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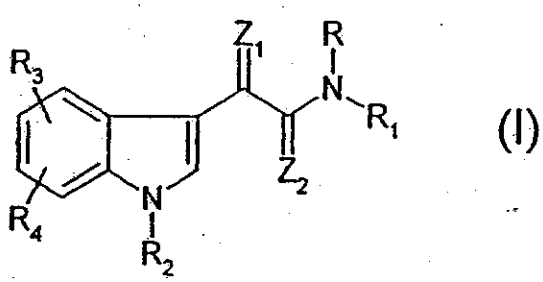
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(54) Title: NOVEL INDOLE DERIVATIVES AND THEIR USE AS MEDICAMENTS

(54) Bezeichnung: NEUE INDOLDERIVATE UND DEREN VERWENDUNG ALS ARZNEIMITTEL

WO 02/10152 A2



(I)

(57) Abstract: The invention relates to novel indole derivatives of general formula (I), to the production of said derivatives and to their use as medicaments, especially for treating tumours.

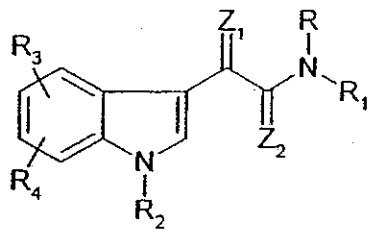
(57) Zusammenfassung: Die Erfindung betrifft neue Indol-Derivate der allgemeinen Formel 1, deren Herstellung und Verwendung als Arzneimittel, insbesondere zur Behandlung von Tumoren. (Formula 1)

Novel indole derivatives and their use as medicaments

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

Indol-3-yl derivatives having certain 2-, 3-, 4- and 8-quinoline radicals are described in the German application DE 198 14 838.0. However, indol-3-yl derivatives having 5-, 6- or 7-quinoline substituents are neither described nor suggested in this publication.

According to a first aspect of the invention, there is provided indole derivatives of the general formula 1



Formula 1

in which

R denotes hydrogen or (C_2-C_6)-alkynyl;

R_1 denotes quinolyl which is optionally substituted by C_{1-6} alkyl; pyrido[2,3-b]pyrazinyl, or indazolyl;

R_2 denotes (C_1-C_6)-alkyl which is mono- or polysubstituted by phenyl, where the phenyl radical may be unsubstituted or mono- to pentasubstituted by identical or different halogen substituents;

R_3 and R_4 denote hydrogen;

Z_1 denotes oxygen or sulfur or geminally attached hydrogen and hydroxyl;

Z_2 denotes oxygen;

their tautomers, stereoisomers, including the diastereomers and enantiomers, and the physiologically acceptable salts thereof.

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

Furthermore, the indole derivatives of the formula (1) according to the invention can be converted into their salts with inorganic or organic acids, in particular, for pharmaceutical use, into their physiologically acceptable salts. Acids which are suitable for this

purpose are, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, malic acid, embonic acid, malonic acid, citric acid, acetic acid, tartaric acid, trifluoroacetic acid, methanesulfonic acid, sulfoacetic acid or maleic acid.

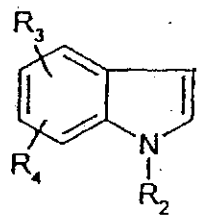
Moreover, the compounds of the formula (1) according to the invention can, if they contain a sufficiently acidic group, such as a carboxyl group, be converted, if desired, into their salts with inorganic or organic bases, in particular, for pharmaceutical use, into their physiologically acceptable salts.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

According to an embodiment, indole derivatives of the general formula (1) are provided which may be characterized in that R, R_2, R_3, R_4, Z_1 and Z_2 have the meanings described above and R_1 represents quinolyl which may be mono- or polysubstituted by straight-chain or branched (C_1-C_6-alkyl) or (C_1-C_6)-alkoxy.

According to a further embodiment, indole derivatives of the general formula (1) are provided which may be characterized in that R, R_2, R_3, R_4, Z_1 and Z_2 have the meanings described above and R_1, represents 2-methyl-6-quinolyl.

