a manner known *per se*, e.g. by means of conventional mixing, granulating, dragée-forming, dissolving or lyophilisation processes. Thus, pharmaceutical preparations for oral application may be obtained by combining the active ingredient with solid carrier substances, optionally granulating the mixture obtained, and processing the mixture or granulate into tablets or dragée cores, if desired or if necessary after adding appropriate excipients.

Appropriate carriers are in particular fillers such as sugar, e.g. lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, e.g. tricalcium phosphate or calcium hydrogen phosphate, furthermore binding agents such as starch paste using e.g. corn, wheat, rice or potato starch, gelatin, tragacanth, methyl cellulose and/or polyvinylpyrrolidone, if desired, disintegrants such as the above-mentioned starches, furthermore carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof such as sodium alginate. Excipients are primarily mobile phases, mobile phase regulators and lubricants, e.g. silicic acid, talc, stearic acid or salts thereof such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with appropriate coatings that are resistant to gastric juices if required. Those used include *inter alia* concentrated sugar solutions which optionally contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or lacquer solutions in appropriate organic solvents or solvent mixtures, or to produce coatings that are resistant to gastric juices, solutions of appropriate cellulose preparations such as acetyl cellulose phthalate or hydroxypropylmethyl cellulose phthalate. Dyes or pigments may be added to the tablets or dragée coatings, e.g. to identify or characterise different dosages of active ingredient.

Further orally applicable pharmaceutical preparations are hard two-piece gelatin capsules, as well as soft, closed capsules consisting of gelatin and a softener such as glycerol or sorbitol. The hard capsules may contain the active ingredient in the form of a granulate, e.g. mixed with fillers such as lactose, binding agents such as starches, and/or lubricants such as talc or magnesium stearate, and optionally stabilizers. In soft capsules, the active ingredient is preferably dissolved or suspended in appropriate liquids such as fatty oils, paraffin oil or liquid polyethylene glycols, whereby stabilizers may similarly be added.

Suppositories may be considered e.g. as rectally applicable pharmaceutical preparations. These consist of a combination of the active ingredient with a suppository base. Suitable

suppository bases may be e.g. natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. In addition, rectal capsules of gelatin may also be used, which contain a combination of the active ingredient with a base substance. The base substances may be e.g. liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

For parenteral administration by infusion and/or injection, aqueous solutions of an active ingredient in water-soluble form are primarily suitable, e.g. a water-soluble salt, also suspensions of the active ingredient, such as appropriate oily suspensions, whereby suitable lipophilic solvents or vehicles are used, such as fatty oils, sesame oil, or synthetic fatty acid esters, e.g. ethyl oleate or triglycerides, or aqueous suspensions which contain viscosity-increasing substances, e.g. sodium carboxymethyl cellulose, sorbitol and/or dextran, and optionally also stabilizers.

The dosage of active substance depends on the species of warm-blooded animal, the age and the individual condition, as well as the method of application. Under normal circumstances, for a patient of about 75 kg weight, an approximately daily dose for oral application is from ca. 10 mg to ca. 500 mg.

The following examples serve to illustrate the invention; temperatures are indicated in degrees celsius, and pressures in mbar.

Example 1: N-(dibenzo[b,f]oxepin-10-ylmethyl)-N-methyl-N-prop-2-ynyl-ammonium-maleinate

Preparation from N-(dibenzo[b,f]oxepin-10-ylmethyl)-N-methyl-N-prop-2-ynyl-amine by reacting with maleic acid in methanol. Recrystallisation from hot methanol. The title compound is the hydrogen maleinate of N-(dibenzo[b,f]oxepin-10-ylmethyl)-N-methyl-N-prop-2-ynyl-amine;

M.p. 158-159°C; Analysis: C 70.73% (70.58); H 5.35% (5.41); N 3.50% (3.58);

¹H-NMR (200 MHz, CD₃OD): 2.84 (s, 3H); 3.31 (t, 1H); 3.99 (m, 2H); 4.42 (s, 2H); 6.25 (s, 2H, maleic acid); 7.15-7.60 (m, 9H).

The starting material may be produced for example as follows:

a) N-(dibenzo[b,f]oxepin-10-ylmethyl-N-methyl-N-prop-2-ynyl-amine

N-methyl-N-propargylamine (4.5 g, 65 mmols) is dissolved in benzene (75 ml) and methanol (25 ml). The solution of 10-bromomethyl-dibenzo[b,f]oxepine (7.0 g, 25 mmols) in benzene (25 ml) is added in drops over the course of half an hour at 40°. When this addition is complete, stirring is effected for another half an hour at 40-50°. The solution is poured onto water, washed three times with water and then extracted with 5% methanesulphonic acid. The acidic aqueous phase is rendered basic with concentrated ammonia and extracted with diethylether. The ethereal phase is dried over sodium sulphate and concentrated by evaporation. Crystallisation of the residue from petroleum ether yields N-(dibenzo[b,f]oxepin-10-ylmethyl-N-methyl-N-prop-2-ynyl-amine (5.3 g, 77%). M.p. 66-67°.

Example 2: N-(dibenzo[b,f]oxepin-10-ylmethyl)-N-methyl-N-prop-2-ynyl-ammonium-fumarate

Preparation from N-(dibenzo[b,f]oxepin-10-ylmethyl)-N-methyl-N-prop-2-ynyl-amine by reacting with fumaric acid in methanol analogously to the manner described in example 1. Recrystallisation from petroleum ether. The title compound is the hydrogen fumarate of N-(dibenzo[b,f]oxepin-10-yl-methyl)-N-methyl-N-prop-2-ynyl-amine; M.p. 118° (decomp.); Analysis: C 70.25% (70.58); H 5.33% (5.41); N 3.52% (3.58); ¹H-NMR (200 MHz, CD₃OD): 2.50 (s, 3H); 2.90 (t, 1H); 3.59 (d, 2H); 3.93 (s, 2H); 6.72 (s, 2H, fumaric acid); 7.00 (s, 1H); 7.10-7.41 (m, 7H); 7.56 (dd, 1H).

Beispiel 3: N-benzyl-N-(dibenzo[b,f]oxepin-10-ylmethyl)-N-methyl-ammonium-maleinate

Preparation from N-benzyl-N-(dibenzo[b,f]oxepin-10-ylmethyl)-N-methylamine by reacting with maleic acid in hot methanol analogously to the manner described in example 2. The title compound is the hydrogen maleinate of N-benzyl-N-(dibenzo[b,f]oxepin-10-ylmethyl)-N-methylamine;

M.p. 161-162°; ¹H-NMR (200 MHz, CD₃OD): 2.81 (s, 3H); 4.38 (s, 2H); 4.40 (sbr, 2H); 6.25 (s, 2H, maleic acid); 7.15-7.55 (m, 9H).

The starting material is produced for example as follows:

a) N-benzyl-N-(dibenzo[b,f]oxepin-10-ylmethyl)-N-methylamine

A solution of 1.0 g (3.48 mmols) of 10-bromomethyl-dibenzo[b,f]oxepine in 6.5 ml of methanol is mixed with a solution of 1.02 ml (8 mmols) of N-benzyl-N-methylamine in 10 ml

of toluene, and stirred for 4 hours at room temperature. After drawing off the solvent, flash-chromatography is carried out directly on 70 g of silica gel with hexane/ethyl acetate (9:1). 1.01 g (89%) of crystallizing N-benzyl-N-(dibenzo[b,f]oxepin-10-ylmethyl)-N-methylamine are obtained;

$^1\text{H-NMR}$ (200 MHz, CDCl_3): 2.28 (s, 3H); 3.53 (s, 2H); 3.60 (s, 2H); 6.90 (s, 1H); 7.05-7.45 (m, 8H); MS: 327 (M^+); 236, 208, 207M; thin-layer chromatography (silica gel, hexane/ethyl acetate (9:1)): $R_f = 0.14$

Example 4: 2-[(dibenzo[b,f]oxepin-10-ylmethyl)-ammonio]-3-phenyl-propionic acid ethyl ester maleinate

Preparation from free base (2-[(dibenzo[b,f]oxepin-10-ylmethyl)-amino]-3-phenyl-propionic acid ethyl ester) with maleic acid in hot methanol. The title compound is the hydrogen maleinate of 2-[(dibenzo[b,f]oxepin-10-ylmethyl)-amino]-3-phenyl-propionic acid ethyl ester; M.p. 140-141°C; $^1\text{H-NMR}$ (200 MHz, CD_3OD): 1.01 (t, 3H); 3.00-3.30 (m, 2H); 4.08 (q, 2H); 4.20 (m, 1H); 4.32 (d, 2H); 6.25 (s, 2H, maleic acid); 7.10-7.50 (m, 9H); optical rotation ($c = 1.0$, methanol): $\alpha_D = + 4.9^\circ$.

The starting material may be produced for example as follows:

a) 2-[(dibenzo[b,f]oxepin-10-ylmethyl)-amino]-3-phenyl-propionic acid ethyl ester

Preparation analogously to example 4a from 10-bromomethyl-dibenz[b,f]oxepine and L-phenylalanine ethyl ester. 2-[(dibenzo[b,f]oxepin-10-ylmethyl)-amino]-3-phenyl-propionic acid ethyl ester is obtained as a yellow oil;

$^1\text{H-NMR}$ (200 MHz, CDCl_3): 1.20 (t, 3H); 1.76 (sbr, 1H, NH); 2.97 (m, 2H); 3.65 (m, 2H); 3.90 (dd, 1H); 4.14 (q, 2H); 6.75 (s, 1H); 7.02-7.35 (m, 13H); MS: 399 (M^+); 308, 207; thin-layer chromatography (silica gel, hexane/ethyl acetate (9:1)): $R_f = 0.16$

Example 5: 1-benzyl-4-dibenzo[b,f]oxepin-10-ylmethyl-piperazinium-dimaleate

Preparation from 0.5 mmols of 1-benzyl-4-dibenzo[b,f]oxepin-10-ylmethyl-piperazine with 2 equivalents of maleic acid in 10 ml of chloroform/methanol (1:1). After leaving to stand over night, the title compound, the dihydrogen maleinate of 1-benzyl-4-dibenzo[b,f]oxepin-10-ylmethyl-piperazine, is obtained as white crystals in 66% yield; M.p. 207-209°C; $^1\text{H-NMR}$ (200 MHz, d_6 -DMSO): 2.80-3.10 (m br, ca. 8H); 3.76 (s br, 2H); 4.19 (s br, 2H); 6.13 (s, 4H, 2x maleic acid); 6.97 (s, 1H); 7.14-7.65 (m, 13H); ES-MS: 383 ($\text{M}^+ + 1$).

