HETEROCYCLE-SUBSTITUTED CYCLIC UREA DERIVATIVES, PREPARATION THEREOF AND PHARMACEUTICAL USE THEREOF AS KINASE INHIBITORS

The present invention relates to novel cyclic urea derivatives, to a process for preparing them, to their use as medicinal products, to pharmaceutical compositions containing them and to the pharmaceutical use of such derivatives for preventing and treating complaints that may be modulated by inhibiting the activity of protein kinases.

The present invention relates to novel cyclic urea derivatives that have inhibitory effects on protein kinases.

The products of the present invention may thus be used especially for preventing or treating complaints capable of being modulated by inhibiting the activity of protein kinases.

The inhibition and regulation of protein kinases especially constitute a powerful new mechanism of action for treating a large number of solid tumours.
Such complaints that the products of the present patent application can treat are thus most particularly solid tumours.

Such protein kinases belong especially to the following group: IGF1, Raf, EGF, PDGF, VEGF, Tie2, KDR, Flt1-3, FAK, Src, Abl, cKit, cdk1-9, Aurora1-2, cdc7, Akt, Pdk, S6K, Jnk, IR, FLK-1, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, PLK, Pyk2, CDK7, CDK2 et EGFR.

Such protein kinases belong more especially to the following group: IGF1, cdc7, Aurora1-2, Src, Jnk, FAK, KDR, IR, Tie2, CDK7, CDK2 et EGFR.

The protein kinase IGF1-R (Insulin Growth Factor-1 Receptor) is particularly indicated.

The protein kinase FAK is also indicated.

The protein kinase AKT is also indicated.

The present invention thus relates particularly to novel inhibitors of the IGF-1R receptor that may be used for oncology treatments.

The present invention also relates to novel FAK receptor inhibitors that may be used for oncology treatments.

The present invention also relates to novel AKT receptor inhibitors that may be used for oncology treatments.

Cancer remains a disease for which the existing treatments are clearly insufficient. Certain protein kinases, especially including IGF-1R (Insulin Growth Factor 1 Receptor), play an important role in many cancers. The inhibition of such protein kinases is potentially important in the chemotherapy of cancers, especially for suppressing the growth or survival of tumours. The present invention thus relates to the identification of novel products that inhibit such protein kinases.

Protein kinases participate in signalling events that control the activation, growth and differentiation of cells in response either to extracellular mediators or to changes in the environment. In general, these kinases belong to two groups: those that preferentially phosphorylate serine and/or threonine residues and those that preferentially phosphorylate tyrosine residues [S.K. Hanks and T. Hunter, FASEB. J., 1995, 9, pages 576-596]. The serine/threonine kinases are, for example, the

isoforms of the protein kinases C [A.C. Newton, J. Biol. Chem., 1995, 270, pages 28495-28498] and a group of cycline-dependent kinases, for instance cdc2 [J. Pines, Trends in Biochemical Sciences, 1995, 18, pages 195-197]. Tyrosine kinases comprise growth factor receptors, for instance the epidermal growth factor (EGF) receptor [S. Iwashita and M. Kobayashi, Cellular Signalling, 1992, 4, pages 123-132], and cytosol kinases, for instance p56tck, p59fYn and ZAP-70 and the kinases csk [C. Chan et. al., Ann. Rev. Immunol., 1994, 12, pages 555-592].

Abnormally high levels of kinase protein activity have been implicated in many diseases, resulting from abnormal cellular functions. This may arise either directly or indirectly from a dysfunction in the mechanisms for controlling the kinase activity, linked, for example, to a mutation, an overexpression or an inappropriate activation of the enzyme, or an over- or underproduction of cytokines or of growth factors, also involved in the transduction of the signals upstream or downstream of the kinases. In all these cases, a selective inhibition of the action of the kinases offers hope of a beneficial effect.

The type 1 receptor for the insulin-like growth factor (IGF-I-R) is a transmembrane receptor with tyrosine kinase activity, which binds firstly to IGFI, but also to IGFII and to insulin with lower affinity. The binding of IGF1 to its receptor results in oligomerization of the receptor, the activation of tyrosine kinase, intermolecular autophosphorylation and the phosphorylation of cell substrates (main substrates: IRS1 and Shc). The receptor activated by its ligand induces

mitogenic activity in normal cells. However, IGF-I-R plays an important role in "abnormal" growth.

Several clinical reports underline the important role of the IGF-I route in the development of human cancers:

IGF-I-R is often found overexpressed in many types of tumour (breast, colon, lung, sarcoma, etc.) and its presence is often associated with a more aggressive phenotype.

High concentrations of circulating IGF1 are strongly correlated with a risk of prostate cancer, lung cancer and breast cancer.

Furthermore, it has been widely documented that IGF-I-R is necessary for establishing and maintaining the transformed phenotype in vitro as in vivo [Baserga R, Exp. Cell. Res., 1999, 253, pages 1-6]. The kinase activity of IGF-I-R is essential for the transformation activity of several oncogenes: EGFR, PDGFR, the large T antigen of the SV40 virus, activated Ras, Raf, and v-Src. The expression of IGF-I-R in normal fibroblasts induces a neoplastic phenotype, which may then result in the formation of a tumour in vivo. The expression of IGF-I-R plays an important role in substrate-independent growth. IGF-I-R has also been shown to be a protector in chemotherapy-induced and radiation-induced apoptosis, and cytokine-induced apoptosis. Furthermore, the inhibition of endogenous IGF-I-R with a negative dominant, the formation of a triple helix or the expression of an antisense sequence brings about suppression of the transforming activity *in vitro* and reduction of tumour growth in animal models.

Among the kinases for which a modulation of the activity is desired, FAK (Focal Adhesion Kinase) is also a preferred kinase.

FAK is a cytoplasmic tyrosine kinase that plays an important role in transducing the signal transmitted by the integrins, a family of heterodimeric receptors of cellular adhesion. FAK and the integrins are colocalized in perimembrane structures known as adhesion plaques. It has been shown in many cell types that the activation of FAK and its phosphorylation on tyrosine residues and in particular its autophosphorylation on tyrosine 397 were dependent on the binding of the integrins to their extracellular ligands and thus induced during cellular adhesion [Kornberg L, et al. J. Biol. Chem. 267(33): 23439-442 (1992)]. The autophosphorylation on tyrosine 397 of FAK represents a binding site for another tyrosine kinase, Src, via its SH2 domain [Schaller et al. Mol. Cell. Biol. 14: 1680-1688 1994; Xing et al. Mol. Cell. Biol. 5: 413-421 1994]. Src can then phosphorylate FAK on tyrosine 925, thus recruiting the adapter protein Grb2 and inducing in certain cells activation of the ras and MAP kinase pathway involved in controlling cellular proliferation [Schlaepfer et al. Nature; 372: 786-791 1994; Schlaepfer et al. Prog. Biophy. Mol. Biol. 71: 435-478 1999; Schlaepfer and Hunter, J. Biol. Chem. 272: 13189-13195 1997].

The activation of FAK can thus induce the jun NH2-terminal kinase (JNK) signalling pathway and result in the progression of the cells to the G1 phase of the cellular cycle [Oktay et al., J. Cell. Biol. 145: 1461-1469 1999]. Phosphatidylinositol-3-OH kinase (PI3-kinase)

also binds to FAK on tyrosine 397 and this interaction might be necessary for the activation of PI3-kinase [Chen and Guan, Proc. Nat. Acad. Sci. USA. 91: 10148-10152 1994; Ling et al. J. Cell. Biochem. 73: 533-544 1999]. The FAK/Src complex phosphorylates various substrates, for instance paxillin and p130CAS in fibroblasts [Vuori et al. Mol. Cell. Biol. 16: 2606-2613 1996].

The results of numerous studies support the hypothesis that FAK inhibitors might be useful in treating cancer. Studies have suggested that FAK might play an important role in *in vitro* cell proliferation and/or survival. For example, in CHO cells, certain authors have demonstrated that the overexpression of p125FAK induces an acceleration of the G1 to S transition, suggesting that p125FAK promotes cellular proliferation [Zhao J.-H et al. J. Cell Biol. 143: 1997-2008 1998]. Other authors have shown that tumour cells treated with FAK antisense oligonucleotides lose their adhesion and go into apoptosis (Xu and al, Cell Growth Differ. 4: 413-418 1996). It has also been demonstrated that FAK promotes the migration of cells *in vitro*. Thus, fibroblasts that are deficient for the expression of FAK ("knockout" mice for FAK) show a rounded morphology and deficiencies in cell migration in response to chemotactic signals, and these defects are suppressed by reexpression of FAK [DJ. Sieg et al., J. Cell Science. 112: 2677-91 1999]. The overexpression of the C-terminal domain of FAK (FRNK) blocks the stretching of adherent cells and reduces cellular migration *in vitro* [Richardson A. and Parsons J.T. Nature. 380: 538-540 1996]. The overexpression of FAK in CHO or COS cells or in human astrocytoma cells promotes migration of the cells. The involvement of FAK

in promoting the proliferation and migration of cells in numerous cell types *in vitro* suggests the potential role of FAK in neoplastic processes. A recent study has effectively demonstrated the increase in the proliferation of tumour cells *in vivo* after induction of the expression of FAK in human astrocytoma cells [Cary L.A. et al. J. Cell Sci. 109: 1787-94 1996; Wang D et al. J. Cell Sci. 113: 4221-4230 2000]. Furthermore, immunohistochemical studies on human biopsies have demonstrated that FAK is overexpressed in prostate cancer, breast cancer, thyroid cancer, cancer of the colon, melanoma, brain cancer and lung cancer, the level of expression of FAK being directly correlated to the tumours having the most aggressive phenotype [Weiner TM, et al. Lancet. 342 (8878): 1024-1025 1993; Owens et al. Cancer Research. 55: 2752-2755 1995; Maung K. et al. Oncogene 18: 6824-6828 1999; Wang D et al. J. Cell Sci. 113: 4221-4230 2000].

