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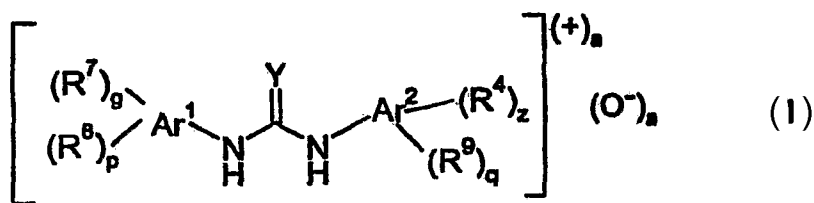
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(54) Title: N-OXIDES OF HETEROCYCLIC SUBSTITUTED BISARYLUREAS FOR TREATING KINASE-MEDIATED DISEASES



(57) Abstract: The present invention relates to heterocyclic substituted N-Oxides of formula (I), the use of the compounds of formula I as inhibitors of one or more kinases, the use of the compounds of formula (I) for the manufacture of a pharmaceutical composition and a method of treatment, comprising administering said pharmaceutical composition to a patient.

N-OXIDES OF HETEROCYCLIC SUBSTITUTED BISARYLUREAS FOR TREATING KINASE-MEDIATED DISEASES

The present invention relates to N-oxides of heterocyclic substituted bisarylureas (in the following referred to as N-oxides), said N-oxides as medicaments, said N-oxides as inhibitors of one or more kinases, the use of N-oxides according to the invention for the manufacture of a pharmaceutical, a method for producing a pharmaceutical composition containing said N-oxides, the pharmaceutical composition obtainable by said method and a method of treatment, comprising administering said pharmaceutical composition.

The instant invention preferably relates to compounds which are able to interact, inhibit, regulate and/or modulate the signal transduction of kinases, especially receptor tyrosine kinases and/or serine/threonine kinases, pharmaceutical preparation which comprises said compounds and the use of said compounds for the treatment of diseases caused, mediated and/or propagated by kinases.

As a mechanistic part of the *hallmarks of cancer* [Hanahan & Weinberg Cell 100, 57-70 (2000)], *Ser/Thr kinases* and *receptor tyrosine kinases* (RTK) are phosphorylating enzymes essential in cellular signaling. Cell cycle, survival, proliferation and cell death are basic cellular processes, regulated by cell signaling, to permit tissue to grow, to regenerate and to be in homeostasis. Some kinases are therefore exquisite targets for mammalian therapy [Dumas Curr.Opin.DrugDiscDev4, 378-389 (2001), Fabbro&Garcia-Echeverria Curr.Opin.DrugDiscDev. 5, 701-712 (2002), Grosios&Traxler Drugs of the Future 28, 679-697 (2003), Shawver Cancer Cell 1, 117-123 (2002), Krause N.Engl.J.Med. 353,172-187(2005)].

Protein phosphorylation is a fundamental process for the regulation of cellular functions. The coordinated action of both protein kinases and phosphatases controls the levels of phosphorylation and, hence, the activity of specific

target proteins. One of the predominant roles of protein phosphorylation is in signal transduction, where extracellular signals are amplified and propagated by a cascade of protein phosphorylation and dephosphorylation events, e.g. in the ras/raf pathway.

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Activated Ras is necessary for the activation of the c-raf-1 proto-oncogene, but the biochemical steps through which Ras activates the Raf-1 protein (Ser/Thr) kinase are now well characterized . It has been shown that inhibiting the effect of active ras by inhibiting the raf kinase signaling pathway by administration of deactivating antibodies to raf kinase or by co-expression of dominant negative raf kinase or dominant negative MEK, the substrate of raf kinase, leads to the reversion of transformed cells to the normal growth phenotype see: Daum et al. (1994) Trends Biochem. Sci., 19, 474-80; Fridman et al. (1994) J Biol. Chem., 269, 30105-8. Kolch et al. (1991) Nature, 349, 426-28) and for review Weinstein-Oppenheim et al. Pharm. & Therap. (2000), 88, 229-279.

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Similarly, inhibition of raf kinase (by antisense oligodeoxynucleotides) has been correlated in vitro and in vivo with inhibition of the growth of a variety of human tumor types (Monia et al., Nat. Med. 1996, 2, 668-75; Geiger et al. (1997), Clin. Cancer Res. 3(7): 1179-85; Lau et al. (2002), Antisense Nucl. Acid. Drug Dev. 12(1): 11-20 ; McPhillips et al. (2001), Br. J. Cancer 85(11): 1753-8).

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Raf serine- and threonine-specific protein kinases are cytosolic enzymes that stimulate cell growth in a variety of cell systems (Rapp, U.R., et al. (1988) in The oncogene handbook; T. Curran, E.P. Reddy, and A. Skalka (ed.) Elsevier Science Publishers; The Netherlands, pp. 213-253; Rapp, U.R., et al. (1988) Cold Spring Harbor Sym. Quant. Biol. 53:173-184; Rapp, U.R., et al. (1990) Inv Curr. Top. Microbiol. Immunol. Potter and Melchers (eds), Berlin, Springer-Verlag 166:129-139).

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Three isozymes have been characterized:

c-Raf (also named Raf-1, c-raf-1 or c-raf1) (Bonner, T.I., et al. (1986) *Nucleic Acids Res.* 14:1009-1015). A-Raf (Beck, T.W., et al. (1987) *Nucleic Acids Res.* 15:595-609), and B-Raf (Qkawa, S., et al. (1998) *Mol. Cell. Biol.* 8:2651-2654; Sithanandam, G. et a. (1990) *Oncogene*:1775). These enzymes differ in their expression in various tissues. Raf-1 is expressed in all organs and in all cell lines that have been examined, and A- and B-Raf are expressed in urogenital and brain tissues, respectively (Storm, S.M. (1990) *Oncogene* 5:345-351).

Raf genes are proto-oncogenes: they can initiate malignant transformation of cells when expressed in specifically altered forms. Genetic changes that lead to oncogenic activation generate a constitutively active protein kinase by removal or interference with an N-terminal negative regulatory domain of the protein (Heidecker, G., et al. (1990) *Mol. Cell. Biol.* 10:2503-2512; Rapp, U.R., et al. (1987) in *Oncogenes and cancer*; S. A. Aaronson, J. Bishop, T. Sugimura, M. Terada, K. Toyoshima, and P. K. Vogt (ed). Japan Scientific Press, Tokyo). Microinjection into NIH 3T3 cells of oncogenically activated but not wild-type versions of the Raf-protein prepared with *Escherichia coli* expression vectors results in morphological transformation and stimulates DNA synthesis (Rapp, U.R., et al. (1987) in *Oncogenes and cancer*; S. A. Aaronson, J. Bishop, T. Sugimura, M. Terada, K. Toyoshima, and P. K. Vogt (ed.) Japan Scientific Press, Tokyo; Smith, M. R., et al (1990) *Mol. Cell. Biol.* 10:3828-3833). Activating mutants of B-Raf have been identified in a wide range of human cancers e.g. colon, ovarian, melanomas and sarcomas (Davies, H., et al. (2002), *Nature* 417 949-945. Published online June 9, 2002, 10.1038/nature00766). The preponderant mutation is a single phosphomimetic substitution in the kinase activation domain (V599E), leading to constitutive kinase activity and transformation of NIH3T3 cells.

Thus, activated Raf-1 is an intracellular activator of cell growth. Raf-1 protein serine kinase is a candidate downstream effector of mitogen signal transduction, since Raf oncogenes overcome growth arrest resulting from a

block of cellular ras activity due either to a cellular mutation (ras revertant cells) or microinjection of anti-ras antibodies (Rapp, U.R., et al. (1988) in The Oncogene Handbook, T. Curran, E.P. Reddy, and A. Skalka (ed.), Elsevier Science Publishers; The Netherlands, pp. 213-253; Smith, M.R., et al. (1986) Nature (London) 320:540-543).

c-Raf function is required for transformation by a variety of membrane-bound oncogenes and for growth stimulation by mitogens contained in serums (Smith, M.R., et al. (1986) Nature (London) 320:540-543). Raf-1 protein serine kinase activity is regulated by mitogens via phosphorylation (Morrison, D.K., et al. (1989) Cell 58:648-657), which also effects sub cellular distribution (Olah, Z., et al. (1991) Exp. Brain Res. 84:403; Rapp, U.R., et al. (1988) Cold Spring Harbor Sym. Quant. Biol. 53:173-184. Raf-1 activating growth factors include platelet-derived growth factor (PDGF) (Morrison, D.K., et al. (1988) Proc. Natl. Acad. Sci. USA 85:8855-8859), colony-stimulating factor (Baccarini, M., et al. (1990) EMBO J. 9:3649-3657), insulin (Blackshear, P.J., et al. (1990) J. Biol. Chem. 265:12115-12118), epidermal growth factor (EGF) (Morrison, R.K., et al. (1988) Proc. Natl. Acad. Sci. USA 85:8855-8859), interleukin 2 (Turner, B.C., et al (1991) Proc. Natl. Acad. Sci. USA 88:1227), and interleukin 3 and granulocytemacrophage colony-stimulating factor (Carroll, M.P., et al (1990) J. Biol. Chem. 265:19812-19817).

There are at least two independent pathways for Raf-1 activation by extracellular mitogens: one involving protein kinase C (PKC) and a second initiated by protein tyrosine kinases (Blackshear, P.J., et al. (1990) J. Biol. Chem. 265:12131-12134; Kovacina, K.S., et al (1990) J. Biol. Chem. 265:12115-12118; Morrison, D.K., et al. (1988) Proc. Natl. Acad. Sci. USA 85:8855-8859; Siegel, J.N., et al (1990) J. Biol. Chem. 265:18472-18480; Turner, B.C., et al (1991) Proc. Natl. Acad. Sci. USA 88:1227). In either case, activation involves Raf-1 protein phosphorylation. Raf-1 phosphorylation may be a consequence of a kinase cascade amplified by autophosphorylation or

may be caused entirely by autophosphorylation initiated by binding of a putative activating ligand to the Raf-1 regulatory domain, analogous to PKC activation by diacylglycerol (Nishizuka, Y. (1986) Science 233:305-312).

5 The process of angiogenesis is the development of new blood vessels, generally capillaries, from pre-existing vasculature. Angiogenesis is defined as involving (i) activation of endothelial cells; (ii) increased vascular permeability; (iii) subsequent dissolution of the basement membrane and extravasation of plasma components leading to formation of a provisional
10 fibrin gel extracellular matrix; (iv) proliferation and mobilization of endothelial cells; (v) reorganization of mobilized endothelial cells to form functional capillaries; (vi) capillary loop formation; and (vii) deposition of basement membrane and recruitment of perivascular cells to newly formed vessels.

15 Normal angiogenesis is activated during tissue growth, from embryonic development through maturity, and then enters a period of relative quiescence during adulthood.

20 Normal angiogenesis is also activated during wound healing, and at certain stages of the female reproductive cycle. Inappropriate or pathological angiogenesis has been associated with several disease states including various retinopathies; ischemic disease; atherosclerosis; chronic inflammatory disorders; rheumatoid arthritis, and cancer. The role of angiogenesis in disease states is discussed, for instance, in Fan et al, Trends
25 in Pharmacol Sci. 16:54-66; Shawver et al, DOT Vol. 2, No. 2 February 1997; Folkman, 1995, Nature Medicine 1:27-31.

30 It has been proposed that various receptor-type tyrosine kinases, and the growth factors binding to them, play a role in angiogenesis, although some may promote angiogenesis indirectly (Mustonen and Alitalo, *J. Cell Biol.* 129:895-898, 1995). One of these receptor-type tyrosine kinases is foetal liver kinase 1, also referred to as FLK-1. The human analogue of FLK-1 is the

kinase insert domain-containing receptor KDR, which is also known as vascular endothelial cell growth factor receptor 2 or VEGFR-2, since it binds VEGF with high affinity. Finally, the murine version of this receptor has also been called NYK (Oelrichs et al., *Oncogene* 8(1):11-15, 1993). VEGF and KDR are a ligand-receptor pair which plays a vital role in the proliferation of vascular endothelial cells and the formation and sprouting of blood vessels, referred to as vasculogenesis and angiogenesis respectively.

Angiogenesis is characterised by excessive activity of vascular endothelial growth factor (VEGF). VEGF actually consists of a family of ligands (Klagsburn and D'Amore, *Cytokine & Growth Factor Reviews* 7:259-270, 1996). VEGF binds the high affinity membrane-spanning tyrosine kinase receptor KDR and the related fms tyrosine kinase-1, also known as Flt-1 or vascular endothelial cell growth factor receptor 1 (VEGFR-1). Cell culture and gene knockout experiments indicate that each receptor contributes to different aspects of angiogenesis. KDR mediates the mitogenic function of VEGF, whereas Flt-1 appears to modulate non-mitogenic functions, such as those associated with cellular adhesion. Inhibiting KDR thus modulates the level of mitogenic VEGF activity. In fact, tumour growth has been shown to be susceptible to the antiangiogenic effects of VEGF receptor antagonists (Kim et al., *Nature* 362, pp. 841- 844, 1993).

Solid tumours can therefore be treated with tyrosine inhibitors since these tumours depend on angiogenesis for the formation of the blood vessels that are necessary to support their growth. These solid tumours include monocytic leukaemia, carcinomas of the brain, urogenital tract, lymphatic system, stomach, larynx and lung, including lung adenocarcinoma and small cell lung carcinoma. Further examples include carcinomas in which overexpression or activation of Raf-activating oncogenes (for example, K-ras, erb-B) is observed. Such carcinomas include pancreatic and breast carcinoma. Inhibitors of these tyrosine kinases are therefore suitable for the prevention and treatment of proliferative diseases caused by these enzymes. The angiogenic activity of VEGF is not limited to tumours. VEGF accounts for the angiogenic activity produced in or near the retina in diabetic retinopathy.

This vascular growth in the retina leads to visual degeneration culminating in blindness. Ocular VEGF mRNA and protein levels are elevated by conditions such as retinal vein occlusion in primates and decreased pO₂ levels in mice that lead to neovascularisation. Intraocular injections of anti-VEGF
5 monoclonal antibodies or VEGF receptor immunofusions inhibit ocular neovascularisation in both primate and rodent models. Irrespective of the cause of induction of VEGF in human diabetic retinopathy, inhibition of ocular VEGF is suitable for treating this disease.

Expression of VEGF is also significantly increased in hypoxic regions of
10 animal and human tumours adjacent to areas of necrosis. In addition, VEGF is upregulated by the expression of the oncogenes Ras, Raf, Src and mutant p53 (all of which are relevant in combating cancer). Anti-VEGF monoclonal antibodies inhibit the growth of human tumours in nude mice. Although the same tumour cells continue to express VEGF in culture, the antibodies do not
15 diminish their mitotic rate. Thus, tumour-derived VEGF does not function as an autocrine mitogenic factor. VEGF therefore contributes to tumour growth in vivo by promoting angiogenesis through its paracrine vascular endothelial cell chemotactic and mitogenic activities. These monoclonal antibodies also inhibit the growth of typically less well vascularised human colon carcinomas
20 in athymic mice and decrease the number of tumours arising from inoculated cells.

The expression of a VEGF-binding construct of Flk-1, Flt-1, the mouse KDR receptor homologue truncated to eliminate the cytoplasmic tyrosine kinase domains but retaining a membrane anchor, in viruses virtually stops the
25 growth of a transplantable glioblastoma in mice, presumably by the dominant negative mechanism of heterodimer formation with membrane-spanning endothelial cell VEGF receptors.

Embryonic stem cells, which normally grow as solid tumours in nude mice, do not produce detectable tumours if both VEGF alleles are knocked out. Taken
30 together, these data indicate the role of VEGF in the growth of solid tumours. Inhibition of KDR or Flt-1 is involved in pathological angiogenesis, and these receptors are suitable for the treatment of diseases in which angiogenesis is

part of the overall pathology, for example inflammation, diabetic retinal vascularisation, as well as various forms of cancer, since tumour growth is known to be dependent on angiogenesis (Weidner et al., N. Engl. J. Med., 324, pp. 1-8, 1991).

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In cancer the growth of solid tumors has been shown to be angiogenesis dependent. (See Folkman, J., J. Nat'l. Cancer Inst., 1990, 82, 4-6.)

Consequently, the targeting of pro-angiogenic pathways is a strategy being widely pursued in order to provide new therapeutics in these areas of great, unmet medical need.

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Raf is involved in angiogenic processes. Endothelial growth factors (e.g. vascular endothelial growth factor VEGF or basic fibroblast growth factor bFGF) activates receptor tyrosine kinases (e.g. VEGFR-2) and signal through the Ras/Raf/Mek/Erk kinase cascade and protects endothelial cells from apoptosis (Alavi et al. (2003), Science 301, 94-96; Hood, J.D. et al. (2002), Science 296, 2404; Mikula, M. et al. (2001), EMBO J. 20, 1952; Hauser, M. et al. (2001), EMBO J. 20, 1940; Wojnowski et al. (1997), Nature Genet. 16, 293). Activation of VEGFR-2 by VEGF is a critical step in the signal transduction pathway that initiates tumor angiogenesis. VEGF expression may be constitutive to tumor cells and can also be upregulated in response to certain stimuli. One such stimulus is hypoxia, where VEGF expression is upregulated in both tumor and associated host tissues. The VEGF ligand activates VEGFR-2 by binding with its extracellular VEGF binding site. This leads to receptor dimerization of VEGFRs and autophosphorylation of tyrosine residues at the intracellular kinase domain of VEGFR-2. The kinase domain operates to transfer a phosphate from ATP to the tyrosine residues, thus providing binding sites for signaling proteins downstream of VEGFR-2 leading ultimately to initiation of angiogenesis (McMahon, G., The Oncologist, Vol. 5, No. 90001, 3-10, April 2000).

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In cancer the growth of solid tumors has been shown to be angiogenesis dependent. (See Folkman, J., J. Nat'l. Cancer Inst., 1990, 82, 4-6.)

Consequently, the targeting of pro-angiogenic pathways is a strategy being widely pursued in order to provide new therapeutics in these areas of great,

5 unmet medical need. The role of tyrosine kinases involved in angiogenesis and in the vascularization of solid tumors has drawn interest. Until recently most interest in this area has focused on growth factors such as vascular endothelial growth factor (VEGF) and its receptors termed vascular endothelial growth factor receptor(s) (VEGFR). VEGF, a polypeptide, is
10 mitogenic for endothelial cells in vitro and stimulates angiogenic responses in vivo. VEGF has also been linked to inappropriate or pathological angiogenesis (Pinedo, H.M. et al The Oncologist, Vol.5, No. 90001, 1-2, April 2000). VEGFR(s) are protein tyrosine kinases (PTKs). PTKs catalyze the phosphorylation of specific tyrosyl residues in proteins involved in the
15 regulation of cell growth and differentiation. (A.F. Wilks, Progress in Growth Factor Research, 1990, 2, 97-111; S.A. Courtneidge, Dev. Supp.I, 1993, 57-64; J. A. Cooper, Semin. Cell Biol., 1994, 5(6)'377-387; R.F. Paulson, Semin. Immunol., 1995, 7(4), 267-277; A.C. Chan, Curr. Opin. Immunol., 1996, 8(3), 394-401).

20 Three PTK receptors for VEGF have been identified: VEGFR-1 (Flt-1); VEGFR-2 (Flk-1 or KDR) and VEGFR-3 (Flt-4). These receptors are involved in angiogenesis and participate in signal transduction (Mustonen, T. et al J. Cell Biol. 1995:129:895-898).

25 Of particular interest is VEGFR-2, which is a transmembrane receptor PTK expressed primarily in endothelial cells. Activation of VEGFR-2 by VEGF is a critical step in the signal transduction pathway that initiates tumor angiogenesis. VEGF expression may be constitutive to tumor cells and can
30 also be upregulated in response to certain stimuli. One such stimulus is hypoxia, where VEGF expression is upregulated in both tumor and associated host tissues. The VEGF ligand activates VEGFR-2 by binding to

its extracellular VEGF binding site. This leads to receptor dimerization of VEGFRs and autophosphorylation of tyrosine residues at the intracellular kinase domain of VEGFR-2. The kinase domain operates to transfer a phosphate from ATP to the tyrosine residues, thus providing binding sites for signaling proteins downstream of VEGFR-2 leading ultimately to initiation of angiogenesis (McMahon, G., *The Oncologist*, Vol. 5, No. 90001, 3-10, April 2000).

Angiopoietin 1 (Ang1), a ligand for the endothelium-specific receptor tyrosine kinase Tie-2 (or TIE-2) is a novel angiogenic factor (Davis et al, *Cell*, 1996, 87:1161-1169; Partanen et al, *Mol. Cell Biol*, 12:1698-1707 (1992); U.S. Patent Nos. 5,521,073; 5,879,672; 5,877,020; and 6,030,831). The acronym Tie (or TIE) represents "tyrosine kinase containing Ig and EGF homology domains". Tie is used to identify a class of receptor tyrosine kinases, which are exclusively expressed in vascular endothelial cells and early hemopoietic cells. Typically, Tie receptor kinases are characterized by the presence of an EGF-like domain and an immunoglobulin (IG) like domain, which consists of extracellular folding units, stabilized by intra-chain disulfide bonds (Partanen et al; *Curr. Topics Microbiol. Immunol.*, 1999, 237:159-172). Unlike VEGF, which functions during the early stages of vascular development, Ang1 and its receptor Tie-2 function in the later stages of vascular development, i.e., during vascular remodeling (remodeling refers to regression of established vasculature and formation of new blood vessels) and maturation (Yancopoulos et al, *Cell*, 1998, 93:661-664; Peters, K.G., *Circ. Res.*, 1998, 83(3):342-3; Suri et al, *Cell* 87, 1171-1180 (1996)).

Endothelial cells (EC) and pericytes (PCs) interact with and are responsible for the maturation, sprouting, bridging, and growth from existing vessels (Jain, *Nat Med.* 2003 Jun; 9(6):685-93).

Ang1 is an agonist of Tie-2 and thus stabilizes or promotes endothelial cells and their formation, whereas Ang2 is an antagonist of Tie-2 and thus

destabilizes endothelial cells and their formation. Tie-2 antagonizes VEGF driven EC proliferation. Otherwise ECs that interact with pericytes are stabilized and do not respond anymore to VEGF.

- 5 Tie-2 inhibitors will lead to vessel regression if VEGF level is low (not sufficient for stimulation) and VEGFR-2 is not activated.

Consequently, inhibition of Tie-2 would be expected to serve to disrupt interaction with pericytes and maturation of new vasculature initiated by angiogenesis thereby disrupting the angiogenic process. Furthermore,
10 inhibition at the kinase domain binding site of VEGFR-2 would block phosphorylation of tyrosine residues and serve to disrupt initiation of angiogenesis. Therefore, inhibition of Tie-2 and/or VEGFR-2 should prevent tumor angiogenesis and serve to retard or eradicate tumor growth.

- 15 The receptor tyrosine kinases comprise a plurality of transmembrane receptors with varying biological activity. More than 20 different subfamilies of receptor tyrosine kinases have been identified. A tyrosine kinase-subfamily, named HER subfamily, consists of EGFR, HER2, HER3 and HER4. To the ligands of this receptor-subfamily belong the epithelial growth factor, TGF- α ,
20 Amphiregulin, HB-EGF, Betacellulin and Heregulin. The insulin-subfamily, to which INS-R, IGF-IR and IR-R are counted, is a further subfamily of the receptor tyrosine kinases. The PDGF subfamily comprises the PDGF- α - and - β -receptor, CSFIR, c-kit and FLK-II. Moreover, there is the FLK-family, which consists of the kinaseinsertdomaine receptor (KDR), the fetal liver
25 kinase-1 (FLK-1), the fetal liver kinase-4 (FLK-4) and the fms-tyrosine kinase-1 (flt-1). Because of the similarities between the PDGF- and FLK-families, both groups are usually discussed commonly. For a more detailed dispassion of the receptor tyrosine kinases see the publication of Plowman et al., *DN & P* 7(6):334-339, 1994, the disclosure of which is incorporated herein by
30 reference.

The cytosolic tyrosine kinases also consist of a plurality of subfamilies, such as Src, Frk, Btk, Csk, Abl, Zap70, Fes/Fps, Fak, Jak, Ack, and LIMK. Every

of the subfamilies is a further divided into different receptors. For example, the Src subfamily is one of the biggest families. It contains Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr und Yrk. The Src enzyme subfamily is discussed in connection with oncogenesis. For a more detailed discussion of the cytosolic tyrosine kinases, see the publication of Bolen *Oncogene*, 8:2025-2031 (1993), the disclosure of which is incorporated herein by reference.

The receptor tyrosine kinases as well as the cytosolic tyrosine kinases are involved in the signal transduction pathways is of the cell, which are relevant for various diseases, such as cancer, psoriasis, hyper immuno reactions and auto immune diseases.

Of the three PTK (protein tyrosine kinases) receptors for VEGFR identified VEGFR-1 (Flt-1); VEGFR-2 (Flk-1 or KDR) and VEGFR-3 (Flt-4), VEGFR-2 is of peculiar interest.

Thus, of the different *families of kinases*, which are part of the human *kinome* [Manning Science 298, 1912-1934 (2002)], the receptor tyrosine kinase *KDR*, also called *VEGF receptor 2*, can stimulate endothelial cell survival and proliferation if ligated extra cellular by VEGF. Ligand binding then can lead to intracellular phosphorylation events, a signaling cascade and ultimately to proliferation. [Zachary IDrugs 6, 224-231(2003)] Inhibition of this KDR signaling is attempted by various therapies [Rosen The Oncologist 10, 382-391 (2005), Hicklin&Ellis J.Clin.Onc. 23, 1011-1027 (2005), McMahon The Oncologist 5 (suppl 5) 3-10 (2000)]. Other kinases and ligands important for function of endothelial cells are *TIE2 kinase* and the *angiopoietins*, *PDGF receptor* and *PDGF* as well as *PIGF*. Ephrin receptor kinase and ephrins, especially EphB4 and ephrin-B2. [Peters Circ.Res. 83, 342-343 (1998), Gale & Yancopoulos Genes&Development 13, 1055-1066 (1999), Pietras Cancer Cell 3, 439-443 (2003)].

Molecular mechanisms of blood vessel formation and the *angiogenic switch* in tumorigenesis are discussed in detail by Hanahan & Folkman Cell 86, 353-

- 364 (1996), Risau Science 386, 671-674 (1997), Bussolino et al. TIBS 22, 251-256 (1997), Augustin Circ. Res. 89, 645-647 (2001), Bergers & Benjamin Nat. Rev. Cancer 3, 401-410 (2003), Carmeliet Nature 438, 932-936 (2005). *Vascular patterning* is regulated by Eph receptor tyrosine kinases and ephrin ligands, f.e. ephrin-B2 signaling via Eph B4 and Eph B1. EphB4 controls
- 5 vascular morphogenesis during postnatal angiogenesis. [Adams Sem. Cell Development Bio 13, 55-60 (2002), Erber EMBO J.25, 628-641 (2006)]. The *maturation* of nascent vasculature, formed by angiogenesis or vasculogenesis, requires mural cells (pericytes, smooth muscle cells),
- 10 generation of extracellular matrix and specialization of the vessel wall for structural support and regulation of vessel function. Regulation of those processes and interaction between endothelial cells and their mural cells involves several ligand kinase pairs, like VEGF / VEGFR1,R2, EphrinB2/EphB4, PDGFR/PDGFR β , Angiopoietins/TIE2, TGF β /TGF β R-
- 15 Alk1/Alk5. Vessel assembly, capillary formation, sprouting, stabilization and destabilization, even regression is regulated by a functional balance of those kinases and ligands [Jain Nat.Med. 9, 685-693 (2003), Saharinen J.Clin.Invest 111, 1277-1280 (2003), Ramsauer&D'Amore J.Clin.Invest 110, 1615-1617 (2002)].
- 20 *Lymphangiogenesis* is regulated via VEGF receptor 3 and its ligands VEGF C, and D, and TIE2 and its ligands angiopoietins 1,2. Inhibition of VEGFR3 and/or TIE2 signaling and therefore inhibition of formation of lymphatic vessels can be a means to stop metastasis of tumor cells [Jones Nat.Rev.Mol.Cell.Biol.2, 257-267 (2001)]
- 25 The whole body of information about pathological vascularisation leads to the assumption for inhibition of angiogenesis being a promising strategy for treatment of cancer and other disorders in addition to [Ferrara & Kerbel Nature 438, 967-974 (2005)].
- 30 Indications and pathologies, direct targeting of tumor, indirect targeting via anti-angiogenesis:

Tumor growth can be characterized by deregulated i.e. autonomous cell growth due to perturbation of RTK signaling by mutations or other genetic alterations. Of the 32000 human coding genes whichn are involved in signal transduction more than 520 protein kinases and 130 protein phosphatases exert tight and reversible control on protein phosphorylation. Selectivity is found for tyrosine and for Ser/threonine phosphorylation. There are more than 90 known PTK genes in the human genome, more than 50 encode transmembrane RPTKs distributed in 20 subfamilies, and 32 encode cytoplasmic, non-receptor PTKs in 10 subfamilies. For example Trk A has a important role in thyroid carcinomas and neuroblastomas, EphB2 and B4 are overexpressed in carcinomas, Axl and Lck are overexpressed in leukaemias [Blume-Jensen & Hunter Nature 411, 355-364 (2001)].

Angiogenesis, the development of new vessels from pre-existing vessels, is critical in vascular development in embryogenesis, organogenesis, and wound healing. [Breier Placenta 21, Suppl. A, Trophoblasr Res. 14, S11-S15 (2000)].

In addition to those physiological processes, angiogenesis is important for tumor growth, metastasis and inflammation, resulting in diseases like tumors of the breast, uterine cervix, uterine corpus (endometrium), ovary, lung, bronchus, liver, kidney, skin, oral cavity and pharynx, prostate, pancreas, urinary bladder, blood cells, colon, rectum, bone, brain, central and peripheral nervous system, exemplified as breast cancer, colorectal cancer, gliomas, lymphomas, and so on, and of inflammatory diseases like rheumatoid arthritis and psoriasis, or diseases of the eye, like macula degeneration, and diabetic retinopathy.

A preferred aspect of the invention therefor relates to methods for the regulation, modulation and/or or inhibition of VEGFR-2, for the prevention and/or treatment of diseases in connection with unregulated or disturbed VEGFR-2-activity.

Also of great interest is the stress activated protein kinase (SAPK) pathway. The SAPK's (also called "jun N-terminal kinases" or "JNK's") are a family of protein kinases that represent the penultimate step in signal transduction pathways that result in activation of the c-jun transcription factor and
5 expression of genes regulated by c-jun. In particular, c-jun is involved in the transcription of genes that encode proteins involved in the repair of DNA that is damaged due to genotoxic insults. As disclosed herein, agents that inhibit SAPK activity in a cell prevent DNA repair and sensitize the cell to those cancer therapeutic modalities that act by inducing DNA damage, such as
10 ionizing radiation; chemical agents that crosslink or otherwise directly damage DNA including cis-platinum and alkylating agents such as N-methyl-N'-nitro-N-nitroso-guanidine (MNNG) and methylmethanesulphonate (MMS); and agents that interfere with DNA synthesis including DNA chain terminating agents such as 1- β -arabinofuranosylcytosine (AraC), topoisomerase
15 inhibitors such as camptothecin, and nucleoside analogs or precursors of such analogs such as methotrexate (MTX) and 5-fluorouracil (5-FU).

Preferably, the SAPK pathway is also involved in the mitogenic response of certain cells, including cancer cells. For example, human A549 tumor cells,
20 which express an EGF receptor on their cell surface, respond mitogenically to EGF. However, the mitogenic response, but not basal growth, is inhibited when the SAPK pathway is inhibited by expressing a dominant negative c-jun mutant in the cells. Thus, in addition to sensitizing tumor cells to a cancer therapeutic modality, inhibition of the SAPK pathway also can block
25 mitogenesis of tumor cells, for example, in response to an autocrine growth factor, thereby providing a therapeutic advantage to an individual treated with a cancer therapeutic modality. In addition, the SAPK pathway can lead to activation of various transcription factors, some of which are involved in cell growth and proliferation.

30

The SAPK pathway is activated in response to genotoxic agents such as ultraviolet radiation and various cancer therapeutic modalities (see, for

example, Derijard et al., *Cell* 76:1025-1037 (1994); Adler et al., *J. Biol. Chem.* 270:26071-26077 (1995); van Dam et al, *EMBO J.* 14:1798-1811 (1995); Kharabanda et al., *Proc. Natl. Acad. Sci., USA* 93:6898-6901 (1996)). SAPK (JNK) phosphorylates c-jun at serine residues 63 and 73 (Smeal et al.,
5 *Nature* 354:494-496 (1991)). In turn, working backwards from c-jun activation in the SAPK pathway, SAPK is activated by phosphorylation of a SAPK kinase (SAPKK; JNKK), which, itself, is activated by phosphorylation of a SAPKK kinase (SAPKKK; JNKKK; also called MEKK1 and referred to herein as "MEKK1;" GenBank Accession No. U29671, which is incorporated herein
10 by reference; see, also, U.S. Pat. No. 5,405,941, which is incorporated herein by reference). Additional steps of the pathway precede the activation of MEKK1 (Liu et al., *Cell* 87:565-576 (1996)) and, as discussed below, MEKK1 also acts as a branch point for a second pathway.

15 Various SAPK's, including SAPK1 (JNK; SAPK1 α 1; GenBank Accession No. 226318; see, also, U.S. Pat. No. 5,534,426, which is incorporated herein by reference), SAPK2 (SAPK2 α 1; U34821) and SAPK3 (SAPK3 α 1; U34820), and related isozymes, SAPK1 α 2 (U34822), SAPK1 β 1 (U35004), SAPK1 β 2 (U35005), SAPK2 β 1 (U35002), SAPK2 β 2 (U35003) and SAPK3 α 2
20 (U34819), each of which is incorporated herein by reference, have been described (see Gupta et al., *EMBO J.* 15:2760-2770 (1996); see, also, Cuenda et al., *EMBO J.* 16:295-305 (1997)). Activation of one or more SAPK's in a cell is associated with the induction of expression of various genes involved in DNA repair and cell survival following a stress, including
25 the genes encoding c-jun (Chu et al., *Mol. Endocrinol.* 8:59 (1994)), p21(Waf1/Cip1) (El-Deiry et al., *Cancer Res.* 55:2910 (1995)), ATF2, ATF3 (Gately et al., *Brit. J. Cancer* 70:1102 (1994)), PCNA (Huang et al., *Mol. Cell. Biol.* 14:4233 (1994)), cyclin-A, cyclin-D1 (Herbert et al., *Oncogene* 9:1295 (1994)), cyclin-G and GADD153 (Luethy and Holbrook, *Cancer Res.*
30 54:1902S (1994); Gately et al., *supra*, 1994).

Accordingly, a composition that inhibits a SAPK pathway as disclosed herein can be useful to inhibit proliferation, growth or DNA repair in cancer cells, thereby increasing the likelihood that cancer cells containing such damage will die.

5

p38 (or P38) (also CSBP or RK) is a serine/threonine mitogen-activated protein kinase (MAPK) that has been shown to regulate pro-inflammatory cytokines. p38 was first identified as a kinase which became tyrosine phosphorylated in mouse monocytes following treatment with

10 lipopolysaccharide (LPS). A link between p38 and the response of cells to cytokines was first established by Saklatvala J., et al., *Cell*, 78: 1039-1049 (1994), who showed that IL-1 activates a protein kinase cascade that results in the phosphorylation of the small heat shock protein, Hsp27, probably by mitogen-activated protein activated protein kinase 2 (MAPKAP kinase-2).

15 Analysis of peptide sequences derived from the purified kinase indicated that it was related to the p38 MAPK activated by LPS in mouse monocytes, Han, J., et al., *Science*, 265: 808-811 (1994). At the same time it was shown that p38 MAPK was itself activated by an upstream kinase in response to a variety of cellular stresses, including exposure to UV radiation and osmotic shock, and the identity of the kinase that directly phosphorylates Hsp27 was confirmed as MAPKAP kinase-2, Rouse, J., et al., *Cell*, 78: 1027- 1037
20 (1994). Subsequently, workers at SmithKline Beecham showed that p38 MAPK was the molecular target of a series of pyridinylimidazole compounds that inhibited the production of TNF from LPS-challenged human monocytes, Lee, J., et al., *Nature*, 372: 739-746. This was a key discovery and has led to the development of a number of selective inhibitors of p38 MAPK and the elucidation of its role in cytokine signaling.
25

30 It is now known that multiple forms of p38 MAPK (α , β , γ , δ), each encoded by a separate gene, form part of a kinase cascade involved in the response of cells to a variety of stimuli, including osmotic stress, UV light and cytokine mediated events. These four isoforms of p38 are thought to regulate different

aspects of intracellular signaling. Its activation is part of a cascade of signaling events that lead to the synthesis and production of pro-inflammatory cytokines like TNF- α . p38 functions by phosphorylating downstream substrates that include other kinases and transcription factors.

5 Agents that inhibit p38 kinase have been shown to block the production of cytokines including but not limited to TNF- α , IL-6, IL-8 and IL-1 β in vitro and in vivo models Adams, J. L., et al., *Progress in Medicinal Chemistry*, 38: 1-60 (2001).

Peripheral blood monocytes (PBMCs) have been shown to express and

10 secrete pro-inflammatory cytokines when stimulated with lipopolysaccharide (LPS) in vitro. p38 inhibitors efficiently block this effect when PBMCs are pretreated with such compounds prior to stimulation with LPS. Lee, J. C., et al., *Int. J. Immunopharmacol.*, 10: 835- 843 (1988). The efficacy of p38 inhibitors in animal models of inflammatory disease has prompted an

15 investigation of the underlying mechanism(s) which could account for the effect of these inhibitors. The role of p38 in the response of cells to IL-1 and TNF has been investigated in a number of cells systems relevant to the inflammatory response using a pyridinyl imidazole inhibitor: endothelial cells and IL- 8, Hashimoto, S., et al., *J. Pharmacol. Exp. Ther.*, 293: 370-375

20 (2001), fibroblasts and IL-6/GM-CSF/PGE2 Beyaert, R., et al., *EMBO J.*, 15: 1914-1923 (1996), neutrophils and IL-8 Albanyan, E. A., et al. , *Infect. Immun.*, 68: 2053-2060 (2000) macrophages and IL-1 Caivano, M. and Cohen, P., *J. Immunol.*, 164: 3018-3025 (2000), and smooth muscle cells and RANTES Maruoka, S., et al., *Am. J. Respir. Crit. Care Med.*, 161: 659-

25 668 (1999). The destructive effects of many disease states are caused by the over production of pro-inflammatory cytokines. The ability of p38 inhibitors to regulate this overproduction makes them excellent candidates for disease modifying agents. Accordingly, p38 inhibitors preferably are useful for the treatment of inflammation, osteoarthritis, rheumatoid arthritis, cancer,

30 autoimmune diseases, and for the treatment of other cytokine mediated diseases.

Mice with a targeted disruption in the Braf gene die of vascular defects during development (Wojnowski, L. et al. 1997, Nature genetics 16, page 293-296). These mice show defects in the formation of the vascular system and in angiogenesis e.g. enlarged blood vessels and increased apoptotic death of differentiated endothelial cells.

For the identification of a signal transduction pathway and the detection of cross talks with other signaling pathways suitable models or model systems have been generated by various scientists, for example cell culture models (e.g. Khwaja et al., EMBO, 1997, 16, 2783-93) and transgenic animal models (e.g. White et al., Oncogene, 2001, 20, 7064-7072). For the examination of particular steps in the signal transduction cascade, interfering compounds can be used for signal modulation (e.g. Stephens et al., Biochemical J., 2000, 351, 95-105). The compounds according to the invention may also be useful as reagents for the examination of kinase dependent signal transduction pathways in animal and/or cell culture models or any of the clinical disorders listed throughout this application.

The measurement of kinase activity is a well known technique feasible for each person skilled in the art. Generic test systems for kinase activity detection with substrates, for example histone (e.g. Alessi et al., FEBS Lett. 1996, 399, 3, page 333-8) or myelin basic protein are well described in the literature (e.g. Campos-González, R. and Glenney, Jr., J.R. 1992 J. Biol. Chem. 267, Page 14535).

For the identification of kinase inhibitors various assay systems are available (see for example Walters et al., Nature Drug Discovery 2003, 2; page 259-266). For example, in scintillation proximity assays (e.g. Sorg et al., J. of Biomolecular Screening, 2002, 7, 11-19) or flashplate assays the radioactive phosphorylation of a protein or peptide as substrate with γ ATP can be measured. In the presence of an inhibitory compound no signal or a decreased radioactive signal is detectable. Furthermore homogeneous time-

resolved fluorescence resonance energy transfer (HTR-FRET), and fluorescence polarization (FP) technologies are useful for assay methods (for example Sills et al., J. of Biomolecular Screening, 2002, 191-214).

Other non-radioactive ELISA based assay methods use specific phospho-antibodies (AB). The phospho-AB binds only the phosphorylated substrate. This binding is detectable with a secondary peroxidase conjugated antibody, measured for example by chemiluminescence (for example Ross et al., Biochem. J., 2002, 366, 977-981).

WO 02/44156 describes benzimidazole derivatives as Tie-2 and/or VEGFR2 inhibitors. WO 99/32436 describes substituted phenyl urea derivatives as Raf-kinase inhibitors. WO 02/062763 and WO 02/085857 describe quinoline-, isoquinoline- und pyridyl or phenyl urea derivatives as raf kinase inhibitors. Hetero aryl ureas are described in WO 02/85859 as p38 kinase inhibitors.

WO 00/42012 and WO 00/41698 describe ω -carboxyaryl-diphenyl-ureas as raf kinase inhibitors and p38 kinase inhibitors, respectively. Furthermore aryl and heteroaryl substituted ureas are described in WO 99/32455 as raf kinase inhibitors and in WO 99/32110 as p38 kinase inhibitors, respectively. Further diphenyl urea derivatives are known from WO 99/32463 and WO 99/32111.

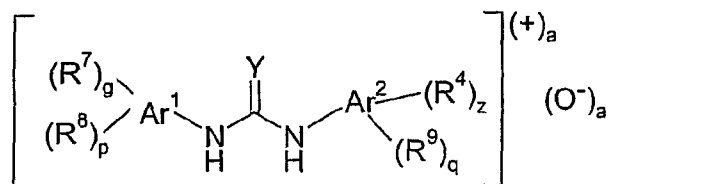
20

The present invention provides compounds generally described as N-oxides, including both aryl and/or heteroaryl derivatives which are preferably kinase inhibitors and more preferably inhibitors of one or more kinases as defined herein. The inhibitors preferably are useful in pharmaceutical compositions for human or veterinary use where inhibition of of one or more kinase pathway is indicated, e.g., in the treatment of tumors and/or cancerous cell growth mediated by one or more kinases. In particular, the compounds preferably are useful in the treatment of human or animal solid cancers, e.g. murine cancer, since the progression of these cancers is dependent upon the respective signal transduction cascades and therefore susceptible to treatment by interruption of one or more of said cascades, i.e., by inhibiting one or more of said kinases. Accordingly, the compound of formula I or a

30

pharmaceutically acceptable salt thereof can be administered for the treatment of diseases mediated by one or more kinase pathways, especially cancers, preferably solid cancers, such as, for example, carcinomas (e.g., of the lungs, pancreas, thyroid, bladder or colon), myeloid disorders (e.g., myeloid leukemia) or adenomas (e.g., villous colon adenoma), pathological angiogenesis and metastatic cell migration. Furthermore the compounds preferably are useful in the treatment of, inter alia, complement activation dependent chronic inflammation (Niculescu et al. (2002) Immunol. Res., 24:191-199) and HIV-1 (human immunodeficiency virus type1) induced immunodeficiency (Popik et al. (1998) J Virol, 72: 6406-6413) and infection disease, Influenza A virus (Pleschka, S. et al. (2001), Nat. Cell. Biol, 3(3):301-5) and Helicobacter pylori infection (Wessler, S. et al. (2002), FASEB J., 16(3): 417-9).

Therefore, subject of the present invention are N-oxides of formula I



wherein

Ar^1, Ar^2 are selected independently from one another from unsaturated or aromatic cyclic hydrocarbons containing 5 to 14 carbon atoms and unsaturated or aromatic heterocyclic residues containing 2 to 10 carbon atoms and one or more heteroatoms, preferably 1 to 5 heteroatoms, independently selected from N, O and S,

R^4 is independently selected from residues of the formula $(\text{X}-\text{Ar}^3)_\alpha-(\text{R}^{10})_r$, wherein

22

- Ar³ is independently selected from the meanings given for Ar¹ and/or Ar²,
- α is 0, 1 or 2,
- 5 R¹⁰ is independently selected from the meanings given for R⁸ and R⁹, and
- r is 0, 1, 2, 3, 4 or 5;
- 10 z is 0, 1, 2, 3, 4 or 5,
- R⁷ is a nitrogen containing heterocyclic moiety, directly bound to Ar¹ via a nitrogen atom, said nitrogen containing heterocyclic moiety being independently selected from Het¹, Het² and Het³, wherein
- 15 Het¹ is an unsaturated or aromatic heterocyclic residue comprising 5, 6 or 7 ring atoms which contains 1 to 4 nitrogen atoms and optionally 1 or 2 additional heteroatoms selected from O and S, whereby said unsaturated or aromatic heterocyclic residue is unsubstituted or substituted by one or more substituents, selected from a group consisting of A, R¹³, =O, =S, =N-R¹⁴, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂NR¹⁵R¹⁶, S(O)_uA and OOCR¹⁵,
- 20
- 25
- 30 Het² is a saturated, unsaturated or aromatic bicyclic residue comprising 3 to 10 carbon atoms, 1 to 4 nitrogen atoms and optionally 1 or 2 additional heteroatoms selected from O and S, whereby said bicyclic residue is unsubstituted or

substituted by one or more substituents, selected from a group consisting of A, R¹³, =O, =S, =N-R¹⁴, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂NR¹⁵R¹⁶, S(O)_uA and OOCR¹⁵,

Het³ is a saturated monocyclic residue comprising 2 to 6 carbon atoms, 1 to 4 nitrogen atoms and optionally 1 or 2 additional heteroatoms selected from O and S, whereby said monocyclic residue is substituted by one or more substituents, selected from a group consisting of =O, =S, =N-R¹⁴, and optionally substituted by one or more substituents, selected from A, R¹³, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂NR¹⁵R¹⁶, S(O)_uA and OOCR¹⁵,

R⁸ and R⁹ are independently selected from a group consisting of H, A, cycloalkyl comprising 3 to 7 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, C(Hal)₃, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nNR¹¹(CH₂)_kNR¹¹R¹², (CH₂)_nO(CH₂)_kOR¹¹, (CH₂)_nNR¹¹(CH₂)_kOR¹², (CH₂)_nCOOR¹³, (CH₂)_nCOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nNR¹¹COR¹³, (CH₂)_nNR¹¹CONR¹¹R¹², (CH₂)_nNR¹¹SO₂A, (CH₂)_nSO₂NR¹¹R¹², (CH₂)_nS(O)_uNR¹¹R¹², (CH₂)_nS(O)_uR¹³, (CH₂)_nOC(O)R¹³, (CH₂)_nCOR¹³, (CH₂)_nSR¹¹, CH=N-OA, CH₂CH=N-OA, (CH₂)_nNHOA, (CH₂)_nCH=N-R¹¹, (CH₂)_nOC(O)NR¹¹R¹², (CH₂)_nNR¹¹COOR¹³, (CH₂)_nN(R¹¹)CH₂CH₂OR¹³, (CH₂)_nN(R¹¹)CH₂CH₂OCF₃, (CH₂)_nN(R¹¹)C(R¹³)HCOOR¹², (CH₂)_nN(R¹¹)C(R¹³)HCOOR¹¹, (CH₂)_nN(R¹¹)CH₂CH₂N(R¹²)CH₂COOR¹¹,

$(CH_2)_nN(R^{11})CH_2CH_2NR^{11}R^{12}$, $CH=CHCOOR^{13}$,
 $CH=CHCH_2NR^{11}R^{12}$, $CH=CHCH_2NR^{11}R^{12}$,
 $CH=CHCH_2OR^{13}$, $(CH_2)_nN(COOR^{13})COOR^{14}$,
 $(CH_2)_nN(CONH_2)COOR^{13}$, $(CH_2)_nN(CONH_2)CONH_2$,
5 $(CH_2)_nN(CH_2COOR^{13})COOR^{14}$,
 $(CH_2)_nN(CH_2CONH_2)COOR^{13}$,
 $(CH_2)_nN(CH_2CONH_2)CONH_2$, $(CH_2)_nCHR^{13}COR^{14}$,
 $(CH_2)_nCHR^{13}COOR^{14}$, $(CH_2)_nCHR^{13}CH_2OR^{14}$, $(CH_2)_nOCN$
 $(CH_2)_nNCO$, Het^9 , $OHet^9$, $N(R^{11})Het^9$, $(CR^5R^6)_kHet^9$,
10 $O(CR^5R^6)_kHet^9$, $N(R^{11})(CR^5R^6)_kHet^9$, $(CR^5R^6)_kNR^{11}R^{12}$,
 $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$,
 $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$,
 $NR^{11}(CR^5R^6)_kOR^{13}$, wherein

15 R^5, R^6 are in each case independently from one another selected from H and A,

R^{11}, R^{12} are independently selected from a group consisting of H, A, $(CH_2)_mAr^7$ and $(CH_2)_mHet^9$, or in $NR^{11}R^{12}$,

20 R^{11} and R^{12} form, together with the N-atom they are bound to, a 5-, 6- or 7- membered heterocyclus which optionally contains 1 or 2 additional hetero atoms, selected from N, O and S; whereby said heterocyclic residue optionally is substituted by one or more substituent, selected from A, R^{13} , $=O$, $=S$ and $=N-R^{14}$,

25 R^{13}, R^{14} are independently selected from a group consisting of H, Hal, A, $(CH_2)_mAr^8$ and $(CH_2)_mHet^9$,

30 A is selected from the group consisting of alkyl, alkenyl, cycloalkyl, alkylencycloalkyl, alkoxy, alkoxyalkyl and

saturated heterocyclyl, preferably from the group consisting of alkyl, alkenyl, cycloalkyl, alkylencycloalkyl, alkoxy and alkoxyalkyl,

- 5 Ar^7, Ar^8 are independently from one another aromatic hydrocarbon residues comprising 5 to 12 and preferably 5 to 10 carbon atoms which are optionally substituted by one or more substituents, selected from a group consisting of A, Hal, NO_2 , CN, OR^{15} , $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, COR^{15} , $SO_2NR^{15}R^{16}$, $S(O)_uA$ and $OOCR^{15}$,
- 10
- 15 Het^9 is a saturated, unsaturated or aromatic heterocyclic residue which preferably contains 1 to 3 heteroatoms, more preferably 1 or 2 heteroatoms, the heteroatoms being preferably selected from N, O and S, more preferably from N and O; whereby said heterocyclic residue is optionally substituted by one ore more substituents, selected from a group consisting of A, R^{13} , $=O$, $=S$, $=N-R^{14}$, Hal, NO_2 , CN, OR^{15} , $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, COR^{15} , $SO_2NR^{15}R^{16}$, $S(O)_uA$ and $OOCR^{15}$,
- 20
- 25 R^{15}, R^{16} are independently selected from a group consisting of H, A, and $(CH_2)_mAr^6$, wherein
- 30 Ar^6 is a 5- or 6-membered aromatic hydrocarbon which is optionally substituted by one or more substituents selected from a group consisting of methyl, ethyl, propyl, 2-propyl, tert.-butyl, Hal, CN, OH, NH_2 and CF_3 ,
- k, n and m are independently of one another 0, 1, 2, 3, 4, or 5,

- X represents a bond or is $(CR^{11}R^{12})_h$, or $(CHR^{11})_h-Q-(CHR^{12})_i$, wherein
- 5 Q is selected from a group consisting of O, S, $N-R^{15}$, $(CHal_2)_j$, $(O-CHR^{18})_j$, $(CHR^{18}-O)_j$, $CR^{18}=CR^{19}$, $(O-CHR^{18}CHR^{19})_j$, $(CHR^{18}CHR^{19}-O)_j$, C=O, C=S, $C=NR^{15}$, $CH(OR^{15})$, $C(OR^{15})(OR^{20})$, $C(=O)O$, $OC(=O)$, $OC(=O)O$, $C(=O)N(R^{15})$, $N(R^{15})C(=O)$, $OC(=O)N(R^{15})$, $N(R^{15})C(=O)O$,
 10 $CH=N-O$, $CH=N-NR^{15}$, $OC(O)NR^{15}$, $NR^{15}C(O)O$, S=O, SO_2 , SO_2NR^{15} and $NR^{15}SO_2$, wherein
- h, i are independently from each other 0, 1, 2, 3, 4, 5, or 6, and
- 15 j is 1, 2, 3, 4, 5, or 6,
- Y is selected from O, S, NR^{21} , $C(R^{22})-NO_2$, $C(R^{22})-CN$ and $C(CN)_2$, wherein
- 20 R^{21} is independently selected from the meanings given for R^{13} , R^{14} and
- 25 R^{22} is independently selected from the meanings given for R^{11} , R^{12} ,
- a is 1, 2 or 3, preferably 1 or 2,
- g is 1, 2 or 3, preferably 1 or 2,
- 30 p is 0, 1, 2, 3, 4 or 5,

q is 0, 1, 2, 3 or 4, preferably 0, 1 or 2,

u is 0, 1, 2 or 3, preferably 0, 1 or 2,

5 and

Hal is independently selected from a group consisting of F, Cl, Br and I;

10 and the pharmaceutically acceptable derivatives, solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, and more preferred the salts and/or solvates thereof, and especially preferred the physiologically acceptable salts and/or solvates thereof.

15 Preferably, the invention also relates to prodrugs and/or metabolites of the N-oxides according to the invention.

N-oxides according to the invention are preferably bisarylurea compounds as given in the brackets of formula I, wherein one or more, especially one, two
20 or three of the nitrogen-atoms, such as one or more of the the nitrogen atoms of the urea group, one or more of the nitrogen atoms optionally contained in Ar¹, one or more of the nitrogen atoms optionally contained in Ar², and/or one or more of the nitrogen atoms optionally contained in the residues R⁷, R⁸, R⁹ and R⁴, are oxidized to the respective N-oxide groups.

25

Accordingly, the term "[]^{(+)^a} (O⁻)_a" around the structures means that the structure within the brackets is N-oxidized once (if a = 1), twice (if a = 2) or three times (if a = 3). Thus, the term "[]^{(+)^b} (O⁻)_b" around a structure already comprising an N-oxide moiety at a specific site of the structure within
30 the brackets means that the respective N-oxide comprises no further N-oxide group beside the one at the specific site (if b = 0), or that it contains one more N-oxide group besides the one at the specific site (if b = 1) or two more

N-oxide groups beside the one at the specific site (if $b = 2$). This also means that if $b = 0$, the term " $(+)_b (O^-)_b$ " becomes moot and thus renders the brackets around the term meaningless or without function. Accordingly, in the case of $b = 0$, the the compound according to the invention is preferably
5 sufficiently characterised by the structure or formula alone, without the brackets/term around it.

More preferably, N-oxides according to the invention are N-oxides as defined above, wherein the one or more nitrogen-atoms that are oxidized into the
10 respective N-oxide groups are secondary amino groups or more preferably tertiary amino groups, such as aliphatic tertiary amino groups, olefinic tertiary amino groups and aromatic tertiary amino groups.

Thus, preferred N-oxides according to the invention are N-oxides as defined
15 above having at least one quaternary N-oxide group derivable from such aliphatic tertiary amino groups, olefinic tertiary amino groups and/or aromatic tertiary amino groups.

However, it is understood that the term "N-oxide" is meant to include the
20 corresponding tautomeric structures, such as the hydroxylamine. Thus, for example the N-oxidised group "pyridine-1-oxide" (which is an example of a quaternary N-oxide group according to the invention) is meant to include those structures referred to in the art as 1-oxo-pyridine and 1-hydroxy-pyridine. The same principles preferably apply in an analogous matter to all
25 N-oxides or N-oxidised groups according to the invention, respectively. The N-oxide of an $-NH-$ group (e.g. one of the $-NH-$ groups of the urea moiety) can be either described in the respective N-oxide form ($-HN^+(O^-)-$) or the hydroxylamine (i.e. $-N(OH)-$) form, which are tautomeric forms of each other. In the case of N-oxides of primary and secondary amines, the hydroxylamine
30 form is regularly the more stable tautomeric form. However, all these forms are preferably within the scope of the present invention.

Preferably, the compound according to the invention is other than 4-(4-{3-[4-(2,5-Dioxo-pyrrolidin-1-yl)-3-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide, and preferably other than the pharmaceutically acceptable derivatives, solvates, salts, tautomers and stereoisomers thereof.

In compounds according to the invention, Het³ is preferably other than unsubstituted and/or substituted succinimidyl.

In compounds according to the invention, Het³ is more preferably other than unsubstituted succinimidyl.

In compounds according to the invention, R⁷, R⁸ and/or R⁹ are preferably other than unsubstituted and/or substituted succinimidyl.

In compounds according to the invention, R⁷, R⁸ and/or R⁹ are preferably other than unsubstituted succinimidyl.

In compounds according to the invention, R⁷, R⁸, R⁹ and/or Het⁹ are more preferably other than unsubstituted and/or substituted succinimidyl.

In compounds according to the invention, R⁷, R⁸, R⁹ and/or Het⁹ are more preferably other than unsubstituted succinimidyl.

In this respect, the term succinimidyl preferably refers to succinimidoyl, 2,5-Dioxo-pyrrolidinyl and/or 2,5-Pyrrolidindionyl, and more preferably to succinimidoyl, succinimid-1-yl, 2,5-Dioxo-pyrrolidin-1-yl and/or 2,5-Pyrrolidindion-1-yl. In this respect, the terms succinimid-1-yl, 2,5-Dioxo-pyrrolidin-1-yl and/or 2,5-Pyrrolidindion-1-yl preferably are to be regarded as equivalent to the terms succinimide-1-yl, 2,5-Dioxo-pyrrolidine-1-yl and/or 2,5-Pyrrolidindione-1-yl, respectively. Also in this respect, the terms

succinimidoyl and succinimido-1-yl preferably are to be regarded as equivalent to the terms succinimidyl and succinimid-1-yl, respectively.

5 As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing,
10 prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

15 As used herein, the term "alkyl" preferably refers to a straight or branched chain hydrocarbon having from one to twelve carbon atoms, optionally substituted with substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylsulfanyl, C₁-C₆ alkylsulfenyl, C₁-C₆ alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or C₁-C₆ perfluoroalkyl, multiple
20 degrees of substitution being allowed. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, and the like.

25 As used herein, the term "C₁-C₆ alkyl" preferably refers to an alkyl group as defined above containing at least 1, and at most 6, carbon atoms. Examples of branched or straight chained "C₁-C₆ alkyl" groups useful in the present invention include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, isobutyl, n-butyl, t-butyl, n-pentyl and isopentyl.
30

As used herein, the term "alkylene" preferably refers to a straight or branched chain divalent hydrocarbon radical having from one to ten carbon atoms,

optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl, optionally substituted by alkyl, nitro, cyano, halogen and lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, n-propylene, n-butylene and the like.

As used herein, the term "C₁-C₆ alkylene" preferably refers to an alkylene group, as defined above, which contains at least 1, and at most 6, carbon atoms respectively. Examples of "C₁-C₆ alkylene" groups useful in the present invention include, but are not limited to, methylene, ethylene and n-Propylene.

As used herein, the term "halogen" or "hal" preferably refers to fluorine (F), chlorine (Cl), bromine (Br) or iodine (I).

As used herein, the term "C₁-C₆ haloalkyl" preferably refers to an alkyl group as defined above containing at least 1, and at most 6, carbon atoms substituted with at least one halogen, halogen being as defined herein. Examples of branched or straight chained "C₁-C₆ haloalkyl" groups useful in the present invention include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl and n-butyl substituted independently with one or more halogens, e.g., fluoro, chloro, bromo and iodo.

As used herein, the term "cycloalkyl" or "C₃-C₇ cycloalkyl" preferably refers to a non-aromatic cyclic hydrocarbon ring having from three to seven carbon atoms and which optionally includes a C₁-C₆ alkyl linker through which it may be attached. The C₁-C₆ alkyl group is as defined above. Exemplary "C₃-C₇ cycloalkyl" groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The term "cycloalkyl", as used herein

preferably also includes saturated heterocyclic groups, which are preferably selected from the cycloalkyl-groups as defined above, wherein one or two carbon atoms are replaced by hetero atoms, selected from the group consisting of O, N and S, which optionally is substituted by one or more
5 substituents, preferably selected from alkyl, =O, =S and substituted or unsubstituted imino groups.