The starting material is produced as follows:

1-benzyl-4-dibenzo[b,f]oxepin-10-ylmethyl-piperazine

1.27 ml (8.0 mmols) of N-benzylpiperazine are slowly sprayed into a solution of 1.0 g (3.48 mmols) of 10-bromomethyl-dibenzo[b,f]oxepine in 7 ml of methanol and 7 ml of toluene. The solution is stirred for 16 hours at room temperature, the solvents drawn off, taken up in methylene chloride, washed with saturated sodium hydrogen carbonate solution, the organic phase dried over magnesium sulphate, the solvent drawn off and the residue chromatographed on silica gel with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (39:1) as the eluant. 1.42 g of 1-di-benzo[b,f]oxepin-10-ylmethyl-1,2,3,6-tetrahydro-pyridine are obtained as a yellowish oil; $^1\text{H-NMR}$ (200 MHz, CD_3Cl): 2.45 (m br, ca. 4H); 2.61 (m br, 4H); 3.50 (s, 4H); 6.83 (s, 1H); 7.03-7.35 (m, 12H); 7.60 (dd, 1H); ES-MS: 383 ($\text{M}^+ + 1$).

Example 6: 1-benzyl-4-dibenzo[b,f]oxepin-10-ylmethyl-piperazinium-difumarate

Preparation from 0.5 mmols of free base 1-benzyl-4-dibenzo[b,f]oxepin-10-ylmethyl-piperazine with 2 equivalents of fumaric acid in 10 ml of chloroform/methanol (1:1). After leaving to stand over night, the title compound, the dihydrogen fumarate of 1-benzyl-4-dibenzo[b,f]oxepin-10-ylmethyl-piperazine, is obtained as white crystals in 80% yield; M.p. 227-229°;

$^1\text{H-NMR}$ (200 MHz, $\text{d}_6\text{-DMSO}$): 2.40-2.60 (m br, ca. 8H); 3.51 (m, 4H); 6.62 (s, 4H, 2x fumaric acid); 6.90 (s, 1H); 7.10-7.40 (m, 12H); 7.63 (dd, 1H); ES-MS: 383 ($\text{M}^+ + 1$).

Example 7: 1-dibenzo[b,f]oxepin-10-ylmethyl-1,2,3,6-tetrahydro-pyridinium-maleate

Preparation from the free base 1-dibenzo[b,f]oxepin-10-ylmethyl-1,2,3,6-tetrahydro-pyridine with 1 equivalent of maleic acid in hot methanol. After leaving to stand over night, the title compound, the hydrogen maleinate of 1-dibenzo[b,f]oxepin-10-ylmethyl-1,2,3,6-tetrahydro-pyridine, is obtained in a 70% yield as light beige crystals; M.p. 188-191°;

$^1\text{H-NMR}$ (200 MHz, CD_3OD): 2.50 (m, 2H); 3.45 (m, 2H); 3.80 (m, 2H); 4.57 (s, 2H); 5.76 (m, 1H); 6.00 (m, 1H); 6.29 (s, 2H, maleic acid); 7.19-7.69 (m, 9H); ES-MS: 290 ($\text{M}^+ + 1$), 207. Elementary analysis: C: 70.61% (calculated: 71.10%); H: 5.72% (5.72%); N: 3.32% (3.45%).

The starting material is produced as follows:

a) 1-dibenzo[b,f]oxepin-10-ylmethyl-1,2,3,6-tetrahydro-pyridine

1.45 ml (16.0 mmols) of 1,2,5,6-tetrahydropyridine are slowly sprayed into a solution of 2.0 g (6.96 mmols) of 10-bromomethyl-dibenzo[b,f]oxepine in 15 ml of methanol and 15 ml of toluene. The solution is stirred for 16 hours at room temperature, the solvents drawn off, and the residue chromatographed on silica gel with hexane/ethyl acetate (9:1) as the eluant. 1.59 g (79%) of the title compound are obtained as an orange oil;

¹H-NMR (200 MHz, CDCl₃): 2.13 (m, 2H); 2.65 (t, 2H); 3.05 (m, 2H); 3.57 (m, 2H); 5.69 (m, 2H); 6.87 (s, 1H); 7.00-7.30 (m, 7H); 7.58 (dd, 1H);

ES-MS: 285, 287 (M, weak); 207 (M-Br).

Example 8: 1-dibenzo[b,f]oxepin-10-ylmethyl-1,2,3,6-tetrahydro-pyridinium-fumarate

Preparation from the free base 1-dibenzo[b,f]oxepin-10-ylmethyl-1,2,3,6-tetrahydro-pyridine with 1 equivalent of fumaric acid in hot methanol. After leaving to stand over night, light beige crystals are obtained in a 50% yield; M.p. 168-171°;

¹H-NMR (200 MHz, CD₃OD): 2.45 (m, 2H); 3.38 (m, 2H); 3.78 (m, 2H); 4.43 (s, 2H); 5.73 (m, 1H); 5.95 (m, 1H); 6.71 (s, 2H, fumaric acid); 7.18-7.65 (m, 9H); ES-MS: 290 (M⁺+1), 207.

Elementary analysis: C: 71.12% (calculated: 71.10%); H: 5.73% (5.72%); N: 3.38% (3.45%).

Example 9: 1-dibenzo[b,f]oxepin-10-ylmethyl-1,2,3,6-tetrahydro-pyridinium-succinate

Preparation from the free base 1-dibenzo[b,f]oxepin-10-ylmethyl-1,2,3,6-tetrahydro-pyridine with 1 equivalent of succinic acid in hot methanol. After leaving to stand over night, light beige crystals are obtained in a 40% yield; M.p. 133-135°;

¹H-NMR (200 MHz, CD₃OD): 2.33 (m, 2H); 2.57 (s, 4H, succinic acid); 3.10 (t, 2H); 3.45 (m, 2H); 4.15 (s, 2H); 5.70 (m, 1H); 5.89 (m, 1H); 7.10-7.65 (m, 9H); ES-MS: 290 (M⁺+1), 207.

Elementary analysis: C: 70.83% (calculated: 70.75%); H: 6.18% (6.18%); N: 3.43% (3.44%).

Example 10: 1-dibenzo[b,f]oxepin-10-ylmethyl-4-phenyl-piperidinium-4-carbonitrile-maleate

Preparation from 0.5 mmols of free base 1-dibenzo[b,f]oxepin-10-ylmethyl-4-phenyl-piperidine-4-carbonitrile with 1 equivalent of maleic acid in 10 ml of chloroform/methanol (1:1). After drawing off chloroform/methanol and crystallising from ethanol/diethylether, the title compound, the hydrogen maleinate of 1-dibenzo[b,f]oxepin-10-ylmethyl-4-phenyl-piperidine-4-carbonitrile, is obtained as white crystals in a 94% yield; M.p. 202-203°;

¹H-NMR (200 MHz, CD₃OD): 2.45 (m, 4H); 3.35 (m, 2H); 3.78 (m, 2H); 4.63 (s, 2H); 6.28 (s, 2H, maleic acid); 6.97 (s, 1H); 7.20-7.70 (m, 14H); ES-MS: 393 (M⁺+1).

The starting material is produced as follows:

a) 1-dibenzo[b,f]oxepin-10-ylmethyl-4-phenylpiperidine-4-carbonitrile

1.36 ml (9.74 mmols) of triethylamine, followed by 1.78 ml (8.0 mmols) of 4-cyano-4-phenylpiperidine-hydrochloride, are slowly sprayed into a solution of 1.0 g (3.48 mmols) of 10-bromomethyl-dibenzo[b,f]oxepine in 7 ml of methanol and 7 ml of toluene. The solution is stirred for 16 hours at room temperature, the solvents drawn off, CH₂Cl₂ taken up, washed with saturated sodium hydrogen carbonate solution, the organic phase is dried over MgSO₄, the solvent drawn off, and the residue chromatographed on silica gel (CH₂Cl₂). After drawing off chloroform/methanol and crystallising from ethanol/diethylether, 0.93 g (68%) of the title compound are obtained as a pale foam;

¹H-NMR (200 MHz, CD₃Cl): 2.10 (m, 4H); 2.58 (m, 2H); 3.29 (m, 2H); 3.62 (d, 2H); 6.89 (s, 1H); 7.05-7.60 (m, 13H); ES-MS: 393 (M⁺+1).

Example 11: 1-dibenzo[b,f]oxepin-10-ylmethyl-4-phenyl-piperidinium-4-carbonitrile-fumarate

Preparation from 0.5 mmols of free base 1-dibenzo[b,f]oxepin-10-ylmethyl-4-phenylpiperidine-4-carbonitrile with 1 equivalent of fumaric acid in 10 ml of chloroform/methanol (1:1). After drawing off chloroform/methanol and crystallising from ethanol/diethylether, the title compound, the hydrogen fumarate of 1-dibenzo[b,f]oxepin-10-ylmethyl-4-phenylpiperidine-4-carbonitrile, is obtained as white crystals in a 75% yield;

M.p. 232-234°; ¹H-NMR (200 MHz, CD₃OD): 1.90-3.70 (m br, ca. 10H); 6.71 (s, 2H, fumaric acid); 6.99 (s, 1H); 7.10-7.70 (m, 13H); ES-MS: 393 (M⁺+1).

Example 12: 1-dibenzo[b,f]oxepin-10-ylmethyl-4-(4-chlorophenyl)-piperazinium-maleate

Preparation from 0.5 mmols of free base 1-dibenzo[b,f]oxepin-10-ylmethyl-4-(4-chlorophenyl)-piperazine with 1 equivalent of maleic acid in 10 ml of chloroform/methanol (1:1). After drawing off chloroform/methanol and crystallising from ethanol/diethylether, the title compound, the maleinate of 1-chloro-4-dibenzo[b,f]oxepin-10-ylmethyl-piperazine, is obtained as white crystals in an 84% yield;

M.p. 180-183°; ¹H-NMR (200 MHz, CD₃OD): 2.40-2.60 (m, 8H); 4.52 (s, 2H); 6.28 (s, 2H, maleic acid); 6.99 (m, 2H); 7.20-7.70 (m, 11H); ES-MS: 403 (M⁺+1).

