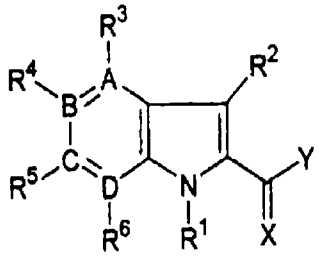
2-acyl indole derivatives and their use as antitumor agents

The invention relates to novel indole and heteroindole derivatives of the formula I



(I)

to their tautomers, their stereoisomers, their mixtures and their salts, to their preparation and to the use of indole derivatives of the formula I as antitumor agents.

It is an object of the present invention to provide novel active compounds for the treatment of tumors in mammals.

The German Offenlegungsschrift [German published specification] No. DE 2 501 468 describes 1-alkyl-2-pyridylcarbonyl-substituted indole compounds, their preparation and their use as fibrinolytics or thrombolytics. An antitumor action is neither described nor suggested.

In the Belgian patent No. BE 637355, 2-benzoyl-substituted indole compounds as intermediates in a Grignard reaction are converted into the corresponding 1-aminoalkyl-1-hydroxy derivatives (phenylindolyl-alkanolamines). A biological action of the intermediates is neither described nor suggested to a person of ordinary skill in the art.

The German Offenlegungsschrift No. DE 2 037 998 describes a process for preparing 2-benzoyl-, 2-acetyl, 2-propionyl and 2-p-toluoylindole, the class of the 2-acylindoles being described as "relatively inaccessible". Reference is made to the use of the 2-acylindoles as intermediates in the preparation of phenylindolylalkanolamine sedatives according to the abovementioned Belgian patent No. 637 355. Without further details being given, the use of the 2-acylindoles for preparing dyes, alkaloids, plant hormones and proteins is merely mentioned. A use of the 2-acylindoles as medicaments is neither disclosed nor suggested.

In the publication with the title "Nucleophilic Substitution of C-Hydrogen on the Five-membered Ring of Indoles" by John A. Joule in *Progress in Heterocyclic Chemistry*, 86VK, 7200.6-11, pages 45-65, the preparation of hydroxy-2-indolyl-(2-hydroxymethyl)-phenylmethane is described on page 50, the preparation of 2-benzoylindole is described on page 54 and the preparation of 2-cyclopropycarbonylindole is described on page 55. A medicinal use of the compounds mentioned is neither disclosed nor suggested.

The publication by David St. C. Black et al., *J. Chem. Soc., Chem. Commun.*, 1989, pp. 425-426 describes the preparation of 2-(p-chlorophenylcarbonyl-)-3-methyl-4,6-dimethoxyindole and its use as an intermediate in the synthesis of indole-containing macrocycles.

US patent No. 3,660,430 by Meier E. Freed et al., granted on 2 May 19972, describes 3-phenyl-substituted 2-benzoylindole compounds, their preparation and their use as CNS sedatives.

US patent No. 3,838,167 by Charles D. Jones, granted on 24 September 1974, describes a process for preparing 2-acylindole compounds. The only example given for a

2-benzoylindole that is unsubstituted in the 3-position is 2-(3-bromobenzoyl)-7-trifluoromethylindole. With respect to the use as CNS sedative, reference is made to the abovementioned US patent 3,660,430.

The publication by Michael D. Varney et al., J. Med. Chem. 1994, 37, pages 2274-2284, describes 2-benzoyl-(metaposition: H, trifluoromethyl or methyl) and 2-cyclohexylcarbonyl indole compounds as intermediates for the preparation of HIV protease inhibitors. A biological action of the intermediates is neither disclosed nor suggested.

The publication by Gordon W. Gribble et al., *J. Org. Chem. 1992, 57, 5891-5899* describes 2-(2-carboxy)-benzoyl and 2-(5-carboxypyridin-4-yl indole derivatives, the latter being substituted in the 5-position by hydrogen or methoxy, as intermediates for the synthesis of benzo[b]carbazole and 6H-pyrido-[4,3-b]carbazoles respectively. A biological action of the intermediates is neither disclosed nor suggested.

The publication by S. Cenini, *Journal of Molecular Catalysis A: Chemical* 111 (1996) 37-41 describes the palladium- or ruthenium-catalyzed synthesis of 2-benzoylindoles which are unsubstituted in the indole ring, where the phenyl ring is substituted in positions 3, 4 or 5 by hydrogen, halogen, methyl or methoxy. A biological action of the 2-acylindoles that are prepared is not disclosed.

The publication by David St. C. Black and L.C.H. Wong, *J.C.S. Comm.* 1980, page 200, describes the synthesis of 2-acylindoles which are substituted in indole positions 4 to 7 by chlorine, methyl or methoxy. A biological action of the 2-acylindoles that are prepared is neither disclosed nor suggested.

The publication by David St. C. Black et al.,

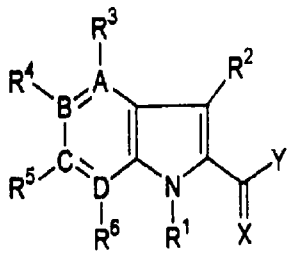
Tetrahedron Letters, Vol. 32, No. 12, pages 1587-1590, 1991 describes the reaction of 3-methyl-4,7-dimethoxy-2-benzoylindole with methyl iodide with formation of the corresponding carbinol compound. A biological action of the starting material is neither disclosed nor suggested.

The publication by Tetsuji Kametani et al., Yakugaku-zasshi, 91 (9) 1033-1036 (1971) describes a process for preparing the compound 2-benzoyl-5,6-methylenedioxy-indole from β-(benzoyl)-4,5-methylenedioxy-2-nitro-styrene.

The publication by Charles D. Jones and Tulio Suarez, J. Org. Chem., Vol. 37, No. 23, 1972, pages 3622-3623 describes a process for preparing 2-acylindoles. A biological action of the compounds that are prepared is neither disclosed nor suggested.

The publication by V.I. Gorgos et al., Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1490-1492 (English translation in UDC 547.756'757.07; pp. 1179-1182) describes a process for preparing 2-benzoyl-indoles substituted in the 5- or 7-position by bromine or methoxy. A biological action of the compounds that are prepared is not disclosed. The same applies to the Soviet patent No. 696016, which names the authors of the publication mentioned above as inventors.

Surprisingly, it has now been found that the compounds of the formula I



(I)

in which

R1 is hydrogen, (C1-C6)-alkylcarbonyl, preferably acetyl, (C_1-C_6)-alkyl, mono-(C_1-C_6)-alkylamino-(C_1-C_4)-alkyl, di-(C_1-C_6)-alkylamino-(C_1-C_4)-alkyl, where the two (C_1-C_6)-alkyl radicals together may form a ring, which optionally contains one or more NH, N-(C1-C6)-alkyl, O or S members, (C6-C14)-aryl-(C1-C6)-alkyl or (C6-C14)-aryl-(C1-C6)-alkoxy-(C1-C6)-alkyl;

R2 is a hydrogen atom, halogen, cyano, nitro, (C1-C6)-alkyl, (C1-C6)-alkyl which is substituted by one or more halogen atoms, preferably trifluoromethyl, (C1-C6)-alkoxy which is substituted by one or more halogen atoms, preferably trifluoromethoxy, (C2-C6)-alkenyl, (C2-C6)-alkynyl, (C3-C8)-cycloalkyl, (C1-C6)-alkoxy, (C1-C6)-alkoxycarbonyloxy, (C1-C6)-alkylcarbonyloxy, (C1-C4)-alkylthio, (C1-C4)-alkylsulfinyl, (C1-C4)-alkylsulfonyl, (C1-C6)-alkoxy-(C1-C6)-alkyl, amino, mono-(C1-C6)-alkylamino, di-N,N-(C1-C6)-alkylamino, where the two (C1-C6)-alkyl radicals together may form a ring, which optionally contains one or more NH, N-(C1-C6)-alkyl, O or S, (C6-C14)-aryl, (C6-C14)-aryloxy, (C6-C14)-aryl-(C1-C4)-alkyl, (C6-C14)-aryl-(C1-C4)-alkoxy-(C1-C4)-alkyl, (C1-C6)-alkylcarbonyl, (C1-C6)-alkoxycarbonyl or hydroxyl;

A, B, C and D independently of one another are a nitrogen atom (in which case R3, R4, R5 and R6 represent the free electron pair at the nitrogen atom) or are a carbon atom substituted by one of the radicals R3-R6;

R3, R4, R5 and R6 independently of one another are, when attached to nitrogen, a free electron pair, or,

when attached to carbon, hydrogen, halogen, cyano, nitro, straight-chain or branched (C1-C6)-alkyl, straight-chain or branched (C1-C6)-alkyl which is substituted by one or more halogen atoms, preferably trifluoromethyl, straight-chain or branched (C1-C6)-alkoxy which is substituted by one or more halogen atoms, preferably trifluoromethoxy, (C2-C6)-alkenyl, (C2-C6)-alkynyl, (C3-C8)-cycloalkyl, straight-chain or branched (C1-C6)-alkoxy, preferably methoxy, straight-chain or branched (C1-C6)-alkylenedioxy, preferably methylenedioxy, (C1-C6)-alkoxycarbonyloxy, (C1-C6)-alkylcarbonyloxy, (C1-C4)-alkylthio, (C1-C4)-alkylsulfinyl, (C1-C4)-alkylsulfonyl, carboxyl, (C1-C6)-alkyl carboxylate, carboxamide, N-(C1-C4)-alkyl carboxamide, N,N-di-(C1-C4)-alkyl carboxamide, (C1-C6)-alkoxy-(C1-C6)-alkyl, amino, mono-(C1-C6)-alkylamino, N,N-di-(C1-C6)-alkylamino, where the two C1-C6-alkyl radicals together may form a ring, which optionally contains one or more NH, N-(C1-C6)-alkyl, O or S, (C6-C14)-aryl, (C6-C14)-aryloxy, (C6-C14)-aryl-(C1-C4)-alkyl, (C6-C14)-aryl-(C1-C4)-alkoxy-(C1-C4)-alkyl, (C1-C6)-alkylcarbonyl, (C1-C6)-alkylcarbonyloxy, (C1-C6)-alkoxycarbonyl, hydroxyl, where two directly adjacent radicals may be attached to one another;

Y is unsubstituted (C6-C14)-aryl or (C6-C14)-aryl which is fully or partially substituted by identical or different substituents, preferably phenyl or 1- or 2-naphthyl, or is unsubstituted (C1-C13)-heteroaryl or (C1-C13)-heteroaryl which is fully or partially substituted by identical or different substituents and has in each case at least one to four N, NH, N-(C1-C6)-alkyl, O and/or S as ring members, or is unsubstituted (C3-C8)-cycloalkyl or (C3-C8)-cycloalkyl which is fully or partially substituted by identical or different substituents, where the identical or different

substituents are selected independently of one another from the group consisting of halogen, preferably fluorine, chlorine, bromine or iodine; cyano; straight-chain or branched cyano-(C1-C6)-alkyl; hydroxyl; straight-chain or branched (C1-C6)-alkyl which is substituted by one or more hydroxyl substituents; carboxyl; (C1-C6)-alkyl carboxylate, carboxamide; N-(C1-C6)-alkyl carboxamide, N,N-di-(C1-C4)-alkyl carboxamide, nitro, straight-chain or branched (C1-C6)-alkyl, straight-chain or branched (C1-C6)-alkyl which is substituted by one or more halogen atoms, preferably trifluoromethyl, straight-chain or branched (C1-C6)-alkoxy which is substituted by one or more halogen atoms, preferably trifluoromethoxy, straight-chain or branched (C2-C6)-alkenyl, straight-chain or branched (C2-C6)-alkynyl, (C3-C8)-cycloalkyl, straight-chain or branched (C1-C6)-alkoxy, preferably methoxy, straight-chain or branched (C1-C6)-alkylenedioxy, preferably methylenedioxy, thio (-SH), straight-chain or branched (C1-C6)-alkylthio, (C1-C6)-alkylsulfinyl, (C1-C6)-alkylsulfonyl, (C1-C6)-alkoxy-(C1-C6)-alkyl, amino, straight-chain or branched mono-(C1-C6)-alkylamino, straight-chain or branched N,N-di-(C1-C6)-alkylamino, where the two (C1-C6)-alkyl radicals together may form a ring, which may optionally contain one or more NH, N-(C1-C6)-alkyl, O and/or S, (C6-C14)-aryl, (C6-C14)-aryloxy, (C6-C14)-aryl-(C1-C6)-alkyl, (C6-C14)-aryl-(C1-C6)-alkoxy-(C1-C6)-alkyl, (C1-C6)-alkylcarbonyl, (C1-C6)-alkylcarbonyloxy, (C1-C6)-alkoxycarbonyl, (C1-C6)-alkoxycarbonyloxy, straight-chain or branched mono- and N,N-di-(C1-C6)-alkylcarbonylamino, straight-chain or branched mono- and N,N-di-(C1-C6)-alkoxycarbonylamino, straight-chain or branched N-(C1-C6)-alkylcarbonyl-N-(C1-C6)-alkylamino, straight-chain

or branched N-(C1-C6)-alkoxycarbonyl-N-(C1-C6)-alkylamino, formylamino, formyl, where two directly adjacent radicals may be attached to one another;

X is an oxygen or sulfur atom, is NH, or is a geminally (at the same C atom) substituted hydroxyl and hydrogen (-CH(OH)-);

their stereoisomers, their tautomers, mixtures thereof and the pharmaceutically acceptable salts thereof can be used for preparing a medicament for the treatment of oncoses in mammals.

A particular embodiment of the present invention provides the use of at least one compound of the formula I according to claim 1, characterized in that R1-R6, A, B, C, D, X and Y are as defined in claim 1, with the proviso that at least one of the radicals R3-R6 is straight-chain or branched (C1-C6)-alkoxy, preferably methoxy; straight-chain or branched (C1-C6)-alkyl, preferably methyl; straight-chain or branched (C1-C6)-alkylenedioxy, preferably methylenedioxy, hydroxyl; straight-chain or branched (C1-C6)-alkoxy which is substituted by one or more halogen atoms, preferably trifluoromethoxy; straight-chain or branched (C1-C6)-alkyl which is substituted by one or more halogen atoms, preferably trifluoromethyl.

A further embodiment of the invention provides the use of at least one compound of the formula I according to claim 1, characterized in that that R1, R2, R3, R5, R6, A, B, C, D, X and Y are as defined above and the radical R4 is straight-chain or branched (C1-C6)-alkoxy, preferably methoxy; straight-chain or branched (C1-C6)-alkyl, preferably methyl; straight-chain or branched (C1-C6)-alkylenedioxy (where the second oxygen atom may optionally be the radical R4 or R6), preferably methylenedioxy, hydroxyl; straight-chain or

branched (C1-C6)-alkoxy which is substituted by one or more halogen atoms, preferably trifluoromethoxy; straight-chain or branched (C1-C6)-alkyl which is substituted by one or more halogen atoms, preferably trifluoromethyl.

A further embodiment of the invention provides the use of at least one compound of the abovementioned formula I, characterized in that R1, R2, R3, R5, R6, A, B, C, D, X and Y are as defined above and the radical R4 is straight-chain or branched (C1-C6)-alkoxy, preferably methoxy.

A further embodiment of the invention provides the use of at least one compound of the abovementioned formula I according to any of the preceding embodiments, characterized in that R1, R2, R3, R5, R6, A, B, C, D, X and Y are as defined above and the radical R4 is methoxy.

A further embodiment of the invention provides the use of at least one compound of the formula I according to any of the preceding embodiments, characterized in that R1-R6, A, B, C, D and X are as defined above and the radical Y is substituted or unsubstituted (C6-C14)-aryl or is (C1-C13)-heteroaryl which contains at least one to four N, NH, O and/or S as ring member.

