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(54) Title: 3-SUBSTITUTED PYRROLO (2.1-A) ISOQUINOLINE DERIVATIVES

(57) Abstract: The present invention relates to pyrrolo[2.1-a]dihydroisoquinolines which are inhibitors of phosphodiesterase 10a and can be used for combating cancer.

3-SUBSTITUTED PYRROLO (2.1-A) ISOQUINOLINE DERIVATIVES

The present invention relates to 3-substituted pyrrolo[2.1-a]isoquinoline derivatives which are inhibitors of phosphodiesterase 10a, a process for preparing those compounds and a method of treating cancer by administering those compounds.

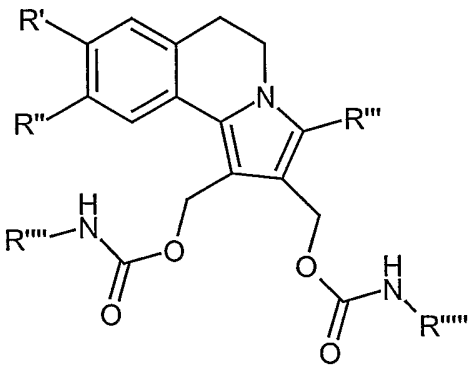
Cyclic AMP metabolism is regulated by the opposing activities of adenylyl cyclase, which generates cAMP in response to extracellular stimuli (e.g. engagement of G-protein coupled receptors by their cognate ligands), and 3', 5' cyclic nucleotide phosphodiesterases (PDEs), which hydrolyze cAMP to 5'-AMP. Signal transduction via cAMP is associated with transcriptional events that can result in the inhibition of cellular proliferation (W.L. Lowe et al., Endocrinology. 138, 2219 (1997)); D.A. Albert, J. Clin. Invest. 95, 1490 (1995); M.I. Mednieks et al., FEBS Lett. 254, 83 (1989). Indeed, elevation of intracellular cAMP concentration is growth inhibitory for several human tumor cell lines, including those derived from breast, lung and colorectal carcinomas (I.S. Fentimen et al., Mol. Biol. Med. 2, 81 (1984); P. Cassoni et al., Int. J. Cancer 72, 340 (1997); S. Shafer et al., Biochem. Pharmacol. 56, 1229 (1998); N.M. Hoosein et al., Regul. Peptides 24, 15 (1989)). In several human breast carcinoma cell lines, increased cAMP production through stimulation of adenylate cyclase activity and/or reduction in cAMP catabolism through inhibition of phosphodiesterase activity has been shown to result in increased steady state levels of cAMP and growth inhibition (N. Veber et al., Eur. J. Cancer. 30A, 1352 (1994); J.A. Fontana et al., J. Natl. Cancer Inst. 78, 1107 (1987); T.A. Slotkin et al., Breast Cancer Res. and Treatment. 60, 153 (2000)). In contrast to breast tumor cell lines, normal human mammary epithelial cells are stimulated to proliferate by elevation of intracellular cAMP (I.S. Fentimen et al., Mol. Biol. Med. 2, 81 (1984)). These observations suggest that elevation of intracellular cAMP may selectively inhibit breast tumor cell proliferation. Interestingly, it has been reported that neoplastic mammary tissues have higher levels of low-Km phosphodiesterase activity compared to normal breast tissue, suggesting that tumors may gain a growth or survival

advantage by keeping intracellular cAMP levels in check (A.L. Singer et al., Cancer Res. 36, 60 (1976)).

The ICAST (Inhibitor of Cyclic AMP Signal Transduction) gene encodes a specific 3',5'-cyclic nucleotide phosphodiesterase. Compared to corresponding normal tissues, ICAST mRNA is overexpressed in breast carcinoma specimens, liver metastases of colorectal carcinoma and non-small cell lung carcinomas. The ICAST cDNA was also recently cloned by other groups and named PDE10a (K. Fujishige et al., J. Biol. Chem. 274, 18 438 (1999); S.H. Soderling et al., Proc. Natl. Acad. Sci. USA 96, 7071 (1999); K. Loughney et al., Gene 234, 109 (1999)). Published expression data for ICAST mRNA show a very limited distribution across adult human tissues, with highest levels observed in the testis, caudate nucleus and putamen (K. Fujishige et al., 1999). Increased expression of ICAST mRNA in human tumor specimens indicates that ICAST may play an important role in tumor cell growth and/or survival under conditions of elevated cAMP generation. Selective inhibition of ICAST activity in tumor cells should lead to increased cAMP concentrations and growth inhibition. The expression profile of ICAST and the published reports indicating that breast, lung and colon carcinomas are particularly sensitive to elevation of intracellular cAMP indicate that ICAST may play critical roles specifically in those tumor types. In addition to elevation of cAMP, inhibition of ICAST activity should also decrease the intracellular concentration of 5-AMP, which could limit purine pools and DNA synthesis in rapidly dividing tumor cells.

Certain pyrrolo[2.1-a]isoquinoline derivatives are known from the literature as, for example, hypotensive agents or psychotropic agents (e.g. GB-A 1,153,670; U.S. 4,694,085; H. Meyer, Liebigs Ann. Chem. 9, 1534-1544 (1981)). Pyrrolo[2.1-a]-isoquinoline derivatives for the treatment of dermatologic diseases such as psoriasis are disclosed in WO 98/55118. However, the compounds disclosed in WO 98/55118 are described as having virtually no cytotoxic activity.

Pyrrolo[2.1-a]isoquinoline derivatives of the formula (A) are described in J. Med. Chem. 27, 1321 (1984) and in J. Med. Chem. 31, 2097 (1988):

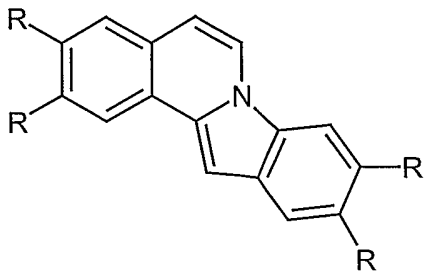


(A)

R' = H, OMe, Cl
R'' = H, Cl
R''' = H, Me
R'''', R''''' = Me, Et, i-Pr, C_6H_{11}

These compounds are described as having antineoplastic activity, which however is stated to be due to the carbamate moieties being electrophilic centers enabling the compounds (A) to react via an alkyl-oxygen cleavage mechanism. It is not mentioned that these compounds have any PDE 10a inhibitory activity.

Tetracyclic compounds of the formula (B) containing a pyrrolo[2.1-a]isoquinoline moiety are described in Arch. Pharm. 321, 481 (1988):



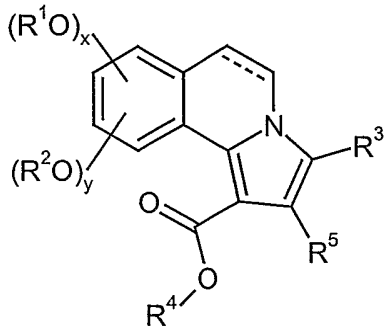
(B)

R = H, OMe

The compounds B are described as having anti-tumor activity due to their ability to intercalate into DNA. It is not mentioned that these compounds have any PDE 10a inhibitory activity.

Surprisingly, it has been found that the pyrrolo[2.1-a]isoquinoline derivatives of the present invention inhibit PDE 10a and exhibit an antiproliferative activity.

The present invention relates to a compound of the formula



(I)

wherein

x and y independently from each other denote zero or 1 and

x+y is 1 or 2;

R^1 and R^2 independently from each other denote hydrogen, C_{1-4}-alkyl or CF_3 or

R^1 and R^2 together form a C_{1-4}-alkylene bridge;

R^3 denotes hydrogen, formyl, (C_{1-4}-alkyl)-carbonyl, (C_{1-4}-alkoxy)-carbonyl, NO_2, NR^6R^7, C_{1-4}-alkyl-NR^6R^7, C_{1-4}-alkyl-OR^8, C_{1-4}-alkyl-$COOR^8$, C_{6-10}-aryl-C_{1-4}-alkyl wherein the aryl moiety is optionally substituted with 1 to 3 radicals selected from the group consisting of OH, C_{1-4}-alkyl and C_{1-4}-alkoxy;

wherein

R^6 and R^7 independently from each other denote hydrogen, C_{1-4}-alkyl, C_{3-8}-cycloalkyl, C_{6-10}-aryl-C_{1-4}-alkyl wherein the aryl moiety is optionally substituted with 1 to 3 radicals selected from the group consisting of OH, C_{1-4}-alkyl and C_{1-4}-alkoxy; or

R^6 and R^7 together with the nitrogen atom to which they are attached, form a 5- to 7-membered heterocyclyl which may contain up to 2 further hetero atoms selected from the group consisting of N, O and S, which heterocyclyl can further be substituted with 1 to 3 radicals selected from the group consisting of OH, C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{6-10}-aryl and aromatic 4- to 9-membered heterocyclyl with 1 to 4 hetero atoms selected from the group consisting of N, O and S;

R^8 denotes hydrogen or C_{1-4}-alkyl;

R^4 denotes C_{1-4}-alkyl;

R^5 is

i) C_{6-14}-aryl optionally containing 1 to 3 further substituents selected from the group consisting of

halogen;

C_{1-6}-alkyl which can be further substituted with one or more radicals selected from the group consisting of C_{1-6}-alkoxy, OH and NH_2;

C_{1-6}-alkoxy which can be further substituted with one or more radicals selected from the group consisting of C_{1-6}-alkoxy,OH and NH_2;

C_{6-10}-aryloxy-C_{1-6}-alkoxy;

OH;

NO_2;

CN;

CF_3;

OCF_3;

NR^9R^{10};

$CONR^9R^{10}$;

$COOR^{11}$;

SR^{11};

SOR^{11};

SO_2R^{11};

OSO_2R^{11};

-O-$(CH_2)_{1-4}$-O- wherein the oxygen atoms are bound to the aryl moiety in ortho-position to each other;

phenyloxy or benzyloxy wherein the phenyl moieties can contain one further substituent selected from the group consisting of C_{1-6}-alkyl, C_{1-6}-alkoxy, halogen and NO_2;

phenyl optionally substituted with CN;

aromatic 4- to 9-membered heterocyclyl with 1 to 4 hetero atoms selected from the group consisting of N, O and S;

and

saturated 5- to 7-membered nitrogen-containing heterocyclyl which is linked to the C_{6-10}-aryl moiety via the nitrogen atom and may contain up to 2 further hetero atoms selected from the group consisting of N, O and S and which saturated heterocyclyl can be further substituted with one or more radicals selected from the group consisting of C_{1-6}-alkoxy, OH and NH_2;

wherein

R^9 and R^{10} independently from each other denote hydrogen, C_{1-6}-alkyl, (C_{1-6}-alkyl)-carbonyl, (C_{1-6}-alkoxy)-carbonyl, C_{1-6}-alkylsulfonyl, (C_{1-6}-alkylamino)-carbonylamino, (C_{6-10}-arylamino)-carbonylamino, or

R^9 and R^{10} together with the nitrogen atom to which they are attached, form a 5- to 7-membered saturated, partially unsaturated or aromatic heterocyclyl which can contain up to 3 further hetero atoms selected from the group consisting of N, O and S, and which heterocyclyl can contain 1 to 3 substituents selected from the group consisting of

C_{1-6}-alkyl, C-$_{1-6}$-alkoxy, C_{6-10}-aryl and aromatic 4- to 9-membered heterocyclyl with 1 to 4 hetero atoms selected from the group consisting of N, O and S;

R^{11} is hydrogen, C_{1-6}-alkyl or C_{6-10}-aryl;

or

ii) C_{1-12}-alkyl which can contain 1 to 3 substituents selected from the group consisting of C_{1-6}-alkyl, C_{-1-6}-alkoxy, C_{6-10}-aryl and aromatic 4- to 9-membered heterocyclyl with 1 to 4 hetero atoms selected from the group consisting of N, O and S;

or

iii) C_{3-8}-cycloalkyl which can contain 1 to 3 substituents selected from the group consisting of C_{1-6}-alkyl, C_{-1-6}-alkoxy, $COOR^{11}$ wherein R^{11} is as defined above, C_{6-10}-aryl and aromatic 4- to 9-membered heterocyclyl with 1 to 4 hetero atoms selected from the group consisting of N, O and S;

or

iv) aromatic C_{2-9}-heterocyclyl with 1 to 4 hetero atoms selected from the group consisting of N, O and S which aromatic heterocyclyl can contain 1 to 3 further substituents selected from the group consisting of OH, C_{1-6}-alkyl, C_{-1-6}-alkoxy, C_{6-10}-aryl which can contain 1 to 3 halogen radicals, COR^{11} or $COOR^{11}$ wherein R^{11} is as defined above, halogen, CN, and saturated 5- to 7-membered nitrogen-containing heterocyclyl which is linked to the C_{6-10}-aryl moiety via the nitrogen atom and can contain up to 2 further hetero atoms selected from the group consisting of N, O and S and which saturated heterocyclyl can be further substituted with one or more radicals selected from the group consisting of C_{1-6}-alkoxy, OH and NH_2;

with the proviso that ethyl 8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2.1-a]isoquinoline-1-carboxylate is excluded;

and an isomer, a (pharmaceutically acceptable) salt, a hydrate or a hydrate of a (pharmaceutically acceptable) salt thereof.

An alternative embodiment of the present invention relates to a compound of the formula (I), wherein

x and y independently from each other denote zero or 1 and

x+y is 1 or 2;

R^1 and R^2 independently from each other denote C_{1-4}-alkyl or CF_3;

R^3 denotes hydrogen, formyl, (C_{1-4}-alkyl)-carbonyl, (C_{1-4}-alkoxy)-carbonyl, NO_2, NR_6R_7, C_{1-4}-alkyl-NR^6R^7, C_{1-4}-alkyl-OR^8, C_{1-4}-alkyl-$COOR^8$, C_{6-10}-aryl-C_{1-4}-alkyl wherein the aryl moiety can be substituted with 1 to 3 radicals selected from the group consisting of OH, C_{1-4}-alkyl and C_{1-4}-alkoxy;

wherein

R^6 and R^7 independently from each other denote hydrogen, C_{1-4}-alkyl, C_{3-8}-cycloalkyl, C_{6-10}-aryl-C_{1-4}-alkyl wherein the aryl moiety can be substituted with 1 to 3 radicals selected from the group consisting of OH, C_{1-4}-alkyl and C_{1-4}-alkoxy; or

R^6 and R^7 together with the nitrogen atom to which they are attached, form a 5- to 7-membered heterocyclyl which may contain up to 2 further hetero atoms selected from the group consisting of N, O and S and which heterocyclyl can be further substituted with 1 to 3 radicals selected from the group consisting of OH, C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{6-10}-aryl and aromatic 4- to 9-membered heterocyclyl with 1 to 3 hetero atoms selected from the group consisting of N, O and S;

R^8 denotes hydrogen or C_{1-4}-alkyl;

R^4 denotes C_{1-4}-alkyl;

R^5 is

i) phenyl optionally having 1 to 3 further substituents selected from the group consisting of F, Cl, Br; C_{1-6}-alkyl; C_{1-6}-alkoxy; OH; NR^9R^{10} and $COOR^{11}$; or
naphthyl optionally containing one further OH group;

or

iv) indolyl optionally having 1 to 3 further substituents selected from the group consisting of F, Cl, Br; C_{1-6}-alkyl; C_{1-6}-alkoxy; OH; NR^9R^{10} and $COOR^{11}$;

wherein

R^9 to R^{11} independently from each other denote C_{1-6}-alkyl;

with the proviso that ethyl 8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2.1-a]isoquinoline-1-carboxylate is excluded;

and an isomer, a (pharmaceutically acceptable) salt, a hydrate or a hydrate of a (pharmaceutically acceptable) salt thereof.

