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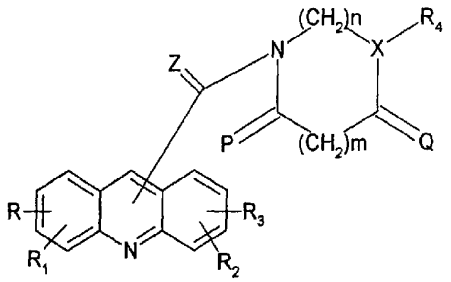
(54) **Title:** NOVEL HETEROARYL DERIVATIVES AND THE USE THEREOF AS PHARMACEUTICALS

(54) **Bezeichnung:** ACRIDIN-DERIVATE UND DEREN VERWENDUNG ALS ARZNEIMITTEL



(1)

(57) **Abstract:** The invention relates to novel acridine derivatives of general formula (1), the production thereof and the use of the same as pharmaceuticals, especially for treating tumours.

(57) **Zusammenfassung:** EP0108261dung betrifft neue Acridin-Derivate der allgemeinen Formel (1), deren Herstellung und Verwendung als Arzneimittel, insbesondere zur Behandlung von Tumoren.

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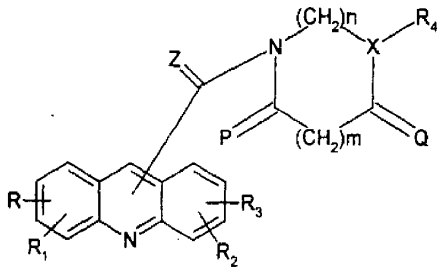
ACRIDINE DERIVATIVES AND THEIR USE AS MEDICAMENTS

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



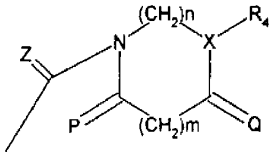
formula 1

in which

R, R_1, R_2, R_3 can be attached to any of the acridine carbon atoms C_1 to C_9, are identical or different and independently of one another denote hydrogen, straight-chain or branched (C_1-C_8)-alkyl, (C_3-C_7)-cycloalkyl, straight-chain or branched (C_1-C_8)-alkylcarbonyl, preferably acetyl, straight-chain or branched (C_1-C_8)-alkoxy, halogen, aryl-(C_1-C_8)-alkoxy, preferably benzyloxy or phenylethyloxy, nitro, amino, mono-(C_1-C_4)-alkylamino, di-(C_1-C_4)-alkylamino, (C_1-C_8)-alkoxycarbonyl-amino, (C_1-C_6)-alkoxycarbonylamino-(C_1-C_8)-alkyl, cyano, straight-chain or branched cyano-(C_1-C_6)-alkyl, carboxyl, (C_1-C_8)-alkoxy-carbonyl, (C_1-C_4)-alkyl which is substituted

by one or more fluorine atoms, preferably the trifluoromethyl group, carboxy-(C_1-C_8)-alkyl or (C_1-C_8)-alkoxycarbonyl-(C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, preferably allyl, (C_2-C_6)-alkynyl, preferably ethynyl or propargyl, straight-chain or branched cyano-(C_1-C_6)-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 (C_1-C_8)-alkyl, (C_3-C_7)-cycloalkyl, carboxyl, straight-chain or branched (C_1-C_8)-alkoxycarbonyl, preferably tert-butoxycarbonyl, by trifluoromethyl, hydroxyl, straight-chain or branched (C_1-C_8)-alkoxy, preferably methoxy or ethoxy, benzyloxy, nitro, amino, mono-(C_1-C_4)-alkylamino, di-(C_1-C_4)-alkylamino, cyano, straight-chain or branched cyano-(C_1-C_6)-alkyl,

Z is oxygen or sulfur, where the radical



substituted on the acridine heterocycle may be attached to C atoms C_1-C_9 of the acridine ring skeleton;

P, Q independently of one another represent oxygen or in each case two hydrogen atoms (i.e. $-CH_2-$);

X is nitrogen or C-R_5, where R_5 represents hydrogen or (C_1-C_6)-alkyl;

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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 (C_1-C_6)-alkyl and that the nitrogen atom adjacent to the C=Z group is substituted by a hydrogen atom or a $(C-C_6)$-alkyl group;

