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Indolyl-3-glyoxylic acid derivatives having therapeutically valuable properties

The invention relates to the further advantageous development of the German Patent Application indole-3-glyoxylamides having the reference 19814 838.0.

In connection with chemotherapy, in oncoses the greatest problems result due to the occurrence of pharmaceutical resistance on the one hand and due to the serious side effects of these agents on the other hand.

It is furthermore known that many primary tumors, after reaching a certain size, have a premature tendency to form metastases via the bloodstream and lymph tracts. The continuing process of tumor invasion and the formation of metastases is the most frequent cause of death of cancer patients.

There are various starting points to explain this spread, inter alia intensified angiogenesis, increased extracellular matrix degradation, tumor cell migration and modulation of cell adhesion. These factors can also act in combination, but until now have been only partially explained.

The metastasis of a tumor is usually accompanied by poor prognoses in the tumor treatment. The prerequisite for metastasis is the detachment of cells from the primary tumor, the migration of the cells to the blood vessels, the invasion into the blood vessels and the invasion of the cells from the blood vessels into other tissue.

An inhibitory action of certain antitumor agents such as tamoxoifen [sic] on the migration and invasion of cancer cells is known [J Clin Endocrinol Metab 1995 jan;80(1):308-13).

The inhibition of tumor cell invasion by verapamil has been reported [Pigment Cell Res 1991 Dec;4(5-6):225-33.]

The influence of melantonin [sic] on invasive and metastatic properties of MCF-7 human breast cancer cells has been reported [Cancer res 1998 Oct1;58(19):4383-90]

The published PCT Application WO 96/23506 demonstrated the overcoming of pharmaceutical resistance with certain tumor pharmaceuticals as a result of the gene amplification of the multi-drug resistance gene (MDR gene) brought about by such antitumor agents. Antitumor agents such as vincristine and taxol furthermore have a not inconsiderable neurotoxicity, which proves disadvantageous in chemotherapy.

The object of the invention is now to widen the area of use of N-substituted indole-3-glyoxylamides and thus to enrich the available pharmaceutical wealth. The possibility of a lower, longer-lasting and more tolerable medication for the class of substance having antitumor action described in German Patent Application 19814 838.0 should thereby be opened up. In particular, the disadvantageous development of resistance, such as is known of many antitumor agents, should be circumvented.
Development and spread of the tumor by metastases should moreover be counteracted.

Since, according to more recent knowledge, angiogenesis is obviously also responsible for tumor growth and the development of metastases, the property of inhibition of angiogenesis is a further advantageous pharmaceutical potential, for example in cancer therapy.

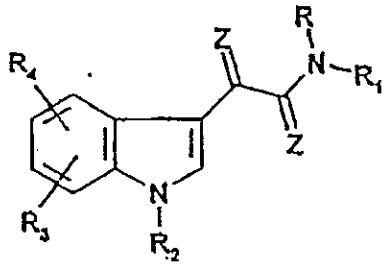
The intensification of action achieved with the N-substituted indole-3-glyoxylamides should make pharmaceutical use in tumor therapy more effective. Moreover, it should be possible to shorten the treatment time and to extend it to therapy-resistant cases. Recurrences and metastases should furthermore be restricted or prevented and thus the survival time of the patients should additionally be increased. The aim is to develop medicaments which can intervene in the

metastatic process.

It has surprisingly been found that the N-substituted indole-3-glyoxylamides described in German Patent Application 19814 838.0 and of the general formula 1 indicated below, which are suitable for the treatment of oncoses, further have advantageous properties for tumor treatment of the type which can widen their area of use.