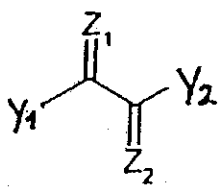
According to a further embodiment, indole derivatives of the general formula (1) are provided which may be characterized in that R, R_3, and R_4, have the meanings described above and R_1, denotes (2-methyl)-6-quinolyl, R_2 denotes 4-chlorobenzyl, and Z_1 and Z_2 each denote oxygen.

According to a second aspect of the invention, there is provided a process for preparing indole derivatives of the general formula (1) as defined above characterized in that an indole precursor of the general formula (2)



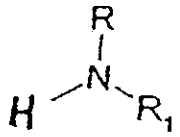
Formula 2

in which R_2, R_3, and R_4, have the meanings mentioned above is reacted with a compound of the general formula (3)

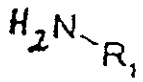


Formula 3

in which Z_1 and Z_2 have the meanings mentioned and Y_1 and Y_2 independently of one another represent a suitable leaving group, such as halogen, ((C_1-C_6)-alkoxy, -O-tosyl, -O-mesyl or -N1-imidazole, and then with an amine of the general formula (4) or (5)

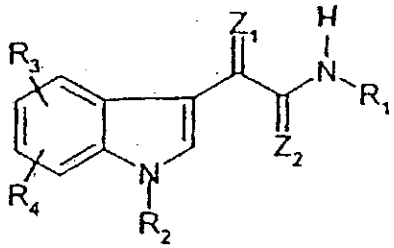


Formula 4



Formula 5

in which R and R_1 have the meanings mentioned above, giving the desired compound of the general formula (1) (with amine 4) or the compound of the general formula (6) (with amine 5)



Formula 6

in which R_1, R_2, R_3, R_4, Z_1 and Z_2 have the meanings mentioned above, using, if appropriate, diluents and auxiliaries, where the compound of the general formula (6) may subsequently be reacted with a compound of the general formula (7)

$$R-Y_3 \qquad (7)$$

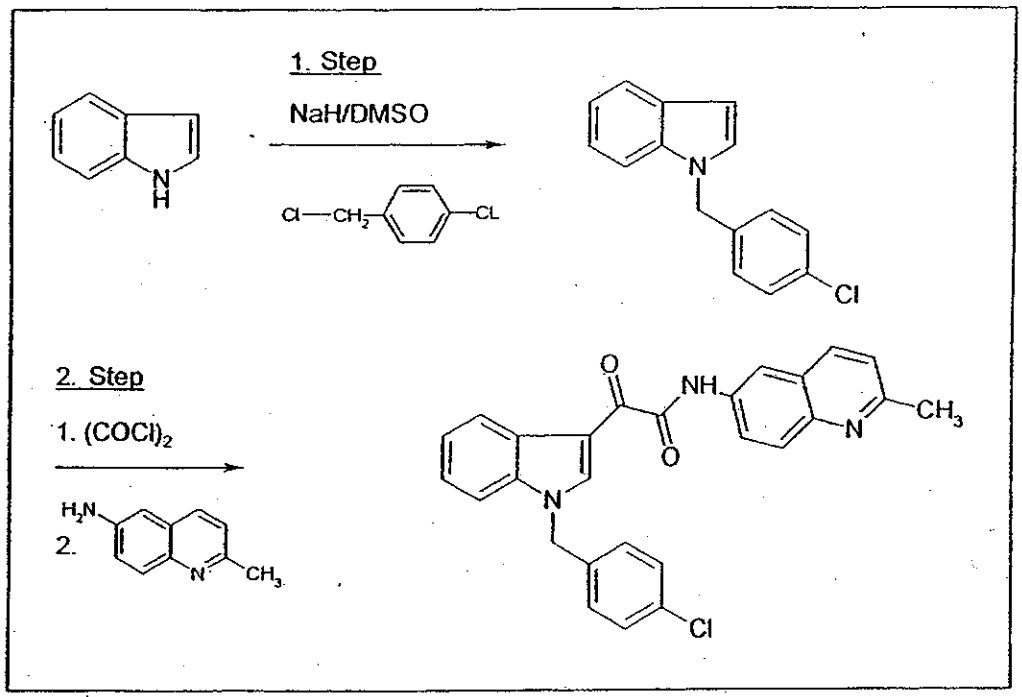
in which R has the meaning mentioned above and Y_3 represents a suitable electrophilic leaving group, such as halogen, (C_1-C_6)-alkoxy, -O-tosyl, -O-mesyl or -N1-

