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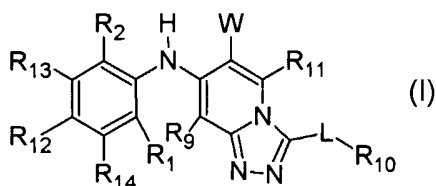
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(54) Title: [1,2,4]TRIAZOLO[4,3-A]PYRIDINE DERIVATIVES FOR THE TREATMENT OF HYPERPROLIFERATIVE DIS-
 EASES



(57) Abstract: The invention provides novel, substituted 7-arylamino[1,2,4]triazolo[4,3-a]pyridine compounds Formula (I): pharmaceutically acceptable salts, solvates and prodrug compounds thereof, wherein W, R₁, R₂, R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄ and L are as defined in the specification. Such compounds are MEK inhibitors and useful in the treatment of hyperproliferative diseases, such as cancer, restenosis and inflammation. Also disclosed is the use of such compounds in the treatment of hyperproliferative diseases in mammals, especially humans, and pharmaceutical compositions containing such compounds.

**[1,2,4] triazolo [4,3-A] PYRIDINE DERIVATIVES FOR THE TREATMENT OF
HYPERPROLIFERATIVE DISEASES**

Field of the invention

The invention relates to a series of substituted 7-arylamino[1,2,4]triazolo[4,3-a]pyridine derivatives that are useful in the treatment of hyperproliferative diseases, such as cancer and inflammation, in mammals. Also disclosed is the use of such compounds in the treatment of hyperproliferative diseases in mammals, especially humans, and pharmaceutical compositions containing such compounds.

Summary of the related art

The Ras/Raf/MEK/ERK pathway is a central signal transduction pathway, which transmits signals from multiple cell surface receptors to transcription factors in the nucleus, which regulate gene expression. This pathway is frequently referred to as the MAP kinase pathway as MAPK stands for mitogen-activated protein kinase indicating that this pathway can be stimulated by mitogens, cytokines and growth factors (Steelman et al., Leukemia **2004**, 18, 189-218). Depending upon the stimulus and cell type, this pathway can transmit signals, which result in the prevention or induction of apoptosis or cell cycle progression. The Ras/Raf/MEK/ERK pathway has been shown to play important roles in cell proliferation and the prevention of apoptosis. Aberrant activation of this pathway is commonly observed in malignantly transformed cells. Amplification of *ras* proto-oncogenes and activating mutations that lead to the expression of constitutively active Ras proteins are observed in approximately 30% of all human cancers (Stirewalt et al., Blood **2001**, 97, 3589-95). Mutated, oncogenic forms of Ras are found in 50% of colon and >90% pancreatic cancers as well as many other types of cancers (Kohl et al., Science **1993**, 260, 1834-1837). The effects of Ras on proliferation and tumorigenesis have been documented in immortal cell lines (McCubrey et al., Int J Oncol **1995**, 7, 295-310). *bRaf* mutations have been identified in more than 60% of malignant melanoma (Davies, H et al., Nature **2002**, 417, 949-954). Given the high level of mutations that have been detected at Ras, this pathway has always been considered a key target for therapeutic intervention (Chang et al., Leukemia **2003**, 17, 1263-93).

The Ras/Raf/MEK/ERK signaling pathway can exert proliferative or antiproliferative effects through downstream transcription factor targets including NF- κ B, CREB, Ets-1, AP-1 and c-Myc. ERKs can directly phosphorylate Ets-1, AP-1 and c-Myc, which lead to their activation. Alternatively, ERKs can phosphorylate and activate a downstream kinase target RSK, which then phosphorylates and activates transcription factors, such as

CREB. These transcription factors induce the expression of genes important for cell cycle progression, for example, Cdk's, cyclins, growth factors, and apoptosis prevention, for example, antiapoptotic Bcl-2 and cytokines. Overall, treatment of cells with growth factors leads to the activation of ERKs which results in proliferation and, in some cases, differentiation (Lewis et al., Adv. Cancer Res, **1998**, 74, 49-139).

MEK proteins are the primary downstream targets of Raf. The MEK family of genes consists of five genes: MEK1, MEK2, MEK3, MEK4 and MEK5. This family of dual-specificity kinases has both serine/threonine and tyrosine kinase activity. The structure of MEK consists of an amino-terminal negative regulatory domain and a carboxy-terminal MAP kinase-binding domain, which is necessary for binding and activation of ERKs. Deletion of the regulatory MEK1 domain results in constitutive MEK1 and ERK activation (Steelman et al., Leukemia **2004**, 18, 189-218).

MEK1 is a 393-amino-acid protein with a molecular weight of 44 kDa (Crews et al., Science **1992**, 258, 478-80). MEK1 is modestly expressed in embryonic development and is elevated in adult tissue with the highest levels detected in brain tissue. MEK1 requires phosphorylation of S218 and S222 for activation, and substitution of these residues with D or glutamic acid (E) led to an increase in activity and foci formation in NIH3T3 cells (Huang et al., Mol Biol Cell, **1995**, 6, 237-45). Constitutive activity of MEK1 in primary cell culture promotes senescence and induces p53 and p16^{INK4a}, and the opposite was observed in immortalized cells or cells lacking either p53 or p16^{INK4a} (Lin et al., Genes Dev, **1998**, 12, 3008-3019). Constitutive activity of MEK1 inhibits NF- κ B transcription by negatively regulating p38^{MAPK} activity (Carter et al., J Biol Chem **2000**, 275, 27858-64). The main physiological substrates of MEK are the members of the ERK (extracellular signal-regulated kinase) or MAPK (mitogen activated protein kinase) family of genes. Aberrant expression of MEK1 has been detected in many different types of cancer, and mutated forms of MEK1 will transform fibroblast, hematopoietic and other cell types.

Constitutive activation of MEK1 results in cellular transformation. It therefore represents a likely target for pharmacological intervention in proliferative and inflammatory diseases (Lee et al., Nature **1994**, 372, 739-746; Dudley et al., Proc. Natl. Acad. Sci. U.S.A. **1995**, 92, 7686-7689).

Useful inhibitors of MEK have been developed that show potential therapeutic benefit in several studies. For example, small molecule MEK inhibitors have been shown to inhibit human tumor growth in nude mouse xenografts (Yeh, T. et al, *Proceedings of the*

American Association of Cancer Research **2004**, 45, Abs 3889 and Lee, P. et al., *Proceedings of the American Association of Cancer Research* **2004**, 45, Abs 3890). MEK inhibitors also entered clinical trials, i.e. ARRY142886 (Wallace, E. et al, *Proceedings of the American Association of Cancer Research* **2004**, 45, Abs 3891), PD-0325901 (Swanton C, Johnston S *IDDB MEETING REPORT* **2003**, February 13-1) and PD-184352 (Waterhouse et al., *Proceedings of the American Society for Clinical Oncology* **2003**, 22, Abs 816).

Compounds suitable as MEK inhibitors are also disclosed in US 5,525,625; WO 98/43960; WO 99/01421; WO 99/01426; WO 00/41505; WO 00/42002; WO 00/42003; WO 00/41994; WO 00/42022; WO 00/42029; WO 00/68201; WO 01/68619; WO 02/06213; WO03/035626; A2; WO 03/077855; WO03/077914; WO2004/005284; WO2004/056789.

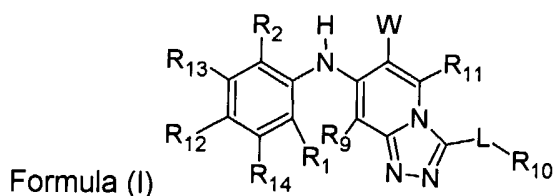
However, PD-184352 was lacking efficacy in clinical phase II trials. Tumors were much less responsive, as no partial responses and only a few patients with stable disease were observed. As a result, the clinical trials of this molecule were suspended (McInnes C *IDDB MEETING REPORT* 2003). PD-184352 was limited by poor solubility, high metabolic clearance and low bioavailability. This exemplifies the need for novel MEK inhibitors with superior pharmacological properties.

Description of the invention

In view of the foregoing it is the object of the present invention to provide novel MEK inhibitors useful in the treatment of hyperproliferative diseases related to the hyperactivity of MEK as well as diseases modulated by the MEK cascade, such as cancer and inflammation, in mammals with superior pharmacological properties both with respect to their activities as well as their solubility, metabolic clearance and bioavailability characteristics.

As a result, this invention provides novel, substituted 7-arylamino[1,2,4]triazolo[4,3-a]pyridine derivatives and pharmaceutically acceptable salts, solvates or prodrugs thereof, that are MEK inhibitors and useful in the treatment of the above mentioned diseases.

The compounds are defined by Formula (I):



a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein:

R_1 , R_2 , R_9 , R_{11} , R_{12} , R_{13} and R_{14} are independently selected from hydrogen, halogen, cyano, nitro, azido, $-OR_3$, $-C(O)R_3$, $-C(O)OR_3$, $-NR_4C(O)OR_6$, $-OC(O)R_3$, $-NR_4S(O)_jR_6$, $-S(O)_jNR_3R_4$, $-S(O)_jNR_4C(O)R_3$, $-C(O)NR_4S(O)_jR_6$, $S(O)_jR_6$, $-NR_4C(O)R_3$, $-C(O)NR_3R_4$, $-NR_5C(O)NR_3R_4$, $-NR_5C(NCN)NR_3R_4$, $-NR_3R_4$ and C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkylalkyl, $-S(O)_j(C_1$ - C_6 alkyl), $-S(O)_j(CR_4R_5)_m$ -aryl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclalkyl, $-O(CR_4R_5)_m$ -aryl, $-NR_4(CR_4R_5)_m$ -aryl, $-O(CR_4R_5)_m$ -heteroaryl, $-NR_4(CR_4R_5)_m$ -heteroaryl, $-O(CR_4R_5)_m$ -heterocyclyl, $-NR_4(CR_4R_5)_m$ -heterocyclyl, and $-S(C_1$ - C_2 alkyl) substituted with 1 to 5 F, where each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is substituted or unsubstituted;

R_{10} is selected from hydrogen, $-OR_3$, $-C(O)R_3$, $-C(O)OR_3$, $-NR_4C(O)OR_6$, $-OC(O)R_3$, $-NR_4S(O)_jR_6$, $-S(O)_jNR_3R_4$, $-S(O)_jNR_4C(O)R_3$, $-C(O)NR_4S(O)_jR_6$, $S(O)_jR_6$, $-NR_4C(O)R_3$, $-C(O)NR_3R_4$, $-NR_5C(O)NR_3R_4$, $-NR_5C(NCN)NR_3R_4$, $-NR_3R_4$; $-S(O)_j(C_1$ - C_6 alkyl), $-S(O)_j(CR_4R_5)_m$ -aryl, $-O(CR_4R_5)_m$ -aryl, $-NR_4(CR_4R_5)_m$ -aryl, $-O(CR_4R_5)_m$ -heteroaryl, $-NR_4(CR_4R_5)_m$ -heteroaryl, $-O(CR_4R_5)_m$ -heterocyclyl, $-NR_4(CR_4R_5)_m$ -heterocyclyl, and $-S(C_1$ - C_2 alkyl) substituted with 1 to 5 F, where each, aryl, heteroaryl and heterocyclyl is substituted or unsubstituted;

L is selected from a bond, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclalkyl, where each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is unsubstituted or substituted;

R_3 is selected from hydrogen, trifluoromethyl, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclalkyl, where each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is substituted or unsubstituted;

R_4 is selected from hydrogen or C_1 - C_6 alkyl whereby alkyl may be substituted or unsubstituted; or

R₃ and R₄ can be taken together with the atom to which they are attached to form a 4 to 10 membered heteroaryl or heterocyclic ring, each of which is substituted or unsubstituted;

R₅ is selected from hydrogen or C₁-C₆ alkyl whereby alkyl may be substituted or unsubstituted; or

R₄ and R₅ can be taken together with the atom to which they are attached to form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring, each of which is substituted or unsubstituted;

R₆ is selected from trifluoromethyl, C₁-C₁₀ alkyl, C₃-C₁₀ cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, where each alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl substituted or unsubstituted;

W is selected from heteroaryl containing 1-4 heteroatoms or heterocyclyl containing 1-4 heteroatoms each of which is unsubstituted or substituted by 1 to 5 substituents ZR₁₅; or W is -C(O)OR₁₅, -C(O)NR₄R₁₅, -C(O)NR₄OR₁₅, -C(O)(C₃-C₁₀ cycloalkyl), -C(O)(C₂-C₁₀ alkyl), -C(O)(aryl), -C(O)(heteroaryl), -C(O)(heterocyclyl), -S(O)_jNR₄R₁₅, -S(O)_jNR₄OR₁₅, -S(O)_jNR₄C(O)R₁₅, or -C(O)NR₄S(O)_jR₆, whereby R₄ and R₁₅ are as defined herein or may form together a 3 to 7 membered ring with 1 or 2 N atoms and optionally an O atom,

Z is a bond, NR₁₆, O, NR₁₆SO₂ or S,

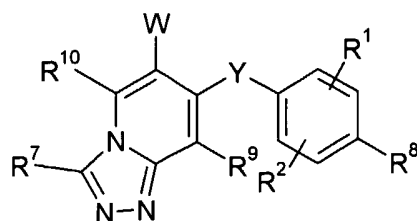
R₁₅ is independently selected from hydrogen, trifluoromethyl, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, where each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is substituted or unsubstituted;

R₁₆ is selected from hydrogen or C₁-C₁₀ alkyl, or R₁₅ and R₁₆ form together a 4 to 10 membered cyclic ring with 1 or 2 N atoms and optionally an O atom, said ring being substituted or unsubstituted;

m is 0, 1, 2, 3, 4 or 5 ;and

j is 1 or 2.