R_4 represents a straight-chain or branched (C_1-C_{20})-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, (C_1-C_6)-alkoxycarbonylamino, (C_1-C_6)-alkoxy, amino, mono-(C_1-C_4)-alkylamino or di-(C_1-C_4)-alkylamino; a (C_6-C_{14})-aryl radical, (C_6-C_{14})-aryl-(C_1-C_4)-alkyl radical or a (C_2-C_{10})-heteroaryl or (C_2-C_{10})-heteroaryl-(C_1-C_4)-alkyl radical which contains one or more heteroatoms selected from the group consisting of N, O and S, where the (C_1-C_4)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-alkyl, halogen and oxo (=O) and where the (C_6-C_{14})-aryl or (C_2-C_{10})-heteroaryl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of straight-chain or branched (C_1-C_8)-alkyl, (C_3-C_7)-cycloalkyl, halogen, cyano, (C_1-C_6)-alkoxycarbonylamino, (C_1-C_6)-alkoxy, carboxyl, (C_1-C_8)-alkoxycarbonyl, straight-chain or branched (C_1-C_6)-alkyl which is substituted by one or more fluorine atoms, preferably trifluoromethyl, hydroxyl, straight-chain or branched (C_1-C_8)-alkoxy, preferably methoxy or ethoxy, where adjacent oxygen atoms may also be linked by (C_1-C_2)-alkylene groups, preferably by a methylene group, benzyloxy, nitro,

amino, mono-(C_1-C_4)-alkylamino, di-(C_1-C_4)-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 (C_1-C_8)-alkyl, (C_3-C_7)-cycloalkyl, carboxyl, straight-chain or branched (C_1-C_8)-alkoxycarbonyl, by trifluoromethyl, hydroxyl, straight-chain or branched (C_1-C_8)-alkoxy, preferably methoxy or ethoxy, benzyloxy, nitro, amino, mono-(C_1-C_4)-alkylamino, di-(C_1-C_4)-alkylamino, cyano, straight-chain or branched cyano-(C_1-C_6)-alkyl;

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

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 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 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 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.

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 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.

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

R_4 denotes a straight-chain or branched (C_1-C_{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, halogen, (C1-C6)-alkoxy, amino, mono-(C_1-C_4)-alkylamino or di-(C_1-C_4)-alkylamino;

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 (C_1-C_8)-alkyl, (C_3-C_7)-cycloalkyl, halogen, cyano, (C_1-C_6)-alkoxycarbonylamino, (C_1-C_6)-alkoxy, carboxyl, (C_1-C_8)-alkoxycarbonyl, straight-chain or branched (C_1-C_6)-alkyl which is substituted by one or more fluorine atoms, preferably trifluoromethyl, hydroxyl, straight-chain or branched

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(C_1-C_8)-alkoxy, preferably methoxy or ethoxy, where adjacent oxygen atoms may also be linked by (C_1-C_2)-alkylene groups, preferably a methylene group, benzyloxy, nitro, amino, mono-(C_1-C_4)-alkylamino, di-(C_1-C_4)-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 (C_1-C_8)-alkyl, (C_3-C_7)-cycloalkyl, carboxyl, straight-chain or branched (C_1-C_8)-alkoxycarbonyl, by trifluoromethyl, hydroxyl, straight-chain or branched (C_1-C_8)-alkoxy, preferably methoxy or ethoxy, benzyloxy, nitro, amino, mono-(C_1-C_4)-alkylamino, di-(C_1-C_4)-alkylamino, cyano, straight-chain or branched cyano-(C_1-C_6)-alkyl;

a 2-, 4-, 5- or 6-pyrimidinyl radical or 2-, 4-, 5- or 6-pyrimidinyl-(C_1-C_4)-alkyl radical, where the (C_1-C_4)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxy-carbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 3-, 4-, 5- or 6-pyridazinyl radical or 3-, 4-, 5- or 6-pyridazinyl-(C_1-C_4)-alkyl radical, where the (C_1-C_4)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxy-carbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

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a 2-, 3-, 5- or 6-pyrazinyl radical or 2-, 3-, 5- or 6-pyrazinyl-(C_1-C_4)-alkyl radical, where the (C_1-C_4)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 3-, 4-, 5-, 6-, 7-, or 8-cinnolinyl radical or 3-, 4-, 5-, 6-, 7-, or 8-cinnolinyl-(C_1-C_4)-alkyl radical, where the (C_1-C_4)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

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a 2-, 4-, 5-, 6-, 7-, or 8-quinazolinyl radical or 2-, 4-, 5-, 6-, 7-, or 8-quinazolinyl-(C_1-C_4)-alkyl radical, where the (C_1-C_4)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of hydrogen, (C_1-C_6)-alkyl, halogen and oxo (=O) and the 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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 2-, 3-, 5-, 6-, 7-, or 8-quinoxalinyl radical or 2-, 3-, 5-, 6-, 7-, or 8-quinoxalinyl-(C_1-C_4)-alkyl radical, where the (C_1-C_4)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-alkyl, halogen and oxo (=O) and the 2-, 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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 1-, 4-, 5-, 6-, 7-, or 8-phthalazinyl radical or 1-, 4-, 5-, 6-, 7-, or 8-phthalazinyl-(C_1-C_4)-alkyl radical, where the (C_1-C_4)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-alkyl, halogen and oxo (=O) and the 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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

