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(54) Title: NOVEL 4,5-DIHYDRO-IMIDAZO[4,5,1-IJ]QUINOLIN-6-ONES

(57) Abstract: Compounds of a certain formula 1, in which A, R1 and R2 have the meanings indicated in the description, are novel active PARP inhibitors.

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Novel 4,5-Dihydro-imidazo[4,5,1-ij]quinolin-6-ones

Field of application of the invention

The invention relates to novel 4,5-Dihydro-imidazo[4,5,1-ij]quinolin-6-ones, which are used in the pharmaceutical industry for the production of pharmaceutical compositions.

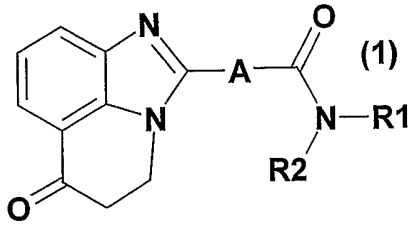
Known technical background

In the International patent applications WO00/42040, WO01/23386 and WO01/23390 3,4-Dihydro-1,2a,4-triaza-acenaphthylen-5-one derivatives are described as poly(ADP-ribosyl)transferase (PARP) inhibitors. In the European patent application EP 0405442 4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one derivatives are described with hypotensive, anti-oedematous and diuretic effects. In the European patent application EP 0646583 4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one derivatives are described as inhibitors for types 5-HT_3 and 5-HT_4 serotoninergic receptors. In the International patent application WO01/16136 8,9-Dihydro-7H-2,7,9a-triaza-benzo[cd]azulen-6-one derivatives are disclosed as poly-(ADP-ribosyl)transferase (PARP) inhibitors; in this application 4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one derivatives are mentioned as possible intermediates. In the International patent application WO02/12239 4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one derivatives which are substituted by piperazinyl- or piperidinyl groups are disclosed as poly(ADP-ribosyl)transferase (PARP) inhibitors.

Description of the invention

It has now been found that the novel 4,5-Dihydro-imidazo[4,5,1-ij]quinolin-6-ones described in greater detail below have surprising and particularly advantageous properties.

The invention thus relates to compounds of formula 1,



in which

A is furanylene, thienylene, pyrrolylene, imidazolylene, pyrazolylene, oxazolylene, isoxazolylene, thiazolylene, isothiazolylene, oxadiazolylene, thiadiazolylene, phenylene, pyrindinylene, pyridazinylene, pyrimidinylene, pyrazinylene, pyrrolidinylene, pyrazolidinylene, piperidinylene, piperazinylene, imidazolidinylene or 3-7C-cycloalkylene, and

in which either

R1 is hydrogen and

R2 is 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, phenyl, phenyl substituted by R3 and/or R4, phenyl-1-4C-alkyl, phenyl-1-4C-alkyl substituted in the phenyl moiety by R3 and/or R4, hetaryl, hetaryl-1-4C-alkyl, R5(R6)N-1-4C-alkyl, dihydrofuran-2-on-3-yl or tetrahydrofuran-2-ylmethyl,

or

R1 and R2 together and with inclusion of the nitrogen atom to which they are both attached form a pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl or hexahydroazepinyl ring, a piperidinyl ring substituted by R7 or a piperazinyl ring substituted by R8,

R3 is halogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy completely or predominantly substituted by fluorine, amino or mono-or di-1-4C-alkylamino,

R4 is halogen or 1-4C-alkoxy,

R5 and R6 are independently from each other hydrogen or 1-4C-alkyl, or R5 and R6 together and with inclusion of the nitrogen atom to which they are both attached form a pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl or hexahydroazepinyl ring,

hetaryl is pyridyl, imidazolyl, 1-methyl-1H-imidazol-2-yl, pyrazolyl, 1-methyl-1H-pyrazol-3-yl, 3-methyl-1H-pyrazol-5-yl, 3-phenyl-1H-pyrazol-5-yl, 3-tert-butyl-1H-pyrazol-5-yl, 3-(furan-2-yl)-1H-pyrazol-5-yl, 1,3-dimethyl-1H-pyrazol-5-yl, triazolyl, 4-(5-yl-1H-[1,2,4]triazol-3-yl)morpholine, furanyl, 2-methoxycarbonylfuran-5-yl, indolyl, thiophenyl, 2-methoxycarbonylthiophen-3-yl, 2-methoxycarbonyl-4-methylthiophen-3-yl, 3-methoxycarbonylpyrimidin-2-yl, 1-methyl-4-ethoxycarbonyl-1H-pyrazol-5-yl or 5-methylisoxazol-3-yl ,

R7 is pyrimidin-2-yl or tert-butoxycarbonylamino, and

R8 is 1-4C-alkyl, formyl or tert-butoxycarbonyl,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

1-4C-Alkyl represents a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl and preferably the ethyl and methyl radicals.

1-4C-Alkoxy represents radicals which, in addition to the oxygen atom, contain a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy and preferably the ethoxy and methoxy radicals.

1-4C-Alkoxy which is completely or predominantly substituted by fluorine is, for example, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,2,2-trifluoroethoxy and in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and the difluoromethoxy radical, of which the difluoromethoxy radical is preferred. "Predominantly" in this connection means that more than the half of the hydrogen atoms of the 1-4C-alkoxy group is replaced by fluorine atoms.

Halogen within the meaning of the invention is bromine, chlorine or fluorine.

Mono- or Di-1-4C-alkylamino radicals contain in addition to the nitrogen atom, one or two of the abovementioned 1-4C-alkyl radicals. Preferred are the di-1-4C-alkylamino radicals, especially the dimethylamino, the diethylamino and the diisopropylamino radical.

3-7C-Cycloalkylene stands for 1,2-cyclopropylene, 1,2-cyclobutylene, 1,3-cyclobutylene, 1,2-cyclopentylene, 1,3-cyclopentylene, 1,2-cyclohexylene, 1,3-cyclohexylene, 1,4-cyclohexylene, 1,2-cycloheptylene, 1,3-cycloheptylene and 1,4-cyloheptylene, of which 1,2-cyclopropylene is preferred.

3-7C-Cycloalkyl represents cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, of which cyclopropyl, cyclobutyl and cyclopentyl are preferred.

3-7C-Cycloalkyl-1-4C-alkyl alkyl stands for one of the abovementioned 1-4C-alkyl radicals which is substituted by one of the abovementioned 3-7C-cycloalkyl radicals. Examples which may be mentioned are the cyclopropylmethyl and the cyclohexylmethyl radical.

1-4C-Alkoxy-1-4C-alkyl stands for one of the abovementioned 1-4C-alkyl radicals, which is substituted by one of the abovementioned 1-4C-alkoxy radicals. Examples which may be mentioned are the methoxyethyl and the butoxyethyl radical.

Phenyl-1-4C-alkyl stands for one of the abovementioned 1-4C-alkyl radicals, which is substituted by phenyl. Examples which may be mentioned are the benzyl or the phenylethyl radicals.

Hetaryl stands for pyridyl, imidazolyl, 1-methyl-1H-imidazol-2-yl, pyrazolyl, 1-methyl-1H-pyrazol-3-yl, 3-methyl-1H-pyrazol-5-yl, 3-phenyl-1H-pyrazol-5-yl, 3-tert-butyl-1H-pyrazol-5-yl, 3-(furan-2-yl)-1H-pyrazol-5-yl, 1,3-dimethyl-1H-pyrazol-5-yl, triazolyl, 4-(5-yl-1H-[1,2,4]triazol-3-yl)morpholine, furanyl, 2-methoxycarbonylfuran-5-yl, indolyl, thiophenyl, 2-methoxycarbonylthiophen-3-yl, 2-methoxycarbonyl-4-methylthiophen-3-yl, 3-methoxycarbonylpyrimidin-2-yl, 1-methyl-4-ethoxycarbonyl-1H-pyrazol-5-yl or 5-methylisoxazol-3-yl.

Hetaryl-1-4C-alkyl stands for one of the abovementioned 1-4C-alkyl radicals, which is substituted by one of the abovementioned hetaryl radicals. Examples which may be mentioned are the pyridylmethyl, the pyridylethyl, the furanylmethyl and the imidazolylethyl radicals.

"N-oxides of these compounds" stands for any single or multiple N-oxide(s) which can be formed starting from the compounds of formula 1. Preferred are the single N-oxides.

Examples for a phenyl radical substituted by R3 and/or R4 which may be mentioned are the 4-dimethylaminophenyl and the 3-trifluoromethoxyphenyl and the 3,5-dimethoxyphenyl radical.

Examples for a phenyl-1-4C-alkyl radical substituted in the phenyl moiety by R3 and/or R4 which may be mentioned are the 3-aminophenylmethyl, the 2-fluorophenylmethyl, the 4-methoxyphenylmethyl the 3,5-dimethoxyphenylmethyl and the 3,4-dichlorophenylmethyl radical.

Possible salts for compounds of the formula 1 - depending on substitution - are all acid addition salts or all salts with bases. Particular mention may be made of the pharmacologically tolerable salts of the inorganic and organic acids and bases customarily used in pharmacy. Those suitable are, on the one hand, water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 3-hydroxy-2-naphthoic acid, it being possible to employ the acids in salt preparation - depending on whether a mono- or polybasic acid is concerned and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

On the other hand, salts with bases are also suitable. Examples of salts with bases which may be mentioned are alkali metal (lithium, sodium, potassium) or calcium, aluminum, magnesium, titanium, ammonium, meglumine or guanidinium salts, where here too the bases are employed in salt preparation in an equimolar quantitative ratio or one differing therefrom.

Pharmacologically intolerable salts which can initially be obtained, for example, as process products in the preparation of the compounds according to the invention on an industrial scale are converted into pharmacologically tolerable salts by processes known to the person skilled in the art.