imidazole, giving the desired compound (1), where R does not denote hydrogen, using, if appropriate, diluents and auxiliaries.

Synthesis routes:

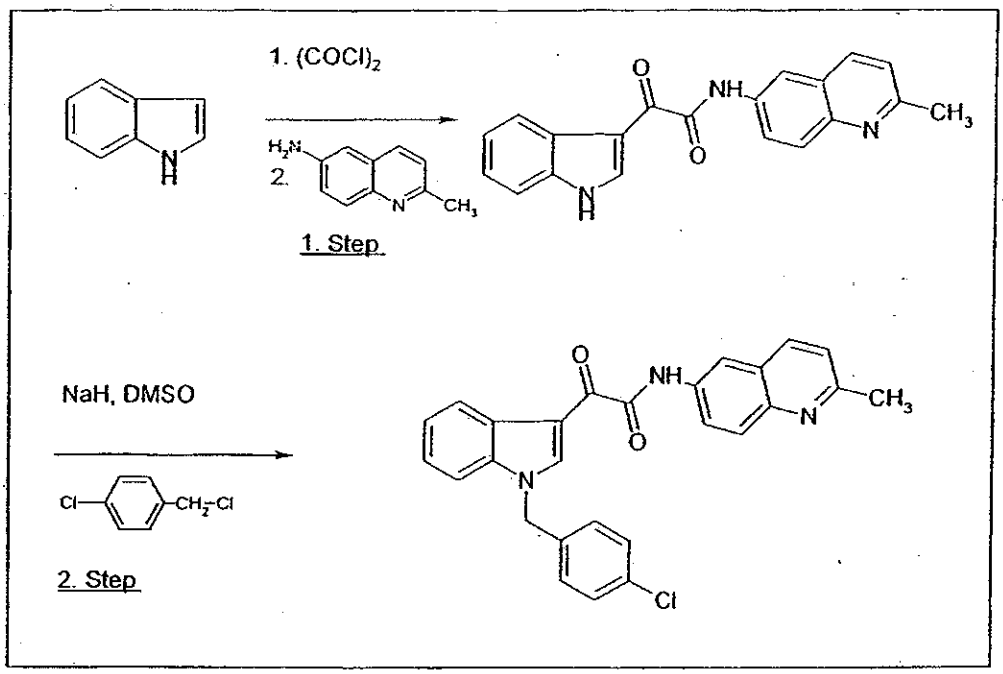
The compounds of the general formula 1 can be obtained according to Scheme 1 below:

Scheme 1



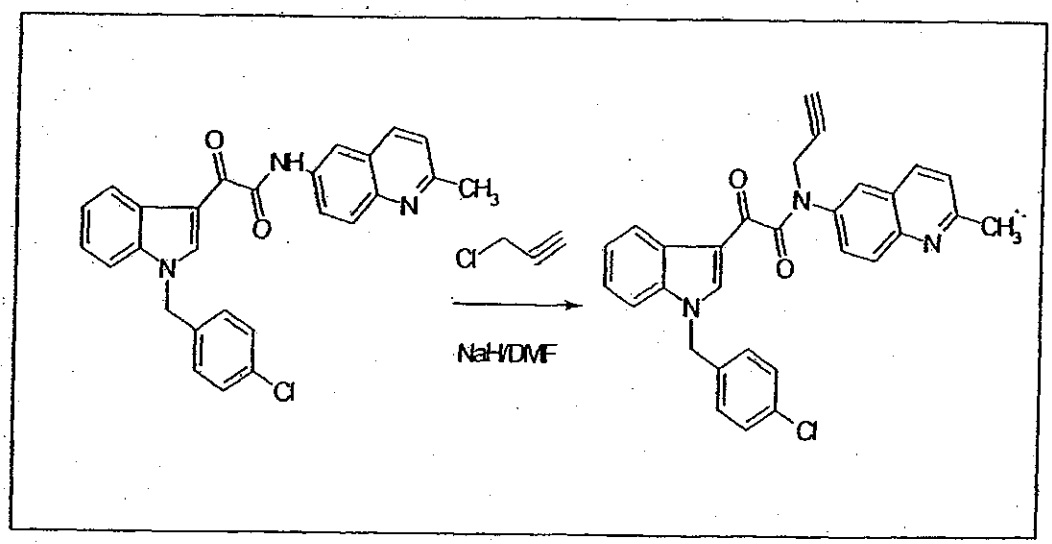
Furthermore, the compounds of the general formula 1 can also be obtained by the synthesis route of Scheme 2:

Scheme 2



The compounds of the general formula 1 in which R= methyl, benzyl, propargyl or cyanomethyl and R_1, R_2, R_3 and R_4 have the meanings given for the general formula 1 can also be prepared according to the synthesis route of Scheme 3:

Scheme 3



The starting materials (2), (3) and (4) are either commercially available or can be prepared by procedures known per se. The starting materials (2), (3) and (4)

are useful intermediates for preparing the indole derivatives of the formula (1).

For the preparation of starting materials and target compounds, reference may be made, for example, to the following standard works of organic synthesis, the content of which is hereby explicitly included into the disclosure of the present application:

1) Houben-Weyl, Volume E 7a (part 1) pp. 290-492, pp. 571-740
Houben-Weyl, Volume E 7a (part 2) pp. 119-156, pp. 205-686, pp. 157-204

2) Monograph "Heterocyclic Compounds" (Elderfield),
Volume 1, pp. 119-207, pp. 397-616
Volume 3, pp. 1-274
Volume 6, pp. 101-135, pp. 234-323

3) Monograph "Comprehensive Organic Chemistry" (S.D. Barton, W.D. Ollis)
Volume 4, pp. 155-204, pp. 205-232, pp. 493-564

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

The indole derivatives of the general formula (1) according to one embodiment may be suitable as medicaments, in particular as antitumor agents, for treating mammals, in particular man, but also domestic animals such as horses, cattle, dogs, cats, hares, sheep, poultry and the like.

Another embodiment may also provide indole derivatives as described above for use in therapy.

According to a third aspect of the invention, there is provided a use of the indole derivatives as defined above for the manufacture of a medicament for treating tumors in mammals.At least one indole derivative of the general formula (1) may be administered to a mammal in an amount effective for the treatment of the tumor. The therapeutically effective dose of the indole derivative which may be administered for the treatment depends inter alia on the nature and the stage of the oncosis, the age and the sex of the patient, the type of administration and the duration of the treatment. Administration can take place orally, rectally, buccally (for example sublingually), parenterally (for example subcutaneously, intramuscularly, intradermally or intravenously), topically or transdermally.

According to a fourth aspect of the invention, there is provided medicament characterized in that it comprises, as active ingredient, at least one indole derivative as defined above. These can be solid, semisolid, liquid or aerosol preparations. Suitable solid preparations are, for example, capsules, powders, granules, tablets. Suitable semisolid preparations are, for example, ointments, creams, gels, pastes, suspensions, oil-in-water and water-in-oil emulsions. Suitable liquid preparations are, for example, sterile aqueous preparations for parenteral administration which are isotonic with the blood of the patient.