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a 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl radical or 2-, 3-, 4-, 5-, 6-, 7 or 8-quinolyl-(C_1-C_4)-alkyl radical, where the (C_1-C_4)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, preferably methyl, particularly preferably 2-methyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxy

carbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl radical or 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl-(C_1-C_4)-alkyl radical, where the (C_1-C_4)-alkyl radical may be unsubstituted or mono- or polysubstituted by identidal or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 2-, 6-, 8- or 9-[9*H*]-purinyl radical or 2-, 6-, 8- or 9-[9*H*]-purinyl-(C_1-C_4)-alkyl radical, where the (C_1-C_4)-alkyl radical may be unsubstituted or mono- or polysubstituted by identidal or different substituents from the group consisting of (C_1-C_6)-alkyl, halogen and oxo (=O) and the 2-, 6-, 8- or 9-[9*H*]-purinyl radical may be unsubstituted or mono- to trisubstituted by identical or different substituents from the group consisting of hydrogen, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 2-, 6-, 7- or 8-[7*H*]-purinyl radical or 2-, 6-, 7- or 8-[7*H*]-purinyl-(C_1-C_4)-alkyl radical, where the (C_1-C_4)-alkyl radical may be unsubstituted or mono- or polysubstituted by identidal or different substituents from the group consisting of (C_1-C_6)-alkyl, halogen and oxo (=O) and the 2-, 6-, 7- or 8-[7*H*]-purinyl radical may be unsubstituted or mono- to trisubstituted by identical or different substituents from the group consisting of hydrogen, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-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-(C_1-C_4)-alkyl radical, where the (C_1-C6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identidal or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-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-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identidal or different substituents from the group consisting of hydrogen, (C_1-C_6)-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 (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkyl-amino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, (C_6-C_{10})-aryl-(C_1-C_6)-alkoxy, preferably benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxy-carbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoro-methyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 2-, 3-, 4-, 5- or 6-pyridinyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_5)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 2-, 3-, 4- or 5-thienyl radical or 2-, 3-, 4- or 5-thienyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identidal or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 2-, 4-, or 5-thiazolyl radical or 2-, 4-, or 5-thiazolyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identidal or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino

or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 3-, 4-, or 5-isothiazolyl radical or 3-, 4-, or 5-isothiazolyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identidal or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 2-, 4-, 5-, 6-, or 7-benzothiazolyl radical or 2-, 4-, 5-, 6-, or 7-benzothiazolyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identidal or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 1-, 2-, 4-, or 5-imidazolyl radical or 1-, 2-, 4-, or 5-imidazolyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identidal or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 1-, 3-, 4-, or 5-pyrazolyl radical or 1-, 3-, 4- or 5-pyrazolyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identidal or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 1-, 2-, 3-, 4-, or 5-pyrrolyl radical or 1-, 2-, 3-, 4-, or 5-pyrrolyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identidal or different substituents from the group consisting of (C_1-C_6)-

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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 1-, 3-, or 5-[1.2.4]-triazolyl radical or 1-, 3-, or 5-[1.2.4]-triazolyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identidal or different substituents from the group consisting of hydrogen, (C_1-C_6)-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 (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkyl-amino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxy-carbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 1-, 4-, or 5-[1.2.3]-triazolyl radical or 1-, 4-, or 5-[1.2.3]-triazolyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identidal or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 1- or 5-[1*H*]-tetrazolyl radical or 1-, or 5-[1*H*]-tetrazolyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identidal or different substituents from the group consisting of (C_1-C_6)-alkyl, halogen and oxo (=O) and the 1-, or 5-[1*H*]-tetrazolyl radical may be unsubstituted or substituted by hydrogen, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 2- or 5-[2*H*]-tetrazoyl radical or 2- or 5-[2*H*]-tetrazolyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identidal or different substituents from the group consisting of (C_1-C_6)-alkyl, halogen and oxo (=O) and the 2- or 5-[2*H*]-tetrazolyl radical may be unsubstituted or substituted by hydrogen, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoro-

methyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 2-, 4-, or 6-[1.3.5]-triazinyl radical or 2-, 4-, or 6-[1.3.5]-triazinyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identidal or different substituents from the group consisting of hydrogen, (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 2-, 4-, or 5-oxazolyl radical or 2-, 4-, or 5-oxazolyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identidal or different substituents from the group consisting of (C_1-C_6)-alkyl, halogen and oxo (=O) and the 2-, 4-, or 5-oxazolyl radical may be unsubstituted or mono- or disubstituted by identical or different substituents from the group consisting of hydrogen, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 3-, 4-, or 5-isoxazolyl radical or 3-, 4-, or 5-isoxazolyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identidal or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl radical or 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identidal or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, preferably trifluoromethyl, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl and the isomers, in particular tautomers, diastereomers and enantiomers, and the pharmaceutically acceptable salts, in particular acid addition salts, thereof.

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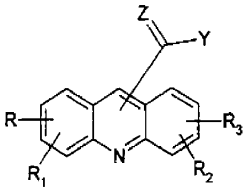
According to a further embodiment, acridine derivatives of the formula (1) are provided which are characterized in that R, R_1, R_2, R_3, X, Z, P, Q, n and m have the meanings given above and R_4 represents phenyl which is unsubstituted or substituted by one to five identical or different (C_1-C_6)-alkoxy groups, where adjacent oxygen atoms may also be linked by (C_1-C_2)-alkylene groups.

According to a further embodiment, acridine derivatives of the formula (1) are provided which are characterized in that R, R_1, R_2, R_3, X, Z, P, Q, n and m have the meanings given above and R_4 represents 3,5-dimethoxyphenyl.

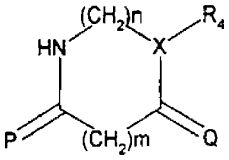
According to a further embodiment, acridine derivatives of the formula (1) are provided which are characterized in that R_4 has the meaning given above, R, R_1, R_2, R_3 each represent a hydrogen atom, Z represents an oxygen atom and X represents a nitrogen atom, P and Q each represent two hydrogen atoms (i.e. -CH_2-), m is zero and n is the integer 2.

According to a further embodiment, acridine derivatives of the formula (1) are provided which are characterized in that R, R_1, R_2 and 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. -CH_2-), m is zero, n represents the integer 2 and R_4 represents a 3,5-dimethoxyphenyl radical.

According to a further aspect of the invention, a process for preparing acridine derivatives of formula (1) is provided, 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, (C_1-C_6)-alkoxy, preferably methoxy or ethoxy, -O-tosyl, -O-mesyl or imidazolyl,



Formula 2



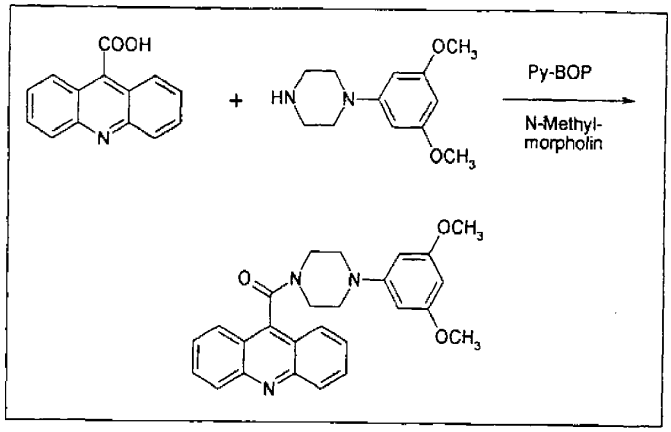
Formula 3

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



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 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 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, in particular man, but also domestic animals such as horses, cattle, dogs, cats, hares, sheep, poultry and the like.

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 formula (1), or a medicament comprising an acridine derivative of formula (1) optionally together with pharmaceutically acceptable auxiliaries, is administered to a mammal in an amount effective for the treatment of the tumor. The therapeutically effective 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 the treatment. Administration can take place orally, rectally, buccally (for example sublingually), parenterally (for example subcutaneously, intramuscularly, intradermally or intravenously), topically or transdermally.

According to another aspect of the invention there is provided the use of acridine derivatives of formula (1) for preparing a medicament for treating tumors in mammals.

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 of formula (1) 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 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 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 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-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 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).

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

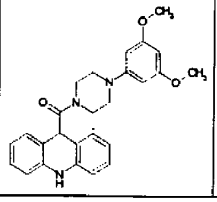
1. Antiproliferative action in various tumor cell lines

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 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 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.

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 µg/ml; thus stated as >3.16).