It is known to the person skilled in the art that the compounds according to the invention and their salts, when they are isolated, for example, in crystalline form, can contain various amounts of solvents. The invention therefore also comprises all solvates and in particular all hydrates of the compounds of the formula 1, and also all solvates and in particular all hydrates of the salts of the compounds of the formula 1.

One embodiment (embodiment A) of the invention are compounds of formula 1 in which

A is furanylene, thienylene, pyrrolylene, imidazolylene, pyrazolylene, oxazolylene, isoxazolylene, thiazolylene, isothiazolylene, oxadiazolylene, thiadiazolylene, phenylene, pyrindinylene, pyridazinylene, pyrimidinylene, pyrazinylene, pyrrolidinylene, pyrazolidinylene, piperidinylene, piperazinylene, imidazolidinylene or 3-7C-cycloalkylene, and

in which either

R1 is hydrogen and

R2 is 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, phenyl-1-4C-alkyl, phenyl-1-4C-alkyl substituted in the phenyl moiety by R3 and/or R4, hetaryl, hetaryl-1-4C-alkyl, R5(R6)N-1-4C-alkyl, dihydrofuran-2-on-3-yl or tetrahydrofuran-2-ylmethyl,

or

R1 and R2 together and with inclusion of the nitrogen atom to which they are both attached form a pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl or hexahydroazepinyl ring, a piperidinyl ring substituted by R7 or a piperazinyl ring substituted by R8,

R3 is halogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy completely or predominantly substituted by fluorine, amino or mono-or di-1-4C-alkylamino,

R4 is halogen or 1-4C-alkoxy,

R5 and R6 are independently from each other hydrogen or 1-4C-alkyl, or R5 and R6 together and with inclusion of the nitrogen atom to which they are both attached form a pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl or hexahydroazepinyl ring,

hetaryl is pyridyl, imidazolyl, 1-methyl-1H-imidazol-2-yl, pyrazolyl, 1-methyl-1H-pyrazol-3-yl, 3-methyl-1H-pyrazol-5-yl, 3-phenyl-1H-pyrazol-5-yl, 3-tert-butyl-1H-pyrazol-5-yl, 3-(furan-2-yl)-1H-pyrazol-5-yl, 1,3-dimethyl-1H-pyrazol-5-yl, triazolyl, 4-(5-yl-1H-[1,2,4]triazol-3-yl)morpholine, furanyl, 2-methoxycarbonylfuran-5-yl, indolyl, thiophenyl, 2-methoxycarbonylthiophen-3-yl, 2-methoxycarbonyl-4-methylthiophen-3-yl, 3-methoxycarbonylpyrimidin-2-yl, 1-methyl-4-ethoxycarbonyl-1H-pyrazol-5-yl or 5-methylisoxazol-3-yl ,

R7 is pyrimidin-2-yl or tert-butoxycarbonylamino, and

R8 is 1-4C-alkyl, formyl or tert-butoxycarbonyl,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Compounds of formula 1 to be emphasized are those in which

A is 1,4-phenylene or 1,2-cyclopropylene, and

in which either

R1 is hydrogen and

R2 is 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, phenyl, phenyl substituted by R3 and/or R4, phenyl-1-4C-alkyl, phenyl-1-4C-alkyl substituted by R3 and/or R4, hetaryl, hetaryl-1-4C-alkyl, R5(R6)N-1-4C-alkyl, dihydrofuran-2-on-3-yl or tetrahydrofuran-2-ylmethyl,

or

R1 and R2 together and with inclusion of the nitrogen atom to which they are both attached form a pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl morpholinyl, thiomorpholinyl or hexahydroazepinyl ring, a piperidinyl ring substituted in 4-position by R7 or a piperazinyl ring substituted in 4-position by R8,

R3 is halogen, 1-4C-alkyl, 1-4C-alkoxy, trifluoromethoxy, amino or mono-or di-1-4C-alkylamino,

R4 is halogen or 1-4C-alkoxy,

R5 and R6 are independently from each other hydrogen or 1-4C-alkyl, or R5 and R6 together and with inclusion of the nitrogen atom to which they are both attached form a pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl or hexahydroazepinyl ring,

hetaryl is pyridyl, imidazolyl, 1-methyl-1H-imidazol-2-yl, pyrazolyl, 1-methyl-1H-pyrazol-3-yl, 3-methyl-1H-pyrazol-5-yl, 3-phenyl-1H-pyrazol-5-yl, 3-tert-butyl-1H-pyrazol-5-yl, 3-(furan-2-yl)-1H-pyrazol-5-yl, 1,3-dimethyl-1H-pyrazol-5-yl, triazolyl, 4-(5-yl-1H-[1,2,4]triazol-3-yl)morpholine, furanyl, 2-methoxycarbonylfuran-5-yl, indolyl, thiophenyl, 2-methoxycarbonylthiophen-3-yl, 2-methoxycarbonyl-4-methylthiophen-3-yl, 3-methoxycarbonylpyrimidin-2-yl, 1-methyl-4-ethoxycarbonyl-1H-pyrazol-5-yl or 5-methylisoxazol-3-yl,

R7 is pyrimidin-2-yl or tert-butoxycarbonylamino, and

R8 is formyl or tert-butoxycarbonyl,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Compounds of formula 1 of embodiment A which are to be emphasized are those in which

A is 1,4-phenylene or 1,2-cyclopropylene, and

in which either

R1 is hydrogen and

R2 is 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, phenyl-1-4C-alkyl, phenyl-1-4C-alkyl substituted by R3 and/or R4, hetaryl-1-4C-alkyl, R5(R6)N-1-4C-alkyl, dihydrofuran-2-on-3-yl or tetrahydrofuran-2-ylmethyl,

or

R1 and R2 together and with inclusion of the nitrogen atom to which they are both attached form a pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl morpholinyl, thiomorpholinyl or hexahydroazepinyl ring, a piperidinyl ring substituted in 4-position by R7 or a piperazinyl ring substituted in 4-position by R8,

R3 is halogen, 1-4C-alkyl, 1-4C-alkoxy, trifluoromethoxy, amino or mono-or di-1-4C-alkylamino,

R4 is halogen or 1-4C-alkoxy,

R5 and R6 are independently from each other hydrogen or 1-4C-alkyl, or R5 and R6 together and with inclusion of the nitrogen atom to which they are both attached form a pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl or hexahydroazepinyl ring,

hetaryl is pyridyl, imidazolyl or furanyl,

R7 is pyrimidin-2-yl or tert-butoxycarbonylamino, and

R8 is formyl or tert-butoxycarbonyl,
and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Compounds of formula 1 particularly to be emphasized are those in which
A 1,4-phenylene,
R1 is hydrogen and
R2 is 3-aminobenzyl, cyclopropyl, cyclopentyl, tetrahydrofuran-2-ylmethyl, methoxyethyl, cyclopropylmethyl, cyclohexyl, morpholin-4-yleth-2-yl, pyridin-2-ylmethyl, pyridin-3-ylmethyl, piperidin-1-yleth-2-yl, furan-2-ylmethyl, pyridin-4-ylmethyl, pyridin-4-yleth-2-yl, pyridin-3-yleth-2-yl,
or
R1 and R2 together and with inclusion of the nitrogen atom to which they are both attached form a pyrrolidinyl ring, a piperidinyl ring substituted in 4-position by R7 or a piperazinyl ring substituted in 4-position by R8,
R7 is pyrimidin-2-yl or tert-butoxycarbonylamino, and
R8 is tert-butoxycarbonyl,
and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Further compounds of formula 1 particularly to be emphasized are those in which
A 1,2-cyclopropylene,
R1 is hydrogen and
R2 is 1H-imidazol-5-yl-eth-2-yl, cyclopropyl, cyclopentyl, cyclohexylmethyl, methoxyethyl, cyclopropylmethyl, pyridin-2-ylmethyl, pyridin-3-ylmethyl, piperidin-1-yleth-2-yl, 2-fluorobenzyl, 4-methoxybenzyl, 3,5-dimethoxybenzyl, 3,4-dichlorobenzyl, furan-2-ylmethyl, pyridin-4-ylmethyl, pyridin-4-yleth-2-yl or pyridin-3-yleth-2-yl,
or
R1 and R2 together and with inclusion of the nitrogen atom to which they are both attached form a pyrrolidinyl or morpholinyl ring, a piperidinyl ring substituted in 4-position by R7 or a piperazinyl ring substituted in 4-position by R8,
R7 is pyrimidin-2-yl or tert-butoxycarbonylamino, and
R8 is formyl,
and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Preferred compounds of formula 1 are
2-(4-Cyclopropylaminocarbonyl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(4-(4-tert-Butyloxycarbonylamino-piperazin-1-yl-carbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(4-tert-Butyloxycarbonylamino-piperidin-1-yl-carbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(3-Amino-benzylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,

