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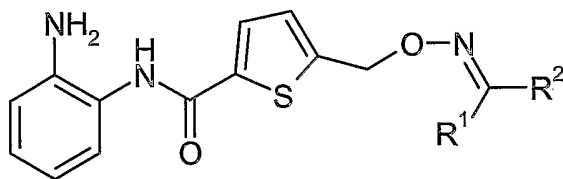
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(54) Title: OXIME DERIVATIVES AND THEIR USE AS PHARMACEUTICALLY ACTIVE AGENTS



(I)

(57) Abstract: Objects of the present
invention are the compounds of formula I, their
pharmaceutically acceptable salts as well as
their enantiomeric forms, diastereoisomers and
racemates; the preparation of the above-men-
tioned compounds, medicaments containing them
and their manufacture, as well as the use of the
above-mentioned compounds as inhibitors of
histone deacetylase (HDAC) and therefore in the

control or prevention of illnesses and disorders as mentioned above, or in the manufacture of corresponding medicaments.



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OXIME DERIVATIVES AND THEIR USE AS PHARMACEUTICALLY ACTIVE AGENTS

Objects of the present invention are new oxime derivatives and pharmaceutically acceptable salts thereof. The invention also relates to processes for the manufacturing of these compounds of formula I, to pharmaceutical compositions containing said compounds and to their use in the manufacture of drugs for the treatment of diseases such as cancer.

Cancer is one of the major causes of death, exceeding heart and cerebrovascular diseases, and so many studies have been conducted with enormous expense and time to overcome cancer. However, in spite of a variety of therapies such as surgical operation, radiation therapy and chemotherapy, there is still a great need for improved anticancer therapeutics. Among these therapies, chemotherapy is one of the main areas for cancer treatment. Most drugs show their effect by affecting mainly DNA to express their cytotoxicity and then, in consequence injuring tumor cells. However, lacking selectivity, they do not sufficiently differentiate between tumor cells and normal cells, and therefore, adverse reactions expressed in normal cells have limited their use in therapy. Up to now, no satisfactory drugs have been discovered, and thus an anticancer drug with reduced toxicity, better tolerability and a high therapeutic effect is very much desired.

The compounds according to this invention are inhibitors of histone deacetylase (HDAC) and therefore show antiproliferative and differentiation-inducing activity, which results in inhibition of tumor cell proliferation, induction of apoptosis and inhibition of invasion.

Transcriptional regulation is a major event in cell differentiation, proliferation, and apoptosis. Transcriptional activation of a set of genes determines cell destination and for this reason transcription is tightly regulated by a variety of factors. One of its regulatory mechanisms involved in the process is an alteration in the tertiary structure of DNA, which affects transcription by modulating the accessibility of transcription factors to their target DNA segments. Nucleosomal integrity is regulated by the acetylation status of the core histones. In a hypoacetylated state, nucleosomes are tightly compacted and thus are nonpermissive for transcription. On the other hand, nucleosomes are relaxed by acetylation of the core histones, with the result being permissiveness to transcription. The acetylation status of the histones is governed by the balance of the activities of histone acetyl transferase

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(HAT) and histone deacetylase (HDAC). Recently, HDAC inhibitors have been found to arrest growth and induce apoptosis in several types of cancer cells, including colon cancer cells, T-cell lymphoma cells, and erythroleukemic cells. Given that apoptosis is a crucial factor for cancer progression, HDAC inhibitors are promising reagents for cancer therapy as effective inducers of apoptosis (Koyama, Y., et al., Blood 96 (2000) 1490-1495).

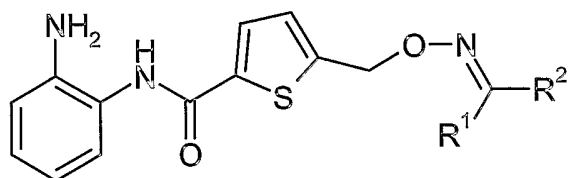
EP-A 0 847 992 describes monoacylated o-phenyldiamine derivatives as cell differentiation inducers. The same type of compounds is also the subject of EP-A 0 242 851. The compounds described in these applications are almost exclusively o-phenylene derivatives monoacylated with derivatives of benzoic acid. WO 03/013484 discloses N-monoacylated carbocyclic but non-aromatic or heteroaromatic o-phenylene diamines as anti-proliferative and differentiation inducing agents. However, there is still a need to provide compounds with improved therapeutical properties such as improved activity, tolerability, selectivity, stability, less toxicity and / or less side effects to name only a few.

Monoacylated o-phenyldiamines are known in the art as precursors for the preparation of the corresponding benzimidazoles, such preparation methods are e.g. described in DE-A 2 062 265; FR 2 167 954; Rastogi, R., and Sharma, S., Indian J. Chem., Sect. B, 21B (5) (1982) 485-487; Moll, R., et al., Z. Chem. 17 (1977) 133-134; and Hassan, H., et al., Indian J. Chem. 39B (2000) 764-768.

