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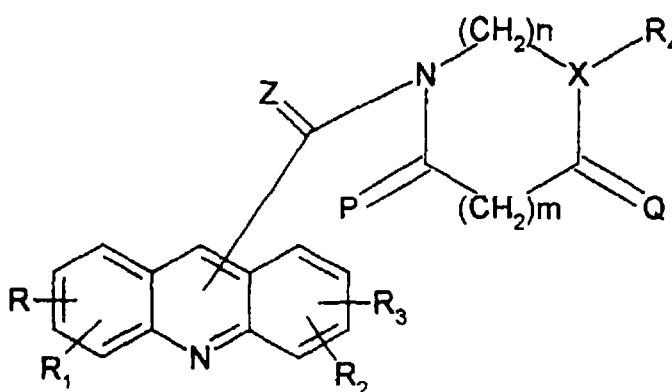
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ACRIDINE DERIVATIVES AND THEIR USE AS MEDICAMENTS

The invention relates to novel heteroaryl derivatives of the formula 1, to their preparation and to their use as medicaments, in particular for treating tumors.

According to one aspect of the invention, novel acridine derivatives of the formula 1



formula 1

in which

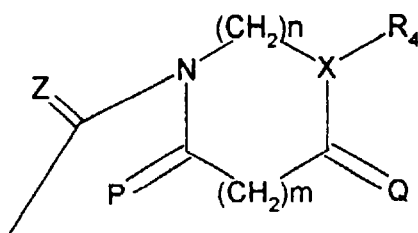
- 15 R, R₁, R₂, R₃ can be attached to any of the acridine carbon atoms C₁ to C₉, are identical or different and independently of one another denote hydrogen, straight-chain or branched (C₁-C₈)-alkyl, (C₃-C₇)-cycloalkyl, straight-chain or branched (C₁-C₈)-alkylcarbonyl, preferably acetyl, straight-chain or branched (C₁-C₈)-alkoxy, halogen, aryl-(C₁-C₈)-alkoxy, preferably benzyloxy or phenylethyloxy, nitro, amino, mono-(C₁-C₄)-alkylamino, di-
- 20 (C₁-C₄)-alkylamino, (C₁-C₈)-alkoxycarbonylamino, (C₁-C₆)-alkoxycarbonylamino-(C₁-C₈)-alkyl, cyano, straight-chain or branched cyano-(C₁-C₆)-alkyl, carboxyl, (C₁-C₈)-alkoxycarbonyl, (C₁-C₄)-alkyl which is substituted
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by one or more fluorine atoms, preferably the trifluoromethyl group, carboxy-(C₁-C₈)-alkyl or (C₁-C₈)-alkoxycarbonyl-(C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, preferably allyl, (C₂-C₆)-alkynyl, preferably ethynyl or propargyl, straight-chain or branched cyano-(C₁-C₆)-alkyl, preferably cyanomethyl, aryl, where the aryl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of halogen, straight-chain or branched (C₁-C₈)-alkyl, (C₃-C₇)-cycloalkyl, carboxyl, straight-chain or branched (C₁-C₈)-alkoxycarbonyl, preferably tert-butoxycarbonyl, by trifluoromethyl, hydroxyl, straight-chain or branched (C₁-C₈)-alkoxy, preferably methoxy or ethoxy, benzyloxy, nitro, amino, mono-(C₁-C₄)-alkylamino, di-(C₁-C₄)-alkylamino, cyano, straight-chain or branched cyano-(C₁-C₆)-alkyl,

Z is oxygen or sulfur, where the radical



substituted on the acridine heterocycle may be attached to C atoms C₁-C₉ of the acridine ring skeleton;

P, Q independently of one another represent oxygen or in each case two hydrogen atoms (i.e. -CH₂-);

X is nitrogen or C-R₅, where R₅ represents hydrogen or (C₁-C₆)-alkyl;

- n,m independently of one another denotes an integer between 0-3, with the proviso that in the case n = 0, X denotes a CR_5R_6 group where R_5 and R_6 independently of one another represent hydrogen or (C₁-C₆)-alkyl and that the nitrogen atom adjacent to the C=Z group is substituted by a hydrogen atom or a (C-C₆)-alkyl group;
- 5
- 10 R₄ [lacuna] a straight-chain or branched (C₁-C₂₀)-alkyl radical which may be saturated or unsaturated, with one to three double and/or triple bonds, and which may be unsubstituted or may optionally be substituted at the same or different C atoms by one, two or more aryl, heteroaryl, halogen, cyano, (C₁-C₆)-alkoxy-carbonylamino, (C₁-C₆)-alkoxy, amino, mono-(C₁-C₄)-alkylamino or di-(C₁-C₄)-alkylamino; a (C₆-C₁₄)-aryl radical, (C₆-C₁₄)-aryl-(C₁-C₄)-alkyl radical or a (C₂-C₁₀)-heteroaryl or (C₂-C₁₀)-heteroaryl-(C₁-C₄)-alkyl radical which contains one or more hetero-atoms selected from the group consisting of N, O and S, where the (C₁-C₄)-alkyl radical may be unsubstituted or mono- [lacuna] polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and where the (C₆-C₁₄)-aryl or (C₂-C₁₀)-heteroaryl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of straight-chain or branched (C₁-C₈)-alkyl, (C₃-C₇)-cycloalkyl, halogen, cyano, (C₁-C₆)-alkoxycarbonylamino, (C₁-C₆)-alkoxy, carboxyl, (C₁-C₈)-alkoxycarbonyl, straight-chain or branched (C₁-C₆)-alkyl which is substituted by one or more fluorine atoms, preferably trifluoromethyl, hydroxyl, straight-chain or branched (C₁-C₈)-alkoxy, preferably methoxy or ethoxy, where adjacent oxygen atoms may also be linked by (C₁-C₂)-alkylene groups, preferably by a methylene group, benzyloxy, nitro,
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amino, mono-(C₁-C₄)-alkylamino, di-(C₁-C₄)-alkyl-
amino, aryl, which for its part may be
unsubstituted or mono- or polysubstituted by
identical or different substituents from the group
5 consisting of straight-chain or branched (C₁-C₈)-
alkyl, (C₃-C₇)-cycloalkyl, carboxyl, straight-chain
or branched (C₁-C₈)-alkoxycarbonyl, by trifluoro-
methyl, hydroxyl, straight-chain or branched (C₁-
C₈)-alkoxy, preferably methoxy or ethoxy,
10 benzyloxy, nitro, amino, mono-(C₁-C₄)-alkylamino,
di-(C₁-C₄)-alkylamino, cyano, straight-chain or
branched cyano-(C₁-C₆)-alkyl;

and their structural isomers and stereoisomers, in
15 particular tautomers, diastereomers and
enantiomers, and their pharmaceutically acceptable
salts, in particular acid addition salts, are
provided.

20 Thus, for example, the compounds of the formula (1)
according to the invention which have one or more
centers of chirality and which are present as racemates
can be separated by methods known per se into their
optical isomers, i.e. enantiomers or diastereomers. The
25 separation can be carried out by column separation on
chiral phases or by recrystallization from an optically
active solvent or using an optically active acid or
base or by derivatization with an optically active
reagent, such as, for example, an optically active
30 alcohol, and subsequent removal of the radical.

Furthermore, the acridine derivatives of the formula
(1) according to the invention can be converted into
their salts with inorganic or organic acids, in
35 particular, for pharmaceutical use, into their
physiologically acceptable salts. Acids which are
suitable for this purpose are, for example,
hydrochloric acid, hydrobromic acid, sulfuric acid,
phosphoric acid, fumaric acid, succinic acid, lactic

acid, citric acid, acetic acid, tartaric acid, malic acid, malonic acid, embonic acid, trifluoroacetic acid or maleic acid.

