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(54) **Title**: DIPHENYLPROPANE COMPOUNDS AND THEIR CYTOTOXIC ACTIVITY

(57) **Abstract**: The invention relates to new derivatives of 1,3-diphenylpropane described by general formula (I), demonstrating cytotoxic activity against cancer cells, to be used as drugs in anticancer therapy, and characterized by reduced undesired side effects in comparison to related derivatives of chalcones.

DIPHENYLPROPANE COMPOUNDS AND THEIR CYTOTOXIC ACTIVITY

The invention relates to new derivatives of 1,3-diphenylpropane that from a chemical point of view can be considered as derivatives of chalcone with various degree of reduction of the enone system, to pharmaceutical compositions containing the same, and to their use in therapy of cancer related diseases.

Chalcones can be defined as compounds composed of two phenyl rings connected with a propen-3-one unit. They belong to the class of unsaturated aromatic ketones and are known as by-products in biosynthesis of flavonoids. In the prior art, various chalcone derivatives are disclosed, displaying diverse biological activity, including antiinflammatory, anticancer or antibacterial.

From publications WO01/72980, WO99/22728, WO99/00114, WO98/58913, WO91/17749, WO03/048106 various chalcone derivatives substituted in both rings with substituents like OH, OCH_3, F, Cl, Br, SCH_3, CF_3, NH_2, NR_2, and displaying anticancer activity are known. WO03/076407 discloses derivatives of 1-(4-methoxyphenyl)-3-(3,5-dimethoxyphenyl)prop-1-en-3-one possessing anticancer and antiangiogenic activity. Publication WO11/009826 discloses derivatives of chalcone with anticancer activity wherein one of the phenyl rings is fused with oxathiole, oxathiine, dioxole or dioxane ring.

In the prior art, an opinion prevails that the presence of enone group is necessary for cytotoxic activity of chalcones, as its reduction results in one – two orders decrease in activity. (E. Venkateswararao et al., A SAR study on a series of synthetic lipophilic chalcones as Inhibitor of transcription factor NF- κB; Eur. J. Med. Chem. 54 (2012) 379-386; D. Maydt et al., Chemical reactivity and biological activity of chalcones and other α,β-unsaturated carbonyl compounds: Xenobiotica 43(8) (2013) 711-718). The enone group, while necessary for cytotoxic activity, can lead, in case of eventual application of chalcones as anticancer drugs, to severe side effects, related to reactions of the reactive enone moiety with nucleic acids or proteins. Such interactions can effect synthesis of DNA, enzymes activations, regulations of cell cycle, and other processes vital for normal functions of organism (P. Perjesi i inn. „Comparison of effects of some cyclic chalcone analogues on selected mitochondrial functions" Pharmazie 63 (2008) 899-903; P. Perjesi i inn. (E)-2-Benzylidenebenzocyclanones: Part VII. Investigation of the conjugation reaction of two

cytotoxic cyclic chalcone analogues with glutathione: an HPLC–MS study" Monatsh. Chem. 143 (2012) 1107–1114).

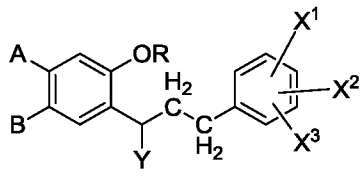
For the above reasons, in spite of existence of numerous known chalcone derivatives bearing cytotoxic activity, there is still a need for new derivatives of chalcones with cytotoxic activity against cancer cells that can extend our arsenal of anticancer drugs, but at the same time will be free of undesired side effects present in currently available chemotherapies.

Reduced derivatives of chalcone do not have the enone moiety responsible for the potentially unfavorable side effects, and it can be expected that they will exhibit much less of the undesired side effects than their analogs with unmodified enone group. However, the known applications of the reduced derivatives of chalcone do not suggest their use as cytotoxic agents, as they are known as antiarrhythmic drugs (for example Propafenon, Diprafenon, Alprafenon) or as artificial sweeteners, used on a large scale in food industry (neohesperidine dihydrochalcone = additive E959).

The present invention solves the presented above problems providing new anticancer compounds that do not lead to the undesired side effects and retain high, at nanomolar level activity.

It was unexpectedly found that some derivatives of 1,3-diphenylpropane display cytotoxic activity against cancer cells, similar to the activity of the analogous chalcones. At the same time, due to the lack of the reactive enone moiety, it can be expected that side effects associated with application of the cytostatic agents to patients, will be minimized, in comparison with effects of the analogous chalcones.

The invention relates to new derivatives of 1,3-diphenylpropane of general formula (I), and their pharmaceutically acceptable salts,



(I)

wherein:

A and **B** are linked together and form a a moiety selected from $-O-(CH_2)_n-S(O)_m-$, $-S(O)_m-(CH_2)_n-O-$ or $-O-(CH_2)_n-O-$

or

one of **A** and **B** is $-S(O)_m-C_1-C_6$-alkyl, and the second is selected from a group consisting of OH and $-O-C_1-C_6$-alkyl;

R is H, C_1-C_6-alkyl, $CO-C_1-C_6$-alkyl, or $-(CH_2)_p-NR^1R^2$, wherein

$\mathbf{R^1}$ and $\mathbf{R^2}$ are independently of each other, H, C_1-C_6-alkyl, or

$\mathbf{R^1}$ and $\mathbf{R^2}$ are linked together by a polymethylene linker $-(CH_2)_q-$, to form along with the nitrogen atom to which they are attached, a five or six- membered ring, wherein one of carbon atoms may be optionally replaced by O, N, or S.

Y is: O, H, OH, NH_2

$\mathbf{X^1}$, $\mathbf{X^2}$, $\mathbf{X^3}$ are, independently of each other, H, halogen atom, OH, $-O-C_1-C_6$alkyl, $-O-CO-C_1-C_6$alkyl, $-O-C_1-C_6$alkyl($N(C_1-C_6$ alkyl$)_2$), $O-PO(OH)_2$, NO_2, NH_2 or NHR^3, wherein $\mathbf{R_3}$ is C_1-C_6alkyl

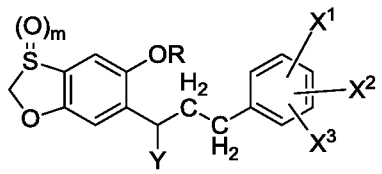
m= 0, 1, or 2

n= 1 or 2;

p=2 to 6

q= 4 or 5

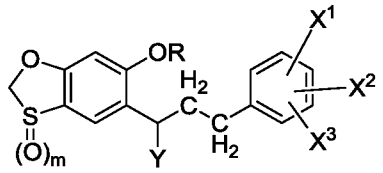
In one of the embodiments of the invention, derivatives of 1,3-diphenylpropane are compounds of formula (IA)



(IA)

wherein R, m, X^1, X^2, X^3, Y have the same meanings as defined for general formula (I).

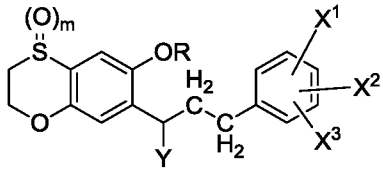
In one of the embodiments of the invention, derivatives of 1,3-diphenylpropane are compounds of formula (IB)



(IB)

wherein R, m, X^1, X^2, X^3, Y have the same meanings as defined for general formula (I).

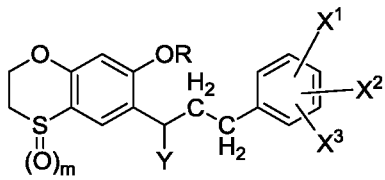
In one of the embodiments of the invention, derivatives of 1,3-diphenylpropane are compounds of formula (IC)



(IC)

wherein R, m, X^1, X^2, X^3, Y have the same meanings as defined for general formula (I).

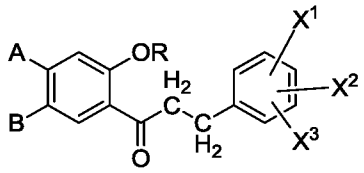
In one of the embodiments of the invention, derivatives of 1,3-diphenylpropane are compounds of formula (ID)



(ID)

wherein R, m, X^1, X^2, X^3, Y have the same meanings as defined for general formula (I).

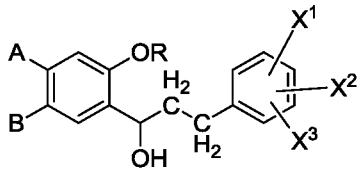
In one of the embodiments of the invention, derivatives of 1,3-diphenylpropane are compounds of formula (IIA)



(IIA)

wherein A, B, R, X^1, X^2, X^3 have the same meanings as defined for general formula (I).

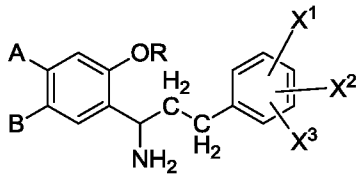
In another embodiment of the invention, derivatives of 1,3-diphenylpropane can be presented by formula (IIB)



(IIB)

wherein A,B, R, X^1, X^2, X^3 have the same meanings as defined for general formula (I).

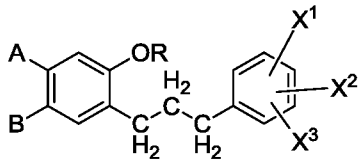
In another embodiment of the invention, derivatives of 1,3-diphenylpropane can be presented by formula (IIC)



(IIC)

wherein A,B, R, X^1, X^2, X^3 have the same meanings as defined for general formula (I).

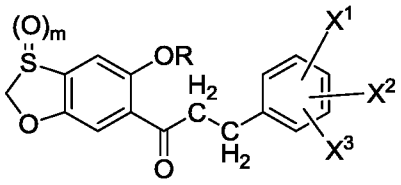
In still another embodiment of the invention, derivatives of 1,3-diphenylpropane are compounds of formula (IID)



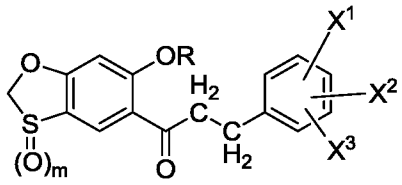
(IID)

wherein A,B, R, X^1, X^2, X^3 have the same meanings as defined for general formula (I).

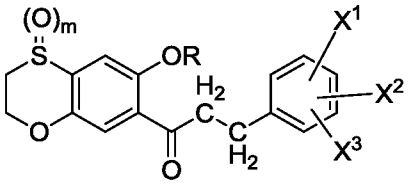
In subsequent embodiments of the invention, derivatives of 1,3-diphenylpropane are compounds of formulas IIA1 – IIA4; IIB1 – IIB4; IIC1 – IIC4; IID1 – IID4, wherein R, m, X^1, X^2, X^3 have the same meanings as defined for general formula (I).



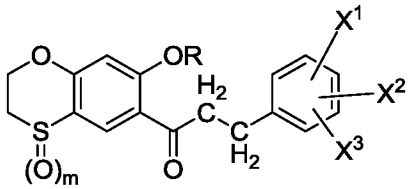
IIA1



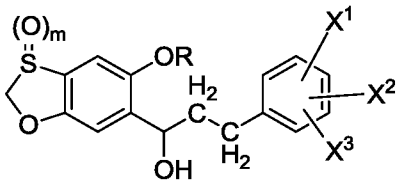
IIA2



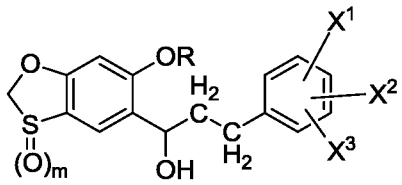
IIA3



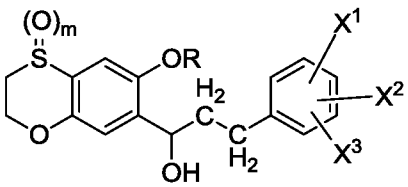
IIA4



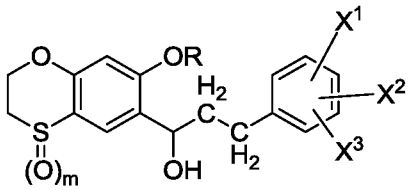
IIB1



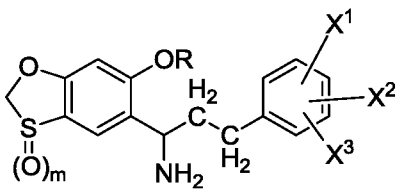
IIB2



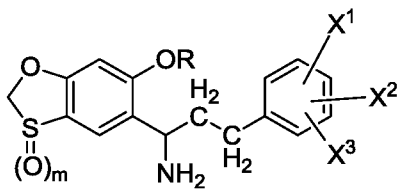
IIB3



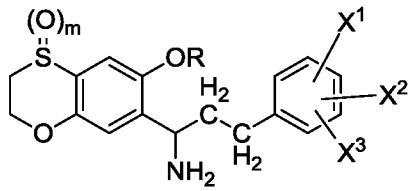
IIB4



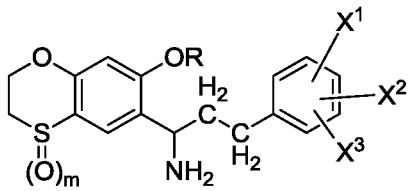
IIC1



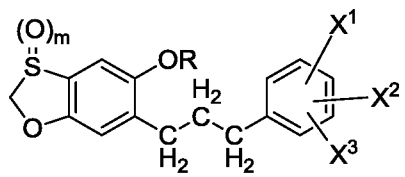
IIC2



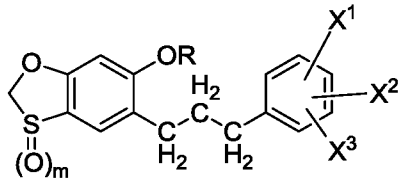
IIC3



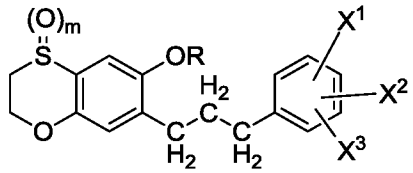
IIC4



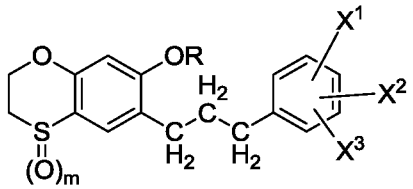
IID1



IID2

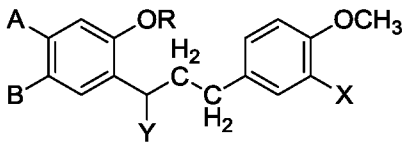


IID3



IID4

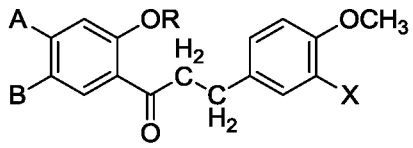
In particularly preferred embodiment of the invention derivative of 1,3-diphenylpropane is compound of formula (III)



(III)

wherein A, B, R, Y have the same meanings as defined for general formula (I), X is H, halogen atom, OH, -O-C_1-C_6alkyl, -O-CO-C_1-C_6 alkyl, -O-C_1-C_6alkyl(N(C_1-C_6alkyl)$_2$), O-$PO(OH)_2$, NO_2, NH_2 or NHR^3, wherein R_3 is C_1-C_6alkyl.

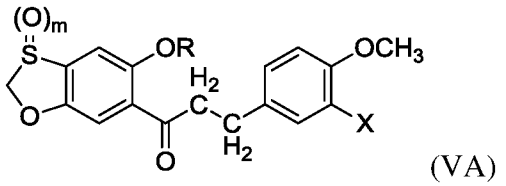
In another, particularly preferred embodiment of the invention derivative of 1,3-diphenylpropane is compound of formula (IV)



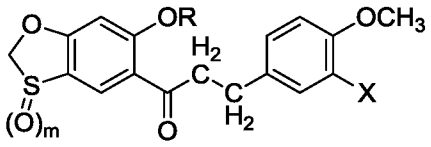
(IV)

wherein A, B, R have the same meanings as defined for general formula (I), X is H, halogen atom, OH, -O-C_1-C_6alkyl, -O-CO-C_1-C_6 alkyl, -O-C_1-C_6alkyl(N(C_1-C_6alkyl)$_2$), O-PO(OH)$_2$, NO_2, NH_2 or NHR^3, wherein R_3 is C_1-C_6alkyl.