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

Working examples

Example 1 (Reaction according to Scheme 1, 1. step):

Preparation of 1-(4-chlorobenzyl)indole

A solution of 5.86 g (0.05 mol) of indole in 25 ml of DMSO is added to a mixture of 1.32 g of sodium hydroxide (0.055 mol, suspension in mineral oil) in 50 ml of dimethyl sulfoxide. The mixture is heated at 60°C for 1.3 hours and then allowed to cool, and 17.7 g (0.11 mol) of 4-chlorobenzyl chloride are added dropwise. The solution is heated at 60°C, allowed to stand overnight and then poured with stirring into 200 ml of water. The mixture is extracted repeatedly with a total of 75 ml of CH_2Cl_2, the organic phase is dried with anhydrous sodium sulfate and filtered and the filtrate is concentrated under reduced pressure.
Yield: 11.5 g (95% of theory)

Example 2 (Reaction according to the 2. step of Scheme 1):

Preparation of N-(2-methyl-6-quinolyl)-[1-(4-chlorobenzyl)indole-3-yl]glyoxylamide (D-69429)

At 0°C and under nitrogen, a solution of 10.2 g (42.2 mmol) of 1-(4-chlorobenzyl)indole in 50 ml of ether is added dropwise to a solution of 5.50 ml of oxalyl chloride in 50 ml of ether. The mixture is heated at reflux for 2 hours and the solvent is then evaporated. 100 ml of tetrahydrofuran were then added to the residue and the solution was cooled to -4°C and treated dropwise with a solution of 15.66 g (99.0 mmol) of 6-amino-2-methylquinoline in 350 ml of THF. The mixture is heated at reflux for 4 hours and allowed to stand at room temperature overnight. The 6-amino-2-methylquinoline hydrochloride is filtered off with suction, the precipitate is washed with THF, the filtrate is concentrated under reduced pressure and the residue is recrystallized from methyl ethyl ketone/ methylene chloride.

Yield: 14.8 g (77.3% of theory)

Melting point: 182-185°C

Preparation of the hydrochloride:

The equivalent amount of hydrochloric acid, dissolved in isopropanol, is added to 0.453 g (1 mmol) of N-(2-methyl-6-quinolyl)-[1-(4-chlorobenzyl)indol-3-yl]glyoxylamide in 20 ml of hot ethanol, the mixture is heated at 70-80°C and the solution is, at 40°C and under reduced pressure, evaporated to dryness. Repeated additional evaporation with toluene gave the colorless and crystalline hydrochloride.

Yield: 0.49 g (100% of theory)
m.p.: 196°C

Preparation of the methanesulfonate:

A mixture of 0.453 g (1 mmol) of N-(2-methyl-6-quinolyl)-[1-(4-chlorobenzyl)indol-3-yl]glyoxylamide and 0.67 ml of methanesulfonic acid in 15 ml of dichloromethane is heated at 50°C for 30 minutes, the resulting solution is concentrated at 35°C under reduced pressure, the residue is additionally evaporated with methyl tert-butyl ether repeatedly, and the resulting residue is dried at 35°C under reduced pressure.

Yield: 0.46 g (84% of theory)
m.p.: > 230°C

Example 3 (Reaction according to Scheme 3):

Preparation of N-propargyl-N-(2-methyl-6-quinolyl)-[1-(4-chlorobenzyl)indol-3-yl]glyoxylamide

At room temperature and under nitrogen, a suspension of 2.32 g (5.13 mmol) of N-(2-methyl-6-quinolyl))-[1-(4-chlorobenzyl)indol-3-yl]glyoxylamide in 20 ml of DMF is added to a suspension of 0.154 g of sodium hydride (5.13 mmol, suspension in mineral oil) in 10 ml of DMF.

Melting point: 182-185°C

Preparation of the hydrochloride:

The equivalent amount of hydrochloric acid, dissolved in isopropanol, is added to 0.453 g (1 mmol) of N-(2-methyl-6-quinolyl)-[1-(4-chlorobenzyl)indol-3-yl]glyoxylamide in 20 ml of hot ethanol, the mixture is heated at 70-80°C and the solution is, at 40°C and under reduced pressure, evaporated to dryness. Repeated additional evaporation with toluene gave the colorless and crystalline hydrochloride.