Tab. 1 In-vitro cytotoxicity in tumor cell lines (values determined from 5 substance concentrations)

		XTT - Assay IC^{50} [µg/ml]				
D number	Structure	MW	SKOV-3	L1210	KB/HeLa	MCF7
D-43411		429	<0.0003	<0.0003	<0.0003	>3.16

2. Method

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% CO_2 and 95% atmospheric humidity. On Test Day 1, the adherent cells are detached using trypsine/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.

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

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.

Example II

Capsule containing 50 mg of active compound

Composition:

(1)	Active compound	50.0 mg

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

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, filled into hard gelatine capsules size 3.

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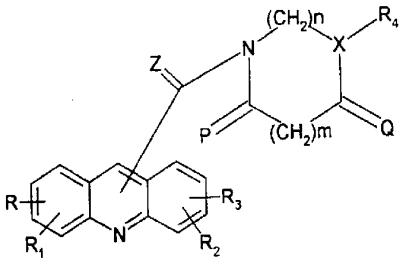
The claims defining the invention are as follows:

1. Acridine derivatives according to the formula 1

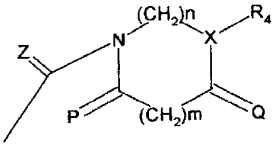


formula 1

in which

R, R_1, R_2, R_3 can be attached to any of the acridine carbon atoms C_1 to C_9, are identical or different and independently of one another denote hydrogen, straight-chain or branched (C_1-C_8)-alkyl, (C_3-C_7)-cycloalkyl, straight-chain or branched (C_1-C_8)-alkylcarbonyl, straight-chain or branched (C_1-C_8)-alkoxy, halogen, aryl-(C_1-C_8)-alkoxy, nitro, amino, mono-(C_1-C_4)-alkylamino, di-(C_1-C_4)-alkylamino, (C_1-C_8)-alkoxycarbonyl-amino, (C_1-C_6)-alkoxycarbonylamino-(C_1-C_8)-alkyl, cyano, straight-chain or branched cyano-(C_1-C_6)-alkyl, carboxyl, (C_1-C_8)-alkoxy-carbonyl, (C_1-C_4)-alkyl which is substituted by one or more fluorine atoms, carboxy-(C_1-C_8)-alkyl or (C_1-C_8)-alkoxycarbonyl-(C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, straight-chain or branched cyano-(C_1-C_6)-alkyl, 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 (C_1-C_8)-alkyl, (C_3-C_7)-cycloalkyl, carboxyl, straight-chain or branched (C_1-C_8)-alkoxycarbonyl, by trifluoromethyl, hydroxyl, straight-chain or branched (C_1-C_8)-alkoxy, benzyloxy, nitro, amino, mono-(C_1-C_4)-alkylamino, di-(C_1-C_4)-alkylamino, cyano, straight-chain or branched cyano-(C_1-C_6)-alkyl,

Z is oxygen or sulfur, where the radical



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substituted on the acridine heterocycle may be attached to C atoms C_1-C_9 of the acridine ring skeleton;

P,Q independently of one another represent oxygen or in each case two hydrogen atoms (i.e. -CH_2-);

X is nitrogen or C-R_5, where R_5 represents hydrogen or (C_1-C_6)-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 (C_1-C_6)-alkyl and that the nitrogen atom adjacent to the C=Z group is substituted by a hydrogen atom or a (C_1-C_6)-alkyl group;

R_4 represents a straight-chain or branched (C_1-C_{20})-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 C atoms by one, two or more aryl, heteroaryl, halogen, cyano, (C_1-C_6)-alkoxycarbonylamino, (C_1-C_6)-alkoxy, amino, mono-(C_1-C_4)-alkylamino or di-(C_1-C_4)-alkylamino; a (C_6-C_{14})-aryl radical, (C_6-C_{14})-aryl-(C_1-C_4)-alkyl radical or a (C_2-C_{10})-heteroaryl or (C_2-C_{10})-heteroaryl-(C_1-C_4)-alkyl radical which contains one or more heteroatoms selected from the group consisting of N, O and S, where the (C_1-C_4)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-alkyl, halogen and oxo (=O) and where the (C_6-C_{14})-aryl or (C_2-C_{10})-heteroaryl radical may be unsubstituted or mono- or poly-substituted by identical or different substituents from the group consisting of straight-chain or branched (C_1-C_8)-alkyl, (C_3-C_7)-cycloalkyl, halogen, cyano, (C_1-C_6)-alkoxycarbonylamino, (C_1-C_6)-alkoxy, carboxyl, (C_1-C_8)-alkoxycarbonyl, straight-chain or branched (C_1-C_6)-alkyl which is substituted by one or more fluorine atoms, hydroxyl, straight-chain or branched (C_1-C_8)-alkoxy, where adjacent oxygen atoms may also be linked by (C_1-C_2)-alkylene groups, benzyloxy, nitro, amino, mono-(C_1-C_4)-alkylamino, di-(C_1-C_4)-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 (C_1-C_8)-alkyl, (C_3-C_7)-cycloalkyl, carboxyl, straight-chain or branched (C_1-C_8)-alkoxycarbonyl, by trifluoromethyl, hydroxyl, straight-chain or branched (C_1-C_8)-alkoxy, benzyloxy, nitro, amino, mono-(C_1-C_4)-alkylamino, di-(C_1-C_4)-alkylamino, cyano, straight-chain or branched cyano-(C_1-C_6)-alkyl;