5 Moreover, the compounds of the formula (1) according to the invention can, if they contain a sufficiently acidic group, such as a carboxyl group, be converted, if desired, into their salts with inorganic or organic bases, in particular, for pharmaceutical use, into
10 their physiologically acceptable salts. Bases which are suitable for this purpose are, for example, sodium hydroxide, potassium hydroxide, calcium hydroxide, lysine, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

15 According to a preferred embodiment, acridine derivatives of the formula 1 are provided in which R, R₁, R₂, R₃, X, Z, P, Q, n and m have the meanings given above and

20 R₄ denotes a straight-chain or branched (C₁-C₂₀)-alkyl radical which may be saturated or unsaturated, with one to three double and/or triple bonds, and which may be unsubstituted or optionally
25 substituted on the same or different C atoms by one, two or more aryl, heteroaryl, halogen, (C₁-C₆)-alkoxy, amino, mono-(C₁-C₄)-alkylamino or di-(C₁-C₄)-alkylamino;

30 a phenyl ring or a naphthyl ring, each of which may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of straight-chain or branched (C₁-C₈)-alkyl, (C₃-C₇)-cycloalkyl, halogen, cyano,
35 (C₁-C₆)-alkoxycarbonylamino, (C₁-C₆)-alkoxy, carboxyl, (C₁-C₈)-alkoxycarbonyl, straight-chain or branched (C₁-C₆)-alkyl which is substituted by one or more fluorine atoms, preferably trifluoromethyl, hydroxyl, straight-chain or branched

(C₁-C₈)-alkoxy, preferably methoxy or ethoxy, where adjacent oxygen atoms may also be linked by (C₁-C₂)-alkylene groups, preferably a methylene group, benzyloxy, nitro, amino, mono-(C₁-C₄)-alkyl-amino, di-(C₁-C₄)-alkylamino, aryl, which for its part may be unsubstituted or mono- or poly-substituted by identical or different substituents from the group consisting of straight-chain or branched (C₁-C₈)-alkyl, (C₃-C₇)-cycloalkyl, carboxyl, straight-chain or branched (C₁-C₈)-alkoxy-carbonyl, by trifluoromethyl, hydroxyl, straight-chain or branched (C₁-C₈)-alkoxy, preferably methoxy or ethoxy, benzyloxy, nitro, amino, mono-(C₁-C₄)-alkylamino, di-(C₁-C₄)-alkylamino, cyano, straight-chain or branched cyano-(C₁-C₆)-alkyl;

a 2-, 4-, 5- or 6-pyrimidinyl radical or 2-, 4-, 5- or 6-pyrimidinyl-(C₁-C₄)-alkyl radical, where the (C₁-C₄)-alkyl radical may be unsubstituted or mono- [lacuna] polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 2-, 4-, 5- or 6-pyrimidinyl radical may be unsubstituted or mono- to trisubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 3-, 4-, 5- or 6-pyridazinyl radical or 3-, 4-, 5- or 6-pyridazinyl-(C₁-C₄)-alkyl radical, where the (C₁-C₄)-alkyl radical may be unsubstituted or mono- [lacuna] polysubstituted by identical or different substituents from the group consisting

of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 3-, 4-, 5- or 6-pyridazinyl radical may be unsubstituted or mono- to trisubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 2-, 3-, 5- or 6-pyrazinyl radical or 2-, 3-, 5- or 6-pyrazinyl-(C₁-C₄)-alkyl radical, where the (C₁-C₄)-alkyl radical may be unsubstituted or mono- [lacuna] polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 2-, 3-, 5- or 6-pyrazinyl radical may be unsubstituted or mono- to trisubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 3-, 4-, 5-, 6-, 7-, or 8-cinnolinyl radical or 3-, 4-, 5-, 6-, 7-, or 8-cinnolinyl-(C₁-C₄)-alkyl radical, where the (C₁-C₄)-alkyl radical may be unsubstituted or mono- [lacuna] polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 3-, 4-, 5-, 6-, 7-, or 8-cinnolinyl radical may be unsubstituted or mono- to pentasubstituted by identical or different

- substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;
- 10 a 2-, 4-, 5-, 6-, 7-, or 8-quinazolinyl radical or 2-, 4-, 5-, 6-, 7-, or 8-quinazolinyl-(C₁-C₄)-alkyl radical, where the (C₁-C₄)-alkyl radical may be unsubstituted or mono- [lacuna] polysubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen and
- 15 oxo (=O) and the or [sic] 2-, 4-, 5-, 6-, 7-, or 8-quinazolinyl radical may be unsubstituted or mono- to pentasubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by
- 20 fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;
- 25 a 2-, 3-, 5-, 6-, 7-, or 8-quinoxalinyl radical [lacuna] 2-, 3-, 5-, 6-, 7-, or 8-quinoxalinyl-(C₁-C₄)-alkyl radical, where the (C₁-C₄)-alkyl radical may be unsubstituted or mono- [lacuna] polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the or [sic] 2-,
- 30 3-, 5-, 6-, 7-, or 8-quinoxalinyl radical may be unsubstituted or mono- to pentasubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-
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alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 1-, 4-, 5-, 6-, 7-, or 8-phthalazinyl radical or 1-, 4-, 5-, 6-, 7-, or 8-phthalazinyl-(C₁-C₄)-alkyl radical, where the (C₁-C₄)-alkyl radical may be unsubstituted or mono- [lacuna] polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the or [sic] 1-, 4-, 5-, 6-, 7-, or 8-phthalazinyl radical may be unsubstituted or mono- to pentasubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl radical or 2-, 3-, 4-, 5-, 6-, 7 or 8-quinolyl-(C₁-C₄)-alkyl radical, where the (C₁-C₄)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl radical may be unsubstituted or mono- to hexasubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, preferably methyl, particularly preferably 2-methyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxy-

carbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

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a 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl radical or 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl-(C₁-C₄)-alkyl radical, where the (C₁-C₄)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl radical may be unsubstituted or mono- to hexasubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 2-, 6-, 8- or 9-[9H]-purinyl radical or 2-, 6-, 8- or 9-[9H]-purinyl-(C₁-C₄)-alkyl radical, where the (C₁-C₄)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 2-, 6-, 8- or 9-[9H]-purinyl radical may be unsubstituted or mono- to trisubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

5 a 2-, 6-, 7- or 8-[7H]-purinyl radical or 2-, 6-,
 7- or 8-[7H]-purinyl-(C₁-C₄)-alkyl radical, where
 the (C₁-C₄)-alkyl radical may be unsubstituted or
 mono- or polysubstituted by identical or different
 substituents from the group consisting of (C₁-C₆)-
 alkyl, halogen and oxo (=O) and the 2-, 6-, 7- or
 8-[7H]-purinyl radical may be unsubstituted or
 mono- to trisubstituted by identical or different
 10 substituents from the group consisting of
 hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino,
 mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino,
 hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-
 C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or
 15 (C₁-C₆)-alkyl which is mono- or polysubstituted by
 fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl
 and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

