BENZYLHYDROXYDE DERIVATIVES, PREPARATION THEREOF AND THERAPEUTIC USE THEREOF

The present invention relates to benzylhydroxyde derivatives, to their preparation and to their therapeutic use.

The compounds according to the present invention are direct safe inhibitors of the complex 1 of the mitochondrial respiratory chain and indirect inhibitors of Hypoxia Inducible Factor (HIF-1) stabilization under hypoxic stress.

Mitochondrial complex I, also called NADH: Ubiquinone oxidoreductase, is a key component of the respiratory chain. Mitochondrial complex 1 contributes to the formation of membrane potential coupled to ATP synthesis at the origin of the energy supporting cellular processes. Composed of 45 subunits coded by both the genomic and mitochondrial DNAs, the complex 1 is present in the inner mitochondrial membrane of all the mammalian cells and is the main consumer of the NADH generated in the Krebs cycle and the regulator of NADH/NAD+ homeostasis in the cell.

Due to its function, the complex 1 is responsible for the indirect modulation of many different cellular metabolites (AMP/ATP and NADH/NAD+ ratios, alpha ketoglutarate, succinate and oxygen for examples) involved in the pathways which support cellular proliferation, growth and adaptation under specific stress.

Under oxidative stress, the mitochondrial complex 1 participates as the major source of the radical oxygen species (ROS) production in the mitochondrial respiratory chain to the induction of apoptosis (Li et al, 2003).

Through the indirect modulation of alpha ketoglutarate, succinate and oxygen concentrations, the mitochondrial complex 1 also participates to the regulation of prolyl hydroxylase activity (PHD) which leads to the degradation of hypoxia inducible factor (HIF) under normoxia. Under hypoxia or dysfunction of some enzymes of the TCA (succinate dehydrogenase, fumarate hydratase), PHD is inhibited, HIF-1a stabilized and translocated to the nucleus. HIF1a acts as a transcription factor which leads to the upregulation of target genes involved in many aspects of cancer progression, angiogenesis, cell survival, glucose metabolism and invasion. More than 70 putative HIF-1 target genes have currently been identified (S.S. Hong & al., 2004).

In the 1920s, Otto Warburg demonstrated tumor cells present a specific metabolism compared to primary cells: an increase of cellular glucose avidity (Warburg effect) under

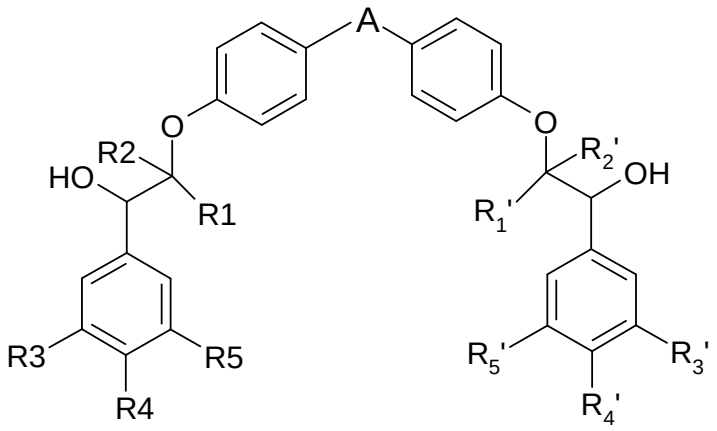
normoxic conditions (aerobic glycolysis). Since few years, metabolism deregulation has finally been defined as an emerging hallmark of cancer (Hanahan et al. (2011) Cell, 144). And this observation has been even more translated to clinics where aggressive tumors are nowadays commonly diagnosed thanks to their glucose avidity (FDG Petscan). Understanding metabolic adaptation under stress and developing strategy to target specific tumor cell metabolism appears now an evidence for the community.

Many cancers demonstrate a glycolytic shift (Warburg effect) which correlates with tumor aggressiveness and poor prognostic. It is for example the case of most of the glioblastoma or triple negative breast cancers, metastatic head and neck cancers or metastatic melanomas. On the other hand, some tumors depend on oxidative phosphorylation metabolism (OXPHOS, mitochondria) to grow. Tumors relying on pyruvate, glutamine or lipids to grow may depend on OXPHOS metabolism to support ATP generation, oxidoreduction homeostasis and aminoacids providing. For example, hormone-dependent breast tumors, some lung tumors, hepatocarcinomas, gastrointestinal tumors, overexpressing c-Myc tumors such as some lymphomas should almost be considered as OXPHOS depending tumors. Furthermore, new evidence support the fact that treatment resistance occurring after some “targeted therapies” targeting pathways which support glycolytic metabolism can be reached by a shift of tumor metabolism to OXPHOS dependency. Researches are performed to identify some new ways to diagnose those tumor types through specific innovative biopsies respiration assay, or specific development of PET-Scan biomarkers as ^{18}F-Glutamine or ^{11}C-acetate for example.

Beyond its major role in supporting OXPHOS tumors metabolism, the complex 1 participates to the development of the tumor toward the establishment of an aggressive pattern triggered by HIF1 stabilization under hypoxic conditions. It is clear today that modulation of mitochondrial function activity leads to modulation of HIF1 stabilization: inhibition of complex 1 reducing HIF-1a stabilization under hypoxia although complex 2 (succinate dehydrogenase) inhibition leading to increased HIF-1a stabilization under normoxia (SDH or FH mutations leads to cancer development through HIF stabilization). Multiple enzymes responsible for shifting the metabolism toward anaerobic glycolysis (Wenger, R. H., 2000), implicated in the regulation of intracellular pH, tumor invasiveness and metastasis are directly controlled by HIF-1a. And increased HIF-1a levels in diagnostic tumor biopsies are associated with increased risk of mortality in cancers of

bladder, brain, breast, colon, cervix, endometrium, head/neck, lung, ovary, pancreas, prostate, rectum and stomach. Furthermore, experimental manipulations that increase HIF-1a expression result in increased tumor growth, whereas loss of HIF activity results in decreased tumor growth (Semenza, G.L., 2010). In the same way, HIF-1a null tumors exibit retarded growth and reduced pulmonary metastasis (Liao D., et al., 2007). Preventing OXPHOS dependent growth, metabolic adaptation and tumor vascularization through HIF1a destabilization and inducing apoptosis with specific and safe mitochondrial complex 1 inhibitor appears as a consequence to be a new way to address those tumors.

The present invention provides the compounds of the formula (I):



wherein

A represents a 5-membered heteroaryl group comprising between 1 and 3 heteroatoms, at least one heteroatom being selected from a sulfur atom and a nitrogen atom, A being unsubstituted or substituted with one or more (C1-C4)alkyl groups, each (C1-C4) alkyl group unsubstituted or substituted with a heterocyclyl group,

each of R1, R2, R1' and R2' independently represents a hydrogen atom or a (C1-C4 alkyl) group, and

each of R3, R4, R5, R3', R4' and R5' is independently selected from a hydrogen atom, a halogen atom, an –O-fluoromethyl group and a (C1-C4)alkoxy group, wherein at least one from R3, R4 and R5 represents a (C1-C4)alkoxy group and at least one from R3', R4' and R5' represents a (C1-C4)alkoxy group,

in the form of a base, enantiomers, diastereoisomers including racemic mixture, and addition salt with an acid.

The compounds of formula (I) may contain one or more asymmetric carbon atoms. They may therefore exist in the form of enantiomers or diastereoisomers. These enantiomers and diastereoisomers, and also mixtures thereof, including the racemic mixtures, form part of the invention.

Diastereomers can be separated into the individual isomers, for example, by chromatography. Racemates can be separated into the two enantiomers by customary methods, for example by chromatography on chiral phases.

The compounds of formula (I) may exist in the form of bases or addition salts with acids. Such addition salts form part of the invention.

These salts may be prepared with pharmaceutically acceptable acids, although the salts of other acids useful, for example, for purifying or isolating compounds of formula (I) also form part of the invention.

In the context of the present invention, certain terms have the following definitions:

a halogen atom: a fluorine, a chlorine, a bromine or an iodine;

an alkyl group: a linear or branched saturated hydrocarbon group. Examples include the groups methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, etc.;

a fluoroalkyl group: an alkyl group in which one or more hydrogen atoms have been substituted by a fluorine atom;

an alkoxy group: an -O-alkyl radical in which the alkyl group is as defined above;

a heteroaryl group: a cyclic aromatic group containing between 2 and 4 carbon atoms and containing between 1 and 3 heteroatoms, such as nitrogen, oxygen or sulphur. Examples of heteroaryl groups include oxazolyl, thiazol, thienyl, oxadiazolyl, thiadiazolyl or indolyl groups;

a heterocyclyl group: a saturated cyclic group containing between 5 and 10 carbon atoms and containing between 1 and 3 heteroatoms, such as nitrogen, oxygen or sulphur. Examples of heterocyclyl groups include morpholine groups.

Among the compounds of formula (I) that are subject matter of the invention, a first group of compounds is composed of the compounds for which A comprises an oxygen atom.

Among the compounds of formula (I) that are subject matter of the invention, a second group of compounds is composed of the compounds for which A represents an oxazolyl, thiazol, thienyl, oxadiazolyl, thiadiazolyl or imidazolyl group.

Among the compounds of formula (I) that are subject matter of the invention, a third group of compounds is composed of the compounds for which A is unsubstituted.

Among the compounds of formula (I) that are subject matter of the invention, a fourth group of compounds is composed of the compounds for which that A is substituted with one or more methyl groups.

Among the compounds of formula (I) that are subject matter of the invention, a fifth group of compounds is composed of the compounds for which each of R1, R2, R1' and R2' represents a hydrogen atom or a methyl group.

Among the compounds of formula (I) that are subject matter of the invention, a sixth group of compounds is composed of the compounds for which at least two from R3, R4 and R5 represent -OCH_3 and at least two from R3', R4'and R5' represent -OCH_3.

In particular, among the compounds the sixth group of compounds, mention may be made of the compounds for which two from R3, R4 and R5 represent -OCH_3 and two from R3', R4' and R5' represent -OCH_3.

Among the compounds of formula (I) that are subject matter of the invention, a seventh group of compounds is composed of the compounds for which at least one of R3, R4, R5, R3', R4' and R5' represents –$OCHF_2$.

Among the compounds of formula (I) that are subject matter of the invention, an eighth group of compounds is composed of the compounds for which R1=R1', R2=R2', R3=R3', R4=R4' and R5=R5'.

Among the compounds of formula (I) that are subject matter of the invention, mention may be made in particular of the following compounds:

1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-5-methyl-oxazol-4-yl]phenoxy]ethanol;

1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-5-methyl-oxazol-4-yl]phenoxy]-2-methyl-propan-1-ol ;

1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-4-methyl-oxazol-5-yl]phenoxy]ethanol ;

1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-5-methyl-thiazol-4-yl]phenoxy]-2-methyl-propan-1-ol ;

1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-5-methyl-thiazol-4-yl]phenoxy]ethanol ;

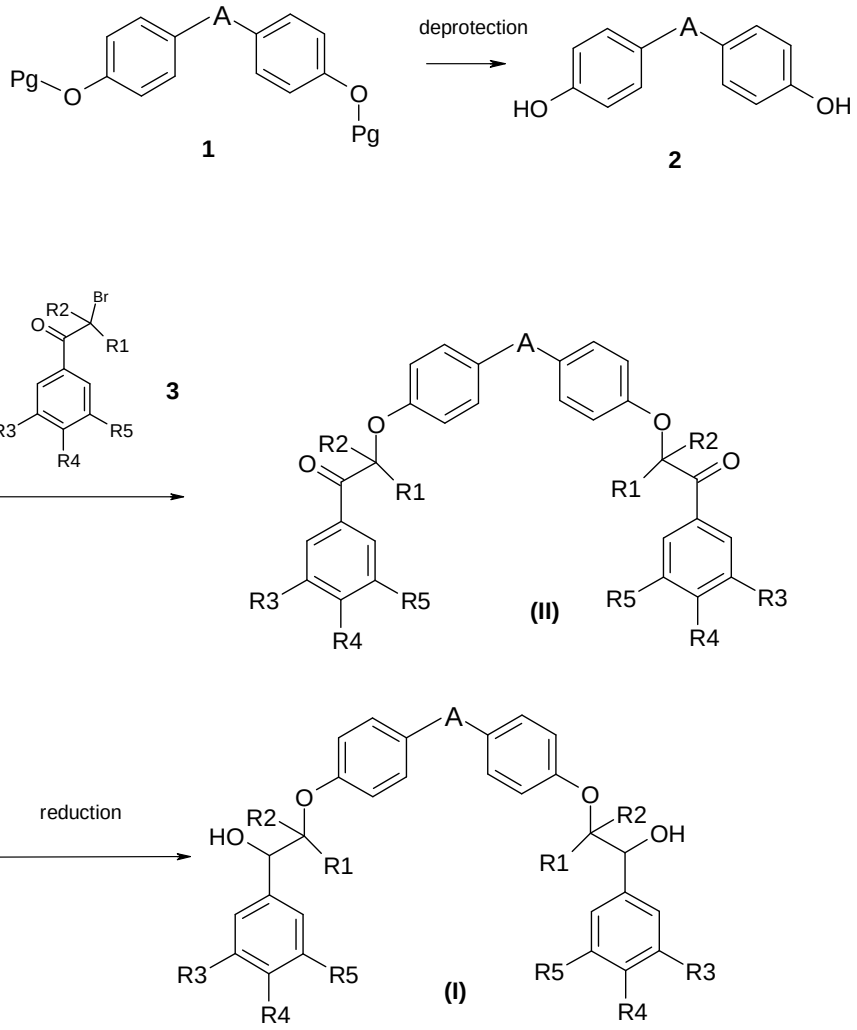
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-5-methyl-thiazol-4-yl]phenoxy]-2-methyl-propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-5-methyl-thiazol-4-yl]phenoxy]ethanol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1-methyl-ethoxy]phenyl]oxazol-4-yl]phenoxy]propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]oxazol-4-yl]phenoxy]ethanol ;
1-(4-chloro-3-methoxy-phenyl)-2-[4-[2-[4-[2-(4-chloro-3-methoxy-phenyl)-2-hydroxy-ethoxy]phenyl]oxazol-4-yl]phenoxy]ethanol ;
1-(4-fluoro-3-methoxy-phenyl)-2-[4-[2-[4-[2-(4-fluoro-3-methoxy-phenyl)-2-hydroxy-ethoxy]phenyl]oxazol-4-yl]phenoxy]ethanol ;
1-(3-fluoro-4-methoxy-phenyl)-2-[4-[2-[4-[2-(3-fluoro-4-methoxy-phenyl)-2-hydroxy-ethoxy]phenyl]oxazol-4-yl]phenoxy]ethanol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]oxazol-4-yl]phenoxy]-2-methyl-propan-1-ol ;
2-[4-[2-[4-[2-hydroxy-2-(3,4,5-trimethoxyphenyl)ethoxy]phenyl]oxazol-4-yl]phenoxy]-1-(3,4,5-trimethoxyphenyl)ethanol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]thiazol-4-yl]phenoxy]ethanol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]thiazol-4-yl]phenoxy]-2-methyl-propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1-methyl-ethoxy]phenyl]thiazol-4-yl]phenoxy]propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]thiazol-4-yl]phenoxy]ethanol ;
1-(3,4-dimethoxyphenyl)-2-[4-[4-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]thiazol-2-yl]phenoxy]-2-methyl-propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]thiazol-4-yl]phenoxy]-2-methyl-propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-3-thienyl]phenoxy]-2-methyl-propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-3-thienyl]phenoxy]ethanol ;

1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-1,2,4-oxadiazol-3-yl]phenoxy]ethanol ;
1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-1,2,4-oxadiazol-3-yl]phenoxy]-2-methyl-propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1-methyl-ethoxy]phenyl]-1,2,4-thiadiazol-3-yl]phenoxy]propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-1,2,4-thiadiazol-3-yl]phenoxy]ethanol ;
1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-1,2,4-thiadiazol-3-yl]phenoxy]-2-methyl-propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-1,2,4-thiadiazol-3-yl]phenoxy]-2-methyl-propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1-methyl-ethoxy]phenyl]oxazol-5-yl]phenoxy]propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-1H-imidazol-4-yl]phenoxy]ethanol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-1H-imidazol-4-yl]phenoxy]-2-methyl-propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-1-methyl-imidazol-4-yl]phenoxy]-2-methyl-propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-1-methyl-imidazol-4-yl]phenoxy]ethanol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-1-(2-morpholinoethyl)imidazol-4-yl]phenoxy]-2-methyl-propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-1-(2-morpholinoethyl)imidazol-4-yl]phenoxy]ethanol hydrochloride ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-4-methyl-oxazol-5-yl]phenoxy]ethanol ;
1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-1,2,4-oxadiazol-3-yl]phenoxy]ethanol ;
1-[3-(difluoromethoxy)-4-methoxy-phenyl]-2-[4-[2-[4-[2-[3-(difluoromethoxy)-4-methoxy-phenyl]-2-hydroxy-ethoxy]phenyl]thiazol-4-yl]phenoxy]ethanol ; and
1-[4-(difluoromethoxy)-3-methoxy-phenyl]-2-[4-[2-[4-[2-[4-(difluoromethoxy)-3-methoxy-phenyl]-2-hydroxy-ethoxy]phenyl]thiazol-4-yl]phenoxy]ethanol .