It has been found that the compounds of formula I are HDAC inhibitors which have anti-proliferative and differentiation-inducing activity, which results in inhibition of tumor cell proliferation, induction of apoptosis and inhibition of invasion. These compounds are therefore useful for the treatment of diseases such as cancer in humans or animals. Examples of tumors which may be treated, but are not limited to, colon cancers, breast carcinoma (including advanced breast cancer), lung cancer (e.g. adenocarcinoma and including non-small cell lung cancer), prostate cancer including advanced disease, pancreatic cancers, hematopoietic tumors of lymphoid lineage (e.g. acute lymphocytic leukemia, B-cell lymphoma, Burkitt's lymphoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome (MSD), tumors of mesenchymal origin, melanomas, teratocarcinomas, neuroblastomas, gliomas, benign tumors of the skin (e.g. keratoacanthomas), kidney carcinoma, ovary carcinoma, bladder carcinoma and epidermal carcinoma.

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The present invention thus concerns new compounds of the general formula I



formula I

wherein

5 R^1 is hydrogen or
 $\text{C}_1\text{-C}_4\text{-alkyl}$;

R^2 is aryl, heteroaryl or heterocyclyl; all of which may optionally be
 substituted once or several times with
10 alkyl;
 halogen;
 -O-alkyl;
 -NH(alkyl);
 -N(alkyl)₂; or

15 R^1 and R^2 , together with the carbon atom to which they are bound form a cyclic
 hydrocarbon;

and pharmaceutically acceptable salts thereof.

20 Objects of the present invention are the compounds of formula I, their
 pharmaceutically acceptable salts as well as their enantiomeric forms,
 diastereoisomers and racemates; the preparation of the above-mentioned
 compounds, medicaments containing them and their manufacture, as well as the
 use of the above-mentioned compounds as inhibitors of histone deacetylase
25 (HDAC) and therefore in the control or prevention of illnesses and disorders as
 mentioned above, or in the manufacture of corresponding medicaments.

The following definitions of the general terms used in the present description apply
irrespective of whether the terms in question appear alone or in combination.

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The term "halogen" denotes fluorine, chlorine, bromine or iodine.

The term "C₁-C₄-alkyl" denotes a saturated straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, 2-butyl, t-butyl.

5 The term "alkyl" denotes a saturated straight- or branched hydrocarbon containing from 1 to 12 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, 2-butyl, t-butyl, pentyl, hexyl and the like. The alkyl group may optionally be mono or multiple substituted by halogen, preferably fluor such as e.g. trifluoromethyl or pentafluoroethyl and the like.

10 The term "aryl" denotes an aromatic 6 to 10 membered mono- or bicyclic hydrocarbon, e.g. a phenyl or naphthyl ring, and the like.

15 The term "heteroaryl" denotes a 5 or 6 membered monocyclic aromatic hydrocarbon, wherein one or two carbon atoms are replaced by oxygen, nitrogen or sulfur. Examples are imidazolyl, pyrazolyl, thiazolyl, oxazolyl, pyridinyl, pyrimidinyl, and the like.

20 The term "heterocyclyl" denotes a 6 to 10 membered, mono- or bicyclic non-aromatic or partially aromatic hydrocarbon, wherein one or two carbon atoms are replaced by oxygen or nitrogen. Examples are morpholinyl, piperidinyl, 2,3-dihydro-benzofuranyl, benzo[1,3]dioxolyl, 2,3-dihydro-benzo[1,4]dioxinyl or 2,3-dihydro-1H-indolyl, and the like.

A used herein the term "cyclic hydrocarbon" denotes a 9 or 10 membered bicyclic, non-aromatic or partially aromatic hydrocarbon, formed by R¹ and R² together with the carbon atom to which they are bound. Examples are 1,2,3,4-tetrahydro-naphthylidene, indanylidene, and the like.

25 The term "pharmaceutically acceptable salt" refers to conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds of formula I and are formed from suitable non-toxic organic or inorganic acids or organic or inorganic bases. Sample acid-addition salts include those derived from inorganic acids such as hydrochloric acid, hydrobromic acid,
30 hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and

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those derived from organic acids such as p-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Sample base-addition salts include those derived from ammonium, potassium, sodium and quaternary ammonium hydroxides, such as for example, tetramethylammonium hydroxide. The chemical modification of a pharmaceutical compound (i.e. a drug) into a salt is a technique well known to pharmaceutical chemists to obtain improved physical and chemical stability, hygroscopicity, flowability and solubility of compounds. See, e.g., Ansel, H., et. al., Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th ed., 1995, at pp. 196 and 1456-1457.

An embodiment of the invention are the compounds of formula I, wherein

R¹ is hydrogen;
R² is pyridinyl;
2,3-dihydro-benzo[1,4]dioxine-6-yl;
benzo[1,3]dioxole-5-yl; or
phenyl, which may optionally be once or several times substituted with
halogen;
-O-alkyl;
-NH(alkyl); or
-N(alkyl)₂;

and pharmaceutically acceptable salts thereof.

Such compounds are for example

5-(3,4-Dichloro-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;
5-Benzylideneaminooxymethyl-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;
5-(Benzo[1,3]dioxol-5-ylmethyleneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;
5-(4-Chloro-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;

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- 5-(3,4-Dimethoxy-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;
5-(4-Fluoro-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;
5 5-(2-Fluoro-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;
5-(3-Methoxy-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;
5-(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethyleneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;
10 5-(4-Trifluoromethoxy-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;
5-(4-Trifluoromethyl-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;
15 5-(4-Diethylamino-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;
5-(4-Dibutylamino-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide; or
5-(Pyridin-3-ylmethyleneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;
20 5-(Pyridin-4-ylmethyleneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide; or
5-(Pyridin-2-ylmethyleneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide.