In a preferred embodiment, the variants R₁-R₁₆, L, W and Z are defined as above on pages 4 to 5 but with the proviso that the compounds with the following formula including resolved enantiomers, diastereomers, solvates and pharmaceutically acceptable salts thereof are excluded:



wherein

Y is NH;

R^1 , R^2 , R^7 , R^8 , R^9 and R^{10} are independently hydrogen, halogen, cyano, nitro, azido, -OR³, -C(O)R³, -C(O)OR³, -NR⁴C(O)OR⁶, -OC(O)R³, -NR⁴SO₂R⁶, -SO₂NR³R⁴, -NR⁴C(O)R³, -C(O)NR³R⁴, -NR⁵C(O)NR³R⁴, -NR⁵C(NCN)NR³R⁴, -NR³R⁴, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkylalkyl, -S(O)_i(C₁-C₆ alkyl), -S(O)_i(CR⁴R⁵)_m-aryl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclalkyl, -O(CR⁴R⁵)_m-aryl, -NR⁵(CR⁴R⁵)_m-aryl, -O(CR⁴R⁵)_m-heteroaryl, -NR⁴(CR⁴R⁵)_m-heteroaryl, -O(CR⁴R⁵)_m-heterocyclyl or -NR⁴(CR⁴R⁵)_m-heterocyclyl, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclalkyl portions are optionally substituted with one or more groups independently selected from oxo, halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, -NR⁴SO₂R⁶, -SO₂NR³R⁴, -C(O)R³, -C(O)OR³, -OC(O)R³, -NR⁴C(O)OR⁶, -NR⁴C(O)R³, -C(O)NR³R⁴, -NR³R⁴, -NR⁵C(O)NR³R⁴, -NR⁵C(NCN)NR³R⁴, -OR³, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclalkyl,

R^3 is hydrogen, trifluoromethyl, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₁₀-cycloalkyl, C₃-C₁₀ cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclalkyl, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclalkyl portions are optionally substituted with one or more groups independently selected from oxo, halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, -NR⁴SO₂R⁶, -SO₂NR³R⁴, -C(O)R³, -C(O)OR³, -OC(O)R³, -NR⁴C(O)OR⁶, -NR⁴C(O)R³, -C(O)NR³R⁴, -SR³, -S(O)R³, -SO₂R⁶, -NR⁴R⁶, -NR⁴C(O)NR³R⁴, -NR⁴C(NCN)NR³R⁴, -OR³, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclalkyl, or

R^3 and R^4 together with the atom to which they are attached form a 4 to 10 membered heteroaryl or heterocyclic ring, wherein any of said heteroaryl or heterocyclic rings are optionally substituted with one or more groups independently selected from

halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, NR'SO₂R''', -SO₂NR'R'', -C(O)R', -C(O)OR', -OC(O)R', -NR'C(O)OR''', -NR'C(O)R'', -C(O)NR'R'', -SO₂R''', -NR'R'', -NR'C(O)NR''R''', -NR'C(NCN)NR''R''', -OR', aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclalkyl;

5 R', R'' and R''' independently are hydrogen, lower alkyl, lower alkenyl, aryl and arylalkyl, and R'''' is lower alkyl, lower alkenyl, aryl or arylalkyl, or any two of R', R'', R''' or R'''' together with the atom to which they are attached form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring, wherein any of said alkyl, alkenyl, aryl, arylalkyl carbocyclic rings, heteroaryl rings or heterocyclic rings are optionally substituted with one or more groups
10 independently selected from halo, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclalkyl;

R⁴ and R⁵ independently are hydrogen or C₁-C₆ alkyl, or

R⁴ and R⁵ together with the atom to which they are attached form a 4 to 10-membered
15 carbocyclic, heteroaryl or heterocyclic ring, wherein said alkyl or any of said carbocyclic, heteroaryl and heterocyclic rings are optionally substituted with one or more groups independently selected from cyano, halogen, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, -NR'SO₂R''', -SO₂NR'R'', -C(O)R'', C(O)OR', -OC(O)R', -NR'C(O)OR''', -NR'C(O)R'', -C(O)NR'R'', -SO₂R''', -NR'R'',
20 -NR'C(O)NR''R''', -NR'C(NCN)NR''R''', -OR', aryl, heteroaryl, arylalkyl, heteroaryl-alkyl, heterocyclyl, and heterocyclalkyl;

R⁶ is trifluoromethyl, C₁-C₁₀ alkyl, C₃-C₁₀ cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclalkyl, wherein any of said alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and
25 heterocyclalkyl portions are optionally substituted with one or more groups independently selected from oxo, halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, -NR'SO₂R''', -SO₂NR'R'', -C(O)R', C(O)OR', -OC(O)R', -NR'C(O)OR''', -NR'C(O)R'', -C(O)NR'R'', -SO₂R''', -NR'R'', -NR'C(O)NR''R''', -NR'C(NCN)NR''R''', -OR', aryl, heteroaryl, arylalkyl,
30 heteroarylalkyl, heterocyclyl, and heterocyclalkyl;

W is heteroaryl, heterocyclyl, -C(O)OR³, -C(O)NR³R⁴, -C(O)NR⁴OR³, -C(O)(C₃-C₁₀ cycloalkyl), -C(O)(C₁-C₁₀ alkyl), -C(O)(aryl), -C(O)(heteroaryl), -C(O)(heterocyclyl), -C(O)NH(SO₂)CH₃, wherein any of said heteroaryl, heterocyclyl, -C(O)OR³, -C(O)NR³R⁴, -C(O)NR⁴OR³, -C(O)(C₃-C₁₀ cycloalkyl),

-C(O)(C₁-C₁₀ alkyl), -C(O)(aryl), -C(O)(heteroaryl), -C(O)(heterocyclyl),
 C(O)NH(SO₂)CH₃ are optionally substituted with one or more groups independently
 selected from -NR³R⁴, -OR³, R², C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, and C₂-C₁₀ alkynyl,
 wherein any of said C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, and C₂-C₁₀ alkynyl, are optionally
 5 substituted with 1 or more groups independently selected from -NR³R⁴ and -OR³;

m is 0, 1, 2, 3, 4 or 5; and

j is 1 or 2.

In preferred embodiments, the variants have the following meanings:

R₁ is as defined above, preferably hydrogen, halo, C₁-C₄ alkyl, C₃-C₄ cycloalkyl, C₂-C₄
 10 alkenyl, C₂-C₄ alkynyl, cyano, nitro, OR₃ or NR₃R₄; more preferably hydrogen, halo or C₁-
 C₄ alkyl, still more preferably hydrogen or halo, most preferably hydrogen or F. In one
 embodiment, R₁ is hydrogen.

In a further embodiment, R₁ is -S(O)_jNR₄C(O)R₃, -C(O)NR₄S(O)_jR₆, or S(O)_jR₆.

R₂ is as defined above, preferably hydrogen, halo, C₁-C₄ alkyl, C₃-C₄ cycloalkyl, C₂-C₄
 15 alkenyl, C₂-C₄ alkynyl, cyano, nitro, OR₃ or NR₃R₄; more preferably hydrogen, halo or C₁-
 C₂ alkyl, still more preferably halo or methyl, most preferably Cl, F or methyl. In one
 embodiment, R₂ is methyl. In another embodiment, methyl is preferably further
 substituted by 1, 2 or 3 fluorines, preferably 3 fluorines. Most preferably, R₂ is F.

In still another embodiment, R₂ is -S(O)_jNR₄C(O)R₃, -C(O)NR₄S(O)_jR₆, or S(O)_jR₆.

20 R₉ is as defined above, preferably hydrogen, halo, C₁-C₄ alkyl, C₃-C₄ cycloalkyl, C₂-C₄
 alkenyl, C₂-C₄ alkynyl, cyano, nitro, OR₃ or NR₃R₄; more preferably hydrogen, halo or C₁-
 C₄ alkyl, still more preferably hydrogen, methyl or halo, most preferably hydrogen,
 methyl, Cl or F. In one embodiment, R₉ is hydrogen.

In another embodiment, R₉ is -S(O)_jNR₄C(O)R₃, -C(O)NR₄S(O)_jR₆, or S(O)_jR₆.

25 R₁₀ is as defined above, preferably hydrogen, -OR₃, -C(O)R₃, -C(O)OR₃, -NR₄C(O)OR₆,
 -OC(O)R₃, -NR₄S(O)₂R₆, -S(O)₂NR₃R₄, S(O)₂R₆, -NR₄C(O)R₃, -C(O)NR₃R₄,
 -NR₅C(O)NR₃R₄, -NR₃R₄, more preferably hydrogen, -OR₃, -NR₄C(O)R₃, -C(O)NR₃R₄,
 -NR₃R₄, still more preferably hydrogen, -OR₃, -NR₃R₄, most preferably hydrogen. In
 preferred embodiments R₃ and R₄ are independently C₁-C₆ alkyl, more preferably C₁-C₄
 30 alkyl, optionally substituted by 1 or 2 alkyl amino, dialkyl amino, amino, O-alkyl, hydroxy,
 or R₃ and R₄ form together a cyclic ring with 1 or 2 N atoms and optionally an O atom,
 said ring being optionally substituted by 1 or 2 alkyl amino, amino, hydroxy or O-alkyl.

In a further embodiment, R_{10} is $-S(O)_jNR_4C(O)R_3$, $-C(O)NR_4S(O)_jR_6$, $-S(O)_jR_6$, $-S(O)_j(C_1-C_6 \text{ alkyl})$, $-S(O)_j(CR_4R_5)_m\text{-aryl}$, $-O(CR_4R_5)_m\text{-aryl}$, $-NR_4(CR_4R_5)_m\text{-aryl}$, $-O(CR_4R_5)_m\text{-heteroaryl}$, $-NR_4(CR_4R_5)_m\text{-heteroaryl}$, $-O(CR_4R_5)_m\text{-heterocyclyl}$, or $-NR_4(CR_4R_5)_m\text{-heterocyclyl}$ and $-S(C_1-C_2\text{alkyl})$ substituted with 1 to 5 F, where each aryl, heteroaryl and heterocyclyl is substituted or unsubstituted.

L is as defined above, preferably a bond, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_3-C_{10} cycloalkylalkyl, arylalkyl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, more preferably a bond, C_1-C_5 alkyl, most preferably a bond, methylene, ethylene, n-propylene or n-butylene. In one embodiment, L is ethylene, n-propylene or n-butylene. In another embodiment, L is a bond or methylene. In the definition of L all moieties are divalent so that L serves as a linker between the nitrogen atom and R_{10} .

R_{11} is as defined above, preferably hydrogen, halo, C_1-C_4 alkyl, C_3-C_4 cycloalkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, cyano, nitro, OR_3 or NR_3R_4 ; more preferably hydrogen, halo or C_1-C_4 alkyl or $O-C_1-C_4$ alkyl, still more preferably hydrogen, methyl, O-methyl or halo, most preferably hydrogen, methyl, Cl, Br or F. In one embodiment, R_{11} is hydrogen. In another embodiment, R_{11} is methyl. In yet another embodiment, methyl is preferably further substituted by 1, 2 or 3 fluorines, preferably 3 fluorines.