A further embodiment of the invention provides the use of at least one compound of the formula I according to any of the preceding embodiments, characterized in that R1-R6, A, B, C, D and X are as defined above and the radical Y is (C6-C14)-aryl or is (C1-C13)-heteroaryl which contains at least one N, NH, O and/or S as ring member and is unsubstituted or substituted by at least one radical selected from the group consisting of hydrogen, amino, halogen, nitro, cyano, straight-chain or branched (C1-C6)-alkoxy, preferably methoxy; straight-chain or branched (C1-C6)-alkyl, preferably

methyl; hydroxyl; (C1-C6)-alkylcarbonyloxy, (C1-C6)-alkoxycarbonyloxy; straight-chain or branched (C1-C6)-alkoxy which is substituted by one or more halogen atoms, preferably trifluoromethoxy; straight-chain or branched (C1-C6)-alkyl which is substituted by one or more halogen atoms, preferably trifluoromethyl.

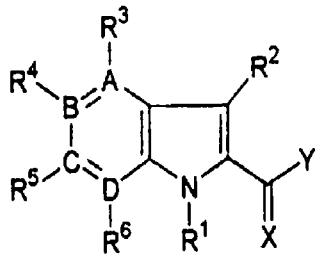
A further embodiment of the invention provides the use of at least one compound of the formula I according to any of the preceding embodiments, characterized in that R1-R6, A, B, C, D and X are as defined above and the radical Y is a 1-phenyl radical which is unsubstituted or substituted by hydrogen, 3,4-dichloro, 2- or 3-methoxy, 2,4-dimethoxy, 3-nitro 3-trifluoromethyl, 2,3,4-trimethoxy, 3,4,5-trimethoxy.

A further embodiment of the invention provides the use of a compound of the formula I according to any of the preceding embodiments for preparing a medicament having antimitotic action in mammals.

A further embodiment of the invention provides the use of a compound of the formula I according to any of the preceding embodiments for preparing a medicament for the direct and/or indirect inhibition of tubulin polymerization in mammalian cells.

A further embodiment of the invention provides the use of a compound of the formula I according to any of the preceding embodiments for preparing a medicament for oral, parenteral or topical treatment of tumor disorders in mammals, preferably in man.

According to a further aspect of the present invention, compounds of the formula I



(I)

in which

R1 is hydrogen, (C1-C6)-alkylcarbonyl, preferably acetyl, (C_1-C_6)-alkyl, mono-(C_1-C_6)-alkylamino-(C_1-C_4)-alkyl, di(C_1-C_6)-amino-(C_1-C4)-alkyl, where the two (C_1-C_4)-alkyl radicals together may form a ring, which optionally contains one or more NH, N-(C1-C)-alkyl, O or S members, (C6-C14)-aryl-(C1-C6)-alkyl or (C6-C14)-aryl-(C1-C6)-alkoxy-(C1-C6)-alkyl;

R2 is a hydrogen atom, halogen, cyano, nitro, (C1-C6)-alkyl, (C1-C6)-alkyl which is substituted by one or more halogen atoms, preferably trifluoromethyl, (C1-C6)-alkoxy which is substituted by one or more halogen atoms, preferably trifluoromethoxy, (C2-C6)-alkenyl, (C2-C6)-alkynyl, (C3-C8)-cycloalkyl, (C1-C)-alkoxy, (C1-C)-alkoxycarbonyloxy, (C1-C)-alkylcarbonyloxy, (C1-C)-alkylthio, (C1-C4)-alkylsulfinyl, (C1-C4)-alkylsulfonyl, (C1-C4)-alkoxy-(C1-C4)-alkyl, amino, mono-(C1-C)-alkylamino, di-(C1-C)-alkyl)-amino, where the two C1-C4-alkyl radicals together may form a ring, which optionally contains one or more NH, N-(C1-C4)alkyl, O or S, (C6-C14)-aryl, (C6-C14)-aryloxy, (C6-C14)-aryl-(C1-C4)-alkyl, (C6-C14)-aryl-(C1-C4)-alkoxy-(C1-C4)-alkyl, (C1-C6)-alkylcarbonyl, (C1-C6)-alkoxycarbonyl or hydroxyl;

A, B, C and D independently of one another are a

nitrogen atom (in which case R3, R4, R5 and R6 represent the free electron pair at the nitrogen atom) or are a carbon atom substituted by one of the radicals R3-R6;

R3, R4, R5 and R6 independently of one another are, when attached to nitrogen, a free electron pair, or, when attached to carbon, hydrogen, halogen, cyano, nitro, straight-chain or branched (C1-C6)-alkyl, straight-chain or branched (C1-C6)-alkyl which is substituted by one or more halogen atoms, preferably trifluoromethyl, straight-chain or branched (C1-C6)-alkoxy which is substituted by one or more halogen atoms, preferably trifluoromethoxy, (C2-C6)-alkenyl, (C2-C6)-alkynyl, (C3-C8)-cycloalkyl, straight-chain or branched (C1-C6)-alkoxy, straight-chain or branched (C1-C6)-alkylenedioxy, (C1-C6)-alkoxycarbonyloxy, (C1-C6)-alkylcarbonyloxy, (C1-C)-alkylthio, (C1-C4)-alkyl-sulfinyl, (C1-C4)-alkylsulfonyl, carboxyl, (C1-C6)-alkyl carboxylate, carboxamide, N-(C1-C4)-alkyl carboxamide, N,N-di-(C1-C4)-alkyl carboxamide, (C1-C6)-alkoxy-(C1-C6)-alkyl, amino, mono-(C1-C6)-alkylamino, di-(C1-C6)-alkyl)-amino, where the two C1-C4-alkyl radicals together may form a ring, which optionally contains one or more NH, N-(C1-C4)-alkyl, O or S, aryl, aryloxy, aryl-(C1-C4)-alkyl, aryl-(C1-C4)-alkoxy-(C1-C4)-alkyl, (C1-C6)-alkylcarbonyl, (C1-C6)-alkoxycarbonyl, hydroxyl, where two directly adjacent radicals may be attached to one another;

Y is unsubstituted (C10-C14)-aryl or (C10-C14)-aryl which is fully or partially substituted by identical or different substituents, preferably 1- or 2-naphthyl, or is unsubstituted (C1-C13)-heteroaryl or (C1-C13)-heteroaryl which is fully or partially substituted by identical or different substituents and has in each case at least one to

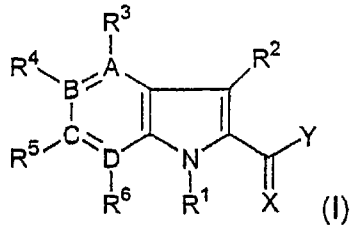
four N, NH, N-(C1-C6)-alkyl, O and/or S as ring members, or is unsubstituted (C3-C8)-cycloalkyl or (C3-C8)-cycloalkyl which is fully or partially substituted by identical or different substituents, where the identical or different substituents are selected independently of one another from the group consisting of halogen, preferably fluorine, chlorine, bromine or iodine; cyano; straight-chain or branched cyano-(C1-C6)-alkyl; hydroxyl; straight-chain or branched (C1-C6)-alkyl which is substituted by one or more hydroxyl groups; carboxyl; (C1-C6)-alkyl carboxylate; carboxamide; N-(C1-C6)-alkyl carboxamide, N,N-di-(C1-C4)-alkyl carboxamide, nitro, straight-chain or branched (C1-C6)-alkyl, straight-chain or branched (C1-C6)-alkyl which is substituted by one or more halogen atoms, preferably trifluoromethyl, straight-chain or branched (C1-C6)-alkoxy which is substituted by one or more halogen atoms, preferably trifluoromethoxy, straight-chain or branched (C2-C6)-alkenyl, straight-chain or branched (C2-C6)-alkynyl, (C3-C8)-cycloalkyl, straight-chain or branched (C1-C6)-alkoxy, preferably methoxy, straight-chain or branched (C1-C6)-alkylenedioxy, preferably methylenedioxy, thio (-SH), straight-chain or branched (C1-C6)-alkylthio, (C1-C6)-alkylsulfinyl, (C1-C6)-alkylsulfonyl, (C1-C6)-alkoxy-(C1-C6)-alkyl, amino, straight-chain or branched mono-(C1-C6)-alkylamino, straight-chain or branched N,N-di-(C1-C6)-alkylamino, where the two (C1-C6)-alkyl radicals together may form a ring, which may optionally contain one or more NH, N-(C1-C6)-alkyl, O and/or S, (C6-C14)-aryl, (C6-C14)-aryloxy, (C6-C14)-aryl-(C1-C6)-alkyl, (C6-C14)-aryl-(C1-C6)-alkoxy-(C1-C6)-alkyl, (C1-C6)-alkylcarbonyl, (C1-C6)-alkylcarbonyloxy, (C1-C6)-alkoxycarbonyl, (C1-C6)-alkoxycarbonyloxy, straight-chain or branched

mono- and N,N-di-(C1-C6)-alkylcarbonylamino, straight-chain or branched mono-N- and N,N-di-(C1-C6)-alkoxycarbonylamino, straight-chain or branched N-(C1-C6)-alkylcarbonyl-N-(C1-C6)-alkylamino, straight-chain or branched N-(C1-C6)-alkoxycarbonyl-N-(C1-C6)-alkylamino, formylamino, formyl, where two directly adjacent radicals may be attached to one another;

X is an oxygen or sulfur atom, is NH, or is a geminally (at the same C atom) substituted hydroxyl and hydrogen (-CH(OH)-);

their stereoisomers, their tautomers, and the pharmaceutically acceptable salts thereof, except for the racemic compounds according to formula I where R1 = R2 = R3 = R5 = R6 = hydrogen, X = oxygen or, if R4 = H, geminally substituted hyroxyl and hydrogen, Y = 3-carboxypyridin-4-yl and R4 = hydrogen or methoxy, and the compounds 2-cyclopropylcarbonylindole and 2-cyclohexylcarbonylindole, are provided.

A further embodiment of the invention provides compounds of the formula I



(I)

in which A, B, C, D, X, Y and R1 to R6 are as defined in claim 13, including the compounds of the formula I where R1 = R2 = R3 = R5 = R6 = hydrogen, X = oxygen or, if R4 = H, geminally substituted hyroxyl and hydrogen, Y = 3-carboxypyridin-4-yl and R4 = hydrogen or methoxy, and the compounds 2-cyclopropylcarbonylindole and

2-cyclohexylcarbonylindole for use as medicaments, in particular as antitumor agents.

A further embodiment of the invention provides compounds of the formula I, characterized in that R1-R6, A, B, C, D, X and Y are as defined in claim 11, with the proviso that at least one of the radicals R3-R6 is straight-chain or branched (C1-C6)alkoxy, preferably methoxy; straight-chain or branched (C1-C6)-alkyl, preferably methyl; straight-chain or branched (C1-C6)-alkylenedioxy, preferably methylenedioxy, hydroxyl; straight-chain or branched (C1-C6)-alkoxy substituted by one or more halogen atoms, preferably trifluoromethoxy; straight-chain or branched (C1-C6)-alkyl substituted by one or more halogen atoms, preferably trifluoromethyl.

A further embodiment of the invention provides compounds of the formula I, characterized in that that R1, R2, R3, R5, R6, A, B, C, D, X and Y are as defined above and the radical R4 is straight-chain or branched (C1-C6)-alkoxy, preferably methoxy; straight-chain or branched (C1-C6)-alkyl, preferably methyl; straight-chain or branched (C1-C6)-alkylenedioxy (where the second oxygen atom may either be the radical R4 or the radical R6), preferably methylenedioxy, hydroxyl; straight-chain or branched (C1-C6)-alkoxy substituted by one or more halogen atoms, preferably trifluoromethoxy; straight-chain or branched (C1-C6)-alkyl having one or more halogen atoms, preferably trifluoromethyl.

A further embodiment of the invention provides compounds of the formula I, characterized in that R1, R2, R3, R5, R6, A, B, C, D, X and Y are as defined above and the radical R4 is straight-chain or branched (C1-C6)-alkoxy, preferably methoxy.

A further embodiment of the invention provides

compounds of the formula I, characterized in that R1, R2, R3, R5, R6, A, B, C, D, X and Y are as defined above and the radical R4 is methoxy.

A further embodiment of the invention provides compounds of the formula I, characterized in that R1-R6, A, B, C, D and X are as defined above and the radical Y is substituted or unsubstituted (C6-C14)-aryl or is (C1-C13)-heteroaryl which contains at least one to four N, NH, O and/or S as ring member.

A further embodiment of the invention provides compounds of the formula I, characterized in that R1-R6, A, B, C, D and X are as defined above and the radical Y is (C6-C14)-aryl or is (C1-C13)-heteroaryl which contains at least one N, NH, O and/or S as ring member and which is unsubstituted or substituted by at least one radical selected from the group consisting of hydrogen, amino, halogen, nitro, cyano, straight-chain or branched (C1-C6)-alkoxy, preferably methoxy; straight-chain or branched (C1-C6)-alkyl, preferably methyl; hydroxyl; (C1-C6)-alkylcarbonyloxy, (C1-C6)-alkoxycarbonyloxy; straight-chain or branched (C1-C6)-alkoxy which is substituted by one or more halogen atoms, preferably trifluoromethoxy; straight-chain or branched (C1-C6)-alkyl which is substituted by one or more halogen atoms, preferably trifluoromethyl.

A further embodiment of the invention provides compounds of the formula I, characterized in that R1-R6, A, B, C, D and X are as defined above and the radical Y is a 1-phenyl radical which is unsubstituted or substituted by hydrogen, 3,4-dichloro, 2- or 3-methoxy, 2,4-dimethoxy, 3-nitro 3-trifluoromethyl, 2,3,4-trimethoxy, 3,4,5-trimethoxy.

A further aspect of the invention provides compounds of the formula I according to the invention for use as medicament.

A further aspect of the invention provides a process for preparing the compounds of the formula I according to the invention, characterized by the following steps:

a) lithiation of the corresponding 1-N-protected indole or heteroindole derivative and reaction with Z-CO-Y, where Z is a suitable leaving group, such as halogen, or H-CO-Y, giving the corresponding methanone derivative or the corresponding tertiary alcohol which is, if appropriate, oxidized to the methanone derivative,

b) if appropriate removal of the protective group and

c) if appropriate further reaction of the reactive radicals by procedures known per se.

A further aspect of the invention provides medicaments, comprising at least one compound of the formula I according to the invention, if appropriate together with customary pharmaceutical auxiliaries and/or excipients.

A further aspect of the invention provides antitumor agents, comprising an effective amount of at least one compound of the formula I according to the invention, if appropriate together with customary pharmaceutical auxiliaries and/or excipients.

A further aspect of the invention provides a process for preparing the medicaments according to the invention, characterized in that at least one compound of the formula I according to the invention is, if appropriate together with customary pharmaceutical auxiliaries and/or excipients, converted into a customary pharmaceutical presentation form.