Yield: 0.49 g (100% of theory)
m.p.: 196°C

Preparation of the methanesulfonate:

A mixture of 0.453 g (1 mmol) of N-(2-methyl-6-quinolyl)-[1-(4-chlorobenzyl)indol-3-yl]glyoxylamide and 0.67 ml of methanesulfonic acid in 15 ml of dichloromethane is heated at 50°C for 30 minutes, the resulting solution is concentrated at 35°C under reduced pressure, the residue is additionally evaporated with methyl tert-butyl ether repeatedly, and the resulting residue is dried at 35°C under reduced pressure.

Yield: 0.46 g (84% of theory)
m.p.: > 230°C

Example 3 (Reaction according to Scheme 3):

Preparation of N-propargyl-N-(2-methyl-6-quinolyl)-[1-(4-chlorobenzyl)indol-3-yl]glyoxylamide

At room temperature and under nitrogen, a suspension of 2.32 g (5.13 mmol) of N-(2-methyl-6-quinolyl))-[1-(4-chlorobenzyl)indol-3-yl]glyoxylamide in 20 ml of DMF is added to a suspension of 0.154 g of sodium hydride (5.13 mmol, suspension in mineral oil) in 10 ml of DMF.

This resulted in strong foaming, with the mixture turning yellow. A solution of 0.382 g (5.13 mmol) of propargyl chloride in 10 ml of DMF is added dropwise, and the mixture is, under nitrogen gas, stirred at room temperature for 24 hours and allowed to stand at room temperature for 4 days. The dark-brown solution is then poured into 120 ml of ice water and extracted in portions with 250 ml of methylene chloride, and the combined organic phases are dried using anhydrous sodium sulfate. The extract is concentrated under reduced pressure and the residue is purified using a silica gel column (silica gel 60, from Merck AG, Darmstadt, Germany) and the mobile phase methylene chloride/ethanol (97:3, v/v).

Yield: 1.98 g (78.6% of theory)
Mass spectrum: m/e= 491.9 (M^+)

Biological tests

1. Antiproliferative action in various tumor cell lines

In a proliferation test, the antiproliferative activity of the substance D-69429 was examined using established tumor cell lines. In the test used, the cellular dehydrogenation activity is determined, which makes it possible to determine the vitality of the cell and, indirectly, the cell count. The cell lines used are the human cervical carcinoma cell line KB/HeLa (ATCC CCL17), the murine lymphocyte leukaemia L1210 (ATCC CCL-219), the human breast adenocarcinoma line MCF7 (ATCC HTB22) and the ovary adenocarcinoma line SKOV-3 (ATCC HTB77). These are established cell lines which are very well characterized and were obtained from ATCC and cultured.

The results shown in Tab. 1 demonstrate the highly potent antiproliferative action of D-69429 in the cell

lines SKOV-3, L-1210 and HeLa/KB. Owing to the particularly slow growth of the MCF7 line, the effect of D-69429 in the test period of 48 h is only small (18% inhibition at 3.16 µg/ml; thus stated as >3.16).

2. Method

XTT Test for cellular dehydrogenase activity

The adherently growing tumor cell lines HeLa/KB, SKOV-3 and MCF7 and the L1210 leukaemia line, which grows in suspension, were cultivated under standard conditions in an incubator with gas inlet at 37°C, 5% CO_2 and 95% atmospheric humidity. On Test Day 1, the adherent cells are detached using trypsin/EDTA and pelleted by centrifugation. The cell pellet is then resuspended in the RPMI 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 stock solutions in DMSO and, on Test Day 2, diluted with culture medium to the corresponding concentrations. The substances in the culture medium are then added to the cells and incubated in the incubator with gas inlet for 45 h. Cells which have not been treated with test substance serve as control.