As used herein, the term "C₃-C₇ cycloalkylene" preferably refers to a non-aromatic alicyclic divalent hydrocarbon radical having from three to seven
10 carbon atoms, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, lower
15 perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "cycloalkylene" as used herein include, but are not limited to, cyclopropyl-1,1-diyl, cyclopropyl-1,2-diyl, cyclobutyl-1,2-diyl, cyclopentyl-1,3-diyl, cyclohexyl-1,4-diyl, cycloheptyl-1,4-diyl, or cyclooctyl-1,5-diyl, and the like.

As used herein, the term "heterocyclic" or the term "heterocyclyl" preferably refers to a three to twelve-membered heterocyclic ring having one or more degrees of unsaturation containing one or more heteroatomic substitutions selected from S, SO, SO₂, O or N, optionally substituted with substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆
25 alkoxy, C₁-C₆ alkylsulfanyl, C₁-C₆ haloalkylsulfanyl, C₁-C₆ alkylsulfenyl, C₁-C₆ alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or C₁-C₆ perfluoroalkyl, multiple degrees of substitution being allowed. Such a ring may be optionally fused to
30 one or more other "heterocyclic" ring(s) or cycloalkyl ring(s). Examples of "heterocyclic" moieties include, but are not limited to, tetrahydrofuran, pyran,

1,4-dioxane, 1,3-dioxane, pyrrolidine, piperidine, morpholine, tetrahydrothiopyran, tetrahydrothiophene, and the like.

As used herein, the term "heterocyclylene" preferably refers to a three to
5 twelve-membered heterocyclic ring diradical having one or more degrees of
unsaturation containing one or more heteroatoms selected from S, SO, SO₂,
O or N, optionally substituted with substituents selected from the group which
includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl,
lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by
10 alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl
optionally substituted by alkyl, nitro, cyano, halogen, lower perfluoroalkyl,
multiple degrees of substitution being allowed. Such a ring may be optionally
fused to one or more benzene rings or to one or more of another
"heterocyclic" rings or cycloalkyl rings. Examples of "heterocyclylene"
15 include, but are not limited to, tetrahydrofuran-2,5-diyl, morpholine-2,3-diyl,
pyran-2,4-diyl, 1,4-dioxane-2,3-diyl, 1,3-dioxane-2,4-diyl, piperidine-2,4-diyl,
piperidine-1,4-diyl, pyrrolidine-1,3-diyl, morpholine-2,4-diyl, and the like.

As used herein, the term "aryl" preferably refers to an optionally substituted
20 benzene ring or to an optionally substituted benzene ring system fused to
one or more optionally substituted benzene rings to form, for example,
anthracene, phenanthrene, or naphthalene ring systems. Exemplary optional
substituents include C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylsulfanyl, C₁-C₆
alkylsulfenyl, C₁-C₆ alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally
25 substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by
alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl,
acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, C₁-
C₆ perfluoroalkyl, heteroaryl, or aryl, multiple degrees of substitution being
allowed. Examples of "aryl" groups include, but are not limited to Phenyl, 2-
30 naphthyl, 1-naphthyl, biphenyl, as well as substituted derivatives thereof.
As used herein, the term "arylene" preferably refers to a benzene ring
diradical or to a benzene ring system diradical fused to one or more

optionally substituted benzene rings, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl and aryl, multiple degrees of substitution being allowed. Examples of "arylene" include, but are not limited to benzene-1,4-diyl, naphthalene-1,8-diyl, anthracene-1,4-diyl, and the like.

10

As used herein, the term "aralkyl" preferably refers to an aryl or heteroaryl group, as defined herein, attached through a C₁-C₆ alkyl linker, wherein C₁-C₆ alkyl is as defined herein. Examples of "aralkyl" include, but are not limited to, benzyl, phenylpropyl, 2-pyridylmethyl, 3-isoxazolylmethyl, 5-methyl-3-isoxazolylmethyl and 2-imidazolylethyl.

15

As used herein, the term "heteroaryl" preferably refers to a monocyclic five to seven-membered aromatic ring, or to a fused bicyclic aromatic ring system comprising two of such monocyclic five to seven-membered aromatic rings.

20 These heteroaryl rings contain one or more nitrogen, sulfur and/or oxygen heteroatoms, where N-Oxides and sulfur Oxides and dioxides are permissible heteroatom substitutions and may be optionally substituted with up to three members selected from a group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ alkylsulfanyl, C₁-C₆ haloalkylsulfanyl, C₁-C₆ alkylsulfenyl, C₁-C₆ alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, C₁-C₆ perfluoroalkyl, heteroaryl or aryl, multiple degrees of substitution being allowed. Examples of "heteroaryl" groups used herein include furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, oxo-pyridyl, thiadiazolyl, isothiazolyl, pyridyl,

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pyridazyl, pyrazinyl, pyrimidyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, indolyl, indazolyl, and substituted versions thereof.

As used herein, the term "heteroarylene" preferably refers to a five - to
5 seven -membered aromatic ring diradical, or to a polycyclic heterocyclic aromatic ring diradical, containing one or more nitrogen, oxygen, or sulfur heteroatoms, where N-Oxides and sulfur monoxides and sulfur dioxides are permissible heteroaromatic substitutions, optionally substituted with
substituents selected from the group consisting of lower alkyl, lower alkoxy,
10 lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxy carbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl, or aryl,
15 multiple degrees of substitution being allowed. For polycyclic aromatic ring system diradicals, one or more of the rings may contain one or more heteroatoms. Examples of "heteroarylene" used herein are furan-2,5-diyl, thiophene-2,4-diyl, 1,3,4-oxadiazole-2,5-diyl, 1,3,4-thiadiazole-2,5-diyl, 1,3-thiazole-2,5-diyl, pyridine-2,4-diyl, pyridine-2,3-diyl, pyridine-2,5-diyl,
20 pyrimidine-2,4-diyl, quinoline-2,3-diyl, and the like.

As used herein, the term "alkoxy" preferably refers to the group R_aO- , where R_a is alkyl as defined above and the term "C₁-C₆ alkoxy" preferably refers to an alkoxy group as defined herein wherein the alkyl moiety contains at least
25 1 and at most 6 carbon atoms. Exemplary C₁-C₆ alkoxy groups useful in the present invention include, but are not limited to methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and t-butoxy.

As used herein, the term "haloalkoxy" preferably refers to the group R_aO- ,
30 where R_a is haloalkyl as defined above and the term "C₁-C₆ haloalkoxy" preferably refers to an haloalkoxy group as defined herein wherein the haloalkyl moiety contains at least 1 and at most 6 carbon atoms. Exemplary

C₁-C₆ haloalkoxy groups useful in the present invention include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and t-butoxy substituted with one or more halo groups, for instance trifluoromethoxy.

- 5 As used herein the term "aralkoxy" preferably refers to the group R_CR_BO-, where R_B is alkyl and R_C is aryl as defined above.
- As used herein the term "aryloxy" preferably refers to the group R_CO-, where R_C is aryl as defined above.
- As used herein, the term "alkylsulfanyl" preferably refers to the group R_AS-,
- 10 where R_A is alkyl as defined above and the term "C₁-C₆ alkylsulfanyl" preferably refers to an alkylsulfanyl group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms.
- As used herein, the term "haloalkylsulfanyl" preferably refers to the group R_DS-, where R_D is haloalkyl as defined above and the term "C₁-C₆
- 15 haloalkylsulfanyl" preferably refers to a haloalkylsulfanyl group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms.
- As used herein, the term "alkylsulfenyl" preferably refers to the group R_AS(O)-, where R_A is alkyl as defined above and the term "C₁-C₆
- 20 alkylsulfenyl" preferably refers to an alkylsulfenyl group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms.
- As used herein, the term "alkylsulfonyl" preferably refers to the group R_ASO₂-, where R_A is alkyl as defined above and the term "C₁-C₆ alkylsulfonyl" preferably refers to an alkylsulfonyl group as defined herein wherein the alkyl
- 25 moiety contains at least 1 and at most 6 carbon atoms.

As used herein, the term "oxo" preferably refers to the group =O.

As used herein, the term "mercapto" preferably refers to the group -SH.

As used herein, the term "carboxy" preferably refers to the group -COOH.

- 30 As used herein, the term "cyano" preferably refers to the group -CN.

As used herein, the term "cyanoalkyl" preferably refers to the group -R_BCN, wherein R_B is alkyl as defined above. Exemplary "cyanoalkyl" groups

useful in the present invention include, but are not limited to, cyanomethyl, cyanoethyl and cyanoisopropyl.

As used herein, the term "aminosulfonyl" preferably refers to the group $-\text{SO}_2\text{NH}_2$.

5 As used herein, the term "carbamoyl" preferably refers to the group $-\text{C}(\text{O})\text{NH}_2$.

As used herein, the term "sulfanyl" shall refer to the group $-\text{S}-$.

As used herein, the term "sulfenyl" shall refer to the group $-\text{S}(\text{O})-$.

As used herein, the term "sulfonyl" shall refer to the group $-\text{S}(\text{O})_2-$ or $-\text{SO}_2-$.

10 As used herein, the term "acyl" preferably refers to the group $\text{R}_\text{F}\text{C}(\text{O})-$, where R_F is alkyl, cycloalkyl or heterocyclyl as defined herein.

As used herein, the term "aroyl" preferably refers to the group $\text{R}_\text{C}\text{C}(\text{O})-$, where R_C is aryl as defined herein.

As used herein, the term "heteroaroyl" preferably refers to the group $\text{R}_\text{E}\text{C}(\text{O})-$
15 where R_E is heteroaryl as defined herein.

As used herein, the term "alkoxycarbonyl" preferably refers to the group $\text{R}_\text{A}\text{OC}(\text{O})-$, where R_A is alkyl as defined herein.

As used herein, the term "acyloxy" preferably refers to the group $\text{R}_\text{F}\text{C}(\text{O})\text{O}-$, where R_F is alkyl, cycloalkyl, or heterocyclyl as defined herein.

20 As used herein, the term "aroyloxy" preferably refers to the group $\text{R}_\text{C}\text{C}(\text{O})\text{O}-$, where R_C is aryl as defined herein.

As used herein, the term "heteroaroyloxy" preferably refers to the group $\text{R}_\text{E}\text{C}(\text{O})\text{O}-$, where R_E is heteroaryl as defined herein.

25 As used herein, the term "carbonyl" or "carbonyl moiety" preferably refers to the group $\text{C}=\text{O}$.

As used herein, the term "thiocarbonyl" or "thiocarbonyl moiety" preferably refers to the group $\text{C}=\text{S}$.

30 As used herein, the term "amino", "amino group" or "amino moiety" preferably refers to the group $\text{NR}_\text{G}\text{R}_\text{G'}$, wherein R_G and $\text{R}_\text{G'}$ are preferably selected, independently from one another, from the group consisting of

hydrogen, halogen, alkyl, haloalkyl, alkenyl, cycloalkyl, alkylencycloalkyl, cyanoalkyl, aryl, aralkyl, heteroaryl, acyl and aroyl. If both R_G and $R_{G'}$ are hydrogen, $NR_G R_{G'}$ is also referred to as "unsubstituted amino moiety" or "unsubstituted amino group". If R_G and/or $R_{G'}$ are other than hydrogen,
5 $NR_G R_{G'}$ is also referred to as "substituted amino moiety" or "substituted amino group".

As used herein, the term "imino" or "imino moiety" preferably refers to the group $C=NR_G$, wherein R_G is preferably selected from the group consisting of
10 hydrogen, halogen, alkyl, haloalkyl, alkenyl, cycloalkyl, alkylencycloalkyl, cyanoalkyl, aryl, aralkyl, heteroaryl, acyl and aroyl. If R_G is hydrogen, $C=NR_G$ is also referred to as "unsubstituted imino moiety". If R_G is a residue other than hydrogen, $C=NR_G$ is also referred to as "substituted imino moiety".

15 As used herein, the term "unsaturated" preferably means ethylenically unsaturated.

As used herein, the terms "group", "residue" and "radical" or "groups", "residues" and "radicals" are usually used as synonyms, respectively, as it is
20 common practice in the art.

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s), which occur, and events that do not occur.

25 As used herein, the term "physiologically functional derivative" preferably refers to any pharmaceutically acceptable derivative of a compound of the present invention, for example, an ester or an amide, which upon administration to a mammal is capable of providing (directly or indirectly) a
30 compound of the present invention or an active metabolite thereof. Such derivatives are clear to those skilled in the art, without undue experimentation, and with reference to the teaching of Burger's Medicinal

Chemistry And Drug Discovery, 5th Edition, Vol 1: Principles and Practice, which is incorporated herein by reference to the extent that it teaches physiologically functional derivatives.

5 As used herein, the term

As used herein, the term "solvate" preferably refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula I or a salt or physiologically functional derivative thereof) and a solvent. Such
10 solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation, water,
15 ethanol and acetic acid. Most preferably the solvent used is water.

As used herein, the term "substituted" preferably refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

20

Certain of the compounds described herein may contain one or more chiral atoms, or may otherwise be capable of existing as two or more stereoisomers, which are usually enantiomers and/or diastereomers. Accordingly, the compounds of this invention include mixtures of
25 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 formulae I above as well as any wholly or
30 partially equilibrated mixtures thereof. The present invention also covers the individual isomers of the compounds represented by the formulas above 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 formulae I are included within the scope of the compounds of formulae I and preferably the formulae and subformulae corresponding thereto.

5

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 β -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.

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

It is of course also possible to obtain optically active compounds of the formula I by the methods described above by using starting materials which are already optically active.

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Unless indicated otherwise, it is to be understood that reference to compounds of formula I preferably includes the reference to the compounds of formula I', I'', I''' and/or I'''. Unless indicated otherwise, it is to be understood that reference to the compounds of formula I, I', I'', I''' and I'''' preferably includes the reference to the sub formulae corresponding thereto, for example the sub formulae I.1 to I.20 and preferably formulae Ia to Iz. It is also understood that the following embodiments, including uses and compositions, although recited with respect to formula I are preferably also

applicable to formulae I', I'', I''' and/or I'''' and/or sub formulae I.1 to I.20 and preferably also to formulae Ia to Iz.

Unless indicated otherwise, it is to be understood that reference to
5 compounds of formula I preferably also includes the reference to the
compounds of formula I'''''. Unless indicated otherwise, it is to be understood
that reference to the compounds of formula I, I', I'', I''', I'''' and/or I'''''
preferably includes the reference to the sub formulae corresponding thereto,
for example the sub formulae I.1 to I.20 and preferably to one or more of
10 formulae Ia to Iz and/or Iaa to Iss. It is also understood that the following
embodiments, including uses and compositions, although recited with respect
to formula I are preferably also applicable to formulae I', I'', I''', I'''' and/or I''''';
preferably also applicable to sub formulae I.1 to I.20; and preferably also
applicable to sub formulae Ia to Iz and/or Iaa to Iss.
15 Even more preferred are compounds of formula I

wherein

Ar¹ is selected independently from aromatic hydrocarbons
20 containing 5 to 12, preferably 6 to 10 and especially 6
carbon atoms and unsaturated or aromatic heterocyclic
residues containing 3 to 8 and especially 4 to 6 carbon
atoms and one, two or three heteroatoms, preferably one
or two heteroatoms, independently selected from N, O and
25 S and especially selected from N and O,

Ar² is selected independently from aromatic hydrocarbons
containing 5 to 12, preferably 6 to 10 and especially 6
carbon atoms and unsaturated or aromatic heterocyclic
30 residues containing 2 to 8, especially 3 to 6 and especially
4 or 5 carbon atoms and 1, 2 or 3 heteroatoms, preferably
1 or 2 heteroatoms, independently selected from N, O and

S and especially selected from N and O,

- R^4 is independently selected from residues of the formula $(Ar^3)_\alpha-(R^{10})_r$, wherein
- 5 Ar^3 is independently selected from the meanings given for Ar^1 and/or Ar^2 , and more preferably is selected independently from unsubstituted or substituted, preferably substituted unsaturated or aromatic cyclic hydrocarbons containing 5 to 14 carbon atoms, preferably 6 to 10 carbon atoms; and unsubstituted or substituted, preferably substituted unsaturated or aromatic heterocyclic residues containing 2 to 10 carbon atoms and one or more heteroatoms, preferably 1 to 4 heteroatoms, more preferably 1, 2 or 3 heteroatoms, independently selected from N, O and S and more preferably from N and O,
- 15 α is 0, 1 or 2, preferably 0 or 1, and especially 1,
- 20 R^{10} is independently selected from the meanings given for R^8 and R^9 , and more preferably selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nS(O)_uNR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$,
- 25 $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$,
- 30 $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$,

- and/or selected from the group consisting Het⁹, OHet⁹,
 N(R¹¹)Het⁹, (CR⁵R⁶)_kHet⁹, O(CR⁵R⁶)_kHet⁹,
 N(R¹¹)(CR⁵R⁶)_kHet⁹, (CR⁵R⁶)_kNR¹¹R¹², (CR⁵R⁶)_kOR¹³,
 O(CR⁵R⁶)_kNR¹¹R¹², NR¹¹(CR⁵R⁶)_kNR¹¹R¹², O(CR⁵R⁶)_kR¹³,
 NR¹¹(CR⁵R⁶)_kR¹³, O(CR⁵R⁶)_kOR¹³, NR¹¹(CR⁵R⁶)_kOR¹³,
 wherein
- R⁵, R⁶ are in each case independently from one another selected from H and A;
- r is 0, 1, 2, 3, 4 or 5, more preferably 0, 1, 2 or 3, and especially 1, 2 or 3,
- z is 0, 1, 2, 3, 4 or 5, preferably 0, 1, 2, 3, 4 or 5, more preferably 0, 1, 2 or 3, even more preferably 1, 2 or 3, and especially 1,
- R⁷ is a nitrogen containing heterocyclic moiety, directly bound to Ar¹ via a nitrogen atom, said nitrogen containing heterocyclic moiety being independently selected from Het¹, Het² and Het³, wherein
- Het¹ is an unsaturated or aromatic heterocyclic residue comprising 5 or 6 ring atoms which contains 1 to 4 nitrogen atoms and optionally 1 or 2 additional heteroatoms selected from O and S, preferably no additional heteroatoms, whereby said unsaturated or aromatic heterocyclic residue is unsubstituted or substituted by one or more substituents, selected from a group consisting of A, R¹³, =O, =S, =N-R¹⁴, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂NR¹⁵R¹⁶, S(O)_uA

and OOCR^{15} , more preferably selected from $=\text{O}$, $=\text{S}$, $=\text{N}-\text{R}^{14}$, Hal , NO_2 , CN , OR^{15} , $\text{NR}^{15}\text{R}^{16}$, COOR^{15} , $\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{15}\text{COR}^{16}$, $\text{NR}^{15}\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{16}\text{SO}_2\text{A}$, COR^{15} , $\text{SO}_2\text{NR}^{15}\text{R}^{16}$ and $\text{S(O)}_u\text{A}$;

5

Het²

is a saturated, unsaturated or aromatic bicyclic residue comprising 4 to 9 carbon atoms, more preferably 5 to 8 carbon atoms, 1 to 4 nitrogen atoms and optionally 1 or 2 additional heteroatoms selected from O and S, whereby said bicyclic residue is unsubstituted or substituted by one or more substituents, preferably substituted by 1 to 6 substituents, selected from a group consisting of A, R^{13} , $=\text{O}$, $=\text{S}$, $=\text{N}-\text{R}^{14}$, Hal , NO_2 , CN , OR^{15} , $\text{NR}^{15}\text{R}^{16}$, COOR^{15} , $\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{15}\text{COR}^{16}$, $\text{NR}^{15}\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{16}\text{SO}_2\text{A}$, COR^{15} , $\text{SO}_2\text{NR}^{15}\text{R}^{16}$, $\text{S(O)}_u\text{A}$ and OOCR^{15} ,

10

15

Het³

is a saturated monocyclic residue comprising 2 to 6 carbon atoms, preferably 3 to 5 carbon atoms, 1 to 4 nitrogen atoms and optionally 1 or 2 additional heteroatoms selected from O and S, whereby said monocyclic residue is substituted by one or more substituents, preferably 1 or 2 substituents selected from a group consisting of $=\text{O}$, $=\text{S}$ and $=\text{N}-\text{R}^{14}$, and optionally substituted by one or more substituents, selected from A, R^{13} , Hal , NO_2 , CN , OR^{15} , $\text{NR}^{15}\text{R}^{16}$, COOR^{15} , $\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{15}\text{COR}^{16}$, $\text{NR}^{15}\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{16}\text{SO}_2\text{A}$, COR^{15} , $\text{SO}_2\text{NR}^{15}\text{R}^{16}$ and $\text{S(O)}_u\text{A}$,

20

25

30 R⁸ and R⁹

are independently selected from a group consisting of H, A, cycloalkyl comprising 3 to 7 carbon atoms, Hal , CH_2Hal , $\text{CH}(\text{Hal})_2$, $\text{C}(\text{Hal})_3$, NO_2 , $(\text{CH}_2)_n\text{CN}$, $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$,

$(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{NR}^{11}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$,
 $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{OR}^{11}$, $(\text{CH}_2)_n\text{NR}^{11}(\text{CH}_2)_k\text{OR}^{12}$,
 $(\text{CH}_2)_n\text{COR}^{13}$, $(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$,
 $(\text{CH}_2)_n\text{NR}^{11}\text{COR}^{13}$, $(\text{CH}_2)_n\text{NR}^{11}\text{CONR}^{11}\text{R}^{12}$,
5 $(\text{CH}_2)_n\text{NR}^{11}\text{SO}_2\text{A}$, $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$,
 $(\text{CH}_2)_n\text{S}(\text{O})_u\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{S}(\text{O})_u\text{R}^{13}$, $(\text{CH}_2)_n\text{OC}(\text{O})\text{R}^{13}$,
 $(\text{CH}_2)_n\text{COR}^{13}$, $(\text{CH}_2)_n\text{SR}^{11}$, $(\text{CH}_2)_n\text{NHOA}$,
 $(\text{CH}_2)_n\text{NR}^{11}\text{COOR}^{13}$, $(\text{CH}_2)_n\text{N}(\text{R}^{11})\text{CH}_2\text{CH}_2\text{OR}^{13}$,
10 $(\text{CH}_2)_n\text{N}(\text{R}^{11})\text{CH}_2\text{CH}_2\text{OCF}_3$, $(\text{CH}_2)_n\text{N}(\text{R}^{11})\text{C}(\text{R}^{13})\text{HCOOR}^{12}$,
 $(\text{CH}_2)_n\text{N}(\text{R}^{11})\text{C}(\text{R}^{13})\text{HCOR}^{11}$, $(\text{CH}_2)_n\text{N}(\text{COOR}^{13})\text{COOR}^{14}$,
 $(\text{CH}_2)_n\text{N}(\text{CONH}_2)\text{COOR}^{13}$, $(\text{CH}_2)_n\text{N}(\text{CONH}_2)\text{CONH}_2$,
 $(\text{CH}_2)_n\text{N}(\text{CH}_2\text{COOR}^{13})\text{COOR}^{14}$,
 $(\text{CH}_2)_n\text{N}(\text{CH}_2\text{CONH}_2)\text{COOR}^{13}$,
15 $(\text{CH}_2)_n\text{N}(\text{CH}_2\text{CONH}_2)\text{CONH}_2$, $(\text{CH}_2)_n\text{CHR}^{13}\text{COR}^{14}$,
 $(\text{CH}_2)_n\text{CHR}^{13}\text{COOR}^{14}$ and $(\text{CH}_2)_n\text{CHR}^{13}\text{CH}_2\text{OR}^{14}$,
and/or selected from the group consisting Het⁹, OHet⁹,
 $\text{N}(\text{R}^{11})\text{Het}^9$, $(\text{CR}^5\text{R}^6)_k\text{Het}^9$, $\text{O}(\text{CR}^5\text{R}^6)_k\text{Het}^9$,
 $\text{N}(\text{R}^{11})(\text{CR}^5\text{R}^6)_k\text{Het}^9$, $(\text{CR}^5\text{R}^6)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CR}^5\text{R}^6)_k\text{OR}^{13}$,
 $\text{O}(\text{CR}^5\text{R}^6)_k\text{NR}^{11}\text{R}^{12}$, $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{NR}^{11}\text{R}^{12}$, $\text{O}(\text{CR}^5\text{R}^6)_k\text{R}^{13}$,
20 $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{R}^{13}$, $\text{O}(\text{CR}^5\text{R}^6)_k\text{OR}^{13}$, $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{OR}^{13}$,
wherein R⁵ and R⁶ are as defined above/below, and
wherein

n and/or k independently are 0, 1, 2, 3 or 4, preferably 0, 1, 2 or 3,
25 and even more preferred are 0 or 2;

X represents a bond or is $(\text{CR}^{11}\text{R}^{12})_h$, or $(\text{CHR}^{11})_h\text{-Q-}$
 $(\text{CHR}^{12})_i$, wherein

30 Q is selected from a group consisting of O, S, N-R¹⁵,
 $(\text{CHAl}_2)_j$, $(\text{O-CHR}^{18})_j$, $(\text{CHR}^{18}\text{-O})_j$, $\text{CR}^{18}=\text{CR}^{19}$, $(\text{O-CHR}^{18}\text{CHR}^{19})_j$, $(\text{CHR}^{18}\text{CHR}^{19}\text{-O})_j$, C=O, C=NR¹⁵,

CH(OR¹⁵), C(OR¹⁵)(OR²⁰), C(=O)N(R¹⁵), N(R¹⁵)C(=O),
CH=N-NR¹⁵, S=O, SO₂, SO₂NR¹⁵ and NR¹⁵SO₂, wherein

h, i are independently from each other 0, 1, 2, 3, 4, 5 or 6,
5 preferably 0, 1, 2 or 3 and

j is 1, 2, 3, 4, 5 or 6, preferably 1, 2, 3 or 4,

q is 0, 1 or 2, preferably 0 or 1,

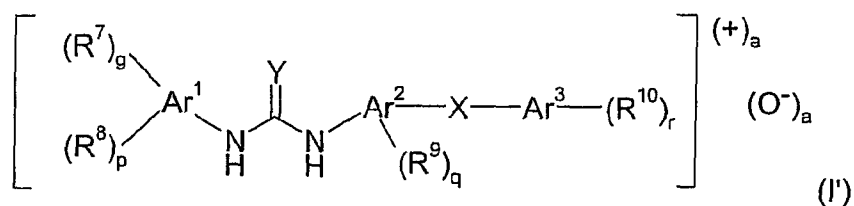
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g is 1 or 2, preferably 1, and

p is 1, 2 or 3, preferably 1 or 2;

15 and the pharmaceutically acceptable derivatives, solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, and more preferred the salts and/or solvates thereof, and especially preferred the physiologically acceptable salts and/or solvates thereof.

20 More preferred as compounds of formula I are compounds of formula I',

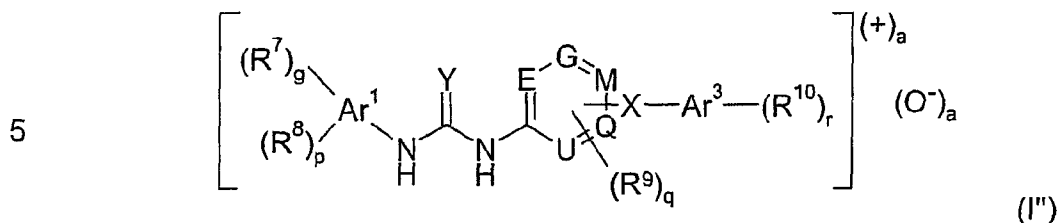


25 wherein Ar¹, R⁷, g, R⁸, p, Y, R⁹, q, Ar³, X, R¹⁰, r and a are as defined above/below,

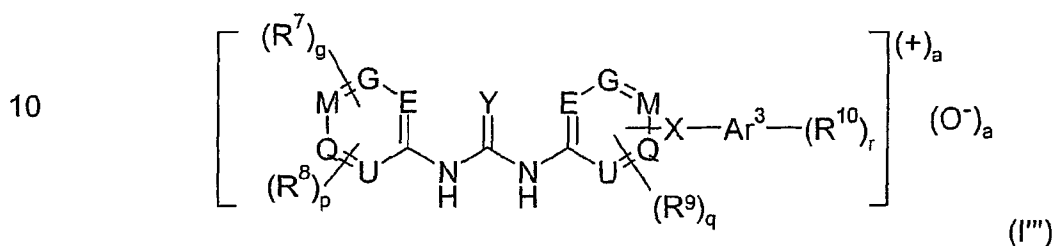
and preferably wherein X is a bond or is selected from CR¹¹R¹², (CR¹¹R¹²)_j, O, S, N-R¹⁵, (CHHal)_j, (CHAl₂)_j, (O-CHR¹⁸)_j, (CHR¹⁸-O)_j, CR¹⁸=CR¹⁹, (O-CHR¹⁸CHR¹⁹)_j, (CHR¹⁸CHR¹⁹-O)_j, C=O, C=NR¹⁵, CH(OR¹⁵), and especially

30 wherein X is a bond or is selected from CR¹¹R¹², O, S, N-R¹⁵, (CHHal)_j, (CHAl₂)_j, (O-CHR¹⁸)_j, (CHR¹⁸-O)_j, C=O, C=NR¹⁵, CH(OR¹⁵) and j is preferably 1 or 2.

More preferred as compounds of formula I are compounds of formula I'',



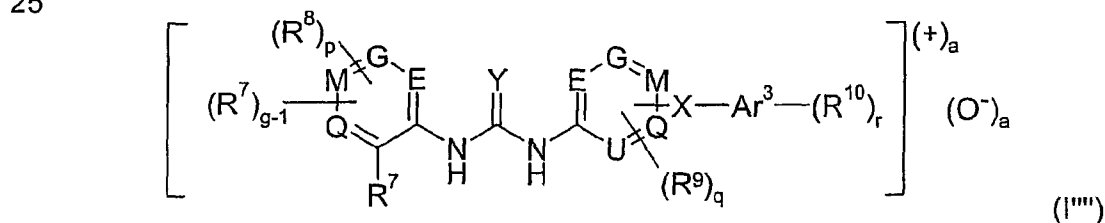
and especially compounds of formula I''',



wherein Ar^1 , R^7 , g , R^8 , p , Y , R^9 , q , Ar^3 , X , R^{10} , r and a are as defined above/below,

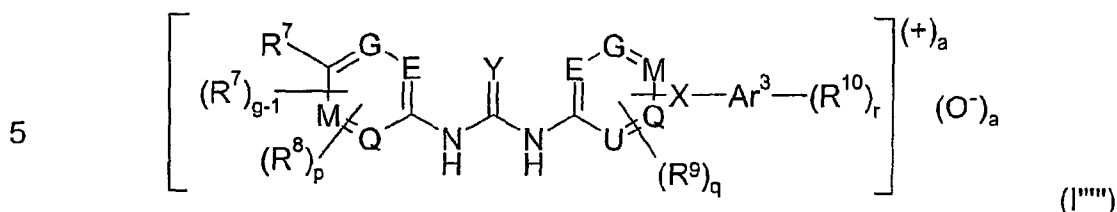
15 and wherein each of E , G , M , Q and U is independently from one another selected from carbon atoms and nitrogen atoms, with the proviso that in each of the E , G , M , Q and U containing 6-membered rings, one or more of E , G , M , Q and U are carbon atoms, and the further proviso that X and preferably substituents $(R^7)_g$ and $(R^8)_p$ are bonded to a carbon atom, respectively. More preferably, in the E , G , M , Q and U containing 6-membered ring one or more times substituted by R^7 , U is CR^7 , where R^7 is as defined above/below.

Accordingly, especially preferred as compounds of formula I are compounds of formula I''',



30 wherein each residue R^7 is independently selected from the meanings given above/below. In this formula, g is preferably 1 or 2 and especially is 1.

Accordingly, further especially preferred as compounds of formula I are compounds of formula I^{'''},



wherein each residue R⁷ is independently selected from the meanings given above/below. In this formula, g is preferably 1 or 2 and especially is 1.

- 10 Preferably, E, G, M, Q and U constitute, together with the carbon atom that E and U are bound to, a bivalent 6-membered aromatic or nitrogen containing heteroaromatic ring. Preferably, one or more of E, G, M, Q and U, more preferably two or more of E, G, M, Q and U and especially three or more of E, G, M, Q and U are carbon atoms. Especially preferred, none or one of E, G, M, Q and U is a nitrogen atom. Especially preferred, E, G, M, Q and U constitute, together with the carbon atom that E and U are bound to, a 6-membered aromatic or nitrogen containing heteroaromatic ring, selected from the group consisting of phenylen, pyridinylen and pyrimidylen, wherein X is preferably bonded to a carbon atom. The substituents R⁹ are preferably bound to a carbon atom.
- 15
- 20

In compounds of formula I, the term alkyl preferably refers to an unbranched or branched alkyl residue, preferably an unbranched alkyl residue comprising 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, preferably 1, 2, 3, 4, 5 or 6, more preferred 1, 2, 3 or 4 and especially 1 or 2 carbon atoms, or a branched alkyl residue comprising 3, 4, 5, 6, 7, 8, 9 or 10, preferably 3, 4, 5 or 6 more preferred 3 or 4 carbon atoms. The alkyl residues can be optionally substituted, especially by one or more halogen atoms, for example up to perhaloalkyl, by one or more hydroxy groups or by one or more amino groups, all of which can optionally be substituted by alkyl. If an alkyl residue is substituted by halogen, it usually comprises 1, 2, 3, 4 or 5 halogen atoms, depending on the number of carbon atoms of the alkyl residue. For example, a methyl group can

25

30

comprise, 1, 2 or 3 halogen atoms, an ethyl group (an alkyl residue comprising 2 carbon atoms) can comprise 1, 2, 3, 4 or 5 halogen atoms. If an alkyl residue is substituted by hydroxy groups, it usually comprises one or two, preferably one hydroxy groups. If the hydroxy group is substituted by
5 alkyl, the alkyl substituent comprises preferably 1 to 4 carbon atoms and is preferably unsubstituted or substituted by halogen and more preferred unsubstituted. If an alkyl residue is substituted by amino groups, it usually comprises one or two, preferably one amino groups. If the amino group is substituted by alkyl, the alkyl substituent comprises preferably 1 to 4 carbon
10 atoms and is preferably unsubstituted or substituted by halogen and more preferred unsubstituted. According to compounds of formula I, alkyl is preferably selected from the group consisting of methyl, ethyl, trifluoro methyl, pentafluoro ethyl, isopropyl, tert.-butyl, 2-amino ethyl, N-methyl-2-amino ethyl, N,N-dimethyl-2-amino ethyl, N-ethyl-2-amino ethyl, N,N-diethyl-
15 2-amino ethyl, 2-hydroxy ethyl, 2-methoxy ethyl and 2-ethoxy ethyl, further preferred of the group consisting of 2-butyl, n-pentyl, neo-nentyl, isopentyl, hexyl and n-decyl, more preferred of methyl, ethyl, trifluoro methyl, isopropyl and tert.-butyl.

20 In compounds of formula I, alkenyl is preferably selected from the group consisting of allyl, 2- or 3-butenyl, isobutenyl, sec-butenyl, furthermore preferably 4-pentenyl, isopentenyl and 5-hexenyl.

25 In compounds of formula I, alkylene is preferably unbranched and is more preferably methylene or ethylene, furthermore preferably propylene or butylene.

30 In compounds of formula I, alkylencycloalkyl preferably has 5 to 10 carbon atoms and is preferably methylenecyclopropyl, methylenecyclobutyl, furthermore preferably methylenecyclopentyl, methylenecyclohexyl or methylenecycloheptyl, furthermore alternatively ethylenecyclopropyl, ethylenecyclobutyl, ethylenecyclopentyl, ethylenecyclohexyl or

ethylenecycloheptyl, propylenecyclopentyl, propylenecyclohexyl, butylenecyclopentyl or butylenecyclohexyl.

In compounds of formula I, the term "alkoxy" preferably comprises groups of formula O-alkyl, where alkyl is an alkyl group as defined above. More preferred, alkoxy is selected from group consisting of methoxy, ethoxy, n-propoxy, isopropoxy, 2-butoxy, tert.-butoxy and halogenated, especially perhalogenated, derivatives thereof. Preferred perhalogenated derivatives are selected from the group consisting of O-CCl₃, O-CF₃, O-C₂Cl₅, O-C₂F₅, O-C(CCl₃)₃ and O-C(CF₃)₃.

In compounds of formula I, the term "alkoxyalkyl" preferably comprises branched and unbranched residues, more preferred unbranched residues, of formula C_uH_{2u+1}-O-(CH₂)_v, wherein u and v are independently from each other 1 to 6. Especially preferred is u = 1 and v 1 to 4.

In compounds of formula I the term "alkoxyalkyl" includes alkoxyalkyl groups as defined above, wherein one or more of the hydrogen atoms are substituted by halogen, for example up to perhalo alkoxyalkyl.

In compounds of formula I, cycloalkyl preferably has 3 – 7 carbon atoms and is preferably cyclopropyl or cyclobutyl, furthermore preferably cyclopentyl or cyclohexyl, furthermore also cycloheptyl, particularly preferably cyclopentyl. The term "cycloalkyl", as used herein preferably also includes saturated heterocyclic groups, wherein one or two carbon atoms are substituted by hetero atoms, selected from the group consisting of O, NH, NA and S, wherein A is as defined as above/below. Cycloalkyl residues as defined herein can optionally be substituted, the substituents preferably selected from A, R¹³, =O, =S, =N-R¹⁴, CN and hal.

In compounds of formula I, Ar⁶ to Ar⁸ are preferably selected independently from one another from phenyl, naphthyl and biphenyl which is optionally

substituted by one or more substituents, selected from the group consisting of A, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂NR¹⁵R¹⁶, S(O)_uA and OOCR¹⁵.

- 5 In compounds of formula I, Het⁹ is preferably an optionally substituted aromatic heterocyclic residue and even more preferred and optionally substituted saturated heterocyclic residue. In substituted saturated heterocyclic residues, the substituents are preferably selected from A, R¹³, =O, =S, =N-R¹⁴, CN and hal. Even more preferred, Het⁹ is selected from the
- 10 group consisting of 1-piperidyl, 4-piperidyl, 1-methyl-piperidin-4-yl, 1-piperazyl, 1-(4-methyl)-piperazyl, 4-methylpiperazin-1-yl amine, 1-(4-(2-hydroxyethyl))-piperazyl, 4-morpholinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-pyrazolidinyl 1-(2-methyl)-pyrazolidinyl, 1-imidazolidinyl or 1-(3-methyl)-imidazolidinyl, thiophen-2-yl, thiophen-3-yl, 2-pyridyl, 3-pyridyl, 4-
- 15 pyridyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, chinolinyl, isochinolinyl, 2-pyridazyl, 4-pyridazyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 2-pyrazinyl and 3-pyrazinyl. Further preferred, Het⁹ as defined above is optionally substituted by one or more substituents preferably selected from A, R¹³, =O, =S, =N-R¹⁴, CN and hal. More preferred, Het⁹ is
- 20 either unsubstituted or substituted once or twice by =O.

- In compounds of formula I, saturated heterocyclyl is preferably a substituted or unsubstituted saturated heterocyclic residue, more preferred an unsubstituted saturated heterocyclic residue, preferably selected from the
- 25 saturated groups given above in the definition of Het⁹. Further preferred, saturated heterocyclyl as defined above is optionally substituted by one or more substituents preferably selected from A, R¹³, =O, =S, =N-R¹⁴, CN and hal. More preferred, saturated heterocyclyl is either unsubstituted or substituted once or twice by =O.

30

In compounds of formula I, aromatic hydrocarbons containing 6 to 14 carbon atoms and unsaturated or aromatic heterocyclic residues containing 3 to 10

carbon atoms and one or two heteroatoms, independently selected from N, O and S, are preferably selected from the definitions given herein for aryl, heteroaryl and/or Het⁹. Heteroaryl is more preferably furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, oxo-pyridyl, thiadiazolyl, isothiazolyl, pyridyl, pyridazyl, pyrazinyl, pyrimidyl, quinoliny, isoquinoliny, benzofuranyl, benzothiophenyl, indolyl, indazolyl and even more preferably pyridinyl, pyrimidyl, chinoliny, isochinoliny, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl and/or imidazolyl. Aryl more preferably refers to an optionally substituted benzene ring or to an optionally substituted benzene ring system fused to one or more optionally substituted benzene rings to form, for example, anthracene, phenanthrene, or naphthalene ring systems. Even more preferably, aryl is selected from the group consisting of phenyl, 2-naphthyl, 1-naphthyl, biphenyl.

In compounds of formula I, Ar¹ is preferably selected from the group consisting of phenyl, pyridinyl, pyrimidyl, chinoliny, isochinoliny, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl and imidazolyl, and especially from phenyl, pyridinyl, chinoliny, isochinoliny, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl and oxazolyl. Especially preferred, Ar¹ is phenyl or pyridinyl. In compounds of formula I, Ar¹ is also preferably selected from the =O, =S, and/or =N-R¹⁴ substituted derivatives thereof.

In compounds of formula I, Ar² is preferably selected from the group consisting of phenyl, pyridinyl, pyrimidyl, chinoliny, isochinoliny, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl and imidazolyl, even more preferably from phenyl, pyridinyl and pyrimidyl and especially preferred from phenyl and pyridinyl. In compounds of formula I, Ar² is preferably also selected from the =O, =S, and/or =N-R¹⁴ substituted derivatives thereof.

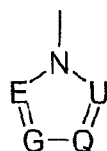
In compounds of formula I, Ar³ is preferably selected from the group consisting of phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl and imidazolyl, and carbon anelated and hetero anelated derivatives thereof, even more preferably from phenyl, pyridinyl and pyrimidyl, and carbon anelated and hetero anelated derivatives thereof, and especially preferred from phenyl and pyridinyl, and carbon anelated and hetero anelated derivatives thereof. In this respect, carbon anelated derivatives thereof refer to anelated or fused ring systems, wherein the unsaturated or aromatic carbocyclic or heterocyclic moiety as given above is fused with an unsaturated or aromatic carbocyclic ring, preferably a 5- or 6-membered unsaturated or aromatic carbocyclic ring, for example cyclopentadienyl-fused derivatives and benzo-fused derivatives, and the dihydro- and tetrahydro-derivatives of said cyclopentadienyl-fused derivatives and benzo-fused derivatives. In compounds of formula I, Ar³ is preferably also selected from the =O, =S, and/or =N-R¹⁴ substituted derivatives thereof.

In compounds of formula I, Ar³ is more preferably selected from the group consisting of phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl and imidazolyl, even more preferably from phenyl, pyridinyl and pyrimidyl and especially preferred from phenyl and pyridinyl. In compounds of formula I, Ar³ is preferably also selected from the =O, =S, and/or =N-R¹⁴ substituted derivatives thereof.

In compounds of formula I, Ar⁷ is preferably selected from the group consisting of phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl and imidazolyl, even more preferably from phenyl, pyridinyl and pyrimidyl and especially preferred from phenyl and pyridinyl. In compounds of formula I, Ar⁷ is preferably also selected from the =O, =S, and/or =N-R¹⁴ substituted derivatives thereof.

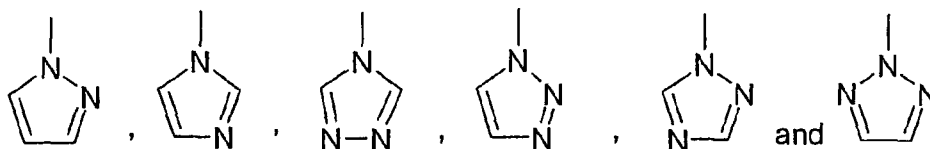
- In compounds of formula I, Ar⁸ is preferably selected from the group consisting of phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl and imidazolyl, even more preferably from phenyl, pyridinyl and pyrimidyl and especially preferred from phenyl and pyridinyl. In compounds of formula I, Ar⁸ is preferably also selected from the =O, =S, and/or =N-R¹⁴ substituted derivatives thereof.
- 10 If R⁵ and/or R⁶ is A, then A is preferably selected, independently from one another in each case, from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl and saturated heterocyclyl, more preferably preferably from the group consisting of alkyl, cycloalkyl, alkoxy and alkoxyalkyl, and especially is alkyl.
- 15 Preferably, the sum of h and i in one residue exceeds 0.
Preferably, the sum of n and k in one residue exceeds 0.
- 20 In R⁷, Het¹ is preferably an unsaturated or aromatic heterocyclic residue comprising 5 or 6 ring atoms which contains 1 to 4 nitrogen atoms and optionally 1 or 2 additional heteroatoms selected from O and S, preferably no additional heteroatoms.
- 25 If Het¹ is an unsubstituted unsaturated or aromatic heterocyclic residue, it is preferably selected from 5-membered unsaturated or aromatic heterocyclic residues comprising 1 to 4 nitrogen atoms and preferably no other hetero atoms, and more preferably is selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl and tetrazolyl, and even more preferably is selected from imidazolyl, pyrazolyl, triazolyl and tetrazolyl, and especially is selected from imidazolyl, pyrazolyl and triazolyl. If Het¹ is an unsubstituted unsaturated or aromatic heterocyclic residue, it is even more preferably selected from
- 30

55



5 wherein E, G, Q and U are selected independently from one another from nitrogen atoms and carbon atoms and especially from N and CH, with the proviso, that one or more of E, G, Q and U are other than nitrogen atoms and especially other than N.

10 If Het¹ is an unsubstituted unsaturated or aromatic heterocyclic residue, it is even more preferably selected from

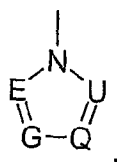


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If Het¹ is a substituted unsaturated or aromatic heterocyclic residue, it is preferably selected from 5- or 6-membered unsaturated or aromatic heterocyclic residues comprising 1 to 4 nitrogen atoms and preferably no other hetero atoms, comprising one or more, preferably 1 to 4 substituents
 20 selected from the group =O, =S, and =N-R¹⁴, and/or selected from the group A, R¹³, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂NR¹⁵R¹⁶ and S(O)_uA.

25 If Het¹ is a substituted unsaturated or aromatic heterocyclic residue, it is even more preferably selected from a), a1), b), b1), b2), b3), c), c1) and d) as given below:

a)



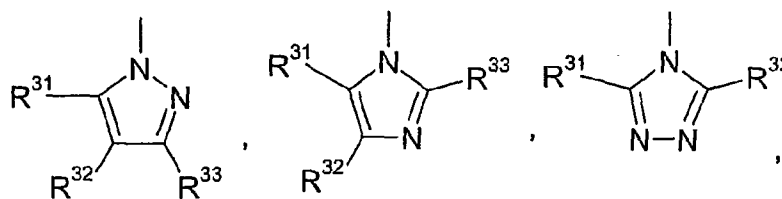
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wherein E, G, Q and U are selected independently from one another from nitrogen atoms and carbon atoms and especially from N and CR³⁰, wherein R³⁰ is independently selected from A, R¹³, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂NR¹⁵R¹⁶ and S(O)_uA and especially from A, H, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵ and CONR¹⁵R¹⁶, with the proviso, that one or more of E, G, Q and U are other than nitrogen atoms and especially other than N, and with the further proviso that one or more of the residues R³⁰ and/or R³¹ is other than H,

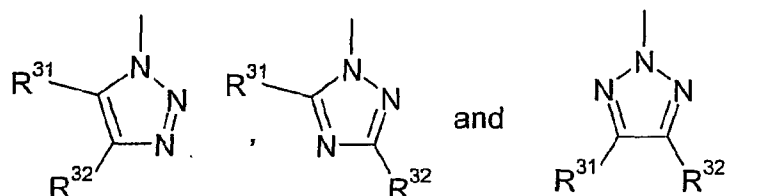
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a1)

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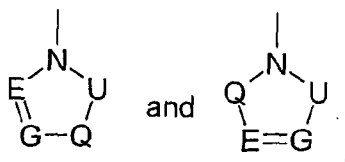


25

wherein R³¹, R³² and R³³ are independently selected from A, R¹³, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂NR¹⁵R¹⁶ and S(O)_uA and especially from A, H, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵ and CONR¹⁵R¹⁶, with the proviso that one or more of the residues R³¹, R³² and R³³ is other than H;

b)

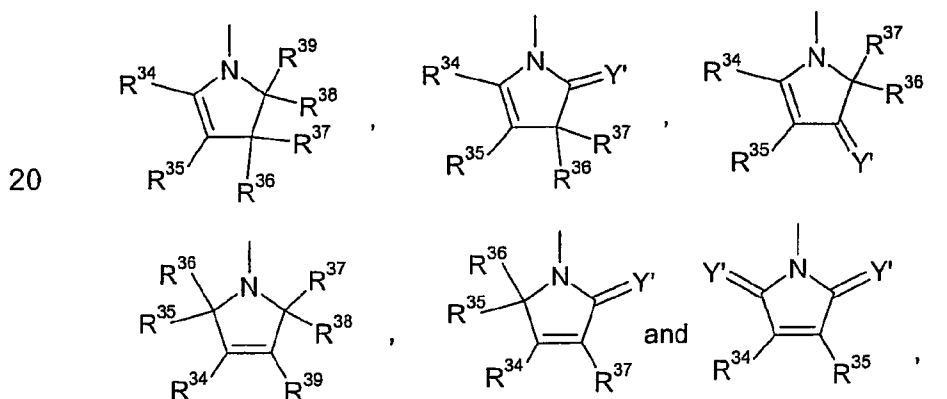
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wherein E and G are selected independently from one another from N and CR^{30} , wherein R^{30} is independently selected from A, R^{13} , Hal, NO_2 , CN, OR^{15} , $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, COR^{15} , $SO_2NR^{15}R^{16}$ and $S(O)_uA$ and especially from A, H, Hal, NO_2 , CN, OR^{15} , $NR^{15}R^{16}$, $COOR^{15}$ and $CONR^{15}R^{16}$,
 5 and wherein Q and U are selected independently from one another from NR^{30} , $CR^{31}R^{32}$, $C=O$, $C=S$ and $C=N-R^{14}$, wherein R^{14} is as defined above/below and R^{30} , R^{31} and R^{32} are independently selected from A, R^{13} , Hal, NO_2 , CN, OR^{15} , $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$,
 10 $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, COR^{15} , $SO_2NR^{15}R^{16}$ and $S(O)_uA$ and especially from A, H, Hal, NO_2 , CN, OR^{15} , $NR^{15}R^{16}$, $COOR^{15}$ and $CONR^{15}R^{16}$,
 with the proviso, that one or more of E, G, Q and U are other than nitrogen atoms, and with the further proviso that one or more of the residues R^{30} , R^{31} and R^{32} is other than H,

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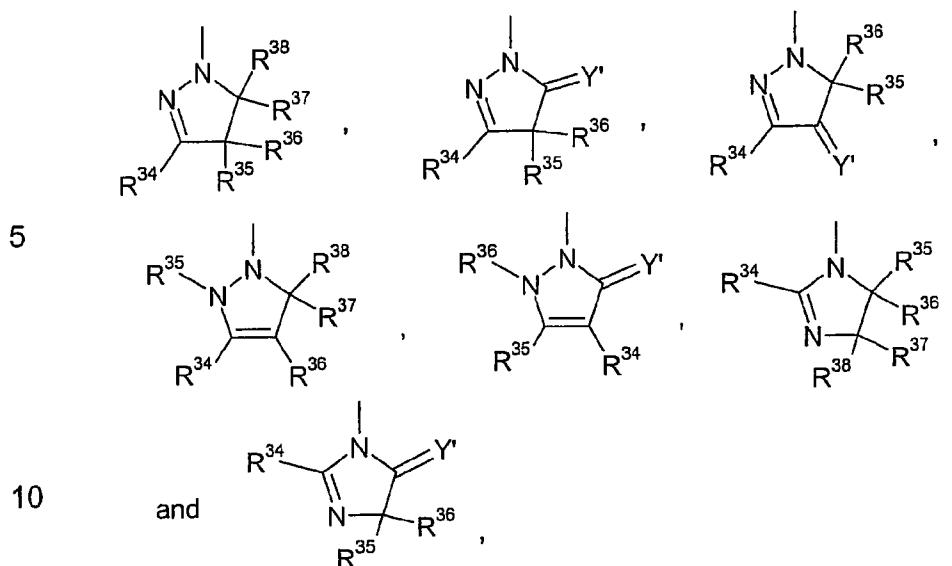
b1)



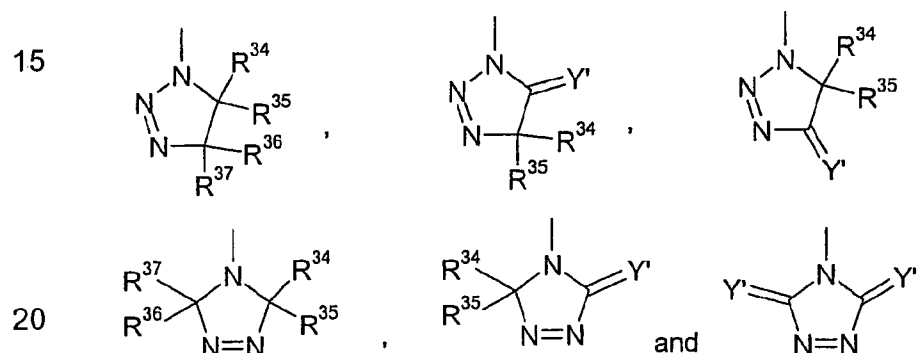
b2)

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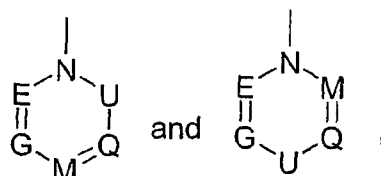


b3)



wherein in b1), b2) and b3), the substituents R^{34} , R^{35} , R^{36} , R^{37} , R^{38} and R^{39} are independently selected from A, R^{13} , Hal, NO_2 , CN, OR^{15} , $\text{NR}^{15}\text{R}^{16}$, COOR^{15} , $\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{15}\text{COR}^{16}$, $\text{NR}^{15}\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{16}\text{SO}_2\text{A}$, COR^{15} , $\text{SO}_2\text{NR}^{15}\text{R}^{16}$ and $\text{S(O)}_u\text{A}$ and especially from A, H, Hal, NO_2 , CN, OR^{15} , $\text{NR}^{15}\text{R}^{16}$, COOR^{15} and $\text{CONR}^{15}\text{R}^{16}$, with the proviso that one or more of the residues R^{34} , R^{35} , R^{36} , R^{37} , R^{38} and R^{39} is other than H, and Y' is independently selected from $=\text{O}$, $=\text{S}$ and $=\text{N-R}^{14}$, wherein R^{14} is as defined above/below;

c)



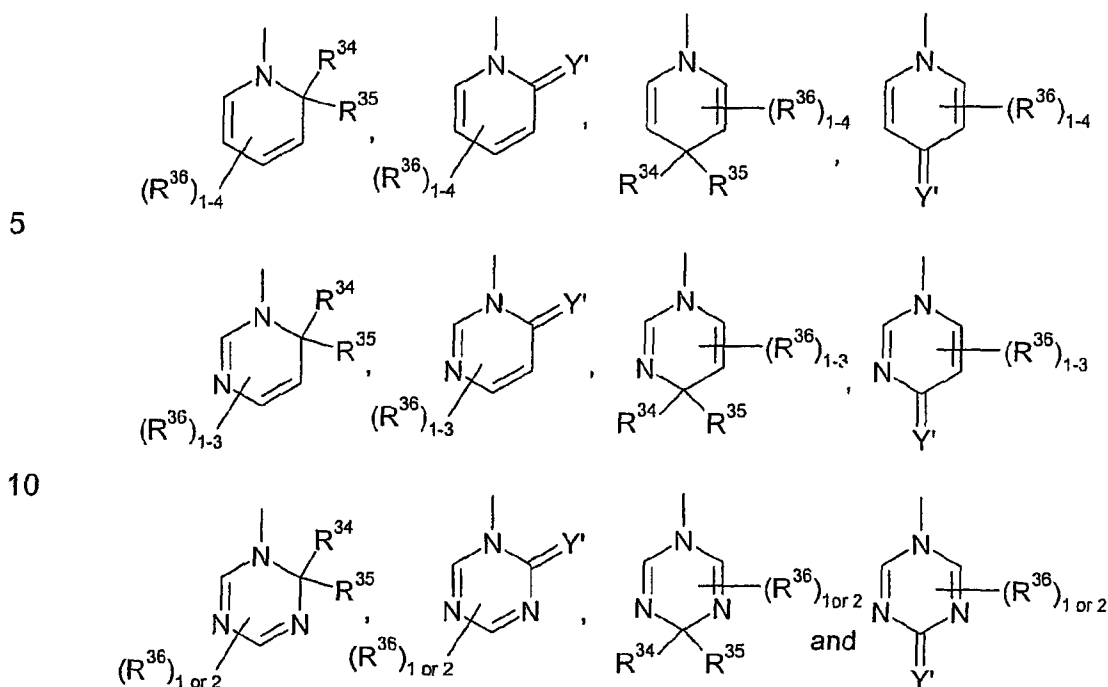
- 5 wherein E, G, M and Q are selected independently from one another from N and CR³⁰, wherein R³⁰ is independently selected from A, R¹³, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂NR¹⁵R¹⁶ and S(O)_uA and especially from A, H, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵ and CONR¹⁵R¹⁶,
- 10 and U is selected from NR³⁰, CR³¹R³², C=O, C=S and C=N-R¹⁴, wherein R¹⁴ is as defined above/below and R³⁰, R³¹ and R³² are independently selected from A, R¹³, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂NR¹⁵R¹⁶ and S(O)_uA and especially from A, H, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵ and
- 15 CONR¹⁵R¹⁶, with the proviso, that one or more of E, G, M, Q and U and preferably two or more of E, G, M, Q and U are other than nitrogen atoms, and with the further proviso that one or more of the residues R³⁰, R³¹ and R³² is other than H,

20 c1)

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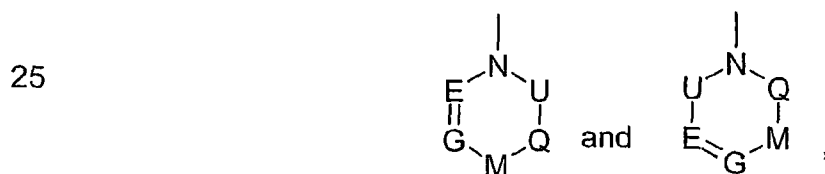
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wherein in c1), the substituents R^{34} , R^{35} and R^{36} are independently selected from A, R^{13} , Hal, NO_2 , CN, OR^{15} , $\text{NR}^{15}\text{R}^{16}$, COOR^{15} , $\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{15}\text{COR}^{16}$, $\text{NR}^{15}\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{16}\text{SO}_2\text{A}$, COR^{15} , $\text{SO}_2\text{NR}^{15}\text{R}^{16}$ and $\text{S(O)}_u\text{A}$ and especially from A, H, Hal, NO_2 , CN, OR^{15} , $\text{NR}^{15}\text{R}^{16}$, COOR^{15} and $\text{CONR}^{15}\text{R}^{16}$, with the proviso that one or more of the residues R^{34} , R^{35} and R^{36} is other than H, and Y' is independently selected from $=\text{O}$, $=\text{S}$ and $=\text{N-R}^{14}$, wherein R^{14} is as defined above/below;

d)



wherein E and G are selected independently from one another from N and CR^{30} , wherein R^{30} is independently selected from A, R^{13} , Hal, NO_2 , CN, OR^{15} , $\text{NR}^{15}\text{R}^{16}$, COOR^{15} , $\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{15}\text{COR}^{16}$, $\text{NR}^{15}\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{16}\text{SO}_2\text{A}$, COR^{15} , $\text{SO}_2\text{NR}^{15}\text{R}^{16}$ and $\text{S(O)}_u\text{A}$ and especially from A, H, Hal, NO_2 , CN, OR^{15} , $\text{NR}^{15}\text{R}^{16}$, COOR^{15} and $\text{CONR}^{15}\text{R}^{16}$,

and M, Q and U are selected independently from one another from NR^{30} , $\text{CR}^{31}\text{R}^{32}$, $\text{C}=\text{O}$, $\text{C}=\text{S}$ and $\text{C}=\text{N}-\text{R}^{14}$, wherein R^{14} is as defined above/below and R^{30} , R^{31} and R^{32} are independently selected from A, R^{13} , Hal, NO_2 , CN, OR^{15} , $\text{NR}^{15}\text{R}^{16}$, COOR^{15} , $\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{15}\text{COR}^{16}$, $\text{NR}^{15}\text{CONR}^{15}\text{R}^{16}$,
 5 $\text{NR}^{16}\text{SO}_2\text{A}$, COR^{15} , $\text{SO}_2\text{NR}^{15}\text{R}^{16}$ and $\text{S}(\text{O})_u\text{A}$ and especially from A, H, Hal, NO_2 , CN, OR^{15} , $\text{NR}^{15}\text{R}^{16}$, COOR^{15} and $\text{CONR}^{15}\text{R}^{16}$, with the proviso, that one or more of E, G, M, Q and U and preferably two or more of E, G, M, Q and U are other than nitrogen atoms, and with the further proviso that one or more of the residues R^{30} , R^{31} and R^{32} is other than H.