and their structural isomers and stereoisomers, and their pharmaceutically acceptable salts.

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2. Acridine derivatives according to claim 1, wherein said straight-chain or branched (C_1-C_8)-alkylcarbonyl is acetyl.

3. Acridine derivatives according to claim 1, wherein said aryl-(C_1-C_8)-alkoxy is benzyloxy or phenylethyloxy.

4. Acridine derivatives according to claim 1, wherein said (C_2-C_6)-alkenyl group is allyl.

5. Acridine derivatives according to claim 1, wherein said (C_2-C_6)-alkynyl group is ethynyl or propargyl.

6. Acridine derivatives according to claim 1, wherein said straight-chain or branched cyano-(C_1-C_6)-alkyl group is cyanomethyl.

7. Acridine derivatives according to claim 1, wherein said straight-chain or branched (C_1-C_8)-alkoxycarbonyl group is tert-butoxycarbonyl.

8. Acridine derivatives according to claim 1, wherein said (C_1-C_2)-alkylene group is methylene.

9. Acridine derivatives according to claim 1, wherein said structural isomers and stereoisomers are tautomers, diastereomers or enantiomers.

10. Acridinc derivatives according to claim 1, wherein said salts are acid addition salts.

11. Acridine derivatives according to claim 1, wherein R, R1, R2, R3, X, Z, P, Q, n and m have the meanings given in any one of claims 1 to 10 and

R4 denotes a straight-chain or branched (C_1-C_{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, halogen, (C_1-C_6)-alkoxy, amino, mono-(C_1-C_4)-alkylamino or di-(C_1-C_4)-alkylamino;

a phenyl ring or a naphthyl ring, each of which may be unsubstituted or mono- or poly-substituted by identical or different substituents from the group consisting of straight-chain or branched (C_1-C_8)-alkyl, (C_3-C_7)-cycloalkyl, halogen, cyano, (C_1-C_6)-alkoxycarbonylamino, (C_1-C_6)-alkoxy, carboxyl, (C_1-C_8)-alkoxycarbonyl, straight-chain or branched (C_1-C_6)-alkyl which is substituted by one or more fluorine atoms, hydroxyl, straight-chain or branched (C_1-C_8)-alkoxy, benzyloxy, nitro, amino, mono-(C_1-C_4)-alkylamino, di-(C_1-C_4)-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 (C_1-C_8)-alkyl, (C_3-C_7)-cycloalkyl, carboxyl, straight-chain or branched (C_1-C_8)-alkoxycarbonyl, by trifluoromethyl, hydroxyl, straight-chain or

branched (C_1-C_8)-alkoxy, benzyloxy, nitro, amino, mono-(C_1-C_4)-alkylamino, di-(C_1-C_4)-alkylamino, cyano, straight-chain or branched cyano-(C_1-C_6)-alkyl;

a 2-, 4-, 5- or 6-pyrimidinyl radical or 2-, 4-, 5- or 6-pyrimidinyl-(C_1-C_4)-alkyl radical, where the (C_1-C_4)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonyl-amino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 3-, 4-, 5- or 6-pyridazinyl radical or 3-, 4-, 5- or 6-pyridazinyl-(C_1-C_4)-alkyl radical, where the (C_1-C_4)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonyl-amino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 2-, 3-, 5- or 6-pyrazinyl radical or 2-, 3-, 5- or 6-pyrazinyl-(C_1-C_4)-alkyl radical, where the (C_1-C_4)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 3-, 4-, 5-, 6-, 7-, or 8-cinnolinyl radical or 3-, 4-, 5-, 6-, 7-, or 8-cinnolinyl-(C_1-C_4)-alkyl radical, where the (C_1-C_4)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-

alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 2-, 4-, 5-, 6-, 7-, or 8-quinazolinyl radical or 2-, 4-, 5-, 6-, 7-, or 8-quinazolinyl-(C_1-C_4)-alkyl radical, where the (C_1-C_4)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of hydrogen, (C_1-C_6)-alkyl, halogen and oxo (=O) and the 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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benz-yloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 2-, 3-, 5-, 6-, 7-, or 8-quinoxalinyl radical or 2-, 3-, 5-, 6-, 7-, or 8-quinoxalinyl-(C_1-C_4)-alkyl radical, where the (C_1-C_4)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-alkyl, halogen and oxo (=O) and the 2-, 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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonyl-amino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 1-, 4-, 5-, 6-, 7-, or 8-phthalazinyl radical or 1-, 4-, 5-, 6-, 7-, or 8-phthalazinyl-(C_1-C_4)-alkyl radical, where the (C_1-C_4)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-alkyl, halogen and oxo (=O) and the 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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonyl-amino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl radical or 2-, 3-, 4-, 5-, 6-, 7 or 8-quinolyl-(C_1-C_4)-alkyl radical, where the (C_1-C_4)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl radical or 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl-(C_1-C_4)-alkyl radical, where the (C_1-C_4)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 2-, 6-, 8- or 9-[9*H*]-purinyl radical or 2-, 6-, 8- or 9-[9*H*]-purinyl-(C_1-C_4)-alkyl radical, where the (C_1-C_4)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-alkyl, halogen and oxo (=O) and the 2-, 6-, 8- or 9-[9*H*]-purinyl radical may be unsubstituted or mono- to trisubstituted by identical or different substituents from the group consisting of hydrogen, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonyl-amino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 2-, 6-, 7- or 8-[7*H*]-purinyl radical or 2-, 6-, 7- or 8-[7*H*]-purinyl-(C_1-C_4)-alkyl radical, where the (C_1-C_4)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-alkyl, halogen and oxo (=O) and the 2-, 6-, 7- or 8-[7*H*]-purinyl radical may be unsubstituted or mono- to trisubstituted by identical or different substituents from the group consisting of hydrogen, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-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-(C_1-C_4)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-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-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of hydrogen, (C_1-C_6)-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 (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, (C_6-C_{10})-aryl-(C_1-C_6)-alkoxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 2-, 3-, 4-, 5- or 6-pyridyl radical where the 2-, 3-, 4-, 5- or 6-pyridiyl radical may be unsubstituted or mono- to tetrasubstituted by identical or different substituents from the group consisting of hydrogen, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 2-, 3-, 4-, 5- or 6-pyridyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonyl-amino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 2-, 3-, 4- or 5-thienyl radical or 2-, 3-, 4- or 5-thienyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl,

halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 2-, 4-, or 5-thiazolyl radical or 2-, 4-, or 5-thiazolyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 3-, 4-, or 5-isothiazolyl radical or 3-, 4-, or 5-isothiazolyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 2-, 4-, 5-, 6-, or 7-benzothiazolyl radical or 2-, 4-, 5-, 6-, or 7-benzothiazolyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 1-, 2-, 4-, or 5-imidazolyl radical or 1-, 2-, 4-, or 5-imidazolyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-alkyl, halogen and oxo (=O) and the 1-, 2-, 4-, or 5-imidazolyl radical may be unsubstituted or mono- to

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trisubstituted by identical or different substituents from the group consisting of hydrogen, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonyl-amino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 1-, 3-, 4-, or 5-pyrazolyl radical or 1-, 3-, 4- or 5-pyrazolyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 1-, 2-, 3-, 4-, or 5-pyrrolyl radical or 1-, 2-, 3-, 4-, or 5-pyrrolyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonyl-amino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 1-, 3-, or 5-[1.2.4]-triazolyl radical or 1-, 3-, or 5-[1.2.4]-triazolyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of hydrogen, (C_1-C_6)-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 (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 1-, 4-, or 5-[1.2.3]-triazolyl radical or 1-, 4-, or 5-[1.2.3]-triazolyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-alkyl, halogen

