USE OF THIAZOLIDINONE DERIVATIVES AS ANTIANGIOGENIC AGENTS

Field of the invention

The invention relates to thiazolidinone compounds capable of inhibiting the interaction between HIF-1α transcription factor and its coactivator p300 and of preventing the production of Vascular Endothelial cell Growth Factor.

Background of the invention

Vascular Endothelial Cell Growth Factor plays a key role in the processes of physiological and physiopathological angiogenesis. A number of mechanisms are involved in the regulation of the VEGF gene, among which a fundamental role is played by the tissue oxygen tension, as proved by the reversible increase in VEGF mRNA levels under *in vivo* and *in vitro* hypoxia conditions. Increased expression of VEGF mRNA is mainly mediated by the transcription factor HIF-1 (hypoxia-inducible factor-1), which binds to a recognition site in the promoter region of the VEGF gene.

A great number of experimental data show that HIF-1 is a global regulator of oxygen homeostasis and that an impaired activity of HIF-1 promotes survival, proliferation, invasion and metastatization of tumoral cells (1). It has been therefore suggested that therapeutic strategies focusing on the inhibition of HIF-1 activity could increase the survival of cancer patients (2).

HIF-1 is a heterodimer consisting of HIF-1α and HIF-1β sub-units, which dimerize and bind to DNA through the bHLH-PAS domain (3). The expression of the HIF-1α sub-unit is strictly regulated by the tissue oxygen tension (4) through processes of ubiquitination and proteasome degradation, mediated by the binding of VHL protein to HIF-1α. Such interaction only takes place when HIF-1α has been hydroxylated at the 402 and 564 proline residues. Oxygen is the limiting substrate for prolyl-hydroxylase which

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modifies HIF-1α (5). The expression of HIF-1α exponentially increases as O_2 concentration decreases and determines the HIF-1 global activity levels.

The function of HIF-1α transactivation domain is also subject to negative regulation, controlled by oxygen partial pressure. The N-terminal transactivation domain is negatively regulated through the recruitment of hystone deacylase by VHL and by HIF-1 inhibiting factor (FIH-1), which binds to both VHL and HIF-1α (6).

HIF-1 activation takes place through p300/CBP coactivators which physically interact with the activation of the HIF-1 domain to promote transcription of genes like VEGF (7). Both p300 and CBP are co-activators also for other transcription factors, such as Stat-3, NF-κB, p53.

The interaction of p300/CBP with HIF-1 is essential to transcription, and recent publications have proved the importance of the HIF-1/p300 interaction for tumor growth (8). HIF-1α C-terminal trans-activation domain (C-TAD) binds to a p300 and CBP domain known as CH1. The binding of CBP and p300 to HIF-1α is negatively regulated through oxygen-dependent hydroxylation of asparagine 803 in the C-terminal activation domain by FIH-1. Thus, hypoxia causes both stabilization to proteasome degradation and transcriptional activity of HIF-1.

Structural details of the interaction between HIF-1α TAD-C and the CH1 domain of p300 or CBP have been elucidated (9, 10). Details of the interaction between p300/CBP and the CITED2 protein (also known as $p35^{srj}$), which is considered a negative regulator of Hif-1α activity (11), have also been published.

HIF-1 activation induces the transcription of a number of genes involved in the production of angiogenic factors, glucose carriers, glycolytic enzymes, survival, migration and invasion factors, which are particularly important for tumor progression.

Aberrant expression of Hif-1α was observed in more than 70% of human tumors and their metastases and was connected with an increase in vascularization and tumor progression (12-14). In clinical practice, aberrant expression of Hif-1α was associated to therapy failure and mortality increase in a number of tumoral pathologies, such as non-small cells lung carcinoma (15), oropharyngeal squamous cell cancer (16), early-stage cervical cancer (17), head-and-neck cancer (18), mutated p53 ovary cancer (19), oligodendrioglioma (20) and BCL-2 positive esophageal cancer (21).

Various approaches for inhibiting HIF-1 activity have been described in the literature. Some of them suggested the use of antisense oligonucleotides for Hif-1α or negative dominant forms of Hif-1α.

Among the pharmacological approaches, Hif-1α activity inhibitors acting through indirect mechanisms have been described, such as PI3K-mTOR inhibitors (22-23) and MEKK (24) inhibitors which act on the transduction of signals controlling Hif-1α activity; inhibitors of HSP90 chaperone protein (25); thioredoxin reductase inhibitors, which act modifying the cell redox state (26); molecules which destabilize microtubules, such as 2-methoxyestradiol (27) and epothilones (28). Recently, both constitutive and hypoxia-induced inhibition of Hif-1α levels by PX-478 (Melphalan N-oxide) in human tumors transplanted in nude mice was reported. The compound shows marked antitumoral effects. However, the mechanism of action of this compound has yet to be completely clarified (29).

Finally, chaetomine, a dithiodioxopiperazine metabolite of Chaetomium sp fungi, has recently been reported to interfere with the binding of Hif-1α to p300. The compound acts altering the CH1 domain structure of p300, thus preventing its interaction with Hif-1α. Chaetomine administration to tumor-bearing mice inhibits hypoxia-induced transcription in the tumor and tumor growth (30). It would therefore be advantageous to provide further

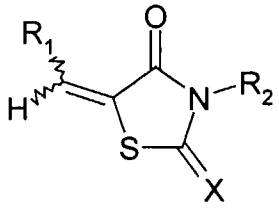
compounds capable of inhibiting the binding between HIF-1α to p300.

US 2004/002526 A1 discloses thiazolidinone compounds for use as inhibitors of phospholipase D and WO 98/53790 discloses thiazolidinones useful as antitumor agents.

Disclosure of the invention

It has now been found that some thiazolidinones inhibit the interaction between Hif-1α and p300 and prevent VEGF production in tumour cells under hypoxia conditions. The compounds are therefore useful for the control of angiogenesis and tumor growth.

Accordingly, the present invention relates to the use of compounds of general formula (**I**)



(**I**)

in which

R_1 is aryl or heteroaryl;

R_2 is alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl;

X is oxygen or sulphur

for the preparation of pharmaceutical compositions for the treatment of pathologies in which inhibition of interaction between HIF-1α and p300 is beneficial.

For the purposes of the present application:

"alkyl" is a straight or branched hydrocarbon comprising 1 to 10 carbon atoms, preferably 1 to 8 carbon atoms, optionally substituted with one or more groups independently selected from cycloalkyl, heterocycloalkyl, aryl, heteroaryl, haloalkyl, halogen, hydroxy, alkoxy, mercapto, cyano, sulfonamido, aminosulfonyl, acyl, acyloxy and substituted amino;

"aryl" is an unsaturated cyclic aromatic hydrocarbon comprising 6 to 14 carbon atoms, optionally substituted with one or more substituents independently selected from alkyl, aryl, haloalkyl, halogen, hydroxy, alkoxy, mercapto, cyano, sulfonamido, aminosulfonyl, acyl, acyloxy, nitro and substituted amino.