2-(4-(Cyclopentylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Tetrahydrofuran-2-yl-methylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Methoxyethylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Cyclopropylmethylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Cyclohexylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(2-Morpholin-4-yl-ethylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Pyridin-2-yl-methylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Pyridin-3-yl-methylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(2-Piperidin-1-yl-ethylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(1-Pyrrolidin-1-yl-carbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Furan-2-yl-methylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Pyridin-4-yl-methylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Pyridin-4-yl-ethylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Pyridin-3-yl-ethylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(4-Pyrimidin-2-yl-piperidin-1-yl-carbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(2-(2-(3*H*-Imidazol-4-yl)-ethylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(4-tert-Butyl-oxycarbonylamino)-piperidin-1yl-carbonyl-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]-quinolin-6-one,
2-(2-(Cyclopropylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Cyclopentylaminocarbonyl-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Cyclohexylaminocarbonyl-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(2-Methoxyethylamino)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Cyclopropylmethylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Pyridin-2-yl-methylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Pyridin-3-yl-methylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Piperidin-1-yl-ethylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(2-Fluorobenzylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(4-Methoxybenzylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(2,4-Dimethoxybenzylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Morpholin-1-yl-carbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Pyrrolidin-1-yl-carbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(4-Formyl-piperazin-1-yl-carbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Furan-1-yl-methylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Pyridin-4-yl-methylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(2,4-Dichlorobenzylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Pyridin-4-yl-ethylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Pyridin-3-yl-ethylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(4-Pyrimidin-2-yl-piperidin-1-yl-carbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Particularly preferred compounds of formula 1 are
2-(4-Cyclopropylaminocarbonyl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(4-(4-tert-Butyloxycarbonylamino-piperazin-1-yl-carbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(4-tert-Butyloxycarbonylamino-piperidin-1-yl-carbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(3-Amino-benzylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Cyclopentylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Tetrahydrofuran-2-yl-methylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Methoxyethylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Cyclopropylmethylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Pyridin-2-yl-methylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(1-Pyrrolidin-1-yl-carbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Furan-2-yl-methylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Pyridin-4-yl-methylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(4-Pyrimidin-2-yl-piperidin-1-yl-carbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(2-(Cyclopropylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Cyclopentylaminocarbonyl-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Cyclohexylaminocarbonyl-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Cyclopropylmethylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Pyridin-2-yl-methylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Pyridin-3-yl-methylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Piperidin-1-yl-ethylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(4-Methoxybenzylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(4-Formyl-piperazin-1-yl-carbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Furan-1-yl-methylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Pyridin-4-yl-methylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(2,4-Dichlorobenzylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Pyridin-4-yl-ethylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
and the salts, the N-oxides and the salts of the N-oxides of these compounds.

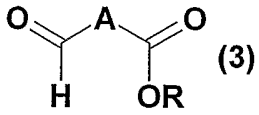
A special embodiment of the compounds of the present invention include those compounds of formula 1 in which A is 1,4-phenylene.

Another special embodiment of the compounds of the present invention include those compounds of formula 1 in which A is 1,2-cyclopropylene.

The preparation of the compounds of the formula 1 in which A, R1 and R2 have the meanings indicated above and their salts can be carried out, for example, by the processes described in greater detail below in the reaction schemes 1, 2 and 3.

Reaction scheme 1 shows the preparation of the intermediate products A1 and A2. In a first step 2-nitroaniline is reacted with acrylonitrile to yield 3-(2-nitrophenylamino)propionitrile (intermediate product A8). The propionitrile is then saponified to give the corresponding propionic acid (intermediate product A7). Cyclocondensation of intermediate product A7 results in 2,3-dihydro-8-nitro-1H-quinolin-4-one (intermediate product A6). Selective reduction of the 8-nitro-group yields 2,3-dihydro-8-amino-1H-quinolin-4-one (intermediate product A5).

Intermediate product A5 is then condensed with compounds of formula 3, wherein A has the meanings indicated above and R is preferably 1-4C-alkyl,



(3)

for example, 4-formyl-benzoic acid methyl ester or 2-formyl-cyclopropancarboxylic ethyl ester, to give the intermediate products A4 and A3, respectively. These are saponified to give the intermediate products A1 and A2, respectively.

In reaction scheme 2 the final step in the preparation of compounds of formula 1, wherein A is 1,4-phenylene is shown. Intermediate product A1 is reacted with compounds of the formula (2) to give the compounds of formula 1.

(2)

Furthermore, it is possible to additionally activate the intermediate product A1 (A2) prior to the reaction with compounds of the formula (2), for example by forming an acid halide or an acid anhydride, or by using coupling agents known to the person skilled in the art, such as, for example, N,N'-dicyclohexylcarbodiimide or N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide.

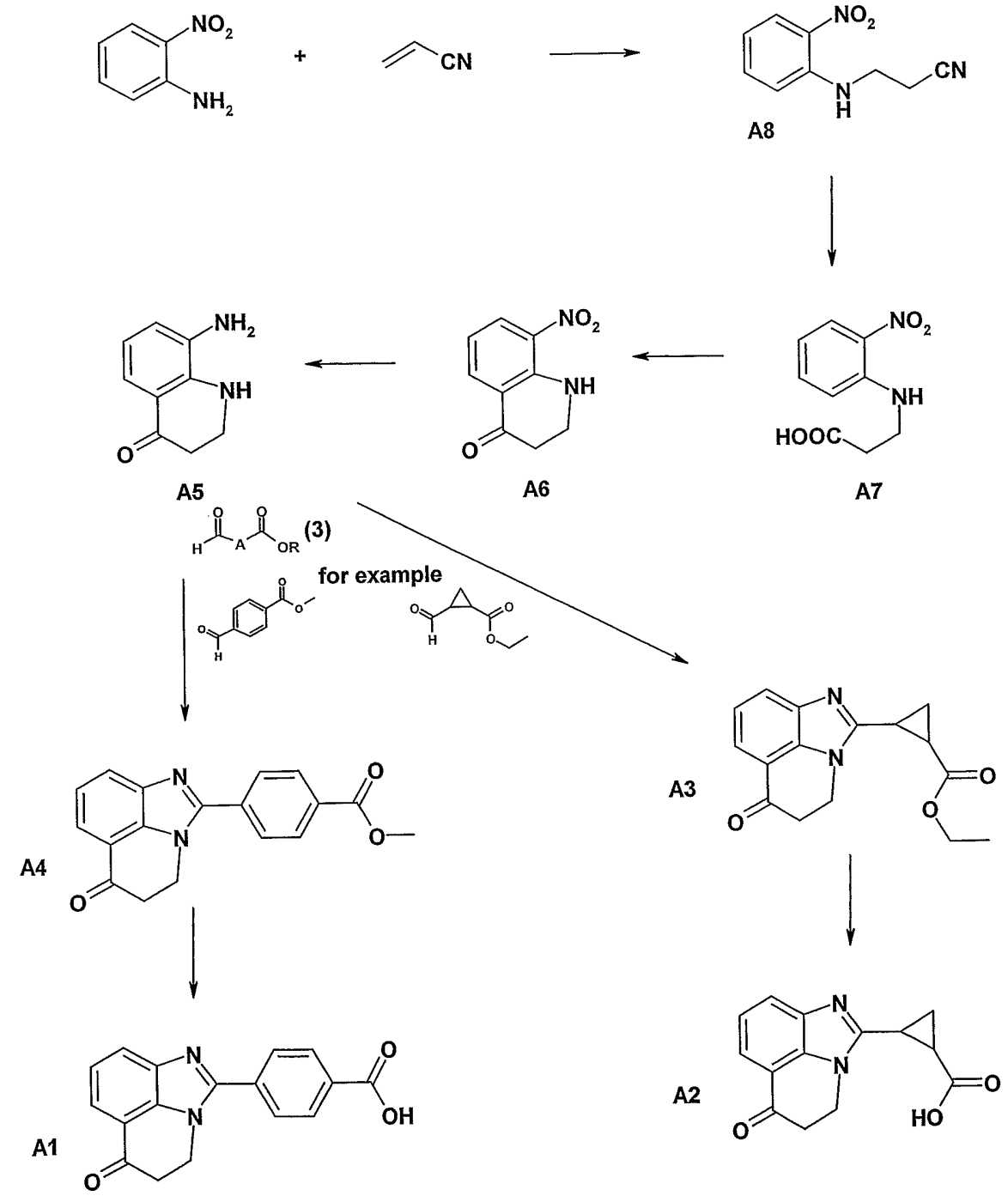
Compounds of formula 1, wherein A is 1,2-cyclopropylene are prepared analogously (Reaction scheme 3).

Likewise, further compounds of formula 1, wherein A has one of the above indicated meanings furanylene, thienylene, pyrrolylene, imidazolylene, pyrazolylene, oxazolylene, isoxazolylene, thiazolylene, isothiazolylene, oxadiazolylene, thiadiazolylene, pyrindinylene, pyridazinylene, pyrimidinylene, pyrazinylene or 4-7C-cycloalkylene, can be prepared analogously, using a suitable compound of formula 3 instead of 4-formyl-benzoic acid methyl ester or 2-formyl-cyclopropancarboxylic ethyl ester as shown exemplarily in reaction scheme 1.

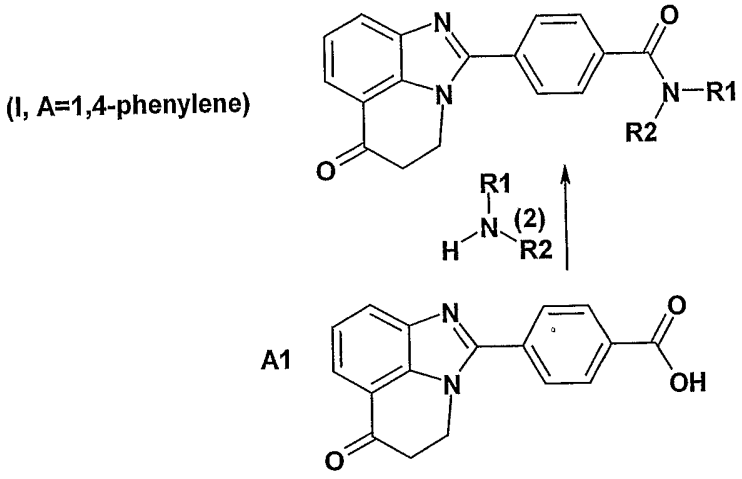
Compounds of formulae 2 and 3 are known or can be prepared according to methods known to the person skilled in the art.

The compounds of formula 1 prepared by the processes described above can, if desired, be converted into their salts, or salts of the compounds of formula 1 obtained can, if desired, be converted into the free compounds. Corresponding processes are known to the person skilled in the art.

