

TOLUIDINE SULFONAMIDES AND THEIR USE

The present invention provides novel compounds that inhibit cell proliferation and cell division
5 and that inhibit the activation of Hypoxia Inducible Factor (HIF)-mediated transcription and
signaling under hypoxic conditions. In one aspect, the compounds of the present invention are
useful for the preparation of a medicament for the treatment or prevention of a disease or
disorder selected from the group consisting of an inflammatory disease, a hyperproliferative
disease or disorder, a hypoxia-related pathology and a disease characterized by excessive
10 vascularisation. Also provided is a pharmaceutical composition, comprising a compound of the
invention and a second therapeutic agent or radiation, useful for the treatment or prevention of
the mentioned diseases or disorders.

BACKGROUND OF THE INVENTION

15 The normal response of cells to inadequate oxygen supply is mediated by the hypoxia
signaling pathway. This response is important for a number of physiological functions such as
tumor development and metastasis, resistance to apoptosis, induction of new blood vessel
formation, and metabolism among others. For a general review on hypoxia signaling see e.g.
Qingdong Ke and Max Costa, Molecular Pharmacology (2006), vol. 70, no. 5.

20 As a result of hypoxia, augmented levels of a heterodimeric complex of transcription
factors (Hypoxia Inducible Factor, HIF), most notably HIF-1 α and HIF-1 β , are observed in e.g.
tumors to compensate in cooperation with additional co-factors for the reduced availability of
oxygen and nutrients in this fast growing tissue type. Under anaerobic conditions, homeostasis of
HIF-1 α is imbalanced by its reduced degradation, thus enabling enhanced signaling through the
25 Hypoxia Responsive Element (HRE) and resulting in increased expression of a large number of
survival and growth factors.

Hypoxic conditions are also found in non-tumor tissue. For example, retinopathy is a
general term that refers to non-inflammatory damage to the retina of the eye. This condition is
most commonly caused by an insufficient blood supply leading to hypoxia. Particularly people
30 with diabetes mellitus are at risk of retinopathy. The lack of oxygen in the retina of diabetics
causes fragile, new, blood vessels to grow along the retina and in the clear, gel-like vitreous
humour that fills the inside of the eye. Without timely treatment, these new blood vessels can
bleed, cloud vision, and destroy the retina. Fibrovascular proliferation can also cause fractional

retinal detachment. The new blood vessels can also grow into the anterior chamber of the eye and cause neovascular glaucoma.

Recently, evidence has accumulated that inhibition of HIF-1 activity could also act to prevent inflammation, by virtue of its role in the activation and infiltration of macrophages and neutrophils into affected tissues (see e.g. Giaccia et al., Drug Discovery, vol. 2, October 2003).

For the above-outlined reasons, compounds that inhibit HIF function are valuable medicaments for the treatment or prevention of a disease or disorder selected from the group consisting of an inflammatory disease, a hyperproliferative disease or disorder, a hypoxia-related pathology and a disease characterized by excessive vascularisation.

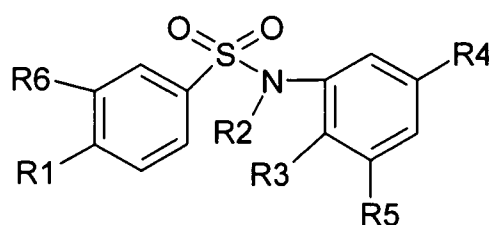
Because of the importance of HIF-1 in tumor development, progression and metastasis, a considerable amount of effort has been devoted to identify HIF-1 inhibitors for cancer therapy. A number of small molecules and RNA constructs, like siRNA, have been reported to exhibit inhibition of the HIF-1 pathway, e.g. Kung AL et al, Cancer Cell (2004), vol. 6, p. 33 ff; Rapisarda A, et al. Cancer Res. (2002), vol. 62, p. 4316 ff.; Tan C. et al, Cancer Res. (2005), vol. 65, p. 605 ff; Mabjeesh NJ, et al, Cancer Cell, (2003), vol. 3, p. 363ff.; Kong X, et al, Mol Cell Biol (2006) , vol. 26, p. 2019 ff.; Kong D, et al, Cancer Res. (2005), vol. 65, p. 9047 ff.; Chau N. et al., Cancer Res. (2005), vol. 65, p. 4918 ff; Welsh S, et al., Mol Cancer Ther (2004), vol. 3, p. 233 ff. However, these compounds often have activities other than HIF-1 inhibition, and most of them lack the desired pharmacokinetic properties or toxicity profiles required for a useful pharmaceutical agent. Furthermore, some of the compounds have the disadvantage that they can not be administered orally, such as the HIF-1 inhibitor EZN-2968, which is a locked nucleic acid antisense oligonucleotide.

The scientific literature cited above emphasizes the high medical need for new therapeutic agents to provide more efficient treatment of different proliferative and inflammatory diseases or disorders, hypoxia-related pathologies and diseases characterized by excessive vascularisation.

SUMMARY OF THE INVENTION

The present invention provides novel compounds capable of prevention or treatment of a disease or disorder. Data presented herein establish that compounds according to the present invention are surprisingly very potent inhibitors of (i) the activation of HIF mediated transcription under hypoxic conditions, of (ii) cell cycle and cell proliferation, of (iii) estrogen response element – mediated transcriptional activity, and (iv) that these compounds induce apoptosis.

In a first aspect the present invention relates to a compound having a structure according to formula I:



(I)

wherein

R^1 is selected from a group consisting of H, alkyl, alkenyl, alkynyl, -CN, halogen, -OH, alkoxy, -SH, S-alkyl, -NH₂, NH-alkyl, N-bis-alkyl, NHOH, NMeOH, NMe(OMe), -NO₂, -CF₃, -OCF₃ and C₁-C₄ hydroxyalkyl.

R^2 is H or C₁-C₄ alkyl;

R^3 is H or -CH₃;

R^4 is phenyl or monocyclic 5- or 6-membered heteroaryl; optionally substituted with one or more substituents selected from the group consisting of:

alkyl, alkenyl, alkynyl, alkoxy, halogen, -CN, -CF₃, -OCF₃, C₁-C₄

hydroxyalkyl, -OH, -SH, S-alkyl, -CN, N-bis-alkyl, cyanoacetylene, -NO₂, -

NR⁷R⁸, -C(O)R²⁰, N-O (wherein the nitrogen atom is integral part of the monocyclic 5- or 6-membered heteroaryl)

and two substituents which form together a dioxymethylene bridge (-O-CH₂-O-);

R^5 is H or -CH₃;

R^6 is selected from the group consisting of H, halogen, alkyl, alkoxy, alkenyl, alkynyl, S-alkyl, -OH, -NR⁷R⁸, -CN, N-bis-alkyl, -SH, -CF₃ and -OCF₃;
or R^6 forms together with R^1 a dioxymethylene bridge (-O-CH₂-O-);

R^7 is H or alkyl;

R^8 is H or C₁-C₄ alkyl; and

R^{20} is C₁-C₄ alkyl;

with the proviso that R^4 is not 3-alkoxy-pyridazine-5-yl; that if R^4 is phenyl, then the 2- and 5-position of the phenyl ring may not be substituted with two methoxy substituents at the same time; and that R^3 and R^5 are not at the same time H.

In a further aspect the present invention relates to a pharmaceutical composition comprising a compound according to the invention or pharmaceutically acceptable salt thereof and a second therapeutic agent useful for the treatment or prevention of a disease or disorder selected from the

group consisting of an inflammatory disease, a hyperproliferative disease or disorder, a hypoxia related pathology and a disease characterized by pathophysiological hyper-vascularisation, and, optionally, a pharmaceutically acceptable carrier or excipient.

In a further aspect the present invention is directed at the use of a compound according to the invention or the composition according to the invention for the preparation of a medicament for the treatment or prevention of a disease or disorder selected from the group consisting of an inflammatory disease, a hyperproliferative disease or disorder, a hypoxia related pathology and a disease characterized by pathophysiological hyper-vascularisation.

In another aspect, the invention provides a method for treating a hyperproliferative disease or disorder comprising administering a compound or composition according to the invention to a patient prior to, during and/or after he was subjected to a radiation therapy, a chemotherapy, an immunotherapy, a laser/microwave thermotherapy or a gene therapy using antisense DNA and RNA.

DETAILED DESCRIPTION

It is to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art.

Preferably, the terms used herein are defined as described in "A multilingual glossary of biotechnological terms: (IUPAC Recommendations)", Leuenberger, H.G.W, Nagel, B. and Kibl, H. eds. (1995), Helvetica Chimica Acta, CH-4010 Basel, Switzerland).

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

Several documents are cited throughout the text of this specification. Each of the documents cited herein (including all patents, patent applications, scientific publications, manufacturer's specifications, instructions, etc.), whether supra or infra, are hereby incorporated by reference in their entirety. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

In the following definitions of the terms: alkyl, heteroalkyl, heteroaryl, alkenyl, and alkynyl are provided. These terms will in each instance of its use in the remainder of the specification have the respectively defined meaning and preferred meanings. Nevertheless in

some instances of their use throughout the specification preferred meanings of these terms are indicated.

The term "alkyl" refers to a saturated straight or branched carbon chain. Preferably, the chain comprises from 1 to 10 carbon atoms, i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms, e.g. methyl, ethyl methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, hexyl, heptyl, octyl. Alkyl groups are optionally substituted where indicated.

The term "C₁-C₄ hydroxyalkyl" refers to a mono- or poly-hydroxylated C₁-C₄ alkyl, i.e. comprising 1, 2, 3 or 4 carbon atoms. Preferably, this term refers to a mono-hydroxylated C₁-C₄ alkyl group, e.g. hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxyl-*iso*-propyl, 1-hydroxybutyl or 2-hydroxybutyl.

The term "heteroalkyl" refers to a saturated straight or branched carbon chain. Preferably, the chain comprises from 1 to 9 carbon atoms, i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9 carbon atoms, e.g. methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, heptyl, octyl, which is interrupted one or more times, e.g. 1, 2, 3, with the same or different heteroatoms. Preferably the heteroatoms are selected from O, S, and N, e.g. CH₂-O-CH₃, CH₂-O-C₂H₅, C₂H₄-O-CH₃, C₂H₄-O-C₂H₅ etc. Heteroalkyl groups are optionally substituted.

The term "heteroaryl" preferably refers to a five or six-membered aromatic monocyclic ring wherein at least one of the carbon atoms are replaced by 1, 2, 3 or 4 (for the five membered ring) or 1, 2, 3, or 4, (for the six membered ring) of the same or different heteroatoms, preferably selected from O, N and S; Examples are furanyl, thiophenyl, oxazolyl, isoxazolyl, 1,2,5-oxadiazolyl, 1,2,3-oxadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, thiazolyl, isothiazolyl, 1,2,3-thiadiazolyl, 1,2,5-thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl and 1,3,5-triazinyl.

As used herein, "monocyclic" refers to substituents having only one aromatic or heteroaromatic ring, excluding any multiple fused aromatic or heteroaromatic rings.

The terms "alkenyl" refer to olefinic unsaturated carbon atoms containing one or more double bonds. One example is propenyl. Preferably, the alkenyl chain comprises from 2 to 8 carbon atoms, i.e. 2, 3, 4, 5, 6, 7, or 8 carbon atoms, e.g. ethenyl, 1-propenyl, 2-propenyl, *iso*-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, *iso*-butenyl, *sec*-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, hexenyl, heptenyl, octenyl.

The term "alkynyl" refers to unsaturated carbon atoms with one or more triple bonds. An example is the propargyl radical. Preferably, the alkynyl chain comprises from 2 to 8 carbon atoms, i.e. 2, 3, 4, 5, 6, 7, or 8 carbon atoms, e.g. ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 1-pentylnyl, 2-pentylnyl, 3-pentylnyl, 4-pentylnyl, hexynyl, pentynyl or octynyl.

In one preferred embodiment of the compounds of the invention, hydrogen atoms in an alkyl, aryl, alkenyl or alkynyl radical may be substituted independently from each other with one or more halogen atoms. One radical is the trifluoromethyl radical.

If two or more radicals can be selected independently from each other, then the term
5 "independently" means that the radicals may be the same or may be different.

The term "pharmaceutically acceptable salt" refers to a salt of the compound of the present invention. Suitable pharmaceutically acceptable salts of the compound of the present invention include acid addition salts which may, for example, be formed by mixing a solution of the compounds of the present invention with a solution of a pharmaceutically acceptable acid
10 such as hydrochloric acid, sulfuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compound of the invention carries an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts (e.g., sodium or potassium salts); alkaline earth metal salts (e.g., calcium or magnesium salts); and salts formed with suitable organic ligands (e.g.,
15 ammonium, quaternary ammonium and amine cations formed using counteranions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl sulfonate and aryl sulfonate). Illustrative examples of pharmaceutically acceptable salts include but are not limited to: acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium edetate, camphorate, camphorsulfonate, camsylate,
20 carbonate, chloride, citrate, clavulanate, cyclopentanepropionate, digluconate, dihydrochloride, dodecylsulfate, edetate, edisylate, estolate, esylate, ethanesulfonate, formate, fumarate, gluceptate, glucoheptonate, gluconate, glutamate, glycerophosphate, glycolylarsanilate, hemisulfate, heptanoate, hexanoate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, hydroxynaphthoate, iodide, isothionate,
25 lactate, lactobionate, laurate, lauryl sulfate, malate, maleate, malonate, mandelate, mesylate, methanesulfonate, methylsulfate, mucate, 2-naphthalenesulfonate, napsylate, nicotinate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, pectinate, persulfate, 3-phenylpropionate, phosphate/diphosphate, picrate, pivalate, polygalacturonate, propionate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate,
30 teoate, tosylate, triethiodide, undecanoate, valerate, and the like (see, for example, Berge, S. M., et al, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, 1977, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

The neutral forms of the compounds may be regenerated by contacting the salt with a
35 base or acid and isolating the parent compound in the conventional manner. The parent form of

the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

In addition to salt forms, the present invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide a compound of general formula (I) – (III). A prodrug is a pharmacologically active or inactive compound that is modified chemically through *in vivo* physiological action, such as hydrolysis, metabolism and the like, into a compound of this invention following administration of the prodrug to a patient.

Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme. The suitability and techniques involved in making and using prodrugs are well known by those skilled in the art. For a general discussion of prodrugs involving esters see Svensson and Tunek Drug Metabolism Reviews 16.5 (1988) and Bundgaard Design of Prodrugs, Elsevier (1985). Examples of a masked acidic anion include a variety of esters, such as alkyl (for example, methyl, ethyl), cycloalkyl (for example, cyclohexyl), aralkyl (for example, benzyl, p-methoxybenzyl), and alkylcarbonyloxyalkyl (for example, pivaloyloxymethyl). Amines have been masked as arylcarbonyloxymethyl substituted derivatives which are cleaved by esterases *in vivo* releasing the free drug and formaldehyde (Bungard J. Med. Chem. 2503 (1989)). Also, drugs containing an acidic NH group, such as imidazole, imide, indole and the like, have been masked with N-acyloxymethyl groups (Bundgaard Design of Prodrugs, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers. EP 0 039 051 (Sloan and Little, Apr. 11, 1981) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use.

Compounds of the present invention and also the starting materials for their preparation according to the invention can be synthesized as shown herein, and, alternatively, by methods and standard procedures known to those skilled in the art, i. e. as described in the literature (for example in the standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), under reaction conditions which are known to those skilled in the art and suitable for the said reactions.

If desired, the starting materials can also be formed *in situ* by not isolating them from the reaction mixture, but instead immediately converting them further into the compounds of the present invention. On the other hand, it is possible to carry out the reaction stepwise. It should be noted that the general procedures are shown as it relates to preparation of compounds having

unspecified stereochemistry. However, such procedures are generally applicable to those compounds of a specific stereochemistry, e.g., where the stereochemistry at a stereogenic center is (S) or (R). In addition, the compounds having one stereochemistry (e.g., (R)) can often be utilized to produce those having opposite stereochemistry (i.e., (S)) using well-known methods, for example, by inversion.

Certain compounds of the present invention can exist in unsolvated forms as well as in solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds. The racemates, enantiomers, diastereomers, geometric isomers and individual isomers are all intended to be encompassed within the scope of the present invention. Accordingly, the compounds of this invention include mixtures of stereoisomers, especially mixtures of enantiomers, as well as purified stereoisomers, especially purified enantiomers, or stereoisomerically enriched mixtures, especially enantiomerically enriched mixtures. Also included within the scope of the invention are the individual isomers of the compounds represented by formulas (I) to (III) below as well as any wholly or partially equilibrated mixtures thereof. The present invention also covers the individual isomers of the compounds represented by the formulas below as mixtures with isomers thereof in which one or more chiral centers are inverted. Also, it is understood that all tautomers and mixtures of tautomers of the compounds of formulas (I) to (III) are included within the scope of the compounds of formulas (I) to (III) and preferably the formulas and subformulas corresponding thereto.

Racemates obtained can be resolved into the isomers mechanically or chemically by methods known per se. Diastereomers are preferably formed from the racemic mixture by reaction with an optically active resolving agent.

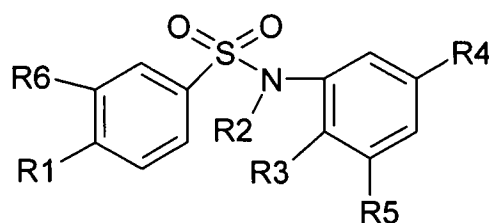
Examples of suitable resolving agents are optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids, such as -camphorsulfonic acid. Also advantageous is enantiomer resolution with the aid of a column filled with an optically active resolving agent (for example dinitrobenzoylphenylglycine); an example of a suitable eluent is a hexane/isopropanol/acetonitrile mixture.

The diastereomer resolution can also be carried out by standard purification processes, such as, for example, chromatography or fractional crystallization.

It is also possible to obtain optically active compounds of formulas (I) to (III) by the methods described above by using starting materials which are already optically active.

The present invention provides novel compositions, compounds and uses of these compounds and compositions for the prevention or treatment of a disease or disorder.

In a first aspect the present invention relates to a compound having a structure according to formula I:



(I)

wherein

- 10 R^1 is selected from a group consisting of H; alkyl, preferably the alkyl chain comprises from 1 to 10 carbon atoms, i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms e.g. methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, hexyl, heptyl or octyl; alkenyl, particularly an alkenyl chain comprising from 2 to 8 carbon atoms, i.e. 2, 3, 4, 5, 6, 7, or 8 carbon atoms, e.g. ethenyl, 1-propenyl, 2-propenyl, *iso*-propenyl, 1-butenyl, 2-butenyl, 15 3-butenyl, *iso*-butenyl, *sec*-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, hexenyl, heptenyl or octenyl; alkynyl, preferably an alkynyl comprising from 2 to 8 carbon atoms, i.e. 2, 3, 4, 5, 6, 7, or 8 carbon atoms, e.g. ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 1-pentylnyl, 2-pentylnyl, 3-pentylnyl, 4-pentylnyl, hexynyl, pentynyl or octynyl; -CN; halogen, in particular F, Cl, Br or I; -OH; alkoxy, in particular C_1 - C_6 alkoxy, e.g. C_1 , C_2 , C_3 , C_4 , C_5 , or C_6 alkoxy, preferably methoxy, 20 ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, *tert*-butoxy, pentoxy, or hexoxy; -SH; S-alkyl, in particular C_1 - C_6 S-alkyl, e.g. C_1 , C_2 , C_3 , C_4 , C_5 , or C_6 S-alkyl; -NH₂; NH-alkyl, in particular C_1 - C_6 NH-alkyl, e.g. C_1 , C_2 , C_3 , C_4 , C_5 , or C_6 NH-alkyl; N-bis-alkyl, preferably C_1 - C_6 N-bis-alkyl, e.g. C_1 , C_2 , C_3 , C_4 , C_5 , or C_6 N-bis-alkyl; NHOH; NMeOH; 25 NMe(OMe); -NO₂; -CF₃; -OCF₃ and C_1 - C_4 hydroxyalkyl, in particular C_1 - C_4 hydroxyalkyl, e.g. C_1 , C_2 , C_3 or C_4 hydroxyalkyl, e.g. hydroxymethyl, hydroxyethyl, hydroxypropyl or hydroxyl-*iso*-propyl, 1-hydroxybutyl or 2-hydroxybutyl;
- R^2 is H or C_1 - C_4 alkyl, i.e. an alkyl group comprising from 1 to 4 carbon atoms, i.e. 1, 2, 3 or 4 carbon atoms e.g. methyl, ethyl, propyl, *iso*-propyl, butyl or *iso*-butyl;
- 30 R^3 is H or -CH₃;
- R^4 is phenyl or monocyclic 5- or 6-membered heteroaryl; optionally substituted with one or more substituents selected from the group consisting of:

alkyl, preferably the alkyl the chain comprises from 1 to 10 carbon atoms, i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms e.g. methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, hexyl, heptyl or octyl; alkenyl, particularly an alkenyl chain comprising from 2 to 8 carbon atoms, i.e. 2, 3, 4, 5, 6, 7, or 8 carbon atoms, e.g. ethenyl, 1-propenyl, 2-propenyl, *iso*-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, *iso*-butenyl, *sec*-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, hexenyl, heptenyl or octenyl; alkynyl, preferably an alkynyl comprising from 2 to 8 carbon atoms, i.e. 2, 3, 4, 5, 6, 7, or 8 carbon atoms, e.g. ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 1-pentylnyl, 2-pentylnyl, 3-pentylnyl, 4-pentylnyl, hexynyl, pentynyl or octynyl; alkoxy, in particular C₁-C₆ alkoxy, e.g. C₁, C₂, C₃, C₄, C₅, or C₆ alkoxy, preferably methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, *tert*-butoxy, pentoxy, or hexoxy; halogen, in particular F, Cl, Br or I; -CN; -CF₃; -OCF₃; C₁-C₄ hydroxyalkyl, in particular C₁-C₄ hydroxyalkyl, e.g. C₁, C₂, C₃ or C₄ hydroxyalkyl, e.g. hydroxymethyl, hydroxyethyl, hydroxypropyl or hydroxyl-*iso*-propyl, 1-hydroxybutyl or 2-hydroxybutyl; -OH; -SH; S-alkyl, in particular C₁-C₆ S-alkyl, e.g. C₁, C₂, C₃, C₄, C₅, or C₆ S-alkyl; -CN; N-bis-alkyl, preferably C₁-C₆ N-bis-alkyl, e.g. C₁, C₂, C₃, C₄, C₅, or C₆ N-bis-alkyl; cyanoacetylene; -NO₂; -NR⁷R⁸, preferably -NH₂ or NH-alkyl, more preferably -NH₂ or -NH-C₁-C₄ alkyl, i.e. -NH-CH₃, -NH-ethyl, -NH-C₃ alkyl or -NH-C₄ alkyl and most preferably -NH₂, NH(CH₃) or N(CH₃)₂; -C(O)R²⁰, preferably acetyl, propionyl, *iso*-propionyl, butyryl or *iso*-butyryl; N-O (wherein the nitrogen atom is integral part of the monocyclic 5- or 6-membered heteroaryl) and two substituents which form together a dioxymethylene bridge (-O-CH₂-O-);

R⁵ is H or -CH₃;

R⁶ is selected from the group consisting of H; halogen, in particular F, Cl, Br or I; alkyl, preferably the alkyl the chain comprises from 1 to 10 carbon atoms, i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms e.g. methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, hexyl, heptyl or octyl; alkoxy, in particular C₁-C₆ alkoxy, e.g. C₁, C₂, C₃, C₄, C₅, or C₆ alkoxy, preferably methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, *tert*-butoxy, pentoxy, or hexoxy; alkenyl, particularly an alkenyl chain comprising from 2 to 8 carbon atoms, i.e. 2, 3, 4, 5, 6, 7, or 8 carbon atoms, e.g. ethenyl, 1-propenyl, 2-propenyl, *iso*-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, *iso*-butenyl, *sec*-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, hexenyl, heptenyl or octenyl; alkynyl,

preferably an alkynyl comprising from 2 to 8 carbon atoms, i.e. 2, 3, 4, 5, 6, 7, or 8 carbon atoms, e.g. ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, hexynyl, pentynyl or octynyl; S-alkyl, in particular C₁-C₆ S-alkyl, e.g. C₁, C₂, C₃, C₄, C₅, or C₆ S-alkyl; -OH; -NR⁷R⁸, preferably -NH₂ or NH-alkyl, more preferably -NH₂ or -NH-C₁-C₄ alkyl, i.e. -NH-CH₃, -NH-ethyl, -NH-C₃ alkyl or -NH-C₄ alkyl and most preferably -NH₂, NH(CH₃) or N(CH₃)₂; -CN; N-bis-alkyl, preferably C₁-C₆ N-bis-alkyl, e.g. C₁, C₂, C₃, C₄, C₅, or C₆ N-bis-alkyl; -SH; -CF₃ and -OCF₃;

or R⁶ forms together with R¹ a dioxymethylene bridge (-O-CH₂-O-), optionally substituted at the methylene;

R⁷ is H or alkyl, preferably the alkyl the chain comprises from 1 to 10 carbon atoms, i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms e.g. methyl, ethyl, propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, hexyl, heptyl or octyl;

R⁸ is H or C₁-C₄ alkyl, in particular methyl, ethyl, propyl, *iso*-propyl, butyl or *iso*-butyl; and

R²⁰ is C₁-C₄ alkyl, in particular methyl, ethyl, propyl, *iso*-propyl, butyl or *iso*-butyl;

with the proviso that R⁴ is not 3-alkoxy-pyridazine-5-yl; if R⁴ is phenyl, then the 2- and 5-position of the phenyl ring may not be substituted with two methoxy substituents at the same time; and that R³ and R⁵ are not at the same time H.

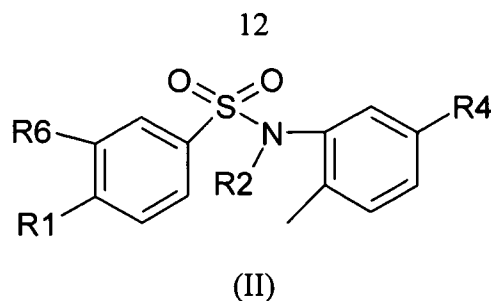
Also preferred is a compound, wherein R¹ is selected from the group consisting of -CH₃, -OCH₃, -CF₃, F and -NH₂.