The starting material is produced as follows:

a) 1-dibenzo[b,f]oxepin-10-ylmethyl-4-(4-chlorophenyl)-piperazine

2.43 ml (17.4 mmols) of triethylamine, followed by 2.16 g (8.0 mmols) of 1-(4-chlorophenyl)piperazine-dihydrochloride, are slowly added to a solution of 1.0 g (3.48 mmols) of 10-bromomethyl-dibenzo[b,f]oxepine in 7 ml of methanol and 7 ml of toluene. The solution is stirred for 16 hours at room temperature, the solvents drawn off, CH_2Cl_2 taken up, washed with saturated sodium hydrogen carbonate solution, the organic phase dried over MgSO_4 , the solvent drawn off and the residue chromatographed on silica gel (CH_2Cl_2). 0.46 g (33%) of the title compound are obtained as a sticky, beige foam;

$^1\text{H-NMR}$ (200 MHz, CD_3Cl): 2.70 (m, 4H); 3.15 (m, 4H); 3.58 (s, 2H); 6.80-6.90 (m, 3H); 7.05-7.35 (m, 9H); 7.60 (dd, 1H); ES-MS: 403 ($\text{M}^+ + 1$).

Example 13: 1-dibenzo[b,f]oxepin-10-ylmethyl-4-(4-chlorophenyl)-piperazinium-fumarate

Preparation from 0.5 mmols of free base 1-dibenzo[b,f]oxepin-10-ylmethyl-4-(4-chlorophenyl)-piperazine with 1 equivalent of fumaric acid in 10 ml of chloroform/methanol (1:1). After drawing off chloroform/methanol and crystallising from ethanol/diethylether, the title compound, the fumarate of 1-chloro-4-dibenzo[b,f]oxepin-10-ylmethyl-piperazine, is obtained as white crystals in a 58% yield;

M.p. 195-198°; $^1\text{H-NMR}$ (200 MHz, d_6 -DMSO): 2.40-3.60 (m br, 10H); 6.62 (s, 2H, fumaric acid); 7.10 (m, 2H); 7.20-7.40 (m, 10H); 7.67 (dd, 1H); ES-MS: 403 ($\text{M}^+ + 1$).

Example 14: (dibenzo[b,f]oxepin-10-ylmethyl-methyl-ammonio)-acetonitrile-maleate

Preparation from 0.5 mmols of free base (dibenzo[b,f]oxepin-10-ylmethyl-methyl-amino)-acetonitrile with 1 equivalent of maleic acid in 10 ml of chloroform/methanol (1:1). After drawing off chloroform/methanol and crystallising from ethanol/diethylether, the title compound, the hydrogen maleinate of (dibenzo[b,f]oxepin-10-ylmethyl-methyl-amino)-acetonitrile, is obtained as white crystals in a 61% yield;

M.p. 137-139°; $^1\text{H-NMR}$ (200 MHz, d_6 -DMSO): 2.28 (s, 3H); 3.63 (s, 2H); 3.75 (s, 2H); 6.27 (s, 2H, maleic acid); 6.95 (s, 1H); 7.12-7.42 (m, 7H); 7.55 (dd, 1H); ES-MS: 277 ($\text{M}^+ + 1$).

The starting material may be obtained as follows:

a) (dibenzo[b,f]oxepin-10-ylmethyl-methyl-amino)-acetonitrile

1.36 ml (9.74 mmols) of triethylamine, followed by 0.85 g (8.0 mmols) of methylamino-acetonitrile-hydrochloride, are slowly added to a solution of 1.0 g (3.48 mmols) of 10-bromo-methyl-dibenzo[b,f]oxepine in 7 ml of methanol and 7 ml of toluene. The solution is stirred for 16 hours at room temperature, the solvents drawn off, CH_2Cl_2 taken up, washed with saturated sodium hydrogen carbonate solution, the organic phase dried over MgSO_4 , the solvent drawn off, and the residue chromatographed on silica gel (CH_2Cl_2). 0.96 g (100%) of (dibenzo[b,f]oxepin-10-ylmethyl-methyl-amino)-acetonitrile are obtained as a beige oil; $^1\text{H-NMR}$ (200 MHz, CD_3Cl): 2.49 (s, 3H); 3.59 (s, 2H); 3.66 (s, 2H); 6.92 (s, 1); 7.05-7.5 (m, 8H); ES-MS: 277 ($\text{M}^+ + 1$).

Example 15: (dibenzo[b,f]oxepin-10-ylmethyl-methyl-ammonio)-acetonitrile-fumarate

Preparation from 0.5 mmols of free base (dibenzo[b,f]oxepin-10-ylmethyl-methyl-amino)-acetonitrile with 1 equivalent of fumaric acid in 10 ml of chloroform/methanol (1:1). After drawing off chloroform/methanol and crystallising from ethanol/diethylether, the title compound, the hydrogen fumarate of (dibenzo[b,f]oxepin-10-ylmethyl-methyl-amino)-acetonitrile, is obtained as white crystals in a 57% yield; M.p. 100-105°; $^1\text{H-NMR}$ (200 MHz, CD_3OD): 2.45 (s, 3H); 3.69 (s, 2H); 3.71 (s, 2H); 6.78 (s, 2H, fumaric acid); 6.95 (s, 1H); 7.12-7.42 (m, 7H); 7.55 (dd, 1H); ES-MS: 277 ($\text{M}^+ + 1$).

Example 16: 2-(4-dibenzo[b,f]oxepin-10-ylmethyl-piperazin-1-yl)-pyrimidinium-maleate

Preparation from 0.5 mmols of free base 2-(4-dibenzo[b,f]oxepin-10-ylmethyl-piperazin-1-yl)-pyrimidine with 1 equivalent of maleic acid in 10 ml of chloroform/methanol (1:1). The title compound, the maleinate of 2-(4-dibenzo[b,f]oxepin-10-ylmethyl-piperazin-1-yl)-pyrimidine, is obtained as white crystals in a 41% yield; M.p. 199-204°; $^1\text{H-NMR}$ (200 MHz, d_6 -DMSO): 2.40-4.20 (m br, 10H); 6.12 (s, 2H, maleic acid); 6.69 (t, 1H); 7.10-7.70 (m, 10H); 8.40 (d, 1H); ES-MS: 371 ($\text{M}^+ + 1$).

The starting material is produced as follows:

a) 2-(4-dibenzo[b,f]oxepin-10-ylmethyl-piperazin-1-yl)-pyrimidine

2.43 ml (17.4 mmols) of triethylamine, followed by 1.9 g (8.0 mmols) of 1-(2-pyrimidyl)-piperazine-dihydrochloride, are slowly added to a solution of 1.0 g (3.48 mmols) of

10-bromomethyl-dibenzo[b,f]oxepine in 7 ml of methanol and 7 ml of toluene. The solution is stirred for 16 hours at room temperature, the solvents drawn off, CH_2Cl_2 taken up, washed with saturated sodium hydrogen carbonate solution, the organic phase dried over MgSO_4 , the solvent drawn off, and the residue chromatographed on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 39:1). 0.62 g (48%) of 2-(4-dibenzo[b,f]oxepin-10-ylmethyl-piperazin-1-yl)-pyrimidine are obtained as a light brown oil;

$^1\text{H-NMR}$ (200 MHz, CD_3Cl): 2.61 (t, 4H); 3.53 (s, 2H); 3.82 (t, 4H); 6.46 (m, 1H); 6.89 (s, 1H); 7.03-7.35 (m, 7H); 7.65 (m, 1H); 8.29 (dd, 2H); ES-MS: 371 ($\text{M}^+ + 1$).

Example 17: 2-(4-dibenzo[b,f]oxepin-10-ylmethyl-piperazin-1-yl)-pyrimidinium-fumarate

Preparation from 0.5 mmols of free base (2-(4-dibenzo[b,f]oxepin-10-ylmethyl-piperazin-1-yl)-pyrimidine with 1 equivalent of fumaric acid in 10 ml of chloroform/methanol (1:1). The title compound, the fumarate of 2-(4-dibenzo[b,f]oxepin-10-ylmethyl-piperazin-1-yl)-pyrimidine, is obtained as white crystals in a 58% yield;

M.p. 234-237°; $^1\text{H-NMR}$ (200 MHz, d_6 -DMSO): 2.51 (m, 4H); 3.57 (s, 2H); 3.71 (m, 4H); 6.71 (m, 1H); 6.72 (s, 2H, fumaric acid); 6.92 (s, 1H); 7.10-7.40 (m, 8H); 7.67 (dd, 1H); 8.32 (d, 1H); ES-MS: 371 ($\text{M}^+ + 1$).

Example 18: 1-dibenzo[b,f]oxepin-10-ylmethyl-4-(4-methoxy-phenyl)-piperazinium-maleate

Preparation from 0.5 mmols of free base 1-dibenzo[b,f]oxepin-10-ylmethyl-4-(4-methoxy-phenyl)-piperazine with 1 equivalent of maleic acid in 10 ml of chloroform/methanol (1:1). The title compound, the maleinate of 1-dibenzo[b,f]oxepin-10-ylmethyl-4-(4-methoxy-phenyl)-piperazine, is obtained as white crystals in a 29% yield;

M.p. 193-194°; $^1\text{H-NMR}$ (200 MHz, d_6 -DMSO): 2.40-4.20 (m br, 10H); 6.10 (s, 2H, maleic acid); 6.80-7.75 (m, 13H); ES-MS: 399 ($\text{M}^+ + 1$).