Disclosed herein is the use of N-substituted indole-3-glyoxylamides according to Claim 1 general formula la for tumor treatment in particular in the case of pharmaceutical resistance and metastatic carcinoma and for the suppression of metastasis formation, as well as angiogenesis inhibitors

Disclosed herein is



formula 1

where the radicals R, R_1, R_2, R_3, R_4 and Z have the following meaning:

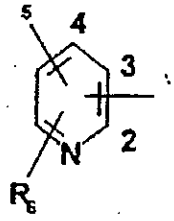
R = hydrogen, (C_1-C_6) -alkyl, where the alkyl group can be mono- or polysubstituted by the phenyl ring and this phenyl ring, for its part, can be mono- or polysubstituted by halogen, (C_1-C_6) -alkyl, (C_3-C_7) -cycloalkyl, by carboxyl groups/ carboxyl groups esterified with C_1-C_6-alkanols, trifluoro-methyl groups , hydroxyl groups , methoxy groups , ethoxy groups,

bensyloxy groups, and by a benzyl group which is mono- or polysubstituted in the phenyl moiety by (C_1-C_6) -alkyl groups, halogen atoms or trifluoromethyl groups,

R is furthermore the benzyloxycarbonyl group (Z group) or the tertiary butoxycarbonyl radical

(Boc radical), furthermore the acetyl group.

R_1 can be the phenyl ring which is mono- or polysubstituted by (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, cyano, halogen, trifluoromethyl, hydroxyl, benzyloxy, nitro, amino, (C_1-C_6)-alkylamino, (C_1-C_6)-alkoxycarbonylamino and by the carboxyl group or by the carboxyl group esterified with C_1-C_6-alkanols, or is a pyridine structure of the formula 2 and its N-oxide [sic]



formula 2

and its N-oxide, where the pyridine structure is alternatively bonded to the ring carbon atoms 2, 3 and 4 and can be substituted by the substituents R_5 and R_6. The radicals R_5 and R_6 can be identical or different and have the meaning (C_1-C_6)-alkyl, and the meaning (C_3-C_7)-cycloalkyl, (C_1-C_6)-alkoxy, nitro, amino, hydroxyl, halogen and trifluoromethyl and are furthermore the ethoxycarbonylamino radical and the group carboxyalkyloxy in which the alkyl group can have 1-4 C atoms.

R_1 can furthermore be a 2- or 4-pyrimidinyl heterocycle, where the 2-pyrimidinyl ring can be mono- or polysubstituted by the methyl group, furthermore the 2-, 3-, 4- and 8-quinolyl structure substituted by (C_1-C_6)-alkyl, halogen, the nitro group, the amino group and the (C_1-C_6)-alkylamino radical, a 2-, 3- or 4-quinolylmethyl group, where the ring carbons of the pyridylmethyl radical of the quinolyl group and of the quinolylmethyl radical can be substituted by (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, nitro, amino and (C_1-C_6)-alkoxycarbonylamino.

R_1 can furthermore be, in the case where

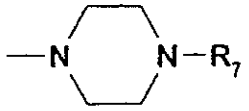
R = hydrogen, the methyl or benzyl group and the benzyloxycarbonyl radical (Z radical), the tert-butoxycarbonyl radical (BOC radical) and the acetyl group, the following radicals:

$-CH_2COOH$; $-CH(CH_3)-COOH$; $-(CH_3)_2-CH-(CH_2)_2-CH-COO$; $H_3C-H_2C-CH(CH_3)-CH(COOH)-$; $HO-H_2C-CH(COOH)-$; phenyl-$CH_2-CH(COOH)-$; (4-imidazolyl)-$CH_2-CH-COOH)-$; $HN=C(NH_2)-NH-(CH_2)_3-CH(COOH)-$; $H_2N-(CH_2)_4-CH(COOH)-$; $H_2N-CO-CH_2-CH-(COOH)-$; $HOOC(CH_2)_2-CH(COOH)-$;

R_1 can furthermore be, in the case where R is hydrogen, the Z group, the BOC radical, the acetyl or the benzyl group, the acid radical of a natural or unnatural amino acid, e.g. the α-glycyl, the α-sarcosyl, the α-alanyl, the α-leucyl, the α-isoleucyl, the α-seryl, the α-phenylalanyl, the α-histidyl, the α-prolyl, the α-arginyl, the α-lysyl, the α-asparagyl and the α-glutamyl radicals, where the amino groups of the respective amino acids can be present in unprotected or protected form. Possible protective groups for the amino function are the carbobenzoxy radical (Z radical) and the tert-butoxycarbonyl radical (BOC radical) as well as the acetyl group. In the case of the asparagyl and glutamyl radical claimed for R_1, the second, unbonded carboxyl group is present as a free carboxyl group or in the form of an ester with C_1-C_6-alkanols, e.g. as a methyl, ethyl or as a tert-butyl ester.