In accordance with the invention the compounds of general formula (I) can be prepared by the following processes, depending on the nature of the substituent A.

In the text below, a protective group Pg is a group which makes it possible on the one hand to protect a reactive function such as a hydroxyl or an amine during a synthesis and on the other hand allows the reactive function to be restored intact at the end of synthesis. Examples of protective groups and also of methods of protection and deprotection are given in “Protective Groups in Organic Synthesis”, Greene et al., 4° Edition (John Wiley & Sons, Inc., New York).

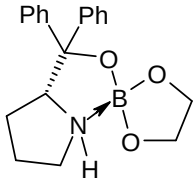
Scheme 1 suitable for compounds having a substituent A different from imidazole and for which R1=R1’, R2=R2’, R3=R3’, R4=R4’ and R5=R5’



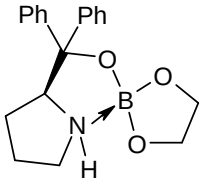
The first synthetic pathway starts from mono or diprotected diphenol **1** which is deprotected in diphenol **2** using classical and well known method depending on the protecting group used (Pg can for example be methyl, Bn, acetyl, TBPS or H) . The diphenol **2** is dialkylated with the corresponding bromo ketone **3**. The resulting diketone of formula (**II**) is then reduced using appropriate reductive agent. In this respect two methods can be used for the synthesis of compounds of formula (**I)**:

- an enantioselective reduction of the diketone of formula (**II)** can be performed using an appropriate chiral Catalyst **4a, 4b**. This method is inspired by a literature method (J. Org. Chem. 2009, 74, 4195–4202) but a double reduction of the diketone of formula (II) is performed in order to obtain chiral compounds of formula (**I**). All the enantioselective reductions described in the examples below were performed using one of the 2 isomers spiroborane **4a** and **4b** as

chiral reductive catalyst. Their syntheses were performed using protocols already described in the literature.



4a

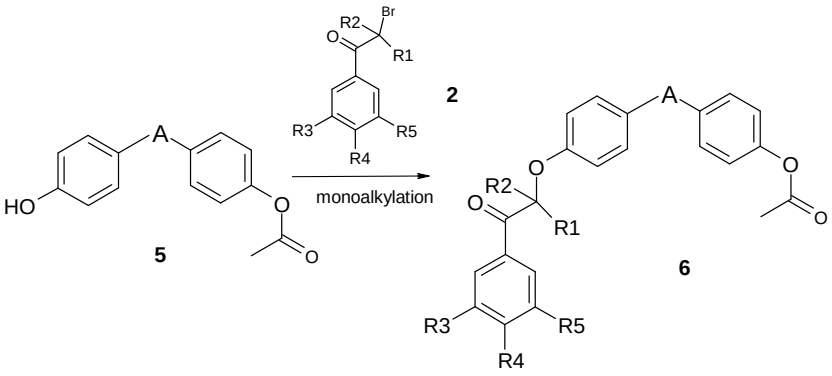


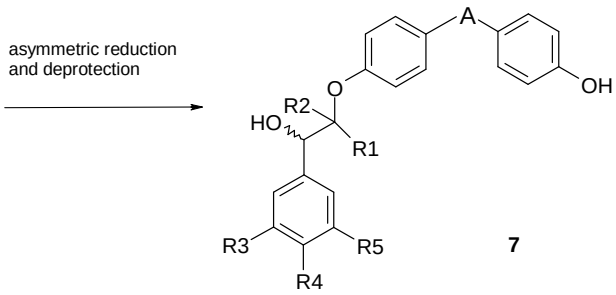
4b

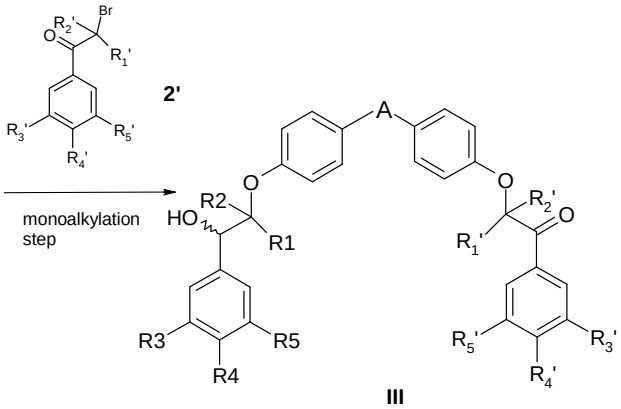
- A racemic reduction of the diketone of formula (II) can be performed with $NaBH_4$ in order to obtain the racemic compound of formula (**I)**.

Scheme 2 suitable for compounds having a substituent A different from imidazole

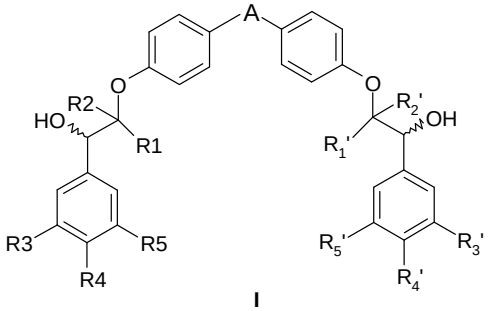
In order to be able to obtain derivatives with different substitutions on each side of the molecule, we have identified two different routes which allow a sequential substitution of the phenol and creation of the asymmetric carbons.


HO
A
O
O
5
R2
Br
O
R1
R3
R5
R4
2
monoalkylation
A
O
O
R2
O
R1
O
R3
R5
R4
6


asymmetric reduction
and deprotection
A
OH
O
HO
R2
R1
R3
R5
R4
7


R2'
Br
O
R1'
R3'
R5'
R4'
2'
monoalkylation
step
A
O
O
HO
R2
R1
R2'
O
R1'
R3
R5
R4
R5'
R3'
R4'
III

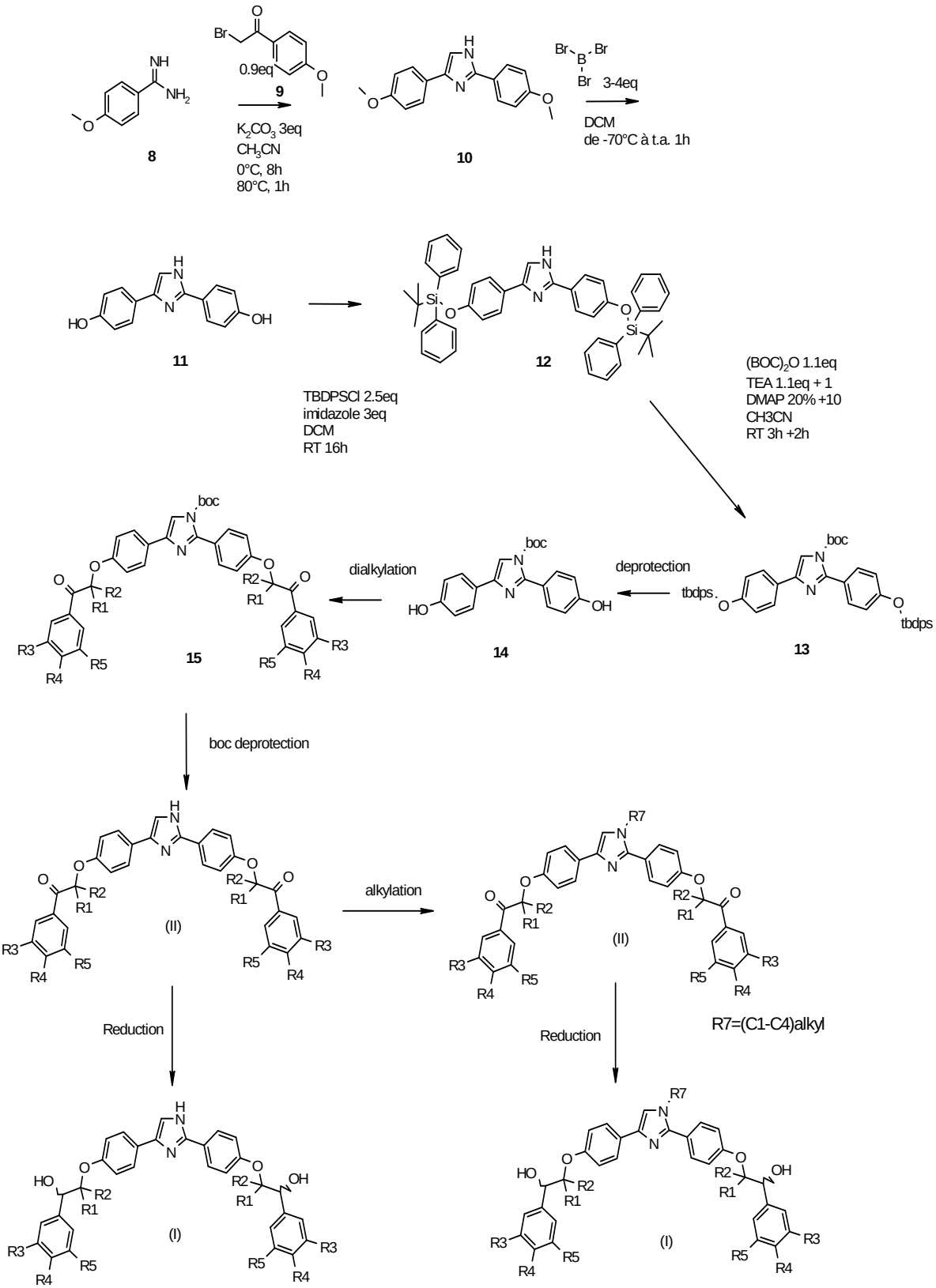
reduction


A
O
O
HO
R2
R1
R2'
OH
R1'
R3
R5
R4
R5'
R3'
R4'
I

Starting from the mono acetate protected phenol **5**, the first step of scheme 2 is an alkylation under basic conditions (ex: K_2CO_3) with the corresponding bromoketone **2**. This ketone 6 is then subjected to an assymetric reduction step with the reductive agent previously described (**4a** or **4b** of scheme 1) and deprotected also in the same step. The resulting phenol **7** is then alkylated under basic conditions (ex: K_2CO_3) with the corresponding bromoketone **2'** which leads to a compound of formula (**III**) and another reduction step, identical to the last reduction step described in scheme 1 is then performed in order to get final compound of formula (**I**).

Scheme 3 suitable for compounds having an imidazol A substituent

Compounds for which A = 2,4-diarylimidazol are prepared with a specific pathway to take into account the reactivity of the imidazole ring.

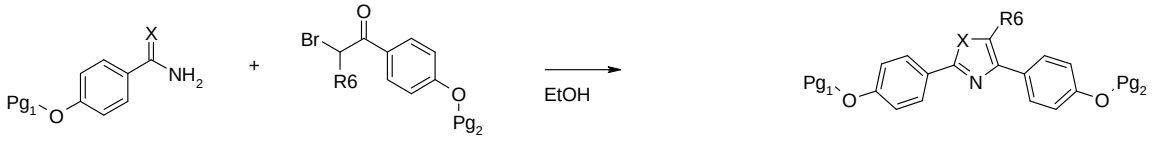


The commercially available amidine **8** is cyclized under basic conditions (K_2CO_3) with the

commercially available bromoketone **9** in order to obtain compound **10**. The deprotection of compound **10** in the diphenol **11** is performed using BBr_3 conditions. The diphenol **11** is then protected with a silyl protective group (compound **12**) and the imidazol ring is protected with Boc group (compound **13**). Deprotection of the sylil group and alkylation of the diphenol **14** gives the diketone of formula (**II**) which can be reduced in the compound of formula (**I**) or alkylated and then reduced using conditions identical to the last reduction step described in scheme 1 is then performed in order to get final compound of formula (**I**)

SYNTHESIS OF HETEROCYCLE DIPHENOL COMPOUNDS

2,4-DIARYLOXAZOL AND 2,4-DIARYLTHIAZOL RING SYNTHESIS

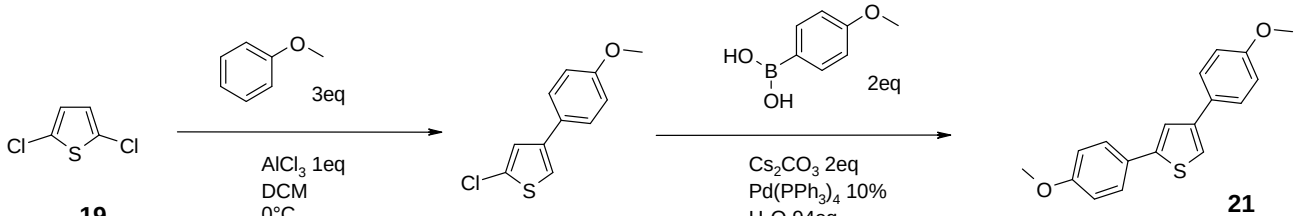


16 **17** **18**

X = O,S
R6 = H, Me

The commercially available substituted amide or thioamine **16** is reacted with the bromoketone **17** in appropriate conditions in order to cyclize in oxazole or thiazole derivatives **18** and those compounds can be directly used as starting material of the general synthesis of the final compounds of formula (**I**).

2,4-DIARYLTHIOPHEN RING SYNTHESIS

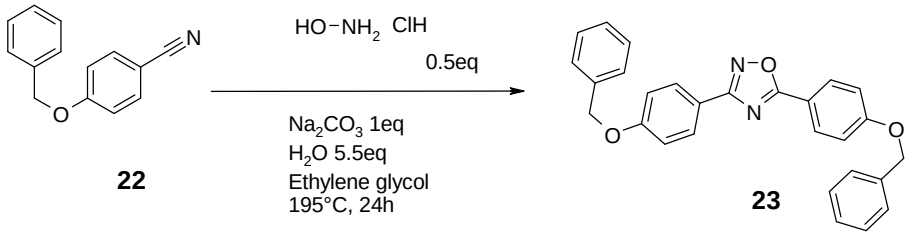


19 **20** **21**

Commercially available dichlorothiophen **19** is reacted with methoxyphenyl in presence of $AlCl_3$ and gives the 4-aryl thiophen **20** which is reacted with boronic acid in a

Suzuki reaction to obtain the 2,4-diarylthiophene **21**. This compound can be directly used as starting material in scheme 1.