In a further preferred embodiment of the compound, R⁶, R² and R⁵ is H and R¹ is selected from the group consisting of -CH₃, -OCH₃, -CF₃, F and -NH₂.

The R⁴ substituent of a compound of the invention may have in preferred embodiments only a single heteroatom and/or may be substituted with less than two or less than three substituents.

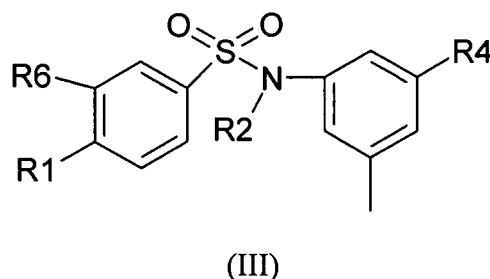
A further preferred embodiment of the compound of the invention has the following substituents: R⁶, R² and R⁵ is H and R¹ is selected from the group consisting of -CH₃, -OCH₃, -CF₃, F and -NH₂ and the R⁴ group is substituted with less than two or less than three substituents and/or, if R⁴ is a monocyclic 5- or 6-membered heteroaryl, then it is preferred in this context that it comprises only a single heteroatom.

In a preferred embodiment the compound of the invention has a structure according to formula II:



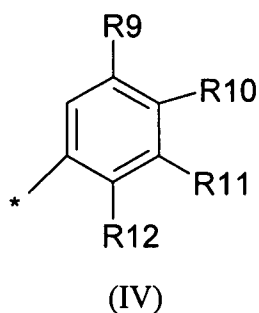
Also preferred is a compound of the invention having a structure according to formula

5 III:



In the context of formulas (II) and (III) R^1 , R^2 , R^4 and R^6 have the above indicated meaning and preferred meanings. Particularly preferred is a compound of formula (II) or (III), wherein R^1 is selected from the group consisting of $-CH_3$, $-OCH_3$, $-CF_3$, F and $-NH_2$. In a further preferred embodiment of the compound according to formula (II) or (III) R^2 is H. In an even more preferred embodiment R^6 and R^2 are H and R^1 is selected from the group consisting of $-CH_3$, $-OCH_3$, $-CF_3$, F and $-NH_2$.

15 In a preferred embodiment of the compound of the invention, preferably a compound according to formula (II) or (III), R^4 has a structure according to formula IV:



wherein

20 R^9 and R^{10} are each individually selected from the group consisting of H; C_1 - C_4 alkyl, in particular methyl, ethyl, propyl, *iso*-propyl, butyl or *iso*-butyl; C_1 - C_4 alkenyl, e.g. ethenyl, 1-propenyl, 2-propenyl, *iso*-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, *iso*-butenyl or *sec*-butenyl; C_1 - C_4 alkynyl, e.g. ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl or 3-butylnyl; $-CN$; $-C(O)R^{20}$, preferably acetyl, propionyl, *iso*-propionyl, butyryl or *iso*-butyryl; cyanoacetylene; halogen, in particular F, Cl, Br or I; $-OH$; C_1 - C_4 alkoxy, e.g.

25

methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy or *tert*-butoxy; -SH; C₁-C₄ S-alkyl, e.g. C₁, C₂, C₃ or C₄ S-alkyl; -NH₂; C₁-C₄ NH-alkyl, e.g. C₁, C₂, C₃ or C₄ NH-alkyl; C₁-C₄ N-bis-alkyl, e.g. C₁, C₂, C₃ or C₄ N-bis-alkyl; -NO₂; -CF₃; -OCF₃; and C₁-C₄ hydroxyalkyl, e.g. hydroxymethyl, hydroxyethyl, hydroxypropyl or hydroxyl-*iso*-propyl, 1-hydroxybutyl or 2-hydroxybutyl; or R⁹ and R¹⁰ form together a dioxymethylene bridge (-O-CH₂-O-);

R¹¹ and R¹² are each individually selected from the group consisting of H; C₁-C₄ alkyl in particular methyl, ethyl, propyl, *iso*-propyl, butyl or *iso*-butyl; C₁-C₄ alkenyl, e.g. ethenyl, 1-propenyl, 2-propenyl, *iso*-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, *iso*-butenyl or *sec*-butenyl; C₁-C₄ alkynyl, e.g. ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl or 3-butylnyl; -CN; halogen, in particular F, Cl, Br or I; -OH; C₁-C₄ alkoxy, e.g. methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy or *tert*-butoxy; -SH; C₁-C₄ S-alkyl, e.g. C₁, C₂, C₃ or C₄ S-alkyl; -CF₃; -OCF₃; -NH₂; -N(CH₃)₂ and C₁-C₄ hydroxyalkyl, e.g. hydroxymethyl, hydroxyethyl, hydroxypropyl or hydroxyl-*iso*-propyl, 1-hydroxybutyl or 2-hydroxybutyl;

with the proviso that R⁹ and R¹² may not be methoxy at the same time;

R²⁰ has the above indicated meaning, e.g. methyl, ethyl, propyl, *iso*-propyl, butyl or *iso*-butyl; and

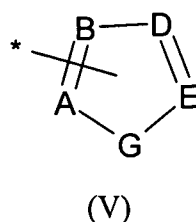
* indicates the bond between R⁴ and the compound according to any of formulas (I) through (III).

In the preferred embodiment wherein R⁴ has the structure of formula (IV) it is particularly preferred that (a) R⁹ is CN, R¹⁰, R¹¹ and R¹² is H; (b) R¹⁰ is CN and R⁹, R¹¹ and R¹² is H, (c) R⁹, R¹⁰ and R¹¹ is H and R¹² is CN; (d) R⁹ is ethynyl, R¹⁰, R¹¹ and R¹² is H; (e) R¹⁰ is ethynyl, R⁹, R¹¹ and R¹² is H, (f) R⁹, R¹⁰ and R¹¹ is H and R¹² is ethynyl; (g) R⁹ is CN and one of R¹⁰, R¹¹ and R¹² is OH or C₁-C₄ alkoxy, e.g. methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy or *tert*-butoxy; (h) R¹⁰ is CN and one of R⁹, R¹¹ and R¹², preferably R⁹ is halogen, in particular F, OH or C₁-C₄ alkoxy, e.g. methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy or *tert*-butoxy or (i) one of R⁹, R¹⁰ and R¹¹ is OH or C₁-C₄ alkoxy, e.g. methoxy, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy or *tert*-butoxy and R¹² is CN; preferably R¹⁰ is CN and R⁹ is OH or C₁-C₄ alkoxy, preferably methoxy.

Further preferred is a compound of the invention, wherein R¹¹ and R¹² are H.

In another preferred embodiment of the compound of the invention, R³ is methyl; R² is H, methyl or ethyl, preferably H; and R⁵ and R⁶ are H.

In a preferred embodiment of the compound of the invention, R⁴ has a structure according to formula V:



wherein

A, B, D and E are each individually selected from the group consisting of a nitrogen atom, CR¹³ and N-O;

G is selected from the group consisting of an oxygen atom, a sulphur atom and NR¹⁴;

R¹³ is selected from the group consisting of H; C₁-C₃ alkyl, in particular methyl, ethyl, propyl or *iso*-propyl; C₁-C₃ alkoxy, e.g. methoxy, ethoxy, propoxy or *iso*-propoxy; -OH; -SH; S-alkyl, e.g. C₁, C₂ or C₃ S-alkyl; -CF₃; -OCF₃; halogen, in particular F, Cl, Br or I; -NR¹⁵R¹⁶, preferably -NH₂ or -NH-C₁-C₄ alkyl, i.e. -NH-CH₃, -NH-ethyl, -NH-C₃ alkyl or -NH-C₄ alkyl and most preferably -NH₂, NH(CH₃) or N(CH₃)₂; -NO₂; -CN; -C(O)R²⁰; acetylene; cyanoacetylene; C₁-C₄ hydroxyalkyl, e.g. hydroxymethyl, hydroxyethyl, hydroxypropyl or hydroxyl-*iso*-propyl, 1-hydroxybutyl or 2-hydroxybutyl and a σ (sigma) bond connecting R⁴ to the compound according to any of formulas (I) through (III); and

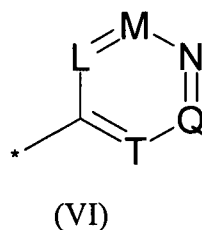
R¹⁴ is selected from the group consisting of H, C₁-C₄ alkyl, in particular methyl, ethyl, propyl, *iso*-propyl, butyl or *iso*-butyl and more preferably methyl, ethyl, propyl or *iso*-propyl; and a σ (sigma) bond connecting R⁴ to the compound according to any of formulas (I) through (III); and

R¹⁵ and R¹⁶ are each individually either H or C₁-C₄ alkyl, in particular methyl, ethyl, propyl, *iso*-propyl, butyl or *iso*-butyl;

R²⁰ has the above indicated meaning, e.g. methyl, ethyl, propyl, *iso*-propyl, butyl or *iso*-butyl; and

* indicates the bond between R⁴ and the compound according to any of formulas (I) through (III).

In another preferred embodiment of the compound of the invention, R⁴ has a structure according to formula VI:



wherein

L and T are each individually either a CH group or a nitrogen atom or N-O;

M, N and Q are each individually selected from the group consisting of a nitrogen atom, a CR¹⁷ group and N-O;

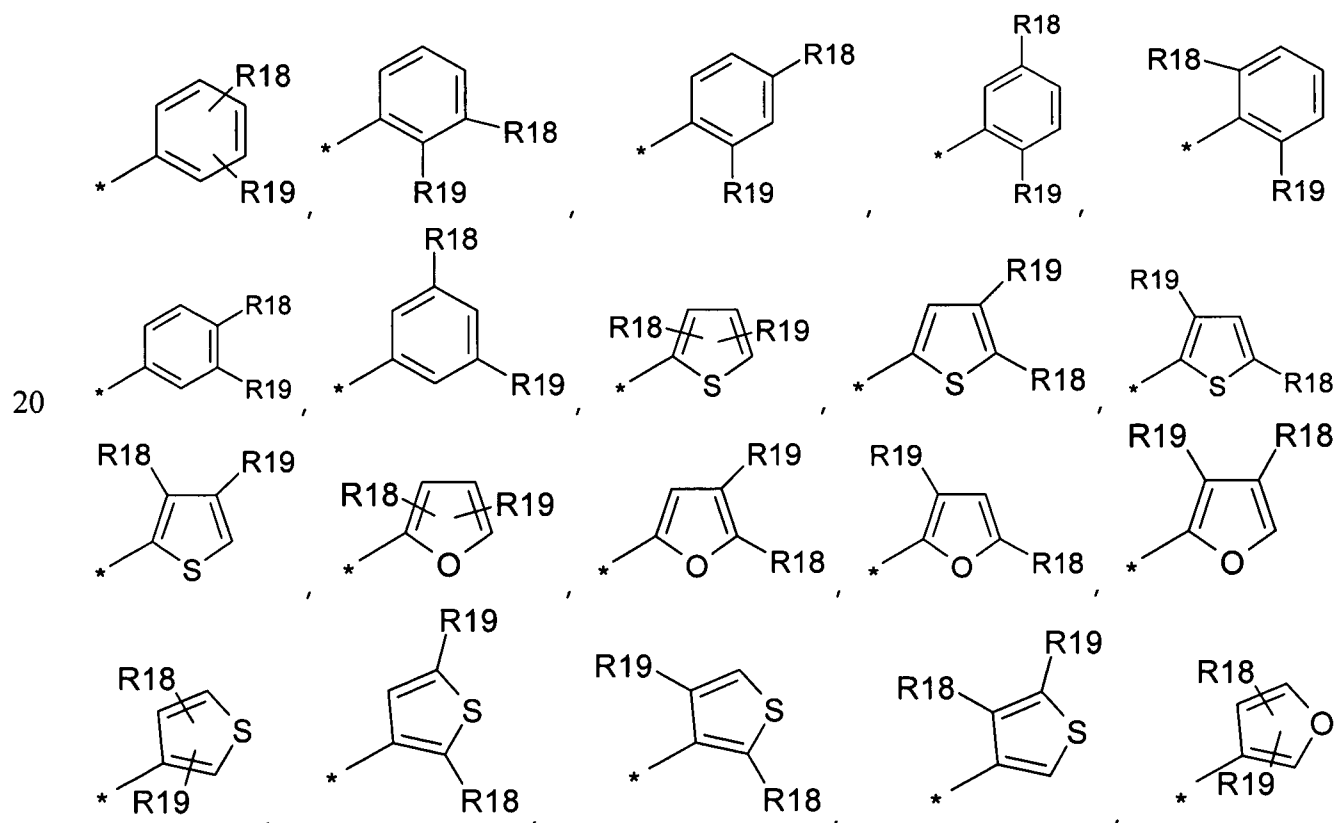
R¹⁷ is selected from the group consisting of H; C₁-C₃ alkyl, in particular methyl, ethyl, propyl or *iso*-propyl; C₁-C₃ alkoxy, e.g. methoxy, ethoxy, propoxy or *iso*-propoxy; -CF₃; -OCF₃; halogen, in particular F, Cl, Br or I; -OH; -NO₂; -SH; C₁-C₃ S-alkyl, e.g. C₁, C₂ or C₃ S-alkyl; -NR¹⁵R¹⁶, preferably -NH₂ or -NH-C₁-C₄ alkyl, i.e. -NH-CH₃, -NH-ethyl, -NH-C₃ alkyl or -NH-C₄ alkyl and most preferably -NH₂, NH(CH₃) or N(CH₃)₂; C₁-C₄ hydroxyalkyl, e.g. hydroxymethyl, hydroxyethyl, hydroxypropyl or hydroxyl-*iso*-propyl, 1-hydroxybutyl or 2-hydroxybutyl; -C(O)R²⁰, preferably acetyl, propionyl, *iso*-propionyl, butyryl or *iso*-butyryl; acetylene; cyanoacetylene and -CN;

R¹⁵ and R¹⁶ are each individually either H or C₁-C₄ alkyl;

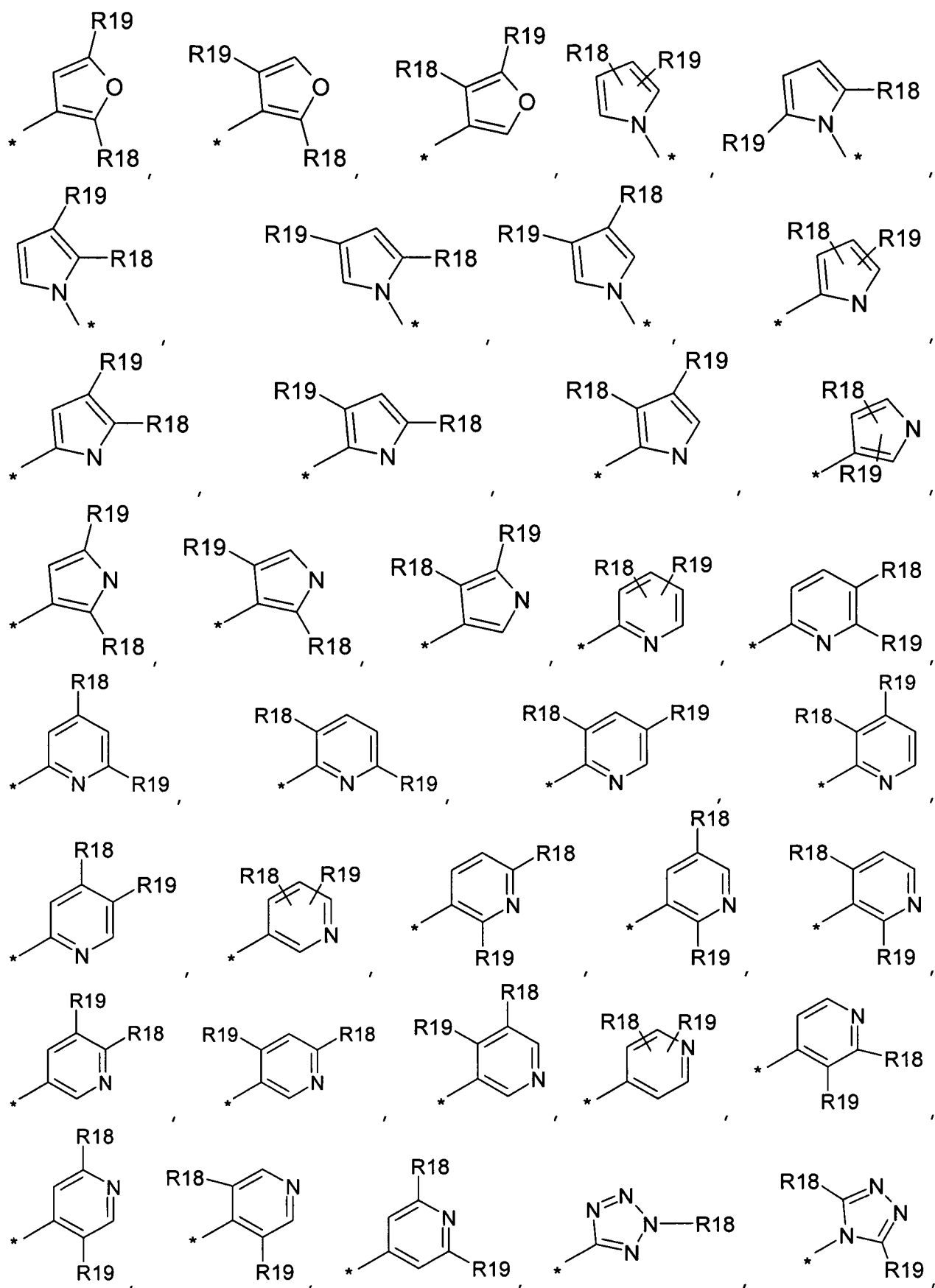
R²⁰ has the above indicated meaning, e.g. methyl, ethyl, propyl, *iso*-propyl, butyl or *iso*-butyl; and

* indicates the bond between R⁴ and the compound according to any of formulas (I) through (III).

Also preferred is a compound of the invention, wherein R⁴ is selected from the group consisting of:



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butenyl, *iso*-butenyl, *sec*-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, hexenyl, heptenyl or octenyl; alkynyl, preferably an alkynyl comprising from 2 to 8 carbon atoms, i.e. 2, 3, 4, 5, 6, 7, or 8 carbon atoms, e.g. ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, hexynyl, pentynyl or octynyl; -C(O)R⁶ preferably acetyl, propionyl, *iso*-propionyl, butyryl or *iso*-butyryl; cyanoacetylene and -CN;

and R¹⁵ and R¹⁶ have the above indicated meaning and preferred meaning.

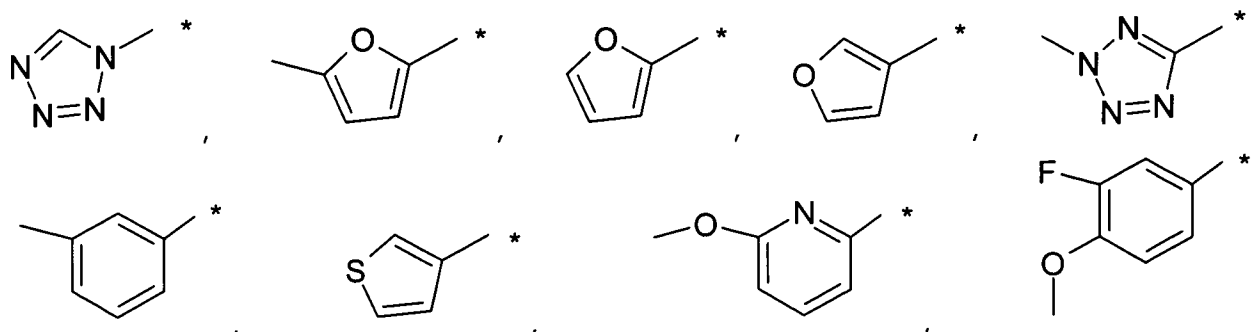
In a preferred embodiment R¹⁸ is H and R¹⁹ in above indicated structures is selected from the group consisting of C₁-C₃ alkyl, in particular methyl, ethyl, propyl or *iso*-propyl; C₁-C₃ alkoxy, e.g. methoxy, ethoxy, propoxy or *iso*-propoxy; -CF₃; -OCF₃; halogen, in particular F, Cl, Br or I; -OH; -NO₂; -SH; C₁-C₃ S-alkyl, e.g. C₁, C₂ or C₃ S-alkyl; -NR¹⁵R¹⁶, preferably -NH₂ or -NH-C₁-C₄ alkyl, i.e. -NH-CH₃, -NH-ethyl, -NH-C₃-alkyl or -NH-C₄-alkyl and most preferably -NH₂, NH(CH₃) or N(CH₃)₂; C₁-C₄-hydroxyalkyl, e.g. hydroxymethyl, hydroxyethyl, hydroxypropyl or hydroxyl-*iso*-propyl, 1-hydroxybutyl or 2-hydroxybutyl; alkenyl, particularly an alkenyl chain comprising from 2 to 8 carbon atoms, i.e. 2, 3, 4, 5, 6, 7, or 8 carbon atoms, e.g. ethenyl, 1-propenyl, 2-propenyl, *iso*-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, *iso*-butenyl, *sec*-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, hexenyl, heptenyl or octenyl; alkynyl, preferably an alkynyl comprising from 2 to 8 carbon atoms, i.e. 2, 3, 4, 5, 6, 7, or 8 carbon atoms, e.g. ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, hexynyl, pentynyl or octynyl; -C(O)R⁶ preferably acetyl, propionyl, *iso*-propionyl, butyryl or *iso*-butyryl; cyanoacetylene and -CN. The most preferred meanings of R¹⁹ in this context are C₁-C₃ alkyl, in particular methyl, ethyl, propyl or *iso*-propyl; C₁-C₃ alkoxy, in particular methoxy, ethoxy, propoxy or *iso*-propoxy; -CF₃; -OCF₃, -CN, -NO₂, or halogen, in particular F, Cl, Br or I, with methyl, methoxy, CF₃ or -CN being the most preferred meanings.

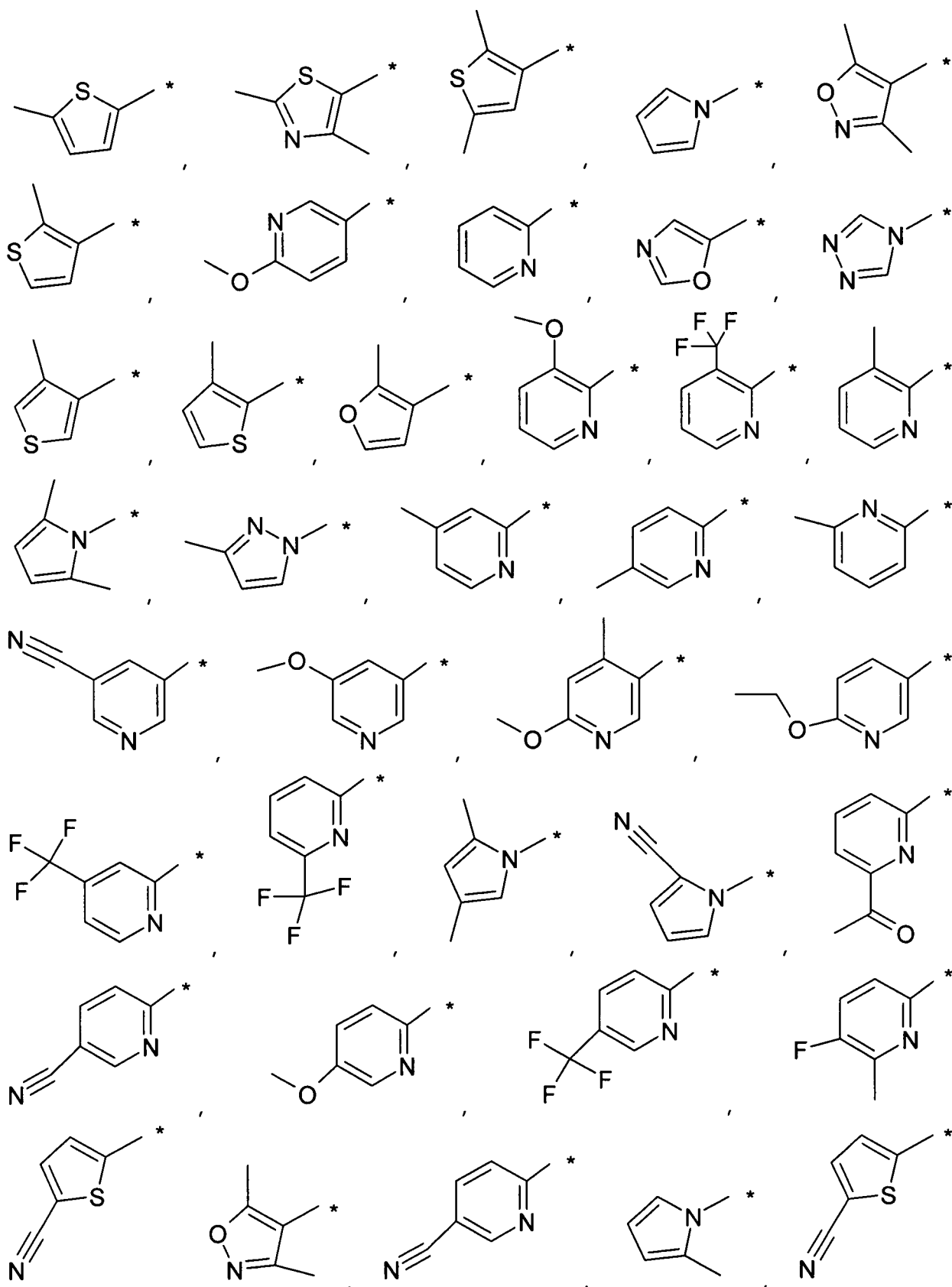
In another preferred embodiment R¹⁹ is H and R¹⁸ in above indicated structures is selected from the group consisting of C₁-C₃ alkyl, in particular methyl, ethyl, propyl or *iso*-propyl; C₁-C₃ alkoxy, e.g. methoxy, ethoxy, propoxy or *iso*-propoxy; -CF₃; -OCF₃; halogen, in particular F, Cl, Br or I; -OH; -NO₂; -SH; C₁-C₃ S-alkyl, e.g. C₁, C₂ or C₃ S-alkyl; -NR¹⁵R¹⁶, preferably -NH₂ or -NH-C₁-C₄ alkyl, i.e. -NH-CH₃, -NH-ethyl, -NH-C₃-alkyl or -NH-C₄-alkyl and most preferably -NH₂, NH(CH₃) or N(CH₃)₂; C₁-C₄-hydroxyalkyl, e.g. hydroxymethyl, hydroxyethyl, hydroxypropyl or hydroxyl-*iso*-propyl, 1-hydroxybutyl or 2-hydroxybutyl; alkenyl, particularly an alkenyl chain comprising from 2 to 8 carbon atoms, i.e. 2, 3, 4, 5, 6, 7, or 8 carbon atoms, e.g. ethenyl, 1-propenyl, 2-propenyl, *iso*-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, *iso*-butenyl, *sec*-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, hexenyl,