Protein kinase AKT (also known as PKB) and phosphoinositide 3-kinase (PI3K) are involved in a cell signalling pathway that transmits signals from growth factors activating membrane receptors.

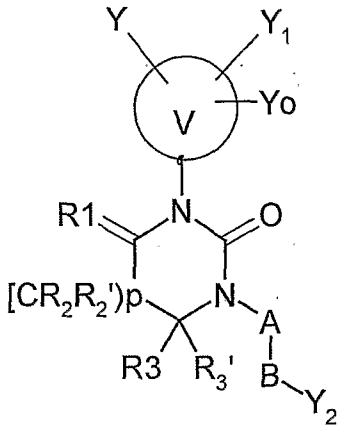
This transduction pathway is involved in numerous cellular functions: regulation of apoptosis, control of transcription and translation, glucose metabolism, angiogenesis and mitochondrial integrity. First identified as an important component of insulin-dependent signalling pathways regulating metabolic responses, serine/threonine kinase AKT was then identified as a mediator playing a key role in survival induced with growth factors. It has been shown that AKT can inhibit

death by apoptosis induced by various stimuli, in a certain number of cell types and tumour cells. In accordance with these findings, it has been shown that AKT can, by phosphorylation of given serine residues, inactivate BAD, GSK3□, caspase-9, and Forkhead transcription factor, and can activate IKKalpha and e-NOS. It is interesting to note that the protein BAD is found hyper-phosphorylated in 11 human tumour cell lines out of 41 studied. Furthermore, it has been shown that hypoxia modulates the induction of VEGF in cells transformed with Ha-ras by activating the PI3K/AKT pathway and by involving the binding sequence of the HIF-1 (hypoxia inducible factor-1) transcription factor known as HRE for "hypoxy-responsive element".

AKT plays a very important role in cancer pathologies. The amplification and/or overexpression of AKT has been reported in many human tumours, for instance gastric carcinoma (amplification of AKT1), ovary carcinoma, breast carcinoma or pancreatic carcinoma (amplification and overexpression of AKT2) and breast carcinomas deficient in oestrogen receptors, and also androgen-independent prostate carcinomas (overexpression of AKT3). Furthermore, AKT is constitutively activated in all the PTEN (-/-) tumours, the PTEN phosphatase being deleted or inactivated by mutations in many types of tumours, for instance carcinomas of the ovary, of the prostate, of the endometrium, glioblastomas and melanomas. AKT is also involved in the oncogenic activation of bcr-abl (references: Khawaja A., Nature 1999, 401, 33-34; Cardone et al. Nature 1998, 282, 1318-1321; Kitada S. et al., Am. J. Pathol. 1998 Jan; 152(1): 51-61; Mazure NM et al.

Blood 1997, *90*, 3322-3331; Zhong H. et al. Cancer Res. 2000, 60, 1541-1545).

One subject of the present invention is thus the products of general formula (I):



(I)

in which

V represents an unsaturated or partially or totally saturated monocyclic or bicyclic heterocyclic 5- to 11-membered radical, containing one or more other hetero atoms, which may be identical or different, chosen from O, N, NR4 and S, optionally substituted with one or more substituents, which may be identical or different, chosen from the values of Y and Y1;

the atom S that V can contain, being optionally oxidized by one or two oxygen,

Yo, Y and Y1, which may be identical or different, are such that Yo represents hydrogen or alkyl and one from among Y and Y1 is chosen from OCF3; -O-CF2-CHF2; -O-CHF2; -O-CH2-CF3; -SO2NR5R6; SF5; -S(O)n-alkyl; alkyl containing 1 to 7 carbon atoms optionally substituted with one or more fluorine atoms or cycloalkyl radicals; 3- to 7-membered cycloalkyl optionally substituted with one or more radicals, which may be identical or

different, chosen from fluorine atoms and alkyl radicals containing 1 to 3 carbon atoms; alkylamino, optionally substituted with one or more flourine atoms; dialkylamino, optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and alkoxy radicals and in which the two alkyl residues may optionally form, together with the nitrogen atom to which they are attached, a 4- to 10-membered heterocycle optionally containing one or more other hetero atoms, which may be identical or different, chosen from O, N, NR4 and S and optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and alkyl and alkoxy radicals; phenyl, phenoxy; arylmercapto or heteroarylmercapto, optionally substituted with one or more radicals, which may be identical or different, chosen from fluorine atoms and alkyl and alkoxy radicals;

and the other from among Y and Y1 is chosen from these same values and in addition from the following values: hydrogen; halogen; hydroxyl; oxo; acyl; alkoxy; nitro; CN; NR5R6; optionally substituted alkyl; optionally substituted aryl and heteroaryl; CF3; O-alkenyl; O-alkynyl; O-cycloalkyl; S(O)n-alkenyl; S(O)n-alkynyl; S(O)n-cycloalkyl; free, salified or esterified carboxyl and CONR5R6;

p represents the integers 0, 1 and 2;

R1 represents O or NH;

R2, R2′, R3 and R3′, which may be identical or different, represent hydrogen, halogen; alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl and heteroaryl, all optionally substituted, or alternatively two of the

residues R2, R2', R3 and R3' form, together with the carbon atom(s) to which they are attached, a carbocyclic or heterocyclic radical, these radicals being 3- to 10-membered and the heterocyclic radical containing one or more hetero atoms chosen from O, S, N and NR4, all these radicals optionally being substituted;

A represents a single bond; an alkylene radical; an alkenyl radical; alkynyl; CO; SO2; O; NH; NH-alkyl;

B represents a saturated or unsaturated monocyclic or bicyclic heterocyclic radical containing one or more hetero atoms, which may be identical or different, chosen from O, S, N and NR4, optionally substituted with one or more substituents, which may be identical or different, chosen from the values of Y2;

Y2 represents hydrogen; halogen; hydroxyl; cyano; alkyl; alkoxy; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; -O-alkenyl; -O-alkynyl; -O-cycloalkyl; -S(O)n-alkyl; -S(O)n-alkenyl; -S(O)n-alkynyl; S(O)n-cycloalkyl; COOR13; -OCOR13; NR5R6; CONR5R6; S(O)n-NR5R6; -NR10-CO-R13; -NR10-SO2-R13; NH-SO2-NR5R6; -NR10-CO-NR5R6; -NR10-CS-NR5R6 and -NR10-COOR13; all these radicals being optionally substituted;

R4 represents a hydrogen atom or an alkyl, alkenyl, alkynyl, cycloalkyl, alkylCO, alkylSO_2, or aryle radical, all optionally substituted with one or more substituents, which may be identical or different, chosen from halogen atoms; hydroxyl; alkoxy; dialkylamino; aryl and heteroaryl radicals, these last two radicals optionally substituted with one or more substituents, which may be identical or different, chosen from halogen atoms and alkyl and alkoxy radicals;

R5 and R6, which may be identical or different, are chosen from hydrogen; alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl and heteroaryl, all optionally substituted or alternatively R5 and R6 form, with the nitrogen atom to which they are attached, a 3- to 10-membered heterocyclic radical containing one or more hetero atoms chosen from O, S, N and optionally substituted NR4;

all the above alkyl, alkenyl, alkynyl and alkoxy radicals being linear or branched and containing up to 6 carbon atoms;

all the above cycloalkyl and heterocycloalkyl radicals containing up to 7 carbon atoms;

all the above aryl and heteroaryl radicals containing up to 10 carbon atoms;

all the above alkyl, alkenyl, alkynyl and alkoxy radicals cycloalkyl, heterocycloalkyl, aryl and heteroaryl radicals, carbocyclic and heterocyclic radicals, and also the ring formed by R5 and R6 with the atom to which they are attached, being optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms; cyano; hydroxyl; alkoxy; CF3; nitro; aryl, heteroaryl and heterocycloalkyl themselves optionally substituted by one or more radicals chosen among halogen, alkyl, OH or alcoxy; -C(=O)-OR9; -C(=O)-R8; -NR11R12; -C(=O)-NR11R12; -N(R10)-C(=O)-R8; -N(R10)-C(=O)-OR9; N(R10)-C(=O)-NR11R12; -N(R10)-S(O)n-R8; -S(O)n-R8; -N(R10)-S(O)n-NR11R12 and -S(O)n-NR11R12 radicals;

all the above heterocycloalkyl, aryl and heteroaryl radicals being also optionally substituted with one or more radicals chosen from alkyl, phenylalkyl and

alkylenedioxy radicals;

all the above cyclic radicals and also the ring formed by R5 and R6 with the atom to which they are attached being also optionally substituted with one or more radicals chosen from oxo and thioxo;

n represents an integer from 0 to 2,

R8 represents alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl; all these radicals being optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and cyano, hydroxyl, alkoxy, alkyl, CF3, nitro, phenyl and free, salified, esterified or amidated carboxyl radicals;

R9 represents the values of R8 and hydrogen;

R10 represents hydrogen or alkyl;

R11 and R12, which may be identical or different, represent hydrogen; alkyl, cycloalkyl and phenyl optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and cyano, hydroxyl, alkoxy, alkyl, CF3, nitro, phenyl and free, salified, esterified or amidated carboxyl radicals;

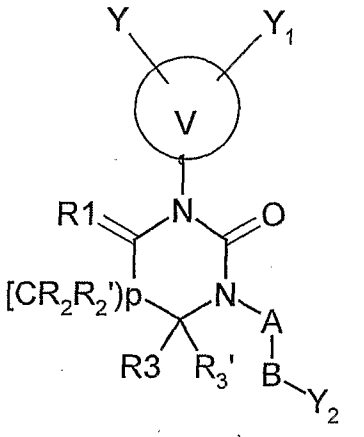
or alternatively R11 and R12 form, with the nitrogen atom to which they are attached, a 5- to 7-membered cyclic radical containing one or more hetero atoms chosen from O, S, N and NR14 and preferably a cyclic amine, optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and cyano, hydroxyl, alkoxy, alkyl, CF3, nitro, phenyl, phenylalkyl and free, salified, esterified or amidated carboxyl radicals;

R13, which may be identical to or different from R5 or R6, being chosen from the values of R5 or R6;

the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

In formula (I) as above defined, Yo can then represent hydrogen.