A further alternative embodiment of the present invention relates to a compound of the formula (I), wherein

x and y independently from each other denote zero or 1 and

x+y is 1 or 2;

R^1 and R^2 independently from each other denote CH_3 or C_2H_5;

R^3 denotes hydrogen, formyl, (C_{1-4}-alkyl)-carbonyl, (C_{1-4}-alkoxy)-carbonyl, NO_2, NR^6R^7, C_{1-4}-alkyl-NR^6R^7, C_{1-4}-alkyl-OR^8, C_{1-4}-alkyl-$COOR^8$, C_{6-10}-aryl-C_{1-4}-alkyl wherein the aryl moiety can be substituted with 1 to 3 radicals selected from the group consisting of OH, C_{1-4}-alkyl and C_{1-4}-alkoxy;

wherein

R^6 and R^7 independently from each other denote hydrogen, C_{1-4}-alkyl, C_{3-8}-cycloalkyl, C_{6-10}-aryl-C_{1-4}-alkyl wherein the aryl moiety can be substituted with 1 to 3 radicals selected from the group consisting of OH, C_{1-4}-alkyl and C_{1-4}-alkoxy; or

R^6 and R^7 together with the nitrogen atom to which they are attached, form a 5- to 7-membered heterocyclyl which may contain up to 2 further hetero atoms selected from the group consisting of N, O and S and which heterocyclyl can be further substituted with 1 to 3 radicals selected from the group consisting of OH, C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{6-10}-aryl and aromatic 4- to 9-membered heterocyclyl with 1 to 3 hetero atoms selected from the group consisting of N, O and S;

R^8 denotes hydrogen or C_{1-4}-alkyl;

R^4 denotes CH_3 or C_2H_5;

R^5 is

i) phenyl optionally having 1 to 3 further substituents selected from the group consisting of Cl; C_{1-4}-alkyl; C_{1-4}-alkoxy; OH; NR^9R^{10} and $COOR^{11}$; or

naphthyl optionally containing one further OH group;

wherein

R^9 to R^{11} independently from each other denote C_{1-4}-alkyl;

or

iv) indolyl;

with the proviso that ethyl 8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2.1-a]isoquinoline-1-carboxylate is excluded;

and an isomer, a (pharmaceutically acceptable) salt, a hydrate or a hydrate of a (pharmaceutically acceptable) salt thereof.

A further alternative embodiment of the present invention relates to a compound of the formula (I), wherein

x and y independently from each other denote zero or 1 and

x+y is 1 or 2;

R^1 and R^2 independently from each other denote CH_3 or C_2H_5;

R^3 denotes hydrogen, formyl, (C_{1-4}-alkyl)-carbonyl, (C_{1-4}-alkoxy)-carbonyl, NO_2, NH_2, C_{1-4}-alkyl-NR^6R^7, C_{1-4}-alkyl-OR^8, C_{1-4}-alkyl-$COOR^8$, phenyl-C_{1-4}-alkyl wherein the phenyl moiety can be substituted with 1 to 3 C_{1-4}-alkyl or C_{1-4}-alkoxy moieties;

wherein

R^6 and R^7 independently from each other denote hydrogen, C_{1-4}-alkyl, C_{3-6}-cycloalkyl, phenyl-C_{1-4}-alkyl wherein the phenyl moiety can be substituted with 1 to 3 C_{1-4}-alkyl or C_{1-4}-alkoxy radicals; or

R^6 and R^7 together with the nitrogen atom to which they are attached, form a saturated 5- to 7-membered heterocyclyl which may contain up to 2 further hetero atoms selected from the group consisting of N, O and S and which saturated heterocyclyl can be further substituted with 1 to 3 radicals selected from the group consisting of C_{1-4}-alkyl, C_{1-4}-alkoxy, phenyl and pyridyl;

R^8 denotes hydrogen or C_{1-4}-alkyl;

R^4 denotes CH_3 or C_2H_5;

R^5 is

i) phenyl optionally having 1 to 3 further substituents selected from the group consisting of Cl; C_{1-4}-alkyl; C_{1-4}-alkoxy; OH; NR^9R^{10}; and $COOR^{11}$; or

naphthyl optionally containing one further OH group;

wherein

R^9 to R^{11} independently from each other denote C_{1-4}-alkyl;

or

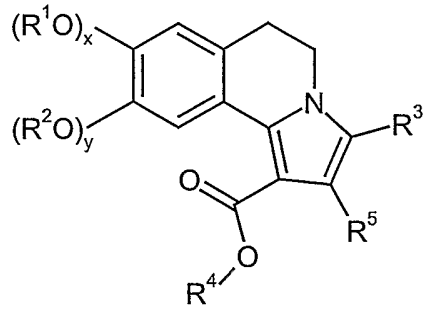
iv) indolyl;

with the proviso that ethyl 8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2.1-a]isoquinoline-1-carboxylate is excluded;

and an isomer, a (pharmaceutically acceptable) salt, a hydrate or a hydrate of a (pharmaceutically acceptable) salt thereof.

A bond with a dotted line thereunder, ---- denotes a bond which alternatively is a single bond or a double bond.

Compounds (I) wherein the radicals $(R^1O)_x$ and $(R^2O)_y$ are attached to the phenyl ring in the following positions, are particularly preferred:



Furthermore, according to the present invention the respective 5,6-dihydro pyrrolo derivatives of formula (I) are preferred.

Furthermore, the compounds of Examples 2, 5, 23 and 27 are particularly preferred.

Pharmaceutically acceptable salts according to the invention are non-toxic salts which in general are accessible by reaction of the compounds (I) with an inorganic or organic base or acid conventionally used for this purpose. Non-limiting examples of pharmaceutically acceptable salts of compounds (I) include the alkali metal salts, e.g.

lithium, potassium and sodium salts, the alkaline earth metal salts such as the magnesium and calcium salts, the quaternary ammonium salts such as, for example, the triethyl ammonium salt, acetates, benzene sulphonates, benzoates, dicarbonates, disulphates, ditartrates, borates, bromides, carbonates, chlorides, citrates, dihydrochlorides, fumarates, gluconates, glutamates, hexyl resorcinates, hydrobromides, hydrochlorides, hydroxynaphthoates, iodides, isothionates, lactates, laurates, malates, maleates, mandelates, mesylates, methylbromides, methylnitrates, methylsulphates, nitrates, oleates, oxalates, palmitates, pantothenates, phosphates, diphosphates, polygalacturonates, salicylates, stearates, sulphates, succinates, tartrates, tosylates, valerates, and other salts used for medicinal purposes.

The present invention includes both the individual enantiomers or diastereomers and the corresponding racemates, diastereomer mixtures and salts of the compounds according to the invention. In addition, all possible tautomeric forms of the compounds described above are included according to the present invention. The diastereomer mixtures can be separated into the individual isomers by chromatographic processes. The racemates can be resolved into the respective enantiomers either by chromatographic processes on chiral phases or by resolution.

In the context of the present invention, the substituents, if not stated otherwise, in general have the following meaning:

Alkyl per se as well as the prefixes "alkyl" and "alk" in the terms "alkylcarbonyl", "alkylsulphonyl", "alkylaminocarbonylamino", "alkoxy", and "alkoxycarbonyl" represent a linear or branched alkyl radical preferably having 1 to 12, more preferably 1 to 6 carbon atoms. Non-limiting examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, hexyl, and isohexyl.

Non-limiting examples of "alkylcarbonyl" include acetyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl, butylcarbonyl, and isobutylcarbonyl. The terms “alkylcarbonyl” and “acyl” are used synonymously.

Non-limiting examples of "alkylsulphonyl" include methylsulphonyl, ethylsulphonyl, propylsulphonyl, isopropylsulphonyl, butylsulphonyl, and isobutylsulphonyl.

Non-limiting examples of "alkylaminocarbonylamino" include methylamino-carbonylamino, ethylaminocarbonylamino, propylaminocarbonylamino, isopropyl-aminocarbonylamino, butylaminocarbonylamino, and isobutylaminocarbonylamino.

Non-limiting examples of "alkoxy" include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentoxy, isopentoxy, hexoxy, and isohexoxy.

Non-limiting examples of "alkoxycarbonyl" include methoxycarbonyl, ethoxy-carbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, and isobutoxy-carbonyl.

Alkylene represents a linear or branched (bivalent) alkylene radical preferably having 1 to 4 carbon atoms. Non-limiting examples include methylene, ethylene, propylene, α-methylethylene, ß-methylethylene, α-ethylethylene, ß-ethylethylene, butylene, α-methylpropylene, ß-methylpropylene, and γ-methylpropylene.

Cycloalkyl represents a saturated cycloalkyl radical preferably having 3 to 8 carbon atoms. Non-limiting examples include cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl; cyclopropyl, cyclopentyl and cyclohexyl are preferred.

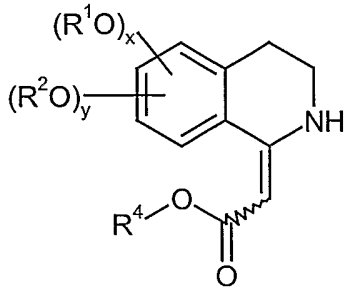
Aryl per se and in the terms "aryloxy", "aryl-alkyl", and "arylaminocarbonylamino" represents an aromatic radical preferably having from 6 to 14, more preferably 6 to 10 carbon atoms. Non-limiting examples of aryl radicals include phenyl, benzyl, naphthyl, and phenanthrenyl. Non-limiting examples of aryloxy radicals include phenyloxy and benzyloxy. Non-limiting examples of aryl-alkyl radicals include benzyl. Non-limiting examples of arylaminocarbonylamino radicals include phenyl-

aminocarbonylamino, benzylaminocarbonylamino, naphthylaminocarbonylamino, and phenanthrenylaminocarbonylamino.

Heterocyclyl in the context of the invention represents a saturated, partially saturated or aromatic 4- to 9-membered, for example 5- to 6-membered ring which can contain from 1 to 3 hetero atoms selected from the group consisting of S, N and O and which ring can be bound via a carbon atom or a nitrogen atom, if such an atom is present. Non-limiting heterocyclyl examples include: oxadiazolyl, thiadiazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, quinolinyl, isoquinolinyl, indolyl, thienyl, furyl, pyrrolyl, N-methylpyrrolyl, indazolyl, benzimidazolyl, pyrrolidinyl, piperazinyl, tetrahydropyranyl, tetrahydrofuranyl, 1,2,3 triazolyl, thiazolyl, oxazolyl, imidazolyl, morpholinyl, thiomorpholinyl or piperidyl. Preferred examples include thiazolyl, furyl, oxazolyl, pyrazolyl, triazolyl, pyridyl, pyrimidinyl, pyridazinyl and tetrahydropyranyl. The terms "heteroaryl" and "hetaryl" denotes an aromatic heterocyclic radical.

Halogen in the context of the invention represents fluorine, chlorine, bromine, and iodine.

The present invention also relates to a process for manufacturing the compounds according to the invention comprising the reaction of a compound of the formula



(IV)

wherein

x, y, R^1, R^2 and R^4 are as defined above,

[A] with the compounds of the formulae

R^5-CHO and R^3-CH_2-NO_2

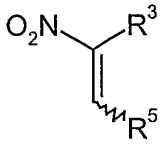
(II) (III)

wherein

$R^3$and R^5 are as defined above,

or

[B] with a compound of the formula



(V)

wherein

R^3 and R^5 are as defined above,

and optionally

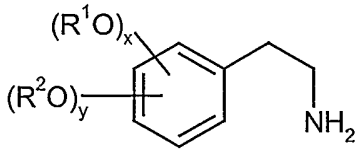
[C] the conversion of the compound obtained through either process [A] or [B] into an isomer, a pharmaceutically acceptable salt, a hydrate or a hydrate of a pharmaceutically acceptable salt thereof.

The compounds (II) are commercially available or can be synthesized according to methods commonly known to those skilled in the art (I.T. Harrison and S. Harrison, Compendium of Organic Synthetic Methods, pp. 132-176, Wiley-Interscience; T.D.

Harris and G.P. Roth, J. Org. Chem. 44, 146 (1979); E. Müller (ed.), " Methoden der Organischen Chemie" (Houben-Weyl), Vol. VII/1 Sauerstoff-Verbindungen II, Georg Thieme Verlag, Stuttgart 1954).

The compounds (III) are commercially available.

The compounds (IV) can be synthesized by reacting compounds of the formula

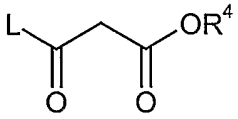


(VI)

wherein

x, y, R^1 and R^2 are as defined above,

with compounds of the formula

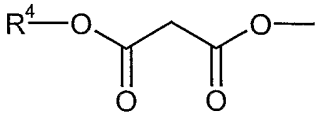


(VII)

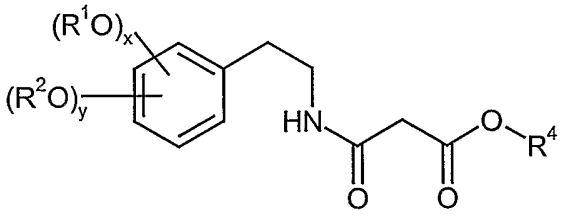
wherein

R^4 is as defined above, and

L is a leaving group, for example a halogen radical such as Cl, or a radical of the formula



to give compounds of the formula



(VIII)

wherein

x, y, R^1, R^2 and R^4 are as defined above,

and reacting compound (VIII) with a dehydrating agent.

The compounds (VI) are commercially available or can be synthesized according to methods commonly known to those skilled in the art (H. Mayer et al., Heterocycles 31, 1035 (1990); E. Müller (ed.), "Methoden der Organischen Chemie" (Houben-Weyl), 4th ed., Vol. 11/1 Stickstoff-Verbindungen II, Georg Thieme Verlag, Stuttgart 1957; Shepard et al. in J. Org. Chem. 17, 568 (1952) and in J. Am. Chem. Soc. 72, 4364 (1950)).

The compounds (VII) are commercially available or can be synthesized according to methods commonly known those skilled in the art [e.g. via acylation of acetic acid with an alkyl chloroformate or dialkyl carbonate (March, Advanced Organic Chemistry, 3rd ed., p. 440-441, Wiley 1985) and converting the resulting monoester of malonic acid into e.g. the corresponding acid chloride or anhydride by methods commonly known to those skilled in the art (see e.g. March, Advanced Organic Chemistry, 3rd ed., p. 355, 388, Wiley 1985)].