R_1 can furthermore be the allylaminocarbonyl-2-methylprop-1-yl group.

R and R_1 can furthermore, together with the nitrogen atom to which they are bonded, form a piperazine ring of the formula 3 or a homopiperazine ring, if R_1 is an aminoalkylene group in which



formula 3

R_7 is an alkyl radical, a phenyl ring which can be mono- or polysubstituted by (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, halogen, the nitro group, the amino function and by the (C_1-C_6)-alkylamino group. R_7 is furthermore the benzhydryl group and the bis-p-fluorobenzylhydryl group.

R_2 can be hydrogen or the (C_1-C_6)-alkyl group, where the alkyl group is mono- or polysubstituted by halogen and phenyl, which for its part can be mono- or polysubstituted by halogen, (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, carboxyl groups, carboxyl groups esterified with C_1-C_6-alkanols, trifluoromethyl groups, hydroxyl groups, methoxy groups, ethoxy groups or benzyloxy groups. The (C_1-C_6)-alkyl group applying for R_2 can furthermore be substituted by the 2-quinolyl group and the 2-, 3- or 4-pyridyl structure, which can both each be mono- or polysubstituted by halogen, (C_1-C_4)-alkyl groups or (C_1-C_4)-alkoxy groups. R_2 is furthermore the aroyl radical, where the aryl moiety on which this radical is based is the phenyl ring, which can be mono- or polysubstituted by halogen, (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, carboxyl groups, carboxyl groups esterified with C_1-C_6-alkanols, trifluoromethyl groups, hydroxyl groups, methoxy groups, ethoxy groups or benzyloxy groups.

R_3 and R_4 can be identical or different and are hydrogen (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, (C_1-C_6)-alkanoyl, (C_1-C_6)-alkoxy, halogen and benzyloxy. R_3 and R_4 can furthermore be the nitro group, the amino group, the (C_1-C_4)-mono- or dialkyl-substituted amino group, and the (C_1-C_6)-alkoxycarbonylamino

function or (C_1-C_6)-alkoxycarbonylamino-(C_1-C_6)-alkyl function.

Z is O or S.

According to one aspect of the invention, there is provided, the use of one or more N-substituted indol-3-glyoxylamides of the general formula 1, their physiologically tolerable acid addition salts and/or their N-oxides for the production of a medicament for the treatment of a disease selected from the group consisting of resistant and/or multidrug resistant (MDR) tumors, development, migration and/or invasion of metastasizing carcinoma, and diseases in which an angiogenesis-inhibitory effect is functionally desirable, whereby the treatment involves markedly lower side effects, in particular markedly lower neurotoxicity.

The designation alkyl, alkanol, alkoxy or alkylamino group for the radicals R, R_1, R_2, R_3, R_4, R_5, R_6, R_7 is normally to be understood as meaning either "straight-chain" or "branched" alkyl groups, where "straight-chain alkyl groups" can be, for example, radicals such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl and "branched alkyl groups" designates, for example, radicals such as isopropyl or tert-butyl. "Cycloalkyl" is understood as meaning radicals such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

The designation "halogen" stands for fluorine, chlorine, bromine or iodine. The designation "alkoxy group" represents radicals such as, for example, methoxy, ethoxy, propoxy, butoxy, isopropoxy, isobutoxy or pentoxy.

The compounds can also be employed as acid addition salts, for example as salts of mineral acids, such as, for example, hydrochloric acid, sulfuric acid, phosphoric acid, salts of organic acids, such as, for example, acetic acid, lactic acid, malonic acid, maleic acid, fumaric acid, gluconic acid, glucuronic acid, citric acid, embonic acid, methanesulfonic acid, trifluoroacetic acid, succinic acid and 2-hydroxyethanesulfonic acid.

Both the compounds of the formula 1 and their salts are biologically active.

The compounds of the formula I can be administered in free form or as salts with physiologically tolerable acids.

Administration can be carried out perorally, parenterally, intravenously, transdermally or by inhalation.

The invention furthermore relates to

pharmaceutical preparations containing at least one of the compounds of the formula 1 or their salts with physiologically tolerable inorganic or organic acids and, if appropriate, pharmaceutically utilizable vehicles and/or diluents or excipients.