One subject of the present invention is thus the products of general formula (I) as above defined:



(I)

in which V represents an unsaturated or partially or totally saturated monocyclic or bicyclic heterocyclic 5- to 11-membered radical, containing one or more other hetero atoms, which may be identical or different, chosen from O, N, NR4 and S, optionally substituted with one or more substituents, which may be identical or different, chosen from the values of Y and Y1;

Y and Y1, which may be identical or different, are such that one from among Y and Y1 is chosen from OCF3; -O-CF2-CHF2; -O-CHF2; -O-CH2-CF3; -SO2NR5R6; SF5; -S(O)n-alkyl;

alkyl containing 1 to 7 carbon atoms optionally

substituted with one or more fluorine atoms or cyclalkyl radicals; 3- to 7-membered cycloalkyl optionally substituted with one or more radicals, which may be identical or different, chosen from fluorine atoms and alkyl radicals containing 1 to 3 carbon atoms;

alkylamino, optionally substituted with one or more flourine atoms; dialkylamino, optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and alkoxy radicals and in which the two alkyl residues may optionally form, together with the nitrogen atom to which they are attached, a 4- to 10-membered heterocycle optionally containing one or more other hetero atoms, which may be identical or different, chosen from O, N, NR4 and S and optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and alkyl and alkoxy radicals; phenyl, phenoxy;

arylmercapto or heteroarylmercapto, optionally substituted with one or more radicals, which may be identical or different, chosen from fluorine atoms and alkyl and alkoxy radicals;

and the other from among Y and Y1 is chosen from these same values and in addition from the following values: hydrogen; halogen; hydroxyl; oxo; alkoxy; nitro; CN; NR5R6; optionally substituted alkyl; optionally substituted aryl and heteroaryl; CF3; O-alkenyl; O-alkynyl; O-cycloalkyl; S(O)n-alkenyl; S(O)n-alkynyl; S(O)n-cycloalkyl; free, salified or esterified carboxyl and CONR5R6;

p represents the integers 0, 1 and 2;

R1 represents O or NH;

R2, R2', R3 and R3', which may be identical or different, represent hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl and heteroaryl which are optionally substituted, or alternatively two of the residues R2, R2', R3 and R3' form, together with the carbon atom(s) to which they are attached, a carbocyclic or heterocyclic radical, these radicals being 3- to 10-membered and the heterocyclic radical containing one or more hetero atoms chosen from O, S, N and NR4, all these radicals optionally being substituted;

A represents a single bond; an alkylene radical; an alkenyl radical; alkynyl; CO; SO2; O; NH; NH-alkyl;

B represents a saturated or unsaturated monocyclic or bicyclic heterocyclic radical containing one or more hetero atoms, which may be identical or different, chosen from O, S, N and NR4, optionally substituted with one or more substituents, which may be identical or different, chosen from the values of Y2;

Y2 represents hydrogen; halogen; hydroxyl; cyano; alkyl; alkoxy; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; -O-alkenyl; -O-alkynyl; -O-cycloalkyl; -S(O)n-alkyl; -S(O)n-alkenyl; -S(O)n-alkynyl; S(O)n-cycloalkyl; COOR13; -OCOR13; NR5R6; CONR5R6; S(O)n-NR5R6; -NR10-CO-R13; -NR10-SO2-R13; NH-SO2-NR5R6; -NR10-CO-NR5R6; -NR10-CS-NR5R6 and -NR10-COOR13; all these radicals being optionally substituted;

R4 represents a hydrogen atom or an alkyl, alkenyl, alkynyl, cycloalkyl, alkylCO, alkylSO_2, or aryle radical, all optionally substituted with one or more substituents, which may be identical or different, chosen from halogen atoms; hydroxyl; alkoxy; dialkylamino; aryl and

heteroaryl radicals, these last two radicals optionally substituted with one or more substituents, which may be identical or different, chosen from halogen atoms and alkyl and alkoxy radicals;

R5 and R6, which may be identical or different, are chosen from hydrogen; alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, optionally substituted aryl and heteroaryl; or alternatively R5 and R6 form, with the nitrogen atom to which they are attached, a 3- to 10-membered heterocyclic radical containing one or more hetero atoms chosen from O, S, N and optionally substituted NR4;

all the above alkyl, alkenyl, alkynyl and alkoxy radicals being linear or branched and containing up to 6 carbon atoms;

all the above cycloalkyl and heterocycloalkyl radicals containing up to 7 carbon atoms;

all the above aryl and heteroaryl radicals containing up to 10 carbon atoms;

all the above alkyl, alkenyl, alkynyl and alkoxy radicals cycloalkyl, heterocycloalkyl, aryl and heteroaryl radicals, carbocyclic and heterocyclic radicals, and also the ring formed by R5 and R6 with the atom to which they are attached being optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms; cyano; hydroxyl; alkoxy; CF3; nitro; aryl; heteroaryl; -C(=O)-OR9; -C(=O)-R8; -NR11R12; -C(=O)-NR11R12; -N(R10)-C(=O)-R8; -N(R10)-C(=O)-OR9; N(R10)-C(=O)-NR11R12; -N(R10)-S(O)n-R8; -S(O)n-R8; -N(R10)-S(O)n-NR11R12 and -S(O)n-NR11R12 radicals;

all the above aryl and heteroaryl radicals also being

optionally substituted with one or more radicals chosen from alkyl, phenylalkyl, alkoxy and alkylenedioxy radicals;all the above cyclic radicals and also the ring formed by R5 and R6 with the atom to which they are attached being also optionally substituted with one or more radicals chosen from oxo and thioxo;

n represents an integer from 0 to 2,

R8 represents alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl; all these radicals being optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and cyano, hydroxyl, alkoxy, alkyl, CF3, nitro, phenyl and free, salified, esterified or amidated carboxyl radicals;

R9 represents the values of R8 and hydrogen;

R10 represents hydrogen or alkyl;

R11 and R12, which may be identical or different, represent hydrogen; alkyl, cycloalkyl and phenyl optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and cyano, hydroxyl, alkoxy, alkyl, CF3, nitro, phenyl and free, salified, esterified or amidated carboxyl radicals;

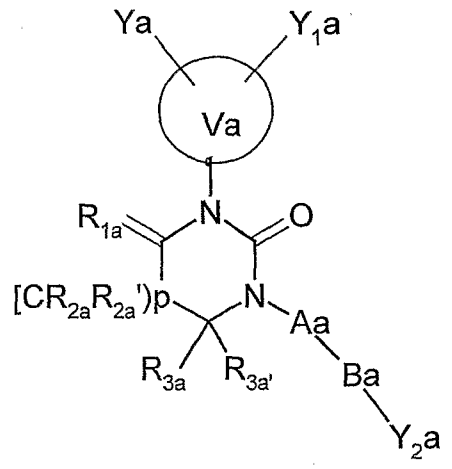
or alternatively R11 and R12 form, with the nitrogen atom to which they are attached, a 5- to 7-membered cyclic radical containing one or more hetero atoms chosen from O, S, N and NR14 and preferably a cyclic amine, optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and cyano, hydroxyl, alkoxy, alkyl, CF3, nitro, phenyl, phenylalkyl and free, salified, esterified or amidated

carboxyl radicals;

R13, which may be identical to or different from R5 or R6, being chosen from the values of R5 or R6;

the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

A subject of the present invention is, more specifically, the products of formula (I) as defined above corresponding to formula (Ia):



(Ia)

in which:

p represents an integer from 0 to 2,

Va represents a 5- or 6-membered heteroaryl radical or a 9- to 11-membered fused heterocyclic radical, containing one or more other hetero atoms, which may be identical or different, chosen from O, N, NR4a and S; optionally substituted with one or more substituents, which may be identical or different, chosen from the values of Ya and Y1a;

Ya and Y1a, which may be identical or different, are such that one from among Ya and Y1a is chosen from OCF3; -O-

CF2-CHF2; -O-CHF2; -O-CH2-CF3; SO2NR5aR6a; SF5; -S(O)n-alkyl;

alkyl containing 1 to 7 carbon atoms optionally substituted with one or more fluorine atoms; 3- to 7-membered cycloalkyl optionally substituted with one or more radicals, which may be identical or different, chosen from fluorine atoms , alkyl radicals containing 1 to 3 carbon atoms, cyclopropyl;

alkylamino, optionally substituted with one or more fluorine atoms; dialkylamino, optionally substituted with one or more radicals, which may be identical or different, chosen from fluorine atoms and alkoxy radicals and in which the two alkyl residues may optionally form, together with the nitrogen atom to which they are attached, a 4- to 10-membered heterocycle optionally containing one or more other hetero atoms, which may be identical or different, chosen from O, N, Nalkyl and S and optionally substituted with one or more radicals, which may be identical or different, chosen from fluorine atoms and alkyl and alkoxy radicals; ; phenyl, phenoxy;5- to 6-membered phenylmercapto or heteroarylmercapto, optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and alkyl and alkoxy radicals;

and the other from among Ya and Y1a is chosen from these same values and in addition from the following values:

hydrogen; halogen; hydroxyl; oxo; nitro; CN; alkenyl; alkoxy; O-allyl; O-propynyl; O-cycloalkyl; CF3; optionally substituted phenyl and heteroaryl; - S(O)nCF3; SO2CHF2, SO2CF2CF3 S(O)n-allyl; S(O)n-propynyl; S(O)n-cycloalkyl; free, salified or esterified carboxyl;