"heteroaryl" is a 5- to 10-membered monocyclic or condensed aromatic ring containing one or more atoms preferably selected from nitrogen, oxygen and sulphur, optionally substituted with one or more groups independently selected from alkyl, aryl, haloalkyl, halogen, hydroxy, alkoxy, mercapto, cyano, sulfonamido, aminosulfonyl, acyl, acyloxy, nitro and substituted amino;

"cycloalkyl" means cyclic alkyl groups which contain from 3 to 8 carbon atoms, optionally substituted with one or more substituents selected from alkyl, aryl, haloalkyl, halogen, hydroxy, alkoxy, mercapto, cyano, sulfonamido, aminosulfonyl, acyl, acyloxy, nitro and substituted amino;

"heterocycloalkyl" is a saturated or partially unsaturated monocyclic or condensed ring, containing one or more atoms preferably selected from nitrogen, oxygen and sulphur, and optionally substituted with one or more groups independently selected from alkyl, aryl, haloalkyl, halogen, hydroxy, alkoxy, mercapto, cyano, sulfonamido, aminosulfonyl, acyl, acyloxy, nitro and substituted amino;

"alkenyl" is a straight, cyclic or branched monovalent hydrocarbon radical, comprising at least one carbon-carbon double bond, optionally substituted with one or more groups independently selected from alkyl, acyl, cycloalkyl, heterocycloalkyl, aryl, haloalkyl, alkoxy and substituted amino;

"alkoxy" is a straight or branched C_1-C_4 alkoxy group;

"substituted amino" is a -NRR group, in which each R group is independently selected from from hydrogen, acyl, alkyl, cycloalkyl, aryl, or

the R groups can form, together with the nitrogen atom, a 5- or 6-membered heterocyclic ring;

"halogen" or the prefix "halo" indicate fluorine, chlorine, bromine and iodine;

"acyl" means a -C(O)-R" group, in which R" is preferably selected from hydrogen, hydroxy, alkyl, haloalkyl, cycloalkyl, aryl optionally substituted with one or more alkyl groups, haloalkyl, alkoxy, halogen and substituted amino groups, heteroaryl optionally substituted with one or more alkyl groups, haloalkyl, alkoxy, halo and substituted amino groups and rings optionally substituted with one or more alkyl, haloalkyl, alkoxy, halo and substituted amino groups. Preferred compounds according to the invention are those in which:

R_1 is substituted or unsubstituted furan;

R_2 is substituted or unsubstituted phenyl or benzyl, or

(2-thienyl)-methyl, morpholinyl-propyl, phenylethyl and (3,4-dimethoxyphenyl)ethyl and

X is sulphur.

"Substituted furan" preferably means a furan group substituted with a phenyl group, optionally substituted with one or more groups selected from those indicated above, preferably carboxy, methoxycarbonyl, cyano, sulfonamido and hydroxyethoxy. "Substituted phenyl or benzyl" preferably means phenyl or benzyl substituted with one or more groups selected from methyl, trifluoromethyl, methoxy, methylenedioxy.

Most preferred are the following compounds:

2-[5-(3-benzyl-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl)-furan-2-yl]benzoic acid methyl ester (**1**);

4-{5-[3-(3,4,5-trimethoxybenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid (**2**);

4-{5-[3-(3,4,5-trimethoxybenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid methyl ester (**3**);

4-{5-[3-(2-trifluoromethylbenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid methyl ester (**4**);

4-[5-(3-benzyl-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl)furan-2-yl-]benzonitrile (**5**);

4-{5-[3-(4-methylbenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]furan-2-yl-}benzonitrile (**6**);

4-[5-(3-benzyl-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl)-furan-2-yl]benzenesulfonamide (**7**);

4-{5-[3-(4-methylbenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzenesulfonamide (**8**);

4-{5-[3-(4-methylbenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid methyl ester (**9**);

4-{5-[3-(4-methylbenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid (**10**);

4-{5-[3-(3,4-methylenedioxybenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzenesulfonamide (**11**);

4-{5-[3-(3,4-methylenedioxybenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid methyl ester (**12**);

4-{5-[3-(2-thienyl)methyl-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid methyl ester (**13**);

4-{5-[3-(2-thienyl)methyl-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzonitrile (**14**);

4-{5-[3-(2-thienyl)methyl-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzenesulfonamide (**15**);

4-{5-[3-(morpholine-4yl-propyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid methyl ester (**16**);

4-{5-[3-(3,4-dimethoxyphenyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid (**17**);

4-{5-[3-[2-(3,4-dimethoxyphenyl)ethyl]-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzonitrile (**18**);

4-{5-[3-(2-phenyl)ethyl-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzonitrile (**19**);

4-{5-[3-[2-(phenyl)ethyl]-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid methyl ester (**20**);

4-{5-[3-[2-(3,4-dimethoxyphenyl)ethyl]-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid methyl ester (**21**);

2-{5-[4-[3-(2-phenyl)ethyl-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl]phenoxy}ethanol (**22**);

3-benzyl-5-[[5-(2-methoxyphenyl)furan-2-ylidenemethyl]-4-oxo-2-thioxo-thiazolidine (**23**);

2-[5-(3-benzyl-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl)-furan-2-yl]benzoic acid (**24**).

Among these compounds, the most preferred is 2-{5-[3-(4-methylbenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid methyl ester.

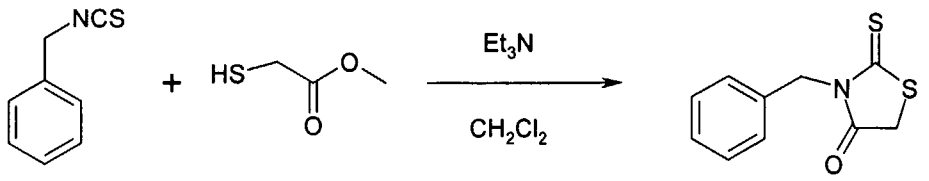
The above-mentioned compounds, except for compounds **1** and **16**, are a further object of the invention.

The compounds of the invention can be synthesised according to known methods, for example those described in US 2004/0002526 A1, which comprise the condensation between a 2-thioxo-thiazolidine-4-one, suitably substituted at the 3- position and a suitably substituted furanaldehyde, or according to the methods described in *Tetrahedron Lett.*, **44**, 4257 (2003), *Bioorg. Med. Chem. Lett.*, **12**, 2681 (2002), *J. Med. Chem.*, **41**, 2390 (1998).