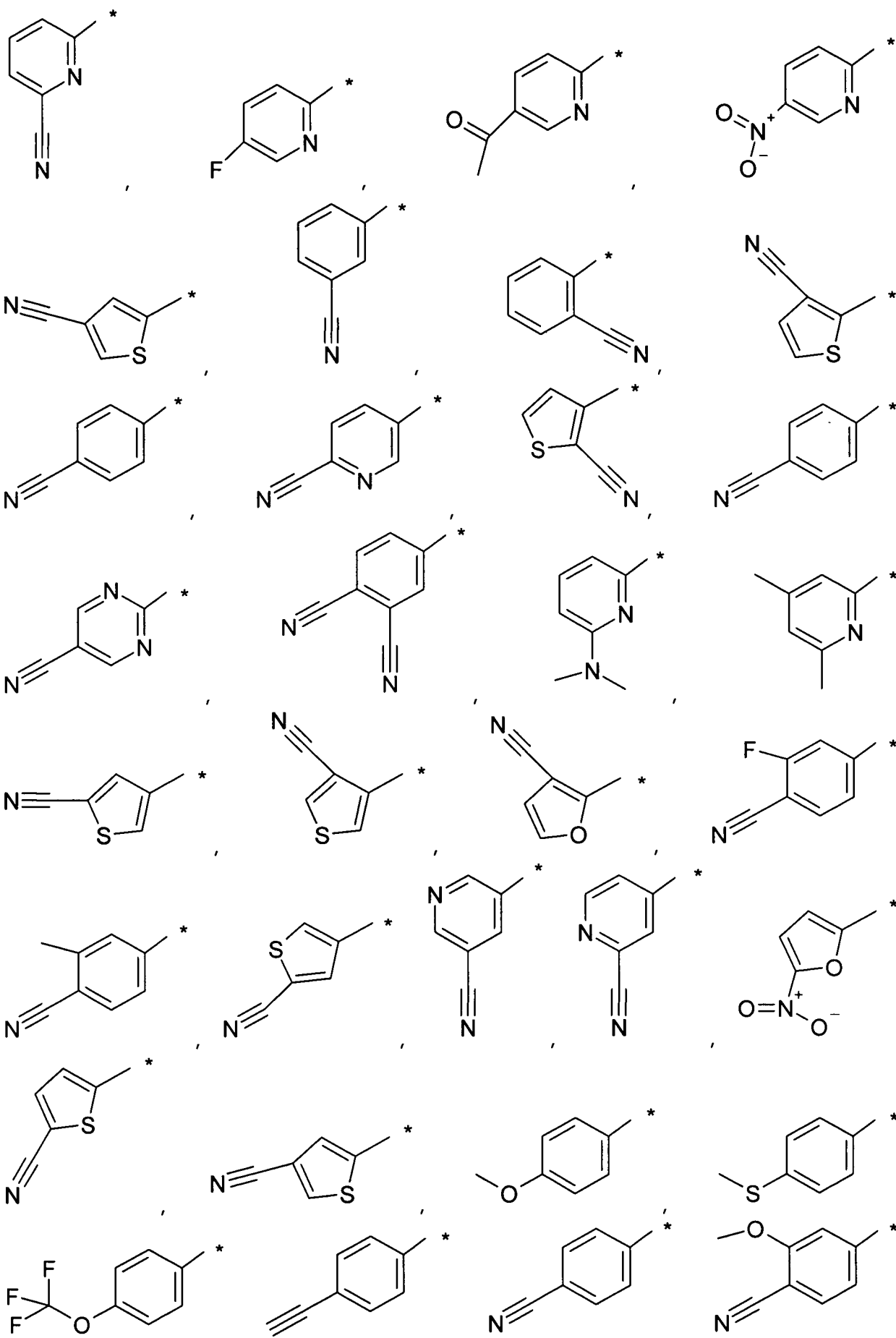
heptenyl or octenyl; alkynyl, preferably an alkynyl comprising from 2 to 8 carbon atoms, i.e. 2, 3, 4, 5, 6, 7, or 8 carbon atoms, e.g. ethynyl, 1-propynyl, 2-propynyl, 1-butyryl, 2-butyryl, 3-butyryl, 1-pentyryl, 2-pentyryl, 3-pentyryl, 4-pentyryl, hexynyl, pentyryl or octynyl; $-C(O)R^6$ preferably acetyl, propionyl, iso-propionyl, butyryl or iso-butyryl; cyanoacetylene and $-CN$. The most preferred meanings of R^{18} in this context are C_1 - C_3 alkyl, in particular methyl, ethyl, propyl or *iso*-propyl; C_1 - C_3 alkoxy, in particular methoxy, ethoxy, propoxy or *iso*-propoxy; $-CF_3$; $-OCF_3$, $-CN$, NO_2 , or halogen, in particular F, Cl, Br or I, with methyl, methoxy, CF_3 or $-CN$ being the most preferred meanings.

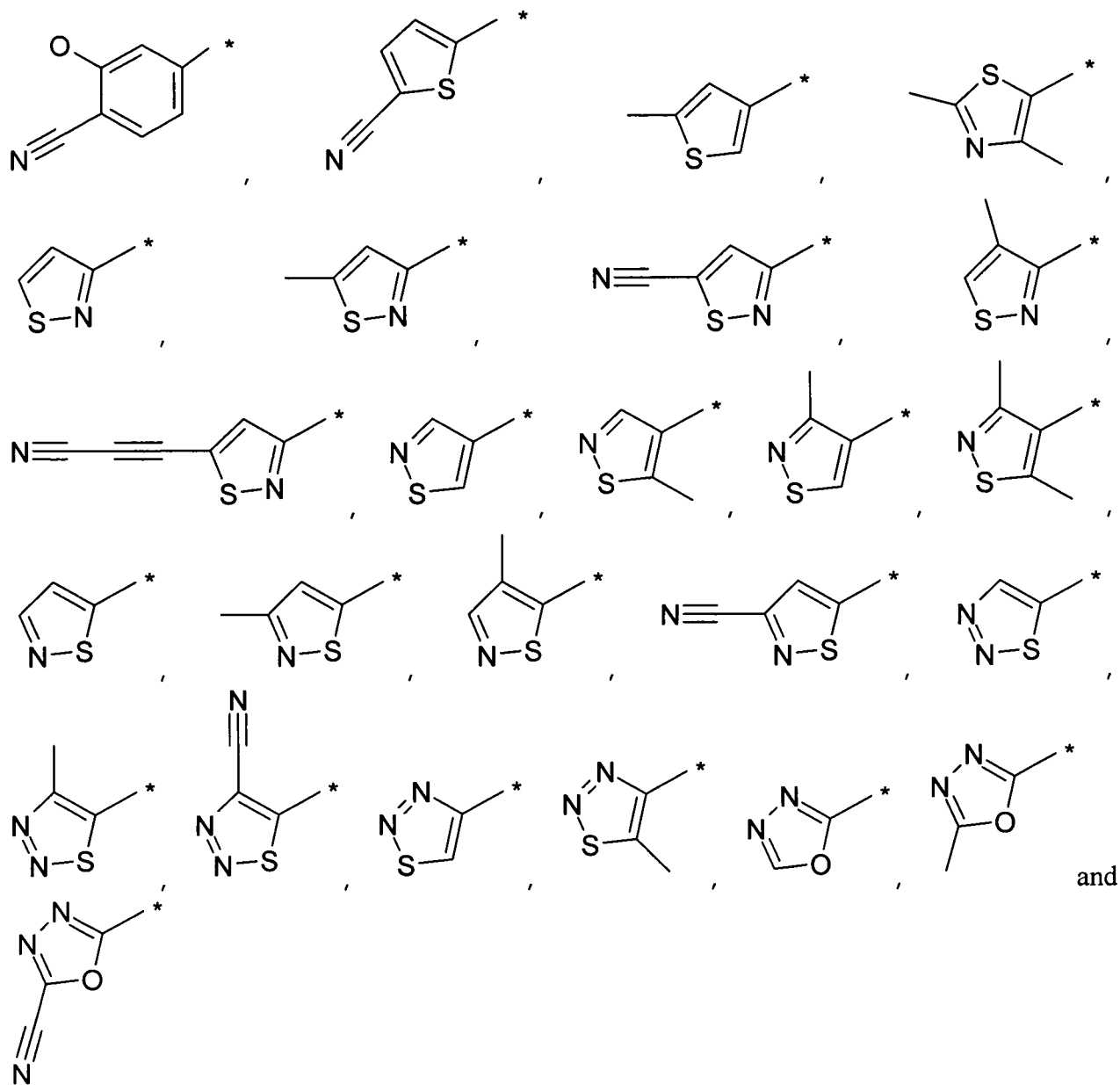
In another preferred embodiment R^{18} and R^{19} are each individually selected from the group consisting of C_1 - C_3 alkyl, in particular methyl, ethyl, propyl or *iso*-propyl; C_1 - C_3 alkoxy, e.g. methoxy, ethoxy, propoxy or *iso*-propoxy; $-CF_3$; $-OCF_3$; halogen, in particular F, Cl, Br or I; $-OH$; $-NO_2$; $-SH$; C_1 - C_3 S-alkyl, e.g. C_1 , C_2 or C_3 S-alkyl; $-NR^{15}R^{16}$, preferably $-NH_2$ or $-NH$ - C_1 - C_4 alkyl, i.e. $-NH-CH_3$, $-NH$ -ethyl, $-NH$ - C_3 -alkyl or $-NH$ - C_4 -alkyl and most preferably $-NH_2$, $NH(CH_3)$ or $N(CH_3)_2$; C_1 - C_4 -hydroxyalkyl, e.g. hydroxymethyl, hydroxyethyl, hydroxypropyl or hydroxyl-*iso*-propyl, 1-hydroxybutyl or 2-hydroxybutyl; alkenyl, particularly an alkenyl chain comprising from 2 to 8 carbon atoms, i.e. 2, 3, 4, 5, 6, 7, or 8 carbon atoms, e.g. ethenyl, 1-propenyl, 2-propenyl, *iso*-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, *iso*-butenyl, *sec*-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, hexenyl, heptenyl or octenyl; alkynyl, preferably an alkynyl comprising from 2 to 8 carbon atoms, i.e. 2, 3, 4, 5, 6, 7, or 8 carbon atoms, e.g. ethynyl, 1-propynyl, 2-propynyl, 1-butyryl, 2-butyryl, 3-butyryl, 1-pentyryl, 2-pentyryl, 3-pentyryl, 4-pentyryl, hexynyl, pentyryl or octynyl; $-C(O)R^6$ preferably acetyl, propionyl, iso-propionyl, butyryl or iso-butyryl; cyanoacetylene and $-CN$. The most preferred meanings of R^{18} and R^{19} in this context are C_1 - C_3 alkyl, in particular methyl, ethyl, propyl or *iso*-propyl; C_1 - C_3 alkoxy, in particular methoxy, ethoxy, propoxy or *iso*-propoxy; $-CF_3$; $-OCF_3$, $-CN$, NO_2 , or halogen, in particular F, Cl, Br or I, with methyl, methoxy, CF_3 or $-CN$ being the most preferred meanings.

In another preferred embodiment of the compound of the invention, R^2 is H and R^4 is selected from the group consisting of:









wherein * indicates the bond between R^4 and the compound according to any of formulas (I) through (III).

In a further preferred embodiment of the compound of the invention R^2 and/or R^6 is H.

The following Table 1 lists further preferred combinations of specific substituents of the compound of the invention:

Table 1

R^1	R^2	R^3	R^4	R^5	R^6	R^{11}	R^{12}
as defined herein	H	methyl	as defined herein	H	H	as defined herein	as defined herein
as defined herein	H	methyl	as defined herein	H	as defined herein	as defined	as defined

						herein	herein
as defined herein	H	as defined herein	as defined herein	as defined herein	H	as defined herein	as defined herein
as defined herein	H	as defined herein	as defined herein	as defined herein	as defined herein	as defined herein	as defined herein
as defined herein	as defined herein	as defined herein	as defined herein	as defined herein	H	as defined herein	as defined herein
as defined herein	H	methyl	as defined herein	H	H	H	H
as defined herein	H	methyl	as defined herein	H	as defined herein	H	H
as defined herein	H	as defined herein	as defined herein	as defined herein	H	H	H
as defined herein	H	as defined herein	as defined herein	as defined herein	as defined herein	H	H
as defined herein	as defined herein	as defined herein	as defined herein	as defined herein	H	H	H

In a particularly preferred embodiment of the compound of the invention, the compound is selected from the group of compounds listed in Table 2A or Table 7.

In a further aspect the invention provides a compound according to the invention or
5 pharmaceutically acceptable salt thereof, for the prevention or treatment of a disease or disorder.

As shown in the examples below, the advantageous properties of the compounds of the invention include their ability of effectively inhibiting cell proliferation and their activity as HIF inhibitors. For example, the compounds of the present invention were shown to inhibit the activation of HIF-mediated transcription under hypoxic conditions. Thus, the compounds of the
10 invention can be used for the preparation of a medicament for the treatment of a disorder characterized by pathophysiological HIF signaling. A person skilled in the art of medical, biological and/or pharmacological science can determine with routine methodology if a disorder is characterized by undesirable HIF signaling. Tissues affected by such diseases will overexpress genes that are induced by activation of the HIF responsive element (HRE). HIF-1 acts by binding
15 to HIF-responsive elements (HREs) in promoters that generally contain the sequence NCGTG.

The genes affected by HIF activity which are regulated by said promoters are well known in the art and were also described in multiple reviews (see e.g. figure 3 of Gregg L. Semenza, Nature Reviews, Oct. 2003, vol. 3).

In animal studies, HIF-1 overexpression is associated with increased tumor growth, increased vascularisation, metastasis and fibrosis, e.g. renal fibrosis (see: Semenza, G, Drug Discovery Today, vol. 12, no. 19/20, October 2007; Kimura, Kuniko, et al., American Journal of Physiology (2008), 295(4, Pt. 2), F1023-F1029 and for a review see N.J. Mabeesh et al., Histol. Histopathol (2007) 22:559-572). Fibrosis is the formation or development of excess fibrous connective tissue in an organ or tissue. Recently, it has become clear that inhibition of HIF-1 activity also acts to prevent inflammation, by virtue of its essential role in the activation and infiltration of macrophages and neutrophils into affected tissues (see e.g. Giaccia et al., Drug Discovery, vol. 2, October 2003).

Pharmaceutical compositions

For the above mentioned reasons, a compound of the present invention can be used to treat an inflammatory disease, a hyperproliferative disease or disorder, a hypoxia related pathology and also diseases characterized by pathophysiological hyper-vascularisation. Therefore, as a further aspect, the invention provides a therapeutical composition wherein the compound of the invention is combined with at least one further pharmaceutically active compound that is useful to treat one of the aforementioned diseases or disorders. Such therapeutical compositions are useful because the therapeutic efficiency of the compounds of the invention can be amplified by the presence of said at least one further pharmaceutically active compound and *vice versa*. For example, it was shown that inhibiting HIF1 α activity via antisense gene therapy enhances the therapeutic efficacy of doxorubicin to combat hepatocellular carcinoma (see Liu, Fengjun et. al., Cancer Science (2008), 99(10), 2055-2061).

Thus, in a further aspect, the present invention relates to a pharmaceutical composition comprising a compound according to the invention or pharmaceutically acceptable salt thereof and a second therapeutic agent useful for the treatment or prevention of a disease or disorder selected from the group consisting of an inflammatory disease, a hyperproliferative disease or disorder, a hypoxia related pathology and a disease characterized by pathophysiological hyper-vascularisation, and, optionally, a pharmaceutically acceptable carrier or excipient. Such compositions are also useful to obtain synergistic therapeutic effects and also to prevent drug resistance of tumor cells, for example. It is also for these reasons, that current chemotherapy generally involves administering a cocktail of different cytotoxic and/or cytostatic compounds to improve the effectiveness of the treatment and reduce the possibility of tumor cell adaptation.

In a further aspect, the present invention relates to a pharmaceutical composition comprising a compound according to the invention or pharmaceutically acceptable salt thereof in combination with radiation therapies.

Any composition of the present invention may be admixed with a pharmaceutically acceptable diluent, excipient or carrier, or a mixture thereof.

Even though the compounds of the present invention (including their pharmaceutically acceptable salts, esters and pharmaceutically acceptable solvates) can be administered alone, they will generally be administered in admixture with a pharmaceutical carrier, excipient or diluent, particularly for human therapy. The pharmaceutical compositions may be for human or animal usage in human and veterinary medicine. Examples of such suitable excipients for the various different forms of pharmaceutical compositions described herein may be found in the "Handbook of Pharmaceutical Excipients", 2nd Edition, (1994), Edited by A Wade and PJ Weller. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co. (A. R Gennaro edit. 1985).

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from 5% to 80%, more preferably from 20% to 70% of the active compound or active compounds. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as

by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. Liquid forms are particularly preferred for topical applications to the eye. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations, which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Interestingly, HIF inhibitors, such as the compounds of the invention, can prevent the development of tumor resistance towards chemotherapeutic drugs and can make cancer cells more sensitive towards radiotherapy (see e.g. Palayoor ST, et al., Int J Cancer. 2008 Nov 15;123(10):2430-7 and Gregg L. Semenza, Nature Reviews, Oct. 2003, vol. 3). Thus, useful second therapeutic agents that can be combined with a compound of the invention to produce the pharmaceutical composition of the invention include, without limitation, a (further) HIF-1 inhibitor, a cytotoxic compound and cytostatic compounds.

A HIF-1 inhibitor can be, e.g. selected from the group consisting of PX-478 (*S*-2-amino-3-[4'-*N,N*,-bis(2-chloroethyl)amino]phenyl propionic acid *N*-oxide dihydrochloride); a topoisomerase-1 inhibitor such as 8,9-Dimethoxy-5-(2-*N,N*-dimethylaminoethyl)-2,3-methylenedioxy-5*H*-dibenzo[*c,h*][1,6] naphthyridin-6-one (also known as ARC-111 or topovale) or (*S*)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1*H*-pyrano[3',4':6,7] indolizino [1,2-*b*]quinoline-3,14-(4*H* ,12*H*)-dione monohydrochloride (also referred to as tropotecan);

echinomycin; chetomin (NSC289491); cyclosporine A; 3-[2-[4-[bis(4-fluorophenyl)methylene]-1-piperidinyl]-2,3-dihydro-2thioxo-4(1H)-quinazolinone (R59949); an inhibitor of the PIK3K/Akt/mTor signalling cascade, e.g., LY294002, wortmannin or rapamycin; an inhibitor of the MAPK signalling cascade, e.g. the MEK1 inhibitor PD98059; a soluble guanyl cyclase stimulator such as 3-(5'-hydroxymethyl-2'-furyl)-1-benzylindazole (YC-1); a heat-shock protein 90 inhibitor, in particular radicicol, the radicicol analogue KF58333 or geldanamycin; a microtubule disrupting agent, in particular e.g. taxol, vincristine or 2-methoxyestradiol; a histone deacetylase inhibitor, e.g. FK228; a thioredoxin inhibitor, in particular PX-12 or pleurotin; UCNO-1; diphenylene iodonium, genestein and carboxyamido-triazole.

Many cytotoxic or cytostatic compounds are known to the expert artisan skilled in the therapy of hyperproliferative diseases or disorders such as a tumor or cancer disease. For example, cytotoxic and cytostatic compounds include, but are not limited to, pure or mixed anti-estrogens such as faslodex, tamoxifen or raloxifen; any inhibitors of topoisomerase I or II, such as camptothecin (topo I) or etoposide (topo II); any compound that acts through inhibiting aromatase activity, such as anastrozole or letrozole; any preparation that interferes with HER2 signalling such as herceptin; any compound that interchelates DNA, such as doxorubicin. Particularly preferred cytostatic or cytotoxic drugs, which can be combined with the compounds of the present invention are alkylating substances, anti-metabolites, antibiotics, epothilones, nuclear receptor agonists and antagonists, anti-androgens, anti-estrogens, platinum compounds, hormones and antihormones, interferons and inhibitors of cell cycle-dependent protein kinases (CDKs), inhibitors of cyclooxygenases and/or lipoxygenases, biogenic fatty acids and fatty acid derivatives, including prostanoids and leukotrienes, inhibitors of protein kinases, inhibitors of protein phosphatases, inhibitors of lipid kinases, platinum coordination complexes, ethyleneimines, methylmelamines, triazines, vinca alkaloids, pyrimidine analogs, purine analogs, alkylsulfonates, folic acid analogs, anthracendiones, substituted urea, methylhydrazine derivatives, in particular acediasulfone, aclarubicin, ambazone, aminoglutethimide, L-asparaginase, azathioprine, bleomycin, busulfan, calcium folinate, carboplatin, carpecitabine, carmustine, celecoxib, chlorambucil, cis-platin, cladribine, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, dapsone, daunorubicin, dibrompropamide, diethylstilbestrol, docetaxel, doxorubicin, enediyne, epirubicin, epothilone B, epothilone D, estramucine phosphate, estrogen, ethinylestradiol, etoposide, flavopiridol, floxuridine, fludarabine, fluorouracil, fluoxymesterone, flutamide, fosfestrol, furazolidone, gemcitabine, gonadotropin releasing hormone analog, hexamethylmelamine, hydroxycarbamide, hydroxymethylnitrofurantoin, hydroxyprogesterone caproate, hydroxyurea, idarubicin, idoxuridine, ifosfamide, interferon γ , irinotecan, leuprolide, lomustine, lurtotecan, mafenide

sulfate olamide, mechlorethamine, medroxyprogesterone acetate, megastrolacetate, melphalan, mepacrine, mercaptopurine, methotrexate, metronidazole, mitomycin C, mitopodozide, mitotane, mitoxantrone, mithramycin, nalidixic acid, nifuratel, nifuroxazide, nifuralazine, nifurtimox, nimustine, ninorazole, nitrofurantoin, nitrogen mustards, oleomucin, oxolinic acid, pentamidine, pentostatin, phenazopyridine, phthalylsulfathiazole, pipobroman, prednimustine, prednisone, preussin, procarbazine, pyrimethamine, raltitrexed, rapamycin, rofecoxib, rosiglitazone, salazosulfapyridine, scriflavinium chloride, semustine streptozocine, sulfacarbamide, sulfacetamide, sulfachlopyridazine, sulfadiazine, sulfadicramide, sulfadimethoxine, sulfaethidole, sulfafurazole, sulfaguanidine, sulfaguanole, sulfamethizole, sulfamethoxazole, cotrimoxazole, sulfamethoxydiazine, sulfamethoxypyridazine, sulfamoxole, sulfanilamide, sulfaperin, sulfaphenazole, sulfathiazole, sulfisomidine, staurosporin, tamoxifen, taxol, teniposide, tertiposide, testolactone, testosteronepropionate, thioguanine, thiotepa, tinidazole, topotecan, triaziquone, treosulfan, trimethoprim, trofosfamide, UCN-01, vinblastine, vincristine, vindesine, vinblastine, vinorelbine, and zorubicin, or their respective derivatives or analogs thereof. Several of the above indicated drugs are now administered simultaneously for cancer therapy and, consequently, it is also envisioned that more than one cytostatic and/or cytotoxic drug can be comprised in compositions of the present invention.

As mentioned above, HIF inhibitors render cancer cells more vulnerable to chemotherapy and radiation therapy. Thus, to effectively treat a hyperproliferative disease or disorder, the compounds of the present invention can be co-administered with other active medicinal agents and/or administered in conjunction with other anticancer, antitumor, or antiproliferative disease therapies. In one aspect, the invention provides a method for treating a hyperproliferative disease or disorder comprising administering a compound according to the invention to a patient prior to, during and/or after said patient was subjected to a radiation therapy, a chemotherapy, an immunotherapy, a laser/microwave thermotherapy or a gene therapy using antisense DNA and RNA (for examples see Moeller et al., Cancer Cell 2004 5429-441).

In a further aspect the invention provides, as already outlined above, the use of a compound according to the invention or a composition according to the invention for the preparation of a medicament for the treatment or prevention of a disease or disorder selected from the group consisting of an inflammatory disease, a hyperproliferative disease or disorder, a hypoxia related pathology such as e.g. diabetic retinopathy, ischemic reperfusion injury, ischemic myocardial and limb disease, ischemic stroke, sepsis and septic shock (see, e.g. Liu FQ, et al., Exp Cell Res. 2008 Apr 1;314(6):1327-36); and a disease characterized by pathophysiological hyper-vascularisation, such as e.g. angiogenesis in osteosarcoma (see, e.g.: Yang, Qing-cheng et al., Dier Junyi Daxue Xuebao (2008), 29(5), 504-508), macular

degeneration, in particular, age-related macular degeneration and vasoproliferative retinopathy (see e.g. Kim JH, et al., J Cell Mol Med. 2008 Jan 19).