10

In R^7 , Het^2 is preferably a saturated, unsaturated or aromatic bicyclic residue comprising 4 to 10 and preferably 5 to 9 carbon atoms, 1 to 4 and preferably 1 to 3 nitrogen atoms and preferably no other hetero atoms, which comprises one or more, preferably 1 to 4 substituents selected independently from one
 15 another from the group $=\text{O}$, $=\text{S}$, and $=\text{N}-\text{R}^{14}$, and/or selected from the group A, R^{13} , Hal, NO_2 , CN, OR^{15} , $\text{NR}^{15}\text{R}^{16}$, COOR^{15} , $\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{15}\text{COR}^{16}$, $\text{NR}^{15}\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{16}\text{SO}_2\text{A}$, COR^{15} , $\text{SO}_2\text{NR}^{15}\text{R}^{16}$ and $\text{S}(\text{O})_u\text{A}$. Saturated bicyclic residues are preferably selected from unsubstituted and substituted monoaza-, diaza-, triaza- and tetraaza-derivatives of bicyclo[3.1.0]hexanes,
 20 bicyclo[3.2.0]heptanes, bicyclo[4.1.0]heptanes, bicyclo[3.3.0]octanes, bicyclo[4.3.0]nonanes and bicyclo[4.4.0]decenes.

Unsaturated or aromatic bicyclic residues are preferably selected from unsubstituted and substituted monoaza-, diaza-, triaza- and tetraaza-derivatives of bicyclo[3.1.0]hexenes, bicyclo[3.2.0]heptenes,
 25 bicyclo[4.1.0]heptenes, bicyclo[3.3.0]octenes, bicyclo[4.3.0]nonenes and bicyclo[4.4.0]decenes, bicyclo[3.2.0]heptadienes, bicyclo[4.1.0]heptadienes, bicyclo[3.3.0]octadienes, bicyclo[4.3.0]nonadienes and bicyclo[4.4.0]decadienes, bicyclo[4.3.0]nonatrienes and bicyclo[4.4.0]decatrienes and bicyclo[4.4.0]decatetraenes. Unsaturated or
 30 aromatic bicyclic bicyclic residues are more preferably selected from unsubstituted and substituted quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, quinazolinyl, phthalazinyl, and the dihydro-, tetrahydro-, hexahydro- and

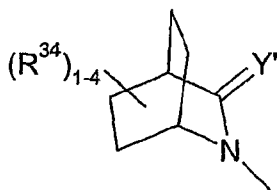
octahydro-derivatives thereof; indolyl, isoindolyl, benzimidazolyl, indazolyl, and the dihydro-, tetrahydro- and hexahydro-derivatives thereof; and the oxo- and dioxo-derivatives thereof. A preferred example for dioxo-derivative of an aza bicyclo[4.3.0]nonatriene or a dioxo-derivative of a dihydro-isoindole is the phthalimidoyl residue.

If Het² is a saturated or unsaturated bicyclic residue, it is preferably also selected from unsubstituted and substituted monoaza-, diaza- and triaza-derivatives of bicyclo[2.2.2]octanes, bicyclo[2.2.2]octenes and bicyclo[2.2.2]octadienes, which comprise one or more, preferably 1 to 4 substituents selected independently from one another from the group =O, =S, and =N-R¹⁴, and/or selected from the group A, R¹³, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂NR¹⁵R¹⁶ and S(O)_uA. A preferred example of an unsubstituted derivative of a bicyclo[2.2.2]octane as described above is the 3-Oxo-2-aza-bicyclo[2.2.2]oct-2-yl residue.

Het² is more preferably selected from

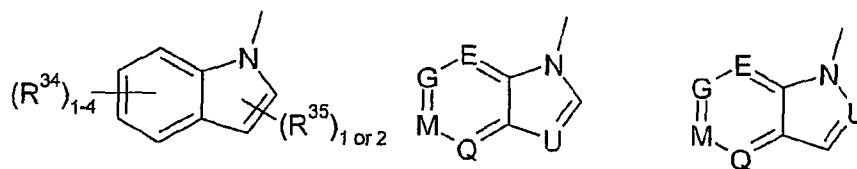
e)

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f)

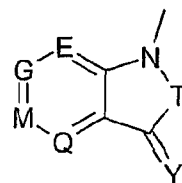
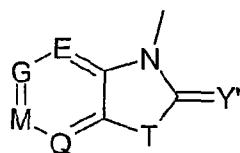
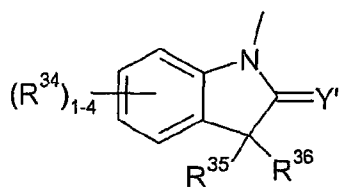
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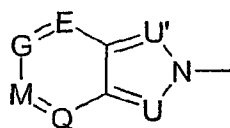
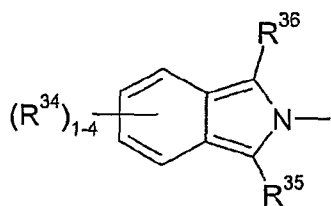
g)

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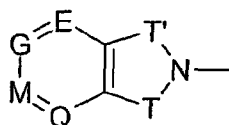
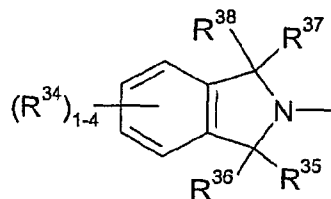
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h)



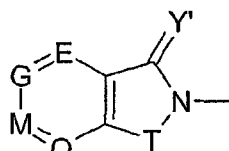
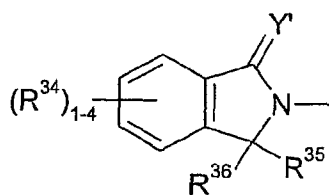
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i)



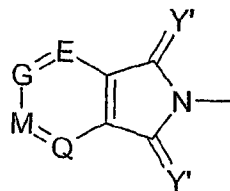
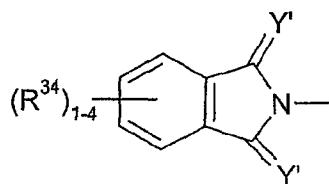
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j)



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25 and k)



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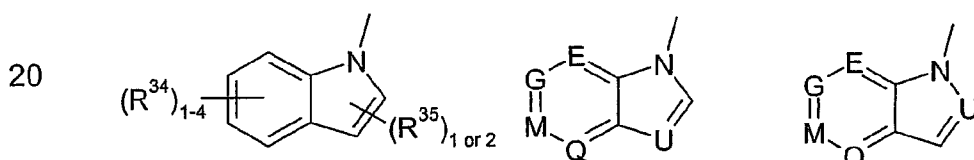
wherein E, G, M, Q, U and U' are selected independently from one another from N and CR³⁰, wherein R³⁰ is independently selected from A, R¹³, Hal,

NO_2 , CN , OR^{15} , $\text{NR}^{15}\text{R}^{16}$, COOR^{15} , $\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{15}\text{COR}^{16}$,
 $\text{NR}^{15}\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{16}\text{SO}_2\text{A}$, COR^{15} , $\text{SO}_2\text{NR}^{15}\text{R}^{16}$ and $\text{S(O)}_u\text{A}$ and especially
 from A , H , Hal , NO_2 , CN , OR^{15} , $\text{NR}^{15}\text{R}^{16}$, COOR^{15} and $\text{CONR}^{15}\text{R}^{16}$,
 and T and T' are selected from NR^{30} , $\text{CR}^{31}\text{R}^{32}$, Y' is selected independently
 5 from one another from $=\text{O}$, $=\text{S}$ and $=\text{N-R}^{14}$, wherein R^{14} is as defined
 above/below and R^{34} , R^{35} , R^{36} , R^{37} and R^{38} are independently selected from
 A , R^{13} , Hal , NO_2 , CN , OR^{15} , $\text{NR}^{15}\text{R}^{16}$, COOR^{15} , $\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{15}\text{COR}^{16}$,
 $\text{NR}^{15}\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{16}\text{SO}_2\text{A}$, COR^{15} , $\text{SO}_2\text{NR}^{15}\text{R}^{16}$ and $\text{S(O)}_u\text{A}$ and especially
 from A , H , Hal , NO_2 , CN , OR^{15} , $\text{NR}^{15}\text{R}^{16}$, COOR^{15} and $\text{CONR}^{15}\text{R}^{16}$, with the
 10 proviso, that one or more, two or more and especially 3 or more of E , G , M ,
 Q , U , U' , T and T' are other than nitrogen atoms, and with the further proviso
 that the residues Het^2 do not contain more than 4 and preferably not more
 than three nitrogen atoms. Even more preferably, Het^2 contains 1, 2 of 3 and
 especially 1 or 2 nitrogen atoms in total.

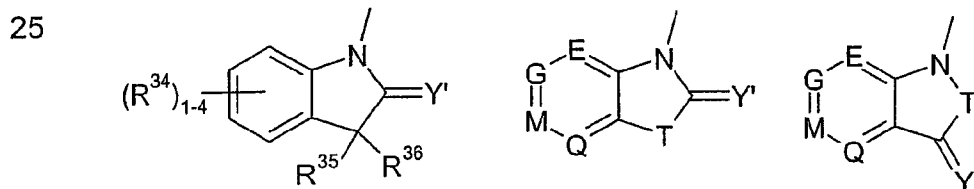
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Het^2 is more preferably selected from

f)



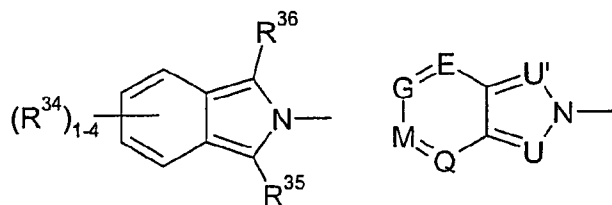
g)



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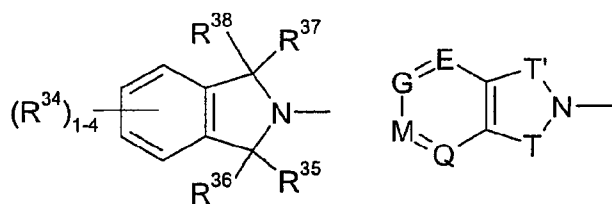
h)

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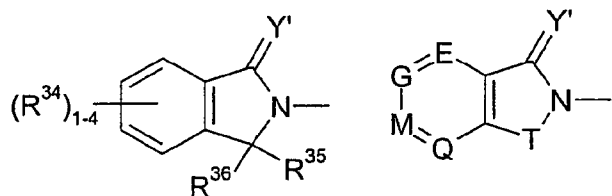
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i)



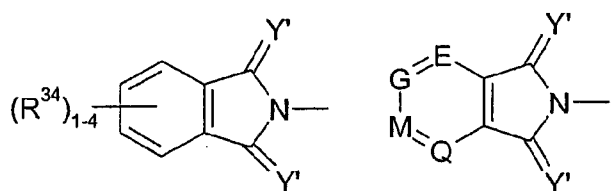
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j)



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and k)



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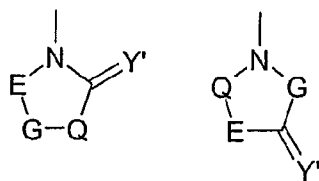
- 25 wherein E, G, M, Q, U and U' are selected independently from one another from N and CR³⁰, wherein R³⁰ is independently selected from A, R¹³, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂NR¹⁵R¹⁶ and S(O)_uA and especially from A, H, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵ and CONR¹⁵R¹⁶,
- 30 and T and T' are selected from NR³⁰, CR³¹R³², Y' is selected independently from one another from =O, =S and =N-R¹⁴, wherein R¹⁴ is as defined above/below and R³⁰, R³¹ and R³² are independently selected from A, R¹³,

- Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶,
 NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂NR¹⁵R¹⁶ and S(O)_uA and especially
 from A, H, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵ and CONR¹⁵R¹⁶, with the
 proviso, that one or more, two or more and especially 3 or more of E, G, M,
 5 Q, U, U', T and T' are other than nitrogen atoms, and with the further proviso
 that the residues Het² do not contain more than 4 and preferably not more
 than three nitrogen atoms. Even more preferably, Het² contains 1, 2 of 3 and
 especially 1 or 2 nitrogen atoms in total.
- 10 In R⁷, Het³ is preferably a saturated 5-, 6- or seven-membered monocyclic
 residue, comprising 1 to 3 and preferably 1 or 2 nitrogen atoms and
 optionally 1 or 2 additional hetero atoms selected from O and S, which is
 substituted by one or two, preferably two substituents selected from the
 group consisting of =O, =S and =N-R¹⁴. Het³ optionally comprises 1 to 6,
 15 preferably 1 to 4 additional substituents, selected from A, R¹³, Hal, NO₂, CN,
 OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶,
 NR¹⁶SO₂A, COR¹⁵, SO₂NR¹⁵R¹⁶ and S(O)_uA and especially from A and Hal.

More preferably, Het³ is selected from

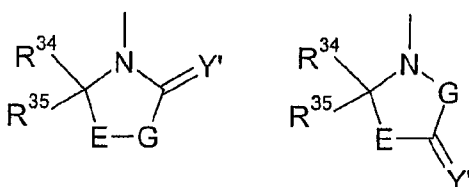
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e)



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e1)

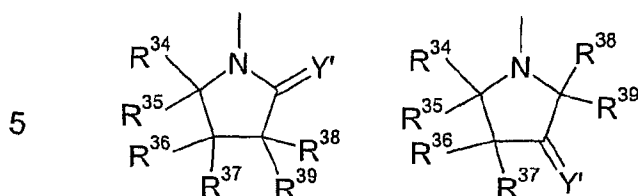


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and

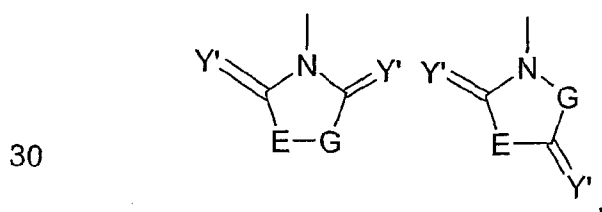
e2)



wherein E, G and Q are selected independently from one another from NR³⁰ and CR³¹R³², wherein R³⁰, R³¹ and R³² are independently selected from A, R¹³, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂NR¹⁵R¹⁶ and S(O)_uA and especially from A, H, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵ and CONR¹⁵R¹⁶, Y' is selected independently from one another from =O, =S and =N-R¹⁴, wherein R¹⁴ is as defined above/below, and R³⁴, R³⁵, R³⁶, R³⁷ and R³⁸ are independently selected from A, R¹³, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂NR¹⁵R¹⁶ and S(O)_uA and especially from A, H, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵ and CONR¹⁵R¹⁶, with the proviso that one or more, preferably two or more of E, G and Q are other than nitrogen atoms, and with the further proviso that the residues Het³ according to e), e1) and e2) do not contain more than 4 and preferably not more than three nitrogen atoms. Even more preferably, Het³ according to e), e1) and e2) contains 1, 2 of 3 and especially 1 or 2 nitrogen atoms in total.

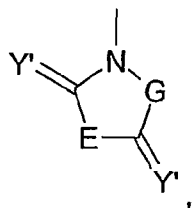
Even more preferably, Het³ is selected from

f)



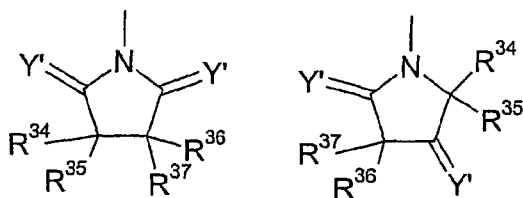
especially

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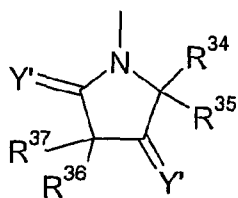
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f1)



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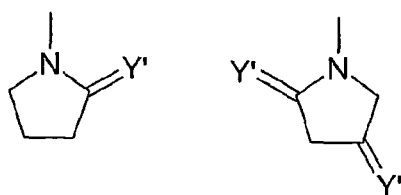
especially



15

and

f2)



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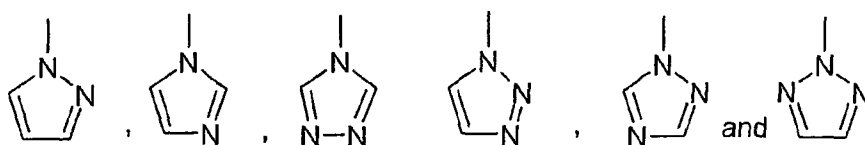
25

wherein E and G are selected independently from one another from NR^{30} and $\text{CR}^{31}\text{R}^{32}$, wherein R^{30} , R^{31} and R^{32} are independently selected from A, R^{13} , Hal, NO_2 , CN, OR^{15} , $\text{NR}^{15}\text{R}^{16}$, COOR^{15} , $\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{15}\text{COR}^{16}$, $\text{NR}^{15}\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{16}\text{SO}_2\text{A}$, COR^{15} , $\text{SO}_2\text{NR}^{15}\text{R}^{16}$ and $\text{S(O)}_u\text{A}$ and especially from A, H, Hal, NO_2 , CN, OR^{15} , $\text{NR}^{15}\text{R}^{16}$, COOR^{15} and $\text{CONR}^{15}\text{R}^{16}$, Y' is selected independently from one another from $=\text{O}$, $=\text{S}$ and $=\text{N-R}^{14}$, wherein R^{14} is as defined above/below, and R^{34} , R^{35} , R^{36} and R^{37} are independently

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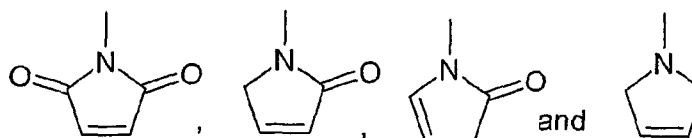
- selected from A, R^{13} , Hal, NO_2 , CN, OR^{15} , $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, COR^{15} , $SO_2NR^{15}R^{16}$ and $S(O)_uA$ and especially from A, H, Hal, NO_2 , CN, OR^{15} , $NR^{15}R^{16}$, $COOR^{15}$ and $CONR^{15}R^{16}$, with the proviso that one or more of E and G are other than nitrogen atoms.; and with the further proviso that the residues Het³ according to f), f1) and f2) do not contain more than 4 and preferably not more than three nitrogen atoms. Even more preferably, Het³ according to e), e1) and e2) contains 1, 2 or 3 and especially 1 or 2 nitrogen atoms in total.
- 5
- 10 Preferably, the residues Het³ according to e), e1) and e2) do not contain more than 4 and preferably not more than three nitrogen atoms. Even more preferably, Het³ according to e), e1) and e2) contains 1, 2 or 3 and especially 1 or 2 nitrogen atoms in total.
- 15 Preferably, the residues Het³ according to f), f1) and f2) do not contain more than 3 and preferably not more than two nitrogen atoms. Even more preferably, Het³ according to f), f1) and f2) contains 1 or 2 and especially 1 nitrogen atom in total.

- 20 Especially preferably, Het¹ is selected from



and/or

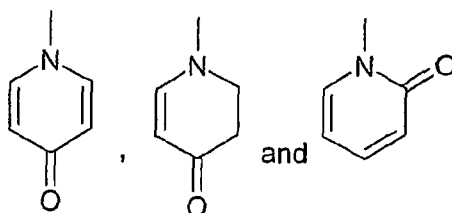
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and/or

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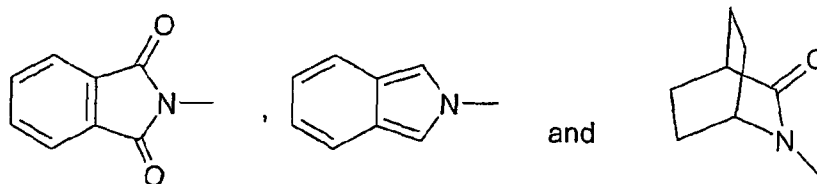


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and/or derivatives thereof that comprise 1 to 4, preferably 1 to 3 and especially 1 or 2 substituents, selected from A, R^{13} , Hal, NO_2 , CN, OR^{15} , $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, $SO_2NR^{15}R^{16}$ and $S(O)_uA$ and especially from A, Hal, NO_2 , CN, OR^{15} , $NR^{15}R^{16}$, $COOR^{15}$ and $CONR^{15}R^{16}$.

10

Especially preferably, Het^2 is selected from

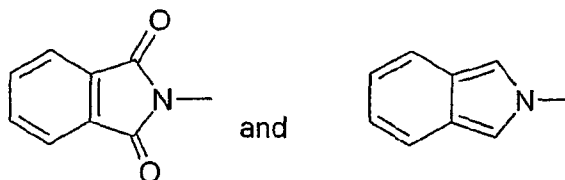


15

and/or derivatives thereof that comprise 1 to 4, preferably 1 to 3 and especially 1 or 2 substituents, selected from A, R^{13} , Hal, NO_2 , CN, OR^{15} , $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, $SO_2NR^{15}R^{16}$ and $S(O)_uA$ and especially from A, Hal, NO_2 , CN, OR^{15} , $NR^{15}R^{16}$, $COOR^{15}$ and $CONR^{15}R^{16}$.

20

Even more preferably, Het^2 is selected from

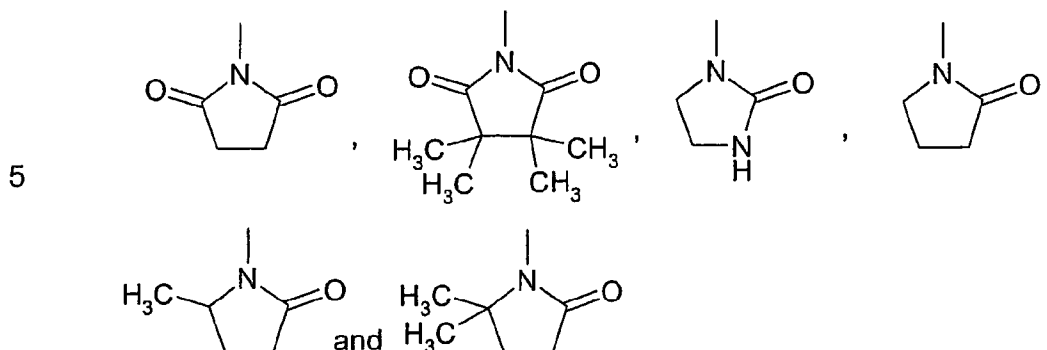


25

and/or derivatives thereof that comprise 1 to 4, preferably 1 to 3 and especially 1 or 2 substituents, selected from A, R^{13} , Hal, NO_2 , CN, OR^{15} , $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, $SO_2NR^{15}R^{16}$ and $S(O)_uA$ and especially from A, Hal, NO_2 , CN, OR^{15} , $NR^{15}R^{16}$, $COOR^{15}$ and $CONR^{15}R^{16}$.

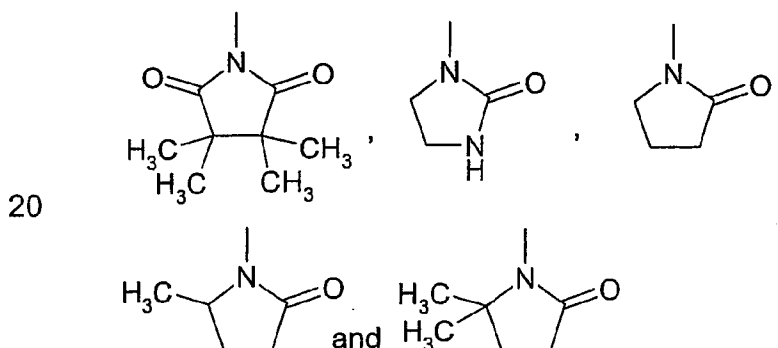
30

Especially preferably, Het³ is selected from



10 and/or derivatives thereof that comprise 1 to 4, preferably 1 to 3 and especially 1 or 2 substituents, selected from A, R¹³, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, SO₂NR¹⁵R¹⁶ and S(O)_uA and especially from A, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵ and CONR¹⁵R¹⁶.

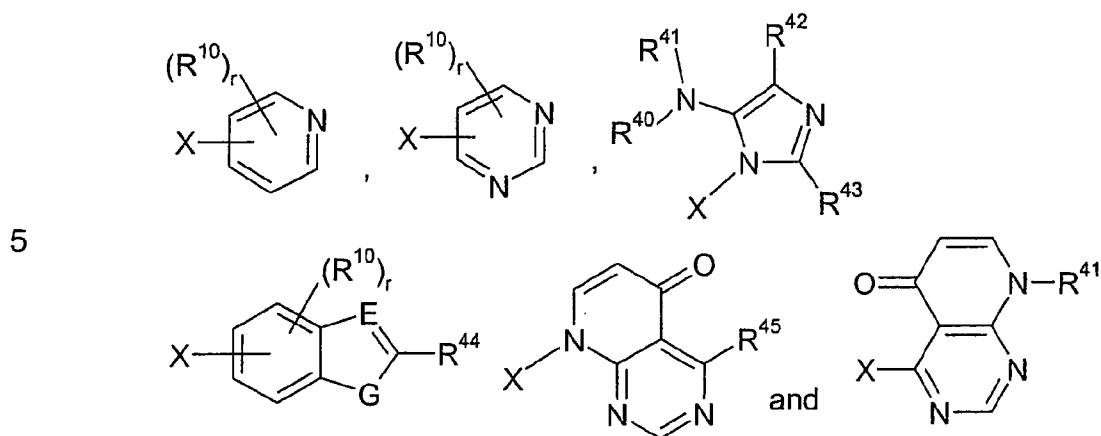
15 Especially preferably, Het³ is selected from



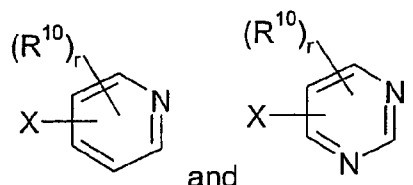
25 and/or derivatives thereof that comprise 1 to 4, preferably 1 to 3 and especially 1 or 2 substituents, selected from A, R¹³, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, SO₂NR¹⁵R¹⁶ and S(O)_uA and especially from A, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵ and CONR¹⁵R¹⁶.

30 According to the invention, X-Ar³ is preferably selected from the group consisting of

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10 and more preferably of



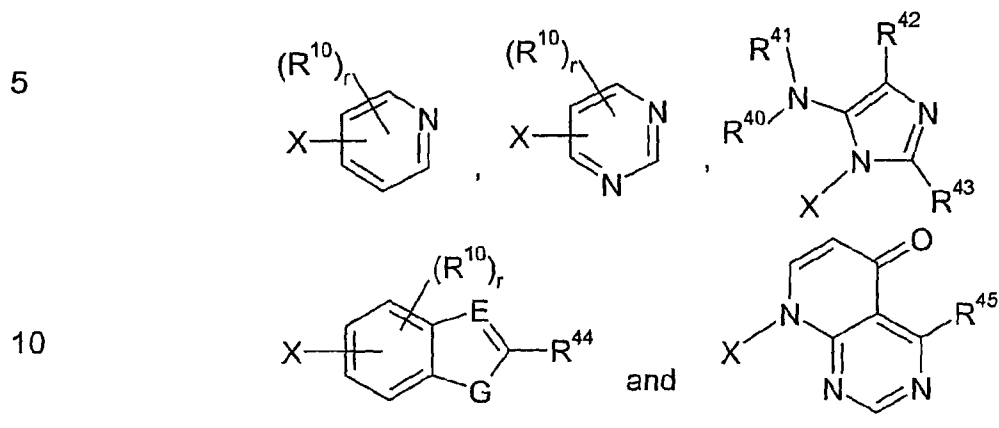
15 wherein X, R^{10} and r are as defined above/below; E is selected from N and CR^{30} , wherein R^{30} is as defined above/below and especially is H or A; G is selected from NR^{30} and $CR^{31}R^{32}$, wherein R^{30} , R^{31} and R^{32} are as defined above/below; and R^{40} , R^{41} , R^{42} , R^{43} , R^{44} and R^{45} are selected independently from one another from the meanings given for R^8 , R^9 and R^{10} . More preferably, X is a bond or O; R^{10} is H or preferably selected from A, Hal, $(CH_2)_nCONR^{11}R^{12}$ and especially from $CONR^{11}R^{12}$; r is 0, 1 or 2, and especially 1 or 2; R^{40} , R^{41} and R^{43} are selected independently from one another from H, A and R^{13} ; R^{10} and R^{42} are selected independently from one another from H, R^{13} , A, Hal and $(CH_2)_nCONR^{11}R^{12}$ and especially from H, A, $CONR^{11}R^{12}$, CONHA and CONHMe; R^{44} is preferably selected from $(CH_2)_nNR^{11}R^{12}$, $NR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$, $(CH_2)_nNR^{11}CONR^{11}R^{12}$ and $(CH_2)_nNR^{11}COOR^{13}$ and especially from $NR^{11}R^{12}$, $NR^{11}CONR^{11}R^{12}$, $NR^{11}COOR^{13}$ and $NR^{11}COOA$; R^{45} is preferably selected from A, Hal, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$, $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}COOR^{13}$ and $NR^{11}R^{12}$ and especially from $NR^{11}R^{12}$, NHA and NH_2 .

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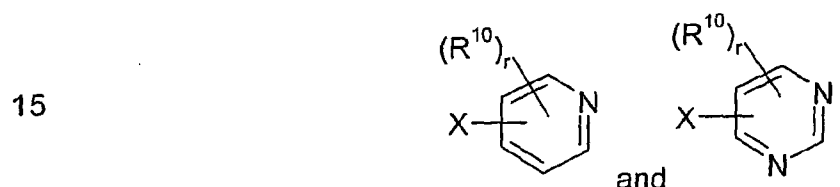
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According to the invention, $X-Ar^3$ is preferably selected from the group consisting of



and more preferably of



wherein X , R^{10} and r are as defined above/below; E is selected from N and CR^{30} , wherein R^{30} is as defined above/below and especially is H or A ; G is selected from NR^{30} and $CR^{31}R^{32}$, wherein R^{30} , R^{31} and R^{32} are as defined above/below; and R^{40} , R^{41} , R^{42} , R^{43} , R^{44} and R^{45} are selected independently from one another from the meanings given for R^8 , R^9 and R^{10} . More preferably, X is a bond or O ; R^{10} is H or preferably selected from A , Hal , $(CH_2)_nCONR^{11}R^{12}$ and especially from $CONR^{11}R^{12}$; r is 0 , 1 or 2 , and especially 1 or 2 ; R^{40} , R^{41} and R^{43} are selected independently from one another from H , A and R^{13} ; R^{10} and R^{42} are selected independently from one another from H , R^{13} , A , Hal and $(CH_2)_nCONR^{11}R^{12}$ and especially from H , A , $CONR^{11}R^{12}$, $CONHA$ and $CONHMe$; R^{44} is preferably selected from $(CH_2)_nNR^{11}R^{12}$, $NR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$, $(CH_2)_nNR^{11}CONR^{11}R^{12}$ and $(CH_2)_nNR^{11}COOR^{13}$ and especially from $NR^{11}R^{12}$, $NR^{11}CONR^{11}R^{12}$, $NR^{11}COOR^{13}$ and $NR^{11}COOA$; R^{45} is preferably selected from A , Hal , $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$, $(CH_2)_nNR^{11}CONR^{11}R^{12}$,

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$(\text{CH}_2)_n\text{NR}^{11}\text{COOR}^{13}$ and $\text{NR}^{11}\text{R}^{12}$ and especially from $\text{NR}^{11}\text{R}^{12}$, NHA and NH_2 .

5 Preferably, $(\text{CR}^5\text{R}^6)_n$ and/or $(\text{CR}^5\text{R}^6)_k$ is linear or branched alkylen, preferably linear or branched $\text{C}_1\text{-C}_4$ alkylen, which is optionally substituted as described above/below and preferably is unsubstituted.

10 Another preferred aspect of the instant invention relates to compounds of formula I, wherein n is 0 in the residues R^8 , R^9 and/or R^{10} and especially in R^{10} .

Another preferred aspect of the instant invention relates to compounds of formula I, wherein in the residues R^8 , n is 1, 2 or 3 and especially is 2.

15 Another preferred aspect of the instant invention relates to compounds of formula I that comprise one or two, preferably one residue R^7 which is preferably bonded to Ar^1 in the ortho, meta or para position relative to the urea moiety Ar^1 is bonded to. More preferably, the residue R^7 is bonded to Ar^1 in the ortho or para position, and especially in the ortho position, relative
20 to the urea moiety that Ar^1 is bonded to.

Another preferred aspect of the instant invention relates to compounds of formula I that comprise one residue R^7 that is bonded to Ar^1 in the para position

25

Another preferred aspect of the instant invention relates to compounds of formula I, wherein X represents a bridging group, selected from $(\text{CR}^{11}\text{R}^{12})_h$ or $(\text{CHR}^{11})_h\text{-Q-(CHR}^{12})_i$.

30 The invention relates in particular to compounds of the formula I in which at least one of said radicals has one of the preferred meanings given above.

Some more preferred groups of compounds may be expressed by the following sub-formulae I.1) to I.20), which correspond to the formula I and in which radicals not denoted in greater detail are as defined in the formula I, but in which

5

I.1) Ar^1 is phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, chinolinyl, isochinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl;

10

15

I.2) Ar^1 is phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, chinolinyl, isochinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl, and

20

p is 1, 2 or 3;

25

I.3) Ar^1 is phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, chinolinyl, isochinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl,

30

p is 1, 2 or 3, and

R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms,

- Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nNR¹¹(CH₂)_kNR¹¹R¹², (CH₂)_nO(CH₂)_kOR¹¹, (CH₂)_nNR¹¹(CH₂)_kOR¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nS(O)_uNR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and (CH₂)_nS(O)_uR¹³;
- 5
- 1.4) Ar¹ is phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, chinolinyl, isochinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl,
- 10
- p is 1, 2 or 3,
- 15
- R⁸ is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nNR¹¹(CH₂)_kNR¹¹R¹², (CH₂)_nO(CH₂)_kOR¹¹, (CH₂)_nNR¹¹(CH₂)_kOR¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nS(O)_uNR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and (CH₂)_nS(O)_uR¹³;
- 20
- 25
- 1.5) Ar¹ is phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, chinolinyl, isochinolinyl, thiophenyl,
- 30

benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl,

- 5 p is 1, 2 or 3,
- R⁸ is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹²,
 10 (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nNR¹¹(CH₂)_kNR¹¹R¹²,
 (CH₂)_nO(CH₂)_kOR¹¹, (CH₂)_nNR¹¹(CH₂)_kOR¹²,
 (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹²,
 (CH₂)_nS(O)_uNR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and
 (CH₂)_nS(O)_uR¹³, wherein
 15 n is 0 or 1;
- I.6) Ar¹ is phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl,
 20 isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, chinolinyl, isochinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl,
- 25 p is 1, 2 or 3,
- R⁸ is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹²,
 30 (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nNR¹¹(CH₂)_kNR¹¹R¹²,
 (CH₂)_nO(CH₂)_kOR¹¹, (CH₂)_nNR¹¹(CH₂)_kOR¹²,

$(\text{CH}_2)_n\text{COR}^{13}$, $(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$,
 $(\text{CH}_2)_n\text{S(O)}_u\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$ and
 $(\text{CH}_2)_n\text{S(O)}_u\text{R}^{13}$, wherein

5 n is 0 or 1, and

u is 0;

1.7) Ar¹ is phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, chinolinyl, isochinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl,

15 p is 1, 2 or 3,

R⁸ is selected from the group consisting of alkyl comprising 1
 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms,
 Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4
 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹²,
 (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nNR¹¹(CH₂)_kNR¹¹R¹²,
 (CH₂)_nO(CH₂)_kOR¹¹, (CH₂)_nNR¹¹(CH₂)_kOR¹²,
 (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹²,
 (CH₂)_nS(O)_uNR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and
 (CH₂)_nS(O)_uR¹³, wherein

n is 0 or 1,

30 u is 0, and

q is 0 or 1, and

- 5 X is a bond or is selected from the group consisting of O, S, NR¹¹, CHOR¹¹, CH₂, CH₂CH₂, OCH₂, CH₂O, OCH₂CH₂, CH₂CH₂O, preferably O, S and CH₂ and especially O and S;
- 10 I.8) Ar¹ is phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, chinolinyl, isochinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl,
- 15 p is 1, 2 or 3,
- 20 R⁸ is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nNR¹¹(CH₂)_kNR¹¹R¹², (CH₂)_nO(CH₂)_kOR¹¹, (CH₂)_nNR¹¹(CH₂)_kOR¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nS(O)_uNR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and (CH₂)_nS(O)_uR¹³, wherein
- 25 n is 0 or 1,
- u is 0, and
- 30 q is 0 or 1, and

- 5 X is a bond or is selected from the group consisting of O, S, NR¹¹, CHOR¹¹, CH₂, CH₂CH₂, OCH₂, CH₂O, OCH₂CH₂, CH₂CH₂O, preferably O, S and CH₂ and especially O and S,
- Ar² is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl;
- 10 I.9) Ar¹ is phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, chinolinyl, isochinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl,
- 15 p is 1, 2 or 3,
- R⁸ is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nNR¹¹(CH₂)_kNR¹¹R¹², (CH₂)_nO(CH₂)_kOR¹¹, (CH₂)_nNR¹¹(CH₂)_kOR¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nS(O)_uNR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and (CH₂)_nS(O)_uR¹³, wherein
- 20 n is 0 or 1,
- u is 0, and
- 30 q is 0 or 1, and

- 5 X is a bond or is selected from the group consisting of O, S, NR¹¹, CHOR¹¹, CH₂, CH₂CH₂, OCH₂, CH₂O, OCH₂CH₂, CH₂CH₂O, preferably O, S and CH₂ and especially O and S,
- 10 Ar² is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl; and
- 15 R¹⁰ is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nNR¹¹(CH₂)_kNR¹¹R¹², (CH₂)_nO(CH₂)_kOR¹¹, (CH₂)_nNR¹¹(CH₂)_kOR¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nS(O)_uNR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and (CH₂)_nS(O)_uR¹³, preferably alkyl comprising 1 to 4 carbon atoms, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹² and especially (CH₂)_nCONR¹¹R¹²;
- 20 1.10) Ar¹ is phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, chinolinyl, isochinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl,
- 30 p is 1, 2 or 3,

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- R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$,
 5 $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nS(O)_uNR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, wherein
- n is 0 or 1,
- 10 u is 0, and
- q is 0 or 1, and
- 15 X is a bond or is selected from the group consisting of O, S, NR^{11} , $CHOR^{11}$, CH_2 , CH_2CH_2 , OCH_2 , CH_2O , OCH_2CH_2 , CH_2CH_2O , preferably O, S and CH_2 and especially O and S,
- 20 Ar^2 is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl; and
- R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$,
 25 $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$,
 30 $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nS(O)_uNR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$,

$(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{COR}^{13}$, $(\text{CH}_2)_n\text{COOR}^{13}$,
 $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ and especially $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$,
 wherein

5 n is 0, 1 or 2, preferably 0 or 1;

1.11) Ar¹ is phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl,
 thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl,
 isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl,
 10 pyridinyl, chinolinyl, isochinolinyl, thiophenyl,
 benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even
 more preferably phenyl or pyridinyl,

15 p is 1, 2 or 3,

 R⁸ is selected from the group consisting of alkyl comprising 1
 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms,
 Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4
 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹²,
 20 (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nNR¹¹(CH₂)_kNR¹¹R¹²,
 (CH₂)_nO(CH₂)_kOR¹¹, (CH₂)_nNR¹¹(CH₂)_kOR¹²,
 (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹²,
 (CH₂)_nS(O)_uNR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and
 (CH₂)_nS(O)_uR¹³, wherein

25 n is 0 or 1,

 u is 0, and

30 q is 0 or 1, and

- 5 X is a bond or is selected from the group consisting of O, S, NR¹¹, CHOR¹¹, CH₂, CH₂CH₂, OCH₂, CH₂O, OCH₂CH₂, CH₂CH₂O, preferably O, S and CH₂ and especially O and S,
- Ar² is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl; and
- 10 R¹⁰ is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nNR¹¹(CH₂)_kNR¹¹R¹², (CH₂)_nO(CH₂)_kOR¹¹, 15 (CH₂)_nNR¹¹(CH₂)_kOR¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nS(O)_uNR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and (CH₂)_nS(O)_uR¹³, preferably alkyl comprising 1 to 4 carbon atoms, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, 20 (CH₂)_nCONR¹¹R¹² and especially (CH₂)_nCONR¹¹R¹², wherein
- n is 0, 1 or 2, preferably 0 or 1 and
- 25 r is 0, 1 or 2, preferably 0 or 1;
- l.12) p is 1, 2 or 3,
- 30 R⁸ is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹²,

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- $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$,
 $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$,
 $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$,
 $(CH_2)_nS(O)_uNR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and
 $(CH_2)_nS(O)_uR^{13}$, wherein
- n is 0 or 1,
- u is 0, and
- q is 0 or 1, and
- X is a bond or is selected from the group consisting of O, S,
 NR^{11} , $CHOR^{11}$, CH_2 , CH_2CH_2 , OCH_2 , CH_2O , OCH_2CH_2 ,
 CH_2CH_2O , preferably O, S and CH_2 and especially O and S,
- Ar^2 is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl; and
- R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$,
 $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$,
 $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$,
 $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$,
 $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nS(O)_uNR^{11}R^{12}$,
 $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$,
 $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$,

$(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ and especially $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$,
wherein

- 5 n is 0, 1 or 2, preferably 0 or 1 and
- r is 0, 1 or 2, preferably 0 or 1;
- l.13) R^8 is selected from the group consisting of alkyl comprising 1
 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms,
10 Hal, CH_2Hal , $\text{CH}(\text{Hal})_2$, perhaloalkyl comprising 1 to 4
 carbon atoms, NO_2 , $(\text{CH}_2)_n\text{CN}$, $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$,
 $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{NR}^{11}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$,
 $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{OR}^{11}$, $(\text{CH}_2)_n\text{NR}^{11}(\text{CH}_2)_k\text{OR}^{12}$,
 $(\text{CH}_2)_n\text{COR}^{13}$, $(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$,
15 $(\text{CH}_2)_n\text{S}(\text{O})_u\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$ and
 $(\text{CH}_2)_n\text{S}(\text{O})_u\text{R}^{13}$, wherein
- n is 0 or 1,
- 20 u is 0, and
- q is 0 or 1, and
- X is a bond or is selected from the group consisting of O, S,
25 NR^{11} , CHOR^{11} , CH_2 , CH_2CH_2 , OCH_2 , CH_2O , OCH_2CH_2 ,
 $\text{CH}_2\text{CH}_2\text{O}$, preferably O, S and CH_2 and especially O and
 S,
- Ar^2 is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or
30 pyridinyl; and

- R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nS(O)_uNR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$, wherein
- n is 0, 1 or 2, preferably 0 or 1 and
- r is 0, 1 or 2, preferably 0 or 1;
- I.14) R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nS(O)_uNR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, wherein
- u is 0, and
- q is 0 or 1, and

- $(\text{CH}_2)_n\text{COR}^{13}$, $(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$,
 $(\text{CH}_2)_n\text{S(O)}_u\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$ and
 $(\text{CH}_2)_n\text{S(O)}_u\text{R}^{13}$, wherein
 q is 0 or 1, and
 5 X is a bond or is selected from the group consisting of O, S,
 NR^{11} , CHOR^{11} , CH_2 , CH_2CH_2 , OCH_2 , CH_2O , OCH_2CH_2 ,
 $\text{CH}_2\text{CH}_2\text{O}$, preferably O, S and CH_2 and especially O and
 S,
 10 Ar^2 is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or
 pyridinyl; and
 15 R^{10} is selected from the group consisting of H, alkyl
 comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4
 carbon atoms, Hal, CH_2Hal , $\text{CH}(\text{Hal})_2$, perhaloalkyl
 comprising 1 to 4 carbon atoms, NO_2 , $(\text{CH}_2)_n\text{CN}$,
 $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$,
 $(\text{CH}_2)_n\text{NR}^{11}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{OR}^{11}$,
 20 $(\text{CH}_2)_n\text{NR}^{11}(\text{CH}_2)_k\text{OR}^{12}$, $(\text{CH}_2)_n\text{COR}^{13}$, $(\text{CH}_2)_n\text{COOR}^{13}$,
 $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{S(O)}_u\text{NR}^{11}\text{R}^{12}$,
 $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$ and $(\text{CH}_2)_n\text{S(O)}_u\text{R}^{13}$, preferably alkyl
 comprising 1 to 4 carbon atoms, $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$,
 $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{COR}^{13}$, $(\text{CH}_2)_n\text{COOR}^{13}$,
 25 $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ and especially $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$,
 wherein
 n is 0, 1 or 2, preferably 0 or 1 and
 30 r is 0, 1 or 2, preferably 0 or 1;
 I.16) q is 0 or 1, and

- 5 X is a bond or is selected from the group consisting of O, S, NR¹¹, CHOR¹¹, CH₂, CH₂CH₂, OCH₂, CH₂O, OCH₂CH₂, CH₂CH₂O, preferably O, S and CH₂ and especially O and S,
- Ar² is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl; and
- 10 R¹⁰ is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nNR¹¹(CH₂)_kNR¹¹R¹², (CH₂)_nO(CH₂)_kOR¹¹, (CH₂)_nNR¹¹(CH₂)_kOR¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nS(O)_uNR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and (CH₂)_nS(O)_uR¹³, preferably alkyl comprising 1 to 4 carbon atoms, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹² and especially (CH₂)_nCONR¹¹R¹², wherein
- 20 n is 0, 1 or 2, preferably 0 or 1 and
- 25 r is 0, 1 or 2, preferably 0 or 1;
- l.17) X is a bond or is selected from the group consisting of O, S, NR¹¹, CHOR¹¹, CH₂, CH₂CH₂, OCH₂, CH₂O, OCH₂CH₂, CH₂CH₂O, preferably O, S and CH₂ and especially O and S,
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- Ar² is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl; and
- 5 R¹⁰ is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nNR¹¹(CH₂)_kNR¹¹R¹², (CH₂)_nO(CH₂)_kOR¹¹, 10 (CH₂)_nNR¹¹(CH₂)_kOR¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nS(O)_uNR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and (CH₂)_nS(O)_uR¹³, preferably alkyl comprising 1 to 4 carbon atoms, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, 15 (CH₂)_nCONR¹¹R¹² and especially (CH₂)_nCONR¹¹R¹², wherein
- n is 0, 1 or 2, preferably 0 or 1 and
- 20 r is 0, 1 or 2, preferably 0 or 1;
- 1.18) Ar² is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl; and
- 25 R¹⁰ is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nNR¹¹(CH₂)_kNR¹¹R¹², 30 (CH₂)_nO(CH₂)_kOR¹¹, (CH₂)_nNR¹¹(CH₂)_kOR¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nS(O)_uNR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and

$(\text{CH}_2)_n\text{S}(\text{O})_u\text{R}^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{COR}^{13}$, $(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ and especially $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$,

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n is 0, 1 or 2, preferably 0 or 1 and

r is 0, 1 or 2, preferably 0 or 1;

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I.19) R^{10}

is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $\text{CH}(\text{Hal})_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(\text{CH}_2)_n\text{CN}$, $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{NR}^{11}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{OR}^{11}$, $(\text{CH}_2)_n\text{NR}^{11}(\text{CH}_2)_k\text{OR}^{12}$, $(\text{CH}_2)_n\text{COR}^{13}$, $(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{S}(\text{O})_u\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$ and $(\text{CH}_2)_n\text{S}(\text{O})_u\text{R}^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{COR}^{13}$, $(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ and especially $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$,

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n is 0, 1 or 2, preferably 0 or 1 and

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r is 0, 1 or 2, preferably 0 or 1;

I.20) R^{10}

is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $\text{CH}(\text{Hal})_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(\text{CH}_2)_n\text{CN}$, $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{NR}^{11}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{OR}^{11}$,

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$(\text{CH}_2)_n\text{NR}^{11}(\text{CH}_2)_k\text{OR}^{12}$, $(\text{CH}_2)_n\text{COR}^{13}$, $(\text{CH}_2)_n\text{COOR}^{13}$,
 $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{S(O)}_u\text{NR}^{11}\text{R}^{12}$,
 $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$ and $(\text{CH}_2)_n\text{S(O)}_u\text{R}^{13}$, preferably alkyl
 comprising 1 to 4 carbon atoms, $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$,
 5 $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{COR}^{13}$, $(\text{CH}_2)_n\text{COOR}^{13}$,
 $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ and especially $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$, and

r is 0, 1 or 2, preferably 0 or 1.

10 One preferred embodiment of the instant invention relates to compounds of
 formula I and preferably one or more of sub formulae I.1) to I.20), wherein p
 is 1, 2 or 3 and R^8 is independently selected from the group consisting of
 methyl, ethyl, isopropyl, tert.-butyl, F, Cl, Br, CF_3 , $\text{C}(\text{CF}_3)_3$, SO_2CF_3 , methoxy,
 ethoxy, tert.-butoxy, perfluoro tert.-butoxy ($\text{OC}(\text{CF}_3)_3$), methyl sulfanyl
 15 (SCH_3), ethyl sulfanyl (SCH_2CH_3), acetyl (COCH_3), propionyl (COCH_2CH_3),
 butyryl ($\text{COCH}_2\text{CH}_2\text{CH}_3$). If p is 2 or 3, all substituents can be the same or
 different.

20 Another preferred embodiment of the instant invention relates to compounds
 of formula I and preferably one or more of sub formulae I.1) to I.20), wherein
 X is selected from the group consisting of S, N-R^{21} , CH_2 , CH_2CH_2 , OCH_2 and
 CH_2O .

25 Another preferred embodiment of the instant invention relates to compounds
 of formula I and preferably one or more of sub formulae I.1) to I.20), wherein
 X is bond, i. e. Ar^3 is directly bonded to Ar^2 .

30 Another preferred embodiment of the instant invention relates to compounds
 of formula I and preferably one or more of sub formulae I.1) to I.20), wherein
 X is selected from the group consisting of S, CH_2 .

Another even more preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein X is O.

5 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Y is selected from the group consisting of $C(R^{22})-NO_2$, $C(R^{22})-CN$ and $C(CN)_2$.

10 Another more preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Y is selected from the group consisting of O, S and NR^{21} .

Another even more preferred embodiment of the instant invention relates to
15 compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Y is selected from the group consisting of O and S.

Another even more preferred embodiment of the instant invention relates to
20 compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Y is O.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Ar^3 is pyridinyl.

25 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein r is either 0 or 1. If r is 1, R^{10} is preferably $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$, wherein n is 0. In this embodiment, R^{11} is preferably
30 selected from the group consisting of H and A and more preferred from H and alkyl, and R^{12} is preferably selected from the group consisting of H and A and more preferred from H and alkyl. Especially preferred as residue R^{10} are

carbamoyl, more preferred alkyl carbamoyl or dialkyl carbamoyl, even more preferred methyl carbamoyl or dimethyl carbamoyl, ethyl carbamoyl or diethyl carbamoyl and especially preferred methyl carbamoyl (-CONHCH₃). This embodiment is especially preferred when Ar² is pyridinyl. When Ar² is pyridinyl, R¹⁰ is preferably bonded in a vicinal position to the nitrogen atom of the pyridinyl residue, i.e. in 2- and/or 6-position of the pyridinyl residue.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Ar¹ is phenyl.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Ar¹ is a 6-membered aryl or heteroaryl moiety which is substituted by one or more, preferably one residue CF₃, preferably in the 3- and/or 5-position relative to the urea moiety Ar¹ is bonded to.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Ar² is phenyl.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein q is 0, i.e. Ar² or the 6-membered aromatic, E, G, M, Q and U containing group bound to the urea moiety is unsubstituted.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein the definition of residues R⁸, R⁹ and/or R¹⁰ does not comprise H. This embodiment preferably is not applicable to sub formulae Ia to Iz and especially not applicable to the definition of R¹⁰ in sub formulae Ia to Iz, since the definition in said sub formulae explicitly incorporates H.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein q is 1, i.e. Ar² or the 6-membered aromatic, E, G, M, Q and U containing group bound to the urea moiety is substituted by one substituent, preferably a substituent as defined above and more preferably a substituent selected from alkyl and hal, and especially selected from CH₃, CH₂CH₃ and hal.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of formulae I.1) to I.20), wherein (R⁸)_p-Ar¹ is selected from the group consisting of 5-trifluoromethyl-phenyl-, 3-trifluoromethyl-phenyl, 4-methyl-5-chloro-phenyl, 4-chloro-5-methyl-phenyl, 4-chloro-5-methyl-phenyl, 4-chloro-5-trifluoro methyl-phenyl, 3-acetyl-phenyl, 4-acetyl-phenyl, 2-bromo-phenyl, 3-bromo-phenyl, 4-bromo-phenyl, 4-bromo-2-chloro-phenyl, 4-bromo-3-methyl-phenyl, 4-bromo-3-trifluoromethyl-phenyl, 2-chloro-phenyl, 2-chloro-4-trifluoromethyl-phenyl, 2-chloro-5-trifluoromethyl-phenyl, 3-chloro-phenyl, 3-chloro-4-methyl-phenyl, 3-chloro-4-methoxy-phenyl, 3-chloro-4-methoxy-phenyl, 4-chloro-phenyl, 4-chloro-2-trifluoromethyl-phenyl, 4-chloro-3-trifluoromethyl-phenyl, 4-chloro-2-methyl-phenyl, 5-chloro-2-methyl-phenyl, 5-chloro-2-methoxy-phenyl, 2,3-dichloro-phenyl, 2,4-dichloro-phenyl, 2,5-dichloro-phenyl, 3,4-dichloro-phenyl, 3,5-dichloro-phenyl, 2,4,5-trichloro-phenyl, 4-fluoro-phenyl, 4-fluoro-3-trifluoromethyl-phenyl, 4-ethoxy-phenyl, 2-methoxy-phenyl, 2-methoxy-5-trifluoromethyl-phenyl, 4-methoxy-phenyl, 2,5-dimethoxy-phenyl, 2-trifluoromethyl-phenyl, 3-trifluoromethyl-phenyl, 3-trifluoromethoxy-phenyl, 4-trifluoromethyl-phenyl, 4-trifluoromethoxy-phenyl, 3,5-bis-trifluoromethyl-phenyl, 3-methoxy-phenyl, 3-methylsulfanyl-phenyl, 4-methylsulfanyl-phenyl, o-tolyl (2-methyl-phenyl), m-tolyl (3-methyl-phenyl), p-tolyl (4-methyl-phenyl), 2,3-dimethyl-phenyl, 2,3-dimethyl-phenyl, 2,5-dimethyl-phenyl, 3,4-dimethyl-phenyl, 3,5-dimethyl-phenyl, 2-ethyl-phenyl, 3-ethyl-phenyl, 4-ethyl-phenyl, 4-isopropyl-phenyl, 4-tert-butyl-phenyl and 5-tert-butyl-isoxazol-3-yl.

Additionally preferred are compounds of formula I and preferably one or more of formulae I.1) to I.20), wherein (R⁸)_p-Ar¹ is selected from the the residues

given above and comprises one or two, preferably one substituent R^7 and especially one or two, preferably one substituent R^7 indicated herein as preferred, more preferred or especially preferred.

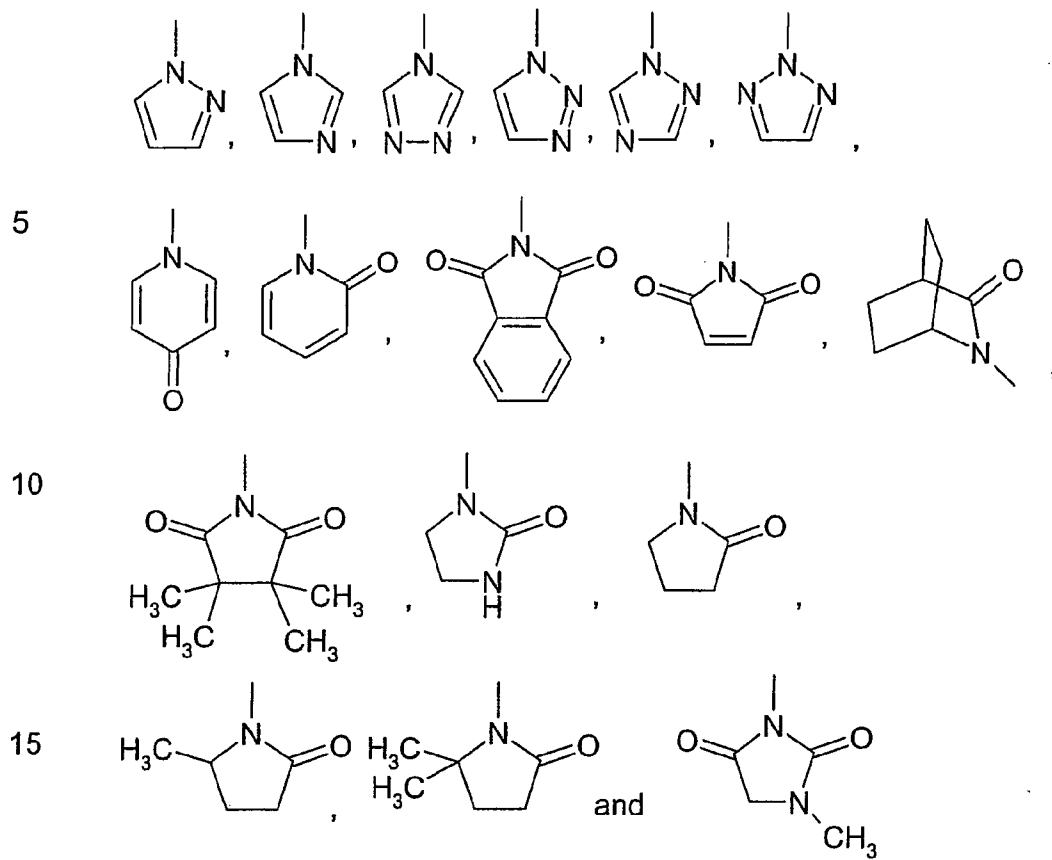
5 Another more preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of formulae I.1) to I.20), wherein $(R^8)_p-Ar^1$ is selected from the group consisting of 5-trifluoromethyl-phenyl, 3-trifluoromethyl-phenyl, 4-methyl-5-chloro-phenyl, 4-chloro-5-methyl-phenyl, 4-chloro-5-methyl-phenyl, and 4-chloro-5-trifluoro methyl-phenyl.

10 Additionally more preferred are compounds of formula I and preferably one or more of formulae I.1) to I.20), wherein $(R^8)_p-Ar^1$ is selected from the the residues given above and comprises one or two, preferably one substituent R^7 and especially one or two, preferably one substituent R^7 indicated herein as preferred, more preferred or especially preferred.

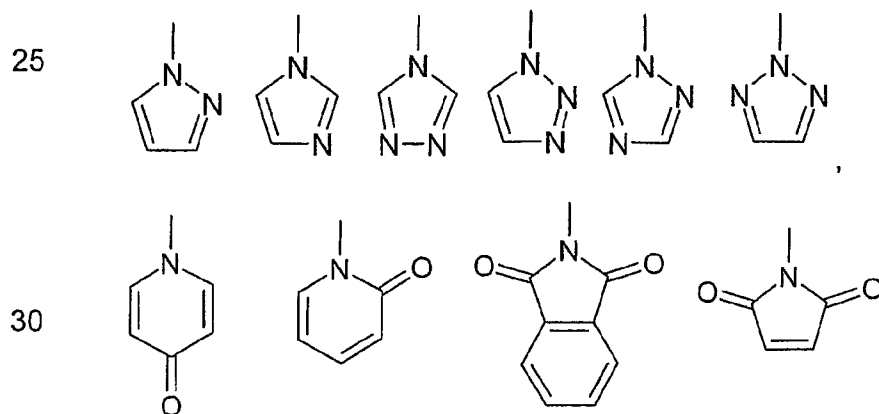
15 Another especially preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of formulae I.1) to I.20), wherein $(R^8)_p-Ar^1$ is selected from the group consisting of 5-trifluoromethyl-phenyl and 3-trifluoromethyl-pheny. Additionally especially preferred are
20 compounds of formula I and preferably one or more of formulae I.1) to I.20), wherein $(R^8)_p-Ar^1$ is selected from the the residues given above and comprises one or two, preferably one substituent R^7 and especially one or two, preferably one substituent R^7 indicated herein as preferred, more preferred or especially preferred.