The starting material is produced as follows:

a) 1-dibenzo[b,f]oxepin-10-ylmethyl-4-(4-methoxyphenyl)-piperazine

2.43 ml (17.4 mmols) of triethylamine, followed by 2.12 g (8.0 mmols) of 1-(p-methoxy-phenyl)-piperazine-dihydrochloride, are slowly added to a solution of 1.0 g (3.48 mmols) of 10-bromomethyl-dibenzo[b,f]oxepine in 7 ml of methanol and 7 ml of toluene. The solution is stirred for 16 hours at room temperature, the solvents drawn off, CH_2Cl_2 taken up, washed with saturated sodium hydrogen carbonate solution, the organic phase dried over

MgSO₄, the solvent drawn off and the residue chromatographed on silica gel (CH₂Cl₂-MeOH 39:1). 19.0 g (14%) of 1-dibenzo[b,f]oxepin-10-ylmethyl-4-(4-methoxyphenyl)-piperazine are obtained as light beige crystals;

¹H-NMR (200 MHz, CD₂Cl): 2.71 (m, 4H); 3.10 (m, 4H); 3.58 (s, 2H); 3.75 (s, 3H) 6.78-6.92 (m, 5H); 7.05-7.35 (m, 7H); 7.65 (m, 1H); ES-MS: 399 (M⁺+1).

Example 19: 1-dibenzo[b,f]oxepin-10-ylmethyl-4-(4-methoxy-phenyl)-piperazinium-fumarate

Preparation from 0.5 mmols of free base 1-dibenzo[b,f]oxepin-10-ylmethyl-4-(4-methoxy-phenyl)-piperazine with 1 equivalent of fumaric acid in 10 ml of chloroform/methanol (1:1). The title compound, the fumarate of 1-dibenzo[b,f]oxepin-10-ylmethyl-4-(4-methoxyphenyl)-piperazine, is obtained as white crystals; M.p. 176-179°;

¹H-NMR (200 MHz, d₆-DMSO): 2.40-4.20 (m br, 10H); 6.72 (s, 2H, maleic acid); 6.70-7.70 (m, 13H); ES-MS: 399 (M⁺+1).

Example 20: Tablets, each containing 50 mg: N-(dibenzo[b,f]oxepin-10-ylmethyl)-N-methyl-N-prop-2-ynyl-ammonium fumarate may be produced as follows:

Composition (10,000 tablets)

active ingredient	500.0 g
lactose	500.0 g
potato starch	352.0 g
gelatin	8.0 g
talc	60.0 g
magnesium stearate	10.0 g
silicon dioxide (highly disperse)	20.0 g
ethanol	q.s.

The active ingredient is mixed with the lactose and 292 g of potato starch, the mixture moistened with an ethanolic solution of the gelatin and granulated through a sieve. After drying, the remainder of the potato starch, the magnesium stearate, the talc and the silicon dioxide are mixed in, and the mixture is pressed into tablets each of 145.0 mg weight and 50.0 mg active ingredient content. If desired, they may be provided with partial notches for finer adjustment of the dosage.

Example 21: A sterile-filtered aqueous gelatin solution with 20% cyclodextrins as dissolving intermediary, each containing 3 mg of N-(dibenzo[b,f]oxepin-10-ylmethyl)-N-methyl-N-prop-2-ynyl-ammonium fumarate as active ingredient, is mixed whilst heating, under aseptic conditions, with a sterile gelatin solution containing phenol as a preservative, such that 1.0 ml of solution has the following composition:

active ingredient	3 mg
gelatin	150.0 mg
phenol	4.7 mg
dist. water with 20% cyclodextrins as dissolving intermediary	1.0 ml

Example 22: To produce a sterile dry substance for injection, each containing 5 mg of N-(dibenzo[b,f]oxepin-10-ylmethyl)-N-methyl-N-prop-2-ynyl-ammonium oxalate, 5 mg of one of the compounds of formula I named in the preceding examples as the active ingredient are dissolved in 1 ml of an aqueous solution with 20 mg of mannitol and 20% cyclodextrins as dissolving intermediary. The solution is sterile-filtered and filled into a 2 ml ampoule under aseptic conditions, deep-frozen and lyophilized. Prior to usage, the lyophilizate is dissolved in 1 ml of distilled water or 1 ml of physiological sodium chloride solution. The solution is used intramuscularly or intravenously. This formulation may also be filled into double-chamber injection ampoules.

Example 23: For the production of 10,000 lacquer-coated tablets, each containing 100 mg of N-(dibenzo[b,f]oxepin-10-ylmethyl)-N-methyl-N-prop-2-ynyl-ammonium fumarate, the following procedure may be followed:

active ingredient	1000 g
corn starch	680 g
colloidal silicic acid	200 g
magnesium stearate	20 g
stearic acid	50 g
sodium carboxymethyl starch	250 g
water	q.s.

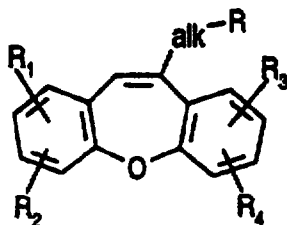
A mixture of the active ingredient, 50 g of corn starch and the colloidal silicic acid is worked into a moist mass with starch paste consisting of 250 g of corn starch and 2.2 kg of demineralised water. This mass is forced through a sieve of 3 mm mesh size, and dried for 30 minutes at 45° in a fluidised bed drier. The dried granulate is pressed through a sieve of 1 mm mesh size, mixed with a previously-sieved mixture (1 mm sieve) of 330 g of corn starch, the magnesium stearate, the stearic acid and the sodium carboxymethyl starch, and then pressed into slightly domed tablets.

Example 24: In addition, pharmaceutical preparations containing another compound according to one of examples 1 to 19 may be produced analogously to the methods described in examples 20 to 23.

**Patent Claims:**

THIS SHEET HAS BEEN
REPLACED

1. An acid addition salt of a 10-aminoalipharyl-dibenz[b,f]oxepine of formula I



(I)

wherein alk signifies a divalent, aliphatic radical,

R represents an amino group, either unsubstituted or mono- or di-substituted by monovalent aliphatic and/or araliphatic radicals, or disubstituted by divalent aliphatic, araliphatic or heteroarylaliphatic radicals, and

R₁, R₂, R₃ and R₄, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl,

with the provision that

- a) R is different from methylamino, dimethylamino, N'-methylpiperazino and N'-(2-hydroxyethyl)-piperazino, or at least one of radicals R₁, R₂ and R₄ is different from hydrogen or R₃ is different from hydrogen and 8-methoxy, or R is different from dimethylamino and diethylamino or at least one of radicals R₁, R₂ and R₄ is different from hydrogen or R₃ is different from 8-chloro, or R is different from pyrrolidino or at least one of radicals R₁, R₂, R₃ or R₄ is different from hydrogen, if alk respectively signifies methylene,
- b) R is different from methylamino or at least one of radicals R₁, R₂ and R₄ is different from hydrogen or R₃ is different from 6-methyl, or R is different from diethylamino, at least one of radicals R₁, R₂ and R₄ is different from hydrogen or R₃ is different from 7-methyl or at least one of radicals R₂, R₃ and R₄ is different from hydrogen or R₁ is different from 3-methyl, if alk is ethylene,
- c) R is different from methylamino and dimethylamino or at least one of radicals R₁, R₂, R₃ and R₄ is different from hydrogen, if alk signifies ethylidene, and
- d) R is different from dimethylamino or at least one of radicals R₂ and R₄ is different from hydrogen or R₁ is different from hydrogen, 3-chloro and 3-trifluoromethyl, or R₃ is different from hydrogen, 8-chloro and 8-trifluoromethyl, or R is different from diethylamino or at least one of radicals R₁, R₂, R₃ and R₄ is different from hydrogen, or R is different from piperidino, at least one of radicals R₂, R₃ and R₄ is different from hydrogen, or R₁ is different





from 1-bromo or R_2 and R_4 are different from hydrogen and R_1 is different from 1-bromo and R_3 is different from hydrogen, or R_1 is different from hydrogen and R_3 is different from 9-bromo, if alk signifies propylene, with an organic carboxylic acid, with the exception of the hydrogenoxalate of N-(Dibenzo[b,f]oxepin-10-ylmethyl-N-methyl-N-prop-2-ynyl-amine).

2. An acid addition salt of a compound of formula I according to claim 1, wherein alk signifies lower alkylidene,

R represents amino, lower-alkylamino; a phenyl-lower-alkylamino, phenyl(carboxy-lower-alkyl)amino, phenyl(lower-alkoxycarbonyl-lower-alkyl)amino or phenyl-lower-alkyl-lower-alkylamino radical either unsubstituted or substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl; hydroxy-lower-alkylamino, carboxy-lower-alkylamino, lower-alkoxy-carbonyl-lower-alkylamino, carbamoyl-lower-alkylamino, lower-alkoxy-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, lower-alkyleneamino-lower-alkylamino, lower-alkenylamino, hydroxy-lower-alkenylamino, lower-alkoxy-lower-alkenylamino, lower-alkanoyloxy-lower-alkenylamino, di-lower-alkylamino-lower-alkenylamino, lower-alkinylamino, hydroxy-lower-alkinylamino, lower-alkoxy-lower-alkinylamino, lower-alkanoyloxy-lower-alkinylamino, di-lower-alkylamino-lower-alkinylamino, di-lower-alkylamino, di(hydroxy-lower-alkyl)amino, hydroxy-lower-alkyl-lower-alkylamino, di(lower-alkoxy-lower-alkyl)amino, lower-alkoxy-lower-alkyl-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkanoyloxy-lower-alkyl-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkyl-lower-alkylamino, di-lower-alkenylamino, lower-alkenyl-lower-alkylamino, hydroxy-lower-alkenyl-lower-alkylamino, di(lower-alkoxy-lower-alkenyl)amino, lower-alkoxy-lower-alkenyl-lower-alkylamino, lower-alkanoyloxy-lower-alkenyl-lower-alkylamino, di-lower-alkylamino-lower-alkenyl-lower-alkylamino, lower-alkinyl-lower-alkylamino, lower-alkoxy-lower-alkinyl-lower-alkylamino, lower-alkanoyloxy-lower-alkinyl-lower-alkylamino, di-lower-alkylamino-lower-alkinyl-lower-alkylamino; respectively 3- to 8-membered lower-alkyleneamino, lower-alkenyleneamino or lower-alkadienylene-amino either unsubstituted or substituted by carboxy, lower-alkoxycarbonyl or carbamoyl or cyano; cyano(phenyl)lower-alkylene-amino either unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl; 3- or 4-aza-lower-alkylene-amino either unsubstituted or N-substituted by lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, pyridinyl, pyrimidinyl, triazinyl or lower-alkanoyl; 3- or 4-oxa-lower-alkylene-amino, optionally S-



oxidised 3- or 4-thia-lower-alkylene-amino; or a N'-phenylaza-lower-alkylene-amino or N'-benzylaza-lower-alkylene-amino radical either unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl, and

R₁, R₂, R₃ and R₄, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl,

with the provision that

R is different from amino either unsubstituted or mono- or di-substituted by lower alkyl; pyrrolidino, piperidino, morpholino, N'-methylpiperazino, N'-(2-hydroxyethyl)piperazino, N'-(2-acetoxyethyl)piperazino, N'-(2-pivaloyloxyethyl)piperazino and N'-methylhomopiperazino, if alk is methylene or ethylidene, and R₁, R₂, R₃ and R₄ signify hydrogen, lower alkyl, lower alkoxy and/or halogen,

with a pharmaceutically applicable, optionally hydroxylated lower alkanolic acid, optionally hydroxylated, aminated and/or oxo-substituted lower alkane-dicarboxylic acids, optionally hydroxylated and/or oxo-substituted lower alkane-tricarboxylic acids, optionally hydroxylated and/or oxo-substituted lower alkene-dicarboxylic acids, optionally hydroxylated and/or oxo-substituted lower alkene-dicarboxylic acid, with the exception of the hydrogenoxalate of N-(Dibenzo[b,f]oxepin-10-ylmethyl-N-methyl-N-prop-2-ynyl-amine.