The following schemes illustrate in particular the synthesis of 4-{5-[3-

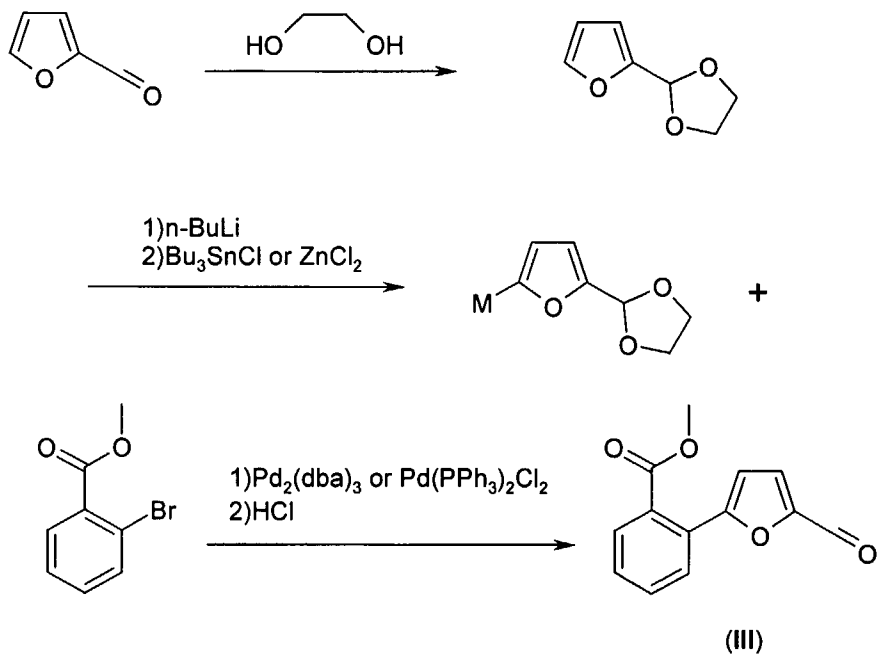
(4-methylbenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid methyl ester.

Scheme 1



(II)

Scheme 2

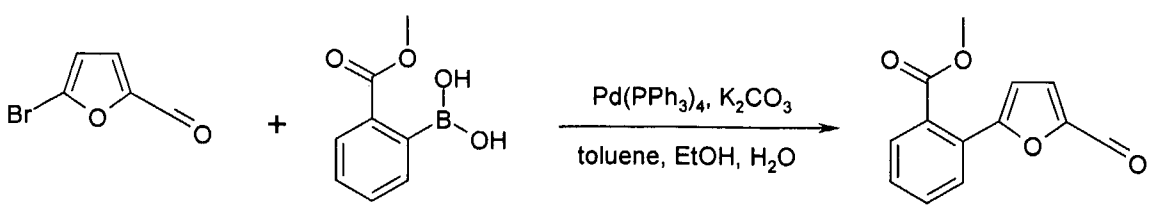


(III)

Wherein M is Li, Zn or Bu_3Sn and DBA is dibenzylidenacetone

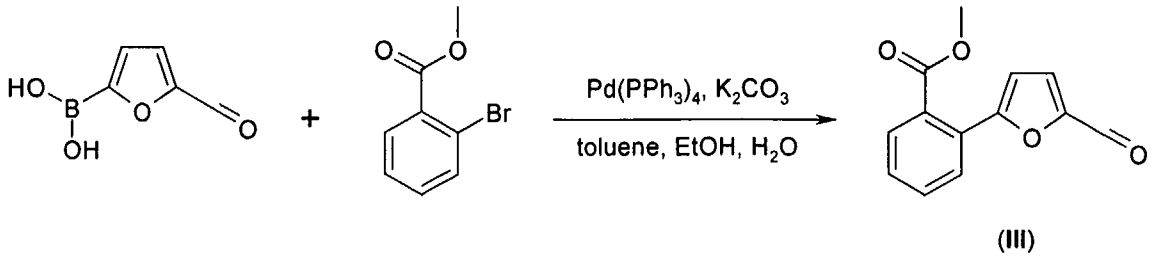
Alternatively, compound (**III**) can be synthesized according to the following schemes:

Scheme 3



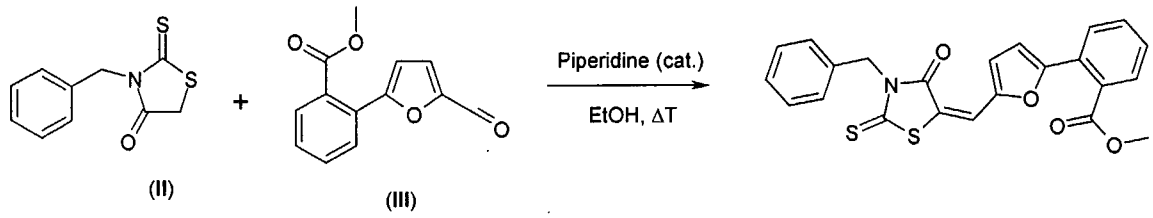
(III)

Scheme 4



(III)

Scheme 5



(II) (III)

All the reagents reported in Schemes 1-5 can be prepared with known methods and are commercially available.

The compounds of the invention inhibit the interaction between HIF-1α and p300 with IC_{50} ranging from 0.5 to 25 μM and the production of VEGF in tumour cells under hypoxia conditions with IC_{50} ranging from 0.10 to 100 μM.

The compounds can therefore be used for the preparation of pharmaceutical compositions for the treatment of pathologies in which inhibition of the interaction between HIF-1α and p300 is beneficial. The compositions can be solid, semi-solid or liquid, preferably in the form of solutions, suspensions, powders, granules, tablets, capsules, syrups, suppositories, aerosol or controlled-release systems. The compositions can be administered through different routes, in particular through the oral, transdermal, subcutaneous, intravenous, intramuscular, rectal and intranasal route. The amount of active ingredient per dosage unit depends on the form and on the administration route, the compound, the disease to treat, but in general ranges from 0.1 to 1000 mg, preferably from 1 to 600 mg. The principles and methods for the preparation of pharmaceutical compositions are known to those

skilled in the art and are described, for example, in Remington's Pharmaceutical Science, Mack Publishing Company, Easton (PA).

The compounds of the invention, suitably formulated, can be used for the treatment of a number of pathologies in which angiogenesis is involved as pathogenesis factor, for example different forms of solid tumors, diabetic retinopathy, rheumatoid arthritis, psoriasis, emangioma, sclerodermia, neovascular glaucoma. Solid tumors particularly sensitive to the compounds of formula (**I**) comprise lung carcinoma, mammary carcinoma, prostate carcinoma, neuroblastoma, glioblastoma multiforme, melanoma, central nervous system cancer, squamous cell oropharyngeal cancer, cervical cancer, ovary, esophageal, kidney, colon, head-and-neck cancer and oligodendrioglioma.

Therefore, the invention relates also to a method for inhibiting VEGF production in a cell, which method comprises contacting said cell with an effective amount of a compound of formula (**I**).

The invention will be illustrated in greater detail in the following experimental section.

EXPERIMENTAL SECTION

Synthesis of the compounds

General procedure A

Example - 4-(5-Formyl-furan-2-yl)-benzoic acid methyl ester

A solution of 5-bromofuraldehyde (2.43 g, 13.9 mmoles), 4-(methoxycarbonyl)phenylboronic acid (2.50 g, 13.9 mmoles), tris(dibenzylideneacetone)palladium (0) (192 mg, 0.2 mmoles) and potassium fluoride (2.42 g, 41.7 mmoles) in 1,4-dioxane (100 ml) was added with a solution of tri-*tert*-butylphosphine in hexane (10% by weight, 101 mg, 0.5 mmoles). After heating at 65-70°C for 4 hours, the mixture was cooled to room temperature and treated with methylene chloride (150 ml). After stirring for 10 minutes, the mixture was filtered through Celite and the filtrate was

concentrated under reduced pressure. The residue was purified by flash silica gel chromatography eluting with an ethyl acetate-hexane mixture (1:1) to give 4-(5-formyl-furan-2-yl)-benzoic acid methyl ester (2.6 g, 81% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.70 (s, 1H), 8.10 (d, 2H), 7.90 (d, 2H), 7.35 (d, 1H), 6.95 (d, 1H), 3.98 (s, 3H).