25

Another embodiment of the invention are the compounds of formula I, wherein

R¹ is C₁-C₄-alkyl;

30 R² is phenyl or 2,3-dihydro-benzofuran-4-yl; both of which are optionally once or several times substituted with
halogen;
alkyl; or
-O-alkyl;

35 and pharmaceutically acceptable salts thereof.

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Such compounds are for example

5-[1-(4-Propyl-phenyl)-ethylideneaminooxymethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;

5-[1-(2-Methyl-2,3-dihydro-benzofuran-4-yl)-ethylideneaminooxymethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;

5-[1-(2,4-Dichloro-phenyl)-ethylideneaminooxymethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;

5-[1-(3,4-Dichloro-phenyl)-ethylideneaminooxymethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;

5-[1-(3,4-Dimethoxy-phenyl)-ethylideneaminooxymethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;

5-(1-Phenyl-ethylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide; or

5-[1-(4-Fluoro-phenyl)-ethylideneaminooxymethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide.

Yet another embodiment of the invention are the compounds of formula I, wherein

R¹ and R², together with the carbon atom to which they are bound form a cyclic hydrocarbon;

and pharmaceutically acceptable salts thereof.

Such compounds are for example

5-(Indan-2-ylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;

5-(Indan-2-ylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide hydrochloride;

5-(Indan-2-ylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide methanesulfonate; or

5-(Indan-1-ylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide.

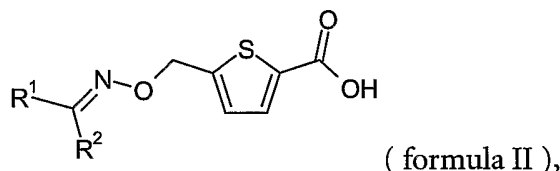
An oxime derivative of the formula I, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of

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chemically-related compounds. Such processes, when used to prepare oxime derivative of the formula I, or a pharmaceutically-acceptable salt thereof, are provided as a further feature of the invention and are illustrated by the following representative examples in which, unless otherwise stated, R^1 and R^2 have the meanings defined above. Starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described within the accompanying examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

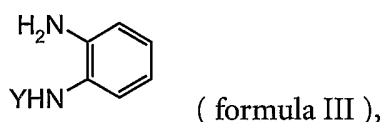
A preferred method, and yet another embodiment of the invention is the process for the manufacture of the compounds of formula I, wherein

(a) a compound of formula II



wherein R^1 and R^2 are as defined above,

is reacted with a compound of the formula III



wherein Y represents hydrogen or a suitable amino protecting group;

(b) the amino protecting group in Y, if present, is cleaved to give a compound of formula I; and

(c) said compound of formula I is isolated from the reaction mixture and, if desired, turned into a pharmaceutically acceptable salt.

The "amino protecting groups" as used herein are known from peptide chemistry. Such protecting groups are for example, benzyloxycarbonyl (cleavage by hydrogenation or hydrobromic acid in acetic acid), t-butoxycarbonyl (cleavage by

strong acids, such as trifluoroacetic acid (neat or in dichloromethane) or hydrochloric acid (HCL) in dioxane), 9-fluorenmethoxycarbonyl (cleavage by secondary amines, such as, piperidine).

5 The reaction typically involves a two-step one-pot procedure. In the first step, the carboxylate of the formula II is activated by reaction of the compound in an inert solvent or diluent, for example, in dichloromethane, dioxane, or tetrahydrofuran (THF), in the presence of an activating agent.

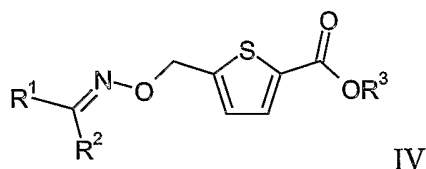
10 A suitable reactive derivative of an acid is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid chloride, for example thionyl chloride or oxalic acid dichloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid and a chloroformate such as isobutyl chloroformate; an active ester, for example an ester formed by the reaction of the acid and a phenol such as pentafluorophenol; an active ester formed by the reaction of the acid and N-hydroxybenzotriazole; an acyl azide, for example
15 an azide formed by the reaction of the acid and an azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid and a carbodiimide such as N-3-dimethylaminopropyl-N-ethylcarbodiimid or dicyclohexylcarbodiimide; or the product of the reaction of
20 the acid with N,N'-carbonyldiimidazole; or the product of the reaction of the acid and uroniumsalts such as O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate; or the product of the reaction of the acid and phosphorus based reagents, e.g. bis-(2-oxo-3-oxazolidinyl)-phosphorylchloride. The reaction is carried out between -30°C and 60°C, conveniently at or below 0°C.

25 In the second step, compound III is added to the solution containing the activated acid. If Y is a protecting group it finally has to be cleaved (methods see above) to yield a compound of formula I.