25 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein $(R^8)_p-Ar^1$ is as defined above, but comprises one or more additional residues, preferably one additional residue. The additional residues are preferably
30 selected from the meanings given for R^7 and more preferably from

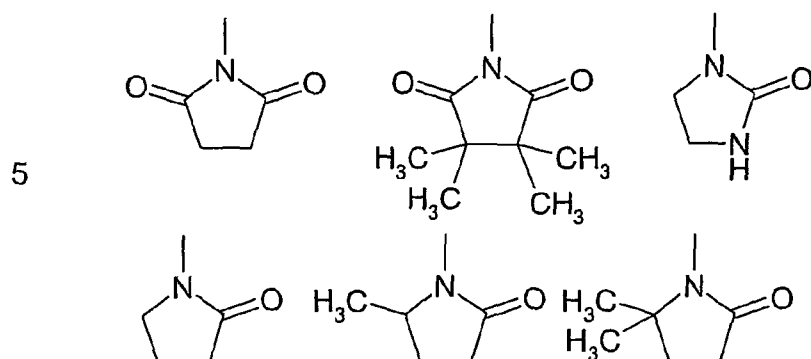
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Another preferred embodiment of the instant invention relates to compounds
 20 of formula I and preferably one or more of sub formulae I.1) to I.20), wherein
 $(R^6)_p-Ar^1$ is as defined above, but comprises one or more additional residues,
 preferably one additional residue. The additional residues are preferably
 selected from the meanings given for R^7 and more preferably from

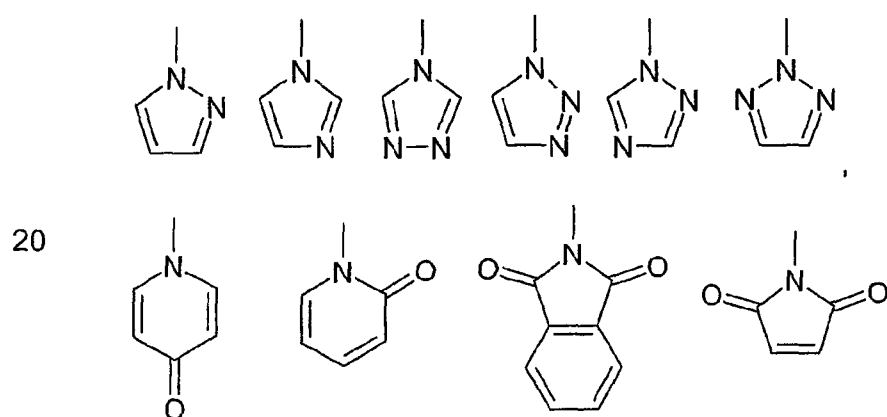


and/or

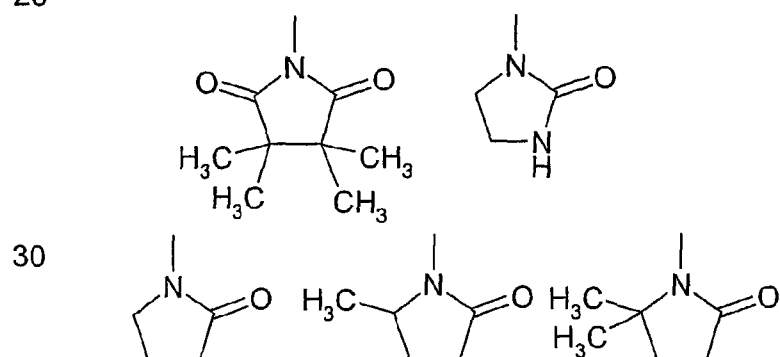


Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein $(R^8)_p-Ar^1$ is as defined above, but comprises one or more additional residues, preferably one additional residue. The additional residues are preferably selected from the meanings given for R^7 and more preferably from

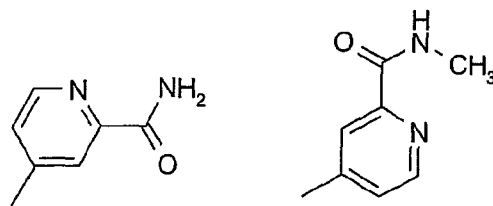
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and/or

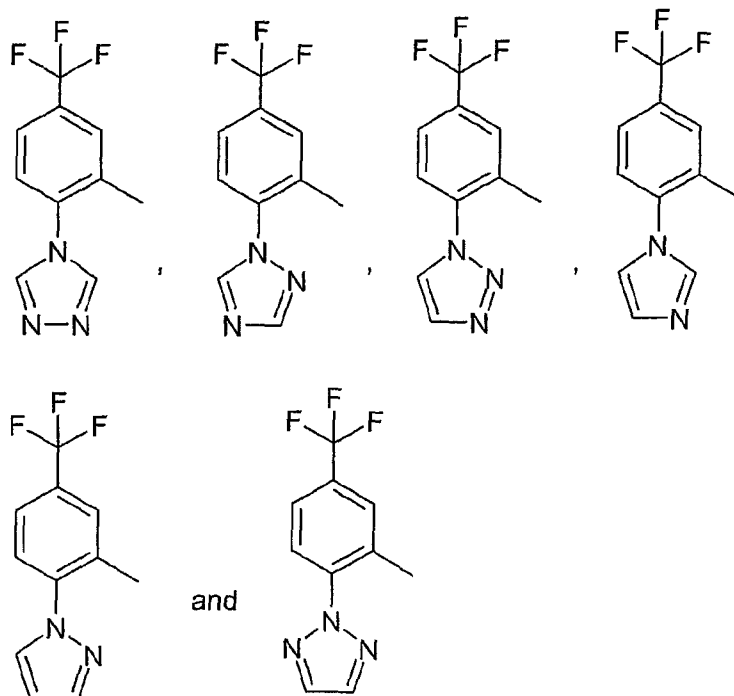


Another preferred embodiment of the instant invention relates to compounds of formula I and the subformulae related thereto and preferably one or more of formulae I.1) to I.20), wherein the residues $\text{Ar}^3-(\text{R}^{10})_r$ are selected from the group consisting of the following formulae:



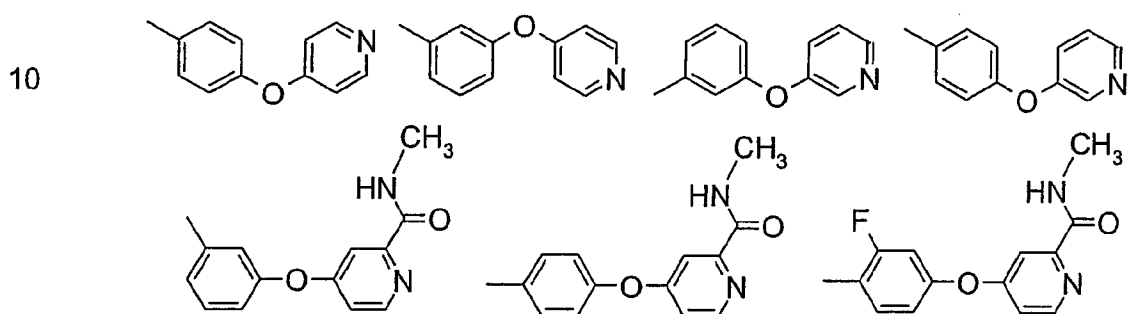
and/or residues of the structures given above that comprise one or two, preferably one additional substituent, independently selected from the meanings given for R^{10} .

Another preferred embodiment of the instant invention relates to compounds of formula I and the subformulae related thereto and preferably one or more of formulae I.1) to I.20), wherein the residues $(\text{R}^8)_p-\text{Ar}^1-(\text{R}^7)_g$ are selected from the following formulae:

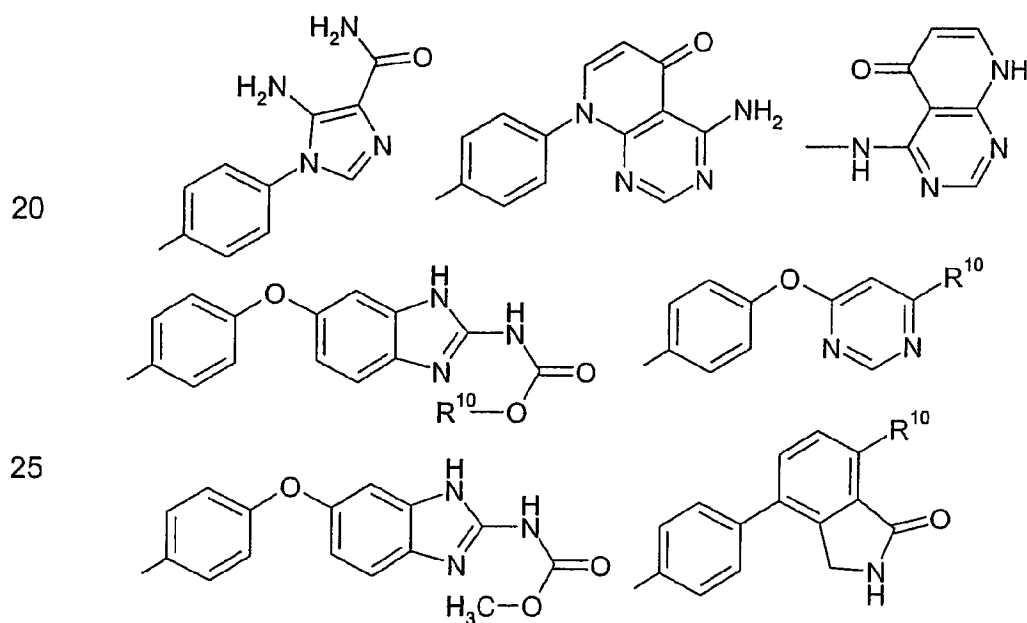


and/or residues of the structures given above that comprise one or two, preferably one additional substituent, independently selected from the meanings given for R⁷ and/or R⁸.

5 Another preferred embodiment of the instant invention relates to compounds of formula A-NH-CO-NH-B, wherein A is selected from the meanings of (R⁸)_p-Ar¹-(R⁷)_g as defined in the paragraph related thereto above, and B is selected from formulae

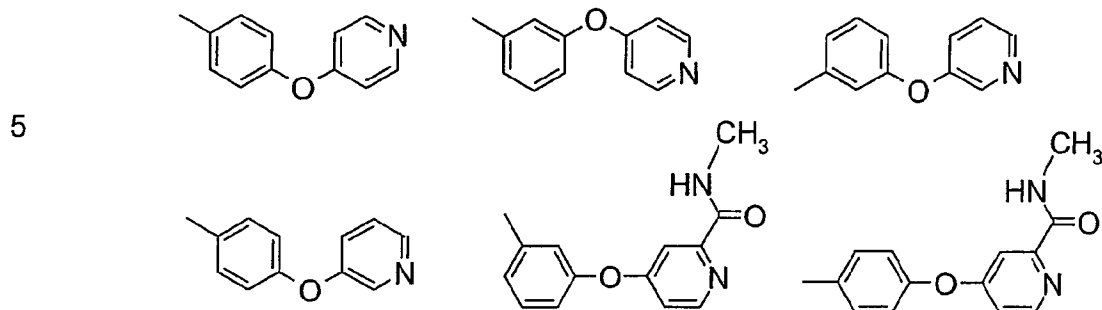


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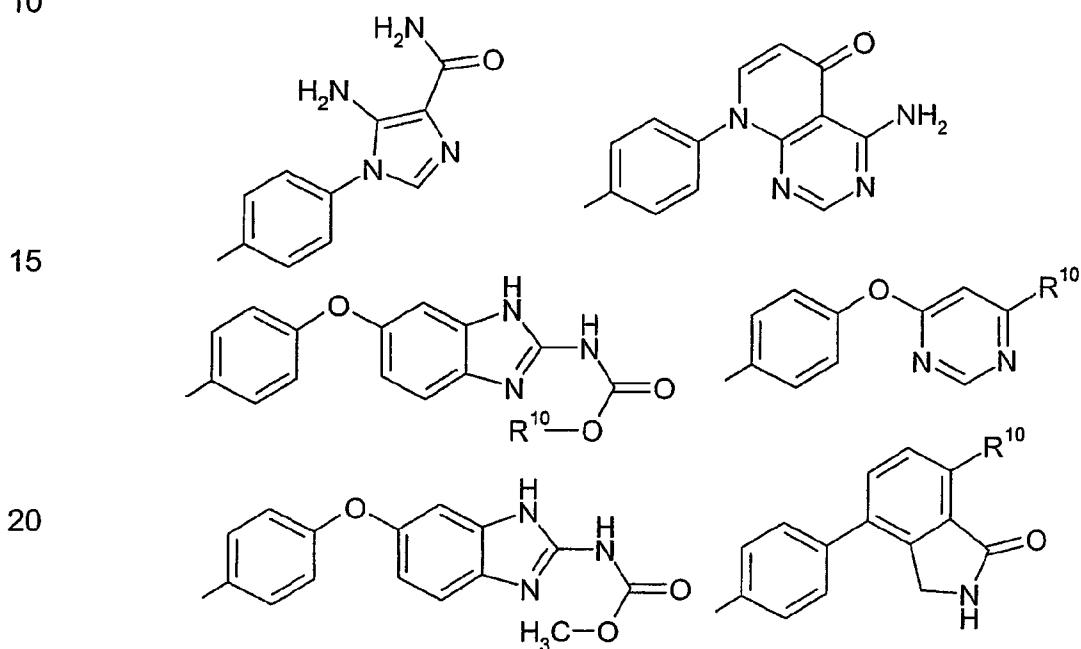


30 Another preferred embodiment of the instant invention relates to compounds of formula A-NH-CO-NH-B, wherein A is selected from the meanings of $(R^B)_p$.

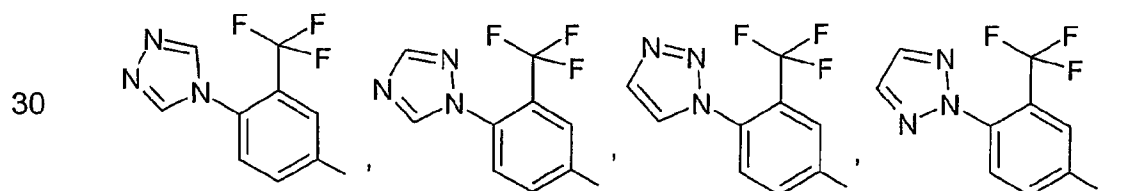
$\text{Ar}^1-(\text{R}^7)_g$ as defined in the paragraph above related thereto, and B is selected from formulae



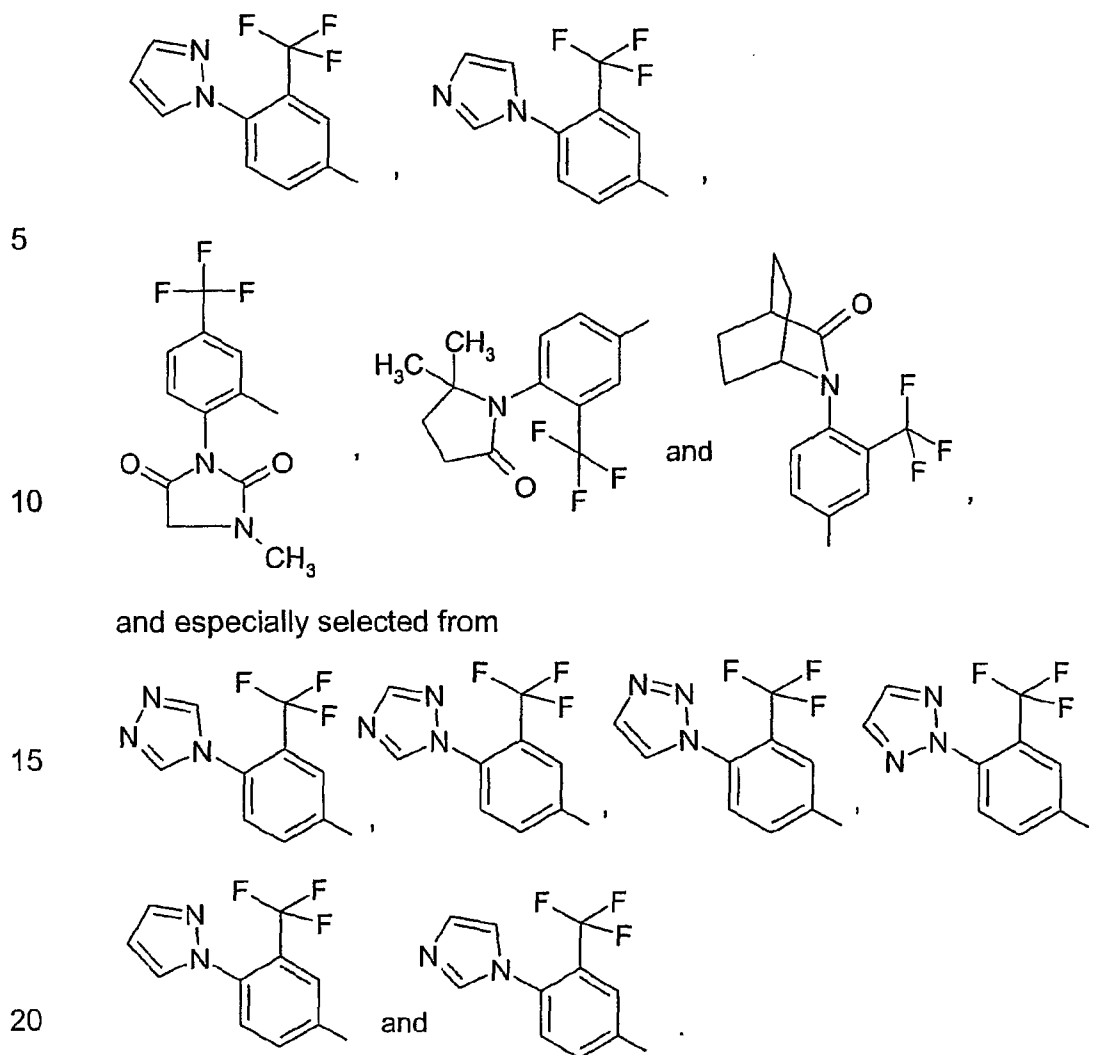
10 and/or



25 Another preferred embodiment of the instant invention relates to compounds of formula $\text{A}-\text{NH}-\text{CO}-\text{NH}-\text{B}$, wherein B is selected from one or more of the two paragraphs above relating thereto, and A is a group of the formula $(\text{R}^8)_p-\text{Ar}^1-(\text{R}^7)_g$ which is preferably selected from



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Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein X is bonded in the para- (p-) or metha- (m-)position to the 6-membered aromatic, E, G, M, Q and U containing group that is bonded directly to the urea moiety.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Ar³ is a pyridinyl residue and wherein said pyridinyl residue is bonded to X in

the 3- or 4-position, preferably the 4-position, relative to the nitrogen atom of the pyridinyl residue.

5 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Ar¹ comprises one or more substituents R⁸ and wherein one or two, preferably one substituent R⁸ is selected from the group consisting of SO₂CH₃, SO₂CF₃, OSO₂CH₃, OSO₂CF₃, SO₂NH₂, SO₂NHCH(CH₃)₂, SO₂N(CH₃)₂, SO₂N(CH₂CH₃)₂ and 4-Morpholine-4-sulfonyl.

10 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably the sub formulae related thereto, wherein Ar³ does not comprise two or more fused 6-membered ringsystems (i.e it does not comprise two or more 6-membered ringsystems fused (or anelated) to each other).

15 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably the sub formulae related thereto, wherein Ar³ does not comprise a 6-membered and a 5-membered ringsystems fused (or anelated) to each other.

20 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably the sub formulae related thereto, wherein Ar³ does not comprise fused or anelated ringsystems.

25 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Ar³ comprises one or more substituents R¹⁰ and wherein one or two, preferably one substituent R¹⁰ is selected from unsubstituted or substituted carbamoyl moieties. Substituted carbamoyl moieties are preferably selected from CONHR²³ or CONR²³R²⁴, preferably CONHR²³, wherein R²³ and R²⁴ are independently selected from the definitions given for R⁸, more preferably

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selected from alkyl, preferably methyl, ethyl, propyl and butyl, $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$ and $(\text{CH}_2)_n\text{OR}^{12}$, wherein R^{11} , R^{12} and n are as defined above. In this embodiment, n is preferably not 0 and more preferred 1 to 3 and especially 1 or 2. Preferred examples for R^{23} are selected from the group consisting of

5 methyl, ethyl, $\text{CH}_2\text{CH}_2\text{NH}_2$, $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{OH}$, $\text{CH}_2\text{CH}_2\text{OCH}_3$ and $\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein

10 Ar^3 comprises one or more substituents R^{10} and wherein one or two, preferably one substituent R^{10} is selected from substituted carbamoyl moieties. Substituted carbamoyl moieties are preferably selected from CONHR^{23} , wherein R^{23} is preferably unsubstituted C_1 - C_4 -alkyl and especially methyl.

15 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Ar^3 comprises one or more substituents R^{10} and wherein one or two, preferably one substituent R^{10} is selected from substituted carbamoyl

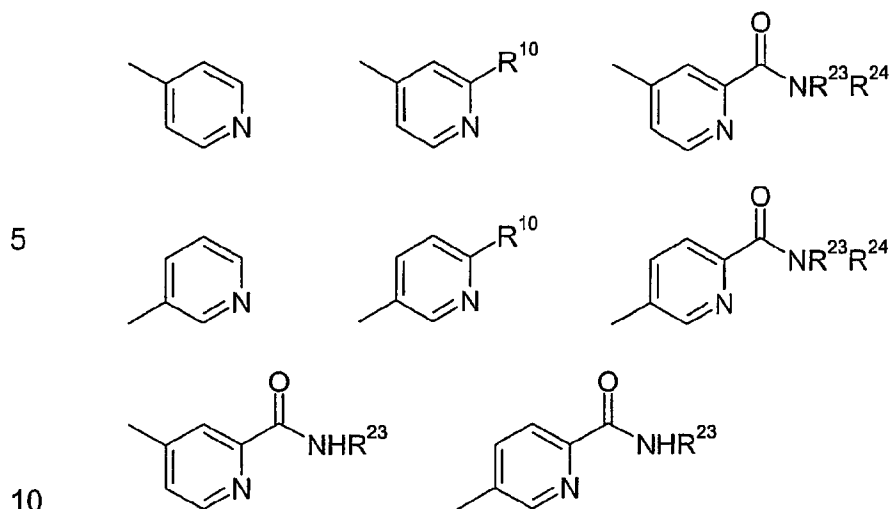
20 moieties. Substituted carbamoyl moieties are preferably selected from CONHR^{23} , wherein R^{23} is selected from $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$ and $(\text{CH}_2)_n\text{OR}^{12}$, wherein R^{11} , R^{12} and n are as defined above. In this embodiment, n is preferably not 0 and more preferred 1 to 3 and especially 1 or 2. Preferred examples for R^{23} are selected from the group consisting of $\text{CH}_2\text{CH}_2\text{NH}_2$,

25 $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{OH}$, $\text{CH}_2\text{CH}_2\text{OCH}_3$ and $\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein

30 $-\text{Ar}^3-(\text{R}^{10})$ is selected from the formulae

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wherein R^{10} , R^{23} and R^{24} are as defined above and below.

15 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably the subformulae related thereto, wherein R^7 is 3-Oxo-2-aza-bicyclo[2.2.2]oct-2-yl.

20 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably the subformulae related thereto, wherein R^7 is 3-Methyl-2,5-dioxo-imidazolidin-1-yl.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably the subformulae related thereto, wherein R^9 is F and q is as defined above/below and preferably is 1.

25 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably the sub formulae related thereto, wherein the residues R^7 do not comprise OH, NH and/or NH_2 groups.

30 Another preferred embodiment of the instant invention relates to compounds of formula I and the sub formulae related thereto, wherein the residues R^8 do not comprise OH, NH and/or NH_2 groups.

Another preferred embodiment of the instant invention relates to compounds of formula I and the sub formulae related thereto, wherein the residues R⁹ do not comprise OH, NH and/or NH₂ groups.

- 5 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably the sub formulae related thereto, wherein Ar¹ and /or Ar² (and the 6-membered aromatic, E, G, M, Q and U containing group or phenyl group bound to the urea moiety that are preferred meanings of Ar², respectively), do not comprise a OH group in the ortho position to the urea
10 moiety.

- Another preferred embodiment of the instant invention relates to compounds of formula I and preferably the sub formulae related thereto, wherein Ar¹ and /or Ar² (and the 6-membered aromatic, E, G, M, Q and U containing group or
15 phenyl group bound to the urea moiety that are preferred meanings of Ar², respectively), do not comprise a -NHSO₂- moiety in the ortho position to the urea moiety.

- Another preferred embodiment of the instant invention relates to compounds
20 of formula I and preferably the sub formulae related thereto, wherein Ar¹ and /or Ar² (and the 6-membered aromatic, E, G, M, Q and U containing group or phenyl group bound to the urea moiety that are preferred meanings of Ar², respectively), do not comprise a moiety in the ortho position to the urea moiety having an ionizable hydrogen and a pKa of 10 or less.

- 25 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably the sub formulae related thereto, wherein both the aromatic groups bound directly to the urea moiety do not comprise a substituent in the ortho position to the urea moiety, selected from OH,
30 substituents comprising a -NHSO₂- moiety, and substituents comprising moieties having an ionizable hydrogen and a pKa of 10 or less.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably the subformulae related thereto, wherein R⁷ is not a 2,5-dimethyl pyrrol-1-yl moiety that is bonded in the ortho position relative to the urea moiety Ar¹ is bonded to.

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Another preferred embodiment of the instant invention relates to compounds of formula I and preferably the subformulae related thereto, wherein R⁷, R⁸, R⁹ and/or Het⁹ is not 2,5-dimethyl pyrrol-1-yl.

10 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably the subformulae related thereto, wherein R⁷, R⁸, R⁹ and/or Het⁹ is not a substituted and/or unsubstituted pyrrol-1-yl moiety.

15 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably the subformulae related thereto, wherein R⁷ is not 2,5-dimethyl pyrrol-1-yl.

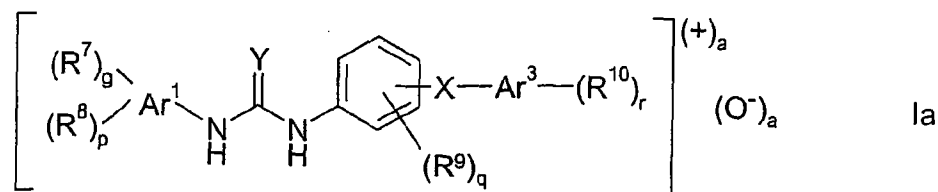
20 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably the subformulae related thereto, wherein R⁷ is not a substituted and/or unsubstituted pyrrol-1-yl moiety.

25 Another especially preferred embodiment of the instant invention relates to compounds of formula I, preferably the sub formulae related thereto and more preferably one or more of the sub formulae I.1) to I.20) and/or Ia to Iz, wherein one or more features of the above and below mentioned embodiments are combined in one compound.

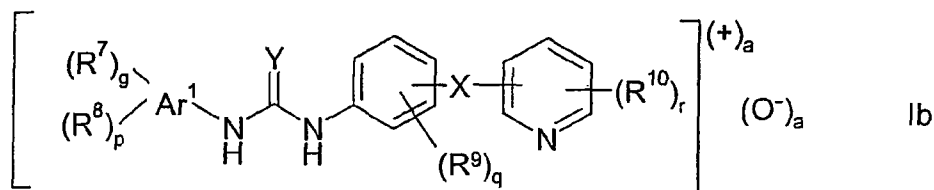
Subject of the present invention are therefore preferably compounds of formula I according to one or more of the formulae Ia, Ib and Ic,

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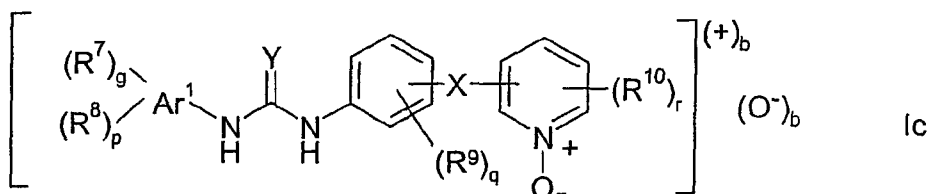
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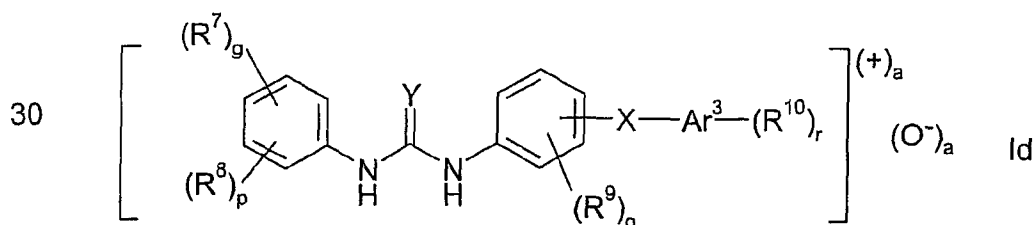
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wherein in formula Ic, b is 0, 1 or 2, preferably 0 or 1, and wherein in formulae Ia, Ib and Ic the meanings Ar¹, R⁷, R⁸, p, g, Y, X, R⁹, q, Ar³, R¹⁰, a and r are as defined above and below, and preferably as defined in sub formulae I.1) to I.20) and/or the embodiments related thereto, and the pharmaceutically acceptable derivatives, solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, and more preferred the salts and/or solvates thereof, and especially preferred the physiologically acceptable salts and/or solvates thereof.

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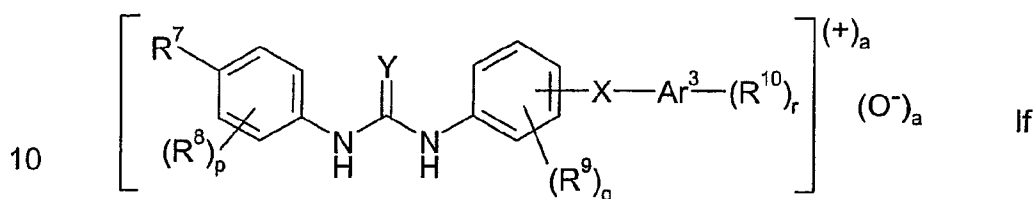
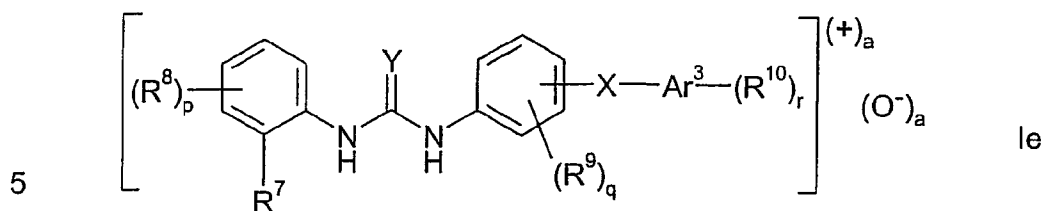
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Subject of the present invention are therefore especially preferred compounds of formula I according to one or both or more of the formulae Id, Ie and If,



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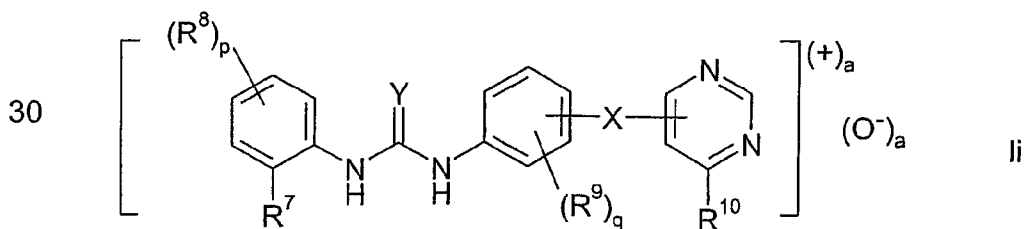
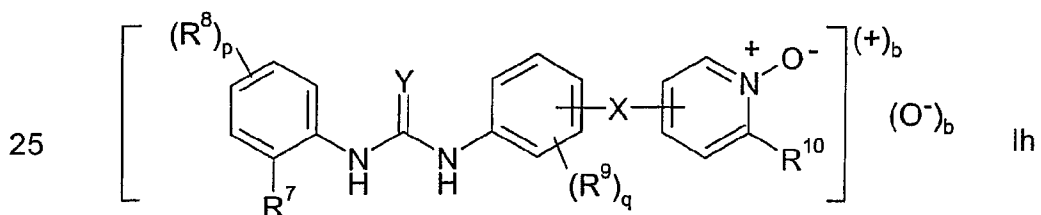
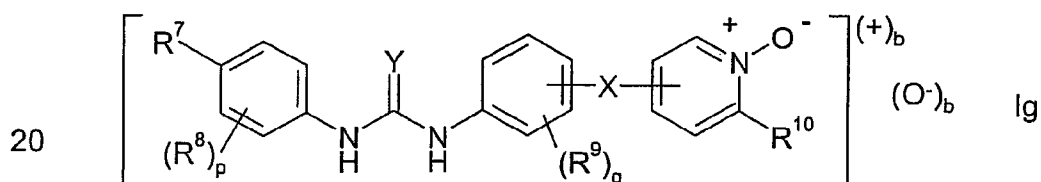
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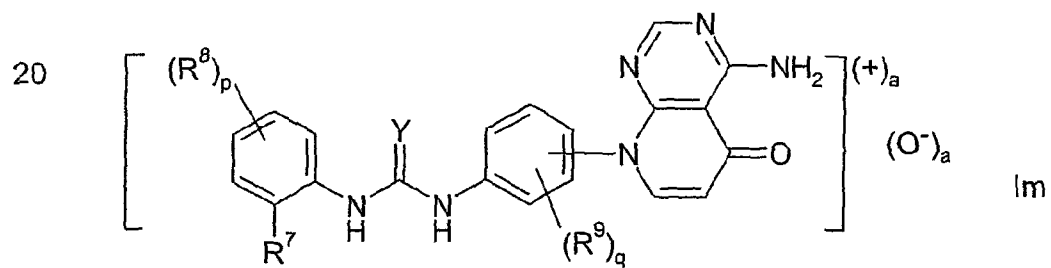
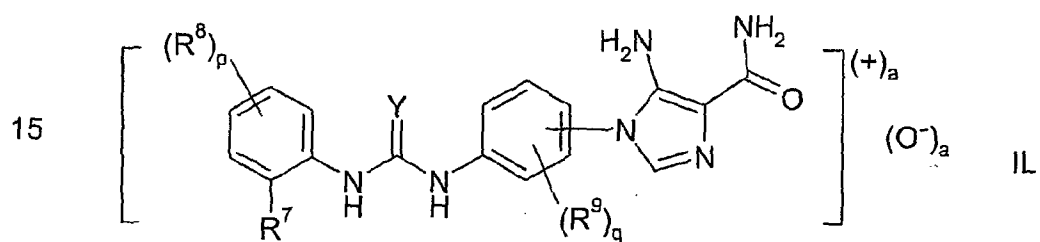
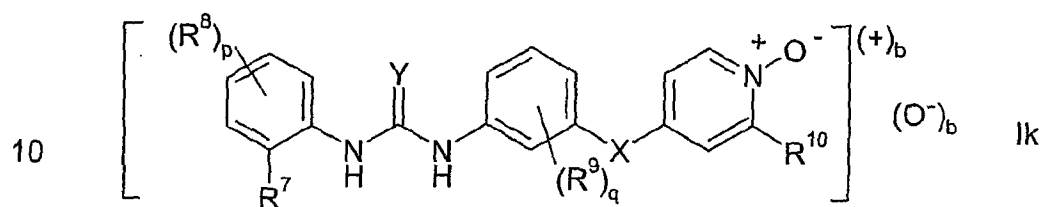
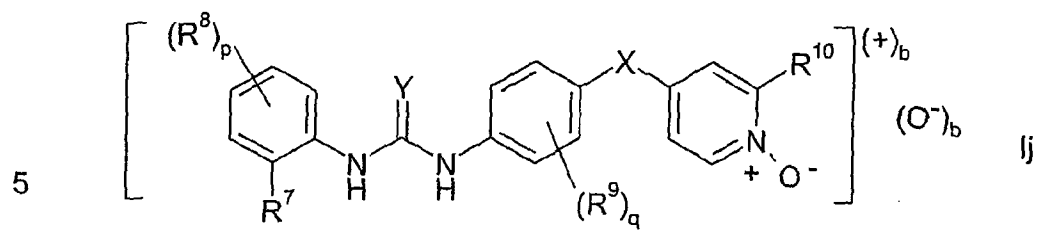
wherein R^7 , g , R^8 , p , Y , X , R^9 , q , Ar^3 , R^{10} and a are as defined above and below, preferably R^{10} is as defined in sub formulae I.1) to I.20) and/or the embodiments related thereto;

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and/or compounds of formula I according to one or more of the formulae lg to lz,



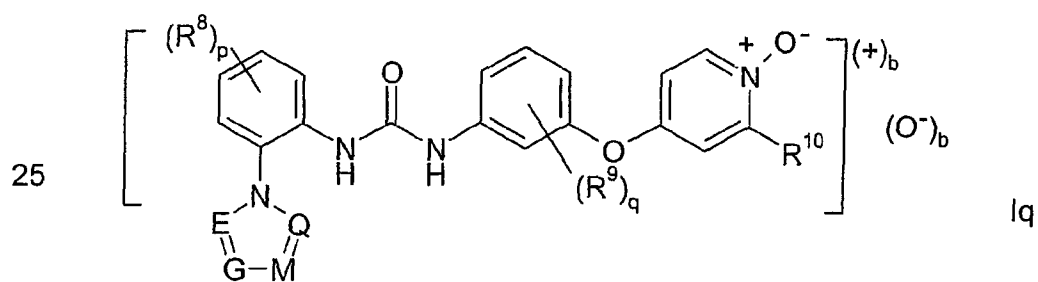
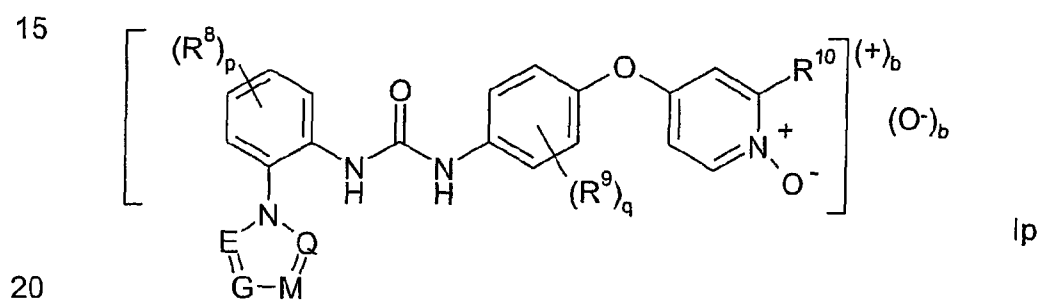
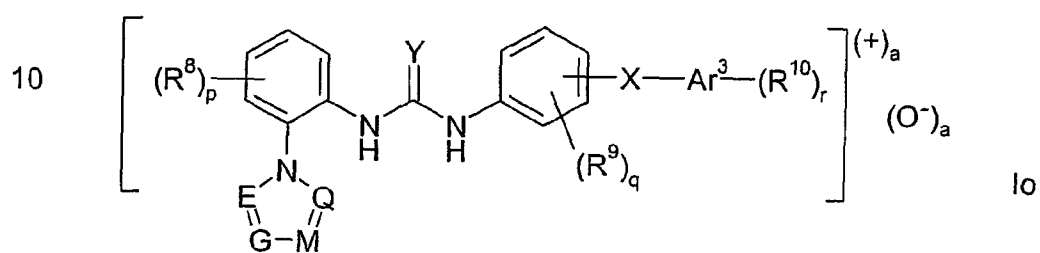
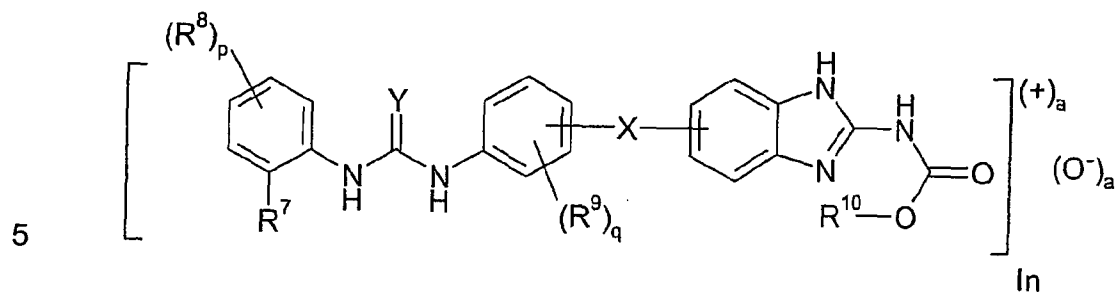
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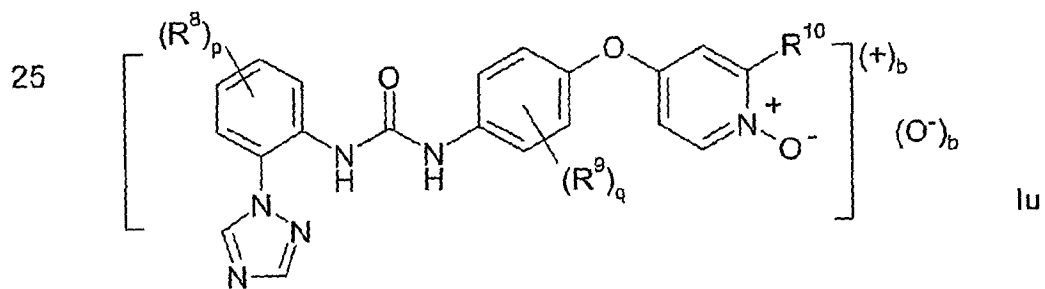
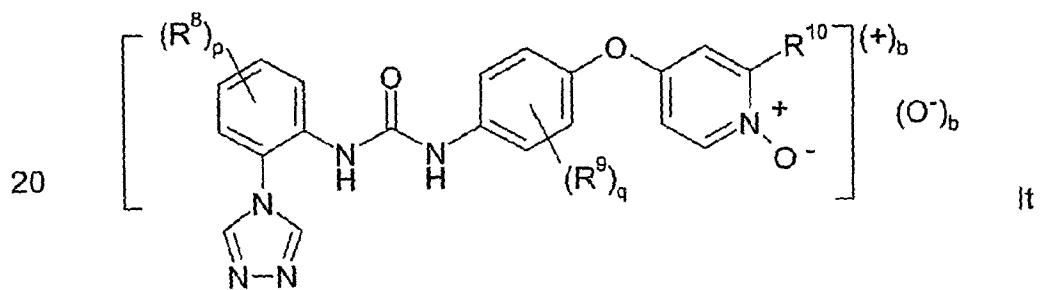
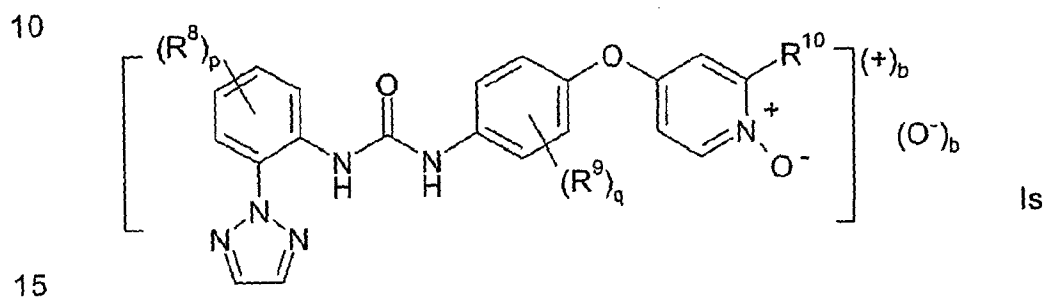
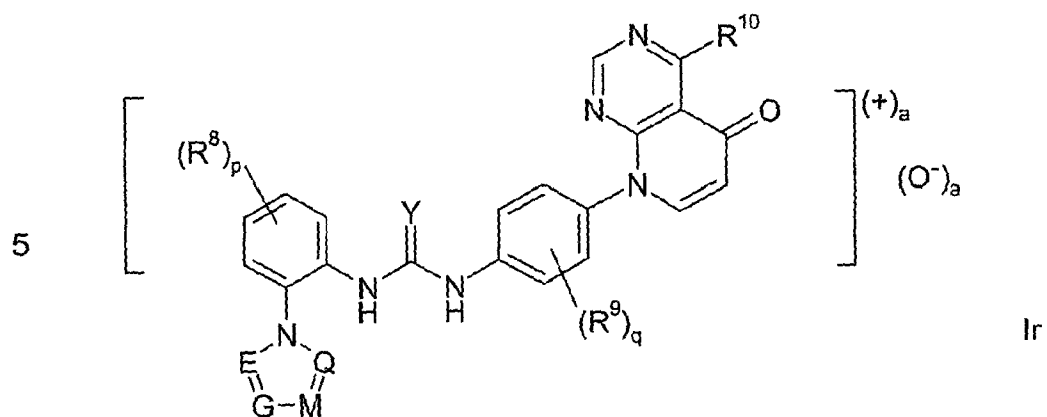
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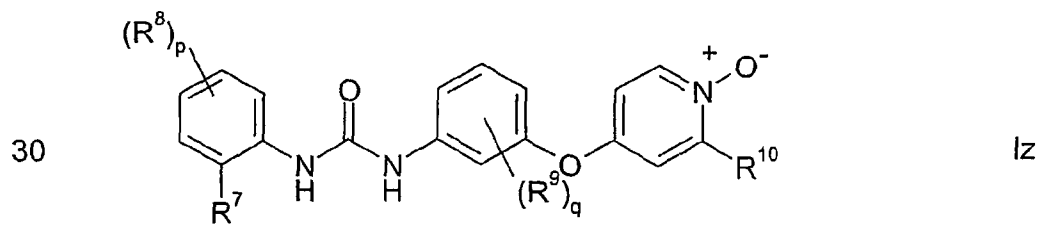
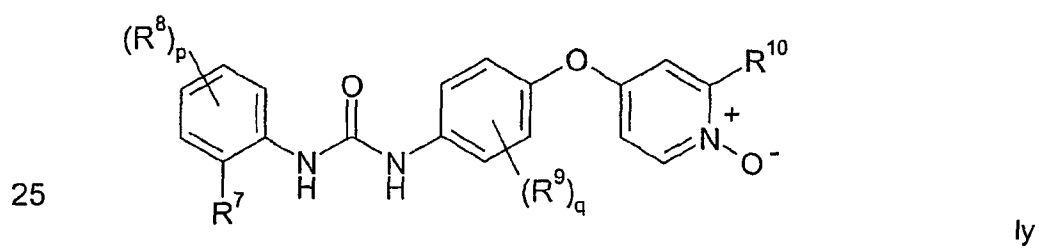
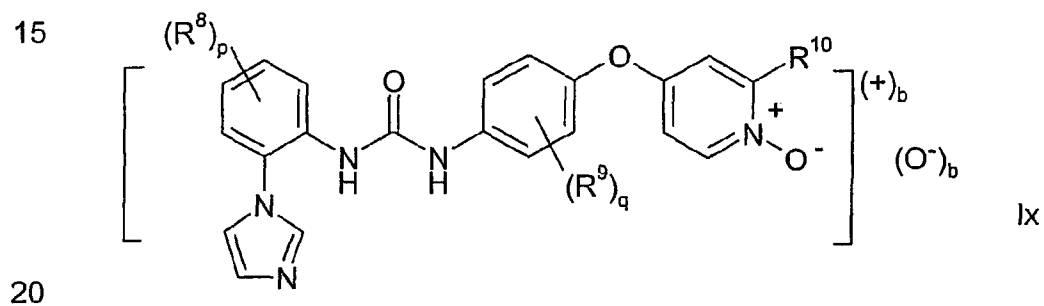
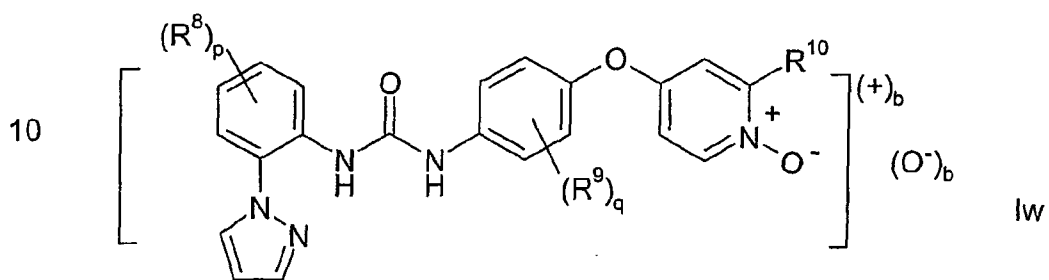
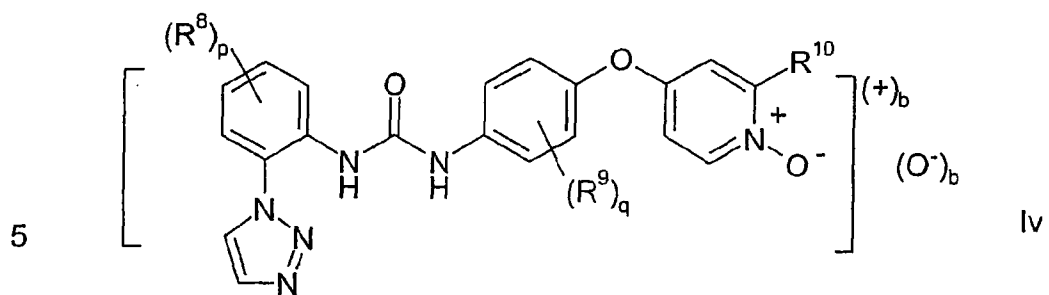


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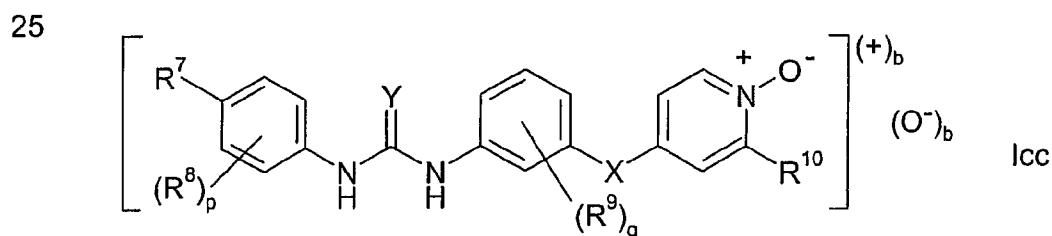
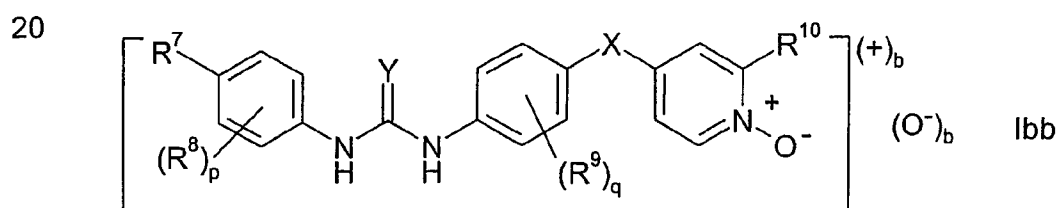
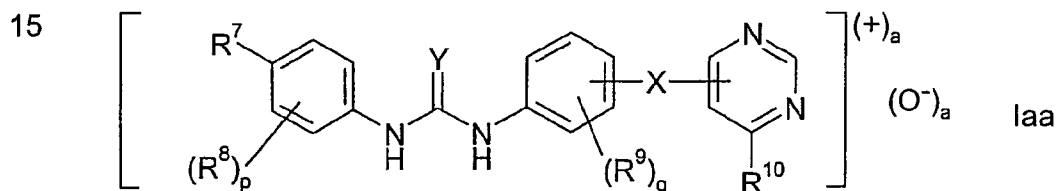
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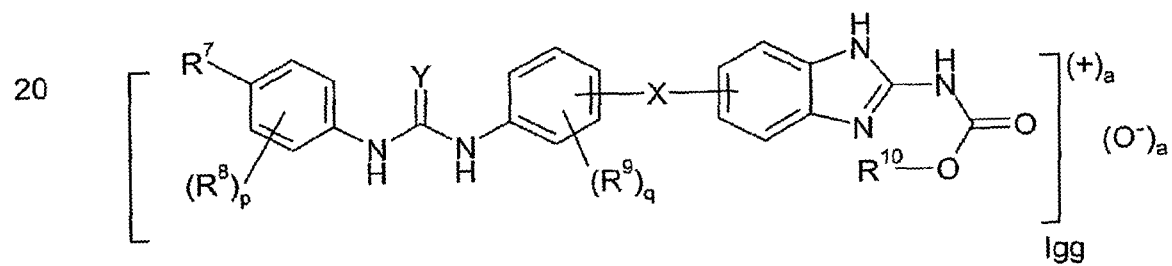
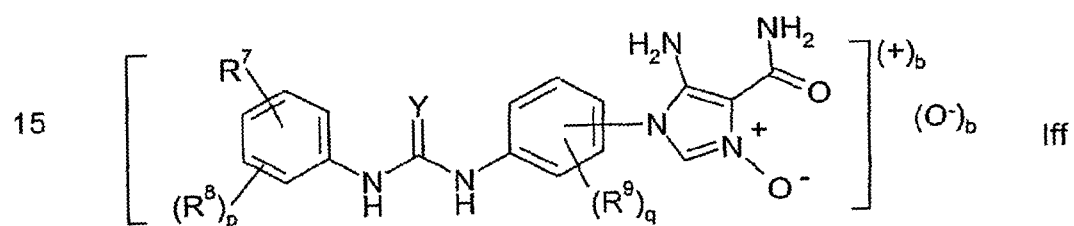
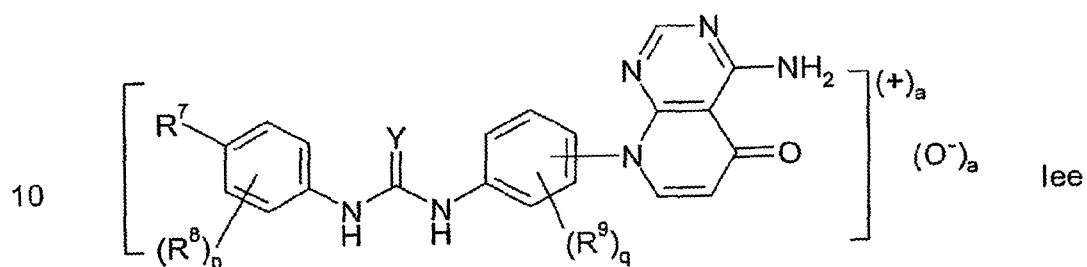
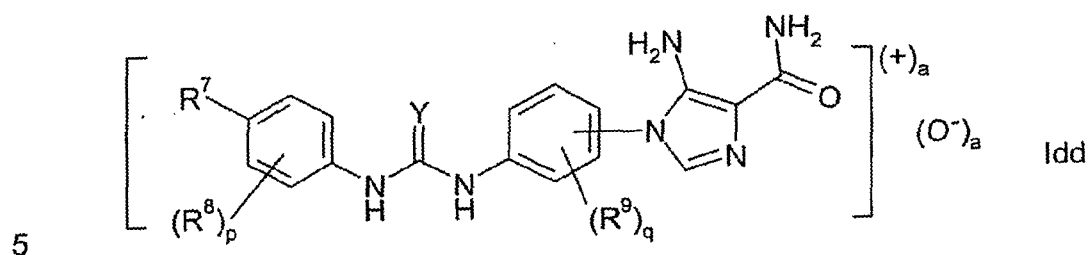
wherein b is 0, 1 or 2, preferably 0 or 1, and wherein R^7 , R^8 , Ar^3 , Y , X , R^9 , p , a , q and R^{10} are as defined above and below, more preferably R^{10} is H or as defined above/below, and preferably as defined in sub formulae I.1) to I.20) and/or the embodiments related thereto, and wherein E, G, M and Q are
 5 selected independently from one another from N and CR^{30} and especially from N and CH; with the proviso that one or more, preferably two or more and especially two or three of E, G, M and Q are other than nitrogen atoms; and the pharmaceutically acceptable derivatives, solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, and more
 10 preferred the salts and/or solvates thereof, and especially preferred the physiologically acceptable salts and/or solvates thereof.