20 a 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-acridinyl
 radical or 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-
 acridinyl-(C₁-C₄)-alkyl radical, where the (C₁-C₆)-
 alkyl radical may be unsubstituted or mono- or
 polysubstituted by identical or different
 substituents from the group consisting of (C₁-C₆)-
 25 alkyl, halogen and oxo (=O) and the 1-, 2-, 3-, 4-
 , 5-, 6-, 7-, 8- or 9-acridinyl radical may be
 unsubstituted or mono- to octasubstituted by
 identical or different substituents from the group
 consisting of hydrogen, (C₁-C₆)-alkyl, halogen,
 30 nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-
 alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy,
 carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxy-
 carbonylamino or (C₁-C₆)-alkyl which is mono- or
 polysubstituted by fluorine, preferably trifluoro-
 35 methyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-
 alkyl;

a 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-
 phenanthridinyl radical or 1-, 2-, 3-, 4-, 5-, 6-,

7-, 8- or 9-phenanthridinyl-(C₁-C₆)-alkyl radical, where the (C₁-C₆)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen and oxo (=O) and the 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-phenanthridinyl radical may be unsubstituted or mono- to octasubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkyl-amino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, (C₆-C₁₀)-aryl-(C₁-C₆)-alkoxy, preferably benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 2-, 3-, 4-, 5- or 6-pyridyl radical where the 2-, 3-, 4-, 5- or 6-pyridyl radical may be unsubstituted or mono- to tetrasubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 2-, 3-, 4-, 5- or 6-pyridinyl-(C₁-C₆)-alkyl radical, where the (C₁-C₆)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 2-, 3-, 4-, 5- or 6-pyridinyl radical may be unsubstituted or mono- to tetrasubstituted by identical or different substituents from the group

- consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;
- 10 a 2-, 3-, 4- or 5-thienyl radical or 2-, 3-, 4- or 5-thienyl-(C₁-C₆)-alkyl radical, where the (C₁-C₆)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 2-, 3-, 4- or 5-thienyl radical may be unsubstituted or mono- to trisubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;
- 20 a 2-, 4-, or 5-thiazolyl radical or 2-, 4-, or 5-thiazolyl-(C₁-C₆)-alkyl radical, where the (C₁-C₆)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 2-, 4-, or 5-thiazolyl radical may be unsubstituted or mono- or disubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino

or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

5 a 3-, 4-, or 5-isothiazolyl radical or 3-, 4-, or 5-isothiazolyl-(C₁-C₆)-alkyl radical, where the (C₁-C₆)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 3-, 4-, or 5-isothiazolyl radical may be unsubstituted or mono- or disubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, 10 mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 2-, 4-, 5-, 6-, or 7-benzothiazolyl radical or 2-, 4-, 5-, 6-, or 7-benzothiazolyl-(C₁-C₆)-alkyl radical, where the (C₁-C₆)-alkyl radical may be 25 unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 2-, 4-, 5-, 6-, or 7-benzothiazolyl radical may be unsubstituted or mono- to tetrasubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, 30 mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 1-, 2-, 4-, or 5-imidazolyl radical or 1-, 2-, 4-, or 5-imidazolyl-(C₁-C₆)-alkyl radical, where the (C₁-C₆)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 1-, 2-, 4-, or 5-imidazolyl radical may be unsubstituted or mono- to trisubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 1-, 3-, 4-, or 5-pyrazolyl radical or 1-, 3-, 4- or 5-pyrazolyl-(C₁-C₆)-alkyl radical, where the (C₁-C₆)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 1-, 3-, 4- or 5-pyrazolyl radical may be unsubstituted or mono- to trisubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 1-, 2-, 3-, 4-, or 5-pyrrolyl radical or 1-, 2-, 3-, 4-, or 5-pyrrolyl-(C₁-C₆)-alkyl radical, where the (C₁-C₆)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-

alkyl, halogen and oxo (=O) and the 1-, 2-, 3-, 4- or 5-pyrrolyl radical may be unsubstituted or mono- to tetrasubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 1-, 3-, or 5-[1.2.4]-triazolyl radical or 1-, 3-, or 5-[1.2.4]-triazolyl-(C₁-C₆)-alkyl radical, where the (C₁-C₆)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen and oxo (=O) and the 1-, 3-, or 5-[1.2.4]-triazolyl radical may be unsubstituted or mono- or disubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 1-, 4-, or 5-[1.2.3]-triazolyl radical or 1-, 4-, or 5-[1.2.3]-triazolyl-(C₁-C₆)-alkyl radical, where the (C₁-C₆)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 1-, 4-, or 5-[1.2.3]-triazolyl radical may be unsubstituted or mono- or disubstituted by identical or different substituents from the group

- consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxy-carbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;
- 5
- 10 a 1- or 5-[1H]-tetrazolyl radical or 1-, or 5-[1H]-tetrazolyl-(C₁-C₆)-alkyl radical, where the (C₁-C₆)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 1-, or 5-[1H]-tetrazolyl radical may be unsubstituted or
- 15 substituted by hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxy-carbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;
- 20
- 25 a 2- or 5-[2H]-tetrazoyl radical or 2- or 5-[2H]-tetrazolyl-(C₁-C₆)-alkyl radical, where the (C₁-C₆)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 2- or 5-[2H]-tetrazolyl radical may be unsubstituted or
- 30 substituted by hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxy-carbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoro-
- 35

methyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

5 a 2-, 4-, or 6-[1.3.5]-triazinyl radical or 2-,
4-, or 6-[1.3.5]-triazinyl-(C₁-C₆)-alkyl radical,
where the (C₁-C₆)-alkyl radical may be
unsubstituted or mono- or polysubstituted by
identical or different substituents from the group
consisting of hydrogen, (C₁-C₆)-alkyl, halogen and
10 oxo (=O) and the 2-, 4-, or 6-[1.3.5]-triazinyl
radical may be unsubstituted or mono- or
disubstituted by identical or different
substituents from the group consisting of
hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino,
15 mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino,
hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl,
(C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino
or (C₁-C₆)-alkyl which is mono- or polysubstituted
by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-
20 aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 2-, 4-, or 5-oxazolyl radical or 2-, 4-, or
5-oxazolyl-(C₁-C₆)-alkyl radical, where the
(C₁-C₆)-alkyl radical may be unsubstituted or mono-
25 or polysubstituted by identical or different
substituents from the group consisting of (C₁-C₆)-
alkyl, halogen and oxo (=O) and the 2-, 4-, or
5-oxazolyl radical may be unsubstituted or mono-
or disubstituted by identical or different
30 substituents from the group consisting of
hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino,
mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino,
hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl,
(C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino
35 or (C₁-C₆)-alkyl which is mono- or polysubstituted
by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-
aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 3-, 4-, or 5-isoxazolyl radical or 3-, 4-, or 5-isoxazolyl-(C₁-C₆)-alkyl radical, where the (C₁-C₆)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 3-, 4-, or 5-isoxazolyl radical may be unsubstituted or mono- or disubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl radical or 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl-(C₁-C₆)-alkyl radical, where the (C₁-C₆)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl radical may be unsubstituted or mono- to hexasubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl and the isomers, in particular tautomers, diastereomers and enantiomers, and the pharmaceutically acceptable salts, in particular acid addition salts, thereof.

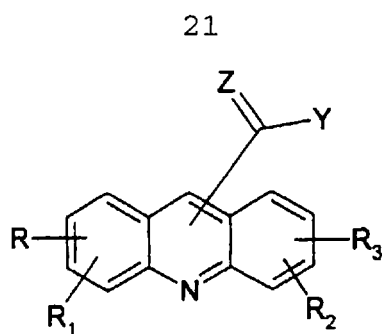
According to a further embodiment, acridine derivatives of the formula (1) are provided which are characterized in that R, R₁, R₂, R₃, X, Z, P, Q, n and m have the meanings given above and R₄ represents phenyl which is
5 unsubstituted or substituted by one to five identical or different (C₁-C₆)-alkoxy groups, where adjacent oxygen atoms may also be linked by (C₁-C₂)-alkylene groups.

