(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) **EP 1 580 188 B9**

(12) **CORRECTED EUROPEAN PATENT SPECIFICATION**

(15) Correction information:
Corrected version no 1 (W1 B1)
Corrections, see
Description Paragraph(s) 9, 24, 29

(48) Corrigendum issued on:
23.05.2012 Bulletin 2012/21

(45) Date of publication and mention of the grant of the patent:
19.10.2011 Bulletin 2011/42

(21) Application number: **05007027.5**

(22) Date of filing: **11.02.2003**

(51) Int Cl.:
C07D 213/79 *(2006.01)* ***C07D 213/81*** *(2006.01)*
C07D 213/89 *(2006.01)* ***A61K 31/44*** *(2006.01)*
A61P 11/00 *(2006.01)* ***A61P 19/00*** *(2006.01)*
A61P 25/00 *(2006.01)* ***A61P 29/00*** *(2006.01)*

(54) **Aryl ureas as kinase inhibitors**

Aryl-Harnstoffe als Kinase Inhibitoren

Aryle urées en tant qu'inhibiteurs de Kinase

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PT SE SI SK TR

(30) Priority: **11.02.2002 US 354937 P**

(43) Date of publication of application:
28.09.2005 Bulletin 2005/39

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
03707848.2 / 1 474 393

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(56) References cited:
WO-A-00/41698 **WO-A-00/42012**

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Description

Field of the Invention

[0001] This invention relates to aryl ureas and methods for their synthesis. The inventive compounds are useful in the treatment of

(i) raf mediated diseases, for example, cancer,
(ii) p38 mediated diseases such as inflammation and osteoporosis, and
(iii) VEGF mediated diseases such as angiogenesis disorders.

Background of the Invention

[0002] Activation of the Ras signal transduction pathway indicates a cascade of events that have a profound impact on cellular proliferation, differentiation, and transformation. Raf kinase, a downstream effector of Ras, is a key mediator of these signals from cell surface receptors to the cell nucleus (Lowy, D. R.; Willumsen, B. M. Ann. Rev. Biochem. 1993, 62, 851; Bos, J. L. Cancer Res. 1989, 49, 4682). 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. Trends Biochem. Sci. 1994, 19, 474-80; Fridman et al. J. Biol. Chem. 1994, 269, 30105-8. Kolch et al. (Nature 1991, 349, 426-28),have further indicated that inhibition of raf expression by antisense RNA blocks cell proliferation in membrane-associated oncogenes. 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). Thus, small molecule inhibitors of Raf kinase activity are important agents for the treatment of cancer (Naumann, U.; Eisenmann-Tappe, I.; Rapp, U. R. Recent Results Cancer Res. 1997, 143, 237; Monia, B. P.; Johnston, J. F.; Geiger, T.; Muller, M.; Fabbro, D. Nature Medicine 1996, 2, 668).

[0003] Inhibition of p38 has been shown to inhibit both cytokine production (eg., TNFα, IL-1, IL-6, IL-8) and proteolytic enzyme production (eg., MMP-1, MMP-3) *in vitro* and/or in *vivo.* The mitogen activated protein (MAP) kinase p38 is involved in IL-1 and TNF signaling pathways (Lee, J. C.; Laydon, J. T.; McDonnell, P. C.; Gallagher, T- F.; Kumar, S.; Green, D.; McNulty, D.; Blumenthal, M. J.; Heys, J. R.; Landvatter, S. W.; Stricker, J. E.; McLaughlin, M. M.; Siemens, I. R.; Fisher, S. M.; Livi, G. P.; White, J. R.; Adams, J. L.; Yound, P. R. Nature 1994, 372, 739).

[0004] Clinical studies have linked TNFα production and/or signaling to a number of diseases including rheumatoid arthritis (Maini. J. Royal Coll. Physicians London 1996, 30, 344). In addition, excessive levels of TNFα have been implicated in a wide variety of inflammatory and/or immunomodulatory diseases, including acute rheumatic fever (Yegin et al. Lancet 1997, 349, 170), bone resorption (Pacifici et al. J. Clin. Endocrinol. Metabol. 1997, 82, 29), postmenopausal osteoperosis (Pacifici et al. J. Bone Mineral Res. 1996, 11, 1043), sepsis (Blackwell et al. Br. J. Anaesth. 1996, 77, 110), gram negative sepsis (Debets et al. Prog. Clin. Biol. Res. 1989, 308, 463), septic shock (Tracey et al. Nature 1987, 330, 662; Girardin et al. New England J. Med. 1988, 319, 397), endotoxic shock (Beutler et al. Science 1985, 229, 869; Ashkenasi et al Proc. Nat 'l. Acad. Sci. USA 1991, 88, 10535), toxic shock syndrome, (Saha et al. J. Immunol. 1996, 157, 3869; Lina et al. FEMS Immunol. Med. Microbiol. 1996, 13, 81), systemic inflammatory response syndrome (Anon. Crit. Care Med. 1992, 20, 864), inflammatory bowel diseases (Stokkers et al. J. Inflamm 1995-6, 47, 97) including Crohn's disease (van Deventer et al. Aliment. Pharmacol. Therapeu. 1996, 10 (Suppl. 2), 107; van Dullemen et al. Gastroenterology 1995, 109, 129) and ulcerative colitis (Masuda et al. J. Clin. Lab. Immunol. 1995, 46, 111), Jarisch-Herxheimer reactions (Fekade et al. New England J. Med. 1996, 335, 311), asthma (Amrani et al. Rev. Malad. Respir. 1996, 13, 539), adult respiratory distress syndrome (Roten et al. Am. Rev. Respir. Dis. 1991, 143, 590; Suter et al. Am. Rev. Respir. Dis. 1992, 145, 1016), acute pulmonary fibrotic diseases (Pan et al. Pathol. Int. 1996, 46, 91), pulmonary sarcoidosis (Ishioka et al. Sarcoidosis Vasculitis Diffuse Lung Dis. 1996, 13, 139), allergic respiratory diseases (Casale et al. Am. J. Respir. Cell Mol. Biol. 1996, 15, 35), silicosis (Gossart et al. J. Immunol. 1996, 156, 1540; Vanhee et al. Eur. Respir. J. 1995, 8, 834), coal worker's pneumoconiosis (Borm et al. Am. Rev. Respir. Dis- 1988, 138, 1589), alveolar injury (Horinouchi et al. Am. J. Respir. Cell Mol. BioL 1996, 14, 1044), hepatic failure (Gantner et al. J. Pharmacol. Exp. Therap. 1997, 280, 53), liver disease during acute inflammation (Kim et al. J. Biol. Chem. 1997, 272, 1402), severe alcoholic hepatitis (Bird et al. Ann. Intern. Med. 1990, 112, 917), malaria (Grau et al, Immunol. Rev. 1989. 112, 49; Taverne et al. Parasitol. Today 1996, 12, 290) including Plasmodium falciparum malaria (Perlmann et al. Infect. Immunit. 1997, 65, 116) and cerebral malaria (Rudin et al. Am. J. Pathol. 1997, 150, 257), non-insulin-dependent diabetes mellitus (NIDDM; Stephens et al J. Biol. Chem. 1997, 272, 971; Ofei et al- Diabetes 1996, 45, 881), congestive heart failure (Doyama et al. Int. J. Cardiol. 1996, 54, 217; McMurray et al. Br. Heart J. 1991, 66, 356), damage following heart disease (Malkiel et al. Mol. Med. Today 1996, 2, 336), atherosclerosis (Parums et al. J. Pathol. 1996, 179, A46), Alzheimer's disease (Fagarasan et al. Brain Res. 1996, 723, 231; Aisen et al. Gerontology 1997, 43, 143), acute encephalitis (Ichiyama

et al. J. Neurol. 1996, 243, 457), brain injury (Cannon et al. Crit. Care Med. 1992, 20, 1414; Hansbrough et al. Surg. Clin. N. Am 1987, 67, 69; Marano et al. Surg. Gynecol. Obsetr. 1990, 170, 32), multiple sclerosis (M.S.; Coyle. Adv. Neuroimmunol. 1996, 6, 143; Matusevicius et al. J Neuroimmunol. 1996, 66, 115) including demyelation and oligiodendrocyte loss in multiple sclerosis (Brosnan et al. Brain Pathol. 1996, 6, 243), advanced cancer (MucWierzgon et al. J. Biol. Regulators Homeostatic Agents 1996, 10, 25), lymphoid malignancies (Levy et al. Crit. Rev. Immunol. 1996, 16, 3 1), pancreatitis (Exley et al. Gut 1992, 33, 1126) including systemic complications in acute pancreatitis (McKay et al Br. J. Surg. 1996, 83, 919), impaired wound healing in infection inflammation and cancer (Buck et al. Am. J. Pathol. 1996, 149, 195), myelodysplastic syndromes (Raza et aL Int. J. Hematol. 1996, 63, 265), systemic lupus erythematosus (Maury et al. Arthritis Rheum. 1989, 32, 146), biliary cirrhosis (Miller et aL Am. J. Gasteroenterolog. 1992, 87, 465), bowel necrosis (Sun et al. J. Clin. Invest. 1988, 81, 1328), psoriasis (Christophers. Austr. J Dermatol. 1996, 37, S4), radiation injury (Redlich et al. J. Immunol. 1996, 157, 1705), and toxicity following administration of monoclonal antibodies such as OKT3 (Brod et al. Neurology 1996, 46, 1633). TNFα levels have also been related to host-versus-graft reactions (Piguet et al. Immunol. Ser. 1992, 56, 409) including ischemia reperfusion injury (Colletti et al. J. Clin Invest. 1989, 85, 1333) and allograft rejections including those of the kidney (Maury et al. J. Exp. Med. 1987, 166, 1132), liver (Imagawa et al. Transplantation 1990, 50, 219), heart (Bolling et al. Transplantation 1992, 53, 283), and skin (Stevens et al. Transplant. Proc. 1990, 22, 1924), lung allograft rejection (Grossman et al. Immunol. Allergy Clin. N. Am. 1989, 9, 153) including chronic lung allograft rejection (obliterative bronchitis; LoCicero et al. J. Thorac. Cardiovasc. Surg. 1990, 99, 1059), as well as complications due to total hip replacement (Cirino et al. Life Sci. 1996, 59, 86). TNFα has also been linked to infectious diseases (review: Beutler et al. Crit. Care Med. 1993, 21, 5423; Degre. Biotherapy 1996, 8, 219) including tuberculosis (Rook et al. Med. Malad. Infect. 1996, 26, 904); Helicobacter pylori infection during peptic ulcer disease (Beales et al. Gastroenterology 1997, 112, 136), Chaga's disease resulting from Trypanosoma cruzi infection (Chandrasekar et al. Biochem. Biophys. Res. Commun. 1996, 223, 365), effects of Shiga-like toxin resulting from E. coli infection (Harel et al. J. Clin. Invest. 1992, 56, 40), the effects of enterotoxin A resulting from Staphylococcus infection (Fischer et al. J. Immunol. 1990, 144, 4663), meningococcal infection (Waage et al. Lancet 1987, 355; Ossege et al. J. Neurolog. Sci 1996, 144; 1), and infections from Borrelia burgdorferi (Brandt et al. Infect. Immunol. 1990, 58, 983), Treponema pallidum (Chamberlin et al. Infect. Immunol 1989, 57, 2872), cytomegalovirus (CMV; Geist et al. Am, J. Respir. Cell Mol. Biol. 1997, 16, 31), influenza virus (Beutler et al. Clin. Res. 1986, 34, 491a), Sendai virus (Goldfield et al. Proc. Nat'l. Acad. Sci. USA 1989, 87, 1490), Theiler's encephalomyelitis virus (Sierra et al. Immunology 1993, 78, 399), and the human immunodeficiency virus (HIV; Poli. Proc. Nat'l. Acad. Sci. USA 1990, 87, 782; Vyakaram et al. AIDS 1990, 4. 21; Badley et al. J. Exp. Med. 1997, 185, 55).

[0005] A number of diseases are thought to be mediated by excess or undesired matrix-destroying metalloprotease (MMP) activity or by an imbalance in the ratio of the MMPs to the tissue inhibitors of metalloproteinases (TIMPs). These include osteoarthritis (Woessner et al. J. Biol. Chem. 1984, 259, 3633), rheumatoid arthritis (Mullins et al. Biochim. Biophys- Acta 1983, 695, 117; Woolley et al. Arthritis Rheum. 1977, 20, 1231; Gravallese et al. Arthritis Rheum: 1991, 34, 1076), septic arthritis (Williams et al. Arthritis Rheum. 1990, 33, 533), tumor metastasis (Reich et al. Cancer Res. 1988, 48, 3307; Matrisian et al. Proc Nat'l. Acad. Sci., USA 1986, 83, 9413), periodontal diseases (Overall et al. J. Periodontal Res. 1987, 22, 81), corneal ulceration (Burns et al. Invest. Opthalmol. Vis. Sci. 1989, 30, 1569), proteinuria (Baricos et al Biochem. J. 1988, 254, 609), coronary thrombosis from atherosclerotic plaque rupture (Henney et al. Proc. Nat'l. Acad. Sci., USA 1991, 88, 8154), aneurysmal aortic disease (Vine et al. Clin. Sci. 1991, 81, 233), birth control (Woessner et al. Steroids 1989, 54, 491), dystrophobic epidermolysis bullosa (Kronberger et al- J. Invest. Dermatol. 1982, 79, 208), degenerative cartilage loss following traumatic joint injury, osteopenias mediated by MMP activity, tempero mandibular joint disease, and demyelating diseases of the nervous system (Chantry et al. J. Neurochem. 1988, 50, 688).

[0006] Because inhibition of p38 leads to inhibition of TNFα production and MMP production, inhibition of mitogen activated protein (MAP) kinase p38 enzyme provides an approach to the treatment of the above listed diseases including osteoporosis and inflammatory disorders such as rheumatoid arthritis and COPD (Badger, A. M.; Bradbeer, J. N.; Votta, B.; Lee, J. C.; Adams. J. L.; Griswold, D. E. J. Pharm. Exper. Ther. 1996,279, 1453).

[0007] Vasculogenesis involves the *de novo* formation of blood vessels from endothelial cell precursors or angioblasts. The first vascular structures in the embryo are formed by vasculogenesis. Angiogenesis involves the development of capillaries from existing blood vessels, and is the principle mechanism by which organs, such as the brain and the kidney are vascularized. While vasculogenesis is restricted to embryonic development, angiogenesis can occur in the adult, for example during pregnancy, the female cycle, or wound healing.

[0008] One major regulator of angiogenesis and vasculogenesis in both embryonic development and some angiogenic-dependent diseases is vascular endothelial growth factor (VEGF; also called vascular permeability factor, VPF). VEGF represents a family of isoforms of mitogens existing in homodimeric forms due to alternative RNA splicing. The VEGF isoforms are highly specific for vascular endothelial cells (for reviews, see: Farrara et al. Endocr. Rev. 1992, 13, 18; Neufield et al. FASEB J. 1999, 13, 9). VEGF expression is induced by hypoxia (Sbweiki et al. Nature 1992, 359, 843), as well as by a variety of cytokines and growth factors, such as interleukin-1, interleukin-6, epidermal growth factor and

transforming growth factor.

[0009] To date, VEGF and the VEGF family members have been reported to bind to one or more of three transmembrane receptor tyrosine kinases (Mustonen et al. J. Cell Biol., 1995, 129, 895), VEGF receptor-1 (also known as flt-1 (fms-like tyrosine kinase-1)), VEGFR-2 (also known as kinase insert domain containing receptor (KDR); the murine analogue of KDR is known as fetal liver kinase-1 (fik-1)), and VEGFR-3 (also known as flt-4). KDR and flt-1 have been shown to have different signal transduction properties (Waltenberger et al. J. Biol. Chem. 1994, 269, 26988); Park et al. Oncogene 1995, 10, 135). Thus, KDR undergoes strong ligand-dependant tyrosine phosphorylation in intact cells, whereas flt-1 displays a weak response. Thus, binding to KDR is a critical requirement for induction of the full spectrum of VEGF-mediated biological responses.