CONR5aR6a;

R1a stands for O;

R2a, R2a', R3a, R3a' represent hydrogen and alkyl, it being understood that two of the substituents R2a, R2a', R3a, R3a' can form, together with the carbon atom to which they are attached, a 3- to 6-membered cycloalkyl or heterocycloalkyl radical containing a nitrogen atom, all these radicals being optionally substituted;

Aa represents a single bond; an alkylene radical; CO; SO2; O; NH; NH-alkyl;

Ba represents pyridyl, pyrimidinyl, quinolyl, azaindolyl, quinazolyl, thiazolyl, imidazolyl, pyrazolyl, furazanyl, isoxazolyl, morpholinyl, pyrrolidinyl, furyl, piperidyl, thienyl, chromenyl, oxochromenyl, indolyl, pyrrolyl, purinyl, benzoxazinyl, benzimidazolyl, indazolyl and benzofuryl radicals, these radicals being optionally substituted with one or more radicals chosen from the values of Y2a;

Y2a represents hydrogen; halogen; hydroxyl; alkyl; alkoxy; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; O-allyl; O-propynyl; O-cycloalkyl; S(O)n-alkyl; S(O)n-allyl; S(O)n-propynyl; S(O)n-cycloalkyl; COOR9a; OCOR8a; NR5aR6a; CONR5aR6a; S(O)n-R5aR6a; NHCOR8a; -NR10a-CO-NR5aR6a NH-S(O)nR8a; NH-S(O)nCF3; NH-SO2-NR5aR6a, all these radicals being optionally substituted;

R4a represents a hydrogen atom; an alkyl; cycloalkyl; or phenyl, all optionally substituted;

R5a and R6a, which may be identical or different, are chosen from hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, optionally substituted

aryl and heteroaryl; or alternatively R5a and R6a form, with the nitrogen atom to which they are attached, a 3- to 10-membered heterocyclic radical containing one or more hetero atoms chosen from O, S, N and optionally substituted NR4a;

all the above alkyl, alkenyl, alkynyl and alkoxy radicals being linear or branched and containing up to 6 carbon atoms;

all the above cycloalkyl and heterocycloalkyl radicals containing up to 7 carbon atoms,

all the above aryl and heteroaryl radicals containing up to 10 carbon atoms;

all the above alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, carbocyclic and heterocyclic radicals being optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms; cyano; hydroxyl; alkoxy; CF3; nitro; aryl; heteroaryl; -C(=O)-OR9a; -C(=O)-R8a; -NR11aR12a; -C(=O)-NR11aR12a; -N(R10a)-C(=O)-R8a; -N(R10a)-C(=O)-OR9a; N(R10a)-C(=O)-NR11aR12a; -N(R10a)-S(O)n-R8a; -S(O)n-R8a; -N(R10a)-S(O)n-NR11aR12a and -S(O)n-NR11aR12a radicals;

all the above aryl and heteroaryl radicals also being optionally substituted with one or more radicals chosen from alkyl, phenylalkyl and alkylenedioxy radicals;

n represents an integer from 0 to 2;

R8a represents alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkyl-alkyl, phenyl, phenylalkyl, heteroaryl and heteroarylalkyl; all these radicals being optionally substituted with one or more radicals, which may be

identical or different, chosen from halogen atoms and hydroxyl, alkoxy, alkyl, CF3, nitro, phenyl and free, salified, esterified or amidated carboxyl radicals;

R9a represents the values of R8 and hydrogen;

R10a represents hydrogen or alkyl;

R11a and R12a, which may be identical or different, represent hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl and phenylalkyl optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and cyano, hydroxyl, alkoxy, alkyl, CF3, nitro, phenyl and free, salified, esterified or amidated carboxyl radicals;

or alternatively R11a and R12a form, with the nitrogen atom to which they are attached, a cyclic radical chosen from pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, indolinyl, pyrindolinyl, tetrahydroquinolyl, thiazolidinyl and naphthyridyl; optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and alkyl, phenyl and phenylalkyl radicals;

the said products of formula (Ia) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (Ia).

In the products of formula (I) and subsequently, the terms indicated have the following meanings:

- the term "Hal", "Halo" or halogen denotes fluorine, chlorine, bromine or iodine atoms,
- the term "alkyl radical", "alk", "Alk" or "ALK" denotes a linear or branched radical containing up to 12 carbon

atoms, chosen from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, sec-pentyl, tert-pentyl, neopentyl, hexyl, isohexyl, sec-hexyl, tert-hexyl, heptyl, octyl, nonyl, decyl, undecyl and dodecyl radicals, and also the linear or branched positional isomers thereof.

Mention is made more particularly of alkyl radicals containing up to 6 carbon atoms, and especially methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, linear or branched pentyl and linear or branched hexyl radicals.

- the term "alkenyl radical" denotes a linear or branched radical containing up to 12 carbon atoms and preferably 4 carbon atoms, chosen, for example, from the following values: ethenyl or vinyl, propenyl or allyl, 1-propenyl, n-butenyl, i-butenyl, 3-methyl-2-butenyl, n-pentenyl, hexenyl, heptenyl, octenyl, cyclohexylbutenyl and decenyl, and also the linear or branched positional isomers thereof.

Among the alkenyl values that may be mentioned more particularly are the values allyl or butenyl.

- the term "alkynyl radical" denotes a linear or branched radical containing up to 12 carbon atoms and preferably 4 carbon atoms, chosen, for example, from the following values: ethynyl, propynyl or propargyl, butynyl, n-butynyl, i-butynyl, 3-methyl-2-butynyl, pentynyl or hexynyl, and also the linear or branched positional isomers thereof.

Among the alkynyl values that are mentioned more particularly is the propargyl value.

- the term "alkoxy radical" denotes a linear or branched radical containing up to 12 carbon atoms and preferably 6 carbon atoms chosen, for example, from methoxy, ethoxy, propoxy, isopropoxy, linear, secondary or tertiary butoxy, pentoxy, hexoxy and heptoxy radicals, and also the linear or branched positional isomers thereof,

- the term "alkoxycarbonyl radical" or alkyl-O-CO- denotes a linear or branched radical containing up to 12 carbon atoms, in which the alkyl radical has the meaning given above: examples that may be mentioned include methoxycarbonyl and ethoxycarbonyl radicals,

- the term "alkylenedioxy radical" or -O-alkylene-O- denotes a linear or branched radical containing up to 12 carbon atoms, in which the alkylene radical has the meaning given above: examples that may be mentioned include methylenedioxy and ethylenedioxy radicals,

- the term "alkylsulfinyl" or alkyl-SO- denotes a linear or branched radical containing up to 12 carbon atoms, in which the alkyl radical has the meaning given above and preferably contains 4 carbon atoms,

- the term "alkylsulfonyl" or alkyl-SO2- denotes a linear or branched radical containing up to 12 carbon atoms, in which the alkyl radical has the meaning given above and preferably contains 4 carbon atoms,

- the term "alkylsulfonylcarbamoyl" or alkyl-SO2-NH-C(=O)- denotes a linear or branched radical containing up to 12 carbon atoms, in which the alkyl radical has the meaning given above and preferably contains 4 carbon atoms,

- the term "alkylthio" or alkyl-S- denotes a linear or branched radical containing up to 12 carbon atoms and

especially represents methylthio, ethylthio, isopropylthio and heptylthio radicals,

- the term "cycloalkyl radical" denotes a 3- to 10-membered monocyclic or bicyclic carbocyclic radical and especially denotes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl radicals,

- the term "-O-cycloalkyl radical" denotes a radical in which the cycloalkyl radical has the meaning given above,

- the term "cycloalkenyl radical" denotes a 3- to 10-membered monocyclic or bicyclic nonaromatic carbocyclic radical containing at least one double bond, and especially denotes cyclobutenyl, cyclopentenyl and cyclohexenyl radicals,

- the term "cycloalkylalkyl radical" denotes a radical in which cycloalkyl and alkyl are chosen from the values indicated above: this radical thus denotes, for example, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl and cycloheptylmethyl radicals,

- the term "acyl radical" or r-CO- denotes a linear or branched radical containing up to 12 carbon atoms, in which the radical r represents a hydrogen atom or an alkyl, cycloalkyl, cycloalkenyl, cycloalkyl, heterocycloalkyl or aryl radical, these radicals having the values indicated above and being optionally substituted as indicated: examples that are mentioned include the formyl, acetyl, propionyl, butyryl or benzoyl radicals, or alternatively valeryl, hexanoyl, acryloyl, crotonoyl or carbamoyl,

- the term "acyloxy radical" means acyl-O- radicals in which acyl has the meaning given above: examples that are mentioned include acetoxy or propionyloxy radicals,

- the term "acylamino radical" means acyl-NH- radicals in which acyl has the meaning given above,
- the term "aryl radical" denotes unsaturated monocyclic radicals or unsaturated radicals consisting of fused carbocyclic rings. Examples of such aryl radicals that may be mentioned include phenyl or naphthyl radicals.