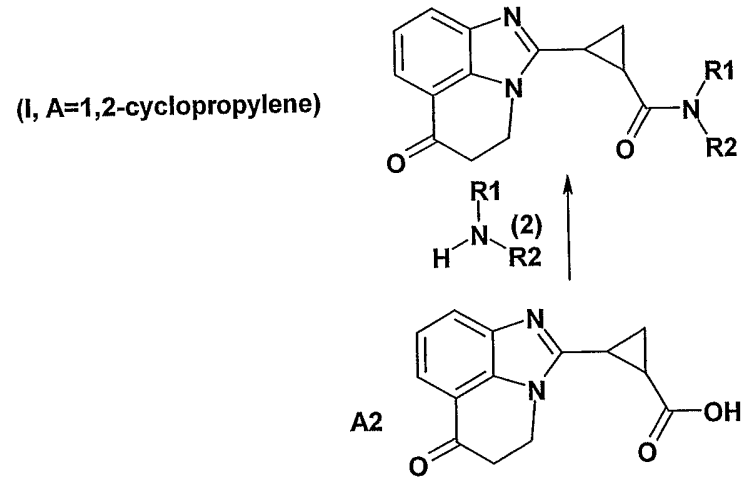
Reaction scheme 1:



Reaction scheme 2:



Reaction scheme 3:



In addition, the compounds of formula 1 can be converted by derivatisation into further compounds of formula 1. Thus, for example, compounds of formula 1 can be converted, if desired, into their N-oxides.

The N-oxidation is carried out in a manner which is known to the person skilled in the art, for example with the aid of hydrogen peroxide in methanol or with the aid of m-chloroperoxybenzoic acid in dichloromethane. The person skilled in the art is familiar on the basis of his/her expert knowledge with the reaction conditions which are specifically necessary for carrying out the N-oxidation.

It is furthermore known to the person skilled in the art that in the case of a number of reactive centers on a starting or intermediate compound it may be necessary to block one or more reactive centers temporarily by protective groups in order to allow a reaction to proceed specifically at the desired reaction center. A detailed description of the use of a large number of proven protective groups is found, for example, in T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991.

The isolation and purification of the substances according to the invention is carried out in a manner known per se, e.g. by distilling off the solvent in vacuo and recrystallizing the resulting residue from a suitable solvent or subjecting it to one of the customary purification methods, such as, for example, column chromatography on suitable support material.

Salts are obtained by dissolving the free compound in a suitable solvent (e.g. a ketone, such as acetone, methyl ethyl ketone or methyl isobutyl ketone, an ether, such as diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol such as ethanol or isopropanol) which contains the desired acid or base, or to which the desired acid or base is then added. The salts are obtained by filtering, reprecipitating, precipitating with a nonsolvent for the addition salt or by evaporating the solvent. Salts obtained can be converted by alkalization or by acidification into the free compounds, which in turn can be converted into salts. In this way, pharmacologically intolerable salts can be converted into pharmacologically tolerable salts.

The following examples serve to illustrate the invention further without restricting it. Likewise, further compounds of formula 1, whose preparation is not explicitly described, can be prepared in an analogous manner or in a manner familiar per se to the person skilled in the art using customary process techniques.

The following methods are used for characterizing the compounds:
MS: atmospheric pressure chemical ionization mass spectrometry (APCI-MS) or electron impact ionization mass spectrometry (EI-MS).

In the examples, h stands for hour(s), RT for room temperature, calc. for calculated, fnd. for found. The compounds mentioned in the examples and their salts are a preferred subject of the invention.

Examples

Final products

1. 2-(4-Cyclopropylaminocarbonyl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

29.2 mg 2-(4-Hydroxycarbonyl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one (intermediate product A1) and 6.8 mg cyclopropylamine are dissolved in 1000 µl of dichloromethane. 400 µl of a 0.55 molar solution of N-dimethylaminoethyl-N'-ethyl-carbodiimide in dichloromethane are added and the reaction mixture is stirred at RT for 16 h. Purification is performed by reversed phase (C18) prep. HPLC to give after evaporation 15.1 mg of the title compound.

MS: calc: $C_{20}H_{17}N_3O_2$ (331.37) fnd: [M+1] 332.3 HPLC [min]: 5.89

The following examples are prepared analogously to example 1:

2. 2-(4-(4-tert-Butyloxycarbonylamino-piperazin-1-yl-carbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one

MS: calc: $C_{26}H_{28}N_4O_4$ (460.53) fnd: [M+1] 461.2 HPLC [min]: 8.93

3. 2-(4-(4-tert-Butyloxycarbonylamino-piperidin-1-yl-carbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one

MS: calc: $C_{27}H_{30}N_4O_4$ (474.56) fnd: [M+1] 475.2 HPLC [min]: 8.64

4. 2-(4-(3-Amino-benzylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one

MS: calc: $C_{24}H_{20}N_4O_2$ (396.45) fnd: [M+1] 397.4 HPLC [min]: 6.67

5. 2-(4-(Cyclopentylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one

MS: calc: $C_{22}H_{21}N_3O_2$ (359.43) fnd: [M+1] 360.4 HPLC [min]: 8.03

6. 2-(4-(Tetrahydrofuran-2-yl-methylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]-quinolin-6-one

MS: calc: $C_{22}H_{21}N_3O_3$ (375.43) fnd: [M+1] 376.4 HPLC [min]: 6.19

7. **2-(4-(Methoxyethylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one**

MS: calc: $C_{20}H_{19}N_3O_3$ (349.39) fnd: [M+1] 350.3 HPLC [min]: 5.36

8. **2-(4-(Cyclopropylmethylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one**

MS: calc: $C_{21}H_{19}N_3O_2$ (345.40) fnd: [M+1] 346.4 HPLC [min]: 7.09

9. **2-(4-(Cyclohexylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one**

MS: calc: $C_{23}H_{23}N_3O_2$ (373.45) fnd: [M+1] 347.4 HPLC [min]: 8.75

10. **2-(4-(2-Morpholin-4-yl-ethylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one**

MS: calc: $C_{23}H_{24}N_4O_3$ (404.47) fnd: [M+1] 405.2 HPLC [min]: 5.57

11. **2-(4-(Pyridin-2-yl-methylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one**

MS: calc: $C_{23}H_{18}N_4O_2$ (382.42) fnd: [M+1] 383.3 HPLC [min]: 6.48

12. **2-(4-(Pyridin-3-yl-methylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one**

MS: calc: $C_{23}H_{18}N_4O_2$ (382.42) fnd: [M+1] 383.3 HPLC [min]: 6.29

13. **2-(4-(2-Piperidin-1-yl-ethylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one**

MS: calc: $C_{24}H_{26}N_4O_2$ (402.5) fnd: [M+1] 403.3 HPLC [min]: 9.44

14. **2-(4-(1-Pyrrolidin-1-yl-carbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one**

MS: calc: $C_{21}H_{19}N_3O_2$ (345.40) fnd: [M+1] 346.3 HPLC [min]: 6.48

15. **2-(4-(Furan-2-yl-methylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one**

MS: calc: $C_{22}H_{17}N_3O_3$ (371.39) fnd: [M+1] 372.4 HPLC [min]: 7.15

16. **2-(4-(Pyridin-4-yl-methylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one**

MS: calc: $C_{23}H_{18}N_4O_2$ (382.42) fnd: [M+1] 383.3 HPLC [min]: 6.08

17. **2-(4-(Pyridin-4-yl-ethylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one**

MS: calc: $C_{24}H_{20}N_4O_2$ (396.45) fnd: [M+1] 397.4 HPLC [min]: 6.51

18. **2-(4-(Pyridin-3-yl-ethylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one**

MS: calc: $C_{24}H_{20}N_4O_2$ (396.45) fnd: [M+1] 397.4 HPLC [min]: 6.51

19. **2-(4-(4-Pyrimidin-2-yl-piperidin-1-yl-carbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]-quinolin-6-one**

MS: calc: $C_{26}H_{23}N_5O_2$ (437.50) fnd: [M+1] 439.3 HPLC [min]: 7.28

20. **2-(2-(2-(3*H*-Imidazol-4-yl)-ethylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]-quinolin-6-one**

MS: calc: $C_{19}H_{19}N_5O_2$ (349.40) fnd: [M+1] 350.1 HPLC [min]: 2.72

21. **2-(2-(4-tert-Butyl-oxycarbonylamino)-piperidin-1yl-carbonyl-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one**

MS: calc: $C_{24}H_{30}N_4O_4$ (438.53) fnd: [M+1] 439.0 HPLC [min]: 5.28

22. **2-(2-(Cyclopropylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one**

MS: calc: $C_{17}H_{17}N_3O_2$ (295.34) fnd: [M+1] 296.1 HPLC [min]: 7.9

23. **2-(2-(Cyclopentylaminocarbonyl-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one**

MS: calc: $C_{19}H_{21}N_3O_2$ (323.40) fnd: [M+1] 324.1 HPLC [min]: 7.8

24. **2-(2-(Cyclohexylaminocarbonyl-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one**

MS: calc: $C_{21}H_{25}N_3O_2$ (351.45) fnd: [M+1] 352.1 HPLC [min]: 6.1

25. **2-(2-(2-Methoxyethylamino)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one**

MS: calc: $C_{17}H_{19}N_3O_3$ (313.36) fnd: [M+1] 314.0 HPLC [min]: 2.27

26. **2-(2-(Cyclopropylmethylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one**

MS: calc: $C_{18}H_{19}N_3O_2$ (309.37) fnd: [M+1] 310.0 HPLC [min]: 4.01

27. **2-(2-(Pyridin-2-yl-methylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one**

MS: calc: $C_{20}H_{18}N_4O_2$ (346.39) fnd: [M+1] 347.0 HPLC [min]: 4.85

28. **2-(2-(Pyridin-3-yl-methylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one**

MS: calc: $C_{20}H_{18}N_4O_2$ (346,39) fnd: [M+1] 347.1 HPLC [min]: 4.48

29. **2-(2-(Piperidin-1-yl-ethylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one**