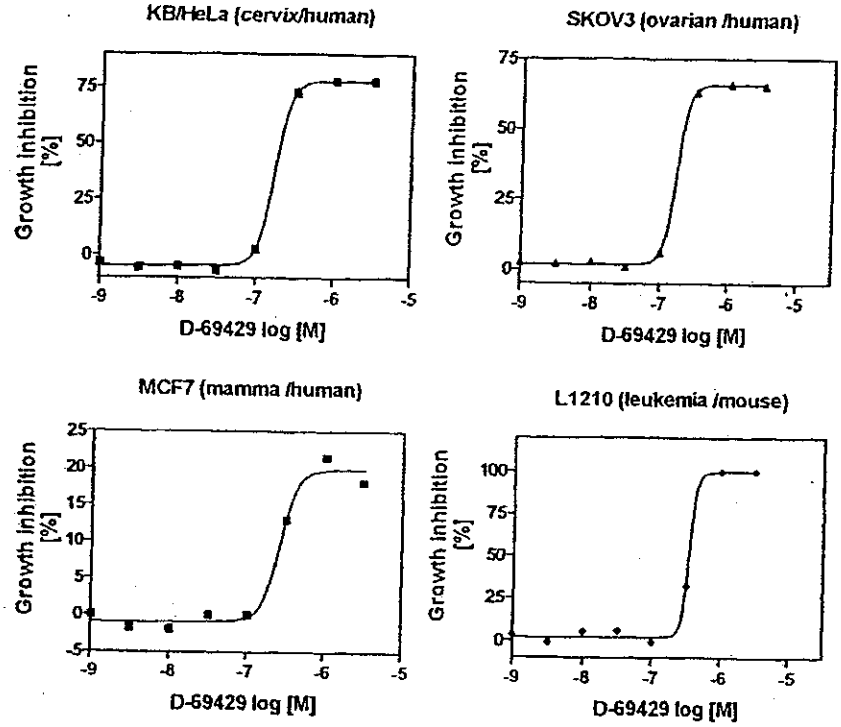
For the XTT assay, 1 mg/ml of XTT (sodium 3'-[1-(phenylaminocarbonyl)-3,4-tetrazolium]-bis(4-methoxy-6-nitro)benzenesulfonic acid) is dissolved in RPMI-1640 medium without Phenol Red. Additionally, a 0.383 mg/ml solution of PMS (N-methyldibenzopyrazine methyl sulfate) in phosphate-buffered saline (PBS)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

with gas inlet for a further 3 h, and the optical density (OD_{490nm}) is determined in a photometer.

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

Tab. 1 In vitro cytotoxicity of D-69429 in tumor cell lines (Curves determined for 8 substance concentrations)

D-69429 induces growth inhibition of various tumor cells



Growth inhibiton, IC50 [µM]	
KB/Hela	0.17
SKOV3	0.17
MCF7	0.26
L1210	0.35

Example I

Tablet containing 50 mg of active compound

Composition:

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

Preparation:

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

Example II

Capsule containing 50 mg of active compound

Composition:

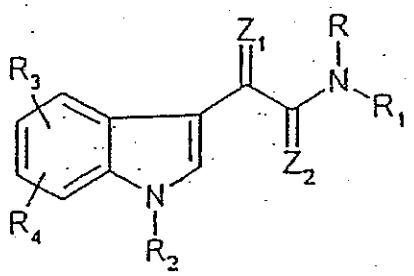
(1)	Active compound	50.0 mg
(2)	Maize starch, dried	58.0 mg
(3)	Lactose powder	50.0 mg
(4)	Magnesium stearate	2.0 mg
Total:		160.0 mg

Preparation:

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

Claims

1. Indole derivatives of the general Formula 1



Formula 1

in which

R denotes hydrogen or (C_2-C_6)-alkynyl;

R_1 denotes quinolyl which is optionally substituted by C_{1-6} alkyl; pyridol[2,3-b]pyrazinyl or indazolyl;

R_2 denotes (C_{1-6})-alkyl which is mono- or polysubstituted by phenyl, where the phenyl radical may be unsubstituted or mono- to pentasubstituted by identical or different halogen substituents;

R_3 and R_4 denote hydrogen;

Z_1 denotes oxygen or sulfur or geminally attached hydrogen and hydroxyl;

Z_2 denotes oxygen;

their tautomers, stereoisomers, including the diastereomers and enantiomers, and the physiologically acceptable salts thereof.