A further aspect of the invention provides a process for preparing the antitumor agents according to the invention, characterized in that an effective amount of

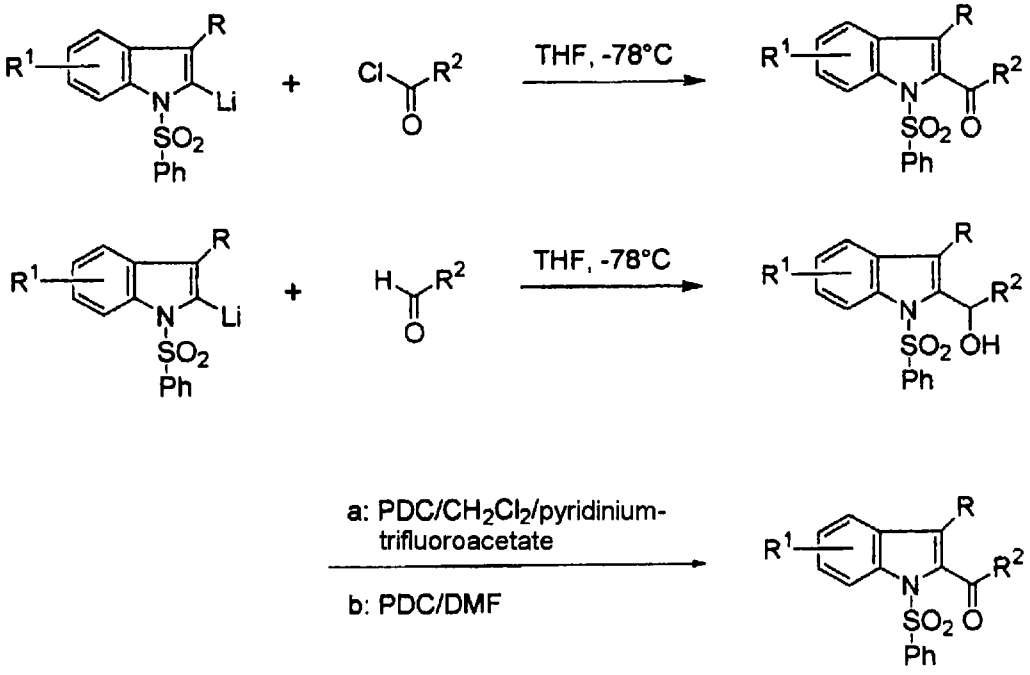
at least one compound of the formula I according to the invention is, if appropriate with customary pharmaceutical auxiliaries and/or excipients, converted into a customary pharmaceutical presentation form.

A further aspect of the invention provides medicaments according to the invention, characterized in that they can be administered orally, perorally or topically to a mammal.

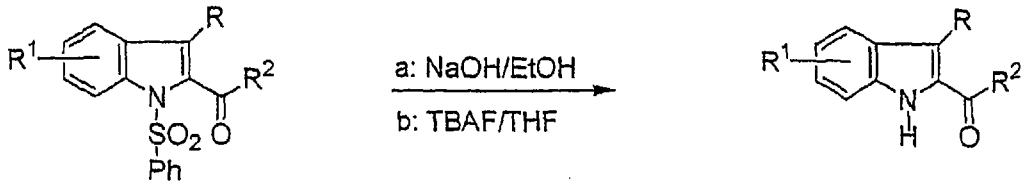
A further aspect of the invention provides antitumor agents according to the invention, characterized in that they can be administered orally, perorally or topically to a mammal.

The compounds according to the invention of the formula I can be prepared by processes known per se, for example by the following processes:

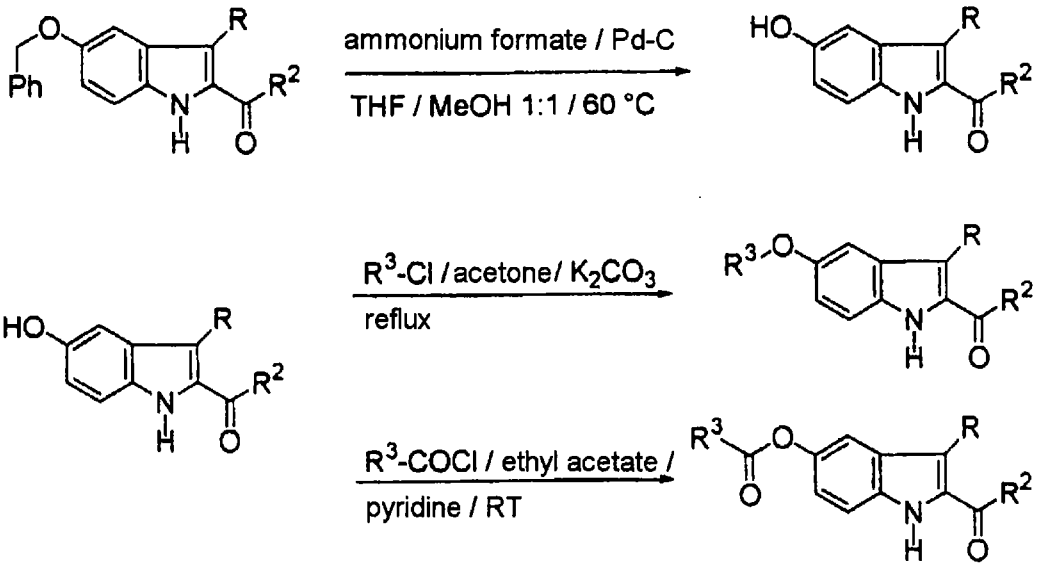
a) Lithiation of the indole derivatives and conversion into the corresponding methanones:



b) Removal of the phenylsulfonyl protective group:



c) Further reaction of the methanones for R^1 = 5-benzyloxy:



The compounds of the above formula I in which R1 is hydrogen or a phenylsulfonyl radical are useful intermediates for preparing the other compounds of the formula I.

The compounds used as starting materials, some of which are commercially available or known from the literature, are obtained by processes known from the literature; furthermore, their preparation is described in the examples. The processes known from the literature are described, for example, in L. and M. Fieser, *Organische Chemie* [Organic Chemistry], 2nd edition, 1979, pages 1417 to 1483 and in the literature cited therein on pages 1481-1483, in *Houben-Weyl-Müller*, Methoden der organischen Chemie [Methods of Organic Chemistry] and in *Ullmanns Encyklopädie der technischen Chemie* [Ullmann's Encyclopedia of Technical

Chemistry].

Furthermore, the resulting compounds of the formula I can be separated into their enantiomers and/or diastereomers. Thus, for example, the resulting compounds of the formula I which occur as racemates can be separated into their optical antipodes by methods known per se, and compounds of the formula I having at least two asymmetrically substituted carbon atoms can be separated owing to their physico-chemical differences by methods known per se, for example by chromatography and/or fractional crystallization, into their diastereomers which, if obtained in racemic form, can then be separated into the enantiomers as mentioned above.

Separation of enantiomers is preferably carried out by column chromatography on chiral phases or by recrystallization from an optically active solvent or by reaction with an optically active substance which forms salts or derivatives, such as, for example, esters or amides, with the racemic compound.

Furthermore, the resulting compounds of the formula I can be converted into their salts with inorganic or organic acids, in particular, for pharmaceutical use, into their pharmacologically and 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, tartaric acid or maleic acid.

Moreover, if they contain an acidic group, such as a carboxyl group, the compounds of the formula I can, if desired, be converted 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, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

As mentioned at the outset, the novel compounds of the formula I and their salts have useful properties. Thus, the compounds of the formula I according to the invention have, for example, useful pharmacological properties. In particular, the compounds of the formula I can be used as antitumor agents and for the chemotherapy of tumor patients. The compounds of the formula I inhibit cell division (anti-mitosis action) and thus tumor growth. In addition, the compounds according to the invention can inhibit tubulin polymerization indirectly or directly. Inhibition of cell division may be effected by stopping the cell cycle of the tumor cells, resulting in the death of the cells (apoptosis). The compounds of the formula I are furthermore suitable for preventing or reducing formation and proliferation of metastases in the body. Moreover, they have anti-angiogenic potential and may therefore be suitable for use as antitumor agents, by inhibiting tumor vascularization.

The examples below illustrate the invention without limiting it.

General procedure for preparing the 1-phenylsulfonyl-1*H*-2-indolylphenyl-1-methanols according to the invention

At -78°C, 9.9 ml (15.9 mmol) of n-butyllithium are added dropwise to 2.23 ml (15.9 mmol) of abs. diisopropylamine in 15 ml of abs. THF. The mixture is stirred at this temperature for 10 min and then warmed to 0°C and stirred for a further 30 min. A solution of the appropriate 1-phenylsulfonylindole (component A) (14.0 mmol) in 22 ml of abs. THF is added over a period of 10 min. The reaction mixture is stirred at 0°C for 30 min and then cooled to -78°C. The appropriate

aldehyde (component B) (15.4 mmol) is dissolved in 15 ml of abs. THF and added dropwise. After warming to room temperature (overnight), the mixture is poured into into 100 ml of 1% HCl. The organic phase is separated off and the aqueous phase is extracted three times with in each case 50 ml of ethyl acetrate. The combined organic phases are washed with 10% sodium bicarbonate solution and water and dried over sodium sulfate. The solvent is removed under reduced pressure and the crude product is then purified by column chromatography or recrystallized from ethanol.

Example 1:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: benzaldehyde
5-methoxy-1-phenylsulfonyl-1*H*-2-indolylphenyl-1-methanol
Mp.: 51-52°C

Example 2:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 2-methoxy-benzaldehyde
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(2-methoxyphenyl)-1-methanol
Mp.: 75-76°C

Example 3:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 3-methoxy-benzaldehyde
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(3-methoxyphenyl)-1-methanol
Mp.: 121-122°C

Example 4:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 4-methoxy-benzaldehyde
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(4-methoxyphenyl)-1-methanol
Mp.: 78-79°C

Example 5:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 2,4-dimethoxy-benzaldehyde
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(2,4-dimethoxyphenyl)-1-methanol
Mp.: 119-120°C

Example 6:
Component A: 1-phenylsulfonyl-1*H*-2-indole
Component B: 3-pyridinyl-carbaldehyde
1-phenylsulfonyl-1*H*-2-indolyl(3-pyridinyl)-1-methanol
Mp.: 146°C (decomp.)

Example 7:
Component A: 4-hydroxy(1-phenylsulfonyl-1*H*-2-indole)
Component B: 4-cyanobenzaldehyde
4-hydroxy(1-phenylsulfonyl-1*H*-2-indolyl)methyl-1-benzenecarbonitrile
Mp.: 150°C (decomp.)

Example 8:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 4-isoquinolinyl-carbaldehyde
4-isoquinolinyl(5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl)-1-methanol
Mp.: 138-139°C

Example 9:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 1-isoquinolinylcarbaldehyde
1-isoquinolinyl(5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl)-1-methanol
Mp.: 167-168°C

General procedure for preparing the 1-phenylsulfonyl-1*H*-2-indolylphenyl-1-methanones according to the invention

17.8 ml (28.6 mmol) of n-butyllithium are added dropwise to 4.01 ml (28.6 mmol) of abs. diisopropylamine in 30 ml of abs. THF. The mixture is stirred at this temperature for 10 min and then warmed to 0°C. A solution of the appropriate 1-phenylsulfonylindole (component A) (26.0 mmol) in 35 ml of abs. THF is added over a period of 10 min. The reaction mixture is stirred at 0°C for 60 min and then cooled to -78°C.

This mixture is added to a solution, precooled to -78°C, of the appropriate carbonyl chloride (component B) (30 mmol) in 40 ml of abs. THF. The mixture is stirred at this temperature for 60 min and then poured into 200 ml of 5% sodium bicarbonate solution and extracted with ethyl acetate. The organic phase is dried over sodium sulfate and the solvent is removed under reduced pressure. The residue is dissolved in ether and mixed with petroleum ether until crystallization sets in. The product is filtered off, washed with petroleum ether and dried.

Example 10:
Component A: 1-phenylsulfonyl-1*H*-2-indole
Component B: benzoyl chloride
1-phenylsulfonyl-1*H*-2-indolylphenyl-1-methanone
Mp.: 142-143°C

Example 11:
Component A: 1-phenylsulfonyl-1*H*-2-indole
Component B: 2-methoxy-benzoyl chloride
1-phenylsulfonyl-1*H*-2-indolyl(2-methoxyphenyl)-1-methanone
Mp.: 141-143°C

Example 12:
Component A: 1-phenylsulfonyl-1*H*-2-indole
Component B: 3-methoxy-benzoyl chloride
1-phenylsulfonyl-1*H*-2-indolyl(3-methoxyphenyl)-1-methanone
Mp.: 101-103°C

Example 13:
Component A: 1-phenylsulfonyl-1*H*-2-indole
Component B: 2,4-dimethoxy-benzoyl chloride
1-phenylsulfonyl-1*H*-2-indolyl(2,4-dimethoxyphenyl)-1-methanone
Mp.: 66-68°C

Example 14:
Component A: 1-phenylsulfonyl-1*H*-2-indole
Component B: 3,4,5-trimethoxy-benzoyl chloride
1-phenylsulfonyl-1*H*-2-indolyl(3,4,5-trimethoxyphenyl)-1-methanone
Mp.: 152-153°C

Example 15:
Component A: 3-methyl-1-phenylsulfonyl-1*H*-2-indole
Component B: 2-methoxy-benzoyl chloride
3-methyl-1-phenylsulfonyl-1*H*-2-indolyl(2-methoxyphenyl)-1-methanone
Mp.: 167-169°C

Example 16:
Component A: 3-methyl-1-phenylsulfonyl-1*H*-2-indole
Component B: 3-methoxy-benzoyl chloride
3-methyl-1-phenylsulfonyl-1*H*-2-indolyl(3-methoxyphenyl)-1-methanone
Mp.: 113°C

Example 17:
Component A: 3-methyl-1-phenylsulfonyl-1*H*-2-indole
Component B: 2,4-dimethoxy-benzoyl chloride
3-methyl-1-phenylsulfonyl-1*H*-2-indolyl(2,4-

dimethoxyphenyl)-1-methanone
Mp.: 155-157°C

Example 18:
Component A: 3-methyl-1-phenylsulfonyl-1*H*-2-indole
Component B: 3,4,5-trimethoxy-benzoyl chloride
3-methyl-1-phenylsulfonyl-1*H*-2-indolyl(3,4,5-trimethoxyphenyl)-1-methanone

Example 19:
Component A: 5-methyl-1-phenylsulfonyl-1*H*-2-indole
Component B: 2-methoxy-benzoyl chloride
5-methyl-1-phenylsulfonyl-1*H*-2-indolyl(2-methoxyphenyl)-1-methanone
Mp.: 157-158°C

Example 20:
Component A: 5-methyl-1-phenylsulfonyl-1*H*-2-indole
Component B: 3-methoxy-benzoyl chloride
5-methyl-1-phenylsulfonyl-1*H*-2-indolyl(3-methoxyphenyl)-1-methanone
Mp.: 124-127°C

Example 21:
Component A: 5-methyl-1-phenylsulfonyl-1*H*-2-indole
Component B: 2,4-dimethoxy-benzoyl chloride
5-methyl-1-phenylsulfonyl-1*H*-2-indolyl(2,4-dimethoxyphenyl)-1-methanone

Example 22:
Component A: 5-methyl-1-phenylsulfonyl-1*H*-2-indole
Component B: 3,4,5-trimethoxy-benzoyl chloride
5-methyl-1-phenylsulfonyl-1*H*-2-indolyl(3,4,5-trimethoxyphenyl)-1-methanone

Example 23:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolylphenyl-1-

methanone
Mp.: 148°C

Example 24:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 2-methoxy-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(2-methoxy-phenyl)-1-methanone
Mp.: 179°C

Example 25:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 3-methoxy-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(3-methoxy-phenyl)-1-methanone
Mp.: 181°C

Example 26:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 4-methoxy-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(4-methoxy-phenyl)-1-methanone
Mp.: 129-130°C

Example 27:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 2,4-dimethoxy-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(2,4-dimethoxy-phenyl)-1-methanone
Mp.: 62-64°C

Example 27A:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 3,4-dimethoxybenzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(3,4-dimethoxyphenyl)-1-methanone
Mp.: 75°C (Decomp.)