[0010] *In vivo,* VEGF plays a central role in vasculogenesis, and induces angiogenesis and permeabilization of blood vessels. Deregulated VEGF expression contributes to the development of a number of diseases that are characterized by abnormal angiogenesis and/or hyperpermeability processes. Regulation of the VEGF-mediated signal transduction cascade will therefore provide a useful mode for control of abnormal angiogenesis and/or hyperpermeability processes.

[0011] Angiogenesis is regarded as an absolute prerequisite for growth of tumors beyond about 1-2 mm. Oxygen and nutrients may be supplied to cells in tumor smaller than this limit through diffusion. However, every tumor is dependent on angiogenesis for continued growth after it has reached a certain size. Tumorigenic cells within hypoxic regions of tumors respond by stimulation of VEGF production, which.triggers activation of quiescent endothelial cells to stimulate new blood vessel formation. (Shweiki et al. Proc. Nat'l. Acad. Sci., 1995, 92, 768). In addition, VEGF production in tumor regions where there is no angiogenesis may proceed through the ras signal transduction pathway (Grugel et al. J. Biol. Chem, 1995, 270, 25915; Rak et al. Cancer Res. 1995, 55, 4575). In situ hybridization studies have demonstrated VEGF mRNA is strongly upregulated in a wide variety of human tumors, including lung (Mattern et al- Br. J. Cancer 1996, 73, 931), thyroid (Viglietto et al, Oncogene 1995, 11, 1569), breast (Brown et al. Human Pathol. 1995, 26, 86), gastrointestional tract (Brown et al. Cancer Res. 1993, 53. 4727; Suzuki et al. Cancer Res. 1996, 56, 3004), kidney and bladder (Brown et al. Am. J. Pathol. 1993, 143I, 1255), ovary (Olson et al. Cancer Res. 1994, 54, 1255), and cervical (Guidi et al. J. Nat'l Cancer Inst. 1995, 87, 12137) carcinomas, as well as angiosacroma (Hashimoto et al. Lab. Invest 1995, 73, 859) and several intracranial tumors (Plate et al. Nature 1992, 359, 845; Phillips et al. Int. J. Oncol. 1993, 2, 913; Berkman et al. J. Clin. Invest., 1993, 91, 153). Neutralizing monoclonal antibodies to KDR have been shown to be efficacious in blocking tumor angiogenesis (Kim et al. Nature 1993, 362, 841; Rockwell et al. Mol. Cell. Differ. 1995, 3, 315).

[0012] Overexpression of VEGF, for example under conditions of extreme hypoxia, can lead to intraocular angiogenesis, resulting in hyperproliferation of blood vessels, leading eventually to blindness. Such a cascade of events has been observed for a number of retinopathies, including diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity (Aiello et al. New Engl. J. Med. 1994, 331, 1480; Peer et al. Lab. Invest. 1995, 72, 638), and age-related macular degeneration (AMD; see, Lopez et al. Invest. Opththalmol. Vis. Sci. 1996, 37, 855).

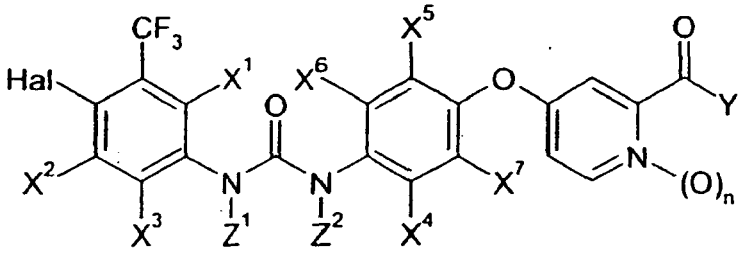
[0013] In rheumatoid arthritis (RA), the in-growth of vascular pannus may be mediated by production of angiogenic factors. Levels of immunoreactive VEGF are high in the synovial fluid of RA patients, while VEGF levels are low in the synovial fluid of patients with other forms of arthritis of with degenerative joint disease (Koch et al. J. Immunol. 1994, 152, 4149). The angiogenesis inhibitor AGM-170 has been shown to prevent neovascularization of the joint in the rat collagen arthritis model (Peacock et al. J. Exper. Med. 1992, 175, 1135).

[0014] Increased VEGF expression has also been shown in psoriatic skin, as well as bullous disorders associated with subepidermal blister formation, such as bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis (Brown et al. J. Invest. Dermatol. 1995, 104, 744).

[0015] Because inhibition of KDR leads to inhibition of VEGF-mediated angiogenesis and permeabilization, KDR inhibitors will be useful in treatment of diseases characterized by abnormal angiogenesis and/or hyperpermeability processes, including the above listed diseases.

Summary of the Invention

[0016] The invention relates to a compound of formula (I)



(I)

wherein,

Y	is OR^1 or NHR^2,	
Hal	is chlorine or bromine,	
R^1	is H or C_1-C_6 alkyl	
R^2	is H, OH, CH_3 or CH_2OH,	
Z^1 and Z^2	are each H or OH, wherein only one of Z^1 or Z^2 can be OH.	
X^1 to X^7	are each, independently, H, OH or $O(CO)C_1$-C_4 alkyl, and	
n	is 0 or 1,	

with the proviso that at least one of conditions a-c is met,

a) Z^1 or Z^2 is OH,
b) R^2 is OH,
c) n is 1, or a salt thereof, e.g., a pharmaceutically acceptable salt thereof, or an isolated stereoisomer thereof (collectively referred to hereinafter as the compounds of the invention). The term stereoisomer is understood to encompass diastereoisomers, enantiomers, geometric isomers, etc.

[0017] One of ordinary skill in the art will recognize that some of the compounds of Formula (I) can exist in different geometrical isomeric forms. In addition, some of the compounds of the present invention possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers, as well as in the form of racemic or nonracemic mixtures thereof, and in the form of diastereomers and diastereomeric mixtures. All of these compounds, including *cis* isomers, *trans* isomers, diastereomic mixtures, racemates, nonracemic mixtures of enantiomers, substantially pure, and pure enantiomers, are considered to be within the scope of the present invention. Herein, substantially pure enantiomers is intended to mean that no more than 5% w/w of the corresponding opposite enantiomer is present.

[0018] The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric and camphorsulfonic acid. Mixtures of diastereoisomers can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known to those skilled in the art, for example, by chromatography or fractional crystallization. The optically active bases or acids are liberated from the separated diastereomeric salts. A different process for separation of optical isomers involves the use of a chiral chromatography column (e.g., chiral HPLC columns) optimally chosen to maximize the separation of the enantiomers. Suitable chiral HPLC columns are manufactured by Diacel, e.g., Chiracel OD and Chiracel OJ. The optically active compounds of Formula (I) can likewise be obtained by utilizing optically active starting materials.

[0019] Regarding the compounds of the invention when n is 1. These compounds particularly include compounds of the invention wherein n is 1 in formula (I), Y is NHR^2 and R^2 is H or CH_3, compounds of the invention wherein n is 1 in formula (I) and X^1 to X^7 are each H, compounds of the invention wherein n is 1 in formula (I) and Z^1 and Z^2 are each H, compounds of the invention wherein n is 1 in formula (I) and Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2 is H, compounds of the invention wherein n is 1 in formula (I) and at least one of X^1 to X^7 is OH or $O(CO)C_1$-C_4 alkyl, compounds of the invention wherein n is 1 in formula (I), Y is NHR^2 and R^2 is CH_2OH, compounds of the invention wherein n is 1 in formula (I), Y is NHR^2 and R^2 is OH, and compounds of the invention wherein n is 1 in formula (I) and Y is OH.

[0020] Other compounds of the invention of interest are those wherein in formula (I) Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2 is H. These particularly include compounds of the invention wherein in formula (I) Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2 is H, and n is 0, compounds of the invention wherein in formula (I) Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2 is H, n is O, Y is NHR^2 and R^2 is H or CH_3, compounds of the invention wherein in formula (I) Z^1 is H and Z^2 is OH or

Z^1 is OH and Z^2 is H, and n is 0 and X^1 to X^7 are each H, compounds of the invention wherein in formula (I) Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2 is H, and n is 0 and at least one of X^1 to X^7 is OH or $O(CO)C_1$-C_4 alkyl, compounds of the invention wherein in formula (I) Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2 is H, n is O, Y is NHR^2 and R^2 is CH_2OH, compounds of the invention wherein in formula (I) Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2 is H, n is 0. Y is NHR^2 and R^2 is OH, and compounds of the invention wherein in formula (I) Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2 is H, and n is 0 and Y is OH.

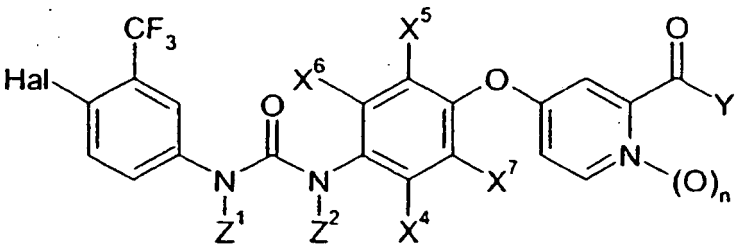
[0021] Further compounds of the invention of interest are those wherein in formula (I), Y is NHR^2 and R^2 is OH. These compounds particularly include compounds of the invention wherein in formula (I), Y is NHR^2 and R^2 is OH and n is 0, compounds of the invention wherein in formula (I), Y is NHR^2 and R^2 is OH and n is 0 and X^1 to X^7 are each H, compounds of the invention wherein in formula (I), Y is NHR^2 and R^2 is OH and n is 0 and Z^1 and Z^2 are each H, compounds of the invention wherein in formula (I), Y is NHR^2 and R^2 is OH and n is 0 and Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2 is H, and compounds of the invention wherein in formula (I). Y is NHR^2 and R^2 is OH and n is 0 and at least one of X^1 to X^7 is OH or $O(CO)C_1$-C_4 alkyl.

[0022] Compounds of the invention of interest are also those wherein in formula (I) Y is OH. These compounds particularly include compounds of the invention wherein in formula (I) Y is OH and n is 0, compounds of the invention wherein in formula (I) Y is OH and n is 0 and X^1 to X^7 are each H, compounds of the invention wherein in formula (I) Y is OH and n is 0 and Z^1 and Z^2 are each H, compounds of the invention wherein in formula (I) Y is OH and n is 0 and Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2 is H, and compounds of the invention wherein in formula (I) Y is OH and n is 0 and at least one of X^1 to X^7 is OH or $O(CO)C_1$-C_4 alkyl.

[0023] Particularly preferred compounds include:

4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide.
4-{4-[({[4-bromo-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide.
4- {4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-2-pyridine carboxamide 1-oxide.
4-{4-[({[4-bromo-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-2-pyridine carboxamide 1-oxide.
4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-N-hydroxymethyl-2-pyridine carboxamide 1-oxide.
4-{4-[({[4-bromo-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-N-hydroxymethyl,-2-pyridine carboxamide 1-oxide, and salts, stereoisomers and prodrugs thereof.

A subgroup of the compounds of the invention which are of interest include compounds of formula (II), or a salt or stereoisomer thereof,



II

wherein,

Y	is OR^1 or NHR^2,
Hal	is chlorine or bromine,
R^1	is H or C_1-C_6 alkyl
R^2	is H, OH, CH_3 or CH_2OH.
Z^1 and Z^2	are each H or OH, wherein only one of Z^1 or Z^2 can be OH,
X^4 to X^7	are each, independently, H , OH or $O(CO)C_1$-C_4 alkyl, and
n	is 0 or 1,

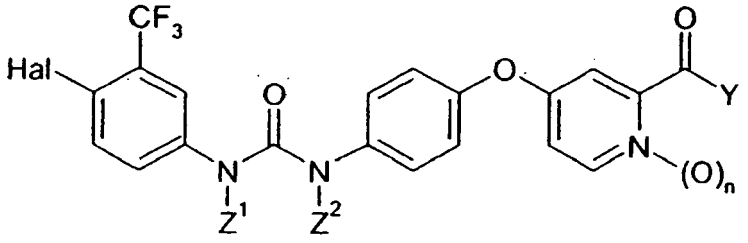
with the proviso that at least one of conditions a-c is met,

a) Z^1 or Z^2 is OH,

b) R^2 is OH,
c)n is 1.

[0024] These include compounds of the invention wherein in formula (II) n is 1, compounds of the invention wherein in formula (II) n is 1 and Z^1 and Z^2 are each H, compounds of the invention wherein in formula (II) n is 1, Z^1 and Z^2 are H and at least one of X^4 to X^7 is OH, compounds of the invention wherein in formula (II) n is 1, Z^1 and Z^2 are H and Y is NHR^2 and R^2 is H or CH_3, compounds of the invention wherein in formula (II) n is 0, compounds of the invention wherein in formula (II) n is 0 and Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2 is H , compounds of the invention wherein in formula (II) n is 0, Z^1 and Z^2 are each H, and at least one of X^4 to X^7 is OH, compounds of the invention wherein in formula (II) n is 0 and Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2 is H and at least one of X^4 to X^7 is OH, compounds of the invention wherein in formula (II) n is 0 and Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2 is H and Y is NHR^2 and R^2 is H or CH_3, compounds of the invention wherein in formula (II) n is 0 and Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2 is H, Y is NHR^1 R^2 is OH, and compounds of the invention wherein in formula (II), Y is NHR^2, R^2 is OH, n is 0 and at least one of X^4 to X^7 is OH.

Another subgroup of the compounds of the invention which are of interest include compounds of formula (III), or a salt or isolated stereoisomer thereof,



III

wherein,

Y	is OR^1 or NHR^2,
Hal	is chlorine or bromine,
R^1	is H or C_1-C_6 alkyl
R^2	is H, OH, CH_3 or CH_2OH,
Z^1 and Z^2	are each H or OH, wherein only one of Z^1 or Z^2 can be OH, and
n	is 0 or 1,

with the proviso that at least one of conditions a-c is met,

a) Z^1 or Z^2 is OH,
b) R^2 is OH,
c) n is 1.

[0025] These include compounds of the invention wherein in formula (III) n is 1 and Z^1 and Z^2 are each H, compounds of the invention wherein in formula (III) n is 1, Z^1 and Z^2 are each H, Y is NHR^2 and R^2 is H or CH_3, compounds of the invention wherein in formula (III) n is 0 and Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2 is H, compounds of the invention wherein in formula (III) n is 0, Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2 is H, Y is NHR^2 and R^2 is H or CH_3, and compounds of the invention wherein in formula (III) Y is OH.

[0026] The invention further relates to processes and methods of preparing the novel compounds of the invention. Such processes and methods include, but are not limited to, the oxidation of the pyridyl ring of 4-{4-[({[4-chloro-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide and 4-{4-[({[4-bromo-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide into their corresponding pyridine-1-oxides, the formal oxidation of any of the urea nitrogens of compounds of the invention into an N-hydroxyurea, the oxidation of any of the positions represented by X^1 to X^7 of compounds of the invention whereby a hydrogen atom is replaced by a hydroxyl group, the hydroxylation of the N-methyl amides of 4-{(4-[({[4-chloro-3-(trifluoromethyl)phenyl] amino} carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide and 4-{4-[({[4-bromo-3-(trifluoromethyl) phenyl]amino}carbonyl)amino] phenoxy}-N-methyl-2-pyridine carboxamide into the corresponding hydroxymethyl amides, the hydroxylation of said N-methyl amides into hydroxamic acids, the demethylation of said N-methyl amides into unsubstituted

amides, the hydrolysis of said N-methyl amides into carboxylic acids and combinations thereof. Furthermore, the invention relates to the esterification of hydroxyl groups in the X^1 to X^7 positions to, for example, acetates.