The reaction between the compounds (VI) and (VII) is preferably carried out in a solvent. Suitable solvents comprise the customary organic solvents which are inert under the reaction conditions. Non-limiting examples include ethers such as diethyl ether, dioxane, tetrahydrofuran, 1,2-dimethoxy ethane; hydrocarbons such as benzene, toluene, xylene, hexane, cyclohexane, mineral oil fractions; halogenated hydrocarbons

such as dichloromethane, trichloromethane, carbon tetrachloride, dichloroethane, trichloroethylene, chlorobenzene; ketones such as acetone; esters such as ethyl acetate; nitriles such as acetonitrile; heteroaromatics such as pyridine; polar solvents such as dimethyl formamide and hexamethyl phosphoric acid tris-amide; and mixtures of the above-mentioned solvents. Dichloromethane is particularly preferred.

The compound (VII) is generally employed in an amount of from 1 to 4 mol per mol of compound (VI); an equimolar amount or slight excess of compound (VII) is preferred.

The reaction between the compounds (VI) and (VII) is preferably carried out in the presence of a base. Non-limiting examples include alkali metal hydrides and alkali metal alkoxides such as, for example, sodium hydride and potassium tert-butoxide; C_1-C_4-alkyl amines such as, for example, triethyl amine; cyclic amines such as, for example, piperidine, pyridine, dimethylamino pyridine and -preferably - 1,8-diaza-bicyclo[4.3.0]undec-7-ene (DBU). The base is generally employed in an amount of from 1 to 4 mol per mol of compound (VI); an equimolar amount or slight excess of the base is preferred.

The reaction of the compounds (VI) and (VII) can generally be carried out within a relatively wide temperature range. In general, the reaction is carried out within a range of from -20 to 200°C, preferably from 0 to 70°C, and more preferably at room temperature.

For the cyclization of the compounds (VIII) to yield compounds (IV), dehydrating agents such as, for example, P_2O_5 or $POCl_3$ are generally employed in an amount of from 1 to 10 mol, preferably from 3 to 8 mol, per mol of compound (VIII).

The cyclization reaction of the compounds (VIII) to yield the compounds (IV) is also preferably carried out in a solvent. Non-limiting examples comprise the customary organic solvents which are inert under the reaction conditions. They preferably include ethers such as diethyl ether, dioxane, tetrahydrofuran, 1,2-dimethoxy ethane; hydro-

carbons such as benzene, toluene, xylene, hexane, cyclohexane, mineral oil fractions; halogenated hydrocarbons such as dichloromethane, trichloromethane, carbon tetrachloride, dichloroethane, trichloroethylene, chlorobenzene; esters such as ethyl acetate; ketones such as acetone; nitriles such as acetonitrile; heteroaromatics such as pyridine; polar solvents such as dimethyl formamide and hexamethyl phosphoric acid tris-amide; and mixtures thereof. Toluene is preferred, if the reaction is carried out with P_2O_5, and acetonitrile is preferred, if the reaction is carried out with $POCl_3$ (Benovsky, Stille, Tetrahedron Lett. 38, 8475-8478 (1997)).

The temperature for the cyclization reaction of compounds (VIII) is preferably within a range of from 60 to 200°C and more preferably within a range of from 80 to 120°C.

The above process steps are generally carried out under atmospheric pressure. However, it is also possible to carry them out under superatmospheric pressure or under reduced pressure (for example, in a range of from 0.5 to 5 bar). The reaction time can generally be varied within a relatively wide range. In general, the reaction is finished after a period of from 2 to 24 hours, preferably from 6 to 12 hours.

The reaction of the compounds (IV) with either compounds (II) and (III) or with compound (V) can be carried out as a one-pot synthesis, preferably in a solvent. Suitable solvents comprise the customary organic solvents which are inert under the reaction conditions. Non-limiting examples include ethers such as diethyl ether, dioxane, tetrahydrofuran, 1,2-dimethoxy ethane; hydrocarbons such as benzene, toluene, xylene, hexane, cyclohexane, mineral oil fractions; halogenated hydrocarbons such as dichloromethane, trichloromethane, carbon tetrachloride, dichloroethane, trichloroethylene, chlorobenzene; alcohols such as methanol, ethanol, n-propanol, isopropanol; esters such as ethyl acetate; ketones such as acetone; nitriles such as acetonitrile; heteroaromatics such as pyridine; polar solvents such as dimethyl formamide and hexamethyl phosphoric acid tris-amide; and mixtures thereof. Ethanol/isopropanol (approximately 1:1 vol/vol) mixtures are preferred.

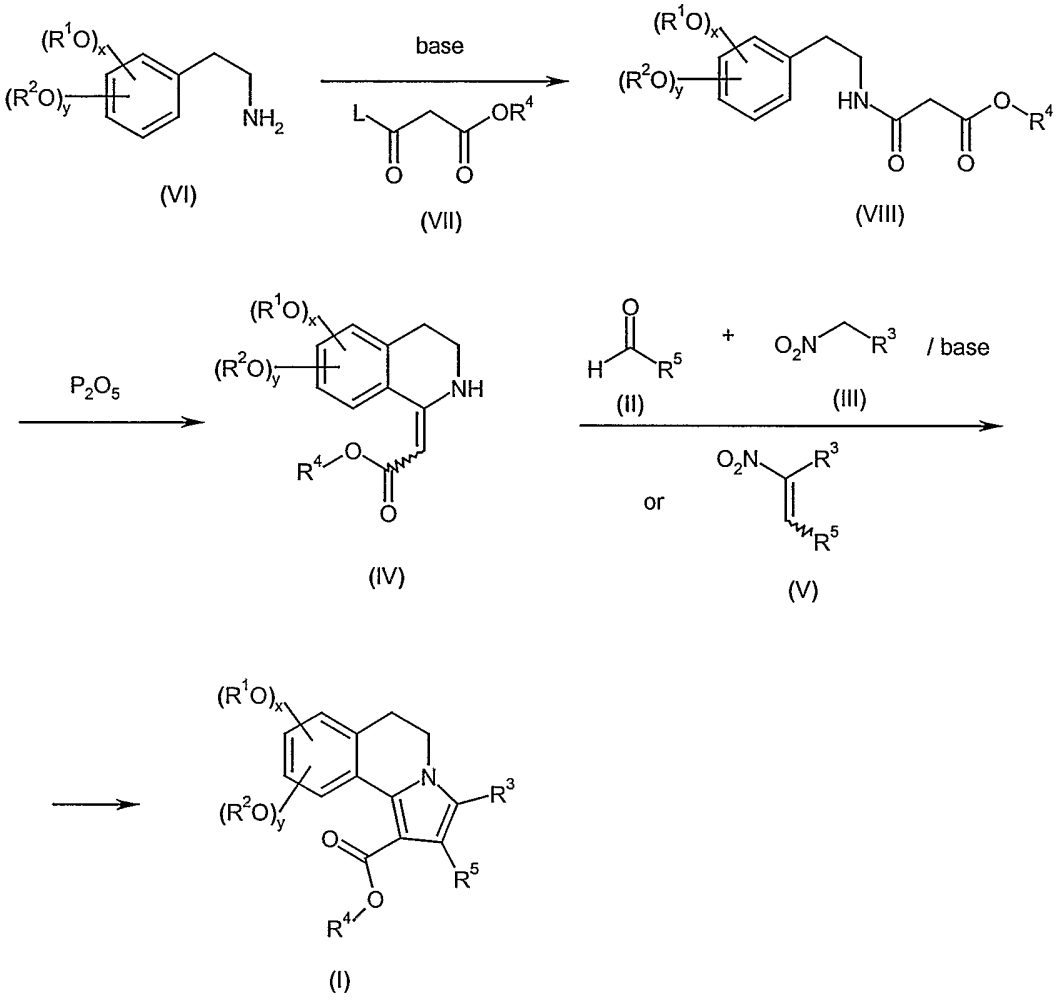
The compounds (III) are generally employed in an amount of from 1 to 3 mol per mol of compound (II); an equimolar amount or slight excess of compound (III) is particularly preferred. The compounds (IV) are generally employed in an amount of from 0.1 to 1 mol, preferably from 0.3 to 1 mol, per mol of compounds (II).

The reactions of the compounds (IV) with either compounds (II) and (III) or with compound (V) are preferably carried out in the presence of a base. Non-limiting examples include alkali metal hydrides and alkali metal alkoxides such as, for example, sodium hydride and potassium tert.-butoxide; C_{1-4}-alkyl amines such as, for example, triethyl amine; cyclic amines such as, for example, pyridine, dimethylamino pyridine, 1,8-diazabicyclo[4.3.0]undec-7-ene (DBU) and - preferably - piperidine. The base is generally employed in an amount of from 0.1 to 1 mol, preferably from 0.3 to 1 mol, per mol of compound (II) or compound (V), respectively.

The reactions of the compounds (IV) with either compounds (II) and (III) or with compound (V) are generally carried out within a relatively wide temperature range. In general, they are carried out in a range of from -20 to 200°C, preferably from 0 to 100°C, and more preferably from 50 to 90°C. The steps of this reaction are generally carried out under atmospheric pressure. However, it is also possible to carry them out under superatmospheric pressure or under reduced pressure (for example, in a range of from 0.5 to 5 bar). The reaction time can generally be varied within a relatively wide range. In general, the reaction is finished after a period of from 2 to 24 hours, preferably from 6 to 12 hours.

The compounds (V) are commercially available or can be synthesized in analogy to the reaction of compounds (II) and (III) described above (in the absence of compound (IV).

The process according to the present invention can be illustrated by the following scheme:



wherein

x, y, R^1 to R^5 and L are as defined above.

If the compounds (I) are not directly obtained by reacting the compounds (II), (III) and (IV) or (IV) and (V), the compounds thus obtained have to be converted into the compounds (I) by further reactions known to the man skilled in the art.

For example, compounds (I) wherein R^3 is C_{1-4}-alkyl-NR^6R^7, C_{1-4}-alkyl-OR^8, C_{1-4}-alkyl-$COOR^8$ or C_{6-10}-aryl-C_{1-4}-alkyl can be synthesized from compounds wherein R^3 is C_{1-4}-alkyl (which themselves can be obtained according to one of the above processes A or B) by reaction with a halogenating agent such as sulfuryl chloride

(SO_2Cl_2), thionyl chloride ($SOCl_2$) or N-chlorosuccinimide (NCS), preferably in an organic solvent commonly used for such reactions, for example in a halogenated alkane such as dichloromethane, under conditions known to the skilled man, and a consecutive nucleophilic substitution reaction with an appropriate nucleophile such as the respective amine HNR^6R^7, the respective alkoholate R^8O^- or OH^-, under conditions commonly used for such reactions and known to the skilled man. The halogenated intermediate obtained after the first of the above reaction steps can either be isolated and then reacted with the desired nucleophile or directly be converted into the desired product by reaction with a respective nucleophile.

Compounds (I) wherein R^3 is hydrogen can be synthesized by process A or B using compound (III) or (V) respectively wherein R^3 is hydrogen.

Compounds (I) wherein R^3 is formyl can be synthesized from the compounds wherein R^3 is methyl (which themselves can be obtained according to one of the above processes A or B) by reaction with manganese dioxide in an organic solvent commonly used for such reactions such as, for example, an ether such as dioxane under conditions known to the skilled man. The formyl compounds thus obtained can also be converted into compounds (I) wherein R^3 is $CH_2NR^6R^7$ by a reductive amination reaction commonly known to the skilled man.

Compounds (I) wherein R^3 is C_{1-4}-alkylcarbonyl can be synthesized preferably by reaction of compounds (IV) with compounds (V), wherein R^3 is C_{1-4}-alkylcarbonyl (these derivatives can be prepared from nitromethyl-alkylketones (compare D.C. Baker et al., Synthesis 1978; 478-479) and activated aldehydes, e.g. benzylidene-butyl-amines (see Dornow et al.; Liebigs Ann. Chem. 602; 14, 19 (1957)).

Compounds (I) wherein R^3 is NO_2 can be synthesized from the compounds wherein R^3 is methyl (which themselves can be obtained according to one of the above processes A or B) by reaction with HNO_3 in acetic acid under conditions commonly used for such reactions and known to the skilled man. These nitro compounds can

further be converted into compounds wherein R^3 is NR^6R^7 by a hydrogenation of the nitro group to the respective amino group under conditions commonly used for such reactions and known to the skilled man, and optionally alkylating the amino group under conditions commonly used for such reactions and known to the skilled man.

The compounds of the present invention are inhibitors of phosphodiesterase 10a (PDE 10a). As outlined above, the inhibition of PDE 10a is a promising approach for the treatment of cancer. The biological tests described below show that the compounds (I) exhibit a pronounced anti-proliferation activity against tumor cells; they are therefore useful for the treatment of cancer. Furthermore, our investigations showed that they are also useful for treatment of conditions of pain and/or for the lowering of the temperature of the body in fever conditions.

The compounds according to the invention can be used as active ingredients for the production of medicaments against carcinomatous disorders. For this, they can be converted into the customary formulations such as tablets, coated tablets, aerosols, pills, granules, syrups, emulsions, suspensions and solutions using inert, non-toxic, pharmaceutically suitable excipients or solvents. Preferably, the compounds according to the invention are used in an amount such that their concentration is approximately 0.5 to approximately 90% by weight, based on the ready-to-use formulations, the concentration being dependent, inter alia, on the indication of the medicament.

The formulations can be produced, for example, by extending the active compounds with solvents and/or excipients having the above properties, where, if appropriate, additionally emulsifiers or dispersants and, in the case of water as the solvent, an organic solvent can additionally be added.

Administration can be carried out in a customary manner, preferably orally, transdermally or parenterally, for example perlingually, buccally, intravenously, nasally, rectally or inhalationally.

For human use, in the case of oral administration, it is recommended to administer doses of from 0.001 to 50 mg/kg, preferably from 0.01 to 20 mg/kg. In the case of parenteral administration such as, for example, intravenously or via mucous membranes nasally, buccally or inhalationally, it is recommended to use doses of from 0.001 to 0.5 mg/kg.

If appropriate, it may be necessary to depart from the amounts mentioned above, namely depending on the body weight or the type of administration route, on the individual response towards the medicament, the manner of its formulation and the time or interval at which administration takes place. Thus, in some cases it may be sufficient to manage with less than the above mentioned minimum amount, while in other cases the upper limit mentioned must be exceeded. In the case of the administration of relatively large amounts, it may be recommended to divide these into several individual doses over the course of the day.

The compounds according to the invention are also suitable for use in veterinary medicine. For use in veterinary medicine, the compounds or their non-toxic salts can be administered in a suitable formulation in accordance with general veterinary practice. Depending on the kind of animal to be treated, the veterinary surgeon can determine the nature of use and the dosage.