MS: calc: $C_{21}H_{26}N_4O_2$ (366.47) fnd: [M+1] 367.1 HPLC [min]: 7.33

30. **2-(2-(2-Fluorobenzylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one**

MS: calc: $C_{21}H_{18}FN_3O_2$ (363.39) fnd: [M+1] 364.0 HPLC [min]: 5.71

31. **2-(2-(4-Methoxybenzylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one**

MS: calc: $C_{22}H_{21}N_3O_3$ (375.43) fnd: [M+1] 376.0 HPLC [min]: 5.48

32. **2-(2-(2,4-Dimethoxybenzylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]-quinolin-6-one**

MS: calc: $C_{23}H_{23}N_3O_4$ (405.46) fnd: [M+1] 406.0 HPLC [min]: 5.76

33. **2-(2-(Morpholin-1-yl-carbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one**

MS: calc: $C_{18}H_{19}N_3O_3$ (325.37) fnd: [M+1] 326.0 HPLC [min]: 2.83

34. **2-(2-(Pyrrolidin-1-yl-carbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one**

MS: calc: $C_{18}H_{19}N_3O_2$ (309.37) fnd: [M+1] 310.0 HPLC [min]: 5.04

35. **2-(2-(4-Formyl-piperazin-1-yl-carbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one**

MS: calc: $C_{19}H_{20}N_4O_3$ (352.40) fnd: [M+1] 353.1 HPLC [min]: 2.03

36. **2-(2-(Furan-1-yl-methylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one**

MS: calc: $C_{19}H_{17}N_3O_3$ (335.37) fnd: [M+1] 336.0 HPLC [min]: 4.63

37. **2-(2-(Pyridin-4-yl-methylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one**

MS: calc: $C_{20}H_{18}N_4O_2$ (346.39) fnd: [M+1] 347.1 HPLC [min]: 4.32

38. **2-(2-(2,4-Dichlorobenzylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one**

MS: calc: $C_{21}H_{17}Cl_2N_3O_2$ (414.29) fnd: [M+1] 414.0 HPLC [min]: 6.80

39. **2-(2-(Pyridin-4-yl-ethylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one**

MS: calc: $C_{21}H_{20}N_4O_2$ (360.42) fnd: [M+1] 361.0 HPLC [min]: 3.97

40. **2-(2-(Pyridin-3-yl-ethylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one**

MS: calc: $C_{21}H_{20}N_4O_2$ (360.42) fnd: [M+1] 361.1 HPLC [min]: 2.91

41. **2-(2-(4-Pyrimidin-2-yl-piperidin-1-yl-carbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]-quinolin-6-one**

MS: calc: $C_{23}H_{23}N_5O_2$ (401.47) fnd: [M+1] 403.0 HPLC [min]: 5.23

Starting compounds and intermediate products

A1. 2-(4-Hydroxycarbonyl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

1.37 g 2-(4-Methoxycarbonyl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one (**A4**) are dissolved in 5 ml dioxane and 5 ml water and 197 mg sodium hydroxide in 5 ml water are added. The reaction mixture is stirred for 16 h and evaporated. Water, dichloromethane and isopropanol are added and the mixture is acidified. The organic layer is separated, dried and evaporated to yield 1.16 g of the product.

^{1}H-NMR (200MHz, D_6-DMSO): δ = 3.12 (t,J=6.7Hz,2H), 4.83 (t,J=6.7Hz,2H), 7.38 (m, 1H), 7.62 (d,J=7.4Hz,1H), 7.98-8.10 (m,5H).

A2. 2-(2-Hydroxycarbonyl-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

2.31 g 2-(2-Ethoxycarbonyl-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one (**A3**) are dissolved in 10 ml dioxane and 10 ml water and 358 mg sodium hydroxide in 8 ml water are added. The reaction mixture is stirred for 16 h and evaporated. Water, dichloromethane and isopropanol are added and the mixture is acidified. The organic layer is separated, dried and evaporated to yield 2.0 g of the product.

^{1}H-NMR (200MHz, D_6-DMSO): δ = 1.59-1.73 (m,2H), 2.26-2.35 (m,1H), 2.74-2.83 (m,1H), 3.08 (t, J=6.9Hz,2H), 4.71 (d,J=6.9Hz,2H), 7.31-7.39 (m,1H), 7.57 (d,J=7.5Hz, 1H), 7.84 (d,J=7.9Hz,1H).

A3. 2-(2-Ethoxycarbonyl-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

1.19 g 2-Formyl-cyclopropanecarboxylic ethyl ester and 973 mg diamine (**A5**) are dissolved in 70 ml methanol. 4.2 ml of 2 N aqueous hydrochloric acid and 24 g silica are added. The mixture is stirred for 16 h at RT and for 3 h at 90°C and evaporated to dryness. The crude product on dry silica is purified by flash chromatography using strong cation exchange silica to give after evaporation 627 mg of the product.

^{1}H-NMR (200MHz, D_6-DMSO): δ = 1.23 (t,J=7.1Hz,3H), 1.60-1.68 (m,2H), 2.27-2.36 (m,1H), 2.73 (m,1H), 3.06 (t, J=7.0Hz, 2H), 4.15 (q,J=7.1Hz,2H), 4.66 (t,J=7.0Hz,2H), 7.27 (m,1H), 7.51 (d, J=7.5Hz,1H), 7.79 (d, J=7.9Hz,1H).

A4. 2-(4-Methoxycarbonyl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

1.38 g 4-Formyl-benzoic acid methyl ester and 973 mg diamine (**A5**) are dissolved in 70 ml methanol. 4.2 ml of 2 N aqueous hydrochloric acid and 24 g silica are added. The mixture is stirred for 16 h at RT

and for 3 h at 90°C and evaporated to dryness. The crude product on dry silica is purified by flash chromatography using strong cation exchange silica to give after evaporation 849 mg of the product.

^{1}H-NMR (200MHz, D_6-DMSO): δ = 3.13 (t,J=6.9Hz,2H), 3.92 (s, 3H), 4.84 (t, J=6.9Hz), 7.40 (m,1H), 7.64 (d, J=7.1Hz,1H), 8.01 (d,J=7.4Hz,1H), 8.15 (s,4H).

A5. 2,3-Dihydro-8-amino-1*H*-quinolin-4-one

8.6 g 2,3-Dihydro-8-nitro-1*H*-quinolin-4-one (**A6**) is dissolved in 600 ml methanol and 0.85 g Pd/C (10%) is added under an atmosphere of nitrogen. The mixture is hydrogenated under atmospheric pressure for 16 h. The mixture is filtered over celite and evaporated to dryness. The residue is purified by flash chromatography to yield 5.95 g of the product.

^{1}H-NMR (200MHz, D_6-DMSO): δ = 2.45-2.52 (m,2H), 3.41-3.49 (m,2H), 4.75 (s, 2H), 5.83 (s,1H), 6.42 (t, 1H), 6.67 (dd, 1H), 6.98 (dd,1H).

A6. 2,3-Dihydro-8-nitro-1*H*-quinolin-4-one

A mixture of 21.0 g 3-(2-nitrophenylamino)-propionic acid (**A7**) and 42.5 g phosphorus pentoxide in 300 ml absolute toluene is heated at reflux for 2 h. The mixture is filtered and the residue extracted three times with 300 ml of boiling ethyl acetate. The filtrates and extracts are evaporated to dryness to give 10.9 g of the desired product.

^{1}H-NMR (200MHz, D_6-DMSO): δ = 2.70 (t, 2H), 3.62-3.75 (m, 2H), 6.74 (t, 1H), 8.04 (dd, 1H), 8.30 (dd, 1H), 8.61 (s, 1H).

A7. 3-(2-Nitrophenylamino)propionic acid

66.0 g 3-(2-nitrophenylamino)-propionitrile (**A8**) are suspended in 500 ml 10% KOH and stirred at 130°C for 1.5 h. The clear orange solution is cooled and brought to pH=3 with conc. HCl. After cooling the yellow precipitate is filtered off, washed with water and dried, yielding 63 g.

^{1}H-NMR (200MHz, D_6-DMSO): δ = 2.61 (t, 2H), 3.58 (q, 2H), 6.63-6.72 (m, 1H), 7.09 (dd, 1H), 7.49-7.60 (m, 1H), 8.08 (dd, 1H), 8.19 (t, 1H).

A8. 3-(2-Nitrophenylamino)propionitrile

A solution of 104 g of 2-nitroaniline and 15 ml of Triton B in 500 ml absolute ethanol is heated to 80°C and 140 ml acrylonitrile are addded over a period of 5 h. Stirring at 80°C is continued for 24 h. EtOH is removed in vacuo, the oily residue dissolved in 300 ml ethyl acetate, treated with charcoal and 400 ml petrolether are added. After cooling coarse brown crystals are filtered off, yielding 61 g of the desired product.

^{1}H-NMR (200MHz, D_6-DMSO): δ = 2.89 (t, 2H), 3.72 (q, 2H), 6.70-6.78 (m, 1H), 7.18 (dd, 1H), 7.49-7.50 (m, 1H), 8.07 (dd, 1H), 8,25 (t, 1H).

Determination of HPLC-Values

A Superspher 60 RP-Select B 75 x 4 mm column from Merck was used; the chromatography was carried out at a column temperature of 40°C using a flow of 1 ml/min. The solvent system employed was solvent A (water + 0.5% NH_3) and solvent B (acetonitrile + 0.5% NH_3), with the following gradient course being used:

a) Examples 1-19:

min	%A	%B
0.0	**80**	**20**
1.0	**80**	**20**
8.0	**50**	**50**
12.0	**50**	**50**
14.0	**80**	**20**
16.0	**80**	**20**

b) Examples 20-41:

min	%A	%B
0.0	**80**	**20**
1.0	**80**	**20**
8.0	**20**	**80**
12.0	**20**	**80**
14.0	**80**	**20**
16.0	**80**	**20**

Detection was carried out by UV at 254 nm.