30 These methods are well known to those skilled in the art. In principle, all methods for the synthesis of amides as used in peptide chemistry as described e.g. by Houben-Weyl, In: Methoden der organischen Chemie, Vols. XV/1 and XV/2, are also applicable. Monoacylation of unprotected phenylene diamine is described in EP 0 974 576.

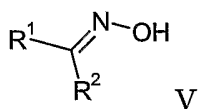
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Compounds of formula II can be prepared by cleavage of the R^3 group of compounds of formula IV

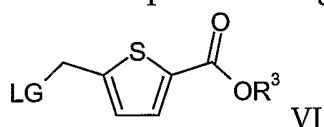


5 wherein R^3 is alkyl and said alkyl has the significance given herein before. Examples for R^3 are methyl and ethyl. The reaction is carried out in the presence of a base, for example, lithium hydroxide, sodium hydroxide, or potassium hydroxide in an inert solvent or diluent, for example in methanol, ethanol, dioxane, THF, water.

10 Compounds of the general formula IV can be prepared for example by a substitution reaction of oximes of the general formula V



15 with a compound of the general formula VI

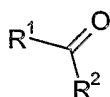


wherein LG is a suitable leaving group for this substitution; examples for LG are Br, Cl, I, tosylate, mesylate.

20

The reaction is carried out in an inert solvent, for example in dichloromethane, acetone, dimethylformamide (DMF), THF, acetonitrile, ethyl acetate, dimethyl sulfoxide (DMSO) and preferably in the presence of a base, e.g. potassium carbonate (K_2CO_3), sodium hydroxide (NaOH), sodium hydride (NaH). Addition
25 of potassium iodide or tetrabutylammonium hydrogen sulfate to the reaction mixture may have a favourable effect in certain cases. If necessary the reaction mixture is heated.

A number of compounds of the general formula V are commercially available. In other cases they can be prepared by known methods e.g. condensation reaction of the corresponding aldehydes or ketones VII



with hydroxylamine or hydroxylamine hydrochloride in an inert solvent e.g. ethanol, , methanol, water, dioxane and preferably in the presence of a base e.g. pyridine, potassium hydroxide, sodium hydroxide, sodium acetate. If necessary the reaction mixture is heated.

10 Some compounds of formula VI are described in the literature. For example 5-Bromomethyl-thiophene-2-carboxylic acid methyl ester is described in e.g Curtin, M.L., et al., J. Med. Chem. 41 (1998) 74-95.

15 The compounds of the general formula I can contain one or several chiral centres and can then be present in a racemic or in an optically active form. The racemates can be separated according to known methods into the enantiomers. Preferably diastereomeric salts which can be separated by crystallization are formed from the racemic mixtures by reaction with an optically active acid such as e.g. D- or L-
20 tartaric acid, mandelic acid, malic acid, lactic acid or camphorsulfonic acid. Furthermore, the racemic compounds can be separated into their enantiomers by chromatography on an analytical, semipreparative or preparative scale using suitable optically active stationary phases with suitable eluents. Suitable optically active stationary phases include, but are not limited to, silica (e.g. ChiraSper,Merck;
25 Chiralpak OT/OP, Baker), cellulose esters or carbamates (e.g. Chiracel OB/OY, Baker) or others (e.g. Crownpak, Daicel or Chiracel OJ-R, Baker).

30 The compounds of formula I, as well as their pharmaceutically usable addition salts possess valuable pharmacological properties. It has been found that they possess antiproliferative and differentiation-inducing activity, which results in inhibition of tumor cell proliferation, induction of apoptosis and inhibition of invasion. Therefore these compounds are useful for the treatment of diseases such as cancer in humans or animals. Consequently a further embodiment of the present invention is the use of a compound of formula I for the treatment of cancer. Yet

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another embodiment is the use of a compound of formula I for the manufacture of corresponding medicaments for the inhibition of tumor growth.

5 The activity of the compounds according to this invention as HDAC inhibitors is demonstrated using a cellular acetylation assay. Therein acetylation of histones is monitored in PC3 cells. High acetylation correlates with inhibition of histone deacetylase by compounds. Cell viability is monitored in parallel to estimate the cytotoxicity of compounds.

10 PC3 cells, a human prostate carcinoma cell line, are seeded as 1800 cells per well of a 384-well microtiterplate in RPMI 1640 (including 5% FCS, 2mM glutamine and pen / strep).

After 48 h at 37 °C pre-diluted compounds are added to a final concentration of 1 uM. Compounds are pre-diluted in dimethyl sulfoxide (DMSO) resulting in a final concentration of DMSO of 0.5 % per well.

15 After 24 h incubation cell viability is determined by adding cell proliferation reagent WST-1 (Roche Molecular Biochemicals). Another 60 min later the optical density (OD) is measured (450 nm versus 690 nm).

20 After measurement the cell layer is prepared for the ELISA reaction. Medium is aspirated and cells are fixed in ethanol at -20 °C for 60 min. After washing with PBS / Tween the blocking solution (PBS/ 5% FCS / Tween) is added and the cell layer is washed again. Antibodies against acetylated histone H3 or H4 (rabbit polyklonal IgG, Upstate Biotechnologie) are added at a dilution of 1:200 for 60 min at 37 °C. As a second antibody goat anti rabbit IgG (H+L) humanIgG adsorbed-HRP conjugate (Dako) is used (1:2000 diluted). Cells are washed 3 times and the peroxidase substrate ABTS is allowed to react for 30-60 min at 37 °C. The OD is
25 measured at 405 nm.