10 According to a further embodiment, acridine derivatives of the formula (1) are provided which are characterized in that R, R₁, R₂, R₃, X, Z, P, Q, n and m have the meanings given above and R₄ represents 3,5-
dimethoxyphenyl.

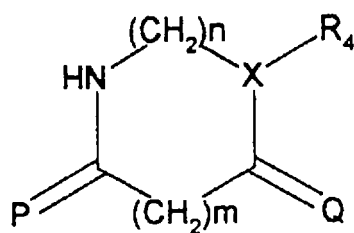
15 According to a further embodiment, acridine derivatives of the formula (1) are provided which are characterized in that and [sic] R₄ has the meanings given above, R, R₁, R₂, R₃ each represent a hydrogen atom, Z represents
20 an oxygen atom and X represents a nitrogen atom, P and Q each represent two hydrogen atoms (i.e. -CH₂-), m is zero and n is the integer 2.

According to a further embodiment, acridine derivatives
25 of the formula (1) are provided which are characterized in that R, R₁, R₂ and R₃ each represent a hydrogen atom, Z represents an oxygen atom and X represents a nitrogen atom, P and Q each represent two hydrogen atoms (i.e. -CH₂-), m is zero, n represents the integer 2 and R₄
30 represents a 3,5-dimethoxyphenyl radical.

According to a further aspect of the invention, a process for preparing acridine derivatives according to any of claims 1 to 6 [lacuna], characterized in that an
35 acridine carboxylic acid of the formula (2) in which R, R₁, R₂, R₃ have the meanings given above, Z denotes an oxygen or sulfur atom and Y represents a leaving group such as halogen, hydroxyl, (C₁-C₆)-alkoxy, preferably methoxy or ethoxy, -O-tosyl, -O-mesyl or imidazolyl,



Formula 2



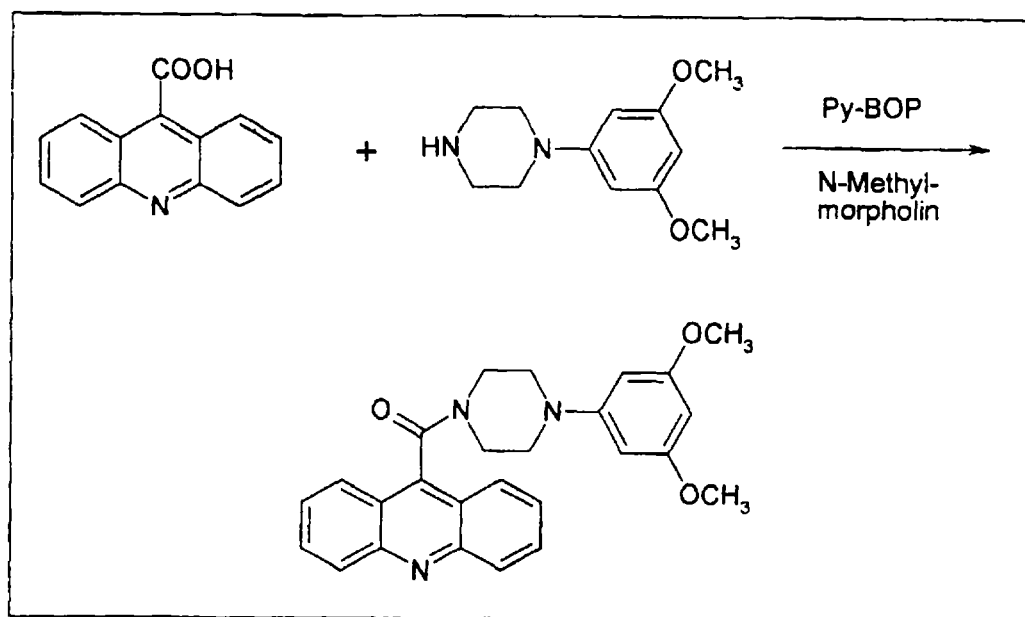
Formula 3

is reacted with an amine of the formula (3) in which R₄, P, Q, X, m and n are as defined above, using, if appropriate, diluents and auxiliaries, and the desired acridine derivatives are formed.

Synthesis route:

The compounds of the formula 1 can be obtained according to Scheme 1 below:

Scheme 1



5 The starting materials (2) and (3) are either commercially available or can be prepared by procedures known per se. The starting materials (2) and (3) are useful intermediates for preparing the acridine derivatives of the formula (1) according to the
10 invention.

The solvents and auxiliaries to be used, if appropriate, and the reaction parameters to be used, such as reaction temperature and reaction time, are
15 known to the person skilled in the art owing to his expert knowledge.

The acridine derivatives of the formula (1) according to the invention are suitable as medicaments, in particular as antitumor agents, for treating mammals,
20 in particular man, but also domestic animals such as horses, cattle, dogs, cats, hares, sheep, poultry and the like.

25 According to a further aspect of the invention, a method for controlling tumors in mammals, in particular

man, is provided which is characterized in that at least one acridine derivative of the formula (1) is administered to a mammal in an amount effective for the treatment of the tumor. The therapeutically effective
5 dose of the acridine derivative according to the invention in question which is to be administered for the treatment depends inter alia on the nature and the stage of the oncosis, the age and the sex of the patient, the type of administration and the duration of
10 the treatment. Administration can take place orally, rectally, buccally (for example sublingually), parenterally (for example subcutaneously, intramuscularly, intradermally or intravenously), topically or transdermally.

15 According to a further aspect of the invention, medicaments for the treatment of tumors are provided which are characterized in that they comprise, as active ingredient, at least one acridine derivative
20 according to any of Claims 1 to 4 or a pharmaceutically acceptable salt thereof, if appropriate together with customary pharmaceutically acceptable auxiliaries, additives and carriers. These can be solid, semisolid, liquid or aerosol preparations. Suitable solid
25 preparations are, for example, capsules, powders, granules, tablets. Suitable semisolid preparations are, for example, ointments, creams, gels, pastes, suspensions, oil-in-water and water-in-oil emulsions. Suitable liquid preparations are, for example, sterile
30 aqueous preparations for parenteral administration which are isotonic with the blood of the patient.

The invention is to be illustrated in more detail by the example below, without being restricted to the
35 example.

Working Example

**1-(3,5-Dimethoxyphenyl)-4-(9-acridinyl)-
(D-43411) carbonyl)piperazine**

8 g (35.84 mmol) of acridine-9-carboxylic acid were charged to 300 ml of DMF with stirring. 5.79 g (57.34 mmol) of N-methylmorpholine, then a solution of 24.24 g (46.59 mmol) of Py-BOP (1-benzotriazolyltri-
5 pyrrolidinophosphonium hexafluorophosphate) and 7.96 g [lacuna] (35.81 mmol) of 1-(3,5-dimethoxyphenyl)-piperazine in 50 ml of DMF were added successively to the mixture with further stirring. The mixture was stirred at room temperature for 12 hours, the DMF was
10 distilled off under reduced pressure and the residue was purified on a silica gel column (Kieselgel 60, from Merck AG, Darmstadt) using the mobile phase dichloromethane/methanol/ (95:5 v/v).