3. An acid addition salt of a compound of formula I according to claim 1, wherein alk signifies methylene or ethylidene,

R represents amino, lower-alkylamino; a phenyl-lower-alkylamino, phenyl(carboxy-lower-alkyl)amino, phenyl(lower-alkoxycarbonyl-lower-alkyl)amino or phenyl-lower-alkyl-lower-alkylamino radical either unsubstituted or substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl; hydroxy-lower-alkylamino, lower-alkoxy-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, lower-alkylene-amino-lower-alkylamino, lower-alkenylamino, hydroxy-lower-alkenylamino, lower-alkoxy-lower-alkenylamino, lower-alkanoyloxy-lower-alkenylamino, di-lower-alkylamino-lower-alkenylamino, lower-alkinylamino, hydroxy-lower-alkinylamino, lower-alkoxy-lower-alkinylamino, lower-alkanoyloxy-lower-alkinylamino, di-lower-alkylamino-lower-alkinylamino, di-lower-alkylamino, di(hydroxy-lower-alkyl)amino, hydroxy-lower-alkyl-lower-alkylamino, di(lower-alkoxy-lower-alkyl)amino, lower-alkoxy-lower-alkyl-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkanoyloxy-lower-alkyl-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkyl-lower-alkylamino, di-lower-alkenylamino, lower-alkenyl-lower-alkylamino, hydroxy-lower-alkenyl-



lower-alkylamino, di(lower-alkoxy-lower-alkenyl)amino, lower-alkoxy-lower-alkenyl-lower-alkylamino, lower-alkanoyloxy-lower-alkenyl-lower-alkylamino, di(lower-alkylamino-lower-alkenyl-lower-alkylamino, lower-alkinyl-lower-alkylamino, lower-alkoxy-lower-alkinyl-lower-alkylamino, lower-alkanoyloxy-lower-alkinyl-lower-alkylamino, di-lower-alkylamino-lower-alkinyl-lower-alkylamino, 3- to 8-membered lower-alkylene-amino; 3- or 4-aza-lower-alkylene-amino either unsubstituted or N-substituted by lower alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl or lower-alkanoyl; 3- or 4-oxa-lower-alkylene-amino or optionally S-oxidised 3- or 4-thia-lower-alkyleneamino, and

R₁, R₂, R₃ and R₄, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl,

with a pharmaceutically applicable, optionally hydroxylated lower alkanoic acid, optionally hydroxylated and/or oxo-substituted lower alkane-dicarboxylic acid, fumaric acid, maleic acid, tartaric acid, citric acid, pyroacemic acid, malic acid, furthermore with an aromatic, heteroaromatic or araliphatic carboxylic acid.

4. An acid addition salt of a compound of formula I according to claim 1, wherein alk signifies lower alkylidene,

R represents amino, lower-alkylamino, cyano-lower-alkylamino; a phenyl-lower-alkylamino, phenyl(carboxy-lower-alkyl)amino, phenyl(lower-alkoxycarbonyl-lower-alkyl)amino or phenyl-lower-alkyl-lower-alkylamino radical either unsubstituted or substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl; lower-alkinylamino, di-lower-alkylamino, 3- to 8-membered lower-alkylene-amino or cyano(phenyl)lower-alkylene-amino, 3- to 8-membered lower-alkenylene-amino; 3- or 4-aza-lower-alkylene-amino either unsubstituted or N-substituted by lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl or lower-alkanoyl; 3- or 4-oxa-lower-alkylene-amino, optionally S-oxidised 3- or 4-thia-lower-alkylene-amino or a respectively 3- to 8-membered N'-pyrimidinylaza-lower-alkylene-amino radical; a phenyl-lower-alkylene, phenyl(cyano)lower-alkylene, N'-phenylaza-lower-alkylene-amino or N'-benzylaza-lower-alkylene-amino radical either unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl, and

R₁, R₂, R₃ and R₄, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl,

with a pharmaceutically applicable, optionally hydroxylated lower alkanoic acid, optionally hydroxylated, aminated and/or oxo-substituted lower alkane-dicarboxylic acid, optionally hydroxylated and/or oxo-substituted lower alkane-tricarboxylic acid, optionally hydroxylated



and/or oxo-substituted lower alkene-dicarboxylic acid, optionally hydroxylated and/or oxo-substituted lower alkene-dicarboxylic acid, furthermore with an aromatic, heteroaromatic or araliphatic carboxylic acid.

5. An acid addition salt of a compound of formula I according to claim 1, wherein alk signifies methylene,

R represents C₁-C₄-alkylamino, cyano-C₁-C₄-alkylamino, a phenyl-C₁-C₄-alkylamino, phenyl-C₁-C₄-alkyl-C₁-C₄-alkylamino, phenyl-(1-carboxy-C₁-C₄-alkyl)amino or phenyl-(1-C₁-C₄-alkoxycarbonyl-C₁-C₄-alkylamino radical either unsubstituted or substituted by C₁-C₄-alkyl such as methyl, C₁-C₄-alkoxy, halogen with an atomic number up to and including 35 and/or by trifluoromethyl; C₂-C₇-alkenylamino, C₂-C₇-alkinylamino, N-C₂-C₇-alkenyl-N-C₁-C₄-alkylamino, N-C₂-C₇-alkinyl-N-C₁-C₄-alkylamino, di-C₁-C₄-alkylamino, pyrrolidino, piperidino, 1,2,3,6-tetrahydropyridino; 4-cyano-4-phenylpiperidino either unsubstituted or substituted by C₁-C₄-alkyl, C₁-C₄-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl; morpholino, piperazino, N'-C₁-C₄-alkylpiperazino, N'-(hydroxy-C₂-C₄-alkyl)piperazino, N'-pyrimidinylpiperazino; or a N'-phenylpiperazino or N'-phenyl-C₁-C₄-alkylpiperazino radical either unsubstituted or substituted by C₁-C₄-alkyl, C₁-C₄-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl, and R₁, R₂, R₃ and R₄, independently of one another, denote hydrogen, C₁-C₄-alkyl, C₁-C₄-alkoxy, halogen with an atomic number up to and including 35 or trifluoromethyl, with a pharmaceutically applicable, optionally hydroxylated C₁-C₇-alkanoic acid, optionally hydroxylated, aminated and/or oxo-substituted C₂-C₇-alkane-dicarboxylic acid, optionally hydroxylated and/or oxo-substituted C₄-C₇-alkane-tricarboxylic acid, optionally hydroxylated and/or oxo-substituted C₄-C₇-alkene-dicarboxylic acid, optionally hydroxylated and/or oxo-substituted C₄-C₇-alkyne-dicarboxylic acid, furthermore with benzoic acid, salicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid or nicotinic acid.

6. An acid addition salt of a compound of formula I according to claim 1, wherein alk is methylene,

R represents C₁-C₄-alkylamino; a phenyl-C₁-C₄-alkylamino, phenyl-C₁-C₄-alkyl-C₁-C₄-alkylamino, phenyl-(1-carboxy-C₁-C₄-alkyl)amino or phenyl-(1-C₁-C₄-alkoxycarbonyl-C₁-C₄-alkylamino radical either unsubstituted or substituted by C₁-C₄-alkyl, C₁-C₄-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl; C₂-C₇-alkenylamino, C₂-C₇-alkinylamino, N-C₂-C₇-alkenyl-N-C₁-C₄-alkylamino, N-C₂-C₇-alkinyl-N-C₁-C₄-alkylamino,



di-C₁-C₄-alkylamino, pyrrolidino, piperidino, morpholino, piperazino, N'-C₁-C₄-alkylpiperazino, or N'-(hydroxy-C₂-C₄-alkyl)piperazino, and

R₁, R₂, R₃ and R₄, independently of one another, denote hydrogen, C₁-C₄-alkyl, C₁-C₄-alkoxy, halogen with an atomic number up to and including 35, or trifluoromethyl, with acetic acid, propionic acid, pivalic acid, glycolic acid, pyroacemic acid, lactic acid, oxalic acid, succinic acid, tartaric acid or malic acid, citric acid, fumaric acid, maleic acid, furthermore with benzoic acid, mandelic acid or nicotinic acid.

7. An acid addition salt of a compound of formula I according to claim 1, wherein alk is methylene,

R represents C₂-C₇-alkenylamino, C₂-C₇-alkinylamino, N-C₂-C₇-alkenyl-N-C₁-C₄-alkylamino, N-C₂-C₇-alkinyl-N-C₁-C₄-alkylamino; or phenyl-C₁-C₄-alkylamino either unsubstituted or substituted by C₁-C₄-alkyl, C₁-C₄-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl, and

R₁, R₂, R₃ and R₄, independently of one another, denote hydrogen, C₁-C₄-alkyl, C₁-C₄-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl, with a pharmaceutically applicable, optionally hydroxylated C₁-C₇-alkanoic acid, optionally hydroxylated, aminated and/or oxo-substituted C₂-C₇-alkane-dicarboxylic acid, optionally hydroxylated and/or oxo-substituted C₄-C₇-alkane-tricarboxylic acid, optionally hydroxylated and/or oxo-substituted C₄-C₇-alkene-dicarboxylic acid, optionally hydroxylated and/or oxo-substituted C₄-C₇-alkyne-dicarboxylic acid, with benzoic acid, salicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid or nicotinic acid.