In one of the embodiment of the invention derivatives of 1,3-diphenylpropanes can be presented by formulas VA-VD, VIA-VID, VIIA-VIID, VIIIA-VIIID:



(VA)



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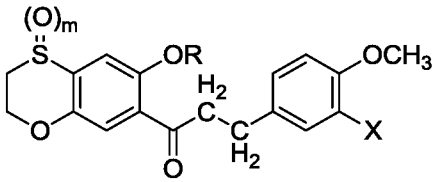

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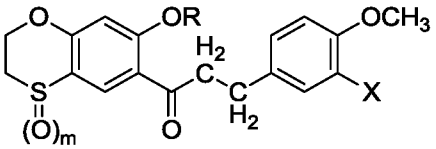

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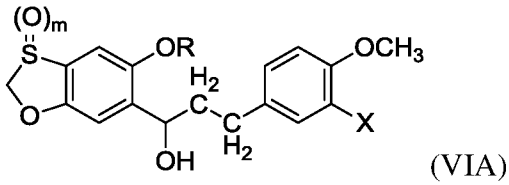

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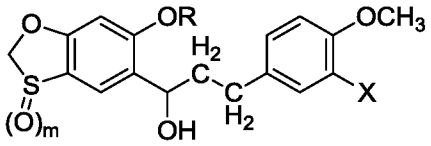

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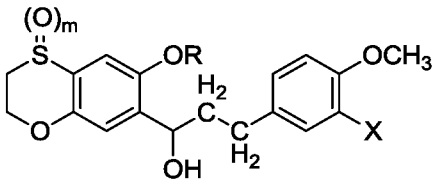
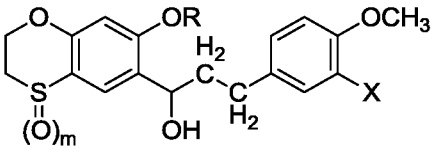


(VIC)



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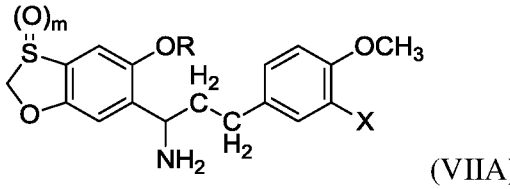
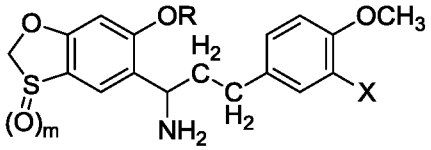


(VIIA)



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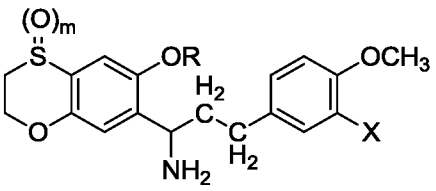

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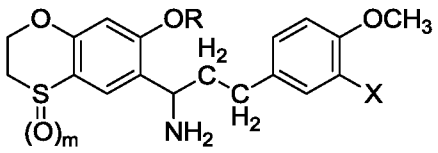

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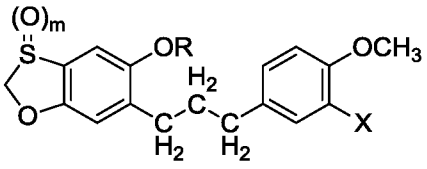

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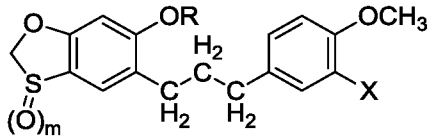

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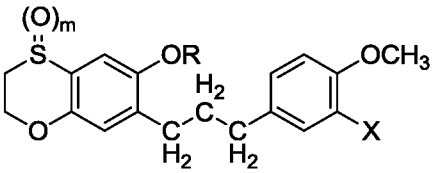
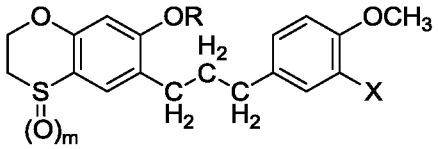


(VIIIC)



(VIIID)

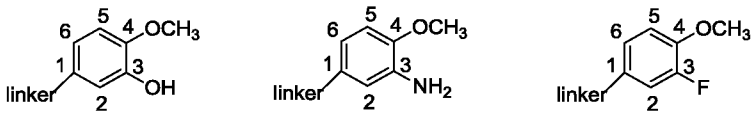
wherein R and m have the same meanings as defined for general formula (I), X is H, halogen atom, OH, -O-C_1-C_6alkyl, -O-CO-C_1-C_6 alkyl, -O-C_1-C_6alkyl(N(C_1-C_6alkyl)$_2$), O-PO(OH)$_2$, NO_2, NH_2 or NHR^3, wherein R_3 is C_1-C_6alkyl.

A particular group of the defined above compounds of formulas IIA1-IIA4, IIB1-IIB4, IIC1-IIC4, IID1-IID4 and VA-VD, VIA-VID, VIIA-VIID, VIIIA-VIIID are compounds wherein m = 1, that means compounds with sulfoxide group –SO.

Another particular group of the defined above compounds of formulas IIA1-IIA4, IIB1-IIB4, IIC1-IIC4, IID1-IID4 and VA-VD, VIA-VID, VIIA-VIID, VIIIA-VIIID are compounds wherein m = 2, that means compounds with sulfone group –SO_2.

Preferably, in the above compounds R is C_1-C_4-alkyl group, particularly ethyl and propyl group.

Preferably, system of substituents X^1, X^2, X^3 in the general formula (I) is as demonstrated on the Scheme below:



Derivatives of 1,3-diphenylpropane with the above systems of substituents demonstrated the highest cytotoxic activity.

The term „C_1-C_4-alkyl" relates to acyclic, saturated hydrocarbon group, with the indicated number of the carbon atoms that can be either a straight-chain or branched chain. Specific examples of groups included in the definition are methyl, ethyl, n-propyl, iso-propyl, n-butyl, tert-butyl, and sec-butyl groups.

The term "halogen" relates to a substituent selected from Cl, F, and Br.

Compounds of general formula (I), having -O-$PO(OH)_2$ group, may form salts with bases. The salts also constitute a subject of the invention. Particularly, the invention includes sodium, potassium and lithium salts of compounds of general formula (I).

Compounds of general formula (I), having an amino group or nitrogen heterocyclic group, may form addition salts with acids. The salts also constitute a subject of the invention.

Salts with acids may be pharmaceutically acceptable salts, especially in case they are intended to be used as component of pharmaceutical composition. The invention encompasses also salts with other than pharmaceutically acceptable acids that may be applied for example, as intermediate products in purification of compounds according to the invention.

Addition salts with acids my be formed with inorganic (mineral) acids or with organic acids. As examples of the acids, the hydrochloric, hydrobromic, phosphoric, sulfuric, nitric, succinic, maleic, formic, acetic, glutaminic, asparaginic, p-toluenesulfonic, benzenesulfonic, methanesulfonic, ethanesulfonic, naphtalenesulfonic such as 2-naphtalenesulfonic, or hexanoic acid can be listed.

Addition salt with acid may be produced by reaction of compound of general formula (I) with a suitable inorganic or organic acid, ewentually in a suitable solvent, such as an organic solvent, usually the formed salt is isolated by crystallization and filtration. For example, free bases of compounds can be transformed into related hydrochlorides by reaction of solution of the compounds, for example in methanol, with a suitable amount of hydrochloric acid or its solution in methanol, ethanol, or diethyl ether, and evaporation of the solvents. Also for example, free bases of compounds can be tansformed into related methanesufonates by addition of a suitable amount of methanesulfonic acid in methanol, ethanol or diethyl ether sulution to a solution of the compound, and subsequent evaporation of solvents or precipitation of the product.

Pharmacological properties of the compounds according to the invention depend to much extend on possibility of their transformation into pro-drugs. Compounds of general formula (I) may form pharmaceutically acceptable esters and amides that can be used as pro-drugs. The simplest effect that can be achieved in result is water solubility. Derivatives substituted with hydroxyl group can be transformed into esters with phosphoric acid (compound AMG-414), and compounds with amino group into amides of amino acids (compounds AMG-415, AMG-421). Compounds according to the invention can form in case of phenol group carbamates, and in case of an amino group derivatives with other amino acids.

The used here term "pro-drug" relates to a compound that is transformed *in vivo* into the parent drug, in result of particular physiological processes (for example the parent drug is formed under influence of enzymes or physiological pH).

Pro-drugs are needed, as under some circumstances, they can be applied easier than the parent drug. Pro-drug can have better than the parent drug solubility in pharmaceutical compositions, for example the pro-drug may have better water solubility, what facilitate an intravenous apllication of the drug. Pro-drug may have a better bioavailability in per-os application. After application, the pro-drug is enzymatically or chemicaly cleaved, to give the parent drug in blood or other tissues.

Exemplary pro-drugs of compounds according to the invention, include compounds wherein a hydrogen atom of amine or hydroxy group of the parent drug is replaced by a moiety such as (C_1-C_6)alkanoiloxymethyl, 1-((C_1-C_6)alkanoiloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoiloxy)ethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonyloaminomethyl, arylacyl and α-aminoacyl or α-aminoacyl-α-aminoacyl, wherein the above α-aminoacyl groups are independently selected from any natural, existing in proteins L-amino acids, -P(O)$(OH)_2$, -P(O)$(O(C_1$-$C_6)alkyl)_2$ or glycoside (a radical formed by elimination of hydroxy group from a hemiacetal form of carbohydrate).

The invention relates also to pharmaceutical compositions containing compounds described by the formula (I), and pharmaceutically acceptable excipient, such like vehicle.

The term "pharmaceutically acceptable vehicle" relates to any vehicle used in preparation of a desired pharmaceutical dosage form. The pharmaceutically acceptable vehicle can include one or more solvents, diluents or other liquid disperging agents, additives used to prepare dispersion or suspension, detergents, isotonic agants, binders, emulgants, preservatives,

lubricants and others. Remington's Pharmaceutical Sciences, XV-th Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1975) and Handbook of Pharmaceutical Excipients, III-rd Ediition, A. H. Kibbe ed. (American Pharmaceutical Assoc. 2000) disclose various vehicles used in pharmaceutical compositions and known procedures for their preparation.

The invention relates also to compounds described by the above formulas for use as medicaments.

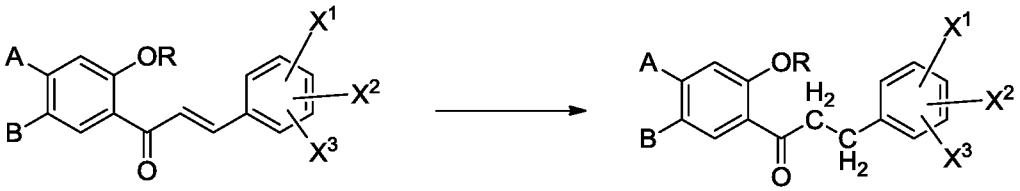
Subsequent invention relates to compounds described by the above formulas for use in treatment of cancer.

Reduction of the double bond in chalcone derivatives containing fused oxathiole, oxathiin, dioxole or dioxane ring results in compounds according to the invention that still display very strong cytotoxic activity. At the same time, due to the reduction of the double bond, the compounds according to the invention will not react nonenzymatically with cellular nucleophiles, and subsequently will cause lesser amount of adverse side effects. Chalcones may react *in vivo* with thiols, e.g. GSH, to give potentially severe biological consequences. The enone group of chalcones can conjugate with thiols by the Michael addition. The reactions can lead to many undesired side effects. Particularly, thiols are involved in regulation of redox equilibrium of cell, and its destabilizations may results in destabilization of synthesis of DNA, affects activation of enzymes, selectivity of genes expression, and regulation of cell cycle (P. Perjesi et al (Monatsh Chem (2012) 143:1107–1114). Elimination of the double bond from the chalcone molecule resulted in elimination of possibility of reaction with the protein derived thiol groups, and subsequently in elimination of eventuall undesired side effects.

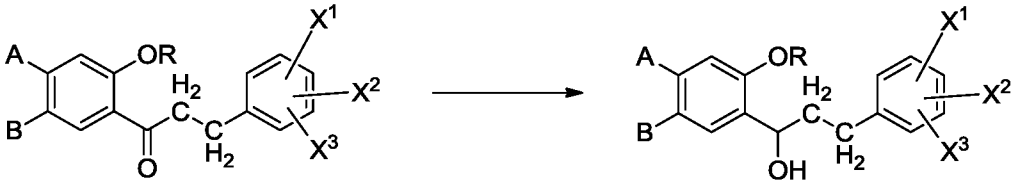
The presented solution is contrary to believe that cytotoxic activity of chalcones depends on their ability to react with thiols that depends on the presence of the double bond (Z. Rozmer et al., Toxicology in Vitro 2006, 20, 1354-1362).

The reduced derivatives of 1,3-diphenylpropane will display much less of side effects than their analogs with enone moiety. The effect, besides of cytotoxic activity is characteristic for compounds according to the said invention.

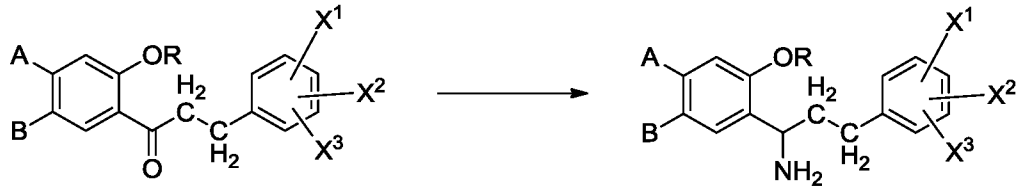
The compounds according to the invention are produced using methods generally known in the state of the art, according to the Schemes below.



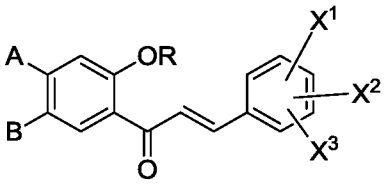
chalcone IIA



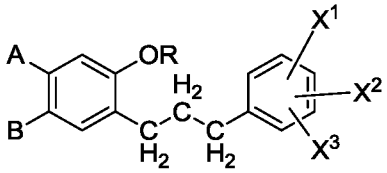
IIA IIB



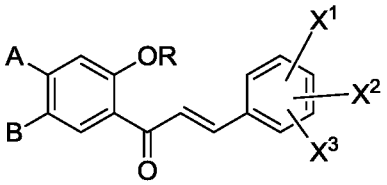
IIA IIC



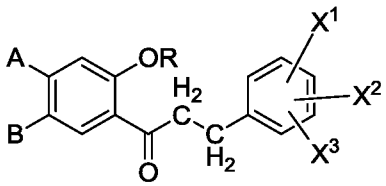
chalcone



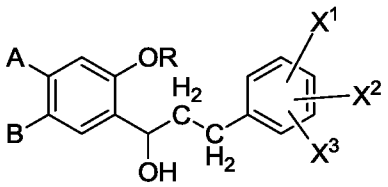
IID



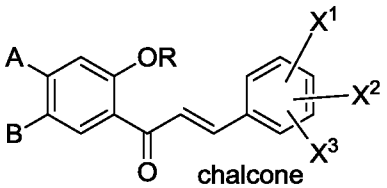
chalcone



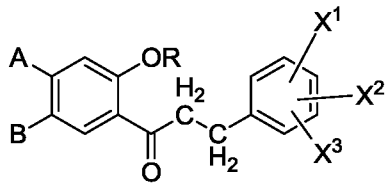
IIA



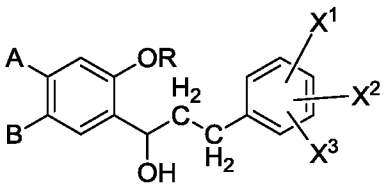
IIB



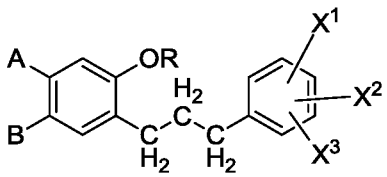
chalcone



IIA



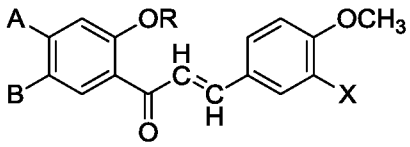
IIB



IID

Compounds prepared as demonstrated on the above Schemes can be transformed further, as demonstrated in Examples. Especially, the degree of oxidation of sulfur atom in compounds of general formula (I) can be modified using the known in the state of the art methods of oxidation of sulfur compounds. Compounds of general formula (I) can be transformed into their pro-drugs of eter, carbamate, ester or amide character, using methods known in the state of the art, as demonstrated in Examples.