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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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonyl-amino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 1- or 5-[1*H*]-tetrazolyl radical or 1-, or 5-[1*H*]-tetrazolyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-alkyl, halogen and oxo (=O) and the 1-, or 5-[1*H*]-tetrazolyl radical may be unsubstituted or substituted by hydrogen, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonyl-amino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 2- or 5-[2*H*]-tetrazoyl radical or 2- or 5-[2*H*]-tetrazolyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-alkyl, halogen and oxo (=O) and the 2- or 5-[2*H*]-tetrazolyl radical may be unsubstituted or substituted by hydrogen, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonyl-amino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 2-, 4-, or 6-[1.3.5]-triazinyl radical or 2-, 4-, or 6-[1.3.5]-triazinyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of hydrogen,(C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benz-yloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 2-, 4-, or 5-oxazolyl radical or 2-, 4-, or 5-oxazolyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-alkyl, halogen and oxo (=O) and the 2-, 4-, or 5-oxazolyl radical may be unsubstituted or mono- or disubstituted by

identical or different substituents from the group consisting of hydrogen, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 3-, 4-, or 5-isoxazolyl radical or 3-, 4-, or 5-isoxazolyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl;

a 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl radical or 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl-(C_1-C_6)-alkyl radical, where the (C_1-C_6)-alkyl radical may be unsubstituted or mono- or polysubstituted by identical or different substituents from the group consisting of (C_1-C_6)-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, (C_1-C_6)-alkyl, halogen, nitro, amino, mono-(C_1-C_6)-alkylamino, di-(C_1-C_6)-alkylamino, hydroxyl, (C_1-C_6)-alkoxy, benzyloxy, carboxyl, (C_1-C_6)-alkoxycarbonyl, (C_1-C_6)-alkoxycarbonylamino or (C_1-C_6)-alkyl which is mono- or polysubstituted by fluorine, (C_6-C_{10})-aryl and (C_6-C_{10})-aryl-(C_1-C_6)-alkyl.

12. Acridine derivatives according to any one of claims 1 to 11, wherein said alkyl group which is substituted by one or more fluorine atoms is a trifluoromethyl group.

13. Acridine derivatives according to any one of claims 1 to 11, wherein said straight-chain or branched (C_1-C_8)-alkoxy group is methoxy or ethoxy.

14. Acridine derivatives according to claim 11, wherein said quinolyl radical is mono- to hexasubstituted by methyl substituents.

15. Acridine derivatives according to claim 11, wherein said quinolyl radical comprises a 2-methyl substituent.

16. Acridine derivatives according to claim 11, wherein said (C_6-C_{10})-aryl-(C_1-C_6)-alkoxy group is benzyloxy.

17. Acridine derivatives according to any one of claims 1 to 16, wherein R, R_1, R_2, R_3, X, Z, P, Q, n and m have the meanings given above and R4 represents phenyl

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which is unsubstituted or substituted by one to five identical or different (C_1-C_6)-alkoxy groups, where adjacent oxygen atoms may also be linked by (C_1-C_2)-alkylene groups.

18. Acridine derivatives according to any one of claims 1 to 17, wherein R, R_1, R_2, R_3, P, Q, X, Z, n and m have the meanings given above and R_4 represents 3,5-dimethoxyphenyl.

19. Acridine derivatives according to any one of claims 1 to 18, wherein 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. $-CH_2-$) and m is zero and n represents the integer 2.

20. Acridine derivatives according to any one of claims 1 to 19, wherein 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. $-CH_2-$) and m is zero and n represents the integer 2, and R_4 represents 3,5-dimethoxyphenyl.

21. An acridine derivative of formula (1) as defined in claim 1, substantially as hereinbefore described with reference to any one of the examples.

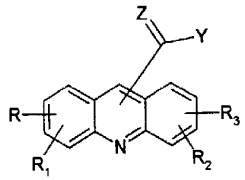
22. Acridine derivatives according to any one of claims 1 to 21 when used as medicaments.

23. A medicament comprising as active ingredient at least one acridine derivative according to any one of claims 1 to 21, if appropriate together with customary pharmaceutically acceptable auxiliaries, additives and carriers.

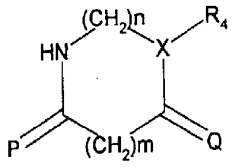
24. A method for treating tumors in mammals, comprising administering to said mammal at least one acridine derivative according to any one of claims 1 to 21, or a medicament according to claim 23, in a dose effective for tumor treatment.

25. Use of the acridine derivatives according to any one of claims 1 to 21 for preparing a medicament for treating tumors in mammals.

26. A process for preparing acridine derivatives according to any one of claims 1 to 21, wherein an 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, (C_1-C_6)-alkoxy, -O-tosyl, -O-mesyl or imidazolyl,



formula 2



formula 3

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.

27. The process according to claim 26, wherein said (C_1-C_6)-alkoxy group is methoxy or ethoxy.

28. A process for preparing acridine derivatives of formula (1) as defined in claim 1, substantially as hereinbefore described with reference to any one of the examples.

29. An acridine derivative of formula (1) prepared according to the process of any one of claims 26 to 28.

Dated 21 March, 2005
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