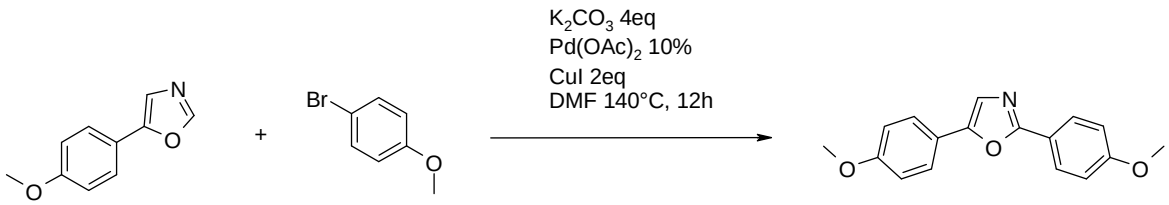
3,5-DIARYLOXADIAZOL RING SYNTHESIS



22 **23**

Oxadiazol compound **23** is prepared using a dimerization reaction of the cyano derivate **22** in presence of hydroxylamine and this compound can be directly used as starting material in scheme 1.

2,5-DIARYLOXAZOL RING SYNTHESIS



24 **25** **26**

Compound **26** is obtained with a palladium coupling reaction of compound **24** with the bromo anisole **25** in presence of CuI and this compound can be directly used as starting material in scheme 1.

In schemes 1-3, the starting compounds and the reactants, when the way in which they are prepared is not described, are available commercially or are described in the literature, or else may be prepared by methods which are described therein or which are known to a person skilled in the art.

In another of its aspects the invention also provides the compounds of formulae (II) and (III). These compounds are useful as synthesis intermediates for the compounds of formula (I).

Examples

The examples which follow describe the preparation of certain compounds in accordance with the invention. These examples are not limitative, and merely illustrate the present invention. The numbers of the compounds exemplified match those given in the table hereinafter, which illustrates the chemical structures and physical properties of some compounds according to the invention.

The following abbreviations and empirical formulae are used:

AcOEt	ethyl acetate
Boc	tert-butyloxycarbonyl
CuI	copper iodide
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
EtSNa	sodium ethyl sulfide
EtOH	ethanol
HCl	hydrogen chloride
HPLC	high-performance liquid chromatography
LCMS	liquid chromatography/mass spectrometry
MeOH	methanol
NaCl	sodium chloride
$NaBH_4$	sodium borohydride
Na_2SO_4	sodium sulfate
TBDPSiCl	tert-butyldiphenylsilyl chloride
TBPS	tris(biphenyl-4-yl)silyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
°C	degrees Celsius
RT	room temperature
Rt	retention time
min	minute(s)

mL	millilitre(s)
mmol	millimole(s)
ppm	parts per million

The chiral HPLC method able to separate the compounds was identified using a mixture of isomers obtained according to the racemic reduction described in scheme 1 and was then used to determine the chiral UV purity of all described compounds.

In the examples described herein below the following analytical methods were used:

The proton nuclear magnetic resonance spectra (1H NMR) were recorded on Bruker spectrometers (250, 400 and 500 MHz) in DMSO-d6 or $DCCl_3$. The chemical shifts δ were expressed in parts per million (ppm). The following abbreviations were used for interpreting the spectra: s: singlet, d: doublet, t: triplet, q: quadruplet, quint: quintuplet, sext: sextuplet, m: multiplet, dd: doublet of doublets, br: broad peak.

The different LCUVMS methods which were used are detailed below.

Method 1:

UPLC 220nm

Column Acquity UPLC BEH C18 (2.1x50mm) 1.7µm

Eluent A=H2O+0.02%HCOOH.

Eluent B=CH3CN+0.02%HCOOH.

T°C: 55°C.

Gradient : t0 2% de B, t4 min98% de B, t4.5 min 98% de B, t4.6 min 2% de B , t5.0. min 2% de B .

Flow rate=1ml/min

Method 2:

HPLC 1100 polar mode UV = 220 nM, column DAICEL Chiralpak IB (250 mm x 4.6) 5 µm, 100% methanol, flowrate 1 mL/min, T= 25°C, injection 10µL at 0.5 mg/mL of MeOH

Method 3:

HPLC 1100 polar mode UV = 210 nM, column DAICEL Chiralpak IC (250 mm x 4.6) 5 µm, 100% acetonitrile, flowrate 1 mL/min, T= 25°C, injection 10µL at 0.5 mg/mL of MeOH

Method 4:

HPLC Agilent 1100 UV = 210 nM, column DAICEL Chiralpak OD-H (100 mm x 4.6) 5 µm, 100% MeOH, flowrate 0.8 mL/min, T= 25°C, injection 2µL at 0.5 mg/mL of MeOH

Method 5:

Instrument: Waters HPLC: Alliance 2695, UV : PDA 996, MS : ZQ (simple Quad) ZQ2

Software: Masslynx , OpenLynx

LC Conditions:

Column: Luna C18 (2)-HST Phenomenex (30 x 2 mm) 2.5µm

Column temperature: 50°C

Eluent A: H2O + 0.05% TFA (v/v)

Eluent B: CH3CN + 0.035% TFA (v/v)

Gradient: t0 0% de B, t2.5min 100% de B, t3.5min 100% de B, t3.6min 0% de B, t5min 0% de B

Flow rate: 1ml/min

Split: 1/3 to the MS source

Injection: 2µl

UV detection: extraction 220nm

MS Conditions:

Ionization mode: positive electrospray ES+

Capillary tension: 3.5kV

Cone Tension: 30V

Desolvation Temperature: 300°C

Source Temp.: 130°C

Method 6:

Instrument: Waters UPLC: Acquity, UV: Acquity PDA, MS: SQD (simple Quad) SQW

Software: Masslynx, OpenLynx

LC Conditions:

Column: BEH C18 Waters (50 x 2.1 mm) 1.7µm

Temp. Column: 55°C

Eluent A: H2O + 0.05% TFA (v/v)

Eluent B: CH3CN+0.035% TFA(v/v)

Gradient: t0 2% de B, t2.4min 98% de B, t3.0min 98% de B, t3.03min 2% de B, t3.5min 2% de B

Flow rate: 0.8ml/min

Injection: 0.3µl

UV Detection: extraction 220nm

MS conditions:

Ionization mode: positive electrospray ES+

Capillary tension: 3kV

Cone tension: 30V

Desolvation Temperature: 500°C

Source Temp.: 150°C

Examples prepared according to scheme 1

Example 1: Synthesis of 2,4-Bis-(4-hydroxyphenyl)-thiazole

2,4-Bis-(4-methoxyphenyl)-thiazole **1** (1 eq, 5 g, 16.81 mmol) was dissolved in 50 mL of DMF then EtSNa (6 eq, 8.49 g, 100.88 mmol) was added and stirring at RT. The reaction mixture was warmed to 120°C for 12h, and then cooled to RT. 200 mL of AcOEt were added and the suspension obtained was filtered. The solid was stirred with 200 mL of AcOEt and 200 mL of 1M solution of HCl for 16h at RT then the suspension was filtered and the solid was dried under reduced pressure to give 3.5 g (77% yield) of 2,4-Bis-(4-hydroxyphenyl)-thiazole.

1H NMR (400 MHz, DMSO-d6) δ ppm 9.20 (br. s, 2 H) 7.84 (d, J=1.8 Hz, 2 H) 7.82 (d, J=1.8 Hz, 2 H) 7.76 (s, 1 H) 6.89 (d, J=8.7 Hz, 2 H) 6.84 (d, J=8.7 Hz, 2 H)

LCMS (Method 3): 100% (purity at 210 nM) Rt = 5 min

Example 2: Synthesis of 1-(3,4-Dimethoxy-phenyl)-2-[4-(4-{4-[2-(3,4-dimethoxy-phenyl)-2-oxo-ethoxy]-phenyl}-thiazol-2-yl)-phenoxy]-ethanone **II-1**

The diphenol obtained in example 1 (1eq, 500 mg, 1.86 mmol) was dissolved in 10 mL of DMF at RT, K_2CO_3 (6 eq, 1.54 g, 11.16 mmol) was added and 2-Bromo-1-(3,4-dimethoxy-phenyl)-ethanone (1.16 g, 4.46 mmol). The reaction mixture was stirred at RT 16 h then filtered. The solution was evaporated under reduced pressure. The solid was then dissolved in DCM and washed with saturated solution of Na_2CO_3 then water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The

residue was purified by silica gel chromatography (eluent: heptane/AcOEt 1/0 to 1/1) to give, after evaporation, 228 mg of **II-1** (20% yield).

1H NMR (400 MHz, CHLOROFORM-d δ ppm 7.97 (d, J=8.3 Hz, 2 H) 7.91 (d, J=8.3 Hz, 2 H) 7.67 (t, J=6.0 Hz, 2 H) 7.58 (br. s., 2 H) 7.28 (s, 1 H) 7.01 (d, J=8.3 Hz, 4 H) 6.93 (d, J=8.3 Hz, 2 H) 5.30 (s, 2 H) 5.27 (s, 2 H) 3.97 (s, 6 H) 3.95 (s, 6 H)

LCMS (Method 1): 91.4% (purity at 220 nM) Rt = 2.64 min m/z= 626.1

Example 3: Synthesis of 1-(3,4-Dimethoxy-phenyl)-2-[4-(4-{4-[2-(3,4-dimethoxy-phenyl)-2-hydroxy-ethoxy]-phenyl}-thiazol-2-yl)-phenoxy]-ethanol (isomer 2) compound **I-23**

The borane catalyst **4a** (33.3 mg, 0.1 mmol) was dissolved in 1 mL of THF then 0.34 ml (0.69 mmol) of 2 M solution of BH_3/Me_2S was added dropwise and the reaction mixture was stirred 1h at RT. A suspension of the diketone **II-1** obtained in example 2 (0.215 g, 0.34 mmol) in 1.5 mL of THF was added at -20°C under nitrogen. The reaction was allowed to warm to RT and stirred at this temperature for 20 h. 5 mL of methanol were added and the mixture was concentrated under vacuum. 20 mL of AcOEt was added and the mixture was washed with 1M solution of HCl in water (2x20 ml), 30 mL of water and 30 mL of NaCl (saturated solution) and then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: AcOEt/cyclohexane 15/85 to 1/1) to afford, after evaporation, 1-(3,4-Dimethoxy-phenyl)-2-[4-(4-{4-[2-(3,4-dimethoxy-phenyl)-2-hydroxy-ethoxy]-phenyl}-thiazol-2-yl)-phenoxy]-ethanol (compound I-23).

Yield: 301 mg, 75 %

1H NMR (400 MHz, DMSO-d6) δ ppm 7.94 (d, J=6.7 Hz, 2 H) 7.92 (d, J=6.7 Hz, 2 H) 7.90 (s, 1 H) 7.05 - 7.10 (m, 4 H) 7.02 (d, J=8.8 Hz, 2 H) 6.98 (dd, J=8.3, 1.4 Hz, 2 H) 6.93 (d, J=8.3 Hz, 2 H) 5.59 (d, J=4.5 Hz, 1 H) 5.56 (d, J=4.5 Hz, 1 H) 4.89 (quin, J=4.9 Hz, 2 H) 4.07 (d, J=5.8 Hz, 2 H) 4.04 (d, J=5.8 Hz, 2 H) 3.77 (s, 6 H) 3.74 (s, 6 H)

Chiral chromatography (Method 3): 98.9% (purity at 210 nM) Rt = 10.1 min.

Example 4: Synthesis of 1-(3,4-Dimethoxy-phenyl)-2-[4-(4-{4-[2-(3,4-dimethoxy-phenyl)-2-hydroxy-ethoxy]-phenyl}-thiazol-2-yl)-phenoxy]-ethanol (isomer 1) compound **I-24**

This compound was obtained using the method described in example 3 for compound **I-23** but with **4b** instead of **4a** as chiral catalyst agent

1H NMR (400 MHz, DMSO-d6) δ ppm 7.94 (d, J=6.7 Hz, 2 H) 7.92 (d, J=6.7 Hz, 2 H) 7.90 (s, 1 H) 7.05 - 7.10 (m, 4 H) 7.02 (d, J=8.8 Hz, 2 H) 6.98 (dd, J=8.3, 1.4 Hz, 2 H) 6.93 (d,

J=8.3 Hz, 2 H) 5.59 (d, J=4.5 Hz, 1 H) 5.56 (d, J=4.5 Hz, 1 H) 4.89 (quin, J=4.9 Hz, 2 H) 4.07 (d, J=5.8 Hz, 2 H) 4.04 (d, J=5.8 Hz, 2 H) 3.77 (s, 6 H) 3.74 (s, 6 H)
Chiral chromatography (Method 3): 81.2% (purity at 210 nM) Rt = 13.6 min

Example 5: Synthesis of 1-(3,4-Dimethoxy-phenyl)-2-[4-(4-{4-[2-(3,4-dimethoxy-phenyl)-2-hydroxy-ethoxy]-phenyl}-thiazol-2-yl)-phenoxy]-ethanol (isomer 1, 2, 3 and 4) compound **I-69**

To a suspension of the diketone **II-1** (0.4 mg, 1 eq.) in MeOH 13 mL $NaBH_4$ (0.241 mg, 10 eq.) were added at RT under N_2. After 3 days 5 eq. of $NaBH_4$ was added and the reaction mixture stirred 24h at RT. 10 ml of HCl 1N was then added, the MeOH was evaporated and DCM was added. The organic layer was separated and washed with water. After separation, the organic phase was dried over Na_2SO_4 filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: AcOEt/cyclohexane 15/85 to 1/1) to afford, after evaporation, 1-(3,4-Dimethoxy-phenyl)-2-[4-(4-{4-[2-(3,4-dimethoxy-phenyl)-2-hydroxy-ethoxy]-phenyl}-thiazol-2-yl)-phenoxy]-ethanol (compound I-69).
Yield: 301 mg, 75 %
1H NMR (400 MHz, DMSO-d6) δ ppm 7.92 (5 H) 6.91 - 7.10 (15 H) 5.56 (2 H) 4.89 (2 H) 4.06 (4 H) 3.77 (s, 6 H) 3.74 (s, 6 H)
Chiral chromatography (Method 3):
Isomer 1: 25.8% (purity at 210 nM) Rt = 10.3 min.
Isomer 2: 24.5% (purity at 210 nM) Rt = 11.5 min.
Isomer 3: 25.1% (purity at 210 nM) Rt = 11.8 min.
Isomer 4: 24.6% (purity at 210 nM) Rt = 13.6 min.

Examples prepared according to scheme 2

Example 6: Synthesis of acetic acid 4-[2-(4-hydroxy-phenyl)-thiazol-4-yl]-phenyl ester

1.66 g of 4-hydroxythiobenzamide (1 eq, 6.46 mmol) and 0.99 g of Acetic acid 4-(2-bromo-acetyl)-phenyl ester (1 eq, 6.46 mmol) were dissolved in 25 mL of CH_3CN and heated at reflux for 1h. After cooled down to RT over a 2h period the solid formed was filtered off, washed with a minimum of EtOH and dried under vaccum at 40°C overnight. 1.99 g of acetic acid 4-[2-(4-hydroxy-phenyl)-thiazol-4-yl]-phenyl ester were obtained (99% yield).