Compound of formula (IIA) is prepared by reaction of chalcone,



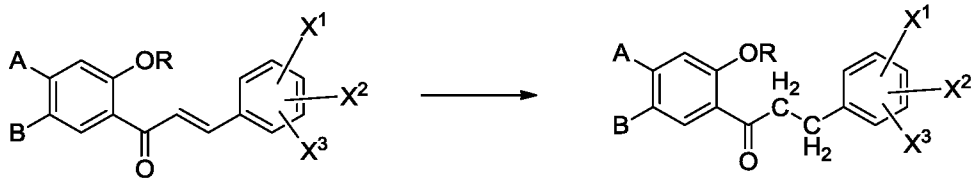
wherein A, B, R, X have the same meanings as defined for a related compound (IIA), with hydrogen, in a presence of a catalyst.

The reaction is performed by stirring a mixture, for example of solution of a suitable chalcone in solvent like ethyl acetate, in the presence of a catalyst such as palladium on charcoal, under atmosphere of hydrogen, at room temperature, until chromatographic analysis demonstrate that the substrate have reacted completely. The product is isolated using generaly known methods.

Derivatives of 1,3-diphenylpropane of formulas VA to VD and VIIIA to VIIID, wherein R and m have the same meanings as defined above for formula (I), and X is -O-PO(OH)$_2$, and their salts with alkali metals, may by obtained from related compounds of general formula (I), wherein X is OH, by reaction with phosphorous oxychloride P(O)Cl$_3$ or by an alternative methods described in the state of the art for similar derivatives of phenol.

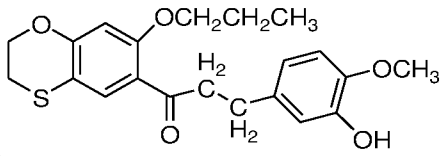
The invention is explained below in Examples.

Example 1. Preparation of compounds of formula (I) wherein Y = O



A mixture of a suitable starting compound, obtained according to a method known from WO11/009826A2, and palladium on charcoal as catalyst (in case of substrates with non-oxidized sulfur atom, largel than usuall amount of the catalyst has to be used), in ethyl

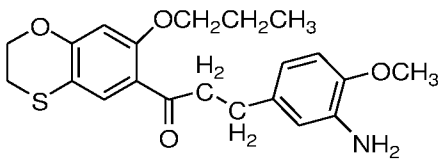
acetate is hydrogenated with gaseous hydrogen, at room temperature. When a control demonstrate that the substrate reacted completely, the catalyst is filtered off, and the filtrate is evaporated to dryness. The residue is crystallized from a suitable solvent or purified on silica gel chromatographic column, to give the product.



AMG-391

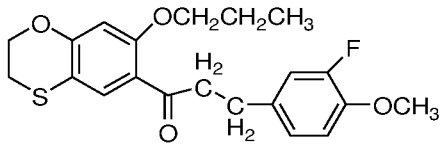
Using the described above procedure of synthesis of compounds of general formula (I), wherein Y = O, 3-(3-hydroxy-4-methoxyphenyl)-1-(7-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-6-yl)propen-1-one (193 mg, 0,5 mmol), and 10 % palladium on charcoal (250 mg) in ethyl acetate were stirred at room temperature, under hydrogen, for 50 hours. The catalyst was filtered off, and the filtrate was evaporated to give a colorless oil. The crude product was purified on silica gel chromatographic column in methylene chloride, and next crystallized from methanol to give 3-(3-hydroxy-4-methoxyphenyl)-1-(7-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-6-yl)propan-1-one as a colorless solid, yield 104 mg (53 %), mp. (^{o}C): 116 – 118. NMR (500 MHz, DMSO-d_6): δ 8,79 (s, 1 H, OH), 7,32 (s, 1 H, H-5), 6,79 (d, 1 H, J = 8,2 Hz, H-5'), 6,62 (d, 1 H, J = 2,0 Hz, H-2'), 6,60 (s, 1 H, H-8), 6,56 (dd, 1 H, J_1 = 8,2 Hz, J_2 = 2,0 Hz, H-6'), 4,43 (m, 2 H, H-2), 3,98 (t, 2 H, J = 6,3 Hz, OCH_2), 3,72 (s, 3 H, OCH_3), 3,17 (m, 4 H, H-3 + H-β) 2,74 (t, 2 H, J = 7,6 Hz, H-α), 1,73 (m, 2 H, CH_2), 0,96 (t, 3 H, J = 7,4 Hz, CH_3). IR (KBr, cm^{-1}): 3405, 1657, 1596, 1513, 1269, 1193, 1173, 1086.

Using the described above procedure of synthesis of compounds of general formula (I), wherein Y = O, and demonstrated for compound AMG-391, the following compounds were obtained:



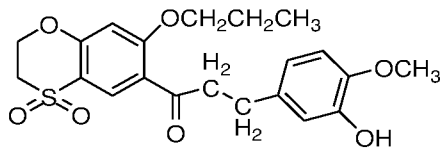
AMG-407

3-(3-amino-4-methoxyphenyl)-1-(7-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-6-yl)propan-1-one. NMR (500 MHz, DMSO-d_6): δ 7,29 (s, 1 H, H-5), 6,64 (d, 1 H, J = 8,1 Hz, H-5'), 6,57 (s, 1 H, H-8), 6,45 (d, 1 H, J = 1,9 Hz, H-2'), 6,31 (dd, 1 H, J_1 = 8,1 Hz, J_2 = 1,9 Hz, H-6'), 4,57 (s, 2 H, NH_2), 4,40 (m, 2 H, H-2), 3,96 (t, 2 H, J = 6,3 Hz, OCH_2), 3,69 (s, 3 H, OCH_3), 3,13 (m, 4 H, H-3 + CH_2CO), 2,67 (t, 2 H, J = 7,6 Hz, CH_2Ph), 1,71 (m, 2 H, CH_2), 0,94 (t, 3 H, J = 7,4 Hz, CH_3).



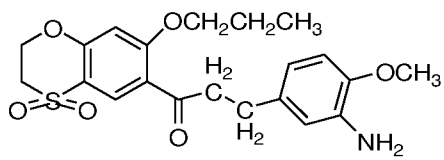
AMG-395

3-(3-fluoro-4-methoxyphenyl)-1-(7-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-6-yl)propan-1-one. NMR (500 MHz, DMSO-d_6): δ 7,33 (s, 1 H, H-5), 7,02 – 7,08 (m, 2 H, H-2', H-6'), 6,96 (d, 1 H, J = 8,3 Hz, H-5'), 6,59 (s, 1 H, H-8), 4,43 (m, 2 H, H-2), 3,97 (t, 2 H, J = 6,3 Hz, OCH_2), 3,80 (s, 3 H, OCH_3), 3,22 (t, 2 H, J = 7,5 Hz, $COCH_2$), 3,17 (m, 2 H, H-3), 2,82 (t, 2 H, J = 7,5 Hz, CH_2Ph), 1,72 (m, 2 H, CH2), 0,94 (t, 3 H, J = 7,4 Hz, CH_3).



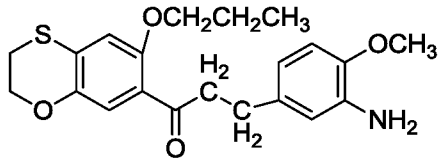
AMG-401

3-(3-hydroxy-4-methoxyphenyl)-1-(4,4-dioxo-7-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-6-yl)propan-1-one. NMR (500 MHz, DMSO-d_6): δ 8,79 (s, 1 H, OH), 7,93 (s, 1 H, H-5), 6,79 (m, 2 H, H-6', H-8), 6,63 (s, 1 H, H-2'), 6,56 (d, 1 H, J = 8,2 Hz, H-5'), 4,84 (m, 2 H, H-3), 4,10 (t, 2 H, J = 6,3 Hz, OCH_2), 3,85 (m, 2 H, H-2), 3,72 (s, 3 H, OCH_3), 3,21 (t, 2 H, J = 7,4 Hz, $COCH_2$), 2,76 (t, 2 H, J = 7,4 Hz, CH_2Ar), 1,76 (m, 2 H, CH_2), 0,96 (t, 3 H, J = 7,4 Hz, CH_3).



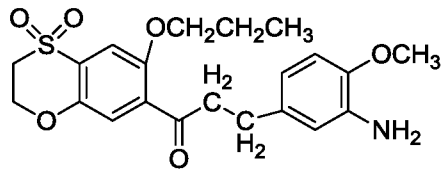
AMG-409

3-(3-amino-4-methoxyphenyl)-1-(4,4-dioxo-7-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-6-yl)propan-1-one. NMR (500 MHz, DMSO-d_6): δ 7,90 (s, 1 H, H-5), 6,76 (s, 1 H, H-8), 6,64 (d, 1 H, J = 8,1 Hz, H-5'), 6,46 (d, 1 H, J = 1,4 Hz, H-2'), 6,32 (dd, 1 H, J_1 = 8,1 Hz, J_2 = 1,4 Hz, H-6'), 4,82 (m, 2 H, H-3), 4,58 (s, 2 H, NH_2), 4,08 (t, 2 H, J = 6,3 Hz, OCH_2), 3,83 (m, 2 H, H-2), 3,69 (s, 3 H, OCH_3), 3,16 (t, 2 H, J = 7,6 Hz, CH_2CO), 2,70 (t, 2 H, J = 7,6 Hz, CH_2Ph), 1,75 (m, 2 H, CH_2), 0,95 (t, 3 H, J = 7,4 Hz, CH_3).



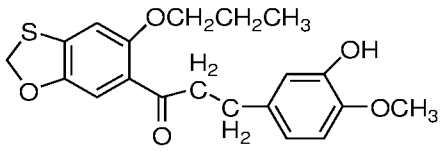
AMG-482

3-(3-amino-4-methoxyphenyl)-1-(6-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-7-yl)propan-1-one. NMR (500 MHz, DMSO-d_6): δ 6,98 (s, 1H, H-8), 6,84 (s, 1H, H-5), 6,64 (d, 1H, J = 8,1 Hz, H-5'), 6,45 (d, 1H, J = 2.1 Hz, H-2'), 6,32 (dd, 1H, J_1 = 8,1 Hz, J_2 = 2.1 Hz, H-6'), 4,58 (s, 2H, NH_2), 4,28 (m, 2H, H-2), 3,95 (t, 2H, J = 6,4 Hz, OCH_2), 3,69 (s, 3H, OCH_3), 3,20 (m, 2H, H-3), 3,14 (t, 2H, J = 7,7 Hz, $COCH_2$), 2,68 (t, 2H, J = 7,7 Hz, CH_2Ph), 1,70 (m, 2H, CH_2), 0,93 (t, 3H, J = 7,4 Hz, CH_3).



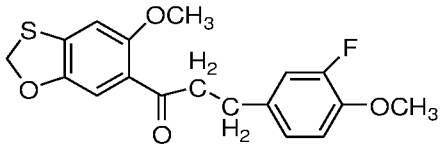
AMG-479

3-(3-amino-4-methoxyphenyl)-1-(4,4-dioxido-6-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-7-yl)propan-1-one. NMR (500 MHz, DMSO-d_6): δ 7,30 (s, 1H, H-5), 7,06 (s, 1H, H-8), 6,64 (d, 1H, J = 8,0 Hz, H-5'), 6,45 (d, 1H, J = 2.0 Hz, H-2'), 6,32 (dd, 1H, J_1 = 8,0 Hz, J_2 = 2.0 Hz, H-6'), 4,71 (m, 2H, H-2), 4,59 (s, 2H, NH_2), 4,03 (t, 2H, J = 6,3 Hz, OCH_2), 3,85 (m, 2H, H-3), 3,69 (s, 3H, OCH_3), 3,13 (t, 2H, J = 7,5 Hz, $COCH_2$), 2,69 (t, 2H, J = 7,7 Hz, CH_2Ph), 1,70 (m, 2H, CH_2), 0,93 (t, 3H, J = 7,3 Hz, CH_3).



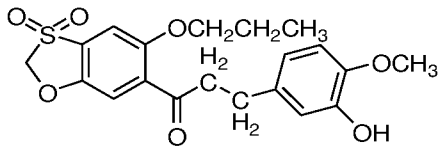
AMG-396

3-(3-hydroxy-4-methoxyphenyl)-1-(5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propan-1-one. NMR (500 MHz, DMSO-d_6): δ 8,78 (s, 1 H, OH), 7,23 (s, 1 H, H-7), 7,01 (s, 1 H, H-4), 6,79 (d, 1 H, J = 8,2 Hz, H-5), 6,62 (d, 1 H, J = 1,7 Hz, H-2'), 6,56 (dd, J_1 = 8,2 Hz, J_2 = 1,7 Hz), 5,77 (s, 2 H, H-2), 4,00 (7, 2 H, J = 6,4 Hz, OCH_2), 3,72 (s, 3 H, OCH_3), 3,18 (t, 2 H, J = 7,5 Hz, $COCH_2$), 2,74 (t, 2 H, J = 7,5 Hz, CH_2Ph), 1,73 (m, 2 H, CH_2), 0,95 (t, 3 H, J = 7,4 Hz, CH_3).



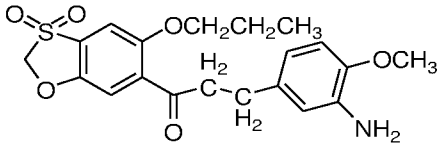
AMG-397

3-(3-fluoro-4-methoxyphenyl)-1-(5-methoxybenzo[*d*][1,3]oxathiol-6-yl)propan-1-one. (500 MHz, DMSO-d_6): δ 7,26 (s, 1 H, H-7), 7,04 – 7,11 (m, 2 H, H-2', H-6'), 7,04 (s, 1 H, H-4), 6,98 (d, 1 H, J = 8,3 Hz, H-5'), 5,78 (s, 2 H, H-2), 3,83 (s, 3 H, OCH_3), 3,80 (s, 3 H, OCH_3), 3,17 (t, 2 H, J = 7,4 Hz, $COCH_2$), 2,81 (t, 2 H, J = 7,4 Hz, CH_2Ph).



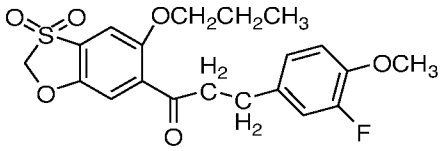
AMG-398

3-(3-hydroxy-4-methoxyphenyl)-1-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propan-1-one. NMR (500 MHz, DMSO-d_6): δ 8,81 (s, 1 H. OH), 7,63 (s, 1 H, H-4), 7,28 (s, 1 H, H-7), 6,79 (d, 1 H, J = 8,2 Hz, H-5'), 6,63 (d, 1 H, J = 1,9 Hz, H-2'), 6,56 (dd, 1 H, J_1 = 8,2 Hz, J_2 = 1,9 Hz, H-6'), 5,42 (s, 2 H, H-2), 4,08 (t, 2 H, J = 6,3 Hz, OCH_2), 3,72 (s, 3 H, OCH_3), 3,18 (t, 2 H, J = 7,5 Hz, $COCH_2$), 2,77 (t, 2 H, J = 7,5 Hz, CH_2Ph), 1,71 (m, 2 H, CH_2), 0,94 (t, 3 H, J = 7,4 Hz, CH_3).



AMG-405

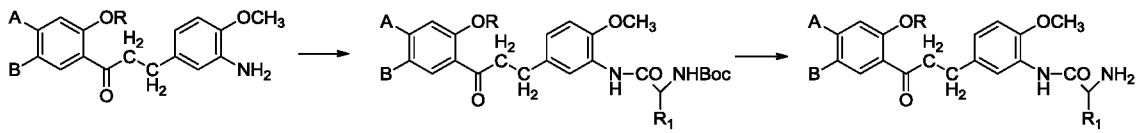
3-(3-amino-4-methoxyphenyl)-1-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propan-1-one. NMR (500 MHz, DMSO-d_6): δ 7,63 (s, 1 H, H-4), 7,28 (s, 1 H, H-7), 6,67 (d, 1 H, J = 8,1 Hz, H-5'), 6,47 (d, 1 H, J = 1,5 Hz, H-2'), 6,34 (dd, 1 H, J_1 = 8,1 Hz, J_2 = 1,5 Hz, H-6'), 5,42 (s, 2 H, H-2), 4,61 (s, 2 H, NH_2), 4,09 (t, 2 H, J = 6,3 Hz, OCH_2), 3,71 (s, 3 H, OCH_3), 3,15 (t, 2 H, J = 7,5 Hz, $COCH_2$), 2,72 (t, 2 H, J = 7,5 Hz, CH_2Ph), 1,72 (m, 2 H, CH_2), 0,95 (t, 3 H, J = 7,4 Hz, CH_3).