Mention is made more particularly of the phenyl radical.
- the term "arylalkyl" means radicals resulting from the combination of the optionally substituted alkyl radicals mentioned above and the optionally substituted aryl radicals also mentioned above: examples that are mentioned include benzyl, phenylethyl, 2-phenethyl, triphenylmethyl or naphthalenemethyl radicals,
- the term "heterocyclic radical" denotes a saturated carbocyclic radical (heterocycloalkyl) or unsaturated carbocyclic radical (heteroaryl) which is at most 6-membered, interrupted with one or more hetero atoms, which may be identical or different, chosen from oxygen, nitrogen and sulfur atoms.

Heterocycloalkyl radicals that may especially be mentioned include dioxolane, dioxane, dithiolane, thiooxolane, thiooxane, oxiranyl, oxolanyl, dioxolanyl, piperazinyl, piperidyl, pyrrolidyl, imidazolidinyl, pyrazolidinyl, morpholinyl, or tetrahydrofuryl, tetrahydrothienyl, chromanyl, dihydrobenzofuranyl, indolinyl, piperidyl, perhydropyranyl, pyrindolinyl, tetrahydroquinolyl, tetrahydroisoquinolyl and thioazolidinyl radicals, all these radicals being optionally substituted.

Among the heterocycloalkyl radicals that may especially be mentioned are optionally substituted piperazinyl,

optionally substituted piperidyl, optionally substituted pyrrolidinyl, imidazolidinyl, pyrazolidinyl, morpholinyl and thioazolidinyl radicals: mention may also be made more particularly of optionally substituted morpholinyl, pyrrolidyl and piperazinyl radicals;

- the term "heterocycloalkylalkyl radical" means radicals in which the heterocycloalkyl and alkyl residues have the above meanings;

- among the 5-membered heteroaryl radicals that may be mentioned are furyl radicals such as 2-furyl, thienyl radicals such as 2-thienyl and 3-thienyl, and pyrrolyl, diazolyl, thiazolyl, thiadiazolyl, thiatriazolyl, isothiazolyl, oxazolyl, oxadiazolyl, 3- or 4-isoxazolyl, imidazolyl, pyrazolyl and isoxazolyl radicals.

Among the 6-membered heteroaryl radicals that may especially be mentioned are pyridyl radicals such as 2-pyridyl, 3-pyridyl and 4-pyridyl, and pyrimidyl, pyrimidinyl, pyridazinyl, pyrazinyl and tetrazolyl radicals;

- as fused heteroaryl radicals containing at least one hetero atom chosen from sulfur, nitrogen and oxygen, examples that may be mentioned include benzothienyl such as 3-benzothienyl, benzofuryl, benzofuranyl, benzopyrrolyl, benzimidazolyl, benzoxazolyl, thionaphthyl, indolyl, purinyl, quinolyl, isoquinolyl and naphthyridinyl.

Among the fused heteroaryl radicals that may be mentioned more particularly are benzothienyl, benzofuranyl, indolyl, quinolyl, benzimidazolyl, benzothiazolyl, furyl, imidazolyl, indolizinyl, isoxazolyl, isoquinolyl, isothiazolyl, oxadiazolyl, pyrazinyl, pyridazinyl,

pyrazolyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, 1.3.4-thiadiazolyl, thiazolyl and thienyl radicals and triazolyl groups, these radicals optionally being substituted as indicated for the heteroaryl radicals;

- the term "cyclic amine" denotes a 3- to 8-membered cycloalkyl radical in which one carbon atom is replaced with a nitrogen atom, the cycloalkyl radical having the meaning given above and also possibly containing one or more other hetero atoms chosen from O, S, SO2, N and NR4 with R4 as defined above; examples of such cyclic amines that may be mentioned include pyrrolidyl, piperidyl, morpholinyl, piperazinyl, indolinyl, pyrindolinyl and tetrahydroquinolyl radicals.

The term "patient" denotes human beings, but also other mammals.

The term "prodrug" denotes a product that may be converted in vivo via metabolic mechanisms (such as hydrolysis) into a product of formula (I). For example, an ester of a product of formula (I) containing a hydroxyl group may be converted by hydrolysis in vivo into its parent molecule. Alternatively, an ester of a product of formula (I) containing a carboxyl group may be converted by in vivo hydrolysis into its parent molecule.

Examples of esters of the products of formula (I) containing a hydroxyl group that may be mentioned include the acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylenebis-β-hydroxynaphthoates, gentisates, isethionates, di-p-tolyltartrates, methanesulfonates, ethanesulfonates, benzenesulfonates, p-toluenesulfonates, cyclohexylsulfamates and quinates.

Esters of products of formula (I) that are particularly useful, containing a hydroxyl group, may be prepared from acid residues such as those described by Bundgaard et. al., J. Med. Chem., 1989, 32, page 2503-2507: these esters especially include substituted (aminomethyl)benzoates, dialkylaminomethylbenzoates in which the two alkyl groups may be linked together or may be interrupted with an oxygen atom or with an optionally substituted nitrogen atom, i.e. an alkylated nitrogen atom, or alternatively (morpholinomethyl)benzoates, eg. 3- or 4-(morpholinomethyl)benzoates, and (4-alkyl-piperazin-1-yl)benzoates, eg. 3- or 4-(4-alkylpiperazin-1-yl)benzoates.

The carboxyl radical(s) of the products of formula (I) may be salified or esterified with various groups known to those skilled in the art, among which nonlimiting examples that may be mentioned include the following compounds:

- among the salification compounds, mineral bases such as, for example, one equivalent of sodium, potassium, lithium, calcium, magnesium or ammonium, or organic bases such as, for example, methylamine, propylamine, trimethylamine, diethylamine, triethylamine, N,N-dimethylethanolamine, tris(hydroxymethyl)aminomethane, ethanolamine, pyridine, picoline, dicyclohexylamine, morpholine, benzylamine, procaine, lysine, arginine, histidine or N-methylglucamine,
- among the esterification compounds, alkyl radicals to form alkoxycarbonyl groups such as, for example, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl or benzyloxycarbonyl, these alkyl radicals possibly being substituted with radicals chosen, for example, from

halogen atoms and hydroxyl, alkoxy, acyl, acyloxy, alkylthio, amino or aryl radicals, such as, for example, in chloromethyl, hydroxypropyl, methoxymethyl, propionyloxymethyl, methylthiomethyl, dimethylaminoethyl, benzyl or phenethyl groups.

The term "esterified carboxyl" means, for example, radicals such as alkyloxycarbonyl radicals, for example methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butyl or tert-butyloxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl or cyclohexyloxycarbonyl.

Mention may also be made of radicals formed with readily cleavable ester residues, such as methoxymethyl or ethoxymethyl radicals; acyloxyalkyl radicals such as pivaloyloxymethyl, pivaloyloxyethyl, acetoxymethyl or acetoxyethyl; alkyloxycarbonyloxyalkyl radicals such as methoxycarbonyloxy methyl or ethyl radicals, and isopropyloxycarbonyloxy methyl or ethyl radicals.

A list of such ester radicals may be found, for example, in European patent EP 0 034 536.

The term "amidated carboxyl" means radicals of the type -CONR5R6 as defined above.

The term "alkylamino radical" means linear or branched methylamino, ethylamino, propylamino or butylamino radicals. Alkyl radicals containing up to 4 carbon atoms are preferred, the alkyl radicals possibly being chosen from the alkyl radicals mentioned above.

The term "dialkylamino radical" means, for example, dimethylamino, diethylamino and methylethylamino radicals. As previously, alkyl radicals containing up to 4 carbon atoms, chosen from the list indicated above, are preferred.

The radicals NR5R6 or NR11R12 may also represent a heterocycle which may or may not comprise an additional hetero atom. Mention may be made of pyrrolyl, imidazolyl, indolyl, piperidyl, pyrrolidinyl, morpholinyl and piperazinyl radicals. The piperidyl, pyrrolidinyl, morpholinyl and piperazinyl radicals are preferred.

The term "salified carboxyl" means the salts formed, for example, with one equivalent of sodium, potassium, lithium, calcium, magnesium or ammonium. Mention may also be made of the salts formed with organic bases such as methylamine, propylamine, trimethylamine, diethylamine and triethylamine. The sodium salt is preferred.

When the products of formula (I) comprise an amino radical that may be salified with an acid, it is clearly understood that these acid salts also form part of the invention. Mention may be made of the salts obtained, for example, with hydrochloric acid or methanesulfonic acid.

The addition salts with mineral or organic acids of the products of formula (I) may be, for example, the salts formed with hydrochloric acid, hydrobromic acid, hydriodic acid, nitric acid, sulfuric acid, phosphoric acid, propionic acid, acetic acid, trifluoroacetic acid, formic acid, benzoic acid, maleic acid, fumaric acid, succinic acid, tartaric acid, citric acid, oxalic acid, glyoxylic acid, aspartic acid, ascorbic acid, alkylmonosulfonic acids such as, for example, methanesulfonic acid, ethanesulfonic acid or propanesulfonic acid, alkyldisulfonic acids such as, for example, methanedisulfonic acid or alpha,beta-ethanedisulfonic acid, arylmonosulfonic acids such as benzenesulfonic acid, and aryldisulfonic acids.