[0027] Processes of interest include a process for preparing 4-{4-[({[4-chloro-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide, or 4-{4-[({[4-bromo-3-(trifluoromethyl)phenyl]amino} carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide, or pharmaceutically acceptable salt, or an isolated stereoisomer thereof comprising oxidizing 4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide or 4-{4-[({[4-bromo-3-(trifluoromethyl)phenyl]amino}carbonyl)amino] phenoxy}-N-methyl-2-pyridine carboxamide into the corresponding pyridine-1-oxides and a process for preparing 4-{4-[({(4-chloro-3-(trifluoromethyl)phenyl] amino}carbonyl)amino]phenoxy}2-pyridine carboxamide 1-oxide, or 4-{4-[({(4-bromo-3-(trifluoromethyl)phenyl] amino}carbonyl)amino]phenoxy}2-pyridine carboxamide 1-oxide or pharmaceutically acceptable salt, or an isolated stereoisomer thereof comprising oxidizing 4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino} carbonyl)amino]phenoxy}-2-pyridine carboxamide or 4-{4-[({[4-bromo-3-(trifluoromethyl)phenyl]amino) carbonyl)amino] phenoxy}-2-pyridine carboxamide into the corresponding pyridine-1-oxides.

[0028] Compounds prepared by these methods are included in the invention. Also included are compounds obtained by transformation, including metabolic transformation, of 4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide or 4-{4-(({[4-bromo-3-(trifluoromethyl)phenyl]amino}carbonyl)amino] phenoxy}-N-methyl-2-pyridine carboxamide to either:

a) replace one or more of the phenyl hydrogens with a hydroxyl group,
b) hydroxyate the N-methyl-amide into a hydroxymethyl amide or hydroxamic acid,
c) demethylate the N-methyl amide into an unsubstituted amide,
d) oxidize one or more of the urea nitrogens from =NH to =NOH,
e) hydrolyze the N-methyl amide into a carboxylic acid,
f) oxidize the pyridine nitrogen into a pyridine-1-oxide, or
g) a combination of a-f,

with the proviso that at least one of steps b), d), and f) is performed.

[0029] Of particular interest are compounds obtained by transformation, including metabolic transformation, of 4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl) amino}carbonyl) amino]phenoxy-}-N-methyl-2-pyridine carboxamide or 4-{4-[({[4-bromo-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide to either:

a) hydroxyate the N-methyl amide into a hydroxymethyl amide or hydroxamic acid,
b) demethylate the N-methyl amide into an unsubstituted amide,
c) oxidize one or more of the urea nitrogens from =NH to =NOH,
d) hydrolyze the N-methyl amide into a carboxylic acid,
e) oxidize the pyridine nitrogen into a pyridine-1-oxide, or
f) a combination of a-e,

with the proviso that at least one of steps a), c), and e) is performed.

It is understood that the term "pyridine-1-oxide" used throughout the document includes 1-oxo-pyridine and 1-hydroxy-pyridine, and that for the purposes of this document, all 3 terms are considered interchangeable. For example, ChemInnovation Software, Inc. Nomenclator™ v. 3.01 identifies compounds of formula III where Y = $NHCH_3$, Hal= Cl, Z^1 and Z^7 - H, and n=1, drawn in ChemDraw, as N-[4-chloro-3-(trifluoromelhyl)phenyl]({4-[1-hydroxy-2-(N-methylcarbamoyl) (4-pyridyloxy)]phenyl}amino)carboxamide.

The invention further relates to a pharmaceutical composition comprising one or more compounds of the invention.

[0030] These include a pharmaceutical composition comprising an effective amount of at least one compound of the invention and a physiologically acceptable carrier. Preference is given to a pharmaceutical composition comprising an effective amount of 4-{4-[({[4-chloro-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide, 4-(4-[(([4-bromo-3-(trifluoromethyl)phenyl]amino) carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide, 4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl] amino}carbonyl)amino]phenoxy}2-pyridine carboxamide 1-oxide, or 4-{4-[({[4-bromo-3-(trifluoromethyl)phenyl] amino}carbonyl)amino]phenoxy} 2-pyridine carboxamide 1-oxide or a pharmaceutically acceptable salt, an isolated stereoisomer or a mixture thereof and a physiologically acceptable carrier.

[0031] Pharmaceutically acceptable salts of these compounds are also within the scope of the invention.

[0032] Salts of this invention are especially the pharmaceutically acceptable salts of compounds of formula (I) such as, for example, organic or inorganic acid addition salts of compounds of formula (I). Suitable inorganic acids include but are not limited to halogen acids (such as hydrochloric acid), sulfuric acid, or phosphoric acid. Suitable organic acids include but are not limited to carboxylic, phosphonic, sulfonic, or sulfamic acids, with examples including acetic acid,

propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, 2- or 3-hydroxybutyric acid, γ-aminobutyric acid (GABA), gluconic acid, glucosemonocarboxylic acid, fumaric acid, succinic acid, adipic acid, pimelic acid, suberic acid, azeiaic acid, malic acid, tartaric acid, citric acid, glucaric acid, galactaric acid, amino acids (such as glutamic acid, aspartic acid, N-methylglycine, acetylaminoacetic acid, N-acetylasparagine or N-acetylcysteine), pyruvic acid, acetoacetic acid, methanesulfonic acid, 4-toluene sulfonic acid, benzenesulfonic acid, phosphoserine, and 2- or 3-glyrerophosphoric acid.

[0033] 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)).Commonly used prodrugs of the disclosed oxazolyl-phenyl-2,4-diamino-pyrimidine compounds 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 11-13, (1996)).

[0034] The invention also relates to the use of a compound of the invention, or a pharmaceutical composition comprising a compound of the invention for the manufacture of a medicament for treating and preventing diseases, for example, inflammatory and angiogenesis disorders and osteoporosis in mammals.

[0035] These include the use of an effective amount of a compound of the invention for the manufacture of a medicament for treating or preventing osteoporosis, inflammation, and angiogenesis disorders (other than cancer) in a mammal. Preference is given to the use of an effective amount of 4-{4-[({[4-chloro-3-(trifluoromethyl) phenyl]amino}carbonyl) amino] phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide, 4-{4-[({[4-bromo-3-(trifluoromethyl)phenyl]amino} carbonyl) amino]phenoxy}-N-methyl-2-pyridine carboxamidel-oxide, 4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl] amino}carbonyl) amino]phenoxy}2-pyridine carboxamide 1-oxide, or 4-{4-[({[4-bromo-3-(trifluoromethyl)phenyl] amino}carbonyl)amino] phenoxy}2-pyridine carboxamide, 1-oxide or pharmaceutically acceptable salt, an isolated stereoisomer or a mixture thereof for the manufacture of a medicament for treating or preventing osteoporosis, inflammation, and angiogenesis disorders (other than cancer) in a mammal.

[0036] The invention also relates to the use of a compound of the invention, or a pharmaceutical composition comprising one or more compounds of the invention, in combination with a cytotoxic agent, for the manufacture of a medicament for treating or preventing cancer and other hyperproliferative disorders.

[0037] These include the use of an effective amount of a compound of the invention for the manufacture of a medicament for treating or preventing a hyper-proliferative disorder in a mammal. Preference is given to the use of an effective amount of 4-{4-[({[4-chloro-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide, 4-{4-[({[4-bromo-3-(trifluoromethyl)phenyl]amino} carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide, 4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl] amino}carbonyl)amino]phenoxy}2-pyridine carboxamide 1-oxide, or 4-{4-({[4-bromo-3-(trifluoromethyl)phenyl] amino} carbonyl)amino] phenoxy}2-pyridine carboxamide 1-oxide or a pharmaceutically acceptable salt, or an isolated stereoisomer or a mixture thereof for the manufacture of a medicament for treating or preventing a hyper-proliferative disorder in a mammal.

[0038] One or more additional compounds or compositions may be administered to the mammal, such as for example, an anticancer compound or composition, which is not a compound or composition according to the invention, which is preferably a cytotoxic compound or composition. The pharmaceutical composition also includes an effective amount of 4-{4-[({[4-chloro-3-(trifluoromethyl) phenyl]amino} carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide, 4-{4-[({[4-bromo-3-(trifluoromethyl)phenyl]amino} carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide, 4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl] amino}carbanyl)amino]phenoxy}2-pyridine carboxamide 1-oxide, or 4-{4-[({[4-bromo-3-(trifluoromethyl)phenyl]amino}carbonyl)amino] phenoxy}2-pyridine carboxamide 1-oxide or a pharmaceutically acceptable salt, or an isolated stereoisomer or a mixture thereof together with a cytotoxic compound or composition.

[0039] Optional anti-proliferative agents which can be added to the composition include but are not limited to compounds listed on the cancer chemotherapy drug regimens in the 11th Edition of the Merck Index, (1996), such as asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, and vindesine.

[0040] Other anti-proliferative agents suitable for use with the composition of the invention include but are not limited to those compounds acknowledged to be used in the treatment of neoplastic diseases in Goodman and Gilman's The Pharmacological Basis of Therapeutics (Ninth Edition), editor Molinoff et al., publ. by McGraw-Hill, pages 1225-1287, (1996), such as aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfart, diethylstilbestrol, 2', 2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyladenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorode-

oxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspatrate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

[0041] Other anti-proliferative agents suitable for use with the composition of the invention include but are not limited to other anti-cancer agents such as oxaliplatin, gemcitabone, gefinitib, taxotere, BCNU, CCNU, DTIC, ara A, ara C, herceptin, actinomycin D, epothilone, irinotecan, raloxifen and topotecan.

Description of Treatment of Hyperproliferative Disorders

[0042] Cancer and hyperproliferative disorders are defined as follows. These disorders include but are not limited to solid tumors, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases. Those disorders also include lymphomas, sarcomas, and leukemias.

Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ.

Examples of cancers of the respiratory tract include, but are not limited to small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

Examples of brain cancers include, but are not limited to brain stem and hypophtalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumor.

Tumors of the male reproductive organs include, but are not limited to prostate and testicular cancer.

Tumors of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

Tumors of the digestive tract include, but are not limited to anal, colon, colorectal, esophageal, gallblader, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.

Tumors of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, and urethral cancers.

Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

Skin cancers include, but are not-limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer. Head-and-neck cancers include, but are not limited to laryngeal / hypopharyngeal /nasopharyngeal / oropharyngeal cancer, and lip and oral cavity cancer. Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

Sarcomas include, but are not limited to sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma. Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

These disorders have been well characterized in man, but also exist with a similar etiology in other mammals.

[0043] Generally, the use of cytotoxic and/or cytostatic agents in combination with aryl urea compound raf kinase inhibitors will serve to (1) yield better efficacy in reducing the growth of a tumor or even eliminate the tumor as compared to administration of either agent alone, (2) provide for the administration of lesser amounts of the administered chemomerapeutic agents, (3) provide for a chemotherapeutic treatment that is well tolerated in the patient with fewer deleterious pharmacological complications than observed with single agent chemotherapies and certain other combined therapies, (4) provide for treating a broader spectrum of different cancer types in mammals, especially humans, (5) provide for a higher response rate among treated patients, (6) provide for a longer survival time among treated patients compared to standard chemotherapy treatments, (7) provide a longer time for tumor progression, and/or (8) yield efficacy and tolerability results at least as good as those of the agents used alone, compared to known instances where other cancer agent combinations produce antagonistic effects.

[0044] The present invention relates to a combination comprising (a) a compound according to the invention (b) at least one other chemotherapeutic cytotoxic or cytostatic agent; or pharmaceutically acceptable salts of any component (a) or (b).

[0045] The invention also relates to a pharmaceutical preparation which comprises (1) quantities of (a) a compound according to the invention (b) at least one other cytotoxic or cytostatic agent in amounts which are jointly effective for treating a cancer, where any component (a) or (b) can also be present in the form of a pharmaceutically acceptable salt if at least one salt-forming group is present, with (2) one or more pharmaceutically acceptable carrier molecules.

[0046] The invention also relates to the use of a compound according to the invention and at least one other chemotherapeutic agent which is a cytotoxic or cytostatic agent for the manufacture of a medicament for treating a cancer. The

compound according to the invention and the cytotoxic or cytostatic agent are in quantities which together are therapeutically effective against hyper proliferative diseases as defined above. Thus, the compound according to the invention is effective for raf kinase-mediated cancers. However, these compounds are also effective for cancers not mediated by raf kinase.

[0047] In a preferred embodiment, the present invention relates to the use of a compound according to the invention optionally in combination with a cytotoxic or cytostatic chemotherapeutic agent including but not limited to DNA topoisomerase I and II inhibitors, DNA intercalators, alkylating agents, microtubule disruptors, hormone and growth factor receptor agonists or antagonists, other kinase inhibitors and antimetabolites for the manufacture of a medicament for treating a cancer in a mammal, especially a human patient.

[0048] In another embodiment, the composition comprising a compound according to the invention or the cytotoxic or cytostatic agent can be administered to a patient in the form of a tablet, a liquid, a topical gel, an inhaler or in the form of a sustained release composition.

[0049] In one embodiment of the invention, a compound according to the invention can be administered simultaneously with a cytotoxic or cytostatic agent to a patient with a cancer, in the same formulation or, more typically in separate formulations and, often, using different administration routes. Administration can also be sequentially, in any order.

[0050] In another embodiment, a compound according to the invention can be administered in tandem with the cytotoxic or cytostatic agent, wherein a compound according to the invention can be administered to a patient once or more per day for up to 28 consecutive days with the concurrent or intermittent administration of a cytotoxic or cytostatic agent over the same total time period.

[0051] In another embodiment of the invention, a compound according to the invention can be administered to a patient at an oral, intravenous, intramuscular, subcutaneous, or parenteral dosage which can range from about 0.1 to about 200 mg/kg of total body weight.

[0052] In another embodiment, the cytotoxic or cytostatic agent can be administered to a patient at an intravenous, intramuscular, subcutaneous, or parenteral dosage which can range from about 0.1 mg to 200 mg/kg of patient body weight.

[0053] Further, the invention relates to a method of inhibiting proliferation of cancer cells comprising contacting cancer cells with a pharmaceutical preparation or product of the invention, especially a method of treating a proliferative disease comprising contacting a subject, cells, tissues or a body fluid of said subject, suspected of having a cancer with a pharmaceutical composition or product of this invention.

[0054] This invention also relates to compositions containing both a compound according to the invention and the other cytotoxic or cytostatic agents, in the amounts of this invention.

[0055] This invention further relates to kits comprising separate doses of the two mentioned chemotherapeutic agents in separate containers. The combinations of the invention can also be formed in vivo, e.g., in a patient's body.

[0056] The term "cytotoxic" refers to an agent which can be administered to kill or eliminate a cancer cell. The term "cytostatic" refers to an agent which can be administered to restrain tumor proliferation rather than induce cytotoxic cytoreduction yielding an elimination of the cancer celt from the total viable cell population of the patient. The chemotherapeutic agents described herein, e.g., irinotecan, vinorelbine, gemcitabine, and paclitaxel are considered cytotoxic agents. These cytotoxic and cytostatic agents have gained wide spread use as chemotherapeutics in the treatment of various cancer types and are well known.

[0057] These and other cytotaxic/cytostatic agents can be administered in the conventional formulations and regimens in which they are known for use alone.

General Preparative Methods

[0058] The compounds of the invention may be prepared by use of known chemical reactions and procedures. Nevertheless, the following general preparative methods are presented to aid the reader in synthesizing the compounds of the present invention, with more detailed particular examples being presented below in the experimental section describing the working examples.

[0059] All variable groups of these methods are as described in the generic description if they are not specifically defined below. When a variable group or substituent with a given symbol is used more than once in a given structure, it is to be understood that each of these groups or substituents may be independently varied within the range of definitions for that symbol. It is recognized that compounds of the invention with each claimed optional functional group cannot be prepared, with each of the below-listed methods. Within the scope of each method optional substituents are used which are stable to the reaction conditions, or the functional groups which may participate in the reactions are present in protected form where necessary, and the removal of such protective groups is completed at appropriate stages by methods well known to those skilled in the art.

[0060] The compounds of the invention can be made according to conventional chemical methods, and/or as disclosed below, from starting materials which are either commercially available or producible according to routine, conventional

chemical methods. General methods for the preparation of the compounds are given below, and the preparation of representative compounds is specifically illustrated in Examples 1 and 2.