AMG-420

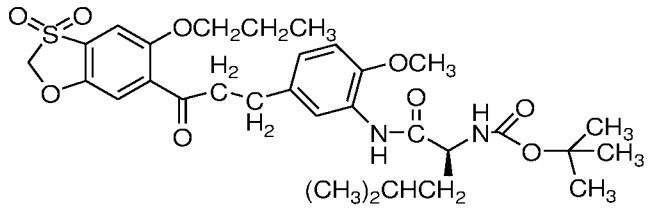
3-(3-fluoro-4-methoxyphenyl)-1-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propan-1-one. NMR (500 MHz, DMSO-d_6): δ 7,61 (s, 1 H, H-4), 7,29 (s, 1 H, H-7), 7,06 (dd, 1 H, J_1 = 13,2 Hz, J_2 = 1,9 Hz, H-2'), 7,02 (d, 1 H, J = 8,6 Hz, H-5'), 6,96 (d, 1 H, J = 8,6 Hz, H-6'), 5,40 (s, 2 H, H-2), 4,05 (t, 2 H, J = 6,3 Hz, OCH_2), 3,78 (s, 3 H, OCH_3), 3,22 (t, 2 H, J = 7,4 Hz, $COCH_2$), 2,83 (t, 2 H, J = 7,4 Hz, CH_2Ph), 1,67 (m, 2 H, CH_2), 0,90 (t, 3 H, J = 7,4 Hz, CH_3).

Example 2. Preparation of derivatives of compounds of general formula (I), wherein Y = O (carbonyl) and one of the substituents X = $NHCOCHR_1NH_2$ (synthesis of pro-drugs with amino acids)



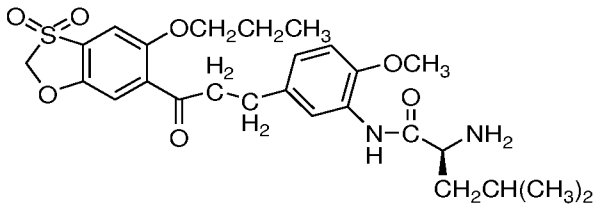
A suitable starting compound, prepared according to the procedure described above, is condensed with a suitable derivative of amino acid with protected amino group, using generally known procedures, for example condensation in a presence of dicyclohexylcarbodiimide in methylene chloride solution. The obtained product is purified

using column chromatography on silica gel column or is crystallized from a suitable solvent. The obtained conjugate is deprotected using generally known methods, for example, deprotection of t-butylcarbamoyl group is carried out with a solution of trifluoroacetic acid in methylene chloride. The obtained product is purified using chromatography on silica gel column or by crystallization from a suitable solvent. Optionally, the obtained product is treated with a protic acid to give a suitable salt.



AMG-419

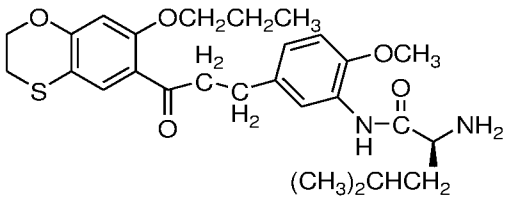
Using the described above procedure for preparation of compounds of formula (I), wherein Y = O (carbonyl) and one of the substituents X = $NHCOCHR_1NH_2$, a solution of 3-(3-amino-4-methoxyphenyl)-1-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propan-1-one (202 mg, 0,5 mmol), Boc-L-leucine (139 mg, 0,6 mmole) and N,N'-dicyclohexylcarbodiimide (165 mg, 0,8 mmole) in anhydrous methylene chloride (5 ml) was stirred at room temperature for 18 hours. The precipitated solid was filtered off, the filtrate was evaporated, and the residue was purified on silica gel chromatographic column in methylene chloride – ethyl acetate 20 : 1 solution. The obtained product was crystallized from ethanol, to give (S)-tert-butyl 1-(2-methoxy-5-(3-oxo-3-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propyl)phenylamino)-4-methyl-1-oxopentan-2-yl carbamate as a colorless solid, yield 200 mg (65 %). NMR (500 MHz, DMSO-d_6): δ 8,89 (s, 1 H, NH), 7,95 (s, 1 H, H-2'), 7,60 (s, 1 H, H-4), 7,37 (d, 1 H, J = 7,6 Hz, NH), 7,28 (s, 1 H, H-7), 6,93 (d, 1 H, J = 8,4 Hz, H-5'), 6,88 (d, 1 H, J = 8,4 Hz, H-6'), 5,40 (s, 2 H, H-2), 4,05 (m, 3 H, OCH_2 + CH), 3,79 (s, 3 H, OCH_3), 3,18 (t, 2 H, J = 7,4 Hz, CH_2CO), 2,81 (t, 2 H, J = 7,4 Hz, CH_2Ph), 1,68 (m, 3 H, CH_2 + CH), 1,52 (m, 2 H, CH_2), 1,40 (s, 9 H, 3 x CH_3), 0,89 (m, 9 H, 3 x CH_3). IR (KBr, cm^{-1}): 3422, 2961, 2930, 1686, 1538, 1463, 1418, 1325, 1255, 1171, 1146, 1014.



AMG-415

Trifluoroacetic acid (2 ml) was added to a solution of (S)-tert-butyl 1-(2-methoxy-5-(3-oxo-3-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propyl)phenylamino)-4-methyl-1-oxopentan-2-yl carbamate (500 mg, 0,81 mmol) in anhydrous methylene chloride (10 ml), and the mixture was stirred at room temperature for 2 hours. The obtained solution was poured into a stirred solution of sodium bicarbonate in ice cooled water, and the resulted mixture was extracted with ethyl acetate (100 ml). The organic layer was washed with sodium bicarbonate solution (1 x 10 ml), brine (1 x 50 ml), and dried (Na_2SO_4). The solution was evaporated to dryness, and the residue was crystallized from ethanol to give (S)-2-amino-N-(2-methoxy-5-(3-oxo-3-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propyl)phenyl)-4-methylpentanamide as a creem solid, yield (71%). NMR (500 MHz, DMSO-d_6): δ 10,13 (bs, 1 H, NH), 8,14 (s, 1 H, H-2'), 7,60 (s, 1 H, H-4), 7,27 (s, 1 H, H-7), 6,92 (d, 1 H, J = 8,4 Hz, H-5'), 6,85 (d, 1 H, J = 8,4 Hz, H-6'), 5,40 (s, 2 H, H-2), 4,05 (t, 2 H, J = 6,3 Hz, OCH_2), 3,80 (s, 3 H, OCH_3), 3,33 (bs, under H_2O, CH), 3,18 (t, 2 H, J = 7,4 Hz, CH_2CO), 2,81 (t, 2 H, J = 7,4 Hz, CH_2Ph), 1,78 (m, 1 H, CH), 1,69 (m, 2 H, CH_2), 1,56 (m, 1 H, CH), 1,33 (m, 1 H, CH), 0,89 (m, 9 H, 3 x CH_3). IR (KBr, cm^{-1}): 3405, 3330, 2954, 1679, 1535, 1463, 1417, 1324, 1147, 1017.

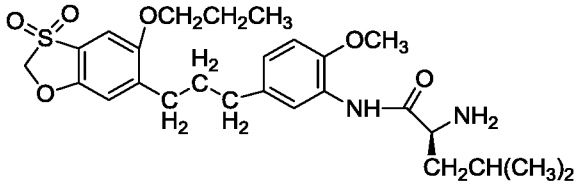
Using the described above procedure for preparation of compounds of general formula (I), wherein Y = O and one of the substituents X = $NHCOCHR_1NH_2$, and demonstrated for compounds AMG-419, and AMG-415, the following compounds were obtained:



AMG-421

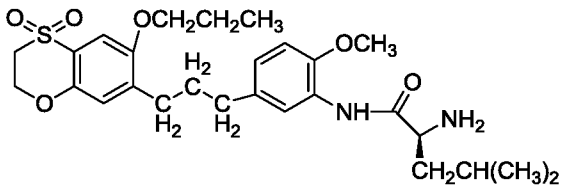
(S)-2-amino-N-(2-methoxy-5-(3-oxo-3-(7-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-6-yl)propyl)phenyl)-4-methylpentanamide. NMR (500 MHz, D_2O) (spectrum for hydrochloride): δ 7,33 (s, 1 H, H-2'), 7,03 (s, 1 H, H-8), 6,71 (bs, 2 H, H-5', H-6'), 6,11 (s,

1 H, H-5), 4,17 (s, 2 H, H-2), 4,09 (m, 1 H, LeuCH), 3,63 (s, 3 H, OCH_3), 3,53 (s, 2 H, OCH_3), 2,91 (s, 2 H, CH_2CO), 2,83 (s, 2 H, H-3), 2,59 (s, 2 H, CH_2Ph), 1,64 (m, 2 H, propylCH_2), 1,54 (m, 1 H, LeuCH), 1,45 (m, 2 H, LeuCH_2), 0,81 (d, 3 H, J = 6,3 Hz, CH_3), 0,79 (d, 3 H, J = 6,3 Hz, CH_3), 0,69 (t, 3 H, J = 7,0 Hz, CH_3).



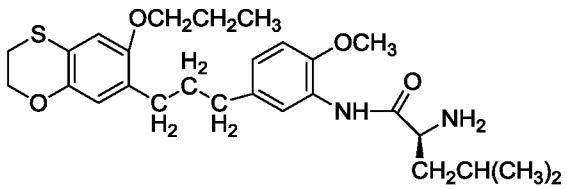
AMG-488

Using compound AMG-487 as a substrate, (S)-2-amino-N-(5-(3-(3,3-dioxido-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propyl)-2-methoxyphenyl)-4-methylpentanamide was obtained. NMR (500 MHz, DMSO-d_6): δ 10,16 (bs, 1H, NH), 8,15 (d, 1H, J = 2,0 Hz, H-2'), 7,28 (s, 1H, H-4), 7,13 (s, 1H, H-7), 6,92 (d, 1H, J = 8,3 Hz, H-5'), 6,81 (dd, 1H, J_1 = 8,2 Hz, J_2 = 2,2 Hz, H-6'), 5,30 (s, 2H, H-2), 3,93 (t, 2H, J = 6,2 Hz, OCH_2), 3,80 (s, 3H, OCH_3), 3,27 (m, 1H, CH), 2,60 (m, 2H, CH_2), 2,51 (t, 2H, J = 7,5 Hz, CH_2), 2,19 (bs, 2H, NH_2), 1,76 (m, 2H, CH_2), 1,67 (m, 2H, CH_2), 1,54 (m, 1H, CH), 1,30 (m, 1H, CH), 0,84 – 0,94 (m, 9H, 3 x CH_3).



AMG-484

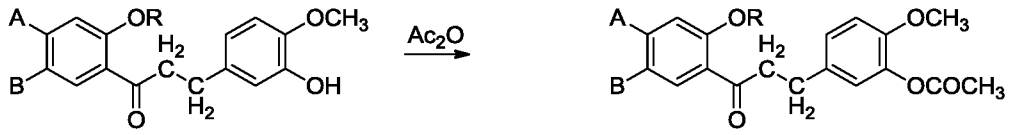
Using compound AMG-483 as a substrate, (S)-2-amino-N-(5-(3-(4,4-dioxido-6-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-7-yl)propyl)-2-methoxyphenyl)-4-methylpentanamide was obtained. NMR (500 MHz, DMSO-d_6) (spectrum for hydrochloride): δ 9,80 (s, 1H, NH), 8,32 (s, 3H, NH_3^+), 7,67 (s, 1H, H-2'), 7,04(s, 1H, H-5), 6,98 (d, 1H, J = 8,3 Hz, H-5'), 6,94 (t, 1H, J = 8,4 Hz, H-6'), 6,88 (s, 1H, H-8), 4,67 (m, 2H, H-2), 4,15 (m, 1H, CH), 3,90 (t, 2H, J = 6,2 Hz, OCH_2), 3,80, s, 3H, OCH_3), 3,75 (m, 2H, H-3), 2,51, m, 4H, 2 x CH_2), 1,76 (m, 2H, CH_2), 1,65 (m, 5 H, 2 x CH_2, CH), 0,91 (m, 9H, 3 x CH_3).

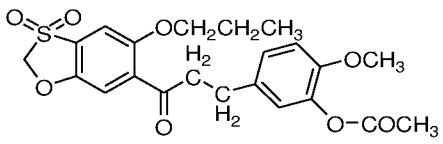


AMG-486

Using compound AMG-485 as a substrate, (S)-2-amino-N-(2-methoxy-5-(3-(6-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-7-yl)propyl)phenyl)-4-methylpentanamide was obtained. NMR (500 MHz, DMSO-d_6) (spectrum for hydrochloride): δ 9,81 (s, 1H, NH), 8,35 (s, 3H, NH_3^+), 7,66 (s, 1H, H-2'), 6,95 (m, 2H, H-5', H-6"), 6,58 (s, 1H, H-8), 6,55 (s, 1H, H-5), 4,24 (m, 1H, H-2), 4,15 (m, 1H, CH), 3,79 (s, 3H, OCH_3), 3.78 (t, 2H, J = 6,4 Hz, OCH_2), 3,12 (m, 2H, H-3), 2.5 (m, under DMSO, CH_2), 2.44 (t, 2H, J = 7,6 Hz, CH_2), 1,72 (m, 3H, CH_2, CH), 1,63 (m, 3H, CH_2, CH), 0,91 (m, 9H, 3x CH_3).

Example 3. Preparation of compounds of general furmula (I), wherein Y = O, (carbonyl) and one of the substituents X = $OCOCH_3$ (synthesis of acyl pro-drugs).





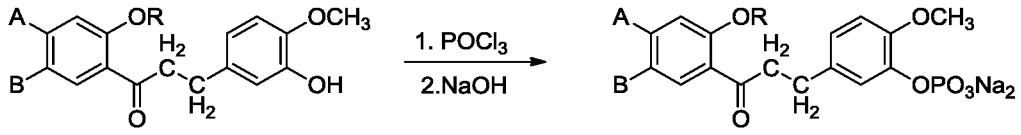
AMG-403

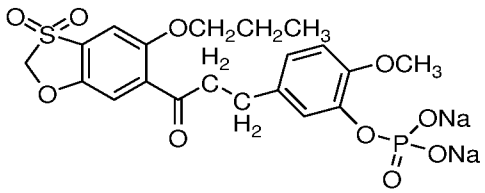
2-methoxy-5-(3-oxo-3-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propyl)phenyl acetate

3-(3-Hydroxy-4-methoxyphenyl)-1-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propan-1-one (404 mg, 1 mmol) was suspended in acetyl anhydride (4 ml), catalytic amount of concentrated sulfuric acid was added, and the mixture was stirred at room temperature for 30 minutes. Water and ice were added to the mixture, and after 1 hour the precipitated solid was filtered off, and crystallized from methanol to give 2-methoxy-5-(3-oxo-3-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propyl)phenyl acetate (360 mg, 80 %), m.p. 98-99 °C. NMR (500 MHz, DMSO-d_6): δ 7,63 (s, 1 H, H-4), 7,30 (s, 1 H, H-7), 7,08 (dd, 1 H, J_1 = 8,4 Hz, J_2 = 1,9 Hz, H-6'), 7,02 (d, 1 H, J = 8,4 Hz, H-5'), 6,94 (d, 1 H, J = 1,9 Hz, H-2'), 5,42 (s, 2 H, H-2), 4,08 (t, 2 H, J = 6,4 Hz, OCH_2), 3,73 (s, 3 H, OCH_3),

3,24 (t, 2 H, J = 7,4 Hz, $COCH_2$), 2,85 (t, 2 H, J = 7,4 Hz, CH_2Ph), 2,24 (s, 3 H, $COCH_3$), 1,70 (m, 2 H, CH_2), 0,93 (t, 3 H, J = 7,5 Hz, CH_3).

Example 4. Preparation of derivatives of compounds of general formula (I), wherein Y = (carbonyl) and one of the substituents X = OPO_3Na_2 (synthesis of phosphate pro-drugs).