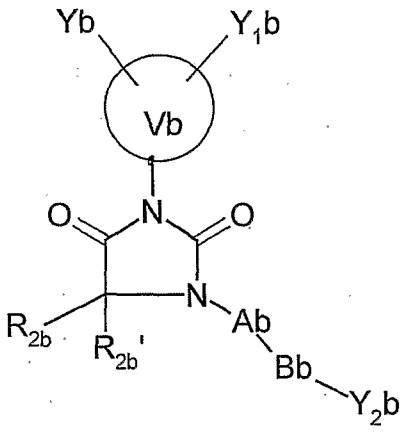
It may be recalled that stereoisomerism may be defined in its broad sense as the isomerism of compounds having the same structural formulae but whose various groups are arranged differently in space, especially such as in monosubstituted cyclohexanes whose substituent may be in an axial or equatorial position, and the various possible rotational conformations of ethane derivatives. However, there is another type of stereoisomerism, due to the different spatial arrangements of fixed substituents, either on double bonds or on rings, which is often referred to as geometrical isomerism or cis-trans isomerism. The term "stereoisomer" is used in the present patent application in its broadest sense and thus relates to all the compounds indicated above.

A subject of the invention is especially the products of formula (I) as defined above, such that p represents the integer 0, the other substituents of the said products of formula (I) having any one of the values defined above.

A subject of the invention is especially the products of formula (I) as defined above, such that p represents the integer 1, the other substituents of the said products of formula (I) having any one of the values defined above.

A subject of the invention is especially the products of formula (I) as defined above, such that p represents the integer 2, the other substituents of the said products of formula (I) having the values defined in the present invention.

A subject of the present invention is especially the products of formula (I) or (Ia) as defined above corresponding to formula (Ib):



(Ib)

in which

Vb represents pyridine; pyrimidine; pyrrole; thiophene; thiazole; imidazole; oxazole; pyrazole; isoxaozole; indole; indazole; benzimidazole; benzothiazole; benzoxazole; 2,3-dihydro-1H-indole; 2,3-dihydro-1H-isoindole; 2,3-dihydrobenzothiazole; 1,2,3,4-tetrahydro-quinoline, 1,2,3,4-Tetrahydro-isoquinoline, triazole; oxadiazole; dihydrobenzothiazine; benzodioxinyl; benzopyranyl; quinolyl; optionally substituted with one or more substituents, which may be identical or different, chosen from the values of Yb and Y1b;

Yb and Y1b, which may be identical or different, are such that one from among Yb and Y1b is chosen from OCF3; S(O)nCF3; S(O)nAlk; SO2CHF2; SO2CF2CF3; SO2NR5bR6b; alkyl containing 1 to 6 carbon atoms optionally substituted by one or more F; 3- to 6-membered cycloalkyl optionally substituted with one or more methyl radicals or one or more F;

alkylamino; dialkylamino, in which the two alkyl residues may optionally form, together with the nitrogen atom to which they are attached, a 5- or 6-membered heterocycle optionally containing one or more other hetero atoms, which may be identical or different, chosen from O, N,

Nalkyl and S and optionally substituted with one or more radicals, which may be identical or different, chosen from fluorine atoms and alkyl radicals; phenyl, phenoxy; 5- to 6-membered phenylmercapto or heteroarylmercapto, optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and alkyl radicals;

and the other from among Yb and Y1b is chosen from the same values and also from hydrogen; halogen; hydroxyl; oxo; nitro; free or esterified carboxyl; NR5bR6b; optionally substituted alkyl, alkoxy and phenyl; -O-CF2-CHF2; -O-CHF2; -O-CH2-CF3; -S-CF2-CF2-CF3; - -S-Alk-O-Alk; -S-Alk-OH; -S-Alk-CN; -S-Alk-heterocycloalkyl; pyrazolyl, pyridyl, morpholino, pyrrolidinyl and piperazinyl optionally substituted with an alkyl, phenyl or phenylalkyl radical;

R2b and R2b' represent hydrogen and alkyl, or two substituents R2b and R2b', can form, together with the carbon atom to which they are attached, a cycloalkyl radical containing from 3 to 6 carbon atoms, or form an azetidinyl, pyrrolidinyl or piperidyl radical.

Ab represents a single bond, an alkylene radical;; O; NH; NH-alkyl;

Bb represents a heterocyclic radical chosen from 3- or 4-pyridyl; pyrimidinyl;; 3- or 4- quinolyl; azaindolyl; quinazolyl;indazolyl; thiazolyl; imidazolyl; pyrazolyl, furazanyl and isoxazolyl radicals; these radicals being optionally substituted with one or more radicals chosen from the values of Yb,

Y2b represents hydrogen; halogen; hydroxyl; alkyl; alkoxy; cycloalkyl; heterocycloalkyl; phenyl; heteroaryl;

O-cycloalkyl; S(O)n-alk; S(O)n-cycloalkyl; COOR9; OCOR8; NR5R6; CONR5R6; S(O)n-R5R6; NHCOR8 -NR10b-CO-NR5bR6b and NH-S(O)nR8; all these radicals being optionally substituted,

R4b represents a hydrogen atom or an alkyl, cycloalkyl or phenyl radical,

R5b and R6b, which may be identical or different, are chosen from hydrogen, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, optionally substituted phenyl and heteroaryl or alternatively R5b and R6b form, with the nitrogen atom to which they are attached, a 3- to 10-membered heterocyclic radical containing one or more hetero atoms chosen from O, S, N and optionally substituted NR4b,

all the above alkyl, alkenyl, alkynyl and alkoxy radicals being linear or branched and containing up to 6 carbon atoms,

all the above cycloalkyl and heterocycloalkyl radicals containing up to 7 carbon atoms,

all the above aryl and heteroaryl radicals containing up to 10 carbon atoms,

all the above radicals being optionally substituted with one or more radicals chosen from halogen, cyano, hydroxyl, alkyl and alkoxy containing 1 to 4 carbon atoms, CF3, nitro, phenyl, carboxyl, free, salified, esterified with an alkyl radical or amidated with a radical NR11bR12b, -C(=O)-R9b, -NR11bR12b or -C(=O)-NR11bR12b,

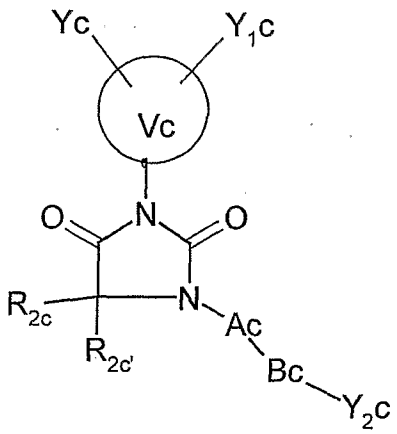
R8b represents alkyl, cycloalkyl, cycloalkylalkyl and phenyl,

R9b, which may be identical to or different from R8b,

represents hydrogen and the values of R8b,
R11b and R12b, which may be identical or different, represent hydrogen, alkyl, cycloalkyl and phenyl or alternatively R11b and R12b form, with the nitrogen atom to which they are attached, a pyrolidine, piperidinyl, morpholinyl or a piperazinyl radical optionally substituted with an alkyl, phenyl or phenylalkyl radical;

the said products of formula (Ib) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (Ib).

A subject of the present invention is especially the products of formula (I), (Ia) or (Ib) as defined above corresponding to formula (Ic):



(Ic)

in which
Vc represents pyrrole, thiophene, thiazole, pyrazole, , indazole, 2,3-dihydro-1H-indole: benzodioxinyl ; benzopyranyl ;
optionally substituted with one or more substituents, which may be identical or different, chosen from the values of Yc and Y1c;

Yc and Y1c, which may be identical or different, are such

that one from among Yc and Y1c is chosen from OCF3; -S(O)nCF3; S(O)n-Alk;SO2CHF2; SO2CF2CF3; SO2NR5cR6c; alkyl especially such as methyl, ethyl, isopropyl, tert-butyl, sec-butyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl; cyclopropyl or cyclobutyl especially such as 1-methyl-cyclopropyl, 2-methylcyclopropyl, 2,2-dimethylcyclo-propyl, cyclobutyl, 2,2,3,3-tetrafluorocyclobutyl;
di(C2-C4-alkyl)amino;
piperid-1-yl, thiomorpholin-4-yl, morpholin-4-yl, pyrrolidin-1-yl optionally substituted with one or more radicals chosen from fluorine atoms and alkyl radicals; phenyl, optionally substituted with one or more halogen atoms, phenoxy, phenyl, optionally substituted with one or more halogen atoms; phenylmercapto, optionally substituted with one or more halogen atoms;
and the other from among Yc and Y1c is chosen from these same values and also from hydrogen; halogen; hydroxyl; oxo; NR5cR6c; optionally substituted alkyl, alkoxy and phenyl; optionally substituted pyrazolyl and pyridyl;

R2 and R2c' represent a hydrogen atom, alkyl of form together with the carbon atom bearing them a 3 to 6 membered cycloalkyl ring;

Ac represents a single bond , -O- or -CH2;

Bc represents a heterocyclic radical chosen from 3- or 4-pyridyl, pyrimidinyl, , 3- or 4- quinolyl, azaindolyl and quinazolyl, indazolyl, these radicals being optionally substituted with one or more radicals chosen from the values of Y2c;

Y2c represents hydrogen; halogen; alkyl; cycloalkyl; hydroxyl; alkoxy; ; NH2; NHalk; N(alk)2; NH-Phenyl-; NH-Heteroaryl; NH-CO-R5c; NH-CO-heteroaryl; NH-CO-NR5cR6c;

and phenyl; all the alkyl, alkoxy phenyl and heteroaryl radicals being optionally substituted;

R5c and R6c, which may be identical or different, represent hydrogen, alkyl, cycloalkyl and phenyl, which are optionally substituted, or alternatively R5c and R6c form, with the nitrogen atom to which they are attached, a cyclic radical chosen from pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, piperazinyl, indolinyl, pyrindolinyl, tetrahydroquinoline and azetidine radicals, all these radicals being optionally substituted with one or more radicals chosen from alkyl, alkoxy and phenyl;

all the above alkyl, alkoxy and phenyl radicals being optionally substituted with one or more radicals chosen from halogen, OH, alk, Oalk, OCF3, S(O)n-CF3, CF3, NH2, NHAlk and N(alk)2; it beeing understood, that all dialkylamino radicals optionally can form a pyrrolidine, piperidine, morpholine or piperazine ring optionally substituted by one or more alkyl;

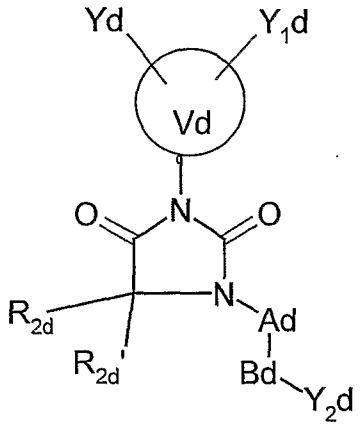
the said products of formula (Ic) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (Ic).In particular, R5c and R6c, which may be identical or different, represent hydrogen, alkyl, cycloalkyl and phenyl, the alkyl and phenyl radicals being optionally substituted, or alternatively R5c and R6c form, with the nitrogen atom to which they are attached, a cyclic radical chosen from pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, piperazinyl and azetidine.