The present invention provides compounds for the use in a medical application, in particular for combating cancer.

The invention further provides a method of manufacturing a pharmaceutical composition by combining at least one of the compounds of the invention with at least one pharmacologically acceptable formulating agent.

The invention further provides a pharmaceutical composition comprising as an active ingredient an effective amount of at least one of the compounds of the invention and at least one pharmacologically acceptable formulating agent.

The invention further provides a pharmaceutical composition comprising as an active ingredient an effective amount of at least one of the compounds of the invention and at least one pharmaceutical active ingredient which is different from the compounds of the invention.

The invention further provides a medicament in dosage unit form comprising an effective amount of a compound according to the invention together with an inert pharmaceutical carrier.

The invention further provides a method of combating cancer in mammals comprising the administration of an effective amount of at least one compound according to the invention either alone or in admixture with a diluent or in the form of a medicament.

The percentages in the description above, in the following tests and in the Examples are - if not stated otherwise - percentages by weight; parts are parts by weight. Solvent ratios, dilution ratios and concentrations in solutions of liquids in liquids are ratios and concentrations by volume.

Biological tests

***In vitro* Enzyme Inhibition Assay**

Full-length recombinant PDE 10a was expressed in Sf9 insect cells (Invitrogen, Carlsbad, California, U.S.A.) using the Bac-to-Bac™ Baculovirus Expression System (Life Technologies, Gaithersburg, MD, U.S.A.). 48 hours post infection, cells were harvested and resuspended in 20 mL (per 1L culture) Lysis Buffer (50 mM Tris-HCl, pH 7.4, 50 mM NaCl, 1 mM $MgCl_2$, 1.5 mM EDTA, 10% glycerol plus 20 µL Protease Inhibitor Cocktail Set III [CalBiochem, La Jolla, CA, U.S.A.]). Cells were sonicated at 4°C for 1 minute and centrifuged at 10,000 RPM for 30 minutes at 4°C. Supernatant was removed and stored at -20°C for activity assays.

The test compounds were serially diluted in DMSO using two-fold dilutions to stock concentrations ranging typically from 200 µM to 1.6 µM (final concentrations in the assay range from 4 µM to 0.032 µM). 96-well assay isoplates (Wallac Inc., Atlanta, GA, U.S.A.) were loaded with 50 µL dilution buffer per well (dilution buffer: 50 mM Tris/HCl pH 7.5, 8.3 mM $MgCl_2$, 1.7 mM EDTA, 0.2% BSA). 2 µL of the serially diluted individual test compounds were added to individual wells, followed by 25 µL of a 1:25,000 dilution of crude recombinant PDE 10a-containing Sf9 cell lysate (diluted in dilution buffer described above). The enzymatic assay was initiated by addition of 25 µL (0.025 µCi) ^3H cyclic AMP tracer [5',8-^3H] adenosine 3',5'-cyclic phosphate (Amersham Pharmacia Biotech., Piscataway, NJ, U.S.A.) that was diluted 1:1000 in assay buffer (assay buffer: 50 mM Tris/HCl pH 7.5, 8.3 mM $MgCl_2$, 1.7 mM EDTA). Reactions were incubated at room temperature for 60 minutes and terminated by addition of 25 µL of 18 mg/mL Yttrium Scintillation Proximity Beads (Amersham Pharmacia Biotech., Piscataway, NJ, U.S.A.). Plates were sealed and incubated at room temperature for 60 minutes. Plates were read for 30 seconds/well using a Microbeta counter (Wallac Inc., Atlanta, GA, U.S.A.). The IC_{50} values were determined by plotting compound concentration versus percent inhibition. Representative results are shown in Table 1:

Table 1

Example No.	IC_{50} (nM)
18	54
23	81
26	56

***In vitro* Proliferation Inhibition Assay**

MDA-MB-231 human breast carcinoma cells (ATCC # HTB26) were cultured in standard growth medium (DMEM), supplemented with 10% heat-inactivated FBS, 10 mM HEPES, 2 mM glutamine, 100 U/mL penicillin, and 100 µg/mL streptomycin) at 37°C in 5% CO_2 (vol/vol) in a humidified incubator. Cells were plated at a density of 3000 cells per well in 100 µL growth medium in a 96 well culture dish. 24 hours after plating, LDH activity was determined using the Cytotox 96 Non-radioactive Cytotoxicity Kit (Promega, Madison, WI, U.S.A.) to yield T_{0h} LDH values. Briefly, cells were lysed with the addition of 200 µL of Lysis Buffer (included in the Promega Kit) and lysates were further diluted so that LDH values fell within the standard curve. 50 µL of diluted cell lysate were transferred to a fresh 96 well culture plate. The assay was initiated with the addition of 50 µL of substrate per well. Color development was allowed to proceed for 10-15 minutes. The assay was terminated with the addition of 50 µL of Stop Solution (included in Promega kit). Optical densities were determined spectrophotometrically at 490 nm in a 96 well plate reader (SpectraMax 250, Molecular Devices, Sunnyvale, CA, U.S.A.).

Test compounds were dissolved in 100% DMSO to prepare 10 mM stocks. Stocks were further diluted 1:250 in growth medium to yield working stocks of 40 µM test compound in 0.4% DMSO. Test compounds were serially diluted in growth medium containing 0.4% DMSO to maintain constant DMSO concentrations for all wells. 50 µL of fresh growth medium and 50 µL of diluted test compound were added to each culture well to give a final volume of 200 µL. The cells with and without

individual test compounds were incubated for 72 hours at which time LDH activity was measured to yield T_{72h} values. Optionally, the IC_{50} values can be determined with a least squares analysis program using compound concentration versus percent inhibition.

% Inhibition = $[1-(T_{72h\ test}-T_{0h})/(T_{72h\ ctrl}-T_{0h})] \times 100$

wherein

$T_{72h\ test}$ = LDH activity at 72 hours in the presence of test compound,

$T_{72h\ ctrl}$ = LDH activity at 72 hours in the absence of test compound and

T_{0h} = LDH activity at Time Zero

Representative results are shown in Table 2 below:

Table 2

Example No.	% inhibition at a concentration of 10 μM
6	80
23	93
26	42

***In vivo* Tumor Growth Inhibition Assay**

Inhibition of tumor growth *in vivo* is readily determined via the following assay:

MDA-MB-231 cells are cultured as described above. The cells were harvested by trypsinization, washed, counted, adjusted to 2.5 x 10^7 cells/mL with ice-cold PBS, and subsequently stored on ice until transplantation. Xenograft experiments are con-

ducted using eight-to-ten week-old female athymic mice with an average body mass of 20-25 g. Approximately 5 x 10^6 cells in a total volume of 0.2 mL PBS were injected subcutaneously in the flank region. Thereafter the mice were randomized and divided into several groups that reflect different dosages or schedules, respectively (n = 10 mice/ group). The test compounds were administered starting at day 1 at different dosages (e.g. 10, 20 and 40 mg/kg) and different schedules (e.g. Q1Dx15, Q2Dx7, Q3Dx5). Test compounds were formulated for oral administration in a vehicle for oral administration composed of polyethylene glycol-400, ™Cremophor, ethanol and 0.9% saline (40:5:5:50). Tumor measurements were performed twice per week. Tumor weights are calculated using the formula $(a \times w^2)/2$. Animals were sacrificed on day 15 after transplantation and plasma was harvested for pharmacokinetic analyses.

Abbreviations used in this specification

BSA	bovine serum albumin
™Cremophor	non-ionic emulsifyer from BASF
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMEM	Dulbecco's Modified Eagle Medium, Life Technologies, Gaithersburg, MD, U.S.A.
DMF	N,N-dimethyl formamide
DMSO	dimethyl sulphoxide
EDTA	ethylene diamine tetraacetate
FBS	fetal bovine serum
HEPES	N-(2-hydroxyethyl)-piperazine-N'-(2-ethane sulphonic acid)
HPLC	high pressure liquid chromatography
LC-MS	liquid chromatography – coupled mass spectroscopy
LDH	lactate dehydrogenase
NMR	nuclear resonance spectroscopy
PBS	phosphate-buffered saline
tlc	thin layer chromatography

Tris/HCl	tris(hydroxymethyl)-aminomethane hydrochloride
™Triton X-100	tert.-octylphenoxypolyethoxyethanol

The yield percentages of the following Examples refer to the starting component which was used in the lowest molar amount.

Examples

LC-MS / HPLC methods

Method A

MS equipment:	Micromass Quattro LCZ			
	ionisation mode:	ESI positive / negative		
HPLC equipment:	HP 1100			
	UV detection:	208-400 nm		
	temperature:	40°C		
Column:	™Symmetry C 18			
	50 mm x 2.1 mm	3.5 µm		
Supplier:	Waters			
Gradient:	Time [min.]	A: %	B: %	Flow [mL/min.]
	0.00	10.0	90.0	0.50
	4.00	90.0	10.0	0.50
	6.00	90.0	10.0	0.50
	6.10	10.0	90.0	1.00
	7.50	10.0	90.0	0.50
	A:	0.1% strength solution of formic acid in acetonitrile		
	B:	0.1% strength aqueous formic acid		

Method B

Column:	™Kromasil C 18			
	60 mm x 2.0 mm			
Gradient:	Time [min.]	A: %	B: %	Flow [mL/min.]
	0.00	90.0	10.0	0.75
	0.50	90.0	10.0	0.75
	4.50	10.0	90.0	0.75
	6.50	10.0	90.0	0.75
	7.50	90.0	10.0	0.75
	A:	0.001 % strength aqueous H_3PO_4		
	B:	acetonitrile		

Method C

MS equipment:	Micromass TOF-MUX-Interface 4-fold parallel injection			
	ionisation mode:	ESI positive		
HPLC equipment:	Waters 600			
	UV detection:	210 nm		
	temperature:	40°C		
Column:	Symmetry C 18			
	50 mm x 2.1 mm	3.5 µm		
Supplier:	Waters			
Gradient:	Time [min.]	A: %	B: %	Flow [mL/min.]
	0.00	10.0	90.0	0.75
	0.50	10.0	90.0	0.75
	4.00	90.0	10.0	0.75
	5.50	90.0	10.0	0.75
	5.60	10.0	90.0	1.25
	6.50	10.0	90.0	0.75
	A:	0.1% strength solution of formic acid in acetonitrile		

B: 0.1% strength aqueous formic acid

Method D

MS equipment:	Micromass Platform LCZ			
	ionisation mode:	ESI positive / negative		
HPLC equipment:	HP 1100			
	UV detection:	208-400 nm		
	temperature:	40 °C		
Column:	Symmetry C 18			
	50 mm x 2.1 mm	3.5 µm		
Supplier:	Waters			
Gradient:	Time [min.]	A: %	B: %	Flow [mL/min.]
	0.00	10.0	90.0	0.50
	4.00	90.0	10.0	0.50
	6.00	90.0	10.0	0.50
	6.10	10.0	90.0	1.00
	7.50	10.0	90.0	0.50
	A:	0.1% strength solution of formic acid in acetonitrile		
	B:	0.1% strength aqueous formic acid		

Method E

Column:	Kromasil C 18			
	60 mm x 2.0 mm			
Gradient:	Time [min.]	A: %	B: %	Flow [mL/min.]
	0.00	98.0	2.0	0.75
	4.50	10.0	90.0	0.75
	6.50	10.0	90.0	0.75
	6.70	98.0	2.0	0.75
	7.50	98.0	2.0	0.75

A: 0.5% strength aqueous $HClO_4$

B: acetonitrile

The present invention is illustrated below with the aid of the following non-limiting examples:

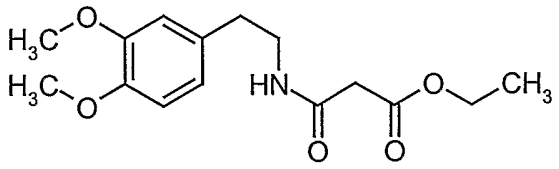
Starting Materials

I. Phenethyl amines

The substituted 2-phenethyl amines are commercially available or can be prepared in analogy to any one of the following procedures, e.g. starting from the corresponding benzaldehydes (see also Shepard et al. in J. Org. Chem. 17, 568 (1952) and in J. Am. Chem. Soc. 72, 4364 (1950)).

II. Amides

IIa: Ethyl 3-{[2-(3,4-dimethoxyphenyl)-ethyl]-amino}-3-oxopropanoate



A solution of 12.4 g (82.7 mmol) of ethyl 3-chloro-3-oxopropanoate in 150 mL of dichloromethane was added at room temperature to a solution of 15.0 g (82.7 mmol) of 2-(3,4-dimethoxyphenyl)-ethyl amine and 12.6 g (82.7 mmol) of DBU in 300 mL of dichloromethane. The mixture was stirred at room temperature overnight, then water was added, and the organic layer was washed three times with water. The organic phase was dried over

Na_2SO_4, and the solvent was evaporated under reduced pressure to give the title compound.

Yield: 91.3 %

^1H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.1 Hz, 3H), 2.78 (t, J = 7.0 Hz, 2H), 3.27 (s, 2H), 3.53 (q, J = 6.0 Hz, 2H), 3.86 (s, 3H), 3.88 (s, 3H), 4.16 (q, J = 7.1 Hz, 2H), 6.70 - 6.67 (m, 2H), 6.81 (d, J = 8.7 Hz, 1H), 7.12 (s, 1H).

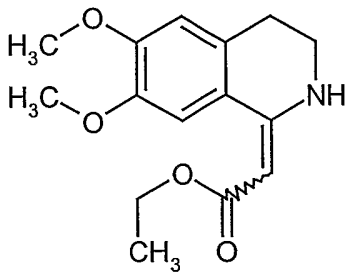
The following amides were obtained in analogy to the described procedure:

IIb: Ethyl 3-{[2-(3-methoxyphenyl)-ethyl]-amino}-3-oxopropanoate

IIc: Ethyl 3-{[2-(4-methoxyphenyl)-ethyl]-amino}-3-oxopropanoate

III. <u>3,4-Dihydro-1(2H)-isoquinolinylidene-ethanoates</u>

Example IIIa: Ethyl (6,7-dimethoxy-3,4-dihydro-1(2H)-isoquinolinylidene-ethanoate



A solution of 22.0 g (74.5 mmol) of ethyl 3-{[2-(3,4-dimethoxyphenyl)-ethyl]-amino}-3-oxopropanoate (Example IIa) in 400 mL of toluene was heated under reflux, and 63.4 g (446.95 mmol) of phosphorus pentoxide were added to the boiling solution in 6 portions at 15-20 min. intervals (following the course of the reaction by tlc using 1:1 cyclohexane/ ethyl acetate as eluant). After cooling to room temperature, the bulk of toluene was decanted, and residual toluene was removed by evaporation under reduced pressure.

Solid ice was added to the residue, and the mixture was stirred at room temperature. The resulting solution was filtered and extracted several times with ethyl acetate. The combined organic phases were dried over Na_2SO_4, filtered through a pad of silicagel, and finally the solvent was evaporated under reduced pressure to give the title compound.