Commercial applicability

The compounds according to the invention have valuable pharmacological properties which make them commercially utilizable. They are inhibitors of the Poly(ADP-ribose)polymerase enzymes, in particular of the PARP-1 isoenzyme. Poly(ADP-ribose) polymerases (PARP, also called PARS, NAD^+-ADP-ribosyl-trans-ferase, pADPRT(EC 2.4.2.30)) are enzymes located in the nuclei of cells of various organs, including muscle, heart, brain and pancreatic cells. PARPs poly-ADP-ribosylate various nuclear proteins and also show auto-poly-ADP-ribosylating properties. PARPs play a physiological role in the maintainance of genomic integrity and stability. While till the late nineties only one PARP-enzyme was known, it is now clear that a whole family of related enzymes exists. Up to now the PARP-family consists of 7 isoenzymes showing high to moderate sequence homologies. High overall homology is found between the isoenzymes PARP-1 to PARP-3. The other isoforms display relevant homologies only at the catalytic site while the other domains of the proteins are completely different. The exact functions of most isoenzymes are not yet known, but it is clear that PARP-1 is physiologically involved in DNA-repair *(Ikai et al., J. Histochem. Cytochem. 11: 1261-1264, 1983)* and transcriptional regulation. PARP-1 is highly expressed in the nuclei of cells and is a member of the base excision repair complex (BER-complex). Once activated by damaged DNA fragments, PARP-1 catalyzes the attachment of up to 100 ADP-ribose units to a variety of nuclear proteins which are involved in DNA repair, including histones, topoisomerases, DNA-polymerases, DNA-ligases and PARP-1 itself. NAD is used as a source of ADP-ribose. Poly–ADP-ribosylation is thought to stabilize the region of the single strand break and to allow the recruitment of other DNA-repair enzymes. Consumed NAD is regenerated by the use of 4 ATP-molecules for every molecule of NAD. After intense auto-ADR-ribosylation PARP-1 becomes negatively charged and dissociates from the DNA.

A high number of DNA strand breaks caused by inflammatory mediators, ischemia/ reperfusion or other stimuli leads to a massive overactivation of PARP-1. It has been shown that overactivation of PARP´s especially PARP-1 leads to an immediate consumption of cellular NAD. Thus, intracellular NAD, the substrate of PARP, and ATP are depleted by massive PARP activation and this energy depletion is thought to be one stimulus leading to cellular damage and cell death.

It is well known that temporary oxygen deprivation as found in situations of ischemia and reperfusion leads to the generation of reactive oxygen species which alone or in combination with nitric oxide lead to massive DNA strand breaks. In an effort to repair these strand breaks PARP-1 is overactivated, resulting in cellular NAD and ATP depletion, cell death and organ damage. In isolated organ systems such as heart or skeletal muscle PARP inhibition diminishes ischemia/reperfusion induced tissue damage *(Thiemerman et al. PNAS 94,: 679-683, 1997)* and contractile dysfunction *(Docherty et al. Br. J. Pharmacol. 127,: 1518-1524, 1999)*. Protection from PARP mediated cell death has been shown in PARP-1 knock-out mice in various in-vivo models of cerebral and myocardial ischemia/reperfusion injury. A massive reduction of the necrotic area in the CNS was reported in PARP-1-knock out mice

after transient occlusion of the middle cerebral artery. Protection from myocardial ischemia/reperfusion damage was also seen in PARP-1 knock out mice after transient coronary occlusion. In models of cardiac ischemia and myocardial infarction PARP inhibitors reduce infarct size. It has been shown in myocytes that PARP inhibition inhibits cellular oxydative damage *(Bowes et al. Br. J. Pharmacol. 124: 1760-1766, 1998).*

Similarly, in models of retinal ischemia/reperfusion PARP inhibition has been shown to reduce cellular and organ damage. Confirming results are available from small molecule inhibitors of PARPs in models of transient cerebral ischemia and transient retinal ischemia *(Lam, Res. Com. Mol. Pathol. Pharmacol. 95, 241-252, 1997).*

Similarly, acute or chronic inflammation in general is characterised among others by massive generation of reactive oxygen species and nitric oxide. As in the case of ischemia/reperfusion these reactive species lead to DNA strand breaks, PARP-1 overactivation and cell death. It has been shown that PARP inhibition by small molecule inhibitors or genetic knock out reduces edema formation after zymosan or carrageenan, inhibits cellular damage in pancreatic islet cells after streptozotocin, inhibits experimental arthritis and reduces intestinal damage in models of intestinal inflammation. Evidence exists that PARP inhibitors are useful for treating inflammatory bowel disorders. *(Salzman et al., Japanese J. Pharm., 75, Supp. I:15, 1997).* In rodent in vivo models experimentally induced colitis was reduced by administration of PARP inhibitors.

Evidence also exists that PARP inhibitors are useful for treating arthritis. *(Szabo et al., Japanese J. Pharm., 75, Supp. I:102, 1997).* Beside an inhibition of cellular damage due to the above mentioned mechanisms it has been demonstrated that PARP inhibition reduces the expression of proinflammatory adhesion molecules such as ICAM-1 and P-selectin.

It has also been reported that PARP activation plays a key role in glutamate-, NMDA-, NO-, reactive oxygen species- and glucose deprivation induced neurotoxicity. The use of PARP inhibitors was reported to prevent neurotoxicity in cortical or cerebellar granule cell cultures and in hippocampal slices *(Wallis et al., NeuroReport, 5:3, 245-48. 1993; Cosi et al, J. Neurosci. Res 39: 38-46, 1994; Eliasson et al. Nature Med. 3: 1089-1095, 1997)*; Inhibition of neurotoxicity by various compounds was found to correspond to their PARP-1 inhibitory potency *(Zhang et al., Science, 263:687-89, 1994)*; Excessive activation of glutamate receptors has been implicated in various neurological diseases. NO together with reactive oxygen species has been shown to be causally involved in in-vivo models for various neurodegenerative diseases of the CNS. During ischemia/reperfusion injury various neurotoxic species including glutamate, NO, reactive oxygen species and others are released leading to massive organ damage. Other pathophysiological stimuli resulting in PARP activation and concomittant cell damage are 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), leading to experimental parkinsonism, immune complexes mediating experimental encephalomyelitis and traumatic head injury.

There are also data showing that PARP inhibitors reduce the severity of septic or hemorrhagic shock in animal models. Survival of mice after a lethal dose of LPS was increased by PARP inhibitors *(Szabo et al. Int. J. Oncology 10, 1093-1101, 1997).* In addition organ dysfunction (shown for lung, liver, intestine) after zymosan in experimental models of shock is reduced by PARP inhibitors *(Szabo et al. J.Exp. Med. 186, 1041-1049, 1997).*

It has also been shown that PARP-1 inhibition protects pancreatic islet cells from NO or reactive oxygene species induced damage *(Uchigata et al. J. Biol. Chem. 257 6084- 6088,1982).* In more complex models of streptozotocin induced diabetes, PARP-1 inhibition reduced cellular damage and increased insulin production *(Uchigata et al. Diabetes 32, 316-318, 1983)*

PARP inhibitors have been reported to be effective in radiosensitizing hypoxic tumor cells and in preventing tumor cells from recovering from potentially lethal damage of DNA after radiation therapy, presumably by their ability to prevent DNA repair *(Griffin et al. J. Med. Chem. 41, 5247-5256, 1998).*

On account of their PARP - in particular their PARP-1 - inhibiting properties, the compounds according to the invention can be employed in human and veterinary medicine and therapeutics, where they can be used for the treatment and prophylaxis of the following diseases: vascular stroke (cerebral stroke), myocardial infarction and other cardiovascular disorders (artherosclerosis), diabetes, head trauma, sepsis and septic shock; hemorrhagic shock, tissue damage resulting from PARP-1 mediated necrosis or apoptosis; any kind of reperfusion injury; especially neuronal (CNS), myocardial, retinal or other tissue damage resulting from ischemia and reperfusion; ischemia/reperfusion injury during organ transplantation surgery, surgery with transient interruption of blood flow to organs or body areas, and surgery when heart-lung/heart-circulation machines are used; renal failure due to ischemia or glomerulonephritis, retinal ischemia; neurological disorders and neurodegenerative diseases caused by free radical generation or other PARP-1 activating stimuli; pancreatic disorders; acute and chronic inflammatory diseases (chronic inflammatory disease of the CNS (Alzheimer, multiple sklerosis, Parkinson´s disease), chronic inflammatory diseases of the gastrointestinal tract (Morbus Crohn, colitis ulcerosa), chronic inflammatory diseases of the lungs (acute lung injury, ARDS), chronic inflammatory diseases of the joints (rheumatoid arthritis, osteoarthritis), acute inflammatory diseases of various organs; traumata of various organs; viral infections which rely on PARP-activity for successful DNA integration; infections by human immune deficiency and other viruses (AIDS); degenerative diseases of skeletal muscle involving replicative senescence, immune senescence, muscular dystrophy, chronic and acute pain (neuropathic pain),and skin aging.

In addition to this, conditions including epilepsy, stroke, Alzheimer's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis (ALS), Huntington's disease, schizophrenia, chronic pain, ischemia and neuronal loss following hypoxia, hypoglycemia, ischemia, trauma, and nervous insult can be expected

to be mitigated by PARP-1 inhibition. Recent studies have also advanced a glutamatergic basis for compulsive disorders, particularly drug dependence.

Furthermore PARP-inhibitors can be used to extend the lifespan and proliferative capacity of cells; to alter gene expression of senescent cells and to enhance the efficacy of chemo- or radiotherapy in cancers. PARP-inhibitors can also be used to potentiate cellular necrosis and/or apoptosis by chemotherapeutic compounds of various classes.

The invention further relates to a method for the treatment of mammals, including humans, which are suffering from one of the abovementioned illnesses. The method is characterized in that a therapeutically active and pharmacologically effective and tolerable amount of one or more of the compounds according to the invention is administered to the ill mammal.