Suitable administration forms are, for example, tablets, coated tablets, capsules, solutions for infusion or ampoules, suppositories, patches, powder preparations which can be employed by inhalation, suspensions, creams and ointments.

The preparation processes for the substances can be taken from the examples of the German Patent DE 196 36 150 A1.

The therapeutically valuable properties found relate specifically to the following advantages:

- no development of resistance was detected
- parameters were detected which are characteristic of the inhibition of metastasis formation (migration)
- parameters were found which confirm the inhibition of angiogenesis
- in various models, no neurotoxicity was found with the N-substituted indole-3-gloxylamides [sic] according to Claim 1, general formula 1a, in contrast to most antitumor preparations

The absent development of resistance is confirmed in the following pharmacological models and cell cultures:

1. The cytotoxic activity of D-24851 (see Claim 4) on the MDR (multidrug-resistant) leukemia cell line of the mouse L 1210/VCR is not influenced in vivo and in vitro. See Figure 1, 2 and 3.

D-24851 (see Claim 4) has an unchanged cytotoxic activity against the multidrug-resistant mouse leukemia cell subline L1210/VCR in contrast to taxol, doxirubicin, vincristine or epotholone B [sic].

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Experimental procedure:

The mouse leukemia cell lines [sic] L 1210 was adapted to vincristine. The unadapted (L 1210) and the adapted (L 1210/VCR) cells were exposed to cytostatic agents and the cell growth, which was determined by the metabolic activity, was determined (XTT test).
The curves which connect the XTT data points were calculated using a nonlinear regression program.
These experimental results are also confirmed in vitro on the human resistant LT12/MDR cell line, see Figure 4.

2. The proof of lacking metastasis formation was furnished by means of the inhibition of migration of MO4 cells. See Figure 5.
D-24 851 (see Claim 4) inhibits the migration of MO4 cells in a dose-dependent manner. An antiinvasive and an antimetastatic action for D-24851 can be derived therefrom.
In vitro, the migration ability of MO4 cells can be measured by inoculating the cells in the center of a cell culture dish and determining the migration by means of radius or the covered area of the cells after different numbers of days with and without D-24851. Figure 4 shows that the migration of the cells decreases with increasing D-24851 concentration.

In order to test whether D-24851 also acts antiinvasively, the invasion of MO4 fibrosarcoma cells was investigated in chicken heart. It is also seen here that at a concentration of 260 and 1000 nM the invasion is completely inhibited while at lower concentrations the invasiveness of the MO4 cells increases. On the basis of these findings, it is seen that D-24851 inhibits both the migration and the invasion of tumor cells and thereby has a strong antimetastatic potential.

3. From comparison experiments of the compound

according to the invention D-24851 (see Claim 4) with vincristine and taxol on rats, in which ataxia, traction and reaction were assessed (see Figure 6), it emerges that this compound has no neurotoxic effect, in contrast to taxol and vincristine.
In comparison to taxol and vincristine, D-24851 furthermore has no adverse effect on the nerve conduction velocity, see Figure 7.
This confirms that D-24851, on account of the lacking neurotoxicity, has markedly lower side effects than other chemotherapeutics.

4. From further investigations, according to Figure 8 and 9 it is evident that the compound D-24851 (see Claim 4) has a potential as an angiogenesis inhibitor.
As a result of the physiological relationship to tumor growth, angiogenesis inhibitors are at the same time also agents for the inhibition of tumor growth, in that the formation of new blood vessels, which should feed the tumor, is inhibited.
In an antiangiogenesis model on endothelial cells, D-24851 causes a complete inhibition of the formation of blood vessels, which is not based on a cytotoxic effect.
In Figure 8, it can be seen that 0.1 µMol/L D 24851 almost completely breaks up existing cell-cell contact (see vital staining). Normally, the cells maintain at least partial contact. Cell migration is markedly reduced and many cells are rounded.
Lethal staining in the monolayer before angiogenesis induction did not show any increased cell mortality with D-24851. Increased cell mortality was also still not detectable in the first 22 hours after induction in comparison to the control.
(see lethal staining in Figure 9, white dots)

The cells originated from human umbilical cord vein (arterial function). They were employed for the investigation in the third and fourth passage. Angiogenesis is induced by a natural stimulus. The

primary inducer of the endothelial migration is a protein which is expressed to an increased extent in vascularizing tissue. The substances are added to the culture medium shortly before the induction of angiogenesis.