General procedure B

Example - 3-(3-Morpholino-4-yl-propyl)-2-thioxo-thiazolidine-4-one

A suspension of bis(carboxymethyl)trithiocarbonate (498 mg, 2.2 mmoles), potassium carbonate (138 mg, 1.0 mmoles) and 4-(3-aminopropyl)morpholine (288 mg, 2.0 mmoles) in water (20 ml) was refluxed for 12 hours. After addition of water (10 ml), the mixture was cooled to room temperature and extracted with 10% methanol-methylene chloride (3x50 ml). The combined extracts were dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography eluting with 10% methanol-methylene chloride to give 3-(3-morpholino-4-yl-propyl)-2-thioxo-thiazolidine-4-one (252 mg, 48% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.10 (dd, 2H), 3.95 (s, 2H), 3.55-3.70 (m, 4H), 2.30-2.50 (m, 6H), 1.70-1.90 (m, 2H).

General procedure C

Example - 4{5-[3-(3-Morpholino-4-yl-propyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}-benzoic acid methyl ester

A solution of 4-(5-formyl-furan-2-yl)-benzoic acid methyl ester (59 mg, 0.27 mmoles) and 3-(3-morpholino-4-yl-propyl)-2-thioxo-thiazolidine-4-one (72 mg, 0.27 mmoles) in ethanol (10 ml) was added with piperidine (1 drop). After heating under reflux for 6 hours, the mixture was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography eluting with 10% methanol-methylene chloride to give the title compound (32 mg, 25%yield).

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.15 (d, 2H), 7.75 (d, 2H), 7.50 (s, 1H), 6.95-7.05 (m, 2H), 4.20 (t, 2H), 3.95 (s, 3H), 3.90 (t, 2H), 3.58-3.75 (m, 2H), 2.30-2.60 (m, 6H), 1.80-2.00 (m, 2H).

4-(5-Formyl-furan-2-yl)benzenesulfonyl amide

A mixture 4-(tributylstannyl)benzenesulfonyl amide (2.77 g, 6.21 mmoles) and bis(triphenylphosphine) palladium (II) chloride (436 mg, 0.62 mmoles) in ethanol (65 ml) was refluxed for 18 hours under argon atmosphere. After cooling to room temperature, ethyl ether (200 ml) was added and the mixture was vacuum filtered through Celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash silica gel chromatography eluting with 20% ethyl acetate-hexane to give the title compound (450 mg, 29% yield).

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.70 (s, 1H), 7.90-8.10 (m, 4H), 7.40 (d, 1H), 7.00 (d, 1H), 4.90 (br s, 2H).

3-Benzyl-2-thioxo-thiazolidine-4-one

Following general procedure B, bis(carboxymethyl)-trithiocarbonate (2.50 g, 11.0 mmoles), was reacted with benzylamine (1.07 g, 10.0 mmoles). The title compound was obtained after flash silica gel chromatography eluting with 70% methylene chloride-hexane, (960 mg, 43% yield).

4-[5-(3-Benzyl-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl)-furan-2-yl]-benzene sulfonamide

A solution of 4-(5-formyl-furan-2-yl)benzenesulfonyl amide (50 mg, 0.2 mmoles) and 3-benzyl-2-thioxo-thiazolidine-4-one (44.6 mg. 0.2 mmoles) in ethanol (5 ml) was added with piperidine (1 drop) and the mixture was refluxed for 30 minutes. After cooling to 0-5°C, the solid was filtered, washed with cold ethanol (2x5 ml) and dried under vacuum to give the title compound (73 mg, 80% yield).

^{1}H NMR (300 MHz, DMSO-d_6): d 7.95-8.25 (m, 4H), 7.75 (s, 1H),

7.20-7.55 (m, 10H), 5.25 (s, 2H).

4-(5-Formyl-furan-2-yl)-benzonitrile

Following general procedure A, 5-bromo furaldehyde (3.50 g, 0.2 moles) was reacted with 4-cyanoboronic acid (2.94 g, 0.2 moles). After usual work-up of the mixture and chromatographic purification on silica gel column eluting with 50% ethyl acetate-hexane the title compound was obtained (2.60 g, 66% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.70 (s, 1H), 8.00 (d, 2H), 7.80 (d, 2H), 7.40 (d, 1H), 7.00 (d, 1H).

2-Thioxo-3-(3,4-dimethoxy-phenylethyl)-thiazolidine-4-one

Following general procedure B, bis(carboxymethyl) thiocarbonate (905 mg, 4.0 mmoles), was reacted with 3,4-dimethoxy-benzylamine (363 mg, 2.0 mmoles) and, after flash silica gel chromatography eluting with 70% methylene chloride-hexane, the title compound was obtained (420 mg, 71% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.70-6.90 (m, 3H), 4.20 (t, 2H), 4.00 (s, 2H), 3.90 (s, 3H), 3.85 (s, 3H), 2.95 (t, 2H).

4-(5-{3-[2-(3,4-Dimethoxy-phenyl)-ethyl]-oxo-2-thioxo-thiazolidine-5-ylidenemethyl}-furan-2-yl)-benzonitrile

Following general procedure C, 4-(5-formyl-furan-2-yl)-benzonitrile (39.4 mg, 0.2 mmoles) was reacted with 2-thioxo-3-(3,4-dimethoxy-benzyl)-thiazolidine-4-one (59.4 mg, 0.2 mmoles) to give the title compound (58 mg, 61% yield).

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.95-8.25 (m, 4H), 7.75 (s, 1H), 7.60 (d, 1H), 7.40 (d, 1H), 6.7-6.90 (m, 3H), 4.25 (t, 2H), 3.75 (s, 3H), 3.70 (s, 3H), 2.95 (s, 2H).

3-(2-Phenylethyl)-2-thioxo-thiazolidine-4-one

Following general procedure B, bis(carboxymethyl)trithiocarbonate

(905 mg, 4.0 mmoles), was reacted with 2-phenylethylamine (242.4 mg, 2.0 mmoles). The title compound was obtained after flash silica gel chromatography eluting with 70% methylene chloride-hexane, (246 mg, 52% yield).

^{1}HMR (300 MHz, $CDCl_3$): δ 7.15-7.40 (m, 5H), 4.20 (t, 2H), 3.95 (s, 2H), 3.00 (t, 2H).