Example 27B:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 3,5-dimethoxybenzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(3,5-dimethoxyphenyl)-1-methanone
Mp.: 122-123°C

Example 28:
Component A: 1-phenylsulfonyl-1*H*-2-indole
Component B: 3-pyridinyl-carbonyl chloride
1-phenylsulfonyl-1*H*-2-indolyl(3-pyridinyl)-1-methanone
Mp.: 124-125°C

Example 29:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 2-pyridinyl-carbonyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(2-pyridinyl)-1-methanone
Mp.: 207°C

Example 30:
Component A: 4-(1-phenylsulfonyl-1*H*-2-indole
Component B: 4-cyano-benzoyl chloride
4-(1-phenylsulfonyl-1*H*-2-indolylcarbonyl)-1-benzol-carbonitrile
Mp.: 175-177°C

Example 31:
Component A: 2-fluorophenyl(5-methoxy-1-phenylsulfonyl-1*H*-2-indole)
Component B: 2-fluoro-benzoyl chloride
2-fluorophenyl(5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl)-1-methanone
Mp.: 199-205°C

Example 32:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 2,6-difluoro-benzoyl chloride
2,6-difluorophenyl(5-methoxy-1-phenylsulfonyl-1*H*-2-

indolyl)-1-methanone
Mp.: 124°C

Example 33:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 2-methyl-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(2-methylphenyl)-1-methanone
Mp.: 149-153°C

Example 34:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 3-trifluoromethylphenyl-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(3-trifluoromethylphenyl)-1-methanone
Mp.: 175-177°C

Example 35:
Component A: 4-fluorophenyl(5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 4-fluoro-benzoyl chloride
4-fluorophenyl(5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl)-1-methanone
Mp.: 123-128°C

Example 36:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 3,4-dichloro-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(3,4-dichlorophenyl)-1-methanone
Mp.: 141-144°C

Example 37:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 4-chloro-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(4-chlorophenyl)-1-methanone
Mp.: 146-148°C

Example 38:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 4-bromo-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(4-bromophenyl)-1-methanone
Mp.: 145-148°C

Example 39:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 3,4,5-trimethoxy-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(3,4,5-trimethoxyphenyl)-1-methanone
Mp.: 140-142°C

Example 40:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 4-pentyloxy-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(4-pentyloxyphenyl)-1-methanone
Mp.: 118-120°C

Example 41:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 1-naphthyl-carbonyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(1-naphthalenyl)-1-methanone
Mp.: 225-228°C

Example 42:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 4-tert-buty-benzoyl chloride
4-*tert*-butylphenyl(5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl-1-methanone)
Mp.: 161-163°C

Example 43:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 2,3-dimethoxy-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(2,3-

dimethoxyphenyl)-1-methanone
Mp.: 128°C

Example 44:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 2,3,4-trimethoxy-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(2,3,4-trimethoxyphenyl)-1-methanone
Mp.: 57-59°C

Example 45:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 4-methyl-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(4-methylphenyl)-1-methanone
Mp.: 126-127°C

Example 46:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 4-ethyl-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(4-ethylphenyl)-1-methanone
Mp.: 107-108°C

Example 47:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 4-propyl-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(4-propylphenyl)-1-methanone
Mp.: 112-114°C

Example 48:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 2-chloro-6-fluoro-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(2-chloro-6-fluorophenyl)-1-methanone
Mp.: 130°C

Example 49:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 2,5-dimethyl-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(2,5-dimethylphenyl)-1-methanone
Mp.: 164°C

Example 50:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 2-nitro-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(2-nitrophenyl)-1-methanone
Mp.: 190-191°C

Example 51:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 2-amino-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(2-aminophenyl)-1-methanone

Example 52:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 3-nitro-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(3-nitrophenyl)-1-methanone
Mp.: 228-230°C

Example 53:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 3-amino-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(3-aminophenyl)-1-methanone
Mp.: 188-189°C

Example 54:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 4-nitro-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(4-nitrophenyl)-

1-methanone
Mp.: 161-162°C

Example 55:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 4-amino-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(4-aminophenyl)-1-methanone

Example 56:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 3-methoxy-2-nitro-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(3-methoxy-2-nitrophenyl)-1-methanone
Mp.: 180°C

Example 57:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 2-amino-3-methoxy-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(2-amino-3-methoxyphenyl)-1-methanone

Example 58:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 2-methyl-3-nitro-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(2-methyl-3-nitrophenyl)-1-methanone
Mp.: 210-211°C

Example 59:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 3-amino-2-methyl-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(3-amino-2-methylphenyl)-1-methanone
Mp.: 206-207°C

Example 60:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: cyclopropylcarbonyl chloride

Cyclopropyl(5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl)-1-methanone
Mp.: 118-120°C

Example 61:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: cyclobutylcarbonyl chloride
Cyclobutyl(5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl)-1-methanone
Mp.: 146-147°C

Example 62:
Component A: 5-benzyloxy-1-phenylsulfonyl-1*H*-2-indole
Component B: benzoyl chloride
5-benzyloxy-1-phenylsulfonyl-1*H*-2-indolylphenyl-1-methanone
Mp.: 205-207°C

Example 63:
Component A: 5-benzyloxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 3-chloro-benzoyl chloride
5-benzyloxy-1-phenylsulfonyl-1*H*-2-indolyl(3-chlorophenyl)-1-methanone
Mp.: 150-152°C

Example 64:
Component A: 5-benzyloxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 4-chloro-benzoyl chloride
5-benzyloxy-1-phenylsulfonyl-1*H*-2-indolyl(4-chlorophenyl)-1-methanone
Mp.: 63-65°C

Example 65:
Component A: 5-benzyloxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 4-methoxy-benzoyl chloride
5-benzyloxy-1-phenylsulfonyl-1*H*-2-indolyl(4-methoxyphenyl)-1-methanone
Mp.: 70-72°C

Example 66:
Component A: 5-benzyloxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 3,4,5-trimethoxy-benzoyl chloride
5-benzyloxy-1-phenylsulfonyl-1*H*-2-indolyl(3,4,5-trimethoxyphenyl)-1-methanone
Mp.: 150-152°C

Example 67:
Component A: 5-benzyloxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 2-methoxy-benzoyl chloride
5-benzyloxy-1-phenylsulfonyl-1*H*-2-indolyl(2-methoxyphenyl)-1-methanone
Mp.: 115-116°C

Example 68:
Component A: 5-benzyloxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 3-methoxy-benzoyl chloride
5-benzyloxy-1-phenylsulfonyl-1*H*-2-indolyl(3-methoxyphenyl)-1-methanone
Mp.: 129-131°C

Example 69:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 4-isoquinolyl-carbonyl chloride
4-isoquinolyl(5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl)-1-methanone
Mp.: 189-190°C

Example 70:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-2-indole
Component B: 1-isoquinolyl-carbonyl chloride
1-isoquinolyl(5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl)-1-methanone
Mp.: 200°C

Example 71:
Component A: 1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine
Component B: 2-methoxy-benzoyl chloride

1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl(2-methoxyphenyl)-1-methanone
Mp.: 124-125°C

Example 72:
Component A: 1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine
Component B: 3-methoxy-benzoyl chloride
1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl(3-methoxyphenyl)-1-methanone
Mp.: 139-140°C

Example 73:
Component A: 1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine
Component B: 3,4,5-trimethoxy-benzoyl chloride
1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl(3,4,5-trimethoxyphenyl)-1-methanone
Mp.: 180-181°C

Example 74:
Component A: 1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine
Component B: 2,4-dimethoxy-benzoyl chloride
1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl(2,4-dimethoxyphenyl)-1-methanone
Mp.: 190-195°C (decomp.) °C

Example 75:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine
Component B: 2-methoxy-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl(2-methoxyphenyl)-1-methanone

Example 76:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine
Component B: 3-methoxy-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl(3-methoxyphenyl)-1-methanone

Example 77:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine
Component B: 3,4,5-trimethoxy-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl(3,4,5-trimethoxyphenyl)-1-methanone

Example 78:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine
Component B: 2,4-dimethoxy-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl(2,4-dimethoxyphenyl)-1-methanone

Example 79:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-pyrrolo[3,2-*b*]pyridine
Component B: benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-pyrrolo[3,2-*b*]pyridin-2-ylphenyl-1-methanone

Example 80:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-pyrrolo[3,2-*b*]pyridine
Component B: 2-methoxy-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl(2-methoxyphenyl)-1-methanone

Example 81:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*c*]pyridine
Component B: 3-methoxy-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl(3-methoxyphenyl)-1-methanone

Example 82:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*c*]pyridine
Component B: 2,4-dimethoxy-benzoyl chloride

5-methoxy-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl(2,4-dimethoxyphenyl)-1-methanone

Example 83:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*c*]pyridine
Component B: 3,4,5-trimethoxy-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl(3,4,5-trimethoxyphenyl)-1-methanone

Example 84:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine
Component B: 2-methoxy-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl(2-methoxyphenyl-1-methanones
Mp.: 197-198°C

Example 85:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-pyrrolo[3,2-*b*]pyridine
Component B: 3-methoxy-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl(3-methoxyphenyl-1-methanones
Mp.: 147-149°C

Example 86:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-pyrrolo[3,2-*b*]pyridine
Component B: 2,4-dimethoxy-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl(2,4-dimethoxyphenyl-1-methanones
Mp.: 132°C

Example 87:
Component A: 5-methoxy-1-phenylsulfonyl-1*H*-pyrrolo[3,2-*b*]pyridine
Component B: 3,4,5-trimethoxy-benzoyl chloride
5-methoxy-1-phenylsulfonyl-1*H*-pyrrolo[3,2-*b*]pyridin-2-

yl(3,4,5-trimethoxyphenyl-1-methanones
Mp.: 190-191°C

General procedures for preparing the 1*H*-2-indolylphenyl-1-methanones according to the invention

Method A: The appropriate N-protected methanone derivative (starting component) (1.8 mmol) is, in a mixture of 10% sodium hydroxide (20 ml) and ethanol (40 ml), heated at reflux for 2 to 15 hours (TLC). The solution is cooled to room temperature and then poured into 100 ml of water and extracted with ethyl acetate. The organic phase is dried over sodium sulfate and the solvent is removed. The crude product is recrystallized from ethyl acetate.

Method B: A mixture of the appropriate N-protected methanone derivative (starting component) (1.8 mmol) and 0.79 g (2.5 mmol) of tetrabutylammonium fluoride trihydrate in 20 ml of THF/methanol 1:1 is heated at reflux. After the reaction has ended (30 min - 4 hours, TLC), the mixture is cooled and poured into 100 ml of water. The mixture is extracted with ethyl acetate and the organic phase is dried over sodium sulfate. The solvent is concentrated slowly until the product begins to crystallize out.

Example 88:
Starting component: compound according to Example 10
Method A or B
1*H*-2-indolylphenyl-1-methanone
Mp.: 145-147°C

Example 89:
Starting component: compound according to Example 11
Method A or B
1*H*-2-indolyl(2-methoxyphenyl)-1-methanone
Mp.: 129-130°C

Example 90:
Starting component: compound according to Example 12
Method A or B
1*H*-2-indolyl(3-methoxyphenyl)-1-methanone
Mp.: 124-126°C

Example 91:
Starting component: compound according to Example 13
Method A or B
1*H*-2-indolyl(2,4-dimethoxyphenyl)-1-methanone
Mp.: 134-135°C

Example 92:
Starting component: compound according to Example 14
Method A or B
1*H*-2-indolyl(3,4,5-trimethoxyphenyl)-1-methanone
Mp.: 148-150°C

Example 93:
Starting component: compound according to Example 15
Method A or B
3-methyl-1*H*-2-indolyl(2-methoxyphenyl)-1-methanone
Mp.: 152-153°C

Example 94:
Starting component: compound according to Example 16
Method A or B
3-methyl-1*H*-2-indolyl(3-methoxyphenyl)-1-methanone
Mp.: 131°C

Example 95:
Starting component: compound according to Example 17
Method A or B
3-methyl-1*H*-2-indolyl(2,4-dimethoxyphenyl)-1-methanone
Mp.: 124-126°C

Example 96:
Starting component: compound according to Example 18
Method A or B

3-methyl-1*H*-2-indolyl(3,4,5-trimethoxyphenyl)-1-methanone
Mp.: 138-144°C

Example 97:
Starting component: compound according to Example 19
Method A or B
5-methyl-1*H*-2-indolyl(2-methoxyphenyl)-1-methanone
Mp.: 165-167°C

Example 98:
Starting component: compound according to Example 20
Method A or B
5-methyl-1*H*-2-indolyl(3-methoxyphenyl)-1-methanone
Mp.: 192-202°C

Example 99:
Starting component: compound according to Example 21
Method A or B
5-methyl-1*H*-2-indolyl(2,4-dimethoxyphenyl)-1-methanone

Example 99A:
Starting component: compound according to Example XX
Method A or B
5-methyl-1*H*-2-indolyl(3,4-dimethoxyphenyl)-1-methanone
Mp.: 187°C

Example 99B:
Starting component: compound according to Example YY
Method A or B
5-methyl-1*H*-2-indolyl(3,5-dimethoxyphenyl)-1-methanone
Mp.: 141-142°C

Example 100:
Starting component: compound according to Example 22
Method A or B
5-methyl-1*H*-2-indolyl(3,4,5-trimethoxyphenyl)-1-methanone
Mp.: 202-203°C

Example 101:
Starting component: compound according to Example 23
Method A or B
5-methoxy-1*H*-2-indolylphenyl-1-methanone
Mp.: 162°C

Example 102:
Starting component: compound according to Example 24
Method A or B
5-methoxy-1*H*-2-indolyl(2-methoxyphenyl)-1-methanone
Mp.: 127°C

Example 103:
Starting component: compound according to Example 25
Method A or B
5-methoxy-1*H*-2-indolyl(3-methoxyphenyl)-1-methanone
Mp.: 147-148°C

Example 104:
Starting component: compound according to Example 26
Method A or B
5-methoxy-1*H*-2-indolyl(4-methoxyphenyl)-1-methanone
Mp.: 165°C

Example 105:
Starting component: compound according to Example 27
Method A or B
5-methoxy-1*H*-2-indolyl(2,4-dimethoxyphenyl)-1-methanone
Mp.: 160-161°C

Example 106:
Starting component: compound according to Example 29
Method A or B
5-methoxy-1*H*-2-indolyl(2-pyridinyl)-1-methanone
Mp.: 201°C

Example 107:
Starting component: compound according to Example 30 (?)