8. An acid addition salt of a compound of formula I according to claim 1, wherein alk is methylene,

R represents C₂-C₇-alkenylamino, C₂-C₇-alkinylamino, N-C₂-C₇-alkenyl-N-C₁-C₄-alkylamino or N-C₂-C₇-alkinyl-N-C₁-C₄-alkylamino and

R₁, R₂, R₃ and R₄ signify hydrogen, C₁-C₄-alkyl, C₁-C₄-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl,

with a pharmaceutically applicable, optionally hydroxylated C₁-C₇-alkanoic acid, optionally hydroxylated, aminated and/or oxo-substituted C₂-C₇-alkane-dicarboxylic acid, optionally hydroxylated and/or oxo-substituted C₄-C₇-alkane-tricarboxylic acid, optionally hydroxylated and/or oxo-substituted C₄-C₇-alkene-dicarboxylic acid, optionally hydroxylated and/or oxo-substituted C₄-C₇-alkyne-dicarboxylic acid, e.g. acetylene-dicarboxylic acid, with benzoic

acid, salicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid or nicotinic acid.

9. An acid addition salt of a compound of formula I according to claim 1, wherein alk is methylene,

R represents C₂-C₇-alkenylamino, C₂-C₇-alkynylamino, N-C₂-C₇-alkenyl-N-C₁-C₄-alkylamino, or N-C₂-C₇-alkynyl-N-C₁-C₄-alkylamino,

R₁ and R₃, independently of one another, signify hydrogen, C₁-C₄-alkyl, C₁-C₄-alkoxy, halogen or trifluoromethyl and

R₂, R₄ signify hydrogen,

with glycolic acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, tartaric acid, citric acid, pyroacemic acid, malic acid, benzoic acid, nicotinic acid or mandelic acid.

10. An acid addition salt selected from

N-(dibenzo[b,f]oxepin-10-ylmethyl)-N-methyl-N-prop-2-ynyl-ammonium-maleinate,

N-(dibenzo[b,f]oxepin-10-ylmethyl)-N-methyl-N-prop-2-ynyl-ammonium-fumarate,

N-benzyl-N-(dibenzo[b,f]oxepin-10-ylmethyl)-N-methyl-ammonium-maleinate,

2-[(dibenzo[b,f]oxepin-10-ylmethyl)-ammonio]-3-phenyl-propionic acid ethyl ester-maleinate

1-dibenzo[b,f]oxepin-10-ylmethyl-1,2,3,6-tetrahydro-pyridinium-maleate,

1-dibenzo[b,f]oxepin-10-ylmethyl-1,2,3,6-tetrahydro-pyridinium-fumarate,

1-dibenzo[b,f]oxepin-10-ylmethyl-1,2,3,6-tetrahydro-pyridinium-succinate,

1-benzyl-4-dibenzo[b,f]oxepin-10-ylmethyl-piperazinium-dimaleate,

1-benzyl-4-dibenzo[b,f]oxepin-10-ylmethyl-piperazinium-difumarate

1-dibenzo[b,f]oxepin-10-ylmethyl-4-phenyl-piperidinium-4-carbonitrile-maleate,

1-dibenzo[b,f]oxepin-10-ylmethyl-4-phenyl-piperidinium-4-carbonitrile-fumarate,

1-dibenzo[b,f]oxepin-10-ylmethyl-4-(4-chlorophenyl)-piperazinium-maleate,

1-dibenzo[b,f]oxepin-10-ylmethyl-4-(4-chlorophenyl)-piperazinium-fumarate,

(dibenzo[b,f]oxepin-10-ylmethyl-methyl-ammonio)-acetonitrile-maleate,

(dibenzo[b,f]oxepin-10-ylmethyl-methyl-ammonio)-acetonitrile-fumarate,

2-(4-dibenzo[b,f]oxepin-10-ylmethyl-piperazin-1-yl)-pyrimidinium-maleate,

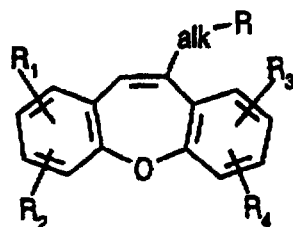
2-(4-dibenzo[b,f]oxepin-10-ylmethyl-piperazin-1-yl)-pyrimidinium-fumarate,

1-dibenzo[b,f]oxepin-10-ylmethyl-4-(4-methoxy-phenyl)-piperazinium-maleate or

1-dibenzo[b,f]oxepin-10-ylmethyl-4-(4-methoxy-phenyl)-piperazinium-fumarate.



11. A compound of formula



(I),

wherein alk is lower alkylidene,

R signifies an amino group mono-substituted by cyano-lower-alkyl or by a phenyl-lower-alkyl radical, either unsubstituted in the phenyl moiety or substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl and in the lower-alkyl moiety by optionally esterified carboxy; or an amino group disubstituted by lower-alkylene, lower-alkenylene or lower-alkadienylene radicals or by phenyl-lower-alkylene, cyano(phenyl)lower-alkylene, phenyl-lower-alkyl-lower-alkylene, N'-phenylaza-lower-alkylene or N'-phenyl-lower-alkylaza-lower-alkylene radicals, either unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl, and

R₁, R₂, R₃ and R₄, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl, in free form.

12. A compound according to claim 13, wherein

alk is lower alkylidene,

R represents cyano-C₁-C₄-alkylamino; a phenyl-(1-carboxy-C₁-C₄-alkyl)amino, phenyl-(1-C₁-C₄-alkoxycarbonyl-C₁-C₄-alkylamino, 4-cyano-4-phenyl-piperidino, phenyl-C₁-C₄-alkylpiperidino, phenyl-C₁-C₄-alkylpiperazino, phenylpiperazino or phenyl-C₁-C₄-alkylpiperazino radical either unsubstituted or substituted by C₁-C₄-alkyl, C₁-C₄-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl; 1,2,3,6-tetrahydropyridino or N'-pyrimidinylpiperazino, and

R₁, R₂, R₃ and R₄, independently of one another, denote hydrogen, C₁-C₄-alkyl, C₁-C₄-alkoxy, halogen with an atomic number up to and including 35 or trifluoromethyl, in free form.

13. A compound according to claim 13, selected from

2-[(dibenzo[b,f]oxepin-10-ylmethyl)-amino]-3-phenyl-propionic acid ethyl ester;

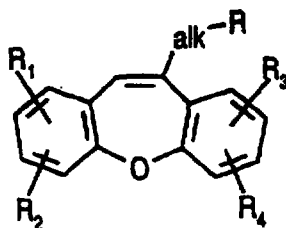


1-(dibenzo[b,f]oxepin-10-ylmethyl)-1,2,3,6-tetrahydro-pyridine;
 1-(dibenzo[b,f]oxepin-10-ylmethyl)-4-phenylpiperidine-4-carbonitrile;
 1-(dibenzo[b,f]oxepin-10-ylmethyl)-4-(4-chlorophenyl)-piperazine;
 (dibenzo[b,f]oxepin-10-ylmethyldiamino)acetonitrile;
 1-(dibenzo[b,f]oxepin-10-ylmethyl)-4-(4-methoxyphenyl)-piperazine;
 2-[4-(dibenzo[b,f]oxepin-10-ylmethyl)-piperazin-1-yl]-pyrimidine and
 1-benzyl-4-dibenzo[b,f]oxepin-10-ylmethyl-piperazine.

14. A compound according to one of claims 1 to 13, for treating the human or animal body.

15. A pharmaceutical preparation, containing an acid addition salt according to one of claims 1 to 10 or a compound according to one of claims 11 to 13, as well as the usual pharmaceutical excipients and carriers.

16. Process for the production of acid addition salts of compounds of formula I



(I)

wherein alk signifies a divalent, aliphatic radical,

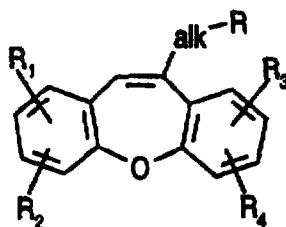
R represents an amino group, either unsubstituted or mono- or di-substituted by monovalent aliphatic and/or araliphatic radicals, or disubstituted by divalent aliphatic, araliphatic or heteroarylaliphatic radicals, and

R₁, R₂, R₃ and R₄, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl, with the provision that

a) R is different from methylamino, dimethylamino, N'-methylpiperazino and N'-(2-hydroxyethyl)-piperazino, or at least one of radicals R₁, R₂ and R₄ is different from hydrogen or R₃ is different from hydrogen and 8-methoxy, or R is different from dimethylamino and diethylamino or at least one of radicals R₁, R₂ and R₄ is different from hydrogen or R₃ is different from 8-chloro, or R is different from pyrrolidino or at least one of radicals R₁, R₂, R₃ or R₄ is different from hydrogen, if alk respectively signifies methylene,



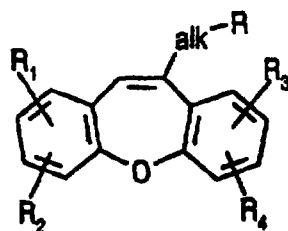
- b) R is different from methylamino or at least one of radicals R_1 , R_2 and R_4 is different from hydrogen or R_3 is different from 6-methyl, or R is different from diethylamino, at least one of radicals R_1 , R_2 and R_4 is different from hydrogen or R_3 is different from 7-methyl or at least one of radicals R_2 , R_3 and R_4 is different from hydrogen or R_1 is different from 3-methyl, if alk is ethylene,
- c) R is different from methylamino and dimethylamino or at least one of radicals R_1 , R_2 , R_3 and R_4 is different from hydrogen, if alk signifies ethylidene, and
- d) R is different from dimethylamino or at least one of radicals R_2 and R_4 is different from hydrogen or R_1 is different from hydrogen, 3-chloro and 3-trifluoromethyl, or R_3 is different from hydrogen, 8-chloro and 8-trifluoromethyl, or R is different from diethylamino or at least one of radicals R_1 , R_2 , R_3 and R_4 is different from hydrogen, or R is different from piperidino, at least one of radicals R_2 , R_3 and R_4 is different from hydrogen, or R_1 is different from 1-bromo or or R_2 and R_4 are different from hydrogen and R_1 is different from 1-bromo and R_3 is different from hydrogen, or R_1 is different from hydrogen and R_3 is different from 9-bromo, if alk signifies propylene,
- with organic carboxylic acids, with the exception of the hydrogenoxalate of N-(Dibenzo[b,f]oxepin-10-ylmethyl-N-methyl-N-prop-2-ynyl-amine, characterised in that a compound of formula I



(I)

in free form is reacted with at least the quantity of an organic carboxylic acid that is required for salt formation, and the desired salt is isolated.