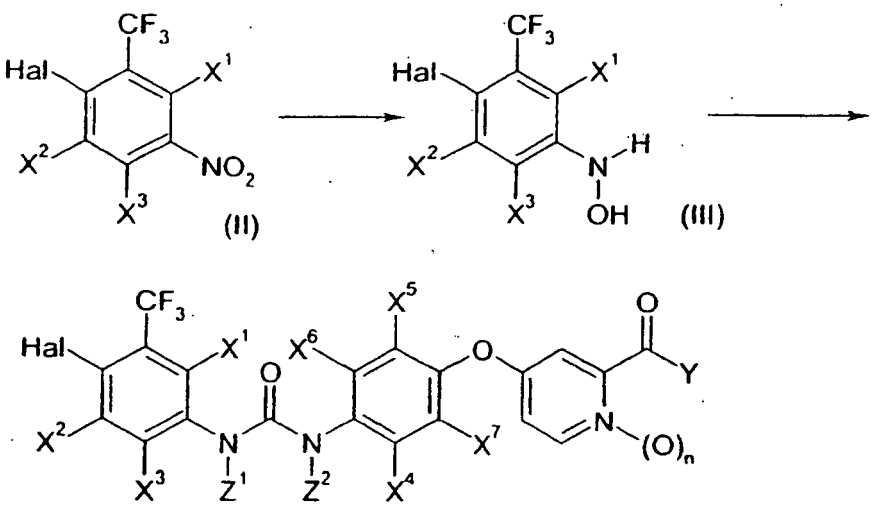
[0061] Ureas and hydroxyureas of formula (I) can be prepared by a variety of simple methods known in the art General approaches for the formation of those compounds can be found in "Advanced Organic Chemistry". by J. Match, John Wiley and Sons, 1985 and in "Comprehensive Organic Transformations ", by R. C. Larock VCH Publishers, 1989).

[0062] More specifically, the pyridine-1-oxides (n = 1 in Formula (I)) of the present invention can be prepared from the corresponding pyridines using oxidation conditions known in the art Some examples are as follows;

- peracids such as meta chloroperbenzoic acids in chlorinated solvents such as dichloromemane, dichloroethane, or chloroform (Markgraf et al., Tetrahedron 1991, 47, 183).
- $(Me_3SiO)_2$ in the presence of a catalytic amount of perrhenic acid in chlorinated solvents such as dichloromethane (Coperet et al., Tetrahedron Lett. 1998, 39 761)
- Perfluoro-cis-2-butyl-3-propyloxaziridine in several combinations of halogenated solvents (Amone et al., Tetrahedron 1998, 54 7831).
- 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 water and acetic acid (Lin A.J., Org. Prep. Proced. Int. 1991, 23(1), 114).
- Dimethyldioxirane in acetone (Boyd et al., J. Chem. Soc., Perkin Trans. 1991, 9, 2189).

[0063] The starting materials for the above-mentioned oxidations are bis aryl ureas, which contain a 2-acyl-pyridine in their side chains. Specific preparations of these ureas are already described in the patent literature, and can be adapted to the compounds of the present invention. For example, Riedl, B., et al., "O-Carboxy Aryl Substituted Diphenyl Ureas as raf Kinase Inhibitors" *PCT Int. Appl.,* WO 00 42012, Riedl, B., et al., "O-Carboxy Aryl Substituted Diphenyl Ureas as p38 Kinase Inhibitors" *PCT Int. Appl,* WO 0041698.

[0064] Hydroxyureas of formula (I), where Z^1 is OH and Z^2 is H can be prepared as follows:



[0065] Substituted nitrobenzenes of Formula (II), which are known in the art, are converted to hydroxyanilines of Formula (III), using a variety of conditions known in the art, for example sodium borohydride in the presence of transition metal catalysts (Yanada et al., Chem. Lett. 1989, 951 and references cited therein), or N-methyldihydroacridine in the presence of perchloric acid (Fukuzumi et al., J. Chem. Soc. Perkin Trans. II 1991, 9, 1393, and references cited therein).

[0066] In the second step, hydroxyanilines of Formula (III) can be converted to the corresponding hydroxyureas by reaction with an isocyanate, or equivalent, in the same way ureas are being prepared. Examples of such reactions can be found in the art (Hoffman et al., J. Med. Chem. 1964, 7, 665, and Stoffel et al., Ber. Disch. Chem. Ges. 1972, 105. 3115).

[0067] Similarly, hydroxyureas of formula (I), where Z^1 is H and Z^2 is OH can be prepared according to the same methods, by substituting the reagents in the appropriate way.

[0068] In both cases, the preparation of the arylamine fragment is illustrated in detail in the patent literature. For'

example, Miller S. et al, "Inhibition of p38 Kinase using Symmetrical and Unsymmetrical Diphenyl Ureas" *PCT Int. Appl.* WO 99 32463, Miller, S et al. "Inhibition of raf Kinase using Symmetrical and Unsymmetrical Substituted. Diphenyl Ureas" *PCT Int. Appl.,* WO 99 32436, Dumas, J. et al., "Inhibition of p38 Kinase Activity using Substituted Heterocyclic Ureas" *PCT Int. Appl.,* WO 99 32111, Dumas, J. et al., "Method for the Treatment of Neoplasm by Inhibition of raf Kinase using N-Reteroaryl-N'-(hetero)arylureas" *PCT Int. Appl.,* WO 99 32106, Dumas, J. et al., "Inhibition of p38 Kinase Activity using Aryl- and Heteroaryl- Substituted Heterocyclic Ureas" *PCT Int. Appl.,* WO 99 32110, Dumas, J., et al., "Inhibition of raf Kinase using Aryl- and Heterearyl- Substituted Heterocyclic Ureas" *PCT Int. Appl.,* WO 99 32455, Riedl, B., et al., "O-Carboxy Aryl Substituted Diphenyl Ureas as raf Kinase Inhibitors" *PCT Int. Appl.,* WO 00 42012, Riedl, B., et al., "O-Carboxy Aryl Substituted Diphenyl Ureas as p38 Kinase Inhibitors" *PCT Int. Appl.,* WO 00 41698.

[0069] Hydroxymethyl amides of Formula (I) where Y is $NHCH_2OH$ can be prepared by hydroxylation of the corresponding unsubstituted amides (Y = NH_z) by a variety of methods known in the art, for example aqueous formaldehyde in the presence of ethanol and sodium hydroxide (Weaver et al., J. Org. Chem. 1951, 16, 1111), or in the presence of potassium carbonate (Haworth et al., J. Chem. Soc. 1946, 1003).

[0070] Hydroxamic acids of Formula (I) where Y is NHOH can be prepared by amidation of the corresponding esters (Y = O alkyl) by a variety of methods known in the art, for example hydroxylamine in the presence of acetic acid and water (Boshagen, H., Ber. Disch. Chem. Ges. 1967, 100, 954), The same compounds can be obtained from the corresponding acids (Y = OH) by one pot activation of the acid with ethyl chloroformate, followed by reaction with hydroxylamine in methanol (Reddy et al., Tetrahedron Lett. 2000, 41(33), 6285), or by activation of the acid into an 1-acylimidazole, followed by reaction with hydroxylamine hydrochloride (Staab et al., Angewandte Chem., 1962, 74, 407).

[0071] Finally, ureas may be further manipulated using methods familiar to those skilled in the art.

[0072] The invention also includes pharmaceutical compositions including a compound of the invention, and a physiologically acceptable carrier.

[0073] The compound may be administered orally, topically, parenterally, by injection, by inhalation or spray or rectally in dosage unit formulations. Administration by injection includes intravenous, intramuscular, subcutaneous and parenteral injections, as well as use of infusion techniques. One or more compounds may be present in association with one or more non-toxic pharmaceutically acceptable carriers and if desired other active ingredients.

[0074] Compositions intended for oral use may be prepared according to any suitable method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from the group consisting of diluents, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; and binding agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. These compounds may also be prepared in solid, rapidly released form.

[0075] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

[0076] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example, lecithin, or condensation products or an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl *p*-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[0077] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents, may also be present.

[0078] The compounds may also be in the form of non-aqueous liquid formulations, e.g., oily suspensions which may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or peanut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example

beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0079] Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

[0080] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

[0081] The compounds may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

[0082] For all regimens of use disclosed herein for compounds of the invention, the daily oral dosage regimen will preferably be from 0.01 to 200 mg /kg of total body weight. The daily dosage for administration by injection, including.intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg / kg of total body weight. The daily rectal dosage regime will preferably be from 0.01 to 200 mg / kg of total body weight. The daily topical dosage regime will preferably be from 0.1 to 200 mg administered between one to four times daily. The daily inhalation dosage regime will preferably be from 0.01 to 10 mg / kg of total body weight. The dosage units employed to provide these dosage regimes can be administered on a daily basis, one or more times, or for extended periods, such as on a weekly or monthly basis.

[0083] It will be appreciated by those skilled in the art that the particular method of administration will depend on a variety of factors, all of which are considered routinely when administering therapeutics. It will also be appreciated by one skilled in the art that the specific dose level for a given patient depends on a variety of factors, including specific activity of the compound administered, age, body weight, health, sex, diet, time and route of administration, rate of excretion, etc. It will be further appreciated by one skilled in the art that the optimal course of treatment, i.e., the mode of treatment and the daily number of doses of a compound of the invention for a defined number of days, can be ascertained by those skilled in the art using conventional treatment tests.

[0084] The compounds can be produced from known compounds (or from starting materials which, in turn, can be produced from known compounds), e.g., through the general preparative methods disclosed herein. The activity of a given compound to inhibit raf, p38, or KDR (VEGFR2) kinases can be routinely assayed, e.g., according to procedures disclosed herein.

[0085] Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following examples are, therefore, to be construed as merely illustrative and not limitative of the remainder of the disclosure in any way whatsoever.

EXAMPLES

[0086] All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of dry argon or dry nitrogen, and were stirred magnetically unless otherwise indicated. Sensitive liquids and solutions were transferred via syringe or cannula, and introduced into reaction vessels through rubber septa. Unless otherwise stated, the term 'concentration under reduced pressure' refers to use of a Buchi rotary evaporator at approximately 15 mmHg. Unless otherwise stated, the term 'under high vacuum' refers to a vacuum of 0.4 - 1.0 mmHg.

[0087] All temperatures are reported uncorrected in degrees, Celsius (°C). Unless otherwise indicated, all parts and percentages are by weight. Commercial grade reagents and solvents were used without further purification.

[0088] Thin-layer chromatography (TLC) is performed using Whatman® precoated glass-backed silica gel 60A F-254 250, μm plates. Visualization of plates is effected by one or more of the following techniques: (a) ultraviolet illumination, (b) exposure to iodine vapor, (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating, (d) immersion of the plate in a cerium sulfate solution followed by heating, and/or (e) immersion of the plate in an acidic ethanol solution of 2,4-dinitrophenylhydrazine- followed by heating. Column chromatography (flash chromatography) is performed using 230-400 mesh EM Science® silica gel.

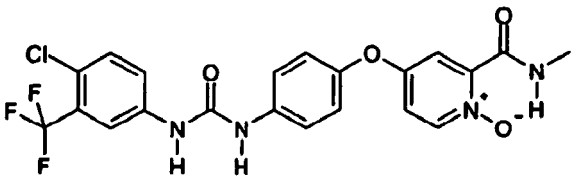
[0089] Melting points (mp) are determined using a Thomas-Hoover melting point apparatus or a Mettler FP66 automated melting point apparatus and are uncorrected. Fourier transform infrared spectra are obtained using a Mattson 4020 Galaxy Series spectrophotometer. Proton (^{1}H) nuclear magnetic resonance (NMR) spectra are measured with a General Electric GN-Omega 300 (300 MHz) spectrometer with either Me_4Si (δ 0.00) or residual protonated solvent

($CHCl_3$ δ 7.26; MeOH δ 3.30; DMSO δ 2.49) as standard. Carbon (^{13}C) NMR spectra are measured with a General Electric GN-Omega 300 (75 MHz) spectrometer with solvent ($CDCl_3$ δ 77.0; MeOD-d_3; δ 49.0; DMSO-d_6 δ 39.5) as standard. Low resolution mass spectra (MS) and high resolution mass spectra (HRMS) are either obtained as electron impact (EI) mass spectra or as fast atom bombardment (FAB) mass spectra. Electron impact mass spectra (EI-MS) are obtained with a Hewlett Packard 5989A mass spectrometer equipped with a Vacumetrics Desorption Chemical Ionization Probe for sample introduction. The ion source is maintained at 250 °C. Electron impact ionization is performed with electron energy of 70 eV and a trap current of 300 μA. Liquid-cesium secondary ion mass spectra (FAB-MS), an updated version of fast atom bombardment are obtained using a Kratos Concept 1-H spectrometer. Chemical ionization mass spectra (CI-MS) are obtained using a Hewlett Packard MS-Engine (5989A) with methane or ammonia as the reagent gas (1×10^{-4} torr to 2.5×10^{-4} torr). The direct insertion desorption chemical ionization (DCI) probe (Vaccumetrics, Inc.) is ramped from 0-1.5 amps in 10 sec and held at 10 amps until all traces of the sample disappeared (~1-2 min). Spectra are scanned from 50-800 amu at 2 sec per scan. HPLC - electrospray mass spectra (HPLC ES-MS) are obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector, a C-18 column, and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra are scanned from 120-800 amu using a variable ion time according to the number of ions in the source. Gas chromatography - ion selective mass spectra (GC-MS) are obtained with a Hewlett Packard 5890 gas chromatograph equipped with an HP-1 methyl silicone column (0.33 mM coating; 25 m x 0.2 mm) and a Hewlett Packard 5971 Mass Selective Detector (ionization energy 70 eV). Elemental analyses are conducted by Robertson Microlit Labs, Madison NJ.

[0090] All compounds displayed NMR spectra, LRMS and either elemental analysis or HRMS consistent with assigned structures.

EXAMPLE 1

[0091] Preparation of N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-(N-methylcarbamoyl)-1-oxo-(4-pyridyloxy)]phenyl} urea



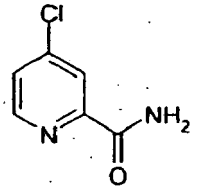
[0092] To a stirred mixture of N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} urea (500 mg, 1.08 mmol), in a mixture of anh CH_2Cl_2 (2.2 mL) and anh THF (2.2 mL) was added 3-chloroperbenzoic acid (77% pure, 1.09 g, 4.86 mmol, 4.5 equiv.), and the resulting mixture was heated at 40°C for 33 h. The resulting mixture was concentrated under reduced pressure, and the crude product was purified by MPLC (Biotage®; gradient from 20% acetone / hexane to 50% acetone /hexane). Recrystallization from EtOAc afforded N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-(N-methylcarbamoyl)-1-oxo-(4-pyridyloxy)]phenyl} urea as a white solid (293 mg, 57%): mp (uncorrected) 232-234°C; TLC (50% acetone/hexane) R_f 0.13; ^1H-NMR (DMSO-d_6) δ 11.48 (broad s, 1H), 9.19 (s, 1H), 8.98 (s, 1H), 8.38 (d, J = 5.8 Hz, 1H), 8.10 (d, J = 2.5 Hz, 1H), 7.64 (dd, J = 8.2 Hz, 2.6 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 2.6 Hz, 1H), 7.28 (dd, J = 5.7 Hz, 2.5 Hz, 1H), 7.18 (d, J = 8.8 Hz, 2H), 2.86 (d, J =5.0 Hz, 3H); HPLC EI-MS m/z 481 ($(M+H)^+$). Anal. calcd for $C_{21}H_{16}ClFN_4O_4$: C 52.46% H 3.33% N 11.65%. Found: C 52.22% H 3.39% N 11.49%.