Method A or B
4-(1*H*-2-indolylcarbonyl)-1-benzenecarboxylic acid
Mp.: > 220°C

Example 108:
Starting component: compound according to Example 31
Method A or B
2-fluorophenyl(5-methoxy-1*H*-2-indolyl)-1-methanone
Mp.: 145°C

Example 109:
Starting component: compound according to Example (?)
Method A or B
5-methoxy-1-phenylsulfonyl-1*H*-2-indolyl(3-trifluoromethylphenyl)-1-methanone
Mp.: 165°C

Example 110:
Starting component: compound according to Example 33
Method A or B
5-methoxy-1*H*-2-indolyl(2-methylphenyl)-1-methanone
Mp.: 120°C

Example 111:
Starting component: compound according to Example 34
Method A or B
5-methoxy-1*H*-2-indolyl(3-trifluoromethylphenyl)-1-methanone
Mp.: 193-195°C

Example 112:
Starting component: compound according to Example 35
Method A or B
4-fluorophenyl(5-methoxy-1*H*-2-indolyl)-1-methanone
Mp.: 168°C

Example 113:
Starting component: compound according to Example 36
Method A or B

5-methoxy-1*H*-2-indolyl(3,4-dichlorophenyl)-1-methanone
Mp.: 190-192°C

Example 114:
Starting component: compound according to Example 37
Method A or B
5-methoxy-1*H*-2-indolyl(4-chlorophenyl)-1-methanone
Mp.: 191-193°C

Example 115:
Starting component: compound according to Example 38
Method A or B
5-methoxy-1*H*-2-indolyl(4-bromophenyl)-1-methanone
Mp.: 188-190°C

Example 116:
Starting component: compound according to Example 39
Method A or B
5-methoxy-1*H*-2-indolyl(3,4,5-trimethoxyphenyl)-1-methanone
Mp.: 210-211°C

Example 117:
Starting component: compound according to Example 40
Method A or B
5-methoxy-1*H*-2-indolyl(4-pentyloxyphenyl)-1-methanone
Mp.: 139-141°C

Example 118:
Starting component: compound according to Example 41
Method A or B
5-methoxy-1*H*-2-indolyl(1-naphthalenyl)-1-methanone
Mp.: 174-175°C

Example 119:
Starting component: compound according to Example 42
Method A or B
4-*tert*-butylphenyl(5-methoxy-1*H*-2-indolyl-1-methanone)
Mp.: 204-207°C

Example 120:
Starting component: compound according to Example 43
Method A or B
5-methoxy-1*H*-2-indolyl(2,3-dimethoxyphenyl)-1-methanone

Example 121:
Starting component: compound according to Example 44
Method A or B
5-methoxy-1*H*-2-indolyl(2,3,4-trimethoxyphenyl)-1-methanone
Mp.: 156°C

Example 122:
Starting component: compound according to Example 45
Method A or B
5-methoxy-1*H*-2-indolyl(4-methylphenyl)-1-methanone
Mp.: 200°C

Example 123:
Starting component: compound according to Example 46
Method A or B
5-methoxy-1*H*-2-indolyl(4-ethylphenyl)-1-methanone
Mp.: 154-155°C

Example 124:
Starting component: compound according to Example 47
Method A or B
5-methoxy-1*H*-2-indolyl(4-propylphenyl)-1-methanone
Mp.: 145-146°C

Example 125:
Starting component: compound according to Example 48
Method A or B
5-methoxy-1*H*-2-indolyl(2-chloro-6-fluorophenyl)-1-methanone
Mp.: 168-170°C

Example 126:
Starting component: compound according to Example 49
Method A or B
5-methoxy-1*H*-2-indolyl(2,5-dimethylphenyl)-1-methanone
Mp.: 152-153°C

Example 127:
Starting component: compound according to Example 50
Method A or B
5-methoxy-1*H*-2-indolyl(2-nitrophenyl)-1-methanone
Mp.: 185-187°C

Example 128:
Starting component: compound according to Example 51
Method A or B
5-methoxy-1*H*-2-indolyl(2-aminophenyl)-1-methanone
Mp.: 144-145°C

Example 129:
Starting component: compound according to Example 52
Method A or B
5-methoxy-1*H*-2-indolyl(3-nitrophenyl)-1-methanone
Mp.: 221-222°C

Example 130:
Starting component: compound according to Example 53
Method A or B
5-methoxy-1*H*-2-indolyl(3-aminophenyl)-1-methanone

Example 131:
Starting component: compound according to Example 54
Method A or B
5-methoxy-1*H*-2-indolyl(4-nitrophenyl)-1-methanone

Example 132:
Starting component: compound according to Example 55
Method A or B
5-methoxy-1*H*-2-indolyl(4-aminophenyl)-1-methanone

Example 133:
Starting component: compound according to Example 56
Method A or B
5-methoxy-1*H*-2-indolyl(3-methoxy-2-nitrophenyl)-1-methanone
Mp.: 212°C (decomp.)

Example 134:
Starting component: compound according to Example 57
Method A or B
5-methoxy-1*H*-2-indolyl(2-amino-3-methoxyphenyl)-1-methanone

Example 135:
Starting component: compound according to Example 58
Method A or B
5-methoxy-1*H*-2-indolyl(2-methyl-3-nitrophenyl)-1-methanone
Mp.: 199-200°C

Example 136:
Starting component: compound according to Example 59
Method A or B
5-methoxy-1*H*-2-indolyl(3-amino-2-methylphenyl)-1-methanone
Mp.: 163-165°C

Example 137:
Starting component: compound according to Example 60
Method A or B
cyclopropyl(5-methoxy-1*H*-2-indolyl)-1-methanone
Mp.: 205-207°C

Example 138:
Starting component: compound according to Example 61
Method A or B
cyclobutyl(5-methoxy-1*H*-2-indolyl)-1-methanone
Mp.: 175-179°C

Example 139:
Starting component: compound according to Example 62
Method A or B
5-benzyloxy-1*H*-2-indolylphenyl-1-methanone
Mp.: 187-188°C

Example 140:
Starting component: compound according to Example 63
Method A or B
5-benzyloxy-1*H*-2-indolyl(3-chlorophenyl)-1-methanone
Mp.: 163-165°C

Example 141:
Starting component: compound according to Example 64
Method A or B
5-benzyloxy-1*H*-2-indolyl(4-chlorophenyl)-1-methanone
Mp.: 188-190°C

Example 142:
Starting component: compound according to Example 65
Method A or B
5-benzyloxy-1*H*-2-indolyl(4-methoxyphenyl)-1-methanone
Mp.: 155-157°C

Example 143:
Starting component: compound according to Example 66
Method A or B
5-benzyloxy-1*H*-2-indolyl(3,4,5-trimethoxyphenyl)-1-methanone
Mp.: 165-167°C

Example 144:
Starting component: compound according to Example 67
Method A or B
5-benzyloxy-1*H*-2-indolyl-(2-methoxyphenyl)-1-methanone
Mp.: 150-151°C

Example 145:
Starting component: compound according to Example 68

Method A or B
5-benzyloxy-1*H*-2-indolyl-(3-methoxyphenyl)-1-methanone
Mp.: 153-154°C

Example 146:
Starting component: compound according to Example 69
Method A or B
4-isoquinolinyl(5-methoxy-1*H*-2-indolyl)-1-methanone
Mp.: 228-230°C

Example 147:
Starting component: compound according to Example 70
Method A or B
1-isoquinolinyl(5-methoxy-1*H*-2-indolyl)-1-methanone
Mp.: 175°C

Example 148:
Starting component: compound according to Example 71
Method A or B
1*H*-pyrrolo[2,3-*b*]pyridin-2-yl(2-methoxyphenyl)-1-methanone
Mp.: 211-213°C

Example 149:
Starting component: compound according to Example 72
Method A or B
1*H*-pyrrolo[2,3-*b*]pyridin-2-yl(3-methoxyphenyl)-1-methanone
Mp.: 166-168°C

Example 150:
Starting component: compound according to Example 73
Method A or B
1*H*-pyrrolo[2,3-*b*]pyridin-2-yl(3,4,5-trimethoxyphenyl)-1-methanone
Mp.: 205-206°C

Example 151:
Starting component: compound according to Example 74

Method A or B
1*H*-pyrrolo[2,3-*b*]pyridin-2-yl(2,4-dimethoxyphenyl)-1-methanone
Mp.: 208-210°C (decomp.)

Example 152:
Starting component: compound according to Example 75
Method A or B
5-methoxy-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl(2-methoxyphenyl)-1-methanone

Example 153:
Starting component: compound according to Example 76
Method A or B
5-methoxy-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl(3-methoxyphenyl)-1-methanone

Example 154:
Starting component: compound according to Example 77
Method A or B
5-methoxy-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl(3,4,5-trimethoxyphenyl)-1-methanone

Example 155:
Starting component: compound according to Example 78
Method A or B
5-methoxy-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl(2,4-dimethoxyphenyl)-1-methanone

Example 156:
Starting component: compound according to Example 79
Method A or B
5-methoxy-1*H*-pyrrolo[3,2-*b*]pyridin-2-ylphenyl-1-methanone

Example 157:
Starting component: compound according to Example 80
Method A or B
5-methoxy-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl(2-

methoxyphenyl)-1-methanone

Example 158:
Starting component: compound according to Example 81
Method A or B
5-methoxy-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl(3-methoxyphenyl)-1-methanone

Example 159:
Starting component: compound according to Example 82
Method A or B
5-methoxy-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl(2.4-dimethoxyphenyl)-1-methanone

Example 160:
Starting component: compound according to Example 83
Method A or B
5-methoxy-1*H*-pyrrolo[2,3-*c*]pyridin-2-yl(3,4,5-trimethoxyphenyl)-1-methanone

Example 161:
Starting component: compound according to Example 84
Method A or B
5-methoxy-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl(2-methoxyphenyl-1-methanone
Mp.: 190°C

Example 162:
Starting component: compound according to Example 85
Method A or B
5-methoxy-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl(3-methoxyphenyl-1-methanone
Mp.: 150°C

Example 163:
Starting component: compound according to Example 86
Method A or B
5-methoxy-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl(2,4-dimethoxyphenyl-1-methanone

Mp.: 100°C (decomp.)

Example 164:
Starting component: compound according to Example 87
Method A or B
5-methoxy-1*H*-pyrrolo[3,2-*b*]pyridin-2-yl(3,4,5-trimethoxyphenyl-1-methanone
Mp.: 233°C

Alternatively, the compounds according to the invention can also be prepared by reacting an N-protected substituted indole derivative with an appropriate nitrile compound according to the exemplary procedure below.

Example 147 (prepared by an alternative process):

Compound: 1-isoquinolinyl(5-methoxy-1*H*-2-indolyl)-1-methanone

n-Butyllithium (5.5 mmol, 1.6 M in hexane, from Aldrich) was added dropwise to a solution, cooled to -78°C, of 1-(tert-butyloxycarbonyl)-5-methoxyindole (5 mmol) in 10 ml of dry THF. After 30 minutes at -78°C, a solution of 1-cyanoisoquinoline (7.5 mmol) dissolved in 2 ml of THF, was slowly added dropwise. The mixture was allowed to warm slowly to room temperature overnight (16 hours). The dark-brown solution was admixed with 50 ml of a mixture of trifluoroacetic acid:dichloromethane = 4:1, stirred at room temperature for 90 minutes and extracted with 30 ml of dichloromethane, the organic phase was washed with water, saturated potassium carbonate solution and again water (20 ml each) and the solvent was removed under reduced pressure. The resulting brown oil was suspended in 10 ml of ethanol and poured into 300 ml of ice-water. The green-brown precipitate was isolated by filtration and purified by column chromatography under atmospheric pressure on silica gel 60 (mobile phase

diethyl ether:hexane = 1:1).
Yield: 160 mg (10%) yellow needles

General procedure for preparing N-oxides of the azaindoles and their derivatization

Preparation of the N-oxides:
At 0°C, 1.00 mmol of the pyridine derivative in 20 ml of dichloromethane are admixed with 2 mmol of meta-chloroperbenzoic acid. The mixture is allowed to warm to r.t. and stirred at this temperature for 24 h. 10 ml of conc. $NaHCO_3$ sltn are added, the organic phase is separated off and the aqueous phase is extracted 10 times with 25 ml of dichloromethane each. The combined org. phases are dried over $MgSO_4$ and the solvent is removed. The residue that remains is admixed with a little diethyl ether, giving the product as a powdery precipitate (yld: 65%).

Example 164:
Starting component: compound according to Example 150
1*H*-pyrrolo[2,3-*b*]pyridin-2-yl(3,4,5-trimethoxyphenyl)-1-methanone N-oxide
Mp.: 90-92°C

Reaction of the N-oxides with acetic anhydride:
0.5 mmol of the N-oxide are mixed with 15 ml of acetic anhydride. A drop of water is added, and the mixture is then refluxed for 12 h. Once all of the starting material has reacted according to TLC, the solvent is removed under reduced pressure and the residue is taken up in a little dichloromethane and washed with $NaHCO_3$ solution.

The solvent is removed and the residue is admixed with diethyl ether, giving the product as a powdery precipitate (60%)

Example 165:
Starting component: compound according to Example XXX
6-[2-(3,4,5-trimethoxybenzoyl)-1-acetyl-1*H*-pyrrolo[2,3*b*]pyridine]ethanoate
Mp.: 151-152°C

General procedure for preparing the N-substituted 1*H*-2-indolylphenyl-1-methanones according to the invention

A mixture of the appropriate 1*H*-2-indolylphenyl-1-methanone (starting material) (5.0 mol), the hydrochloride of the appropriate aminoalkyl chloride (15.0 mmol) and 40.0 mmol of potassium carbonate in 50 ml of abs. acetone is heated at reflux for 14 hours. After cooling, the reaction mixture is poured into 250 ml of water and extracted with dichloromethane. The organic phase is dried over sodium sulfate. The solvent is removed and the residue is then purified by column chromatography.

Example 166:
Starting material according to Example 101
5-methoxy-1-(2-dimethylaminoethyl)-1*H*-2-indolylphenyl-1-methanone
Mp.: 38-40°C

Example 167:
Starting material according to Example 101
5-methoxy-1-(3-dimethylaminopropyl)-1*H*-2-indolylphenyl-1-methanone
Mp.: 51-52°C

Example 168:
Starting material according to Example 101
5-methoxy-1-(2-pyrrolidinoethyl)-1*H*-2-indolylphenyl-1-methanone
Mp.: 68-71°C

Example 169:
Starting material according to Example 101
5-methoxy-1-(2-piperidinoethyl)-1*H*-2-indolylphenyl-1-methanone
Mp.: 55-57°C

Example 170:
Starting material according to Example 101
5-methoxy-1-(2-morpholinoethyl)-1*H*-2-indolylphenyl-1-methanone
Mp.: 66-68°C

Example 171:
Starting material according to Example 101
5-methoxy-1-(2-phenylmethyloxyethyl)-1*H*-2-indolylphenyl-1-methanone
Mp.: 95-97°C

Further examples are:

Example 172:
3-ethoxy-5-methoxy-1*H*-2-indolyl(2-nitrophenyl)-1-methanone

Example 173:
5-methoxy-1*H*-2-indolyl(2-thienyl)-1-methanone

Example 174:
5-methoxy-1*H*-2-indolyl(3-fluorophenyl)-1-methanone

Example 175:
5-methoxy-1*H*-2-indolyl(3-trifluoromethoxyphenyl)-1-methanone

Example 176:
5-methoxy-1*H*-2-indolyl(3-difluoromethylthiophenyl)-1-methanone

Example 177:

5-methoxy-1*H*-2-indolyl(3-hydroxyphenyl)-1-methanone

Example 178:

5-methoxy-1*H*-2-indolyl(3-butanoyloxyphenyl)-1-methanone

Results of the pharmacological tests

The in vitro test in selected tumor models revealed the pharmacological activities shown below.

Example 1: Antitumor action

The substances D-64131 (Ex. 101), D-68143 (Ex. 102), D-68144 (Ex. 103), D-68150 (Ex. 116) and D-68172 (Ex. 105) were tested for antiproliferative activity in a proliferation test on established tumor cell lines. In the test used, the cellular dehydrogenase activity is determined as a measure of cell vitality and, indirectly, cell numbers. The cell lines used were the human glioma cell lines A-172 (ATCC CRL-1620), U118 (ATCC HTB-15) and U373 (ATCC HTB-17), the rat glioma cell line C6 (ATCC CCL107) and the human cervical carcinoma cell line KB/HeLa (ATCC CCL17). These were very well characterized established cell lines which were obtained from ATCC and cultured.

The results summarized in Tab. 1 and Fig. 1 show a highly potent antitumor action of the substances mentioned. It has to be emphasized that the action is concentration-dependent, resulting in comparable maximum inhibitions. It was possible to determine defined activities: D-68144 > D-68150 ≥ D-64131 + D-68143 > D-68172 (increasing antitumor potency from D-68172 to D-68144). This order in the activity was observed in all cell lines examined and is to be judged as an indication for a defined molecular mechanism of action.

Table 1.