Subject of the present invention are therefore especially preferred compounds of formula I according to one or more of the formulae Iaa to Icc

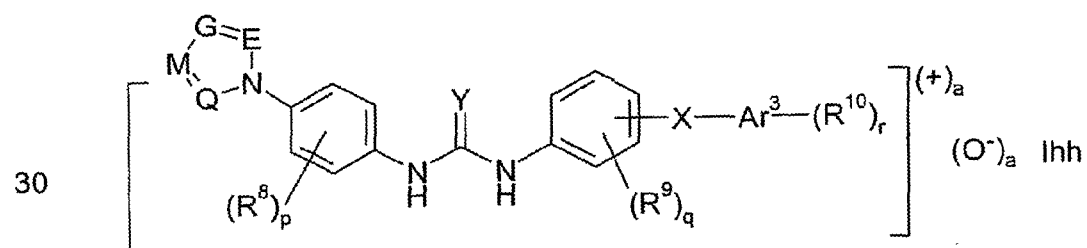


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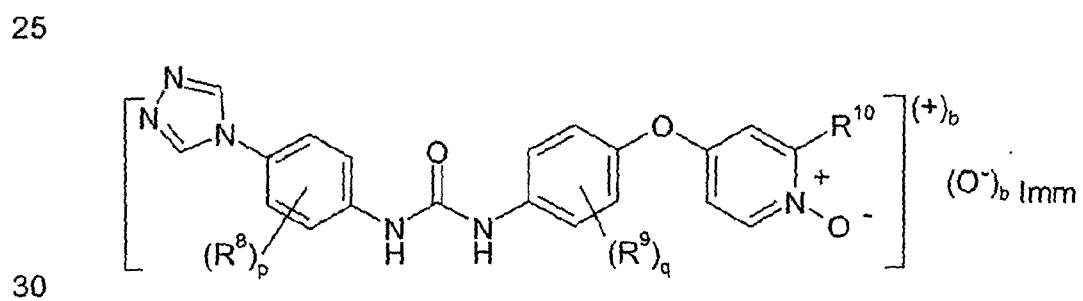
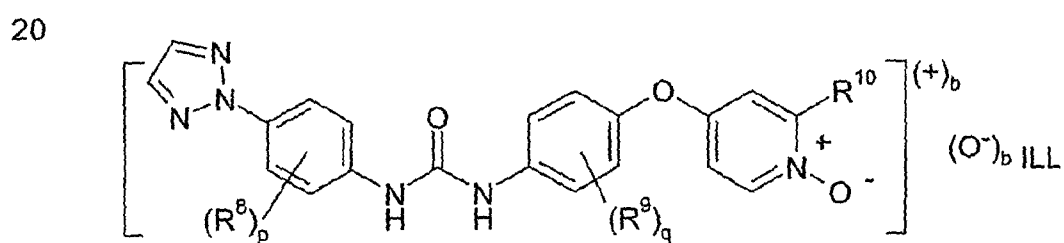
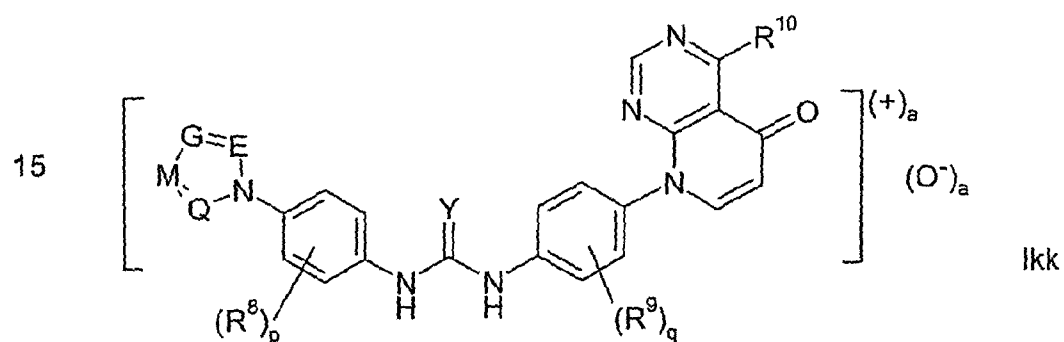
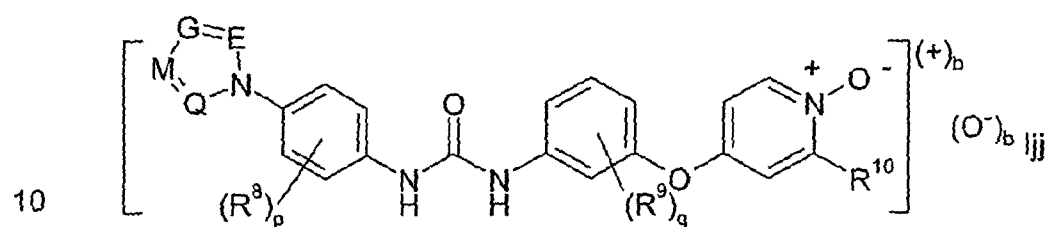
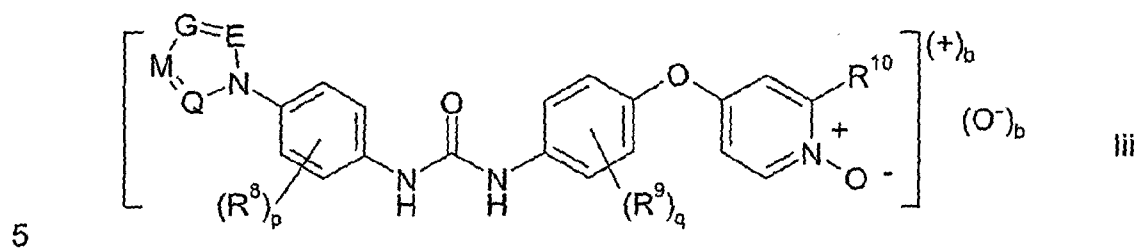
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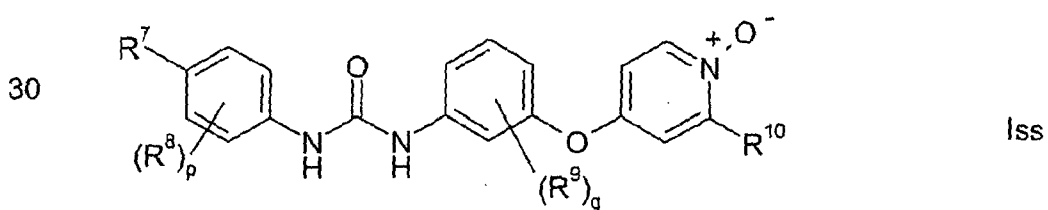
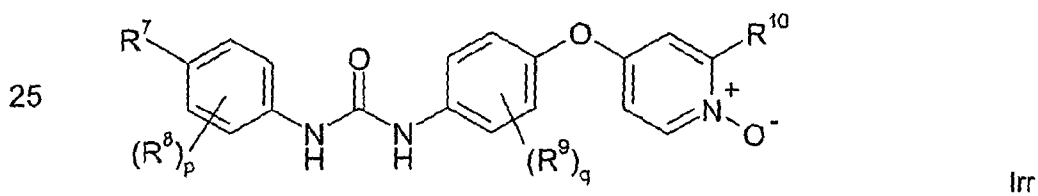
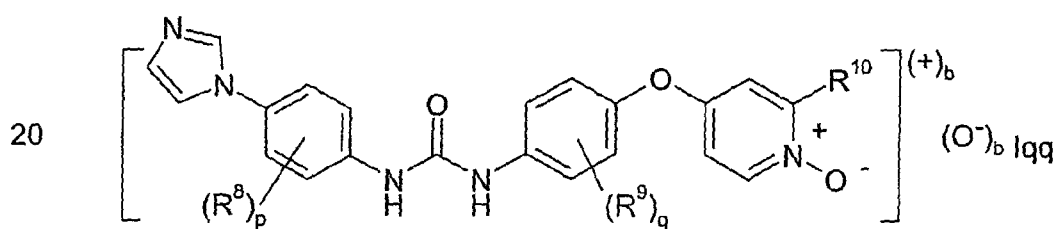
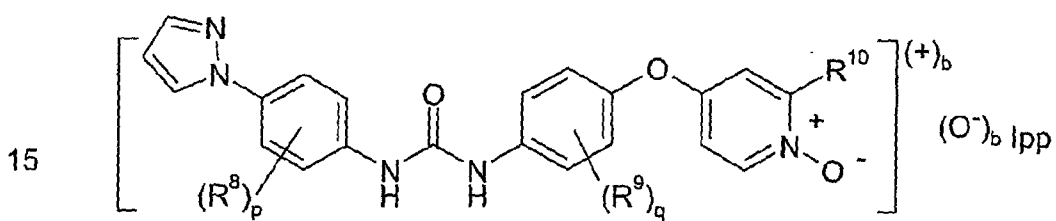
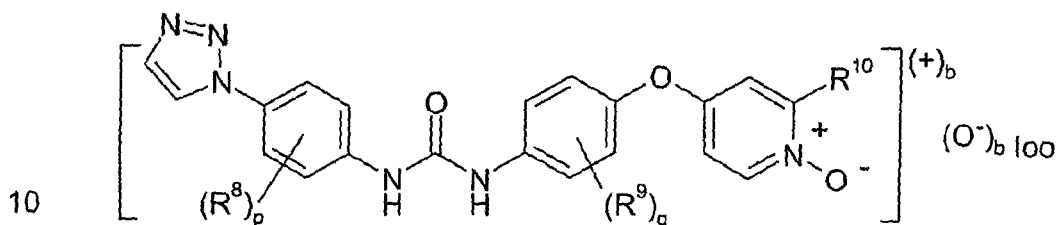
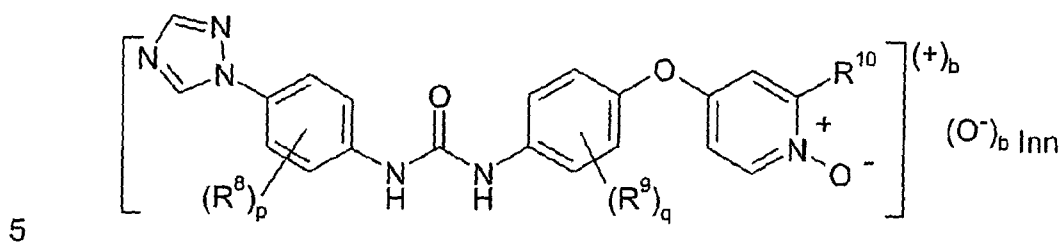
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wherein b is 0, 1 or 2, preferably 0 or 1, and wherein R^7 , R^8 , Ar^3 , Y, X, R^9 , p, a, q and R^{10} are as defined above and below, more preferably R^{10} is H or as defined above/below, and preferably as defined in sub formulae I.1) to I.20) and/or the embodiments related thereto, and wherein E, G, M and Q are
 5 selected independently from one another from N and CR^{30} and especially from N and CH; with the proviso that one or more, preferably two or more and especially two or three of E, G, M and Q are other than nitrogen atoms; and the pharmaceutically acceptable derivatives, solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, and more
 10 preferred the salts and/or solvates thereof, and especially preferred the physiologically acceptable salts and/or solvates thereof.

Preferably, b is 0 or 1, and especially is 0.

15 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20) and Ib, Ie, If, Ig, Ih, In, Io, Iq, Ir, Is, It, Iu, Iv, Iw, Ix, Iy and Iz, wherein R^{10} is a substituted carbamoyl moiety $CONHR^{23}$ or $CONR^{23}R^{24}$, preferably $CONHR^{23}$, wherein R^{23} and R^{24} are independently selected from the definitions given for
 20 R^8 , more preferably selected from CH_3 and $(CH_2)_nNR^{11}R^{12}$, wherein R^{11} , R^{12} and n are as defined above. In this embodiment, n is preferably not 0 and more preferred 1 to 3 and especially 1 or 2. Preferred examples for R^{23} are selected from the group consisting of CH_3 , $CH_2CH_2NH_2$, $CH_2CH_2N(CH_3)_2$, $CH_2CH_2N(CH_2CH_3)_2$, CH_2CH_2OH , $CH_2CH_2OCH_3$ and $CH_2CH_2OCH_2CH_3$.
 25 Preferably, this embodiment also relates to one or more of sub formulae Iaa, Ibb, Icc, and Igg to Iss.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20) and Ia to
 30 In, Iy and Iz, wherein R^7 is selected from [1,2,3]triazol-2-yl, [1,2,4]triazol-4-yl, [1,2,4]triazol-1-yl, [1,2,3]triazol-1-yl, 2-imidazol-1-yl, 2-pyrazol-1-yl, phthalimido-1-yl, succinimido-1-yl, maleinimido-1-yl, pyrrolidin-2-on-1-yl,

pyridin-2-on-1-yl, pyridin-4-on-1-yl, pyrrolidin-2, 5-dion-1-yl, 3,3',4,4'-tetramethyl-pyrrolidin-2,5-dion-1-yl, 5-methyl-pyrrolidin-2-on-1-yl, 5,5'-dimethyl-pyrrolidin-2-on-1-yl, and imiazolidin-2-on-1-yl. Preferably, this embodiment also relates to one or more of sub formulae laa to lgg, lrr and lss.

Another especially preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae l.1) to l.20) and la to ln, ly and lz, wherein R^7 is selected from [1,2,3]triazol-2-yl, [1,2,4]triazol-4-yl, [1,2,4]triazol-1-yl, [1,2,3]triazol-1-yl, 2-imidazol-1-yl, 2-pyrazol-1-yl, phthalimido-1-yl, maleinimido-1-yl, pyrrolidin-2-on-1-yl, pyridin-2-on-1-yl, pyridin-4-on-1-yl, pyrrolidin-2, 5-dion-1-yl, 3,3',4,4'-tetramethyl-pyrrolidin-2,5-dion-1-yl, 5-methyl-pyrrolidin-2-on-1-yl, 5,5'-dimethyl-pyrrolidin-2-on-1-yl, and imiazolidin-2-on-1-yl. Preferably, this embodiment also relates to one or more of sub formulae laa to lgg, lrr and lss.

Another preferred embodiment of the instant invention relates to compounds of sub formulae lm, ln and lp, wherein in each case R^{10} is independently selected from H, Hal, A, $NR^{11}R^{12}$ and NH_2 . Preferably, this embodiment also relates to one or more of sub formulae lff, lgg, lii and lkk.

Another preferred embodiment of the instant invention relates to compounds according to one or more formulae selected from formulae la, lb, lc, ld, le, lf, lg, lh, li, lj, lk, ll, lm, ln, lo, lp, lq, lr, ls, lt, lu, lv, lw, lx, ly, lz, laa, lbb, lcc, ldd, lee, lff, lgg, lhh, lii, ljj, lkk, lll, lmm, lnn, loo, lpp, lqq, lrr and lss, wherein

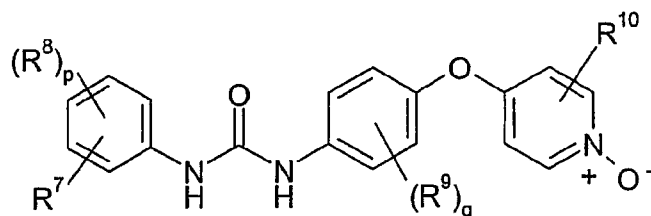
R^7 is azole, preferably [1,2,3]-triazole, 1,2,4]-triazole, [1,3,4]-triazole or [1,3]-imidazole,

R^8 is independently selected from CF_3 , OCF_3 , A, OA and SO_2A , wherein A is preferably an unbranched or branched alkyl residue having 1, 2, 3 or 4 carbon atoms,

- and more preferably is independently selected from CF_3 , OCF_3 , CH_3 , OCH_3 , $\text{C}(\text{CH}_3)_3$ and $\text{OC}(\text{CH}_3)_3$,
 p is 1 or 2, preferably 1;
 R^9 is Hal, preferably F,
 5 q is 0 or 1, and
 R^{10} is H, COOR^{11} , CONH_2 , CONHR^{11} or $\text{CONR}^{11}\text{R}^{12}$,
 preferably COOA , CONH_2 , CONHA or CONA_2 ,
 and the pharmaceutically acceptable derivatives, solvates, salts, tautomers
 and stereoisomers thereof, including mixtures thereof in all ratios, and more
 10 preferred the salts and/or solvates thereof, and especially preferred the
 physiologically acceptable salts and/or solvates thereof.

Another preferred embodiment of the instant invention relates to compounds
 of formula

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- wherein
 20 R^7 is azole, preferably [1,2,3]-triazole, 1,2,4]-triazole, [1,3,4]-
 triazole or [1,3]-imidazole,
 R^8 is independently selected from CF_3 , OCF_3 , A, OA and
 SO_2A , wherein A is preferably an unbranched or
 25 branched alkyl residue having 1, 2, 3 or 4 carbon atoms,
 and more preferably is independently selected from CF_3 ,
 OCF_3 , CH_3 , OCH_3 , $\text{C}(\text{CH}_3)_3$ and $\text{OC}(\text{CH}_3)_3$,
 p is 1 or 2, preferably 1;
 R^9 is Hal, preferably F,
 30 q is 0 or 1, and
 R^{10} is H, COOR^{11} , CONH_2 , CONHR^{11} or $\text{CONR}^{11}\text{R}^{12}$,
 preferably COOA , CONH_2 , CONHA or CONA_2 ,

and the pharmaceutically acceptable derivatives, solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, and more preferred the salts and/or solvates thereof, and especially preferred the physiologically acceptable salts and/or solvates thereof.

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It is understood that when a residue, for example R^8 , R^9 , R^{10} , R^{14} or R^{23} , is comprised twice or more times in one or more of the formulae I and the sub formulae corresponding thereto, it is in each case independently from one another selected from the meanings given for the respective residue. For example, R^{11} and R^{12} are defined to be independently selected from a group consisting of H, A, $(CH_2)_mAr^7$ and $(CH_2)_mHet^9$. Then $(CH_2)_nNR^{11}(CH_2)_mNR^{12}R^{12}$ can be $(CH_2)_nNA(CH_2)_mNA_2$ (if $R^{11} = A$, $R^{12} = A$ and $R^{12} = H$) as well as $(CH_2)_nNA(CH_2)_mNHA$ (if $R^{11} = A$, $R^{12} = H$ and $R^{12} = A$) or $(CH_2)_nNA(CH_2)_mNH(CH_2)_mHet^9$ (if $R^{11} = A$, $R^{12} = H$ and $R^{12} = (CH_2)_mHet^9$). Accordingly, if a compound of formula I comprises one residue R^8 , R^9 and R^{10} , then for example R^8 , R^9 and R^{10} can all be $(CH_2)_nCOOR^{13}$, wherein all residues R^{13} are the same (for example CH_2Hal , wherein Hal is Cl; then all residues R^8 , R^9 and R^{10} are the same) or different (for example CH_2Hal , wherein in R^8 Hal is Cl; in R^9 Hal is F; and in R^{10} Hal is Br; then all residues R^8 , R^9 and R^{10} are different); or for example R^8 is $(CH_2)_nCOOR^{13}$, R^9 is NO_2 and R^{10} is $(CH_2)_nSR^{11}$, wherein R^{11} and R^{13} can be the same (for example both can be H or both can be A which is methyl) or different (for example R^{11} can be H and R^{13} can be A which is methyl).

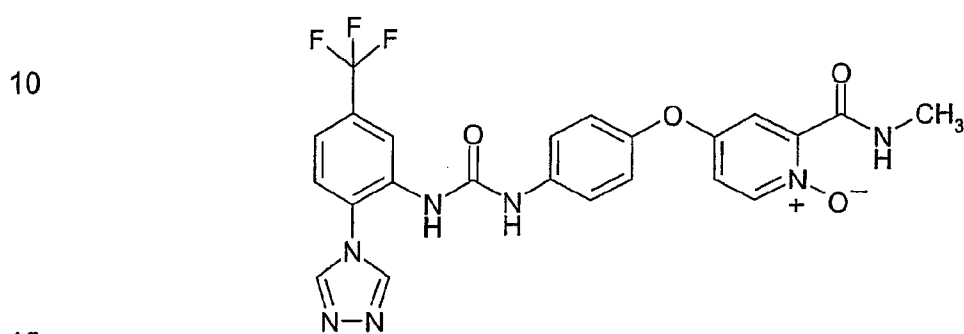
25 If not stated otherwise, reference to compounds of formula I preferably also includes the sub formulae related thereto, especially sub formulae I.1) to I.20) and Ia to Iz.

30 If not stated otherwise, reference to compounds of formula I preferably also includes the sub formulae related thereto, especially sub formulae Iaa to Iss.

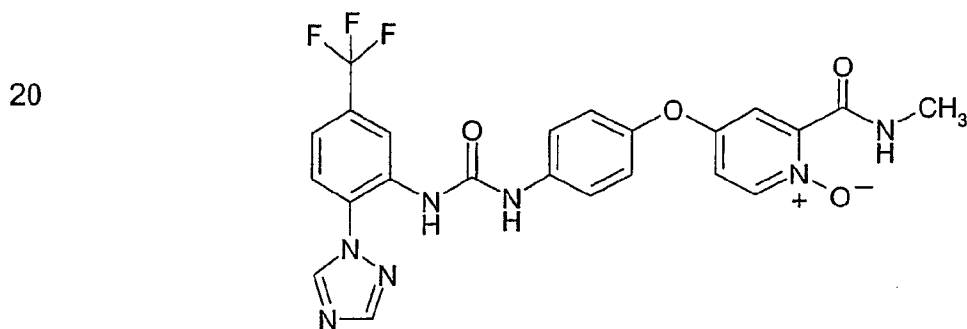
Subject of the instant invention are especially those compounds of formula I and preferably also the sub formulae related thereto, in which at least one of the residues mentioned in said formulae has one of the preferred or especially preferred meanings given above and below.

5

Especially preferred as compounds according to the invention are the compounds given below:



1-Oxy-4-{4-[3-(2-[1,2,4]triazol-4-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide;

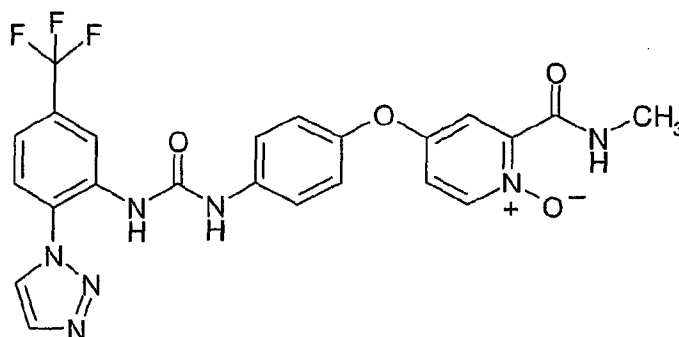


1-Oxy-4-{4-[3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide

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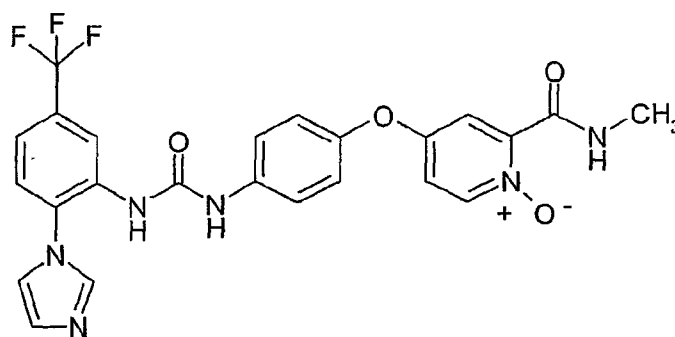
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1-Oxy-4-{4-[3-(2-[1,2,3]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-
pyridine-2-carboxylic acid methylamide;

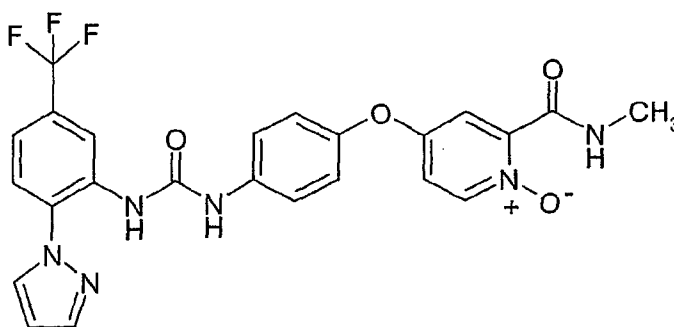
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1-Oxy-4-{4-[3-(2-imidazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-
pyridine-2-carboxylic acid methylamide;

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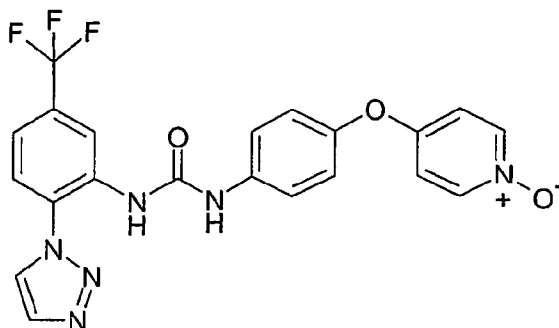
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1-Oxy-4-{4-[3-(2-pyrazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-
pyridine-2-carboxylic acid methylamide;

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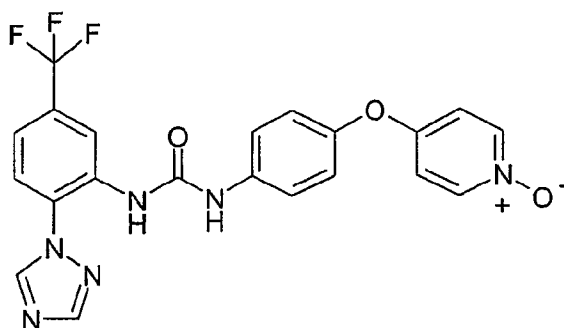
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1-[4-(1-Oxy-pyridin-4-yloxy)-phenyl]-3-(2-[1,2,3]triazol-1-yl-5-trifluoromethyl-phenyl)-urea;

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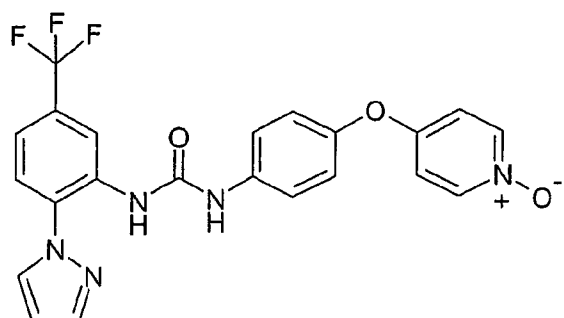
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1-[4-(1-Oxy-pyridin-4-yloxy)-phenyl]-3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-urea;

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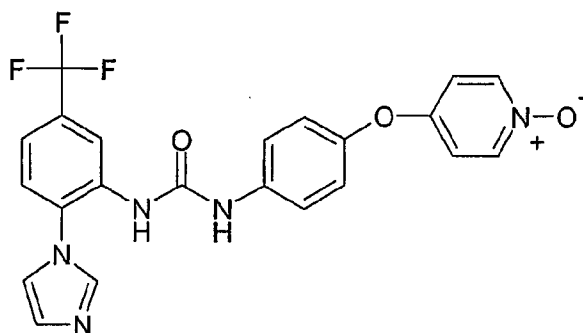


1-[4-(1-Oxy-pyridin-4-yloxy)-phenyl]-3-(2-pyrazol-1-yl-5-trifluoromethyl-phenyl)-urea;

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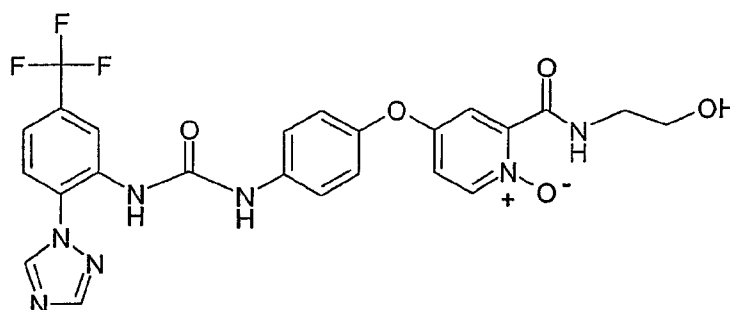
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1-[4-(1-Oxy-pyridin-4-yloxy)-phenyl]-3-(2-imidazol-1-yl-5-trifluoromethyl-phenyl)-urea;

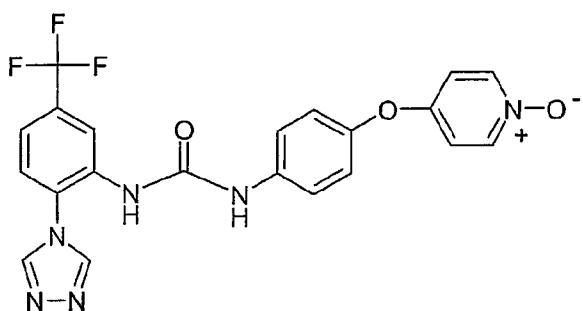
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1-Oxy-4-{4-[3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid (2-hydroxy-ethyl)-amide;

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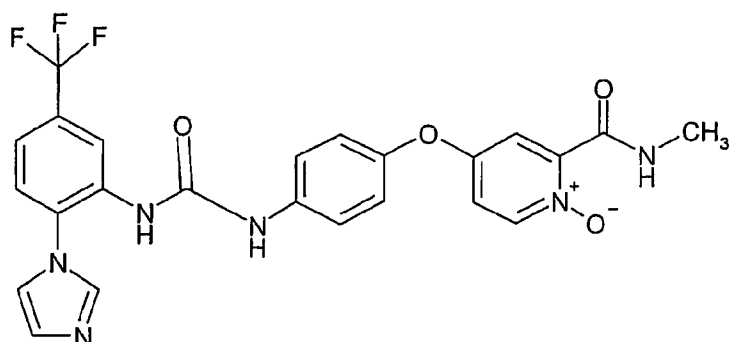
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1-[4-(1-Oxy-pyridin-4-yloxy)-phenyl]-3-(2-[1,2,4]triazol-4-yl-5-trifluoromethyl-phenyl)-urea;

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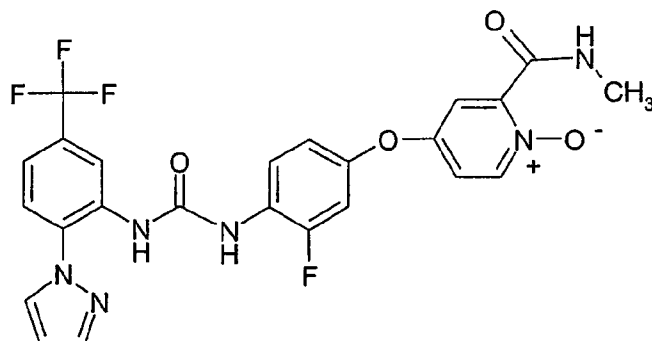
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4-{4-[3-(2-imidazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1-oxy-pyridine-2-carboxylic acid methylamide;

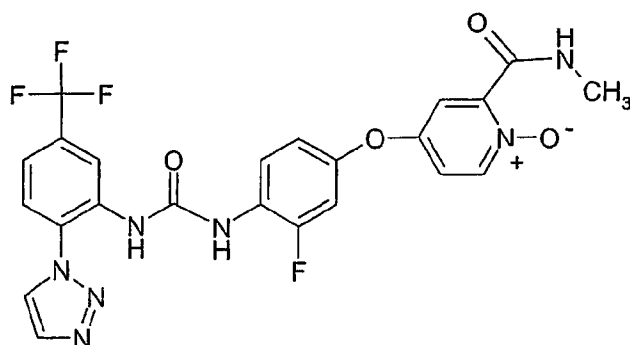
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4-{3-fluoro-4-[3-(2-pyrazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1-oxy-pyridine-2-carboxylic acid methylamide;

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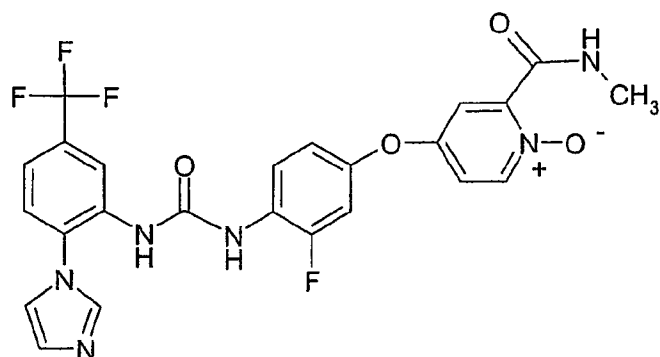


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4-{3-fluoro-4-[3-(2-[1,2,3]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1-oxy-pyridine-2-carboxylic acid methylamide;

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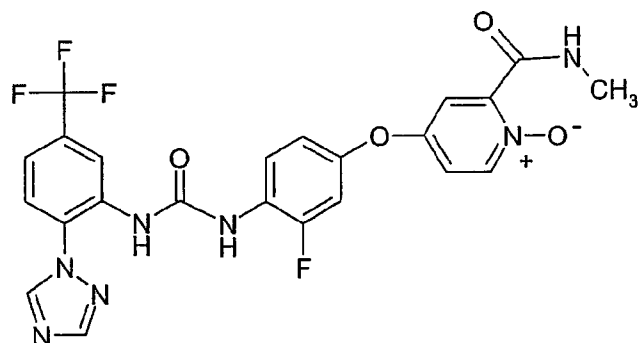
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4-{3-Fluoro-4-[3-(2-imidazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-
1-oxy-pyridine-2-carboxylic acid methylamide;

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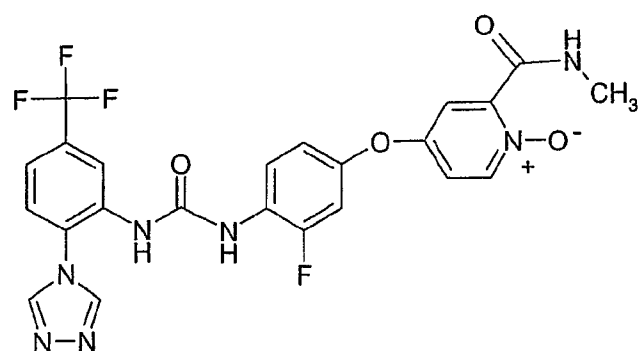
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4-{3-Fluoro-4-[3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-
phenoxy}-1-oxy-pyridine-2-carboxylic acid methylamide;

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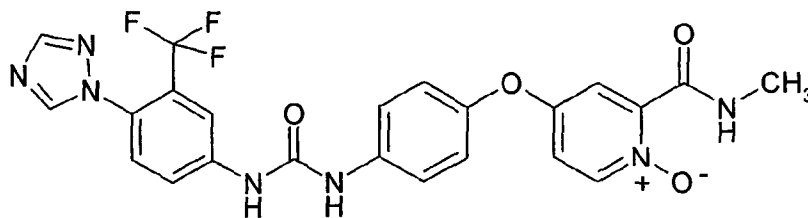
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4-{3-Fluoro-4-[3-(2-[1,2,4]triazol-4-yl-5-trifluoromethyl-phenyl)-ureido]-
phenoxy}-1-oxy-pyridine-2-carboxylic acid methylamide;

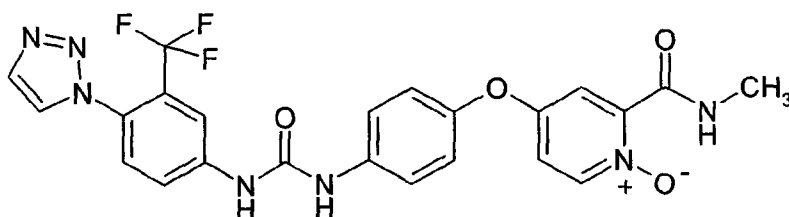
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1-Oxy-4-{4-[3-(4-[1,2,4]triazol-1-yl-3-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide;



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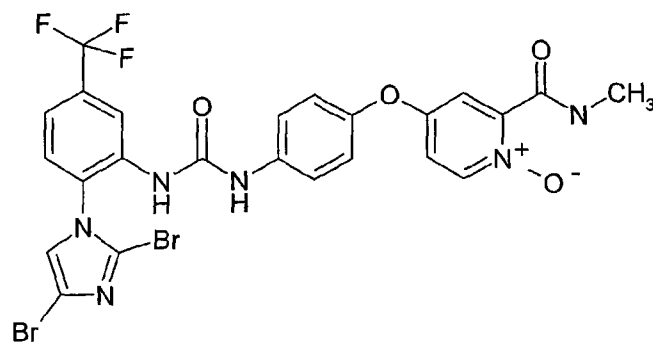
1-Oxy-4-{4-[3-(4-[1,2,3]triazol-1-yl-3-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide;

15

and the pharmaceutically acceptable derivatives, solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, and more preferred the salts and/or solvates thereof, and especially preferred the physiologically acceptable salts and/or solvates thereof.

20

Further especially preferred compounds according to the invention are selected from the compounds given below:

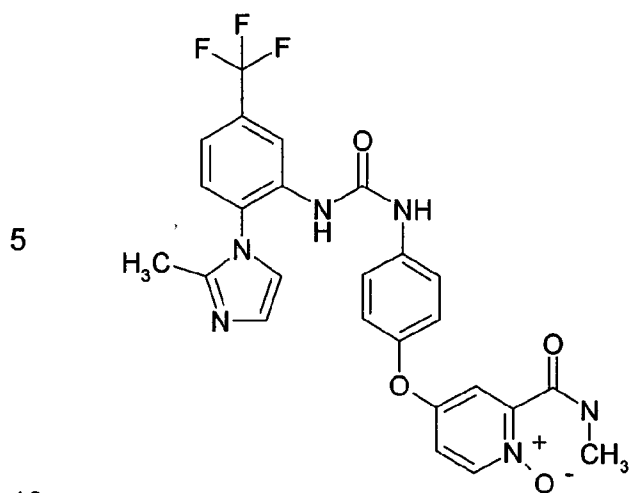


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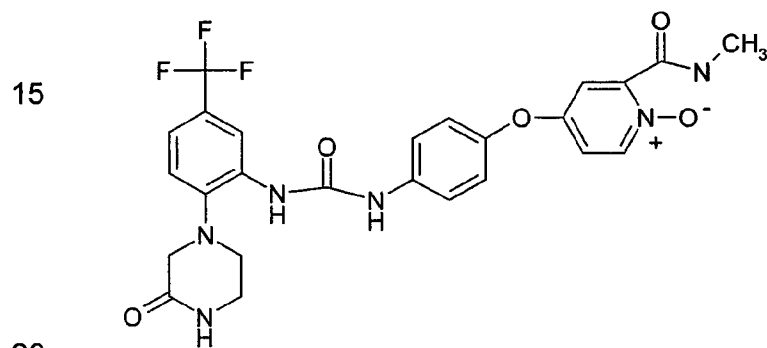
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1-Oxy-4-{4-[3-[2-(2,4-Dibromo-imidazol-1-yl)-5-trifluoromethyl-phenyl]-ureido]-phenoxy}-pyridine-2-carboxylic acid

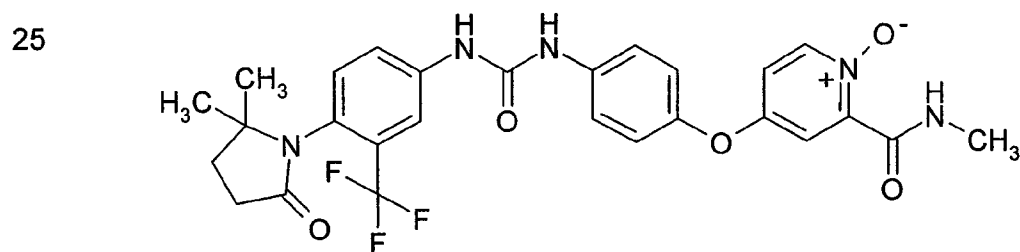
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1-Oxy-4-(4-{3-[2-(2-Methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide



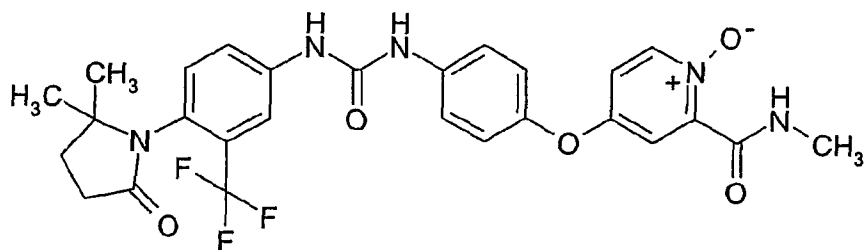
1-Oxy-4-(4-{3-[2-(3-Oxo-piperazin-1-yl)-5-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide



1-Oxy-4-(4-{3-[4-(2,2-Dimethyl-5-oxo-pyrrolidin-1-yl)-3-trifluoromethyl-phenyl]-ureido}-phenoxy)-1-oxy-pyridine-2-carboxylic acid methylamide;

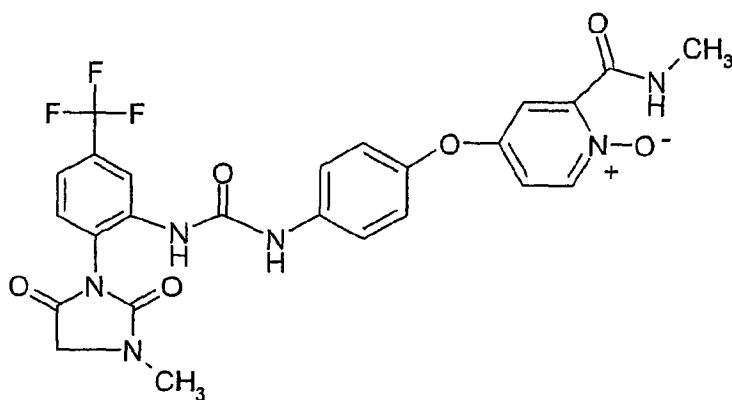
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4-(4-{3-[4-(2,2-Dimethyl-5-oxo-pyrrolidin-1-yl)-3-trifluoromethyl-phenyl]-ureido}-phenoxy)-1-oxy-pyridine-2-carboxylic acid methylamide;

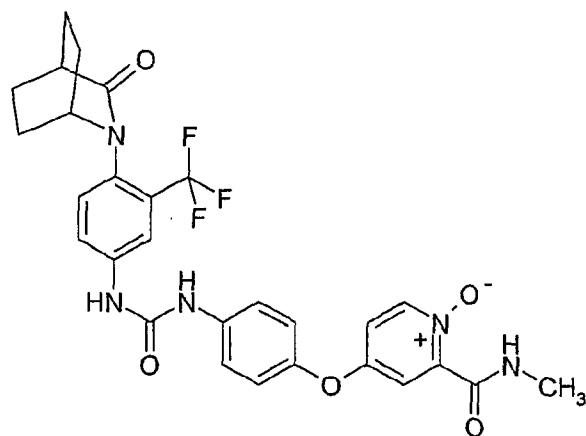
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1-Oxy-4-(4-{3-[2-(3-methyl-2,5-dioxo-imidazolidin-1-yl)-5-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide;

20

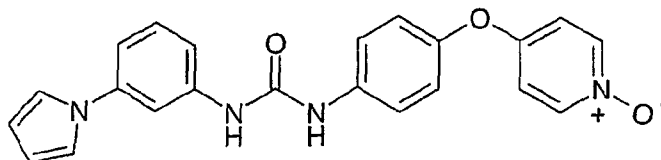


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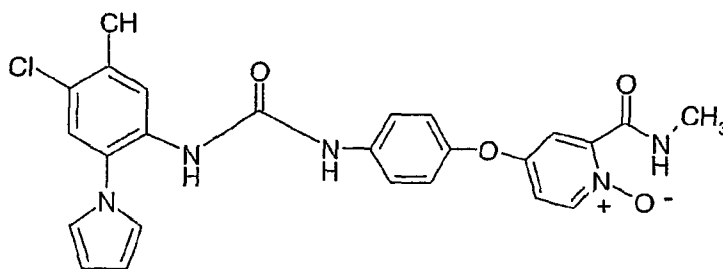
1-Oxy-4-(4-{3-[4-(3-oxo-2-aza-bicyclo[2.2.2]oct-2-yl)-3-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide;

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5 1-[4-(1-Oxy-pyridin-4-yloxy)-phenyl]-3-(3-pyrrol-1-yl-phenyl)-urea;



10

4-{4-[3-(4-Chloro-5-methyl-2-pyrrol-1-yl-phenyl)-ureido]-phenoxy}-1-oxy-pyridine-2-carboxylic acid methylamide;

15 and the pharmaceutically acceptable derivatives, solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, and more preferred the salts and/or solvates thereof, and especially preferred the physiologically acceptable salts and/or solvates thereof.

20 Further especially preferred compounds according to the invention are selected from the compounds given below:

1-[4-(4-Amino-3-oxy-5-oxo-5H-pyrido[2,3-d]pyrimidin-8-yl)-phenyl]-3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-urea;

25 1-[4-(4-Amino-1-oxy-5-oxo-5H-pyrido[2,3-d]pyrimidin-8-yl)-phenyl]-3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-urea;

1-[4-(4-Amino-3-oxy-5-oxo-5H-pyrido[2,3-d]pyrimidin-8-yl)-phenyl]-3-(2-[1,2,3]triazol-1-yl-5-trifluoromethyl-phenyl)-urea;

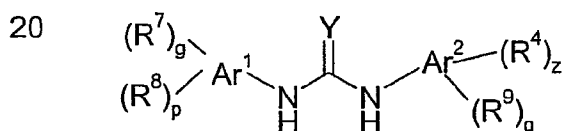
1-[4-(4-Amino-1-oxy-5-oxo-5H-pyrido[2,3-d]pyrimidin-8-yl)-phenyl]-3-(2-[1,2,3]triazol-1-yl-5-trifluoromethyl-phenyl)-urea;

30 1-[4-(4-Amino-3-oxy-5-oxo-5H-pyrido[2,3-d]pyrimidin-8-yl)-phenyl]-3-(2-pyrazol-1-yl-5-trifluoromethyl-phenyl)-urea;

- 1-[4-(4-Amino-1-oxy-5-oxo-5H-pyrido[2,3-d]pyrimidin-8-yl)-phenyl]-3-(2-pyrazol-1-yl-5-trifluoromethyl-phenyl)-urea;
5-Amino-3-oxy-1-{4-[3-(2-[1,2,3]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenyl}-1H-imidazole-4-carboxylic acid amide;
5 5-Amino-3-oxy-1-{4-[3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenyl}-1H-imidazole-4-carboxylic acid amide;
5-Amino-3-oxy-1-{4-[3-(2-pyrazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenyl}-1H-imidazole-4-carboxylic acid amide;
1-[4-(1-Oxy-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidin-4-ylamino)-phenyl]-3-(2-[1,2,3]triazol-1-yl-5-trifluoromethyl-phenyl)-urea;
10 1-[4-(3-Oxy-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidin-4-ylamino)-phenyl]-3-(2-[1,2,3]triazol-1-yl-5-trifluoromethyl-phenyl)-urea;
1-[4-(1-Oxy-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidin-4-ylamino)-phenyl]-3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-urea;
15 1-[4-(3-Oxy-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidin-4-ylamino)-phenyl]-3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-urea;
1-[4-(4-Amino-3-oxy-5-oxo-5H-pyrido[2,3-d]pyrimidin-8-yl)-phenyl]-3-(2-imidazol-1-yl-5-trifluoromethyl-phenyl)-urea;
1-[4-(4-Amino-1-oxy-5-oxo-5H-pyrido[2,3-d]pyrimidin-8-yl)-phenyl]-3-(2-imidazol-1-yl-5-trifluoromethyl-phenyl)-urea;
20 1-[4-(4-Amino-3-oxy-5-oxo-5H-pyrido[2,3-d]pyrimidin-8-yl)-phenyl]-3-(2-[1,2,4]triazol-4-yl-5-trifluoromethyl-phenyl)-urea;
1-[4-(4-Amino-1-oxy-5-oxo-5H-pyrido[2,3-d]pyrimidin-8-yl)-phenyl]-3-(2-[1,2,4]triazol-4-yl-5-trifluoromethyl-phenyl)-urea;
25 (3-Oxy-5-{4-[3-(2-[1,2,4]triazol-4-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1H-benzimidazol-2-yl)-carbamic acid methyl ester;
(3-Oxy-6-{4-[3-(2-[1,2,4]triazol-4-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1H-benzimidazol-2-yl)-carbamic acid methyl ester;
(3-Oxy-5-{4-[3-(2-[1,2,3]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1H-benzimidazol-2-yl)-carbamic acid methyl ester;
30 (3-Oxy-6-{4-[3-(2-[1,2,3]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1H-benzimidazol-2-yl)-carbamic acid methyl ester;

(3-Oxy-5-{4-[3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1H-benzoimidazol-2-yl)-carbamic acid methyl ester;
(3-Oxy-6-{4-[3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1H-benzoimidazol-2-yl)-carbamic acid methyl ester;
5 (3-Oxy-5-{4-[3-(2-imidazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1H-benzoimidazol-2-yl)-carbamic acid methyl ester;
(3-Oxy-6-{4-[3-(2-imidazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1H-benzoimidazol-2-yl)-carbamic acid methyl ester;
(3-Oxy-5-{4-[3-(2-pyrazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1H-
10 benzoimidazol-2-yl)-carbamic acid methyl ester;
(3-Oxy-6-{4-[3-(2-pyrazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1H-benzoimidazol-2-yl)-carbamic acid methyl ester;
and the pharmaceutically acceptable derivatives, solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, and more
15 preferred the salts and/or solvates thereof, and especially preferred the physiologically acceptable salts and/or solvates thereof.

Further especially preferred compounds according to the invention are N-Oxides obtainable by oxidizing a compound of formula



wherein

R⁷, R⁸, R⁹, R⁴, Y, Ar¹, Ar², g, p, q and z are as defined as described herein; at
25 about 25 °C in the presence of an oxidizing agent, selected from 3-
chloroperbenzoic acid and H₂O₂, the oxidizing agent being preferably applied
in a molar ratio between 1.2 to 5 equivalents, more preferably between 2 to 4
equivalents and especially preferably between 2.2 and 3 equivalents, based
on the molar weight of the compound to be oxidized according to the formula;
30 and the pharmaceutically acceptable derivatives, solvates, salts, tautomers
and stereoisomers thereof, including mixtures thereof in all ratios, and more

preferred the salts and/or solvates thereof, and especially preferred the physiologically acceptable salts and/or solvates thereof.

- Further especially preferred compounds according to the invention are N-Oxides obtainable by oxidizing a compound selected from:
- 5 4-{4-[3-(2-[1,2,4]Triazol-4-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide,
4-{4-[3-(2-[1,2,4]Triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide,
- 10 4-{4-[3-(2-[1,2,3]Triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide,
4-{4-[3-(2-Imidazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide,
4-{4-[3-(2-Pyrazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-
- 15 carboxylic acid methylamide,
1-[4-(4-Amino-5-oxo-5H-pyrido[2,3-d]pyrimidin-8-yl)-phenyl]-3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-urea;
1-[4-(4-Amino-5-oxo-5H-pyrido[2,3-d]pyrimidin-8-yl)-phenyl]-3-(2-[1,2,3]triazol-1-yl-5-trifluoromethyl-phenyl)-urea;
- 20 1-[4-(Pyridin-4-yloxy)-phenyl]-3-(2-[1,2,3]triazol-1-yl-5-trifluoromethyl-phenyl)-urea;
1-[4-(Pyridin-4-yloxy)-phenyl]-3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-urea;
5-Amino-1-{4-[3-(2-[1,2,3]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenyl}-1H-imidazole-4-carboxylic acid amide;
- 25 5-Amino-1-{4-[3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenyl}-1H-imidazole-4-carboxylic acid amide;
1-[4-(4-Amino-5-oxo-5H-pyrido[2,3-d]pyrimidin-8-yl)-phenyl]-3-(2-pyrazol-1-yl-5-trifluoromethyl-phenyl)-urea;
- 30 1-(2-Pyrazol-1-yl-5-trifluoromethyl-phenyl)-3-[4-(pyridin-4-yloxy)-phenyl]-urea;
5-Amino-1-{4-[3-(2-pyrazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenyl}-1H-imidazole-4-carboxylic acid amide;

- 1-(2-Imidazol-1-yl-5-trifluoromethyl-phenyl)-3-[4-(pyridin-4-yloxy)-phenyl]-urea;
- 1-[4-(5-Oxo-5,8-dihydro-pyrido[2,3-d]pyrimidin-4-ylamino)-phenyl]-3-(2-[1,2,3]triazol-1-yl-5-trifluoromethyl-phenyl)-urea;
- 5 1-[4-(5-Oxo-5,8-dihydro-pyrido[2,3-d]pyrimidin-4-ylamino)-phenyl]-3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-urea;
- 4-{4-[3-(2-[1,2,4]Triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid (2-hydroxy-ethyl)-amide;
- 1-[4-(4-Amino-5-oxo-5H-pyrido[2,3-d]pyrimidin-8-yl)-phenyl]-3-(2-imidazol-1-yl-5-trifluoromethyl-phenyl)-urea;
- 10 1-[4-(Pyridin-4-yloxy)-phenyl]-3-(2-[1,2,4]triazol-4-yl-5-trifluoromethyl-phenyl)-urea;
- 1-[4-(4-Amino-5-oxo-5H-pyrido[2,3-d]pyrimidin-8-yl)-phenyl]-3-(2-[1,2,4]triazol-4-yl-5-trifluoromethyl-phenyl)-urea;
- 15 (5-{4-[3-(2-[1,2,4]Triazol-4-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1H-benzimidazol-2-yl)-carbamic acid methyl ester;
- (5-{4-[3-(2-[1,2,3]Triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1H-benzimidazol-2-yl)-carbamic acid methyl ester;
- (5-{4-[3-(2-[1,2,4]Triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1H-benzimidazol-2-yl)-carbamic acid methyl ester;
- 20 (5-{4-[3-(2-Imidazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1H-benzimidazol-2-yl)-carbamic acid methyl ester;
- (5-{4-[3-(2-Pyrazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1H-benzimidazol-2-yl)-carbamic acid methyl ester;
- 25 4-{3-Fluoro-4-[3-(2-pyrazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide;
- 4-{3-Fluoro-4-[3-(2-[1,2,3]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide;
- 4-{3-Fluoro-4-[3-(2-imidazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide;
- 30 4-{3-Fluoro-4-[3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide;

- 4-{3-Fluoro-4-[3-(2-[1,2,4]triazol-4-yl)-5-trifluoromethyl-phenyl]-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide;
- 4-{4-[3-(4-[1,2,4]Triazol-1-yl)-3-trifluoromethyl-phenyl]-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide;
- 5 4-{4-[3-(4-[1,2,3]Triazol-1-yl)-3-trifluoromethyl-phenyl]-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide;
- 4-(4-{3-[4-(2,2-Dimethyl-5-oxo-pyrrolidin-1-yl)-3-trifluoromethyl-phenyl]-ureido]-phenoxy})-pyridine-2-carboxylic acid methylamide;
- 4-(4-{3-[2-(3-Methyl-2,5-dioxo-imidazolidin-1-yl)-5-trifluoromethyl-phenyl]-ureido]-phenoxy})-pyridine-2-carboxylic acid methylamide;
- 10 4-(4-{3-[4-(3-Oxo-2-aza-bicyclo[2.2.2]oct-2-yl)-3-trifluoromethyl-phenyl]-ureido]-phenoxy})-pyridine-2-carboxylic acid methylamide;
- 1-[4-(Pyridin-4-yloxy)-phenyl]-3-(3-pyrrol-1-yl-phenyl)-urea;
- 4-{4-[3-(4-Chloro-5-methyl-2-pyrrol-1-yl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide,
- 15 in the presence of an oxidizing agent, selected from 3-chloroperbenzoic acid and H_2O_2 , the oxidizing agent being preferably applied in a molar ratio between 1.2 to 5 equivalents, more preferably between 2 to 4 equivalents and especially preferably between 2.2 and 3 equivalents, based on the molar
- 20 weight of the compound to be oxidized according to the formula; and the pharmaceutically acceptable derivatives, solvates, salts, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, and more preferred the salts and/or solvates thereof, and especially preferred the physiologically acceptable salts and/or solvates thereof.
- 25 More preferably, said N-oxides are obtainable by oxidization with 3-chloroperbenzoic acid, preferably using 2.3, 2.6 or 2.8 equivalents thereof, at about 25 °C for a reaction time in the range of 3 to 10 days, preferably 4 to 9 days, more preferably 6 to 8 days and especially about 7 days, preferably
- 30 using a suitable solvent, such as dichloromethane and/or acetic acid.

Especially preferably, said N-oxides are obtainable by oxidation with 2.3 equivalents (preferably based on the molar weight of the compound to be oxidized) of 3-chloroperbenzoic acid in CH_2Cl_2 (10ml/g) and acetic acid (4 ml/g) for 7 d at ambient temperature, such as described in the experimental section.

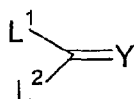
Further compounds that can be advantageously oxidised into N-oxides according to the invention are disclosed in PCT/EP2005/010744, the disclosure of which is incorporated herein by reference.

The nomenclature as used herein for defining compounds, especially the compounds according to the invention, is in general based on the rules of the IUPAC-organisation for chemical compounds and especially organic compounds.

Another aspect of the invention relates to a method for producing compounds of formula I, characterised in that

a) a compound of formula II,

20



wherein
25 L^1 and L^2 either independently from one another represent a leaving group, or together represent a leaving group, and Y is as defined above/below,

30 is reacted with

b) a compound of formula III

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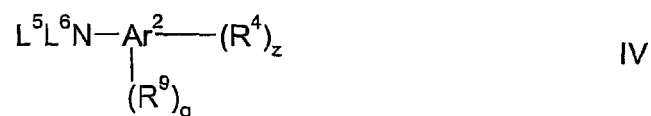


wherein

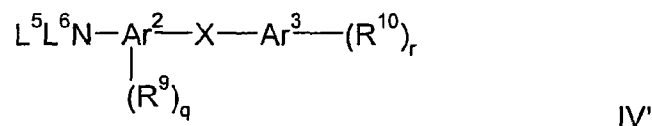
L^3 and L^4 are independently from one another H or a metal ion, and wherein R^7 , R^8 , g , p and Ar^1 are as defined above and below,

and

c) a compound of formula IV,



and more preferably a compound of formula IV',



wherein

L^5 and L^6 are independently from one another H or a metal ion, and R^9 , q , Ar^2 , R^4 , and z and more preferably R^9 , q , Ar^2 , X , Ar^3 , R^{10} and r are as defined above and below,

- d) treating the compound obtained by said reaction with an oxidizing agent to obtain the N-oxide of formula I, and optionally
- e) isolating and/or treating the N-oxide of formula I obtained by said reaction with an acid, to obtain the salt thereof.

The compounds of the formula I and also the starting materials for their preparation can be prepared by methods known per se, 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), to be precise under reaction conditions which are known and suitable for the said reactions. Use can also be made here of
5 variants which are known per se, but are not mentioned here in greater detail.

Oxidizing agents and reaction conditions and reagents, such as solvents, for the treatment according to step d) are known in the art. Preferred oxidizing
10 agents include, but are not limited to peroxy carboxylic acids, such as perbenzoic acids, preferably 3-chloroperbenzoic, and peroxides, such as H_2O_2 . Suitable solvents include, but are not limited to organic solvents, such as chlorinated hydrocarbons, alcohols, acetonitrile and DMSO, and organic acids, such as acetic acid and formic acid, and mixtures thereof. Preferably,
15 mixtures of dichloromethane and one organic acid, selected from acetic acid and formic acid, is applied together with 3-chloroperbenzoic as the oxidizing agent.

However, various suitable oxidation conditions and oxidizing agents are known
20 in the art. Some examples are as follows: peracids such as meta chloroperbenzoic acids in chlorinated solvents such as dichloromethane, dichloroethane, or chloroform (Markgraf et al., *Tetrahedron* 1991, 47, 183). $(Me_3SiO)_2$ in the presence of a catalytic amount of perhenic acid in chlorinated solvents such as dichloromethane (Coperet et al., *Tetrahedron*
25 *Lett.* 1998, 39, 76 1). Perfluoro-cis-2-butyl-3-propyloxaziridine in several combinations of halogenated solvents (Amone et al., *Tetrahedron* 1998, 54, 783 1). Hypofluoric acid - acetonitrile complex in chloroform (Dayan et al., *Synthesis* 1999, 1427). Oxone, in the presence of a base such as KOH, in water (Robker et al., *J. Chem. Res., Synop.* 1993, 10, 412). Magnesium monoperoxyphthalate, in the presence of glacial acetic acid (Klemm et al., *J. Heterocyclic Chem.* 1990, 6, 1537). Hydrogen peroxide, in the presence of
30 water and acetic acid (Lin A.J., *Org. Prep. Proced. Int.* 1991, 23(1), 1 114).

Dimethyldioxirane in acetone (Boyd et al., *J. Chem. Soc., Perkin Trans.* 1991, 9, 2 159).

5 The starting materials for the above mentioned oxidations are preferably non-N-oxidised heterocyclic substituted bisaryl ureas as described herein and/or described in PCT/EP2005/010744, the disclosure of which is incorporated herein by reference.

10 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 formula I. On the other hand, it is possible to carry out the reaction stepwise.

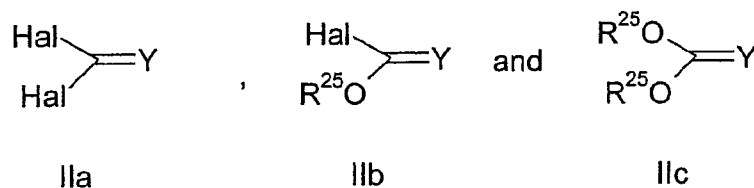
15 The compounds according to the invention can be manufactured or produced in an advantageous manner according to the methods of manufacture as described herein.

20 The reaction for the manufacture of compounds of formula I as described herein can be characterised as a carbonylation reaction of amines or the reaction of amines with carbon dioxide, carbon disulphide or derivatives or analogues thereof.

25 According to one aspect of the method according to the invention, in the compounds of formula II, L^1 and L^2 are preferably selected independently from one another from suitable leaving groups. Suitable leaving groups L^1 and L^2 for this type of reaction are known in the art, for example from the literature cited above. More preferably, L^1 and L^2 are independently selected from halogen, OR^{25} and $O-SO_2-R^{25}$. The residue R^{25} is preferably selected from substituted or unsubstituted alkyl groups and substituted or
30 unsubstituted aryl groups, preferably substituted alkyl groups and substituted aryl groups. Preferred as alkyl groups in this respect are C1-C4- alkyl groups. Preferred as aryl group in this respect is phenyl. Suitable substituents for

substituted alkyl groups are preferably selected from electronegative and/or electron withdrawing groups. Examples of electronegative and/or electron withdrawing groups for substituted alkyl groups include, but are not limited to halogen, especially Cl and/or F, cyano groups and nitro groups. Suitable substituents for substituted aryl groups are preferably selected from alkyl groups, preferably C₁–C₄ alkyl groups, and electronegative and/or electron withdrawing groups. Examples of electronegative and/or electron withdrawing groups for substituted aryl groups include, but are not limited to halogen, especially Cl and/or F, cyano groups and nitro groups. If R²⁵ is an unsubstituted alkyl group, it is preferably methyl. If R²⁵ is a substituted alkyl group, it is preferably CF₃ or CCl₃. If R²⁵ is an unsubstituted aryl group, it is preferably phenyl. If R²⁵ is a substituted aryl group, it is preferably selected from para-tolyl- (i. e. p-Me-C₆H₄) and para-Nitro-phenyl (i.e the p-O₂N-C₆H₄).