15 Yield: 12.9 (84.2% of theory)
m.p.: 172-175°C

1. Antiproliferative action in various tumor cell lines

20

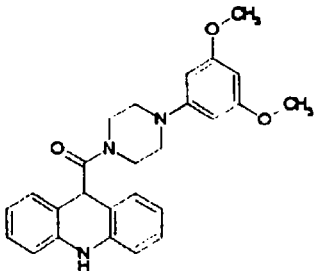
In a proliferation test, the antiproliferative activity of the substance D-43411 was examined using established tumor cell lines. In the test used, the cellular dehydrogenation activity is determined, which makes it
25 possible to determine the vitality of the cell and, indirectly, the cell count. The cell lines used are the human cervical carcinoma cell lines KB/HeLa (ATCC/CCL17), the murine lymphocyte leukaemia L1210 (ATCC CCL-219), the human breast adenocarcinoma line
30 MCF7 /ATCC HTB22) and the ovary adenocarcinoma line SKOV-3 (ATCC HTB77). These are established cell lines which are very well characterized and were obtained from ATCC and cultured.

35 The results shown in Tab. 1 demonstrate the highly potent antiproliferative action of D-43411 in the cell lines SKOV-3, L-1210 and HeLa/KB. Owing to the particularly slow growth of the MCF7 line, the effect

of D-43411 in the test period of 48 h is only small (18% inhibition at 3.16 $\mu\text{g/ml}$; thus stated as >3.16).

Tab. 1 In-vitro cytotoxicity in tumor cell lines

5 (values determined from 5 substance concentrations)

D number	Structure	XTT - Assay IC ⁵⁰ [$\mu\text{g/ml}$]				
		MW	SKOV-3	L1210	KB/HeLa	MCF7
D-43411		429	<0.0003	<0.0003	<0.0003	>3.16

2. Method

10 XTT Test for cellular dehydrogenase activity

The adherently growing tumor cell lines HeLa/KB, SKOV-3 and MCF7 and the L1210 leukaemia line, which grows in suspension, were cultivated under standard conditions in an incubator with gas inlet at 37°C, 5% CO₂ and 95% atmospheric humidity. On Test Day 1, the adherent cells are detached using trypsin/EDTA and pelleted by centrifugation. The cell pellet is then resuspended in RPMI culture medium at the appropriate cell count and transferred to a 96-well microtitre plate. The plates are then cultivated overnight in the incubator with gas inlet. The test substances are made up as stock solutions in DMSO and, on Test Day 2, diluted with culture medium to the desired concentrations. The substances in the culture medium are then added to the cells and incubated in the incubator with gas inlet for 45 h. Cells which have not been treated with test substance serve as control.

For the XTT assay, 1 mg/ml of XTT (sodium 3'-[1-(phenylaminocarbonyl)-3,4-tetrazolium]-bis(4-methoxy-6-nitro)benzenesulfonic acid) is dissolved in RPMI-1640 medium without Phenol Red. Additionally, a 0.383 mg/ml solution of PMS (N-methyldibenzopyrazine methyl sulfate) in phosphate-buffered saline (PBS) is prepared. On Test Day 4, 75 µl/well of the XTT-PMS mixture are pipetted onto the cell plates, which by now have been incubated with the test substances for 45 h. To this end, the XTT solution is mixed with the PMS solution in a ratio of 50:1 (v/v) shortly before use. The cell plates are then incubated in the incubator with gas inlet for a further 3 h, and the optical density (OD_{490nm}) is determined in a photometer.

Using the OD_{490nm} obtained, the inhibition in percent relative to the control is calculated. The antiproliferative activity is estimated using regression analysis.

20

Example I

Tablet containing 50 mg of active compound

Composition:

(1) Active compound	50.0 mg
(2) Lactose	98.0 mg
(3) Maize starch	50.0 mg
(4) Polyvinylpyrrolidone	15.0 mg
(5) Magnesium stearate	2.0 mg
Total:	215.0 mg

30

Preparation:

(1), (2) and (3) are mixed and granulated with an aqueous solution of (4). The dried granules are admixed with (5). This mixture is tabletted.

35

Example II

Capsule containing 50 mg of active compound

Composition:

(1) Active compound	50.0 mg
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(2) Maize starch, dried	58.0 mg
(3) Lactose powder	50.0 mg
(4) Magnesium stearate	2.0 mg
Total:	160.0 mg

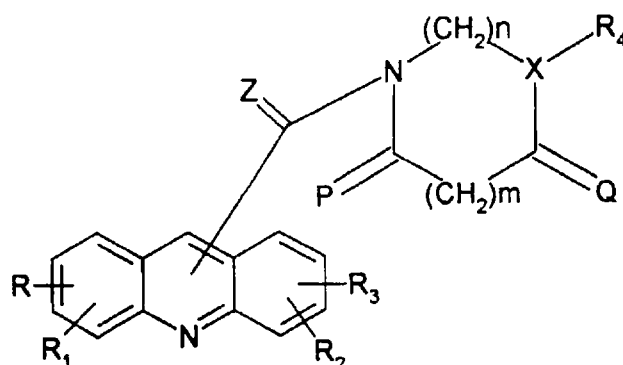
5

Preparation:

(1) is ground with (3). This ground material is added with vigorous mixing to the mixture of (2) and (4). This powder mixture is, on a capsule filling machine,
10 filled into hard gelatine capsules size 3.

Patent Claims

1. Acridine derivatives according to the formula 1



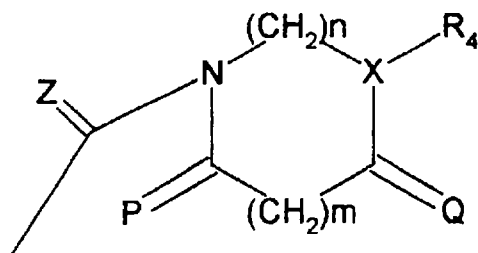
formula 1

in which

- 10 R, R₁, R₂, R₃ can be attached to any of the acridine carbon atoms C₁ to C₉, are identical or different and independently of one another denote hydrogen, straight-chain or branched (C₁-C₈)-alkyl, (C₃-C₇)-cycloalkyl, straight-chain or branched (C₁-C₈)-alkylcarbonyl, preferably acetyl, straight-chain or branched (C₁-C₈)-alkoxy, halogen, aryl-(C₁-C₈)-alkoxy, preferably benzyloxy or phenylethyloxy, nitro, amino, mono-(C₁-C₄)-alkylamino, di-
- 15 (C₁-C₄)-alkylamino, (C₁-C₈)-alkoxycarbonylamino, (C₁-C₆)-alkoxycarbonylamino-(C₁-C₈)-alkyl, cyano, straight-chain or branched cyano-(C₁-C₆)-alkyl, carboxyl, (C₁-C₈)-alkoxycarbonyl, (C₁-C₄)-alkyl which is substituted by one or more fluorine atoms, preferably the trifluoromethyl group, carboxy-(C₁-C₈)-alkyl or (C₁-C₈)-alkoxycarbonyl-(C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, preferably allyl, (C₂-C₆)-alkynyl, preferably ethynyl or propargyl,
- 20 straight-chain or branched cyano-(C₁-C₆)-
- 25
- 30

alkyl, preferably cyanomethyl, aryl, where the aryl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of halogen, straight-chain or branched (C₁-C₈)-alkyl, (C₃-C₇)-cycloalkyl, carboxyl, straight-chain or branched (C₁-C₈)-alkoxycarbonyl, preferably tert-butoxycarbonyl, by trifluoromethyl, hydroxyl, straight-chain or branched (C₁-C₈)-alkoxy, preferably methoxy or ethoxy, benzyloxy, nitro, amino, mono-(C₁-C₄)-alkylamino, di-(C₁-C₄)-alkylamino, cyano, straight-chain or branched cyano-(C₁-C₆)-alkyl,