As was already mentioned above, HIF inhibitors, such as the compounds of the invention, are useful to treat inflammatory disease or disorder. For example, it was shown that oxygen-dependent HIF isoforms are strongly upregulated in psoriatic skin (see e.g. Rosenberger C, et al., J Invest Dermatol. 2007 Oct;127(10):2445-52). Furthermore it was shown that a HIF inhibitor, neovastat, inhibits the airway inflammation in asthma (see e.g., Lee SY, et al., Vascu Pharmacol. 2007 Nov-Dec; 47(5-6):313-8). Furthermore, recent evidence also shows that HIF participates under hypoxic conditions in joint inflammation and destruction in rheumatoid arthritis (see e.g., Ahn, J. K., et al., Rheumatology (Oxford, United Kingdom) (2008), 47(6), 834-839). Thus, in a preferred embodiment of the use of the invention, the inflammatory disease is selected from the group consisting of atherosclerosis, rheumatoid arthritis, asthma, inflammatory bowel disease, psoriasis, in particular psoriasis vulgaris, psoriasis capitis, psoriasis guttata, psoriasis inversa; neurodermatitis; ichthyosises; alopecia areata; alopecia totalis; alopecia subtotalis; alopecia universalis; alopecia diffusa; atopic dermatitis; lupus erythematoses of the skin; dermatomyositis of the skin; atopic eczema; morphea; scleroderma; alopecia areata Ophiasis type; androgenic alopecia; allergic dermatitis; irritative contact dermatitis; contact dermatitis; pemphigus vulgaris; pemphigus foliaceus; pemphigus vegetans; scarring mucous membrane pemphigoid; bullous pemphigoid; mucous membrane pemphigoid; dermatitis; dermatitis herpetiformis Dühring; urticaria; necrobiosis lipoidica; erythema nodosum; prurigo simplex; prurigo nodularis; prurigo acuta; linear IgA dermatosis; polymorphic light dermatosis; erythema solaris; exanthema of the skin; drug exanthema; purpura chronica progressiva; dihydrotic eczema; eczema; fixed drug exanthema; photoallergic skin reaction; and periorale dermatitis. Therefore, a further preferred embodiment of the present invention encompasses a combination of one or more compounds of the present invention and medication in current use for treating such inflammatory diseases or conditions, which can be determined by a person skilled in the art of pharmacological sciences. Such therapeutics for combination can be selected e.g. from a group of anti-inflammatory steroids, antioxidants, therapeutic antibodies or fusion proteins that sequester or bind to certain cytokines or cellular epitopes associated with inflammatory processes, or a dihydrofolate reductase inhibitor like methotrexate.

The compounds of the invention show anti-proliferative effects. Furthermore, HIF inhibitors, such as the compounds of the invention are effective medicaments for the treatment of various cancer diseases (see review article by e.g. Gregg L. Semenza, Nature Reviews, Oct. 2003, vol. 3 and also review article by N.J. Mabeesh et al., Histol. Histopathol (2007), 22:559-572). Thus, also preferred is the use of the invention wherein the hyperproliferative disease is

selected from the group consisting of a tumour or cancer disease, precancerosis, dysplasia, histiocytosis, a vascular proliferative disease and a virus-induced proliferative disease. Thus, in one preferred embodiment of the use of the invention the hyperproliferative disease is a tumor or cancer disease selected from the group consisting of diffuse large B-cell lymphoma (DLBCL), T-cell lymphomas or leukemias, e.g., cutaneous T-cell lymphoma (CTCL), noncutaneous peripheral T-cell lymphoma, lymphoma associated with human T-cell lymphotropic virus (HTLV), adult T- cell leukemia/lymphoma (ATLL), as well as acute lymphocytic leukemia, acute nonlymphocytic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, myeloma, multiple myeloma, mesothelioma, childhood solid tumors, glioma, bone cancer and soft-tissue sarcomas, common solid tumors of adults such as head and neck cancers (e.g., oral, laryngeal and esophageal), genitourinary cancers (e.g., prostate, bladder, renal (in particular malignant renal cell carcinoma (RCC)), uterine, ovarian, testicular, rectal, and colon), lung cancer (e.g., small cell carcinoma and non-small cell lung carcinoma, including squamous cell carcinoma and adenocarcinoma), breast cancer, pancreatic cancer, melanoma and other skin cancers, basal cell carcinoma, metastatic skin carcinoma, squamous cell carcinoma of both ulcerating and papillary type, stomach cancer, brain cancer, liver cancer, adrenal cancer, kidney cancer, thyroid cancer, medullary carcinoma, osteosarcoma, soft-tissue sarcoma, Ewing's sarcoma, veticulum cell sarcoma, and Kaposi's sarcoma, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, leiomyosarcoma, rhabdomyosarcoma, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, seminoma, embryonal carcinoma, Wilms' tumor, small cell lung carcinoma, epithelial carcinoma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, neuroblastoma, retinoblastoma, glaucoma, hemangioma, heavy chain disease and metastases.

The precancerosis treatable with the compounds of the present invention are preferably selected from the group consisting of precancerosis, in particular actinic keratosis, cutaneous horn, actinic cheilitis, tar keratosis, arsenic keratosis, x-ray keratosis, Bowen's disease, bowenoid papulosis, lentigo maligna, lichen sclerosus, and lichen rubber mucosae; precancerosis of the digestive tract, in particular erythroplakia, leukoplakia, Barrett's esophagus, Plummer-Vinson syndrome, crural ulcer, gastropathia hypertrophica gigantea, borderline carcinoma, neoplastic intestinal polyp, rectal polyp, porcelain gallbladder; gynaecological precancerosis, in particular

carcinoma ductale in situ (CDIS), cervical intraepithelial neoplasia (CIN), leukoplakia, endometrial hyperplasia (grade III), vulvar dystrophy, vulvar intraepithelial neoplasia (VIN), hydatidiform mole; urologic precancerosis, in particular bladder papillomatosis, Queyrat's erythroplasia, testicular intraepithelial neoplasia (TIN), leukoplakia; carcinoma in situ (CIS);
5 precancerosis caused by chronic inflammation, in particular pyoderma, osteomyelitis, acne conglobata, lupus vulgaris, and fistula.

Dysplasia is frequently a forerunner of cancer, and is can be found in e.g. the epithelia; it is the most disorderly form of non-neoplastic cell growth, involving a loss in individual cell uniformity and in the architectural orientation of cells. Dysplastic cells often have abnormally
10 large, deeply stained nuclei, and exhibit pleomorphism. Dysplasia characteristically occurs where there exists chronic irritation or inflammation. Dysplastic disorders which can be treated with the compounds of the present invention include, but are not limited to, anhidrotic ectodermal dysplasia, anterofacial dysplasia, asphyxiating thoracic dysplasia, atriadigital dysplasia, bronchopulmonary dysplasia, cerebral dysplasia, cervical dysplasia,
15 chondroectodermal dysplasia, cleidocranial dysplasia, congenital ectodermal dysplasia, craniodiaphysial dysplasia, craniocarpotarsal dysplasia, craniometaphysial dysplasia, dentin dysplasia, diaphysial dysplasia, ectodermal dysplasia, enamel dysplasia, encephalo-ophthalmic dysplasia, dysplasia epiphysialis heminelia, dysplasia epiphysialis multiplex, dysplasia epiphysialis punctata, epithelial dysplasia, faciodigitogenital dysplasia, familial fibrous dysplasia
20 of jaws, familial white folded dysplasia, fibromuscular dysplasia, fibrous dysplasia of bone, florid osseous dysplasia, hereditary renal-retinal dysplasia hidrotic ectodermal dysplasia, hypohidrotic ectodermal dysplasia, lymphopenic thymic dysplasia, mammary dysplasia, mandibulofacial dysplasia, metaphysical dysplasia, Mondini dysplasia, monostotic fibrous dysplasia, mucoepithelial dysplasia, multiple epiphysial dysplasia, oculoauriculovertebral
25 dysplasia, oculodentodigital dysplasia, oculovertbral dysplasia, odontogenic dysplasia, ophthalmomandibulomelic dysplasia, periapical cemental dysplasia, polyostotic fibrous dysplasia, pseudoachondroplastic spondyloepiphysial dysplasia, retinal dysplasia, septo-optic dysplasia, spondyloepiphysial dysplasia, and ventriculoradial dysplasia.

Estrogen receptor refers to a group of receptors which are activated by the hormone 17 β -
30 estradiol (estrogen). Two types of estrogen receptor exist: ER which is a member of the nuclear hormone family of intracellular receptors and the estrogen G protein coupled receptor GPR30 (GPER), which is a G-protein coupled receptor. Estrogen and the estrogen receptors have been implicated in breast cancer, ovarian cancer, colon cancer, prostate cancer and endometrial cancer and other diseases. As the compounds of the invention are capable of inhibiting estrogen
35 receptor-mediated transcriptional activity, they can be used to treat said diseases.

Thus, in a further preferred embodiment, the hyperproliferative disorders treatable according to the invention are those which benefit from a reduced estrogen receptor signalling, i.e. disorders associated with an increased estrogen receptor signaling, if compared to healthy tissue. This particular suitability of the compounds of the present invention is based on the fact, that the compounds of the present invention potentially through inhibiting cellular replication but possibly also through an additional activity of the compounds of the present invention exert an inhibition of estrogen receptor signaling. Thus, preferred diseases, conditions and/or disorders which can be treated are selected from the group consisting of mammary tumors, endometrial tumors and tumors of the uterus. Whether a disease is associated an increased estrogen receptor activity can be measured by a variety of art known methods including determination of ER expression level in the diseased tissue by, e.g. immunological methods, which determine the amount of expressed protein, by methods determining the amount of transcribed ER encoding nucleic acids, e.g. RT-PCR, Northern-blot, nuclear run-ons etc., and determining the activity of a nucleic acid construct comprising an ER-receptor recognition element, which drives expression of a detectable reporter, e.g. CAT, luciferase, GFP etc as described in more detail in the Experimental Section below. Preferably, the disorders which benefit from a reduced estrogen receptor signaling are those, which show in the diseased tissue an increase in estrogen receptor signaling by at least 10%, preferably by at least 20%, 30%, 40%, 50%, 60%, 70%, if compared to healthy tissue. Preferably this increase is measured on the basis of a nucleic acid comprising an ER-receptor recognition element and the increase of the expression of a reporter driven by this element.

In therapeutic use as an antagonist of estrogen receptor signaling, acting through inhibition of cellular replication, the compounds utilized in the use of the invention are administered at the initial dosage of about 0.02 mg/kg to about 20 mg/kg daily. A daily dose range of about 0.05 mg/kg to about 2 mg/kg is preferred, with a daily dose range of about 0.05 mg/kg to about 1 mg/kg being most preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

Salts / esters

The compounds within the compositions or compounds usable according to the present invention can be present as salts or esters, in particular pharmaceutically acceptable salts or esters. Pharmaceutically acceptable salts of the compounds of the invention include suitable acid addition or base salts thereof. A review of suitable pharmaceutical salts may be found in Berge et al, J Pharm Sci, 66, 1-19 (1977). Salts are formed, for example with strong inorganic acids such as mineral acids, e.g. sulphuric acid, phosphoric acid or hydrohalic acids; with strong organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms which are unsubstituted or substituted (e.g., by halogen), such as acetic acid; with saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or tetraphthalic; with hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid; with aminoacids, for example aspartic or glutamic acid; with benzoic acid; or with organic sulfonic acids, such as (C1-C4)-alkyl- or aryl-sulfonic acids which are unsubstituted or substituted (for example, by a halogen) such as methane- or p-toluene sulfonic acid.

Esters are formed either using organic acids or alcohols/hydroxides, depending on the functional group being esterified. Organic acids include carboxylic acids, such as alkanecarboxylic acids of 1 to 12 carbon atoms which are unsubstituted or substituted (e.g., by halogen), such as acetic acid; with saturated or unsaturated dicarboxylic acid, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or tetraphthalic; with hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid; with aminoacids, for example aspartic or glutamic acid; with benzoic acid; or with organic sulfonic acids, such as (C1-C4)-alkyl- or aryl-sulfonic acids which are unsubstituted or substituted (for example, by a halogen) such as methane- or p-toluene sulfonic acid. Suitable hydroxides include inorganic hydroxides, such as sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminium hydroxide. Alcohols include alkanealcohols of 1-12 carbon atoms which may be unsubstituted or substituted, e.g. by a halogen).

Isotopes

The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. An isotopic variation of an agent of the present invention or a pharmaceutically acceptable salt thereof is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes that can be incorporated into the agent and pharmaceutically acceptable salts thereof

include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, fluorine and chlorine such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl , respectively. Certain isotopic variations of the agent and pharmaceutically acceptable salts thereof, for example, those in which a radioactive isotope such as ^3H or ^{14}C is incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium, i.e., ^2H , may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of the agent of the present invention and pharmaceutically acceptable salts thereof of this invention can generally be prepared by conventional procedures using appropriate isotopic variations of suitable reagents.

All isotopic variations of the compounds and compositions of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

Solvates

The present invention also includes solvate forms of the compounds within the compositions or compounds according to any of general formulas (I) through (III) usable according to the present invention. The terms used in the claims encompass these forms.

Polymorphs

The invention furthermore relates to compounds within the compositions of the present invention or compounds according to formula (I) usable according to the present invention in their various crystalline forms, polymorphic forms and (an)hydrous forms. It is well established within the pharmaceutical industry that chemical compounds may be isolated in any of such forms by slightly varying the method of purification and or isolation from the solvents used in the synthetic preparation of such compounds.

Administration

A compound according to the invention can be administered by various well known routes, including oral, rectal, intragastrical, intracranial and parenteral administration, e.g. intravenous, intramuscular, intranasal, intradermal, subcutaneous, and similar administration routes. Parenteral administration and particular intravenous administration, preferably by depot injection, is preferred. Depending on the route of administration different pharmaceutical

formulations are required and some of those may require that protective coatings are applied to the drug formulation to prevent degradation of a compound of the invention in, for example, the digestive tract.

Thus, preferably, a compound of the invention is formulated as a syrup, an infusion or injection solution, a tablet, a capsule, a capslet, lozenge, a liposome, a suppository, a plaster, a band-aid, a retard capsule, a powder, or a slow release formulation. Preferably the diluent is water, a buffer, a buffered salt solution or a salt solution and the carrier preferably is selected from the group consisting of cocoa butter and vitebesole.

Particular preferred pharmaceutical forms for the administration of a compound of the invention are forms suitable for injectionable use and include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. In all cases the final solution or dispersion form must be sterile and fluid. Typically, such a solution or dispersion will include a solvent or dispersion medium, containing, for example, water-buffered aqueous solutions, e.g. biocompatible buffers, ethanol, polyol, such as glycerol, propylene glycol, polyethylene glycol, suitable mixtures thereof, surfactants or vegetable oils. A compound of the invention can also be formulated into liposomes, in particular for parenteral administration. Liposomes provide the advantage of increased half life in the circulation, if compared to the free drug and a prolonged more even release of the enclosed drug.

Sterilization of infusion or injection solutions can be accomplished by any number of art recognized techniques including but not limited to addition of preservatives like anti-bacterial or anti-fungal agents, e.g. parabene, chlorobutanol, phenol, sorbic acid or thimersal. Further, isotonic agents, such as sugars or salts, in particular sodium chloride may be incorporated in infusion or injection solutions.

Production of sterile injectable solutions containing one or several of the compounds of the invention is accomplished by incorporating the respective compound in the required amount in the appropriate solvent with various ingredients enumerated above as required followed by sterilization. To obtain a sterile powder the above solutions are vacuum-dried or freeze-dried as necessary. Preferred diluents of the present invention are water, physiological acceptable buffers, physiological acceptable buffer salt solutions or salt solutions. Preferred carriers are cocoa butter and vitebesole. Besides the preferred excipients mentioned already above, also the following excipients can be chosen, without limitation, to be used with the various pharmaceutical forms of a compound of the invention:

- a) binders such as lactose, mannitol, crystalline sorbitol, dibasic phosphates, calcium phosphates, sugars, microcrystalline cellulose, carboxymethyl cellulose, hydroxyethyl cellulose, polyvinyl pyrrolidone and the like;

- b) lubricants such as magnesium stearate, talc, calcium stearate, zinc stearate, stearic acid, hydrogenated vegetable oil, leucine, glycerids and sodium stearyl fumarates,
- c) disintegrants such as starches, croscarmellose, sodium methyl cellulose, agar, bentonite, alginic acid, carboxymethyl cellulose, polyvinyl pyrrolidone and the like.

5 Other suitable excipients can be found in the Handbook of Pharmaceutical Excipients, published by the American Pharmaceutical Association, which is herein incorporated by reference.

It is to be understood that depending on the severity of the disorder and the particular type which is treatable with one of the compounds of the invention, as well as on the respective
10 patient to be treated, e.g. the general health status of the patient, etc., different doses of the respective compound are required to elicit a therapeutic or prophylactic effect. The determination of the appropriate dose lies within the discretion of the attending physician. It is contemplated that the average daily dosage of a compound of the invention in the therapeutic or prophylactic use of the invention should be in the range of about 0.1 mg to about 3 g. However, in a preferred
15 use of the present invention a compound of the invention is administered to a subject in need thereof in an amount ranging from 1.0 to 1000 mg, preferably ranging from 10 to 500 mg preferably ranging from 50 to 200 mg. The duration of therapy and the dosing frequency with a compound of the invention will vary, depending on the severity of the disease being treated and the condition and idiosyncratic response of each individual patient.

20 As is known in the art, the pharmaceutically effective amount of a given composition will also depend on the administration route. In general the required amount will be higher, if the administration is through the gastrointestinal tract; e.g. by suppository, rectal, or by an intragastric probe, and lower if the route of administration is parenteral, e.g. intravenous. Typically, a compound of the invention will be administered in ranges of 50 mg to 3 g, preferably 50 mg to 500 mg, if rectal or intragastric administration is used and in ranges of 10 to
25 500 mg, if parenteral administration is used.

If a person is known to be at risk of developing a disorder treatable with a compound of the invention, a prophylactic administration of the pharmaceutical composition according to the invention may be possible. In these cases, the respective compound of the invention is preferably
30 administered in above outlined preferred and particular preferred doses on a daily basis. This administration can be continued until the risk of developing the respective disorder has lessened. In most instances, however, a compound of the invention will be administered once a disease/disorder has been diagnosed. In these cases it is preferred that a first dose of a compound of the invention is administered one, two, three or four times daily. Preferably the administration

is discontinued for one day, one week or one month and then repeated until the symptoms of the respective disease are no longer worsening or until they are improving.

Within the meaning of this invention, a combination of substituents or variables is permissible only if such a combination results in a stable or chemically feasible compound. A stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization.

Various modifications and variations of the invention will be apparent to those skilled in the art without departing from the scope of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in the relevant fields are intended to be covered by the present invention.

The following examples and figures are merely illustrative of the present invention and should not be construed to limit the scope of the invention as indicated by the appended claims in any way.

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1: Depicts the fluorescence-assisted cell sorting (FACS) data obtained in example 8 described below.

EXPERIMENTAL SECTION

All starting materials used in the examples are either commercially available or can be synthesized by the average skilled person trained in organic chemistry without undue burden following routine laboratory practice as outlined, for example in example 1.

Besides the guidance provided in example 1, alternative synthetic transformations that may be employed in the synthesis of compounds of formulas I-III and in the synthesis of intermediates involved in the synthesis of compounds of formulas I-III are known by or accessible to one skilled in the art. Collections of synthetic transformations may be found in compilations, such as: J. March. Advanced Organic Chemistry, 4th ed.; John Wiley : New York (1992) R. C. Larock. Comprehensive Organic Transformations, 2nd ed.; Wiley-VCH : New York (1999); F. A. Carey; R. J. Sundberg. Advanced Organic Chemistry, 2nd ed.; Plenum Press:

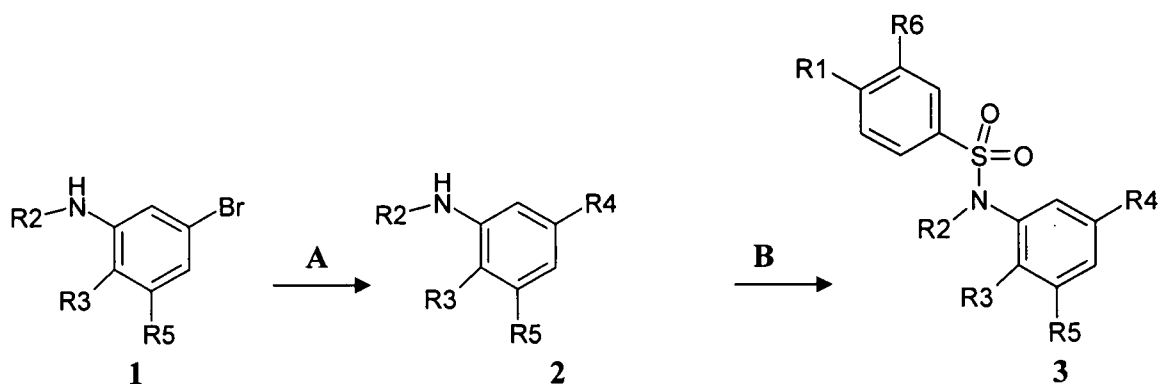
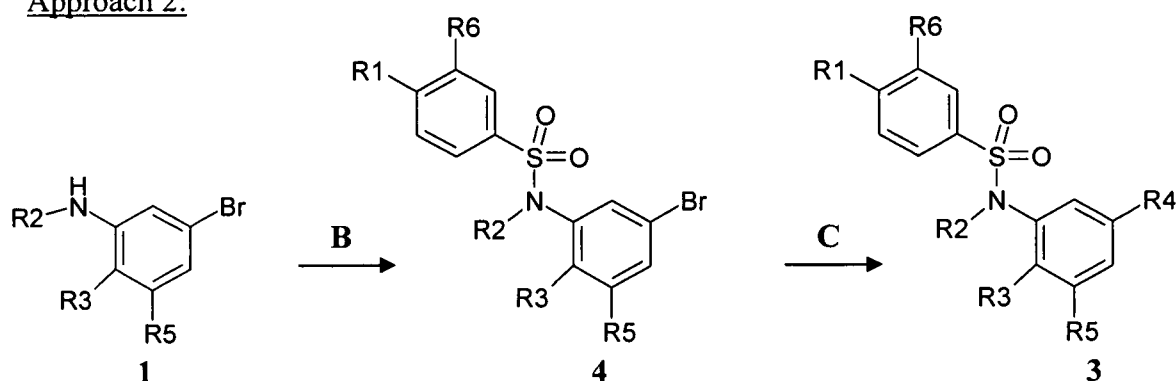
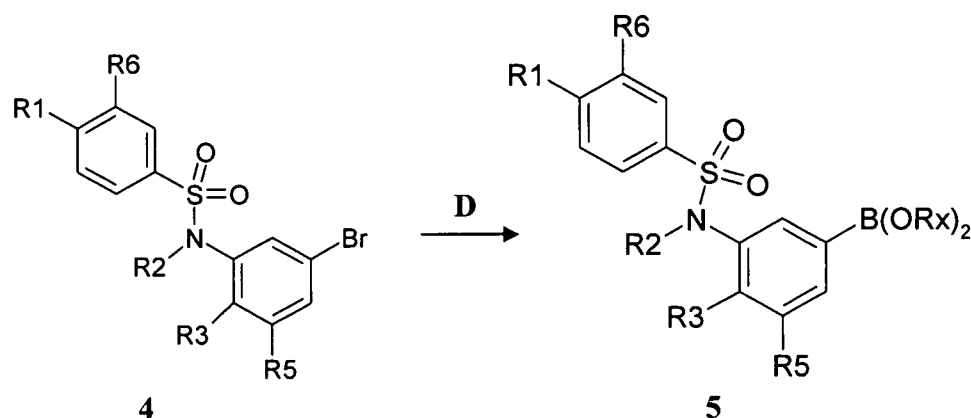
New York (1984) T. W. Greene; P. G. M. Wuts. Protective Groups in Organic Synthesis, 3rd ed.; John Wiley : New York (1999) . L. S. Hegedus. Transition Metals in the Synthesis of Complex Organic Molecules, 2nd ed.; University Science Books: Mill Valley, CA (1994) L. A. Paquette, Ed. The Encyclopedia of Reagents for Organic Synthesis ; John Wiley : New York
5 (1994) . A. R. Katritzky; O. Meth-Cohn; C. W. Rees, Eds. Comprehensive Organic Functional Group Transformations ; Pergamon Press: Oxford, UK (1995). G. Wilkinson ; F. G A. Stone; E. W. Abel, Eds. Comprehensive Organometallic Chemistry ; Pergamon Press: Oxford, UK (1982) . B. M. Trost; I. Fleming. Comprehensive Organic Synthesis ; Pergamon Press: Oxford, UK (1991) A. R. Katritzky ; C. W. Rees Eds. Comprehensive Heterocyclic Chemistry ; Pergamon
10 Press: Oxford, UK (1984) A. R. Katritzky; C. W. Rees ; E. F. V. Scriven, Eds. Comprehensive Heterocyclic Chemistry; Pergamon Press : Oxford, UK (1996) . C. Hansch; P. G. Sammes; J. B. Taylor, Eds. Comprehensive Medicinal Chemistry : Pergamon Press: Oxford, UK (1990).

In addition, recurring reviews of synthetic methodology and related topics include Organic Reactions ; John Wiley : New York; Organic Syntheses ; John Wiley : New York;
15 Reagents for Organic Synthesis : John Wiley : New York; The Total Synthesis of Natural Products ; John Wiley : New York; The Organic Chemistry of Drug Synthesis ; John Wiley : New York ; Annual Reports in Organic Synthesis ; Academic Press: San Diego CA; and Methoden der Organischen Chemie (Houben- Weyl) ; Thieme : Stuttgart, Germany. Furthermore, databases of synthetic transformations include Chemical Abstracts, which may be
20 searched using either CAS OnLine or SciFinder, Handbuch der Organischen Chemie (Beilstein), which may be searched using SpotFire, and REACCS.

The compounds herein were named according to IUPAC standard using the software AutoNom Standard For ISIS/Draw Add-In.

25 **Example 1: Synthesis of the Compounds of the Invention**

The compounds according to general formulas (I) through (III) according to the present invention may be prepared for example according to the following scheme:

Approach 1:5 Approach 2:10 Extra step:

15 wherein R¹ through R⁶ are as defined in the claims, or have the particularly preferred meanings as defined herein and R_x is H and/or pinacolato.