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The percentage of acetylation is calculated after subtraction of blank O.D.s:

$$\frac{\frac{\text{mean O.D. acetylation}}{\text{mean O.D. DMSO control}}}{\frac{\text{mean O.D. WSTI}}{\text{mean O.D. DMSO control}}} \times 100\%$$

Ex-No.	Compound Name	cell acetylation (PC3, 1 μ M) [% of control]
	4-acetylamino-N-(2-amino-phenyl)-benzamide (Reference Compound, from EP0242851, Example 1)	152
4-6	5-Benzylideneaminooxymethyl-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	180
4-7	5-(Indan-2-ylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	182
4-9	5-[1-(3,4-Dimethoxy-phenyl)-ethylideneaminooxymethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	158
4-12	5-(3,4-Dimethoxy-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	137
3	5-(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethylenaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	116
4-17	5-(4-Trifluoromethoxy-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	127
4-21	5-(Pyridin-3-ylmethylenaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	135

5 The effect of the compounds according to the present invention may further be assessed by the following test:

Male NMRI nu/nu-mice(n = 15 per group), aged 8-10 weeks, were subcutaneously injected with 5*10⁶ PC-3 prostate carcinoma cells. On day 10, animals with tumor volumes of about 150 mm³ were randomly assigned to treatment groups. The test compound was administered as a microsuspension in 7,5% gelatine - 0,22% NaCl-Suspension with an application volume of 10 ml/kg based on actual body weights.

10

Once daily oral treatment was performed from approximately day 10 to day 27 on a, 5-7 times per week treatment schedule.

The volume of the tumor is determined from the following equation:

5 Volume of a tumor = $1/2ab^2$, where "a" and "b" are the long and the short diameters of the tumor, respectively

10 Still another embodiment of the invention is a medicament containing as an active ingredient a compound of formula I as described herein before, if desired together with pharmaceutically acceptable adjuvants. Said medicaments, e.g. in the form of pharmaceutical preparations, can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

15 The above-mentioned pharmaceutical preparations can be obtained by processing the compounds according to this invention with pharmaceutically inert, inorganic or organic carriers. Lactose, corn starch or derivatives thereof, talc, stearic acids or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oil and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

25 The pharmaceutical preparations can, moreover, contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

- 15 -

Preferred pharmaceutical preparations comprise the following:

a) Tablet Formulation (Wet Granulation):

Item	Ingredients	mg/tablet			
1.	Compound of formula I	5	25	100	500
2.	Lactose Anhydrous DTG	125	105	30	150
3.	Sta-Rx 1500	6	6	6	30
4.	Microcrystalline Cellulose	30	30	30	150
5.	Magnesium Stearate	1	1	1	1
	Total	167	167	167	831

Manufacturing Procedure:

- 5
 1. Mix items 1, 2, 3 and 4 and granulate with purified water.
 2. Dry the granules at 50°C.
 3. Pass the granules through suitable milling equipment.
 4. Add item 5 and mix for three minutes; compress on a suitable press.

10 b) Capsule Formulation:

Item	Ingredients	mg/capsule			
1.	Compound of formula I	5	25	100	500
2.	Hydrous Lactose	159	123	148	---
3.	Corn Starch	25	35	40	70
4.	Talc	10	15	10	25
5.	Magnesium Stearate	1	2	2	5
	Total	200	200	300	600

Manufacturing Procedure:

1. Mix items 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add items 4 and 5 and mix for 3 minutes.
- 15 3. Fill into a suitable capsule.

The dosage depends on various factors such as manner of administration, species, age and/or individual state of health.

5 The following examples and references are provided to aid the understanding of the present invention, the true scope of which is set forth in the appended claims. It is understood that modifications can be made in the procedures set forth without departing from the spirit of the invention.

In the following examples, unless otherwise stated:

- 10 i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;
- (ii) operations were carried out at ambient temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon or nitrogen;
- 15 (iii) column chromatography (by the flash procedure) and high pressure liquid chromatography (HPLC) were performed on Merck Kieselgel silica or Merck Lichroprep RP-18 reversed-phase silica obtained from E. Merck, Darmstadt, Germany;
- (iv) yields are given for illustration only and are not necessarily the maximum attainable;
- 20 (v) melting points were determined using a Mettler SP62 automatic melting point apparatus, an oil-bath apparatus or a Kofler hot plate apparatus;
- (vi) the structures of the products of the formula I were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques (Micromass Platform II machine using APCI or Micromass Platform ZMD
- 25 using electrospray);
- (vii) intermediates were not generally fully characterized and purity was assessed by thin layer chromatography;
- (viii) the following abbreviations have been used:
- 30 DMF N,N-dimethylformamide;
DMSO dimethylsulphoxide;
THF tetrahydrofuran;
MeOH methanol;
HCl hydrochloric acid;