1H NMR (400 MHz, DMSO-d6) δ ppm 10.29 (br. s, 1 H) 8.06 (d, J=8.7 Hz, 2 H) 8.03 (s, 1 H) 7.86 (d, J=8.7 Hz, 2 H) 7.23 (d, J=8.7 Hz, 2 H) 6.90 (d, J=8.7 Hz, 2 H) 2.30 (s, 3 H)
LCUV-MS: 99% (purity at 220 nM) Rt = 2.24 min m/z = 312 (method 5)

Example 7: Synthesis of acetic acid 4-(2-{4-[2-(3,4-dimethoxy-phenyl)-2-oxo-ethoxy]-phenyl}-thiazol-4-yl)-phenyl ester

The phenol obtained in example 6 (1eq, 1 g, 3.21 mmol) was dissolved in 16 mL of DMF at RT, K_2CO_3 (4 eq, 1.77 g, 12.85 mmol) was added and 2-Bromo-1-(3,4-dimethoxy-phenyl)-ethanone (1.5 eq, 1.25 g, 4.82 mmol). The reaction mixture was stirred at RT 16h then filtered. The solution was evaporated under reduced pressure. The solid was then dissolved in DCM and washed with saturated solution of Na_2CO_3 then water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: DCM/AcOEt 1/0 to 96/4) to give, after evaporation, 736 mg of acetic acid 4-(2-{4-[2-(3,4-dimethoxy-phenyl)-2-oxo-ethoxy]-phenyl}-thiazol-4-yl)-phenyl ester (47% yield).

1H NMR (600 MHz, DMSO-d6) δ ppm 8.09 (s, 1 H) 8.08 (d, J=8.7 Hz, 2 H) 7.97 (d, J=8.8 Hz, 2 H) 7.76 (dd, J=8.5, 2.1 Hz, 1 H) 7.53 (d, J=2.1 Hz, 1 H) 7.25 (d, J=8.7 Hz, 2 H) 7.15 (d, J=8.5 Hz, 1 H) 7.12 (d, J=8.8 Hz, 2 H) 5.65 (s, 2 H) 3.89 (s, 3 H) 3.86 (s, 3 H) 2.31 (s, 3 H)

LCUV-MS: 99% (purity at 220 nm) Rt = 2.56 min m/z = 489.9 (method 5)

Example 8: Synthesis of 4-(2-{4-[2-(3,4-Dimethoxy-phenyl)-2-hydroxy-ethoxy]-phenyl}-thiazol-4-yl)-phenol (isomer 2)

1.86 mL of BH_3-Me_2S 2M in THF (4 eq, 3.72 mmol) and 150.2 mg of boronate **4a** (0.5 eq, 0.464 mmol) were stirred together at RT under N_2 for 30 min. The mixture was cooled to 0°C then the ketone obtained in example 7 (1 eq, 455 mg, 0.929 mmol) in THF suspension was slowly added. The reaction was stirred 72 h at RT. The reaction mixture was poured onto 20 mL of MeOH and the mixture evaporated to dryness. 30 mL of DCM was added and this organic layer washed with HCl 1N (20 mL). Aqueous layer was separated and extracted 2 times with 10 mL of DCM. Organic layers were combined, dried with Na_2SO_4 and evaporated. The residue was purified by silica gel chromatography (eluent: DCM/MeOH 1/0 to 97/3) to afford, after evaporation, 362.8 mg (87% yield) of 4-(2-{4-[2-(3,4-Dimethoxy-phenyl)-2-hydroxy-ethoxy]-phenyl}-thiazol-4-yl)-phenol.

1H NMR (400 MHz, DMSO-d6) δ ppm 9.61 (s, 1 H) 7.92 (d, J=8.8 Hz, 2 H) 7.84 (d, J=8.7 Hz, 2 H) 7.80 (s, 1 H) 7.07 (d, J=8.8 Hz, 2 H) 7.07 (d, J=1.8 Hz, 1 H) 6.98 (dd, J=8.3, 1.8 Hz, 1 H) 6.93 (d, J=8.3 Hz, 1 H) 6.84 (d, J=8.7 Hz, 2 H) 5.59 (d, J=4.7 Hz, 1 H) 4.90 (q, J=5.4 Hz, 1 H) 4.07 (d, J=5.8 Hz, 2 H) 3.77 (s, 3 H) 3.75 (s, 3 H)

Chiral chromatography (Method 4): 93,5% (purity at 210 nM) Rt = 3.9 min.

Example 9: Synthesis of 1-(3,4-Dimethoxy-phenyl)-2-[4-(2-{4-[2-(3,4-dimethoxy-phenyl)-2-hydroxy-ethoxy]-phenyl}-thiazol-4-yl)-phenoxy]-ethanone (isomer 2)

The phenol obtained in example 8 (1 eq, 360 mg, 0.8 mmol) was dissolved in 10 mL of DMF at RT, K_2CO_3 (4 eq, 442.7 mg, 3.2 mmol) was added and 2-Bromo-1-(3,4-dimethoxy-phenyl)-ethanone (1.5 eq, 327.6 mg, 1.2 mmol). The reaction mixture was stirred at RT 16h then filtered. The solution was evaporated under reduced pressure. The solid was then dissolved in DCM and washed with saturated solution of Na_2CO_3 then water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give, after evaporation, 500 mg of 1-(3,4-Dimethoxy-phenyl)-2-[4-(2-{4-[2-(3,4-dimethoxy-phenyl)-2-hydroxy-ethoxy]-phenyl}-thiazol-4-yl)-phenoxy]-ethanone (compound of formula **(III)**, 99% yield).

1H NMR (400 MHz, DMSO-d6) δ ppm 7.89 - 7.98 (m, 5 H) 7.75 (dd, J=8.5, 1.9 Hz, 1 H) 7.51 (d, J=1.9 Hz, 1 H) 7.13 (d, J=8.5 Hz, 1 H) 7.06 (dd, J=13.1, 8.7 Hz, 5 H) 6.98 (dd, J=8.2, 1.7 Hz, 1 H) 6.93 (d, J=8.2 Hz, 1 H) 5.56 - 5.60 (m, 3 H) 4.90 (q, J=5.4 Hz, 1 H) 4.07 (d, J=5.8 Hz, 2 H) 3.87 (s, 3 H) 3.84 (s, 3 H) 3.77 (s, 3 H) 3.75 (s, 3 H)

LCUV-MS: 88 % (purity at 220 nm) Rt = 2.59 min m/z = 628 (method 5)

Chiral chromatography (method 3): 94% (purity at 210 nm) Rt = 8.9 min.

Example 10: Synthesis of 1-(3,4-Dimethoxy-phenyl)-2-[4-(4-{4-[2-(3,4-dimethoxy-phenyl)-2-hydroxy-ethoxy]-phenyl}-thiazol-2-yl)-phenoxy]-ethanol (isomer 3) compound **I-61**

This compound was obtained using the general method of asymmetric reduction previously described. 60% yield.

0.478 mL of BH_3-Me_2S 2M in THF (6 eq, 0.956 mmol) and 46.34 mg of boronate **4a** (0.9 eq, 0.143 mmol) were stirred together at RT under N_2 for 15 min. The mixture was cooled to -20°C then a solution of the ketone of formula (III) obtained in example 9 (1 eq, 100 mg, 0.159 mmol) in THF was slowly added. The reaction was stirred 16 h at RT. The reaction mixture was poured onto 15 mL of MeOH and the mixture evaporated to dryness. 30 mL of DCM was added and this organic layer washed with HCl 1N (20 mL). Aqueous layer

was separated and extracted 2 times with 10 mL of DCM. Organic layers were combined, dried with Na_2SO_4 and evaporated. The residue was purified by silica gel chromatography (eluent: DCM/MeOH 1/0 to 97/3) to afford, after evaporation, 59.9 mg (60% yield) of 1-(3,4-Dimethoxy-phenyl)-2-[4-(4-{4-[2-(3,4-dimethoxy-phenyl)-2-hydroxy-ethoxy]-phenyl}-thiazol-2-yl)-phenoxy]-ethanol (compound **I-61**).

1H NMR (400 MHz, DMSO-d6) δ ppm 7.94 (d, J=6.7 Hz, 2 H) 7.92 (d, J=6.7 Hz, 2 H) 7.90 (s, 1 H) 7.05 - 7.11 (m, 4 H) 7.02 (d, J=8.8 Hz, 2 H) 6.98 (dd, J=8.3, 1.0 Hz, 2 H) 6.93 (d, J=8.3 Hz, 2 H) 5.59 (d, J=4.7 Hz, 1 H) 5.56 (d, J=4.7 Hz, 1 H) 4.89 (quin, J=5.0 Hz, 2 H) 4.07 (d, J=5.8 Hz, 2 H) 4.04 (d, J=5.8 Hz, 2 H) 3.77 (s, 6 H) 3.75 (s, 6 H)

LCUV-MS: 98% (purity at 220 nm) Rt = 2.39 min m/z = 630 (method 1)

Chiral chromatography (method 2): 88.2% (purity at 210 nm) Rt = 22.7 min.

Example 11: Synthesis of 1-(3,4-Dimethoxy-phenyl)-2-[4-(4-{4-[2-(3,4-dimethoxy-phenyl)-2-hydroxy-ethoxy]-phenyl}-thiazol-2-yl)-phenoxy]-ethanol (isomer 3) **I-62**

Same procedure (second synthetic route: scheme 2) was performed as in example 10 but the enantioselective reduction were performed with boronate **4b** instead of **4a** in order to obtained the other enantiomer (isomer 3) compound **I-62**

1H NMR (400 MHz, DMSO-d6) δ ppm 7.94 (d, J=6.7 Hz, 2 H) 7.92 (d, J=6.7 Hz, 2 H) 7.90 (s, 1 H) 7.05 - 7.11 (m, 4 H) 7.02 (d, J=8.8 Hz, 2 H) 6.98 (dd, J=8.3, 1.0 Hz, 2 H) 6.93 (d, J=8.3 Hz, 2 H) 5.59 (d, J=4.7 Hz, 1 H) 5.56 (d, J=4.7 Hz, 1 H) 4.89 (quin, J=5.0 Hz, 2 H) 4.07 (d, J=5.8 Hz, 2 H) 4.04 (d, J=5.8 Hz, 2 H) 3.77 (s, 6 H) 3.75 (s, 6 H)

LCUV-MS: 99.4% (purity at 220 nm) RT = 2.39 min m/z = 630 (method 1)

Chiral chromatography (method 2): 81.5% (purity at 220 nm) Rt = 21 min.

Examples prepared according to scheme 3

Example 12: Synthesis of 2,4-Bis-(4-methoxy-phenyl)-1H-imidazole **10**

To a suspension of the commercially available 4-methoxythiobenzamide **8** (1 eq, 9.1 g, 60.59 mmol) in 200 mL of acetonitrile was added 25 g of K_2CO_3 (3 eq, 181.78 mmol) and at 0°C 12.49 g of bromo-1-(4-methoxyphenyl)-ethanone **9** (0.9 eq, 54.53 mmol). The mixture was stirred at 0°C for 8h then warmed to room temperature overnight. The reaction mixture was warmed to 80°C for 1h, cooled to room temperature and filtered. The solid was washed with acetonitrile then triturated with water and filtered to give 12.6 g of 2,4-Bis-(4-methoxy-phenyl)-1H-imidazole (74% yield).

1H NMR (400 MHz, DMSO-d6) δ ppm 12.35 (br. s., 0.7 H) 12.22 (br. s, 0.3 H) 7.95 (d, J=8.8 Hz, 2 H) 7.76 (d, J=8.0 Hz, 1.4 H) 7.68 (br. s, 0.6 H) 7.56 (s, 0.7 H) 7.28 (br. s., 0.3 H) 7.03 (d, J=8.8 Hz, 2 H) 6.94 (d, J=8.0 Hz, 2 H) 3.81 (s, 3 H) 3.77 (s, 3 H) (2 tautomer's forms 70/30)

LCUV-MS: Rt = 1.64 min m/z = 281 (method 5)

Example 13: Synthesis of 2,4-Bis-(4-hydroxy-phenyl)-1H-imidazole **11**

To a suspension of 2,4-Bis-(4-methoxy-phenyl)-1H-imidazole (1 eq, 1 g, 3.57 mmol) in DCM (90 mL) at -70°C were slowly added 10.7 mL of BBr_3 (3 eq, 10.7 mmol). The solution was warmed to room temperature and stirred 1h. The mixture was cooled to -70°C and water was added (100 mL). At room temperature ethyl acetate and a saturated solution of $NaHCO_3$ was added then the isolated organic layer was washed with water and brine then dried with Na_2SO_4, filtered and concentrated under vacuum pressure. 0.8 g of 2,4-Bis-(4-hydroxy-phenyl)-1H-imidazole was obtained (89% yield).

H NMR (400 MHz, DMSO-d6) δ ppm 12.17 (br. s., 0.7 H) 12.07 (br. s., 0.3 H) 9.61 (br. s., 0.7 H) 9.47 (br. s., 0.3 H) 9.26 (br. s., 1 H) 7.81 - 7.85 (m, 0.6 H) 7.78 (d, J=8.6 Hz, 1.4 H) 7.62 (d, J=8.3 Hz, 1.4 H) 7.51 - 7.58 (m, 0.6 H) 7.43 (s, 0.7 H) 7.17 (br. s., 0.3 H) 6.82 (d, J=8.6 Hz, 2 H) 6.75 (d, J=8.3 Hz, 2 H) (2 tautomer's forms 70/30)

LCUV-MS: Rt = 1.4 min m/z = 253 (method 5)

Example 14: Synthesis of 2,4-Bis-[4-(tert-butyl-diphenyl-silanyloxy)-phenyl]-1H-imidazole **12**

To a suspension of 2,4-Bis-(4-hydroxy-phenyl)-1H-imidazole (1 eq, 1 g, 3.96 mmol) in DCM were added 0.809 g of imidazole (3 eq, 11.89 mmol) and 2.63 mL of TBDPSiCl (2.5 eq, 9.91 mmol). The mixture was stirred at room temperature for 16h then filtered. The filtrate was washed with saturated solution of $NaHCO_3$ water and brine then dried with Na_2SO_4, filtered and concentrated under vacuum pressure. The solid was triturated with MeOH, filtered and the solid was washed with MeOH then dried under vacuum at 50°C. 1.86 g of 2,4-Bis-[4-(tert-butyl-diphenyl-silanyloxy)-phenyl]-1H-imidazole was obtained (64% yield).

1H NMR (400 MHz, DMSO-d6) δ ppm 12.26 (s, 0.7 H) 12.11 (s, 0.3 H) 7.66 - 7.72 (m, 10 H) 7.56 (d, J=8.6 Hz, 2 H) 7.41 - 7.52 (m, 13 H) 6.79 (d, J=8.7 Hz, 2 H) 6.72 (d, J=8.6 Hz, 2 H) 1.06 (s, 9 H) 1.06 (s, 9 H) (2 tautomer's forms 70/30)

LCUV-MS: Rt = 2.91 min m/z = 729 (method 5)

Example 15: Synthesis of 2,4-Bis-[4-(tert-butyl-diphenyl-silanyloxy)-phenyl]-imidazole-1-carboxylic acid tert-butyl ester **13**

To a suspension of 2,4-Bis-[4-(tert-butyl-diphenyl-silanyloxy)-phenyl]-1H-imidazole (1eq, 1.3 g, 1.82 mmol) in 25 mL of acetonitrile was added at room temperature triethylamine (1.1 eq, 280 µL, 2 mmol), $(Boc)_2O$ (2 eq, 0.82 g, 3.64 mmol) and DMAP (0.2 eq, 44.5 mg, 0.36 mmol). The mixture was stirred 4h then filtered and the solid was washed with acetonitrile. The solid was dried under vacuum at 50°C. 2,4-Bis-[4-(tert-butyl-diphenyl-silanyloxy)-phenyl]-imidazole-1-carboxylic acid tert-butyl ester was obtained in 41% yield.