Even more preferably, the leaving groups OR²⁵ are selected from the para-Tosyl- (i. e. p-Me-C₆H₄-SO₃-) group, the para-Nitro-phenolate- (i.e the p-O₂N-C₆H₄-O-) group and the triflate- (i. e. the F₃C-SO₃-) group. Preferably, compounds of formula II, wherein L¹ and L² are selected independently from one another from suitable leaving groups, are selected from compounds IIa, IIb and IIc,



wherein Y, Hal and OR²⁵ are as described above/below.

According to another aspect of the method according to the invention, in the compounds of formula II, L¹ and L² together represent a leaving group. In this aspect, L¹ and L² together preferably represent Y as the leaving group,

wherein the leaving group Y is as defined above/below and more preferably is O or S.

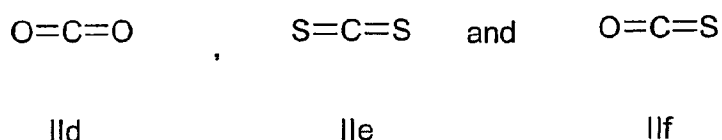
According to this aspect of the method according to the invention, the
 5 compound of formula II is a compound of formula II',



wherein each Y is independently selected from the meaning given
 10 above/below, and especially is independently selected from O and S.

According to this aspect of the method according to the invention, the
 compound of formula II is preferably selected from compounds of formula II d,
 formula II e and formula II f,

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20 more preferably of compounds of formula II d and formula II e. In this aspect, compounds of formula II a are especially preferred.

In compounds of formula II, Y is preferably selected from O and S, and more preferably is O.

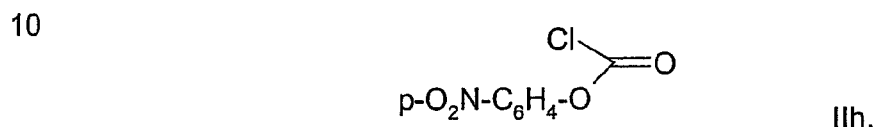
25 If compounds of formula II are desired wherein Y is other than O, it can be advantageous however to carry out the reaction according to the invention selecting a compound of formula II wherein Y is O, and to modify or convert the corresponding C=O group (i. e. the C=Y group, wherein Y is O) in the compound of formula I into a C=NR²¹, C=C(R²²)-NO₂, C=C(R²²)-CN or
 30 C=C(CN)₂ group according to methods known in the art, for example from Houben-Weyl, Methods of Organic Chemistry.

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In the method of manufacture according to the invention, the compound of formula II is even more preferably a compound of formula IIg,



wherein R²⁵ is as defined above/below, and especially a compound of formula IIh,



In the compounds of formula IV, L¹, L² and/or L³ is preferably H or a moiety which activates the amino group it is bonded to, for example a metal ion. Suitable metal ions are preferably selected from the group consisting of alkaline metal ions, alkaline-earth metal ions and aluminium ions. Especially preferred metal ions are alkaline metal ions, of which Li, Na K are especially preferred. In case of multi-valent metal ions, the metal ions and the compounds of formula IV form a complex containing one or more compounds of formula IV and one or more metal ions wherein the ratio between compounds of formula IV and metal ions is depending on the valency of the metal ion(s) according to the rules of stoichiometry and/or electroneutrality. Preferably, at least one of L¹, L² and L³, more preferred at least two of L¹, L² and L³ and even more preferred L¹, L² and L³ are hydrogen.

In detail, the reaction of the compounds of formula II, formula III and formula IV is carried out in the presence or absence of a preferably inert solvent at temperatures between about -20 °C and about 200 °C, preferably between -10 °C and 150 °C and especially between 0 °C or room temperature (25°) and 120°. In many cases, it is advantageous to combine one compound of formula III with one compound of formula IV at the lower end of the given

temperature range, preferably between -20°C and 75°C , more preferred between 0°C and 60°C and especially between 10°C and 40°C , for example at about room temperature, and heat the mixture up to a temperature at the upper end of the given temperature range, preferably
5 between 65°C and 180°C , more preferred between 75°C and 150°C and especially between 80°C and 120°C , for example at about 80°C , at about 90°C or at about 100°C . Proceeding in that manner can be advantageous in the case that pound of formula II is the compounds of formula II'. If the compound of formula II is not a compound of formula II', the reaction can be
10 regularly carried out without prolonged heating to higher temperatures. For example, it can preferably be carried out at a temperature between -10°C and 60°C , more preferably between -5°C and 40°C and even more preferably at about 0°C or at about room temperature. This given temperature range is especially advantageous, if the compound of formula II
15 is selected from compounds of formula IIa, IIb, IIc and especially is a compound of formula IIg or IIh.

The method for manufacture according to the invention is preferably carried out in the presence of an acid binding means, for example one or more
20 bases. This is especially advantageous, if the compound of formula II is selected from compounds of formula IIa – IIc an even preferred if the compound is selected from the compounds of formula IIg or formula IIh.

Suitable acid binding means are known in the art. Preferred as acid binding
25 means are inorganic bases and especially organic bases. Examples for inorganic bases are alkaline or alkaline-earth hydroxides, alkaline or alkaline-earth carbonates and alkaline or alkaline-earth bicarbonates or other salts of a weak acid and alkaline or alkaline-earth metals, preferably of potassium, sodium, calcium or cesium. Examples for organic bases are triethyl amine,
30 diisopropyl ethyl amine (DIPEA), diaza bicyclo undecen (DBU), dimethyl aniline, pyridine or chinoline. If an organic base is used, it is advantageous in general to use a base with a boiling point that is higher than the highest

reaction temperature employed during the reaction. Especially preferred as organic bases are pyridine and DIPEA. In many cases it is advantageous to employ two different organic bases and especially to use pyridine and DIPEA.

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Reaction times are generally in the range between some minutes and several days, depending on the reactivity of the respective compounds and the respective reaction conditions. Suitable reaction times are readily determinable by methods known in the art, for example reaction monitoring.

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Based on the reaction temperatures given above, suitable reaction times generally lie in the range 10 min and 36 hrs, preferably 30 min and 24 hrs and especially between 45 min and 18 hrs, for example about 1 h, about 2 hrs, about 4 hrs, about 6 or about 18 hrs.

15

Preferably, the reaction of the compounds of the formula III with the compounds of the formula IV is carried out in the presence of a suitable solvent, that is preferably inert under the respective reaction conditions. Examples of suitable solvents are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichlorethylene, 1,2-dichloroethane, tetrachloromethane, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide, dimethylformamide (DMF) or N-methyl pyrrolidinone (NMP); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate, or mixtures of the said solvents.

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Polar solvents are in general preferred. Examples for suitable polar solvents are chlorinated hydrocarbons, alcohols, glycol ethers, nitriles, amides and

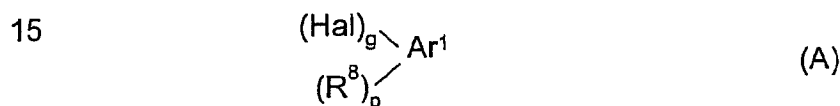
sulfoxides or mixtures thereof. More preferred are chlorinated hydrocarbons, especially dichloromethane, and amides, especially DMF.

In general, the compounds of formula III and/or formula IV are new. In any case, they can be prepared according to methods known in the art.

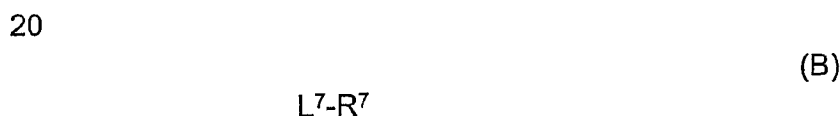
The compounds of formula III can be obtained according to methods known in the art. In an advantageous manner, they can be readily obtained by one or more of the reaction routes given below:

Compounds of formula III can be readily obtained from synthesis sequence as given below:

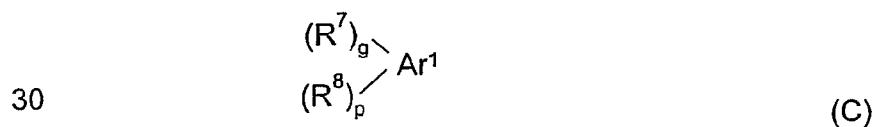
The reaction of derivatives of formula (A)



wherein Hal is Cl, Br or F and especially is F, and wherein g, R⁸, p and Ar¹ are as defined above/below, with p compounds of formula (B)



wherein R⁷ is as defined above/below and L⁷ is preferably selected from H or a metal ion, if L⁷ is bound to an oxygen atom of R⁷ or to a nitrogen atom of R⁷, or selected from carbon atom activating groups, if L⁷ is bound to a carbon atom of R⁷, leads to compounds of formula (C).



Suitable carbon atom activating groups for this type of reaction are known in the art. Suitable metal ions are preferably selected from the group consisting of alkaline metal ions, alkaline-earth metal ions and aluminium ions.

Preferred metal ions are alkaline metal ions, of which Li, Na and/or K are especially preferred. Even more preferred as L^7 is H.

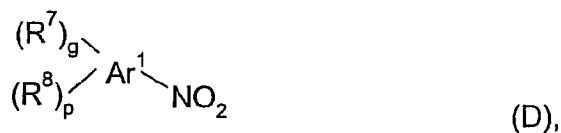
Accordingly, preferred compounds of formula (B) for the method for manufacture according to the invention are compounds that comprise a hydroxy-group, a primary amino group or a secondary amino group. Thus, especially preferred are compounds of formula (B), that comprise an HO-, a H₂N-group, a HNR¹¹-group or a HNR¹²-group, and especially compounds that comprise a terminal HO-, a H₂N-group, a HNR¹¹-group or a HNR¹²-group, wherein R¹¹ and R¹² are as defined above/below.

This type of reaction is generally known as aromatic substitution. Suitable reaction conditions for the reaction of the compounds of formula (A) with the compounds of formula (B) are known in the art.

The compound of formula (C) then can be transferred into the compound of formula III by methods known in the art.

Advantageously, the compound of formula (C) then can be transferred into a compound of formula (D),

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by a nitration reaction. Suitable methods and reaction conditions for nitration reactions are known in the art. Advantageously, the compounds of formula (D) can be obtained by reacting a compound of formula (C) with nitrating acid or a combination of concentrated sulfuric acid and potassium nitrate. If a

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combination of concentrated sulfuric acid and potassium nitrate is used, it can be advantageous to perform the reaction at a relatively low temperature, for example between -20 °C and + 50 °C, preferably between -10 °C and room temperature, more preferred between -5 °C and 0 °C.

5

The compound of formula (D) then can be transferred into a compound of formula III, wherein L^3 and L^4 are hydrogen, preferably by a reduction reaction or hydrogenating reaction, preferably a hydrogenating reaction. Methods and reaction conditions for hydrogenating a NO_2 -moiety into a NH_2 -moiety are known in the art. In general, it is advantageous to carry out the hydrogenation reaction in a hydrogen atmosphere in the presence of a suitable catalyst, for example Pd/C or Raney-nickel, preferably Raney-nickel. In general, such hydrogenation reactions are carried out in a suitable solvent. Suitable solvents for hydrogenation reactions are known in the art. Suitable solvents, for example, are alcohols, especially methanol and ethanol and ethers, especially THF, and mixtures thereof. Preferred as solvent is a mixture of THF/methanol, preferably in about equal measures. In general, the hydrogenation reactions are carried out at about normal pressure or slightly elevated pressure, for example between normal pressure and 3 bar pressure (about 300 kPa). The hydrogenation reaction is usually carried out in the temperature range between -20° and 150°, preferably 0° and 50°. The obtained compound of formula III wherein L^3 and L^4 are hydrogen can optionally be isolated and/or purified and then optionally transferred into a compound of formula III wherein L^3 and L^4 are other than hydrogen, for example according to methods and reaction conditions as described herein.

30

Some of the starting materials of the formula V and/or the formula VI are known and preferably commercially available. If they are not known, they can be prepared by methods known per se.

Generally, the compounds of formula IV and/or IV' can be obtained according to methods known in the art. For example, they can be prepared according to

methods described in Jerchel et al., Chem. Ber. 1956, 2921-2928, WO 02/044156, WO 03/099771, WO 00/42012, Curtin et al., Bioorg. Med. Chem. Lett., in press, or in an analogous manner thereof. Further synthesis methods and strategies that can be applied for the synthesis of the compounds according to the invention are disclosed in PCT/EP2005/010744 and WO 03/068229, the disclosure of which is incorporated herein by reference.

Independently of the chosen reaction route, it is in many cases possible or even feasible to introduce residues R^7 , R^8 , R^9 and/or R^{10} into one or more of the compounds described above, or, if the compound already comprises one or more residues R^7 , R^8 , R^9 and/or R^{10} , to introduce additional residues R^7 , R^8 , R^9 and/or R^{10} into said compound. The introduction of additional residues can be readily performed by methods known in the art and especially by aromatic substitution, for example nucleophilic aromatic substitution or electrophilic aromatic substitution. For example, in compounds comprising Ar^1 , wherein Ar^1 comprises one or more halogen and preferably fluorine substituents, one or more of the halogen/fluorine substituents can be easily substituted by hydroxy, thio and/or amino substituted hydrocarbons and or compounds $H-R^7$ and the metal salts thereof,

On the other hand, it is in many cases possible or even feasible to modify or derivatize one or more of the residues R^7 , R^8 , R^9 and/or R^{10} into residues R^7 , R^8 , R^9 and/or R^{10} other than the ones originally present. For example, CH_3 -groups can be oxidized into aldehyde groups or carboxylic acid groups, thio atom containing groups, for example S-alkyl or S-aryl groups, can be oxidized into SO_2 -alkyl or SO_2 -aryl groups, respectively, carboxylic acid groups can be derivatized to carboxylic acid ester groups or carboxylic acid amide groups and carboxylic acid ester groups or carboxylic acid amide groups can be hydrolysed into the corresponding carboxylic acid groups. Methods for performing such modifications or derivatizations are known in the art, for example from Houben-Weyl, Methods of Organic Chemistry.

Every reaction step described herein can optionally be followed by one or more working up procedures and/or isolating procedures. Suitable such procedures are known in the art, for example from standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart). Examples for such procedures include, but are not limited to evaporating a solvent, distilling, crystallization, fractionised crystallization, extraction procedures, washing procedures, digesting procedures, filtration procedures, chromatography, chromatography by HPLC and drying procedures, especially drying procedures in vacuo and/or elevated temperature.

A base of the formula I can be converted into the associated acid-addition salt using an acid, for example by reaction of equivalent amounts of the base and the acid in a preferably inert solvent, such as ethanol, followed by evaporation. Suitable acids for this reaction are, in particular, those which give physiologically acceptable salts. Thus, it is possible to use inorganic acids, for example sulfuric acid, sulfurous acid, dithionic acid, nitric acid, hydrohalic acids, such as hydrochloric acid or hydrobromic acid, phosphoric acids, such as, for example, orthophosphoric acid, sulfamic acid, furthermore organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic, sulfonic or sulfuric acids, for example formic acid, acetic acid, propionic acid, hexanoic acid, octanoic acid, decanoic acid, hexadecanoic acid, octadecanoic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, trimethoxybenzoic acid, adamantanecarboxylic acid, p-toluenesulfonic acid, glycolic acid, embonic acid, chlorophenoxyacetic acid, aspartic acid, glutamic acid, proline, glyoxylic acid, palmitic acid, parachlorophenoxyisobutyric acid, cyclohexanecarboxylic acid, glucose 1-phosphate, naphthalenemono- and -disulfonic acids or laurylsulfuric acid.

Salts with physiologically unacceptable acids, for example picrates, can be used to isolate and/or purify the compounds of the formula I. On the other hand, compounds of the formula I can be converted into the corresponding metal salts, in particular alkali metal salts or alkaline earth metal salts, or into the corresponding ammonium salts, using bases (for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate). Suitable salts are furthermore substituted ammonium salts, for example the dimethyl-, diethyl- and diisopropylammonium salts, monoethanol-, diethanol- and diisopropanolammonium salts, cyclohexyl- and dicyclohexylammonium salts, dibenzylethylenediammonium salts, furthermore, for example, salts with arginine or lysine.

On the other hand, if desired, the free bases of the formula I can be liberated from their salts using bases (for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate).

The invention relates to compounds of the formula I and physiologically acceptable salts and solvates thereof as medicaments.

The invention also relates to the compounds for the formula I and physiologically acceptable salts and solvates thereof as kinase inhibitors.

The invention furthermore relates to the use of the compounds of the formula I and/or physiologically acceptable salts and/or solvates thereof for the preparation of pharmaceutical compositions and/or pharmaceutical preparations, in particular by non-chemical methods. In this cases, one or more compounds according to the invention can be converted into a suitable dosage form together with at least one solid, liquid and/or semi-liquid excipient or adjuvant and, if desired, in combination with one or more further active ingredients.

The invention further relates to the use of one or more of the compounds according to the invention, selected from the group consisting of compounds of the formula I as free bases, solvates of compounds of the formula I, salts of compounds of formula I, for the production of pharmaceutical compositions and/or pharmaceutical preparations, in particular by a non-chemical route. In general, non-chemical routes for the production of pharmaceutical compositions and/or pharmaceutical preparations comprise processing steps on suitable mechanical means known in the art that transfer one or more compounds according to the invention into a dosage form suitable for administration to a patient in need of such a treatment. Usually, the transfer of one or more compounds according to the invention into such a dosage form comprises the addition of one or more compounds, selected from the group consisting of carriers, excipients, auxiliaries and pharmaceutical active ingredients other than the compounds according to the invention. Suitable processing steps include, but are not limited to combining, milling, mixing, granulating, dissolving, dispersing, homogenizing, casting and/or compressing the respective active and non-active ingredients. In this respect, active ingredients are preferably at least one compound according to this invention and one or more additional compounds other than the compounds according to the invention, which show valuable pharmaceutical properties, preferably those pharmaceutical active agents other than the compounds according to the invention which are disclosed herein.

The process for preparing pharmaceutical compositions and/or pharmaceutical preparations preferably comprises one or more processing steps, selected from the group consisting of combining, milling, mixing, granulating, dissolving, dispersing, homogenizing and compressing. The one or more processing steps are preferably performed on one or more of the ingredients which are to form the pharmaceutical composition and/or pharmaceutical preparation preferably according to the invention. Even more preferred, said processing steps are performed on two or more of the ingredients which are to form the pharmaceutical composition and/or

pharmaceutical preparation, said ingredients comprising one or more compounds according to the invention and, additionally, one or more compounds, preferably selected from the group consisting of active ingredients other than the compounds according to the invention, excipients, auxiliaries, adjuvants and carriers. Mechanical means for performing said processing steps are known in the art, for example from Ullmann's Encyclopedia of Industrial Chemistry, 5th Edition.

The formation of prodrugs is well known in the art in order to enhance the properties of the parent compound; such properties include solubility, absorption, biostability and release time (see "*Pharmaceutical Dosage Form and Drug Delivery Systems*" (Sixth Edition), edited by Ansel et al., published by Williams & Wilkins, pages 27-29, (1995) which is hereby incorporated by reference). Commonly used prodrugs of the N-oxides according to the invention are designed to take advantage of the major drug biotransformation reactions and are also to be considered within the scope of the invention. Major drug biotransformation reactions include N-dealkylation, O-dealkylation, aliphatic hydroxylation, aromatic hydroxylation, N-oxidation, S-oxidation, deamination, hydrolysis reactions, glucuronidation, sulfation and acetylation (see *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Ninth Edition), editor Molinoff et al., publ. by McGraw-Hill, pages 1 1-13, (1996), which is hereby incorporated by reference).

Preferably, one or more compounds according to the invention are converted into a suitable dosage form together with at least one compound selected from the group consisting of excipients, auxiliaries, adjuvants and carriers, especially solid, liquid and/or semi-liquid excipients, auxiliaries, adjuvants and carriers, and, if desired, in combination with one or more further active ingredients.

Suitable dosage forms include, but are not limited to tablets, capsules, semi-solids, suppositories, aerosols, which can be produced according to methods known in the art, for example as described below:

- | | | |
|----|---------------------------------------|---|
| 5 | tablets | mixing of active ingredient/s and auxiliaries, compression of said mixture into tablets (direct compression), optionally granulation of part of mixture before compression |
| 10 | capsules | mixing of active ingredient/s and auxiliaries to obtain a flowable powder, optionally granulating powder, filling powders/granulate into opened capsules, capping of capsules |
| 15 | semi-solids (ointments, gels, creams) | dissolving/dispersing active ingredient/s in an aqueous or fatty carrier; subsequent mixing of aqueous/fatty phase with complementary fatty resp. aqueous phase, homogenisation (creams only) |
| 20 | suppositories (rectal and vaginal) | dissolving/dispersing active ingredient/s in carrier material liquified by heat (rectal: carrier material normally a wax; vaginal: carrier normally a heated solution of a gelling agent), casting said mixture into suppository forms, annealing and withdrawal suppositories from the forms |
| 25 | | |
| 30 | aerosols: | dispersing/dissolving active agent/s in a propellant, bottling said mixture into an atomizer |

The invention thus relates to pharmaceutical compositions and/or pharmaceutical preparations comprising at least one compound of the formula I and/or one of its physiologically acceptable salts and/or solvates.

- 5 Preferably, the pharmaceutical compositions and/or pharmaceutical preparations according to the invention contain a therapeutic effective amount of one or more compounds according to the invention. Said therapeutic effective amount of one or more of the compounds according to the invention is known to the skilled artisan or can be easily determined by
- 10 standard methods known in the art. For example, the compounds according to the invention can be administered to a patient in an analogous manner to other compounds that are effective as raf-kinase inhibitors, especially in an analogous manner to the compounds described in WO 00/42012 (Bayer). Usually, suitable doses that are therapeutically effective lie in the range
- 15 between 0.0005 mg and 1000 mg, preferably between 0.005 mg and 500 mg and especially between 0.5 and 100 mg per dose unit. The daily dose comprises preferably more than 0.001 mg, more preferred more than 0.01 milligram, even more preferred more than 0.1 mg and especially more than 1.0 mg, for example more than 2.0 mg, more than 5 mg, more than 10 mg,
- 20 more than 20 mg, more than 50 mg or more than 100 mg, and preferably less than 1500 mg, more preferred less than 750 mg, even more preferred less than 500 mg, for example less than 400 mg, less than 250 mg, less than 150 mg, less than 100 mg, less than 50 mg or less than 10 mg.
- 25 The specific dose for the individual patient depends, however, on the multitude of factors, for example on the efficacy of the specific compounds employed, on the age, body weight, general state of health, the sex, the kind of diet, on the time and route of administration, on the excretion rate, the kind of administration and the dosage form to be administered, the
- 30 pharmaceutical combination and severity of the particular disorder to which the therapy relates. The specific therapeutic effective dose for the individual

patient can readily be determined by routine experimentation, for example by the doctor or physician which advises or attends the therapeutic treatment.

5 However, the specific dose for each patient depends on a wide variety of factors, for example on the efficacy of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the time and method of administration, on the rate of excretion, medicament combination and severity of the particular illness to which the therapy applies. Parenteral administration is preferred. Oral administration is especially
10 preferred.

These compositions and/or preparations can be used as medicaments in human or veterinary medicine. Suitable excipients are organic or inorganic substances which are suitable for enteral (for example oral), parenteral or
15 topical administration and do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatine, carbohydrates, such as lactose or starch, magnesium stearate, talc or vaseline. Examples for suitable dosage forms, which are especially suitable for oral administration are, in particular, tablets, pills, coated tablets, capsules, powders, granules,
20 syrups, juices or drops. Further examples for suitable dosage forms, which are especially suitable for rectal administration are suppositories, further examples for suitable dosage forms, which are especially suitable for parenteral administration are solutions, preferably oil-based or aqueous solutions, furthermore suspensions, emulsions or implants, and suitable for
25 topical application are ointments, creams or powders. The novel compounds may also be lyophilised and the resultant lyophilisates used, for example, for the preparation of injection preparations. The compositions and/or preparations indicated may be sterilized and/or comprise assistants, such as
30 lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for modifying the osmotic pressure, buffer substances, dyes and flavors

and/or one or more further active ingredients, for example one or more vitamins.

5 For administration as an inhalation spray, it is possible to use sprays in which the active ingredient is either dissolved or suspended in a propellant gas or propellant gas mixture (for example CO₂ or chlorofluorocarbons). The active ingredient is advantageously used here in micronized form, in which case one or more additional physiologically acceptable solvents may be present, for example ethanol. Inhalation solutions can be administered with the aid of
10 conventional inhalers.

The compounds of the formula I and their physiologically acceptable salts and solvates can be employed for combating one or more diseases, for example allergic diseases, psoriasis and other skin diseases, especially
15 melanoma, autoimmune diseases, such as, for example, rheumatoid arthritis, multiple sclerosis, Crohn's disease, diabetes mellitus or ulcerative colitis.

In General, the substances according to the invention are preferably administered in doses corresponding to the compound rolipram of between 1
20 and 500 mg, in particular between 5 and 100 mg per dosage unit. The daily dose is preferably between about 0.02 and 10 mg/kg of body weight. However, the specific dose for each patient depends on a wide variety of factors, for example on the efficacy of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the time
25 and method of administration, on the excretion rate, medicament combination and severity of the particular illness to which the therapy applies. Oral administration is preferred.

The compounds of the formula I according to claim 1 and/or their
30 physiologically acceptable salts are also used in pathological processes which are maintained or propagated by angiogenesis, in particular in tumors,

restenoses, diabetic retinopathy, macular degenerative disease or rheumatoid arthritis.

Those of skill will readily appreciate that dose levels can vary as a function of the specific compound, the severity of the symptoms and the susceptibility of the subject to side effects. Some of the specific compounds are more potent than others. Preferred dosages for a given compound are readily determinable by those of skill in the art by a variety of means. A preferred means is to measure the physiological potency of a given compound.

For use in the subject methods, the subject compounds may be formulated with pharmaceutically active agents other than the compounds according to the invention, particularly other anti-metastatic, antitumor or anti-angiogenic agents. Angiostatic compounds of interest include angiostatin, enclostatin, carboxy terminal peptides of collagen alpha (XV), etc. Cytotoxic and cytostatic agents of interest include adriamycin, aleran, Ara-C, BICNU, busulfan, CNNU, cisplatin, cytoxan, daunorubicin, DTIC, 5-FU, hydrea, ifosfamide, ifosfamide, methotrexate, mithramycin, mitomycin, mitoxantrone, nitrogen mustard, velban, vincristine, vinblastine, VP-16, carboplatin, fludarabine, gemcitabine, idarubicin, irinotecan, leustatin, navelbine, taxol, taxotere, topotecan, etc.

The compounds of the invention preferably show an antiproliferative effect in an in vivo xenograft tumor model. The subject compounds are administered to a subject having a hyperproliferative disorders, e.g., to inhibit tumor growth, to decrease inflammation associated with a lymphoproliferative disorder, to inhibit graft rejection, or neurological damage due to tissue repair, etc. The present compounds are useful for prophylactic or therapeutic purposes. As used herein, the term "treating" is preferably also used to refer to both prevention of disease, and treatment of pre-existing conditions. The prevention of proliferation is accomplished by administration of the subject compounds prior to development of overt disease, e.g., to prevent the

regrowth of tumors, prevent metastatic growth, diminish restenosis associated with cardiovascular surgery, etc. Alternatively the compounds are used to treat ongoing disease, by stabilizing or improving the clinical symptoms of the patient.

5

The host, or patient, may be from any mammalian species, e.g., primate sp., particularly human; rodents, including mice, rats and hamsters; rabbits; equines, bovines, canines, felines; etc. Animal models are of interest for experimental investigations, providing a model for treatment of human disease.

10

The susceptibility of a particular cell to treatment with the subject compounds may be determined by in vitro testing. Typically a culture of the cell is combined with a subject compound at varying concentrations for a period of time sufficient to allow the active agents to induce cell death or inhibit migration, usually between about one hour and one week. For in vitro testing, cultured cells from a biopsy sample may be used. The viable cells left after treatment are then counted.

15

The dose will vary depending on the specific compound utilized, specific disorder, patient status, etc. Typically a therapeutic dose will be sufficient to substantially decrease the undesirable cell population in the targeted tissue, while maintaining patient viability. Treatment will generally be continued until there is a substantial reduction, e.g., at least about 50 %, decrease in the cell burden, and may be continued until there are essentially none of the undesirable cells detected in the body.

20

25

The compounds according to the invention are preferably administered to human or nonhuman animals, more preferred to mammalian animals and especially to humans.

30

The compounds preferably also find use in the specific inhibition of a signaling pathway mediated by protein kinases. Protein kinases are involved in signaling pathways for such important cellular activities as responses to extracellular signals and cell cycle checkpoints. Inhibition of specific protein kinases provided a means of intervening in these signaling pathways, for example to block the effect of an extracellular signal, to release a cell from cell cycle checkpoint, etc. Defects in the activity of protein kinases are associated with a variety of pathological or clinical conditions, where there is a defect in the signaling mediated by protein kinases. Such conditions include those associated with defects in cell cycle regulation or in response to extracellular signals, e.g., immunological disorders, autoimmune and immunodeficiency diseases; hyperproliferative disorders, which may include psoriasis, arthritis, inflammation, endometriosis, scarring, cancer, etc. The compounds of the present invention are active in inhibiting purified kinase proteins, preferably kinases as discussed herein, and especially kinases selected from raf-kinases, Tie-kinases, PDGFR-kinases and VEGFR-kinases, e.g., there is a decrease in the phosphorylation of a specific substrate in the presence of the compound. The compounds of the invention may also be useful as reagents for studying signal transduction or any of the clinical disorders listed throughout this application.

There are many disorders associated with a dysregulation of cellular proliferation. The conditions of interest include, but are not limited to, the following conditions. The subject compounds are useful in the treatment of a variety of conditions where there is proliferation and/or migration of smooth muscle cells, and/or inflammatory cells into the intimal layer of a vessel, resulting in restricted blood flow through that vessel, e.g., neointimal occlusive lesions. Occlusive vascular conditions of interest include atherosclerosis, graft coronary vascular disease after transplantation, vein graft stenosis, peri-anastomatic prosthetic graft stenosis, restenosis after angioplasty or stent placement, and the like.

Diseases where there is hyperproliferation and tissue remodelling or repair or reproductive tissue, e.g., uterine, testicular and ovarian carcinomas, endometriosis, squamous and glandular epithelial carcinomas of the cervix, etc. are reduced in cell number by administration of the subject compounds.

5 The growth and proliferation of neural cells is also of interest.

Tumor cells are characterized by uncontrolled growth, invasion to surrounding tissues, and metastatic spread to distant sites. Growth and expansion requires an ability not only to proliferate, but also to down-
10 modulate cell death (apoptosis) and activate angiogenesis to product a tumor neovasculature.

Tumors of interest for treatment include carcinomas, e.g., colon, duodenal, prostate, breast, melanoma, ductal, hepatic, pancreatic, renal, endometrial,
15 stomach, dysplastic oral mucosa, polyposis, invasive oral cancer, non-small cell lung carcinoma, transitional and squamous cell urinary carcinoma etc.; neurological malignancies; e.g. neuroplastoma, gliomas, etc.; hematological malignancies, e.g., childhood acute leukaemia, non-Hodgkin's lymphomas, chronic lymphocytic leukaemia, malignant cutaneous T-cells, mycosis
20 fungoides, non-MF cutaneous T-cell-lymphoma, lymphomatoid papulosis, T-cell rich cutaneous lymphoid hyperplasia, bullous pemphigoid, discoid lupus erythematosus, lichen planus, etc.; and the like.

Tumors of neural tissue are of particular interest, e.g., gliomas, neuromas,
25 etc. Some cancers of particular interest include breast cancers, which are primarily adenocarcinoma subtypes. Ductal carcinoma in situ is the most common type of noninvasive breast cancer. In DCIS, the malignant cells have not metastasized through the walls of the ducts into the fatty tissue of the breast. Infiltration (or invasive) ductal carcinoma (IDC) has metastasized
30 through the wall of the duct and invaded the fatty tissue of the breast. Infiltrating (or invasive) lobular carcinoma (ILC) is similar to IDC, in that it has

the potential to metastasize elsewhere in the body. About 10 % to 15 % of invasive breast cancers are invasive lobular carcinomas.

Also of interest is non-small cell lung carcinoma. Non-small cell lung cancer (NSCLC) is made up of three general subtypes of lung cancer. Epidermoid carcinoma (also called squamous cell carcinoma) usually starts in one of the larger bronchial tubes and grows relatively slowly. The size of these tumors can range from very small to quite large. Adenocarcinoma starts growing near the outside surface of the lung and may vary in both size and growth rate. Some slowly growing adenocarcinomas are described as alveolar cell cancer. Large cell carcinoma starts near the surface of the lung, grows rapidly, and the growth is usually fairly large when diagnosed. Other less common forms of lung cancer are carcinoid, cylindroma, mucoepidermoid, and malignant mesothelioma.

Melanoma is a malignant tumor of melanocytes. Although most melanomas arise in the skin, they also may arise from mucosal surfaces or at other sites to which neural crest cells migrate. Melanoma occurs predominantly in adults, and more than half of the cases arise in apparently normal areas of the skin. Prognosis is affected by clinical and histological factors and by anatomic location of the lesion. Thickness and/or level of invasion of the melanoma, mitotic index, tumor infiltrating lymphocytes, and ulceration or bleeding at the primary site affect the prognosis. Clinical staging is based on whether the tumor has spread to regional lymph nodes or distant sites. For disease clinically confined to the primary site, the greater the thickness and depth of local invasion of the melanoma, the higher the chance of lymph node metastases and the worse the prognosis. Melanoma can spread by local extension (through lymphatics) and/or by hematogenous routes to distant sites. Any organ may be involved by metastases, but lungs and liver are common sites.

Other hyperproliferative diseases of interest relate to epidermal hyperproliferation, tissue, remodeling and repair. For example, the chronic skin inflammation of psoriasis is associated with hyperplastic epidermal keratinocytes as well as infiltrating mononuclear cells, including CD4+ memory T cells, neutrophils and macrophages.

The proliferation of immune cells is associated with a number of autoimmune and lymphoproliferative disorders. Diseases of interest include multiple sclerosis, rheumatoid arthritis and insulin dependent diabetes mellitus. Evidence suggests that abnormalities in apoptosis play a part in the pathogenesis of systemic lupus erythematosus (SLE). Other lymphoproliferative conditions the inherited disorder of lymphocyte apoptosis, which is an autoimmune lymphoproliferative syndrome, as well as a number of leukemia's and lymphomas. Symptoms of allergies to environmental and food agents, as well as inflammatory bowel disease, may also be alleviated by the compounds of the invention.

Surprisingly, it has been found that N-oxides according to the invention are able to interact with signaling pathways, especially the signaling pathways described herein and preferably the Tie-2, VEGFR-2 and/or raf-kinase signaling pathway. N-Oxides according to the invention preferably show advantageous biological activity which can easily be demonstrated according to methods known in the art, for example by enzyme based assays. Suitable assays are known in the art, for example from the literature cited herein and the references cited in the literature, or can be developed and/or performed in an analogous manner thereof. In such enzyme based assays, N-oxides according to the invention show an effect, preferably a modulating and especially an inhibiting effect which is usually documented by IC_{50} values in a suitable range, preferably in the micromolar range and more preferred in the nanomolar range.

In general, compounds according to the invention are to be regarded as suitable kinase-modulators and especially suitable kinase-inhibitors according to the invention if they show an effect or an activity to one or more kinases, preferably to one or more raf-kinases that preferably lies, determined as IC₅₀-value, in the range of 100 μ mol or below, preferably 10 μ mol or below, more preferably in the range of 3 μ mol or below, even more preferably in the range of 1 μ mol or below and most preferably in the nanomolar range. Especially preferred for use according to the invention are kinase-inhibitors as defined above/below, that show an activity, determined as IC₅₀-value, to one or more kinases, preferably kinases as discussed herein, more preferably one or more kinases including or consisting of Tie-2, VEGFR-2 and/or raf-kinases, in the range of 0.5 μ mol or below and especially in the range of 0.1 μ mol or below. In many cases an IC₅₀-value at the lower end of the given ranges is advantageous and in some cases it is highly desirable that the IC₅₀-value is as small as possible or the IC₅₀-values are as small as possible, but in general IC₅₀-values that lie between the above given upper limits and a lower limit in the range of 0.0001 μ mol, 0.001 μ mol, 0.01 μ mol or even above 0.1 μ mol are sufficient to indicate the desired pharmaceutical activity. However, the activities measured can vary depending on the respective testing system or assay chosen.

Alternatively, the advantageous biological activity of the compounds according to the invention can easily be demonstrated in *in vitro* assays, such as *in vitro* proliferation assays or *in vitro* growth assays. Suitable *in vitro* assays are known in the art, for example from the literature cited herein and the references cited in the literature or can be performed as described below, or can be developed and/or performed in an analogous manner thereof.

As an example for an *in vitro* growth assay, human tumor cell lines, for example HCT116, DLD-1 or MiaPaCa, containing mutated K-ras genes can be used in standard proliferation assays, for example for anchorage dependent growth on plastic or anchorage independent growth in soft agar.

Human tumor cell lines are commercially available, for example from ATCC (Rockville MD), and can be cultured according to methods known in the art, for example in RPMI with 10% heat inactivated fetal bovine serum and 200 mM glutamine. Cell culture media, fetal bovine serum and additives are
5 commercially available, for example from Invitrogen/Gibco/BRL (Karlsruhe, Germany) and/or QRH Biosciences (Lenexa, KS). In a standard proliferation assay for anchorage dependent growth, 3×10^3 cells can be seeded into 96-well tissue culture plates and allowed to attach, for example overnight at 37 °C in a 5% CO₂ incubator. Compounds can be titrated in media in dilution
10 series and added to 96 well cell cultures. Cells are allowed to grow, for example for 1 to 5 days, typically with a feeding of fresh compound containing media at about half of the time of the growing period, for example on day 3, if the cells are allowed to grow 5 days. Proliferation can be monitored by methods known in the art, such as measuring metabolic
15 activity, for example with standard XTT colorimetric assay (Boehringer Mannheim) measured by standard ELISA plate reader at OD 490/560, by measuring ³H-thymidine incorporation into DNA following an 8 h culture with 1 μCi ³H-thymidine, harvesting the cells onto glass fiber mats using a cell harvester and measuring ³H-thymidine incorporation by liquid scintillation
20 counting, or by staining techniques, such as crystal violet staining. Other suitable cellular assay systems are known in the art.

Alternatively, for anchorage independent cell growth, cells can be plated at 1×10^3 to 3×10^3 in 0.4% Seaplaque agarose in RPMI complete media,
25 overlaying a bottom layer containing only 0.64% agar in RPMI complete media, for example in 24-well tissue culture plates. Complete media plus dilution series of compounds can be added to wells and incubated, for example at 37 °C in a 5% CO₂ incubator for a sufficient time, for example 10-14 days, preferably with repeated feedings of fresh media containing
30 compound, typically at 3-4 day intervals. Colony formation and total cell mass can be monitored, average colony size and number of colonies can be quantitated according to methods known in the art, for example using image

capture technology and image analysis software. Image capture technology and image analysis software, such as Image Pro Plus or media Cybernetics.

5 The advantageous properties of the compounds according to the invention can be additionally shown in other suitable assay systems, for example the assay systems described below. Preferably, the compounds according to the invention show an inhibiting activity in one or more of the assay systems. Suitable assays are known from the literature and can be readily performed by the skilled artisan (see for example Dhanabal et al., *Cancer Res.* 59:189-
10 197; Xin et al., *J. Biol. Chem.* 274:9116-9121; Sheu et al., *Anticancer Res.* 18:4435-4441; Ausprunk et al., *Dev. Biol.* 38:237-248; Gimbrone et al., *J. Natl. Cancer Inst.* 52:413-427; Nicosia et al., *In Vitro* 18:538- 549).

15 The compounds according to the invention described in the examples are tested by the assays described below and are found to have kinase inhibitory activity. Other assays are known from the literature and can readily be performed by the person skilled in the art (see, for example, Dhanabal et al., *Cancer Res.* 59:189-197; Xin et al., *J. Biol. Chem.* 274:9116-9121; Sheu et al., *Anticancer Res.* 18:4435-4441; Ausprunk et al., *Dev. Biol.* 38:237-248;
20 Gimbrone et al., *J. Natl. Cancer Inst.* 52:413-427; Nicosia et al., *In Vitro* 18:538- 549).

VEGF receptor kinase assay

VEGF receptor kinase activity is measured by incorporation of radio- labelled phosphate into 4:1 polyglutamic acid/tyrosine substrate (pEY). The
25 phosphorylated pEY product is trapped onto a filter membrane and the incorporation of radiolabelled phosphate is quantified by scintillation counting.

Materials:

VEGF receptor kinase

30 The intracellular tyrosine kinase domains of human KDR (Terman, B. I. et al. *Oncogene* (1991) Vol. 6, pp. 1677-1683.) and Flt-1 (Shibuya, M. et al. *Oncogene* (1990) Vol. 5, pp. 519-524) are cloned as glutathione S-

transferase (GST) gene fusion proteins. This is accomplished by cloning the cytoplasmic domain of the KDR kinase as an in frame fusion at the carboxyl terminus of the GST gene. Soluble recombinant GST-kinase domain fusion proteins are expressed in *Spodoptera frugiperda* (Sf21) insect cells

5 (Invitrogen) using a baculovirus expression vector (pAcG2T, Pharmingen).

Lysis buffer

50 mM Tris pH 7.4, 0.5 M NaCl, 5 mM DTT, 1 mM EDTA, 0.5% triton X-100, 10% glycerol, 10 mg/ml each of leupeptin, pepstatin and aprotinin and 1 mM phenylmethylsulfonyl fluoride (all Sigma).

10 Wash buffer

50 mM Tris pH 7.4, 0.5 M NaCl, 5 mM DTT, 1 mM EDTA, 0.05% triton X-100, 10% glycerol, 10 mg/ml each of leupeptin, pepstatin and aprotinin and 1 mM phenylmethylsulfonyl fluoride.

Dialysis buffer

15 50 mM Tris pH 7.4, 0.5 M NaCl, 5 mM DTT, 1 mM EDTA, 0.05% triton X-100, 50% glycerol, 10 mg/ml each of leupeptin, pepstatin and aprotinin and 1 mM phenylmethylsulfonyl fluoride.

10× reaction buffer

200 mM Tris, pH 7.4, 1.0 M NaCl, 50 mM MnCl₂, 10 mM DTT and 5 mg/ml

20 bovine serum albumin [BSA] (Sigma).

Enzyme dilution buffer

50 mM Tris, pH 7.4, 0.1 M NaCl, 1 mM DTT, 10% glycerol, 100 mg/ml BSA.

10× substrate

750 µg/ml poly(glutamic acid/tyrosine; 4:1) (Sigma).

25 Stop solution

30% trichloroacetic acid, 0.2 M sodium pyrophosphate (both Fisher).

Wash solution

15% trichloroacetic acid, 0.2 M sodium pyrophosphate.

Filter plates

30 Millipore #MAFC NOB, GF/C glass fibre 96 well plate.

Method A – protein purification

1. Sf21 cells are infected with recombinant virus at a multiplicity of infection of 5 virus particles/cell and grown at 27°C for 48 hours.
2. All steps are performed at 4°C. Infected cells are harvested by centrifugation at 1000×g and lysed at 4°C for 30 minutes with 1/10 volume of lysis buffer followed by centrifugation at 100,000×g for 1 hour. The supernatant is then passed over a glutathione Sepharose column (Pharmacia) equilibrated with lysis buffer and washed with 5 volumes of the same buffer followed by 5 volumes of wash buffer. Recombinant GST-KDR protein is eluted with wash buffer/10 mM reduced glutathione (Sigma) and dialysed against dialysis buffer.

Method B – VEGF receptor kinase assay

1. Add 5 µl of inhibitor or control to the assay in 50% DMSO.
2. Add 35 µl of reaction mixture containing 5 µl of 10× reaction buffer, 5 µl of 25 mM ATP/10 µCi [³³P]ATP (Amersham) and 5 µl of 10× substrate.
3. Start the reaction by the addition of 10 µl of KDR (25 nM) in enzyme dilution buffer.
4. Mix and incubate at room temperature for 15 minutes.
5. Stop the reaction by the addition of 50 µl of stop solution.
6. Incubate for 15 minutes at 4°C.
7. Transfer a 90 µl aliquot to filter plate.
8. Aspirate and wash 3 times with wash solution.
9. Add 30 µl of scintillation cocktail, seal plate and count in a Wallace Microbeta scintillation counter.

Human umbilical vein endothelial cell mitogenesis assay

- Expression of VEGF receptors that mediate mitogenic responses to the growth factor is largely restricted to vascular endothelial cells. Human umbilical vein endothelial cells (HUVECs) in culture proliferate in response to VEGF treatment and can be used as an assay system to quantify the effects of KDR kinase inhibitors on VEGF stimulation. In the assay described, quiescent HUVEC monolayers are treated with vehicle or test compound 2 hours prior to addition of VEGF or basic fibroblast growth factor (bFGF). The

mitogenic response to VEGF or bFGF is determined by measuring the incorporation of [³H]thymidine into cellular DNA.

Materials:

5 HUVECs

HUVECs frozen as primary culture isolates are obtained from Clonetics Corp. Cells are maintained in endothelial growth medium (EGM; Clonetics) and are used for mitogenic assays at passages 3-7.

Culture plates

10 NUNCLON 96-well polystyrene tissue culture plates (NUNC #167008).

Assay medium

Dulbecco's modification of Eagle's medium containing 1 g/ml glucose (low-glucose DMEM; Mediatech) plus 10% (v/v) foetal bovine serum (Clonetics).

Test compounds

15 Working stock solutions of test compounds are diluted serially in 100% dimethyl sulfoxide (DMSO) to 400 times greater than their desired final concentrations. Final dilutions to 1× concentration are made into assay medium immediately prior to addition to cells.

10× growth factors

20 Solutions of human VEGF 165 (500 ng/ml; R&D Systems) and bFGF (10 ng/ml; R&D Systems) are prepared in assay medium.

10× [³H]thymidine

[Methyl-³H]thymidine (20 Ci/mmol; Dupont-NEN) is diluted to 80 μCi/ml in low-glucose DMEM.

25 Cell wash medium

Hank's balanced salt solution (Mediatech) containing 1 mg/ml bovine serum albumin (Boehringer-Mannheim).

Cell lysis solution

1 N NaOH, 2% (w/v) Na₂CO₃.

30 Method 1

HUVEC monolayers maintained in EGM are harvested by trypsinisation and plated out at a density of 4000 cells per 100 μl of assay medium per well in

96-well plates. Cell growth is arrested for 24 hours at 37°C in a humidified atmosphere containing 5% CO₂.

Method 2

5 Growth-arrest medium is replaced by 100 µl of assay medium containing either vehicle (0.25% [v/v] DMSO) or the desired final concentration of test compound. All determinations are performed in triplicate. Cells are then incubated at 37°C/5% CO₂ for 2 hours to allow test compounds to enter cells.

Method 3

10 After the 2-hour pre-treatment period, cells are stimulated by addition of 10 µl/well of either assay medium, 10× VEGF solution or 10× bFGF solution. Cells are then incubated at 37°C/5% CO₂.

Method 4

After 24 hours in the presence of growth factors, 10× [³H]thymidine (10 µl/well) is added.

15 Method 5

Three days after addition of [³H]thymidine, medium is removed by aspiration, and cells are washed twice with cell wash medium (400 µl/well followed by 200 µl/well). The washed, adherent cells are then solubilised by addition of cell lysis solution (100 µl/well) and warming to 37°C for 30 minutes. Cell
20 lysates are transferred to 7 ml glass scintillation vials containing 150 µl of water. Scintillation cocktail (5 ml/vial) is added, and cell-associated radioactivity is determined by liquid scintillation spectroscopy.

According to these assays, the compounds of the formula I preferably are inhibitors of VEGF and are thus suitable for the inhibition of angiogenesis,
25 such as in the treatment of ocular diseases, for example diabetic retinopathy, and for the treatment of carcinomas, for example solid tumours. The present compounds preferably inhibit VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC₅₀ values of 0.01-5.0 µM. These compounds preferably also show selectivity over related tyrosine kinases (for
30 example FGFR1 and the Src family; for relationship between Src kinases and VEGFR kinases, see Eliceiri et al., Molecular Cell, Vol. 4, pp.915-924, December 1999).

TIE-2 Enzyme assay (TIE2-E)

The TIE-2 enzyme assay uses the LANCE method (Wallac) and GST-TIE2, baculovirus expressed recombinant constructs of the intracellular domains of human TIE2 (amino acids 762-1104, GenBank Accession # L06139) tagged by GST). The method measures the ability of the purified enzymes to catalyse the transfer of the γ -phosphate from ATP onto tyrosine residues in a biotinylated synthetic peptide, D1-15 (biotin-C6-LEARLVAYEGWVAGKKKamide). This peptide phosphorylation is detected using the following procedure: for enzyme preactivation, GST-TIE2 is incubated for 30mins at room temperature with 2 mM ATP, 5 mM $MgCl_2$ and 12.5 mM DTT in 22.5 mM HEPES buffer (pH7.4). Preactivated GST-TIE2 is incubated for 30mins at room temperature in 96 well plates with 1 μ M D1-15 peptide, 80 μ M ATP, 10 mM $MgCl_2$, 0.1mg/ml BSA and the test compound (diluted from a 10 mM stock in DMSO, final DMSO concentration is 2.4%) in 1 mM HEPES (pH7.4). The reaction is stopped by the addition of EDTA (final concentration 45 mM). Streptavidin linked-APC (allophycocyanin, Molecular Probe) and Europium-labeled anti-phosphorylated tyrosine antibody (Wallac) are then added at the final concentration of 17 μ g/well and 2.1 μ g/well, respectively. The APC signal is measured using an ARVO multilabel counter (e.g. Wallac Berthold Japan). The percent inhibition of activity is calculated relative to blank control wells. The concentration of test compound that inhibits 50% of activity (IC_{50}) is interpolated using nonlinear regression (Levenberg-Marquardt) and the equation, $y = V_{max} (1-x/(K+x)) + Y_2$, where "K" is equal to the IC_{50} . The IC_{50} values are then preferably converted to pIC_{50} values, i.e., $-\log IC_{50}$ in Molar concentration.

As discussed herein, these signaling pathways are relevant for various disorders. Accordingly, by interacting with one or more of said signaling pathways, N-oxides according to the invention are useful in the prevention and/or the treatment of disorders that are dependent from said signaling pathways.

5 The compounds according to the invention are preferably kinase modulators and more preferably kinase inhibitors. The compounds according to the invention are more preferably modulators and especially inhibitors of kinases, preferably kinases selected from the group consisting of serine/threonine kinases and receptor tyrosine kinases.

10 According to the invention, receptor tyrosine kinases are preferably selected from Tie-kinases, VEGFR-kinases and PDGFR-kinases.

According to the invention, serine/threonine kinases are preferably selected from raf-kinases, SAPK-kinases and p38-kinases.

15 According to the invention, kinases include, but are not limited to one or more Raf-kinases, one or more Tie-kinases, one or more VEGFR-kinases, one or more PDGFR-kinases, p38-kinase and/or SAPK2alpha.

Raf-kinases in this respect are respect preferably include or consist of A-Raf, B-Raf and c-Raf1.

20 Tie-kinases in this respect preferably include or consist of Tie-2 kinase.

VEGFR-kinases in this respect preferably include or consist of VEGFR-2 kinase.

25 Accordingly, the compounds according to the invention are preferably modulators and more preferably inhibitors of one or more kinases, selected from the group consisting of A-Raf, B-Raf, c-Raf1, Tie-1, Tie-2, Tie-3, PDGFR, VEGFR-1, VEGFR-2, VEGFR-3, p38-kinase and Ltk-kinase.

30 More preferably, the compounds according to the invention are dual specific or oligo specific modulators and more preferably inhibitors of two or more

kinases, preferably two, three or four kinases, selected from the group consisting of A-Raf, B-Raf, c-Raf1, Tie-1, Tie-2, Tie-3, PDGFR, VEGFR-1, VEGFR-2, VEGFR-3, p38-kinase and Ltk-kinase, more preferably selected from Tie-2, PDGFR, VEGFR-2 and p38-kinase and especially selected from Tie-2, PDGFR and VEGFR-2.

Even more preferably, the compounds according to the invention are highly potent and/or specific inhibitors of Tie-2, VEGFR-2 and/or PDGFR kinases.

Especially preferably, the compounds according to the invention are highly potent and/or specific inhibitors of both Tie-2 and VEGFR-2 kinases.

Especially preferably, the compounds according to the invention are highly potent and/or specific inhibitors of both Tie-2 and KDR.

Due to the kinase modulating or inhibiting properties of the compounds according to the invention, the compounds according to the invention preferably interact with one or more signalling pathways which are preferably cell signalling pathways, preferably by downregulating or inhibiting said signaling pathways. Examples for such signalling pathways include, but are not limited to the raf-kinase pathway, the Tie-kinase pathway, the VEGFR-kinase pathway, the PDGFR-kinase pathway, the p38-kinase pathway, the SAPK2alpha pathway and/or the Ras-pathway.

Modulation of the raf-kinase pathway plays an important role in various cancerous and noncancerous disorders, preferably cancerous disorders, such as dermatological tumors, haematological tumors, sarcomas, squamous cell cancer, gastric cancer, head cancer, neck cancer, oesophageal cancer, lymphoma, ovary cancer, uterine cancer and/or prostate cancer. Modulation of the raf-kinase pathway plays a even more important role in various cancer types which show a constitutive activation of the raf-kinase dependent signalling pathway, such as melanoma, colorectal cancer, lung cancer, brain

cancer, pancreatic cancer, breast cancer, gynaecological cancer, ovarian cancer, thyroid cancer, chronic leukaemia and acute leukaemia, bladder cancer, hepatic cancer and/or renal cancer. Modulation of the raf-kinase pathway plays also an important role in infection diseases, preferably the infection diseases as mentioned above/below and especially in *Helicobacter pylori* infections, such as *Helicobacter pylori* infection during peptic ulcer disease.

Modulation of the Tie-2-kinase pathway plays an important role in various cancerous and noncancerous disorders, preferably cancerous disorders, and especially disorders characterized by cellular proliferation in the area of disorders associated with neo-vascularization and/or vascular permeability; such disorders preferably include blood vessel proliferative disorders, including arthritis and restenosis; fibrotic disorders, including hepatic cirrhosis and atherosclerosis; mesangial cell proliferative disorders, including glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, organ transplant rejection and glomerulopathies; and metabolic disorders, including psoriasis, diabetes mellitus, chronic wound healing, inflammation and neurodegenerative diseases.

One or more of the signalling pathways mentioned above/below and especially the VEGFR-kinase pathway plays an important role in angiogenesis. Accordingly, due to the kinase modulating or inhibiting properties of the compounds according to the invention, the compounds according to the invention are suitable for the prophylaxis and/or treatment of pathological processes or disorders caused, mediated and/or propagated by angiogenesis, for example by inducing anti-angiogenesis. Pathological processes or disorders caused, mediated and/or propagated by angiogenesis include, but are not limited to tumors, especially solid tumors, arthritis, especially rheumatic or rheumatoid arthritis, diabetic retinopathy, psoriasis, restenosis; fibrotic disorders; mesangial cell proliferative disorders, diabetic

nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, organ transplant rejection, glomerulopathies, metabolic disorders, inflammation and neurodegenerative diseases, and especially solid tumors, rheumatic arthritis, diabetic retinopathy and psoriasis.

5

Modulation of the p38-signalling pathway plays an important role in various cancerous and also in various noncancerous disorders, such as fibrosis, atherosclerosis, restenosis, vascular disease, cardiovascular disease, inflammation, renal disease and/or angiogenesis, and especially noncancerous disorders such as rheumatoid arthritis, inflammation, autoimmune disease, chronic obstructive pulmonary disease, asthma and/or inflammatory bowel disease.

10

Modulation of the PDGF-signalling pathway plays an important role in various cancerous and although in various noncancerous disorders, such as rheumatoid arthritis, inflammation, autoimmune disease, chronic obstructive pulmonary disease, asthma and/or inflammatory bowel disease, and especially noncancerous disorders such as fibrosis, atherosclerosis, restenosis, vascular disease, cardiovascular disease, inflammation, renal disease and/or angiogenesis.

15

20

A further preferred subject of the invention are N-oxides according to the invention as promoters or inhibitors, preferably as inhibitors of one or more raf-kinases, selected from the group consisting of A-raf, B-raf and c-raf1.

25

Especially preferred subject of the invention are N-oxides according to the invention as promoters or inhibitors, preferably as inhibitors of c-raf1 or B-raf.

30

Thus, subject of the present invention are N-oxides according to the invention as medicaments. Subject of the present invention are N-oxides according to the invention as medicament active ingredients. Further subject of the present invention is the use of one or more N-oxides according to the invention as a pharmaceutical. Further subject of the present invention is the

use of one or more N-oxides according to the invention in the treatment and/or the prophylaxis of disorders, preferably the disorders described herein, more preferred disorders that are caused, mediated and/ or propagated by signalling pathways discussed herein, even more preferred disorders that are caused, mediated and/or propagated by one or more kinases, preferably selected from serine/threonine kinases and receptor tyrosine kinases, and especially disorders that are caused, mediated and/or propagated by raf-kinases, especially B-raf and/or c-raf1, Tie-kinases, especially Tie-2, and/or VEGFR-kinases, especially VEGFR-2.

Usually, the disorders discussed herein are divided into two groups, hyperproliferative and non hyperproliferative disorders. In this context, psoriasis, arthritis, inflammation, endometriosis, scarring, benign prostatic hyperplasia, immunological diseases, autoimmune diseases and immunodeficiency diseases are to be regarded as noncancerous disorders, of which arthritis, inflammation, immunological diseases, autoimmune diseases and immunodeficiency diseases are usually regarded as non hyperproliferative disorders. In this context, brain cancer, lung cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, hepatic cancer, renal cancer, colorectal cancer, breast cancer, head cancer, neck cancer, oesophageal cancer, gynaecological cancer, thyroid cancer, lymphoma, chronic leukaemia and acute leukaemia are to be regarded as cancerous disorders, all of which are usually regarded as hyperproliferative disorders. Especially cancerous cell growth and especially cancerous cell growth mediated by raf-kinase is a disorder which is a target of the present invention. Subject of the present invention therefore are N-oxides according to the invention as medicaments and/or medicament active ingredients in the treatment and/or the prophylaxis of said disorders and the use of N-oxides according to the invention for the manufacture of a pharmaceutical for the treatment and/or the prophylaxis of said disorders as well as a method of treatment of said disorders, comprising administering one or more N-oxides according to the invention to a patient in need of such an administration.

Subject of the present invention therefore are N-oxides according to the invention as medicaments and/or medicament active ingredients in the treatment and/or the prophylaxis said disorders and the use of N-oxides according to the invention for the manufacture of a pharmaceutical for the treatment and/or the prophylaxis of said disorders as well as a method of treatment of said disorders, comprising administering one or more N-oxides according to the invention to a patient in need of such an administration.

Subject of the present invention is preferably a pharmaceutical composition comprising an N-oxide and optionally a physiologically acceptable vehicle (carrier) to treat a disease in man or other mammal, which is regulated by one or more protein kinases of the receptor tyrosin kinase and serin/threonin kinase families, and thus can be improved by modulation of those kinases.

Subject of the present invention is preferably a pharmaceutical composition comprising an N-oxide and optionally a carrier to treat a disease in man or other mammal, which is regulated by one or more of the protein kinases TIE2, KDR, PDGFR, SAPK2a, SAPK2b, TrkA, TrkB, EphB2, EphB4, VEGFR1, VEGFR3, Lck, Fms, Flt3, RafC, Met.

Subject of the present invention is preferably a method of treatment of diseases by targeting dysregulated kinase signaling with compounds or formulations according to the invention in the areas of cancer, inflammation, cardiovascular system, peripheral and central nervous system.

Subject of the present invention is preferably a method of treatment of diseases by targeting dysregulated kinase signaling with compounds or formulations according to the invention in organs and tissues of man or another mammal, like skin, blood, breast, uterine cervix, uterine corpus (endometrium), ovary, lung, bronchus, stomach, intestines, liver gall bladder, kidney, skin, oral cavity and pharynx, prostate, pancreas, urinary bladder, blood cells, colon, rectum, bone, brain, eye, central and peripheral nervous system, exemplified as breast cancer, colorectal cancer, gliomas, lymphomas, and so on, and of inflammatory diseases like rheumatoid arthritis and psoriasis, or diseases of the eye, like macula degeneration, and diabetic retinopathy.

Subject of the present invention is preferably a method of treatment of cancer by direct targeting kinases of the tumor cells or targeting kinases of the vascular

system, and by targeting kinases of the stromal cells, thus treating or preventing hyper-proliferative, inflammatory and/or angiogenic disorders.