EXAMPLE 2

Preparation of N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-1-oxo-(4-pyridyloxy)]phenyl} urea

Step 1: Preparation of 4-chloro-2-pyndinecarboxamide

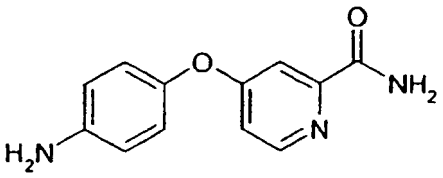
[0093]



[0094] To a stirred mixture of methyl 4-chloro-2-pyridinecarboxylate hydrochloride (1.0 g, 4.81 mmol) dissolved in conc. aqueous ammonia (32 mL) was added ammonium chloride (96.2 mg, 1.8 mmol, 0.37 equiv.), and the heterogeneous reaction mixture was stirred at ambient temperature for 16h. The reaction mixture was poured into EtOAc (500 mL) and water (300 mL). The organic layer was washed with water (2 x 300 mL) and a saturated NaCl solution (1 x 300 mL), dried ($MgSO_4$), concentrated in *vacuo* to give 4-chloro-2-pyridinecarboxamide as a beige solid (604.3 mg, 80.3%): TLC (50% EtOAc / hexane) R_f 0.20; ^{1}H-NMR (DMSO-d_6) δ 8.61 (d, J = 5.4 Hz, 1H), 8.20 (broad s, (1H), 8.02 (d, J = 1.8 Hz, 1H), 7.81 (broad s, I H), 7.76 to 7.73 (m, 1 H).

Step 2: Preparation of 4-(4-aminophenoxy)-2-pyridinecarboxamide

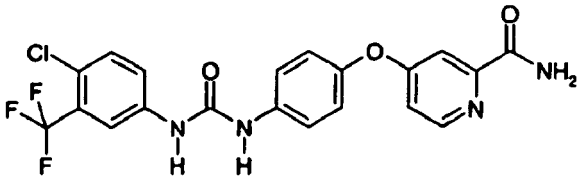
[0095]



[0096] To 4-aminophenol (418 mg, 3.83 mmol) in anh DMF(7.7 mL) was added potassium *tert*-butoxide (447 mg, 3.98 mmol, 1.04 equiv.) in one portion. The reaction mixture was stirred at room temperature for 2 h, and a solution of 4-chloro-2-pyridinecarboxamide (600 mg, 3.83 mmol, 1.0 equiv.) in anh DMF (4 mL) was then added. The reaction mixture was stirred at 80 °C for 3 days and poured into a mixture of EtOAc and a saturated NaCl solution. The organic layer was sequentially washed with a saturated NH_4Cl solution then a saturated NaCl solution, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified using MPLC chromatography (Biotage®; gradient from 100% EtOAc to followed by 10% MeOH /50% EtOAc / 40% hexane) to give the 4-chloro-5-trifluoromethylaniline as a brown solid (510 mg, 58%). ^{1}H-NMR (DMSO-d_6) δ 8.43 (d, J = 5.7 Hz, 1H), 8.07 (br s, 1H), 7.66 (br s, 1H), 7.31 (d, J = 2.7 Hz, 1H), 7.07 (dd, J = 5.7 Hz, 2.7 Hz, 1H), 6.85 (d, J = 9.0 Hz, 2 H), 6.62 (d, J = 8.7 Hz, 2H), 5.17 (broad s, 2H); HPLC EI-MS m/z 230 ($(M+H)^+$.

Step 3: Preparation of N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-(4-pyridyloxy)]phenyl} urea

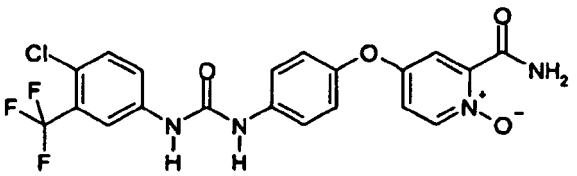
[0097]



[0098] A mixture of 4-chloro-5-trifluoromethylaniline (451 mg, 2.31 mmol, 1.1 equiv.) and 1,1'-carbonyl diimidazole (419 mg, 2.54 mmol, 1.2 equiv.) in anh dichloroethane (5.5 mL) was stirred under argon at 65 °C for 16 h. Once cooled to room temperature, a solution of 4-(4-aminophenoxy)-2-pyridinecarboxamide (480 mg, 2.09 mmol) in anh THF (4.0 mL) was added, and the reaction mixture was stirred at 60°C for 4 h. The reaction mixture was poured into EtOAc, and the organic layer was washed with water (2x) and a saturated NaCl solution (1x), dried ($MgSO_4$), filtered, and evaporated

in vacuo. Purification using MPLC chromatography (Biotage®; gradient from 100% EtOAc to 2% MeOH / EtOAc) gave N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-(4-pyridyloxy)]phenyl} urea as a white solid (770 mg, 82%): TLC (EtOAc) R_f 0.11, 100% ethyl acetate ^{1}H-NMR (DMSO-d_6) δ 9.21 (s, 1H), 8.99 (s, 1H), 8.50 (d, J = 5.6 Hz, 1H), 8.11 (s, 1H), 8.10 (s, 1H), 7.69 (broad s, 1H), 7.64 (dd, J = 8.2 Hz, 2.1 Hz, 1H), 7.61 (s, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 2.5 Hz, 1H), 7.15 (d, J = 8.9 Hz, 2H), 7.14 (m, 1H); MS LC-MS (MH^+ = 451). Anal. calcd for $C_{20}H_{14}ClF_3N_4O_3$: C 53.29% H 3.13% N 12.43%. Found: C 53.33% H 3.21% N 12.60%;.

[0099] Step 4: Preparation of N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-1-oxo-(4-pyridyloxy)]phenyl} urea



[0100] N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-1-oxo-(4-pyridyloxy)]phenyl}urea (125.6 mg, 51%) was prepared as a white solid from N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-(4-pyridyloxy)]phenyl} urea (240.0 mg, 0.53 mmol), in the manner described for N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-(N-methylcarbamoyl)-1-oxo-(4-pyridyloxy)]phenyl} urea: TLC (5% MeOH / CH_2Cl_2) R_f 0.17; ^{1}H-NMR (DMSO-d_6) δ 10.72 (d, J = 4.3 Hz, 1H), 9.21 (s, 1H), 8.99 (s, 1H), 8.36 (d, J = 7.2 Hz, 1H), 8.31 (d, J = 4.1 Hz, 1H), 8.10 (d, J = 2.3 Hz, 1H), 7.65 (dd, J = 8.7 Hz, 2.3 Hz, 1H), 7.60 (d, J = 8.9 Hz, 1H), 7.57 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 3.8 Hz, 1H), 7.28 (dd, J = 7.2 Hz, 3.8 Hz; 1H), 7.18 (d, J = 9.0 Hz, 2 H); HPLC EI-MS *m/z* 467 ($(M+H)^+$; Anal. calcd for $C_{20}H_{14}ClF_3N_4O_4$ $0.5H_2O$: C 50.49% H 3.18% N 11.78%. Found. C 50.69% H 2.86% N 11.47%.

BIOLOGICAL EXAMPLES

P38 Kinase *in vitro* Assay:

[0101] The *in vitro* inhibitory properties of compounds were determined using a p38 kinase inhibition assay. P38 activity was detected using an *in vitro* kinase assay run in 96-well microtiter plates. Recombinant human p38 (0.5 μg/mL) was mixed with substrate (myelin basic protein, 5 μg/mL) in kinase buffer (25 mM Hepes, 20 mM $MgCl_2$ and 150 mM NaCl) and compound. One μCi/well of ^{33}P-labeled ATP (10 μM) was added to a final volume of 100 μL. The reaction was run at 32 °C for 30 min. and stopped with a 1M HCl solution. The amount of radioactivity incorporated into the substrate was determined by trapping the labeled substrate onto negatively charged glass fiber filter paper using a 1% phosphoric acid solution and read with a scintillation counter. Negative controls include substrate plus ATP alone.

LPS Induced TNFα Production in Mice:

[0102] The *in vivo* inhibitory properties of selected compounds can be determined using a murine LPS induced TNFα production *in vivo* model. BALB/c mice (Charles River Breeding Laboratories; Kingston, NY) in groups of ten were treated with either vehicle or compound by the route noted. After one hour, endotoxin (E. coli lipopolysaccharide (LPS) 100 μg) was administered intraperitoneally (i.p.). After 90 min, animals were euthanized by carbon dioxide asphyxiation and plasma was obtained from individual animals by cardiac puncture into heparinized tubes. The samples were clarified by centrifugation at 12,500 x g for 5 min at 4 °C. The supernatants were decanted to new tubes, which were stored as needed at -20 °C. TNFα levels in sera were measured using a commercial murine TNF ELISA kit (Genzyme).

[0103] The two preceding biological examples can be used to demonstrate that the compounds are inhibiting p38 kinase *in vitro* and *in* vivo, and therefore establishes their utility in the treatment of p38 mediated diseases, such as inflammation and osteoporosis.

In Vitro raf Kinase Assay:

[0104] In an *in vitro* kinase assay, raf was incubated with MEK in 20 mM Tris-HCl, pH 8.2 containing 2 mM 2-mercaptoethanol and 100 mM NaCl. This protein solution (20 μL) was mixed with water (5 μL) or with compounds diluted with distilled.water from 10 mM stock solutions of compounds dissolved in DMSO. The kinase reaction was initiated by adding 25 μL [γ-^{33}P]ATP (1000-3000 dpm/pmol) in 80 mM Tris-HCl, pH 7.5, 120 mM NaCl, 1.6 mM DTT, 16 mM $MgCl_2$. The

reaction mixtures were incubated at 32 °C, usually for 22 min. Incorporation of ^{33}P into protein was assayed by harvesting the reaction onto phosphocellulose mats, washing away free counts with a 1% phosphoric acid solution and quantitating phosphorylation by liquid scintillation counting. For high throughput screening, 10 μM ATP and 0.4 μM MEK are used. In some experiments, the kinase reaction is stopped by adding an equal amount of Laemmli sample buffer. Samples are boiled 3 min and the proteins resolved by electrophoresis on 7.5% Laemmli gels. Gels were fixed, dried and exposed to an imaging plate (Fuji). Phosphorylation was analyzed using a Fujix Bio-Imaging Analyzer System. Compounds of Examples 1 and 2 show > 50% inhibition at 10 micromolars in this assay, which is a marked inhibition of raf kinase *in vitro*

Tumor cell proliferation assay:

[0105] For *in vitro* growth assay, human tumor cell lines, including but not limited to HCT116 and DLD-1, containing mutated K-ras genes were used in standard proliferation assays for anchorage dependent growth on plastic or anchorage independent growth in soft agar. Human tumor cell lines were obtained from ATCC (Rockville MD) and maintained in RPMI with 10% heat inactivated fetal bovine serum and 200 mM glutamine. Cell culture media and additives were obtained from Gibco/BRL (Gaithersburg, MD) except for fetal bovine serum (JRH Biosciences, Lenexa, KS). In a standard proliferation assay for anchorage dependent growth, 3 X 10^3 cells were seeded into 96-well tissue culture plates and allowed to attach overnight at 37 °C in a 5% CO_2 incubator. Compounds were titrated in media in dilution series and added to 96 well cell cultures. Cells were allowed to grow 5 days typically with a feeding of fresh compound containing media on day three. Proliferation was monitored by measuring metabolic activity with standard XTT colorimetric assay (Boehringer Mannheim) measured by standard ELISA plate reader at OD 490/560, harvesting the cells onto glass fiber mats using a cell harvester and measuring ^{3}**H**-thymidine incorporation by liquid scintillant counting.

[0106] For anchorage independent cell growth, cells were plated at 1 x 10^3 to 3 x 10^3 in 0.4% Seaplaque agarose in RPMI complete media, overlaying a bottom layer containing only 0.64% agar in RPMI complete media in 24-well tissue culture plates. Complete media plus dilution series of compounds were added to wells and incubated at 37 °C in a 5% CO_2 incubator for 10-14 days with repeated feedings of fresh media containing compound at 3-4 day intervals. Colony formation was monitored and total cell mass, average colony size and number of colonies were quantitated using image capture technology and image analysis software (Image Pro Plus, media Cybernetics).

[0107] The two preceding assays establish that the compounds of Formula I are active to inhibit raf kinase activity and to inhibit oncogenic cell growth:

KDR (VEGFR2) Assay:

[0108] The cytosolic kinase domain of KDR kinase is expressed as a 6His fusion protein in Sf9 insect cells. The KDR kinase domain fusion protein is purified over a Ni++ chelating column. Ninety-six well ELISA plates are coated with 5 μg poly(Glu4;Tyrl) (Sigma Chemical Co., St Louis, MO) in 100 μl HEPES buffer (20 mM HEPES, pH 7.5, 150 mM Nacl, 0.02% Thimerosal) at 4° overnight. Before use, the plate is washed with HEPES, NaCl buffer and the plates are blocked with 1% BSA, 0.1% Tween 20 in HEPES, NaCl buffer.

[0109] Test compounds are serially diluted in 100% DMSO from 4 mM to 0.12 μM in half-log dilutions. These dilutions are further diluted twenty fold in H2O to obtain compound solutions in 5% DMSO. Following loading of the assay plate with 85 μl of assay buffer (20 mM HEPES, pH. 7.5, 100 mM KCl, 10 mM $MgCl_2$, 3 mM $MnCl_2$, 0.05% glycerol, 0.005% Triton X-100, 1 mM -mercaptoethanol, with or without 3.3 μM ATP), 5 μl of the diluted compounds are added to a final assay volume of 100 μl. Final concentrations are between 10 μM, and 0.3 nM in 0.25% DMSO. The assay is initiated by the addition of 10μl (30 ng) of KDR kinase domain.

[0110] The assay is incubated with test compound or vehicle alone with gentle agitation at room temperature for 60 minutes. The wells are washed and phosphotyrosines (PY) are probed with an anti-phosphotyrosine (PY), mAb clone 4G10 (Upstate Biotechnology, Lake Placid, NY). PY/anti-PY complexes are detected with an anti-mouse IgG/HRP conjugate (Amersham International plc, Buckinghamshire, England). Phosphotyrosine is quantitated by incubating with 100 μl 3, 3', 5, 5' tetramethylbenzidine solution (Kirkegaard and Perry, TMB Microwell 1 Component peroxidase substrate). Color development is arrested by the addition of 100 μl 1%, HCl-based stop solution (Kirkegaard and Perry, TMB 1 Component Stop Solution).

[0111] Optical densities are determined spectrophotometrically at 450 nm in a 96-well plate reader, SpectraMax 250 (Molecular Devices). Background (no ATP in assay) OD values are subtracted from all ODs and the percent inhibition is calculated according to the equation:

$$\% \text{ Inhibition} = \frac{(OD(\text{vehicle control}) - OD(\text{with compound})) \times 100}{OD(\text{vehicle control}) - OD(\text{no ATP added})}$$

[0112] The IC_{50} values are determined with a least squares analysis program using compound concentration versus percent inhibition.

Cell mechanistic assay-Inhibition of 3T3 KDR phosphorylation:

[0113] NIH3T3 cells expressing the full length KDR receptor are grown in DMEM (Life Technologies, Inc., Grand Island, NY) supplemented with 10% newborn calf serum, low glucose, 25 mM /L sodium pyruvate, pyridoxine hydrochloride and 0.2 mg/ ml of G418 (Life Technologies Inc., Grand Island, NY). The cells are maintained in collagen I-coated T75 flasks (Becton Dickinson Labware, Bedford, MA) in a humidified 5% CO2 atmosphere at 37°C.
Fifteen thousand cells are plated into each well of a collagen I-coated 96-well plate in the DMEM growth medium. Six hours later, the cells are washed and the medium is replaced with DMEM without serum. After overnight culture to quiesce the cells, the medium is replaced by Dulbecco's phosphate-buffered saline (Life Technologies Inc., Grand Island, NY) with 0.1% bovine albumin (Sigma Chemical Co., St Louis, MO). After adding various concentrations (0-300 nM) of test compounds to the cells in 1% final concentration of DMSO, the cells are incubated at room temperature for 30 minutes. The cells are then treated with VEGF (30.ng / ml) for 10 minutes at room temperature. Following VEGF stimulation, the buffer is removed and the cells are lysed by addition of 150 μl of extraction buffer (50 mM Tris, pH 7.8, supplemented with 10% glycerol, 50 mM BGP, 2 mM EDTA, 10 mM NaF, 0.5 mM NaVO4, and 0.3% TX-100) at 4°C for 30 minutes.
To assess receptor phosphorylation, 100 microliters of each cell lysate is added to the wells of an ELISA plate precoated with 300 ng of antibody C20 (Santa Cruz Biotechnology, Inc., Santa Cruz., CA). Following a 60-minute incubation, the plate is washed and bound KDR is probed for phosphotyrosine using an anti-phosphotyrosine mAb clone 4G10 (Upstate Biotechnology, Lake Placid, NY). The plate is washed and wells are incubated with anti-mouse IgG/HRP conjugate (Amersham International plc, Buckinghamshire, England) for 60 minutes. Wells are washed and phosphotyrosine is quantitated by addition of 100 μl per well of 3,3',5,5' tetramethylbenzidine (Kirkegaard and Perry, TMB Microwell 1 Component peroxidase substrate) solution. Color development is arrested by the addition of 100 μl 1% HCl based stop solu.tion (Kirkegaard and Perry, TMB 1 Component Stop Solution).
Optical densities (OD) are determined spectrophotometrically at 450 nm in a 96-well plate reader (SpectraMax 250, Molecular Devices). Background (no VEGF added) OD values are subtracted from all ODs and percent inhibition is calculated according to the equation:

$$\% \text{ Inhibition} = \frac{(OD(\text{VEGF control}) - OD(\text{with test compound})) \times 100}{OD(\text{VEGF control}) - OD(\text{no VEGF added})}$$

IC_{50}s are determined on some of the exemplary materials with a least squares analysis program using compound concentration versus percent inhibition.