1H NMR (400 MHz, DMSO-d6) δ ppm 7.88 (s, 1 H) 7.65 - 7.73 (m, 8 H) 7.61 (d, J=8.6 Hz, 2 H) 7.40 - 7.53 (m, 12 H) 7.34 (d, J=8.6 Hz, 2 H) 6.78 (d, J=8.7 Hz, 2 H) 6.74 (d, J=8.7 Hz, 2 H) 1.30 (s, 9 H) 1.06 (s, 9 H) 1.05 (s, 9 H)

LCUV-MS: Rt = 2.66 min m/z = 829 (method 6)

Example 16: Synthesis of 2,4-Bis-(4-hydroxy-phenyl)-imidazole-1-carboxylic acid tert-butyl ester **14**

2,4-Bis-[4-(tert-butyl-diphenyl-silanyloxy)-phenyl]-imidazole-1-carboxylic acid tert-butyl ester obtained in example 15 (1 eq, 1.09 g, 1.31 mmol) was dissolved in 20 mL of THF at 0°C, 2.63 mL of TBAF (2 eq, 2.63 mmol) was then added and the reaction mixture was stirred at 0°C 4h. Ethyle acetate and a saturated solution of $NaHCO_3$ was added, then isolated organic layer was washed with water and brine then dried with Na_2SO_4, filtered and concentrated under vacuum pressure. The residue was purified by silica gel chromatography (eluent: CH_2Cl_2/MeOH 98/2 to 90/10) to afford, after evaporation, 72% yield.

1H NMR (400 MHz, DMSO-d6) δ ppm 9.73 (br. s., 1 H) 9.47 (br. s., 1 H) 7.85 (s, 1 H) 7.68 (d, J=8.7 Hz, 2 H) 7.40 (d, J=8.6 Hz, 2 H) 6.82 (d, J=8.7 Hz, 2 H) 6.78 (d, J=8.6 Hz, 2 H) 1.41 (s, 9 H)

LCUV-MS: Rt = 1.85 min m/z = 353 (method 5)

Example 17: Synthesis of 2,4-Bis-{4-[2-(3,4-dimethoxy-phenyl)-2-oxo-ethoxy]-phenyl}-imidazole-1-carboxylic acid tert-butyl **15**

The diphenol obtained in example 16 (1eq, 450 mg, 1.28 mmol) was dissolved in 10 mL of DMF at RT, K_2CO_3 (6 eq, 1.06 g, 7.66 mmol) was added and 2-Bromo-1-(3,4-dimethoxy-phenyl)-ethanone (4 eq, 1.32 g, 5.11 mmol). The reaction mixture was stirred

at RT 16 h then filtered. The solution was evaporated under reduced pressure. The solid was then dissolved in DCM and washed with saturated solution of Na_2CO_3 then water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: heptane/AcOEt 1/0 to 1/1) to afford, after evaporation, 2,4-Bis-{4-[2-(3,4-dimethoxy-phenyl)-2-oxo-ethoxy]-phenyl}-imidazole-1-carboxylic acid tert-butyl in 66% yield.

1H NMR (400 MHz, DMSO-d6) δ ppm 7.98 (s, 1 H) 7.79 (d, J=8.9 Hz, 2 H) 7.74 - 7.77 (m, 1 H) 7.72 - 7.74 (m, 1 H) 7.49 - 7.54 (m, 4 H) 7.12 (d, J=8.6 Hz, 1 H) 7.12 (d, J=8.5 Hz, 2 H) 7.03 (d, J=8.8 Hz, 2 H) 6.99 (d, J=8.9 Hz, 2 H) 5.60 (s, 2 H) 5.55 (s, 2 H) 3.88 (s, 3 H) 3.87 (s, 3 H) 3.85 (s, 3 H) 3.84 (s, 3 H) 1.41 (s, 9 H)

LCUV-MS: Rt = 2.46 min m/z = 709 (method 5)

Example 18: Synthesis of 1-(3,4-Dimethoxy-phenyl)-2-[4-(4-{4-[2-(3,4-dimethoxy-phenyl)-2-oxo-ethoxy]-phenyl}-1H-imidazol-2- yl)-phenoxy]-ethanone

Boc protected diketone **15** (1eq, 0.55 g, 0.78 mmol) was dissolved in 2 mL of DCM then 3.88 mL of a solution of HCl 4N in dioxane (20 eq, 15.52 mmol) was added. The mixture was warmed to 60°C for 2h then cooled to room temperature and filtered. Ethyl acetate and a saturated solution of $NaHCO_3$ were added and the suspension was filtered. The solid was washed with water and dried under vacuum at 50°C. 1-(3,4-Dimethoxy-phenyl)-2-[4-(4-{4-[2-(3,4-dimethoxy-phenyl)-2-oxo-ethoxy]-phenyl}-1H-imidazol-2- yl)-phenoxy]-ethanone (compound of formula (**II**)) was obtained in 79% yield.

1H NMR (400 MHz, DMSO-d6) δ ppm 14.64 (br. s, 2 H) 8.15 (d, J=9.0 Hz, 2 H) 8.10 (s, 1 H) 7.89 (d, J=8.7 Hz, 2 H) 7.74 (dd, J=8.4, 1.9 Hz, 2 H) 7.50 (d, J=1.9 Hz, 2 H) 7.25 (d, J=9.0 Hz, 2 H) 7.14 (d, J=8.7 Hz, 2 H) 7.13 (d, J=8.4 Hz, 2 H) 5.72 (s, 2 H) 5.63 (s, 2 H) 3.88 (s, 6 H) 3.85 (s, 6 H)

LCUV-MS: Rt = 1.97 min m/z = 609 (method 5)

Example 19: Synthesis of 1-(3,4-Dimethoxy-phenyl)-2-[4-(2-{4-[2-(3,4-dimethoxy-phenyl)-2-hydroxy-ethoxy]-phenyl}-1H-imidazol-4-yl)-phenoxy]-ethanol (isomer 1, 2, 3 and 4) compound **I-53**

To a suspension of the diketone obtained in example 18 (1 eq, 0.15 mg, 0.25 mmol) in MeOH 12 mL $NaBH_4$ (10 eq, 0.093 mg, 2.46 mmol) was added at RT under N_2. After 16h at RT, 5 ml of HCl 1N was then added, the MeOH was evaporated and 15 mL of DCM were added. The organic layer was separated and washed with water. After separation,

the organic phase was dried over Na_2SO_4 filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: DCM/MeOH 1/0 to 95/5) to give 54 mg after evaporation, of 1-(3,4-Dimethoxy-phenyl)-2-[4-(2-{4-[2-(3,4-dimethoxy-phenyl)-2-hydroxy-ethoxy]-phenyl}-1H-imidazol-4-yl)-phenoxy]-ethanol (compound I-53).

Yield: 36 %

1H NMR (400 MHz, DMSO-d6) (2 tautomers form) δ ppm 12.34 (s, 0.75H) 12.23 (s, 0.25H) 7.94 (d, J=8.8 Hz, 0.5 H) 7.89 (d, J=8.8 Hz, 1.5 H) 7.74 (d, J=8.7 Hz, 1.5 H) 7.66 (d, J=8.7 Hz, 0.5 H) 7.55 (s, 0.75 H) 7.28 (s, 0.25 H) 7.08 - 7.05 (m, 2 H) 7.02 (d, J=8.8 Hz, 2 H) 6.95 - 7.00 (m, 2 H) 6.91 - 6.95 (m, 4 H) 5.56 (d, J=4.7 Hz, 1.5H) 5.53 (d, J=4.7 Hz, 0.5 H) 4.88 (quin, J=5.4 Hz, 2 H) 4.04 (d, J=5.9 Hz, 2 H) 4.01 (d, J=5.9 Hz, 2 H) 3.77 (s, 6 H) 3.75 (s, 6 H)

LCUV-MS: 95.6% purity at 210 Rt = 1.42 min m/z = 613 (method 2)

Chiral chromatography (Method 2):

isomers 1: 23.7% (purity at 210 nM) Rt = 11.5 min.

Isomer 2+3: 49.6% (purity at 210 nM) Rt = 13.6 min.

Isomer 4: 26.7% (purity at 210 nM) Rt = 16.1 min.

Example 20: Synthesis of 1-(3,4-Dimethoxy-phenyl)-2-[4-(4-{4-[2-(3,4-dimethoxy-phenyl)-2-oxo-ethoxy]-phenyl}-1-methyl-1H-imidazol-2-yl)-phenoxy]-ethanone

To a solution of 1-(3,4-Dimethoxy-phenyl)-2-[4-(4-{4-[2-(3,4-dimethoxy-phenyl)-2-oxo-ethoxy]-phenyl}-1H-imidazol-2- yl)-phenoxy]-ethanone obtained in example 18 (1 eq.) solubilized in DMF was added at room temperature 4 eq. of K_2CO_3. The suspension was stirred 10 min. then appropriate halogenoalkyl derivative (3 eq.) was added and the mixture was warmed to 50-100°C for 2h, cooled to room temperature 16 h then warmed at 50-100°C for 4h. Water and ethyl acetate were added to the reaction mixture and the aquous phase was extracted with ethyl acetate. Organic layers were combined and extracted with water and brine then dried with Na_2SO_4, filtered and concentrated under vacuum pressure. The residue was purified by silica gel chromatography (eluent: CH_2Cl_2/MeOH 100/0 to 95/5) to afford, after evaporation, 1-(3,4-Dimethoxy-phenyl)-2-[4-(4-{4-[2-(3,4-dimethoxy-phenyl)-2-oxo-ethoxy]-phenyl}-1-methyl-1H-imidazol-2-yl)-phenoxy]-ethanone (compound of formula (II)).

1H NMR (400 MHz, DMSO-d6) δ ppm 7.71 - 7.77 (m, 2 H) 7.67 (d, J=8.7 Hz, 2 H) 7.64 (d, J=8.7 Hz, 2 H) 7.57 (s, 1 H) 7.52 (d, J=1.9 Hz, 1 H) 7.50 (d, J=1.9 Hz, 1 H) 7.13 (d, J=4.8

Hz, 1 H) 7.11 (d, J=4.8 Hz, 1 H) 7.07 (d, J=8.8 Hz, 2 H) 6.95 (d, J=8.8 Hz, 2 H) 5.60 (s, 2 H) 5.51 (s, 2 H) 3.87 (s, 3 H) 3.87 (s, 3 H) 3.85 (s, 3 H) 3.84 (s, 3 H) 3.73 (s, 3 H)
LCUV-MS: 99.3% (UV purity at 220 nm) Rt = 1.45 min m/z = 627 (method 1)

Example 21: Synthesis of 1-(3,4-Dimethoxy-phenyl)-2-[4-(4-{4-[2-(3,4-dimethoxy-phenyl)-2-hydroxy-ethoxy]-phenyl}-1-methyl-1H-imidazol-2-yl)-phenoxy]-ethanol compound **I-58**

The reduction method using $NaBH_4$ in route 1 was used in order to obtain **I-58** as racemic mixture starting from 1-(3,4-Dimethoxy-phenyl)-2-[4-(4-{4-[2-(3,4-dimethoxy-phenyl)-2-oxo-ethoxy]-phenyl}-1-methyl-1H-imidazol-2-yl)-phenoxy]-ethanone

1H NMR (400 MHz, DMSO-d6) δ ppm 7.67 (d, J=8.7 Hz, 2 H) 7.63 (d, J=8.7 Hz, 2 H) 7.54 (s, 1 H) 7.02 - 7.09 (m, 4 H) 6.89 - 7.00 (m, 6 H) 5.57 (d, J=4.7 Hz, 1 H) 5.52 (d, J=4.5 Hz, 1 H) 4.82 - 4.92 (m, 2 H) 4.06 (d, J=5.8 Hz, 2 H) 4.00 (d, J=5.8 Hz, 2 H) 3.77 (s, 3 H) 3.77 (s, 3 H) 3.75 (s, 3 H) 3.74 (s, 3 H) 3.72 (s, 3 H)
LCUV-MS: 99.3% purity at 220 nM Rt = 1.45 min m/z = 627 (method 1)
Chiral chromatography (Method 2):
Isomer 1: 24.6% (purity at 210 nM) Rt = 12.1 min.
Isomer 2: 25.3% (purity at 210 nM) Rt = 13.3 min.
Isomer 3: 24.6% (purity at 210 nM) Rt = 15.3 min.
Isomer 4: 25.5% (purity at 210 nM) Rt = 16.9 min.

Preparation of heterocycles

Example 22: Synthesis of 2,4-Bis-(4-methoxy-phenyl)-thiazole

5 g of 4-methoxythiobenzamide (1 eq, 29.9 mmol) and 6.85 g of 2-bromo-1-(4-methoxyphenyl)-ethanone (1 eq, 29.9 mmol) were dissolved in 40 mL of EtOH and heated at reflux for 2h. After cooled down to RT over a 2h period the solid formed was filtered off, washed with a minimum of EtOH and dried under vaccum at 40°C overnight. 7.32 g of compound 2,4-Bis-(4-methoxy-phenyl)-thiazole were obtained (82% yield).
1H NMR (250 MHz, DMSO-d6) δ ppm 7.97 (d, J=8.8 Hz, 2 H) 7.96 (d, J=8.8 Hz, 2 H) 7.91 (s, 1 H) 7.08 (d, J=8.8 Hz, 2 H) 7.03 (d, J=8.8 Hz, 2 H) 3.84 (s, 3 H) 3.81 (s, 3 H)
LCUV-MS: Rt = 6.57 min, m/z = 298, UV (220) purity = 97.7% (method 5)

Example 23: Synthesis of 3-Chloro-4-(4-methoxy-phenyl)-thiophene **20**

10.68 mL of Dichlorothiophene **19** (1 eq, 98.62 mmol) were dissolved in 50 mL of DCM then 32.32 mL of methoxybenzene (3 eq, 295.86 mmol) were added and stirred at 0°C.

12.49 g of $AlCl_3$ (0.95 eq, 93.69 mmol) were added at this temperature by portions and the mixture stirred at 5°C for 1h then warm to RT for 4h. The reaction mixture was poured onto water/ice and extract with DCM. The organic layers were combined and washed with 5% solution of $NaHCO_3$ in water, water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: AcOEt/heptane 0/1 to 3/7) to afford, after evaporation, 8.83 g of 3-Chloro-4-(4-methoxy-phenyl)-thiophene (40% yield).

1H NMR (250 MHz, DMSO-d6) δ ppm 7.63 (d, J=8.8 Hz, 2 H) 7.63 (d, J=1.8 Hz, 1 H) 7.57 (d, J=1.8 Hz, 1 H) 6.97 (d, J=8.8 Hz, 2 H) 3.78 (s, 3 H)

LCUV-MS: Rt = 2.64 min m/z = 225 (method 5)

Example 24: Synthesis of 2,4-Bis-(4-methoxy-phenyl)-thiophene **21**

In a sealed tube 3.33 g of 3-Chloro-4-(4-methoxy-phenyl)-thiophene obtained in example 23 (1 eq, 14.84 mmol) was dissolved in 50 mL of dioxane then 4.51 g of 4-methoxyphenyl boronic acid (2 eq, 29.68 mmol), 25 mL of H_2O (93.5 eq, 1387.7 mmol) and 9.67 g of Cs_2CO_3 (2 eq, 29.68 mmol) were added at RT. The mixture under Ar was warmed to 100°C for 6h and cooled 18h to RT. The precipitate was filtered and washed with AcOEt, H_2O and MeOH. The solid was dried overnight under vacuum pressure at 50°C to afford 3g of 2,4-Bis-(4-methoxy-phenyl)-thiophene (68% yield).