Subject of the present invention is preferably a method for modulating kinase signal transduction by administration of a compounds or formulation according to the invention to a human or other mammal.

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Subject of the present invention is preferably a method for diagnosis, treatment or prevention of a disease in a human or other mammal by administration of a compounds and formulation according to the invention thus modulating kinase signal transduction.

10

Subject of the present invention is preferably a method as described before wherein compounds or formulation according to the invention are administered in combination with another compound of high molecular weight (NBE, protein, antibody, fusion protein, immune cytokine) or low molecular weight (NCE), like an anti-cancer agent, anti-angiogenic agent, cardiovascular agent, PNS agent, CNS agent, immune regulatory agent (like anti-inflammatory, immune stimulating, immune suppressive), or photo-dynamic therapy, or non-drug treatment, like

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excision, radiation, or radio-immuno therapy.

The compounds according the invention are especially advantageous in the above given subjects because of their advantageous kinase modulating properties and especially with respect to the Tie-2 and KDR modulating properties.

20

Accordingly, subject of the present invention are pharmaceutical compositions that contain one or more N-oxides according to the invention. Subject of the present invention are especially pharmaceutical compositions that contain one or more N-oxides according to the invention and one or more additional compounds (other than the compounds of the instant invention), preferably selected from the group consisting of physiologically acceptable excipients, auxiliaries, adjuvants, carriers and pharmaceutically active ingredients other than the compounds according to the invention.

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Accordingly, subject of the present invention is a process for the manufacture of a pharmaceutical composition, wherein one or more N-oxides according to the invention and one or more compounds (other than the compounds of the instant invention), preferably selected from the group consisting of carriers,

excipients, auxiliaries, adjuvants and pharmaceutically active ingredients other than the compounds according to the invention.

Accordingly, the use of the compounds according to the invention in the
5 treatment of Hyperproliferative disorders is a subject of the instant invention.

Accordingly, the use of the compounds according to the invention for
producing a medicament for the treatment of hyperproliferative disorders is a
subject of the instant invention.

10 The compounds according to the invention can preferably be combined in an advantageous manner with known anti-cancer agents. Examples of such known anti-cancer agents comprise:

Estrogen receptor modulators, androgen receptor modulators, retinoid
15 receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA-reductase-inhibitors, HIV-protease-inhibitors, reverse-transcriptase-inhibitors as well as further angiogenesis inhibitors. The compounds according to the invention preferably are especially suitable for administration in combination with radiotherapy.

20 The term „estrogen receptor modulators“ preferably relates to compounds which modulate or preferably inhibit the binding of estrogen to the respective receptor, independently of the respective mode of action. Examples of estrogen receptor modulators in this respect include, but are not limited to Tamoxifen, Raloxifen, Idoxifen, LY353381, LY117081, Toremifen,
25 Fulvestrant, 4-[7-(2,2-Dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyrane-3-yl]phenyl-2,2-dimethylpropanoate, 4,4'-Dihydroxybenzophenone-2,4-dinitrophenylhydrazone and SH646.

The term „androgen receptor modulators“ preferably relates to compounds
30 which modulate or preferably inhibit the binding of androgens to the respective receptor, independently of the respective mode of action.

Androgen receptor modulators in this respect include, but are not limited to

5 α -reductase-inhibitors, Nilutamide, Flutamide, Bicalutamide, Liarozole and Abiraterone-acetate.

5 The term „retinoid receptor modulators“ preferably relates to compounds which modulate or preferably inhibit the binding of retinoids to the respective receptor, independently of the respective mode of action. Retinoid receptor modulators in this respect include, but are not limited to Bexarotene, Tretinoine, 13-cis-retinoic acid, 9-cis-retinoic acid, α -Difluoromethylornithine, ILX23-7553, trans-N-(4'-Hydroxyphenyl)retinamide and N-4-Carboxyphenylretinamide.

10 The term „cytotoxic agents“ preferably relates to compounds which preferably directly interact with the cell functions and thus induce cell death (apoptosis) or which modulate or preferably inhibit cell mitosis. Cytotoxic agents in this respect include, but are not limited to alkylating agents, tumour necrosis factors, intercalating agents, microtubuline inhibitors and topoisomerase inhibitors.

15 Examples of cytotoxic agents in this respect include, but are not limited to Tirapazimine, Sertenef, Cachectine, Ifosfamide, Tasonermine, Lonidamine, Carboplatine, Altretamine, Prednimustine, Dibromdulcit, Ranimustine, Fotemustine, Nedaplatine, Oxaliplatin, Temozolomide, Heptaplatine, Estramustine, Improsulfan-tosylate, Trofosfamide, Nimustine, Dibrospidium-chloride, Pumitepa, Lobaplatine, Satraplatine, Proflomycin, Cisplatin, Irofulvene, Dexifosfamide, cis-Amino dichloro(2-methylpyridine)platin, Benzylguanine, Glufosfamide, GPX100, (trans,trans,trans)-bis- μ -(hexan-1,6-diamine)- μ -[diamine-platin(II)]bis[diamine(chloro)platin(II)]-tetrachloride, 25 Diarizidinylspermine, Arsentrioxide, 1-(11-Dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, Zorubicine, Idarubicine, Daunorubicine, Bisantrene, Mitoxantrone, Pirarubicine, Pinafide, Valrubicine, Amrubicine, Antineoplastone, 3'-Desamino-3'-morpholino-13-desoxo-10-hydroxycarminomycin, Annamycin, Galarubicine, Elinafide, MEN10755 and 4-Desmethoxy-3-desamino-3-aziridinyl-4-methylsulfonyldaunorubicin 30 (see for example WO 00/50032).

Examples of microtubulin inhibitors in this respect include, but are not limited to Paclitaxel, Vindesine-sulfate, 3',4'-Dideshydro-4'-desoxy-8'-norvincal leukoblastine, Docetaxol, Rhizoxine, Dolastatine, Mivobuine-isethionate, Auristatine, Cemadotine, RPR109881, BMS184476, Vinflunine, Cryptophycine, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl)benzene sulfonamide, Anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258 and BMS188797.

Examples of topoisomerase inhibitors in this respect include, but are not limited to Topotecan, Hycaptamine, Irinotecan, Rubitecan, 6-Ethoxypropionyl-3',4'-O-exo-benzyliden-chartreusine, 9-Methoxy-N,N-dimethyl-5-nitropyrzolo[3,4,5-kl]acridine-2-(6H)propanamine, 1-Amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano-[3',4':b,7]indolizino[1,2b]chinoine-10,13(9H,15H)-dione, Lurtotecane, 7-[2-(N-Isopropylamino)ethyl]-(20S)camptothecine, BNP1350, BNPI1100, BN80915, BN80942, Etoposide-phosphate, Teniposide, Sobuzoxane, 2'-Dimethylamino-2'-desoxy-etoposide, GL331, N-[2-(Dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazol-1-carboxamide, Asulacrine, (5a,5aB,8aa,9b)-9-[2-[N-[2-(Dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydroxy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexahydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(Methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]phenanthridinium, 6,9-Bis[(2-aminoethyl)amino]benzo[g]isochinoine-5,10-dione, 5-(3-Aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]-acridine-6-one, N-[1-[2(Diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(Dimethyl-amino)-ethyl)acridine-4-carboxamide, 6-[[2-(Dimethylamino)-ethyl]amino]-3-hydroxy-7H-indeno[2,1-c]chinoine-7-one and Dimesna.

The term „antiproliferative agents“ preferably includes, but is not limited to siRNA, antisense-RNA- and -DNA-Oligonucleotides, such as G3139, ODN698, RVASKRAS, GEM231 and INX3001, as well as antimetabolites, such as Enocitabine, Carmofur, Tegafur, Pentostatine, Doxifluridine, Trimetrexate, Fludarabine, Capecitabine, Galocitabine, Cytarabin-ocfosfate,

Fosteabin-Sodium hydrate, Raltitrexede, Paltitrexide, Emitefur, Tiazofurine,
 Decitabine, Nolatrexede, Pemetrexede, Nelzarabine, 2'-Desoxy-2'-
 methylidencytidine, 2'-Fluoromethylen-2'-desoxycytidine, N-[5-(2,3-
 Dihydrobenzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)harnstoff, N6-[4-Desoxy-
 5 4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-manno-hepto-
 pyranosyl]adenine, Aplidine, Ecteinasidine, Troxacitabine, 4-[2-Amino-4-
 oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazin-6-yl-(S)-ethyl]-2,5-
 thienoyl-L-glutamic acid, Aminopterine, 5-Flurouracil, Alanosine, 11-Acetyl-8-
 (carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo-
 10 (7.4.1.0.0)-tetradeca-2,4,6-trien-9-ylacetic acid ester, Swainsonine,
 Lometrexol, Dexrazoxane, Methioninase, 2'-cyan-2'-desoxy-N4-palmitoyl-1-
 B-D-Arabinofuranosylcytosin and 3-Aminopyridine-2-carboxaldehyde-
 thiosemicarbazone. The „antiproliferative agents“ preferably further include
 monoclonal antibodies against growth factors other than the antibodies cited
 15 with respect to the "angiogenesis inhibitors", such as Trastuzumab, as well
 as tumour suppressor genes, such as p53, which can be administered via
 recombinant virus-driven gene transfer (see for example US 6,069,134).

The compounds according to the invention can preferably be combined in an
 20 advantageous manner with radiotherapy and/or known anti-cancer agents,
 preferably known anti-cancer agents as described herein.

The meaning of the term radiotherapy is known in the art. According to the
 invention, the term radiotherapy preferably includes, but is not limited to
 25 external beam radiation, administration of radioactive materials, such as
 radio isotopes radio nuclides, and/or radio immuno therapy (RIT).

Accordingly, the compounds of the present invention can be used to provide
 additive or preferably synergistic effects with existing cancer chemotherapies,
 30 and/or be used to restore effectiveness of existing cancer chemotherapies
 and radiation.

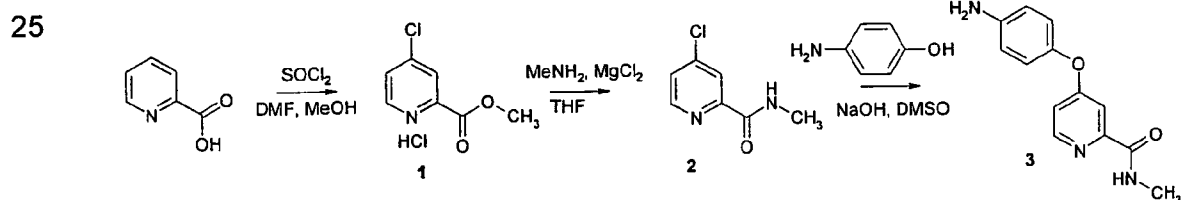
Above and below, all temperatures are given in °C. In the examples below, "conventional work-up" means that the organic phase is washed with saturated NaHCO₃ solution, if desired with water and saturated NaCl solution, the phases are separated, the organic phase is dried over sodium sulfate and evaporated, and the product is purified by chromatography on silica gel, by preparative HPLC and/or by crystallization.

The present invention relates to N-oxides of formula I, the use of the compounds of formula I as inhibitors of one or more kinases, the use of the compounds of formula I for the manufacture of a pharmaceutical composition and a method of treatment, comprising administering said pharmaceutical composition to a patient.

The following examples are given in order to assist the skilled artisan to better understand the present invention by way of exemplification. The examples are not intended to limit the scope of protection conferred by the claims. The features, properties and advantages exemplified for the compounds and uses defined in the examples may be assigned to other compounds and uses not specifically described and/or defined in the examples, but falling under the scope of what is defined in the claims.

Examples

i) Synthesis of the pyridine units



- 30 a) 750 ml of thionyl chloride are heated to 45°C under an N₂ atmosphere, and 23 ml of DMF are added dropwise. 250 g (2.031 mol) of pyridine-2-carboxylic acid are subsequently added in

portions, and the reaction mixture is stirred at 45°C for a further 15 minutes and at 80°C for 24 hours. The yellow suspension is evaporated, and the residue is entrained a number of times with toluene. The oily residue is dissolved in 180 ml of toluene, the solution is cooled to 0°C, and 110 ml of methanol are added dropwise. The suspension is stirred for a further hour, and the precipitated solid is filtered off with suction and rinsed with toluene. The resultant crude product is recrystallised a number of times from acetone and dried in a vacuum drying cabinet.

Yield: 140 g (33%) of **1**, pale crystals

- b) 140 g (0.673 mol) of **1** are stirred with 32 g (0.336 mol) of magnesium chloride and 2 l of THF at room temperature. After 5 minutes, 1.36 l (2.369 mol) of methylamine are added dropwise over the course of 20 minutes. The suspension is stirred at room temperature for a further 16 hours. 1.3 l of water and 680 ml of 1N HCl solution are added to the reaction mixture, and the mixture is extracted with ethyl acetate (3 x 1 l). The combined organic phases are washed with a saturated NaCl solution, dried using sodium sulfate, filtered and evaporated. The crude product is taken up in 300 ml of ethyl acetate and extracted with 200 ml of 1N HCl solution. The aqueous phase is adjusted to pH 9 using a 25% NH₄OH solution and extracted with ethyl acetate (2 x 400 ml). The organic phase is dried using sodium sulfate, filtered and evaporated.

Yield: 93 g (81%) of **2**, brown oil

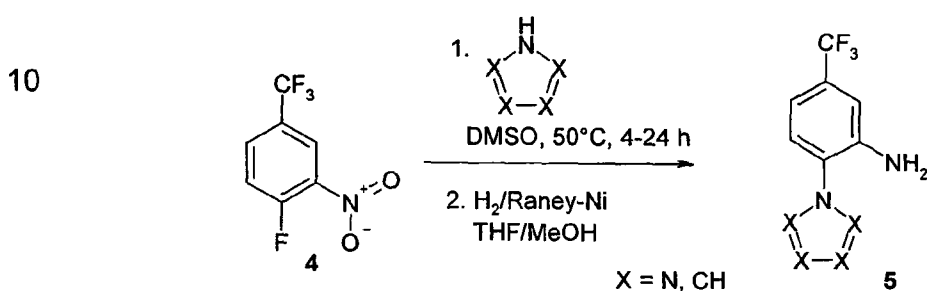
- c) 50 g (0.293 mol) of **2** and 32.6 g (0.293 mol) of 4-aminophenol are dissolved in DMSO, and 29.3 g (0.733 mol) of sodium hydroxide are slowly added. The solution is then heated at 100°C overnight. After a further 29.3 g (0.733 mol) of sodium hydroxide had been added, the reaction mixture is again stirred at 100°C overnight.

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The reaction mixture is cooled to room temperature, ice-water is added, and the mixture is extracted a number of times with diethyl ether. The combined organic phases are dried using sodium sulfate, filtered and evaporated.

5 Yield: 36 g (51%) of **3**, brown oil

ii) Synthesis of the anilines



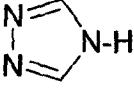
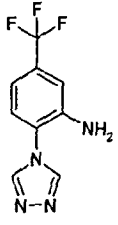
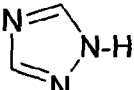
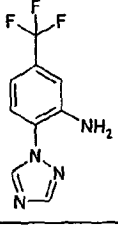
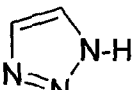
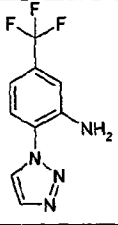
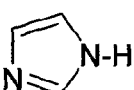
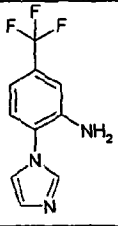
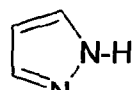
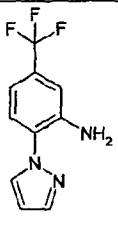
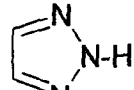
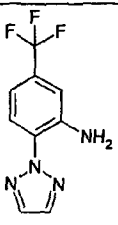
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4-Fluoro-3-nitrobenzotrifluoride is dissolved in DMSO (1.5 ml/mmol), treated with 1 equivalent of the respective azole and stirred at 50 °C for 4-24h. The reaction mixture is cooled to room temperature, treated with water (5-10 ml/mmol) and extracted twice with ethyl acetate (10-20 ml/mmol). The organic phase is washed with brine, dried over Na_2SO_4 , filtered and evaporated to dryness. The residue can be further purified by column chromatography on silica gel.

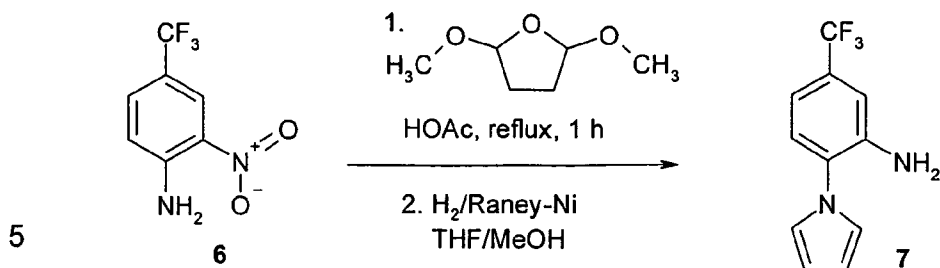
20 The accordingly obtained nitro compound is hydrogenated with H_2 and Pd on charcoal (5%, moisturised with water) in THF at room temperature until a full conversion is achieved. The catalyst is removed by filtration, rinsed with methanol, and the filtrate is evaporated to dryness. The obtained residues can be employed in the next steps without further purification.

30

Table 1

Nr.	R ⁷ -H	Struktur	HPLC	HPLC-MS
5a			2.20 (Method A)	229 (M+H)
5b			2.35 (Method A)	229 (M+H)
5c			2.47 (Method A)	229 (M+H)
5d			2.06 (Method A)	228 (M+H)
5e			2.39 (Method B)	228 (M+H)
5f				

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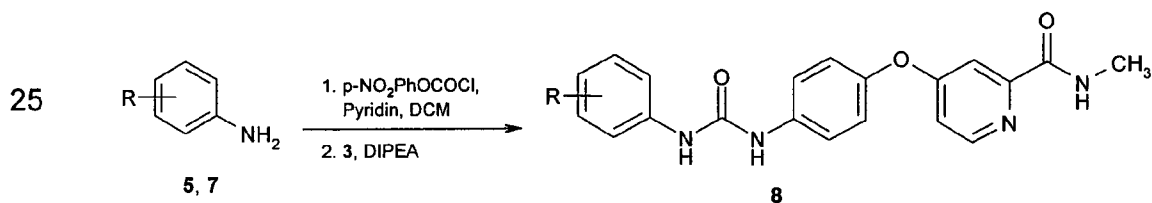
10 4-Fluoro-2-nitroaniline **6** (1.03 g, 5 mmol) is dissolved in 10 ml acetic acid, treated cautiously with 2,5-dimethoxy tetrahydrofuran (647 μ l, 5 mmol) and heated to reflux for 60 min. After cooling down the reaction mixture, the solvent is removed by distillation under reduced pressure. The residue is taken up in 50 ml ethylacetate, the resulting solution washed with 30 ml semi-concentrated NaHCO_3 solution and 30 ml brine, dried using sodium sulfate and evaporated to dryness.

15 Yield: 1.12 g, brown oil, HPLC: 2.85 (Method B), HPLC-MS: 257 (M+H)

The accordingly obtained nitro compound is hydrogenated with H_2 and Pd on charcoal (5%, moisturised with water) in THF at room temperature until a full conversion is achieved. The catalyst is removed by filtration, rinsed with methanol, and the filtrate is evaporated to dryness.

20 Yield: 1.0 g, brown oil, HPLC: 2.81 (Method B), HPLC-MS: 227 (M+H)

Synthesis of the ureas



30 200 μ mol of the respective aniline **5a-e** or **7** is dissolved in dichloromethane together with 220 μ mol p-nitrophenyl chloroformate, treated with 220 μ mol pyridine at room temperature and stirred for 20-35 min. After the reaction is completed, 200 μ mol **3** and 400 μ mol DIPEA are added and the reaction

mixture is stirred at room temperature until a full conversion is achieved (30 min - 17 h). The reaction mixture is diluted with dichloromethane, successively extracted 2x with 1N NaOH, 1x with water and 1x with brine, dried over Na₂SO₄, filtered and evaporated. The accordingly obtained crude product is purified according to the following variants:

Variant A: the residue is purified by column chromatography on silica gel.
Variant B: the residue is purified by preparative HPLC (water/acetonitrile, 0.01% HCOOH).

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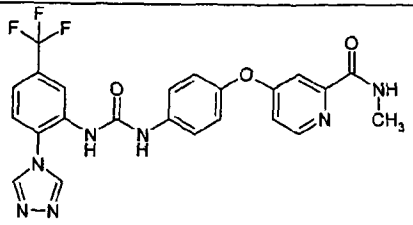
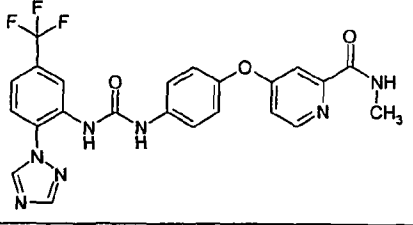
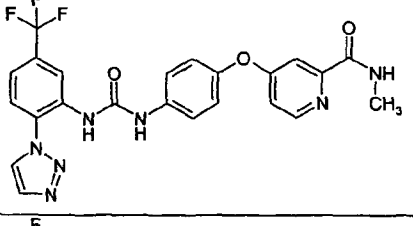
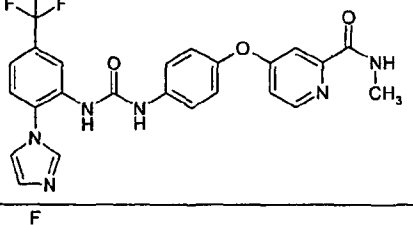
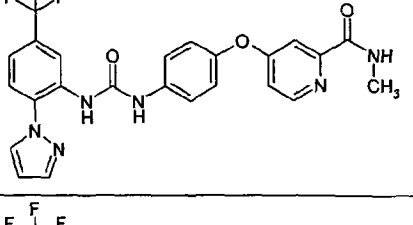
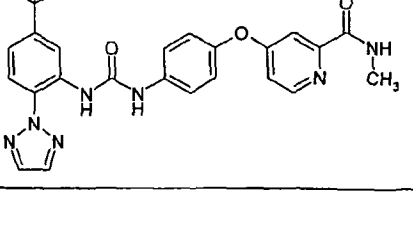
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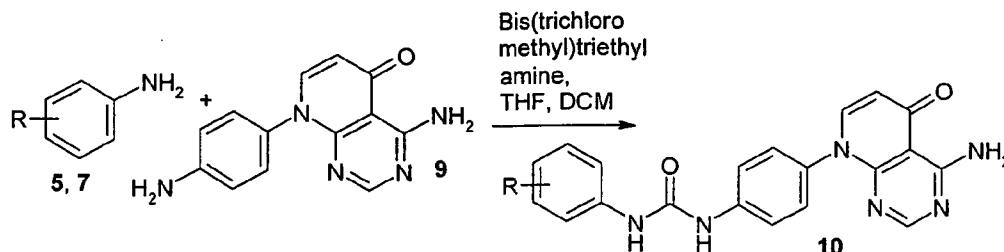
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Table 2:

Nr.	Struktur	HPLC	HPLC-MS
5 8a		2.50 (Method A)	498 (M+H)
10 8b		2.65 (Method A)	498 (M+H)
15 8c		2.47 (Method A)	498 (M+H)
20 8d		2.38 (Method A)	497 (M+H)
25 8e		2.85 (Method B)	497 (M+H)
30 8f			

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The respective aniline **5a-e** or **7** is dissolved in THF (10-20 ml/mmol) and 2.5 equivalents DIPEA and added slowly dropwise to a solution of 0.33 equivalents triphosgen in THF (10-20 ml/mmol aniline). Stirring is continued for 15 min at -70 °C and then a solution of **9** in THF (10-20 ml/mmol; if salts are applied, compound **9** is neutralised with 1.25 equivalents DIPEA) is added dropwise. Stirring is continued for 1 h at -70 °C. Subsequently, the cooling bath is removed and the reaction mixture is slowly warmed up to room temperature under stirring. After 20 h, the reaction mixture is concentrated, taken up in ethylacetate and 5% KHSO₄-solution, washed twice with 5% KHSO₄-solution and 5% NaHCO₃-solution, dried over Na₂SO₄ and evaporated.

Table 3

Nr.	Struktur	HPLC	HPLC-MS
10a		2.65 (Method C)	508 (M+H)

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Retention times (Rt) as disclosed herein are, if not indicated otherwise, HPLC retention times (in minutes), obtained according the following methods:

HPLC-Methods:

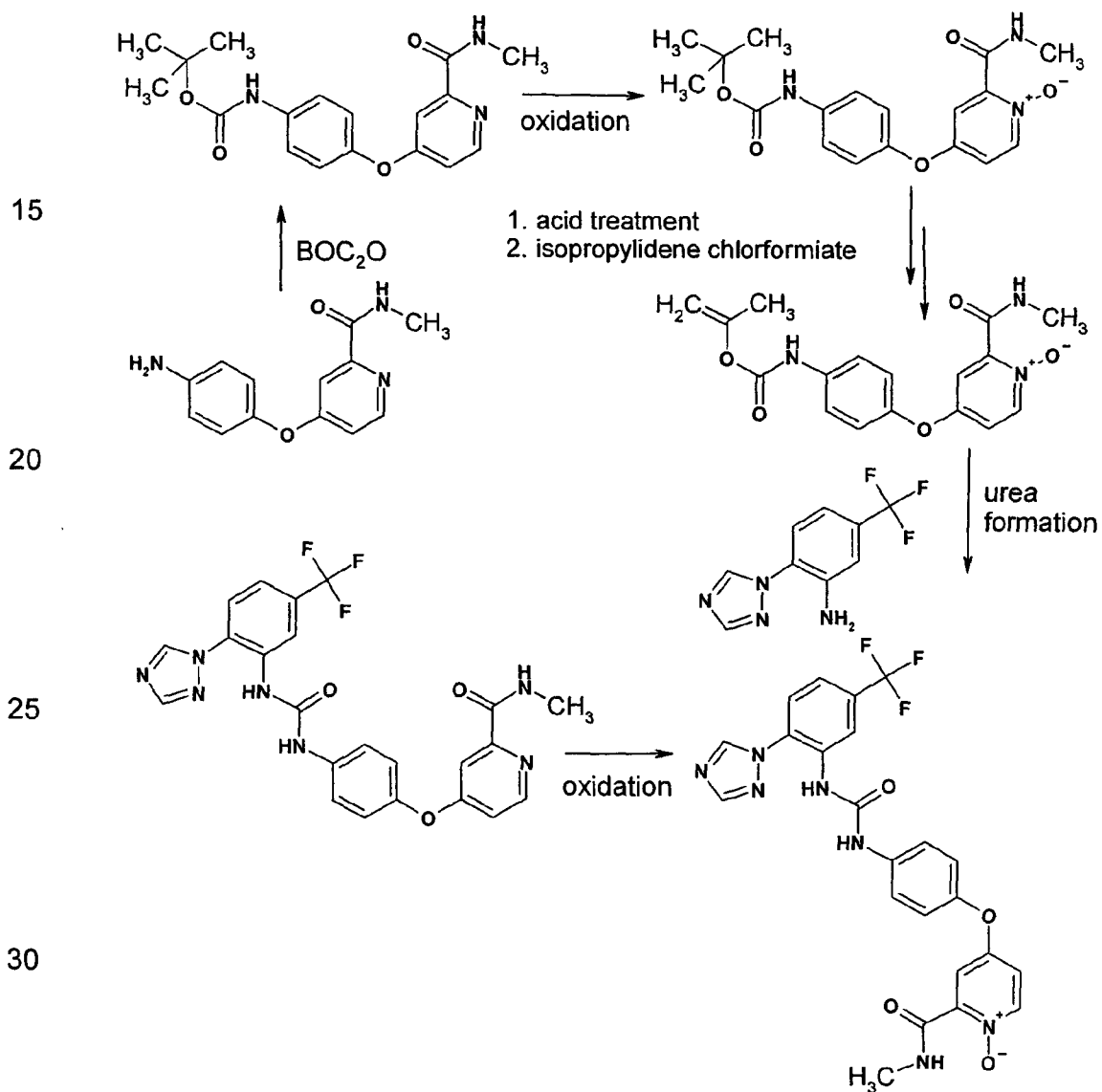
Method A: flow rate: 3 ml/min; 0.0 - 0.5 min: 99:1: (water + 0.1 Vol% TFA):(acetonitrile + 0.1 Vol% TFA); 0.5 - 3.5 min: gradient from 99:1 to 0:100 (water + 0.1 Vol% TFA):(acetonitrile + 0.1 Vol% TFA); 3.5 to 4.5 min: acetonitrile + 0.1 Vol% TFA; column: Chromolith SpeedROD RP18e 50-4.6; wavelength: 220nm.

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Method B: flow rate: 3 ml/min; 0.0 - 3.5 min: gradient from 90:10 to 0:100 (water + 0.1 Vol% TFA):(acetonitrile + 0.1 Vol% TFA); 3.5 to 4.3 min: acetonitrile + 0.1 Vol% TFA; column: Chromolith SpeedROD RP18e 50-4.6; wavelength: 220nm.

5 Method C: flow rate: 2 ml/min; 0.0 - 3.5 min: gradient von 80:200 auf 0:100 (water + 0.1 Vol% TFA):(acetonitrile/water 9:1 + 0.1 Vol% TFA); 3.5 to 5 min: acetonitrile/water 9:1 + 0.1 Vol% TFA; column: Chromolith SpeedROD RP18e 50-4.6; wavelength: 220nm.

10 Synthesis of N-oxides:



Synthesis of the N-oxide 1-Oxy-4-{4-[3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide by treatment of 500 mg of 4-{4-[3-(2-[1,2,4]Triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide with 2.3 equ 3-chloroperbenzoic acid in CH₂Cl₂ (10ml/g) and acetic acid (4 ml/g) for 7 d at ambient temperature yielded the pyridine N-oxide after purification by chromatography on silica gel in CH₂Cl₂ / methanol. The same procedure was applied for the manufacture of 4-{4-[3-(2-Imidazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1-oxy-pyridine-2-carboxylic acid methylamide, 1-Oxy-4-{4-[3-(2-[1,2,3]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide, 1-Oxy-4-{4-[3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide, and various further compounds according to the invention.

Alternatively, the N-oxidation is possible to the skilled person with other oxidizing agents, like H₂O₂ in suitable solvents, such as acids like acetic acid or formic acid.

An alternative preparation of 1-Oxy-4-{4-[3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide was possible by treatment of 10 g 4-amino-phenoxy-pyridine-2-carboxylic acid methylamide in 500 ml THF with 2 equ di-tert.butyl dicarbonate (BOC₂O) for 5 days at ambient temperature to get 4-BOC-amino-phenoxy-pyridine-2-carboxylic acid methylamide, which was oxidized with 2.6 equ 3-chloroperbenzoic acid (MCPB) in CH₂Cl₂ (10ml/g) for 5 days at ambient temperature to yield the N-oxide 1-oxy-4-BOC-amino-phenoxy-pyridine-2-carboxylic acid methylamide. After treatment with 4 m HCl/dioxane (12 ml/g) for 2 hrs at ambient temperature 1-oxy-4-amino-phenoxy-pyridine-2-carboxylic acid methylamide could be isolated, which was reacted to the corresponding urea by treatment with 1 equ 1-oxy-4-isopropylidene-oxycarbonyl-amino-phenoxy-pyridine-2-carboxylic acid methylamide in THF

(20ml/g) in presence of a catalytic amount of N-methylpyrrolidine (50 ul/g) for 10 days at 45 C.

Example 8

Stability against oxygen in air

5 The compounds

4-{4-[3-(2-[1,2,4]Triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide,

4-{4-[3-(2-[1,2,3]Triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide, 525946

10 4-{4-[3-(2-Imidazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide, and

1-[4-(Pyridin-4-yloxy)-phenyl]-3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-urea, respectively,

15 were dissolved either in DMSO / water or in acetic acid / water and stirred on air for more than a week. No N-oxide formation could be detected.

The compounds were analysed by the following methods

Method D)

20 HPLC / MS on a Chromolith Speed ROD RP-18e 50-46 mm column (Merck KGaA) with a gradient of 5-100% B in 2.6 min of a system A: water containing 0.1% TFA B: CH₃CN containing 0.1% TFA at 2.4 ml/min. Monitoring is by UV at 220 nm and MS sampling for compounds of mass 50 – 1000 g/mol.

25 Method E)

HPLC on a Chromolith Performance RP-18e 100-46 mm column (Merck KGaA) with a gradient of 1-99% B in 10 min of a system A: water containing 0.1% TFA B: CH₃CN / water 90/10 (vol) containing 0.1% TFA at 3 ml/min, with monitoring by UV at 215 nm

30

Biological activity of pyridine N-oxides:

The biological activity of N-oxide compounds according the invention are tested in one or more standard kinase assay systems as described in the art. Preferably, the compounds according the invention are tested in a kinase assay as described below, or in analogous manner thereof:

5

In this assay the inhibitory action of the compounds according to the invention on the phosphorylation of the substrates Biotin-poly-Glu-Tyr (4:1) by VEGFR2 (KDR) or poly-Glu-Tyr (4:1) by Tie-2, respectively, is tested. In the wells of a streptavidin-coated microtiter flashplate, VEGFR2, or a microtiter flashplate, Tie-2, respectively, phosphorylate the substrates in the presence of ATPyS and small amounts of radioactive ^{33}P -ATP. Phosphorylated substrates bind during enzymatic reaction to the walls of the wells. The phosphorylation reaction is stopped by addition of a stopping reagent, the liquid is removed from the wells and the wells are rinsed. The amount of radioactivity incorporated into the substrate bound to the well is then measured. The reaction is done in presence of different concentrations of the compound and in absence of the compound. The inhibitory action of the compounds according to the invention is determined on the basis of the ratio of radioactivity found in the presence of a compound according to the invention in comparison to the radioactivity found in the enzymatic reaction in the absence of a compound according to the invention. The catalytic sections of the corresponding tyrosine kinases are preferably expressed as GST fusion proteins.

25 The following materials and amounts are used:

Final concentration per well (assay volume = 100 μl):

30	VEGFR2 or Tie-2	10 or 150	ng/well
	Biotin-Poly Glu,Tyr (4:1) for VEGFR2	100	ng/well
	Poly Glu,Tyr (4:1) for Tie2	500	ng/well
	Hepes /NaOH pH 7,5	50	mM

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	MgCl ₂ ·6H ₂ O	3	mM
	MnCl ₂ ·4H ₂ O	3	mM
	Na-Orthovanadate	3	μM
	DTT	1,85	mM
	ATPγS (total) for VEGFR2	1	μM
	ATPγS (total) for Tie2	0,1	μM
5	³³ P-ATP (does not contribute to the total amount of ATPγS)	0,3	μCi/well
	DMSO	1	%
	Staurosporine Standard 1 (VEGFR2/Tie2)	10/100	nM
	Staurosporine Standard 2 (VEGFR2/Tie2)	1/10	nM
10	Staurosporin pharm. Blank	10	μM

IC₅₀ determination:

100 μL of the compound to be tested are applied to a well (starting concentration: 1E-3 mol/L in 100% DMSO); the dilution for the determination of the IC₅₀ values is performed on a BiomekFX robot in 10 steps (range of concentration is 1E-5 to 1E-10 mol/L in the assay, i.e. 1E-5, 1E-6, 3E-7, 1E-7, 3E-8, 1E-8, 3E-9, 1E-9, 3E-10, 1E-10 mol/L).

The compounds tested show IC₅₀s on TIE2 and/or KDR kinases below 1 μM (see for example Table 4).

Table 4:

Compound	MW	Rf	TIE2 [IC ₅₀] nM	KDR [IC ₅₀] nM
11	M 513.44 M+H~ 514	Rf D)~1.93 min Rf E)~5.64 min	52	14
12	M 513.44 M+H~514	Rf D)~1.78 Rf E)~4.51min	30	49
13	M 512.45 M+H ~513	Rf D)~1.67 min Rf E)~4.72 min	49	56
14	M 456.39 M+H~457	Rf D)~1.81 min Rf E)~	740	1200

Compound 11:

1-Oxy-4-{4-[3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide

Compound 12:

1-Oxy-4-{4-[3-(2-[1,2,3]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide

Compound 13:

4-{4-[3-(2-Imidazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1-oxy-pyridine-2-carboxylic acid methylamide

Compound 14:

1-[4-(1-Oxy-pyridin-4-yloxy)-phenyl]-3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-urea

- 10 Alternatively, the compounds according to the invention are preferably tested according the tyrosine kinase assay method given below or in analog manner thereof:

The catalytic sections of the corresponding tyrosine kinases are expressed as GST fusion proteins . The assay are performed in white 96 well microtiter plates which are coated at 4°C for 16 h with 12.5µg polyGlu-Tyr 4:1 sodium salt (Sigma) in 125 µL of PBS (phosphate buffered saline, Gibco) per well. The coating solution is flicked off and the plates are washed twice with PBST (PBS + 0.5% Tween-20). Kinases are diluted in kinase buffer (100 mM HEPES pH 7.4, 100 mM NaCl) and added at 20 ng protein in 50µL of buffer.

20 Stock solutions of the test compounds are made in DMSO and diluted to a final concentration of 5% DMSO with water (working solution). Twenty five microliters of the working solutions are added to each well. The kinase reaction is started by addition of 25 µL of ATP (100 µM in 40 mM MnCl₂) using a multichannel pipet. Negative controls receive 40 mM MnCl₂ without

25 ATP. The plates are incubated at RT for 90 min. The microtiter plates are washed three times with PBST. One hundred microliters of anti phosphotyrosine antibody (PY20, Calbiochem) conjugated to horseradish peroxidase (POD) is added at 1:5000 dilution in PBST + 0.1% BSA (bovine serum albumin, Calbiochem) and incubated for 1 h at RT. Plates are washed

30 five times with PBST. For detection, 100µL of POD chemiluminescence substrate (Roche) is added. The resulting light emission is detected with an Orion luminescence reader.

The compounds disclosed herein can preferably be produced according to the procedures described herein or in an analogous manner thereof.

5 **Example A: Injection vials**

A solution of 100 g of an active compound of the formula I and 5 g of disodium hydrogenphosphate is adjusted to pH 6.5 in 3 l of double-distilled water using 2N hydrochloric acid, sterile-filtered, dispensed into injection vials, lyophilized under sterile conditions and aseptically sealed. Each
10 injection vial contains 5 mg of active compound.

Example B: Suppositories

A mixture of 20 g of an active compound of the formula I is fused with 100 g
15 of soya lecithin and 1400 g of cocoa butter, poured into moulds and allowed to cool. Each suppository contains 20 mg of active compound.

Example C: Solution

A solution of 1 g of an active compound of the formula I, 9.38 g of $\text{NaH}_2\text{PO}_4 \cdot 2 \text{H}_2\text{O}$, 28.48 g of $\text{Na}_2\text{HPO}_4 \cdot 12 \text{H}_2\text{O}$ and 0.1 g of benzalkonium chloride in
20 940 ml of double-distilled water is prepared. It is adjusted to pH 6.8, made up to 1 l and sterilized by irradiation. This solution can be used in the form of eye drops.

25 **Example D: Ointment**

500 mg of an active compound of the formula I is mixed with 99.5 g of petroleum jelly under aseptic conditions.

Example E: Tablets

30 A mixture of 1 kg of active compound of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is

compressed to give tablets in a customary manner such that each tablet contains 10 mg of active compound.

Example F: Coated tablets

- 5 Analogously to Example E, tablets are pressed and are then coated in a customary manner using a coating of sucrose, potato starch, talc, tragacanth and colourant.

Example G: Capsules

- 10 2 kg of active compound of the formula I are dispensed into hard gelatin capsules in a customary manner such that each capsule contains 20 mg of the active compound.

Example H: Ampoules

- 15 A solution of 1 kg of active compound of the formula I in 60 l of double-distilled water is sterile-filtered, dispensed into ampoules, lyophilized under sterile conditions and aseptically sealed. Each ampoule contains 10 mg of active compound.

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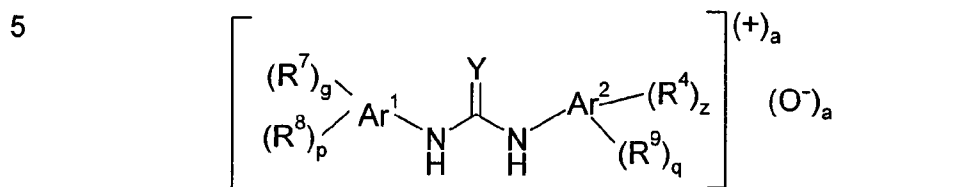
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Claims

1. N-Oxides of formula I



10 wherein

Ar^1, Ar^2 are selected independently from one another from unsaturated or aromatic cyclic hydrocarbons containing 5 to 14 carbon atoms and unsaturated or aromatic heterocyclic residues containing 2 to 10 carbon atoms and one or more heteroatoms, preferably 1 to 5 heteroatoms, independently selected from N, O and S,

20 R^4 is independently selected from residues of the formula $(\text{X}-\text{Ar}^3)_\alpha-(\text{R}^{10})_r$, wherein

Ar^3 is independently selected from the meanings given for Ar^1 and/or Ar^2 ,

25 α is 0, 1 or 2,

R^{10} is independently selected from the meanings given for R^8 and R^9 , and

30 r is 0, 1, 2, 3, 4 or 5;

z is 0, 1, 2, 3, 4 or 5,

- 5 R^7 is a nitrogen containing heterocyclic moiety, directly bound to Ar^1 via a nitrogen atom, said nitrogen containing heterocyclic moiety being independently selected from Het^1 , Het^2 and Het^3 , wherein
- 10 Het^1 is an unsaturated or aromatic heterocyclic residue comprising 5, 6 or 7 ring atoms which contains 1 to 4 nitrogen atoms and optionally 1 or 2 additional heteroatoms selected from O and S, whereby said unsaturated or aromatic heterocyclic residue is unsubstituted or substituted by one or more substituents, selected from a group consisting of A, R^{13} , =O, =S, =N-
15 R^{14} , Hal, NO_2 , CN, OR^{15} , $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, COR^{15} , $SO_2NR^{15}R^{16}$, $S(O)_uA$ and $OOCR^{15}$,
- 20 Het^2 is a saturated, unsaturated or aromatic bicyclic residue comprising 3 to 10 carbon atoms, 1 to 4 nitrogen atoms and optionally 1 or 2 additional heteroatoms selected from O and S, whereby said bicyclic residue is unsubstituted or substituted by one or more substituents, selected from a group consisting of A, R^{13} , =O, =S, =N- R^{14} , Hal, NO_2 , CN,
25 OR^{15} , $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, COR^{15} , $SO_2NR^{15}R^{16}$, $S(O)_uA$ and $OOCR^{15}$,
- 30 Het^3 is a saturated monocyclic residue comprising 2 to 6 carbon atoms, 1 to 4 nitrogen atoms and optionally 1 or 2 additional heteroatoms selected from O and S, whereby said monocyclic residue is substituted by one or more

substituents, selected from a group consisting of =O, =S, =N-R¹⁴, and optionally substituted by one or more substituents, selected from A, R¹³, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶,
 5 NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂NR¹⁵R¹⁶, S(O)_uA and OOCR¹⁵,

R⁸ and R⁹ are independently selected from a group consisting of H, A, cycloalkyl comprising 3 to 7 carbon atoms, Hal, CH₂Hal,
 10 CH(Hal)₂, C(Hal)₃, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nNR¹¹(CH₂)_kNR¹¹R¹², (CH₂)_nO(CH₂)_kOR¹¹, (CH₂)_nNR¹¹(CH₂)_kOR¹², (CH₂)_nCOOR¹³, (CH₂)_nCOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nNR¹¹COR¹³, (CH₂)_nNR¹¹CONR¹¹R¹²,
 15 (CH₂)_nNR¹¹SO₂A, (CH₂)_nSO₂NR¹¹R¹², (CH₂)_nS(O)_uNR¹¹R¹², (CH₂)_nS(O)_uR¹³, (CH₂)_nOC(O)R¹³, (CH₂)_nCOR¹³, (CH₂)_nSR¹¹, CH=N-OA, CH₂CH=N-OA, (CH₂)_nNHOA, (CH₂)_nCH=N-R¹¹, (CH₂)_nOC(O)NR¹¹R¹², (CH₂)_nNR¹¹COOR¹³, (CH₂)_nN(R¹¹)CH₂CH₂OR¹³,
 20 (CH₂)_nN(R¹¹)CH₂CH₂OCF₃, (CH₂)_nN(R¹¹)C(R¹³)HCOOR¹², (CH₂)_nN(R¹¹)C(R¹³)HCOR¹¹, (CH₂)_nN(R¹¹)CH₂CH₂N(R¹²)CH₂COOR¹¹, (CH₂)_nN(R¹¹)CH₂CH₂NR¹¹R¹², CH=CHCOOR¹³, CH=CHCH₂NR¹¹R¹², CH=CHCH₂NR¹¹R¹²,
 25 CH=CHCH₂OR¹³, (CH₂)_nN(COOR¹³)COOR¹⁴, (CH₂)_nN(CONH₂)COOR¹³, (CH₂)_nN(CONH₂)CONH₂, (CH₂)_nN(CH₂COOR¹³)COOR¹⁴, (CH₂)_nN(CH₂CONH₂)COOR¹³, (CH₂)_nN(CH₂CONH₂)CONH₂, (CH₂)_nCHR¹³COR¹⁴,
 30 (CH₂)_nCHR¹³COOR¹⁴, (CH₂)_nCHR¹³CH₂OR¹⁴, (CH₂)_nOCN (CH₂)_nNCO, Het⁹, OHet⁹, N(R¹¹)Het⁹, (CR⁵R⁶)_kHet⁹, O(CR⁵R⁶)_kHet⁹, N(R¹¹)(CR⁵R⁶)_kHet⁹, (CR⁵R⁶)_kNR¹¹R¹²,

$(\text{CR}^5\text{R}^6)_k\text{OR}^{13}$, $\text{O}(\text{CR}^5\text{R}^6)_k\text{NR}^{11}\text{R}^{12}$, $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{NR}^{11}\text{R}^{12}$,
 $\text{O}(\text{CR}^5\text{R}^6)_k\text{R}^{13}$, $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{R}^{13}$, $\text{O}(\text{CR}^5\text{R}^6)_k\text{OR}^{13}$,
 $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{OR}^{13}$, wherein

- 5 R^5, R^6 are in each case independently from one another selected from H and A,
- $\text{R}^{11}, \text{R}^{12}$ are independently selected from a group consisting of H, A, $(\text{CH}_2)_m\text{Ar}^7$ and $(\text{CH}_2)_m\text{Het}^9$, or in $\text{NR}^{11}\text{R}^{12}$,
- 10 R^{11} and R^{12} form, together with the N-atom they are bound to, a 5-, 6- or 7- membered heterocyclus which optionally contains 1 or 2 additional hetero atoms, selected from N, O and S; whereby said heterocyclic residue optionally is substituted by one or more substituent, selected from A, R^{13} , =O, =S and =N- R^{14} ,
- 15 $\text{R}^{13}, \text{R}^{14}$ are independently selected from a group consisting of H, Hal, A, $(\text{CH}_2)_m\text{Ar}^8$ and $(\text{CH}_2)_m\text{Het}^9$,
- 20 A is selected from the group consisting of alkyl, alkenyl, cycloalkyl, alkylencycloalkyl, alkoxy, alkoxyalkyl and saturated heterocyclyl, preferably from the group consisting of alkyl, alkenyl, cycloalkyl, alkylencycloalkyl, alkoxy and alkoxyalkyl,
- 25 Ar^7, Ar^8 are independently from one another aromatic hydrocarbon residues comprising 5 to 12 and preferably 5 to 10 carbon atoms which are optionally substituted by one or more substituents, selected from a group consisting of A, Hal, NO_2 , CN, OR^{15} , $\text{NR}^{15}\text{R}^{16}$, COOR^{15} , $\text{CONR}^{15}\text{R}^{16}$,
- 30

$\text{NR}^{15}\text{COR}^{16}$, $\text{NR}^{15}\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{16}\text{SO}_2\text{A}$, COR^{15} ,
 $\text{SO}_2\text{NR}^{15}\text{R}^{16}$, $\text{S(O)}_u\text{A}$ and OOCR^{15} ,

- 5 Het^9 is a saturated, unsaturated or aromatic heterocyclic residue which preferably contains 1 to 3 heteroatoms, more preferably 1 or 2 heteroatoms, the heteroatoms being preferably selected from N, O and S, more preferably from N and O; whereby said heterocyclic residue is optionally substituted by one or more
- 10 substituents, selected from a group consisting of A, R^{13} , $=\text{O}$, $=\text{S}$, $=\text{N-R}^{14}$, Hal, NO_2 , CN, OR^{15} , $\text{NR}^{15}\text{R}^{16}$, COOR^{15} , $\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{15}\text{COR}^{16}$, $\text{NR}^{15}\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{16}\text{SO}_2\text{A}$, COR^{15} , $\text{SO}_2\text{NR}^{15}\text{R}^{16}$, $\text{S(O)}_u\text{A}$ and OOCR^{15} ,
- 15 R^{15} , R^{16} are independently selected from a group consisting of H, A, and $(\text{CH}_2)_m\text{Ar}^6$, wherein
- Ar^6 is a 5- or 6-membered aromatic hydrocarbon which is optionally substituted by one or more substituents selected
- 20 from a group consisting of methyl, ethyl, propyl, 2-propyl, tert.-butyl, Hal, CN, OH, NH_2 and CF_3 ,
- k, n and m are independently of one another 0, 1, 2, 3, 4, or 5,
- 25 X represents a bond or is $(\text{CR}^{11}\text{R}^{12})_h$, or $(\text{CHR}^{11})_h\text{-Q-}(\text{CHR}^{12})_i$, wherein
- Q is selected from a group consisting of O, S, N-R^{15} , $(\text{CHal}_2)_j$, $(\text{O-CHR}^{18})_j$, $(\text{CHR}^{18}\text{-O})_j$, $\text{CR}^{18}=\text{CR}^{19}$, $(\text{O-CHR}^{18}\text{CHR}^{19})_j$, $(\text{CHR}^{18}\text{CHR}^{19}\text{-O})_j$, C=O , C=S , C=NR^{15} , $\text{CH(OR}^{15})$, $\text{C(OR}^{15})(\text{OR}^{20})$, C(=O)O , OC(=O) , OC(=O)O , $\text{C(=O)N(R}^{15})$, $\text{N(R}^{15})\text{C(=O)}$, $\text{OC(=O)N(R}^{15})$, $\text{N(R}^{15})\text{C(=O)O}$,
- 30

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CH=N-O, CH=N-NR¹⁵, OC(O)NR¹⁵, NR¹⁵C(O)O, S=O, SO₂, SO₂NR¹⁵ and NR¹⁵SO₂, wherein

5 h, i are independently from each other 0, 1, 2, 3, 4, 5, or 6, and

 j is 1, 2, 3, 4, 5, or 6,

10 Y is selected from O, S, NR²¹, C(R²²)-NO₂, C(R²²)-CN and C(CN)₂, wherein

 R²¹ is independently selected from the meanings given for R¹³, R¹⁴ and

15 R²² is independently selected from the meanings given for R¹¹, R¹²,

 a is 1, 2 or 3,

20 g is 1, 2 or 3, ,

 p is 0, 1, 2, 3, 4 or 5,

25 q is 0, 1, 2, 3 or 4, ,

 u is 0, 1, 2 or 3,

and

30 Hal is independently selected from a group consisting of F, Cl, Br and I;

and the pharmaceutically acceptable derivatives, salts, solvates and tautomers thereof.

2. N-Oxides according to claim 1,

5

wherein

10

Ar¹ is selected independently from aromatic hydrocarbons containing 5 to 12 carbon atoms and unsaturated or aromatic heterocyclic residues containing 3 to 8 carbon atoms and one, two or three heteroatoms, independently selected from N, O and S,

15

Ar² is selected independently from aromatic hydrocarbons containing 5 to 12 carbon atoms and unsaturated or aromatic heterocyclic residues containing 2 to 8 carbon atoms and 1, 2 or 3 heteroatoms, independently selected from N, O and S,

20

R⁴ is independently selected from residues of the formula (Ar³)_α-(R¹⁰)_r, wherein

25

Ar³ is independently selected from the meanings given for Ar¹ and/or Ar², and more preferably is selected independently from unsubstituted or substituted unsaturated or aromatic cyclic hydrocarbons containing 5 to 14 carbon atoms; and unsubstituted or substituted unsaturated or aromatic heterocyclic residues containing 2 to 10 carbon atoms and one or more heteroatoms independently selected from N, O and S,

30

α is 0, 1 or 2,

- 5 R^{10} is independently selected from the meanings given for R^8 and R^9 , and more preferably selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nS(O)_uNR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$,
- 10 r is 0, 1, 2, 3, 4 or 5,
- 15 z is 0, 1, 2, 3, 4 or 5, s 0, 1, 2, 3, 4 or 5, more preferably 0, 1, 2 or 3, and especially 1, 2 or 3,
- 20 R^7 is a nitrogen containing heterocyclic moiety, directly bound to Ar^1 via a nitrogen atom, said nitrogen containing heterocyclic moiety being independently selected from Het^1 , Het^2 and Het^3 , wherein
- 25 Het^1 is an unsaturated or aromatic heterocyclic residue comprising 5 or 6 ring atoms which contains 1 to 4 nitrogen atoms and optionally 1 or 2 additional heteroatoms selected from O and S, whereby said unsaturated or aromatic heterocyclic residue is unsubstituted or substituted by one or more substituents, selected from a group consisting of A, R^{13} , $=O$, $=S$, $=N$ - R^{14} , Hal, NO_2 , CN, OR^{15} , $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, COR^{15} , $SO_2NR^{15}R^{16}$, $S(O)_uA$ and $OOCR^{15}$;
- 30

- 5 Het² is a saturated, unsaturated or aromatic bicyclic residue comprising 4 to 9 carbon atoms, 1 to 4 nitrogen atoms and optionally 1 or 2 additional heteroatoms selected from O and S, whereby said bicyclic residue is unsubstituted or substituted by one or more substituents, selected from the group consisting of A, R¹³, =O, =S, =N-R¹⁴, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂NR¹⁵R¹⁶, S(O)_uA and OOCR¹⁵,
- 15 Het³ is a saturated monocyclic residue comprising 2 to 6 carbon atoms, 1 to 4 nitrogen atoms and optionally 1 or 2 additional heteroatoms selected from O and S, whereby said monocyclic residue is substituted by one or more substituents, selected from a group consisting of =O, =S and =N-R¹⁴, and optionally substituted by one or more substituents, selected from A, R¹³, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂NR¹⁵R¹⁶ and S(O)_uA,
- 25 R⁸ and R⁹ are independently selected from a group consisting of H, A, cycloalkyl comprising 3 to 7 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, C(Hal)₃, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nNR¹¹(CH₂)_kNR¹¹R¹², (CH₂)_nO(CH₂)_kOR¹¹, (CH₂)_nNR¹¹(CH₂)_kOR¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nNR¹¹COR¹³, (CH₂)_nNR¹¹CONR¹¹R¹², (CH₂)_nNR¹¹SO₂A, (CH₂)_nSO₂NR¹¹R¹², (CH₂)_nS(O)_uNR¹¹R¹², (CH₂)_nS(O)_uR¹³, (CH₂)_nOC(O)R¹³, (CH₂)_nCOR¹³, (CH₂)_nSR¹¹, (CH₂)_nNHOA,
- 30

$(\text{CH}_2)_n\text{NR}^{11}\text{COOR}^{13}$, $(\text{CH}_2)_n\text{N}(\text{R}^{11})\text{CH}_2\text{CH}_2\text{OR}^{13}$,
 $(\text{CH}_2)_n\text{N}(\text{R}^{11})\text{CH}_2\text{CH}_2\text{OCF}_3$, $(\text{CH}_2)_n\text{N}(\text{R}^{11})\text{C}(\text{R}^{13})\text{HCOOR}^{12}$,
 $(\text{CH}_2)_n\text{N}(\text{R}^{11})\text{C}(\text{R}^{13})\text{HCOR}^{11}$, $(\text{CH}_2)_n\text{N}(\text{COOR}^{13})\text{COOR}^{14}$,
 $(\text{CH}_2)_n\text{N}(\text{CONH}_2)\text{COOR}^{13}$, $(\text{CH}_2)_n\text{N}(\text{CONH}_2)\text{CONH}_2$,
5 $(\text{CH}_2)_n\text{N}(\text{CH}_2\text{COOR}^{13})\text{COOR}^{14}$,
 $(\text{CH}_2)_n\text{N}(\text{CH}_2\text{CONH}_2)\text{COOR}^{13}$,
 $(\text{CH}_2)_n\text{N}(\text{CH}_2\text{CONH}_2)\text{CONH}_2$, $(\text{CH}_2)_n\text{CHR}^{13}\text{COR}^{14}$,
 $(\text{CH}_2)_n\text{CHR}^{13}\text{COOR}^{14}$ and $(\text{CH}_2)_n\text{CHR}^{13}\text{CH}_2\text{OR}^{14}$,
and/or selected from the group consisting of Het^9 , OHet^9 ,
10 $\text{N}(\text{R}^{11})\text{Het}^9$, $(\text{CR}^5\text{R}^6)_k\text{Het}^9$, $\text{O}(\text{CR}^5\text{R}^6)_k\text{Het}^9$,
 $\text{N}(\text{R}^{11})(\text{CR}^5\text{R}^6)_k\text{Het}^9$, $(\text{CR}^5\text{R}^6)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CR}^5\text{R}^6)_k\text{OR}^{13}$,
 $\text{O}(\text{CR}^5\text{R}^6)_k\text{NR}^{11}\text{R}^{12}$, $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{NR}^{11}\text{R}^{12}$, $\text{O}(\text{CR}^5\text{R}^6)_k\text{R}^{13}$,
 $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{R}^{13}$, $\text{O}(\text{CR}^5\text{R}^6)_k\text{OR}^{13}$, $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{OR}^{13}$,
wherein R^5 and R^6 are as defined above/below, and
15 wherein

n and/or k independently are 0, 1, 2, 3 or 4, preferably 0, 1, 2 or 3,
and even more preferred are 0 or 2;

20 X represents a bond or is $(\text{CR}^{11}\text{R}^{12})_h$, or $(\text{CHR}^{11})_h\text{-Q-}$
 $(\text{CHR}^{12})_i$, wherein

25 Q is selected from a group consisting of O, S, N-R^{15} ,
 $(\text{CHAl}_2)_j$, $(\text{O-CHR}^{18})_j$, $(\text{CHR}^{18}\text{-O})_j$, $\text{CR}^{18}=\text{CR}^{19}$, $(\text{O-CHR}^{18}\text{CHR}^{19})_j$,
 $(\text{CHR}^{18}\text{CHR}^{19}\text{-O})_j$, C=O , C=NR^{15} ,
 $\text{CH}(\text{OR}^{15})$, $\text{C}(\text{OR}^{15})(\text{OR}^{20})$, $\text{C(=O)N}(\text{R}^{15})$, $\text{N}(\text{R}^{15})\text{C(=O)}$,
 CH=N-NR^{15} , S=O , SO_2 , $\text{SO}_2\text{NR}^{15}$ and $\text{NR}^{15}\text{SO}_2$, wherein

30 h, i are independently from each other 0, 1, 2, 3, 4, 5 or 6,
preferably 0, 1, 2 or 3 and

j is 1, 2, 3, 4, 5 or 6, preferably 1, 2, 3 or 4,

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q is 0, 1 or 2, preferably 0 or 1,

g is 1 or 2, preferably 1, and

5

p is 1, 2 or 3, preferably 1 or 2;

and the pharmaceutically acceptable derivatives, solvates, salts, tautomers and stereoisomers thereof

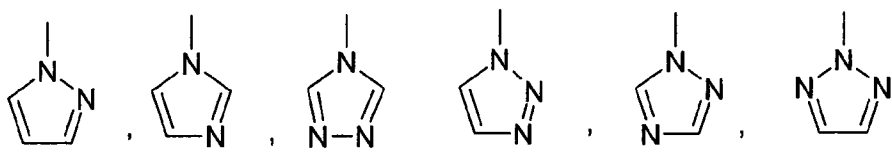
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3. N-Oxides according to claim 1 or 2,

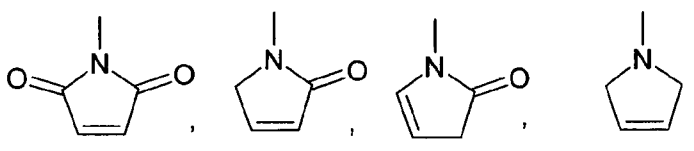
wherein

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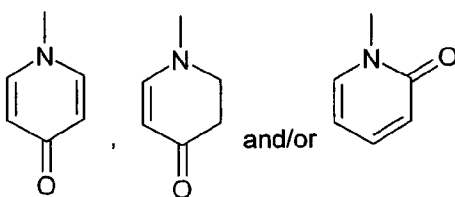
Het¹ is selected from



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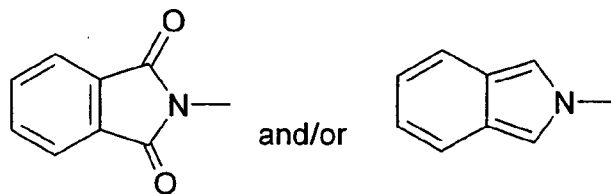


and derivatives thereof that comprise 1 to 4 substituents, selected from A, R¹³, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, SO₂NR¹⁵R¹⁶ and S(O)_uA;

30

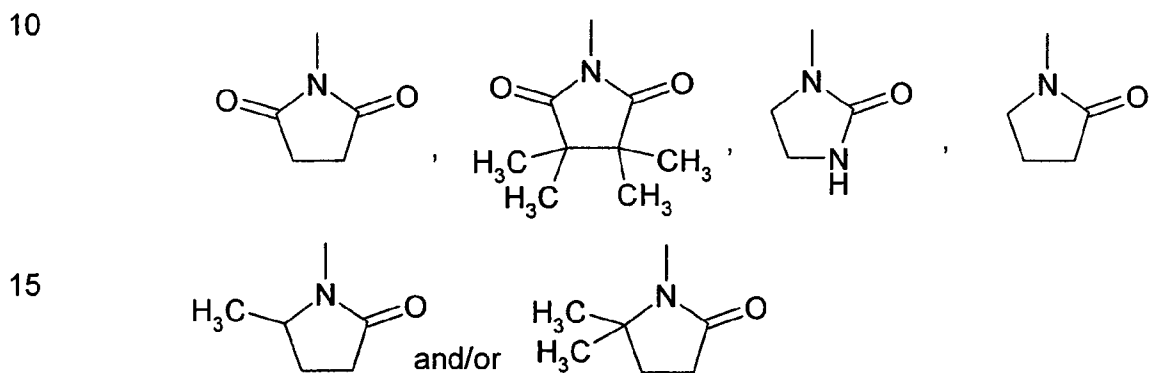
Het² is selected from

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5 and derivatives thereof that comprise 1 to 4 substituents, selected from A, R¹³, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, SO₂NR¹⁵R¹⁶ and S(O)_uA;

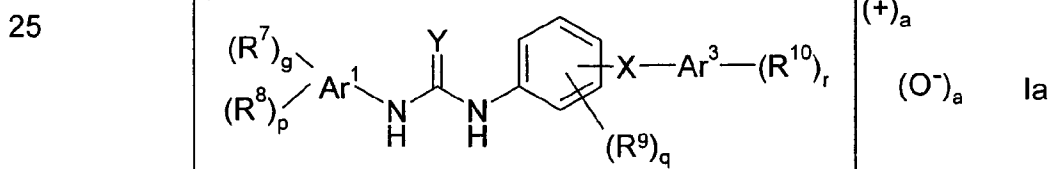
and Het³ is selected from



15 and derivatives thereof that comprise 1 to 4 substituents, selected from A, R¹³, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, SO₂NR¹⁵R¹⁶ and S(O)_uA.