4-[5-(4-Oxo-3-(2-phenylethyl)-2-thioxo-thiazolidine-5-ylidenemethyl)-furan-2-yl]-benzonitrile

Following general procedure C, 4-(5-formyl-furan-2-yl)-benzonitrile (39.4 mg, 0.2 mmoles) was reacted with 3-(2-phenylethyl)-2-thioxo-thiazolidine-4-one (47.4 mg, 0.2 mmoles) to give the title compound (64 mg, 76% yield).

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.95-8.25 (m, 4H), 7.75 (s, 1H), 7.55 (d, 1H), 7.40 (d, 1H), 7.10-7.35 (m, 5H), 4.24 (t, 2H), 3.00 (t, 2H).

3-Thiophenemethyl-2-thioxo-thiazolidine-4-one

Following general procedure B, bis(carboxymethyl)trithiocarbonate (905 mg, 4.0 mmoles), was reacted with 2-(aminomethyl)thiophene (226.4 mg, 2.0 mmoles) to give the title compound (320 mg, 70% yield). ^{1}HNMR ($CDCl_3$): δ 7.15-7.35 (m, 2H), 6.85-7.05 (m, 1H), 5.35 (s, 2H), 4.00 (s, 2H).

4-[5-(4-Oxo-3-thiophene-2-yl-methyl-2-thioxo-thiazolidine-5-ylidenemethyl)-furan-2-yl]-benzoic acid methyl ester

Following general procedure C, 4-(5-formyl-furan-2-yl)-benzoic acid methyl ester (46.0 mg, 0.2 mmoles) was reacted with 3-thiophenemethyl-2-thioxo-thiazolidine-4-one (45.8 mg, 0.2 mmoles) to give the title compound (38.7 mg, 44% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, 2H), 7.85 (d, 2H), 7.50 (s, 1H), 7.20-7.30 (m, 2H), 6.90-7.05 (m, 3H), 5.50 (s, 2H), 3.98 (s, 3H).

4-[5-(4-Oxo-3-(2-phenylethyl)-2-thioxo-thiazolidine-5-ylidenemethyl)-furan-2-yl]-benzoic acid methyl ester

Following general procedure C, 4-(5-formyl-furan-2-yl)-benzoic acid methyl ester (46.0 mg, 0.2 mmoles) was reacted with 3-(2-phenylethyl)-2-thioxo-thiazolidine-4-one (47.4 mg, 0.2 mmoles) to give the title compound (39.2 mg, 44% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, 2H), 7.65 (d, 2H), 6.70-7.15 (m, 8H), 4.15 (t, 2H), 3.88 (s, 3H), 2.85 (t, 2H).

4-(5-{3-[2-(3,4-Dimethoxyphenyl)-ethyl]-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl}-furan-2-yl)-benzoic acid methyl ester

Following general procedure C, 4-(5-formyl-furan-2-yl)-benzoic acid methyl ester (46.0 mg, 0.2 mmoles) was reacted with 2-thioxo-3-[2-(3,4-dimethoxy-phenylethyl)]-thiazolidine-4-one (59.4 mg, 0.2 mmoles (59.4 mg, 0.20 mmoles) to give the title compound (46.7 mg, 46% yield)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (d, 2H), 7.85 (d, 2H), 7.50 (s, 1H), 6.85-7.05 (m, 5H), 4.45 (t, 2H), 4.00 (s, 3H), 3.88 (s, 3H), 3.85(s, 3H), 2.95 (t, 2H).

3-(4-Methyl-benzyl)-2-thioxo-thiazolidine-4-one

Following general procedure B, bis(carboxymethyl) trithiocarbonate (905 mg, 4.0 mmoles), was reacted with 4-methyl-benzyl amine (242 mg, 2.0 mmoles) to give the title compound (250 mg, 53% yield).

^{1}HNMR ($CDCl_3$): δ 7.40 (d, 2H), 7.15 (d, 2H), 5.20 (s, 2H), 4.00 (s, 2H), 2.35 (s, 3H).

4-{5-[3-(4-Methyl-benzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}-benzoic acid methyl ester

Following general procedure C, 4-(5-formyl-furan-2-yl)-benzoic acid methyl ester (46.0 mg, 0.2 mmoles) was reacted with 3-(4-methyl-benzyl)-2-thioxo-thiazolidine-4-one (47.4 mg, 0.2 mmoles) to give the title compound

(46.7 mg, 46% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (d, 2H), 7.85 (d, 2H), 7.50 (s, 1H), 7.40 (d, 1H), 7.15 (d, 1H), 6.90-7.05 (m, 4H), 5.30 (s, 2H), 3.95 (s, 2H), 2.30 (s, 3H).

Primary biochemical assay for the inhibition of Biot-HIF-1α$^{786-826}$/GST-p300$^{323/423}$

The compounds were evaluated for their ability to inhibit the interaction between Hif-1α and p300 using a fluorescence assay (DELFIA^{TM}). The procedure described by Freedman SJ at al., Nature Structural Biology 2003, 10 (7), 504-512 was suitably modified.

The human biotinylated Hif-1α fragment corresponding to C-terminal 786-826 amino acids (Biotinylated Hif-1α$^{786-826}$) was obtained from AnaSpec Inc (San Josè, California, USA) and used without further purifications.

A construct expressing the GST-p300$^{323-423}$ fragment was transformed in the BL21 strain (DE3) of E. coli. Said construct was obtained by cloning in the expression vector pGEX- 4T-1 (Amersham No. 27-45-80-01) the DNA sequence which encodes for the p300 region ranging from amino acids 323 to 423; the DNA sequence was obtained by PCR (Polymerase Chain Reaction). Protein expression was induced with 1 mM isopropyl-1-thio-ß-D-galactopyranoside (IPTG). The bacteria were lysed by sonication in the presence of a suitable buffer (50 mM Tris.HCl pH 8.00, 100 mM NaCl, 0.1 mM $ZnSO_4$, 1 mM DTT, 0.1 mg/ml lysozyme and a tablet of Complete EDTA-free Protease Inhibitor Cocktail Tablets (Roche, catalogue number 1 873 580)) and the GST fusion protein present in the soluble fraction was purified on a Glutathione-Sepharose 4B resin (Amersham Biosciences; no. 27-4574-01). The protein final concentration was determined according to Bradford with the Biorad assay (Bradford M., Anal. Biochem.,72, 248, (1976)) and sample purity was evaluated by SDS-PAGE. The samples were

stored at -80°C in 50% glycerol.

The assay was carried out using NUNC Maxisorp 96-well plates as follows.

C96 NUNC Maxisorp plates (from Nunc, product No. 446612) were incubated overnight with streptavidin (Sigma; product No. S 4762) at a final concentration of 1 µg/ml in PBS buffer (Phosphate Buffered Saline 10 mM sodium phosphate, 150 mM sodium chloride pH 7.4). Each well was subsequently washed with 3x300 µl of TBST buffer (50 mM Tris-HCl pH 8.0, 150 mM NaCl, 0.05% (v/v) Tween 20). Each well was then added with 100 µl of a 10 nM solution of biotinylated Hif-1$\alpha^{786-826}$ in TBSB (50 mM Tris-HCl pH 8.0, 150 mM NaCl, 5% (w/v) BSA (Sigma, product No. A 2153)) and incubated for 1h at 25°C. In the last row of each plate, TBSB buffer only was added. Each well was subsequently washed with 3 x 300 µl of TBST buffer. The thus prepared plate represented the assay plate.