Z is oxygen or sulfur, where the radical



substituted on the acridine heterocycle may be attached to C atoms C₁-C₉ of the acridine ring skeleton;

P, Q independently of one another represent oxygen or in each case two hydrogen atoms (i.e. -CH₂-);

X is nitrogen or C-R₅, where R₅ represents hydrogen or (C₁-C₆)-alkyl;

n, m independently of one another denotes an integer between 0-3, with the proviso that in the case n = 0, X denotes a CR₅R₆ group where R₅ and R₆ independently of one another represent hydrogen or (C₁-C₆)-alkyl and that the nitrogen atom adjacent

to the C=Z group is substituted by a hydrogen atom or a (C-C₆)-alkyl group;

5 R₄ [lacuna] a straight-chain or branched (C₁-C₂₀)-
alkyl radical which may be saturated or un-
saturated, with one to three double and/or triple
bonds, and which may be unsubstituted or may
optionally be substituted at the same or different
10 C atoms by one, two or more aryl, heteroaryl,
halogen, cyano, (C₁-C₆)-alkoxycarbonylamino,
(C₁-C₆)-alkoxy, amino, mono-(C₁-C₄)-alkylamino or
di-(C₁-C₄)-alkylamino; a (C₆-C₁₄)-aryl radical, (C₆-
C₁₄)-aryl-(C₁-C₄)-alkyl radical or a (C₂-C₁₀)-
heteroaryl or (C₂-C₁₀)-heteroaryl-(C₁-C₄)-alkyl
15 radical which contains one or more heteroatoms
selected from the group consisting of N, O and S,
where the (C₁-C₄)-alkyl radical may be
unsubstituted or mono- [lacuna] polysubstituted by
identical or different substituents from the group
20 consisting of (C₁-C₆)-alkyl, halogen and oxo (=O)
and where the (C₆-C₁₄)-aryl or (C₂-C₁₀)-heteroaryl
radical may be unsubstituted or mono- or poly-
substituted by identical or different substituents
from the group consisting of straight-chain or
25 branched (C₁-C₈)-alkyl, (C₃-C₇)-cycloalkyl,
halogen, cyano, (C₁-C₆)-alkoxycarbonylamino,
(C₁-C₆)-alkoxy, carboxyl, (C₁-C₈)-alkoxycarbonyl,
straight-chain or branched (C₁-C₆)-alkyl which is
substituted by one or more fluorine atoms,
30 preferably trifluoromethyl, hydroxyl, straight-
chain or branched (C₁-C₈)-alkoxy, preferably
methoxy or ethoxy, where adjacent oxygen atoms may
also be linked by (C₁-C₂)-alkylene groups,
preferably by a methylene group, benzyloxy, nitro,
35 amino, mono-(C₁-C₄)-alkylamino, di-(C₁-C₄)-alkyl-
amino, aryl, which for its part may be
unsubstituted or mono- or polysubstituted by
identical or different substituents from the group
consisting of straight-chain or branched (C₁-C₈)-

alkyl, (C₃-C₇)-cycloalkyl, carboxyl, straight-chain or branched (C₁-C₈)-alkoxycarbonyl, by trifluoromethyl, hydroxyl, straight-chain or branched (C₁-C₈)-alkoxy, preferably methoxy or ethoxy, benzyl-
 5 oxy, nitro, amino, mono-(C₁-C₄)-alkylamino, di-(C₁-C₄)-alkylamino, cyano, straight-chain or branched cyano-(C₁-C₆)-alkyl;

and their structural isomers and stereoisomers, in
 10 particular tautomers, diastereomers and enantiomers, and their pharmaceutically acceptable salts, in particular acid addition salts.

2. Acridine derivatives of the formula 1 according to
 15 Claim 1, characterized in that R, R₁, R₂, R₃, X, Z, P, Q, n and m have the meanings given in Claim 1 and

R₄ denotes a straight-chain or branched (C₁-C₂₀)-
 20 alkyl radical which may be saturated or unsaturated, with one to three double and/or triple bonds, and which may be unsubstituted or optionally substituted on the same or different C atoms by one, two or more aryl, heteroaryl,
 25 halogen, (C₁-C₆)-alkoxy, amino, mono-(C₁-C₄)-alkylamino or di-(C₁-C₄)-alkylamino;

a phenyl ring or a naphthyl ring, each of which may be unsubstituted or mono- or poly-
 30 substituted by identical or different substituents from the group consisting of straight-chain or branched (C₁-C₈)-alkyl, (C₃-C₇)-cycloalkyl, halogen, cyano, (C₁-C₆)-alkoxycarbonylamino, (C₁-C₆)-alkoxy, carboxyl,
 35 (C₁-C₈)-alkoxycarbonyl, straight-chain or branched (C₁-C₆)-alkyl which is substituted by one or more fluorine atoms, preferably trifluoromethyl, hydroxyl, straight-chain or branched (C₁-C₈)-alkoxy, preferably methoxy or

- ethoxy, benzyloxy, nitro, amino, mono-(C₁-C₄)-alkylamino, di-(C₁-C₄)-alkylamino, aryl, which for its part may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of straight-chain or branched (C₁-C₈)-alkyl, (C₃-C₇)-cycloalkyl, carboxyl, straight-chain or branched (C₁-C₈)-alkoxycarbonyl, by trifluoromethyl, hydroxyl, straight-chain or branched (C₁-C₈)-alkoxy, preferably methoxy or ethoxy, benzyloxy, nitro, amino, mono-(C₁-C₄)-alkylamino, di-(C₁-C₄)-alkylamino, cyano, straight-chain or branched cyano-(C₁-C₆)-alkyl;
- a 2-, 4-, 5- or 6-pyrimidinyl radical or 2-, 4-, 5- or 6-pyrimidinyl-(C₁-C₄)-alkyl radical, where the (C₁-C₄)-alkyl radical may be unsubstituted or mono- [lacuna] polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 2-, 4-, 5- or 6-pyrimidinyl radical may be unsubstituted or mono- to trisubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;
- a 3-, 4-, 5- or 6-pyridazinyl radical or 3-, 4-, 5- or 6-pyridazinyl-(C₁-C₄)-alkyl radical, where the (C₁-C₄)-alkyl radical may be unsubstituted or mono- [lacuna] polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and

5 oxo (=O) and the 3-, 4-, 5- or 6-pyridazinyl radical may be unsubstituted or mono- to trisubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or
10 polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

15 a 2-, 3-, 5- or 6-pyrazinyl radical or 2-, 3-, 5- or 6-pyrazinyl-(C₁-C₄)-alkyl radical, where the (C₁-C₄)-alkyl radical may be unsubstituted or mono- [lacuna] polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 2-, 3-, 5- or 6-pyrazinyl radical may be unsubstituted or mono- to trisubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and
20 (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;
25
30

35 a 3-, 4-, 5-, 6-, 7-, or 8-cinnolinyl radical or 3-, 4-, 5-, 6-, 7-, or 8-cinnolinyl-(C₁-C₄)-alkyl radical, where the (C₁-C₄)-alkyl radical may be unsubstituted or mono- [lacuna] polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 3-, 4-, 5-, 6-, 7-, or 8-cinnolinyl radical may be