In particular, Bc represents a heterocyclic radical

chosen from 3- or 4-pyridyl, 1H-pyrrolo[2,3-b]pyridin-4-yl pyrimidinyl and 3- or 4-quinolyl.

Most particularly, Bc represents 4-pyridyl and 4-quinolyl radicals, optionally substituted with one or more radicals chosen from the values of Y2c,

A subject of the present invention is especially the products of formula (I) as defined above corresponding to formula (Id):



(Id)

in which

Vd represents pyridine; pyrimidine; pyrrole; thiophene; thiazole; imidazole; oxazole; pyrazole; isoxaozole;; indazole; benzimidazole; benzothiazole; benzoxazole; 2,3-dihydro-1H-indole; 2,3-dihydro-1H-isoindole; 2,3-dihydrobenzothiazole; triazole; oxadiazole; dihydrobenzothiazine; benzodioxinyl; benzopyranyl; quinolyl;

Yd and Y1d, which may be identical or different, are such that one from among Y and Y1 is chosen from alkyl, optionally substituted by one or more fluorine atoms, phenyl, O-phenyl, S(O)n-alkyl, S(O)n-alkylphenyl and morpholino and one or and the other from among Y and Y1 is chosen from these same values and in addition from the following values: F, Cl and Br atoms; hydroxyl; oxo;

cyano; free or esterified carboxyl; COCH3; phenyl; O-phenyl; S(O)n alkyl; S(O)n-alkylphenyl and morpholino radicals;

all the alkyl and phenyl radicals being themselves optionally substituted with one or more radicals , which may be identical or different, chosen from halogen atoms and alkyl, alkoxy, OCF3, cyano, amino, alkylamino and dialkylamino radicals, and a phenyl radical, itself optionally substituted with one or more halogen atoms;

R2d and R2d', which may be identical or different, are chosen from hydrogen, methyl, ethyl or form together with the atom bearing thema cyclopropyl or a cyclobutyl ring;

Ad represents a single bond or CH2;

Bd represents a quinolyl or pyridyl radical optionally substituted with one or more radicals Y2d chosen from halogen, -OH, alk, -Oalk, -CO2H, -CO2alk, -NH2, NHalk, N(alk)2, -CF3, -OCF3 and phenyl,NH-phenyl; NH-heteroaryl NH-CO-phenyl, NH-CO-heteroaryl; NH-CO-NH-alkyl; NH-CO-NH-dialkyl ; NH-CO-NH-phenyl;the alkyl and phenyl radicals being themselves optionally substituted with one or more radicals chosen from halogen atoms and alkyl and alkoxy and dialkylamino radicals; it beeing understood, that all dialkylamino radicals optionally can form a pyrrolidine, piperidine, morpholine or piperazine ring optionally substituted by one or more alkyl;

the said products of formula (Id) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (Id).

A subject of the present invention is especially the products of formula (I) as defined above in which

V represents pyridine; pyrimidine; pyrrole; thiophene; thiazole; dithiazole; imidazole; oxazole; isoxazole; pyrazole; isoxaozole; indazole; benzimidazole; benzothiazole; benzoxazole; 2,3-dihydro-1H-indole; 2,3-dihydro-1H-isoindole; 2,3-dihydrobenzothiazole; triazole; oxadiazole; dihydrobenzothiazine; benzodioxinyl; benzopyranyl; quinolyl; 1,2,3,4 tetrahydroquinolyl;
the atom S that V can contain, being optionally oxidized by one or two oxygen,

Yo, Y and Y1, which may be identical or different, are such that Yo represents hydrogen or alkyl and one from among Y and Y1 is chosen from alkyl optionally substituted by one or more fluorine atoms, phenyl, O-phenyl, S(O)n-alkyl, S(O)n-alkylphenyl and morpholino and the other from among Y and Y1 is chosen from these same values and in addition from the following values: F, Cl and Br atoms; hydroxyl; oxo; cyano; free or esterified carboxyl; COCH3; -alkyl-CO-piperazinyl itself optionally substituted by alkyl; phenyl; O-phenyl; S(O)n-alkyl; S(O)n-alkylphenyl and morpholino radicals;
all the alkyl and phenyl radicals being themselves optionally substituted with one or more radicals , which may be identical or different, chosen from halogen atoms and alkyl, alkoxy, OCF3, cyano, amino, alkylamino and dialkylamino radicals, and a phenyl radical, itself optionally substituted with one or more halogen atoms;

R2 and R2′, which may be identical or different, are chosen from hydrogen and alkyl optionally substituted with aryl or heteroaryl themselves optionally substituted

by one or more radicals chosen among halogen, alkyl, OH or alcoxy;

A represents CH2;

B represents a quinolyl, pyrimidinyle or pyridyl radical optionally substituted by one or more radicals identical or different chosen among halogen; -NH2;

-NH-alkyl and N(alk)2 with alkyl optionally substituted by one or more halogen; -NH-CO-N(alk)2; phenyl, -NH-phenyl, -NH-heteroaryl, NH heterocycloalkyl, -NH-CO-phenyl and -NH-CO-heteroaryl themselves optionally substituted by one or more radicals identical or different chosen among halogen, alkyl, alcoxy, N(alk)2, CO2H, CO2ethyl and CO-N(alk)2;

the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

More particularly, in the products of formula (I), R2 and R2', which may be identical or different, can be chosen from hydrogen and alkyl optionally substituted with benzothienyle.

More particularly, in the products of formula (I), B can represent a quinolyl, pyrimidinyle or pyridyl radical with pyrimidinyle optionally substituted by NH2 and pyridyl optionally substituted by halogen; -NH-CH2-CF3; -NH-CO-N(alk)2; -NH-pyridyl; -NH-thiazolyl; -NH-pyrimidinyle and -NH-pyrazolyl optionally substituted by one or more radicals identical or different chosen among halogen, alkyl and alcoxy; phenyl and -NH-phenyl

optionally substituted by one or more radicals identical or different chosen among alkyl, alcoxy, CO2H, CO2ethyl, N(alk)2(ex42) and CO-N(alk)2; -NH-CO-phenyl and -NH-CO-pyridyl optionally substituted by one or more radicals identical or different chosen among alcoxy.

By another embodiment, B represents a 4-quinolyl or 4-pyridyl radical optionally substituted with one or more radicals chosen from F, Cl, OH, CH3, CH2CH3, OCH3, NH2, NHAlk and N(alk)2, and phenyl, NH-phenyl; NH-heteroaryl NH-CO-phenyl, NH-CO-heteroaryl; NH-CO-NH-alkyl; NH-CO-NH-dialkyl the alkyl and phenyl radicals being themselves optionally substituted with one or more radicals chosen from halogen atoms and alkyl and alkoxy radicals.

Most particularly, B represents 4-pyridyl and 4-quinolyl radicals substituted with one or two radicals chosen from F, Cl, OH ; NH2 and OCH3.

A subject of the present invention is especially the products of formula (I) as defined above in which V is chosen from all the values defined above,

R2 and R2′, which may be identical or different, are chosen from hydrogen and alkyl;

A represents CH2;

B represents a quinolyl or pyridyl radical;

the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

A subject of the present invention is, most particularly, the products of formula (I) as defined above in which

V represents pyridine; pyrimidine; pyrrole; thiophene; thiazole; imidazole; oxazole; pyrazole; isoxaozole;; indazole; benzimidazole; benzothiazole; benzoxazole; 2,3-dihydro-1H-indole; 2,3-dihydro-1H-isoindole; 2,3-dihydrobenzothiazole; triazole; oxadiazole; dihydrobenzothiazine; benzodioxinyl; benzopyranyl; quinolyl;

Y and Y1, which may be identical or different, are such that one from among Y and Y1 is chosen from alkyl, optionally substituted by one or more fluorine atoms, phenyl, O-phenyl, S(O)n-alkyl, S(O)n-alkylphenyl and morpholino and one or and the other from among Y and Y1 is chosen from these same values and in addition from the following values: F, Cl and Br atoms; hydroxyl; oxo; cyano; free or esterified carboxyl; COCH3; phenyl; O-phenyl; S(O)n alkyl; S(O)n-alkylphenyl and morpholino radicals;

all the alkyl and phenyl radicals being themselves optionally substituted with one or more radicals , which may be identical or different, chosen from halogen atoms and alkyl, alkoxy, OCF3, cyano, amino, alkylamino and dialkylamino radicals, and a phenyl radical, itself optionally substituted with one or more halogen atoms;

R2 and R2′, which may be identical or different, are chosen from hydrogen and alkyl;

A represents CH2;

B represents a quinolyl or pyridyl radical;

the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, and also the addition salts with mineral and organic acids or with mineral and organic bases of

the said products of formula (I).