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	NaH	sodium hydride
	CH ₂ Cl ₂	dichloromethane;
	H ₂ SO ₄	sulphuric acid
	sat.	saturated
5	sol.	solution
	h	hour
	d	days
	rt	room temperature
	eq	equivalent
10	mp	melting point [°C]
	MW calc'd	molecular weight, calculated [g/mol]
	MW found	molecular weight, determined by mass spectrometry [g/mol]

Example 1

15 5-(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethyleaminooxymethyl)-thiophene-2-carboxylic acid methyl ester

To a solution of 500mg (2.13mmol) 5-bromomethyl-thiophene-2-carboxylic acid methyl ester and 381mg (2.13mmol) 2,3-dihydro-benzo[1,4]dioxine-6-carbaldehyde oxime in 2ml dichloromethane were added 2.0ml 2.2M aqueous sodium hydroxide solution and 902mg (2.55mmol) tetrabutylammonium hydrogen sulfate while vigorously stirring. After 10 minutes another 2.0ml 2.2M aqueous sodium hydroxide solution and 902mg (2.55mmol) tetrabutylammonium hydrogen sulfate were added. This procedure was repeated one more time. After 20 minutes 8ml saturated aqueous bicarbonate solution was added. The aqueous phase was extracted three times with ethyl acetate and the combined organic phases were washed with brine and dried over Na₂SO₄. The solvent was evaporated and the residue was subjected to silica gel chromatography (hexane/ethyl acetate 4:1, then 3:1) to yield 214mg (0.64mmol) 5-(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethyleaminooxymethyl)-thiophene-2-carboxylic acid methyl ester; exact MW [M+H] calc'd: 334.07; MW found [M+H]: 334.2.

Example 2

5-(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethyleaminooxymethyl)-thiophene-2-carboxylic acid

To a solution of 200mg (0.60mmol) 5-(2,3-dihydro-benzo[1,4]dioxin-6-ylmethyleaminooxymethyl)-thiophene-2-carboxylic acid methyl ester in 2.4ml THF were added 1.2ml 1M aqueous LiOH solution and the reaction mixture was heated to 70°C for 5h. Water was added, the mixture was acidified and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over Na₂SO₄ and the solvent was evaporated to give 190mg (0.59mmol) 5-(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethyleaminooxymethyl)-thiophene-2-carboxylic acid; exact MW [M+H] calc'd: 320.06; MW found [M+H]: 320.2.

Example 3

5-(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethyleaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide

A solution of 100mg (0.31mmol) 5-(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethyleaminooxymethyl)-thiophene-2-carboxylic acid, 65mg (0.47mmol) 1-hydroxybenzotriazol, 92mg (0.47mmol) N³-(3-dimethylaminopropyl)-N-ethylcarbodiimide and 65μl (0.47mmol) triethylamine in 3ml dichloromethane was stirred for 15 minutes. After addition of 68mg (0.63mmol) phenylenediamine the reaction mixture was stirred overnight. The solvent was evaporated and the residue was subjected to preparative HPLC to yield 88mg (0.21mmol) 5-(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethyleaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide (17); exact MW [M+H] calc'd: 410.12; MW found [M+H]: 410.2.

¹H-NMR (400 MHz, (CH₃)₂SO): δ = 9.67 (s, 1H), 8.18 (s, 1H), 7.85 (m, 1H), 7.20 (m, 1H), 7.14-7.09 (m, 3H), 6.97 (m, 1H), 6.91 (m, 1H), 6.77 (m, 1H), 6.58 (m, 1H), 5.29 (s, 2H), 4.90 (s, 2H), 4.26 (m, 4H)

Example 4

In an analogous manner to that described in the example 3, and using known methods as described in the literature (e.g. in standard works such as Houben-Weyl, Methoden der Organischen Chemie, Georg Thieme Verlag, Stuttgart;

Organic Reactions, John Wiley & Sons, Inc., New York) the following compounds are prepared :

Cpd. No.	Name	exact MW [M+H] calc'd	MW found [M+H]
4-1	5-[1-(4-Propyl-phenyl)-ethylideneaminooxymethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	408.17	408.2
4-2	5-[1-(2-Methyl-2,3-dihydro-benzofuran-4-yl)-ethylideneaminooxymethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	422.15	422.2
4-3	5-[1-(2,4-Dichloro-phenyl)-ethylideneaminooxymethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	434.05	434.1
4-4	5-[1-(3,4-Dichloro-phenyl)-ethylideneaminooxymethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	434.05	434.3
4-5	5-(3,4-Dichloro-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	420.03	420.3
4-6	5-Benzylideneaminooxymethyl-thiophene-2-carboxylic acid (2-amino-phenyl)-amide ¹ H-NMR (400 MHz, (CH ₃) ₂ SO): δ = 9.68 (s, 1H), 8.32 (s, 1H), 7.87-7.86 (m, 1H), 7.66-7.63 (m, 2H), 7.45-7.43 (m, 3H), 7.22 (m, 1H), 7.10 (m, 1H), 6.97 (m, 1H), 6.77 (m, 1H), 6.58 (m, 1H), 5.34 (s, 2H), 4.89 (s, 2H)	352.11	352.3
4-7	5-(Indan-2-ylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide ¹ H-NMR (400 MHz, (CH ₃) ₂ SO): δ = 9.66 (s, 1H), 7.84 (m, 1H), 7.31-7.29 (m, 2H), 7.24-7.21 (m, 2H), 7.12 (m, 1H), 7.10 (m, 1H), 6.97 (m, 1H), 6.77 (m, 1H), 6.58 (m, 1H), 5.28 (s, 2H), 4.89 (s, 2H), 3.77 (s, 4H)	378.13	378.3
4-8	5-(Benzo[1,3]dioxol-5-ylmethyleneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	396.1	396.2