1H NMR (250 MHz, DMSO-d6) δ ppm 7.79 (d, J=1.5 Hz, 1 H) 7.70 (d, J=8.9 Hz, 2 H) 7.65 (d, J=8.9 Hz, 2 H) 7.63 (d, J=1.5 Hz, 1 H) 7.01 (d, J=4.2 Hz, 2 H) 6.98 (d, J=4.2 Hz, 2 H) 3.80 (s, 3 H) 3.79 (s, 3 H)

LCUV-MS: Rt = 2.76 min m/z = 297 (method 5)

Example 25: Synthesis of 3,5-Bis-(4-benzyloxy-phenyl)-[1,2,4]oxadiazole **23**

To 5 g of the commercially available 4-Benzyloxy-benzonitrile **22** (1 eq, 23.9 mmol) in 10 mL of ethylene glycole were added 1.52 g of Na_2CO_3 (0.6eq, 14.34 mmol), 1.29 mL of water (3 eq, 71.69 mmol) and 0.83 mg of hydroxylamine hydrochloride (0.5 eq, 11.95 mmol) in a sealed tube. The mixture was warmed to 195°C for 24h then water was added and the suspension was filtered. The solid was washed with water and dried under vacuum pressure at 50°C. The solid was triturated with MeOH, filtered and dried under vacuum pressure at 40°C. 3,5-Bis-(4-benzyloxy-phenyl)-[1,2,4]oxadiazole was obtained in 37% yield.

1H NMR (400 MHz, DMSO-d6) δ ppm 8.13 (d, J=8.7 Hz, 2 H) 8.02 (d, J=8.7 Hz, 2 H) 7.32 - 7.54 (m, 10 H) 7.28 (d, J=8.7 Hz, 2 H) 7.22 (d, J=8.7 Hz, 2 H) 5.25 (s, 2 H) 5.21 (s, 2 H)
LCUV-MS: Rt = 3.1 min m/z = 435 (method 5)

Example 26: Synthesis of 2,5-Bis-(4-methoxy-phenyl)-oxazole **26**

1 g of commercially available 5-4-Methoxyphenyl)-oxazole **24** (1 eq, 5,71 mmol) was dissolved in 12 mL of DMF under Ar at RT. Then 1.2 g of 1-bromo-4-methoxyphenyl **25** (1.2 eq, 6.85 mmol), 1.58 g of K_2CO_3 (2 eq, 11.42 mmol), 64.1 mg of $Pd(OAc)_2$ (0.05 eq, 0.29 mmol) and 1.09 g of CuI (1 eq, 5.71 mmol) were added and the reaction mixture was warmed to 140°C for 6 H. The mixture was cooled and filtered through celite washed with AcOEt. The organic layer was washed with H_2O then brine then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: DCM/MeOH 100/0 to 95/5) to afford, after evaporation, 580 mg of 2,5-Bis-(4-methoxy-phenyl)-oxazole (36% yield).

1H NMR (250 MHz, DMSO-d6) δ ppm 8.00 (d, J=8.9 Hz, 2 H) 7.75 (d, J=8.9 Hz, 2 H) 7.61 (s, 1 H) 7.10 (d, J=8.9 Hz, 2 H) 7.06 (d, J=8.9 Hz, 2 H) 3.84 (s, 3 H) 3.82 (s, 3 H)
LCUV-MS: Rt = 9.22 min purity (UV 220 nm) 97% MH^+= 282 (Method 1)

The table below illustrates the chemical structures and the physical properties of some examples of compounds according to the invention.

In general, a reaction mixture containing a final compound of the formula (**I**) or an intermediate is worked up and, if desired, the product is then purified by customary processes known to those skilled in the art. For example, a synthesized compound can be purified using well known methods such as crystallization, chromatography or reverse phase-high performance liquid chromatography (RP-HPLC) or other methods of separation based, for example, on the size, charge or hydrophobicity of the compound. Similarly, well known methods such as NMR, IR and mass spectrometry (MS) can be used for characterizing a compound of the invention.

The compounds of the formula (**I**), which on account of their chemical structure occur in enantiomeric or diastereomeric forms, can be prepared in enantiomeric pure form employing enantiomerically pure starting material or can be resolved into the pure enantiomers by chromatography on chiral stationary phases or derivatization by means of chiral enantiomerically pure compounds such as amino acids, separation of the diastereomers thus obtained, and removal of the chiral auxiliary groups.

It is to be noted that, when the compounds were prepared using a chiral reductive catalyst (as described in scheme 1) their chiral configuration was not determined via direct analytical methods. Therefore when different isomers of the same compound were obtained, they were named ”isomer 1”, “isomer 2” … However, it is well known that the asymmetric catalysts 4a, 4b which were used lead to final compounds having the same chirality as said catalysts.

Column “chiral agent” precises the agent used during the reduction step from compound of formula (II) or (III) into compound of formula (I)

N°	Name and Isomeric form	Chiral chromatography		LCUVMS				Scheme	Chiral agent
		Chiral Purity (%)	Rt(min.)	UV purity (%)	Rt (min.)	m/z	COMMENTS		
I-1	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-5-methyl-oxazol-4-yl]phenoxy]ethanol (equimolar mixture of 4 isomers)			98.3	8.68	628	equimolar mixture of 4 isomers	1	$NaBH_4$
I-2	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-5-methyl-oxazol-4-yl]phenoxy]-2-methyl-propan-1-ol (equimolar mixture of 4 isomers)			97.7	9.93	684	equimolar mixture of 4 isomers	1	$NaBH_4$
I-3	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-5-methyl-oxazol-4-yl]phenoxy]-2-methyl-propan-1-ol (isomer 2)	99.8	4.9	96.8	2.85	684	1 major isomer	1	4a
I-4	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-5-methyl-oxazol-4-yl]phenoxy]-2-methyl-propan-1-ol (isomer 1)	98.3	16.6	94.5	2.85	684	1 major isomer	1	4b
I-5	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-4-methyl-oxazol-5-yl]phenoxy]ethanol (isomer 1)	100	8.9	94.9	8.3	628	1 major isomer	1	4b

I-6	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-5-methyl-thiazol-4-yl]phenoxy]-2-methyl-propan-1-ol (equimolar mixture of 4 isomers)			98.9	10.35	700	equimolar mixture of 4 isomers	1	$NaBH_4$
I-7	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-5-methyl-thiazol-4-yl]phenoxy]ethanol (equimolar mixture of 4 isomers)			97.3	9.05	644	equimolar mixture of 4 isomers	1	$NaBH_4$
I-8	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-5-methyl-thiazol-4-yl]phenoxy]-2-methyl-propan-1-ol (isomer 2)	98.9	4.3	97.9	10.36	700	1 major isomer	1	4a
I-9	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-5-methyl-thiazol-4-yl]phenoxy]-2-methyl-propan-1-ol (isomer 1)	98.7	10.3	98.1	10.36	700	1 major isomer	1	4b
I-10	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-5-methyl-thiazol-4-yl]phenoxy]ethanol (isomer 1)	99.1	3.4	96.3	2.5	644	1 major isomer	1	4b

I-11	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-5-methyl-thiazol-4-yl]phenoxy]ethanol (isomer 2)	94.8	7.2	96.8	2.5	644	1 major isomer	1	4a
I-12	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1-methyl-ethoxy]phenyl]oxazol-4-yl]phenoxy]propan-1-ol (mixture of isomers)			90.4	8.98	642	mixture of isomers	1	$NaBH_4$
I-13	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]oxazol-4-yl]phenoxy]ethanol (isomer 2)	90.9	4	100 % 98.4	5 MINUTES 8.43	614.51 614	1 major isomer	1	4a
I-14	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]oxazol-4-yl]phenoxy]ethanol (isomer 1)	80.2	2.8	91.1	8.44	614	1 major isomer	1	4b
I-15	1-(4-chloro-3-methoxy-phenyl)-2-[4-[2-[4-[2-(4-chloro-3-methoxy-phenyl)-2-hydroxy-ethoxy]phenyl]oxazol-4-yl]phenoxy]ethanol (equimolar mixture of 4 isomers)			98.5	10.64	622.2	equimolar mixture of 4 isomers	1	$NaBH_4$

I-16	1-(4-fluoro-3-methoxy-phenyl)-2-[4-[2-[4-[2-(4-fluoro-3-methoxy-phenyl)-2-hydroxy-ethoxy]phenyl]oxazol-4-yl]phenoxy]ethanol (equimolar mixture of 4 isomers)			93.4	9.41	590.2	equimolar mixture of 4 isomers	1	$NaBH_4$
I-17	1-(3-fluoro-4-methoxy-phenyl)-2-[4-[2-[4-[2-(3-fluoro-4-methoxy-phenyl)-2-hydroxy-ethoxy]phenyl]oxazol-4-yl]phenoxy]ethanol (equimolar mixture of 4 isomers)			97.1	9.28	590.2	equimolar mixture of 4 isomers	1	$NaBH_4$
I-18	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]oxazol-4-yl]phenoxy]-2-methyl-propan-1-ol (isomer 2)	100	15.2	98.6	9.64	670	1 major isomer	1	4a
I-19	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]oxazol-4-yl]phenoxy]-2-methyl-propan-1-ol (isomer 1)	100	21.3	98.2	9.65	670	1 major isomer	1	4b
I-20	2-[4-[2-[4-[2-hydroxy-2-(3,4,5-trimethoxyphenyl)ethoxy]phenyl]oxazol-4-yl]phenoxy]-1-(3,4,5-trimethoxyphenyl)ethanol (equimolar mixture of 4 isomers)			97.7	8.6	674	equimolar mixture of 4 isomers	1	$NaBH_4$
I-21	2-[4-[2-[4-[2-hydroxy-2-(3,4,5-trimethoxyphenyl)ethoxy]phenyl]oxazol-4-yl]phenoxy]-1-(3,4,5-trimethoxyphenyl)ethanol (isomer 1)	88.1	7.1	95.1	8.6	674	1 major isomer	1	4b

I-22	2-[4-[2-[4-[2-hydroxy-2-(3,4,5-trimethoxyphenyl)ethoxy]phenyl]oxazol-4-yl]phenoxy]-1-(3,4,5-trimethoxyphenyl)ethanol (isomer 2)	42.8	13.4	98.3	8.56	674	1 major isomer	1	4a
I-23	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]thiazol-4-yl]phenoxy]ethanol (isomer 2)	95.2	4.1	98.3	9.22	630	1 major isomer	1	4a
I-69	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]thiazol-4-yl]phenoxy]ethanol (isomer 1, 2, 3, and 4)			99.1	18.44	630	equimolar mixture of 4 isomers	1	$NaBH_4$
I-24	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]thiazol-4-yl]phenoxy]ethanol (isomer 1)	95.5	4.2	98.9	8.88	630	1 major isomer	1	4b
I-25	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]thiazol-4-yl]phenoxy]ethanol (isomer 3 and 4)			98.8	8.8	630	Racemic: 2 enantiomers	1*	$NaBH_4$

I-26	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]thiazol-4-yl]phenoxy]-2-methyl-propan-1-ol (equimolar mixture of 4 isomers)			98.31	21.7	686	equimolar mixture of 4 isomers	1	$NaBH_4$
I-27	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]thiazol-4-yl]phenoxy]-2-methyl-propan-1-ol	80.7	4.9	97.4	10.09	686	1 major isomer	1	4a
I-28	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]thiazol-4-yl]phenoxy]-2-methyl-propan-1-ol (isomer 1)	81.8	10.4	97.3	10.08	686	1 major isomer	1	4b
I-29	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1-methyl-ethoxy]phenyl]thiazol-4-yl]phenoxy]propan-1-ol (isomer 6)	99.8	15.4				1 major isomer	1**	$NaBH_4$
I-30	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1-methyl-ethoxy]phenyl]thiazol-4-yl]phenoxy]propan-1-ol (isomer 2)	91.1	9.9	100	19.98	658	1 major isomer	1**	$NaBH_4$

I-31	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1-methyl-ethoxy]phenyl]thiazol-4-yl]phenoxy]propan-1-ol (isomer 3)	95.9	11.1	99.5 99.2	20.08 20.07	658 658	1 major isomer	1**	$NaBH_4$
I-32	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1-methyl-ethoxy]phenyl]thiazol-4-yl]phenoxy]propan-1-ol (isomer 4)	64.8	10.5	97.8	9.4	658	1 major isomer	1**	$NaBH_4$
I-33	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1-methyl-ethoxy]phenyl]thiazol-4-yl]phenoxy]propan-1-ol (isomer 5)	98.5	12.9	100	20.08	658	1 major isomer	1**	$NaBH_4$
I-61	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]thiazol-4-yl]phenoxy]ethanol (isomer 3)	82.2	11.4	99.4	2.39	630	1 major isomer	2	First reduction 4b then 4a
I-62	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]thiazol-4-yl]phenoxy]ethanol (isomer 4)	88.2	22.7	98.5	2.38	630	1 major isomer	2	First reduction 4a then 4b

I-63	1-(3,4-dimethoxyphenyl)-2-[4-[4-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]thiazol-2-yl]phenoxy]-2-methyl-propan-1-ol (equimolar mixture of 4 isomers)			99.25	2.62	658	equimolar mixture of 4 isomers	2	$NaBH_4$
I-64	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]thiazol-4-yl]phenoxy]-2-methyl-propan-1-ol (equimolar mixture of 4 isomers)			100	2.61	658	equimolar mixture of 4 isomers	2	$NaBH_4$
I-65	1-(3,4-dimethoxyphenyl)-2-[4-[4-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]thiazol-2-yl]phenoxy]-2-methyl-propan-1-ol (isomer 2)	94	6.3	99.5	2.61	658	1 major isomer	2	First reduction 4a then 4a
I-66	1-(3,4-dimethoxyphenyl)-2-[4-[4-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]thiazol-2-yl]phenoxy]-2-methyl-propan-1-ol (isomer 1)	95.4	11.5	100	2.61	658	1 major isomer	2	First reduction 4b then 4b
I-67	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]thiazol-4-yl]phenoxy]-2-methyl-propan-1-ol (isomer 2)	97.4	6.6	97.6	2.61	658	1 major isomer	2	First reduction 4a then 4a

I-68	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]thiazol-4-yl]phenoxy]-2-methyl-propan-1-ol (isomer 1)	98	13.3	97.4	2.64	658	1 major isomer	2	First reduction 4b then 4b
I-34	1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-3-thienyl]phenoxy]-2-methyl-propan-1-ol (equimolar mixture of 4 isomers)			99	10.33	685	equimolar mixture of 4 isomers	1	$NaBH_4$
I-35	1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-3-thienyl]phenoxy]ethanol (equimolar mixture of 4 isomers)			99.6	9.1	629	equimolar mixture of 4 isomers	1	$NaBH_4$
I-36	1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-1,2,4-oxadiazol-3-yl]phenoxy]ethanol (equimolar mixture of 4 isomers)			98.9	8.56	615	equimolar mixture of 4 isomers	1	$NaBH_4$
I-37	1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-1,2,4-oxadiazol-3-yl]phenoxy]-2-methyl-propan-1-ol (isomer 1)	98.1	3.7	100	2.71	671	1 major isomer	1	4b