The concentration for the antiangiogenetic action of D-24851 is markedly below the concentration for the cytotoxic activity. It is thereby possible to separate the two qualities of action (cytotoxic activity and antiangiogenetic action) from one another.

Without wanting to restrict the scope of the invention with the following statement, it can be said that doses from approximately 20 mg up to 500 mg daily orally are possible.

In the case of intravenous administration as an injection or as an infusion, up to 250 mg/day or more can be administered depending on the body weight of the patient and individual tolerability.

As a result of the lacking development of resistance and suppression of metastasis, a high effectiveness and wide use of the agents is to be expected to [sic] even in patients who are refractory to tumors.

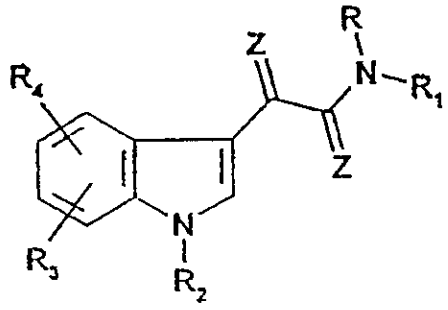
The antiangiogenesis effect is additionally suitable for suppressing the spread of the tumor.

The invention, however, also comprises the use of the N-substituted indole-3-glyoxylamides according to Claim 1 general formula 1a in further diseases in which an angiogenesis-inhibitory effect is functionally desirable. (e.g. wound healing).

The invention furthermore also relates to the fixed or free combination of the N-substituted indole-3-glyoxylamides according to Claim 1 general formula 1a with antitumor agents known per se, and to the replacement of antitumor agents which have become inactive as a result of development of resistance by N-substituted indole-3-glyoxylamides according to Claim 1 general formula 1a.

Patent Claims

1. Use of one or more N-substituted indol-3-gloxylamides of the general formula 1, their physiologically tolerable acid addition salts and/or their N-oxides for the production of a medicament for the treatment of a disease selected from the group consisting of resistant and/or multi drug resistant (MDR) tumors, development, migration and/or invasion of metastasizing carcinoma, and diseases in which an angiogenesis inhibitory effect is functionally desirable, whereby the treatment involves markedly lower side effects in particular markedly lower neurotoxicity,



formula 1

where the radicals R, R_1 , R_2, R_3, R_4 and Z have the following meaning:

R = hydrogen, (Ci-C_6) -alkyl, where the alkyl group can be mono- or polysubstituted by the phenyl ring and this phenyl ring, for its part, can be mono- or

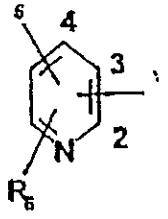
polysubstituted by halogen, (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, by carboxyl groups, carboxyl groups esterified

with C_1-C_6-alkanols, trifluoro-methyl groups, hydroxyl groups, methoxy groups, ethoxy groups, benzyloxy groups, and by a benzyl group which is mono- or polysubstituted in the phenyl moiety by (C_1-C_6)-alkyl groups, halogen atoms or trifluoromethyl groups,

R is furthermore the benzyloxycarbonyl group (Z group) or the tertiary butoxycarbonyl radical (Boc radical), furthermore the acetyl group,

R_1 can be the phenyl ring which is mono- or polysubstituted by (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, cyano, halogen, trifluoromethyl, hydroxyl,

benzyloxy, nitro, amino, (C_1-C_6) -alkylamino, (C_1-C_6) -alkoxycarbonylamino and by the carboxyl group or by the carboxyl group esterified with C_1-C_6-alkanols, or is a pyridine structure of the formula 2 and its N-oxide,



formula 2

and its N-oxide, where the pyridine structure is alternatively bonded to the ring carbon atoms 2, 3 and 4 and can be substituted by the substituents R_5 and R_6. The radicals R_5 and R_6 can be identical or different and have the meaning (C_1-C_6) -alkyl, and the meaning (C_3-C_7) -cycloalkyl, (C_1-C_6) -alkoxy, nitro, amino, hydroxyl, halogen and trifluoromethyl and are furthermore the ethoxycarbonylamino radical and the group carboxyalkyloxy in which the alkyl group can have 1-4 C atoms,