In vivo assay of VEGFR inhibition: Matrigel® Angiogenesis Model:

[0114] Preparation of Matrigel Plugs and *in vivo* Phase: Matrigel® (Collaborative Biomedical Products, Bedford, MA) is a basement membrane extract from a murine tumor composed primarily of laminin, collagen IV and heparan sulfate proteoglycan. It is provided as a sterile liquid at 4° C, but rapidly forms a solid gel at 37° C.
Liquid Matrigel at 4°C is mixed with SK-MEL2 human tumor cells that are transfected with a plasmid containing the murine VEGF gene with a selectable marker. Tumor cells are grown *in vitro* under selection and cells are mixed with cold liquid Matrigel at a ratio of 2×10^6 per 0.5 ml. One half milliliter is implanted subcutaneously near the abdominal midline using a 25 gauge needle. Test compounds are dosed as solutions in Ethanol/Cremaphor EL/saline (12.5%: 12.5%:75%) at 30, 100, and 300 mg/kg po once daily starting on the day of implantation. Mice are euthanized 12 days post-implantation and the Matrigel pellets are harvested for analysis of hemoglobin content.
Hemoglobin Assay: the Matrigel pellets are placed in 4 volumes (w/v) of 4° C Lysis Buffer (20mM Tris pH 7.5, 1mM

EGTA, 1mM EDTA, 1% Triton X-100 [EM Science, Gibbstown, N.J.], and complete, EDTA-free protease inhibitor cocktail [Mannheim, Germany]), and homogenized at 4°C. Homogenates are incubated on ice for 30 minutes with shaking and centrifuged at 14K x g for 30 minutes, at 4°C. Supernatants are transferred to chilled microfuge tubes and stored at 4° C for hemoglobin assay.

Mouse hemoglobin (Sigma Chemical Co., St. Louis, MO) is suspended in autoclaved water (BioWhittaker, Inc, Walkersville, MD.) at 5 mg/ ml. A standard curve is generated from 500 micrograms/ml to 30 micrograms/ml in Lysis Buffer (see above). Standard curve and lysate samples are added at 5 microliters/well in duplicate to a polystyrene 96-well plate. Using the Sigma Plasma Hemoglobin Kit (Sigma Chemical Co., St. Louis, MO), TMB substrate is reconstituted in 50 mls room temperature acetic acid solution. One hundred microliters of substrate is added to each well, followed by 100 microliters /well of Hydrogen Peroxide Solution at room temperature. The plate is incubated at room temperature for 10 minutes.

Optical densities are determined spectrophotometrically at 600 nm in a 96-well plate reader, SpectraMax 250 Microplate Spectrophotometer System (Molecular Devices, Sunnyvale, CA). Background Lysis Buffer readings are subtracted from all wells. Total sample hemoglobin content is calculated according to the following equation:

$$\text{Total Hemoglobin} = (\text{Sample Lysate Volume}) \times (\text{Hemoglobin Concentration})$$

The average Total Hemoglobin of Matrigel samples without cells is subtracted from each Total Hemoglobin Matrigel sample with cells. Percent inhibition is calculated according to the following equation:

$$\%\ \text{Inhibition} = \frac{(\text{Average Total Hemoglobin Drug-Treated Tumor Lysates}) \times 100}{(\text{Average Total Hemoglobin Non-Treated Tumor Lysates})}$$

[0115] The three preceding assays establish that the compounds of Formula I are active to inhibit VEGF receptor kinase activity and to inhibit angiogenesis.

***In Vivo* Assay of antitumor activity:**

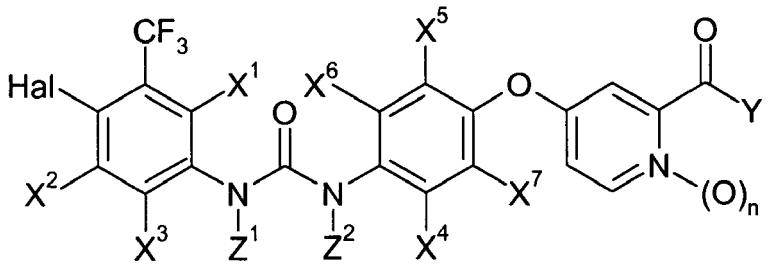
[0116] An *in vivo* assay of the inhibitory effect of the compounds on tumors (e.g., solid cancers) mediated by raf kinase can be performed as follows: CDI nu/nu mice (6-8 weeks old) are injected subcutaneously into the flank at 1 x 10^6 cells with human colon adenocarcinoma cell line. The mice are dosed i.p., i.v. or p.o. at 10, 30, 100, or 300 mg/Kg beginning on approximately day 10, when tumor size is between 50-100 mg. Animals are dosed for 14 consecutive days; tumor size is monitored with calipers twice a week. The inhibitory effect of the compounds on p38, raf and VEGFR kinases and therefore on tumor growth (e.g., solid cancers) can further be demonstrated in vivo according to the technique of Monia et al. (Nat. Med. 1996, 2, 668-75).

[0117] The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

[0118] From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, can make various changes and modifications of the invention to adapt it to various conditions and usages.

Claims

1. A compound of formula (I),



(I)

wherein,

Y is OR^1 or NHR^2,
Hal is chlorine or bromine,
R^1 is H or C_1-C_6 alkyl
R^2 is H, OH, CH_3 or CH_2OH,
Z^1 and Z^2 are each H or OH, wherein only one of Z^1 or Z^2 can be OH.
X^1 to X^7 are each, independently, H, OH or $O(CO)C_1$-C_4 alkyl, and
n is 0 or 1,

with the proviso that at least one of conditions a-c is met,

a) Z^1 or Z^2 is OH,
b) Y is NHR^2 and R^2 is OH,
c) n is 1,

or a salt thereof, or an isolated stereoisomer thereof.

2. A compound of claim 1 wherein n of formula I is 1 and either

a) Y is NHR^2 and R^2 is H or CH_3, and either

i) X^1 to X^7 are each H, or
ii) Z^1 and Z^2 are each H, or
iii) Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2 is H, or
iv) X^1 to X^7 and Z^1 are each H and Z^2 is OH or
v) X^1 to X^7 and Z^2 are each H and Z^1 is OH;

b) Y is NHR^2 and R^2 is CH_2OH or OH or
c) Y is OH.

3. A compound of claim 1, wherein

a) n is 0, and
b) either Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2 is H and
c) either

i) R^2 is H or CH_3, or
ii) X^1 to X^7 are each H, or
iii) at least one of X^1 to X^7 is OH , or
iv) at least one of X^1 to X^7 is $O(CO)C_1$-C_4 alkyl, or
v) R^2 is CH_2OH or OH or
vi) Y is OH.

4. A compound of claim 1, wherein in formula (I),

a) n is 0, and
b) Y is NHR^2 and R^2 is OH and
c) either

i) X^1 to X^7 are each H, or
ii) Z^1 is H and Z^2 is OH, or
iii) Z^1 is OH and Z^2 is H, or
iv) at least one of X^1 to X^7 is OH or
v) at least one of X^1 to X^7 is $O(CO)C_1$-C_4 alkyl.

5. A compound of claim 1, wherein in formula (I),

a) n is 0 and,
b) Y is OH and
c) either

i) X^1 to X^7 are each H, or
ii) Z^2 is H and Z^1 is OH, or
iii) Z^1 is H and Z^2 is OH, or
iv) at least one of X^1 to X^7 is OH, or
v) at least one of X^1 to X^7 is $O(CO)C_1$-C_4 alkyl.

6. A compound of claim 1 selected from the group consisting of :

4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide,
4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-N-hydroxymethyl-2-pyridine carboxamide 1-oxide,
4- {4-[({[4-bromo-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide,
4- {4-[({[4-bromo-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-N-hydroxymethyl-2-pyridine carboxamide 1-oxide,
4- {4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-2-pyridine carboxamide 1-oxide,
4- {4-[({[4-bromo-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-2-pyridine carboxamide 1-oxide,
salts thereof and stereoisomers thereof.

7. A compound of claim 1, wherein each of X^1, X^2 and X^3 is H.

8. A compound of claim 7; wherein in formula (II), n is 1, and either

i) Z^1 and Z^2 are each H, or
ii) at least one of X^4 to X^7 is OH, or
iii) Y is NHR^2 and R^2 is H or CH_3.

9. A compound of claim 7; wherein in formula (II), n is 0 and either

i) Z^1 is H and Z^2 is OH, or
ii) Z^1 is OH and Z^2 is H, or
iii) Z^1 and Z^2 are each H, and at least one of X^4 to X^7 is OH, or
iv) at least one of X^4 to X^7 is OH, or
v) Y is NHR^2 and R^2 is H or CH_3, or
vi) Y is NHR^2 and R^2 is OH.

10. A compound of claim 1, wherein each of X^1-X^7 is H.

11. A compound of claim10 wherein in formula (III), either

a) Y is NHR^2 and R^2 is H or CH_3, and either:

i) n is 1 and Z^1 and Z^2 are each H, or
ii) n is 0 and Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2 is H or

b) Y is OH.

12. A method of preparing compounds of claim 1 comprising the oxidation of
4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide, or
4-{4-[({[4-bromo-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide, or
4- {4-[({[4-chloro-3-trifluoromethyl)
phenyl]amino}carbonyl)amino]phenoxy}-2-pyridine carboxamide, or
4- {4-[({[4-bromo-3-(trifluoromethyl)
phenyl]amino}carbonyl)amino] phenoxy}-2-pyridine carboxamide;
wherein oxidation

a) replaces one or more of the phenyl hydrogens at the positions represented by X^1 to X^7 with a hydroxyl group, which is optionally esterified,
b) hydroxylates the N-methyl amide into a hydroxymethyl amide or hydroxamic acid,
c) demethylates the N-methyl amide into an unsubstituted amide,
d) replaces one or more of the urea nitrogens (=NH) with a hydroxyl group to form an N-hydroxyurea (=NOH),
e) hydrolyzes the N-methyl amide into a carboxylic acid,
f) oxidizes the pyridyl ring nitrogen to form the corresponding pyridine-1-oxide, or
g) provides a combination of two or more of a) - f);

with the proviso that at least one of b), d) and f) is performed.

13. A method as in claim 12 which prepares
4- {4-[({[4-chloro-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide, 4-{4-[({[4-bromo-3-(trifluoromethyl)phenyl]amino} carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide,
4- {4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy} 2-pyridine carboxamide 1-oxide,
4- {4-[({[4-bromo-3-(trifluoromethyl)phenyl] amino} carbonyl)amino]phenoxy} 2-pyridine carboxamide 1-oxide, or a pharmaceutically acceptable salt of one of these oxides, or an isolated stereoisomer of one of these oxides.

14. A pharmaceutical composition comprising an effective amount of at least one compound of any one of claims 1 to 6 and a physiologically acceptable carrier.

15. A pharmaceutical composition comprising an effective amount of

4- {4-[({[4-chloro-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide,
4- {4-[({[4-bromo-3-(trifluoromethyl)phenyl]amino} carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide,
4- {4-[({[4-chloro-3-(trifluoromethyl)phenyl] amino}carbonyl)amino]phenoxy}2-pyridine carboxamide 1-oxide,
4- {4-[({[4-bromo-3-(trifluoromethyl)phenyl] amino}carbonyl)amino]phenoxy} 2-pyridine carboxamide 1-oxide or

a pharmaceutically acceptable salt of one of these oxides, an isolated stereoisomer of one of these oxides or a mixture thereof and a physiologically acceptable carrier.

16. Use of an effective amount of a compound of any one of claims 1 to 6 and optionally, a physiologically acceptable carrier for the manufacture of a medicament for treating or preventing osteoporosis, inflammation, and angiogenesis disorders, with the exclusion of cancer, in a mammal.

17. Use of an effective amount of a compound of any one of claims 1 to 6 for the manufacture of a medicament for treating or preventing a hyper-proliferative disorder in a mammal..

18. Use of a) an effective amount of a compound of any one of claims 1 to 6 and b) an additional anti-proliferative agent, and optionally, c) a physiologically acceptable carrier for the manufacture of a medicament for treating or preventing a hyper-proliferative disorder in a mammal, comprising administering to said mammal.

19. Use according to claim 18 wherein the additional anti-proliferative agent is within a pharmaceutical composition separate from the pharmaceutical composition comprising an effective amount of a compound of any one of claims 1 to 6 and an optional physiologically acceptable carrier.

20. Use according to claim 18 or 19 wherein the additional anti-proliferative agent is selected from the group consisting of asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, vindesine, aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2',2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyladenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, oxaliplatin, gemcitabone, gefinitib, taxotere, BCNU, CCNU, DTIC, ara A, ara C, herceptin, actinomycin D, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

21. Use of

a) an effective amount of a compound of any one of claims 1 to 6, and
b) a cytotoxic agent or cytostatic chemotherapeutic agent, and
c) optionally a physiologically acceptable carrier,

for the manufacture of a medicament for treating or preventing cancer.

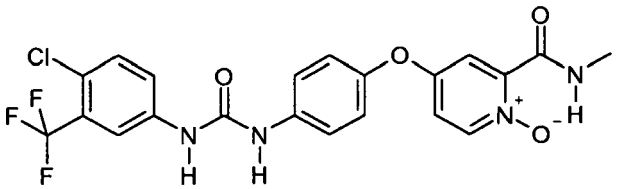
22. Use of claim 21 wherein the cytotoxic agent or cytostatic chemotherapeutic agent administered is within a pharmaceutical composition separate from the pharmaceutical composition comprising an effective amount of a compound of any one of claims 1 to 6, and a physiologically acceptable carrier.

23. Use of a method according to claim 21 or 22 wherein the cytotoxic or cytostatic chemotherapeutic agent is selected from the group consisting of DNA topoisomerase I and II inhibitors, DNA intercalators, alkylating agents, microtubule disruptors, hormone and growth factor receptor agonists or antagonists, other kinase inhibitors and anti-metabolites.

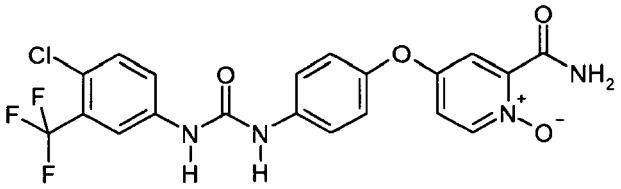
24. A kit comprising a) a dose of a cytotoxic or cytostatic agent and, b) a dose of a compound of any one of claims 1 to 6.