The general reaction schemes indicated above are as follows:

20 **General Procedure A.** A flask charged with **1** (1.0 equiv), Pd(dppf)Cl₂•CH₂Cl₂ (0.1 equiv), and the corresponding heteroaromatic or aromatic boronic acid or boronic ester (1.2 equiv) in 1:1 (v/v) Toluene/MeOH was purged with N₂ under vigorous stirring, and 2.0 M aqueous K₂CO₃ solution (2.5 equiv) were added slowly. The mixture was heated at 90° C for 4 h.

After cooling, the mixture was purified by flash column chromatography (silica gel, EtOAc/heptane, 1:5 to 1:3) to give the derivatives **2** (43-68% yield).

General Procedure B. A flask charged with aniline derivatives **1** or **2** (1.0 equiv), the corresponding sulfonyl chloride (1.1 equiv) and pyridine (10 equiv) in CH₂Cl₂ was stirred at room temperature for 12 h. The mixture was extracted with concentrated aqueous NH₄Cl, washed with brine and dried over MgSO₄. The organic solvents were evaporated and the crude product was purified by preparative HPLC or by flash column chromatography (silica gel, EtOAc/heptane) to give the derivatives **3** or **4** (70% to quantitative yield).

General Procedure C. A 2-5 ml microwave reaction vessel charged with **4** (1.0 equiv), Pd(dppf)Cl₂•CH₂Cl₂ (0.1 equiv), and the corresponding heteroaromatic or aromatic boronic acid or boronic ester (1 equiv) in dry MeOH was purged with N₂ under vigorous stirring and 2.0 M aqueous K₂CO₃ solution (2.5 equiv) were added slowly. The vessel was sealed and the mixture was heated in a microwave oven for 30 min at 90°C (CEM Discover Microwave system, set to P_{max}=150W). After cooling, the mixture was diluted with CH₂Cl₂, filtered through celite and eluted with CH₂Cl₂. The organic solvents were evaporated and the crude product was purified by preparative HPLC or by flash column chromatography (silica gel, EtOAc/heptane,) to give the derivatives **3** (42-90% yield).

General Procedure D. Approach 2 can optionally include an extra step as shown. Bispinacolato diboron (2.5 equiv), Pd(dppf)Cl₂•CH₂Cl₂ (0.1 equiv), and KOAc (3.0 equiv) were added to a flask containing compounds **4** (1.0 equiv) in degassed 1,4-dioxane. The reaction mixture was heated to 95° C and stirred for 4 hours. Upon completion, the reaction mixture was diluted with EtOAc (50 ml), filtered through a short column of silica gel, and further eluted with EtOAc. The combined organic solvent was washed with H₂O and brine, dried over anhydrous MgSO₄ and concentrated in vacuum. The resulting residue was purified by flash column chromatography (silica gel, EtOAc/heptane, 1:3) to yield the boronate esters **5** (50 - 88% yield) as a cream or white solid. In a subsequent step, compounds **5** were transformed with a heteroaromatic or aromatic bromide to **3** following procedures A or C.

Substituents R¹, R⁴ and/or R⁶, which may undergo unwanted reactions when carrying out a synthesis according to approach 1 or 2 may be protected by a conventional protecting group, which is not cleaved during the reactions according to approach 1 or 2 but is cleavable under known conditions. The skilled person is aware of a large variety of protection groups, which can be employed in organic synthesis. Protecting groups are reviewed in, for example, Wuts, P.G.M. and Greene, T.W., *Protective Groups in Organic Chemistry*, 3rd Ed., 1999; Wiley & Sons Inc. and in Kocienski, P.J., *Protecting groups*, 2nd Ed., 2000, Thieme Medical Publishing. Protecting groups are organized in these reference books according to the functionalities that are protected

as well as according to the conditions which remove the respective protecting groups selectively. Particularly preferred protective groups, which can be used, are:

- (i) protective group removed at acidic conditions, preferably at a pH between 4 and 6, which is selected from the group consisting of Boc or Trityl protecting groups;
- 5 (ii) a protecting group removed by a nucleophile, which is selected from the group consisting of Fmoc or Dde protecting groups;
- (iii) a protecting group removed by hydrogenolysis consisting of the allyl type, the tert-butyl type, the benzyl type or Dmab (4-{N-[1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl]amino}benzyl ester);
- 10 (iv) a protecting group removed by radiation, which is selected from the group consisting of nitroveratryloxy carbonyl, nitrobenzyloxy carbonyl, dimethyl dimethoxybenzyloxy carbonyl, 5-bromo-7-nitroindolyl, o-hydroxy- α -methyl cinnamoyl, and 2-oxyethylene anthraquinone.

15 Synthesis of building blocks

The toluidine building blocks (1) are commercially available, but can also be synthesized according to standard functionalization or transformation protocols, described in the literature cited above, and normally known to those ordinary skilled in the art of organic synthesis.

20 Numerous aromatic or heteroaromatic boronic acids or esters useful in **Procedures A and C** for palladium catalyzed coupling reactions are commercially available, or they can be synthesized according to standard functionalization or transformation protocols, described in the literature cited above, and normally known to those ordinary skilled in the art of organic synthesis. In particular, such boronic acid/ester intermediates can be generated e.g. from their corresponding aromatic or heteroaromatic halide precursors, as exemplified in **Procedure D**.

25 Numerous 5- and 6-membered heteroaromatic sulfonic acids and their corresponding activated derivatives, as used in **Procedure B** and there exemplified for sulfonylchlorides, are commercially available or they can be synthesized according to standard functionalization or transformation protocols, described in the literature cited above and normally known to those ordinary skilled in the art of organic synthesis. (Particular methods are e.g. described in:
30 Caldwell, WT et al., J. Med. Chem. (1962), Vol.6., p.58 ff; Caldwell, WT et al., JACS (1959), Vol.81, p.5166 ff; Roblin, RO et al., JACS (1950), Vol.72, p.4890 ff; Hitoshi K et al., US Patent (1998), number 5,811,571; WO 2006/090244, p.38 ff; Janosik T et al., THL (2006), Vol.62, p. 1699 ff; Allred GD, SERMACS (2007), Lanny Liebeskind Cope Scholar Award Symposium II, 222. Sulfonyl Fluorides; and references cited therein). If desired, it is also possible to generate

sulfonamides **3** and/or **4** directly from the corresponding thiols (Wright SW et al., JOC (2006), Vol.71, p.1080 ff).

Example 2: HPLC/MS Analysis of the Compounds of the Invention

The compounds were analyzed as follows:

Measured via HPLC/MS, using a Waters X-bridge C₁₈-column, 5 µm particle size, 4.6 x 150 mm (diameter x length) at a flow rate of 1.75 ml/min with a linear gradient (water to acetonitrile, 0.2% formic acid as modifier) from initially 99:1 to 1:99 over 9.10 min, then hold for 1.80 min. Mass signals were determined using a Waters 3100 Mass Detector.

Example 3: General Cell Culture Maintenance and Cell Proliferation Assays

MCF-7 human breast adenocarcinoma cells and HL-60 acute promyelocytic leukaemia cells were obtained from ATCC (LGC Promochem). HG-1 multiple myeloma cells were obtained from Dr. D. Hose (DKFZ Heidelberg). The CellSensor® HRE-bla HCT116 cell line (colorectal carcinoma) was obtained from Invitrogen.

Cells were grown under humidified 95% air, 5% CO₂ at 37°C in Dulbecco's modified Eagle's medium (DMEM: MCF-7) or RPMI 1640 medium (RPMI: HL-60, HG-1) supplemented with 10% fetal bovine serum (FBS), 100U/ml penicillin and 100µg/ml streptomycin, 2mM L-glutamine, and 2ng/ml IL-6 (for the HG-1 cell line only). The HCT116 cell line was grown under the same atmospheric conditions in McCoy's 5A medium supplemented with 10% FBS and penicillin/streptomycin as above, in addition to blasticidin as a selection marker at a final concentration of 5µg/ml.

Cell proliferation experiments were carried out in 96-well tissue culture plates with seeding of 2000 cells/well (MCF-7) or 1000 cells/well (HL-60, HG-1) in 100µl of the relevant medium. Cells were subsequently incubated under the conditions mentioned for 24h prior to addition of compounds.

For the determination of compound EC₅₀ values, 10µl compounds at 11X concentrations in 5.5% DMSO were added to the wells at various concentrations yielding a final constant percentage of 0.5% DMSO at the desired 1X compound concentration. As a positive control, cells were treated with 5.5% DMSO. The cells were then incubated for a further 72h prior to the measurement.

To determine the degree of inhibition of cell proliferation, cells were treated with ATPlite solution according to the manufacturer's instructions (PerkinElmer, ATPlite 1-step Luminescence ATP Detection Assay System) and luciferase readout measured on an Envision HTS multilabel plate reader (PerkinElmer) in luminescence mode according to established protocols. Raw data were imported into an ActivityBase database (IDBS, ID Business Solutions)

and EC₅₀ values calculated using the IDBS program ActivityBase XE. Table 2A and 2B show the IC₅₀ values obtained in the above-outlined cell proliferation assay for exemplary compounds of the invention. The cell proliferation assay data show that the compounds of the invention can inhibit cell proliferation in cancer cell lines.

5

Reference: EC₅₀ < 500 nM: +++
 500 – 1000 nM: ++
 1 – 10 µM: +

Table 2A - MCF7 cells				
Example no.	IUPAC Name	EC ₅₀	Retention time (HPLC) [min]	Mass Spectrometry MH+
1	4-Methyl-N-[2-methyl-5-(1H-tetrazol-5-yl)-phenyl]-benzenesulfonamide	" + "	5,87	330
2	4-Methyl-N-(2-methyl-5-tetrazol-1-yl-phenyl)-benzenesulfonamide	" + "	6,27	330
3	4-Methyl-N-[2-methyl-5-(5-methyl-furan-2-yl)-phenyl]-benzenesulfonamide	" + + + "	8,27	343
4	N-(5-Furan-2-yl-2-methyl-phenyl)-4-methyl-benzenesulfonamide	" + + + "	7,92	328
5	N-(5-Furan-3-yl-2-methyl-phenyl)-4-methyl-benzenesulfonamide	" + + + "	7,73	328
6	4-Methyl-N-[2-methyl-5-(2-methyl-2H-tetrazol-5-yl)-phenyl]-benzenesulfonamide	" + "	6,88	344
7	N-(4,3'-Dimethyl-biphenyl-3-yl)-4-methyl-benzenesulfonamide	" + + "	8,7	352
8	4-Methyl-N-(2-methyl-5-thiophen-3-yl-phenyl)-benzenesulfonamide	" + + + "	8,12	344
9	N-[5-(6-Methoxy-pyridin-2-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide	" + + "	8,2	370
10	N-(4,4'-Dimethyl-biphenyl-3-yl)-4-methyl-benzenesulfonamide	" + "	8,72	352
11	4-Methyl-N-[2-methyl-5-(5-methyl-thiophen-2-yl)-phenyl]-benzenesulfonamide	" + + + "	8,65	358
12	N-[5-(2,4-Dimethyl-thiazol-5-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide	" + + + "	7,07	373
13	N-[5-(2,5-Dimethyl-thiophen-3-yl)-2-methyl-phenyl]-4-methoxy-benzenesulfonamide	" + "	8,63	388
14	4-Methoxy-N-(2-methyl-5-thiophen-3-yl-phenyl)-benzenesulfonamide	" + + + "	7,72	360
15	4-Methyl-N-(2-methyl-5-pyrrol-1-yl-phenyl)-benzenesulfonamide	" + + + "	7,92	327
16	N-[5-(3,5-Dimethyl-isoxazol-4-yl)-2-methyl-phenyl]-4-methoxy-benzenesulfonamide	" + + + "	7,03	373
17	4-Methoxy-N-[2-methyl-5-(2-methyl-thiophen-3-yl)-phenyl]-benzenesulfonamide	" + + + "	8,23	374
18	N-[5-(6-Methoxy-pyridin-3-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide	" + "	7,73	368,94

19	4-Methyl-N-(2-methyl-5-pyridin-2-yl-phenyl)-benzenesulfonamide	" + + "	5,94	338, 340
20	4-Methoxy-N-(2-methyl-5-oxazol-5-yl-phenyl)-benzenesulfonamide	" + + + "	6,36	345
21	4-Methoxy-N-(2-methyl-5-pyrrol-1-yl-phenyl)-benzenesulfonamide	" + + + "	n.d.	n.d.
22	4-Methyl-N-(2-methyl-5-[1,2,4]triazol-4-yl-phenyl)-benzenesulfonamide	" + "	5,26	329
23	4-Methyl-N-[2-methyl-5-(4-methyl-thiophen-3-yl)-phenyl]-benzenesulfonamide	" + + + "	8,46	358
24	4-Methyl-N-[2-methyl-5-(3-methyl-thiophen-2-yl)-phenyl]-benzenesulfonamide	" + + + "	8,53	358
25	4-Methyl-N-[2-methyl-5-(2-methyl-furan-3-yl)-phenyl]-benzenesulfonamide	" + + + "	8,11	342
26	N-[5-(3-Methoxy-pyridin-2-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide	" + "	5,8	368,98
27	4-Methyl-N-[2-methyl-5-(3-trifluoromethyl-pyridin-2-yl)-phenyl]-benzenesulfonamide	" + "	7,55	407
28	4-Methyl-N-[2-methyl-5-(3-methyl-pyridin-2-yl)-phenyl]-benzenesulfonamide	" + "	4,95	353
29	N-[5-(2,5-Dimethyl-pyrrol-1-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide	" + "	8,36	355
30	4-Methoxy-N-[2-methyl-5-(3-methyl-pyrazol-1-yl)-phenyl]-benzenesulfonamide	" + + + "	7,14	358
31	4-Methyl-N-[2-methyl-5-(4-methyl-pyridin-2-yl)-phenyl]-benzenesulfonamide	" + "	5,28	352,98
32	4-Methyl-N-[2-methyl-5-(5-methyl-pyridin-2-yl)-phenyl]-benzenesulfonamide	" + "	5,88	353
33	4-Methyl-N-[2-methyl-5-(6-methyl-pyridin-2-yl)-phenyl]-benzenesulfonamide	" + + "	5,4	353
34	N-[5-(5-Cyano-pyridin-3-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide	" + + + "	7	364
35	N-[5-(5-Methoxy-pyridin-3-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide	" + "	5,88	369
36	N-[5-(6-Methoxy-4-methyl-pyridin-3-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide	" + "	7,83	382,99
37	N-[5-(6-Ethoxy-pyridin-3-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide	" + "	8,18	383
38	4-Methyl-N-[2-methyl-5-(4-trifluoromethyl-pyridin-2-yl)-phenyl]-benzenesulfonamide	" + "	8,29	407
39	4-Methyl-N-[2-methyl-5-(6-trifluoromethyl-pyridin-2-yl)-phenyl]-benzenesulfonamide	" + + "	8,36	407
40	N-[5-(2,4-Dimethyl-pyrrol-1-yl)-2-methyl-phenyl]-4-methoxy-benzenesulfonamide	" + "	n.d.	n.d.
41	N-[5-(2-Cyano-pyrrol-1-yl)-2-methyl-phenyl]-4-methoxy-benzenesulfonamide	" + + "	7,95*	368
42	N-[5-(6-Acetyl-pyridin-2-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide	" + + "	7,7	381
43	N-[5-(5-Cyano-pyridin-2-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide	" + + + "	7,38	364
44	N-[5-(5-Methoxy-pyridin-2-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide	" + + + "	6,91	369
45	4-Methyl-N-[2-methyl-5-(5-trifluoromethyl-pyridin-2-yl)-phenyl]-benzenesulfonamide	" + "	8,39	407
46	N-[5-(5-Fluoro-6-methyl-pyridin-2-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide	" + + "	8,12	371
47	N-[5-(5-Cyano-thiophen-2-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide	" + + + "	7,93	369

48	N-[5-(3,5-Dimethyl-isoxazol-4-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide	" + + + "	7,34	357
49	N-[5-(5-Cyano-pyridin-2-yl)-2-methyl-phenyl]-4-methoxy-benzenesulfonamide	" + + + "	7,06	380
50	4-Methoxy-N-[2-methyl-5-(2-methyl-pyrrol-1-yl)-phenyl]-benzenesulfonamide	" + + + "	7,81	357
51	N-[5-(5-Cyano-thiophen-2-yl)-2-methyl-phenyl]-4-methoxy-benzenesulfonamide	" + + + "	7,64	385
52	N-[5-(6-Cyano-pyridin-2-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide	" + + "	7,5	364
53	N-[5-(5-Fluoro-pyridin-2-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide	" + + + "	7,63	356,75
54	N-[5-(5-Acetyl-pyridin-2-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide	" + "	7,07	381
55	4-Methyl-N-[2-methyl-5-(5-nitro-pyridin-2-yl)-phenyl]-benzenesulfonamide	" + + + "	7,71	384
56	N-[5-(4-Cyano-thiophen-2-yl)-2-methyl-phenyl]-4-methoxy-benzenesulfonamide	" + + + "	7,45	385
57	N-(3'-Cyano-4-methyl-biphenyl-3-yl)-4-methoxy-benzenesulfonamide	" + + "	7,49	379
58	N-(2'-Cyano-4-methyl-biphenyl-3-yl)-4-methoxy-benzenesulfonamide	" + + "	7,38	379
59	N-[5-(3-Cyano-thiophen-2-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide	" + + "	7,67	369
60	N-(4'-Cyano-4-methyl-biphenyl-3-yl)-4-methyl-benzenesulfonamide	" + + + "	7,83	363
61	N-[5-(6-Cyano-pyridin-3-yl)-2-methyl-phenyl]-4-methoxy-benzenesulfonamide	" + + + "	7,02	380
62	N-[5-(2-Cyano-thiophen-3-yl)-2-methyl-phenyl]-4-methoxy-benzenesulfonamide	" + + + "	7,41	384
63	N-(4'-Cyano-4-methyl-biphenyl-3-yl)-4-methoxy-benzenesulfonamide	" + + + "	7,53	379
64	N-[5-(5-Cyano-pyrimidin-2-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide	" + + "	7,27	365
65	N-(3',4'-Dicyano-4-methyl-biphenyl-3-yl)-4-methoxy-benzenesulfonamide	" + + + "	8,06	404
66	N-[5-(6-Dimethylamino-pyridin-2-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide	" + + "	6,8	383
67	N-[5-(4,6-Dimethyl-pyridin-2-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide	" + "	5,14	367
68	N-[5-(5-Cyano-thiophen-3-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide	" + + + "	7,9	369
69	N-[5-(4-Cyano-thiophen-3-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide	" + + + "	7,55	369
70	N-[5-(3-Cyano-furan-2-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide	" + + + "	7,55	353
71	N-(4'-Cyano-3'-fluoro-4-methyl-biphenyl-3-yl)-4-methyl-benzenesulfonamide	" + + + "	8	381
72	N-(4'-Cyano-4,3'-dimethyl-biphenyl-3-yl)-4-methyl-benzenesulfonamide	" + + + "	8,13	377
73	N-[5-(5-Cyano-thiophen-3-yl)-2-methyl-phenyl]-4-methoxy-benzenesulfonamide	" + + + "	7,53	385
74	N-[5-(5-Cyano-pyridin-3-yl)-2-methyl-phenyl]-4-methoxy-benzenesulfonamide	" + + + "	5,98	338,92
75	N-[5-(2-Cyano-pyridin-4-yl)-2-methyl-phenyl]-4-methoxy-benzenesulfonamide	" + + "	6,95	380
76	4-Methyl-N-[2-methyl-5-(5-nitro-furan-2-yl)-phenyl]-benzenesulfonamide	" + + + "	7,62	373

77	4-Chloro-N-[5-(5-cyano-thiophen-2-yl)-2-methyl-phenyl]-benzenesulfonamide	" + + + "	8,26	389
78	N-[5-(5-Cyano-thiophen-2-yl)-2-methyl-phenyl]-4-trifluoromethyl-benzenesulfonamide	" + + "	8,4	423
79	N-[5-(5-Cyano-thiophen-2-yl)-2-methyl-phenyl]-4-trifluoromethoxy-benzenesulfonamide	" + "	8,48	439
80	N-[5-(4-Cyano-thiophen-2-yl)-2-methyl-phenyl]-4-methoxy-benzenesulfonamide	" + + + "	8,21	385
81	4-Methoxy-N-(4'-methoxy-4-methyl-biphenyl-3-yl)-benzenesulfonamide	" + + + "	7,92	384
82	4-Methoxy-N-(4-methyl-4'-methylsulfanyl-biphenyl-3-yl)-benzenesulfonamide	" + "	8,38	400
83	4-Methoxy-N-(4-methyl-4'-trifluoromethoxy-biphenyl-3-yl)-benzenesulfonamide	" + "	8,74	438
84	N-(4'-Ethynyl-4-methyl-biphenyl-3-yl)-4-methyl-benzenesulfonamide	" + + "	8,48	362
85	N-(4'-Cyano-4-methyl-biphenyl-3-yl)-3-fluoro-4-methoxy-benzenesulfonamide	" + + + "	7,67	397
86	N-(4'-Cyano-4-methyl-biphenyl-3-yl)-4-nitro-benzenesulfonamide	" + "	7,67	392 (M-1)
87	4-Amino-N-(4'-cyano-4-methyl-biphenyl-3-yl)-benzenesulfonamide	" + + + "	6,85	364
88	N-(4'-Cyano-4-methyl-biphenyl-3-yl)-3-fluoro-4-methyl-benzenesulfonamide	" + + + "	8,04	381
89	N-(4'-Cyano-3'-methoxy-4-methyl-biphenyl-3-yl)-4-methoxy-benzenesulfonamide	" + + + "	7,56	409
90	N-(4'-Cyano-3'-hydroxy-4-methyl-biphenyl-3-yl)-4-methoxy-benzenesulfonamide	" + + + "	6,89	395
91	N-[5-(5-Cyano-thiophen-2-yl)-2-methyl-phenyl]-4-fluoro-benzenesulfonamide	" + + "	7,78	373
92	N-[5-(5-Cyano-thiophen-2-yl)-2-methyl-phenyl]-3-fluoro-4-methoxy-benzenesulfonamide	" + + + "	7,71	403
93	4-Amino-N-[5-(5-cyano-thiophen-2-yl)-2-methyl-phenyl]-benzenesulfonamide	" + + + "	6,86	370
94	4-Methyl-N-[3-methyl-5-(5-methyl-thiophen-3-yl)-phenyl]-benzenesulfonamide	" + + + "	8,56	358
95	N-(5-(5-cyanothiophen-3-yl)-2-methylphenyl)-3-fluoro-4-methylbenzenesulfonamide	" + + + "	8,09	385 (M-1)
96	N-(5-(5-cyanothiophen-3-yl)-2-methylphenyl)-4-nitrobenzenesulfonamide	" + "	7,77	398 (M-1)
97	4-chloro-N-(4'-cyano-4-methylbiphenyl-3-yl)benzenesulfonamide	" + + + "	8,10	381 (M-1)
98	N-(5-(5-cyanothiophen-2-yl)-2-methylphenyl)-4-hydroxybenzenesulfonamide	" + + "	6,83	369 (M-1)
99	N-(4'-cyano-3'-methoxy-4-methylbiphenyl-3-yl)-3-fluoro-4-methylbenzenesulfonamide	" + + + "	7,99	409 (M-1)
100	N-(4'-cyano-4-methylbiphenyl-3-yl)-4-hydroxybenzenesulfonamide	" + "	6,38	363 (M-1)
101	N-(4'-cyano-3'-methoxy-4-methylbiphenyl-3-yl)-4-nitrobenzenesulfonamide	" + "	7,63	422 (M-1)
102	4-amino-N-(4'-cyano-3'-methoxy-4-methylbiphenyl-3-yl)benzenesulfonamide	" + + + "	7,58	392 (M-1)
103	N-(4'-cyano-3'-methoxy-4-methylbiphenyl-3-yl)-3-fluoro-4-methoxybenzenesulfonamide	" + + + "	8,46*	425 (M-1)
104	N-(4'-cyano-4-methylbiphenyl-3-yl)-3-fluorobenzenesulfonamide	" + "	8,55*	365 (M-1)

105	N-(4'-cyano-4-methylbiphenyl-3-yl)-3-fluoro-4-nitrobenzenesulfonamide	" + "	8,69*	410 (M-1)
106	N-(5-(5-aminopyridin-2-yl)-2-methylphenyl)-4-methylbenzenesulfonamide	" + "	6,24*	352 (M-1)
107	N-(5-(2-methoxypyrimidin-4-yl)-2-methylphenyl)-4-methylbenzenesulfonamide	" + "	8,43*	368 (M-1)
108	N-(5-(5-cyanothiophen-2-yl)-2-methylphenyl)-3,4-dimethoxybenzenesulfonamide	" + + "	8,15*	415
109	N-(5-(5-cyanothiophen-2-yl)-2-methylphenyl)-4-methoxy-3-methylbenzenesulfonamide	" + + + "	8,79*	399
110	4-amino-N-(4'-cyano-4-methylbiphenyl-3-yl)-3-fluorobenzenesulfonamide	" + + + "	7,77*	380 (M-1)
111	4-methyl-N-(2-methyl-5-(6-methyl-5-nitropyridin-2-yl)phenyl)benzenesulfonamide	" + + + "	8,96*	398
112	N-(5-(5-cyanothiophen-2-yl)-2-methylphenyl)-4-fluoro-3-methylbenzenesulfonamide	" + + + "	8,96*	387
113	N-(5-(5-cyanothiophen-2-yl)-2-methylphenyl)-4-fluoro-3-methoxybenzenesulfonamide	" + + "	8,68*	401 (M-1)
114	N-(5-(5-cyanothiophen-2-yl)-2-methylphenyl)benzo[d][1,3]dioxole-5-sulfonamide	" + + + "	8,44*	399
115	N-(4'-cyano-4-methylbiphenyl-3-yl)-4-(dimethylamino)benzenesulfonamide	" + + + "	8,60*	392
116	4-cyano-N-(5-(5-cyanothiophen-2-yl)-2-methylphenyl)benzenesulfonamide	" + + "	8,36*	378 (M-1)

Retention times marked with "*" were measured using an alternative method to the one given in Example 2. These retention times were determined as follows:

Measured via HPLC/MS, using a Waters X-bridge C₁₈-column, 5 µm particle size, 4.6 x 150 mm (diameter x length) at a flow rate of 1.75 ml/min with a linear gradient (water to methanol, 0.2% formic acid as modifier) from initially 99:1 to 1:99 over 9.10 min, then hold for 1.80 min. Mass signals were determined using a Waters 3100 Mass Detector.