R_1 can furthermore be a 2- or 4-pyrimidinyl heterocycle, where the 2-pyrimidinyl ring can be mono- or polysubstituted by the methyl group, furthermore the 2 -, 3 -, 4 - and 8 - quinolyl structure substituted by (C_1-C_6) -alkyl, halogen, the nitro group, the amino group and the (C_1-C_6)-alkylamino radical, a 2-, 3- or 4-quinolylmethyl group, where the ring carbons of the pyridylmethyl radical of the quinolyl group and of the quinolylmethyl radical can be substituted by (C_1-C_6) -alkyl, (C_1-C_6) -alkoxy, nitro, amino and (C_1-C_6) -alkoxycarbonylamino,

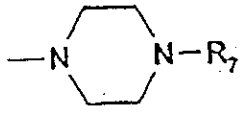
R_1 can furthermore be, in the case where R = hydrogen, the methyl or benzyl group and the benzyloxycarbonyl radical (Z radical), the tert-butoxycarbonyl radical (BOC radical) and the acetyl group, the following radicals;

$-CH_2COOH$; $-CH(CH_3)-COOH$; $-(CH_3)_2-CH-(CH_2)_2-CH-COO$; $H_3C-H_2C-CH(CH_3)-CH(COOH)-$; $HO-H_2C-CH(COOH)-$; phenyl-$CH_2-CH(COOH)-$; (4-imidazolyl)-$CH_2-CH-COOH)-$; $HN=C(NH_2)-NH-(CH_2)_3-CH(COOH)-$; $H_2N-(CH_2)_4-CH(COOH)-$; $H_2N-CO-CH_2-CH-(COOH)-$; $HOOC(CH_2)_2-CH(COOH)-$;

R_1 can furthermore be, in the case where R is hydrogen, the Z group, the BOC radical, the acetyl or the benzyl group, the acid radical of a natural or unnatural amino acid, e.g. the α-glycyl, the α-sarcosyl, the α-alanyl, the α-leucyl, the α-isoleucyl, the α-seryl, the α-phenylalanyl, the α-histidyl, the α-prolyl, the α-arginyl, the α-lysyl, the α-asparagyl and the α-glutamyl radicals, where the amino groups of the respective amino acids can be present in unprotected or protected form. Possible protective groups for the amino function are the carbobenzoxy radical (Z radical and the tert-butoxycarbonyl radical (BOC radical) as well as the acetyl group. In the case of the asparagyl and glutamyl radical claimed for R_1, the second, unbonded carboxyl group is present as a free carboxyl group or in the form of an ester with C_1-C_6-alkanols, e.g. as a methyl, ethyl or as a tert-butyl ester.

R_1 can furthermore be the allylaminocarbonyl-2-methylprop-1-yl group,

R and R_1 can furthermore, together with the nitrogen atom to which they are bonded, form a piperazine ring of the formula 3 or a homopiperazine ring, if R_1 is an aminoalkylene group in which



formula 3

R_7 is an alkyl radical, a phenyl ring which can be mono- or polysubstituted by $(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-

alkoxy, halogen, the nitro group, the amino function and by the (C_1-C_6) -alkylamino group. R_7 is furthermore the benzhydryl group and the bis-p-fluorobenzylhydryl group.

R_2 can be hydrogen or the (C_1-C_6) -alkyl group, where the alkyl group is mono- or polysubstituted by halogen and phenyl, which for its part can be mono- or polysubstituted by halogen, (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, carboxyl groups, carboxyl groups esterified with C_1-C_6-alkanols, trifluoromethyl groups, hydroxyl groups, methoxy groups, ethoxy groups or benzyloxy groups. The (C_1-C_6) -alkyl group applying for R_2 can furthermore be substituted by the 2-quinolyl group and the 2-, 3- or 4-pyridyl structure, which can both each be mono- or polysubstituted by halogen, (C_1-C_4) -alkyl groups or (C_1-C_4) -alkoxy groups. R_2 is furthermore the aroyl radical, where the aryl moiety on which this radical is based is the phenyl ring, which can be mono- or polysubstituted by halogen, (C_1-C_6)-alkyl, (C_3-C_7) -cycloalkyl, carboxyl groups, carboxyl groups esterified with C_1-C_6-alkanols, trifluoromethyl groups, hydroxyl groups, methoxy groups, ethoxy groups or benzyloxy groups,