The invention further relates to the compounds according to the invention for use in the treatment and/or prophylaxis of illnesses, especially the illnesses mentioned.

The invention also relates to the use of the compounds according to the invention for the production of pharmaceutical compositions which are employed for the treatment and/or prophylaxis of the illnesses mentioned.

The invention furthermore relates to pharmaceutical compositions for the treatment and/or prophylaxis of the illnesses mentioned, which contain one or more of the compounds according to the invention.

The pharmaceutical compositions are prepared by processes which are known per se and familiar to the person skilled in the art. As pharmaceutical compositions, the compounds according to the invention (= active compounds) are either employed as such, or preferably in combination with suitable pharmaceutical auxiliaries and/or excipients, e.g. in the form of tablets, coated tablets, capsules, caplets, suppositories, patches (e.g. as TTS), emulsions, suspensions, gels or solutions, the active compound content advantageously being between 0.1 and 95% and where, by the appropriate choice of the auxiliaries and/or excipients, a pharmaceutical administration form (e.g. a delayed release form or an enteric form) exactly suited to the active compound and/or to the desired onset of action can be achieved.

The person skilled in the art is familiar with auxiliaries or excipients which are suitable for the desired pharmaceutical formulations on account of his/her expert knowledge. In addition to solvents, gel formers, ointment bases and other active compound excipients, for example antioxidants, dispersants, emulsifiers, preservatives, solubilizers, colorants, complexing agents or permeation promoters, can be used.

The administration of the pharmaceutical compositions according to the invention may be performed in any of the generally accepted modes of administration available in the art. Illustrative examples of suitable modes of administration include intravenous, oral, nasal, parenteral, topical, transdermal and rectal delivery. Oral and intravenous delivery is preferred.

The pharmaceutical compositions according to the invention are prepared by processes known per se. Dosage of the active compounds takes place in the order of magnitude customary for PARP inhibitors. Thus topical application forms (such as, for example, ointments) contain the active compounds in a concentration of, for example, 0.1-99%. For oral administration, e.g., the dosage that may be employed is from about 0.1 to about 100 mg/kg body weight, with courses of treatment repeated at appropriate intervals.

Biological investigations

The potency of the compounds according to the invention to inhibit PARP-1 activity is tested by measuring the auto-ADP-ribosylation reaction at the level of partially purified human PARP-1. Cellular PARP-activity was measured by quantification of nuclear poly-ADP-ribose polymer.

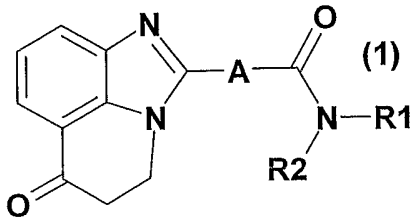
Measurement of enzymatic PARP-1 activity

100 ng of a crude cytosolic fraction of Sf9-cells expressing PARP-1 are incubated in a total volume of 200 µl in the presence of 100 mM Tris/HCl ph=7.4, 1 µM NAD, 1.5 µg Oligonucleotide (GGAATTCC) and 100000 to 200000 dpm of [^{3}H]NAD for various times. Radiolabelled poly-ADP-ribose is measured by adding 50 to 500 ng of an anti polyADP-ribose antibody or an anti-PARP-1 antibody linked to scintillation proximity beads (Protein-A-beads, Amersham-Pharmacia). Bead bound radioactivity is measured in a Wallac Trilux Microbeta counter. Inhibition of PARP activity by compounds is calculated from control values in the absence of compounds and IC_{50}-values (concentration of compound yielding 50 % inhibition are generated by nonlinear least square fitting.

The inhibitory values [measured as -logIC_{50} (mol/l)] determined for the compounds 1-41 according to the invention are all about 5 or greater. The number of the compounds correspond to the number of the examples.

Patent claims

1. A compound of formula 1,



in which

A is furanylene, thienylene, pyrrolylene, imidazolylene, pyrazolylene, oxazolylene, isoxazolylene, thiazolylene, isothiazolylene, oxadiazolylene, thiadiazolylene, phenylene, pyrindinylene, pyridazinylene, pyrimidinylene, pyrazinylene, pyrrolidinylene, pyrazolidinylene, piperidinylene, piperazinylene, imidazolidinylene or 3-7C-cycloalkylene, and

in which either

R1 is hydrogen and

R2 is 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, phenyl, phenyl substituted by R3 and/or R4, phenyl-1-4C-alkyl, phenyl-1-4C-alkyl substituted in the phenyl moiety by R3 and/or R4, hetaryl, hetaryl-1-4C-alkyl, R5(R6)N-1-4C-alkyl, dihydrofuran-2-on-3-yl or tetrahydrofuran-2-ylmethyl,

or

R1 and R2 together and with inclusion of the nitrogen atom to which they are both attached form a pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl or hexahydroazepinyl ring, a piperidinyl ring substituted by R7 or a piperazinyl ring substituted by R8,

R3 is halogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy completely or predominantly substituted by fluorine, amino or mono-or di-1-4C-alkylamino,

R4 is halogen or 1-4C-alkoxy,

R5 and R6 are independently from each other hydrogen or 1-4C-alkyl, or R5 and R6 together and with inclusion of the nitrogen atom to which they are both attached form a pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl or hexahydroazepinyl ring,

hetaryl is pyridyl, imidazolyl, 1-methyl-1H-imidazol-2-yl, pyrazolyl, 1-methyl-1H-pyrazol-3-yl, 3-methyl-1H-pyrazol-5-yl, 3-phenyl-1H-pyrazol-5-yl, 3-tert-butyl-1H-pyrazol-5-yl, 3-(furan-2-yl)-1H-pyrazol-5-yl, 1,3-dimethyl-1H-pyrazol-5-yl, triazolyl, 4-(5-yl-1H-[1,2,4]triazol-3-yl)morpholine, furanyl, 2-methoxycarbonylfuran-5-yl, indolyl, thiophenyl, 2-methoxycarbonylthiophen-3-yl, 2-methoxycarbonyl-4-methylthiophen-3-yl, 3-methoxycarbonylpyrimidin-2-yl, 1-methyl-4-ethoxycarbonyl-1H-pyrazol-5-yl or 5-methylisoxazol-3-yl ,

R7 is pyrimidin-2-yl or tert-butoxycarbonylamino, and

R8 is 1-4C-alkyl, formyl or tert-butoxycarbonyl,

or a salt, a N-oxide or a salt of the N-oxide thereof.

2. A compound of formula 1 as claimed in claim 1, in which

A is furanylene, thienylene, pyrrolylene, imidazolylene, pyrazolylene, oxazolylene, isoxazolylene, thiazolylene, isothiazolylene, oxadiazolylene, thiadiazolylene, phenylene, pyrindinylene, pyridazinylene, pyrimidinylene, pyrazinylene, pyrrolidinylene, pyrazolidinylene, piperidinylene, piperazinylene, imidazolidinylene or 3-7C-cycloalkylene, and

in which either

R1 is hydrogen and

R2 is 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, phenyl-1-4C-alkyl, phenyl-1-4C-alkyl substituted in the phenyl moiety by R3 and/or R4, hetaryl, hetaryl-1-4C-alkyl, R5(R6)N-1-4C-alkyl, dihydrofuran-2-on-3-yl or tetrahydrofuran-2-ylmethyl,

or

R1 and R2 together and with inclusion of the nitrogen atom to which they are both attached form a pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl or hexahydroazepinyl ring, a piperidinyl ring substituted by R7 or a piperazinyl ring substituted by R8,

R3 is halogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy completely or predominantly substituted by fluorine, amino or mono-or di-1-4C-alkylamino,

R4 is halogen or 1-4C-alkoxy,

R5 and R6 are independently from each other hydrogen or 1-4C-alkyl, or R5 and R6 together and with inclusion of the nitrogen atom to which they are both attached form a pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl or hexahydroazepinyl ring,

hetaryl is pyridyl, imidazolyl, 1-methyl-1H-imidazol-2-yl, pyrazolyl, 1-methyl-1H-pyrazol-3-yl, 3-methyl-1H-pyrazol-5-yl, 3-phenyl-1H-pyrazol-5-yl, 3-tert-butyl-1H-pyrazol-5-yl, 3-(furan-2-yl)-1H-pyrazol-5-yl, 1,3-dimethyl-1H-pyrazol-5-yl, triazolyl, 4-(5-yl-1H-[1,2,4]triazol-3-yl)morpholine, furanyl, 2-methoxycarbonylfuran-5-yl, indolyl, thiophenyl, 2-methoxycarbonylthiophen-3-yl, 2-methoxycarbonyl-4-methylthiophen-3-yl, 3-methoxycarbonylpyrimidin-2-yl, 1-methyl-4-ethoxycarbonyl-1H-pyrazol-5-yl or 5-methylisoxazol-3-yl ,

R7 is pyrimidin-2-yl or tert-butoxycarbonylamino, and

R8 is 1-4C-alkyl, formyl or tert-butoxycarbonyl,

or a salt, a N-oxide or a salt of the N-oxide thereof.