Cpd. No.	Name	exact MW [M+H] calc'd	MW found [M+H]
4-9	5-[1-(3,4-Dimethoxy-phenyl)-ethylideneaminooxymethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide ¹ H-NMR (400 MHz, (CH ₃) ₂ SO): δ = 9.67 (s, 1H), 7.85 (m, 1H), 7.33 (m, 1H), 7.24-7.20 (m, 2H), 7.10 (m, 1H), 7.00-6.95 (m, 2H), 6.77 (m, 1H), 6.58 (m, 1H), 5.34 (s, 2H), 4.89 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 2.19 (s, 3H)	426.15	426.2
4-10	5-(1-Phenyl-ethylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	366.13	366.3
4-11	5-(4-Chloro-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	386.07	386.2
4-12	5-(3,4-Dimethoxy-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	412.13	412.2
4-13	5-(4-Fluoro-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	370.1	370.2
4-14	5-(2-Fluoro-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	370.1	370.2
4-15	5-[1-(4-Fluoro-phenyl)-ethylideneaminooxymethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	384.12	384.3
4-16	5-(3-Methoxy-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	382.12	382.2
4-17	5-(4-Trifluoromethoxy-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide ¹ H-NMR (400 MHz, (CH ₃) ₂ SO): δ = 9.69 (s, 1H), 8.38 (s, 1H), 7.87 (m, 1H), 7.78 (m, 2H), 7.45 (m, 2H), 7.23 (m, 1H), 7.10 (m, 1H), 6.97 (m, 1H), 6.77 (m, 1H), 6.58 (m, 1H), 5.36 (s, 2H), 4.90 (s, 2H)	436.09	436.1
4-18	5-(4-Trifluoromethyl-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	420.1	420.2
4-19	5-(4-Diethylamino-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	423.19	423.2
4-20	5-(4-Dibutylamino-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	479.25	479.3

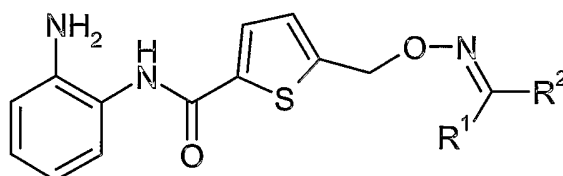
Cpd. No.	Name	exact MW [M+H] calc'd	MW found [M+H]
4-21	5-(Pyridin-3-ylmethyleneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide ¹ H-NMR (400 MHz, (CH ₃) ₂ SO): δ = 9.69 (s, 1H), 8.80 (m, 1H), 8.62 (m, 1H), 8.40 (m, 1H), 8.04 (m, 1H), 7.87 (m, 1H), 7.47 (m, 1H), 7.24 (m, 1H), 7.10 (m, 1H), 6.97 (m, 1H), 6.77 (m, 1H), 6.58 (m, 1H), 5.37 (s, 2H), 4.91 (s, 2H)	353.11	353.1
4-22	5-(Pyridin-4-ylmethyleneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	353.11	353.1
4-23	5-(Pyridin-2-ylmethyleneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	353.11	353.1
4-24	5-(Indan-2-ylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide hydrochloride	413.93	413.9
4-25	5-(Indan-2-ylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide methanesulfonate	473.57	473.6
4-26	5-(Indan-1-ylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	378,13	378,1

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WO 03/013484

Patent Claims

1. A compound of formula I



formula I

wherein,

5 R¹ is hydrogen or
 C₁-C₄-alkyl;

 R² is aryl, heteroaryl or heterocyclyl; all of which may optionally
10 be substituted once or several times with
 alkyl;
 halogen;
 -O-alkyl;
 -NH(alkyl);
 -N(alkyl)₂; or

15 R¹ and R², together with the carbon atom to which they are bound form a
 cyclic hydrocarbon;

and pharmaceutically acceptable salts thereof.

- 20 2. A compound according to claim 1, wherein

 R¹ is hydrogen;

 R² is pyridinyl;

 2,3-dihydro-benzo[1,4]dioxine-6-yl;

 benzo[1,3]dioxole-5-yl; or

25 phenyl, which may optionally be once or several times
 substituted with

 halogen;

- 24 -

-O-alkyl;
-NH(alkyl); or
-N(alkyl)₂;

5 and pharmaceutically acceptable salts thereof.