I-38	1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-1,2,4-oxadiazol-3-yl]phenoxy]-2-methyl-propan-1-ol (isomer 2)	96.7	3	100	2.71	671	1 major isomer	1	4a
I-39	1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1-methyl-ethoxy]phenyl]-1,2,4-thiadiazol-3-yl]phenoxy]propan-1-ol (mixture of isomers)			97.6	19.98	659.3	mixture of isomers	1	$NaBH_4$
I-40	1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-1,2,4-thiadiazol-3-yl]phenoxy]ethanol (isomer 2)	93.5	15.5	98.7	18.5	631	1 major isomer	1	4a
I-41	1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-1,2,4-thiadiazol-3-yl]phenoxy]ethanol (isomer 1)	96.5	11.7	99.3	18.5	631	1 major isomer	1	4b
I-42	1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-1,2,4-thiadiazol-3-yl]phenoxy]-2-methyl-propan-1-ol (equimolar mixture of 4 isomers)			97.4	10.21	687	equimolar mixture of 4 isomers	1	$NaBH_4$

I-43	1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-1,2,4-thiadiazol-3-yl]phenoxy]-2-methyl-propan-1-ol (isomer 2)	99.7	6.3	98.2	2.87	687	1 major isomer	1	4a
I-44	1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-1,2,4-thiadiazol-3-yl]phenoxy]-2-methyl-propan-1-ol (isomer 1)	97.8	19	98.3	2.87	687	1 major isomer	1	4b
I-45	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1-methyl-ethoxy]phenyl]oxazol-5-yl]phenoxy]propan-1-ol (mixture of isomers)			97.5	8.67	642	mixture of isomers	1	$NaBH_4$
I-53	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-1H-imidazol-4-yl]phenoxy]ethanol (equimolar mixture of 4 isomers)			95.6	1.42	613	equimolar mixture of 4 isomers	3	$NaBH_4$
I-54	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-1H-imidazol-4-yl]phenoxy]-2-methyl-propan-1-ol (equimolar mixture of 4 isomers)			98.6	1.71	669	equimolar mixture of 4 isomers	3	$NaBH_4$

I-55	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-1H-imidazol-4-yl]phenoxy]-2-methyl-propan-1-ol (isomer 1)	94.8	15.8	94.05	1.7	669	1 major isomer	3	4b
I-56	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-1H-imidazol-4-yl]phenoxy]-2-methyl-propan-1-ol (isomer 2)	95.2	5	92.06	1.71	669	1 major isomer	3	4a
I-57	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-1-methyl-imidazol-4-yl]phenoxy]-2-methyl-propan-1-ol (equimolar mixture of 4 isomers)			94.23	1.76	683	equimolar mixture of 4 isomers	3	$NaBH_4$
I-58	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-1-methyl-imidazol-4-yl]phenoxy]ethanol (equimolar mixture of 4 isomers)			99.3	1.45	627	equimolar mixture of 4 isomers	3	$NaBH_4$
I-59	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-1-(2-morpholinoethyl)imidazol-4-yl]phenoxy]-2-methyl-propan-1-ol (equimolar mixture of 4 isomers)			100	1.68	782	equimolar mixture of 4 isomers	3	$NaBH_4$

I-60	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-1-(2-morpholinoethyl)imidazol-4-yl]phenoxy]ethanol hydrochloride (equimolar mixture of 4 isomers)			95.7	1.37	726	equimolar mixture of 4 isomers	3	$NaBH_4$
I-46	1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-4-methyl-oxazol-5-yl]phenoxy]ethanol (isomer 2)	89.1	13.8	95	8.3	628	1 major isomer	3	4a
I-47	1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-1,2,4-oxadiazol-3-yl]phenoxy]ethanol (isomer 1)	97.2	10.6	98	2.26	615	1 major isomer	1	4b
I-48	1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-1,2,4-oxadiazol-3-yl]phenoxy]ethanol (isomer 2)	97.2	6.7	98	2.26	615	1 major isomer	1	4a
I-49	1-[3-(difluoromethoxy)-4-methoxy-phenyl]-2-[4-[2-[4-[2-[3-(difluoromethoxy)-4-methoxy-phenyl]-2-hydroxy-ethoxy]phenyl]thiazol-4-yl]phenoxy]ethanol (isomer 2)	94.3	9.2	99	2.76	702	1 major isomer	1	4a

I-50	1-[3-(difluoromethoxy)-4-methoxy-phenyl]-2-[4-[2-[4-[2-[3-(difluoromethoxy)-4-methoxy-phenyl]-2-hydroxy-ethoxy]phenyl]thiazol-4-yl]phenoxy]ethanol (isomer 1)	91.1	9.4	98.5	2.76	702	1 major isomer	1	4b
I-51	1-[4-(difluoromethoxy)-3-methoxy-phenyl]-2-[4-[2-[4-[2-[4-(difluoromethoxy)-3-methoxy-phenyl]-2-hydroxy-ethoxy]phenyl]thiazol-4-yl]phenoxy]ethanol (isomer 2)	72	7.6	96.6	2.8	702	1 major isomer	1	4a
I-52	1-[4-(difluoromethoxy)-3-methoxy-phenyl]-2-[4-[2-[4-[2-[4-(difluoromethoxy)-3-methoxy-phenyl]-2-hydroxy-ethoxy]phenyl]thiazol-4-yl]phenoxy]ethanol (isomer 1)	55.6	6.6	97.7	2.8	702	1 major isomer	1	4b

*Purification method: LC preparative chromatography with 2 columns Chiralpak IC (300x4.6mm) 20µm. Conditions : 100% MeOH - 1ml/min – 210nm – 25°C

**purification method: LC preparative chromatography with Berger Prep SFC (150 x 21 mm 5µm) UV=210 nm. Conditions: 2-Ethylpyridine - CO2/Methanol 75% / 25% 70 mL/min 100 bar 260 inj de 4,1 mg

Some compounds according to the invention underwent biochemical studies in order to demonstrate their capacity to inhibit the mitochondrial complex 1 activity on isolated proteins with a commercial assay according to the protocol described (ab109903: MitoTox Complex 1 OXPHOS Activity Microplate Assay).

In order to evaluate the inhibitory activity of the all compounds, an *in vitro* assay was developed which read out is directly linked to mitochondrial complex 1 inhibition. Since

mitochondrial complex 1 contributes to the formation of membrane potential coupled to the mitochondrial ATP synthesis, complex 1 inhibition directly leads in cells to the inhibition of mitochondrial ATP production. Cellular ATP contents were measured in presence of either glycolysis inhibitor (sodium iodocetate) and/or mitochondrial inhibitors (F0F1-ATPase inhibitor: oligomycin or mitochondrial uncoupler: FCCP) to determine the ATP production part relying either on glycolytic or on mitochondrial metabolism. The compounds according to the invention were evaluated in dose effect in order to demonstrate their capacity to inhibit the mitochondrial ATP production.

Mitochondrial ATP analysis

The compounds of the invention were evaluated for their ability to inhibit mitochondrial ATP production on non-small cell lung carcinoma cell lines NCI-H460, demonstrated for their oxidative pattern.

Sample preparation

ATP was measured using the Promega Cell Titer Glo kit and protocol. In summary, 1,000 cells were plated in 40µL in a 384 well plate. 24 hours later, medium was replaced by 20µl culture medium in presence of compounds: cells were treated in replicates of five with control (PBS), oligomycin A (10µg/ml), FCCP (30µM), or the compounds of the invention in dose effect both alone or in combination with sodium iodoacetate (100µM). Following a 1-hour incubation, 20µL of CellTtiter-glo™ reaction mix were added to each well for a final volume of 40µL. Plates were then analyzed for luminescence with a Perkin Elmer EnVision. By comparing the different conditions, global ATP and percentages of both glycolytic and mitochondrial ATP were determined.

Calculation of results

The mitochondrial ATP production was calculated as the remaining ATP under iodoacetate treatment minus basal ATP (ATP content under iodoacetate and oligomycin treatment). Inhibitory activity of the compounds on mitochondrial ATP in NCI-H460 cells is expressed as the concentration needed to inhibit 50% of mitochondrial ATP production (IC50, M).

N°	**IC_{50} (mito ATP) M**
I-1	3.53E-07
I-2	2.30E-08

I-3	8.85E-09
I-4	1.20E-08
I-5	8.27E-06
I-6	2.13E-08
I-7	2.84E-07
I-8	2.06E-09
I-9	3.86E-09
I-10	1.46E-07
I-11	5.57E-07
I-12	1.28E-07
I-13	6.90E-08
I-14	6.79E-07
I-15	1.55E-06
I-16	3.54E-07
I-17	3.96E-06
I-18	6.28E-08
I-19	2.45E-07
I-20	1.42E-06
I-21	2.65E-06
I-22	1.28E-06
I-23	1.97E-07
I-24	2.54E-07
I-25	1.95E-07
I-26	7.32E-09
I-27	3.68E-09
I-28	4.18E-08
I-29	1.59E-07
I-30	1.67E-07
I-31	3.00E-07
I-32	4.76E-08
I-33	3.01E-08
I-34	6.00E-09
I-35	3.03E-07

I-36	6.76E-07
I-37	9.43E-08
I-38	1.33E-07
I-39	9.25E-08
I-40	2.81E-07
I-41	5.39E-07
I-42	3.00E-08
I-43	3.70E-08
I-44	5.44E-08
I-45	4.26E-07
I-46	> 10 E-06
I-47	> 10 E-06
I-48	> 10 E-06
I-49	> 10 E-06
I-50	1.34E-06
I-51	> 10 E-06
I-52	> 10 E-06
I-53	9.56E-07
I-54	6.72E-07
I-55	4.35E-07
I-56	7.60E-07
I-57	5.19E-08
I-58	4.58E-07
I-59	2.75E-06
I-60	> 10 E-06
I-61	3.26E-07
I-62	4.92E-07
I-63	4.29E-08
I-64	1.80E-07
I-65	2.38E-08
I-66	2.65E-08
I-67	1.56E-07
I-68	3.28E-08

N°	Complex I (IC_{50}) nM
I-1	257
I-2	2.93
I-3	3.53
I-4	25.7
I-5	>10µM
I-6	13.5
I-8	15.6
I-9	37.3
I-10	196
I-11	146
I-12	15.7
I-13	222
I-14	220
I-15	1240
I-16	839
I-17	1710
I-18	12.6
I-19	2.24
I-20	351
I-21	602
I-22	1280
I-23	381
I-24	38.2
I-25	82.5
I-26	4.9
I-27	1.4
I-28	2.2
I-29	61.9
I-30	30.0
I-31	63.2
I-32	6
I-33	28.5
I-34	26.5
I-35	361
I-36	335
I-37	13.1

I-39	35.7
I-40	664
I-41	281
I-43	9.3
I-44	12.9
I-45	696
I-53	>1µM
I-54	240
I-58	239
I-59	>10µM
I-61	44.1
I-62	135
I-63	29.2
I-64	39.0
I-65	16.2
I-66	24.4
I-67	51.4
I-68	52.6

The IC50 values are generally below 10^{-06} M, and more particularly between 2.6 10^{-9} M and 8.3 10^{-6} M for ATP and are generally below 10^{-06} M, and more particularly between 1.4 and 1710 nM for Complex 1.

Other tests involving the *in vitro* activity of the compounds of the invention were carried out.

Since it was sought to determine the efficacy of the compounds to inhibit HIF1a stabilization under hypoxia, the compounds according to the invention underwent biochemical studies in order to determine their capacity to decrease HIF stabilization in Hep3b cells under hypoxia (western blot model).

Western blot model

Sample preparation

Hep3B cells are seeded at a rate of 300000 cells per well in 6-wells culture plate in 2ml of MEM supplemented with glutamin (2mM) and 10% FCS (foetal calf serum) and incubated at 37°C in the presence of 5% CO2. The next day, the cells are placed in contact with the compound and an incubation under hypoxia at 1% O_2 is carried out at 37°C in 95%

humidity and 5% CO2 in a sealed anaerobic workstation (Hypoxystation H35 - Don Whitley - AES Chemunex) during 6 hours.

Immunoblotting

Cells were washed (PBS) and lysed in SDS sample buffer. Proteins (25µg) were separated on 4 -12% Bis-Tris gels and transferred onto polyvinylidene difluoride membranes (Millipore). Membranes were blotted with a mouse monoclonal antibody to HIF-1a (BD transduction) and a mouse monoclonal anti-βactin (Sigma). Immunoreactive bands were detected with a horse radish peroxydase (HRP) anti-mouse antibody (Sigma) by enhanced chemiluminescence (Promega).

Calculation of results

The inhibitory activity of the compounds for their capacity to decrease HIF1-a stabilization in Hep3b under hypoxia is expressed as range of percentage relative to control with:

- represents a decrease of HIF1-a stabilization is less than 30%

* represents a decrease of HIF-a stabilization between 30 to 50%

** represents a decrease of HIF-a stabilization between 50 to 70%

*** represents a decrease of HIF-a stabilization higher than 70%

N°	Western Blot	
I-1	48	*
I-2	54	**
I-3	70	***
I-4	72	***
I-6	43	*
I-7	63	**
I-8	47	*
I-9	58.5	**
I-10	62	**
I-11	65	**
I-12	38	*
I-13	51	**
I-14	59	**
I-18	71	***
I-19	56	**
I-21	52	**
I-22	57	**
I-24	49	*

I-25	41	*
I-26	39	*
I-27	40	*
I-29	67	**
I-30	56	**
I-31	64	**
I-32	45	*
I-33	52	*
I-34	64	**
I-35	68	**
I-36	62	**
I-37	74	***
I-38	79	***
I-39	51	**
I-42	56	**
I-43	32	*
I-44	45	*
I-45	87	***
I-47	51	**
I-48	87	***
I-55	62	**
I-56	75	***
I-57	18	-
I-58	56	**
I-61	46	*
I-62	43	*
I-63	64	**
I-64	58	**
I-65	41	*
I-66	54	**

Most of the compounds induced a decrease of HIF1-a stabilization of at least 30%.

It is therefore apparent that the compounds of the invention have an inhibitory activity for the complex 1 of the mitochondrial respiratory chain and for HIF1-a.

The compounds according to the invention can therefore be used for preparing medicaments, especially medicaments which are inhibitors of the complex 1 of the mitochondrial respiratory chain.

Accordingly, in another of its aspects, the invention provides medicaments which comprise a compound of formula (I), or an addition salt thereof with a pharmaceutically acceptable acid of the compound of formula (I).

These medicaments are employed therapeutically, especially in the treatment and prevention of cancer, in particular carcinomas which have a metabolism dependent on oxidative phosphorylation, such as lung tumors and more specifically non-small cell lung cancers, hormone-dependent breast tumors, ovarian tumors, hepatocarcinomas, gastroinstestinal, pancreatic, and colon tumors, overexpressing c-Myc tumor such as lymphomas, breast or colon cancer, well to medium differentiated tumors, cancers which induce primary lymph node and lung metastases, early grades of cancers described to present hypoxic regions during their development and metabolic adaptation (glycolytic shift) such as melanomas, gliomas, head and neck carcinomas, leukemias.

According to another of its aspects, the present invention relates to pharmaceutical compositions comprising as active principle a compound according to the invention. These pharmaceutical compositions comprise an effective dose of at least one compound according to the invention, or a pharmaceutically acceptable salt of the said compound, and also at least one pharmaceutically acceptable excipient.

The said excipients are selected, in accordance with the pharmaceutical form and method of administration desired, from the customary excipients, which are known to a person skilled in the art.

In the pharmaceutical compositions of the present invention for oral, sublingual, subcutaneous, intramuscular, intravenous, topical, local, intra-tracheal, intranasal, transdermal or rectal administration, the active principle of formula (I) above, or its salt, may be administered in a unit administration form, in a mixture with conventional pharmaceutical excipients, to animals and to human beings for the treatment of the above disorders or diseases.