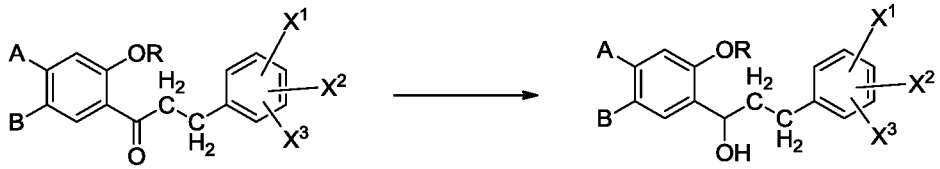
AMG-414

Sodium 2-methoxy-5-(3-oxo-3-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propyl)phenyl phosphate

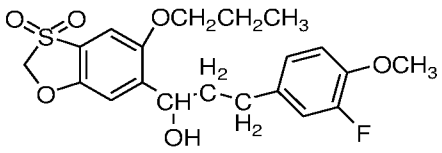
3-(3-Hydroxy-4-methoxyphenyl)-1-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propan-1-one (916 mg, 2.25 mmol) was added to a stirred solution of phosphorous oxychloride (2,3 ml, 25 mmol) and trimethylamine (7 ml, 50 mmol) in anhydrous methylene chloride (90 ml) at room temperature, and the mixture was stirred at room temperature for 40 minutes. The mixture was cooled in ice, 1N solution of sodium hydroxide in water (230 ml) was added, and the whole was stirred at room temperature for 20 hours. The obtained layers were separated, the aqueous one was washed with methylene chloride, acidified with 1N hydrochloric acid, and extracted twice with ethyl acetate (200 ml). The organic layer was washed with brine, dried with anhydrous sodium sulfate, and evaporated. Methanol (7 ml), followed by 1N solution of sodium hydroxide in methanol were added to the residue, and the obtained suspension was diluted with ethanol (20 ml). The solid was filtered off and washed with ethanol to give a yellow solid of sodium 2-methoxy-5-(3-oxo-3-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propyl)phenyl phosphate (700 mg 95 %), m.p. 165 – 168 °C. NMR (500 MHz, D_2O): δ 7,30 (s, 1 H, H-4), 7,16 (s, 1 H, H-2'), 7,07 (s, 1 H, H-7), 6,75 (d, 1 H, J = 8,3 Hz, H-5'), 6,63 (d, 1 H, J = 8,3 Hz, H-6'), 5,15 (s, 2 H, H-2), 3,89 (t, 2 H, J =

6,3 Hz, OCH_2), 3,67 (s, 3 H, OCH_3), 3,21 (t, 2 H, J = 7,2 Hz, CH_2CO), 2,77 (t, 2 H, J = 7,2 Hz, CH_2Ph), 1,61 (m, 2 H, CH_2), 0,81 (t, 3 H, J = 7,4 Hz, CH_3). IR (KBr, cm^{-1}): 3428, 1685, 1515, 1462, 1416, 1305, 1157, 988.

Example 5. Preparation of compounds of general formula (I), wherein Y = OH



Suitable starting compound, prepared as described above in Examples 1 – 4, is reduced using generally known methods, for example reduction with zinc in acetic acid solution, or reduction with sodium borohydride or its derivative in a solution in protic solvent. The obtained product is purified using silica gel column chromatography, or by crystallization from a suitable solvent.



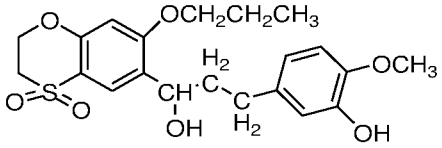
AMG-430

3-(3-fluoro-4-methoxyphenyl)-1-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propan-1-ol

Using the described above procedure for preparation of compounds of general formula (I), wherein Y = OH, a mixture of 3-(3-fluoro-4-methoxyphenyl)-1-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propan-1-one (110 mg, 0,27 mmol) and zinc dust (150 mg, 2,3 mmol) in acetic acid (3 ml) and water (1 ml) was stirred at room temperature for 19 hours, and next extracted with methylene chloride (50 ml). The organic solution was washed with water (3 x 20 ml), dried (Na_2SO_4), and evaporated to dryness. The residue was crystallized from methanol to give 3-(3-fluoro-4-methoxyphenyl)-1-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propan-1-ol as a colorless solid, (60 mg, 54 %). M.p. (^oC): 139 – 140. NMR (500 MHz, DMSO-d_6): δ 7,29 (s, 1 H, H-4 or H-7), 7,27 (s, 1 H, H-4 or H-7), 6,92 – 7,05 (m, 2 H, H-2', H-6'), 6,93 (d, 1 H, J = 8,3 Hz, H-5'), 5,42 (d, 1 H, J = 4,8 Hz, OH), 5,33 (d, 1 H, J = 10,6 Hz, H-2), 5,31 (d, 1 H, J = 10,6 Hz, H-2), 4,77 (m, 1 H,

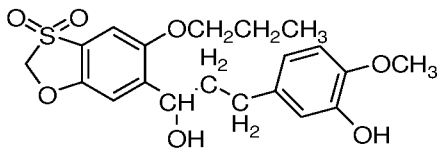
CHOH), 3,95 (m, 1 H, OCH_2), 3,88 (m, 1 H, OCH_2), 3,78 (s, 3 H, OCH_3), 2,64 (t, 2 H, J = 7,2 Hz, CH_2Ph), 1,84 (m, 1 H, CH(OH)CH_2), 1,61 (m, 3 H, CH(OH)CH_2 + CH_2propyl), 0,85 (,t, 3 H, J = 7,4 Hz, CH_3). IR (KBr, cm^{-1}): 3569, 1521, 1463, 1313, 1277, 1143, 1068, 1027, 964.

Using the described above procedure for preparation of compounds of general formula (I), wherein Y = OH, and demonstrated for compound AMG-430, the following compounds were obtained:



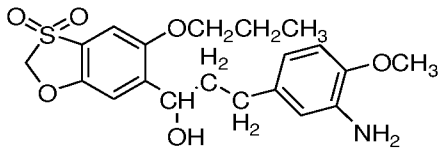
AMG-402

5-(3-hydroxy-3-(4,4-dioxo-7-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-6-yl)propyl)-2-methoxyphenol. NMR (500 MHz, DMSO-d_6): δ 8,75 (s, 1 H, OH), 7,71 (s, 1 H, H-5), 6,78 (d, 1 H, J = 8,2 Hz, H-5'), 6,59 (d, 1 H, J = 2,0 Hz, H-2'), 6,53 (m, 2 H, H-6' + H-8), 5,28 (d, 1 H, J = 5,2 Hz, OH), 4,73 (m, 3 H, H-a + H-3), 3,85 – 3,98 (m, 2 H, OCH_2), 3,75 (m, 2 H, H-2), 3,72 (s, 3 H, OCH_3), 2,56 (m, 2 H, H-c), 1,83 (m, 1 H, H-b), 1,67 (m, 2 H, CH_2), 1,60 (m, 1 H, H-b), 0,91 (t, 3 H, J = 7,3 Hz, CH_3).



AMG-399

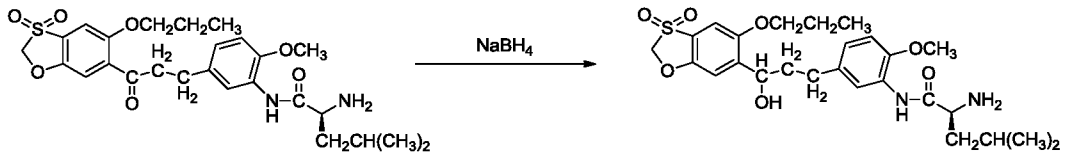
5-(3-hydroxy-3-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propyl)-2-methoxyphenol. NMR (500 MHz, DMSO-d_6): δ 8,75 (s, 1 H, OH), 7,32 (s, 1 H, H-4), 7,28 (s, 1 H, H-7), 6,78 (d, 1 H, J = 8,0 Hz, H-5'), 6,60 (s, 1 H, H-2'), 6,55 (d, 1 H, J = 8,0 Hz, H-6'), 5,40 (s, 1 H, OH), 5,35 (s, 2 H, H-2), 4,83 (m, 1 H, H-a), 3,96 (m, 2 H, OCH_2), 3,72 (s, 3 H, OCH_3), 2,56 (m, 2 H, H-c), 1,85 (m, 1 H, H-b), 1,65 (m, 3 H, H-b + CH_2), 0,91 (t, 3 H, J = 7,2 Hz, CH_3).

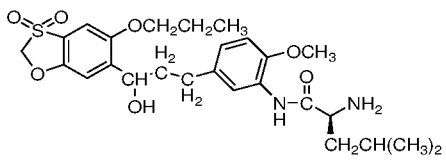


AMG-431

3-(3-hydroxy-3-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propyl)-2-methoxyaniline. NMR (500 MHz, DMSO-d_6): δ 7,30 (s, 1 H, H-4), 7,26 (s, 1 H, H-7), 6,63 (d, 1 H, J = 8,2 Hz, H-5'), 6,43 (d, 1 H, J = 2,0 Hz, H-2'), 6,31 (dd, 1 H, J_1 = 8,2 Hz, J_2 = 2,0 Hz, H-6'), 5,36 (d, 1 H, J = 5,0 Hz, OH), 5,34 (d, 1 H, J = 10,6 Hz, H-2), 5,31 (d, 1 H, J = 10,6 Hz, H-2), 4,83 (m, 1 H, H-a), 4,55 (s, 2 H, NH_2), 3,88 – 4,00 (m, 2 H, OCH_2), 3.68 (s, 3 H, OCH_3), 2,40 – 2,55 (m, under DMSO, H-c), 1,82 (m, 1 H, H-b), 1,66 (m, 2 H, CH_2), 1,59 (m, 1 H, H-b), 0,91 (t, 3 H, J = 7,3 Hz, CH_3).

Example 6. An example of preparation of pro-drug of compound of general formula (I), wherein Y = OH, and one of the substituents X = $NHCOCHR_1NH_2$ (synthesis of pro-drug with aminoacid)





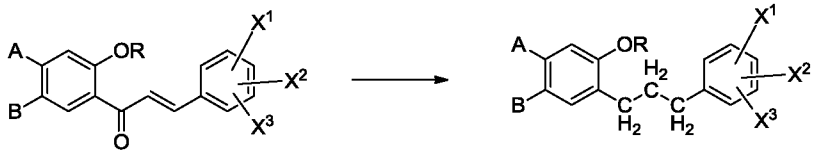
AMG-432

(2S)-2-amino-N-(5-(3-hydroxy-3-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propyl)-2-methoxyphenyl)-4-methylpentanamide

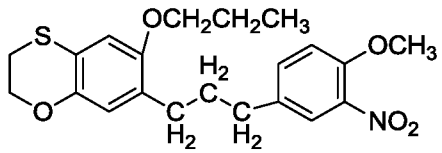
(S)-2-amino-N-(2-methoxy-5-(3-oxo-3-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propyl)phenyl)-4-methylpentanamide (300 mg, 0,58 mmol), prepared as described in the Example 2, was dissolved in hot ethanol (20 ml), cooled in ice, and sodium borohydride (44 mg, 1,16 mmol) was added to the stirred solution. The mixture was stirred for 80 minutes, while the temperature raised to room temperature. Next, water was added (20 ml), the precipitated solid was filtered off, washed with water, and crystallized from ethanol to give

(2S)-2-amino-N-(5-(3-hydroxy-3-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propyl)-2-methoxyphenyl)-4-methylpentanamide as a colorless solid (253 mg, 84 %). The solid was suspended in anhydrous methanol (2 ml), and solution of methanesulfonic acid (0,1 ml, 1,5 mmol) in anhydrous methanol (1 ml) was added. The obtained solution was gradually diluted with ethyl ether (40 ml). The precipitated solid was filtered off, and washed with ethyl ether to give (2S)-2-amino-N-(5-(3-hydroxy-3-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propyl)-2-methoxyphenyl)-4-methylpentanamide methanesulfonate as a colorless solid, yield 255 mg, 69 %. NMR (500 MHz, D_2O): δ 10,16 (bs, 1 H, NH), 8,15 (2 x d, 1 H, J = 2,1 Hz, H-2'), 7,29 (s, 1 H, H-4 or H-7), 7,27 (s, 1 H, H-4 or H-7), 6,90 (d, 1 H, J = 8,2 Hz, H-5'), 6,81 (m, 1 H, H-6'), 5,42 (m, 1 H, OH), 5,34 (d, 1 H, J = 10,5 Hz, H-2), 5,31 (d, 1 H, J = 10,5 Hz, H-2), 4,81 (m, 1 H, CH), 3,95 (m, 1 H, OCH), 3,90 (m, 1 H, OCH), 3,80 (s, 3 H, OCH_3), 3,28 (bd, 1 H, CH), 2,60 (m, 2 H, CH_2), 2,20 (bs, 2 H, NH_2), 1,85 (m, 1 H, CH), 1,78 (m, 1 H, CH), 1,5 – 1,69 (m, 4 H, CH_2 + CH + CH), 1,30 (m, 1 H, CH), 0,88 (m, 9 H, 3 x CH_3). IR (KBr, cm^{-1}): 3410, 2961, 1674, 1548, 1464, 1314, 1161, 1043.

Example 7. Preparation of compounds of formula (I), wherein Y = H



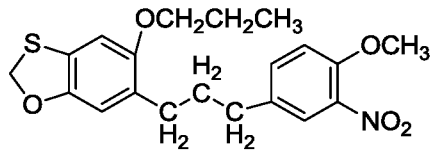
An excess of triethylsilane is added dropwise to a stirred mixture of suitable chalcone and trifluoroacetic acid, and the whole is stirred at room temperature until the end of the reduction. The product is isolated using generally known methods, for example the reaction mixture is poured into a stirred solution of sodium carbonate in water, and product is filtered off or extracted with an organic solvent, for example with ethyl acetate. The crude product is purified by crystallization or using chromatographic methods.



3-(4-methoxy-3-nitrophenyl)-1-(6-propoxybenzo[*b*][1,4]-oxathian-7-yl)propane

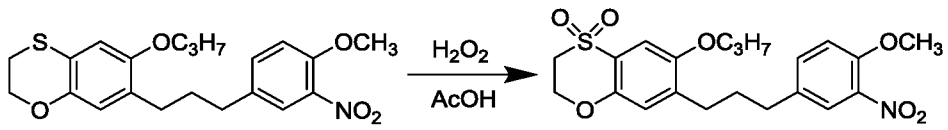
Using the described above procedure for preparation of compounds of general formula (I), wherein Y = H, (*E*)-3-(4-methoxy-3-nitrophenyl)-1-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)prop-2-en-1-one (0,433 g, 1 mmol) was dissolved in trifluoroacetic acid (4 ml). The solution was cooled in ice-water bath, and triethylsilane (1 ml, 6,28 mmol) was added dropwise, with stirring. Next, the solution was stirred at room temperature for 40 minutes, and poured into a stirred solution of sodium carbonate 10 g (0,09 mola) in water (100 ml). The precipitated solid was filtered off, washed with water, and crystallized from ethyl acetate, to give 3-(4-methoxy-3-nitrophenyl)-1-(6-propoxybenzo[*b*][1,4]-oxathian-7-yl)propane, m.p. 183-185°C. ^{1}H NMR (DMSO-d_6) δ 7.68 (d, 1H, J = 2,0 Hz, H-2'), 7.47 (dd, 1H, J_1 = 8,6 Hz, J_2 = 2,1 Hz, H-6'), 7.26 (m, 3H, H-4, H-7, H-5'), 5.49 (d, 1H, J = 5,0 Hz, OH), 5.34 (d, 1H, J = 9,5 Hz, H-2), 5.31 (d, 1H, J = 9,5 Hz, H-2), 4.76 (bs, CHOH), 3.87 (m, 5H, OCH_2, OCH_3), 2.72 (t, 2H, J = 7,2 Hz, CH_2), 1.84-1.9 (m, 1H, CH), 1.65-1.75 (m, 1H, CH), 1.5-1.6 (m, 2H, CH_2), 0.81 (t, 3 H, J=7,4 Hz, CH_3). IR (cm^{-1}): 3425, 2925, 1623, 1531, 1464, 1304, 1278, 1163.

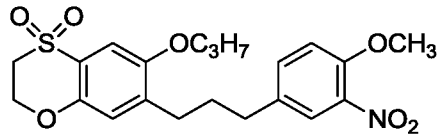
Using the described above procedure for preparation of compounds of general formula (I), wherein Y = H, the following compounds were obtained:



3-(4-methoxy-3-nitrophenyl)-1-(5-propoxybenzo[*b*][1,4]-oxathiol-6-yl)propane. M.p. 53-56°C. ^{1}H NMR (DMSO-d_6) δ 7.67 (d, 1H, J=2,1 Hz, H-2'), 7.46 (dd, 1H, J_1=8,7 Hz, J_2=2,3 Hz, H-6'), 7.25 (d, 1H, J=8,7 Hz, H-5'), 6.92 (s, 1H, H-7), 6.69 (s, 1H, H-4), 3.87 (s, 3H, OCH_3), 3.80 (t, 2H, J=6,3 Hz, OCH_2), 2.59 (t, 2H, J=7,4 Hz, CH_2), 2.43-2.50 (m, 5H, 2x CH_2, CH), 1.71 (m, 2H, CH_2), 1.61 (m, 2H, CH_2), 0.89 (t, 3H, J=7,3 Hz, CH_3). IR (cm^{-1}): 2933, 1622, 1530, 1408, 1353, 1279, 1181, 1020, 824.