17. Process for the treatment of neurodegenerative disorders, in which apoptotic cytolysis plays a role, such as cerebral ischaemia, Alzheimer's disease, Huntington's and Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, types of glaucoma, retina degeneration, especially retinitis pigmentosa, as well as general or diabetic peripheral neuropathia, characterised in that a therapeutically effective quantity of an acid addition salt of a 10-aminoalipharyl-dibenz[b,f]oxepine of formula I



(I)

wherein alk signifies a divalent, aliphatic radical,

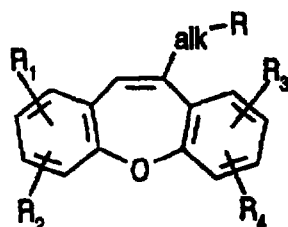
R represents an amino group, either unsubstituted or mono- or di-substituted by monovalent aliphatic and/or araliphatic radicals, or disubstituted by divalent aliphatic, araliphatic or heteroarylaliphatic radicals, and

R₁, R₂, R₃ and R₄, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl,

with an organic carboxylic acid, with the exception of the hydrogenoxalate of N-(Dibenzo[b,f]oxepin-10-ylmethyl-N-methyl-N-prop-2-ynyl-amine, or a compound according to claim 11,

is administered to a warm-blooded person or animal requiring such treatment.

18. Usage of an acid addition salt of a 10-aminoalipharyl-dibenz[b,f]oxepine of formula I



(I)

wherein alk signifies a divalent, aliphatic radical,

R represents an amino group, either unsubstituted or mono- or di-substituted by monovalent aliphatic and/or araliphatic radicals, or disubstituted by divalent aliphatic, araliphatic or heteroarylaliphatic radicals, and

R₁, R₂, R₃ and R₄, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl,

with an organic carboxylic acid, with the exception of the hydrogenoxalate of N-(Dibenzo[b,f]oxepin-10-ylmethyl-N-methyl-N-prop-2-ynyl-amine, as an anti-neurogenerative medicament, or to produce such a medicament.



19. Usage of an acid addition salt of a compound of formula I according to claim 18, wherein

alk signifies lower alkylidene,

R represents amino, lower-alkylamino; a phenyl-lower-alkylamino, phenyl(carboxy-lower-alkyl)amino, phenyl(lower-alkoxycarbonyl-lower-alkyl)amino or phenyl-lower-alkyl-lower-alkylamino radical either unsubstituted or substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl; hydroxy-lower-alkylamino, carboxy-lower-alkylamino, lower-alkoxy-carbonyl-lower-alkylamino, carbamoyl-lower-alkylamino, lower-alkoxy-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, lower-alkyleneamino-lower-alkylamino, lower-alkenylamino, hydroxy-lower-alkenylamino, lower-alkoxy-lower-alkenylamino, lower-alkanoyloxy-lower-alkenylamino, di-lower-alkylamino-lower-alkenylamino, lower-alkinylamino, hydroxy-lower-alkinylamino, lower-alkoxy-lower-alkinylamino, lower-alkanoyloxy-lower-alkinylamino, di-lower-alkylamino-lower-alkinylamino, di-lower-alkylamino, di(hydroxy-lower-alkyl)amino, hydroxy-lower-alkyl-lower-alkylamino, di(lower-alkoxy-lower-alkyl)amino, lower-alkoxy-lower-alkyl-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkanoyloxy-lower-alkyl-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkyl-lower-alkylamino, di-lower-alkenylamino, lower-alkenyl-lower-alkylamino, hydroxy-lower-alkenyl-lower-alkylamino, di(lower-alkoxy-lower-alkenyl)amino, lower-alkoxy-lower-alkenyl-lower-alkylamino, lower-alkanoyloxy-lower-alkenyl-lower-alkylamino, di-lower-alkylamino-lower-alkenyl-lower-alkylamino, lower-alkinyl-lower-alkylamino, lower-alkoxy-lower-alkinyl-lower-alkylamino, lower-alkanoyloxy-lower-alkinyl-lower-alkylamino, di-lower-alkylamino-lower-alkinyl-lower-alkylamino; respectively 3- to 8-membered lower-alkyleneamino either unsubstituted or substituted by carboxy, lower-alkoxycarbonyl or carbamoyl or cyano, 3- to 8-membered lower-alkenyleneamino, lower-alkenyleneamino or lower-alkadienylene-amino; 3- or 4-aza-lower-alkylene-amino either unsubstituted or N-substituted by lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, pyridinyl, pyrimidinyl, triazinyl or lower-alkanoyl; 3- or 4-oxa-lower-alkylene-amino, optionally S-oxidised 3- or 4-thia-lower-alkylene-amino; or a N'-phenylaza-lower-alkylene-amino or N'-benzylaza-lower-alkylene-amino radical either unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl, and

R₁, R₂, R₃ and R₄, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl,



with a pharmaceutically applicable, optionally hydroxylated lower alkanolic acid, optionally hydroxylated, aminated and/or oxo-substituted lower alkane-dicarboxylic acids, optionally hydroxylated and/or oxo-substituted lower alkane-tricarboxylic acids, optionally hydroxylated and/or oxo-substituted lower alkene-dicarboxylic acids, optionally hydroxylated and/or oxo-substituted lower alkine-dicarboxylic acids, furthermore with an aromatic, heteroaromatic or araliphatic carboxylic acid, as an anti-neurodegenerative medicament, or to produce such a medicament.

20. Usage of an acid addition salt of a compound of formula I according to claim 18, wherein

alk signifies methylene or ethylidene,

R represents amino, lower-alkylamino; phenyl-lower-alkylamino, phenyl(carboxy-lower-alkyl)amino, phenyl(lower-alkoxycarbonyl-lower-alkyl)amino or phenyl-lower-alkyl-lower-alkylamino radicals either unsubstituted or substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl; hydroxy-lower-alkylamino, lower-alkoxy-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, lower-alkylene-amino-lower-alkylamino, lower-alkenylamino, hydroxy-lower-alkenylamino, lower-alkoxy-lower-alkenylamino, lower-alkanoyloxy-lower-alkenylamino, di-lower-alkylamino-lower-alkenylamino, lower-alkinylamino, hydroxy-lower-alkinylamino, lower-alkoxy-lower-alkinylamino, lower-alkanoyloxy-lower-alkinylamino, di-lower-alkylamino-lower-alkinylamino, di-lower-alkylamino, di(hydroxy-lower-alkyl)amino, hydroxy-lower-alkyl-lower-alkylamino, di(lower-alkoxy-lower-alkyl)amino, lower-alkoxy-lower-alkyl-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkanoyloxy-lower-alkyl-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkyl-lower-alkylamino, di-lower-alkenylamino, lower-alkenyl-lower-alkylamino, hydroxy-lower-alkenyl-lower-alkylamino, di(lower-alkoxy-lower-alkenyl)amino, lower-alkoxy-lower-alkenyl-lower-alkylamino, lower-alkanoyloxy-lower-alkenyl-lower-alkylamino, di-lower-alkylamino-lower-alkenyl-lower-alkylamino, lower-alkinyl-lower-alkylamino, lower-alkoxy-lower-alkinyl-lower-alkylamino, lower-alkanoyloxy-lower-alkinyl-lower-alkylamino, di-lower-alkylamino-lower-alkinyl-lower-alkylamino, 3- to 8-membered lower-alkylene-amino; 3- or 4-aza-lower-alkylene-amino either unsubstituted or N-substituted by lower alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl or lower-alkanoyl; 3- or 4-oxa-lower-alkylene-amino or optionally S-oxidised 3- or 4-thia-lower-alkyleneamino, and



R_1 , R_2 , R_3 and R_4 , independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl,
with a pharmaceutically applicable, optionally hydroxylated lower alkanolic acid, optionally hydroxylated and/or oxo-substituted lower alkane-dicarboxylic acid, fumaric acid, maleic acid, tartaric acid, citric acid, pyroacetic acid, malic acid, furthermore with an aromatic, heteroaromatic or araliphatic carboxylic acid,
as an anti-neurodegenerative medicament, or to produce such a medicament.

21. Usage of an acid addition salt of a compound of formula I according to claim 18, wherein

alk signifies lower alkylidene,

R represents amino, lower-alkylamino, cyano-lower-alkylamino; a phenyl-lower-alkylamino, phenyl(carboxy-lower-alkyl)amino, phenyl(lower-alkoxycarbonyl-lower-alkyl)amino or phenyl-lower-alkyl-lower-alkylamino radical either unsubstituted or substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl; lower-alkinylamino, di-lower-alkylamino, 3- to 8-membered lower-alkylene-amino or cyano(phenyl)lower-alkylene-amino, 3- to 8-membered lower-alkenylene-amino; 3- or 4-aza-lower-alkylene-amino either unsubstituted or N-substituted by lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl or lower-alkanoyl; 3- or 4-oxa-lower-alkylene-amino, optionally S-oxidised 3- or 4-thia-lower-alkylene-amino or a respectively 3- to 8-membered N'-pyrimidinylaza-lower-alkylene-amino radical; a phenyl-lower-alkylene, phenyl(cyano)lower-alkylene, N'-phenylaza-lower-alkylene-amino or N'-benzylaza-lower-alkylene-amino radical either unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl, and

R_1 , R_2 , R_3 and R_4 , independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl,
with a pharmaceutically applicable, optionally hydroxylated lower alkanolic acid, optionally hydroxylated, aminated and/or oxo-substituted lower alkane-dicarboxylic acid, optionally hydroxylated and/or oxo-substituted lower alkane-tricarboxylic acid, optionally hydroxylated and/or oxo-substituted lower alkene-dicarboxylic acid, optionally hydroxylated and/or oxo-substituted lower alkyne-dicarboxylic acid, furthermore with an aromatic, heteroaromatic or araliphatic carboxylic acid,
as an anti-neurodegenerative medicament, or to produce such a medicament.