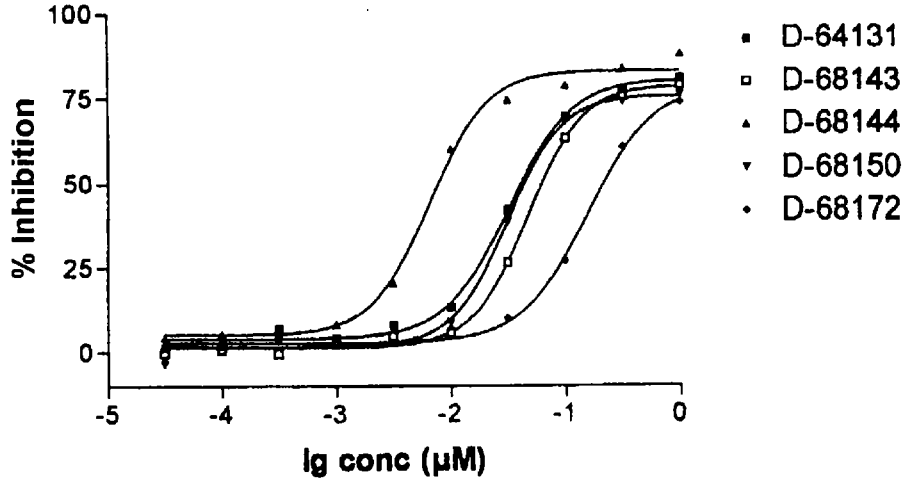
Antitumor potency of various derivatives in the XTT cytotoxicity test with the glioma cell lines C6, A-172, U118, U373 and the cervical carcinoma cell line HeLa/KB. What is stated is the IC_{50} from concentration/activity experiments in nM. If the

experiments were carried out more than once, the number of independent experiments is given in brackets.

Example	Code No.	C6	A-172	U118	U373	KB/HeLa
101	D-64131	96.5 (2)	51	24	22	24 (2)
102	D-68143	98 (2)	73	28	29	35 (2)
103	D-68144	9.6 (2)	15	8.3	5.0	6.6
116	D-68150	77	18.5 (2)	19.4	19.7	32
105	D-68172	180	330 (2)	119 (2)	75 (2)	107 (2)

Fig. 1

Graphic representation of the concentration-dependent antitumor activity of different derivatives in the XTT cytotoxicity test with the KB/HeLa cervical carcinoma cell line.

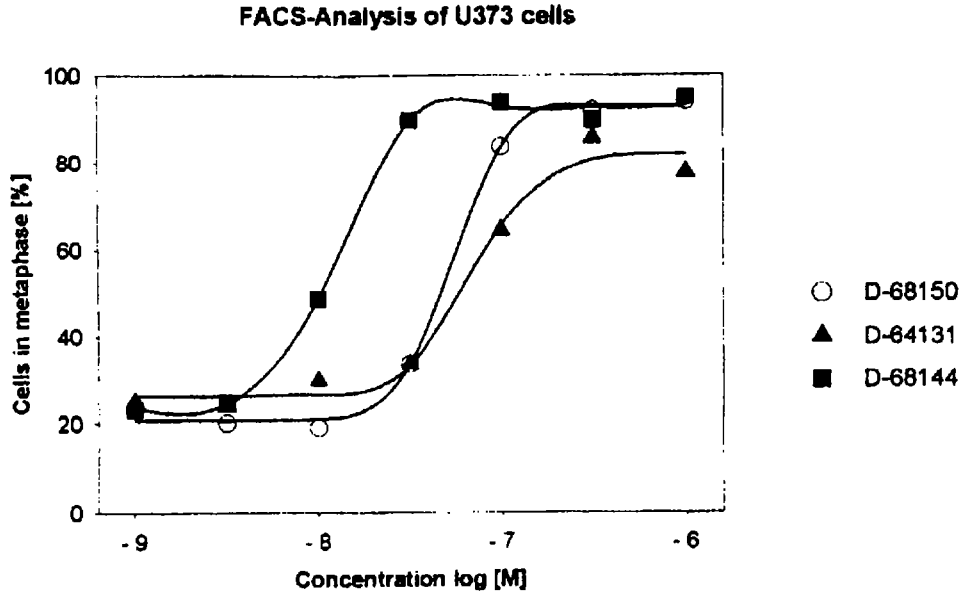


Example 2: Cell cycle analysis using fluorescence-activated cell sorting

The substances D-64131 (Ex. 101), D-68144 (Ex. 103) and D-68150 (Ex. 116) were examined further by fluorescence-activated cell sorting (FACS) using the human glioblastoma cell line U373. The chosen method allowed the detection of a cell-cycle-specific action of the substance. To this end, the proportion of cells in phases G1, S, G2 and M of the cell cycle was

determined by measuring the DNA content. The result of this analysis is summarized in Fig. 2. What is shown is the proportion of cells in the metaphase of mitotic division (M-phase of the cell cycle; 2N chromosomes). For all of the substances tested, a concentration-dependent arrest of the cells in mitosis, which correlates with the antiproliferative action shown in Table 1 and Fig. 1, is clearly detectable. Thus, the substances arrest growth by inhibiting cell division, which subequently results in the death of the tumor cells (apoptosis).

Fig. 2
Cell cycle analysis of substance-treated U373 glioma cells by FACS. What is shown is the percentage of cells having 2N chromosomes, i.e. cells in the metaphase of mitotic cell division, as a function of substance concentration.



Comparison of the biological activity of the compound D-68144 (Example 103) according to the invention with the compounds 1d/4d according to the publication by Medarde et al.

The publication by M. Medarde et al. 1998, Eur. J. Med.

Chem. Vol. 33, pp. 71-77 describes combretastatin analogs which have antitumor action in a proliferation assay with the tumor cell lines P388 (leukemia, murine), A549 (pulmonary carcinoma, human), HT29 (colon carcinoma, human) and Mel28 (melanoma, human). The test system used is comparable to the test system described above. The tumor cells mentioned are treated with the substances for 72 h, and the cell count is determined directly (P388) or indirectly via staining with Crystal Violet (Mel28, A549, HT29). In this test, the known compound 1-methyl-2-(3,4,5-trimethoxyphenyl)carbonylmethylindole (compound 4d) shows an inhibitory activity of IC_{50} = 0.3 to 0.6 µM and the known compound 1-methyl-3-(3-hydroxy-4-methoxyphenyl)carbonylmethylindole (compound 1d) shows an inhibitory activity of IC_{50} = 3.6 to 8.9 µM. In contrast, the compound D-68144 according to the invention shows an inhibitory activity in various glioma lines of IC_{50} = 0.005 to 0.015 µM. Surprisingly, the compound D-68144 according to the invention is, by a factor of 40-60, more active than the compound 4d described in the publication of Medarde et al.

Description of the methods used

XTT test for cellular dehydrogenase activity

The adherently growing tumor cell lines C6, A-172, U118, U373 and HeLa/KB 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 cells are detached using trypsine/EDTA and pelleted by centrifugation. The cell pellet is then resuspended in the respective culture medium at the appropriate cell count and transferred to a 96-well microtiter plate. The plates are then cultivated overnight in the incubator with gas inlet. The test substances are made up as 10 mM 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 and plotted semilogarithmically in the form of a concentration-activity curve. The IC_{50} is calculated from the concentration-activity curve by regression analysis using the program Graphpad.

Cell cycle analysis by FACS

U373 glioma cells in adherent subconfluent culture are treated with substance for 24 h and then detached and washed 1× with PBS. A total of 5×10^6 cells/data point are fixed in 1 ml of 80% methanol (-20°C), kept on ice for 30 min and stored at 4°C. For FACS analysis, the cells are incubated in PBS with 0.1% of saponin, 20 µg/ml of propidium iodide and 1 mg/ml of RNAse A at 37°C for 30 min. The cells are washed in PBS/saponin buffer and then analyzed in a Calibur flow cytometer (Becton Dickinson).

The in vitro tests in selected tumor models showed the following pharmacological activities:

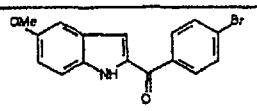
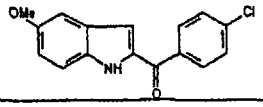
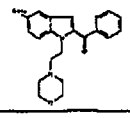
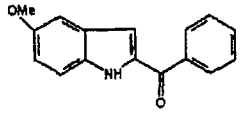
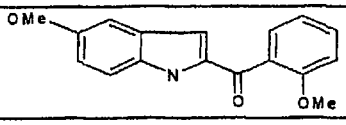
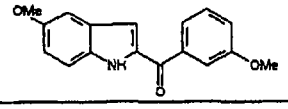
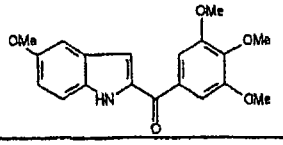
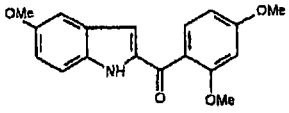
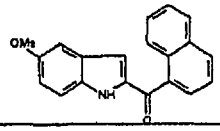
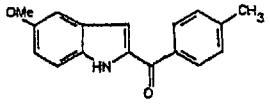
Example 3: Tubulin-inhibitory and cytotoxic activity of selected compounds

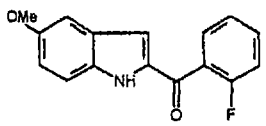
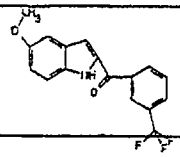
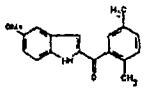
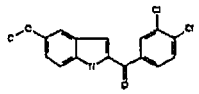
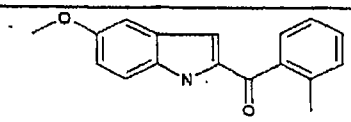
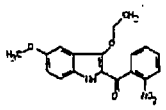
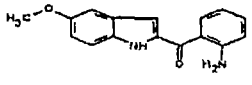
Selected compounds were tested in an in vitro test for inhibition of polymerization of bovine brain. In this test, tubulin purified by polymerization and depolymerization cycles was used and polymerized by addition of GTP and heating. The IC_{50} values of the inhibition of the polymerization of tubulin are stated in table 1. The known tubulin inhibitors vincristine and colchicine are included as reference substances. Highly potent inhibitors which are to be mentioned are, for example, D-70316 and D-81187 with IC_{50} values of 0.81 and 0.39 µM.

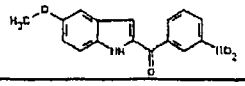
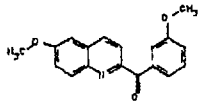
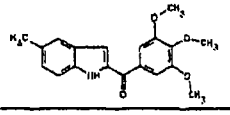
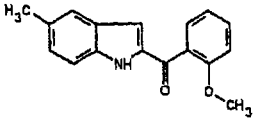
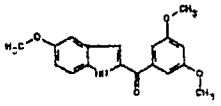
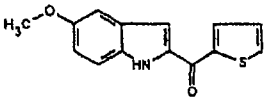
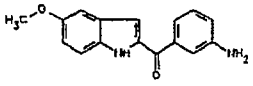
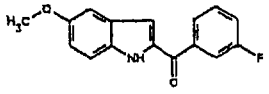
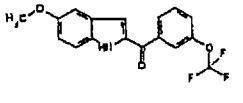
Table 1 furthermore states the cytotoxic or growth-inhibiting activities of the compounds which were tested using the human cervical carcinoma cell line HeLa/KB. Here, some of the compounds are found to be compounds with high cytotoxic activity. D-64131, D-68144, D-70316 and D-81187 may be mentioned by way of example.

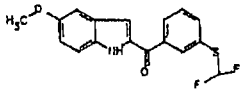
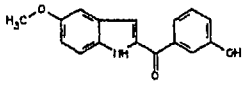
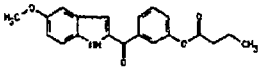
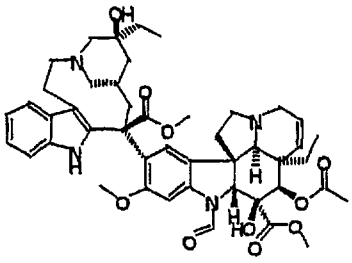
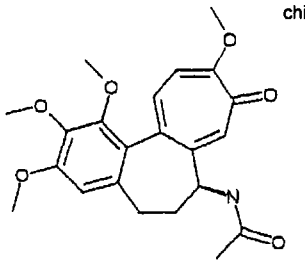
Table 1

Inhibition of tubulin polymerization and cytotoxic activity in the HeLa/KB cervical carcinoma cell line for selected compounds. The cytotoxicity or growth inhibition is stated as IC_{50} in the concentration µg/ml or nM.

Example	Structure	Tubulin inhibition/ IC50 [µM]	Cytotoxicity **KB/HeLa IC50 [µg/ml]**
D-65499 (Ex. 115)		4.3 (2)	~ 0.3
D-65500 (Ex. 114)		4.98 (2)	~ 1.0
D-65502 (Ex. 170)		5.58 (2)	~0.5
D-64131 (Ex. 101)		2.2	24nM (2)
D-68143 (Ex. 102)		2.12 (3)	35nM (2)
D-68144 (Ex. 103)		2.42 (2)	6.6nM
D-68150 (Ex. 116)		10 (1)	32nM
D-68172 (Ex. 105)		<10 (1)	107nM (2)
D-68213 (Ex. 118)		2.93(2)	~0.1
D-68887 (Ex. 122)		1.5 (2)	~0.3

D-68888 (Ex. 108)		1.03 (2)	~0.2
D-68901 (Ex. 111)		1.46(2)	~0.01
D-68906 (Ex. 126)		5.19 (2)	~0.2
D-70026 (Ex. 113)		2.49 (2)	~0.1
D-70038 (Ex. 110)		4.84 (2)	~0.5
D-70046 (Ex. 172)		2.44 (2)	~2
D-70047 (Ex. 128)		6.68 (2)	~2

D-70048 (Ex. 129)		0.85 (2)	~0.03
D-70261 (Ex. 103)		3.2 (2)	n.d.
D-70288 (Ex. 100)		0.86 (2)	~0.01
D-70289 (Ex. 97)		3.54 (2)	~0.1
D-70316 (Ex. 99B)		0.81 (2)	18.6nM (2)
D-70438 (Ex. 173)		2.7 (2)	n.d.
D-81167 (Ex. 130)		0.99 (2)	0.089
D-81187 (Ex. 174)		0.39 (2)	19.7nM (2)
D-81194 (Ex. 175)		1.74 (2)	0.086

D-81196 (Ex. 176)		2,05 (2)	0,134
D-81755 (Ex. 177)		0.66 (2)	0.063
D-81756 (Ex. 178)		0.85 (2)	0.093
vincristine		0.09 (3)	1.5nM (2)
cholchicine	 chiral	1.0 (2)	18.7nM (2)

Example 4 Cell-cycle-specific action in the RKOp21 model

The RKOp21 cell system (M. Schmidt et al. Oncogene 19(20):2423-9, 2000) was used as a model for examining the cell-cycle-specific action. RKO is a human colon carcinoma line in which the cell cycle inhibitor $p21^{waf1}$ is expressed, induced by the Ecdyson expression system, leading to a cell cycle arrest specifically in G1 and G2. An unspecifically acting substance inhibits proliferation independently of whether the RKO cell is arrested in G1 or G2 or not. In contrast, cell-cycle-specific substances, such as, for example, tubulin inhibitors, are only cytotoxic if the cells are not arrested and the cell cycle is progressing. Table 2 shows the cytotoxic and growth-inhibiting activity of selected compounds with/without expression of $p21^{waf1}$. When $p21^{waf1}$ was induced, all compounds tested showed low cytotoxic activity, if any at all. This underlines the fact, already determined in the FACS analyses, that the cell cycle is arrested in G2/M and that the action of the compounds examined is cell-cycle-specific.