Example 8. Preparation of compounds of general formula (I), wherein Y = H, n = 2 and m = 2, from compounds wherein m = 0

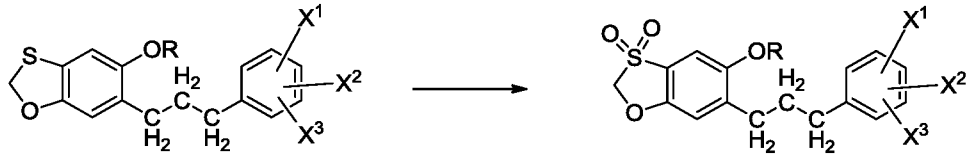


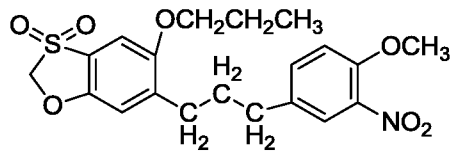


3-(4-methoxy-3-nitrophenyl)-1-(4,4-dioxo-6-propoxybenzo[*b*][1,4]-oxathian-7-yl)propane

3-(4-Methoxy-3-nitrophenyl)-1-(6-propoxy-2,3-dihydrobenzo[*b*][1,4]-oxathiin-7-yl)propane (1,0 g, 2,48 mmol), prepared as described in Example 7, was dissolved in acetic acid (15 ml), 30 % hydrogen peroxide (12 ml) was added, and the mixture was stirred at 75 °C for 5 hours. Next, the mixture was cooled down, diluted with water (20 ml), and extracted with ethyl acetate (2 x 40 ml). The organic layer was washed with sodium carbonate solution, brine, dried over sodium sulfate, and evaporated. The residue was purified on silica gel column in methylene chloride – ethyl acetate 10 : 1 solution, and next crystallized from methanol to give 3-(4-methoxy-3-nitrophenyl)-1-(4,4-dioxo-6-propoxybenzo[*b*][1,4]-oxathian-7-yl)propane (0,85 g, 79 %), m.p. 104-107 °C. ^{1}H NMR (DMSO-d_6) δ 7.68 (d, 1H, J=2,2 Hz, H-2'), 7.46 (dd, 1H, J_1=8,7 Hz, J_2=2,3 Hz, H-6'), 7.24 (d, 1H, J=8,5 Hz, H-5'), 7.02 (s, 1H, H-8 lub H-5), 6.89 (s, 1H, H-8 lub H-5), 4.66 (t, 2H, J=5,3 Hz, OCH_2), 3.88 (t, 5H, J=6,3 Hz, OCH_3, OCH_2), 3.74 (t, 2H, J=5,3 Hz, SCH_2), 2.61 (t, 2H, J=7,3 Hz, CH_2), 2.56 (t, 2H, J=7,5 Hz, CH_2), 1.81 (m, 2H, CH_2), 1.65 (m, 2H, CH_2), 0.90 (t, 3H, J=7,3 Hz, CH_3). IR (cm^{-1}): 2933, 1621, 1525, 1296, 480.

Example 9. Preparation of compounds of general formula (I), wherein Y = H, n = 1 and m = 2, from compounds wherein m = 0

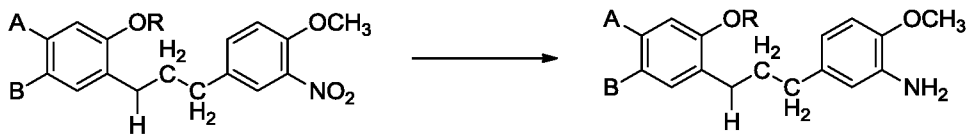




1-(4-methoxy-3-nitrophenyl)-3-(3,3-dioxo-5-propoxybenzo[*b*][1,4]-oxathiol-6-yl)propane

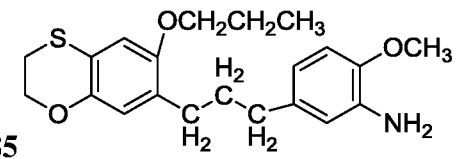
1-(4-Methoxy-3-nitrophenyl)-3-(6-propoxybenzo[*b*][1,4]-oxathiol-6-yl)propane (1,445 g, 3,7 mmol), prepared as described in Example 7, was dissolved in acetic acid (20 ml), the solution was warmed up 75 °C, and 30 % hydrogen peroxide (10 ml) was added portionwise, with stirring. The mixture was stirred at 75 °C until the reaction ended, the precipitated solid was filtered off, and washed with hot methanol to give 3-(4-methoxy-3-nitrophenyl)-1-(3,3-dioxo-6-propoxybenzo[*b*][1,4]-oxathiol-6-yl)propane. NMR (500 MHz, DMSO-d_6): δ 7,69 (d, 1H, J = 2,3 Hz, H-2'), 7,48 (dd, 1H, J_1 = 8,7 Hz, J_2 = 2,3 Hz, H-6'), 7,29 (s, 1H, H-4), 7,25 (d, 1H, J = 8,5 Hz, H-5), 5,31 (s, 2H, H-2), 3,94 (t, 2H, J = 6,2 Hz, OCH_2), 3,87 (s, 3H, OCH_3), 2,61, 4 H, 2 x CH_2), 1,83 (m, 2H, CH_2), 1,66 (m, 2H, CH_2), 0,91 (t, 3H, J = 7,3 Hz).

Example 10. Preparation of compounds of general formula (I), wherein Y = H, and one of the substituents X = NH_2



General procedure:

A suitable starting compound, prepared as described above in Examples 7 – 10, is reduced with a reducing agent, which is suitable for reduction of nitro group, using procedures generaly known in the state of the art, and the obtained product is isolated using generaly known methods. For example, the substrate is dissolved in an organic solvent, such as ethyl acetate and reacted with hydrogen in the presence of palladium catalyst, and the obtained product is isolated on silica gel chromatography column.

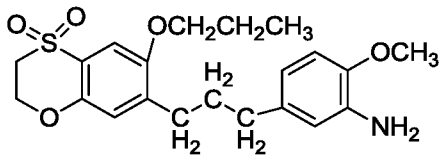


AMG-485

Using the described above procedure for preparation of compounds of general formula (I), wherein Y = H, and one of the substituents X = NH_2, 3-(4-methoxy-3-nitrophenyl)-1-(6-

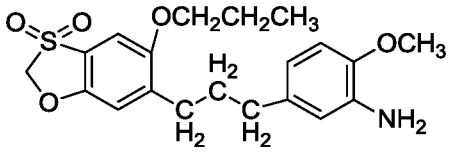
propoxybenzo[*b*][1,4]-oxathian-7-yl)propane (315 mg, 0,72 mmol), prepared as described in Example 7, was dissolved in ethyl acetate (15 ml), 10 % palladium on charcoal (770 mg), was added, and the mixture was stirred at room temperature, under hydrogen, for 19 hours. Next, the mixture was filtered on silica gel column in ethyl acetate, the filtrate was evaporated to give crude product. The product was purified on silica gel column in methylene chloride – ethyl acetate 50 : 1 solution to give a colorless oil (189 mg, 70 %). The oil was dissolved in diethyl ether and a solution of hydrochloride in diethyl ether was added. The precipitated solid was filtered off, washed with diethyl ether and dried, to give 3-(3-amino-4-methoxyphenyl)-1-(6-propoxybenzo[*b*][1,4]-oxathian-7-yl)propane hydrochloride (168 mg). NMR (500 MHz, DMSO-d_6): δ 9,87 (bs, 3H, NH_3^+), 7,20 (s, 1H, H-2'), 7,14 (d, 1H, J = 8,5 Hz, H-6'), 7,08 (d, 1H, J = 8.5Hz, H-5'), 6,59 (s, 1H, H-8, 6,55 (s, 1H, H-5), 4,24 (m, 2H, H-2), 3,84 (s, 3H, OCH_3), 3,79 (t, 2H, J = 6,2 Hz, OCH_2), 3,12 (m, 2H, H-3), 2,51(t, 2H, J = 7,6 Hz, CH_2), 2,44 (t, 2H, J = 7.8 Hz, CH_2), 1,72 (m, 2H, CH_2), 1,64 (m, 2H, CH_2), 0.92 (t, 3H, J = 7,5 Hz, CH_3).

Using the described above procedure for preparation of compounds of general formula (I), wherein Y = H, and one of the substituents X = NH_2, and demonstrated for compound **AMG-485**, the following compounds were obtained:



AMG-483

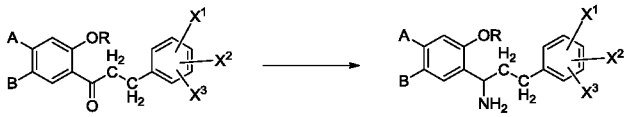
3-(3-amino-4-methoxyphenyl)-1-(4,4-dioxo-6-propoxybenzo[*b*][1,4]-oxathian-7-yl)propane, a clorless solid (0,503 g, 68 %), m.p. 70-79°C. ^{1}H NMR (DMSO-d_6) δ 7.04 (s, 1H, H-5), 6.87 (s, 1H, H-8), 6.65 (d, 1H, J=8,2 Hz, H-5'), 6.43 (d, 1H, J=2,0 Hz, H-2'), 6.30 (dd, 1H, J_1=7,9 Hz, J_2=2,2 Hz, H-6'), 4.67 (m, 2H, OCH_2), 4.57 (s, 2H, NH_2), 3.91 (t, 2H, J=6,2 Hz, OCH_2), 3.75 (m, 2H, SCH_2), 3.69 (s, 3H, OCH_3), 2.54 (t, 2H, J=7,5 Hz, CH_2), 2.39 (t, 2H, J=7,5 Hz, CH_2), 1.71 (m, 4H, 2xCH_2), 0.95 (t, 3H, J=7,4 Hz, CH_3). IR (cm^{-1}): 3468, 3379, 1616, 1515, 1492, 1286, 1227, 1140, 477.

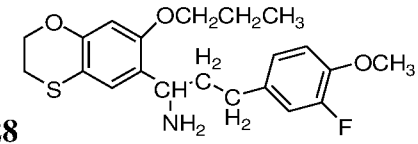


AMG-487

1-(3-amino-4-methoxyphenyl)-3-(3,3-dioxo-5-propoxybenz[*d*][1,3]oxathiol-6-yl)propane, m.p. 96-100°C. ^{1}H NMR (DMSO-d_6) δ 7.29 (s, 1H, H-4), 7.11 (s, 1H, H-7), 6.64 (d, 1H, J=8,0 Hz, H-5'), 6.43 (d, 1H, J=2,1 Hz, H-2'), 6.31 (dd, 1H, J_1=8,2 Hz, J_2=2,1 Hz, H-6'), 5.31 (s, 2H, H-2), 4.57 (s, 2H, NH_2), 3.95 (t, 2H, J=6,1 Hz, OCH_2), 3.69 (s, 3H, OCH_3), 2.60 (t, 2H, J=7,6 Hz, CH_2), 2.40 (t, 2H, J=7,7 Hz, CH_2), 1.71 (t, 4H, J=7,1 Hz, 2xCH_2), 0.94 (t, 3H, J=7,3 Hz, CH_3). IR (cm^{-1}): 3417, 3343, 1621, 1516, 1466, 1300, 1231, 1153, 870.

Example 12. Preparation of compounds of general formula (I), wherein Y = NH_2, using reductive amination method





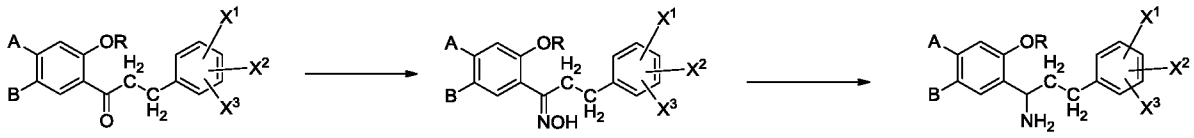
AMG-428

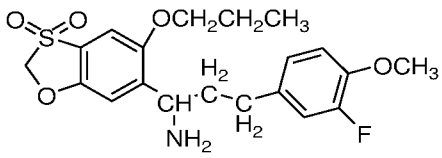
3-(3-fluoro-4-methoxyphenyl)-1-(7-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-6-yl)propan-1-amine

3-(3-Fluoro-4-methoxyphenyl)-1-(7-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-6-yl)propan-1-one (460 mg, 1,17 mmol), prepared as described in Example 1, ammonium acetate (1006 mg, 13,75 mmol), and sodium cyjanoborohydride (62 mg, 1 mmol) in methanol (10 ml) were strred at reflux temperature for 22 hours. The mixture was cooled down, acidified with diluted hydrochloric acid, and washed with diethyl ether. The aqueous layer was alkalized with diluted sodium hydroxide and extracted with methylene chloride. The organic layer was washed with water, dried (sodium sulfate) and evaporated. The residue was purified on silica gel column in methylene chloride – methanol 10 : 1 solution, to give colorless oil (285 mg, 62 %). The product was dissolved in anhydrous ethanol (2 ml) and solution of hydrochloride in diethyl ether (0.7 ml) was added. The solvents were evaporated, and the residue was crystallized from ethanol – water to give a colorless solid of

3-(3-fluoro-4-methoxyphenyl)-1-(7-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-6-yl)propan-1-amine hydrochloride (180 mg, 36 %), m.p. 160 - 161 °C. NMR (500 MHz, $DMSOd_6$): δ 8,30 (bs, 3 H, CNH_3^+), 7,17 (s, 1 H, H-5), 7,04 (t, 1 H, J = 8,7 Hz, H-5'), 6,99 (d, 1 H, J = 2,7 Hz, H-2'), 6,89 (d, 1 H, J = 8,2 Hz, H-6'), 6,52 (s, 1 H, H-8), 4,35 (m, 3 H, H-2 + CH), 3,84 (t, 2 H, J = 6,3 Hz, OCH_2), 3,78 (s, 3 H, OCH_3), 3,15 (m, 2 H, H-3), 2,45 (bm, 2 H, CH_2Ph), 2,16 (m, 1 H, CHCHNH), 2,03 (m, 1 H, CHCHNH), 1,65 (m, 2 H, CH_2), 0,88 (t, 3 H, J = 7,3 Hz, CH_3). IR (KBr, cm^{-1}): 3435, 2922, 1613, 1519, 1275.

Example 13. Preparation of compounds of general formula (I), wherein Y = NH_2, *via* oximes





AMG-433

Step 1.

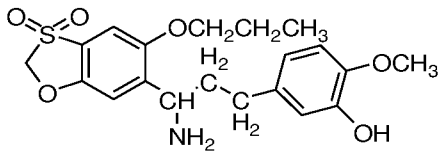
3-(3-Fluoro-4-methoxyphenyl)-1-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propan-1-one (2,98 g, 7,3 mmol), prepared as described in Example 1, hydroxylamine hydrochloride (1,529 g, 22 mmol) and pyridine (1,2 ml, 14,8 mmole) in ethanol (20 ml) were stirred at reflux temperature for 1,5 hour. The mixture was slowly diluted with water (80 ml), the precipitated solid was filtered off, washed with water, and crystallized from ethanol to give 3-(3-fluoro-4-methoxyphenyl)-1-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propan-1-one oxime, (2,234 g, 72 %). NMR demonstrated that this is a mixture of two isomers. NMR (500 MHz, DMSO-d_6): δ 11,42 (s, 1 H, OH isomer A), 10,74 (s, 1 H, OH isomer B), 7,46 (s, 1 H, H-4, isomer A), 7,45 (s, 1 H, H-4, isomer B), 6,92 – 7,08 (m, 8 H, aromatic), 6,90 (s, 1 H, H-7, isomer A), 6,84 (d, 1 H, J = 8,3 Hz, H-6', isomer A), 5,37 (s, 1 H, H-2, isomer B), 5,36 (s, 1 H, H-2, isomer A), 4,02 (t, 2 H, J = 6,4 Hz, OCH_2, isomer A), 3,96 (t, 2 H, J = 6,2 Hz, OCH_2, isomer B), 3,77 (s, 3 H, OCH_3, isomer B), 3,76 (s, 3 H, OCH_3, isomer A), 2,90

(m, 2 H, $NCCH_2$, isomer A), 2,68 (s, 4 H, $NCCH_2$ + CH_2Ph, isomer B), 2,61 (m, 2 H, CH_2Ph), 1,6 – 1,8 (m, 4 H, CH_2, isomers A and B), 0,94 (m, 6 H, CH_3, isomers A and B). IR (KBr, cm^{-1}): 3429, 1521, 1441, 1298, 1134, 1029.