In another embodiment, R_{11} is $-S(O)_jNR_4C(O)R_3$, $-C(O)NR_4S(O)_jR_6$, or $S(O)_jR_6$.

R_{12} is as defined above, preferably hydrogen, halo, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, cyano, nitro, azido; $NR_4SO_2R_6$; $SO_2NR_3R_4$; SO_2R_6 ; $C(O)NR_3R_4$; $C(O)OR_3$; OR_3 , NR_3R_4 or $-S(C_1-C_2 \text{ alkyl})$ substituted with 1 to 5 F, more preferably hydrogen, halo, nitro, C_1-C_4 alkyl, $O-C_1-C_4$ alkyl, SCF_3 , $SCHF_2$, SCH_2F , $SO_2NR_3R_4$ or $C(O)NR_3R_4$, still more preferably hydrogen, F, Cl, Br, I, nitro, methyl, ethyl, n-propyl, i-propyl, cyclopropyl, O-methyl, SCF_3 , $SCHF_2$, SCH_2F , $SO_2NR_3R_4$ or $C(O)NR_3R_4$, most preferably hydrogen, I, Cl, Br, SCF_3 , $SCHF_2$, SCH_2F , methyl or O-methyl. In one embodiment R_{12} is hydrogen. In another embodiment, R_{12} is methyl, SCF_3 , $SCHF_2$, SCH_2F or O-methyl, wherein methyl or O-methyl is preferably unsubstituted or further substituted by 1, 2 or 3 fluorines, preferably 2 or 3 fluorines. In preferred embodiments of R_{12} , R_3 and R_4 are independently C_1-C_6 alkyl, more preferably C_1-C_4 alkyl, optionally substituted by 1 or 2 alkyl amino, dialkyl amino, amino, O-alkyl, hydroxy, or R_3 and R_4 form together a cyclic ring with 1 or 2 N atoms and optionally an O atom, said ring being optionally substituted by 1 or 2 alkyl amino, amino, hydroxy or O-alkyl. Most preferably, R_{12} is Br or I.

In another embodiment, R_{12} is $-S(O)_jNR_4C(O)R_3$, $-C(O)NR_4S(O)_jR_6$, or $S(O)_jR_6$.

R_{13} is as defined above, preferably hydrogen, halo, C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, C_2 - C_4 alkenyl or C_2 - C_4 alkynyl, more preferably hydrogen, F, Cl or methyl, most preferably hydrogen or F. in one embodiment, R_{13} is hydrogen.

In another embodiment, R_{13} is $-S(O)_jNR_4C(O)R_3$, $-C(O)NR_4S(O)_jR_6$, or $S(O)_jR_6$.

5 R_{14} is as defined above, preferably hydrogen, halo, C_1 - C_4 alkyl, C_3 - C_4 cycloalkyl, C_2 - C_4 alkenyl or C_2 - C_4 alkynyl, more preferably hydrogen, F, Cl or methyl, most preferably hydrogen or F. In one embodiment, R_{14} is hydrogen.

In a further embodiment, R_{14} is $-S(O)_jNR_4C(O)R_3$, $-C(O)NR_4S(O)_jR_6$, or $S(O)_jR_6$.

10 In a particular preferred embodiment, at least one of R_1 , R_2 , R_9 , R_{11} , R_{12} , R_{13} and R_{14} is selected from $-S(O)_jNR_4C(O)R_3$, $-C(O)NR_4S(O)_jR_6$, and $S(O)_jR_6$.

As set forth above, the variants of each of R_1 , R_2 , R_9 to R_{14} and L may be substituted. In this case they can be substituted with 1 to 5, preferably 1 to 3, more preferably 1 or 2 groups independently selected from oxo, halogen, cyano, nitro, CF_3 , CHF_2 , CH_2F , OCF_3 , $OCHF_2$, OCH_2F , SCF_3 , $SCHF_2$, SCH_2F , azido, $NR_4SO_2R_6$, $SO_2NR_3R_4$, $C(O)R_3$, $C(O)OR_3$,
 15 $OC(O)R_3$, $NR_4C(O)OR_6$, $NR_4C(O)R_3$, $C(O)NR_3R_4$, NR_3R_4 , $NR_5C(O)NR_3R_4$, $NR_5C(NCN)NR_3R_4$, OR_3 , aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, preferably oxo, halogen, cyano, nitro, CF_3 , CHF_2 , CH_2F , OCF_3 , $OCHF_2$, OCH_2F , SCF_3 , $SCHF_2$, SCH_2F , azido, $NR_4SO_2R_6$, $SO_2NR_3R_4$, $C(O)R_3$, $C(O)OR_3$, $OC(O)R_3$, OR_3 , more preferably oxo, halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy or azido, most preferably halogen, cyano, nitro, CF_3 ,
 20 CHF_2 , CH_2F , OCF_3 , $OCHF_2$, OCH_2F , SCF_3 , $SCHF_2$, SCH_2F , OH, O-methyl, NH_2 or $N(methyl)_2$. When it is described that alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are substituted, this refers to any alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl as a group or sub-structure such as in cycloalkylalkyl,
 25 arylalkyl, heteroarylalkyl, heterocyclalkyl.

R_3 is as defined above, preferably hydrogen, trifluoromethyl, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 cycloalkylalkyl, more preferably hydrogen or C_1 - C_4 alkyl most preferably hydrogen, methyl or ethyl.

30 R_4 is as defined above, preferably hydrogen or C_1 - C_4 alkyl, more preferably hydrogen, methyl or ethyl.

In one preferred embodiment, R_3 and R_4 can be taken together with the atom to which they are attached to form a 4 to 7, preferably 5 or 6, membered heteroaryl or heterocyclic ring.

R₅ is as defined above, preferably hydrogen or C₁-C₄ alkyl, more preferably hydrogen, methyl or ethyl.

In one embodiment, R₄ and R₅ can be taken together with the atom to which they are attached to form a 4 to 7, preferably 5 or 6, membered carbocyclic, heteroaryl or

5 heterocyclic ring.

R₆ is as defined above, preferably trifluoromethyl, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkylalkyl, more preferably C₁-C₄ alkyl, most preferably methyl or ethyl.

As set forth above, the variants of each of R₃, R₄, R₅, R₆ or the rings formed by R₃ and R₄ and R₄ and R₅ may be substituted. In this case they can be substituted with 1 to 5, preferably 1 to 3, more preferably 1 or 2 groups independently selected from oxo, halogen, cyano, nitro, CF₃, CHF₂, CH₂F, OCF₃, OCHF₂, OCH₂F, azido, NR'SO₂R''', SO₂NR'', C(O)R', C(O)OR', OC(O)R', NR'C(O)OR''', NR'C(O)R'', C(O)NR'R'', SR''', S(O)R''', SO₂R', NR'R'', NR'C(O)NR''R'', NR'C(NCN)NR''R'', OR', aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, preferably oxo, halogen, cyano, nitro, CF₃, CHF₂, CH₂F, OCF₃, OCHF₂, OCH₂F, azido, NR'SO₂R''', SO₂NR'', C(O)R', C(O)OR', OC(O)R', NR'C(O)OR''', NR'C(O)R'', C(O)NR'R'', SR''', S(O)R''', SO₂R', NR'R'', NR'C(O)NR''R'', NR'C(NCN)NR''R'' or OR', more preferably oxo, halogen, cyano, nitro, CF₃, CHF₂, CH₂F, OCF₃, OCHF₂, OCH₂F, azido, SR''', S(O)R''', SO₂R', NR'R'' or OR'. In one embodiment, R₃ is preferably oxo, halogen, nitro, trifluoromethyl, OH, O-methyl, NH₂ or N(methyl)₂. When it is described that alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are substituted, this refers to any alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl as a group or sub-structure such as in cycloalkylalkyl, arylalkyl, heteroarylalkyl, heterocyclylalkyl.

25 R' is selected from hydrogen, C₁-C₄ alkyl, C₂-C₄ alkenyl, aryl and arylalkyl, preferably hydrogen or C₁-C₄ alkyl, more preferably hydrogen or methyl.

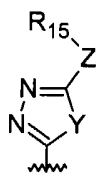
R'' is selected from hydrogen, C₁-C₄ alkyl, C₂-C₄ alkenyl, aryl and arylalkyl, preferably hydrogen or C₁-C₄ alkyl, more preferably hydrogen or methyl.

R''' is selected from hydrogen, C₁-C₄ alkyl, C₂-C₄ alkenyl, aryl and arylalkyl, preferably hydrogen or C₁-C₄ alkyl, more preferably hydrogen or methyl.

R'''' is selected from C₁-C₄ alkyl, C₁-C₄ alkenyl, aryl and arylalkyl, preferably C₁-C₄ alkyl, more preferably methyl.

Alternatively, any two of R', R'', R''' or R'''' can be taken together with the atom to which they are attached to form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring, each of which is optionally substituted with one to three groups independently selected from halogen, cyano; nitro, CF₃, CHF₂, CH₂F, OCF₃, OCHF₂, OCH₂F, azido, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, preferably halogen, cyano; nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy and azido.

W is as defined above, preferably heteroaryl containing 1, 2 or 3 heteroatoms, or heterocyclyl containing 1, 2, or 3 heteroatoms, more preferably heteroaryl, each of which is unsubstituted or substituted by 1 to 5, preferably 1 to 3, more preferably 1, substituents ZR₁₅, or W is -C(O)OR₁₅, -C(O)NR₄R₁₅, -C(O)NR₄OR₁₅, -C(O)(C₃-C₁₀ cycloalkyl), -C(O)(C₂-C₁₀ alkyl), -S(O)_jNR₄C(O)R₁₅, -C(O)NR₄S(O)_jR₆, S(O)_jNR₄R₁₅ or S(O)_jNR₄OR₁₅, more preferably W is heteroaryl containing 1, 2, or 3, specifically 2 or 3 N atoms, C(O)NR₄OR₁₅ or S(O)₂NR₄OR₁₅. R₄ and R₁₅ are as defined herein or may form together a 3 to 7 membered ring with 1 or 2 N atoms and optionally an O atom. When W is heteroaryl, it is preferably



where Z and R₁₅ are as defined above, preferably Z is a bond, NR₁₆, NR₁₆SO₂ or O, more preferably NR₁₆, wherein R₁₆ is as defined above, preferably hydrogen or C₁-C₄ alkyl, more preferably hydrogen. R₁₅ is preferably selected from hydrogen, C₁-C₄ alkyl, C₁-C₄ alkenyl, C₄-C₈ cycloalkylalkyl, each may contain 1 N atom optionally an O atom, where alkyl, alkenyl or cycloalkylalkyl may be further substituted by 1 or 2 of OH, O-C₁-C₄ alkyl or NR'R'', where R' and R'' are independently hydrogen or C₁-C₄ alkyl where R' and R'' may form a 3 to 7 membered ring with 1 or 2 N atoms and optionally an O atom.

Alternatively, R₁₆ and R₁₅ may form together a 4 to 10 membered cyclic ring with 1 or 2 N atoms and optionally an O atom, said ring being optionally substituted by 1 or 2 alkyl amino, amino, hydroxy or O-alkyl. More preferably R₁₅ is C₁-C₄ alkyl or C₁-C₄ alkenyl optionally substituted with 1 substituent OH, O-Me, NH₂, NHmethyl, NHethyl, N(methyl)₂ or N(ethyl)₂.

Y is O or NR', preferably O.

Alternatively, W is preferably $-C(O)OR_{15}$, $-C(O)NR_4R_{15}$, $-C(O)NR_4OR_{15}$, $S(O)_jNR_4R_{15}$ or $S(O)_jNR_4OR_{15}$, more preferably $-C(O)NR_4OR_{15}$ or $S(O)_2NR_4OR_{15}$. In these cases R_{15} is preferably as defined below.

In yet another preferred embodiment, W is $-C(O)NR_4S(O)_jR_6$, or $-S(O)_jNR_4C(O)R_{15}$,

5 whereby R_4 and R_{15} are as defined herein or may form together a 3 to 7 membered ring with 1 or 2 N atoms and optionally an O atom.

Z is as defined above, preferably a bond, NR_{16} , $NR_{16}SO_2$ or O, more preferably NR_{16} .

In another embodiment, Z is S.