2. Indole derivative according to claim 1 wherein R denotes ethynyl or propargyl.

3. Indole derivative according to claim 1 wherein R_2 denotes (C_{1-6})-alkyl which is mono- or polysubstituted by phenyl, where the phenyl radical is mono- to pentasubstituted by identical or different halogen substituents selected from chlorine, bromine or iodine.

4. Indole derivative according to claim 1, characterized in that R, R_2, R_3, R_4, Z_1 and Z_2 have the meanings described above and R_1 represents quinolyl which is mono- or polysubstituted by straight-chain or branched $(C_1$-C_6-alkyl).

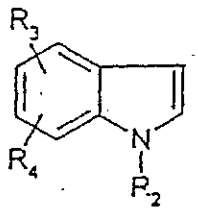
5. Indole derivative according to claim 1, characterized in that R, R_2, R_3, R_4, Z_1 and Z_2 have the meanings described above and R_1 represents 2-methyl-6-quinolyl.

6. Indole derivative according to claim 1, characterized in that R, R_3, R_4 have the meanings described above and R_1 denotes (2-methyl)-6-quinolyl, R_2 denotes 4-chlorobenzyl, and Z_1 and Z_2 each denote oxygen.

7. Indole derivatives according to any of claims 1 to 6 for use in therapy.

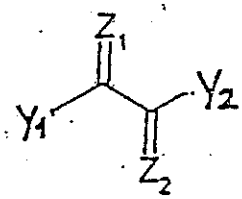
8. Use of the indole derivatives according to any of claims 1 to 6 for the manufacture of a medicament for treating tumors in mammals.

9. Process for preparing indole derivatives of the general formula (1) according to any of claims 1 to 6, characterized in that an indole precursor of the general formula (2)



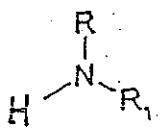
Formula 2

in which R_2, R_3 and R_4 have the meanings mentioned above is reacted with a compound of the general formula (3)

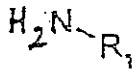


Formula 3

in which Z_1 and Z_2 have the meaning mentioned above and Y_1 and Y_2 independently of one another represent a suitable leaving group, such as halogen, (C_1-C_6)-alkoxy, -O-tosyl, -O-mesyl or –N1-imidazole, and then with an amine of the general formula (4) or (5)

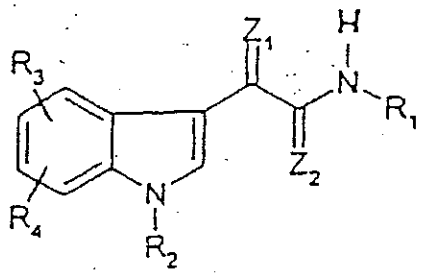


Formula 4



Formula 5

in which R and R_1 have the meanings mentioned above, giving the desired compound of the general formula (1) (with amine 4) or the compound of the general formula (6) (with amine 5)



Formula 6

in which R_1, R_2, R_3, R_4, Z_1 and Z_2 have the meanings mentioned above, using, if appropriate, diluents and auxiliaries, where the compound of the general formula (6) may subsequently be reacted with a compound of the general formula (7)

$$R\text{-}Y_3 \qquad (7)$$

in which R has the meaning mentioned above and Y_3 represents a suitable electrophilic leaving group, such as halogen, (C_1-C_6)-alkoxy, -O-tosyl, -O-mesyl or –N1-imidazole, giving the desired compound (1), where R does not denote hydrogen, using, if appropriate, diluents and auxiliaries.

10. Medicament, characterized in that it comprises, as active ingredient, at least one indole derivative according to any of claims 1 to 6.