Table 2B - HG1 cells

Example no.	EC ₅₀
8	+++
15	+++
19	+++
22	+++
47	+++
51	+++
73	+++

Example 4: Inhibition of Estrogen Receptor (ER) Signaling

To determine the effect of the compounds on estrogen receptor (ER)-mediated transcriptional activity a transfection assay using the MCF-7 cell line was performed. A luciferase-coupled ERE-tk-*luc* construct was obtained from Dr. G. Reid (EMBL).

In brief, MCF-7 cells were maintained as described previously and seeded on the first experimental day at a concentration of 3500 cells/well in 100µl medium and incubated under standard conditions for 24h. Following this initial incubation period, transfection was carried out using 5ng of the ERE-tk-*luc* construct (per well) and Exgene 500 transfection reagent (Fermentas) in a final buffered solution containing 150mM NaCl and 20mM Tris pH 8.4. The plates were then maintained for 3-4 hours until cell culture conditions in the incubator before compounds were added at 11X concentrations to yield the final desired compound concentrations in 0.5% DMSO (in the same manner as for the proliferation assays described previously).

After an additional 24h incubation period the degree of inhibition of ER-signaling was determined via a luciferase readout. Cells were treated with britelite™ plus solution according to the manufacturer's instructions (PerkinElmer, britelite plus, Ultra-High Sensitivity Luminescence Reporter Gene Assay System) and luciferase levels measured on an Envision HTS multilabel plate reader (PerkinElmer) in luminescence mode according to established protocols. Raw data were imported into an ActivityBase database (IDBS, ID Business Solutions) and IC₅₀ values calculated using the IDBS program ActivityBase XE.

The results are depicted in Table 3. As shown in these experiments, the compounds of the invention are capable of inhibiting estrogen receptor element-mediated transcriptional activity in an ERα-positive cell line. The utility of ER-modulating agents for the treatment of breast, uterine or prostate cancer, as well as metastatic bone disease, is known from the literature (see for example, Park & Jordan (2002) Trends Mol. Med. 8(2): 82-88; Steiner *et al.* (2001) Urology 57(4 Suppl 1): 68-72 and Campisi *et al.* (1993) Eur. J. Gynaecol. Oncol. 14(6): 479-483.)).

Reference: IC₅₀ < 500 nM: +++
 500 – 1000 nM: ++
 1 – 10 µM: +

Table 3	
Example no.	IC ₅₀
4	+++
5	+++
15	+++
43	+++

47	+++
49	+++
60	+++
72	+++

Example 5: Inhibition of *In Vitro* Tubulin Polymerization

To assess the degree of inhibition of *in vitro* tubulin polymerization, a tubulin solution (prepared in-house from porcine brain using a standard procedure involving cycles of polymerization/de-polymerization, see Castoldi & Popov (2003) Protein Expr. Purif. 32(1): 83-88) was incubated with varying concentrations of compounds under polymerizing conditions and kinetic experiments performed to determine the amount of polymerization (as measured by changes in OD at 340nm) taking place over a 90min period.

Compound solutions were diluted in double-distilled water to yield final 10X solutions containing 5% DMSO. 5µl solutions were then added to the wells on a 384-well clear-bottom plate (Corning #3711, Corning Inc.) in preparation for the addition of tubulin. The tubulin solution (19.6mg/ml, in 80mM K-PIPES [pH 6.8], 1mM MgCl₂, 1mM EGTA) was re-suspended to a final concentration of 4mg/ml with ice cold G-PEM buffer (80mM PIPES [pH 6.8], 2mM MgCl₂, 0.5mM EGTA, 10% glycerol, 1mM GTP) and maintained on ice for at least 1min. 50µl was then added to the pre-dispensed compound solutions, the plate orbital shaken on a medium setting for 5s, and the first measurement begun immediately.

Experiments were carried out on a Safire²™ monochromator (Tecan) preset to a stable temperature of 37°C; the degree of polymerization was determined by measuring the absorbance of the solutions at 340nm every minute over the 90min cycle. Reported inhibition values were based on the final absorbance at 90min and calculated with reference to a vehicle control (0.5% DMSO) using the minimum and maximum signals obtained for this sample.

As demonstrated by these experiments (see Table 4), changes in the structural properties of the various examples can lead to a selection of compounds that are active in inhibiting cell proliferation and affect HIF-signaling, but that do, or do not, have tubulin inhibition properties, depending on whether this is desired in the target product profile.

Reference:	Inhibition at 10µM	> 50%:	+
		20 – 50%:	+/-
		< 20%	-

Table 4	
Example no.	Inhibition (%)

3	+
11	+/-
16	+/-
23	+
56	+
60	-
63	-
72	-

Example 6: Inhibition of Activation of HIF Mediated Transcription under Hypoxic Conditions

5 Inhibition of an activated HIF signaling response under chemically-induced hypoxic conditions due to compound treatment was determined using the CellSensor® HRE-bla HCT-116 stably transfected reporter cell line from Invitrogen according to the manufacturer's instructions. HIF is a transcriptional factor composed of the constitutively expressed HIF1 β subunit and one of three HIF α subunits (HIF1 α , HIF2 α , HIF3 α). This assay is responsive towards HIF α activity in
10 general. In one example, HIF-1, when stabilized by hypoxic conditions, upregulates several genes to promote cell survival in low-oxygen conditions. These include glycolysis enzymes, which allow ATP synthesis in an oxygen-independent manner, and vascular endothelial growth factor (VEGF), which promotes angiogenesis. HIF-1 acts by binding to HIF-responsive elements (HREs) in promoters that generally contain the sequence NCGTG.

15 Cells were maintained as described previously and seeded into 384-well, clear-bottom plates (Corning 3712) at 15000 cells/well in 32 μ l assay medium (Opti-MEM [Invitrogen], 0.5% FBS, 100U/ml penicillin, 100 μ g/ml streptomycin, 0.1mM non-essential amino acids [NEAA], 1mM sodium pyruvate, 5mM HEPES [pH 7.3]). Following a 2h incubation period, compounds (4 μ l) were subsequently added to the cells at 10X concentrations in 5% DMSO and incubated
20 under normal conditions for 30min. To induce hypoxic conditions, 4 μ l of a 2 mM deferoxamine (DFO) solution was added to the cells followed by 24 h incubation under standard assay conditions (as described). Control wells included wells containing only medium (no cells) and wells treated with 0.5% DMSO instead of compound.

Prior to the readout, the Substrate Loading Solution was prepared as described in the
25 manufacturer's protocol and 10 μ l added to each well. Following a further 2h incubation period at room temperature and in the dark, fluorescence was measured at two wavelengths (blue channel: ex. 409nm, em. 460nm; green channel: ex. 409nm, em. 530 nm) on a PerkinElmer Envision HTS. For the analysis, the average signal of the cell-free wells at 460 nm and 530 nm was first subtracted from the blue and green channel data, respectively. The blue/green emission ratios
30 were then calculated for each well, dividing the background-corrected blue emission values by

the background-corrected green emission values. IC₅₀ values were determined from these ratios using GraphPad Prism (Prism 5, GraphPad software, Inc.).

The results of these experiments (see Table 5) show that the compounds of the invention are capable of inhibiting hypoxia regulated element-mediated transcriptional activity under hypoxic conditions. The compounds of this invention have a potency level that exceeds HIF-inhibitor compounds described in the prior art such as, e.g. the ProlX compound PX-478, the only small molecule HIF-inhibitor currently reported to undergo clinical trials.

Reference: EC₅₀ < 500 nM: +++
500 – 1000 nM: ++
1 – 10 µM: +

Table 5	
Example no.	EC ₅₀
3	+++
8	+++
23	+++
43	+++
51	+++
68	+++
71	+++
73	+++
95	+++
103	+++
112	+++
114	+++

Example 7: Activation of Apoptosis

Activation of caspase-3/7 signal following treatment with test compounds was carried out using a Caspase-Glo® 3/7 kit (Promega). In brief, HG-1 cells were seeded at a concentration of 1000 cells/well in 50µl medium into 96-well plates and incubated for 24h under the conditions described previously. Compounds at various concentrations were then added to the wells (at all final concentrations 0.5% DMSO) and incubated for a further 24h period. The plates were subsequently removed from the incubator and allowed to equilibrate to room temperature, after which 50µl Caspase-Glo reagent was added to all wells, the plate shaken at 300rpm for 30s, and luminescence measured after a 30min incubation period on an Envision HTS (PerkinElmer).

Following treatment with compounds of the invention, a clear activation of the caspase-3/7 response was observed (see Table 6), indicating that apoptosis is one factor in the observed decrease in cell proliferation due to the compound mechanisms of action.

5	Reference:	EC ₅₀	< 500 nM:	+++
			500 – 1000 nM:	++
			1 – 10 μ M:	+

Table 6	
Example no.	EC ₅₀
47	+++
51	+++
56	+++
60	+++
63	+++

10

Example 8: Cell Cycle Analysis

To determine the effect on the cell cycle of HL-60 cells following treatment with compounds, fluorescence-assisted cell sorting (FACS) was used, sorting cells by nuclear staining.

15 A standard protocol using propidium iodide was utilized. In brief, cells were seeded into 6-well tissue culture plates at 2×10^5 cells in 2ml medium and incubated for 24h at 37°C under standard tissue culture conditions (humidified 95% air, 5% CO₂). Following this initial incubation period, compound solutions were added from stock solutions yielding final concentrations of 20 μ M in 0.1% DMSO and the cells incubated after gentle mixing for further 24h.

20 Cells were subsequently harvested, washed, and re-suspended in phosphate-buffered saline (PBS, pH 7.4). Fixation was performed in ice-cold 70% ethanol while vortexing at half-speed and the solutions stored overnight at 4°C. The cells were then spun down, washed 3 times in PBS, and stained with a propidium iodide staining solution (20 μ g/ml propidium iodide, 200 μ g/ml RNase A, 0.1% Triton X-100 in PBS, pH 7.4). Finally, samples were passed through a 25 70 μ m filter (BD Falcon) prior to measurement on a FACScan™ flow cytometer (Beckton Dickinson).

Together with the data showing caspase-3/7 activation, the FACS analysis shown for a representative compound demonstrates the appearance of a sub-2N population indicative of a cell cycle effect leading to apoptosis (see results depicted in figure 1). The ability of the 30 compounds of the invention to induce apoptosis is a useful feature which can be exploited in chemotherapeutical applications.

Example 9: Further Useful Compounds According to the Invention

Further compounds of the invention are exemplified in Table 7, which are of particular use within the scope of the present invention. These compounds can be produced as outlined under example 1 and also according to manufacturing practice well known in organic chemistry as described above. These compounds will have a similar inhibitory activity as shown for the compounds listed in table 2A and tested in examples 3 to 8.

Table 7	
Example Number	IUPAC Name
117	4-Methyl-N-[3-methyl-5-(5-methyl-furan-2-yl)-phenyl]-benzenesulfonamide
118	N-(3-Furan-2-yl-5-methyl-phenyl)-4-methyl-benzenesulfonamide
119	N-(3-Furan-3-yl-5-methyl-phenyl)-4-methyl-benzenesulfonamide
120	4-Methyl-N-(3-methyl-5-thiophen-3-yl-phenyl)-benzenesulfonamide
121	4-Methyl-N-[3-methyl-5-(5-methyl-thiophen-2-yl)-phenyl]-benzenesulfonamide
122	4-Methyl-N-(3-methyl-5-thiophen-2-yl-phenyl)-benzenesulfonamide
123	N-[3-(2,4-Dimethyl-thiazol-5-yl)-5-methyl-phenyl]-4-methyl-benzenesulfonamide
124	4-Methyl-N-(3-methyl-5-pyrrol-1-yl-phenyl)-benzenesulfonamide
125	N-[3-(3,5-Dimethyl-isoxazol-4-yl)-5-methyl-phenyl]-4-methyl-benzenesulfonamide
126	4-Methyl-N-[3-methyl-5-(2-methyl-thiophen-3-yl)-phenyl]-benzenesulfonamide
127	4-Methyl-N-(3-methyl-5-oxazol-5-yl-phenyl)-benzenesulfonamide
128	4-Methyl-N-[3-methyl-5-(3-methyl-pyrazol-1-yl)-phenyl]-benzenesulfonamide
129	N-[3-(6-Cyano-pyridin-3-yl)-5-methyl-phenyl]-4-methyl-benzenesulfonamide
130	N-[3-(5-Cyano-pyridin-2-yl)-5-methyl-phenyl]-4-methyl-benzenesulfonamide
131	N-[3-(5-Methoxy-pyridin-2-yl)-5-methyl-phenyl]-4-methyl-benzenesulfonamide
132	N-[3-(5-Cyano-thiophen-2-yl)-5-methyl-phenyl]-4-methyl-benzenesulfonamide
133	N-[3-(5-Fluoro-pyridin-2-yl)-5-methyl-phenyl]-4-methyl-benzenesulfonamide
134	N-(4'-Cyano-5-methyl-biphenyl-3-yl)-4-methyl-benzenesulfonamide
135	N-(3',4'-Dicyano-5-methyl-biphenyl-3-yl)-4-methyl-benzenesulfonamide
136	N-(4'-Cyano-3'-fluoro-5-methyl-biphenyl-3-yl)-4-methyl-benzenesulfonamide
137	N-(4'-Cyano-5,3'-dimethyl-biphenyl-3-yl)-4-methyl-benzenesulfonamide
138	N-[3-(2-Cyano-pyridin-4-yl)-5-methyl-phenyl]-4-methyl-benzenesulfonamide
139	4-Methyl-N-[3-methyl-5-(5-nitro-furan-2-yl)-phenyl]-benzenesulfonamide
140	4-Chloro-N-[3-(5-cyano-thiophen-2-yl)-5-methyl-phenyl]-benzenesulfonamide
141	N-(4'-Methoxy-5-methyl-biphenyl-3-yl)-4-methyl-benzenesulfonamide
142	N-(4'-Cyano-3'-hydroxy-5-methyl-biphenyl-3-yl)-4-methyl-benzenesulfonamide
143	N-(4'-Cyano-3'-methoxy-5-methyl-biphenyl-3-yl)-4-methyl-benzenesulfonamide
144	N-(4'-Cyano-3'-hydroxy-5-methyl-biphenyl-3-yl)-4-methoxy-benzenesulfonamide
145	N-(4'-Cyano-3'-methoxy-5-methyl-biphenyl-3-yl)-4-methoxy-benzenesulfonamide
146	N-[3-(5-Cyano-pyridin-2-yl)-5-methyl-phenyl]-4-methoxy-benzenesulfonamide

147	4-Methoxy-N-[3-(5-methoxy-pyridin-2-yl)-5-methyl-phenyl]-benzenesulfonamide
148	N-[3-(5-Cyano-thiophen-2-yl)-5-methyl-phenyl]-4-methoxy-benzenesulfonamide
149	N-[3-(5-Fluoro-pyridin-2-yl)-5-methyl-phenyl]-4-methoxy-benzenesulfonamide
150	N-(4'-Cyano-5-methyl-biphenyl-3-yl)-4-methoxy-benzenesulfonamide
151	N-(3',4'-Dicyano-5-methyl-biphenyl-3-yl)-4-methoxy-benzenesulfonamide
152	N-(4'-Cyano-3'-fluoro-5-methyl-biphenyl-3-yl)-4-methoxy-benzenesulfonamide
153	N-(4'-Cyano-5,3'-dimethyl-biphenyl-3-yl)-4-methoxy-benzenesulfonamide
154	N-[3-(2-Cyano-pyridin-4-yl)-5-methyl-phenyl]-4-methoxy-benzenesulfonamide
155	4-Methoxy-N-[3-methyl-5-(5-nitro-furan-2-yl)-phenyl]-benzenesulfonamide
156	4-Methoxy-N-(4'-methoxy-5-methyl-biphenyl-3-yl)-benzenesulfonamide
157	4-Methoxy-N-(3-methyl-5-pyrrol-1-yl-phenyl)-benzenesulfonamide
158	N-[3-(3,5-Dimethyl-isoxazol-4-yl)-5-methyl-phenyl]-4-methoxy-benzenesulfonamide
159	4-Methoxy-N-[3-methyl-5-(2-methyl-thiophen-3-yl)-phenyl]-benzenesulfonamide
160	4-Methoxy-N-(3-methyl-5-oxazol-5-yl-phenyl)-benzenesulfonamide
161	4-Methoxy-N-[3-methyl-5-(3-methyl-pyrazol-1-yl)-phenyl]-benzenesulfonamide
162	N-[3-(6-Cyano-pyridin-3-yl)-5-methyl-phenyl]-4-methoxy-benzenesulfonamide
163	4-Methoxy-N-[3-methyl-5-(5-methyl-furan-2-yl)-phenyl]-benzenesulfonamide
164	N-(3-Furan-2-yl-5-methyl-phenyl)-4-methoxy-benzenesulfonamide
165	N-(3-Furan-3-yl-5-methyl-phenyl)-4-methoxy-benzenesulfonamide
166	4-Methoxy-N-(3-methyl-5-thiophen-3-yl-phenyl)-benzenesulfonamide
167	4-Methoxy-N-[3-methyl-5-(5-methyl-thiophen-2-yl)-phenyl]-benzenesulfonamide
168	4-Methoxy-N-(3-methyl-5-thiophen-2-yl-phenyl)-benzenesulfonamide
169	N-[3-(2,4-Dimethyl-thiazol-5-yl)-5-methyl-phenyl]-4-methoxy-benzenesulfonamide
170	N-[3-(2,4-Dimethyl-thiazol-5-yl)-4-methyl-phenyl]-4-methoxy-N-methyl-benzenesulfonamide
171	4-Methoxy-N-methyl-N-(4-methyl-3-thiophen-2-yl-phenyl)-benzenesulfonamide
172	4,N-Dimethyl-N-[4-methyl-3-(5-methyl-furan-2-yl)-phenyl]-benzenesulfonamide
173	4,N-Dimethyl-N-(4-methyl-3-thiophen-3-yl-phenyl)-benzenesulfonamide
174	4-Methoxy-N-methyl-N-[4-methyl-3-(5-methyl-thiophen-2-yl)-phenyl]-benzenesulfonamide
175	4-Methoxy-N-methyl-N-(4-methyl-3-thiophen-3-yl-phenyl)-benzenesulfonamide
176	N-(3-Furan-3-yl-4-methyl-phenyl)-4-methoxy-N-methyl-benzenesulfonamide
177	N-[3-(6-Cyano-pyridin-3-yl)-4-methyl-phenyl]-4-methoxy-N-methyl-benzenesulfonamide
178	4-Methoxy-N-methyl-N-(4-methyl-3-oxazol-5-yl-phenyl)-benzenesulfonamide
179	4-Methoxy-N-methyl-N-[4-methyl-3-(3-methyl-pyrazol-1-yl)-phenyl]-benzenesulfonamide
180	4-Methoxy-N-methyl-N-[4-methyl-3-(5-methyl-furan-2-yl)-phenyl]-benzenesulfonamide
181	N-(3-Furan-2-yl-4-methyl-phenyl)-4-methoxy-N-methyl-benzenesulfonamide
182	4-Methoxy-N-methyl-N-[4-methyl-3-(5-nitro-furan-2-yl)-phenyl]-benzenesulfonamide

183	4-Methoxy-N-methyl-N-[4-methyl-3-(2-methyl-thiophen-3-yl)-phenyl]-benzenesulfonamide
184	N-[3-(3,5-Dimethyl-isoxazol-4-yl)-4-methyl-phenyl]-4-methoxy-N-methyl-benzenesulfonamide
185	N-[3-(2-Cyano-pyridin-4-yl)-4-methyl-phenyl]-4-methoxy-N-methyl-benzenesulfonamide
186	4-Methoxy-N-(4'-methoxy-6-methyl-biphenyl-3-yl)-N-methyl-benzenesulfonamide
187	4-Methoxy-N-methyl-N-(4-methyl-3-pyrrol-1-yl-phenyl)-benzenesulfonamide
188	N-(4'-Cyano-6,3'-dimethyl-biphenyl-3-yl)-4-methoxy-N-methyl-benzenesulfonamide
189	N-(4'-Cyano-6-methyl-biphenyl-3-yl)-4-methoxy-N-methyl-benzenesulfonamide
190	N-(3',4'-Dicyano-6-methyl-biphenyl-3-yl)-4-methoxy-N-methyl-benzenesulfonamide
191	N-(4'-Cyano-3'-fluoro-6-methyl-biphenyl-3-yl)-4-methoxy-N-methyl-benzenesulfonamide
192	4,N-Dimethyl-N-(4-methyl-3-thiophen-2-yl-phenyl)-benzenesulfonamide
193	4-Methoxy-N-[3-(5-methoxy-pyridin-2-yl)-4-methyl-phenyl]-N-methyl-benzenesulfonamide
194	N-[3-(5-Cyano-thiophen-2-yl)-4-methyl-phenyl]-4-methoxy-N-methyl-benzenesulfonamide
195	N-[3-(5-Fluoro-pyridin-2-yl)-4-methyl-phenyl]-4,N-dimethyl-benzenesulfonamide
196	N-(4'-Cyano-3'-hydroxy-6-methyl-biphenyl-3-yl)-4-methoxy-N-methyl-benzenesulfonamide
197	N-[3-(5-Cyano-pyridin-2-yl)-4-methyl-phenyl]-4-methoxy-N-methyl-benzenesulfonamide
198	N-(4'-Cyano-3'-methoxy-6-methyl-biphenyl-3-yl)-4-methoxy-N-methyl-benzenesulfonamide
199	N-(4'-Cyano-3'-methoxy-6-methyl-biphenyl-3-yl)-4,N-dimethyl-benzenesulfonamide
200	N-(3-Furan-3-yl-4-methyl-phenyl)-4,N-dimethyl-benzenesulfonamide
201	4,N-Dimethyl-N-[4-methyl-3-(3-methyl-pyrazol-1-yl)-phenyl]-benzenesulfonamide
202	N-[3-(3,5-Dimethyl-isoxazol-4-yl)-4-methyl-phenyl]-4,N-dimethyl-benzenesulfonamide
203	N-[3-(2,4-Dimethyl-thiazol-5-yl)-4-methyl-phenyl]-4,N-dimethyl-benzenesulfonamide
204	N-[3-(5-Methoxy-pyridin-2-yl)-4-methyl-phenyl]-4,N-dimethyl-benzenesulfonamide
205	4,N-Dimethyl-N-(4-methyl-3-pyrrol-1-yl-phenyl)-benzenesulfonamide
206	4,N-Dimethyl-N-(4-methyl-3-oxazol-5-yl-phenyl)-benzenesulfonamide
207	4,N-Dimethyl-N-[4-methyl-3-(5-methyl-thiophen-2-yl)-phenyl]-benzenesulfonamide
208	N-[3-(5-Cyano-pyridin-2-yl)-4-methyl-phenyl]-4,N-dimethyl-benzenesulfonamide
209	4,N-Dimethyl-N-[4-methyl-3-(2-methyl-thiophen-3-yl)-phenyl]-benzenesulfonamide
210	N-[3-(5-Cyano-thiophen-2-yl)-4-methyl-phenyl]-4,N-dimethyl-benzenesulfonamide
211	N-(3-Furan-2-yl-4-methyl-phenyl)-4,N-dimethyl-benzenesulfonamide
212	N-[3-(6-Cyano-pyridin-3-yl)-4-methyl-phenyl]-4,N-dimethyl-benzenesulfonamide
213	N-(4'-Cyano-6-methyl-biphenyl-3-yl)-4,N-dimethyl-benzenesulfonamide
214	N-(3',4'-Dicyano-6-methyl-biphenyl-3-yl)-4,N-dimethyl-benzenesulfonamide
215	N-(4'-Cyano-3'-hydroxy-6-methyl-biphenyl-3-yl)-4,N-dimethyl-benzenesulfonamide