R_{15} is as defined above, preferably hydrogen, C_1 - C_4 alkyl, C_1 - C_4 alkenyl, C_4 - C_6

10 cycloalkylalkyl, more preferably C_1 - C_4 alkyl or C_1 - C_4 alkenyl, yet more preferably C_1 - C_4 alkyl. Alkyl, alkenyl cycloalkyl, alkynyl, aryl, heteroaryl or heterocyclyl may be further substituted with 1 to 5, preferably 1, 2 or 3, more preferably 1 or 2, substituents selected from OR_3 or $NR'R''$ wherein R_3 is selected from hydrogen, C_1 - C_4 alkyl or C_1 - C_4 alkenyl, C_4 - C_6 cycloalkylalkyl, more preferably hydrogen, methyl or ethyl, and where R' and R''

15 are independently hydrogen or C_1 - C_4 alkyl, or R' and R'' may form a 3 to 7 membered ring with 1 or 2 N atoms and optionally an O atom, more preferably R' and R'' are independently hydrogen, methyl or ethyl, still more preferably both R' and R'' are methyl. Yet more preferably, R_{15} may be substituted by 1 or 2 of OH, O- C_1 - C_4 alkyl or $NR'R''$.

Most preferably, R_{15} is C_1 - C_4 alkyl or C_1 - C_4 alkenyl optionally substituted with 1

20 substituent OH, O-Me, NH_2 , $N(methyl)_2$ or $N(ethyl)_2$.

Regarding R_{15} , when it is described that alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are substituted, this refers to any alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl as a group or sub-structure such as in cycloalkylalkyl, arylalkyl, heteroarylalkyl, heterocyclalkyl.

25 R_{16} is as defined above, preferably hydrogen or C_1 - C_4 alkyl, more preferably hydrogen.

Alternatively, R_{16} and R_{15} may form together a 4 to 10, preferably 5 to 6, membered cyclic ring with 1 or 2 N atoms and optionally an O atom, said ring being optionally substituted by 1 or 2 alkyl amino, amino, hydroxy or O-alkyl.

m is as defined above, preferably 0, 1, 2 or 3, more preferably 0, 1 or 2, most preferably 1.

30 j is as defined above, preferably 2.

In the above, any of the preferred definitions for each variant can be combined with the preferred definition of the other variants.

The combinations as set forth in the claims are particularly preferred.

In the above and the following, the employed terms have independently the meaning as described below:

Aryl is an aromatic mono- or polycyclic moiety with preferably 6 to 20 carbon atoms which is preferably selected from phenyl, biphenyl, naphthyl, tetrahydronaphthyl, fluorenyl, indenyl or phenanthrenyl, more preferably phenyl or naphthyl.

Heteroaryl is an aromatic moiety having 6 to 20 carbon atoms with at least one ring containing a heteroatom selected from O, N and/or S, or heteroaryl is an aromatic ring containing at least one heteroatom selected from O, N and/or S and 1 to 6 carbon atoms.

Preferably, heteroaryl contains 1 to 4, more preferably 1, 2 or 3 heteroatoms selected from O and/or N and is preferably selected from pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinoliny, isoquinoliny, indolyl, benzimidazolyl, benzofuranyl, cinnoliny, indazolyl, indoliziny, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, triazolyl, thiadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazoliny, quinoxaliny, naphthyridinyl, and furopyridinyl. Spiro moieties are also included within the scope of this definition.

Preferred heteroaryl include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, isoxazolyl, oxazolyl, isothiazolyl, oxadiazolyl, triazolyl. Heteroaryl groups are optionally mono-, di-, or trisubstituted with, e.g., halogen, lower alkyl, lower alkoxy, haloalkyl, aryl, heteroaryl, and hydroxy.

Heterocyclyl is a saturated or unsaturated ring containing at least one heteroatom selected from O, N and/or S and 1 to 6 carbon atoms. Preferably, heterocyclyl contains 1 to 4, more preferably 1, 2 or 3 heteroatoms selected from O and/or N and is preferably selected from pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, homopiperazinyl, azetidiny, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indoliny, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinylimidazolinyl, imidazolidinyl, azetidin-2-one-1-yl, pyrrolidin-2-one-1-yl, piperid-2-one-1-yl, azepan-2-one-1-yl, 3-azabicyco[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, azabicyclo[2.2.2]hexanyl, 3H-indolyl and quinoliziny. Spiro moieties are also included within the scope of this definition.

Carbocyclyl is a monocyclic or polycyclic ring system of 3 to 20 carbon atoms which may be saturated, unsaturated or aromatic.

Alkyl is a saturated hydrocarbon moiety, namely straight chain or branched alkyl having 1 to 10, preferably 1 to 8 carbon atoms, more preferably 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl or heptyl.

Cycloalkyl is an alkyl ring having 3 to 10, preferably 3 to 8 carbon atoms, more preferably 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl.

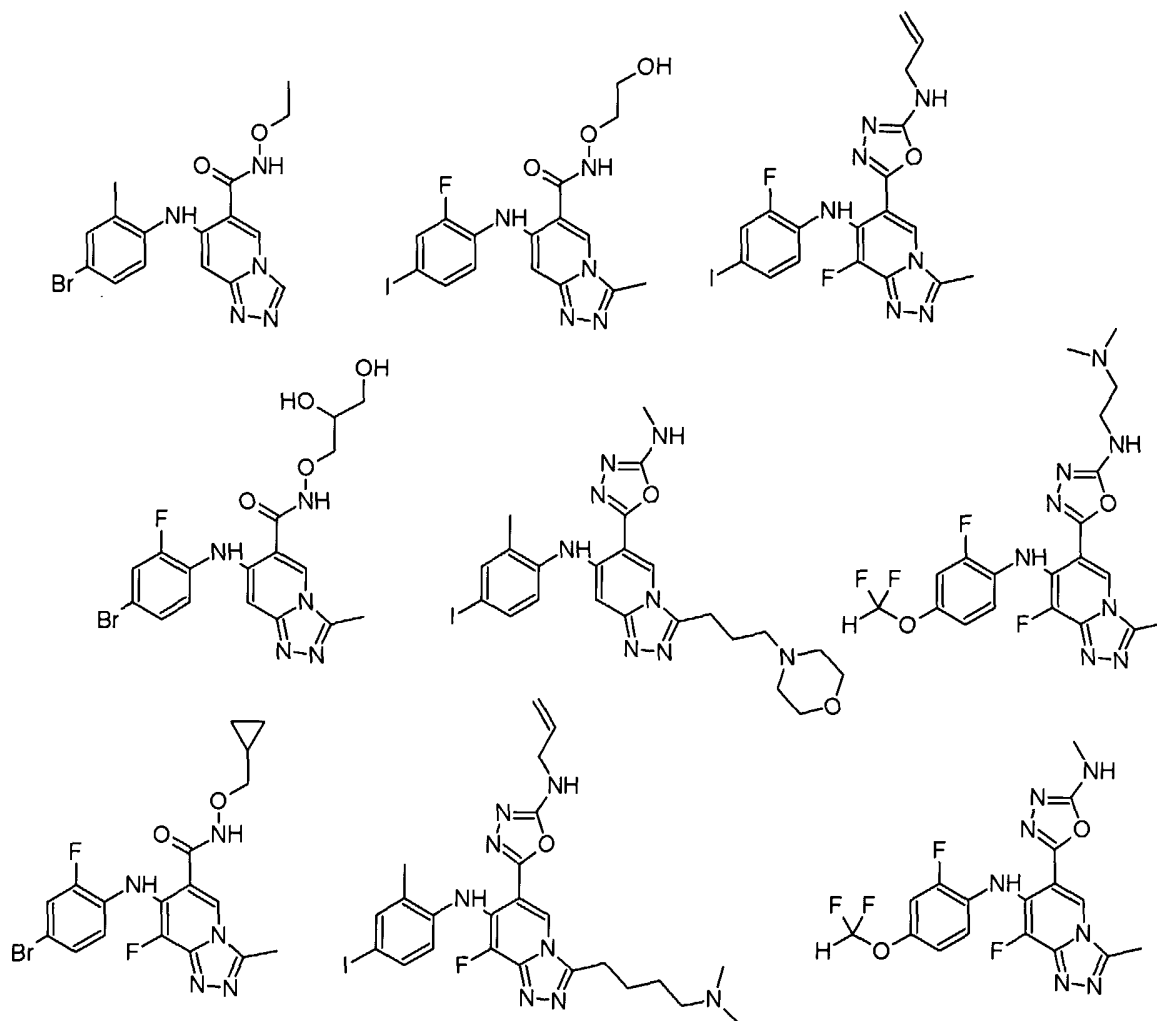
Alkenyl is an unsaturated hydrocarbon moiety with one or more double bonds, preferably one double bond, namely straight chain or branched alkenyl having 1 to 10, preferably 2 to 8 carbon atoms, more preferably 2 to 4 atoms, such as vinyl, allyl, methallyl, buten-2-yl, buten-3-yl, penten-2-yl, penten-3-yl, penten-4-yl, 3-methyl-but-3-enyl, 2-methyl-but-3-enyl, 1-methyl-but-3-enyl, hexenyl or heptenyl.

Alkynyl is an unsaturated hydrocarbon moiety with one or more triple bonds, preferably one triple bond, namely straight chain or branched alkynyl having 1 to 10, preferably 2 to 8 carbon atoms, more preferably 2 to 4 atoms, such as ethynyl, propynyl, butyn-2-yl, butyn-3-yl, pentyn-2-yl, pentyn-3-yl, pentyn-4-yl, 2-methyl-but-3-ynyl, 1-methyl-but-3-ynyl, hexynyl or heptynyl.

Halo or halogen is a halogen atom preferably selected from F, Cl, Br and I, preferably F, Cl and Br.

In the definitions cycloalkylalkyl, arylalkyl, heretoarylalkyl and heterocyclalkyl it is contemplated that cycloalkyl, aryl, heretoaryl and heterocycl are bonded via an alkylene moiety. This alkylene moiety may be a straight chain or branched chain group. Said alkylene moiety preferably has 1 to 6 carbon atoms. Examples thereof include methylene, ethylene, n-propylene, n-butylene, n-pentylene, n-hexylene, iso-propylene, sec.-butylene, tert.-butylene, 1,1-dimethyl propylene, 1,2-dimethyl propylene, 2,2-dimethyl propylene, 1,1-dimethyl butylene, 1,2-dimethyl butylene, 1,3-dimethyl butylene, 2,2-dimethyl butylene, 2,3-dimethyl butylene, 3,3-dimethyl butylene, 1-ethyl butylene, 2-ethyl butylene, 3-ethyl butylene, 1-n-propyl propylene, 2-n-propyl propylene, 1-iso-propyl propylene, 2-iso-propyl propylene, 1-methyl pentylene, 2-methyl pentylene, 3-methyl pentylene and 4-methyl pentylene. More preferably, said alkylene moiety has 1 to 3 carbon atoms, such as methylene, ethylene, n-propylene and iso-propylene. Most preferred is methylene.

Preferred embodiments of the compounds according to present invention are shown in scheme 1.



5 Scheme 1

The compounds of the present invention can be in the form of a prodrug compound.

"Prodrug compound" means a derivative that is converted into a compound according to the present invention by a reaction with an enzyme, gastric acid or the like under a physiological condition in the living body, e.g. by oxidation, reduction, hydrolysis or the like, each of which is carried out enzymatically. Examples of the prodrug are compounds, wherein the amino group in a compound of the present invention is acylated, alkylated or phosphorylated to form, e.g., eicosanoylamino, alanylamino, pivaloyloxymethylamino or wherein the hydroxyl group is acylated, alkylated, phosphorylated or converted into the borate, e.g. acetyloxy, palmitoyloxy, pivaloyloxy, succinyloxy, fumaryloxy, alanyloxy or wherein the carboxyl group is esterified or amidated. These compounds can be produced

from compounds of the present invention according to well-known methods. Other examples of the prodrug are compounds, wherein the carboxylate in a compound of the present invention is for example converted into an alkyl-, aryl-, choline-, amino, acyloxymethylester, linolenoyl-ester.

- 5 Metabolites of compounds of the present invention are also within the scope of the present invention.

Where tautomerism, like e.g. keto-enol tautomerism, of compounds of the present invention or their prodrugs may occur, the individual forms, like e.g. the keto and enol form, are claimed separately and together as mixtures in any ratio. Same applies for
10 stereoisomers, like e.g. enantiomers, cis/trans isomers, conformers and the like.

If desired, isomers can be separated by methods well known in the art, e.g. by liquid chromatography. Same applies for enantiomers by using e.g. chiral stationary phases. Additionally, enantiomers may be isolated by converting them into diastereomers, i.e. coupling with an enantiomerically pure auxiliary compound, subsequent separation of the
15 resulting diastereomers and cleavage of the auxiliary residue. Alternatively, any enantiomer of a compound of the present invention may be obtained from stereoselective synthesis using optically pure starting materials.