Yield: 87.1 %

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.30 (t, J = 7.2 Hz, 3H), 2.83 (t, J = 6.4 Hz, 2H), 3.32-3.52 (m, 2H), 3.89 (s, 3H), 3.91 (s, 3H), 4.17 (q, J = 7.1 Hz, 2H), 5.05 (s, 1H), 6.66 (s, 1H), 7.12 (s, 1H), 9.04 (s, 1H).

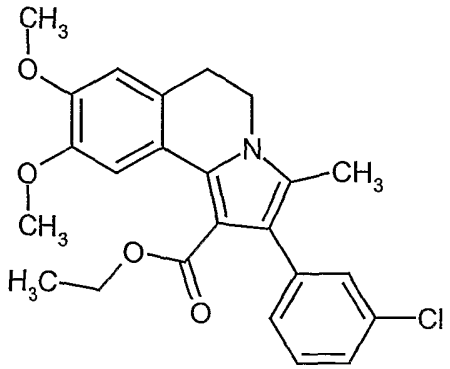
The following 3,4-dihydro-1(2H)-isoquinolinylidene-ethanoates were obtained in analogy to the described procedure:

IIIb: Ethyl (2E,Z)-(6-methoxy-3,4-dihydro-1(2H)-isoquinolinylidene)-ethanoate

IIIc: Ethyl (2E,Z)-(7-methoxy-3,4-dihydro-1(2H)-isoquinolinylidene)-ethanoate

IV. 5,6-Dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylates

Example IVa: Ethyl 2-(3-chlorophenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylate



A mixture of 10.06 g (0.04 mol) of the compound of Example IIIa, 5.1 g (0.04 mol) of 3-chloro-benzaldehyde, 2.72 g (0.04 mol) of nitroethane and

0.54 mL (0.01 mol) of piperidine in 45 mL of ethanol was refluxed for 80 hours. It was cooled, the obtained crystals were sucked off and washed carefully with isopropanol. 10.74 g of a nearly colorless solid compound of melting point 132-133 °C were obtained.

The following 5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylates were obtained in analogy to the described procedure :

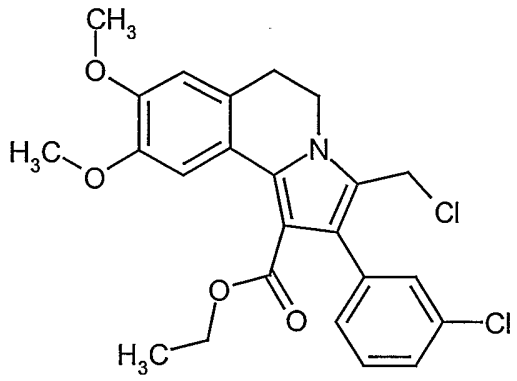
IVb: Ethyl 2-(4-hydroxy-3,5-dimethylphenyl)-8,9-dimethoxy-3-methyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-1-carboxylate using 3,5-dimethyl-4-hydroxy-benzaldehyde instead of 3-chloro-benzaldeyde

IVc: Ethyl 8,9-dimethoxy-2-[4-(methoxycarbonyl)-phenyl]-3-methyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-1-carboxylate using 4-methoxy-carbonyl-benzaldehyde instead of 3-chloro-benzaldehyde

IVd: Ethyl 2-(3-chlorophenyl)-8-methoxy-3-methyl-5,6-dihydro-pyrrolo-[2,1-a]isoquinoline-1-carboxylate using ethyl (6-methoxy-3,4-dihydro-1(2H)-isoquinolinylidene-ethanoate instead of ethyl (6,7-dimethoxy-3,4-dihydro-1(2H)-isoquinolinylidene-ethanoate

Example V

Ethyl 2-(3-chlorophenyl)-8,9-dimethoxy-3-chloromethyl-5,6-dihydro-pyrrolo[2,1-a]-isoquinoline-1-carboxylate

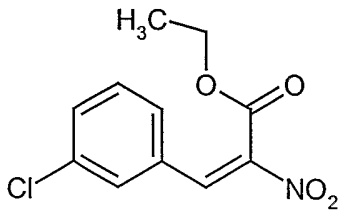


200 mg (0,47 mmol) of ethyl 2-(3-chlorophenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylate from Example IV were dissolved in 1,3 mL of dichloromethane, and a solution of 65,28 mg (0,48 mmol) of sulfuryl chloride in 1 mL of dichloromethane was added dropwise at 0°C. The color of the solution changed from yellow to red and finally to brown. It was stirred for 10 minutes under ice cooling and for 1 hour at room temperature, the solvent was evaporated, and after addition of dichloromethane the solvent evaporated again. The raw chloromethyl compound thus obtained was further reacted without purification.

Instead of sulfurylchloride also thionyl chloride or N-chlorosuccinimide can be used according to this method.

Example VI

Ethyl 2-(3-chlorophenyl)-1-nitroethene-carboxylate

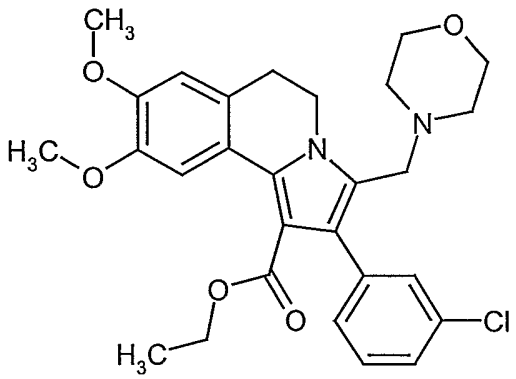


A solution of 28,5 g (150 mmol) of titanium tetrachloride in 40 mL of tetrachloromethane was added dropwise to 300 mL of ice-cooled THF under an argon atmosphere. Into the suspension thus obtained 10,56 g (75,13 mmol) of 3-chlorobenzaldehyde and 10,0 g (75,13 mmol) of nitroacetic acid ethyl ester were added simultaneously from two dropping funnels at 0°C. Thereafter, 30,4 g (300.52 mmol) of N-methyl morpholine were added dropwise within 2 hours at 0°C. It was stirred overnight at 0°C and then allowed to warm up until room temperature. The solution was carefully reacted with water under cooling. 400 mL of diethyl ether were added, the layers separated, the aqueous layer extracted twice with diethyl ether, the combined organic layers washed with sodium chloride solution and dried, and the solvent was evaporated. The residue was crystallized with ethanol/petrolether 1:1. 5,05 g (26,4 %) of crystals having a melting point of 65-66 °C were obtained.

Preparation Examples

Example 1

Ethyl 2-(3-chlorophenyl)-8,9-dimethoxy-3-N-morpholinomethyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-1-carboxylate

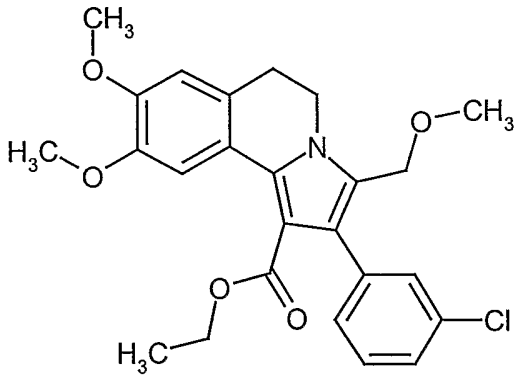


The raw chloromethyl derivative from Example V was dissolved in 3 mL of dichloromethane and reacted dropwise with a solution of 2 mmol (174 mg) of morpholine in 2 mL of dichloromethane. The mixture was stirred overnight, diluted

with dichloromethane, washed with water and dried, and the solvent was evaporated. After a preliminary purification by means of a cartridge 118 mg (49,2 %) of colorless crystals having a melting point of 186-187°C were obtained.

Example 2

Ethyl 2-(3-chlorophenyl)-8,9-dimethoxy-3-methoxymethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylate



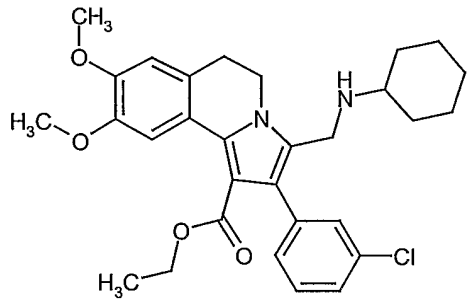
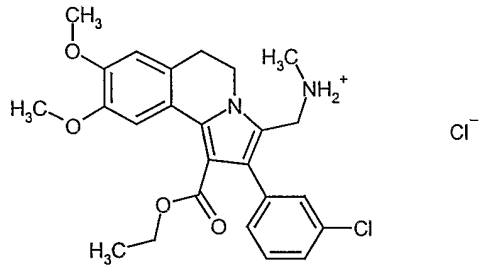
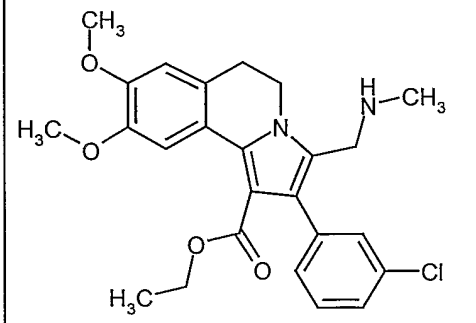
51 mg (0,11 mmol) of the raw chloromethyl derivative of Example V in methanol were reacted with 0,2 mL of a 30 % solution of sodium methylate in methanol. The solvent was evaporated after 2 hours, the residue was taken up in ethyl acetate, the solution was washed with water, and the solvent was evaporated. Purification was conducted by means of a cartridge. 20 mg (40 %) of colorless crystals having a melting point of 116-117°C were obtained.

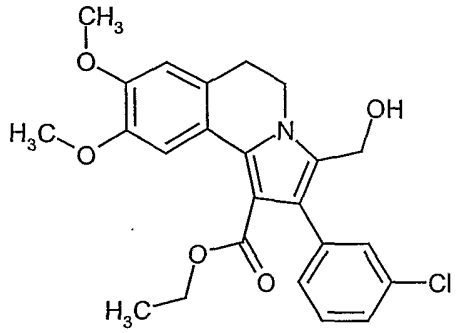
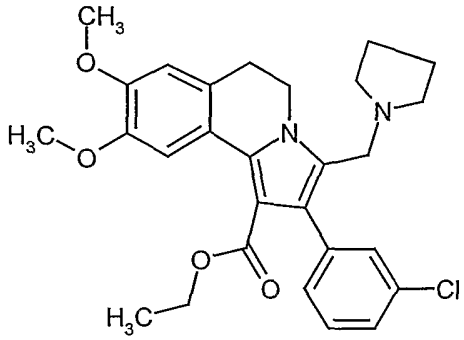
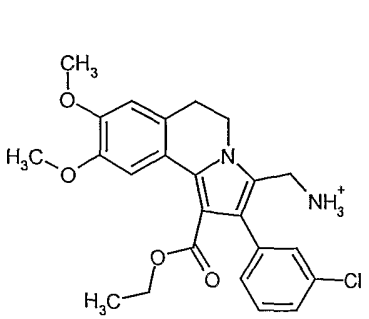
^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.89 (t, 3H), 2.97 (t, 2H), 3.20 (s, 3H), 3.73 (s, 3H), 3.81 (s, 3H), 3.93-4.08 (m, 4H), 4.27 (s, 2H), 6.98 (s, 1H), 7.13-7.19 (m, 1H), 7.22 (s, 1H), 7.33-7.48 (m, 2H), 7.72 (s, 1H).

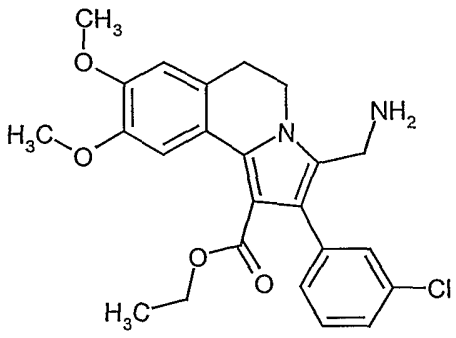
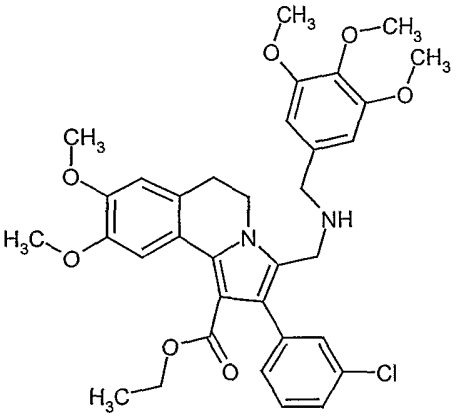
MS: 455 (M^+)

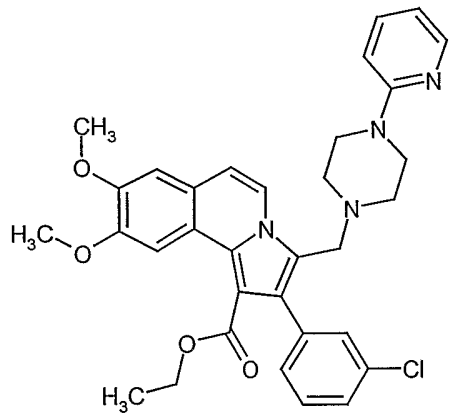
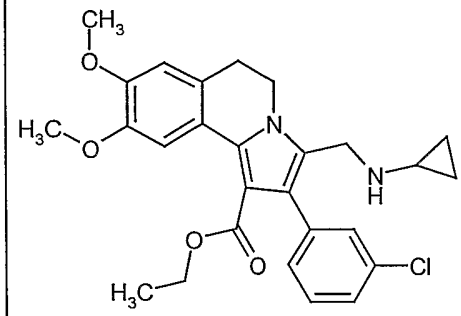
HPLC retention time [min]: 5 (method E)

The following Examples (Nos. 3-12) were carried out in analogy to the description of Examples 1 and 2:

Ex.	Structure	Analytical data
3		**^{1}H-NMR** (200 MHz, DMSO-d_6): δ = 0.89 (t, 3H), 0.92-1.28 (m, 4H), 1.41-1.85 (m, 6H), 2.12-2.36 (m, 1H), 2.96 (t, 2H), 3.58 (d, 2H), 3.75 (s, 3H), 3.81 (s, 3H), 3.99 (q, 2H), 4.10 (t, 2H), 6.95 (s, 1H), 7.17-7.28 (m, 1H), 7.29-7.46 (m, 3H), 7.72 (s, 1H) **MS:** 522 **HPLC retention time [min]:** 3.26 (method D) **Melting point [°C]:** 134-135
4		**^{1}H-NMR** (300 MHz, DMSO-d_6): δ = 0.89 (t, 3H), 1.93-2.03 (m, 1H), 2.21 (s, 3H), 2.96 (t, 2H), 3.42-3.51 (m, 2H), 3.72 (s, 3H), 3.80 (s, 3H), 3.90-4.15 (m, 4H), 6.96 (s, 1H), 7.18-7.27 (m, 1H), 7.28-7.42 (m, 3H), 7.74 (s, 1H) salt from example 5
5		**^{1}H-NMR** (300 MHz, DMSO-d_6): δ = 0.89 (t, 3H), 1.93-2.03 (m, 1H), 2.21 (s, 3H), 2.96 (t, 2H), 3.42-3.51 (m, 2H), 3.72 (s, 3H), 3.80 (s, 3H), 3.90-4.15 (m, 4H), 6.96 (s, 1H), 7.18-7.27 (m, 1H), 7.28-7.42 (m, 3H), 7.74 (s, 1H) **MS:** 454 **HPLC retention time [min]:** 2.96 (method D) **Melting point [°C]:** 121-122