Separately, a plate (daughter plate) containing in each well 10 µl of each test compound dissolved in DMSO to a concentration of 10 µM was prepared. This plate was added with 100 µl of a 111 pM solution of GST-p300$^{323-423}$ diluted in the incubation buffer (TBSB added with 0.1% (v/v) Tween 20, 0.5 mM DTT, 10 µM $ZnCl_2$) and the whole was mixed. 100 µl of the mixture contained in the daughter plate was immediately transferred to the assay plate.

Each daughter plate was prepared with 80 different compounds at a 10 µM concentration, safe for the last two well rows, wherein each well was added with 10 µl of DMSO. These two rows represented the positive (row 11, + Hif-1) and negative (row 12, - Hif-1) controls.

After incubation for 1 h at 25°C, each well was washed with 3 x 300 µl of TBST buffer (50 mM Tris-HCl pH 8.0, 150 mM NaCl, 0.05% (v/v) Tween 20). Each well was then added with 60.8 ng of an europium-labelled anti-GST

antibody (DELFIA Eu-N1 labeled; Perkin Elmer; product no. A D 0251) dissolved in 100 µl of TBST buffer containing 10 µM $ZnCl_2$. After incubation for 1 h at room temperature, each well was washed with 3 x 300 µl of TBST buffer, then 100 µl of signal amplification solution (Enhancement Solution, Perkin Elmer product No. 1244-105) was added.

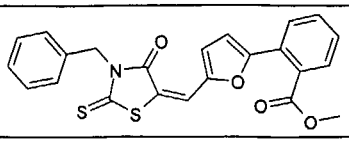
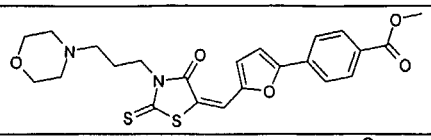
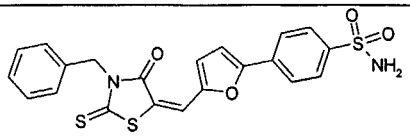
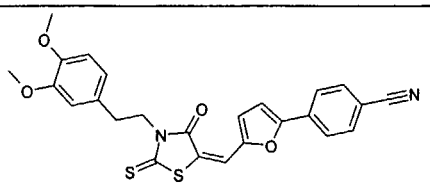
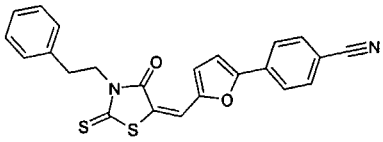
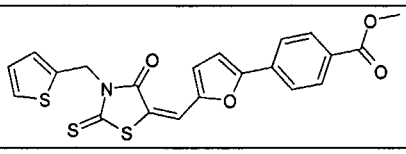
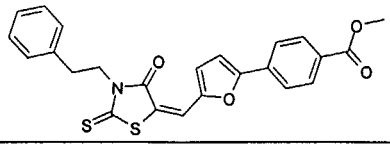
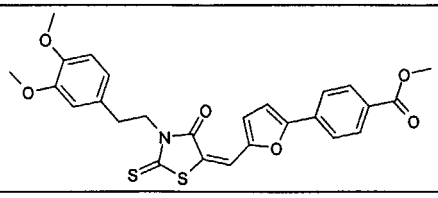
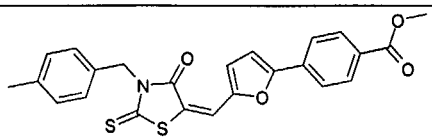
The plates were then read using a FUSION alpha-FP-HT reader (Perkin Elmer) in fluorescence mode for time resolution.

The activity of the compounds was calculated as follows. The fluorescence mean value of negative controls in row 12 of the plate test was subtracted from the fluorescence value of all the other wells. The resulting fluorescence value for each well was then divided by the fluorescence mean value of the positive controls in row 11 (which represent the maximum signal value, 100%) and expressed as percentage value. The inhibition value was expressed as the difference to 100 of the signal percentage calculated for each well.

Using daughter plates in which the compounds were present at 10 different concentrations ranging from 90 µM to 0.178 µM in each row, a dose-response curve could be calculated from which the IC_{50} value (concentration of the compound necessary to inhibit the signal by 50%) was obtained. Rows 11 and 12 containing the vehicle only were the controls.

The IC_{50} values obtained for some compounds of the present invention are reported in Table 1. The data are the mean of two independent experiments.

Table 1

Structure	Compound	HIF/p300 (IC_{50}, μM)
	1	8.6
	16	11.08
	7	4.9
	18	29.9
	19	1.4
	13	14.7
	20	4.2
	21	7.4
	9	5.9

Inhibition of VEGF production

The compounds having inhibitory activity in the Hif-1α/p300 assay described above were evaluated using a cellular test on genetically modified human hepatocarcinoma Hep3B cells (Hep3B-VEGF*Luciferase*) in order to stably express a vector in which the Open Reading Frame of *firefly Luciferase*

is under the control of the rat VEGF gene promoter.

Hif-1 induction by deferoxamine (which causes hypoxia) induces luciferase transcription through activation of the VEGF promoter, which in turn increases luciferase activity, which can be measured with a commercially available kit. The compounds interfering with the Hif-1α/p300 complex inhibit Hif-dependent luciferase activation, resulting in a reduction of luciferase activity. Therefore, this assay allows to evaluate the activity of the compounds towards the VEGF promoter, which is essential to VEGF production and subsequent tumor angiogenesis.

The Hep-3B-VEGF *Luciferase* cell line was obtained according to the following procedure.

Human hepatocarcinoma cells Hep-3B (ATCC reference No. HB-8064) were seeded onto 6-well plates at a concentration of 2.5 x 10^5 cells/well in 2 ml DMEM/10% FCS and the following day were transfected using Fugene 6 (Roche Biochemicals®). In each well, the transfection mixtures contained 6 µl of the transfection reagent Fugene 6, 1 µg of the pxp2-VEGF-luciferase reporter plasmid (VEGF rat promoter, NCBI GenBank No. of accession U22373, Levy et al., J. Biol. Chem. 270 (22), 13333-13340, 1995), and 10 ng of pcDNA3.1(+)plasmid (INVITROGEN) which makes the cells resistant to neomycin. Transfection was carried out according to the manufacturer's instructions.

A suitable cell population (phenotypically resistant to neomycin) was selected by means of a cloning approach based on the "dilution limit" procedure (Sambrook J., Fritsch E.F. and Maniatis T. (1989) Molecular Cloning, A Laboratory Manual; Cold Spring Harbor Laboratories). The subsequent assays for Luciferase expression/activity (Luciferase assay) and for the quantification of secreted VEGF in the supernatant (ELISA secreted VEGF test) were carried out with the stably transfected selected cells.

The following experimental protocol was used:

Day 1. Hep-3B –VEGF Luciferase cells were seeded onto "blank" 96-wells plates (Greiner) at a density of 1 x 10^4 cells/well/125 µl of medium, then left to adhere overnight in thermostat (37°C/5% CO_2).