Step 2

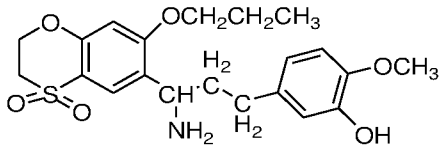
3-(3-Fluoro-4-methoxyphenyl)-1-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propan-1-one oxime (700 mg, 1,65 mmol) and zinc dust (700 mg, 10,7 mmol) in acetic acid (10 ml) were stirred at reflux temperature for 2 hours. The mixture was cooled down, diluted with water, alkalized with sodium bicarbonate (22 g), and extracted with ethyl acetate (200 ml). The organic layer was washed with water, brine, dried with sodium sulfate, and evaporated. The residue was purified on silica gel column in methylene chloride – methanol 20 : 1 solution to give a colorless solid (400 mg). The solid was suspended in anhydrous methanol (3 ml), 2N solution of hydrochloride in diethyl ether (2,5 ml) was added, and the obtained clear solution was diluted with diethyl ether (50 ml). The precipitated solid was filtered off, and washed with diethyl ether to give 3-(3-fluoro-4-methoxyphenyl)-1-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propan-1-amine hydrochloride, 320 mg (43 %). NMR (500 MHz, D_2O): δ 7,05 (s, 1 H, H-4), 6,98 (s, 1 H, H-7), 6,71 (t, 1 H, J = 8,9 Hz, H-5'), 6,62 (d, 1 H, J = 13,2 Hz, H-2'), 6,55 (d, 1 H, J = 8,6 Hz, H-6'), 5,12 (s, 2 H, H-2), 4,41 (m, 1 H, H-a), 3,79 (m, 2 H, OCH_2), 3,67 (s, 3 H, OCH_3), 2,62 (m, 1 H, H-b), 2,41 (m, 2 H, H-c), 2,21 (m, 1 H, H-b), 1,65 (m, 2 H, CH_2), 0,86 (t, 3 H, J = 7,4 Hz, CH_3). IR (KBr, cm^{-1}): 3424, 2961, 2922, 2853, 1604, 1522, 1316, 1178, 1156, 1040.

Analogously, the following compounds were prepared:



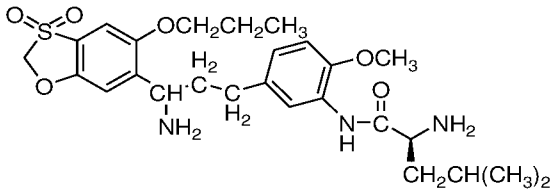
AMG-413

5-(3-amino-3-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propyl)-2-methoxyphenol. NMR (500 MHz, DMSO-d_6): δ 8,73 (s, 1 H, OH), 7,38 (s, 1 H, H-4), 7,27 (s, 1 H, H-7), 6,75 (d, 1 H, J = 8,1 Hz, H-5'), 6,56 (d, 1 H, J = 1,8 Hz, H-2'), 6,50 (dd, 1 H, J_1 = 8,1 Hz, J_2 = 1,8 Hz, H-6'), 5,31 (s, 2 H, H-2), 4,10 (m, 1 H, Ha), 3,92 (m, 2 H, OCH_2), 3,69 (s, 3 H, OCH_3), 2,54 (m, 1 H, Hc), 2,43 (m, 1 H, Hc), 1,92 (bs, 2 H, NH_2), 1,77 (m, 1 H, Hb), 1,66 (m, 2 H, CH_2), 1,58 (m, 1 H, Hb), 0,92 (t, 3 H, J = 7,4 Hz, CH_3



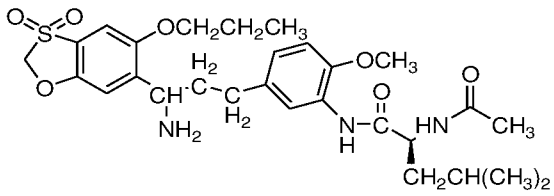
AMG-412

5-(3-amino-3-(4,4-dioxo-7-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-6-yl)propyl)-2-methoxyphenol. NMR (500 MHz, DMSO-d_6): δ 8,73 (s, 1 H, OH), 7,72 (s, 1 H, H-5), 6,75 (d, 1 H, J = 8,2 Hz, H-5'), 6,56 (d, 1 H, J = 1,9 Hz, H-2'), 6,50 (m, 2 H, H-8 + H-6'), 4,71 (m, 2 H, H-3), 4,01 (m, 1 H, Ha), 3,91 (m, 2 H, OCH_2), 3,70 (m, 5 H, OCH_3 + H-2), 2,5 (m, Hc, under DMSO), 2,41 (m, 1 H, Hc), 1,87 (bs, 2 H, NH_2), 1,75 (m, 1 H, Hb), 1,68 (m, 2 H, CH_2), 1,59 (m, 1 H, Hb), 0,92 (t, 3 H, J = 7,2 Hz, CH_3).



AMG-434

(2S)-2-amino-N-(5-(3-amino-3-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propyl)-2-methoxyphenyl)-4-methylpentanamide. NMR (500 MHz, D_2O) (spectrum for hydrochloride): δ 7,13 (s, 1 H), 7,12 (s, 1 H), 7,07 (s, 1 H), 7,04 (s, 1 H), 6,92 (s, 1 H), 6,89 (s, 1 H), 6,72 (s, 2 H), 6,71 (s, 2 H), 5,10 (m, 4 H), 4,45 (m, 2 H), 4,10 (m, 2 H), 3,75 – 3,85 (m, 4 H), 3,65 (s, 6 H), 2,65 (m, 2 H), 2,40 (m, 4 H), 2,25 (m, 2 H), 1,55 – 1,75 (m, 10 H), 0,85 (m, 18 H).



AMG-435

A side product in synthesis of AMG-434 (above) formed in case of prolonged zinc reduction, (2S)-2-acetamido-N-(5-(3-amino-3-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propyl)-2-methoxyphenyl)-4-methylpentanamide. NMR (500 MHz, DMSO-d_6): δ 8,99 (2 x s, 21 H, NHCO), 8,24 (m, 1 H, NHCO), 7,83 (s, 1 H, H-2'), 7,38 (s, 1 H, H-7), 7,27 (s,

1 H, H-4), 6,90 (d, 1 H, J = 8,2 Hz, H-5'), 6,84 (d, 1 H, J = 8,2 Hz, H-6'), 5,33 (d, 1 H, J = 10,0 Hz, H-2), 5,30 (d, 1 H, J = 10,0 Hz, H-2), 4,43 (m, 1 CH), 4,11 (m, 1 H, CH), 3,92 (m, 2 H, CH_2), 3,77 (s, 3 H, OCH_3), 2,60 (m, 1 H, CH), 2,50 (m, 1 H, CH), 2,13 (bs, 2 H, NH_2), 1,88 (s, 3 H, $COCH_3$), 1,79 (m, 1 H, CH), 1,63 (m, 4 H, 2 x CH + CH_2), 1,52 (m, 2 H, CH_2), 0,90 (m, 6 H, 2 x CH_3), 0,85 (d, 3 H, J = 6,5 Hz, CH_3).

MTT cytotoxicity assay

MTT assay is a colorimetric assay used for estimation of cells proliferation and viability as well as cytotoxicity of the substance, for the cells. It consists in decomposition of the yellow tetrazolium salt MTT (methyl 3-(4,5-dimethylthiazo-2-yl)-2,5-diphenyltetrazole bromide) to insoluble in water purple dye formazan, by the mitochondrial succinic-tetrazole reductase. MTT reduction occurs in living cells only. Data analysis consists in determination of concentration of the test compound wherein 50 % reduction in the number of cells in the treated population occurs, in comparison to to the control cells. Results were analyzed using GraphPad Prism 4.0.

The assay was performed according to literature description (Celis, J.E., (1998). Cell biology, a laboratory handbook, second edition, Academic Press, San Diego; Yang, Y., Koh, L.W., Tsai, J-H., (2004), Involvement of viral and chemical factors with oral cancer in Taiwan, Jpn J Clin Oncol, 34(4)176-183).

Human cervix carcinoma cells HeLa (ATCC# CCL-2) were maintained in MEM medium (HyClone, Logan, UT, USA) supplemented with 10 % fetal calf serum (HyClone, Logan, UT, USA), 2mM L-glutamine and antibiotics (penicillin 100 U/ml and streptomycin 100 mg/ml (HyClone, Logan, UT, USA) at temperature 37 ^{o}C, under atmosphere of air supplemented with 5 % of CO_2.

Human colonic epithelial cells HCT-116 (ATCC# CCL-247) were maintained in McCoy's medium (HyClone, Logan, UT, USA) supplemented with 10 % fetal calf serum (HyClone, Logan, UT, USA), 2mM L-glutamine and antibiotics (penicillin 100 U/ml and streptomycin 100 mg/ml (HyClone, Logan, UT, USA) at temperature 37 ^{o}C, under atmosphere of air supplemented with 5 % of CO_2.

Human lung adenocarcinoma epithelial cells A549 (ATCC# CCL-185) were maintained in RPMI1640 medium (HyClone, Logan, UT, USA) supplemented with 10 % fetal calf serum

(HyClone, Logan, UT, USA), 2mM L-glutamine and antibiotics (penicillin 100 U/ml and streptomycin 100 mg/ml (HyClone, Logan, UT, USA) at temperature 37 °C, under atmosphere of air supplemented with 5 % of CO_2.

Cells were subjected to routine checkup for the presence of Mycoplasma by PCR using commercially available Venor®GeM Mycoplasma PCR Detection Kit (Minerva Biolabs, Berlin, Germany).

The cells culture was diluted with the medium to a specified density (10^4 - 10^5 cells per 100 µl). Then 100 µl of appropriately diluted cell suspension was applied in 96-well plate in triplicates, The cells thus prepared were incubated for 24 hours at 37 °C in 5 % CO_2, then to the cells (in 100 µl of medium) another 100 µl of culture medium containing different concentrations of test compounds was added. The cells were incubated with tested compounds for subsequent 72 hours, what corresponds to 3 – 4 times of cell division. Then to the medium with test compounds 20 µl of MTT working solution [5 mg/ml] was added and incubated for 3 hours at 37 °C in 5 % CO_2. Then, medium with the MTT solution was removed, and formazan crystals were dissolved in 100 µl of DMSO. After mixing, the absorbance was measured at a wavelength of 570 nm (reference filter 690 nm). Results of the test are presented in Table 1 as IC_{50} [µM].

Table 2 presents evaluation of anticancer activity of compound AMG-415 against murine Colon 26 carcinoma, inoculated subcutaneously to BALB/C mice.

Table 3 presents evaluation of anticancer activity of compound AMG-432 against murine Colon 26 carcinoma, inoculated subcutaneously to BALB/C mice.

Table 1

Compound no	A549	HCT116	HeLa
Compounds of general formula IIA			
AMG-391	0,019	0,020	0,020
AMG-407	0,075	0,025	0,021
AMG-421	0,156	0,241	0,085
AMG-395	0,356	0,207	0,097

AMG-401	> 4	> 4	1,427
AMG-409	4,20	1,95	1,52
AMG-482	1,70	0,826	1,161
AMG-479	0,15	0,0093	0,045
AMG-396	0,054	0,021	0,012
AMG-397	3,06	2,147	0,257
AMG-398	0,030	0,001	0,005
AMG-403	0,023	0,002	0,004
AMG-414	0,037	0,012	0,013
AMG-405	0,008	0,002	0,004
AMG-415	0,004	0,002	0,001
AMG-419	2,50	1,89	1,64
AMG-417	2,71	0,179	0,200
AMG-420	0,0075	0,0024	0,001
Compounds of general formula IIB			
AMG-402	> 4	> 4	> 4
AMG-399	0,018	0,014	0,0033
AMG-430	0,016	0,018	0,002
AMG-431	0,021	0,026	
AMG-432	0,028	0,037	
Compounds of general formula IID			
AMG-485	68.91	30.66	63.00
AMG-486	6.08	5.96	5.41
AMG-483	6.9	6.36	5.25
AMG-484	4.98	3.45	5.61
AMG-487	0.273	0.117	0.048
AMG-488	0.416	0.214	0.158
Compounds of general formula IIC			
AMG-428	> 4	> 4	
AMG-412	> 4	> 4	

AMG-433	0.179	0.192	
AMG-434	0.363	0.462	
AMG-435	> 4	> 4	
AMG-413	0.198	0.244	0.158

Table 2

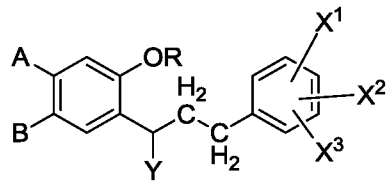
No	Group name	Body weight change from the beginning of treatment (from day 1 to 14)	Mean tumor size on the 14th day [mg]	Tumor growth inhibition after 14th day [%]	Mean tumor size on the 15th day [mg]	Tumor growth inhibition after 15th day [%]	Number of animals per experiment / Number of dead animals
1	CONTROL female	-0,10	385,5		657,40		12/0
2	METHOTREXATE 20 mg/kg	0,80	224,0	41,9	438,60	33	8/0
3	AMG 415 12,5 mg/kg	0,70	253,0	34,4	494,00	25	8/0
4	AMG 415 25mg/kg	0,80	407,0	- 5,6	659,30	0	8/0
5	AMG 415 50 mg/kg	0,40	277,5	28,0	571,30	13	8/0
6	AMG 415 100mg/kg	-0,70	120,6	68,7	186,60	72	8/0

Table 3

No	Group name	Body weight change from the beginning of treatment (from day 1 to 14)	Mean tumor size on the 14th day [mg]	Tumor growth inhibition after 14th day [%]	Mean tumor size on the 15th day [mg]	Tumor growth inhibition after 15th day [%]	Number of animals per experiment / Number of dead animals
1	CONTROL female	-2,10	545,04		695,59		20/7
3	AMG 432 12,5 mg/kg	-2,10	552,37	-1	755,92	-9	8/5
4	AMG 432 25mg/kg	-1,10	520,18	5	814,25	-17	8/0
5	AMG 432 50 mg/kg	-0,70	336,42	38	550,31	21	8/0
6	AMG 432 100mg/kg	-1,00	288,70	47	395,71	43	8/0

Claims

1. Compounds of general formula (I),



(I)

wherein

A and **B** are linked together and form a a moiety selected from -O-$(CH_2)_n$-S$(O)_m$-, -S$(O)_m$-$(CH_2)_n$-O- or -O-$(CH_2)_n$-O-

or

one of **A** and **B** is –S$(O)_m$-C_1-C_6-alkyl, and the second is selected from a group consisting of OH and -O-C_1-C_6-alkyl;

R is H, C_1-C_6-alkyl, CO-C_1-C_6-alkyl, or -(CH_2)p-NR^1R^2, wherein

R^1 and **R^2** are independently of each other, H, C_1-C_6-alkyl, or

R^1 and **R^2** are linked together by a polymethylene linker -$(CH_2)_q$-, to form along with the nitrogen atom to which they are attached a five or six- membered ring, wherein one of carbon atoms may be optionally replaced by O, N, or S.

Y is: O, H, OH, NH_2

X^1, **X^2**, **X^3** are, independently of each other, H, halogen atom, OH, -O-C_1-C_6alkyl, -O-CO-C_1-C_6alkyl, -O-C_1-C_6alkyl(N(C_1-C_6 alkyl)$_2$), O-PO$(OH)_2$, NO_2, NH_2 or NHR^3, wherein **R_3** is C_1-C_6alkyl

m= 0, 1, or 2

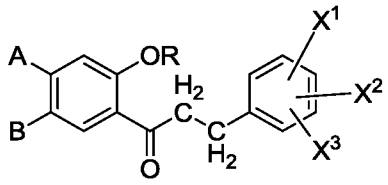
n= 1 or 2;

p=2 to 6

q= 4 or 5,

and their pharmaceutically acceptable salts

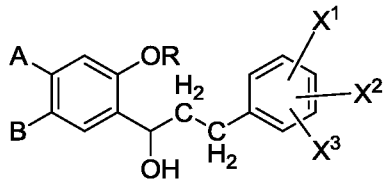
2. Compounds according to Claim 1 described by formula (IIA)



(IIA)

wherein A, B, R, X^1, X^2, X^3 have the same meanings as defined for general formula (I).