The compounds of the present invention can be in the form of a pharmaceutically acceptable salt or a solvate. The term "pharmaceutically acceptable salts" refers to salts
20 prepared from pharmaceutically acceptable non-toxic bases or acids, including inorganic bases or acids and organic bases or acids. In case the compounds of the present invention contain one or more acidic or basic groups, the invention also comprises their corresponding pharmaceutically or toxicologically acceptable salts, in particular their pharmaceutically utilizable salts. Thus, the compounds of the of the present invention
25 which contain acidic groups can be present on these groups and can be used according to the invention, for example, as alkali metal salts, alkaline earth metal salts or as ammonium salts. More precise examples of such salts include sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. Compounds of
30 the present invention which contain one or more basic groups, i.e. groups which can be protonated, can be present and can be used according to the invention in the form of their addition salts with inorganic or organic acids. Examples for suitable acids include hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, oxalic acid,

acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfaminic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid, and other acids known to the

5 person skilled in the art. If the compounds of the present invention simultaneously contain acidic and basic groups in the molecule, the invention also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions). The respective salts can be obtained by customary methods which are known to the person skilled in the art like, for example by contacting these with an organic or inorganic acid or base in a solvent or
10 dispersant, or by anion exchange or cation exchange with other salts. The present invention also includes all salts of the compounds of the present invention which, owing to low physiological compatibility, are not directly suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of pharmaceutically acceptable salts.

15 Furthermore, the present invention provides pharmaceutical compositions comprising a compound of the present invention, or a prodrug compound thereof, or a pharmaceutically acceptable salt or solvate thereof as active ingredient together with a pharmaceutically acceptable carrier.

"Pharmaceutical composition" means one or more active ingredients, and one or more
20 inert ingredients that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made
25 by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the present invention may additionally comprise one or more other compounds as active ingredients like one or more additional compounds of the present invention, or a prodrug compound or other MEK inhibitors.

30 The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently

presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

In one embodiment, said compounds and pharmaceutical composition are for the treatment of cancer such as brain, lung, squamous cell, bladder, gastric, pancreatic, breast, head, neck, renal, kidney, ovarian, prostate, colorectal, oesophageal, testicular, gynecological or thyroid cancer. In another embodiment, said pharmaceutical composition is for the treatment of a noncancerous hyperproliferative disorder such as benign hyperplasia of the skin (e.g., psoriasis), restenosis, or prostate (e.g. benign prostatic hypertrophy (BPH)).

The invention also relates to a compound or pharmaceutical composition for the treatment of pancreatitis or kidney disease (including proliferative glomerulonephritis and diabetes induced renal disease) or pain in a mammal which comprises a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof, and a pharmaceutically acceptable carrier.

The invention also relates to a compound or pharmaceutical composition for the prevention of blastocyte implantation in a mammal which comprises a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof, and a pharmaceutically acceptable carrier. The invention also relates to a compound or pharmaceutical composition for treating a disease related to vasculogenesis or angiogenesis in a mammal which comprises a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof, and a pharmaceutically acceptable carrier.

In one embodiment, said compound or pharmaceutical composition is for treating a disease selected from the group consisting of tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis, inflammatory bowel disease, atherosclerosis, skin diseases such as psoriasis, eczema, and sclerodema, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma, Kaposi's sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer.

The invention also relates to the use for treating a hyperproliferative disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof. In one embodiment, said use relates to the treatment of cancer such

as brain, lung, squamous cell, bladder, gastric, pancreatic, breast, head, neck, renal, kidney, ovarian, prostate, colorectal, oesophageal, testicular, gynecological or thyroid cancer. In another embodiment, said use relates to the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (e.g., psoriasis), restenosis, or prostate (e.g., benign prostatic hypertrophy (BPH)).

The invention also relates to a use for the treatment of a hyperproliferative disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof, in combination with an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, antimetabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzyme inhibitors, topoisomerase inhibitors, biological response modifiers, antihormones, angiogenesis inhibitors, and anti-androgens.

The invention also relates to a use of treating pancreatitis or kidney disease or pain in a mammal that comprises administering to said mammal a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof. The invention also relates to a use of preventing blastocyte implantation in a mammal that comprises administering to said mammal a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof.

The invention also relates to a use of treating diseases related to vasculogenesis or angiogenesis in a mammal that comprises administering to said mammal a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof. In one embodiment, said method is for treating a disease selected from the group consisting of tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis, atherosclerosis, inflammatory bowel disease, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma, Kaposi's sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer. Patients that can be treated with compounds of the present invention, or pharmaceutically acceptable salts, prodrugs and hydrates of said compounds, according to the methods of this invention include, for example, patients that have been diagnosed as having psoriasis, restenosis, atherosclerosis, BPH, lung cancer, bone cancer, CMML, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer,

ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, testicular, gynecologic tumors (e.g., uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's disease, cancer of the esophagus, cancer
5 of the small intestine, cancer of the endocrine system (e.g., cancer of the thyroid, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter (e.g., renal cell carcinoma, carcinoma of the renal pelvis), or neoplasms of the central nervous
10 system (e.g., primary CNS lymphoma, spinal axis tumors, brain stem gliomas or pituitary adenomas).

This invention also relates to a compound or pharmaceutical composition for inhibiting abnormal cell growth in a mammal which comprises an amount of a compound of the present invention, or a pharmaceutically acceptable salt or solvate or prodrug thereof, in
15 combination with an amount of a chemotherapeutic, wherein the amounts of the compound, salt, solvate, or prodrug, and of the chemotherapeutic are together effective in inhibiting abnormal cell growth. Many chemotherapeutics are presently known in the art. In one embodiment, the chemotherapeutic is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth
20 factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, and anti-androgens. This invention further relates to a method for inhibiting abnormal cell growth in a mammal or treating a hyperproliferative disorder which method comprises administering to the mammal an amount of a compound of the present invention, or a pharmaceutically
25 acceptable salt or solvate or prodrug thereof, in combination with radiation therapy, wherein the amounts of the compound, salt, solvate, or prodrug, is in combination with the radiation therapy effective in inhibiting abnormal cell growth or treating the hyperproliferative disorder in the mammal. Techniques for administering radiation therapy are known in the art, and these techniques can be used in the combination
30 therapy described herein. The administration of the compound of the invention in this combination therapy can be determined as described herein. It is believed that the compounds of the present invention can render abnormal cells more sensitive to treatment with radiation for purposes of killing and/or inhibiting the growth of such cells. Accordingly, this invention further relates to a method for sensitizing abnormal cells in a
35 mammal to treatment with radiation which comprises administering to the mammal an

amount of a compound of the present invention or pharmaceutically acceptable salt or solvate or prodrug thereof, which amount is effective is sensitizing abnormal cells to treatment with radiation. The amount of the compound, salt, or solvate in this method can be determined according to the means for ascertaining effective amounts of such compounds described herein. The invention also relates to a method of and to a pharmaceutical composition of inhibiting abnormal cell growth in a mammal which comprises an amount of a compound of the present invention, or a pharmaceutically acceptable salt or solvate thereof, a prodrug thereof, or an isotopically-labeled derivative thereof, and an amount of one or more substances selected from anti-angiogenesis agents, signal transduction inhibitors, and antiproliferative agents.

In practical use, the compounds of the present invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, hard and soft capsules and tablets, with the solid oral preparations being preferred over the liquid preparations.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin.

When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Compounds of the present invention may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dose of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like. Preferably compounds of the present invention are administered orally.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated. Such dosage may be ascertained readily by a person skilled in the art.

When treating or preventing cancer, inflammation or other proliferative diseases for which compounds of the present invention are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily

dosage of from about 0.1 milligram to about 100 milligram per kilogram of animal body weight, preferably given as a single daily dose or in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1.0 milligrams to about 1000 milligrams, preferably from about 1 milligram to about 50 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 milligrams to about 350 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

Some abbreviations that may appear in this application are as follows.

Abbreviations*Designation*

b	Broad peak
Boc	<i>tert.</i> -Butyloxycarbonyl
CDI	N,N-Carbonyldiimidazole
d	Doublet
DCM	Dichloromethane
dd	double doublet
DIPEA	N-Ethyldiisopropylamine
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HPLC	High pressure liquid chromatography
LiHMDS.	Lithium hexamethyldisilazide
NMR	Nuclear Magnetic Resonance
PG	Protecting group
PyBroP	Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
PyBOP	Benzotriazole-1-yl-oxy-trispyrrolidinophosphonium hexafluorophosphate
PPA	Polyphosphoric acid
q	Quartett
rt	Retention time
s	Singlet
tert	Tertiary-butyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofurane
TLC	Thin Layer Chromatography

The compounds of the present invention can be prepared according to the procedures of the following Schemes and Examples, using appropriate materials and are further

exemplified by the following specific examples. Moreover, by utilizing the procedures described herein, in conjunction with ordinary skills in the art, additional compounds of the present invention claimed herein can be readily prepared. The compounds illustrated in the examples are not, however, to be construed as forming the only genus that is

5 considered as the invention. The examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. The instant compounds are generally isolated in the form of their pharmaceutically acceptable salts, such as those

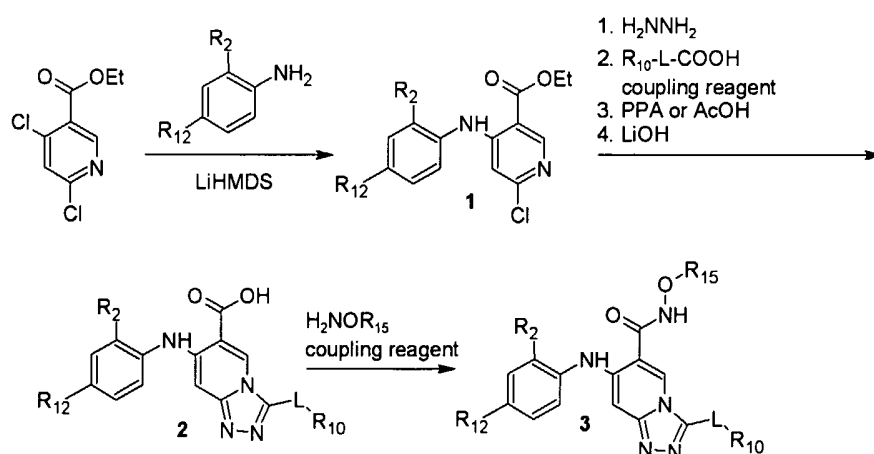
10 described above. The amine-free bases corresponding to the isolated salts can be generated by neutralization with a suitable base, such as aqueous sodium hydrogencarbonate, sodium carbonate, sodium hydroxide and potassium hydroxide, and extraction of the liberated amine-free base into an organic solvent, followed by evaporation. The amine-free base, isolated in this manner, can be further converted into

15 another pharmaceutically acceptable salt by dissolution in an organic solvent, followed by addition of the appropriate acid and subsequent evaporation, precipitation or crystallisation.

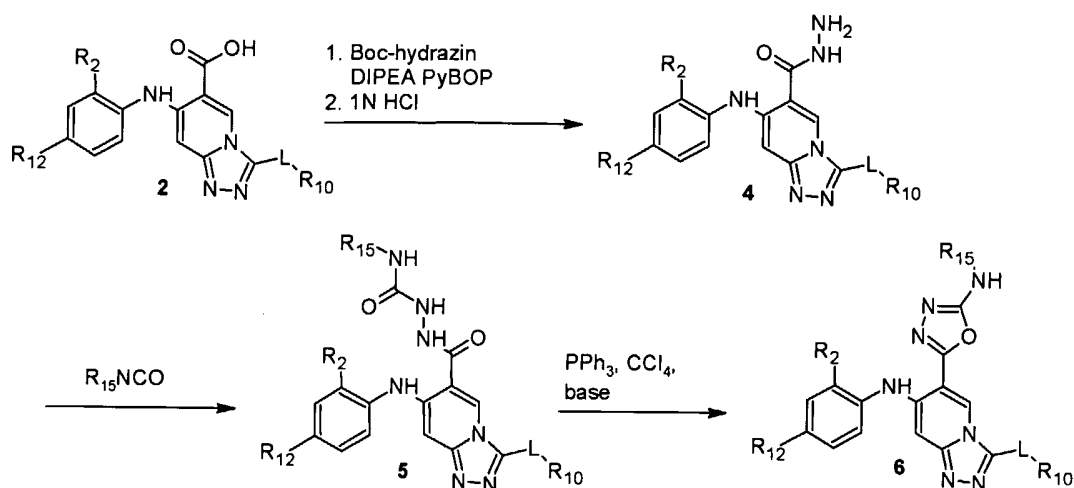
An illustration of the preparation of compounds of the present invention is shown in schemes 2 and 3. Unless otherwise indicated in the schemes, the variables have the

20 same meaning as described above.