Day 2. 75 µl of "3.2x working solutions" of compound (previously prepared in culture medium so that the DMSO concentration is 1.6% v/v) were added to the cells (partial volume/well = 200 µl, partial concentration of compound = 1.2 x, partial concentration of DMSO = 0.6%). After 1 hour incubation in thermostat, hypoxia was induced chemically by addition of 40 µl/well of a 6x (600 µM) stock solution of deferoxamine (final volume/well = 240 µl, final concentration of compound = 1x, final concentration of DMSO = 0.5%, final concentration of deferoxamine = 1x ≈ 100 µM). The plates were then thermostated for further 18-20 hours.

Day 3. The Luciferase assay and the secreted VEGF ELISA test were carried out as follows.

Secreted VEGF ELISA test

Quantification of secreted VEGF was performed using the "DuoSet Elisa Development System human VEGF" kit (R&D Systems). 100 µl/well of the supernatant from the "blank" 96-well plates with the cells of the Hep3B/VEGF Luciferase clone were transferred into transparent 96-well plates (Maxisorp) and assayed according to the indications of the kit manufacturer.

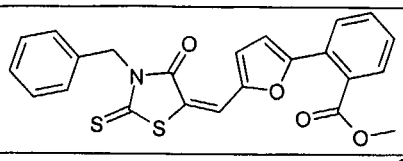
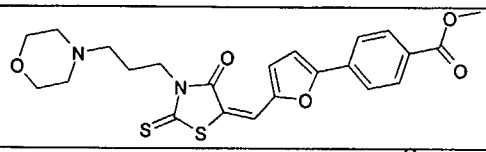
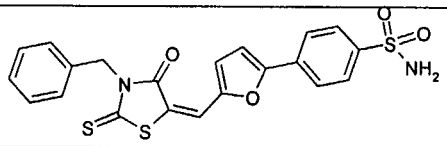
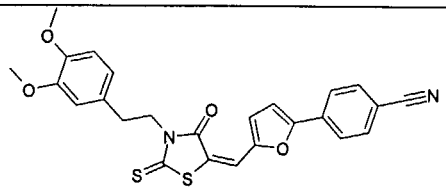
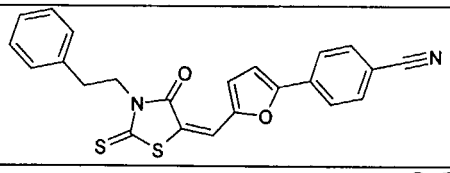
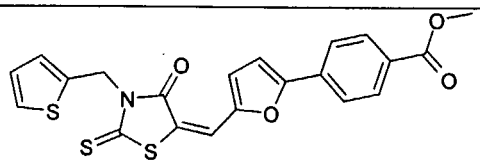
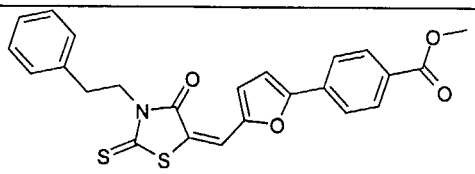
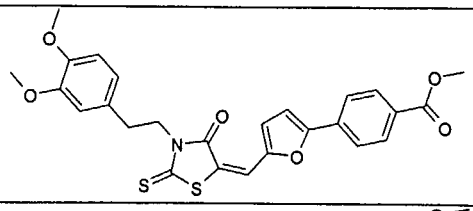
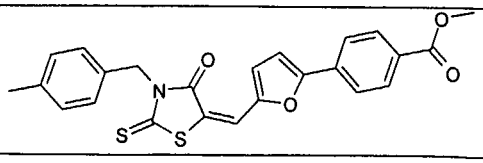
Luciferase assay

Quantification of the expression of the Luciferase reporter gene was performed by means of the Bright Glo Reagent (Promega). After removing the supernatant and washing once with PBS, 40 µl/well of Bright Glo Reagent were added to blank 96-well plates with Hep3B/VEGF-Luciferase cells. The expression levels of the reporter gene were determined by reading the plates with a luminometer.

IC_{50} values (concentration of the compound that causes 50% inhibition

of the luciferase signal or 50% reduction of secreted VEGF) for some compounds of the invention are reported in table 2.

Table 2

Compound	Structure	IC_{50} (μM)	
		Luciferase assay	ELISA test (secreted VEGF)
1		6.66	0.37
16		2.07	0.70
7		3.16	0.87
18		3.17	0.49
19		7.29	0.33
13		9.64	0.58
20		10.47	0.46
21		4.86	0.24
9		> 5.0	0.18

5

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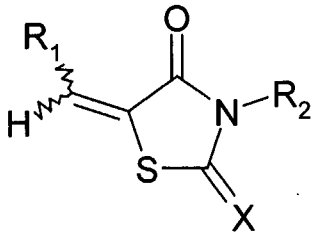
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CLAIMS

1. Use of compounds of general formula (**I**)



(I)

in which

R_1 is aryl or heteroaryl;

R_2 is alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl;

X is oxygen or sulphur

and in which

"alkyl" is a straight or branched hydrocarbon containing 1 to 10 carbon atoms, preferably 1 to 8 carbon atoms, optionally substituted with one or more groups independently selected from cycloalkyl, heterocycloalkyl, aryl, heteroaryl, haloalkyl, halogen, hydroxy, alkoxy, mercapto, cyano, sulfonamido, aminosulfonyl, acyl, acyloxy and substituted amino;

"aryl" is an unsaturated cyclic aromatic hydrocarbon from 6 to 14 carbon atoms, optionally substituted with one or more substituents independently selected from alkyl, aryl, haloalkyl, halogen, hydroxy, alkoxy, mercapto, cyano, sulfonamido, aminosulfonyl, acyl, acyloxy, nitro, and substituted amino;

"heteroaryl" is a monocyclic or fused 5- to 10-membered aromatic ring containing one or more atoms preferably selected from nitrogen, oxygen and sulphur, optionally substituted with one or more groups independently selected from alkyl, aryl, haloalkyl, halogen, hydroxy,

alkoxy, mercapto, cyano, sulfonamido, aminosulfonyl, acyl, acyloxy, nitro and substituted amino;

"cycloalkyl" is a cyclic alkyl group containing 3 to 8 carbon atoms, optionally substituted with one or more substituents selected from alkyl, aryl, haloalkyl, halogen, hydroxy, alkoxy, mercapto, cyano, sulfonamido, aminosulfonyl, acyl, acyloxy, nitro and substituted amino;

"heterocycloalkyl" is a saturated or partially unsaturated monocyclic or condensed ring, containing one or more atoms preferably selected from nitrogen, oxygen and sulphur, and optionally substituted with one or more groups independently selected from alkyl, aryl, haloalkyl, halogen, hydroxy, alkoxy, mercapto, cyano, sulfonamido, aminosulfonyl, acyl, acyloxy, nitro and substituted amino;