5 unsubstituted or mono- to pentasubstituted by
 identical or different substituents from the
 group consisting of hydrogen, (C₁-C₆)-alkyl,
 halogen, nitro, amino, mono-(C₁-C₆)-alkylamino,
 10 di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy,
 benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl,
 (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl
 which is mono- or polysubstituted by fluorine,
 preferably trifluoromethyl, (C₆-C₁₀)-aryl and
 15 (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 2-, 4-, 5-, 6-, 7-, or 8-quinazolinyl radical
 or 2-, 4-, 5-, 6-, 7-, or 8-quinazolinyl-(C₁-
 C₄)-alkyl radical, where the (C₁-C₄)-alkyl
 20 radical may be unsubstituted or mono- [lacuna]
 polysubstituted by identical or different
 substituents from the group consisting of
 hydrogen, (C₁-C₆)-alkyl, halogen and oxo (=O)
 and the or [sic] 2-, 4-, 5-, 6-, 7-, or
 8-quinazolinyl radical may be unsubstituted or
 mono- to pentasubstituted by identical or
 different substituents from the group
 consisting of hydrogen, (C₁-C₆)-alkyl, halogen,
 nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-
 C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benz-
 25 yloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-
 C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which
 is mono- or polysubstituted by fluorine,
 preferably trifluoromethyl, (C₆-C₁₀)-aryl and
 30 (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 2-, 3-, 5-, 6-, 7-, or 8-quinoxaliny radical
 [lacuna] 2-, 3-, 5-, 6-, 7-, or 8-quinoxaliny-
 (C₁-C₄)-alkyl radical, where the (C₁-C₄)-alkyl
 radical may be unsubstituted or mono- [lacuna]
 35 polysubstituted by identical or different
 substituents from the group consisting of
 (C₁-C₆)-alkyl, halogen and oxo (=O) and the or
 [sic] 2-, 3-, 5-, 6-, 7-, or 8-quinoxaliny
 radical may be unsubstituted or mono- to

pentasubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonyl-amino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 1-, 4-, 5-, 6-, 7-, or 8-phthalazinyl radical or 1-, 4-, 5-, 6-, 7-, or 8-phthalazinyl-(C₁-C₄)-alkyl radical, where the (C₁-C₄)-alkyl radical may be unsubstituted or mono- [lacuna] polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the or [sic] 1-, 4-, 5-, 6-, 7-, or 8-phthalazinyl radical may be unsubstituted or mono- to pentasubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonyl-amino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl radical or 2-, 3-, 4-, 5-, 6-, 7 or 8-quinolyl-(C₁-C₄)-alkyl radical, where the (C₁-C₄)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl radical may be

5 unsubstituted or mono- to hexasubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, preferably methyl, particularly preferably 2-methyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by 10 fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

15 a 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl radical or 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl-(C₁-C₄)-alkyl radical, where the (C₁-C₄)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl radical may be unsubstituted or 20 mono- to hexasubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, 25 preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

35 a 2-, 6-, 8- or 9-[9H]-purinyl radical or 2-, 6-, 8- or 9-[9H]-purinyl-(C₁-C₄)-alkyl radical, where the (C₁-C₄)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 2-, 6-, 8- or 9-[9H]-purinyl

radical may be unsubstituted or mono- to trisubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 2-, 6-, 7- or 8-[7H]-purinyl radical or 2-, 6-, 7- or 8-[7H]-purinyl-(C₁-C₄)-alkyl radical, where the (C₁-C₄)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 2-, 6-, 7- or 8-[7H]-purinyl radical may be unsubstituted or mono- to trisubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-acridinyl radical or 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-acridinyl-(C₁-C₄)-alkyl radical, where the (C₁-C₆)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or

9-acridinyl radical may be unsubstituted or mono- to octasubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-phenanthridinyl radical or 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-phenanthridinyl-(C₁-C₆)-alkyl radical, where the (C₁-C₆)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen and oxo (=O) and the 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-phenanthridinyl radical may be unsubstituted or mono- to octasubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, (C₆-C₁₀)-aryl-(C₁-C₆)-alkoxy, preferably benzyl-oxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 2-, 3-, 4-, 5- or 6-pyridyl radical where the 2-, 3-, 4-, 5- or 6-pyridinyl [sic] radical may be unsubstituted or mono- to tetrasubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino,

di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 2-, 3-, 4-, 5- or 6-pyridyl-(C₁-C₆)-alkyl radical, where the (C₁-C₆)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 2-, 3-, 4-, 5- or 6-pyridinyl radical may be unsubstituted or mono- to tetrasubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 2-, 3-, 4- or 5-thienyl radical or 2-, 3-, 4- or 5-thienyl-(C₁-C₆)-alkyl radical, where the (C₁-C₆)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 2-, 3-, 4- or 5-thienyl radical may be unsubstituted or mono- to trisubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl

which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

5 a 2-, 4-, or 5-thiazolyl radical or 2-, 4-, or 5-thiazolyl-(C₁-C₆)-alkyl radical, where the (C₁-C₆)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group
 10 consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 2-, 4-, or 5-thiazolyl radical may be unsubstituted or mono- or disubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl,
 15 halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine,
 20 preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 3-, 4-, or 5-isothiazolyl radical or 3-, 4-, or 5-isothiazolyl-(C₁-C₆)-alkyl radical, where
 25 the (C₁-C₆)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 3-, 4-, or 5-isothiazolyl radical
 30 may be unsubstituted or mono- or disubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy,
 35 benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 2-, 4-, 5-, 6-, or 7-benzothiazolyl radical
 or 2-, 4-, 5-, 6-, or 7-benzothiazolyl-(C₁-C₆)-
 alkyl radical, where the (C₁-C₆)-alkyl radical
 5 may be unsubstituted or mono- or
 polysubstituted by identical or different
 substituents from the group consisting of
 (C₁-C₆)-alkyl, halogen and oxo (=O) and the 2-,
 4-, 5-, 6-, or 7-benzothiazolyl radical may be
 10 unsubstituted or mono- to tetrasubstituted by
 identical or different substituents from the
 group consisting of hydrogen, (C₁-C₆)-alkyl,
 halogen, nitro, amino, mono-(C₁-C₆)-alkylamino,
 di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy,
 15 benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl,
 (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl
 which is mono- or polysubstituted by fluorine,
 preferably trifluoromethyl, (C₆-C₁₀)-aryl and
 (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;
 20

a 1-, 2-, 4-, or 5-imidazolyl radical or 1-,
 2-, 4-, or 5-imidazolyl-(C₁-C₆)-alkyl radical,
 where the (C₁-C₆)-alkyl radical may be
 unsubstituted or mono- or polysubstituted by
 25 identical or different substituents from the
 group consisting of (C₁-C₆)-alkyl, halogen and
 oxo (=O) and the 1-, 2-, 4-, or 5-imidazolyl
 radical may be unsubstituted or mono- to
 trisubstituted by identical or different
 30 substituents from the group consisting of
 hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino,
 mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino,
 hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl,
 (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonyl-
 35 amino or (C₁-C₆)-alkyl which is mono- or
 polysubstituted by fluorine, preferably
 trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-
 (C₁-C₆)-alkyl;