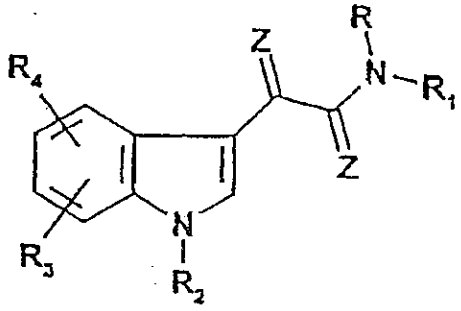
R_3 and R_4 can be identical or different and are hydrogen (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, (C_1-C_6) -alkanoyl, -(C_1-C_6)-alkoxy, halogen or benzyloxy. R_3 and R_4 can furthermore be the nitro group, the amino group, the (C_1-C_4)-mono- or dialkyl-substituted amino group, and the (C_1-C_6)-alkoxycarbonylamino function or (C_1-C_6)-alkoxycarbonylarnino-(C_1-C_6) -alkyl function.

z is O or S

2. Use of one or more N-substituted indole-3-gloxylamides according to Claim 1 of the general formula 1a, their

physiologically tolerable acid addition salts and/or their N-oxides for the production of a medicament for the treatment of a disease selected from the group consisting of resistant and/or multidrug resistant (MDR) tumors, development, migration and/or invasion of metastasizing carcinoma, and diseases in which an angiogenesis-inhibitory effect is functionally desirable, whereby the treatment involves markedly

lower neurotoxicity,



formula Ia

where the radicals

R = hydrogen

R_1 = 4-pyridyl, 4-fluorophenyl

R_2 = benzyl, 4-chlorobenzyl, 4-fluorobenzyl, 3 - pyridylmethyl, 4-bromobenzyl

R_3 and R_4 = hydrogen

and Z is oxygen.

3. Use of one or more N-substituted indole-3-glyoxylamides of the general formula 1 or la according to claims 1 or 2, and their physiologically tolerable acid addition salts and/or their N-oxides, for the production of a medicament for the treatment of a disease selected from the group consisting of resistant and/or multidrug resistant (MDR) tumors, development, migration and/or invasion of metastasizing carcinoma, and diseases in which an angiogenesis-inhibitory effect is functionally desirable, whereby the treatment invloves markedly lower side effects in particular markedly lower neurotoxicity, in particular of the following compounds, their physiologically tolerable acid addition salts and/or their N-oxides:

D 24241 N-(pyridin-4-yl)-[1-(4-fluorobenzyl) indol-3-yl] glyoxylamide

D 24843 N- (pyridin-4-yl) - (1-benzylindol-3-yl) glyoxylamide

D 24850 N- (4-fluorophenyl) -[1- (3-pyridylmethyl) indol-3-yl] glyoxylamide

D 24851 N- (pyridin-4-yl) -[1- (4-chlorobenzyl) indol-3-yl] glyoxylamide

D 25505 N-(pyridin-4-yl)-[1-(4-fluorobenzyl) indol-3-yl] glyoxylamide HCl salt

4. Use of one or more N-substituted indole-3-glyoxylamides according to any one of claims 1 to 3, wherein the acid addition salt is selected from the group consisting of salts of mineral acids, such as hydrochloric acid, sulfuric acid, phosphoric acid, salts of organic acids, such as acetic acid, lactic acid, malonic acid, maleic acid, fumaric acid, gluconic acid, glucoronic acid, citric acid, embonic acid, methanesulfonic acid, trifluoroacetic acid, succinic acid and 2-hydroxyethanesulfonic acid,

5. Use of one or more N-substituted indole-3-glyoxylamides according to any one of claims 1 to 3, wherein the physiologically tolerable N-oxide is a chemically possible N-oxide of an N-substituted indole-3-gloxylamide or an acid addition salt thereof.