216	N-[3-(2-Cyano-pyridin-4-yl)-4-methyl-phenyl]-4,N-dimethyl-benzenesulfonamide
217	N-(4'-Cyano-3'-fluoro-6-methyl-biphenyl-3-yl)-4,N-dimethyl-benzenesulfonamide
218	N-(4'-Cyano-6,3'-dimethyl-biphenyl-3-yl)-4,N-dimethyl-benzenesulfonamide
219	4,N-Dimethyl-N-[4-methyl-3-(5-nitro-furan-2-yl)-phenyl]-benzenesulfonamide
220	N-(4'-Methoxy-6-methyl-biphenyl-3-yl)-4,N-dimethyl-benzenesulfonamide
221	4-Chloro-N-[3-(5-cyano-thiophen-2-yl)-4-methyl-phenyl]-N-methyl-benzenesulfonamide
222	4-Methyl-N-[2-methyl-5-(1-methyl-1H-pyrrol-2-yl)-phenyl]-benzenesulfonamide
223	4-Methoxy-N-[2-methyl-5-(1-methyl-1H-pyrrol-2-yl)-phenyl]-benzenesulfonamide
224	4-Methyl-N-[2-methyl-5-(1-methyl-1H-pyrrol-3-yl)-phenyl]-benzenesulfonamide
225	4-Methoxy-N-[2-methyl-5-(1-methyl-1H-pyrrol-3-yl)-phenyl]-benzenesulfonamide
226	4-Methyl-N-[3-methyl-5-(1-methyl-1H-pyrrol-2-yl)-phenyl]-benzenesulfonamide
227	4-Methoxy-N-methyl-N-[2-methyl-5-(1-methyl-1H-pyrrol-2-yl)-phenyl]-benzenesulfonamide
228	4-Methyl-N-[3-methyl-5-(1-methyl-1H-pyrrol-3-yl)-phenyl]-benzenesulfonamide
229	4-Methoxy-N-methyl-N-[2-methyl-5-(1-methyl-1H-pyrrol-3-yl)-phenyl]-benzenesulfonamide
230	4,N-Dimethyl-N-[2-methyl-5-(1-methyl-1H-pyrrol-2-yl)-phenyl]-benzenesulfonamide
231	4-Methoxy-N-methyl-N-[3-methyl-5-(1-methyl-1H-pyrrol-2-yl)-phenyl]-benzenesulfonamide
232	4,N-Dimethyl-N-[3-methyl-5-(1-methyl-1H-pyrrol-3-yl)-phenyl]-benzenesulfonamide
233	4-Methoxy-N-[3-methyl-5-(1-methyl-1H-pyrrol-3-yl)-phenyl]-benzenesulfonamide
234	4-Amino-N-[2-methyl-5-(1-methyl-1H-pyrrol-2-yl)-phenyl]-benzenesulfonamide
235	4-Hydroxy-N-[2-methyl-5-(1-methyl-1H-pyrrol-2-yl)-phenyl]-benzenesulfonamide
236	4-Chloro-N-[2-methyl-5-(1-methyl-1H-pyrrol-2-yl)-phenyl]-benzenesulfonamide
237	4-Chloro-N-[2-methyl-5-(1-methyl-1H-pyrrol-3-yl)-phenyl]-benzenesulfonamide
238	4-Hydroxy-N-[2-methyl-5-(1-methyl-1H-pyrrol-3-yl)-phenyl]-benzenesulfonamide
239	4-Amino-N-[2-methyl-5-(1-methyl-1H-pyrrol-3-yl)-phenyl]-benzenesulfonamide
240	N-[5-(1,3-Dimethyl-1H-pyrrol-2-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide
241	N-[5-(1,3-Dimethyl-1H-pyrrol-2-yl)-2-methyl-phenyl]-4-methoxy-benzenesulfonamide
242	N-[5-(1,4-Dimethyl-1H-pyrrol-3-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide
243	N-[5-(1,4-Dimethyl-1H-pyrrol-3-yl)-2-methyl-phenyl]-4-methoxy-benzenesulfonamide
244	N-[3-(1,3-Dimethyl-1H-pyrrol-2-yl)-5-methyl-phenyl]-4-methyl-benzenesulfonamide
245	N-[5-(1,3-Dimethyl-1H-pyrrol-2-yl)-2-methyl-phenyl]-4-methoxy-N-methyl-benzenesulfonamide
246	N-[3-(1,4-Dimethyl-1H-pyrrol-3-yl)-5-methyl-phenyl]-4-methyl-benzenesulfonamide
247	N-[5-(1,4-Dimethyl-1H-pyrrol-3-yl)-2-methyl-phenyl]-4-methoxy-N-methyl-benzenesulfonamide
248	N-[5-(1,3-Dimethyl-1H-pyrrol-2-yl)-2-methyl-phenyl]-4,N-dimethyl-benzenesulfonamide

249	N-[3-(1,3-Dimethyl-1H-pyrrol-2-yl)-5-methyl-phenyl]-4-methoxy-N-methyl-benzenesulfonamide
250	N-[3-(1,4-Dimethyl-1H-pyrrol-3-yl)-5-methyl-phenyl]-4,N-dimethyl-benzenesulfonamide
251	N-[3-(1,4-Dimethyl-1H-pyrrol-3-yl)-5-methyl-phenyl]-4-methoxy-benzenesulfonamide
252	4-Hydroxy-N-[2-methyl-5-(5-methyl-furan-2-yl)-phenyl]-benzenesulfonamide
253	4-Amino-N-[2-methyl-5-(5-methyl-furan-2-yl)-phenyl]-benzenesulfonamide
254	4-Chloro-N-[2-methyl-5-(5-methyl-furan-2-yl)-phenyl]-benzenesulfonamide
255	4-Hydroxy-N-[2-methyl-5-(5-methyl-thiophen-2-yl)-phenyl]-benzenesulfonamide
256	4-Amino-N-[2-methyl-5-(5-methyl-thiophen-2-yl)-phenyl]-benzenesulfonamide
257	4-Chloro-N-[2-methyl-5-(5-methyl-thiophen-2-yl)-phenyl]-benzenesulfonamide
258	N-(5-Furan-2-yl-2-methyl-phenyl)-4-hydroxy-benzenesulfonamide
259	4-Amino-N-(5-furan-2-yl-2-methyl-phenyl)-benzenesulfonamide
260	4-Chloro-N-(5-furan-2-yl-2-methyl-phenyl)-benzenesulfonamide
261	4-Hydroxy-N-(2-methyl-5-thiophen-2-yl-phenyl)-benzenesulfonamide
262	4-Amino-N-(2-methyl-5-thiophen-2-yl-phenyl)-benzenesulfonamide
263	4-Chloro-N-(2-methyl-5-thiophen-2-yl-phenyl)-benzenesulfonamide
264	4-Hydroxy-N-(2-methyl-5-thiophen-3-yl-phenyl)-benzenesulfonamide
265	4-Amino-N-(2-methyl-5-thiophen-3-yl-phenyl)-benzenesulfonamide
266	4-Chloro-N-(2-methyl-5-thiophen-3-yl-phenyl)-benzenesulfonamide
267	N-(5-Furan-3-yl-2-methyl-phenyl)-4-hydroxy-benzenesulfonamide
268	4-Amino-N-(5-furan-3-yl-2-methyl-phenyl)-benzenesulfonamide
269	4-Chloro-N-(5-furan-3-yl-2-methyl-phenyl)-benzenesulfonamide
270	4-Hydroxy-N-methyl-N-[2-methyl-5-(5-methyl-furan-2-yl)-phenyl]-benzenesulfonamide
271	4-Amino-N-methyl-N-[2-methyl-5-(5-methyl-furan-2-yl)-phenyl]-benzenesulfonamide
272	4-Chloro-N-methyl-N-[2-methyl-5-(5-methyl-furan-2-yl)-phenyl]-benzenesulfonamide
273	4-Hydroxy-N-methyl-N-[2-methyl-5-(5-methyl-thiophen-2-yl)-phenyl]-benzenesulfonamide
274	4-Amino-N-methyl-N-[2-methyl-5-(5-methyl-thiophen-2-yl)-phenyl]-benzenesulfonamide
275	4-Chloro-N-methyl-N-[2-methyl-5-(5-methyl-thiophen-2-yl)-phenyl]-benzenesulfonamide
276	N-(5-Furan-2-yl-2-methyl-phenyl)-4-hydroxy-N-methyl-benzenesulfonamide
277	4-Amino-N-(5-furan-2-yl-2-methyl-phenyl)-N-methyl-benzenesulfonamide
278	4-Chloro-N-(5-furan-2-yl-2-methyl-phenyl)-N-methyl-benzenesulfonamide
279	4-Hydroxy-N-methyl-N-(2-methyl-5-thiophen-2-yl-phenyl)-benzenesulfonamide
280	4-Amino-N-methyl-N-(2-methyl-5-thiophen-2-yl-phenyl)-benzenesulfonamide
281	4-Chloro-N-methyl-N-(2-methyl-5-thiophen-2-yl-phenyl)-benzenesulfonamide
282	4-Hydroxy-N-methyl-N-(2-methyl-5-thiophen-3-yl-phenyl)-benzenesulfonamide
283	4-Amino-N-methyl-N-(2-methyl-5-thiophen-3-yl-phenyl)-benzenesulfonamide

284	4-Chloro-N-methyl-N-(2-methyl-5-thiophen-3-yl-phenyl)-benzenesulfonamide
285	N-(5-Furan-3-yl-2-methyl-phenyl)-4-hydroxy-N-methyl-benzenesulfonamide
286	4-Amino-N-(5-furan-3-yl-2-methyl-phenyl)-N-methyl-benzenesulfonamide
287	4-Chloro-N-(5-furan-3-yl-2-methyl-phenyl)-N-methyl-benzenesulfonamide
288	N-[5-(5-Cyano-furan-2-yl)-2-methyl-phenyl]-4-hydroxy-N-methyl-benzenesulfonamide
289	4-Amino-N-[5-(5-cyano-furan-2-yl)-2-methyl-phenyl]-N-methyl-benzenesulfonamide
290	4-Chloro-N-[5-(5-cyano-furan-2-yl)-2-methyl-phenyl]-N-methyl-benzenesulfonamide
291	4-Hydroxy-N-methyl-N-[2-methyl-5-(5-nitro-furan-2-yl)-phenyl]-benzenesulfonamide
292	4-Amino-N-methyl-N-[2-methyl-5-(5-nitro-furan-2-yl)-phenyl]-benzenesulfonamide
293	4-Chloro-N-methyl-N-[2-methyl-5-(5-nitro-furan-2-yl)-phenyl]-benzenesulfonamide
294	N-[5-(5-Cyano-thiophen-3-yl)-2-methyl-phenyl]-4-hydroxy-benzenesulfonamide
295	4-Amino-N-[5-(5-cyano-thiophen-3-yl)-2-methyl-phenyl]-benzenesulfonamide
296	4-Chloro-N-[5-(5-cyano-thiophen-3-yl)-2-methyl-phenyl]-benzenesulfonamide
297	N-[5-(5-Cyano-furan-2-yl)-2-methyl-phenyl]-N-methyl-4-trifluoromethoxy-benzenesulfonamide
298	N-[5-(5-Cyano-furan-2-yl)-2-methyl-phenyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide
299	N-[5-(5-Cyano-thiophen-3-yl)-2-methyl-phenyl]-4-trifluoromethoxy-benzenesulfonamide
300	N-[5-(5-Cyano-thiophen-3-yl)-2-methyl-phenyl]-4-trifluoromethyl-benzenesulfonamide
301	N-[5-(5-Cyano-furan-2-yl)-2-methyl-phenyl]-4-trifluoromethoxy-benzenesulfonamide
302	N-[5-(5-Cyano-furan-2-yl)-2-methyl-phenyl]-4-trifluoromethyl-benzenesulfonamide
303	N-[5-(2,4-Dimethyl-thiazol-5-yl)-2-methyl-phenyl]-4-hydroxy-benzenesulfonamide
304	N-[5-(3,5-Dimethyl-isoxazol-4-yl)-2-methyl-phenyl]-4-hydroxy-benzenesulfonamide
305	4-Amino-N-[5-(2,4-dimethyl-thiazol-5-yl)-2-methyl-phenyl]-benzenesulfonamide
306	4-Chloro-N-[5-(2,4-dimethyl-thiazol-5-yl)-2-methyl-phenyl]-benzenesulfonamide
307	4-Amino-N-[5-(3,5-dimethyl-isoxazol-4-yl)-2-methyl-phenyl]-benzenesulfonamide
308	4-Chloro-N-[5-(3,5-dimethyl-isoxazol-4-yl)-2-methyl-phenyl]-benzenesulfonamide
309	4-Hydroxy-N-(2-methyl-5-oxazol-5-yl-phenyl)-benzenesulfonamide
310	4-Amino-N-(2-methyl-5-oxazol-5-yl-phenyl)-benzenesulfonamide
311	4-Chloro-N-(2-methyl-5-oxazol-5-yl-phenyl)-benzenesulfonamide
312	4-Hydroxy-N-(2-methyl-5-pyrrol-1-yl-phenyl)-benzenesulfonamide
313	4-Amino-N-(2-methyl-5-pyrrol-1-yl-phenyl)-benzenesulfonamide
314	4-Chloro-N-(2-methyl-5-pyrrol-1-yl-phenyl)-benzenesulfonamide
315	4-Hydroxy-N-[2-methyl-5-(3-methyl-pyrazol-1-yl)-phenyl]-benzenesulfonamide
316	4-Amino-N-[2-methyl-5-(3-methyl-pyrazol-1-yl)-phenyl]-benzenesulfonamide
317	4-Chloro-N-[2-methyl-5-(3-methyl-pyrazol-1-yl)-phenyl]-benzenesulfonamide
318	4-Hydroxy-N-[2-methyl-5-(2-methyl-pyrrol-1-yl)-phenyl]-benzenesulfonamide

319	4-Amino-N-[2-methyl-5-(2-methyl-pyrrol-1-yl)-phenyl]-benzenesulfonamide
320	4-Chloro-N-[2-methyl-5-(2-methyl-pyrrol-1-yl)-phenyl]-benzenesulfonamide
321	N-(4,2'-Dimethyl-biphenyl-3-yl)-4-hydroxy-benzenesulfonamide
322	4-Amino-N-(4,2'-dimethyl-biphenyl-3-yl)-benzenesulfonamide
323	4-Chloro-N-(4,2'-dimethyl-biphenyl-3-yl)-benzenesulfonamide
324	N-(4,3'-Dimethyl-biphenyl-3-yl)-4-hydroxy-benzenesulfonamide
325	4-Amino-N-(4,3'-dimethyl-biphenyl-3-yl)-benzenesulfonamide
326	4-Chloro-N-(4,3'-dimethyl-biphenyl-3-yl)-benzenesulfonamide
327	N-(4,4'-Dimethyl-biphenyl-3-yl)-4-hydroxy-benzenesulfonamide
328	4-Amino-N-(4,4'-dimethyl-biphenyl-3-yl)-benzenesulfonamide
329	4-Chloro-N-(4,4'-dimethyl-biphenyl-3-yl)-benzenesulfonamide
330	4-Hydroxy-N-(2-methyl-5-pyridin-2-yl-phenyl)-benzenesulfonamide
331	4-Amino-N-(2-methyl-5-pyridin-2-yl-phenyl)-benzenesulfonamide
332	4-Chloro-N-(2-methyl-5-pyridin-2-yl-phenyl)-benzenesulfonamide
333	4-Hydroxy-N-(2-methyl-5-pyridin-3-yl-phenyl)-benzenesulfonamide
334	4-Amino-N-(2-methyl-5-pyridin-3-yl-phenyl)-benzenesulfonamide
335	4-Chloro-N-(2-methyl-5-pyridin-3-yl-phenyl)-benzenesulfonamide
336	4-Hydroxy-N-(2-methyl-5-pyridin-4-yl-phenyl)-benzenesulfonamide
337	4-Amino-N-(2-methyl-5-pyridin-4-yl-phenyl)-benzenesulfonamide
338	4-Chloro-N-(2-methyl-5-pyridin-4-yl-phenyl)-benzenesulfonamide
339	N-[5-(5-Cyano-pyridin-3-yl)-2-methyl-phenyl]-4-hydroxy-benzenesulfonamide
340	4-Amino-N-[5-(5-cyano-pyridin-3-yl)-2-methyl-phenyl]-benzenesulfonamide
341	4-Chloro-N-[5-(5-cyano-pyridin-3-yl)-2-methyl-phenyl]-benzenesulfonamide
342	4-Hydroxy-N-[2-methyl-5-(6-methyl-pyridin-2-yl)-phenyl]-benzenesulfonamide
343	4-Amino-N-[2-methyl-5-(6-methyl-pyridin-2-yl)-phenyl]-benzenesulfonamide
344	4-Chloro-N-[2-methyl-5-(6-methyl-pyridin-2-yl)-phenyl]-benzenesulfonamide
345	N-[5-(5-Cyano-pyridin-2-yl)-2-methyl-phenyl]-4-hydroxy-benzenesulfonamide
346	4-Amino-N-[5-(5-cyano-pyridin-2-yl)-2-methyl-phenyl]-benzenesulfonamide
347	4-Chloro-N-[5-(5-cyano-pyridin-2-yl)-2-methyl-phenyl]-benzenesulfonamide
348	N-[5-(5-Cyano-pyridin-2-yl)-2-methyl-phenyl]-4-trifluoromethoxy-benzenesulfonamide
349	N-[5-(5-Cyano-pyridin-2-yl)-2-methyl-phenyl]-4-trifluoromethyl-benzenesulfonamide
350	4-Hydroxy-N-[5-(5-methoxy-pyridin-2-yl)-2-methyl-phenyl]-benzenesulfonamide
351	4-Amino-N-[5-(5-methoxy-pyridin-2-yl)-2-methyl-phenyl]-benzenesulfonamide
352	4-Chloro-N-[5-(5-methoxy-pyridin-2-yl)-2-methyl-phenyl]-benzenesulfonamide
353	N-[5-(5-Methoxy-pyridin-2-yl)-2-methyl-phenyl]-4-trifluoromethoxy-benzenesulfonamide
354	N-[5-(5-Methoxy-pyridin-2-yl)-2-methyl-phenyl]-4-trifluoromethyl-benzenesulfonamide
355	N-[5-(5-Fluoro-pyridin-2-yl)-2-methyl-phenyl]-4-hydroxy-benzenesulfonamide
356	4-Amino-N-[5-(5-fluoro-pyridin-2-yl)-2-methyl-phenyl]-benzenesulfonamide

357	4-Chloro-N-[5-(5-fluoro-pyridin-2-yl)-2-methyl-phenyl]-benzenesulfonamide
358	N-[5-(5-Fluoro-pyridin-2-yl)-2-methyl-phenyl]-4-trifluoromethoxy-benzenesulfonamide
359	N-[5-(5-Fluoro-pyridin-2-yl)-2-methyl-phenyl]-4-trifluoromethyl-benzenesulfonamide
360	4-Hydroxy-N-[2-methyl-5-(5-nitro-pyridin-2-yl)-phenyl]-benzenesulfonamide
361	4-Amino-N-[2-methyl-5-(5-nitro-pyridin-2-yl)-phenyl]-benzenesulfonamide
362	4-Chloro-N-[2-methyl-5-(5-nitro-pyridin-2-yl)-phenyl]-benzenesulfonamide
363	N-[2-Methyl-5-(5-nitro-pyridin-2-yl)-phenyl]-4-trifluoromethoxy-benzenesulfonamide
364	N-[2-Methyl-5-(5-nitro-pyridin-2-yl)-phenyl]-4-trifluoromethyl-benzenesulfonamide
365	4-Amino-N-(4'-cyano-4-methyl-biphenyl-3-yl)-benzenesulfonamide
366	N-[5-(6-Cyano-pyridin-3-yl)-2-methyl-phenyl]-4-hydroxy-benzenesulfonamide
367	4-Amino-N-[5-(6-cyano-pyridin-3-yl)-2-methyl-phenyl]-benzenesulfonamide
368	4-Chloro-N-[5-(6-cyano-pyridin-3-yl)-2-methyl-phenyl]-benzenesulfonamide
369	N-(3',4'-Dicyano-4-methyl-biphenyl-3-yl)-4-hydroxy-benzenesulfonamide
370	4-Amino-N-(3',4'-dicyano-4-methyl-biphenyl-3-yl)-benzenesulfonamide
371	4-Chloro-N-(3',4'-dicyano-4-methyl-biphenyl-3-yl)-benzenesulfonamide
372	N-(4'-Cyano-3'-fluoro-4-methyl-biphenyl-3-yl)-4-hydroxy-benzenesulfonamide
373	4-Amino-N-(4'-cyano-3'-fluoro-4-methyl-biphenyl-3-yl)-benzenesulfonamide
374	4-Chloro-N-(4'-cyano-3'-fluoro-4-methyl-biphenyl-3-yl)-benzenesulfonamide
375	N-(4'-Cyano-4,3'-dimethyl-biphenyl-3-yl)-4-hydroxy-benzenesulfonamide
376	4-Amino-N-(4'-cyano-4,3'-dimethyl-biphenyl-3-yl)-benzenesulfonamide
377	4-Chloro-N-(4'-cyano-4,3'-dimethyl-biphenyl-3-yl)-benzenesulfonamide
378	3-Fluoro-N-(5-furan-2-yl-2-methyl-phenyl)-4-methyl-benzenesulfonamide
379	3-Fluoro-N-(5-furan-2-yl-2-methyl-phenyl)-4-methoxy-benzenesulfonamide
380	3-Fluoro-4-methyl-N-[2-methyl-5-(5-methyl-furan-2-yl)-phenyl]-benzenesulfonamide
381	3-Fluoro-4-methoxy-N-[2-methyl-5-(5-methyl-furan-2-yl)-phenyl]-benzenesulfonamide
382	N-(4,4'-Dimethyl-biphenyl-3-yl)-3-fluoro-4-methyl-benzenesulfonamide
383	N-(4,4'-Dimethyl-biphenyl-3-yl)-3-fluoro-4-methoxy-benzenesulfonamide
384	3-Fluoro-N-[5-(5-methoxy-pyridin-2-yl)-2-methyl-phenyl]-4-methyl-benzenesulfonamide
385	3-Fluoro-4-methoxy-N-[5-(5-methoxy-pyridin-2-yl)-2-methyl-phenyl]-benzenesulfonamide
386	3-Fluoro-4-methyl-N-(2-methyl-5-pyridin-3-yl-phenyl)-benzenesulfonamide
387	3-Fluoro-4-methoxy-N-(2-methyl-5-pyridin-3-yl-phenyl)-benzenesulfonamide
388	N-[5-(4-Cyano-thiophen-2-yl)-2-methyl-phenyl]-3-fluoro-4-methyl-benzenesulfonamide
389	N-[5-(4-Cyano-thiophen-2-yl)-2-methyl-phenyl]-3-fluoro-4-methoxy-benzenesulfonamide
390	N-[5-(5-Cyano-thiophen-3-yl)-2-methyl-phenyl]-3-fluoro-4-methoxy-benzenesulfonamide

Discussion

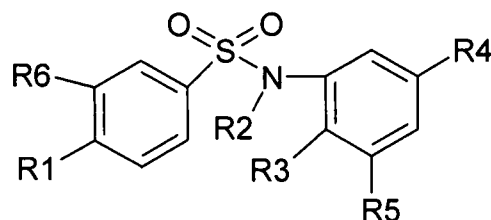
It follows directly from the data shown in the examples above that the compounds of the invention have the common property of inhibiting HIF function and inhibiting cell proliferation.

- 5 Thus, these compounds are useful as therapeutic compounds for the treatment or prevention of a disease or disorder selected from the group consisting of an inflammatory disease, a hyperproliferative disease or disorder, a hypoxia-related pathology and a disease characterized by excessive vascularisation.

- 10 In addition to the above described useful properties that are shared by all compounds of the invention, these compounds also exhibit different degrees of potency with respect to inhibiting tubulin organization. This shows a further valuable contribution of this invention which lies in the provision of therapeutic compounds that can be administered selectively on a case to case basis to patients depending on their disease state, constitution and genetic predisposition. In this context it is further possible to decide if the patient is to be treated with
- 15 compounds of the invention that do or do not possess an additional activity as tubulin inhibitors.

Claims

1. A compound having a structure according to formula I:



(I)

wherein

R^1 is selected from a group consisting of H, alkyl, alkenyl, alkynyl, -CN, halogen, -OH, alkoxy, -SH, S-alkyl, -NH₂, NH-alkyl, N-bis-alkyl, NHOH, NMeOH, NMe(OMe), -NO₂, -CF₃, -OCF₃ and C₁-C₄ hydroxyalkyl.

R^2 is H or C₁-C₄ alkyl;

R^3 is H or -CH₃;

R^4 is phenyl or monocyclic 5- or 6-membered heteroaryl; optionally substituted with one or more substituents selected from the group consisting of:

alkyl, alkenyl, alkynyl, alkoxy, halogen, -CN, -CF₃, -OCF₃, C₁-C₄ hydroxyalkyl, -OH, -SH, S-alkyl, -CN, N-bis-alkyl, cyanoacetylene, -NO₂, -NR⁷R⁸, -C(O)R²⁰, N-O (wherein the nitrogen atom is integral part of the monocyclic 5- or 6-membered heteroaryl) and two substituents which form together a dioxymethylene bridge (-O-CH₂-O-);

R^5 is H or -CH₃;

R^6 is selected from the group consisting of H, halogen, alkyl, alkoxy, alkenyl, alkynyl, S-alkyl, -OH, -NR⁷R⁸, -CN, N-bis-alkyl, -SH, -CF₃ and -OCF₃; or R^6 forms together with R^1 a dioxymethylene bridge (-O-CH₂-O-);

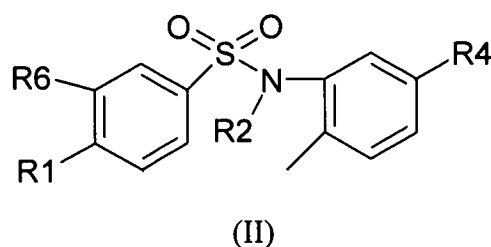
R^7 is H or alkyl;

R^8 is H or C₁-C₄ alkyl; and

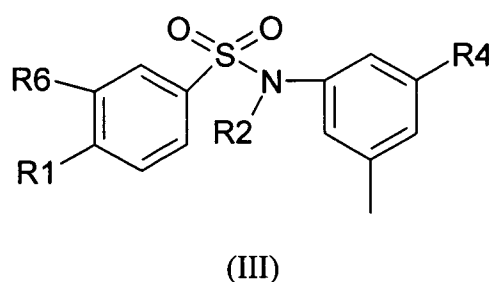
R^{20} is C₁-C₄ alkyl;

with the proviso that R^4 is not 3-alkoxy-pyridazine-5-yl; that if R^4 is phenyl, then the 2- and 5-position of the phenyl ring may not be substituted with two methoxy substituents at the same time; and that R^3 and R^5 are not at the same time H.

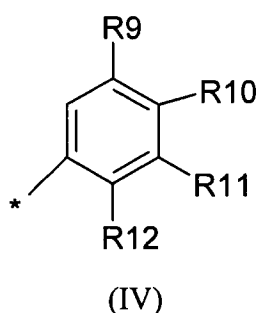
2. Compound according to claim 1, wherein the compound has a structure according to formula II:



3. Compound according to claim 1, wherein the compound has a structure according to formula III:



4. Compound according to any of claims 1-3, wherein R⁴ has a structure according to formula IV:



wherein

R⁹ and R¹⁰ are each individually selected from the group consisting of H, C₁-C₄ alkyl, C₁-C₄ alkenyl, C₁-C₄ alkynyl, -CN, -C(O)R²⁰, cyanoacetylene, halogen, -OH, C₁-C₄ alkoxy, -SH, C₁-C₄ S-alkyl, -NH₂, C₁-C₄ NH-alkyl, C₁-C₄ N-bis-alkyl, -NO₂, -CF₃, -OCF₃, and C₁-C₄ hydroxyalkyl,
or R⁹ and R¹⁰ form together a dioxymethylene bridge (-O-CH₂-O-);

R^{11} and R^{12} are each individually selected from the group consisting of H, C₁-C₄ alkyl, C₁-C₄ alkenyl, C₁-C₄ alkynyl, -CN, halogen, -OH, C₁-C₄ alkoxy, -SH, C₁-C₄ S-alkyl, -CF₃, -OCF₃, -NH₂, -N(CH₃)₂ and C₁-C₄ hydroxyalkyl;

with the proviso that R^9 and R^{12} may not be methoxy at the same time;

5 R^{20} has the above indicated meaning; and

* indicates the bond between R^4 and the compound according to any of formulas (I) through (III).