a 1-, 3-, 4-, or 5-pyrazolyl radical or 1-, 3-,
 4- or 5-pyrazolyl-(C₁-C₆)-alkyl radical, where
 the (C₁-C₆)-alkyl radical may be unsubstituted
 or mono- or polysubstituted by identical or
 5 different substituents from the group
 consisting of (C₁-C₆)-alkyl, halogen and oxo
 (=O) and the 1-, 3-, 4- or 5-pyrazolyl radical
 may be unsubstituted or mono- to trisubstituted
 by identical or different substituents from the
 10 group consisting of hydrogen, (C₁-C₆)-alkyl,
 halogen, nitro, amino, mono-(C₁-C₆)-alkylamino,
 di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy,
 benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl,
 (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl
 15 which is mono- or polysubstituted by fluorine,
 preferably trifluoromethyl, (C₆-C₁₀)-aryl and
 (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 1-, 2-, 3-, 4-, or 5-pyrrolyl radical or 1-,
 20 2-, 3-, 4-, or 5-pyrrolyl-(C₁-C₆)-alkyl radical,
 where the (C₁-C₆)-alkyl radical may be
 unsubstituted or mono- or polysubstituted by
 identical or different substituents from the
 group consisting of (C₁-C₆)-alkyl, halogen and
 25 oxo (=O) and the 1-, 2-, 3-, 4- or 5-pyrrolyl
 radical may be unsubstituted or mono- to
 tetrasubstituted by identical or different
 substituents from the group consisting of
 hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino,
 30 mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino,
 hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl,
 (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonyl-
 amino or (C₁-C₆)-alkyl which is mono- or
 polysubstituted by fluorine, preferably
 35 trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-
 (C₁-C₆)-alkyl;

a 1-, 3-, or 5-[1.2.4]-triazolyl radical or 1-,
 3-, or 5-[1.2.4]-triazolyl-(C₁-C₆)-alkyl

radical, where the (C₁-C₆)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen and oxo (=O) and the 1-, 3-, or 5-[1.2.4]-triazolyl radical may be unsubstituted or mono- or disubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 1-, 4-, or 5-[1.2.3]-triazolyl radical or 1-, 4-, or 5-[1.2.3]-triazolyl-(C₁-C₆)-alkyl radical, where the (C₁-C₆)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 1-, 4-, or 5-[1.2.3]-triazolyl radical may be unsubstituted or mono- or disubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 1- or 5-[1H]-tetrazolyl radical or 1-, or 5-[1H]-tetrazolyl-(C₁-C₆)-alkyl radical, where the (C₁-C₆)-alkyl radical may be unsubstituted or

mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 1-, or 5-[1H]-tetrazolyl radical may be unsubstituted or substituted by hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonyl-amino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 2- or 5-[2H]-tetrazoyl radical or 2- or 5-[2H]-tetrazolyl-(C₁-C₆)-alkyl radical, where the (C₁-C₆)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 2- or 5-[2H]-tetrazolyl radical may be unsubstituted or substituted by hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonyl-amino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 2-, 4-, or 6-[1.3.5]-triazinyl radical or 2-, 4-, or 6-[1.3.5]-triazinyl-(C₁-C₆)-alkyl radical, where the (C₁-C₆)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen and oxo (=O) and the 2-, 4-, or 6-[1.3.5]-triazinyl radical may be unsubstituted

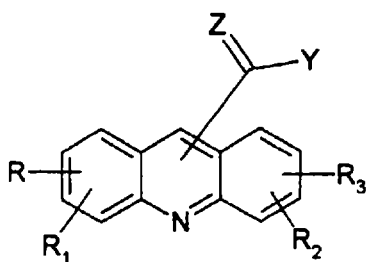
or mono- or disubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-
 5 (C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and
 10 (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

a 2-, 4-, or 5-oxazolyl radical or 2-, 4-, or 5-oxazolyl-(C₁-C₆)-alkyl radical, where the (C₁-C₆)-alkyl radical may be unsubstituted or mono-
 15 or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 2-, 4-, or 5-oxazolyl radical may be unsubstituted or mono- or disubstituted by identical or
 20 different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl
 25 which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;

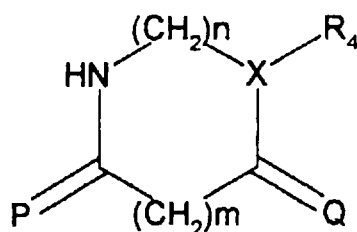
a 3-, 4-, or 5-isoxazolyl radical or 3-, 4-, or 5-isoxazolyl-(C₁-C₆)-alkyl radical, where the (C₁-C₆)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or
 30 different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 3-, 4-, or 5-isoxazolyl radical may be unsubstituted or mono- or disubstituted by identical or different substituents from the
 35 group consisting of hydrogen, (C₁-C₆)-alkyl,

- halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl;
- a 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl radical or 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl-(C₁-C₆)-alkyl radical, where the (C₁-C₆)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C₁-C₆)-alkyl, halogen and oxo (=O) and the 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl radical may be unsubstituted or mono- to hexasubstituted by identical or different substituents from the group consisting of hydrogen, (C₁-C₆)-alkyl, halogen, nitro, amino, mono-(C₁-C₆)-alkylamino, di-(C₁-C₆)-alkylamino, hydroxyl, (C₁-C₆)-alkoxy, benzyloxy, carboxyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkoxycarbonylamino or (C₁-C₆)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C₆-C₁₀)-aryl and (C₆-C₁₀)-aryl-(C₁-C₆)-alkyl.
3. Acridine derivatives according to Claim 1 or 2, characterized in that R, R₁, R₂, R₃, X, Z, P, Q, n and m have the meanings given above and R₄ represents phenyl which is unsubstituted or substituted by one to five identical or different (C₁-C₆)-alkoxy groups, where adjacent oxygen atoms may also be linked by (C₁-C₂)-alkylene groups.
4. Acridine derivatives according to any of Claims 1 to 3, characterized in that R, R₁, R₂, R₃, P, Q, X, Z, n and m have the meanings given above and R₄ represents 3,5-dimethoxyphenyl.

5. Acridine derivatives according to any of the preceding claims, characterized in that R_4 has the meanings given above, R , R_1 , R_2 , R_3 each represent a hydrogen atom, Z represents an oxygen atom and X represents a nitrogen atom, P and Q each represent two hydrogen atoms (i.e. $-\text{CH}_2-$) and m is zero and n represents the integer 2.
6. Acridine derivatives according to any of the preceding claims, characterized in that R , R_1 , R_2 , R_3 each represent a hydrogen atom, Z represents an oxygen atom and X represents a nitrogen atom, P and Q each represent two hydrogen atoms (i.e. $-\text{CH}_2-$) and m is zero and n represents the integer 2, and R_4 represents 3,5-dimethoxyphenyl.
7. Acridine derivatives according to any of Claims 1 to 6 for use as medicaments.
8. Use of the acridine derivatives according to any of Claims 1 to 6 for preparing a medicament for treating tumors in mammals.
9. Process for preparing acridine derivatives according to any of Claims 1 to 6, characterized in that an acridine carboxylic acid of the formula (2) in which R , R_1 , R_2 , R_3 have the meanings given above, Z denotes an oxygen or sulfur atom and Y represents a leaving group such as halogen, hydroxyl, (C1-C6)-alkoxy, preferably methoxy or ethoxy, -O-tosyl, -O-mesyl or imidazolyl,



formula 2



formula 3

- 5 is reacted with an amine of the formula (3) in which R₄, X, P, Q, m and n have the meanings given above, if appropriate using diluents and auxiliaries, and the desired acridine derivative is formed.
- 10
10. Method for treating tumors in mammals, characterized in that at least one acridine derivative according to any of Claims 1 to 6 is administered to the mammal in a dose effective for
- 15 tumor treatment.
11. Medicament, characterized in that it comprises, as active ingredient, at least one acridine derivative according to any of Claims 1 to 6, if
- 20 appropriate together with customary pharmaceutically acceptable auxiliaries, additives and carriers.