The unit administration forms appropriate include oral forms such as tablets, soft or hard gel capsules, powders, granules and oral solutions or suspensions, sublingual, buccal, intratracheal, intra-ocular and intranasal administration forms, forms for inhalative, topical, transdermal, subcutaneous, intra-muscular or intravenous administration, rectal

administration forms and implants. For topical application it is possible to use the compounds according to the invention in creams, gels, ointments or lotions.

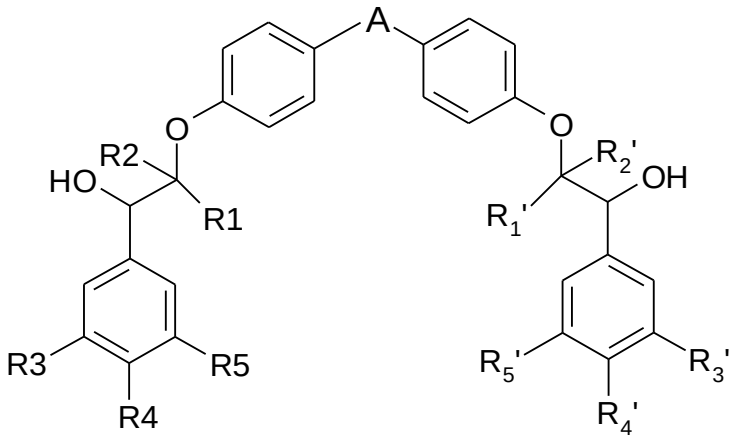
As an example, a unit administration form of a compound according to the invention in tablet form may comprise the following components:

Compound according to the invention	50.0 mg
Mannitol	223.75 mg
Sodium croscarmellose	6.0 mg
Corn starch	15.0 mg
Hydroxypropylmethylcellulose	2.25 mg
Magnesium stearate	3.0 mg

The present invention, according to another of its aspects, also provides a method of treating the pathologies indicated above, which comprises administering to a patient an effective dose of a compound according to the invention, or one of its pharmaceutically acceptable salts.

CLAIMS

1. Compounds of formula (I)



wherein

A represents a 5-membered heteroaryl group comprising between 1 and 3 heteroatoms, at least one heteroatom being selected from a sulfur atom and a nitrogen atom, A being unsubstituted or substituted with one or more (C1-C4)alkyl groups, each (C1-C4) alkyl group unsubstituted or substituted with a heterocyclyl group,

each of R1, R2, R_1' and R_2' independently represents a hydrogen atom or a (C1-C4 alkyl) group, and

each of R3, R4, R5, R_3', R_4' and R_5' is independently selected from a hydrogen atom, a halogen atom, an –O-fluoromethyl group and a (C1-C4)alkoxy group, wherein at least one from R3, R4 and R5 represents a (C1-C4)alkoxy group and at least one from R_3', R_4' and R_5' represents a (C1-C4)alkoxy group,

in the form of a base, enantiomers, diastereoisomers including racemic mixture, and addition salt with an acid.

2. Compounds of formula (I) according to claim 1, characterized in that A represents an oxazolyl, thiazol, thienyl, oxadiazolyl, thiadiazolyl or imidazolyl group, in the form of a base, enantiomers, diastereoisomers including racemic mixture, and addition salt with an acid.

3. Compounds of formula (I) according to any one of claims 1 and 2, characterized in that A is unsubstituted, in the form of a base, enantiomers, diastereoisomers including racemic mixture, and addition salt with an acid.

4. Compounds of formula (I) according to any one of claims 1 and 2, characterized in that A is substituted with one or more methyl group, in the form of a base, enantiomers, diastereoisomers including racemic mixture, and addition salt with an acid.

5. Compounds of formula (I) according to any one of claims 1 to 4, characterized in that each of R1, R2, R_1' and R_2' represents a hydrogen atom or a methyl group, in the form of a base, enantiomers, diastereoisomers including racemic mixture, and addition salt with an acid.

6. Compounds of formula (I) according to claim 5, characterized in that each of R1, R2, R_1' and R_2' represents a hydrogen atom, in the form of a base, enantiomers, diastereoisomers including racemic mixture, and addition salt with an acid.

7. Compounds of formula (I) according to any one of claims 1 to 6, characterized in that at least two from R3, R4 and R5 represent -OCH3 and at least two from R_3', R_4'and R_5' represent -OCH_3, in the form of a base, enantiomers, diastereoisomers including racemic mixture, and addition salt with an acid.

8. Compounds of formula (I) according to claims 7, characterized in that two from R3, R4 and R5 represent -OCH_3 and two from R_3', R_4' and R_5' represent -OCH_3, in the form of a base, enantiomers, diastereoisomers including racemic mixture, and addition salt with an acid.

9. Compounds of formula (I) according to any one of claims 1 to 8, characterized in that at least one of R3, R4, R5, R_3', R_4' and R_5' represents –$OCHF_2$, in the form of a base, enantiomers, diastereoisomers including racemic mixture, and addition salt with an acid .

10. Compounds of formula (I) according to any one of claims 1 to 9, characterized in that R1=R_1', R2=R_2', R3=R_3', R4=R_4' and R5=R_5', in the form of a base, enantiomers, diastereoisomers including racemic mixture, and addition salt with an acid.

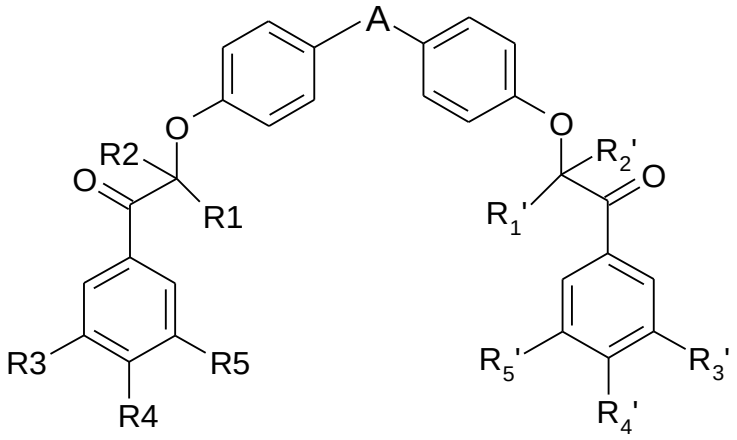
11. Compounds of formula (I) according to claim 1 which are selected from the following list:
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-5-methyl-oxazol-4-yl]phenoxy]ethanol;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-5-methyl-oxazol-4-yl]phenoxy]-2-methyl-propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-4-methyl-oxazol-5-yl]phenoxy]ethanol ;

1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-5-methyl-thiazol-4-yl]phenoxy]-2-methyl-propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-5-methyl-thiazol-4-yl]phenoxy]ethanol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-5-methyl-thiazol-4-yl]phenoxy]-2-methyl-propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-5-methyl-thiazol-4-yl]phenoxy]ethanol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1-methyl-ethoxy]phenyl]oxazol-4-yl]phenoxy]propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]oxazol-4-yl]phenoxy]ethanol ;
1-(4-chloro-3-methoxy-phenyl)-2-[4-[2-[4-[2-(4-chloro-3-methoxy-phenyl)-2-hydroxy-ethoxy]phenyl]oxazol-4-yl]phenoxy]ethanol ;
1-(4-fluoro-3-methoxy-phenyl)-2-[4-[2-[4-[2-(4-fluoro-3-methoxy-phenyl)-2-hydroxy-ethoxy]phenyl]oxazol-4-yl]phenoxy]ethanol ;
1-(3-fluoro-4-methoxy-phenyl)-2-[4-[2-[4-[2-(3-fluoro-4-methoxy-phenyl)-2-hydroxy-ethoxy]phenyl]oxazol-4-yl]phenoxy]ethanol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]oxazol-4-yl]phenoxy]-2-methyl-propan-1-ol ;
2-[4-[2-[4-[2-hydroxy-2-(3,4,5-trimethoxyphenyl)ethoxy]phenyl]oxazol-4-yl]phenoxy]-1-(3,4,5-trimethoxyphenyl)ethanol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]thiazol-4-yl]phenoxy]ethanol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]thiazol-4-yl]phenoxy]-2-methyl-propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1-methyl-ethoxy]phenyl]thiazol-4-yl]phenoxy]propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]thiazol-4-yl]phenoxy]ethanol ;
1-(3,4-dimethoxyphenyl)-2-[4-[4-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]thiazol-2-yl]phenoxy]-2-methyl-propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]thiazol-4-yl]phenoxy]-2-methyl-propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-3-thienyl]phenoxy]-2-methyl-propan-1-ol ;

1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-3-thienyl]phenoxy]ethanol ;
1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-1,2,4-oxadiazol-3-yl]phenoxy]ethanol ;
1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-1,2,4-oxadiazol-3-yl]phenoxy]-2-methyl-propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1-methyl-ethoxy]phenyl]-1,2,4-thiadiazol-3-yl]phenoxy]propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-1,2,4-thiadiazol-3-yl]phenoxy]ethanol ;
1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-1,2,4-thiadiazol-3-yl]phenoxy]-2-methyl-propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-1,2,4-thiadiazol-3-yl]phenoxy]-2-methyl-propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1-methyl-ethoxy]phenyl]oxazol-5-yl]phenoxy]propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-1H-imidazol-4-yl]phenoxy]ethanol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-1H-imidazol-4-yl]phenoxy]-2-methyl-propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-1-methyl-imidazol-4-yl]phenoxy]-2-methyl-propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-1-methyl-imidazol-4-yl]phenoxy]ethanol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1,1-dimethyl-ethoxy]phenyl]-1-(2-morpholinoethyl)imidazol-4-yl]phenoxy]-2-methyl-propan-1-ol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-1-(2-morpholinoethyl)imidazol-4-yl]phenoxy]ethanol ;
1-(3,4-dimethoxyphenyl)-2-[4-[2-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-4-methyl-oxazol-5-yl]phenoxy]ethanol ;
1-(3,4-dimethoxyphenyl)-2-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-ethoxy]phenyl]-1,2,4-oxadiazol-3-yl]phenoxy]ethanol ;
1-[3-(difluoromethoxy)-4-methoxy-phenyl]-2-[4-[2-[4-[2-[3-(difluoromethoxy)-4-methoxy-phenyl]-2-hydroxy-ethoxy]phenyl]thiazol-4-yl]phenoxy]ethanol ; and
1-[4-(difluoromethoxy)-3-methoxy-phenyl]-2-[4-[2-[4-[2-[4-(difluoromethoxy)-3-methoxy-phenyl]-2-hydroxy-ethoxy]phenyl]thiazol-4-yl]phenoxy]ethanol ,

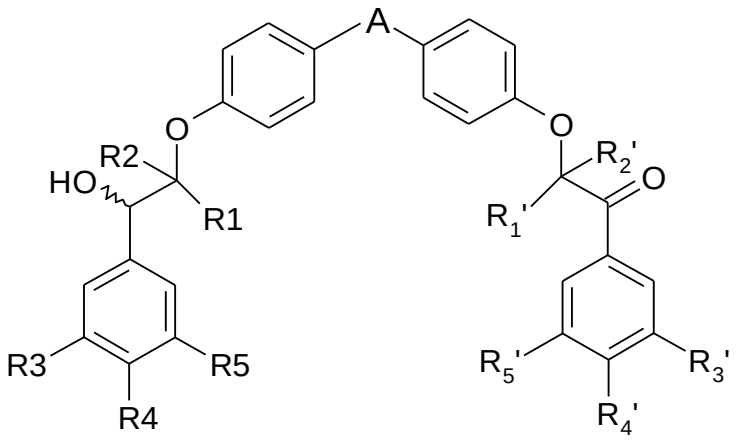
in the form of a base, enantiomers, diastereoisomers including racemic mixture, and addition salt with an acid.

12. Process for preparing a compound of formula (I) according to any one of claims 1 to 11, characterized in that a compound of formula (II)



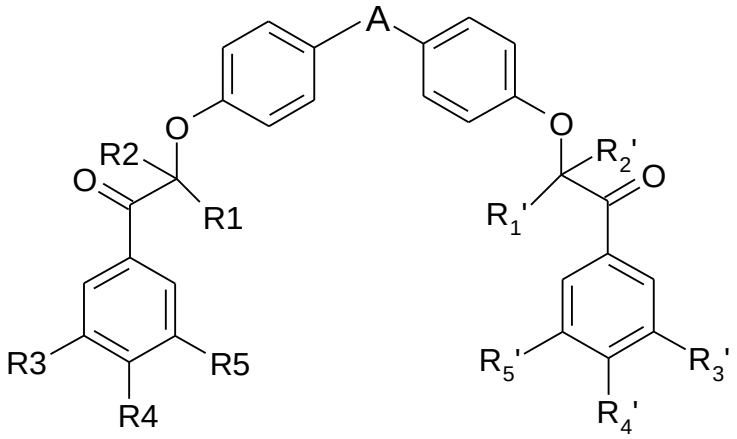
is subjected to a reduction step.

13. Process for preparing a compound of formula (I) according to any one of claims 1 to 11, characterized in that a compound of formula (III):



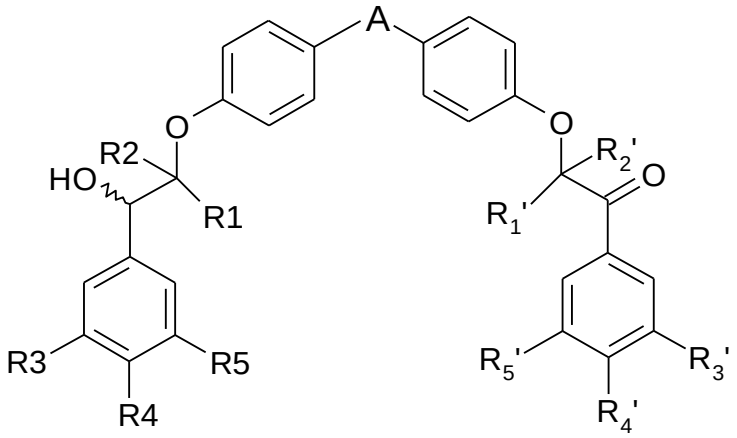
is subjected to a reduction step.

14. Compounds of formula (II)



wherein R1, R2, R3, R4, R5, R_1', R_2', R_3', R_4' and R_5' have the same meanings as in claim 1.

15. Compounds of formula (III)



wherein R1, R2, R3, R4, R5, R_1', R_2', R_3', R_4' and R_5' have the same meanings as in claim 1.

16. Medicament, characterized in that it comprises a compound of formula (I) according to any one of Claims 1 to 11, or an addition salt of this compound with a pharmaceutically acceptable acid.

17. Pharmaceutical composition, characterized in that it comprises a compound of formula (I) according to any one of Claims 1 to 11, or a pharmaceutically acceptable salt of this compound, and also at least one pharmaceutically acceptable excipient.

18. Compound of formula (I) according to any one of Claims 1 to 11 for use as an inhibitor of the complex 1 of the mitochondrial respiratory chain.

19. Compound of formula (I) according to any one of Claims 1 to 11 for use in the treatment of cancer.

20. Compound for use according to claim 19, wherein the cancer is selected from carcinomas which have a metabolism dependent on oxidative phosphorylation, such as lung tumors and more specifically non-small cell lung cancers, hormone-dependent breast tumors, ovarian tumors, hepatocarcinomas, gastroinstestinal, pancreatic, and colon tumors, overexpressing c-Myc tumor such as lymphomas, breast or colon cancer, well to medium differentiated tumors, cancers which induce primary lymph node and lung metastases, early grades of cancers described to present hypoxic regions during their development and metabolic adaptation (glycolytic shift) such as melanomas, gliomas, head and neck carcinomas and leukemias.