Table 2
Cytotoxic activity of selected compounds in the RKO $p21^{waf1}$ cell system.

Substance	**RKO p21 induced**	**RKO p21 induced IC_{50} [nM]**
D-64131	n.c.	15 (1)
D-68143	n.c.	28 (1)
D-68144	n.c.	3.6 (1)
D-68150	n.c.	16.8 (1)
D-68172	n.c.	136 (1)
D-70316	n.c.	17.95 (2)
D-81187	n.c.	16.8 (2)
taxol	n.c.	0.0078 µg/ml

n.c. the IC_{50} could not be calculated

Example 5 Activity of D-64131 in human tumor xenograft experiments in nude mice

Subcutaneously transplanted tumor fragments of the human melanoma MEXF 989 or the rhabdomyosarcoma SXF 463 were used for the in vivo experiments on nude mice. D-64131 was administered orally in doses of 100 and 200 mg/kg (vehicle 10% DMSO in PBS/Tween 80 0.05%) for 2 weeks (5 applications per week; Monday to Friday). In experiments with the two tumors, D-64131 was found to be highly active. In the MEXF989 model, it was possible to obtain a growth inhibition of 81% (200 mg/kg/day) or 66% (100 mg/kg/day). In the SXF463 model, the higher dose of 200 mg/kg was found to effect 83% growth inhibition relative to the control. These results show, in addition to oral bioavailability and very good tolerance, potent antitumor activity in two human tumor xenograft models.

Description of the methods used.

Bovine tubulin polymerization assay

The tubulin used for the assay was isolated from bovine brain by polymerization and depolymerization cycles. 85 µl of a mix comprising 80 µl of PEM buffer pH 6.6 (0.1M pipes, 1 mM EGTA, 1 mM $MgSO_4$ p.H 6.6) and 5 µl of 20 mM GTP stock solution were initially charged per well into the MultiScreen-type filter plate (0.22 µM hydrophilic, low protein binding-Durapore Membrane, from Millipore). The appropriate amount of test substance, dissolved in 100% DMSO, is added using a pipette. This is followed by addition of 10 µl of purified bovine tubulin (50-60 µg of tubulin per well). At room temperature, the filter plate is shaken at 400 rpm for 20 min, and 50 µl/well of stain solution (45% MeOH, 10% acetic acid, 0.1% Naphthol Blue Black/Sigma) are then added using a pipette. After an incubation time of 2 minutes, the stain solution is

aspirated (Eppendorf Event 4160), and the well is then washed twice using a 90% methanol/2% acetic acid solution. 200 µl/well of decolorization solution (25 mM NaOH, 50% ethanol, 0.05 mM EDTA) are then added using a pipette. Following a 20 minute incubation at room temperature on a shaker (400 rpm), the samples are measured in a photometer at an absorption of 600 nM. What is calculated is the inhibition in percent, based on the 100% value of a positive control (without test substance), or, if a concentration activity curve is drawn, the IC_{50} value.

XTT test for cellular dehydrogenase activity

In addition to the tumor cell line HeLa/KB (see table 1), it is possible to use the cell lines C6, A-172, U118, U373, SKOV3 (ATCC HTB 77, human ovarian adenocarcinoma), SF268 (NCI 503138, human glioma), NCI460 (NCI 503473; human non-small-cell lung carcinoma), MCF-7 (ATCC HTB22; human mamma adenocarcinoma) and RKO (human colon adenocarcinoma) for the proliferation experiments.

Cell cycle analysis using the RKOp21 model

The assay is carried out in 96-well plates. Using inducible expression of $p21^{waf1}$, the growth of the cells is completely arrested, but the cells do not die. By comparing the effect on induced and non-induced cells, it is possible to draw conclusions with respect to the mechanism of action (cell cycle specificity) of the therapeutics. Non-induced cells are sown at a cell count which is about four times higher, since, in contrast to non-induced cells, there is no further division during the assay (2×10^4 cells/well induced, about 0.6×10^4 cells/well non-induced). The controls are untreated cells (+/- induction). Induction is carried out using 3 µM of muristerone A. On day 1, the cells are plated (+/- muristerone A) and incubated at 37°C for 24 h. On day 2, the test substance is added

(control DMSO) and incubation is continued at 37°C for a further 48 h, which is then followed by a standard XTT assay.

Oral bioavailability of D-64131:

Initially, D-64131 was examined in vitro for its antitumor activity using 12 permanent human tumor cell lines. The cell lines included intestinal (2), gastric (1), pulmonary (3), breast (2), melanoma (2), ovarial (1), kidney (1) and uterus (1) tumor cell lines. The average IC50 of D-64131 for all cell lines examined using a propidium-iodide-based cytotoxicity assay was 0.34 µM. Melanoma, intestinal and kidney tumor cells were most sensitive (IC50 = 4 nM). The IC50 for the pulmonary and gastric tumor cell lines examined was about 4 µM. Here, D-64131 acted as a cell-cycle-specific active compound via interaction with tubulin. D-64131 inhibited the polymerization of calf brain tubulin with an IC50 of 2.2 µM. The maximum tolerated dose for intraperitoneal (i.p.) injection in nude mice was 400 mg/kg for weekly administration. For peroral (p.o.) administration, 100 and 200 mg/kg of D-64131 were administered at a "Qdx5" dosage (1× per day for 5 successive days) for 2 weeks. Both p.o. dosages were tolerated very well, and no indications of toxicity or loss of body weight were found. The last dosage protocol was used to test the activity of D-64131 in the human melanoma xenograft model MEXF 989. Oral treatment with D-64131 resulted in an 81% inhibition of growth, compared to the control, at 200 mg/kg/d and to 66% inhibition of growth at 100 mg/kg/d. In the rhabdomyosarcoma xenograft model SXF 463, the inhihition of growth at 200 mg/kg/d was found to be 83%. The results confirm that the indole compounds according to the invention are potent cytotoxically active compounds acting in a cell-cycle-specific manner by interfering with the mitotic spindle apparatus. Also to be emphasized is the oral bioavailability of the

indole compounds according to the invention.

Based on the activity and compatibility found for the orally bioavailable low-molecular-weight tubulin inhibitor D-64131, this compound is a candidate for further phases I and II clinical trials.

Examples of pharmaceutical preparations of the indole compounds according to the invention and their preparation are shown below.

Example I

Tablet containing 50 mg of active compound

Composition:

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

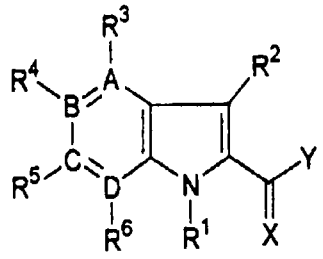
(1) Active compound	50.0 mg
(2) Corn starch, dried	58.0 mg
(3) Lactose powder	50.0 mg
(4) Magnesium stearate	2.0 mg
Sum:	160.0 mg

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 gelatin capsules size 3.

Patent claims:

1. Use of at least one compound of the formula I



(I)

in which

R1 is hydrogen, (C1-C6)-alkylcarbonyl, preferably acetyl, (C_1-C_6)-alkyl, mono-(C_1-C_6)-alkylamino-(C_1-C_4)-alkyl, di-(C_1-C_6)-alkylamino-(C_1-C_4)-alkyl, where the two (C_1-C_6)-alkyl radicals together may form a ring, which optionally contains one or more NH, N-(C1-C6)-alkyl, O or S members, (C6-C14)-aryl-(C1-C6)-alkyl or (C6-C14)-aryl-(C1-C6)-alkoxy-(C1-C6)-alkyl;

R2 is a hydrogen atom, halogen, cyano, nitro, (C1-C6)-alkyl, (C1-C6)-alkyl which is substituted by one or more halogen atoms, preferably trifluoromethyl, (C1-C6)-alkoxy which is substituted by one or more halogen atoms, preferably trifluoromethoxy, (C2-C6)-alkenyl, (C2-C6)-alkynyl, (C3-C8)-cycloalkyl, (C1-C6)-alkoxy, (C1-C6)-alkoxycarbonyloxy, (C1-C6)-alkylcarbonyloxy, (C1-C4)-alkylthio, (C1-C4)-alkylsulfinyl, (C1-C4)-alkylsulfonyl, (C1-C6)-alkoxy-(C1-C6)-alkyl, amino, mono-(C1-C6)-alkylamino, di-N,N-(C1-C6)-alkylamino, where the two (C1-C6)-alkyl radicals together may form a ring, which optionally contains one or more NH, N-(C1-C6)-alkyl, O or S, (C6-C14)-aryl, (C6-C14)-

aryloxy, (C6-C14)-aryl-(C1-C4)-alkyl, (C6-C14)-aryl-(C1-C4)-alkoxy-(C1-C4)-alkyl, (C1-C6)-alkylcarbonyl, (C1-C6)-alkoxycarbonyl or hydroxyl;

A, B, C and D independently of one another are a nitrogen atom (in which case R3, R4, R5 and R6 represent the free electron pair at the nitrogen atom) or are a carbon atom substituted by one of the radicals R3-R6;

R3, R4, R5 and R6 independently of one another are, when attached to nitrogen, a free electron pair, or, when attached to carbon, hydrogen, halogen, cyano, nitro, straight-chain or branched (C1-C6)-alkyl, straight-chain or branched (C1-C6)-alkyl which is substituted by one or more halogen atoms, preferably trifluoromethyl, straight-chain or branched (C1-C6)-alkoxy which is substituted by one or more halogen atoms, preferably trifluoromethoxy, (C2-C6)-alkenyl, (C2-C6)-alkynyl, (C3-C8)-cycloalkyl, straight-chain or branched (C1-C6)-alkoxy, preferably methoxy, straight-chain or branched (C1-C6)-alkylenedioxy, preferably methylenedioxy, (C1-C6)-alkoxycarbonyloxy, (C1-C6)-alkylcarbonyloxy, (C1-C4)-alkylthio, (C1-C4)-alkylsulfinyl, (C1-C4)-alkylsulfonyl, carboxyl, (C1-C6)-alkyl carboxylate, carboxamide, N-(C1-C4)-alkyl carboxamide, N,N-di-(C1-C4)-alkyl carboxamide, (C1-C6)-alkoxy-(C1-C6)-alkyl, amino, mono-(C1-C6)-alkylamino, N,N-di-(C1-C6)-alkylamino, where the two C1-C6-alkyl radicals together may form a ring, which optionally contains one or more NH, N-(C1-C6)-alkyl, O or S, (C6-C14)-aryl, (C6-C14)-aryloxy, (C6-C14)-aryl-(C1-C4)-alkyl, (C6-C14)-aryl-(C1-C4)-alkoxy-(C1-C4)-alkyl, (C1-C6)-alkylcarbonyl, (C1-C6)-alkylcarbonyloxy, (C1-C6)-alkoxycarbonyl, hydroxyl, where two directly adjacent radicals may be attached to one another;

Y is unsubstituted (C6-C14)-aryl or (C6-C14)-aryl which is fully or partially substituted by identical or different substituents, preferably phenyl or 1- or 2-naphthyl, or is unsubstituted (C1-C13)-heteroaryl or (C1-C13)-heteroaryl which is fully or partially substituted by identical or different substituents and has in each case at least one to four N, NH, N-(C1-C6)-alkyl, O and/or S as ring members, or is unsubstituted (C3-C8)-cycloalkyl or (C3-C8)-cycloalkyl which is fully or partially substituted by identical or different substituents, where the identical or different substituents are selected independently of one another from the group consisting of halogen, preferably fluorine, chlorine, bromine or iodine; cyano; straight-chain or branched cyano-(C1-C6)-alkyl; hydroxyl; straight-chain or branched (C1-C6)-alkyl which is substituted by one or more hydroxyl groups; carboxyl; (C1-C6)-alkyl carboxylate, carboxamide; N-(C1-C6)-alkyl carboxamide, N,N-di-(C1-C4)-alkyl carboxamide, nitro, straight-chain or branched (C1-C6)-alkyl, straight-chain or branched (C1-C6)-alkyl which is substituted by one or more halogen atoms, preferably trifluoromethyl, straight-chain or branched (C1-C6)-alkoxy which is substituted by one or more halogen atoms, preferably trifluoromethoxy, straight-chain or branched (C2-C6)-alkenyl, straight-chain or branched (C2-C6)-alkynyl, (C3-C8)-cycloalkyl, straight-chain or branched (C1-C6)-alkoxy, preferably methoxy, straight-chain or branched (C1-C6)-alkylenedioxy, preferably methylenedioxy, thio (-SH), straight-chain or branched (C1-C6)-alkylthio, (C1-C6)-alkylsulfinyl, (C1-C6)-alkylsulfonyl, (C1-C6)-alkoxy-(C1-C6)-alkyl, amino, straight-chain or branched mono-(C1-C6)-alkylamino, straight-chain or branched N,N-di-(C1-C6)-alkylamino, where the two (C1-C6)-alkyl

radicals together may form a ring, which may optionally contain one or more NH, N-(C1-C6)-alkyl, O and/or S, (C6-C14)-aryl, (C6-C14)-aryloxy, (C6-C14)-aryl-(C1-C6)-alkyl, (C6-C14)-aryl-(C1-C6)-alkoxy-(C1-C6)-alkyl, (C1-C6)-alkylcarbonyl, (C1-C6)-alkylcarbonyloxy, (C1-C6)-alkoxycarbonyl, (C1-C6)-alkoxycarbonyloxy, straight-chain or branched mono- and N,N-di-(C1-C6)-alkylcarbonylamino, straight-chain or branched mono- and N,N-di-(C1-C6)-alkoxycarbonylamino, straight-chain or branched N-(C1-C6)-alkylcarbonyl-N-(C1-C6)-alkylamino, straight-chain or branched N-(C1-C6)-alkoxycarbonyl-N-(C1-C6)-alkylamino, formylamino, formyl, where two directly adjacent radicals may be attached to one another;

X is an oxygen or sulfur atom, is NH, or is a geminally (at the same C atom) substituted hydroxyl and hydrogen (-CH(OH)-);

its stereoisomers, its tautomers, mixtures thereof and the pharmaceutically acceptable salts thereof, for preparing a medicament for the treatment of oncoses in mammals.

2. Use of at least one compound of the formula I according to claim 1, characterized in that R1-R6, A, B, C, D, X and Y are as defined in claim 1, with the proviso that at least one of the radicals R3-R6 is straight-chain or branched (C1-C6)-alkoxy, preferably methoxy; straight-chain or branched (C1-C6)-alkyl, preferably methyl; straight-chain or branched (C1-C6)-alkylenedioxy, preferably methylenedioxy, hydroxyl; straight-chain or branched (C1-C6)-alkoxy which is substituted by one or more halogen atoms, preferably trifluoromethoxy; straight-chain or branched (C1-C6)-alkyl which is substituted by one

or more halogen atoms, preferably trifluoromethyl.

3. Use of at least one compound of the formula I according to claim 1 or 2, characterized in that that R1, R2, R3, R5, R6, A, B, C, D, X and Y are as defined above and the radical R4 is straight-chain or branched (C1-C6)-alkoxy, preferably methoxy; straight-chain or branched (C1-C6)-alkyl, preferably methyl; straight-chain or branched (C1-C6)-alkylenedioxy (where the second oxygen atom may optionally be the radical R4 or R6), preferably methylenedioxy, hydroxyl; straight-chain or branched (C1-C6)-alkoxy which is substituted by one or more halogen atoms, preferably trifluoromethoxy; straight-chain or branched (C1-C6)-alkyl which is substituted by one or more halogen atoms, preferably trifluoromethyl.

4. Use of at least one compound of the formula I according to any of claims 1 to 3, characterized in that R1, R2, R3, R5, R6, A, B, C, D, X and Y are as defined above and the radical R4 is straight-chain or branched (C1-C6)-alkoxy, preferably methoxy.