22. Usage of an acid addition salt of a compound of formula I according to claim 18, wherein

alk signifies methylene,

R represents C₁-C₄-alkylamino, cyano-C₁-C₄-alkylamino, a phenyl-C₁-C₄-alkylamino, phenyl-C₁-C₄-alkyl-C₁-C₄-alkylamino, phenyl-(1-carboxy-C₁-C₄-alkyl)amino or phenyl-(1-C₁-C₄-alkoxycarbonyl-C₁-C₄-alkylamino radical either unsubstituted or substituted by C₁-C₄-alkyl such as methyl, C₁-C₄-alkoxy, halogen with an atomic number up to and including 35 and/or by trifluoromethyl; C₂-C₇-alkenylamino, C₂-C₇-alkinylamino, N-C₂-C₇-alkenyl-N-C₁-C₄-alkylamino, N-C₂-C₇-alkinyl-N-C₁-C₄-alkylamino, di-C₁-C₄-alkylamino, pyrrolidino, piperidino, 1,2,3,6-tetrahydropyridino; 4-cyano-4-phenylpiperidino either unsubstituted or substituted by C₁-C₄-alkyl, C₁-C₄-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl; morpholino, piperazino, N'-C₁-C₄-alkylpiperazino, N'-(hydroxy-C₂-C₄-alkyl)piperazino, N'-pyrimidinylpiperazino; or a N'-phenylpiperazino or N'-phenyl-C₁-C₄-alkylpiperazino radical either unsubstituted or substituted by C₁-C₄-alkyl, C₁-C₄-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl, and

R₁, R₂, R₃ and R₄, independently of one another, denote hydrogen, C₁-C₄-alkyl, C₁-C₄-alkoxy, halogen with an atomic number up to and including 35 or trifluoromethyl, with a pharmaceutically applicable, optionally hydroxylated C₁-C₇-alkanoic acid, optionally hydroxylated, aminated and/or oxo-substituted C₂-C₇-alkane-dicarboxylic acid, optionally hydroxylated and/or oxo-substituted C₄-C₇-alkane-tricarboxylic acid, optionally hydroxylated and/or oxo-substituted C₄-C₇-alkene-dicarboxylic acid, optionally hydroxylated and/or oxo-substituted C₄-C₇-alkyne-dicarboxylic acid, furthermore with benzoic acid, salicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid or nicotinic acid, as an anti-neurodegenerative medicament, or to produce such a medicament.

23. Usage of an acid addition salt of a compound of formula I according to claim 18, wherein

R represents C₁-C₄-alkylamino; a phenyl-C₁-C₄-alkylamino, phenyl-C₁-C₄-alkyl-C₁-C₄-alkylamino, phenyl-(1-carboxy-C₁-C₄-alkyl)amino or phenyl-(1-C₁-C₄-alkoxycarbonyl-C₁-C₄-alkylamino radical either unsubstituted or substituted by C₁-C₄-alkyl, C₁-C₄-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl; C₂-C₇-alkenylamino, C₂-C₇-alkinylamino, N-C₂-C₇-alkenyl-N-C₁-C₄-alkylamino, N-C₂-C₇-alkinyl-N-C₁-C₄-alkylamino, di-C₁-C₄-alkylamino, pyrrolidino, piperidino, morpholino, piperazino, N'-C₁-C₄-alkylpiperazino, or N'-(hydroxy-C₂-C₄-alkyl)piperazino, and



R_1 , R_2 , R_3 and R_4 , independently of one another, denote hydrogen, C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, halogen with an atomic number up to and including 35, or trifluoromethyl, with a pharmaceutically applicable, optionally hydroxylated C_1 - C_7 -alkanoic acid, optionally hydroxylated, aminated and/or oxo-substituted C_2 - C_7 -alkane-dicarboxylic acid, optionally hydroxylated and/or oxo-substituted C_4 - C_7 -alkane-tricarboxylic acid, aconitic acid, optionally hydroxylated and/or oxo-substituted C_4 - C_7 -alkene-dicarboxylic acid, optionally hydroxylated and/or oxo-substituted C_4 - C_7 -alkyne-dicarboxylic acid, furthermore with benzoic acid, salicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid or nicotinic acid as an anti-neurodegenerative medicaments, or to produce such a medicament.



REPLACEMENT SHEET

24 NOV 1999

Patent Claims

1. An acid addition salt selected from:

N-(dibenzo[b,f]oxepin-10-ylmethyl)-N-methyl-N-prop-2-ynyl-ammonium -maleinate,
N-(dibenzo[b,f]oxepin-10-ylmethyl)-N-methyl-N-prop-2-ynyl-ammonium-fumarate,
N-benzyl-N-(dibenzo[b,f]oxepin-10-ylmethyl)-N-methyl-ammonium maleinate,
2-[(dibenzo[b,f]oxepin-10-ylmethyl)-ammonio]-3-phenyl-propionic acid ethyl ester-maleinate
1-dibenzo[b,f]oxepin-10-ylmethyl-1,2,3,6-tetrahydro-pyridinium-maleate,
1-dibenzo[b,f]oxepin-10-ylmethyl-1,2,3,6-tetrahydro-pyridinium-fumarate,
1-dibenzo[b,f]oxepin-10-ylmethyl-1,2,3,6-tetrahydro-pyridinium-succinate,
1-benzyl-4-dibenzo[b,f]oxepin-10-ylmethyl-piperazinium-dimaleate,
1-benzyl-4-dibenzo[b,f]oxepin-10-ylmethyl-piperazinium-difumarate,
1-dibenzo[b,f]oxepin-10-ylmethyl-4-phenyl-piperidinium-4-carbonitrile-maleate,
1-dibenzo[b,f]oxepin-10-ylmethyl-4-phenyl-piperidinium-4-carbonitrile-fumarate,
1-dibenzo[b,f]oxepin-10-ylmethyl-4-(chlorophenyl)-piperazinium-maleate,
1-dibenzo[b,f]oxepin-10-ylmethyl-4-(chlorophenyl)-piperazinium-fumarate,
(dibenzo[b,f]oxepin-10-ylmethyl-methyl-ammonio)-acetonitrile-maleate,
(dibenzo[b,f]oxepin-10-ylmethyl-methyl-ammonio)-acetonitrile-fumarate,
2-(4-dibenzo[b,f]oxepin-10-ylmethyl-piperazin-1-yl)-pyrimidinium-maleate,
2-(4-dibenzo[b,f]oxepin-10-ylmethyl-piperazin-1-yl)-pyrimidinium-fumarate,
1-dibenzo[b,f]oxepin-10-ylmethyl-4-(4-methoxy-phenyl)-piperazinium-maleate or
1-dibenzo[b,f]oxepin-10-ylmethyl-4-(4-methoxy-phenyl)-piperazinium-fumarate.

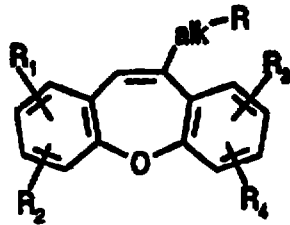
2. A compound selected from:

2-[(dibenzo[b,f]oxepin-10-ylmethyl)-amino]-3-phenyl-propionic acid ethyl ester;
1-(dibenzo[b,f]oxepin-10-ylmethyl)-1,2,3,6-tetrahydro-pyridine;
1-(dibenzo[b,f]oxepin-10-ylmethyl)-4-phenylpiperidine-4-carbonitrile;
1-(dibenzo[b,f]oxepin-10-ylmethyl)-4-(chlorophenyl)-piperazine;
(dibenzo[b,f]oxepin-10-ylmethylamino)acetonitrile;
1-dibenzo[b,f]oxepin-10-ylmethyl-4-(4-methoxyphenyl)-piperazine;
2-[4-dibenzo[b,f]oxepin-10-ylmethyl-piperazin-1-yl]pyrimidine and
1-benzyl-4-dibenzo[b,f]oxepin-10-ylmethyl-piperazine.

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(21) International Application Number: PCT/EP97/02794 (22) International Filing Date: 28 May 1997 (28.05.97) (30) Priority Data: 1352/96 30 May 1996 (30.05.96) CH (71) Applicant (for all designated States except US): NOVARTIS AG [CH/CH]; Schwarzwaldallee 215, CH-4058 Basel (CH). (72) Inventors; and (75) Inventors/Applicants (for US only): ZIMMERMANN, Kaspar [CH/CH]; Immenbachstrasse 20, CH-4125 Riehen (CH). ROGGO, Silvio [CH/CH]; Bahnhofstrasse 10 A/1, CH-4132 Muttenz (CH). BEFSCHART, Claudia [CH/JP]; 2-17-301, Jurakuso, Takarazuma 665 (JP). (74) Agent: ROTH, Bernhard, M.; Novartis AG, Patent- und Markenabteilung, Klybeckstrasse 141, CH-4002 Basel (CH).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, <u>SG</u>, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.
(54) Title: ANTI-NEURODEGENERATIVELY EFFECTIVE 10-AMINOALIPHATYL-DIBENZ[b,f]OXEPINE SALTS (57) Abstract Acid addition salts of 10-aminoaliphatyl-dibenz[b,f]oxepines of formula (I), wherein alk signifies a divalent, aliphatic radical, R represents an amino group, either unsubstituted or mono- or di-substituted by monovalent aliphatic and/or araliphatic radicals, or disubstituted by divalent aliphatic or araliphatic radicals, and R₁, R₂, R₃ and R₄, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl, with organic carboxylic acids, may be employed as anti-neurodegenerative active ingredients for medicaments. The invention also relates to new compounds of formula (I) in free form.  (I)		