3. The compounds according to claim 1 or 2,

5-(3,4-Dichloro-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid
(2-amino-phenyl)-amide;

10 5-Benzylideneaminooxymethyl-thiophene-2-carboxylic acid (2-amino-
phenyl)-amide;

5-(Benzo[1,3]dioxol-5-ylmethylenaminooxymethyl)-thiophene-2-
carboxylic acid (2-amino-phenyl)-amide;

5-(4-Chloro-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-
amino-phenyl)-amide;

15 5-(3,4-Dimethoxy-benzylideneaminooxymethyl)-thiophene-2-carboxylic
acid (2-amino-phenyl)-amide;

5-(4-Fluoro-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-
amino-phenyl)-amide;

20 5-(2-Fluoro-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-
amino-phenyl)-amide;

5-(3-Methoxy-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-
amino-phenyl)-amide;

5-(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethylenaminooxymethyl)-
thiophene-2-carboxylic acid (2-amino-phenyl)-amide;

25 5-(4-Trifluoromethoxy-benzylideneaminooxymethyl)-thiophene-2-
carboxylic acid (2-amino-phenyl)-amide;

5-(4-Trifluoromethyl-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;

5-(4-Diethylamino-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;

5 5-(4-Dibutylamino-benzylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;

5-(Pyridin-3-ylmethyleneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;

10 5-(Pyridin-4-ylmethyleneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide; or

5-(Pyridin-2-ylmethyleneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide.

4. A compound according to claim 1, wherein

15 R¹ is C₁-C₄-alkyl;

R² is phenyl or 2,3-dihydro-benzofuran-4-yl; both of which are optionally once or several times substituted with
halogen;
alkyl; or
20 -O-alkyl;

and pharmaceutically acceptable salts thereof.

5. The compounds according to claim 1 or 4,

25 5-[1-(4-Propyl-phenyl)-ethylideneaminooxymethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;

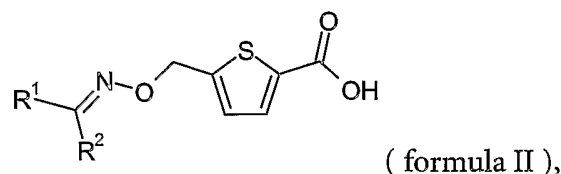
5-[1-(2-Methyl-2,3-dihydro-benzofuran-4-yl)-ethylideneaminooxymethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;

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- 5-[1-(2,4-Dichloro-phenyl)-ethylideneaminooxymethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;
- 5-[1-(3,4-Dichloro-phenyl)-ethylideneaminooxymethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;
- 5 5-[1-(3,4-Dimethoxy-phenyl)-ethylideneaminooxymethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;
- 5-(1-Phenyl-ethylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide; or
- 10 5-[1-(4-Fluoro-phenyl)-ethylideneaminooxymethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide.
6. A compound according to claim 1, wherein
- R^1 and R^2 , together with the carbon atom to which they are bound form a cyclic hydrocarbon;
- and pharmaceutically acceptable salts thereof.
- 15 7. The compounds according to claim 1 or 6,
- 5-(Indan-2-ylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide;
- 5-(Indan-2-ylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide hydrochloride;
- 20 5-(Indan-2-ylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide methanesulfonate; or
- 5-(Indan-1-ylideneaminooxymethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide.

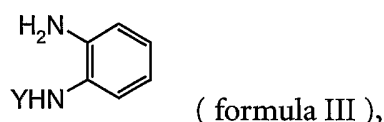
8. The process for the manufacture of the compounds of formula I, wherein

(a) a compound of formula II



5 wherein R¹ and R² are as defined in claim 1,

is reacted with a compound of the formula III



10 wherein Y represents hydrogen or a suitable amino protecting group;

(b) the amino protecting group in Y, if present, is cleaved to give a compound of formula I; and

15 (c) said compound of formula I is isolated from the reaction mixture and, if desired, turned into a pharmaceutically acceptable salt.

9. A medicament containing one or more compounds as claimed in any one of claims 1 to 7 and pharmaceutically acceptable excipients.

20 10. A medicament according to claim 9 for the inhibition of tumor growth.

11. The use of a compound in any one of claims 1 to 7 for the treatment of cancer.

12. The use of a compound in any one of claims 1 to 7 for the manufacture of corresponding medicaments for the inhibition of tumor growth.

INTERNATIONAL SEARCH REPORT

International Application No

EP2004/003498

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D409/12 A61K31/38 A61P35/00 C07D333/38 A61K31/44

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 A61K 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, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/013484 A (HOFFMANN LA ROCHE) 20 February 2003 (2003-02-20) cited in the application Claims 1-10; Formula (I); compounds 21, 53, 84	1-12
A	WO 03/011851 A (HOFFMANN LA ROCHE) 13 February 2003 (2003-02-13) Claims 1-2,5-9; Formula (I); compound n°91	1-12
A	WO 02/46129 A (ABBOTT LAB) 13 June 2002 (2002-06-13) Claims 1-31	1-12
	----- -/-	



Further documents are listed in the continuation of box C.



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

21 June 2004

Date of mailing of the international search report

06/07/2004

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Kirsch, C

INTERNATIONAL SEARCH REPORT

ional Application No
EP2004/003498

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 013, no. 187 (C-592), 2 May 1989 (1989-05-02) & JP 01 013086 A (NIPPON NOHYAKU CO LTD), 17 January 1989 (1989-01-17) Formulas (I) and (II) abstract -----	1-12

INTERNATIONAL SEARCH REPORT

ional Application No

EP2004/003498

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WO 03011851	A	13-02-2003	CA 2449804 A1	13-02-2003
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