The examples presented below are intended to illustrate particular embodiments of the invention.



Scheme 2



Scheme 3

As outlined in scheme2, ethyl 4,6-dichloronicotinate can be reacted with an appropriately substituted aniline in an inert solvent, preferable THF, by addition of a base, preferably but not limited to LiHMDS to yield substituted ethyl 6-chloro-4-arylamonicotinate **1**. Heating with hydrazine hydrate leads to an intermediate hydrazino compound which is acylated by coupling with an activated carboxylic acid building block. Cyclisation is achieved by heating in acidic solvents such as AcOH or PPA. The resulting triazolopyridine is saponified in the next step by heating with lithium hydroxide in a water-alcohol mixture to give triazolopyridine carboxylic acid **2**. The latter can be further derivatised by coupling with a substituted O-alkylhydroxylamine using a coupling reagent such as PyBro, PyBOP or DCC for example to give substituted hydroxamate **3**.

Scheme 3 illustrates the preparation of compounds of the present invention where W is heterocyclic. Triazolopyridine carboxylic acid **2** can be coupled with Boc-hydrazine by using a coupling reagent such as PyBOP or DCC for example and the Boc protecting group is then removed by treatment with an acid such as HCl. The resulting hydrazide **4** is further derivatised by reacting with an appropriately substituted isocyanate. Cyclisation can be achieved by heating with triphenyl phosphine and CCl_4 in a suitable solvent to give oxadiazole compound **6**.

Suitable anilines, carboxylic acids, O-alkyl hydroxylamines, and isocyanates are commercially available from Sigma-Aldrich Chemie GmbH, Munich, Germany or from Acros Organics, Belgium or from Fisher Scientific GmbH, 58239 Schwerte, Germany or can be routinely prepared by procedures described in "March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure", 5th Edition; John Wiley & Sons. O-[(4S)2,2-Dimethyl-[1,3]dioxolan-4-ylmethyl]-hydroxylamine and O-[(4R)2,2-dimethyl-[1,3]dioxolan-4-ylmethyl]-hydroxylamine are prepared according to a procedure described in

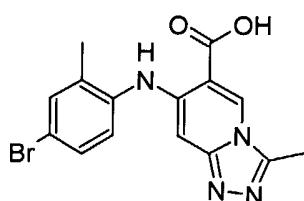
WO02/06213 A2. Ethyl 4,6-dichloronicotinate is synthesised in three steps from diethyl acetone dicarboxylate according to a literature procedure (DenHertog, Recl Trav Chim Pays-Bas **1946**, 65, 129-140).

Compounds with other variants in the position of W can be prepared by derivatizing the COOH group appropriately as known to the person skilled in the art as described in Theophil Eicher, Siegfried Hauptmann "The Chemistry of Heterocycles; Structures, Reactions, Synthesis and Application", 2nd edition, Wiley-VCH 2003. The introduction of alternative heterocyclic or heteroaryl groups is exemplified e.g. in WO 03/077855 and WO 01/05391.

Unless otherwise noted, all non-aqueous reactions were carried out either under an argon or nitrogen atmosphere with commercial dry solvents. Compounds were purified using flash column chromatography using Merck silica gel 60 (230-400 mesh), or by reverse phase preparative HPLC using a Reprosil-Pur ODS3, 5 µm, 20 x 125 mm column with Shimadzu LC8A-Pump and SPD-10Avp UV/Vis diode array detector. The ¹H-NMR spectra were recorded on a Varian VXR-S (300 MHz for ¹H-NMR) using d₆-dimethylsulfoxide or d₄-methanol as solvent; chemical shifts are reported in ppm relative to tetramethylsilane. Analytical LC/MS was performed using Reprosil-Pur ODS3, 5 µm, 1 x 60 mm columns at a flow rate of 250 µl/min, sample loop 2.5µl; retention times are given in minutes. Methods are: (I) runs on a LC10Advp-Pump (Shimadzu) with SPD-M10Avp UV/Vis diode array detector and QP2010 MS-detector in ESI+ modus with UV-detection at 214, 254 and 275 nm with a gradient of 15-95% acetonitrile (B) in water (A) (0.1% formic acid), 5 min. linear gradient; (II) idem but linear gradient 8min 1-30% B; (III) idem but linear gradient 8min 10-60% B; (IV) idem but linear gradient 8min 15-99% B; (V) idem but linear gradient 10min 5-95% B; (VI) idem but linear gradient 10min 10-95% B; (VII) idem but linear gradient 5min 10-90% B; (VIII) idem but linear gradient 5min 5-95% B.

Example 1

7-[(4-Bromo-2-methylphenyl)amino]-3-methyl[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid (2a)



Step A

Ethyl 4,6-dichloronicotinate (2.0g, 9.1mmol) and 4-bromo-2-methylaniline (1.7g, 9.1mmol) are dissolved in dry THF (20ml) under argon and the mixture is cooled to -78°C. A solution of LiHMDS (1.0M in THF, 32ml) is slowly added and the reaction mixture is allowed to warm to ambient temperature. After 18h the reaction is quenched by adding dilute hydrochloric acid (1.0M, 20.0ml) and the mixture is extracted with DCM (3x 60ml). The combined organic extracts are concentrated *in vacuo* and the crude material is purified by flash chromatography using silica gel and a gradient of 0-10% ethylacetate in cyclohexane as eluent to give pure ethyl 4-[(4-bromo-2-methylphenyl)amino]-6-chloronicotinate (**1a**) (900mg, 27% yield).

LC-MS method (I) rt 5.34 min; m/z 369, 371 [M+H]⁺, Br,Cl pattern.

¹H-NMR (300MHz, CDCl₃): δ = 1.42 (t, J = 7.3Hz, 3H), 2.21 (s, 3H), 4.39 (q, J = 7.3Hz, 2H), 6.50 (s, 1H), 7.11 (d, J = 8.1Hz, 1H), 7.35-7.41 (m, 1H), 7.44-7.47 (m, 1H), 8.76 (s, 1H), 9.59 (b, 1H)

Step B

Compound **1a** (500mg, 1.35mmol) is dissolved in dry dioxane (10ml), hydrazine hydrate (985μl, 20.3mmol) is added and the mixture is heated at 150°C with microwave irradiation for 30min. The volatiles are removed *in vacuo* and the crude ethyl 4-[(4-bromo-2-methylphenyl)amino]-6-hydrazinonicotinate is used in the next step.

LC-MS method (I) rt 2.26 min; m/z 365, 367 [M+H]⁺, Br pattern.

Step C

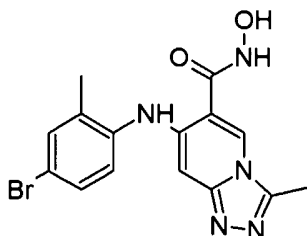
4-[(4-Bromo-2-methylphenyl)amino]-6-hydrazinonicotinate (crude from step B, ~1.35mmol) is dissolved in dry pyridine (8ml) and acetic anhydride (4ml) and the mixture is heated at 60°C for 20 min. The volatiles are removed *in vacuo*, acetic acid (5ml) and acetic anhydride (2.5ml) are added and the mixture is heated for 90min at 170°C with microwave irradiation. The volatiles are removed *in vacuo*, the residue is redissolved in THF (8ml), water (0.8ml) and LiOH (2.1mmol, 71mg) is added and the mixture is heated to 120°C with microwave irradiation for 20minutes. The volatiles are removed *in vacuo*, the residual material is adsorbed on flash silica and purified by flash chromatography using silica gel and a gradient of 0-10% methanol in DCM as eluent to give 361 mg (1.0 mmol, 74%yield for steps B and C) of pure 7-[(4-Bromo-2-methylphenyl)amino]-3-methyl[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid **2a**.

LC-MS method (V) rt 1.86 min; m/z 361, 363 [M+H]⁺, Br pattern.

$^1\text{H-NMR}$ (300MHz, DMSO-d_6): δ = 2.22 (s, 3H), 2.60 (s, 3H), 6.59 (s, 1H), 7.40-7.50 (m, 3H), 8.60 (s, 1H).

Example 2

7-[(4-Bromo-2-methylphenyl)amino]-N-hydroxy-3-methyl[1,2,4]triazolo[4,3-a]pyridine-6-carboxamide (3a)



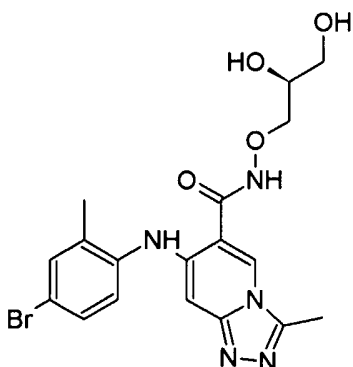
7-[(4-Bromo-2-methylphenyl)amino]-3-methyl[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid (**2a**) (50mg, 0.138mmol) is dissolved in dry DMF and hydroxylamine hydrochloride (19.2mg, 0.277mmol), PyBrOP (83.9mg, 0.180mmol) and DIPEA (96 μ l, 0.554mmol) is added. The mixture is stirred for 6h, the volatiles are evaporated and the crude material is purified by preparative HPLC to give 30 mg (0.080mmol, 58%yield) of pure **3a**.

LC-MS method (VII) rt 1.92 min; m/z 376, 378 $[\text{M}+\text{H}]^+$, Br pattern.

$^1\text{H-NMR}$ (400MHz, MeOH-d_4): δ = 2.28 (s, 3H), 2.75 (s, 3H), .6.42 (s, 1H), 7.30 (d, J = 8.6Hz, 1H), 7.50-7.55 (m, 1H), 7.63 (s, 1H), 8.79 (s, 1H).

Example 3

7-[(4-Bromo-2-methylphenyl)amino]-N-[(2S)-2,3-dihydroxypropyl]oxy]-3-methyl[1,2,4]triazolo[4,3-a]pyridine-6-carboxamide (3b)



Step A

7-[(4-Bromo-2-methylphenyl)amino]-3-methyl[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid (**2a**) (50mg, 0.138mmol) is dissolved in dry DMF (2.0ml) and DIPEA (96 μ l, 0.554mmol),

PyBroP (84mg, 0.180mmol) and O-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}hydroxylamine (27mg, 0.18mmol) are added. The mixture is stirred for 6h at ambient temperature and the volatiles are evaporated. DCM is added and the mixture is washed with saturated NaHCO₃ solution, dried (Na₂SO₄) and evaporated to give the crude hydroxamate which is used without purification in the next step.

LC-MS method (VII) rt 2.64 min; m/z 490, 492 [M+H]⁺, Br pattern.

Step B

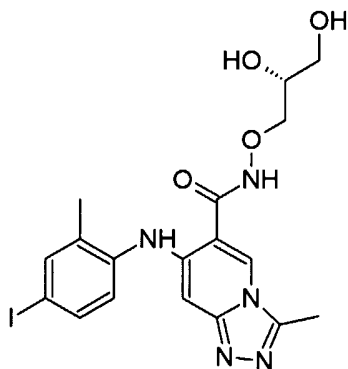
The crude material from step A is dissolved in MeOH (1.8ml) and water (0.2ml). Dowex50X8 resin (20mg) is added and the mixture is heated to 120°C with microwave irradiation for 20min, the solution is filtered and evaporated. The crude material is purified by preparative HPLC to give 18.6mg (41.4μmol, 30%yield, two steps) of pure hydroxamate **3b**.

LC-MS method (II) rt 6.01 min; m/z 450, 452 [M+H]⁺, Br pattern.

¹H-NMR (400MHz, MeOH-d₄): δ = 2.27 (s, 3H), 2.70 (s, 3H), 3.62-3.66 (m, 2H), 3.92-3.99 (m, 1H), 4.01-4.07 (m, 1H), 4.14-4.19 (m, 1H), 6.43 (s, 1H), 7.27 (d, J = 8.6Hz, 1H), 7.40-7.46 (m, 1H), 7.52 (s, 1H), 8.56 (s, 1H).