6. Use of one or more N-substituted indole-3-glyoxylamides according to any one of claims 1 to 5, wherein the resistant and/or multidrug resistant (MDR) tumor is a tumor at least resistant to an antitumor drug selected from the group consisting of taxol, doxirubicine, vincristine and epotholone B.

7. Use of one or more N-substituted indole-3-glyoxylamides according to any one of claims 1 to 5, wherein the diseases in which the functionally desirable angiogenesis-inhibitory effect is wound healing.

8. Use of one or more N-substituted indole-3-gloxylamides according to any one of claims 1 to 7, wherein one or more N-substituted indole-3-glyoxylamides their physiologically tolerable acid addition salts and/or N-oxides, as active ingredients are used together with a pharmaceutically utilizable vehicle and/or diluent or excipient in the form of tablets, coated tablets, capsules, solutions for infusion or

ampoules, suppositories, patches, powder preparations which, can be employed by inhalation/ suspensions, creams and ointments.

9. Use of one or more N-substituted indole-3-glyoxylamides of the general formula 1 or la according to claims 1 or 2, their physiologically tolerable acid addition salts and/or N-oxides for the preparation of a medicament having angiogenesis inhibitor activity, in particular said use of one or more of the following compounds, their physiologically tolerable acid addition salts and/or N-oxides:

D 24241 N-(pyridin-4-yl)-[1-(4-fluorobenzyl)indol-3-yl3 glyoxylamide

D 24843 N-(pyridin-4-yl) - (1-benzylindol-3-yl) glyoxyl-amide

D 24850 N-(4-fluorophenyl) - [1- (3-pyridylmethyl) indol-3 -yl] glyoxylamide

D 24851 N-(pyridin-4-yl)-[1- (4-chlorobenzyl)indol-3-yl] glyoxylamide

D 25505 N-(pyridin-4-yl)-[1-(4-fluorobenzyl)indol-3-yl] glyoxylamide HCl salt.

10. Use of one or more N-substituted indole-3-glyoxylamides of the general formula 1 or la to claims 1 or 2, and their physiologically tolerable acid addition salts, and/or N-oxides for the preparation of a medicament for the treatment of pharmaceutically resistant and/or multidrug resistant (MDR) tumors for replacement of one or more antitumor agents which are no longer active on account of resistance formation, in particular said use of one or more of the following compounds, their physiologically tolerable acid addition salts and/or N-oxides

D 24241 N-(pyridin-4-yl) - [1-(4-fluorobenzyl)indol-3-yl] glyoxylamide

D 24843 N-(pyridin-4-yl) - (1-benzylindol-3-yl)glyoxyl-

amide

D 24850 N-(4-fluorophenyl)-[1-(3-pyridylmethyl)indol-3-yl)glyoxylamide

D 24851 N-(pyridin-4-yl)-[1-(4-chlorobenayl)indol-3-yl] glyoxylamide

D 25505 N-(pyridin-4-yl)-[1-(4-fluorobenzyl)indol-3-yl]

glyoxylamide HCl salt.

11. Use of one or more N-substituted indole-3-glyoxylamides of the general formula 1 or 1a according to claims 1 or 2, their physiologically tolerable acid addition salts and/or N-oxides for the preparation of a medicament comprising a fixed or free combination of said one or more N-substituted indole-3-glyoxylamides of the general formula 1 or 1a according to claims 1 or 2 and one or more known antitumor agents for replacement of one or more antitumor agents which are no longer active on account of resistance formation, in particular said use of one or more of the following compounds, their physiologically tolerable acid addition salts and/or N-oxides

D 24241 N-(pyridin-4-yl)-[1- (4-fluorobensyl)indol-3-yl] glyoxylamide

D 24843 N-(pyridin-4-yl)-(1-benzylindol-3-yl)glyoxyl amide

D 24850 N-(4-fluorophenyl) - [1-(3-pyridylmethyl) indol-3-yl]glyoxylamide

D 24851 N-(pyridin-4-yl)-[1-(4-chlorobenzyl) indol-3-yl]glyoxylamide

D 25505 N-(pyridin-4-yl) - [1-(4-fluorobenzyl) indol-3-yl]glyoxylamide HCl salt.