25. A method of preparing

a) N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-(N-methylcarbamoyl)-1-oxo-(4-pyridyloxy)]phenyl} urea



comprising chemically oxidizing N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} urea in solution, or
b) N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-1-oxo-(4-pyridyloxy)]phenyl} urea



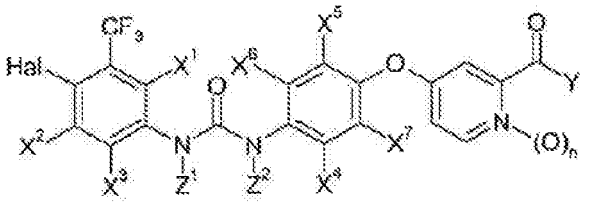
comprising chemically oxidizing N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-(4-pyridyloxy)]phenyl} urea in solution.

26. A pharmaceutical composition according to claim 14 or 15 for its use in treating or preventing osteoporosis, inflammation, and angiogenesis disorders, with the exclusion of cancer, in a mammal.

27. A pharmaceutical composition according to claim 14 or 15 for its use in treating or preventing a hyper-proliferative disorder in a mammal.

Patentansprüche

1. Verbindung gemäß Formel (I),



(I)

worin
Y OR^1 oder NHR^2 ist,
Hal Chlor oder Brom ist,
R_1 H oder C_1-C_6-Alkyl ist,
R_2 H, OH, CH_3 oder CH_2OH ist,
Z_1 und Z_2 jeweils H oder OH sind, wobei nur einer von Z^1 oder Z^2 OH sein kann,
X_1 bis X^7 unabhängig voneinander jeweils H, OH oder O (CO) C_1-C_4-Alkyl sind, und
n 0 oder 1 ist,
mit der Maßgabe, dass mindestens eine der Bedingungen a) bis c) erfüllt ist,

a) Z^1 oder Z^2 ist OH,
b) Y ist NHR^2 und R^2 ist OH,
c) n ist 1,

oder ein Salz davon oder ein isoliertes Stereoisomer davon.

2. Verbindung nach Anspruch 1, wobei n aus Formel I 1 ist und entweder

a) Y NHR^2 ist und R^2 H oder CH_3 ist und entweder

i) X^1 bis X^7 jeweils H sind oder
ii) Z^1 und Z^2 jeweils H sind oder
iii) Z^1 H ist und Z^2 OH ist oder Z^1 OH ist und Z^2 H ist oder
iv) X^1 bis X^7 und Z^1 jeweils H sind und Z^2 OH ist oder
v) X^1 bis X^7 und Z^2 jeweils H sind und Z^1 OH ist;

b) Y NHR^2 ist und R^2 CH_2OH oder OH ist, oder

c) Y OH ist.

3. Verbindung nach Anspruch 1, worin

a) n 0 ist und
b) entweder Z^1 H ist und Z^2 OH ist oder Z^1 OH ist und Z^2 H ist und
c) entweder

i) R^2 H oder CH_3 ist oder
ii) X^1 bis X^7 jeweils H sind oder
iii) mindestens einer von X^1 bis X^7 OH ist oder
iv) mindestens einer von X^1 bis X^7 O (CO) C_1-C_4-Alkyl ist, oder
v) R^2 CH_2OH oder OH ist oder
vi) Y OH ist.

4. Verbindung nach Anspruch 1, worin in Formel (I)

a) n 0 ist und
b) Y NHR^2 ist und R^2 OH ist, und
c) entweder

i) X^1 bis X^7 jeweils H sind oder
ii) Z^1 H ist und Z^2 OH ist, oder
iii) Z^1 OH ist und Z^2 H ist, oder
iv) mindestens einer von X^1 bis X^7 OH ist oder
v) mindestens einer von X^1 bis X^7 O (CO) C_1-C_4-Alkyl ist.

5. Verbindung nach Anspruch 1, worin in Formel (I)

a) n 0 ist und
b) Y OH ist und
c) entweder

i) X^1 bis X^7 jeweils H sind oder
ii) Z^2 H ist und Z^1 OH ist, oder
iii) Z^1 H ist und Z^2 OH ist, oder
iv) mindestens einer von X^1 bis X^7 OH ist oder
v) mindestens einer von X^1 bis X^7 O (CO) C_1-C_4-Alkyl ist.

6. Verbindung nach Anspruch 1, die ausgewählt ist aus der Gruppe, bestehend aus:

4-{4-[({[4-Chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridincarboxamid-1-oxid, 4-{4-[({[4-Chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-N-hydroxymethyl-2-pyridincarboxamid-1-oxid,
4-{4-[({[4-Bromo-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridincarboxamid-1-oxid,
4-{4-[({[4-Bromo-3-(trifluorornethyl)phenyl]amino}carbonyl)amino]phenoxy} -N-hydroxymethyl-2-pyridincarboxamid-1-oxid,
4-{4-[({[4-Chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-2-pyridincarboxamid-1-oxid,
4-{4-[({[4-Bromo-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-2-pyridincarboxamid-1-oxid, Salzen davon und Stereoisomeren davon.

7. Verbindung nach Anspruch 1, wobei jeder von X^1, X^2 und X^3 H ist.

8. Verbindung nach Anspruch 7, wobei in Formel (II) n 1 ist und entweder

i) Z^1 und Z^2 jeweils H sind, oder
ii) mindestens einer von X^4 bis X^7 OH ist oder

iii) Y NHR^2 ist und R^2 H oder CH_3 ist.

9. Verbindung nach Anspruch 7, wobei in Formel (II) n 0 ist und entweder

i) Z^1 H ist und Z^2 OH ist, oder
ii) Z^1 OH ist und Z^2 H ist, oder
iii) Z^1 und Z^2 jeweils H sind und mindestens einer von X^4 bis X^7 OH ist oder
iv) mindestens einer von X^4 bis X^7 OH ist oder
v) Y NHR^2 ist und R^2 H oder CH_3 ist, oder
vi) Y NHR^2 ist und R^2 OH ist.

10. Verbindung nach Anspruch 1, worin jeder von X^1 bis X^7 H ist.

11. Verbindung nach Anspruch 10, worin in Formel (I) entweder

a) Y NHR^2 ist und R^2 H oder CH_3 ist und entweder:

i) n 1 ist und Z^1 und Z^2 jeweils H sind, oder
ii) n 0 ist und Z^1 H ist und Z^2 OH ist oder Z^1 OH ist und Z^2 H ist oder

b) Y OH ist.

12. Verfahren zum Herstellen von Verbindungen nach Anspruch 1, umfassend die Oxidation von 4-{4-[({[4-Chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridincarboxamid oder, 4-{4-[({[4-Bromo-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridincarboxamid oder 4-{4-[({[4-Chloro-3-trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-2-pyridincarboxamid oder 4-{4-[({[4-Bromo-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-2-pyridincarboxamid;
wobei die Oxidation

a) einen oder mehrere der Phenylwasserstoffe an den Positionen, die durch X^1 bis X^7 dargestellt sind, durch eine Hydroxylgruppe ersetzt, die wahlweise verestert wird,
b) das N-Methylamid zu einem Hydroxymethylamid oder einer Hydroxamsäure hydroxyliert,
c) das N-Methylamid zu einem nichtsubstituierten Amid demethyliert,
d) einen oder mehrere der Harnstoffstickstoffe (=NH) durch eine Hydroxylgruppe ersetzt, um einen N-Hydroxyharnstoff (=NOH) zu bilden,
e) das N-Methylamid zu einer Carbonsäure hydrolysiert,
f) den Pyridylringstickstoff oxidiert, um das entsprechende Pyridin-1-oxid zu bilden, oder
g) eine Kombination von zwei oder mehr der Schritte a) bis f) bereitstellt;

mit der Maßgabe, dass mindestens einer der Schritte b), d) und f) ausgeführt wird.

13. Verfahren nach Anspruch 12, durch das Folgendes hergestellt wird
4-{4-[({[4-Chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridincarboxamid-1-oxid,
4-{4-[({[4-Bromo-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridincarboxamid-1-oxid,
4-{4-[({[4-Chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}2 -pyridincarboxamid-1-oxid,
4-{4-[({[4-Bromo-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}2 -pyridincarboxamid-1-oxid oder ein pharmazeutisch verträgliches Salz eines dieser Oxide oder ein isoliertes Stereoisomer eines dieser Oxide.

14. Pharmazeutische Zusammensetzung, umfassend eine wirksame Menge mindestens einer Verbindung nach einem der Ansprüche 1 bis 6 und einen physiologisch verträglichen Träger.

15. Pharmazeutische Zusammensetzung, umfassend eine wirksame Menge von 4-{4-[({[4-Chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridincarboxamide-1-oxid, 4-{4-[({[4-Bromo-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridincarboxamid-1-oxid, 4- {4-[({[4-Chloro-3-(trifiuoromethyl)phenyl]amino}carbonyl)amino]phenoxy}2 -pyridincarboxamid-1-oxid, 4-(4-[({[4-Bromo-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}2 -pyridincarboxamid-1-oxid oder eines pharmazeutisch verträglichen Salzes eines dieser Oxide, eines isolierten Stereoisomers eines dieser Oxide oder einer Mischung davon und einen physiologisch verträglichen Träger.

16. Verwendung einer wirksamen Menge einer Verbindung nach einem der Ansprüche 1 bis 6 und wahlweise eines physiologisch verträglichen Trägers für die Herstellung eines Medikaments zur Behandlung oder Prävention von Osteoporose, Entzündung und Angiogenese-Erkrankungen mit Ausnahme von Krebs bei einem Säugetier.

17. Verwendung einer wirksamen Menge einer Verbindung nach einem der Ansprüche 1 bis 6 für die Herstellung eines Medikaments zur Behandlung oder Prävention einer hyperproliferativen Erkrankung bei einem Säugetier.

18. Verwendung a) einer wirksamen Menge einer Verbindung nach einem der Ansprüche 1 bis 6 und b) eines zusätzlichen antiproliferativen Mittels und wahlweise c) eines physiologisch verträglichen Trägers für die Herstellung eines Medikaments zur Behandlung oder Prävention einer hyperproliferativen Erkrankung bei einem Säugetier, umfassend die Verabreichung dem Säugetier.

19. Verwendung nach Anspruch 18, wobei das zusätzliche antiproliferative Mittel innerhalb einer pharmazeutischen Zusammensetzung vorhanden ist, die von der pharmazeutischen Zusammensetzung getrennt ist, die eine wirksame Menge einer Verbindung nach einem der Ansprüche 1 bis 6 und einen optionalen physiologisch verträglichen Träger umfasst.

20. Verwendung nach Anspruch 18 oder 19, wobei das zusätzliche antiproliferative Mittel ausgewählt ist aus der Gruppe, bestehend aus Asparaginase, Bleomycin, Carboplatin, Carmustin, Chlorambucil, Cisplatin, Colaspase, Cyclophosphamid, Cytarabin, Dacarbazin, Dactinomycin, Daunorubicin, Doxorubicin (Adriamycin), Epirubicin, Etoposid, 5-Fluorouracil, Hexamethylmelamin, Hydroxyharnstoff, Ifosfamid, Irinotecan, Leucovorin, Lomustin, Mechlorethamin, 6-Mercaptopurin, Mesna, Methotrexat, Mitomycin C, Mitoxantron, Prednisolon, Prednison, Procarbazin, Raloxifen, Streptozocin, Tamoxifen, Thioguanin, Topotecan, Vinblastin, Vincristin, Vindesin, Aminoglutethimid, L-Asparaginase, Azathioprin, 5-Azacytidin-Cladribin, Busulfan, Diethylstilbestrol, 2',2'-Difluorodeoxycytidin, Docetaxel, Erythrohydroxynonyladenin, Ethinylestradiol, 5-Fluorodeoxyuridin, 5-Fluorodeoxyuridinmonophosphat, Fludarabinphosphat, Fluoxymesteron, Flutamid, Hydroxyprogesteroncaproat, Idarubicin, Interferon, Medroxyprogesteronacetat, Megestrolacetat, Melphalan, Mitotan, Paclitaxel, Oxaliplatin, Gemcitabon, Gefinitib, Taxoter, BCNU, CCNU, DTIC, Ara-A, Ara-C, Herceptin, Actinomycin-D, Pentostatin, N-Phosphonoacetyl-L-aspartat (PALA), Plicamycin, Semustin, Teniposid, Testosteronpropionat, Thiotepa, Trimethylmelamin, Uridin und Vinorelbin.

21. Verwendung

a) einer wirksamen Menge einer Verbindung nach einem der Ansprüche 1 bis 6 und
b) eines zytotoxischen Mittels oder eines zytotoxischen chemotherapeutischen Mittels und
c) wahlweise eines physiologisch verträglichen Trägers

für die Herstellung eines Medikaments zur Behandlung oder Prävention von Krebs.

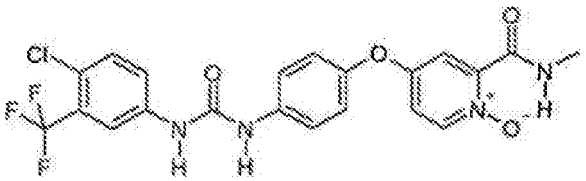
22. Verwendung nach Anspruch 21, wobei das zytotoxische chemotherapeutische Mittel innerhalb einer pharmazeutischen Zusammensetzung verabreicht wird, die von der pharmazeutischen Zusammensetzung getrennt ist, die eine wirksame Menge einer Verbindung nach einem der Ansprüche 1 bis 6 und einen optionalen physiologisch verträglichen Träger umfasst.

23. Verwendung eines Verfahrens nach Anspruch 21 oder 22, wobei das zytotoxische oder zytostatische chemotherapeutische Mittel ausgewählt ist aus der Gruppe, bestehend aus DNA-Topoisomerase-I und -II-Inhibitoren, DNA-Interkalatoren, Alkylierungsmitteln, Mikrotubulus-Disruptoren, Hormon- und Wachstumsfaktor-Rezeptor-Agonisten oder -Antagonisten, anderen Kinase-Inhibitoren und Antimetaboliten.

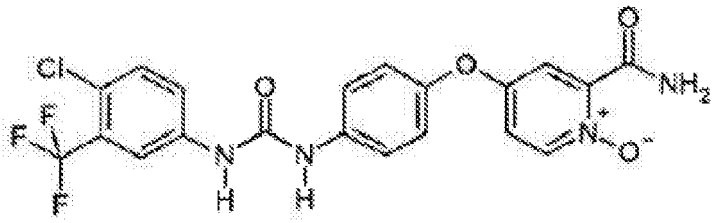
24. Satz, umfassend a) eine Dosis eines zytotoxischen oder zytostatischen Mittels und b) einer Dosis einer Verbindung nach einem der Ansprüche 1 bis 6.

25. Verfahren zum Herstellen von

a) N-[4-Chloro-3-(trifiuoromethyl)phenyl]-N'-{4-[2-(N-methylcarbamoyl)-1-oxo-(4-pyridyloxy)]phenyl}harnstoff



umfassend das chemische Oxidieren von N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl}harnstoff in gelöster Form oder
b) N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-1-oxo-(4-pyridyloxy)]phenyl}harnstoff



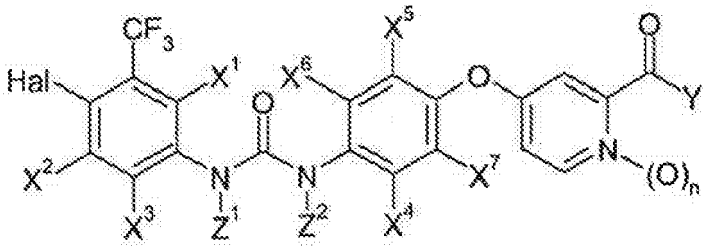
umfassend das chemische Oxidieren von N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-(4-pyridyloxy)]phenyl}harnstoff in gelöster Form.

26. Pharmazeutische Zusammensetzung nach Anspruch 14 oder 15 zur Verwendung bei der Behandlung oder Prävention von Osteoporose, Entzündung, Angiogenese-Erkrankungen mit Ausnahme von Krebs bei einem Säugetier.

27. Pharmazeutische Zusammensetzung nach Anspruch 14 oder 15 zur Verwendung bei der Behandlung oder Prävention einer hyperproliferativen Erkrankung bei einem Säugetier.