"alkenyl" is a straight, cyclic or branched monovalent hydrocarbon radical, comprising at least one carbon-carbon double bond, optionally substituted with one or more groups independently selected from alkyl, acyl, cycloalkyl, heterocycloalkyl, aryl, haloalkyl, alkoxy and substituted amino;

"alkoxy" is a straight or branched C_1-C_4 alkoxy group;

" substituted amino " is a -NRR group, in which each R group is independently selected from hydrogen, acyl, alkyl, cycloalkyl, aryl, or the R groups can form, together with the nitrogen atom, a 5- or 6-membered heterocyclic ring;

"halogen" or the "halo" prefix means fluorine, chlorine, bromine and iodine;

"acyl" is a -C(O)-R" group, in which R" is preferably selected from hydrogen, hydroxy, alkyl, haloalkyl, cycloalkyl, aryl optionally substituted with one or more alkyl groups, haloalkyl, alkoxy, halogen and substituted amino groups, heteroaryl optionally substituted with one

or more alkyl groups, haloalkyl, alkoxy, halo and substituted amino groups and rings optionally substituted with one or more alkyl, haloalkyl, alkoxy, halo and substituted amino groups

for the preparation of pharmaceutical compositions for the treatment of pathologies in which inhibition of the interaction between HIF-1α and p300 is beneficial.

2. Use as claimed in claim 1 wherein in the compound of formula (**I**)

R_1 is furan, optionally substituted with a phenyl or substituted phenyl group with one or more groups selected from carboxy, methoxycarbonyl, cyano, sulfonamido and hydroxyethoxy;

R_2 is phenyl or benzyl, optionally substituted with one or more groups selected from methyl, trifluoromethyl, methoxy, methylenedioxy, or (2-thienyl)-methyl, morpholinyl-propyl, phenylethyl and (3,4-dimethoxyphenyl)ethyl

and X is sulphur.

3. Use as claimed in claim 2 in which the compound of formula (**I**) is selected from

2-[5-(3-benzyl-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl)-furan-2-yl]benzoic acid methyl ester (**1**);

4-{5-[3-(3,4,5-trimethoxybenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid (**2**);

4-{5-[3-(3,4,5-trimethoxybenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid methyl ester (**3**);

4-{5-[3-(2-trifluoromethylbenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid methyl ester (**4**);

4-[5-(3-benzyl-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl)furan-2-yl-]benzonitrile (**5**);

4-{5-[3-(4-methylbenzyl)-4-oxo-2-thioxo-thiazolidine-5-

ylidenemethyl]furan-2-yl-}benzonitrile (**6**);

4-[5-(3-benzyl-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl)-furan-2-yl]benzenesulfonamide (**7**);

4-{5-[3-(4-methylbenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzenesulfonamide (**8**);

4-{5-[3-(4-methylbenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid methyl ester (**9**);

4-{5-[3-(4-methylbenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid (**10**);

4-{5-[3-(3,4-methylenedioxybenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzenesulfonamide (**11**);

4-{5-[3-(3,4-methylenedioxybenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid methyl ester (**12**);

4-{5-[3-(2-thienyl)methyl-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid methyl ester (**13**);

4-{5-[3-(2-thienyl)methyl-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzonitrile (**14**);

4-{5-[3-(2-thienyl)methyl-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzenesulfonamide (**15**);

4-{5-[3-(morpholine-4yl-propyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid methyl ester (**16**);

4-{5-[3-(3,4-dimethoxyphenyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid (**17**);

4-{5-[3-[2-(3,4-dimethoxyphenyl)ethyl]-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzonitrile (**18**);

4-{5-[3-(2-phenyl)ethyl-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzonitrile (**19**);

4-{5-[3-[2-(phenyl)ethyl]-4-oxo-2-thioxo-thiazolidine-5-

ylidenemethyl]-furan-2-yl}benzoic acid (**20**);

4-{5-[3-[2-(3,4-dimethoxyphenyl)ethyl]-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid methyl ester (**21**);

2-{5-[4-[3-(2-phenyl)ethyl-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl]phenoxy}ethanol (**22**);

3-benzyl-5-[[5-(2-methoxyphenyl)furan-2-ylidenemethyl]-4-oxo-2-thioxo-thiazolidine (**23**);

2-[5-(3-benzyl-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl)-furan-2-yl]benzoic acid (**24**).

4. Use according to any one of claims 1 to 3 for the preparation of antiangiogenic medicaments.

5. Use according to any one of claims 1 to 4 for the preparation of medicaments for the therapy of solid tumors.

6. Use as claimed in claim 5 in which the tumors are selected from lung carcinoma, mammary carcinoma, prostate carcinoma, neuroblastoma, glioblastoma multiforme, melanoma, central nervous system cancer, squamous cell oropharyngeal cancer, cervical cancer, ovary, esophageal, kidney, colon, head-and-neck cancer and oligodendrioglioma.

7. A method for inhibiting VEGF production in a cell which comprises contacting said cell with an effective amount of compound of formula (**I**).

8. A compound selected from:

4-{5-[3-(3,4,5-trimethoxybenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid (**2**);

4-{5-[3-(3,4,5-trimethoxybenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid methyl ester (**3**);

4-{5-[3-(2-trifluoromethylbenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid methyl ester (**4**);

4-[5-(3-benzyl-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl)furan-2-yl-]

benzonitrile (**5**);

4-{5-[3-(4-methylbenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]furan-2-yl-} benzonitrile (**6**);

4-[5-(3-benzyl-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl)-furan-2-yl]benzenesulfonamide (**7**);

4-{5-[3-(4-methylbenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzenesulfonamide (**8**);

4-{5-[3-(4-methylbenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid methyl ester (**9**);

4-{5-[3-(4-methylbenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid (**10**);

4-{5-[3-(3,4-methylenedioxybenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzenesulfonamide (**11**);

4-{5-[3-(3,4-methylenedioxybenzyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid methyl ester (**12**);

4-{5-[3-(2-thienyl)methyl-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid methyl ester (**13**);

4-{5-[3-(2-thienyl)methyl-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzonitrile (**14**);

4-{5-[3-(2-thienyl)methyl-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzenesulfonamide (**15**);

4-{5-[3-(3,4-dimethoxyphenyl)-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid (**17**);

4-{5-[3-[2-(3,4-dimethoxyphenyl)ethyl]-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzonitrile (**18**);

4-{5-[3-(2-phenyl)ethyl-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzonitrile (**19**);

4-{5-[3-[2-(phenyl)ethyl]-4-oxo-2-thioxo-thiazolidine-5-

ylidenemethyl]-furan-2-yl}benzoic acid (**20**);

4-{5-[3-[2-(3,4-dimethoxyphenyl)ethyl]-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl}benzoic acid methyl ester (**21**);

2-{5-[4-[3-(2-phenyl)ethyl-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl]-furan-2-yl]phenoxy}ethanol (**22**);

3-benzyl-5-[[5-(2-methoxyphenyl)furan-2-ylidenemethyl]-4-oxo-2-thioxo-thiazolidine (**23**);

2-[5-(3-benzyl-4-oxo-2-thioxo-thiazolidine-5-ylidenemethyl)-furan-2-yl]benzoic acid (**24**).