3. A compound of formula 1 as claimed in claim 1, in which

A is 1,4-phenylene or 1,2-cyclopropylene, and

in which either

R1 is hydrogen and

R2 is 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, phenyl, phenyl substituted by R3 and/or R4, phenyl-1-4C-alkyl, phenyl-1-4C-alkyl substituted by R3 and/or R4, hetaryl, hetaryl-1-4C-alkyl, R5(R6)N-1-4C-alkyl, dihydrofuran-2-on-3-yl or tetrahydrofuran-2-ylmethyl,

or

R1 and R2 together and with inclusion of the nitrogen atom to which they are both attached form a pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl morpholinyl, thiomorpholinyl or hexahydroazepinyl ring, a piperidinyl ring substituted in 4-position by R7 or a piperazinyl ring substituted in 4-position by R8,

R3 is halogen, 1-4C-alkyl, 1-4C-alkoxy, trifluoromethoxy, amino or mono-or di-1-4C-alkylamino,

R4 is halogen or 1-4C-alkoxy,

R5 and R6 are independently from each other hydrogen or 1-4C-alkyl, or R5 and R6 together and with inclusion of the nitrogen atom to which they are both attached form a pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl or hexahydroazepinyl ring,

hetaryl is pyridyl, imidazolyl, 1-methyl-1H-imidazol-2-yl, pyrazolyl, 1-methyl-1H-pyrazol-3-yl, 3-methyl-1H-pyrazol-5-yl, 3-phenyl-1H-pyrazol-5-yl, 3-tert-butyl-1H-pyrazol-5-yl, 3-(furan-2-yl)-1H-pyrazol-5-yl, 1,3-dimethyl-1H-pyrazol-5-yl, triazolyl, 4-(5-yl-1H-[1,2,4]triazol-3-yl)morpholine, furanyl, 2-methoxycarbonylfuran-5-yl, indolyl, thiophenyl, 2-methoxycarbonylthiophen-3-yl, 2-methoxycarbonyl-4-methylthiophen-3-yl, 3-methoxycarbonylpyrimidin-2-yl, 1-methyl-4-ethoxycarbonyl-1H-pyrazol-5-yl or 5-methylisoxazol-3-yl,

R7 is pyrimidin-2-yl or tert-butoxycarbonylamino, and

R8 is formyl or tert-butoxycarbonyl,

or a salt, a N-oxide or a salt of the N-oxide thereof.

4. A compound of formula 1 as claimed in claim 1, in which

A is 1,4-phenylene or 1,2-cyclopropylene, and

in which either

R1 is hydrogen and

R2 is 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, phenyl-1-4C-alkyl, phenyl-1-4C-alkyl substituted by R3 and/or R4, hetaryl-1-4C-alkyl, R5(R6)N-1-4C-alkyl, dihydrofuran-2-on-3-yl or tetrahydrofuran-2-ylmethyl,

or

R1 and R2 together and with inclusion of the nitrogen atom to which they are both attached form a pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl morpholinyl, thiomorpholinyl or hexahydroazepinyl ring, a piperidinyl ring substituted in 4-position by R7 or a piperazinyl ring substituted in 4-position by R8,

R3 is halogen, 1-4C-alkyl, 1-4C-alkoxy, trifluoromethoxy, amino or mono-or di-1-4C-alkylamino,

R4 is halogen or 1-4C-alkoxy,

R5 and R6 are independently from each other hydrogen or 1-4C-alkyl, or R5 and R6 together and with inclusion of the nitrogen atom to which they are both attached form a pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl or hexahydroazepinyl ring,

hetaryl is pyridyl, imidazolyl or furanyl,

R7 is pyrimidin-2-yl or tert-butoxycarbonylamino, and

R8 is formyl or tert-butoxycarbonyl,

or a salt, a N-oxide or a salt of the N-oxide thereof.

5. A compound of formula 1 as claimed in claim 1, in which

A 1,4-phenylene,

R1 is hydrogen and

R2 is 3-aminobenzyl, cyclopropyl, cyclopentyl, tetrahydrofuran-2-ylmethyl, methoxyethyl, cyclopropylmethyl, cyclohexyl, morpholin-4-yleth-2-yl, pyridin-2-ylmethyl, pyridin-3-ylmethyl, piperidin-1-yleth-2-yl, furan-2-ylmethyl, pyridin-4-ylmethyl, pyridin-4-yleth-2-yl, pyridin-3-yleth-2-yl,

or

R1 and R2 together and with inclusion of the nitrogen atom to which they are both attached form a pyrrolidinyl ring, a piperidinyl ring substituted in 4-position by R7 or a piperazinyl ring substituted in 4-position by R8,

R7 is pyrimidin-2-yl or tert-butoxycarbonylamino, and

R8 is tert-butoxycarbonyl,

or a salt, a N-oxide or a salt of the N-oxide thereof.

6. A compound of formula 1 as claimed in claim 1, in which

A 1,2-cyclopropylene,

R1 is hydrogen and

R2 is 1H-imidazol-5-yl-eth-2-yl, cyclopropyl, cyclopentyl, cyclohexylmethyl, methoxyethyl, cyclopropylmethyl, pyridin-2-ylmethyl, pyridin-3-ylmethyl, piperidin-1-yleth-2-yl, 2-fluorobenzyl, 4-methoxybenzyl, 3,5-dimethoxybenzyl, 3,4-dichlorobenzyl, furan-2-ylmethyl, pyridin-4-ylmethyl, pyridin-4-yleth-2-yl or pyridin-3-yleth-2-yl,

or

R1 and R2 together and with inclusion of the nitrogen atom to which they are both attached form a pyrrolidinyl or morpholinyl ring, a piperidinyl ring substituted in 4-position by R7 or a piperazinyl ring substituted in 4-position by R8,

R7 is pyrimidin-2-yl or tert-butoxycarbonylamino, and

R8 is formyl,

or a salt, a N-oxide or a salt of the N-oxide thereof.

7. A compound of formula 1 as claimed in claim 1, selected from

2-(4-Cyclopropylaminocarbonyl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(4-(4-tert-Butyloxycarbonylamino-piperazin-1-yl-carbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(4-tert-Butyloxycarbonylamino-piperidin-1-yl-carbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(3-Amino-benzylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Cyclopentylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Tetrahydrofuran-2-yl-methylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Methoxyethylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Cyclopropylmethylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Cyclohexylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(2-Morpholin-4-yl-ethylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Pyridin-2-yl-methylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Pyridin-3-yl-methylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(2-Piperidin-1-yl-ethylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(1-Pyrrolidin-1-yl-carbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Furan-2-yl-methylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Pyridin-4-yl-methylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Pyridin-4-yl-ethylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Pyridin-3-yl-ethylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(4-Pyrimidin-2-yl-piperidin-1-yl-carbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(2-(2-(3*H*-Imidazol-4-yl)-ethylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(4-tert-Butyl-oxycarbonylamino)-piperidin-1yl-carbonyl-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]-quinolin-6-one,
2-(2-(Cyclopropylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Cyclopentylaminocarbonyl-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Cyclohexylaminocarbonyl-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(2-Methoxyethylamino)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Cyclopropylmethylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Pyridin-2-yl-methylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Pyridin-3-yl-methylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Piperidin-1-yl-ethylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(2-Fluorobenzylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(4-Methoxybenzylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(2,4-Dimethoxybenzylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Morpholin-1-yl-carbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Pyrrolidin-1-yl-carbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(4-Formyl-piperazin-1-yl-carbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Furan-1-yl-methylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Pyridin-4-yl-methylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(2-(2,4-Dichlorobenzylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Pyridin-4-yl-ethylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Pyridin-3-yl-ethylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(4-Pyrimidin-2-yl-piperidin-1-yl-carbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
or a salt, a N-oxide or a salt of the N-oxide thereof.

8. A compound of formula 1 as claimed in claim 1, selected from
2-(4-Cyclopropylaminocarbonyl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(4-(4-tert-Butyloxycarbonylamino-piperazin-1-yl-carbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(4-tert-Butyloxycarbonylamino-piperidin-1-yl-carbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(3-Amino-benzylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Cyclopentylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Tetrahydrofuran-2-yl-methylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Methoxyethylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Cyclopropylmethylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Pyridin-2-yl-methylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(1-Pyrrolidin-1-yl-carbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Furan-2-yl-methylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(Pyridin-4-yl-methylaminocarbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-(4-Pyrimidin-2-yl-piperidin-1-yl-carbonyl)-phenyl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(2-(Cyclopropylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Cyclopentylaminocarbonyl-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Cyclohexylaminocarbonyl-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Cyclopropylmethylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Pyridin-2-yl-methylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Pyridin-3-yl-methylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Piperidin-1-yl-ethylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(4-Methoxybenzylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(4-Formyl-piperazin-1-yl-carbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Furan-1-yl-methylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Pyridin-4-yl-methylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(2,4-Dichlorobenzylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-(Pyridin-4-yl-ethylaminocarbonyl)-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
or a salt, a N-oxide or a salt of the N-oxide thereof.

9. A compound of formula 1 as claimed in claims 1, 2, 3, or 4 in which A is 1,4-phenylene.

10. A compound of formula 1 as claimed in claims 1, 2, 3 or 4 in which A is 1,2-cyclopropylene.

11. A compound of formula 1 as claimed in claim 1 for use in the treatment of illnesses.

12. A compound of formula 1 as claimed in claim 7 for use in the treatment of illnesses.

13. A pharmaceutical composition comprising at least one compound of formula 1 as claimed in claim 1 together with customary pharmaceutical excipients and/or vehicles.

14. Use of a compound of formula 1 as claimed in claim 1 for the production of pharmaceutical compositions for the treatment of cancer, inflammation, ischemia/reperfusion injury during organ transplantation surgery, cerebral stroke, myocardial infarct and diabetes mellitus.

15. Use of a compound of formula 1 as claimed in claim 7 for the production of pharmaceutical compositions for the treatment of cancer, inflammation, ischemia/reperfusion injury during organ transplantation surgery, cerebral stroke, myocardial infarct and diabetes mellitus.

16. A method of treating cancer, inflammation, ischemia/reperfusion injury during organ transplantation surgery, cerebral stroke, myocardial infarct or diabetes mellitus in a patient, comprising administering to said patient a therapeutically effective amount of a compound of formula 1 as claimed in claim 1.

17. A method of treating cancer, inflammation, ischemia/reperfusion injury during organ transplantation surgery, cerebral stroke, myocardial infarct or diabetes mellitus in a patient, comprising administering to said patient a therapeutically effective amount of a compound of formula 1 as claimed in claim 7.