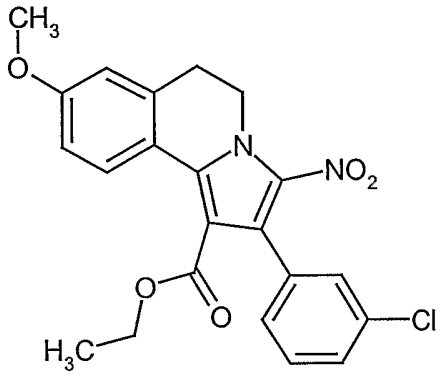
Ex.	Structure	Analytical data
6		**^{1}H NMR (300 MHz, $CDCl_3$):** δ = 0.92 (t, 3H), 3.02 (t, 2H), 3.94 (s, 6H), 4.03 (q, 2H), 4.16 (t, 2H), 4.51-4.59 (m, 2H), 6.74 (s, 1H), 7.12-7.32 (m, 4H), 8.02 (s, 1H) **MS:** 441 **HPLC retention time [min]:** 4.35 (method D) **melting point [°C]:** 97-98 prepared from V and potassium acetate in DMF at room temperature and basic work up
7		**^{1}H NMR (300 MHz, DMSO-d_6):** δ = 0.84 (t, 3H), 1.52-1.68 (m, 4H), 2.21-2.33 (m, 4H), 2.93 (t, 2H), 3.49 (s, 2H), 3.72 (s, 3H), 3.81 (s, 3H), 3.92 (q, 2H), 4.08 (t, 2H), 6.95 (s, 1H), 7.12-7.18 (m, 1H), 7.21-7.28 (m, 1H), 7.31-7.42 (m, 2H), 7.78 (s, 1H) **MS:** 494 **HPLC retention time [min]:** 3.15 (method D) **Melting point [°C]:** 149-150
8		**^{1}H NMR (200 MHz, DMSO-d_6):** δ = 0.89 (t, 3H), 1.73-1.88 (m, 2H), 2.97 (t, 2H), 3.58 (s, 2H), 3.72 (s, 3H), 3.80 (s, 3H), 3.98 (q, 2H), 4.11 (t, 2H), 6.97 (s, 1H), 7.20-7.42 (m, 4H), 7.72 (s, 1H) Salt of example 9

Ex.	Structure	Analytical data
9		**^{1}H NMR (200 MHz, DMSO-d_6):** δ = 0.89 (t, 3H), 1.73-1.88 (m, 2H), 2.97 (t, 2H), 3.58 (s, 2H), 3.72 (s, 3H), 3.80 (s, 3H), 3.98 (q, 2H), 4.11 (t, 2H), 6.97 (s, 1H), 7.20-7.42 (m, 4H), 7.72 (s, 1H) **MS:** 440 (M^+) **HPLC retention time [min]:** 4.2 (method E) From V with ammonia in dioxane at room temperature
10		**^{1}H NMR (200 MHz, DMSO-d_6):** δ = 0.89 (t, 3H), 2.57-2.71 (m, 1H), 2.98 (t, 2H), 3.41-3.54 (m, 2H), 3.55-3.67 (m, 2H), 3.62 (s, 3H), 3.73 (s, 9H), 3.80 (s, 3H), 3.98 (q, 2H), 4.12 (t, 2H), 6.62 (s, 2H), 6.96 (s, 1H), 7.15-7.24 (m, 1H), 7.24-7.36 (m, 3H), 7.72 (s, 1H) **MS:** 620 **HPLC retention time [min]:** 3.91 (method D)

Ex.	Structure	Analytical data
11		**^{1}H NMR (300 MHz, $CDCl_3$):** δ = 0.86 (t, 3H), 1.21-1.34 (m, 4H), 2.39-3.01 (m, 2H), 3.42-3.56 (m, 2H), 3.68 (s, 2H), 3.98-4.10 (m, 2H), 4.01 (s, 3H), 4.08 (s, 3H), 6.53-6.66 (m, 2H), 6.94 (d, 1H), 7.05 (s, 1H), 7.11-7.20 (m, 1H), 7.21-7.35 (m, 3H), 7.39-7.50 (m, 1H), 8.11-8.19 (m, 1H), 8.26 (d, 1H), 9.08 (s, 1H) **MS:** 584 **HPLC retention time [min]:** 3.69 (method D)
12		**^{1}H NMR (300 MHz, DMSO-d_6):** δ = 0.17-0.24 (m, 2H), 0.26-0.38 (m, 2H), 0.89 (t, 3H), 1.95-2.03 (m, 1H), 2.53-2.13 (m, 1H), 2.95 (t, 2H), 3.58 (d, 2H), 3.73 (s, 3H), 3.80 (s, 3H), 3.99 (q, 2H), 4.07 (t, 2H), 6.98 (s, 1H), 7.20-7.26 (m, 1H), 7.80-7.92 (m, 3H), 7.71 (s, 1H) **MS:** 480 **HPLC retention time [min]:** 3.07 (method D) **Melting point [°C]:** 135-136

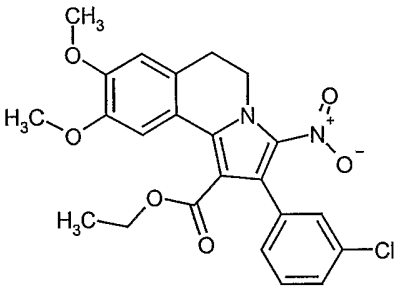
Example 13

Ethyl 2-(3-chlorophenyl)-8-methoxy-3-nitro-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylate



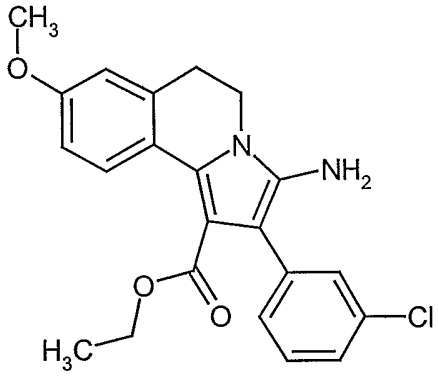
840 mg (2,12 mmol) of ethyl 2-(3-chlorophenyl)-8-methoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylate (Example IV d) were suspended in 16,27 mL of glacial acetic acid, and a mixture of 0,31 mL (4,45 mmol) of 65 % nitric acid in 1 mL of glacial acetic acid was added dropwise at 20°C. The reaction solution changed from green to orange red. After 2 hours the solution was poured into ice water, the mixture was extracted twice with dichloromethane, the combined organic layers were washed with water and dried, and the solvent was evaporated. The purification was made by column chromatography with dichloromethane. 153 mg of crystals having a melting point of 189-190°C were obtained.

Starting from the compound of Example IV, the following compound was prepared in analogy to Example 20:

Ex.	Structure	Analytical data
14		**^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 0.91 (t, 3H), 3.08 (t, 2H), 3.91 (s, 3H), 3.95 (s, 3H), 4.02 (q, 2H), 4.60 (t, 2H), 6.79 (s, 1H), 7.69-7.42 (m, 4H), 7.75 (s, 1H) **MS:** 474 ($M+NH_4$) **HPLC retention time [min]:** 5.1 (method E)

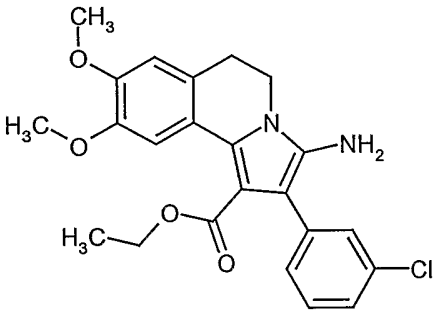
Example 15

Ethyl 3-amino-8-methoxy-2-(3-chlorophenyl)-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylate



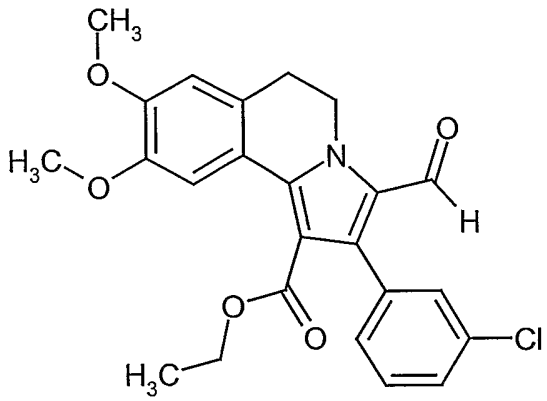
80 mg (0,18 mmol) of the compound of Example 13 were dissolved in a mixture of 1 mL of pyridine and 5 mL of ethanol and, after addition of 40 mg of Pd/C (10%), hydrogenated at normal pressure for 4 hours. The mixture was filtrated, the solvent was evaporated, and the compound was purified with mixtures of cyclohexane/ethyl acetate over a silicagel column. 35 mg (49,6 %) of little yellowish crystals having a melting point of 150-152°C were obtained.

In analogy to Example 15, the following compound was prepared from the compound of Example 14:

Ex.	Structure	Analytical data
16		**^{1}H-NMR** (200 MHz, DMSO-d_6): δ = 0.90 (t, 3H), 2.90 (t, 2H), 3.72 (s, 3H), 3.78 (s, 3H), 3.84 (t, 2H), 4.00 (q, 2H), 4.60 (s, 2H), 6.90 (s, 1H), 7.12-7.22 (m, 2H), 7.27-7.48 (m, 3H), 7.68 (s, 1H) **MS:** 393 (M+H) **HPLC retention time [min]:** 4.1 (method E)

Examples 17a and 17b

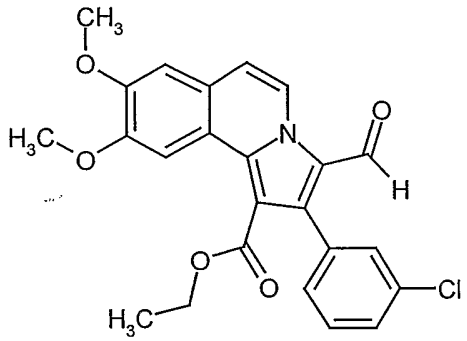
Ethyl 3-formyl-8,9-dimethoxy-2-(3-chlorophenyl)-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylate



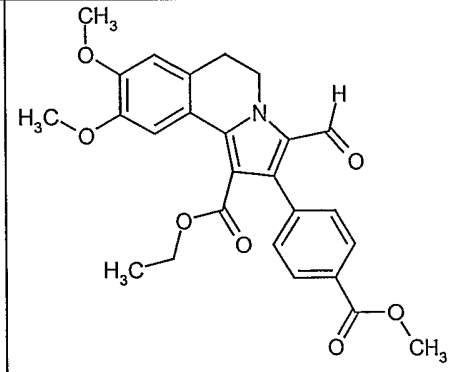
A mixture of 100 mg (0,234 mmol) of ethyl 2-(3-chlorophenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylate from Example IVa and 500 mg of manganese dioxide in 3 mL of dioxane was stirred for 2 hours at 100°C. The mixture was cooled, filtrated, and the solvent was evaporated. The resulting mixture of products was separated with toluene/ ethyl acetate (until 4:1) over a silicagel column. 27 mg (26,2 %) of colorless crystals having a melting point of 180-181°C were obtained.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.94 (t, 3H), 3.02 (t, 2H), 3.89 (s, 3H), 3.93 (s, 3H), 4.08 (q, 2H), 4.69 (t, 2H), 6.78 (s, 1H), 7.13-7.44 (m, 4H), 7.87 (s, 1H), 9.35 (s, 1H).

As a second compound the respective dehydro compound ethyl 3-formyl-8,9-dimethoxy-2-(3-chlorophenyl)-pyrrolo[2,1-a]isoquinoline-1-carboxylate (Example 17b) having a melting point of 155-157°C could be obtained:

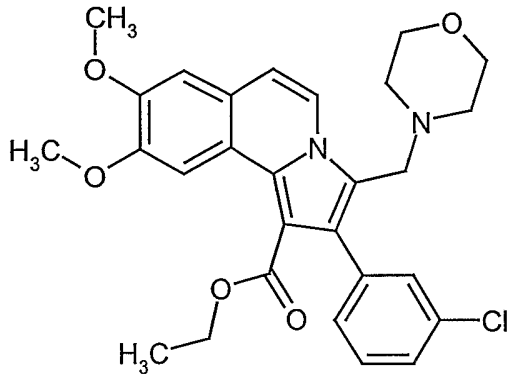


Starting from the compound of Example IVc, the following compound was prepared in analogy to Example 17a:

Ex.	Structure	Analytical data
18		**^{1}H-NMR** (300 MHz, DMSO-d_6): δ = 0.86 (t, 3H), 3.02 (t, 2H), 3.74 (s, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 4.01 (q, 2H), 4.59 (t, 2H), 7.06 (s, 1H), 7.53 (d, 2H), 7.60 (s, 1H), 8.01 (d, 2H) **MS:** 464 (M+H) **Melting point [°C]:** 164-165

Example 19

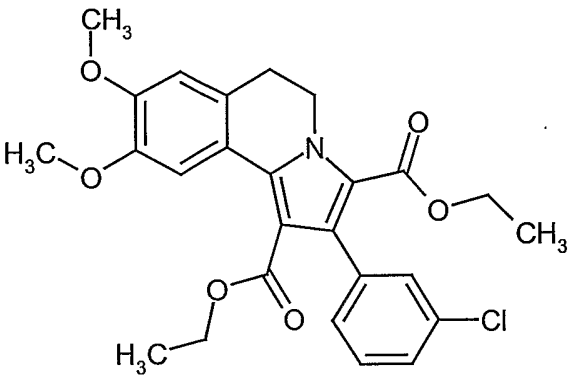
Ethyl 3-N-morpholinomethyl-8,9-dimethoxy-2-(3-chlorophenyl)-pyrrolo[2,1-a]isoquinoline-1-carboxylate



100 mg (0,23 mmol) of ethyl 2-(3-chlorophenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylate (Example IVa) were stirred in 0,4 mL of thionyl chloride for 70 minutes under moderate reflux conditions. The solvent was evaporated, the residue was taken up with dichloromethane, the solvent was evaporated and the residue was dissolved in 4 mL of dichloromethane. 87 mg (1 mmol) of morpholine were added dropwise, it was stirred for 3 hours at 20°C, diluted with dichloromethane and shaken twice with water. The solvent was evaporated and the compound was purified over a short column with dichloromethane/-ethyl acetate (until 1:1). 43 mg (36,7 %) of colorless crystals having a melting point of 176-177°C were obtained.