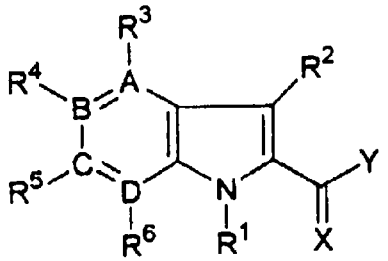
5. Use of at least one compound of the formula I according to any of claims 1 to 4, characterized in that R1, R2, R3, R5, R6, A, B, C, D, X and Y are as defined above and the radical R4 is methoxy.

6. Use of at least one compound of the formula I according to any of claims 1 to 5, characterized in that R1-R6, A, B, C, D and X are as defined above and the radical Y is substituted or unsubstituted (C6-C14)-aryl or (C1-C13)-heteroaryl which contains at least one to four N, NH, O and/or S as ring members.

7. Use of at least one compound of the formula I according to any of claims 1 to 6, characterized in that R1-R6, A, B, C, D and X are as defined above and the radical Y is (C6-C14)-aryl or (C1-C13)-heteroaryl which contains at least one N, NH, O and/or S as ring members, which is unsubstituted or substituted by at least one radical selected from the group consisting of hydrogen, amino, halogen, nitro, cyano, straight-chain or branched (C1-C6)-alkoxy, preferably methoxy; straight-chain or branched (C1-C6)-alkyl, preferably methyl; hydroxyl; (C1-C6)-alkyl-carbonyloxy, (C1-C6)-alkoxycarbonyloxy, straight-chain or branched (C1-C6)-alkoxy which is substituted by one or more halogen atoms, preferably trifluoromethoxy; straight-chain or branched (C1-C6)-alkyl which is substituted by one or more halogen atoms, preferably trifluoromethyl.

8. Use of at least one compound of the formula I according to any of claims 1 to 7, characterized in that R1-R6, A, B, C, D and X are as defined above and the radical Y is a 1-phenyl radical which is unsubstituted or substituted by hydrogen, 3,4-dichloro, 2- or 3-methoxy, 2,4-dimethoxy, 3-nitro 3-trifluoromethyl, 2,3,4-trimethoxy, 3,4,5-trimethoxy.

9. Compounds of the formula I



(I)

in which

R1 is hydrogen, (C1-C6)-alkylcarbonyl, preferably acetyl, (C_1-C_6)-alkyl, mono-(C_1-C_6)-alkylamino-(C_1-C_4)-alkyl, di(C_1-C_6)-amino-(C_1-C4)-alkyl, where the two (C_1-C4)-alkyl radicals together may form a ring, which optionally contains one or more NH, N-(C1-C)-alkyl, O or S members, (C6-C14)-aryl-(C1-C6)-alkyl or (C6-C14)-aryl-(C1-C6)-alkoxy-(C1-C6)-alkyl;

R2 is a hydrogen atom, halogen, cyano, nitro, (C1-C6)-alkyl, (C1-C6)-alkyl which is substituted by one or more halogen atoms, preferably trifluoromethyl, (C1-C6)-alkoxy which is substituted by one or more halogen atoms, preferably trifluoromethoxy, (C2-C6)-alkenyl, (C2-C6)-alkynyl, (C3-C8)-cycloalkyl, (C1-C)-alkoxy, (C1-C)-alkoxycarbonyloxy, (C1-C)-alkylcarbonyloxy, (C1-C)-alkylthio, (C1-C4)-alkylsulfinyl, (C1-C4)-alkylsulfonyl, (C1-C4)-alkoxy-(C1-C4)-alkyl, amino, mono-(C1-C)-alkylamino, di-(C1-C)-alkyl)-amino, where the two C1-C4-alkyl radicals together may form a ring, which optionally contains one or more NH, N-(C1-C4)alkyl, O or S, (C6-C14)-aryl, (C6-C14)-aryloxy, (C6-C14)-aryl-(C1-C4)-alkyl, (C6-C14)-aryl-(C1-C4)-alkoxy-(C1-C4)-alkyl, (C1-C6)-alkyl-carbonyl, (C1-C6)-alkoxycarbonyl or hydroxyl;

A, B, C and D independently of one another are a nitrogen atom (in which case R3, R4, R5 and R6 represent the free electron pair at the nitrogen atom) or are a carbon atom substituted by one of the radicals R3-R6;

R3, R4, R5 and R6 independently of one another are, when attached to nitrogen, a free electron pair, or, when attached to carbon, hydrogen, halogen, cyano, nitro, straight-chain or branched (C1-C6)-

alkyl, straight-chain or branched (C1-C6)-alkyl which is substituted by one or more halogen atoms, preferably trifluoromethyl, straight-chain or branched (C1-C6)-alkoxy which is substituted by one or more halogen atoms, preferably trifluoromethoxy, (C2-C6)-alkenyl, (C2-C6)-alkynyl, (C3-C8)-cycloalkyl, straight-chain or branched (C1-C6)-alkoxy, straight-chain or branched (C1-C6)-alkylenedioxy, (C1-C6)-alkoxy-carbonyloxy, (C1-C6)-alkylcarbonyloxy, (C1-C)-alkylthio, (C1-C4)-alkylsulfinyl, (C1-C4)-alkyl-sulfonyl, carboxyl, (C1-C6)-alkyl carboxylate, carboxamide, N-(C1-C4)-alkyl carboxamide, N,N-di-(C1-C4)-alkyl carboxamide, (C1-C6)-alkoxy-(C1-C6)-alkyl, amino, mono-(C1-C6)-alkylamino, di-(C1-C6)-alkyl)-amino, where the two C1-C4-alkyl radicals together may form a ring, which optionally contains one or more NH, N-(C1-C4)-alkyl, O or S, aryl, aryloxy, aryl-(C1-C4)-alkyl, aryl-(C1-C4)-alkoxy-(C1-C4)-alkyl, (C1-C6)-alkylcarbonyl, (C1-C6)-alkoxycarbonyl, hydroxyl, where two directly adjacent radicals may be attached to one another;

Y is unsubstituted (C10-C14)-aryl or (C10-C14)-aryl which is fully or partially substituted by identical or different substituents, preferably 1- or 2-naphthyl, or is unsubstituted (C1-C13)-heteroaryl or (C1-C13)-heteroaryl which is fully or partially substituted by identical or different substituents and has in each case at least one to four N, NH, N-(C1-C6)-alkyl, O and/or S as ring members, or is unsubstituted (C3-C8)-cycloalkyl or (C3-C8)-cycloalkyl which is fully or partially substituted by identical or different substituents, where the identical or different substituents are selected independently of one another from the group consisting of halogen, preferably fluorine, chlorine, bromine or iodine;

cyano; straight-chain or branched cyano-(C1-C6)-alkyl; hydroxyl; straight-chain or branched (C1-C6)-alkyl which is substituted by one or more hydroxyl substituents; carboxyl; (C1-C6)-alkyl carboxylate; carboxamide; N-(C1-C6)-alkyl carboxamide, N,N-di-(C1-C4)-alkyl carboxamide, nitro, straight-chain or branched (C1-C6)-alkyl, straight-chain or branched (C1-C6)-alkyl which is substituted by one or more halogen atoms, preferably trifluoromethyl, straight-chain or branched (C1-C6)-alkoxy which is substituted by one or more halogen atoms, preferably trifluoromethoxy, straight-chain or branched (C2-C6)-alkenyl, straight-chain or branched (C2-C6)-alkynyl, (C3-C8)-cycloalkyl, straight-chain or branched (C1-C6)-alkoxy, preferably methoxy, straight-chain or branched (C1-C6)-alkylenedioxy, preferably methylenedioxy, thio (-SH), straight-chain or branched (C1-C6)-alkylthio, (C1-C6)-alkylsulfinyl, (C1-C6)-alkylsulfonyl, (C1-C6)-alkoxy-(C1-C6)-alkyl, amino, straight-chain or branched mono-(C1-C6)-alkylamino, straight-chain or branched N,N-di-(C1-C6)-alkylamino, where the two (C1-C6)-alkyl radicals together may form a ring, which may optionally contain one or more NH, N-(C1-C6)-alkyl, O and/or S, (C6-C14)-aryl, (C6-C14)-aryloxy, (C6-C14)-aryl-(C1-C6)-alkyl, (C6-C14)-aryl-(C1-C6)-alkoxy-(C1-C6)-alkyl, (C1-C6)-alkylcarbonyl, (C1-C6)-alkylcarbonyloxy, (C1-C6)-alkoxycarbonyl, (C1-C6)-alkoxycarbonyloxy, straight-chain or branched mono- and N,N-di-(C1-C6)-alkylcarbonylamino, straight-chain or branched mono-N- and N,N-di-(C1-C6)-alkoxy-carbonylamino, straight-chain or branched N-(C1-C6)-alkylcarbonyl-N-(C1-C6)-alkylamino, straight-chain or branched N-(C1-C6)-alkoxycarbonyl-N-(C1-C6)-alkylamino, formylamino, formyl, where two directly adjacent radicals may

be attached to one another;

X is an oxygen or sulfur atom, is NH, or is a geminally (at the same C atom) substituted hydroxyl and hydrogen (-CH(OH)-);

their stereoisomers, their tautomers, and the pharmaceutically acceptable salts thereof, except for the racemic compounds according to formula I where R1 = R2 = R3 = R5 = R6 = hydrogen, X = oxygen or, if R4 = H, geminally substituted hyroxyl and hydrogen, Y = 3-carboxypyridin-4-yl and R4 = hydrogen or methoxy, and the compounds 2-cyclopropylcarbonylindole and 2-cyclohexylcarbonylindole.

10. Compounds of the formula I according to claim 9, characterized in that R1-R6, A, B, C, D, X and Y are as defined in claim 9, with the proviso that at least one of the radicals R3-R6 is straight-chain or branched (C1-C6)-alkoxy, preferably methoxy; straight-chain or branched (C1-C6)-alkyl, preferably methyl; straight-chain or branched (C1-C6)-alkylenedioxy, preferably methylenedioxy, hydroxyl; straight-chain or branched (C1-C6)-alkoxy, substituted by one or more halogen atoms, preferably trifluoromethoxy; straight-chain or branched (C1-C6)-alkyl substituted by one or more halogen atoms, preferably trifluoromethyl.

11. Compounds according to claim 9 or 10, characterized in that that R1, R2, R3, R5, R6, A, B, C, D, X and Y are as defined above and the radical R4 is straight-chain or branched (C1-C6)-alkoxy, preferably methoxy; straight-chain or branched (C1-C6)-alkyl, preferably methyl; straight-chain or branched (C1-C6)-alkylenedioxy (where the second oxygen atom can either be the radical R4 or R6), preferably methylenedioxy, hydroxyl;

straight-chain or branched (C1-C6)-alkoxy substituted by one or more halogen atoms, preferably trifluoromethoxy; straight-chain or branched (C1-C6)-alkyl substituted by one or more halogen atoms, preferably trifluoromethyl.

12. Compounds according to any of claims 9 to 11, characterized in that R1, R2, R3, R5, R6, A, B, C, D, X and Y are as defined above and the radical R4 is straight-chain or branched (C1-C6)-alkoxy, preferably methoxy.

13. Compounds according to any of claims 9 to 12, characterized in that R1, R2, R3, R5, R6, A, B, C, D, X and Y are as defined above and the radical R4 is methoxy.

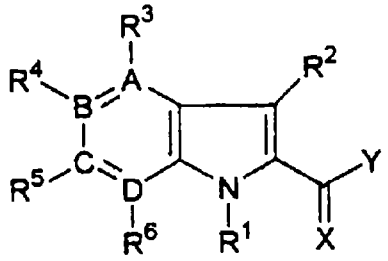
14. Compounds according to any of claims 9 to 13, characterized in that R1-R6, A, B, C, D and X are as defined above and the radical Y is substituted or unsubstituted (C6-C14)-aryl or is (C1-C13)-heteroaryl which contains at least one to four N, NH, O and/or S as ring member.

15. Compounds according to any of claims 9 to 14, characterized in that R1-R6, A, B, C, D and X are as defined above and the radical Y is (C6-C14)-aryl or is (C1-C13)-heteroaryl which contains at least one N, NH, O and/or S as ring member and which is unsubstituted or substituted by at least one radical selected from the group consisting of hydrogen, amino, halogen, nitro, cyano, straight-chain or branched (C1-C6)-alkoxy, preferably methoxy; straight-chain or branched (C1-C6)-alkyl, preferably methyl; hydroxyl; (C1-C6)-alkyl-carbonyloxy, (C1-C6)-alkoxycarbonyloxy; straight-chain or branched (C1-C6)-alkoxy substituted by one or more halogen atoms, preferably trifluoro-methoxy; straight-chain or branched (C1-C6)-alkyl

substituted by one or more halogen atoms, preferably trifluoromethyl.

16. Compounds according to any of claims 9 to 15, characterized in that R1-R6, A, B, C, D and X are as defined above and the radical Y is a 1-phenyl radical which is unsubstituted or substituted by hydrogen, 3,4-dichloro, 2- or 3-methoxy, 2,4-dimethoxy, 3-nitro 3-trifluoromethyl, 2,3,4-trimethoxy, 3,4,5-trimethoxy.

17. Compounds of the formula I



(I)

in which A, B, C, D, X, Y and R1 to R6 are as defined in claim 9, including the compounds of the formula I where R1 = R2 = R3 = R5 = R6 = hydrogen, X = oxygen or, if R4 = H, geminally substituted hydroxyl and hydrogen, Y = 3-carboxypyridin-4-yl and R4 = hydrogen or methoxy, and the compounds 2-cyclopropylcarbonylindole and 2-cyclohexylcarbonylindole for use as medicaments, in particular as antitumor agents.

18. Compounds according to any of claims 10 to 16 for use as medicaments, in particular as antitumor agents.

19. Use of a compound of the formula I according to any of claims 9 to 16 for preparing a medicament having antimitotic action in mammals.

20. Use of a compound of the formula I according to any of claims 9 to 16 for preparing a medicament for direct and/or indirect inhibition of tubulin polymerization in mammalian cells.

21. Use of a compound of the formula I according to any of claims 9 to 16 for preparing a medicament for oral, parenteral or topical treatment of tumor disorders in mammals, preferably in man.

22. Process for preparing compounds according to any of claims 9 to 16, characterized by the following steps

d) lithiation of the corresponding 1-N-protected indole or heteroindole derivative and reaction with Z-CO-Y, where Z is a suitable leaving group, such as halogen, or H-CO-Y, giving the corresponding methanone derivative or the corresponding tertiary alcohol which, if appropriate, can be oxidized to the methanone derivative,

e) if appropriate removal of the protective group and

f) if appropriate further reaction of the reactive radicals by procedures known per se.

23. Medicament comprising at least one compound according to any of claims 9 to 16, if appropriate together with customary pharmaceutical auxiliaries and/or excipients.

24. Antitumor agent, comprising an effective amount of at least one compound according to any of claims 9 to 16, if appropriate together with customary pharmaceutical auxiliaries and/or excipients.

25. Process for preparing medicaments according to claim 23, characterized in that at least one compound according to any of claims 9 to 16, if

appropriate together with customary pharmaceutical auxiliaries and/or excipients, is converted into a customary pharmaceutical presentation form.

26. Process for preparing antitumor agents according to claim 24, characterized in that an effective amount of at least one compound according to any of claims 9 to 16, if appropriate together with customary pharmaceutical auxiliaries and/or excipients, is converted into a customary pharmaceutical presentation form.

27. Medicament according to claim 23, characterized in that it can be administered orally, perorally or topically to a mammal.

28. Antitumor agent according to claim 24, characterized in that it can be administered orally, parenterally or topically to a mammal.