Revendications

1. Composé de formule (I)



(I)

dans laquelle
Y est OR^1 ou NHR^2,
Hal est le chlore ou le brome,
R^1 est H ou un alkyle en C_1 à C_6,
R^2 est H, OH, CH_3 ou CH_2OH,
Z^1 et Z^2 sont chacun H ou OH, un seul de Z^1 et Z^2 pouvant être OH,
X^1 et X^2 sont chacun indépendamment H, OH ou O(CO)alkyle en C_1 à C_4, et n vaut 0 ou 1,
sous réserve qu'au moins l'une des conditions a-c soit satisfaite :

a) Z^1 ou Z^2 est OH,

b) Y est NHR^2 et R^2 est OH,
c) n vaut 1,

ou un sel de celui-ci, ou un stéréoisomère isolé de celui-ci.

2. Composé selon la revendication 1, dans lequel n dans la formule I vaut 1 et soit

a) Y est NHR^2 et R^2 est H ou CH_3, et soit

i) X^1 à X^7 sont chacun H, soit
ii) Z^1 et Z^2 sont chacun H, soit
iii) Z^1 est H et Z^2 est OH ou Z^1 est OH et Z^2 est H, soit
iv) X^1 à X^7 et Z^1 sont chacun H et Z^2 est OH, soit
v) X^1 à X^7 et Z^2 sont chacun H et Z^1 est OH ;

b) Y est NHR^2 et R^2 est CH_2OH ou OH, soit
c) Y est OH.

3. Composé selon la revendication 1, dans lequel

a) n vaut 0, et
b) soit Z^1 est H et Z^2 est OH soit Z^1 est OH et Z^2 est H et
c) soit

i) R^2 est H ou CH_3, soit
ii) X^1 à X^7 sont chacun H, soit
iii) au moins l'un de X^1 à X^7 est OH, soit
iv) au moins l'un de X^1 à X^7 est O(CO)alkyle en C_1 à C_4, soit
v) R^2 est CH_2OH ou OH, soit
vi) Y est OH.

4. Composé selon la revendication 1, dans lequel, dans la formule (I),

a) n vaut 0, et
b) Y est NHR^2 et R^2 est OH et
c) soit

i) X^1 à X^7 sont chacun H, soit
ii) Z^1 est H et Z^2 est OH, soit
iii) Z^1 est OH et Z^2 est H, soit
iv) au moins l'un de X^1 à X^7 est OH, soit
v) au moins l'un de X^1 à X^7 est O(CO)alkyle en C_1 à C_4.

5. Composé selon la revendication 1, dans lequel, dans la formule (I),

a) n vaut 0, et
b) Y est OH et
c) soit

i) X^1 à X^7 sont chacun H, soit
ii) Z^2 est H et Z^1 est OH, soit
iii) Z^1 est H et Z^2 est OH, soit
iv) au moins l'un de X^1 à X^7 est OH, soit
v) au moins l'un de X^1 à X^7 est O(CO)alkyle en C_1 à C_4.

6. Composé selon la revendication 1, choisi dans le groupe constitué par les suivants :

1-oxyde de 4-{4-[({[4-chloro-3-(trifluorométhyl)-phényl]amino}carbonyl)amino]phénoxy}-N-méthyl-2-pyridine-

carboxamide,
1-oxyde de 4-{4-[({[4-chloro-3-(trifluorométhyl)-phényl]amino}carbonyl)amino]phénoxy}-N-hydroxyméthyl-2-pyridinecarboxamide,
1-oxyde de 4-{4-[({[4-bromo-3-(trifluorométhyl)-phényl]amino}carbonyl)amino]phénoxy}-N-méthyl-2-pyridine-carboxamide,
1-oxyde de 4-{4-[({[4-bromo-3-(trifluorométhyl)-phényl]amino}carbonyl)amino]phénoxy}-N-hydroxyméthyl-2-pyridinecarboxamide,
1-oxyde de 4-{4-[({[4-chloro-3-(trifluorométhyl)-phényl]amino}carbonyl)amino]phénoxy}-2-pyridine-carboxamide,
1-oxyde de 4-{4-[({[4-bromo-3-(trifluorométhyl)-phényl]amino}carbonyl)amino]phénoxy}-2-pyridine-carboxamide,
leurs sels et leurs stéréoisomères.

7. Composé selon la revendication 1, dans lequel chacun de X^1, X^2 et X^3 est H.

8. Composé selon la revendication 7, dans lequel, dans la formule (II), n vaut 1, et soit

i) Z^1 et Z^2 sont chacun H, soit
ii) au moins l'un de X^4 à X^7 est OH, soit
iii) Y est NHR^2 et R^2 est H ou CH_3.

9. Composé selon la revendication 7, dans lequel, dans la formule (II), n vaut 0, et soit

i) Z^1 est H et Z^2 est OH, soit
ii) Z^1 est OH et Z^2 est H, soit
iii) Z^1 et Z^2 sont chacun H, et au moins l'un de X^4 à X^7 est OH, soit
iv) au moins l'un de X^4 à X^7 est OH, soit
v) Y est NHR^2 et R^2 est H ou CH_3, soit
vi) Y est NHR^2 et R^2 est OH.

10. Composé selon la revendication 1, dans lequel X^1 à X^7 sont chacun H.

11. Composé selon la revendication 10, dans lequel, dans la formule (III), soit

a) Y est NHR^2 et R^2 est H ou CH_3, et soit :

i) n vaut 1 et chacun de Z^1 et Z^2 est H, soit
ii) n vaut 0 et Z^1 est H et Z^2 est OH ou Z^1 est OH et Z^2 est H, soit

b) Y est OH.

12. Procédé pour préparer des composés de formule 1, comprenant l'oxydation de
4-{4-[({[4-chloro-3-(trifluorométhyl)-phényl]amino}-carbonyl)amino]phénoxy}-N-méthyl-2-pyridinecarboxamide, ou de
4-{4-[({[4-bromo-3-(trifluorométhyl)-phényl]amino}-carbonyl)amino]phénoxy}-N-méthyl-2-pyridinecarboxamide, ou de
4-{4-[({[4-chloro-3-(trifluorométhyl)-phényl]amino}-carbonyl)amino]phénoxy}-2-pyridinecarboxamide, ou de
4-{4-[({[4-bromo-3-(trifluorométhyl)-phényl]amino}-carbonyl)amino]phénoxy}-2-pyridinecarboxamide ;
dans lequel l'oxydation

a) remplace un ou plusieurs des hydrogènes de phényle aux positions représentées par X^1 à X^7 par un groupe hydroxyle, qui est éventuellement estérifié,
b) hydroxyle le N-méthylamide en un hydroxyméthylamide ou acide hydroxamique,
c) déméthyle le N-méthylamide en un amide non substitué,
d) remplace un ou plusieurs des azotes d'urée (=NH) par un groupe hydroxyle pour former une N-hydroxyurée (=NOH),
e) hydrolyse le N-méthylamide en un acide carboxylique,
f) oxyde l'azote du cycle pyridyle pour former le pyridine-1-oxyde correspondant, ou

g) réalise une combinaison de deux ou plusieurs parmi a) à f) ;

sous réserve qu'au moins l'un parmi b), d) et f) soit effectué.

13. Procédé selon la revendication 12, qui prépare
le 1-oxyde de 4-{4-[({[4-chloro-3-(trifluorométhyl)-phényl]amino}carbonyl)amino]phénoxy}-N-méthyl-2-pyridine-carboxamide,
le 1-oxyde de 4-{4-[({[4-bromo-3-(trifluorométhyl)-phényl]amino}carbonyl)amino]phénoxy}-N-méthyl-2-pyridine-carboxamide,
le 1-oxyde de 4-{4-[({[4-chloro-3-(trifluorométhyl)-phényl]amino}carbonyl)amino]phénoxy}-2-pyridine-carboxamide,
le 1-oxyde de 4-{4-[({[4-bromo-3-(trifluorométhyl)-phényl]amino}carbonyl)amino]phénoxy}-2-pyridine-carboxamide,
ou un sel pharmaceutiquement acceptable de l'un de ces oxydes, ou un stéréoisomère isolé de l'un de ces oxydes.

14. Composition pharmaceutique comprenant une quantité efficace d'au moins un composé de l'une quelconque des revendications 1 à 6 et un véhicule physiologiquement acceptable.

15. Composition pharmaceutique comprenant une quantité efficace de
1-oxyde de 4-{4-[({[4-chloro-3-(trifluorométhyl)-phényl]amino}carbonyl)amino]phénoxy}-N-méthyl-2-pyridine-carboxamide,
1-oxyde de 4-{4-[({[4-bromo-3-(trifluorométhyl)-phényl]amino}carbonyl)amino]phénoxy}-N-méthyl-2-pyridine-carboxamide,
1-oxyde de 4-{4-[({[4-chloro-3-(trifluorométhyl)-phényl]amino}carbonyl)amino]phénoxy}-2-pyridine-carboxamide,
1-oxyde de 4-{4-[({[4-bromo-3-(trifluorométhyl)-phényl]amino}carbonyl)amino]phénoxy}-2-pyridine-carboxamide,
ou d'un sel pharmaceutiquement acceptable de l'un de ces oxydes, d'un stéréoisomère isolé de l'un de ces oxydes, ou d'un de leurs mélanges, et un véhicule physiologiquement acceptable.

16. Utilisation d'une quantité efficace d'un composé de l'une quelconque des revendications 1 à 6 et éventuellement d'un véhicule physiologiquement acceptable pour la fabrication d'un médicament pour traiter ou prévenir l'ostéoporose, une inflammation et des troubles de l'angiogenèse, à l'exclusion du cancer, chez un mammifère.

17. Utilisation d'une quantité efficace d'un composé de l'une quelconque des revendications 1 à 6 pour la fabrication d'un médicament pour traiter ou prévenir un trouble hyperprolifératif chez un mammifère.

18. Utilisation de a) une quantité efficace d'un composé de l'une quelconque des revendications 1 à 6 et b) un agent antiprolifératif additionnel et éventuellement c) un véhicule physiologiquement acceptable, pour la fabrication d'un médicament pour traiter ou prévenir un trouble hyperprolifératif chez un mammifère, comprenant l'administration audit mammifère.

19. Utilisation selon la revendication 18, dans lequel l'agent antiprolifératif additionnel se trouve dans une composition pharmaceutique séparée de la composition pharmaceutique comprenant une quantité efficace d'un composé de l'une quelconque des revendications 1 à 6 et un véhicule physiologiquement acceptable facultatif.

20. Utilisation selon la revendication 18 ou 19, dans laquelle l'agent antiprolifératif additionnel est choisi dans le groupe constitué par l'asparaginase, la bléomycine, le carboplatine, la carmustine, le chlorambucil, le cisplatine, la colaspase, le cyclophosphamide, la cytarabine, la dacarbazine, la dactinomycine, la daunorubicine, la doxorubicine (adriamycine), l'épirubicine, l'étoposide, le 5-fluorouracile, l'hexaméthylmélamine, l'hydroxyurée, l'ifosfamide, l'irinotécan, la leucovorine, la lomustine, la méchloréthamine, la 6-mercaptopurine, le mesna, le méthotrexate, la mitomycine C, la mitoxantrone, la prednisolone, la prednisone, la procarbazine, le raloxifen, la streptozocine, le tamofixen, la thioguanine, le topotécan, la vinblastine, la vincristine, la vindésine, l'aminoglutéthimide, la L-asparaginase, l'azathioprine, la 5-azacytidine cladribine, le busulfan, le diéthylstilbestrol, la 2',2'-difluorodésoxycytidine, le docétaxel, l'érythrohydroxynonyladénine, l'éthinyl-oestradiol, la 5-fluorodésoxyuridine, le monophosphate de 5-fluorodésoxyuridine, le phosphate de fludarabine, la fluoxymestérone, le flutamide, le caproate d'hydroxyprogestérone, l'idarubicine, l'interféron, l'acétate de médroxyprogestérone, l'acétate de mégestrol, le melphalan, le mitotane, le paclitaxel, l'oxaliplatine, la gemcitabone, le géfinitib, le taxotère, BCNU, CCNU, DTIC, ara A, ara C, l'herceptine, l'actinomycine D, la pentostatine, le L-aspartate de N-phosphonoacétyle (PALA), la plicamycine, la sémustine, le téniposide, le propionate de testostérone, le thiotépa, la triméthylmélamine, l'uridine, et la vinorelbine.

21. Utilisation de

a) une quantité efficace d'un composé de l'une quelconque des revendications 1 à 6, et
b) un agent cytotoxique ou un agent chimiothérapeutique cytostatique, et
c) éventuellement un véhicule physiologiquement acceptable,

pour la fabrication d'un médicament pour traiter ou prévenir un cancer.

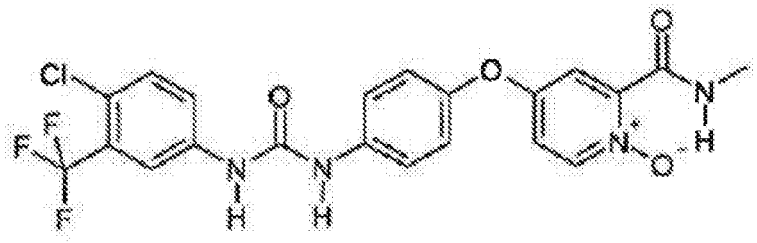
22. Utilisation selon la revendication 21, dans laquelle l'agent cytotoxique ou l'agent chimiothérapeutique cytostatique administré se trouve dans une composition pharmaceutique séparée de la composition pharmaceutique comprenant une quantité efficace d'un composé de l'une quelconque des revendications 1 à 6, et un véhicule physiologiquement acceptable.

23. Utilisation d'un procédé selon la revendication 21 ou 22, dans laquelle l'agent chimiothérapeutique cytotoxique ou cytostatique est choisi dans le groupe constitué par les inhibiteurs d'ADN topoisomérase I et II, les intercalateurs d'ADN, les agents d'alkylation, les rupteurs de microtubules, les agonistes ou antagonistes de récepteurs de facteurs de croissance et d'hormones, d'autres inhibiteurs de kinases, et les antimétabolites.

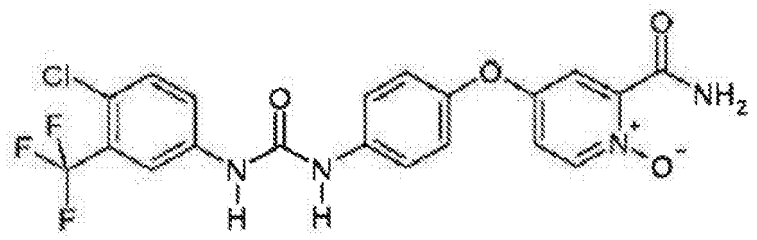
24. Trousse comprenant a) une dose d'agent cytotoxique ou cytostatique et b) une dose d'un composé de l'une quelconque des revendications 1 à 6.

25. Procédé pour préparer

a) de la N-[4-chloro-3-(trifluorométhyl)phényl]-N'-{4-[2-(N-méthylcarbamoyl)-1-oxo-(4-pyridyloxy)]phényl}urée



comprenant l'oxydation chimique de N-[4-chloro-3-(trifluorométhyl)phényl]-N'-{4-[2-(N-méthylcarbamoyl)-(4-pyridyloxy)]phényl}urée en solution, ou
b) de la N-[4-chloro-3-(trifluorométhyl)phényl]-N'-{4-[2-carbamoyl-1-oxo-(4-pyridyloxy)]phényl}urée



comprenant l'oxydation chimique de N-[4-chloro-3-(trifluorométhyl)phényl]-N'-{4-[2-carbamoyl-(4-pyridyloxy)]phényl}urée en solution.

26. Composition pharmaceutique selon la revendication 14 ou 15, pour une utilisation dans le traitement ou la prévention de l'ostéoporose, d'une inflammation et de troubles de l'angiogenèse, à l'exclusion d'un cancer, chez un mammifère.

27. Composition pharmaceutique selon la revendication 14 ou 15, pour une utilisation dans le traitement ou la prévention d'un trouble hyperprolifératif chez un mammifère.

REFERENCES CITED IN THE DESCRIPTION

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