Example 20

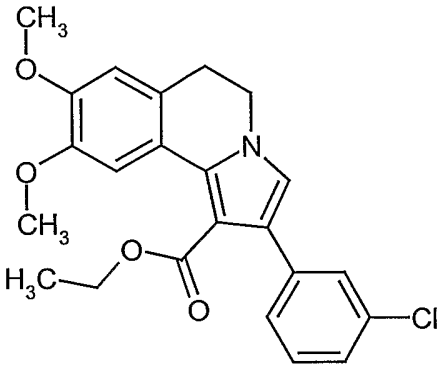
Diethyl 8,9-dimethoxy-2-(3-chlorophenyl)-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1,3-dicarboxylate



1,0 g (3,93 mmol) of the compound of Example VI was added to a solution of 1,09 g (3,93 mmol) of ethyl (6,7-dimethoxy-3,4-dihydro-1(2H)-isoquinolinylidene)-ethanoate from Example III a in 40 mL of isopropanol. The solution was stirred for 17 hours under moderate reflux conditions and then cooled with an ice bath. The precipitated crystals were sucked off and washed with isopropanol. 1,179 g (62 %) of crystals having a melting point of 140-141°C were obtained.

Example 21

Ethyl 8,9-dimethoxy-2-(3-chlorophenyl)-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylate



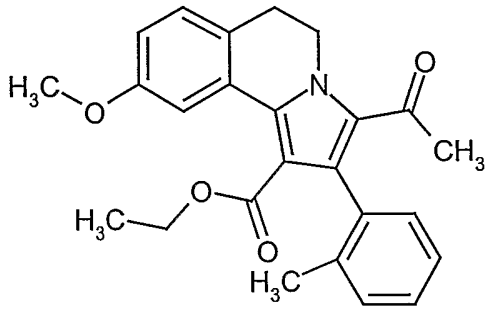
In analogy to the procedure described in Example IV, the title compound was obtained using nitromethane instead of nitroethane.

MS: 412.2 (M+H)

HPLC retention time [min]: 4.86 (method C)

Example 22

Ethyl 9-methoxy-2-(2-methylphenyl)-3-methylcarbonyl-5,6-dihydro-pyrrolo[2,1-a]-isoquinoline-1-carboxylate



150 mg (0,61 mmol) of ethyl (7-methoxy-3,4-dihydro-1(2H)-isoquinolinylidene)-ethanoate (Example III c) and 248,95 mg (1,21 mmol) of 4-(2-methylphenyl)-3-nitro-3-buten-2-one (prepared from 2-methyl-benzaldeyde and 1-nitro-propane-2-one) in 2 mL of ethanol were refluxed for 24 hours. It was evaporated to dryness and separated on a silicagel column with dichloromethane. A yield of 52 mg (21,25 % of theory) was obtained.

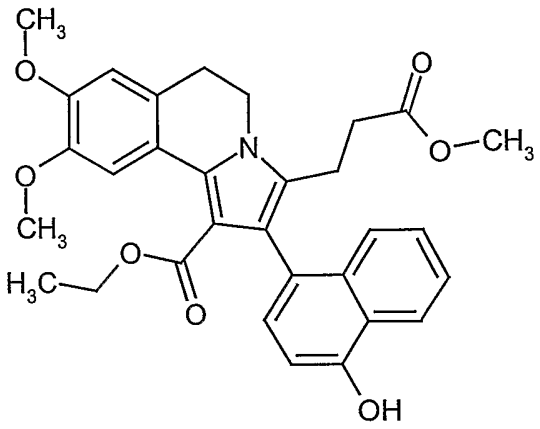
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.84 (t, J = 7.2 Hz, 3H), 1.79 (s, 3H), 2.18 (s, 3H), 2.98 (t, J = 6.4 Hz, 2H), 3.81 (s, 3H), 3.98 (q, J = 7.2 Hz, 2H), 4.43-4.78 (m, 2H), 6.86 (dd, J = 8.2 Hz, J = 2.5 Hz, 1H), 7.03-7.30 (m, 4H), 7.58 (d, J = 2.5 Hz, 1H).

MS: 404.3 (M+H)

HPLC retention time [min]: 4.7 (method C)

Example 23

Ethyl 2-(4-hydroxy-1-naphthyl)-8,9-dimethoxy-3-(3-methoxy-3-oxopropyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-1-carboxylate



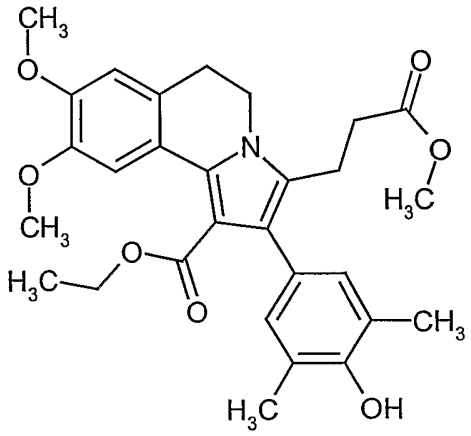
In analogy to the procedure described in Example IVa, the title compound was obtained using ethyl (6,7-dimethoxy-3,4-dihydro-1(2H)-isoquinolinylidene)-ethanoate (Example III a), 4-hydroxy-1-naphthaldehyde and methyl 4-nitrobutanoate.

MS: 530.2 (M+H)

HPLC retention time [min]: 4.33 (method A)

Example 24

Ethyl 2-(4-hydroxy-3,5-dimethylphenyl)-8,9-dimethoxy-3-(3-methoxy-3-oxopropyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-1-carboxylate



In analogy to the procedure described in Example IVa, the title compound was obtained using ethyl (6,7-dimethoxy-3,4-dihydro-1(2H)-isoquinolinylidene)-ethanoate (Example III a), 4-hydroxy-3,5-dimethyl-benzaldehyde and methyl 4-nitrobutanoate.

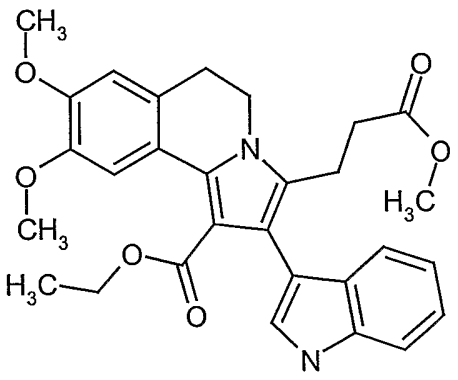
^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.90 (t, J = 7.0 Hz, 3H), 2.15 (s, 6H), 2.38-2.53 (m, 2H), 2.73-2.84 (m, 2H), 2.93 (t, J = 6.1 Hz, 2H), 3.54 (s, 3H), 3.70 (s, 3H), 3.78 (s, 3H), 3.89-4.02 (m, 4H), 6.70 (s, 2H), 6.94 (s, 1H), 7.52 (s, 1H), 8.09 (s, 1H)

MS: 508.4 (M+H), 525.4 ($M+NH_4$)

HPLC retention time [min]: 4.54 (method B)

Example 25

Ethyl 2-(1H-indol-3-yl)-8,9-dimethoxy-3-(3-methoxy-3-oxopropyl)-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylate



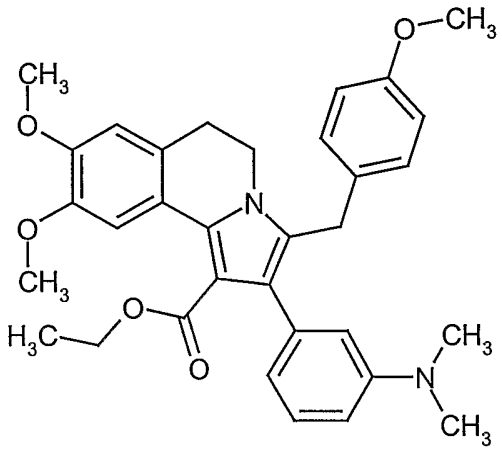
In analogy to the procedure described in Example IVa, the title compound was obtained using ethyl (6,7-dimethoxy-3,4-dihydro-1(2H)-isoquinolinylidene)-ethanoate (Example III a), 1H-indole-3-carbaldehyde and methyl 4-nitrobutanoate.

MS: 503.2 (M+H)

HPLC retention time [min]: 4.34 (method A)

Example 26

Ethyl 2-[3-(dimethylamino)-phenyl]-8,9-dimethoxy-3-(4-methoxybenzyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-1-carboxylate



In analogy to the procedure described in Example IVa, the title compound was obtained using ethyl (6,7-dimethoxy-3,4-dihydro-1(2H)-isoquinolinylidene)-ethanoate (Example III a), 3-(dimethylamino)-benzaldehyde and 1-methoxy-4-(3-nitropropyl)-benzene.

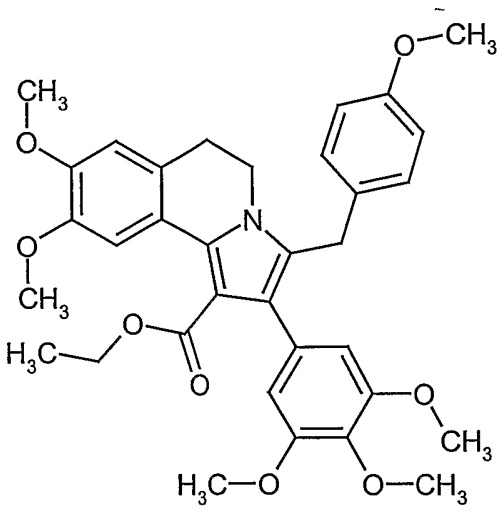
^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.91 (t, J = 7.2 Hz, 3H), 3.24-3.38 (m, 8H), 3.62-3.81 (m, 11H), 3.86-4.07 (m, 4H), 6.44-6.54 (m, 2H), 6.57-6.66 (m, 1H), 6.79-7.01 (m, 5H), 7.05-7.19 (m, 1H), 7.62 (s, 1H)

MS: 541.0 (M+H)

HPLC retention time [min]: 4.5 (method B)

Example 27

Ethyl 8,9-dimethoxy-3-(4-methoxybenzyl)-2-(3,4,5-trimethoxyphenyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline-1-carboxylate



In analogy to the procedure described in Example IVa, the title compound was obtained using ethyl (6,7-dimethoxy-3,4-dihydro-1(2H)-isoquinolinylidene)-ethanoate (Example III a), 3,4,5-trimethoxy-benzaldehyde and 1-methoxy-4-(3-nitropropyl)-benzene.

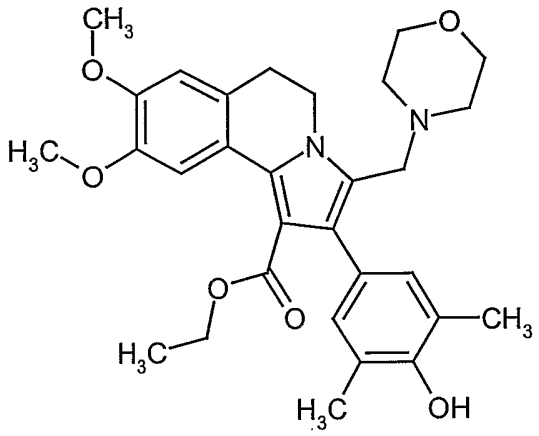
^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.92 (t, J = 7.0 Hz, 3H), 2.79-2.90 (m, 2H), 3.57-3.81 (m, 20H), 3.87-4.09 (m, 4H), 6.43 (s, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.90 (s, 1H), 6.98 (d, J = 8.7 Hz, 2H), 7.68 (s, 1H)

MS: 588.0 (M+H), 610.0 (M+Na)

HPLC retention time [min]: 5.12 (method B)

Example 28

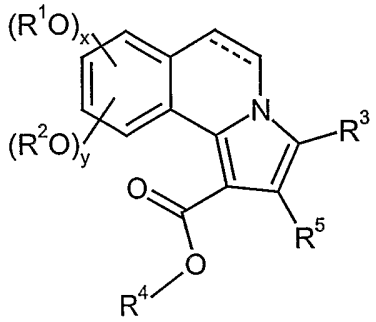
Ethyl 2-(3,5-dimethyl-4-hydroxy-phenyl)-8,9-dimethoxy-3-N-morpholinomethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylate



35 mg (0.08 mmol) of ethyl 2-(4-hydroxy-3,5-dimethylphenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylate (Example IV b) were solved in 1 mL of dichloromethane and treated at 0°C with 10.73 mg (0.08 mmol) of N-chlorosuccinimide. The mixture was stirred for 1 hour at room temperature, the solvent was evaporated in vacuo, the residue was solved again in 1 mL of dichloromethane and treated with 3 drops of morpholine. The mixture was diluted with dichloromethane after 3 hours, washed with water, dried, and the solvent was evaporated. After chromatography on silicagel 10 mg of crystals having a melting point of 195°C were obtained.