Example 4

7-[(4-Iodo-2-methylphenyl)amino]-N-[[[(2R)-2,3-dihydroxypropyl]oxy]-3-methyl[1,2,4]triazolo[4,3-a]pyridine-6-carboxamide (3c)



Step A

Ethyl 4,6-dichloronicotinate (**1**) (3.0g, 14mmol) and 4-iodo-2-methylaniline (3.2g, 14mmol) are dissolved in dry THF (20ml) under argon and the mixture is cooled to -78°C. A solution of LiHMDS (1.0M in THF, 48ml) is slowly added and the reaction mixture is allowed to warm to ambient temperature. The reaction is quenched after 20h by adding dilute hydrochloric acid (1.0M, 20.0ml), the volatiles are evaporated and the residue is extracted with DCM (3x 60ml). The combined organic extracts are concentrated *in vacuo* and the crude material is purified

by flash chromatography using silica gel and a gradient of 0-10% ethylacetate in cyclohexane as eluent to give pure ethyl 4-[(4-iodo-2-methylphenyl)amino]-6-chloronicotinate (700mg, 12% yield).

LC-MS method (VIII) rt 5.64 min; m/z 417 [M+H]⁺, CI pattern.

- 5 ¹H-NMR (400MHz, DMSO-d₆): δ = 1.33 (t, J = 7.1Hz, 3H), 2.13 (s, 3H), 4.35 (q, J = 7.1Hz, 2H), 6.41 (s, 1H), 7.12 (d, J = 8.6Hz, 1H), 7.63 (d, J = 8.1Hz, 1H), 7.76 (s, 1H), 8.65 (s, 1H), 9.52 (b, 1H).

Step B

- 10 4-[(4-iodo-2-methylphenyl)amino]-6-chloronicotinate (350mg, 0.84mmol) is dissolved in dry dioxane (7ml), hydrazine hydrate (611μl, 12.6mmol) is added and the mixture is heated at 150°C with microwave irradiation for 30min. The volatiles are removed *in vacuo* and the crude ethyl 4-[(4-iodo-2-methylphenyl)amino]-6-hydrazinonicotinate is directly used in the next step.

LC-MS method (VII) rt 2.68 min; m/z 413 [M+H]⁺.

- 15 **Step C**

- 4-[(4-iodo-2-methylphenyl)amino]-6-hydrazinonicotinate (crude from step B, ~0.84mmol) is dissolved in dry pyridine (8ml) and acetic anhydride (4ml) and the mixture is heated at 70°C for 20 min with microwave irradiation. The volatiles are removed *in vacuo*, acetic acid (3ml) and acetic anhydride (1.5ml) are added and the mixture is heated for 90min at 170°C with
20 microwave irradiation. The volatiles are removed *in vacuo* and the crude material is purified by flash-chomatography using silica gel and 5% methanol in DCM as eluent to give 130mg (0.30mmol, 35%yield for steps B and C) ethyl 7-[(4-iodo-2-methylphenyl)amino]-3-methyl[1,2,4]triazolo[4,3-a]pyridine-6-carboxylate.

LC-MS method (VII) rt 2.96 min; m/z 437 [M+H]⁺.

- 25 **Step D**

- Ethyl 7-[(4-iodo-2-methylphenyl)amino]-3-methyl[1,2,4]triazolo[4,3-a]pyridine-6-carboxylate (130mg, 0.298mmol) is dissolved in THF (6ml), water (1ml) and LiOH hydrate (68mg, 1.62mmol) are added and the mixture is heated for 30 min at 120°C with microwave irradiation. Hydrochloric acid (1N in dioxane, 4ml) is added and the volatiles are removed
30 under reduced pressure. The residue is partitioned between DCM and water, the organic phase is dried (Na₂SO₄) and evaporated to give crude 7-[(4-iodo-2-methylphenyl)amino]-3-methyl[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid.

LC-MS method (VII) rt 2.60 min; m/z 409 [M+H]⁺.

Step E

The crude carboxylic acid from step D (~0.27mmol) is dissolved in dry DMF, ByBrOP (162mg, 0.348mmol), DIPEA (138mg, 1.07mmol) and O-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}hydroxylamine (51mg, 0.35mmol) are added and the mixture is stirred at 50°C over
 5 night. The volatiles are evaporated, DCM is added and washed with pH7-phosphate buffer and brine, dried (Na₂SO₄) and evaporated. The residue is dissolved in methanol (2.7ml) and water (0.3ml) and Dowex50X8 resin (18mg) is added. The mixture is heated at 120°C for 40min with microwave irradiation, filtered and evaporated. The crude product is purified by preparative HPLC to yield 30mg of hydroxamate **3c**.

Assay

The activity of the compounds of the present invention may be determined by the following procedure: Inhibition of human MEK1 kinase activity was monitored with a homogenous, fluorescence based assay. The assay uses time resolved fluorescence resonance energy transfer to probe for phosphorylation of ERK1 by MEK1. The assay is carried out in low
 15 volume 96 well microtiterplates. In a total volume of 15 µl, compounds are incubated with 100nM MEK1, 15 µM ATP, 300nM ERK2 employing a buffer containing 20mM TRIS/HCl, 10 mM MgCl₂, 100 µM NaVO₄, 1 mM DTT, and 0.005% Tween 20 (pH 7.4). After two hours, 5 nM Europium-anti-PY20 (Perkin Elmer) and 50nM Anti-GST-Allophycocyanin (CisBio) in buffer containing 50mM EDTA and 0,05% BSA are added and the reaction incubated for one
 20 hour in the dark. Time-resolved fluorescence is measured using a LJI-Analyst (Molecular Devices) with an excitation wavelength of 340 nm and an emission wavelength of 665 nm. The final concentration of DMSO is 2 %. To assess the inhibitory potential of the compounds, IC₅₀-values were determined.

In this assay compounds of the invention exhibited IC₅₀s within certain ranges. The following
 25 compounds exemplify such activity with "+" meaning 1µM < IC₅₀ ≤ 10µM and "++" IC₅₀ ≤ 1µM

Table 1: Inhibition of MEK

Compound #	Activity
2a	+
3a	++
3b	+
3c	++

Assay 2: Tumor cell proliferation assays (ATP Lite)

Murine colon C26, human melanoma A375 and human melanoma Mel5 cells were plated in 96 well Corning white plates (1500 cells/well for C26, and 2000 cells/well for A375, and MiaPaCa-2) and cultured overnight at 37°C in 5% CO₂. Inhibitors were serially diluted in 100 % DMSO and subsequently added to cells to reach a final concentration of 0.25% DMSO. The cells were incubated for 4 days in the presence of test compounds in cell growth media (DMEM with 10% fetal bovine serum, 2mM glutamine for C26, and MiaPaCa-2, and RPMI with 10% fetal bovine serum, 2mM glutamine for A375). Cell proliferation was quantitated using the ATP lite cell proliferation kit (Packard). Inhibition of cell proliferation is shown in Table 2. Columns 2-4 show the concentration of compounds required to induce 50% cell death (IC₅₀ in μ M) of human endometriotic cells. With "+" meaning $100\mu\text{M} < \text{IC}_{50} \leq 10\mu\text{M}$ and "++" $\text{IC}_{50} \leq 1\mu\text{M}$ and "n.d." means not determined.

Assay 3: Microsomal stability assay

Compounds were tested on their stability in human, rat and mouse liver microsomal preparations (HLM, RLM and MLM respectively). At a final concentration of 3 μ M, compounds were incubated at 37°C with 0.5 mg/ml human, rat or mouse liver microsomes in a buffer containing 50 mM phosphate, pH 7.4 and 2 mM NADPH. Pooled human liver microsomes or pooled male rat liver microsomes (Sprague Dawley) were obtained from NatuTec (Frankfurt, Germany). Incubations without NADPH served as negative controls. Reactions were stopped after 0, 15, 30, 45 or 60 min by the addition of acetonitrile and microsomes were pelleted by centrifugation (10 min at 6200 x g). Supernatants were analyzed by HPLC regarding the concentration of mother compound. Finally, the half-life of compounds in the regarding microsomal preparation was calculated. Results are shown in Table 2. Wherein "+" means $t_{1/2}$ of 1-30 min, "++" means $t_{1/2}$ of 31-120 min and "+++" means $t_{1/2}$ of >120 min and "n.d." means not determined.

Assay 4: Caco-2 permeability assay

Caco-2 cells obtained from the ATCC at passage number 27 are used. Cells (passage number 40-60) were seeded on to Millipore Multiscreen Caco-2 plates or Falcon HTS inserts at 1×10^5 cells/cm². Cells were cultured for 20 days in DMEM and media was changed every two or three days. On day 20 the permeability study was performed.

Permeability was studied by applying compound to the apical surface of cell monolayers and measuring compound permeation into the basolateral compartment. The experiment

was also performed in the reverse direction (B-A) to investigate active transport. Hanks Balanced Salt Solution (HBSS) pH 7.4 buffer with 25mM HEPES and 10mM glucose at 37°C was used as the medium in permeability studies. Incubations were carried out in an atmosphere of 5% CO₂ with a relative humidity of 95%.

- 5 The monolayers were prepared by rinsing both basolateral and apical surfaces twice with HBSS at 37°C. Cells were then incubated with HBSS in both apical and basolateral compartments for 40 minutes to stabilize physiological parameters.

- HBSS was then removed from the apical compartment and replaced with test compound dosing solutions. The solutions were made by diluting 10mM DMSO concentrates with
10 HBSS to give a final test compound concentration of 10µM (final DMSO concentration adjusted to 1%). The fluorescent integrity marker lucifer yellow was also included in the dosing solution. Analytical standards were made from dosing solutions. Test compound permeability was assessed in duplicate. On each plate compounds of known permeability characteristics were run as controls.

- 15 The apical compartment inserts were then placed into 'companion' plates containing fresh HBSS. For basolateral to apical (B-A) experiments the experiment was initiated by replacing buffer in the inserts then placing them in companion plates containing dosing solutions. At 120 minutes the companion plate was removed and apical and basolateral samples diluted for analysis by LC-MS/MS (the donor compartment was also sampled to
20 permit determination of starting concentration after non-specific binding has occurred).

Analysis

- The integrity of the monolayers throughout the experiment is checked by monitoring lucifer yellow permeation using fluorimetric analysis. Lucifer yellow permeation was low if monolayers have not been damaged. Test and control compounds were quantified by
25 LC-MS/MS cassette analysis using a 5-point calibration with appropriate dilution of the samples. Should lucifer yellow Papps were above QC limits in more than one well per test compound, the compound was re-tested.

The permeability coefficient for each compound (P_{app}) was calculated from the following equation:

30
$$P_{app} = [dQ/dt]/[C_0 \times A]$$

Whereby dQ/dt is the rate of permeation of the drug across the cells, C_0 is the donor compartment concentration at time zero and A is the area of the cell monolayer. C_0 is obtained from analysis of the donor compartment at the end of the incubation period.

Test compounds were grouped into low, medium or high absorption potential based on comparison with control compounds, which have known human absorption.

In addition, permeation was studied in both directions across the cells, and an asymmetry index was reported from mean A-B and B-A data. This was derived from:

$$5 \quad P_{\text{app (B-A)}}/P_{\text{app (A-B)}}$$

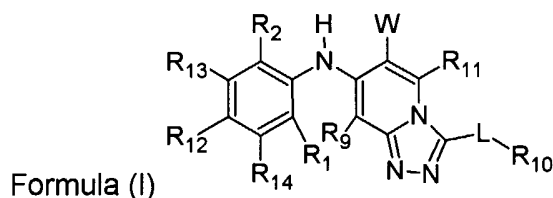
Results are shown in Table 2. Wherein "+" means a caco A-B and caco B-A value of 1-10 and "++" means a caco A-B and caco B-A value of 11-100 and "n.d." means not determined.