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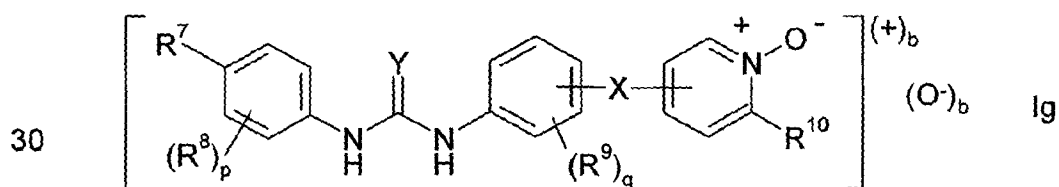
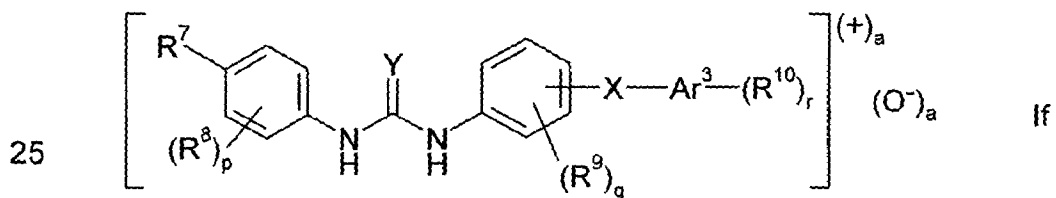
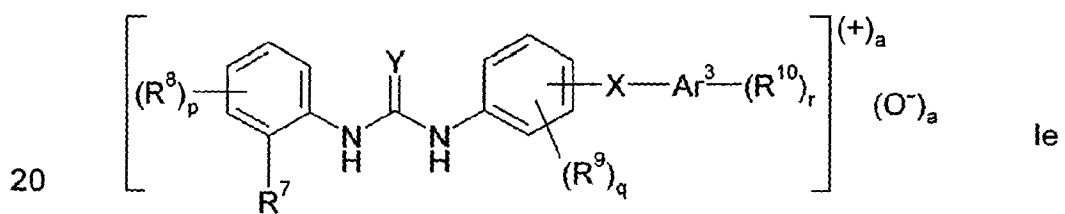
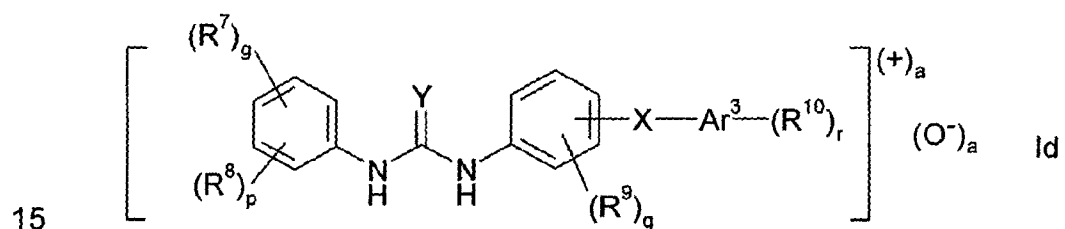
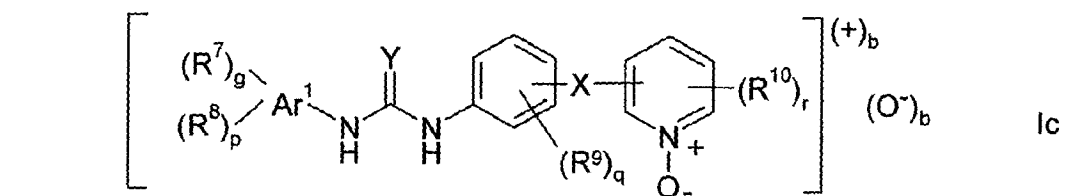
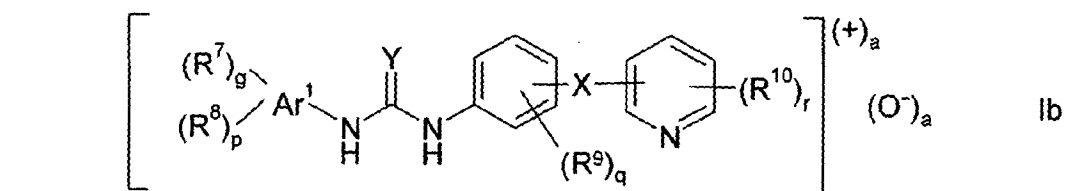
4. N-Oxides according to one of the claims 1 to 3, selected from the compounds of formula Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ii, Ij, Ik, IL, Im, In, Io, Ip, Iq, Ir, Is, It, Iu, Iv, Iw, Ix, Iy, Iz and Iaa to Iss,



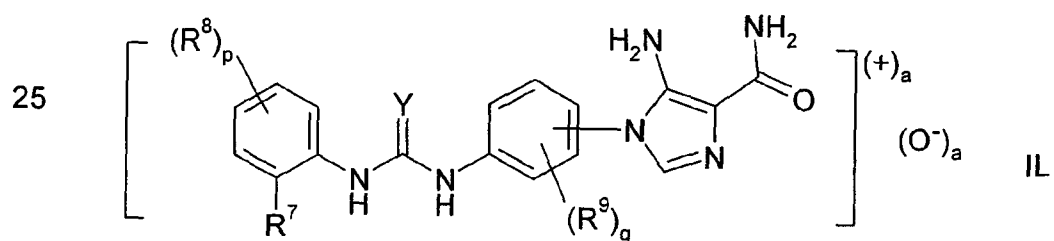
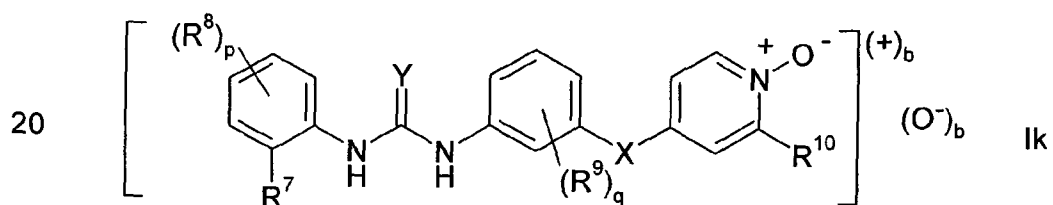
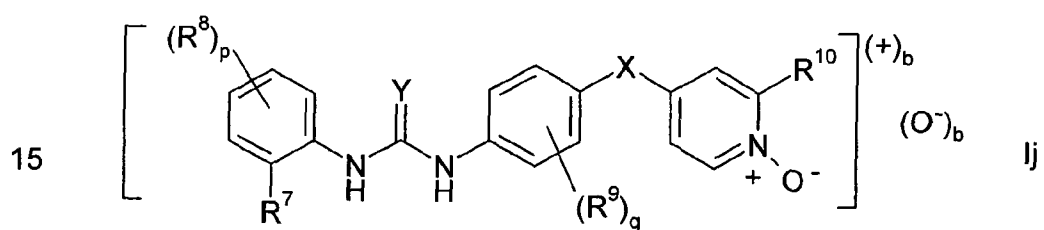
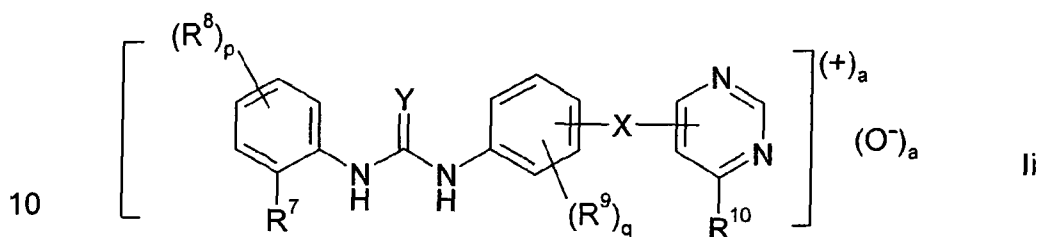
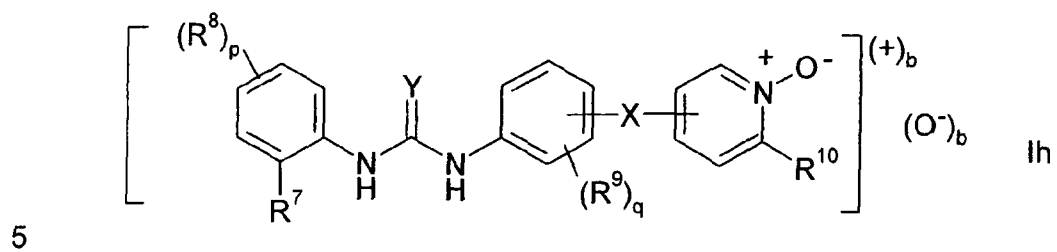
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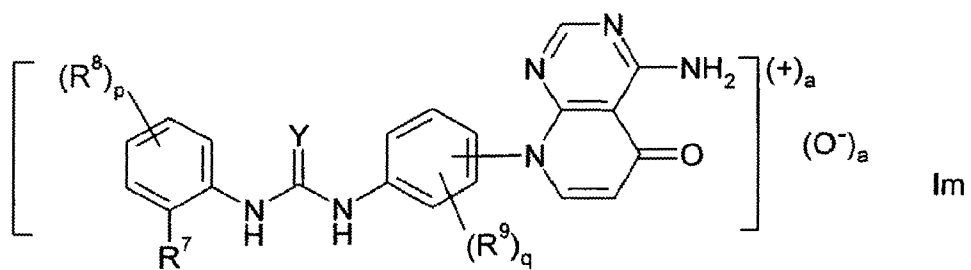


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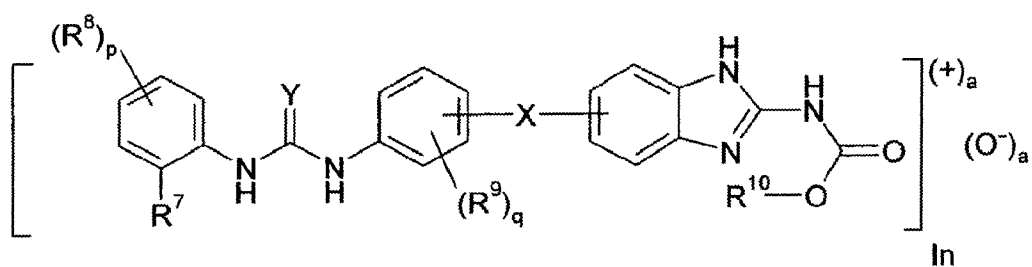


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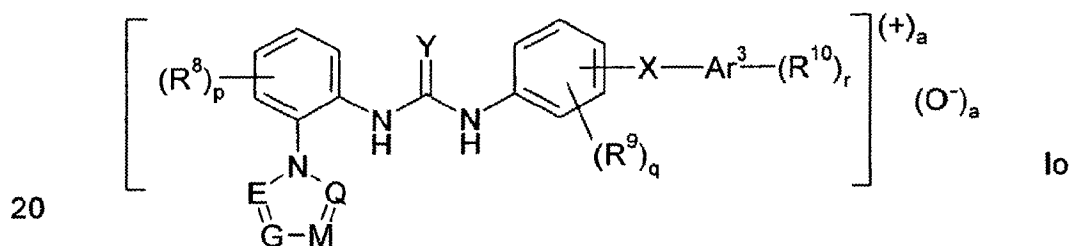
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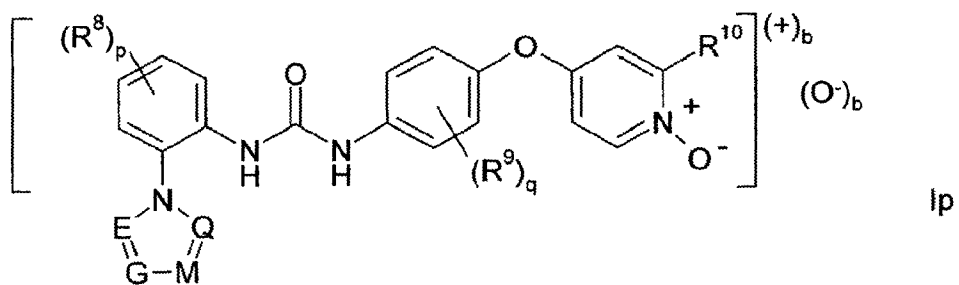
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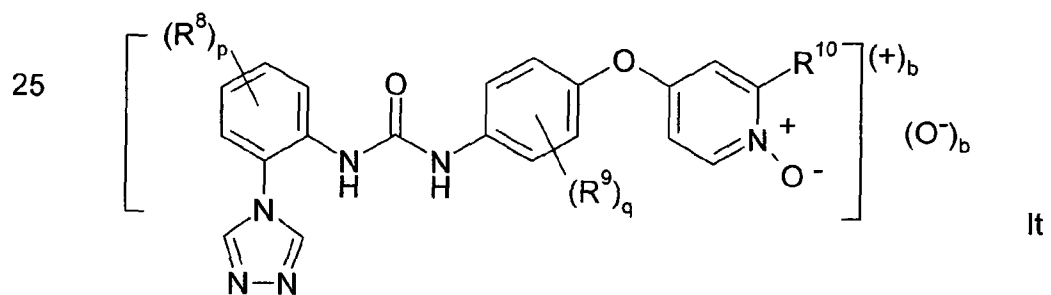
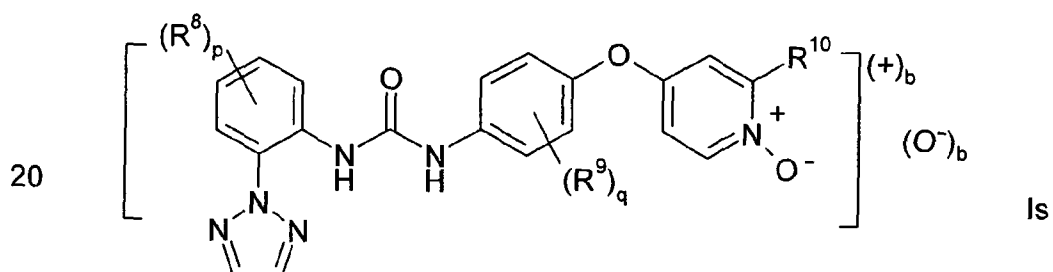
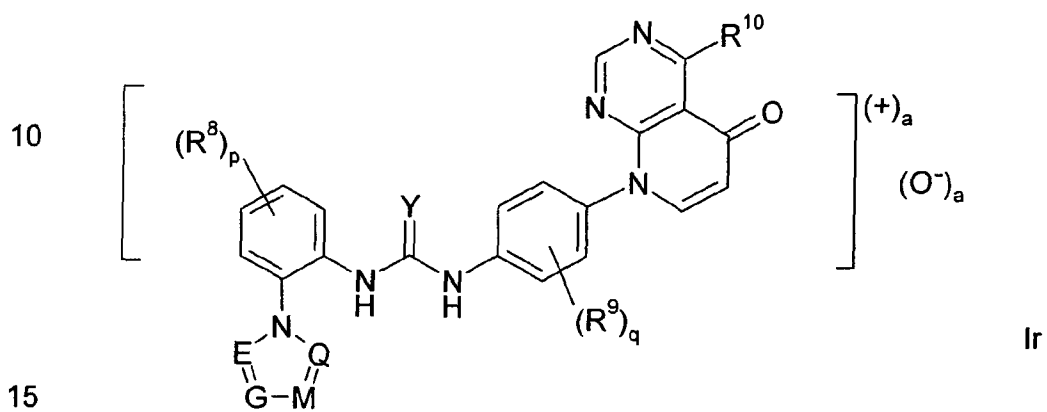
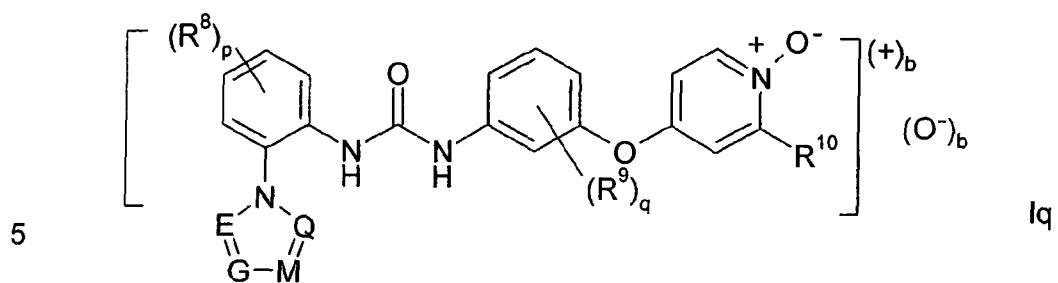


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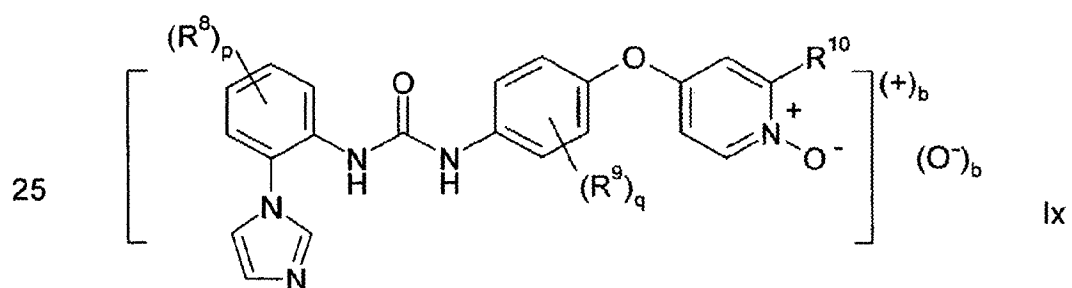
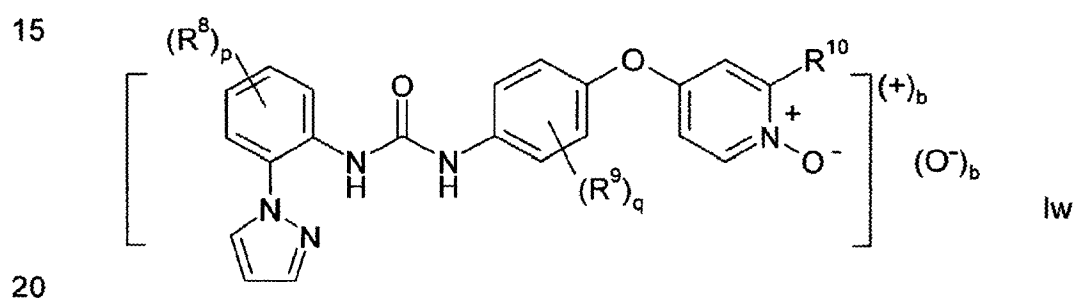
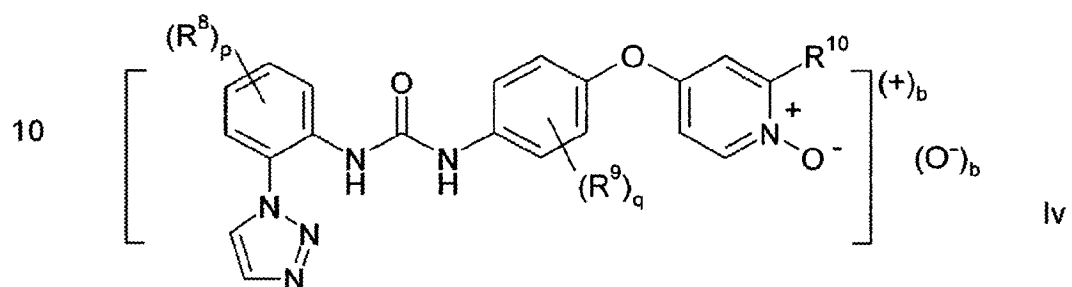
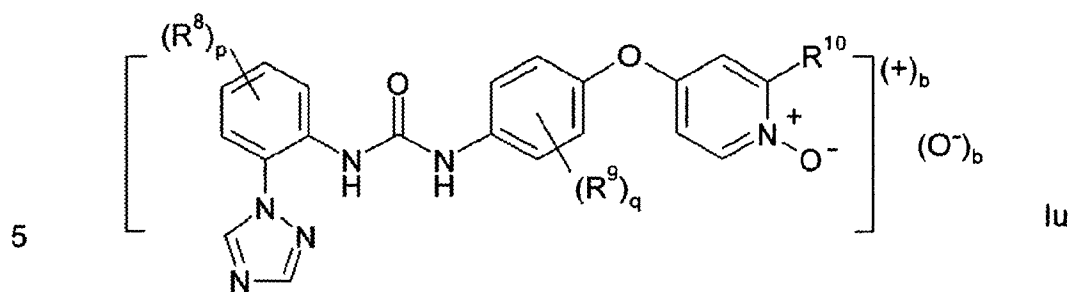


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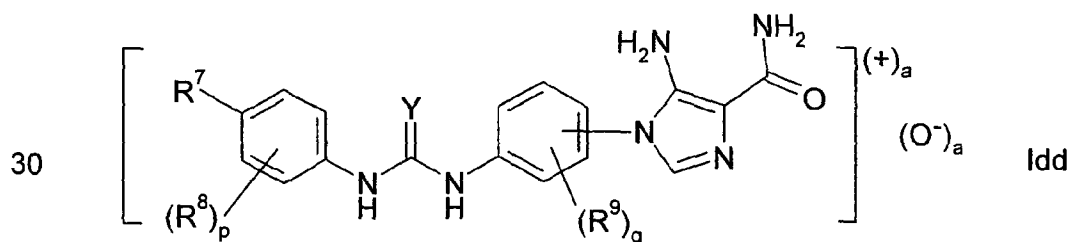
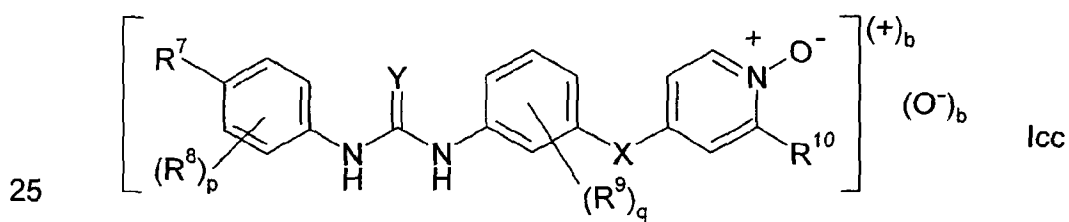
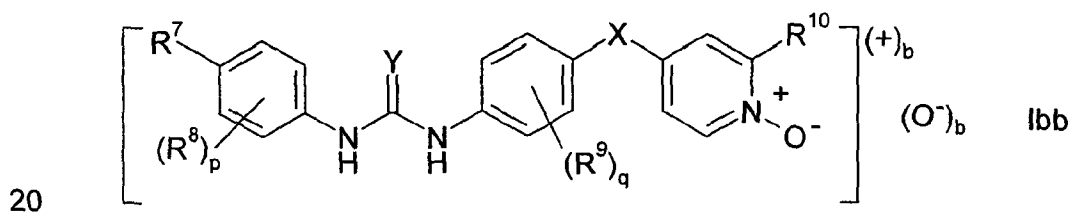
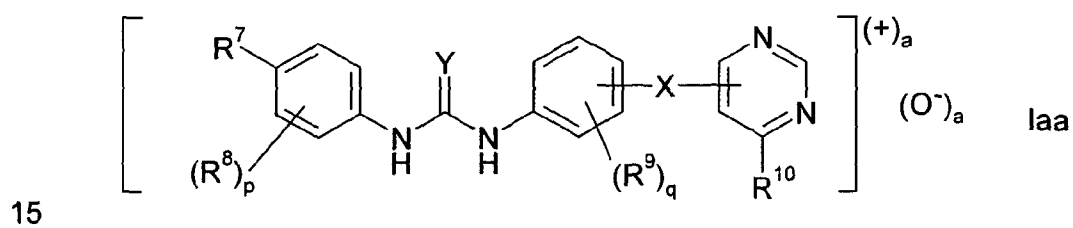
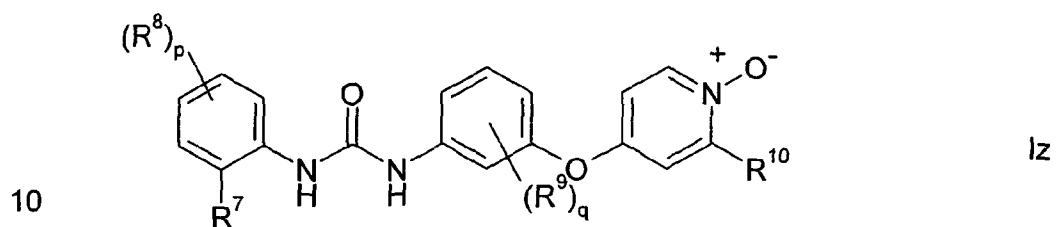
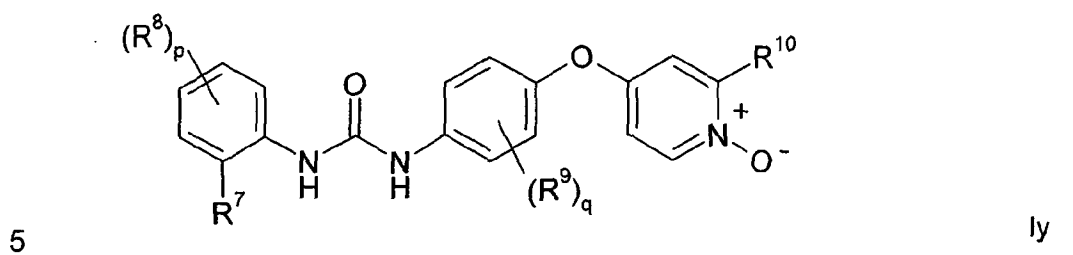
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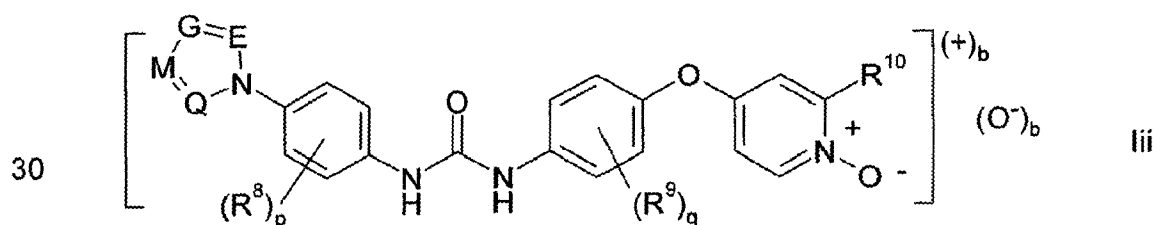
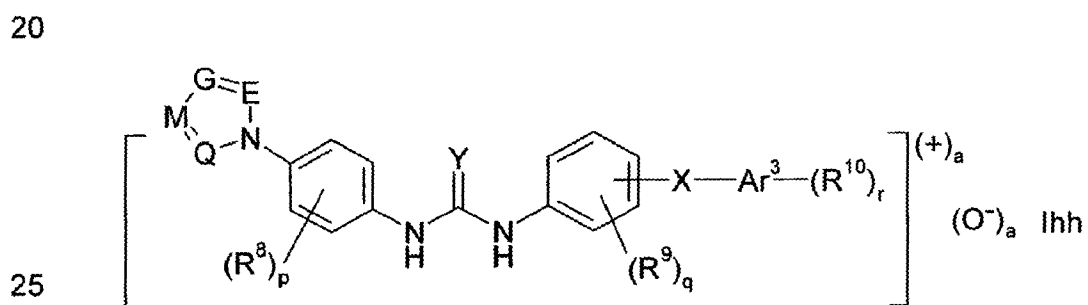
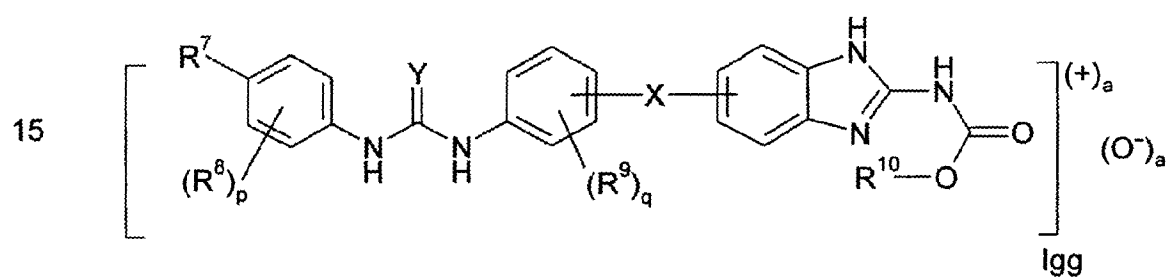
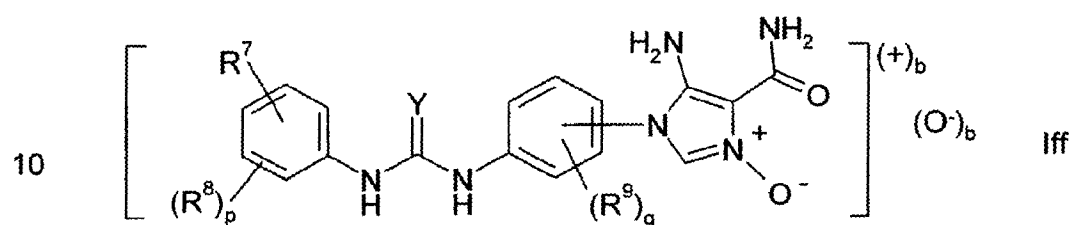
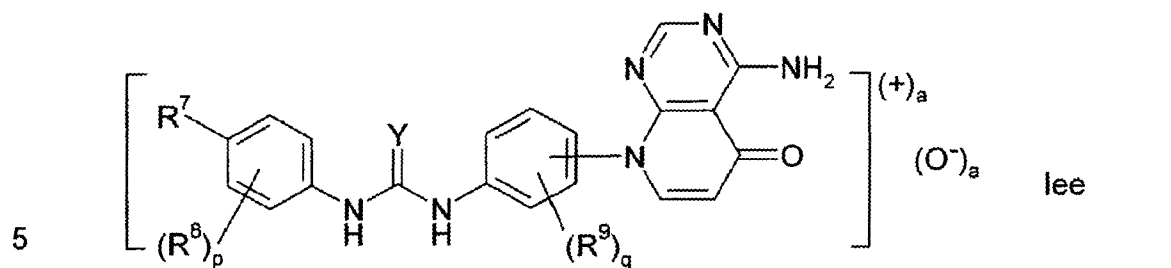
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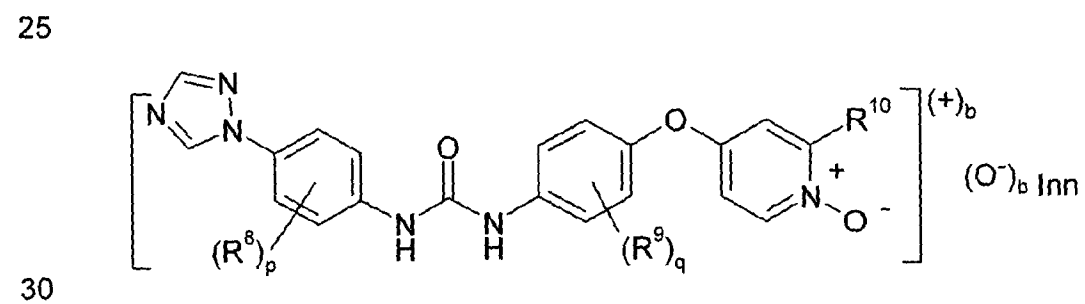
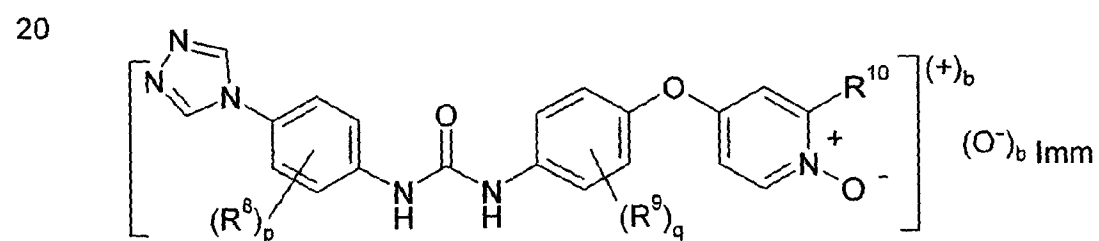
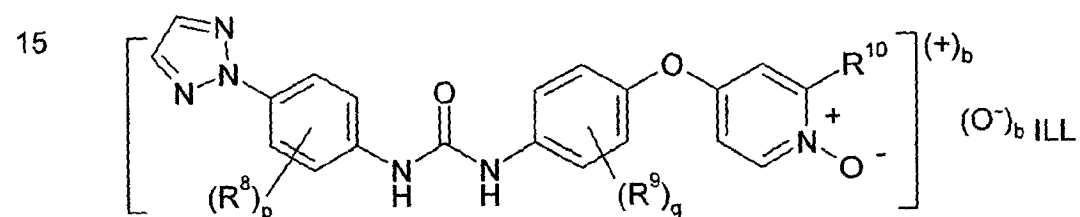
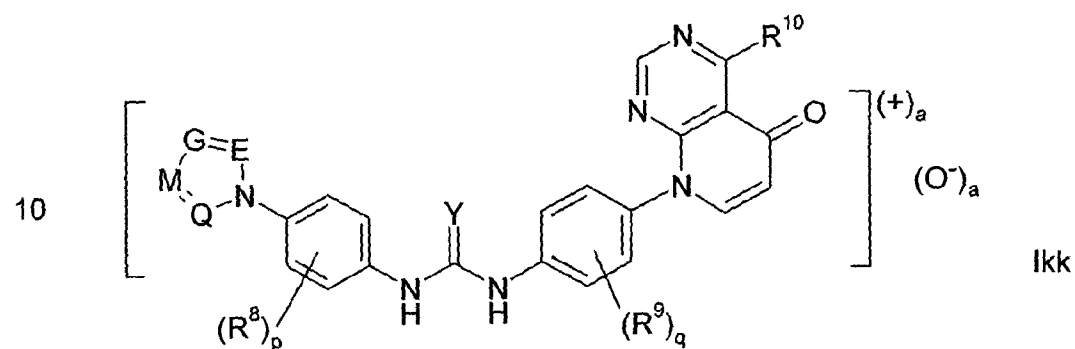
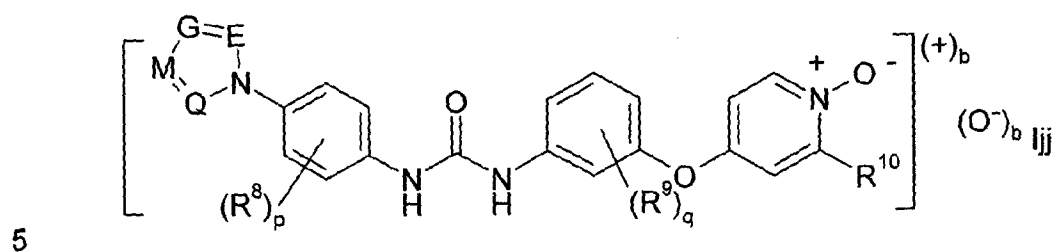


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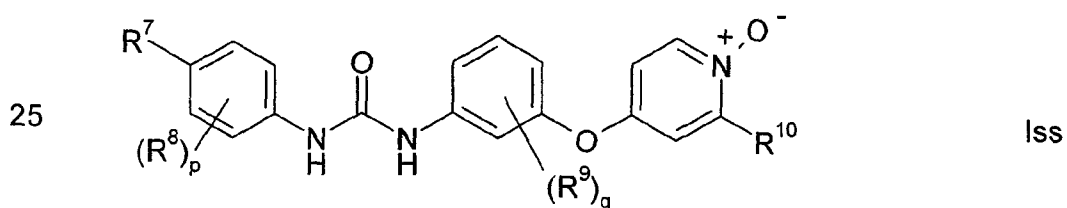
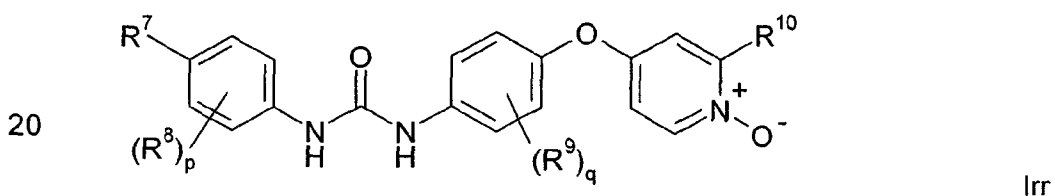
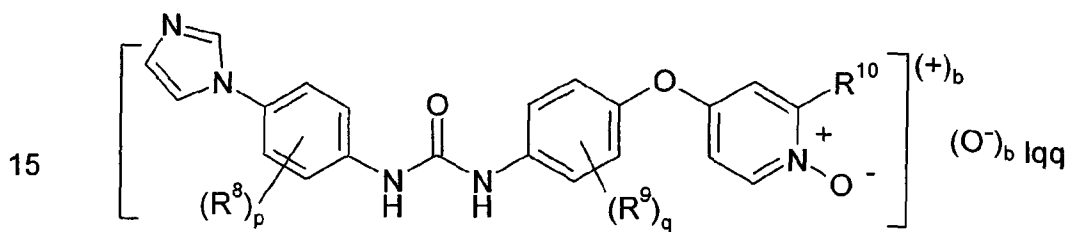
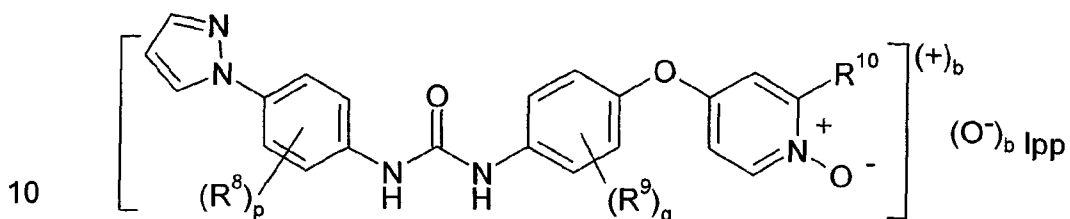
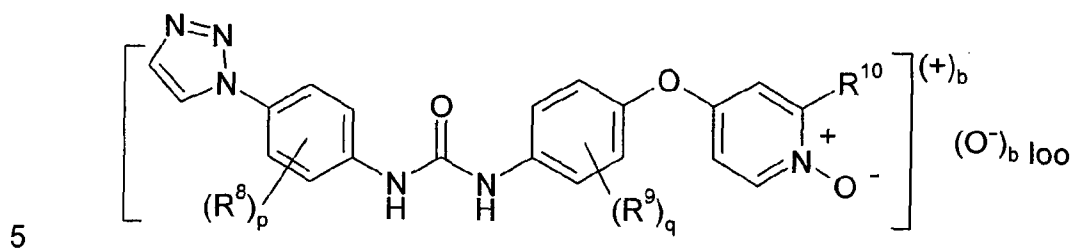


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wherein b is 0, 1 or 2, and wherein R^7 , R^8 , Ar^1 , Ar^3 , Y, X, R^9 , a, g, p, q and r are as defined in one of the claims 1 to 3, R^{10} is H or as defined in one of the claims 1 to 3; and wherein E, G, M and Q are selected independently from one another from N and CR^{30} , with the proviso that

one or more of E, G, M and Q are other than nitrogen atoms; and the pharmaceutically acceptable derivatives, salts, solvates and tautomers thereof.

- 5 5. N-Oxides according to one of the claims 1 to 4, selected from
 - 1-Oxy-4-{4-[3-(2-[1,2,4]triazol-4-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide;
 - 1-Oxy-4-{4-[3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide;
 - 10 1-Oxy-4-{4-[3-(2-[1,2,3]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide;
 - 1-Oxy-4-{4-[3-(2-imidazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide;
 - 1-Oxy-4-{4-[3-(2-pyrazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide;
 - 15 1-[4-(1-Oxy-pyridin-4-yloxy)-phenyl]-3-(2-[1,2,3]triazol-1-yl-5-trifluoromethyl-phenyl)-urea;
 - 1-[4-(1-Oxy-pyridin-4-yloxy)-phenyl]-3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-urea;
 - 20 1-[4-(1-Oxy-pyridin-4-yloxy)-phenyl]-3-(2-pyrazol-1-yl-5-trifluoromethyl-phenyl)-urea;
 - 1-[4-(1-Oxy-pyridin-4-yloxy)-phenyl]-3-(2-imidazol-1-yl-5-trifluoromethyl-phenyl)-urea;
 - 1-Oxy-4-{4-[3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid (2-hydroxy-ethyl)-amide;
 - 25 1-[4-(1-Oxy-pyridin-4-yloxy)-phenyl]-3-(2-[1,2,4]triazol-4-yl-5-trifluoromethyl-phenyl)-urea;
 - 4-{4-[3-(2-Imidazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1-oxy-pyridine-2-carboxylic acid methylamide;
 - 30 4-{3-Fluoro-4-[3-(2-pyrazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1-oxy-pyridine-2-carboxylic acid methylamide;
 - 4-{3-Fluoro-4-[3-(2-[1,2,3]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-

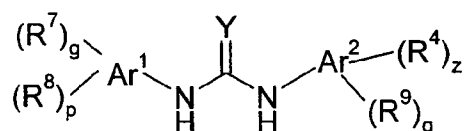
- phenoxy}-1-oxy-pyridine-2-carboxylic acid methylamide;
4-{3-Fluoro-4-[3-(2-imidazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-
phenoxy}-1-oxy-pyridine-2-carboxylic acid methylamide;
4-{3-Fluoro-4-[3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-
5 phenoxy}-1-oxy-pyridine-2-carboxylic acid methylamide;
4-{3-Fluoro-4-[3-(2-[1,2,4]triazol-4-yl-5-trifluoromethyl-phenyl)-ureido]-
phenoxy}-1-oxy-pyridine-2-carboxylic acid methylamide;
1-Oxy-4-{4-[3-(4-[1,2,4]triazol-1-yl-3-trifluoromethyl-phenyl)-ureido]-
phenoxy}-pyridine-2-carboxylic acid methylamide;
10 1-Oxy-4-{4-[3-(4-[1,2,3]triazol-1-yl-3-trifluoromethyl-phenyl)-ureido]-
phenoxy}-pyridine-2-carboxylic acid methylamide;
1-Oxy-4-(4-{3-[2-(2,4-Dibromo-imidazol-1-yl)-5-trifluoromethyl-phenyl]-
ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide;
1-Oxy-4-(4-{3-[2-(2-Methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-
15 ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide;
1-Oxy-4-(4-{3-[2-(3-Oxo-piperazin-1-yl)-5-trifluoromethyl-phenyl]-
ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide;
4-(4-{3-[4-(2,2-Dimethyl-5-oxo-pyrrolidin-1-yl)-3-trifluoromethyl-phenyl]-
ureido}-phenoxy)-1-oxy-pyridine-2-carboxylic acid methylamide;
20 1-Oxy-4-(4-{3-[2-(3-methyl-2,5-dioxo-imidazolidin-1-yl)-5-trifluoromethyl-
phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide;
1-Oxy-4-(4-{3-[4-(3-oxo-2-aza-bicyclo[2.2.2]oct-2-yl)-3-trifluoromethyl-
phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide;
1-[4-(1-Oxy-pyridin-4-yloxy)-phenyl]-3-(3-pyrrol-1-yl-phenyl)-urea;
25 4-{4-[3-(4-Chloro-5-methyl-2-pyrrol-1-yl-phenyl)-ureido]-phenoxy}-1-oxy-
pyridine-2-carboxylic acid methylamide;
1-[4-(4-Amino-3-oxy-5-oxo-5H-pyrido[2,3-d]pyrimidin-8-yl)-phenyl]-3-(2-
[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-urea;
1-[4-(4-Amino-1-oxy-5-oxo-5H-pyrido[2,3-d]pyrimidin-8-yl)-phenyl]-3-(2-
30 [1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-urea;
1-[4-(4-Amino-3-oxy-5-oxo-5H-pyrido[2,3-d]pyrimidin-8-yl)-phenyl]-3-(2-
[1,2,3]triazol-1-yl-5-trifluoromethyl-phenyl)-urea;

- 1-[4-(4-Amino-1-oxy-5-oxo-5H-pyrido[2,3-d]pyrimidin-8-yl)-phenyl]-3-(2-[1,2,3]triazol-1-yl-5-trifluoromethyl-phenyl)-urea;
- 1-[4-(4-Amino-3-oxy-5-oxo-5H-pyrido[2,3-d]pyrimidin-8-yl)-phenyl]-3-(2-pyrazol-1-yl-5-trifluoromethyl-phenyl)-urea;
- 5 1-[4-(4-Amino-1-oxy-5-oxo-5H-pyrido[2,3-d]pyrimidin-8-yl)-phenyl]-3-(2-pyrazol-1-yl-5-trifluoromethyl-phenyl)-urea;
- 5-Amino-3-oxy-1-{4-[3-(2-[1,2,3]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenyl}-1H-imidazole-4-carboxylic acid amide;
- 5-Amino-3-oxy-1-{4-[3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenyl}-1H-imidazole-4-carboxylic acid amide;
- 10 5-Amino-3-oxy-1-{4-[3-(2-pyrazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenyl}-1H-imidazole-4-carboxylic acid amide;
- 1-[4-(1-Oxy-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidin-4-ylamino)-phenyl]-3-(2-[1,2,3]triazol-1-yl-5-trifluoromethyl-phenyl)-urea;
- 15 1-[4-(3-Oxy-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidin-4-ylamino)-phenyl]-3-(2-[1,2,3]triazol-1-yl-5-trifluoromethyl-phenyl)-urea;
- 1-[4-(1-Oxy-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidin-4-ylamino)-phenyl]-3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-urea;
- 1-[4-(3-Oxy-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidin-4-ylamino)-phenyl]-3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-urea;
- 20 1-[4-(4-Amino-3-oxy-5-oxo-5H-pyrido[2,3-d]pyrimidin-8-yl)-phenyl]-3-(2-imidazol-1-yl-5-trifluoromethyl-phenyl)-urea;
- 1-[4-(4-Amino-1-oxy-5-oxo-5H-pyrido[2,3-d]pyrimidin-8-yl)-phenyl]-3-(2-imidazol-1-yl-5-trifluoromethyl-phenyl)-urea;
- 25 1-[4-(4-Amino-3-oxy-5-oxo-5H-pyrido[2,3-d]pyrimidin-8-yl)-phenyl]-3-(2-[1,2,4]triazol-4-yl-5-trifluoromethyl-phenyl)-urea;
- 1-[4-(4-Amino-1-oxy-5-oxo-5H-pyrido[2,3-d]pyrimidin-8-yl)-phenyl]-3-(2-[1,2,4]triazol-4-yl-5-trifluoromethyl-phenyl)-urea;
- (3-Oxy-5-{4-[3-(2-[1,2,4]triazol-4-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1H-benzimidazol-2-yl)-carbamic acid methyl ester;
- 30 (3-Oxy-6-{4-[3-(2-[1,2,4]triazol-4-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1H-benzimidazol-2-yl)-carbamic acid methyl ester;

- (3-Oxy-5-{4-[3-(2-[1,2,3]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1H-benzoimidazol-2-yl)-carbamic acid methyl ester;
 (3-Oxy-6-{4-[3-(2-[1,2,3]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1H-benzoimidazol-2-yl)-carbamic acid methyl ester;
 5 (3-Oxy-5-{4-[3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1H-benzoimidazol-2-yl)-carbamic acid methyl ester;
 (3-Oxy-6-{4-[3-(2-[1,2,4]triazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1H-benzoimidazol-2-yl)-carbamic acid methyl ester;
 (3-Oxy-5-{4-[3-(2-imidazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1H-benzoimidazol-2-yl)-carbamic acid methyl ester;
 10 (3-Oxy-6-{4-[3-(2-imidazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1H-benzoimidazol-2-yl)-carbamic acid methyl ester;
 (3-Oxy-5-{4-[3-(2-pyrazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1H-benzoimidazol-2-yl)-carbamic acid methyl ester;
 15 (3-Oxy-6-{4-[3-(2-pyrazol-1-yl-5-trifluoromethyl-phenyl)-ureido]-phenoxy}-1H-benzoimidazol-2-yl)-carbamic acid methyl ester;
 and the pharmaceutically acceptable derivatives, salts, solvates and tautomers thereof.

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6. N-Oxides obtainable by oxidizing a compound of formula



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wherein

R⁷, R⁸, R⁹, R⁴, Y, Ar¹, Ar², g, p, q and z are as defined in one or more of claims 1, 2 or 3; at about 25 °C in the presence of an oxidizing agent, selected from 3-chloroperbenzoic acid, H₂O₂ in acetic acid and H₂O₂ in formic acid.

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7. N-Oxide according to one of the claims 1 to 6 as a medicament.

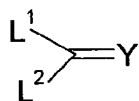
8. N-Oxide according to one of the claims 1 to 6 as a kinase inhibitor.
- 5 9. N-Oxide according to claim 8, characterized in that the kinases are selected from raf-kinases, Tie-kinases, PDGFR-kinases and VEGFR-kinases.
- 10 10. Pharmaceutical composition, characterised in that it contains one or more compounds according to one of the claims 1 to 6.
- 15 11. Pharmaceutical composition according to claim 9, characterised in that it contains one or more additional compounds, selected from the group consisting of physiologically acceptable excipients, auxiliaries, adjuvants, carriers and pharmaceutical active ingredients other than the compounds according to one of the claims 1 to 6.
- 20 12. Process for the manufacture of a pharmaceutical composition, characterised in that one or more compounds according to one of the claims 1 to 6 and one or more compounds, selected from the group consisting of carriers, excipients, auxiliaries and pharmaceutical active ingredients other than the compounds according to one of the claims 1 to 6, is processed by mechanical means into a pharmaceutical composition that is suitable as dosageform for application and/or administration to a patient.
- 25 13. Use of a compound according to one of the claims 1 to 6 as a pharmaceutical.
- 30 14. Use of a compound according to one of the claims 1 to 6 in the treatment and/or prophylaxis of disorders.

15. Use of a compound according to one of the claims 1 to 6 for producing a pharmaceutical composition for the treatment and/or prophylaxis of disorders.
- 5 16. Use according to claim 14 or 15, characterised in that the disorders are caused, mediated and/or propagated by one or more kinases, selected from raf-kinases, Tie-kinases, PDGFR-kinases and VEGFR-kinases.
- 10 17. Use according to claim 14, 15 or 16, characterised in that the disorders are selected from the group consisting of hyperproliferative and nonhyperproliferative disorders.
- 15 18. Use according to claim 14, 15, 16 or 17, characterised in that the disorder is cancer.
19. Use according to claim 14, 15, 16 or 17, characterised in that the disorder is noncancerous.
- 20 20. Use according to claim 14, 15, 16, 17 or 19, characterised in that the disorders are selected from the group consisting of psoriasis, arthritis, inflammation, endometriosis, scarring, Helicobacter pylori infection, Influenza A, benign prostatic hyperplasia, immunological diseases, autoimmune diseases and immunodeficiency diseases.
- 25 21. Use according to one of the claims 14 to 18, characterised in that the disorders are selected from the group consisting of melanoma, brain cancer, lung cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, hepatic cancer, renal cancer, colorectal cancer, breast cancer, head cancer, neck cancer, oesophageal cancer, 30 gynaecological cancer, ovarian cancer, ovary cancer, uterine cancer, prostate cancer, thyroid cancer, lymphoma, chronic leukaemia and acute leukaemia.

22. Use according to one of the claims 14 to 19, characterised in that the disorders are selected from the group consisting of arthritis, restenosis; fibrotic disorders; mesangial cell proliferative disorders, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, organ transplant rejection, glomerulopathies, metabolic disorders, inflammation, solid tumors, rheumatic arthritis, diabetic retinopathy, and neurodegenerative diseases.
23. Use according to one of the claims 14 to 17, characterised in that the disorders are selected from the group consisting of rheumatoid arthritis, inflammation, autoimmune disease, chronic obstructive pulmonary disease, asthma, inflammatory bowel disease, fibrosis, atherosclerosis, restenosis, vascular disease, cardiovascular disease, inflammation, renal disease and angiogenesis disorders.
24. Use of a compound according to one of the claims 1 to 6 as a kinase inhibitor.
25. Use according to claim 24, characterised in that the raf-kinase is selected from the group consisting of raf-kinases, Tie-kinases, PDGFR-kinases, VEGFR-kinases and p38-kinases.
26. Method for the treatment and/or prophylaxis of disorders, characterised in that one or more compounds according to one of the claims 1 to 6 is administered to a patient in need of such a treatment.
27. Method according to claim 26, characterised in that the one or more compounds according to one of the claims claim 1 to 6 are administered as a pharmaceutical composition according to claim 10 or 11.

28. Method for the treatment and/or prophylaxis of disorders according to claim 27, characterised in that the disorders are as defined in one of the claims 16 to 23.
- 5 29. Method for the treatment according to claim 28, characterised in that the disorder is cancerous cell growth mediated by Tie kinases, PDGFR kinases and/or VEGFR kinases.
- 10 30. Use of an N-oxide according to one of the claims 1 to 6 for the preparation of a medicament for the treatment of solid tumours, where a therapeutically effective amount of said heterocyclic substituted bisaryl urea derivative is administered in combination with radiotherapy and/or a compound from the group consisting of 1) an oestrogen receptor
- 15 modulator, 2) an androgen receptor modulator, 3) a retinoid receptor modulator, 4) a cytotoxic agent, 5) an antiproliferative agent, 6) a prenyl-protein transferase inhibitor, 7) an HMG-CoA reductase inhibitor, 8) an HIV protease inhibitor, 9) a reverse transcriptase inhibitor and 10) another angiogenesis inhibitor.
- 20 31. Method for producing compounds of formula I, characterised in that
- a) a compound of formula II,

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wherein

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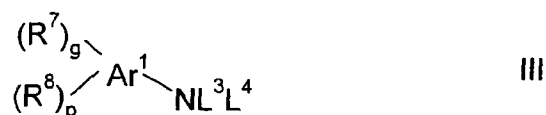
L^1 and L^2 either independently from one another represent a leaving group, or together represent a leaving group,

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and Y is as defined above/below,

is reacted with

- 5 b) a compound of formula III



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wherein

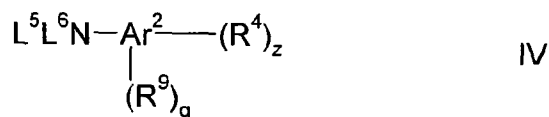
L^3 and L^4 are independently from one another H or a metal ion,
and wherein R^7 , R^8 , g, p and Ar^1 are as defined in claim
1,

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and

- c) a compound of formula IV,

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wherein

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L^5 and L^6 are independently from one another H or a metal ion,
and R^9 , q, Ar^2 , R^4 , and z are as defined in claim 1,

- 30 d) treating the compound obtained by said reaction with an oxidizing agent to obtain the N-oxide of formula I,

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and optionally

- e) isolating and/or treating the N-oxide of formula I obtained by said reaction with an acid, to obtain the salt thereof.

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2007/002647

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/12 C07D471/04 A61K31/435 A61K31/495 A61P35/00
A61P37/00 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/075425 A (MERCK PATENT GMBH [DE]; BUCHSTALLER HANS-PETER [DE]; BURGDORF LARS [DE]) 18 August 2005 (2005-08-18) claim 1; examples 80,89	1-31
X	WO 2005/097755 A (MERCK PATENT GMBH [DE]; HOELZEMANN GUENTER [DE]; CRASSIER HELENE [DE];) 20 October 2005 (2005-10-20) Examples; claim 1	1-31
X	WO 2005/047283 A (MERCK PATENT GMBH [DE]; HOELZEMANN GUENTER [DE]; CRASSIER HELENE [DE];) 26 May 2005 (2005-05-26) Examples, claim 1	1-31

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

1 June 2007

Date of mailing of the international search report

12/06/2007

Name and mailing address of the ISA/

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Authorized officer

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2007/002647

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 13-29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2007/002647

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005075425 A	18-08-2005	AR 047585 A1	25-01-2006
		AU 2005211448 A1	18-08-2005
		CA 2554878 A1	18-08-2005
		KR 20060132882 A	22-12-2006
WO 2005097755 A	20-10-2005	AR 048327 A1	19-04-2006
		AU 2005231907 A1	20-10-2005
		CA 2561585 A1	20-10-2005
		CN 1938282 A	28-03-2007
		DE 102004015099 A1	20-10-2005
		EP 1761503 A2	14-03-2007
WO 2005047283 A	26-05-2005	KR 20060132965 A	22-12-2006
		AR 046929 A1	04-01-2006
		AU 2004288727 A1	26-05-2005
		CA 2545558 A1	26-05-2005
		DE 10352979 A1	09-06-2005
		EP 1682548 A1	26-07-2006
		JP 2007510679 T	26-04-2007
		US 2007099910 A1	03-05-2007