Patent claims

1. A compound of the formula



(I)

wherein

x and y independently from each other denote zero or 1 and

x+y is 1 or 2;

R^1 and R^2 independently from each other denote hydrogen, C_{1-4}-alkyl or CF_3

or

R^1 and R^2 together form a C_{1-4}-alkylene bridge;

R^3 denotes hydrogen, formyl, (C_{1-4}-alkyl)-carbonyl, (C_{1-4}-alkoxy)-carbonyl, NO_2, NR^6R^7, C_{1-4}-alkyl-NR^6R^7, C_{1-4}-alkyl-OR^8, C_{1-4}-alkyl-$COOR^8$, C_{6-10}-aryl-C_{1-4}-alkyl wherein the aryl moiety is optionally substituted with 1 to 3 radicals selected from the group consisting of OH, C_{1-4}-alkyl and C_{1-4}-alkoxy;

wherein

R^6 and R^7 independently from each other denote hydrogen, C_{1-4}-alkyl, C_{3-8}-cycloalkyl, C_{6-10}-aryl-C_{1-4}-alkyl wherein the aryl moiety is optionally substituted with 1 to 3 radicals selected from the group consisting of OH, C_{1-4}-alkyl and C_{1-4}-alkoxy; or

R^6 and R^7 together with the nitrogen atom to which they are attached, form a 5- to 7-membered heterocyclyl which may contain up to 2 further hetero atoms selected from the group consisting of N, O and S, which heterocyclyl can further be substituted with 1 to 3 radicals selected from the group consisting of OH, C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{6-10}-aryl and aromatic 4- to 9-membered heterocyclyl with 1 to 4 hetero atoms selected from the group consisting of N, O and S;

R^8 denotes hydrogen or C_{1-4}-alkyl;

R^4 denotes C_{1-4}-alkyl;

R^5 is

i) C_{6-14}-aryl optionally containing 1 to 3 further substituents selected from the group consisting of

halogen;

C_{1-6}-alkyl which can be further substituted with one or more radicals selected from the group consisting of C_{1-6}-alkoxy, OH and NH_2;

C_{1-6}-alkoxy which can be further substituted with one or more radicals selected from the group consisting of C_{1-6}-alkoxy,OH and NH_2;

C_{6-10}-aryloxy-C_{1-6}-alkoxy;

OH;

NO_2;

CN;

CF_3;

OCF_3;

NR^9R^{10};

$CONR^9R^{10}$;

$COOR^{11}$;

SR^{11};

SOR^{11};

SO_2R^{11};

OSO_2R^{11};

-O-$(CH_2)_{1-4}$-O- wherein the oxygen atoms are bound to the aryl moiety in ortho-position to each other;

phenyloxy or benzyloxy wherein the phenyl moieties can contain one further substituent selected from the group consisting of C_{1-6}-alkyl, C_{1-6}-alkoxy, halogen and NO_2;

phenyl optionally substituted with CN;

aromatic 4- to 9-membered heterocyclyl with 1 to 4 hetero atoms selected from the group consisting of N, O and S;

and

saturated 5- to 7-membered nitrogen-containing heterocyclyl which is bound to the C_{6-10}-aryl moiety via the nitrogen atom and may contain up to 2 further hetero atoms selected from the group consisting of N, O and S and which saturated heterocyclyl can be further substituted with one or more radicals selected from the group consisting of C_{1-6}-alkoxy, OH and NH_2;

wherein

R^9 and R^{10} independently from each other denote hydrogen, C_{1-6}-alkyl, (C_{1-6}-alkyl)-carbonyl, (C_{1-6}-alkoxy)-carbonyl, C_{1-6}-alkylsulfonyl, (C_{1-6}-alkylamino)-carbonylamino, (C_{6-10}-arylamino)-carbonylamino, or

R^9 and R^{10} together with the nitrogen atom to which they are attached, form a 5- to 7-membered saturated, partially unsaturated or aromatic heterocyclyl which can contain up to 3 further hetero atoms selected from the group consisting of N, O and S, and which heterocyclyl can contain 1 to 3 substituents selected from the group consisting of

C_{1-6}-alkyl, C-$_{1-6}$-alkoxy, C_{6-10}-aryl and aromatic 4- to 9-membered heterocyclyl with 1 to 4 hetero atoms selected from the group consisting of N, O and S;

R^{11} is hydrogen, C_{1-6}-alkyl or C_{6-10}-aryl;

or

ii) C_{1-12}-alkyl which can contain 1 to 3 substituents selected from the group consisting of C_{1-6}-alkyl, C_{-1-6}-alkoxy, C_{6-10}-aryl and aromatic 4- to 9-membered heterocyclyl with 1 to 4 hetero atoms selected from the group consisting of N, O and S;

or

iii) C_{3-8}-cycloalkyl which can contain 1 to 3 substituents selected from the group consisting of C_{1-6}-alkyl, C_{-1-6}-alkoxy, $COOR^{11}$ wherein R^{11} is as defined above, C_{6-10}-aryl and aromatic 4- to 9-membered heterocyclyl with 1 to 4 hetero atoms selected from the group consisting of N, O and S;

or

iv) aromatic C_{2-9}-heterocyclyl with 1 to 4 hetero atoms selected from the group consisting of N, O and S which aromatic heterocyclyl can contain 1 to 3 further substituents selected from the group consisting of OH, C_{1-6}-alkyl, C_{-1-6}-alkoxy, C_{6-10}-aryl which can contain 1 to 3 halogen radicals, COR^{11} or $COOR^{11}$ wherein R^{11} is as defined above, halogen, CN, and saturated 5- to 7-membered nitrogen-containing heterocyclyl which is bound to the C_{6-10}-aryl moiety via the nitrogen atom and can contain up to 2 further hetero atoms selected from the group consisting of N, O and S and which saturated heterocyclyl can be further substituted with one or more radicals selected from the group consisting of C_{1-6}-alkoxy, OH and NH_2;

with the proviso that ethyl 8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2.1-a]isoquinoline-1-carboxylate is excluded;

and an isomer, a (pharmaceutically acceptable) salt, a hydrate or a hydrate of a (pharmaceutically acceptable) salt thereof.

2. A compound according to claim 1, wherein

x and y independently from each other denote zero or 1 and

x+y is 1 or 2;

R^1 and R^2 independently from each other denote C_{1-4}-alkyl or CF_3;

R^3 denotes hydrogen, formyl, (C_{1-4}-alkyl)-carbonyl, (C_{1-4}-alkoxy)-carbonyl, NO_2, NR_6R_7, C_{1-4}-alkyl-NR^6R^7, C_{1-4}-alkyl-OR^8, C_{1-4}-alkyl-$COOR^8$, C_{6-10}-aryl-C_{1-4}-alkyl wherein the aryl moiety can be substituted with 1 to 3 radicals selected from the group consisting of OH, C_{1-4}-alkyl and C_{1-4}-alkoxy;

wherein

R^6 and R^7 independently from each other denote hydrogen, C_{1-4}-alkyl, C_{3-8}-cycloalkyl, C_{6-10}-aryl-C_{1-4}-alkyl wherein the aryl moiety can be substituted with 1 to 3 radicals selected from the group consisting of OH, C_{1-4}-alkyl and C_{1-4}-alkoxy; or

R^6 and R^7 together with the nitrogen atom to which they are attached, form a 5- to 7-membered heterocyclyl which may contain up to 2 further hetero atoms selected from the group consisting of N, O and S and which heterocyclyl can be further substituted with 1 to 3 radicals selected from the group consisting of OH, C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{6-10}-aryl and aromatic 4- to 9-membered heterocyclyl with 1 to 3 hetero atoms selected from the group consisting of N, O and S;

R^8 denotes hydrogen or C_{1-4}-alkyl;

R^4 denotes C_{1-4}-alkyl;

R^5 is

i) phenyl optionally having 1 to 3 further substituents selected from the group consisting of F, Cl, Br; C_{1-6}-alkyl; C_{1-6}-alkoxy; OH; NR^9R^{10} and $COOR^{11}$; or

naphthyl optionally containing one further OH group;

or

iv) indolyl optionally having 1 to 3 further substituents selected from the group consisting of F, Cl, Br; C_{1-6}-alkyl; C_{1-6}-alkoxy; OH; NR^9R^{10} and $COOR^{11}$;

wherein

R^9 to R^{11} independently from each other denote C_{1-6}-alkyl;

with the proviso that ethyl 8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2.1-a]isoquinoline-1-carboxylate is excluded;

and an isomer, a (pharmaceutically acceptable) salt, a hydrate or a hydrate of a (pharmaceutically acceptable) salt thereof.

3. A compound according to claim 1, wherein

x and y independently from each other denote zero or 1 and

x+y is 1 or 2;

R^1 and R^2 independently from each other denote CH_3 or C_2H_5;

R^3 denotes hydrogen, formyl, (C_{1-4}-alkyl)-carbonyl, (C_{1-4}-alkoxy)-carbonyl, NO_2, NR^6R^7, C_{1-4}-alkyl-NR^6R^7, C_{1-4}-alkyl-OR^8, C_{1-4}-alkyl-$COOR^8$, C_{6-10}-aryl-C_{1-4}-alkyl wherein the aryl moiety can be substituted with 1 to 3 radicals selected from the group consisting of OH, C_{1-4}-alkyl and C_{1-4}-alkoxy;

wherein

R^6 and R^7 independently from each other denote hydrogen, C_{1-4}-alkyl, C_{3-8}-cycloalkyl, C_{6-10}-aryl-C_{1-4}-alkyl wherein the aryl moiety can be substituted with 1 to 3 radicals selected from the group consisting of OH, C_{1-4}-alkyl and C_{1-4}-alkoxy; or

R^6 and R^7 together with the nitrogen atom to which they are attached, form a 5- to 7-membered heterocyclyl which may contain up to 2 further hetero atoms selected from the group consisting of N, O and S and which heterocyclyl can be further substituted with 1 to 3 radicals selected from the group consisting of OH, C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{6-10}-aryl and aromatic 4- to 9-membered heterocyclyl with 1 to 3 hetero atoms selected from the group consisting of N, O and S;

R^8 denotes hydrogen or C_{1-4}-alkyl;

R^4 denotes CH_3 or C_2H_5;

R^5 is

i) phenyl optionally having 1 to 3 further substituents selected from the group consisting of Cl; C_{1-4}-alkyl; C_{1-4}-alkoxy; OH; NR^9R^{10} and $COOR^{11}$; or

naphthyl optionally containing one further OH group;

wherein

R^9 to R^{11} independently from each other denote C_{1-4}-alkyl;

or

iv) indolyl;

with the proviso that ethyl 8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2.1-a]isoquinoline-1-carboxylate is excluded;

and an isomer, a (pharmaceutically acceptable) salt, a hydrate or a hydrate of a (pharmaceutically acceptable) salt thereof.

4. A compound according to claim 1, wherein

x and y independently from each other denote zero or 1 and

x+y is 1 or 2;

R^1 and R^2 independently from each other denote CH_3 or C_2H_5;

R^3 denotes hydrogen, formyl, (C_{1-4}-alkyl)-carbonyl, (C_{1-4}-alkoxy)-carbonyl, NO_2, NH_2, C_{1-4}-alkyl-NR^6R^7, C_{1-4}-alkyl-OR^8, C_{1-4}-alkyl-$COOR^8$, phenyl-C_{1-4}-alkyl wherein the phenyl moiety can be substituted with 1 to 3 C_{1-4}-alkyl or C_{1-4}-alkoxy moieties;

wherein

R^6 and R^7 independently from each other denote hydrogen, C_{1-4}-alkyl, C_{3-6}-cycloalkyl, phenyl-C_{1-4}-alkyl wherein the phenyl moiety can be substituted with 1 to 3 C_{1-4}-alkyl or C_{1-4}-alkoxy radicals; or

R^6 and R^7 together with the nitrogen atom to which they are attached, form a saturated 5- to 7-membered heterocyclyl which may contain up to 2 further hetero atoms selected from the group consisting of N, O and S and which saturated heterocyclyl can be further substituted with 1 to 3 radicals selected from the group consisting of C_{1-4}-alkyl, C_{1-4}-alkoxy, phenyl and pyridyl;

R^8 denotes hydrogen or C_{1-4}-alkyl;

R^4 denotes CH_3 or C_2H_5;

R^5 is

i) phenyl optionally having 1 to 3 further substituents selected from the group consisting of Cl; C_{1-4}-alkyl; C_{1-4}-alkoxy; OH; NR^9R^{10}; and $COOR^{11}$; or

naphthyl optionally containing one further OH group;

wherein

R^9 to R^{10} independently from each other denote C_{1-4}-alkyl;

or

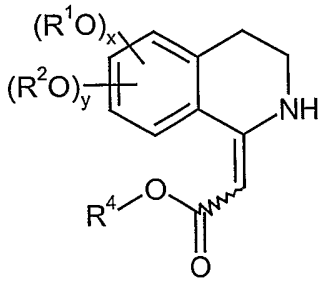
iv) indolyl;

with the proviso that ethyl 8,9-dimethoxy-2-phenyl-5,6-dihydropyrrolo[2.1-a]isoquinoline-1-carboxylate is excluded;

and an isomer, a (pharmaceutically acceptable) salt, a hydrate or a hydrate of a (pharmaceutically acceptable) salt thereof.

5. A compound selected from the group consisting of the compounds of Examples 2, 5, 23 and 27.

6. A process for manufacturing a compound according to claims 1 to 5 comprising the reaction of a compound of the formula



(IV)

wherein

x, y, R^1, R^2 and R^4 are as defined in claims 1 to 4,

[A] with the compounds of the formulae

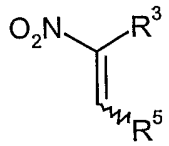
R^5-CHO (II) and R^3-CH_2-NO_2 (III)

wherein

$R^3$and R^5 are as defined in claims 1 to 4,

or

[B] with a compound of the formula



(V)

wherein R^3 and R^5 are as defined in claims 1 to 4,

and optionally

[C] the conversion of the compound obtained through either process [A] or [B] into an isomer, a pharmaceutically acceptable salt, a hydrate or a hydrate of a pharmaceutically acceptable salt thereof.

7. Compounds of claims 1 to 5 for the use in a medical application.

8. Compounds of claims 1 to 5 for combating cancer.

9. Method of manufacturing a pharmaceutical composition by combining at least one of the compounds according to claims 1 to 5 with at least one pharmacologically acceptable formulating agent.

10. Pharmaceutical composition comprising as an active ingredient an effective amount of at least one of the compounds according to claims 1 to 5 and at least one pharmacologically acceptable formulating agent.

11. Pharmaceutical composition comprising as an active ingredient an effective amount of at least one of the compounds according to claims 1 to 5 and at least one pharmaceutical active ingredient which is different from the compounds according to claims 1 to 5.

12. A medicament in dosage unit form comprising an effective amount of a compound according to claims 1 to 5 together with an inert pharmaceutical carrier.

13. A method of combating cancer in mammals comprising the administration of an effective amount of at least one compound according to claims 1 to 5 either alone or in admixture with a diluent or in the form of a medicament.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/08341

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 02 48144 A (ERGUEDEN JENS-KERIM ;FLUBACHER DIETMAR (DE); NIEWOEHNER ULRICH (DE) 20 June 2002 (2002-06-20) page 4, line 5 -page 6, line 12; claims 1-11; examples --- -/--	1-13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 October 2002	06/11/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schmid, A

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/08341

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	ANDERSON W K ET AL: "SYNTHESIS AND MURINE ANTINEOPLASTIC ACTIVITY OF BIS (CARBAMOYLOXY(METHYL DERIVATIVES OF PYRROLO 2,1-AISOQUINOLINE" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 10, no. 27, October 1984 (1984-10), pages 1321-1325, XP001070339 ISSN: 0022-2623 cited in the application abstract; page 1323 "biological evaluation and discussion"; page 1324, table 2; compounds 7-12, 13a-c	1-13
A	WO 98 55118 A (IRILAB LTD ;ROSSI CARLA (IT)) 10 December 1998 (1998-12-10) cited in the application page 3, line 23 -page 5, line 4; claims 1-5; examples	1-13
A	GB 1 153 670 A (G. FERRARI, C. CASAGRANDE) 29 May 1969 (1969-05-29) cited in the application example 3	1-13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/08341

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/08341

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0248144 A	20-06-2002	AU 2798502 A	24-06-2002
		WO 0248144 A1	20-06-2002
WO 9855118 A	10-12-1998	IT MI971329 A1	07-12-1998
		AU 8625598 A	21-12-1998
		WO 9855118 A2	10-12-1998
		EP 0986386 A2	22-03-2000
		JP 2002502410 T	22-01-2002
		US 6323230 B1	27-11-2001
GB 1153670 A	29-05-1969	BE 690792 A	16-05-1967