Table 2: Results of inhibition of tumor cell proliferation and microsomal stability

Compound No.	C26 cells IC ₅₀ [uM]	MeI5 cells IC ₅₀ [uM]	A375 cells IC ₅₀ [uM]	HLM t _{1/2} [min]	RLM t _{1/2} [min]	Caco A-B [10 ⁻⁶ cm/s]	Caco B-A [10 ⁻⁶ cm/s]
2a	+	+	+	n.d.	n.d.	n.d.	n.d.
3a	+	+	+	n.d.	n.d.	n.d.	n.d.
3b	+	+	+	+++	+++	+	+

Claims

1. A compound of formula (I),



a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein:

10 R₁, R₂, R₉, R₁₁, R₁₂, R₁₃ and R₁₄ are independently selected from hydrogen, halogen, cyano, nitro, azido, -OR₃, -C(O)R₃, -C(O)OR₃, -NR₄C(O)OR₆, -OC(O)R₃, -NR₄S(O)_jR₆, -S(O)_jNR₃R₄, -S(O)_jNR₄C(O)R₃, -C(O)NR₄S(O)_jR₆, S(O)_jR₆, -NR₄C(O)R₃, -C(O)NR₃R₄, -NR₅C(O)NR₃R₄, -NR₅C(NCN)NR₃R₄, -NR₃R₄ and C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkylalkyl, -S(O)_j(C₁-C₆ alkyl), -S(O)_j(CR₄R₅)_m-aryl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, -O(CR₄R₅)_m-aryl, -NR₄(CR₄R₅)_m-aryl, -O(CR₄R₅)_m-heteroaryl, -NR₄(CR₄R₅)_m-heteroaryl, -O(CR₄R₅)_m-heterocyclyl, -NR₄(CR₄R₅)_m-heterocyclyl, and -S(C₁-C₂ alkyl) substituted with 1 to 5 F, where each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is substituted or unsubstituted;

20 R₁₀ is selected from hydrogen, -OR₃, -C(O)R₃, -C(O)OR₃, -NR₄C(O)OR₆, -OC(O)R₃, -NR₄S(O)_jR₆, -S(O)_jNR₃R₄, -S(O)_jNR₄C(O)R₃, -C(O)NR₄S(O)_jR₆, S(O)_jR₆, -NR₄C(O)R₃, -C(O)NR₃R₄, -NR₅C(O)NR₃R₄, -NR₅C(NCN)NR₃R₄, -NR₃R₄; -S(O)_j(C₁-C₆ alkyl), -S(O)_j(CR₄R₅)_m-aryl, -O(CR₄R₅)_m-aryl, -NR₄(CR₄R₅)_m-aryl, -O(CR₄R₅)_m-heteroaryl, -NR₄(CR₄R₅)_m-heteroaryl, -O(CR₄R₅)_m-heterocyclyl, -NR₄(CR₄R₅)_m-heterocyclyl, and -S(C₁-C₂ alkyl) substituted with 1 to 5 F, where each, aryl, heteroaryl and heterocyclyl is substituted or unsubstituted;

25 L is selected from a bond, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, where each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is unsubstituted or substituted;

R₃ is selected from hydrogen, trifluoromethyl, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, where each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is substituted or unsubstituted;

- 5 R₄ is selected from hydrogen or C₁-C₆ alkyl whereby alkyl may be substituted or unsubstituted; or

R₃ and R₄ can be taken together with the atom to which they are attached to form a 4 to 10 membered heteroaryl or heterocyclic ring, each of which is substituted or unsubstituted;

- 10 R₅ is selected from hydrogen or C₁-C₆ alkyl whereby alkyl may be substituted or unsubstituted; or

R₄ and R₅ can be taken together with the atom to which they are attached to form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring, each of which is substituted or unsubstituted;

- 15 R₆ is selected from trifluoromethyl, C₁-C₁₀ alkyl, C₃-C₁₀ cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, where each alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl substituted or unsubstituted;

W is selected from heteroaryl containing 1-4 heteroatoms or heterocyclyl containing 1-4 heteroatoms each of which is unsubstituted or substituted by 1 to 5 substituents

- 20 ZR₁₅, or W is -C(O)OR₁₅, -C(O)NR₄R₁₅, -C(O)NR₄OR₁₅, -C(O)(C₃-C₁₀ cycloalkyl), -C(O)(C₂-C₁₀ alkyl), -C(O)(aryl), -C(O)(heteroaryl), -C(O)(heterocyclyl), -S(O)_jNR₄R₁₅, -S(O)_jNR₄OR₁₅, -S(O)_jNR₄C(O)R₁₅, or -C(O)NR₄S(O)_jR₆, whereby R₄ and R₁₅ are as defined herein or may form together a 3 to 7 membered ring with 1 or 2 N atoms and optionally an O atom,

- 25 Z is a bond, NR₁₆, O, NR₁₆SO₂ or S,

R₁₅ is independently selected from hydrogen, trifluoromethyl, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, where each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is substituted or unsubstituted;

- 30 R₁₆ is selected from hydrogen or C₁-C₁₀ alkyl, or R₁₅ and R₁₆ form together a 4 to 10 membered cyclic ring with 1 or 2 N atoms and optionally an O atom, said ring being substituted or unsubstituted;

m is 0, 1, 2, 3, 4 or 5 ;and

j is 1 or 2.

2. The compound of Formula (I) according to claim 1 wherein

5 R₁, R₂, R₉, R₁₁ are selected independently from hydrogen, halo, C₁-C₄ alkyl, C₃-C₄ cycloalkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, cyano, nitro, OR₃ or NR₃R₄ where each alkyl, alkenyl, alkynyl, cycloalkyl is optionally substituted with one to five halogens;

R₁₀ is selected from hydrogen, -OR₃, -NR₄C(O)R₃, -C(O)NR₃R₄, -NR₃R₄;

L is selected from a bond or C₁-C₅ alkyl;

10 R₁₂ is selected independently from hydrogen, halo, C₁-C₁₀ alkyl, C₃-C₁₀ cycloalkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, cyano, nitro, azido; NR₄SO₂R₆; SO₂NR₃R₄; SO₂R₆; C(O)NR₃R₄; -S(O)_jNR₄C(O)R₃, -C(O)NR₄S(O)_jR₆, OR₃, NR₃R₄ or -S(C₁-C₂ alkyl) substituted with 1 to 5 F, where each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is substituted or unsubstituted;

15 R₁₃ and R₁₄ are selected independently from H, F, Cl and C₁-C₄ alkyl, C₃-C₄ cycloalkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl where each alkyl, alkenyl, cycloalkyl, alkynyl is optionally further substituted with one to five halogens;

W is selected from heteroaryl containing 1-4 heteroatoms, heterocyclyl containing 1-4 heteroatoms each of which is unsubstituted or substituted by 1 to 3 substituents

20 ZR₁₅, or W is -C(O)OR₁₅, -C(O)NR₄R₁₅, -C(O)NR₄OR₁₅, -C(O)(C₃-C₁₀ cycloalkyl), -C(O)(C₂-C₁₀ alkyl), -S(O)_jNR₄C(O)R₁₅, -C(O)NR₄S(O)_jR₆, S(O)_jN, NR₄R₁₅ or S(O)_jNR₄OR₁₅;

Z is selected from NR₁₆, NR₁₆SO₂ or O;

25 R₁₅ is selected from hydrogen, C₁-C₄ alkyl, C₁-C₄ alkenyl, C₄-C₆ cycloalkylalkyl, where alkyl or alkenyl may be further substituted by 1 or 2 of OH, O-C₁-C₄ alkyl or NR'R'';

R₁₆ is selected from hydrogen or C₁-C₄ alkyl;

R' and R'' are each independently selected from hydrogen, C₁-C₄ alkyl, C₂-C₄ alkenyl, aryl and arylalkyl.

30 3. The compound of Formula (I) according to claim 1 or 2 wherein

R_1 is selected independently from H and F;

R_2 is selected independently from F, Cl, Me, where the methyl group is optionally substituted with one to three fluorines;

R_9 is selected independently from H, F, Cl;

- 5 R_{10} is selected from hydrogen, $-OR_3$, $-NR_3R_4$, wherein R_3 and R_4 are independently C_1 - C_6 alkyl, optionally substituted by 1 or 2 alkyl amino or O-alkyl, or R_3 and R_4 form together a cyclic ring with 1 or 2 N atoms and optionally an O atom, said ring being optionally substituted by 1 or 2 alkyl amino or O-alkyl

L is selected from a bond, methylene, ethylene, n-propylene or n-butylene;

- 10 R_{11} is selected independently from H, F, Cl, Br, Me, OMe, where the methyl groups are optionally substituted with one to three fluorines;

R_{12} is selected independently from H, F, Cl, Br, I, nitro, methyl, ethyl, n-propyl, i-propyl, cyclopropyl, SCF_3 , $SCHF_2$, SCH_2F , $SO_2NR_3R_4$ or $C(O)NR_3R_4$ or OMe, where the methyl groups are optionally substituted with one to three fluorines, wherein R_3 and

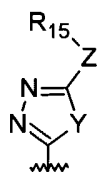
15 R_4 are independently C_1 - C_6 alkyl, optionally substituted by 1 or 2 alkyl amino or O-alkyl, or R_3 and R_4 form together a cyclic ring with 1 or 2 N atoms and optionally an O atom, said ring being optionally substituted by 1 or 2 alkyl amino or O-alkyl;

R_{13} is selected independently from H and F;

R_{14} is selected independently from H and F;

- 20 W is selected from $-C(O)NR_4OR_{15}$ or $SO_2NR_4OR_{15}$;

or W is



wherein

Z is NR_{16} ;

- 25 R_{15} is C_1 - C_4 alkyl or C_1 - C_4 alkenyl optionally substituted with 1 to 3 substituents OH, OMe, NH_2 , $N(methyl)_2$, NHmethyl, NHethyl or $N(ethyl)_2$;

R_{16} is hydrogen or C_1 - C_4 alkyl, or R_{16} and R_{15} form together a 4 to 10 membered ring with 1 or 2 N atoms and optionally an O atom, said ring being optionally substituted by 1 or 2 alkyl amino, amino, hydroxy or O-alkyl.

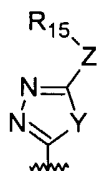
Y is O, S or NR' .

5

4. The compound of Formula (I) according to any of claims 1 to 3 wherein

W is selected from $-C(O)NR_4OR_{15}$ or $SO_2NR_4OR_{15}$,

or W is



10

wherein

R_4 is hydrogen;

Z is NH,

R_{15} is selected from C_1 - C_4 alkyl or C_1 - C_4 alkenyl that may be further substituted by 1 or 2 of OH, O- C_1 - C_4 alkyl or $NR'R''$,

15

R' and R'' are independently hydrogen, methyl or ethyl; and

Y is O.

5. The compound of Formula (I) according to any of claims 1 to 4

wherein LR_{10} are together methyl or hydrogen.

20

6. The compound of any of claims 1 to 5 for use as a medicament.

7. Use of the compound according to any of claims 1 to 5, for the preparation of a medicament for the treatment of hyperproliferative diseases or disorders mediated by aberrant proliferation, including cancer.

25

8. Use of the compound of any of claims 1 to 5 for the preparation of a medicament for the treatment of hyperproliferative diseases related to the hyperactivity of MEK as well as diseases modulated by the MEK cascade in mammals.
- 5 9. Use according to claim 8 for the treatment of diseases selected from the group consisting of cancer, inflammation, pancreatitis or kidney disease, pain, benign hyperplasia of the skin, restenosis, prostate, diseases related to vasculogenesis or angiogenesis, tumor angiogenesis, skin diseases selected from psoriasis, eczema, and sclerodema, diabetes, diabetic retinopathy, retinopathy of prematurity, age-
10 related macular degeneration, hemangioma, glioma, melanoma and Kaposi's sarcoma.
10. Use according to claim 8 or 9 for the treatment of cancer or inflammation.
- 15 11. Use according to any of claims 8 to 10 for the treatment of cancer selected from the group consisting of ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer; or inflammation selected from the group consisting of rheumatoid arthritis, inflammatory bowel disease, atherosclerosis.
- 20 12. A pharmaceutical composition which comprises a compound of any of claims 1 to 5 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/012855

A. CLASSIFICATION OF SUBJECT MATTER

C07D471/04 A61K31/435 A61P35/00
//(C07D471/04,249:00,221:00)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K

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

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

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/077855 A (ARRAY BIOPHARMA, INC; WALLACE, ELI, M; LYSSIKATOS, JOSEPH, P; HURLEY,) 25 September 2003 (2003-09-25) the whole document	1-12
A	WO 03/077914 A (ARRAY BIOPHARMA, INC; WALLACE, ELI, M; LYSSIKATOS, JOSEPH, P; HURLEY,) 25 September 2003 (2003-09-25) the whole document	1-12
A	WO 99/01421 A (WARNER-LAMBERT COMPANY; BARRETT, STEPHEN, DOUGLAS; BRIDGES, ALEXANDER,) 14 January 1999 (1999-01-14) the whole document	1-12

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

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O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

g document member of the same patent family

Date of the actual completion of the international search

24 February 2006

Date of mailing of the international search report

10/03/2006

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2005/012855

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