5. Compound according to claim 4, wherein R^{11} and R^{12} are H.

10

6. Compound according to claim 5, wherein

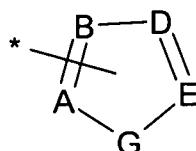
R^3 is methyl;

R^2 is H, methyl or ethyl; and

R^5 and R^6 are H.

15

7. Compound according to any of claims 1-3, wherein R^4 has a structure according to formula V:



(V)

20

wherein

A, B, D and E are each individually selected from the group consisting of a nitrogen atom, CR¹³ and N-O;

G is selected from the group consisting of an oxygen atom, a sulphur atom and NR¹⁴;

25

R¹³ is selected from the group consisting of H, C₁-C₃ alkyl, C₁-C₃ alkoxy, -OH, -SH, -CF₃, -OCF₃, halogen, -NR¹⁵R¹⁶, -NO₂, -CN, -C(O)R²⁰, acetylene, cyanoacetylene, C₁-C₄ hydroxyalkyl and a σ (sigma) bond connecting R^4 to the compound according to any of formulas (I) through (III); and

R¹⁴ is selected from the group consisting of H, C₁-C₄ alkyl and a σ (sigma) bond connecting R^4 to the compound according to any of formulas (I) through (III);

30

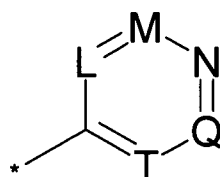
and

R¹⁵ and R¹⁶ are each individually either H or C₁-C₄ alkyl;

R²⁰ has the above indicated meaning; and

* indicates the bond between R⁴ and the compound according to any of formulas (I) through (III).

8. Compound according to any of the claims 1-3, wherein R⁴ has a structure according to formula VI:



(VI)

wherein

L and T are each individually either a CH group or a nitrogen atom or N-O;

M, N and Q are each individually selected from the group consisting of a nitrogen atom, a CR¹⁷ group and N-O;

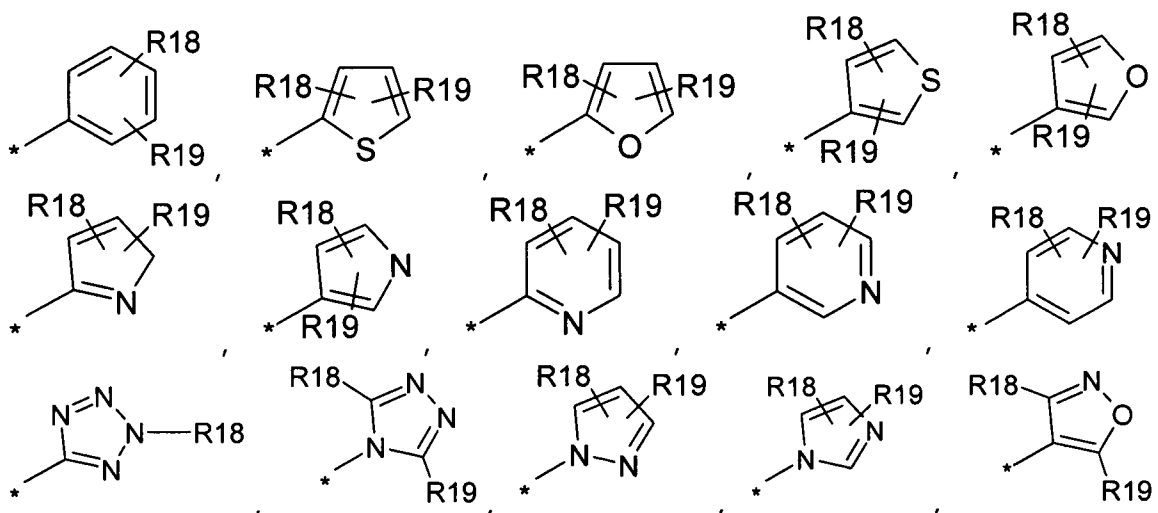
R¹⁷ is selected from the group consisting of H, C₁-C₃ alkyl, C₁-C₃ alkoxy, -CF₃, -OCF₃, halogen, -OH, -NO₂, -SH, C₁-C₃ S-alkyl, -NR¹⁵R¹⁶, C₁-C₄ hydroxyalkyl, -C(O)R²⁰, acetylene, cyanoacetylene and -CN;

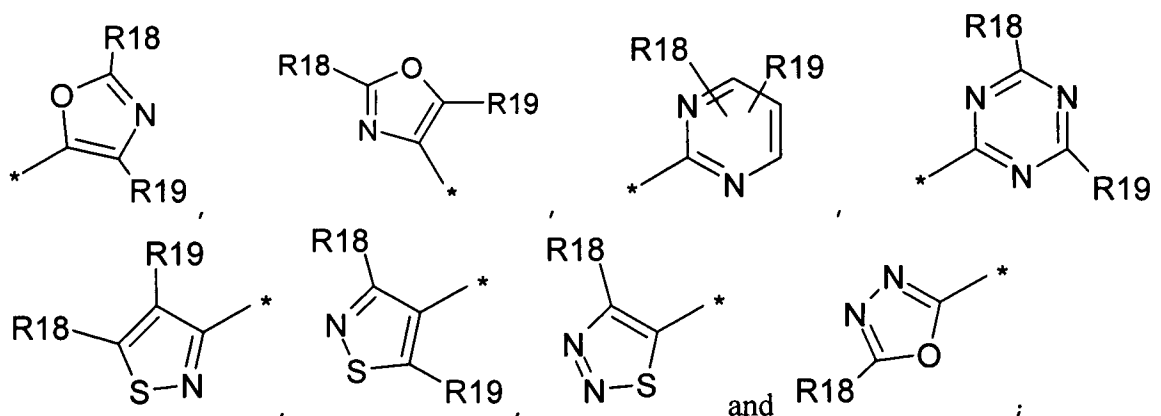
R¹⁵ and R¹⁶ are each individually either H or C₁-C₄ alkyl;

R²⁰ has the above indicated meaning; and

* indicates the bond between R⁴ and the compound according to any of formulas (I) through (III).

9. Compound according to any of claims 1-3, wherein R⁴ is selected from the group consisting of:

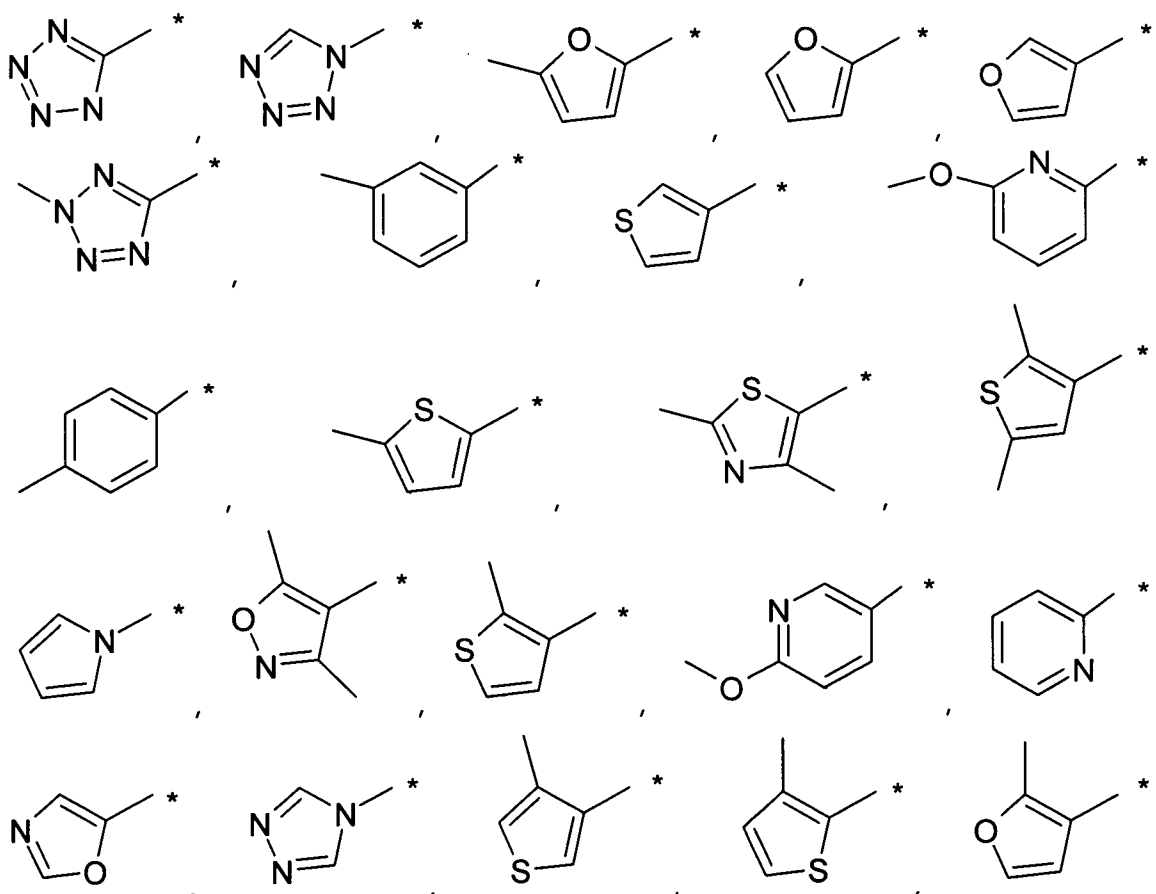


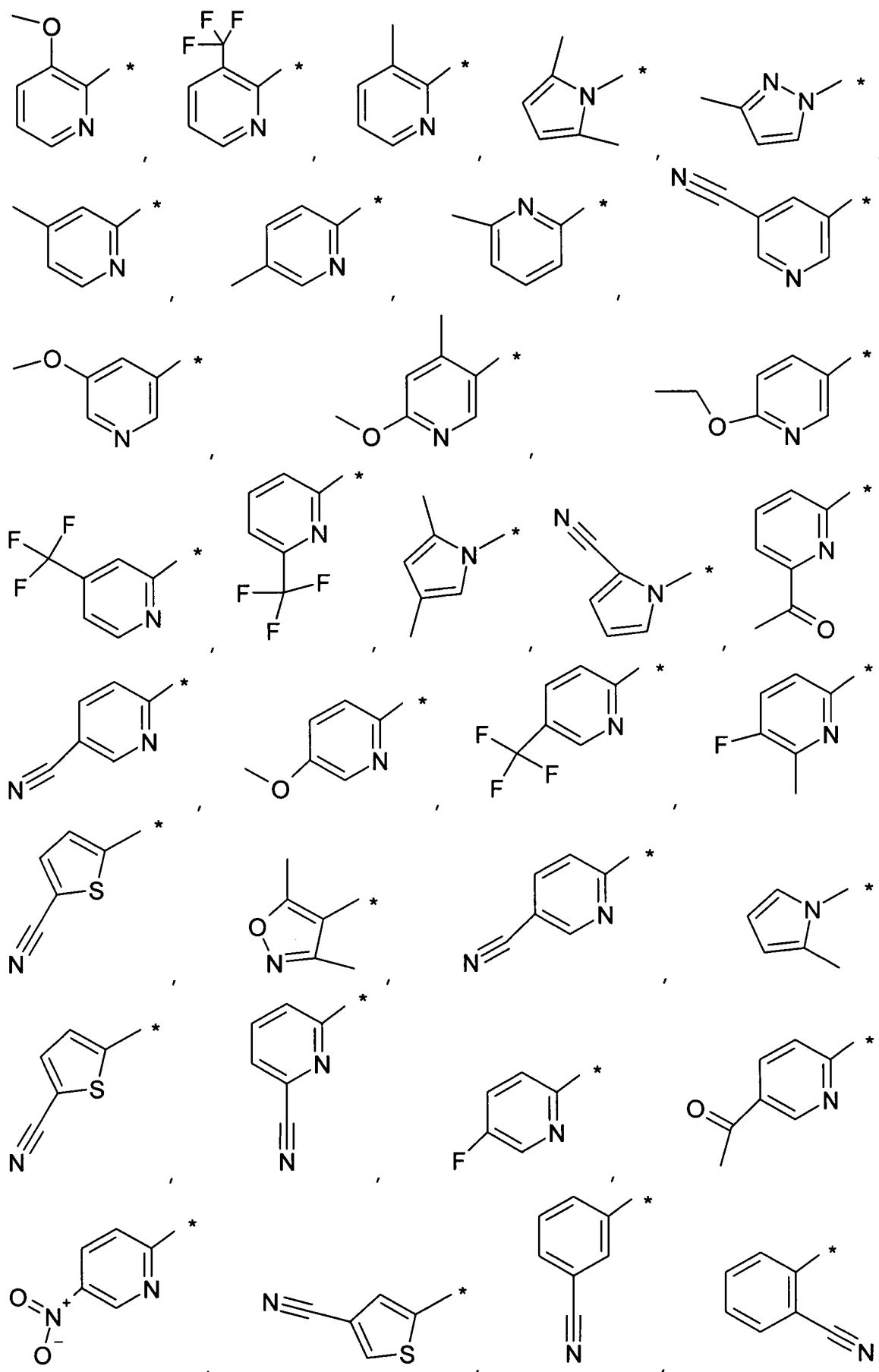


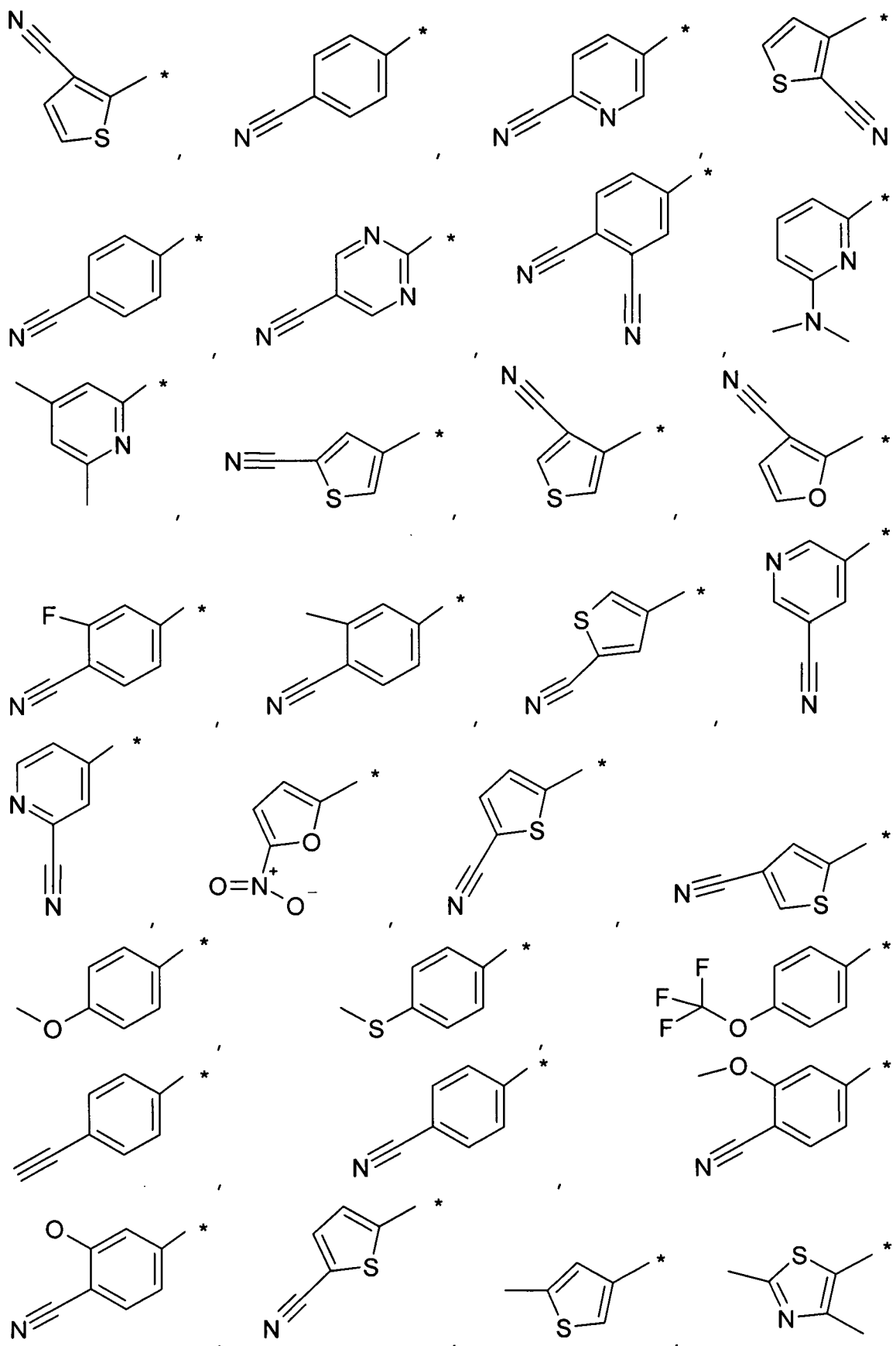
wherein R¹⁸ and R¹⁹ are each individually selected from the group consisting of H, C₁-C₃ alkyl, C₁-C₃ alkoxy, -CF₃, -OCF₃, halogen, -OH, -NO₂, -SH, C₁-C₃ S-alkyl, -NR¹⁵R¹⁶, C₁-C₄ hydroxyalkyl, alkynyl, alkenyl, -C(O)R²⁰, cyanoacetylene and -CN;

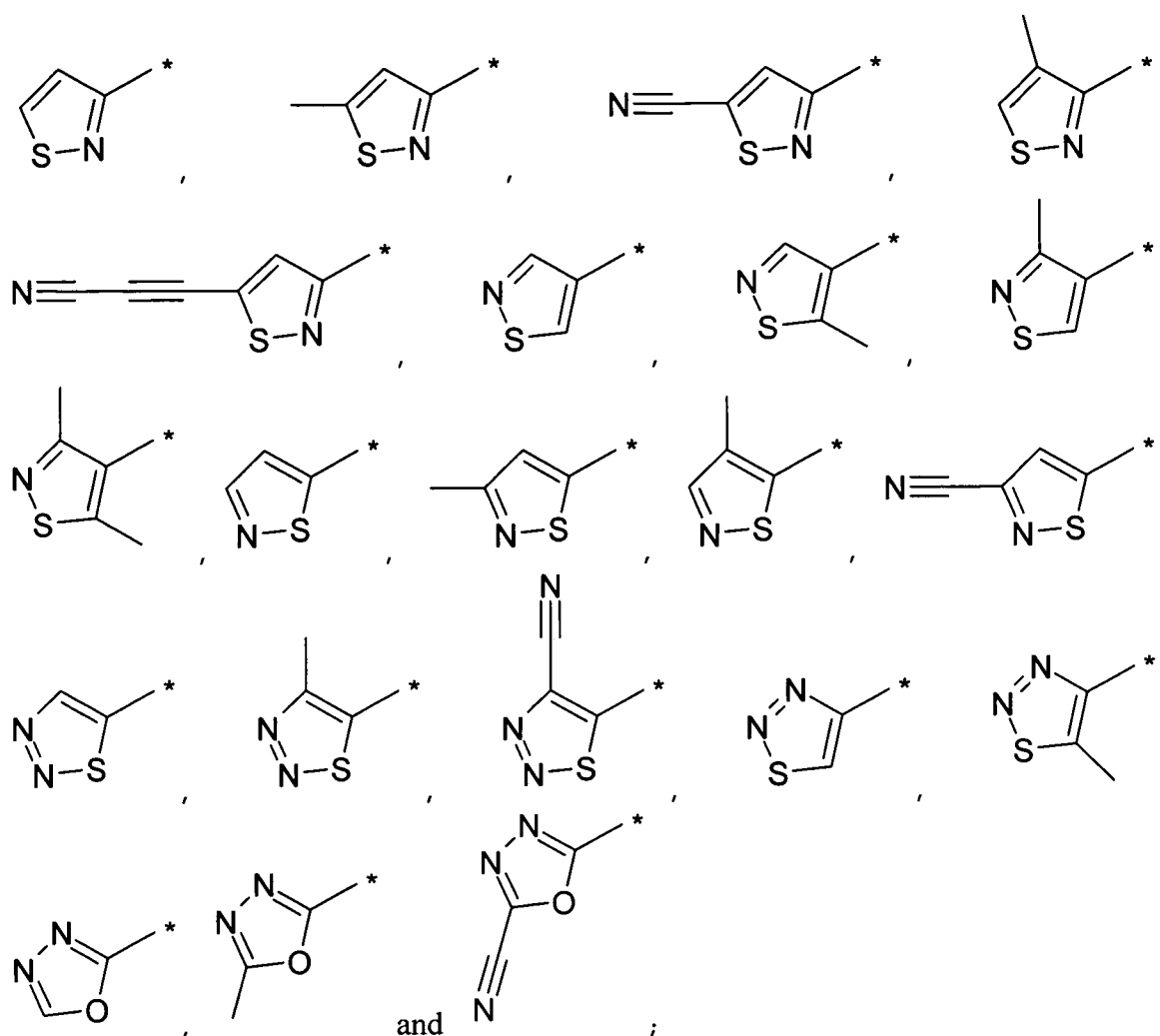
and R¹⁵, R¹⁶ and R²⁰ have the above indicated meaning.

10. Compound according to any of claims 1-3, wherein R² is H and R⁴ is selected from the group consisting of:









wherein * indicates the bond between R⁴ and the compound according to any of formulas (I) through (III).

- 10 11. Compound according to any of claims 1 - 10, wherein R² and/or R⁶ is H.
12. A compound according to any of claims 1-11 or pharmaceutically acceptable salt thereof, for the prevention or treatment of a disease or disorder.
- 15 13. A pharmaceutical composition comprising a compound according to any of claims 1-10 or pharmaceutically acceptable salt thereof and a second therapeutic agent useful for the treatment or prevention of a disease or disorder selected from the group consisting of an inflammatory disease, a hyperproliferative disease or disorder, a hypoxia related pathology and a disease characterized by pathophysiological hyper-vascularisation, and,

20 optionally, a pharmaceutically acceptable carrier or excipient.

14. Use of a compound according to any of claims 1-11 or the composition according to claim 13 for the preparation of a medicament for the treatment or prevention of a disease or disorder selected from the group consisting of
- 5 an inflammatory disease, a hyperproliferative disease or disorder, a hypoxia related pathology and a disease characterized by pathophysiological hyper- vascularisation.
15. Use according to claim 14, wherein the inflammatory disease is selected form the group consisting of atherosclerosis, rheumatoid arthritis, asthma, inflammatory bowel disease,
- 10 psoriasis, in particular psoriasis vulgaris, psoriasis capitis, psoriasis guttata, psoriasis inversa; neurodermatitis; ichthyosises; alopecia areata; alopecia totalis; alopecia subtotalis; alopecia universalis; alopecia diffusa; atopic dermatitis; lupus erythematoses of the skin; dermatomyositis of the skin; atopic eczema; morphea; scleroderma; alopecia areata Ophiasis type; androgenic alopecia; allergic dermatitis; irritative contact dermatitis;
- 15 contact dermatitis; pemphigus vulgaris; pemphigus foliaceus; pemphigus vegetans; scarring mucous membrane pemphigoid; bullous pemphigoid; mucous membrane pemphigoid; dermatitis; dermatitis herpetiformis Dühring; urticaria; necrobiosis lipoidica; erythema nodosum; prurigo simplex; prurigo nodularis; prurigo acuta; linear IgA dermatosis; polymorphic light dermatosis; erythema solaris; exanthema of the skin;
- 20 drug exanthema; purpura chronica progressiva; dihydrotic eczema; eczema; fixed drug exanthema; photoallergic skin reaction; and periorale dermatitis.
16. Use according to claim 14, wherein the hyperproliferative disease is selected from the group consisting of a tumor or cancer disease, precancerosis, dysplasia, histiocytosis, a
- 25 vascular proliferative disease and a virus-induced proliferative disease.
17. Use according to claim 16, wherein the hyperproliferative disease is a tumor or cancer disease selected from the group consisting of diffuse large B-cell lymphoma (DLBCL), T-cell lymphomas or leukemias, e.g., cutaneous T-cell lymphoma (CTCL), noncutaneous peripheral T-cell lymphoma, lymphoma associated with human T-cell lymphotropic virus (HTLV), adult T- cell leukemia/lymphoma (ATLL), as well as acute lymphocytic leukemia, acute nonlymphocytic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, myeloma, multiple myeloma, mesothelioma, childhood solid tumors, glioma, bone
- 30

cancer and soft-tissue sarcomas, common solid tumors of adults such as head and neck cancers (e.g., oral, laryngeal and esophageal), genitourinary cancers (e.g., prostate, bladder, renal, uterine, ovarian, testicular, rectal, and colon), lung cancer (e.g., small cell carcinoma and non-small cell lung carcinoma, including squamous cell carcinoma and adenocarcinoma), breast cancer, pancreatic cancer, melanoma and other skin cancers, basal cell carcinoma, metastatic skin carcinoma, squamous cell carcinoma of both ulcerating and papillary type, stomach cancer, brain cancer, liver cancer, adrenal cancer, kidney cancer, thyroid cancer, medullary carcinoma, osteosarcoma, soft-tissue sarcoma, Ewing's sarcoma, veticulum cell sarcoma, and Kaposi's sarcoma, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, leiomyosarcoma, rhabdomyosarcoma, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, seminoma, embryonal carcinoma, Wilms' tumor, small cell lung carcinoma, epithelial carcinoma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, neuroblastoma, retinoblastoma, glaucoma, hemangioma, heavy chain disease and metastases.

18. Method for treating a hyperproliferative disease or disorder comprising administering a compound according to any of claims 1-11 or a composition according to claim 13 to a patient prior to, during and/or after he was subjected to a radiation therapy, a chemotherapy, an immunotherapy, a laser/microwave thermotherapy or a gene therapy using antisense DNA and/or RNA.