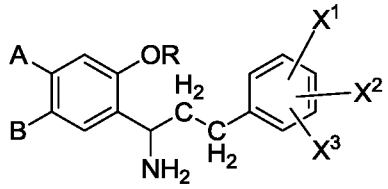
3. Compounds according to Claim 1 described by formula (IIB)



(IIB)

wherein A, B, R, X^1, X^2, X^3 have the same meanings as defined for general formula (I).

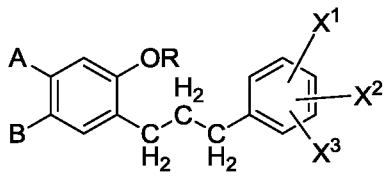
4. Compounds according to Claim 1 described by formula (IIC)



(IIC)

wherein A, B, R, X^1, X^2, X^3 have the same meanings as defined for general formula (I).

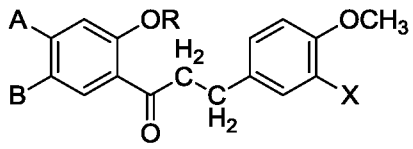
5. Compounds according to Claim 1 described by formula (IID)



(IID)

wherein A, B, R, X^1, X^2, X^3 have the same meanings as defined for general formula (I).

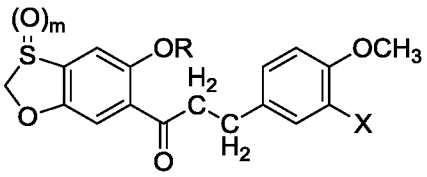
6. Compounds according to Claim 1 described by formula (IV)



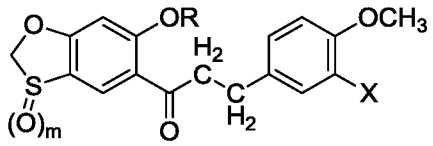
(IV)

wherein A, B, R have the same meanings as defined for general formula (I), X is H, halogen atom, OH, -O-C_1-C_6alkyl, -O-CO-C_1-C_6alkyl, -O-C_1-C_6alkyl(N(C_1-C_6alkyl)$_2$), O-PO(OH)$_2$, NO_2, NH_2 or NHR^3, wherein R_3 is C_1-C_6alkyl.

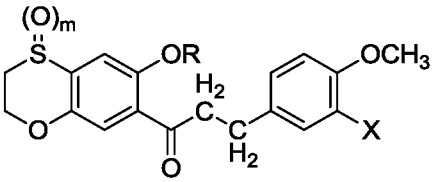
7. Compounds according to Claim 1 described by formulas VA-VD, VIA-VID, VIIA-VIID, VIIIA-VIIID:



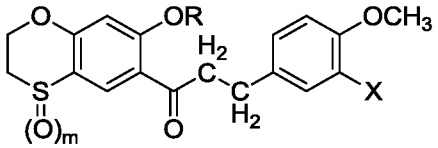
(VA)



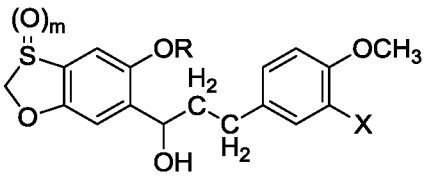
(VB)



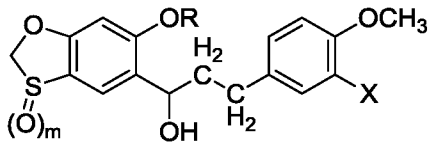
(VC)



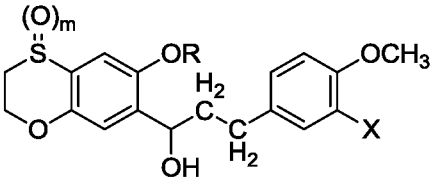
(VD)



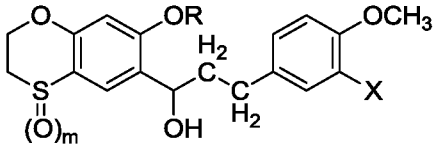
(VIA)



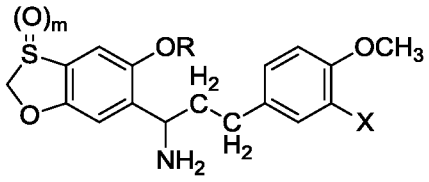
(VIB)



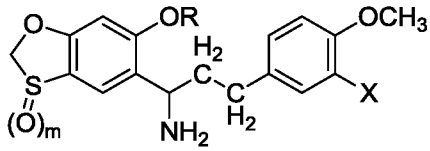
(VIC)



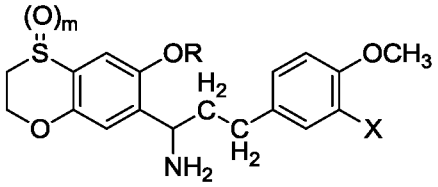
(VID)



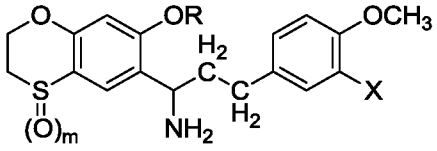
(VIIA)



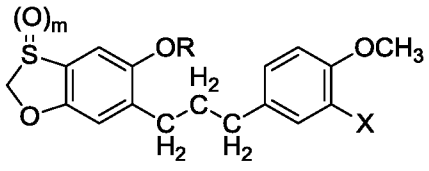
(VIIB)



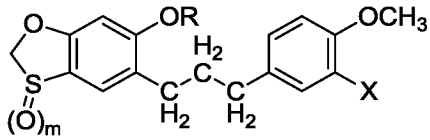
(VIIC)



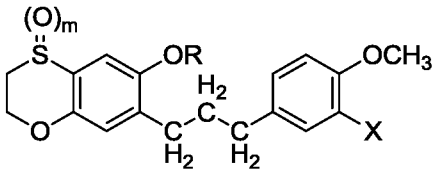
(VIID)



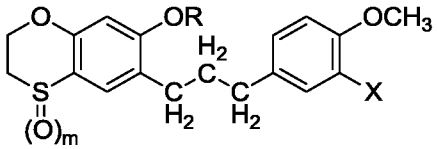
(VIIIA)



(VIIIB)



(VIIIC)



(VIIID)

wherein R and m have the same meanings as defined above for general formula (I), X is H, halogen atom, OH, -O-C_1-C_6alkyl, -O-CO-C_1-C_6alkyl, -O-C_1-C_6alkyl(N(C_1-C_6alkyl)$_2$), O-PO(OH)$_2$, NO_2, NH_2 or NHR^3, wherein R_3 is C_1-C_6alkyl.

8. Compound selected from a group consisting of:

3-(3-hydroxy-4-methoxyphenyl)-1-(7-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-6-yl)propan-1-one (**AMG-391**);

3-(3-amino-4-methoxyphenyl)-1-(7-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-6-yl)propan-1-one (**AMG-407**);

(S)-2-amino-N-(2-methoxy-5-(3-oxo-3-(7-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-6-yl)propyl)phenyl)-4-methylpentanamide (**AMG-421**);

3-(3-fluoro-4-methoxyphenyl)-1-(7-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-6-yl)propan-1-one (**AMG-395**);

3-(3-hydroxy-4-methoxyphenyl)-1-(4,4-dioxo-7-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-6-yl)propan-1-one (**AMG-401**);

3-(3-amino-4-methoxyphenyl)-1-(4,4-dioxo-7-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-6-yl)propan-1-one (**AMG-409**);

3-(3-amino-4-methoxyphenyl)-1-(6-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-7-yl)propan-1-one (**AMG-482**);

3-(3-amino-4-methoxyphenyl)-1-(4,4-dioxido-6-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-7-yl)propan-1-one (**AMG-479**);

3-(3-hydroxy-4-methoxyphenyl)-1-(5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propan-1-one (**AMG-396**);

3-(3-fluoro-4-methoxyphenyl)-1-(5-methoxybenzo[*d*][1,3]oxathiol-6-yl)propan-1-one (**AMG-397**);

3-(3-hydroxy-4-methoxyphenyl)-1-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propan-1-one (**AMG-398**);

2-methoxy-5-(3-oxo-3-(3,3-dioxo-5-propoxybenzo[d][1,3]oxathiol-6-yl)propyl)phenyl acetate (**AMG-403**);

sodium 2-methoxy-5-(3-oxo-3-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propyl)phenyl phosphate (**AMG-414**);

3-(3-amino-4-methoxyphenyl)-1-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propan-1-one (**AMG-405**);

(S)-2-amino-N-(2-methoxy-5-(3-oxo-3-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propyl)phenyl)-4-methylpentanamide (**AMG-415**);

(S)-tert-butyl 1-(2-methoxy-5-(3-oxo-3-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propyl)phenylamino)-4-methyl-1-oxopentan-2-yl carbamate (**AMG-419**);

3-(3-fluoro-4-methoxyphenyl)-1-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propan-1-one (**AMG-420**);

5-(3-hydroxy-3-(4,4-dioxo-7-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-6-yl)propyl)-2-methoxyphenol (**AMG-402**);

5-(3-hydroxy-3-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propyl)-2-methoxyphenol (**AMG-399**);

3-(3-fluoro-4-methoxyphenyl)-1-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propan-1-ol (**AMG-430**);

3-(3-hydroxy-3-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propyl)-2-methoxyaniline (**AMG-431**);

(2S)-2-amino-N-(5-(3-hydroxy-3-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propyl)-2-methoxyphenyl)-4-methylpentanamide (**AMG-432**);

3-(4-methoxy-3-nitrophenyl)-1-(6-propoxybenzo*[b]*[1,4]-oxathian-7-yl)propane;

1-(4-methoxy-3-nitrophenyl)-3-(5-propoxybenzo*[b]*[1,4]-oxathiol-6-yl)propane;

3-(4-methoxy-3-nitrophenyl)-1-(4,4-dioxo-6-propoxybenzo*[b]*[1,4]-oxathian-7-yl)propane;

1-(4-methoxy-3-nitrophenyl)-3-(3,3-dioxo-5-propoxybenzo*[b]*[1,4]-oxathiol-6-yl)propane;

2-methoxy-5-(3-(6-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-7-yl)propyl)aniline (**AMG-485**);

(S)-2-amino-N-(2-methoxy-5-(3-(6-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-7-yl)propyl)phenyl)-4-methylpentanamide (**AMG-486**);

7-(3-(3-amino-4-methoxyphenyl)propyl)-6-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiine 4,4-dioxide (**AMG-483**);

(S)-2-amino-N-(5-(3-(4,4-dioxido-6-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-7-yl)propyl)-2-methoxyphenyl)-4-methylpentanamide (**AMG-484**);

6-(3-(3-amino-4-methoxyphenyl)propyl)-5-propoxybenzo[*d*][1,3]oxathiole 3,3-dioxide (**AMG-487**);

(S)-2-amino-N-(5-(3-(3,3-dioxido-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propyl)-2-methoxyphenyl)-4-methylpentanamide (**AMG-488**);

3-(3-fluoro-4-methoxyphenyl)-1-(7-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-6-yl)propan-1-amine (**AMG-428**);

5-(3-amino-3-(4,4-dioxo-7-propoxy-2,3-dihydrobenzo[*b*][1,4]oxathiin-6-yl)propyl)-2-methoxyphenol (**AMG-412**);

3-(3-fluoro-4-methoxyphenyl)-1-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propan-1-amine (**AMG-433**);

(2S)-2-amino-N-(5-(3-amino-3-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propyl)-2-methoxyphenyl)-4-methylpentanamide (**AMG-434**);

(2S)-2-acetamido-N-(5-(3-amino-3-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propyl)-2-methoxyphenyl)-4-methylpentanamide (**AMG-435**);

5-(3-amino-3-(3,3-dioxo-5-propoxybenzo[*d*][1,3]oxathiol-6-yl)propyl)-2-methoxyphenol (**AMG-413**).

9. Pharmaceutical composition containing compounds as defined in Claims 1 to 8 and a pharmaceutically acceptable carrier.

10. Compounds as defined in Claims 1 to 8 for use as a drug.

11. Compounds as defined in Claims 1 to 8 for use in therapy of cancer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/002409

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D327/04 C07D327/06 A61K31/39 A61P3/00
ADD.

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)
C07D

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 practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GETAHUN, Z. ET AL.: "Synthesis of alkoxy-substituted diaryl compounds and correlation of ring separation with inhibition of tubulin polymerization: differential enhancement of inhibitory effects under suboptimal polymerization reaction conditions", JOURNAL OF MEDICINAL CHEMISTRY., vol. 35, no. 6, 1992, pages 1058-1067, XP002754708, AMERICAN CHEMICAL SOCIETY. WASHINGTON; US ISSN: 0022-2623 page 1058, column 1, lines 1, 2, 16, 22, 23 Scheme V; page 1060; compounds 46, 47 page 1062; table II; compounds 46, 47 ----- -/--	1-3,6, 9-11

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

[X] See patent family 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 application or patent 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
3 March 2016	18/05/2016

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, Fax: (+31-70) 340-3016	Hoepfner, Wolfgang

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/002409

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CONSERVA, L. M. ET AL.: "The chemistry of the Brazilian Myristicaceae. Part 33. Diarylpropanes from Iryanthera ulei.", PHYTOCHEMISTRY, vol. 29, no. 12, 1990, pages 3986-3988, XP002754709, PERGAMON PRESS; GB ISSN: 0031-9422 page 3987; compounds 2a-2d	1-3,6
A	MORAIS, A. A. ET AL.: "Synthesis of three natural 1,3-diarylpropanes: two revised structures", PHYTOCHEMISTRY., vol. 28, no. 1, 1989, pages 239-242, XP055034868, PERGAMON PRESS; UK ISSN: 0031-9422 page 240; compounds 1c-1e	1-3,6
A	DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 17 March 1989 (1989-03-17), XP002754710, retrieved from STN Database accession no. 1989:92107 abstract & SUAREZ, M. ET AL.: "1,3-Diarylpropane and flavonols from Persea sp.", REVISTA LATINOAMERICANA DE QUIMICA, vol. 19, no. 2, 1988, pages 83-84, MONTERREY; MX ISSN: 0370-5943	1-3,6
A	PEDRO, P. ET AL.: "Diarylpropanes from the wood of Iryanthera grandis.", PHYTOCHEMISTRY., vol. 25, no. 10, 1986, pages 2935-2937, XP002754711, PERGAMON PRESS; UK ISSN: 0031-9422 page 2935; compounds 1a, 1c-1e	1-3,6
A	BRAZ FILHO, R. ET AL.: "The chemistry of Brazilian Myristicaceae. Part 14. Flavonoids from Iryanthera laevis", PHYTOCHEMISTRY., vol. 19, no. 6, 1980, pages 1195-1197, XP002754712, PERGAMON PRESS; UK ISSN: 0031-9422 page 1196; compounds 3a, 3b, 3d, 3e, 3g	1-3,6

-/--

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/002409

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ALVES DE LIMA, R. ET AL.: "Chemistry of Brazilian Myristicaceae. 5. Diarylpropanes from Iryanthera coriacea", PHYTOCHEMISTRY., vol. 14, no. 8, 1975, pages 1831-1833, XP002754713, PERGAMON PRESS; UK ISSN: 0031-9422 page 1832; compounds 1a-1f, 1i ----	1-3,6
Y	WO 2011/009826 A2 (ADAMED SP ZOO [PL]; KONIECZNY MAREK [PL]; SKLADANOWSKI ANDRZEJ [PL]; L) 27 January 2011 (2011-01-27) cited in the application page 1, lines 4-7 page 3, line 21 - page 4, line 5 page 5; compounds (IA), (IB) page 6; compounds (IC), (ID) examples page 85 - page 92 ----	1-3,6, 9-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2015/002409

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 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. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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 No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

see additional sheet

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 fees, this Authority did not invite payment of additional fees.

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.:

2, 3, 6(completely); 1, 9-11(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 2, 3, 6(completely); 1, 9-11(partially)

   1,3-Bis(aryl)propanes, wherein variable "Y" is selected from O or OH.

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2. claims: 5(completely); 1, 9-11(partially)

   1,3-Bis(aryl)propanes, wherein variable "Y" is H.

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3. claims: 4(completely); 1, 9-11(partially)

   1,3-Bis(aryl)propanes, wherein variable "Y" is NH2.

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4. claims: 7, 8(completely); 9-11(partially)

   1,3-Bis(aryl)propanes, wherein at least 1 of variables "A" or "B" is selected from S, SO or SO2.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2015/002409

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011009826 A2	27-01-2011	NONE	