In particular, V represents pyridine; pyrimidine; pyrrole; thiophene; thiazole; imidazole; oxazole; pyrazole; isoxaozole; ; indazole; benzimidazole; benzothiazole; benzoxazole 2,3-dihydro-1H-indole; 2,3-dihydro-1H-isoindole; 2,3-dihydrobenzothiazole; all these radicals being optionally substituted as indicated above.

Most particular V represents 2,3-dihydro-1H-indole and pyrazole.

Among the preferred products of the invention, mention may be made more specifically of the products of formula (I) as defined above, the names of which are given hereinbelow:

- 3-(5-Isopropyl-thiazol-2-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl-imidazolidine-2,4- dione

- 3-(5-tert-Butyl-2H-pyrazol-3-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl-imidazolidine-2,4- dione

- 3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl- imidazolidine-2,4-dione

- 3-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl- imidazolidine-2,4-dione

- 5,5-Dimethyl-3-(2-oxo-4-trifluoromethyl-2H-1-benzopyran-7-yl)-1-pyridin-4-ylmethyl-imidazolidine-2,4-dione trifluoroacetate

- 3-(2,2-Dimethyl-4-oxo-4H-1,3-benzodioxin-7-yl)-5,5-dimethyl-1-pyridin-4-ylmethyl-imidazolidine-2,4-dione trifluoroacetate

- 3-(1-Acetyl-2,3-dihydro-1H-indol-5-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl-imidazolidine- 2,4-dione

the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

Among the preferred products of the invention, mention may be made more specifically of the products of formula (I) as defined above, the names of which are given hereinbelow:

- 3-(5-Isopropyl-thiazol-2-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl-imidazolidine-2,4- dione

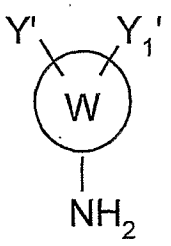
- 3-(5-tert-Butyl-2H-pyrazol-3-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl-imidazolidine-2,4- dione

- 3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl- imidazolidine-2,4-dione

- 3-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl- imidazolidine-2,4-dione

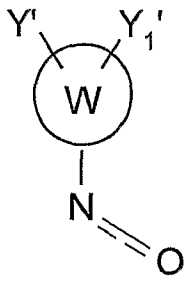
the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

The compounds of the general formula I can be prepared by initially converting a heterocyclic amino compound of the general formula 1 in which Y′ and Y1′ have the meanings stated for Y and Y1

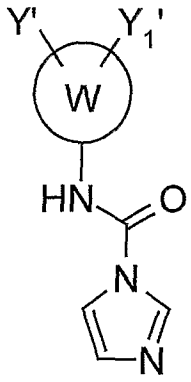


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by reaction with phosgene, diphosgene or triphosgene, or by activation with carbonyldiimidazole or a reagent of a similar type, into a reactive intermediate such as, for example, the isocyanate 2 or the carbonylimidazole derivative 3.



2



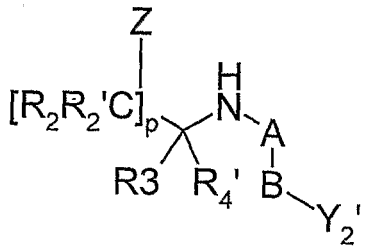
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These reactive derivatives are prepared in an inert organic solvent such as, for example, toluene, 1,2-dichloroethane or THF, at a temperature between -20°C and the reflux temperature of the particular solvent. Preferred solvents are toluene and 1,2-dichlorethane, and preferred reaction temperatures are from -20 to +5°C during the addition and reflux temperature for completion of the reaction. The reaction can be assisted by addition of a base, but is preferably carried out without addition of base.

The reactive derivatives of the general formula 2 can be isolated, but the intermediates are preferably used without further purification, where appropriate after

replacement of the solvent, directly for further reaction.

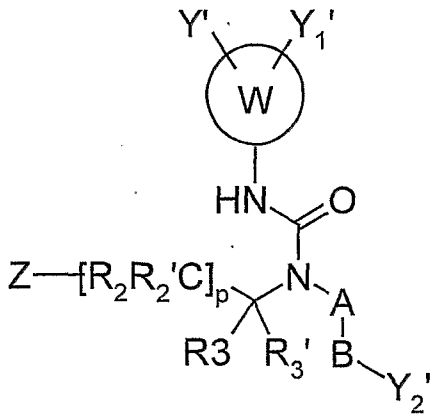
Reaction of the intermediates with a structural unit of the general formula 4 in which Z is COOR or CN is carried out in an inert organic solvent such as, for example, toluene, chlorobenzene, THF, dioxane or ethyl acetate, at a temperature between room temperature and the reflux temperature of the solvent. The reaction can be assisted by addition of a base such as, for example, triethylamine or potassium tert-butoxide, but is preferably carried out without addition of base. The initial linkage of the reactive intermediates 2 or 3 with the amino derivative of the general formula 4 and the subsequent ring closure to form the central heterocycle is preferably carried out in one step.



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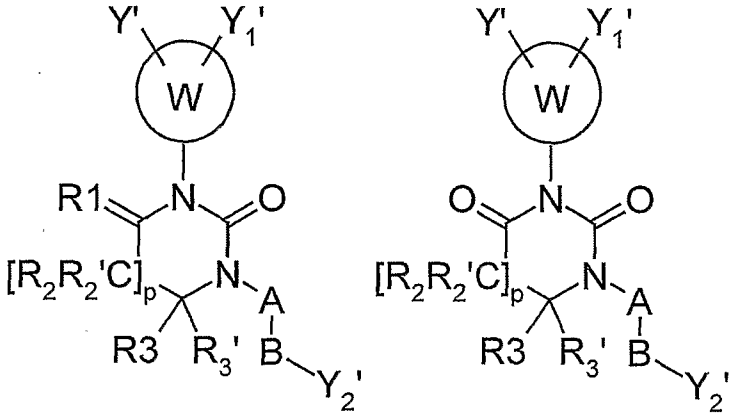
However, it is also possible alternatively to form the central heterocycle in a second step by heating the open-chain intermediate of the general formula 5 in a higher-boiling solvent or in aqueous mineral acids.

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In the case where Z is CN, the products of the general formula Ia (R1 = N) are obtained and can be converted through the action of aqueous mineral acid into compounds of the general formula Ib.

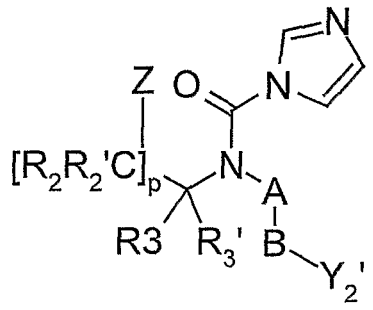


Ia Ib

The compounds of the general formulae Ia and Ib prepared in this way, in which the variables have the meanings stated above for the compound of the general formula I, can be converted by derivatization reactions known to the skilled worker into compounds of the general formula I.

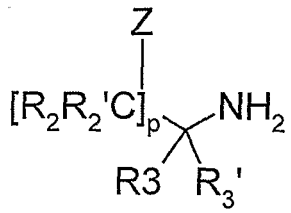
An alternative approach to compounds of the general formula I is provided by reaction of the structural unit 4 with carbonyldiimidazole, phosgene, diphosgene or triphosgene to give a reactive intermediate. The reaction is preferably carried out with carbonyldiimidazole in an inert organic solvent such as, for example, toluene, 1,2-

dichloroethane or THF at a temperature between -20°C and RT. THF is the particularly preferred solvent. The intermediates such as, for example, the derivatives of the general formula 6 (from reaction of 4 with carbonyldiimidazole) are then reacted in a solvent such as, for example, DMF, toluene, 1,2-dichloroethane or THF with a heterocyclic amino compound of the general formula 1. The reaction is preferably carried out at a temperature between RT and the boiling point of the solvent. Open-chain intermediates are preferably cyclized directly to compounds of the general formula Ia and b, which can be converted by further derivatization reactions known to the skilled worker into compounds of the general formula I.

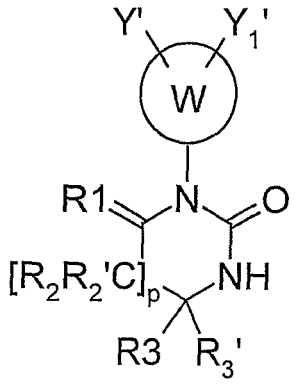


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The compounds of the general formula Ia can additionally be obtained by reacting compounds of the general formulae 2 and 3 with a structural unit of the general formula 7.



7



8

The resulting derivatives of the general formula 8 are then converted by the action of a halide Hal-A'-B'-Y_2' or a related reagent of similar reactivity in which A', B' and Y_2' have the meanings mentioned for A, B and Y_2, and which are obtainable by conventional processes known to the skilled worker, into compounds of the general formula Ia.

The reactions are preferably carried out in an organic solvent such as, for example, dimethylformamide, N-methylpyrrolidone, ethyl acetate or acetone in the presence of a base such as, for example, potassium carbonate, caesium carbonate, sodium hydride or potassium tert-butoxide. Dimethylformamide and caesium carbonate are preferably used.

All reactions for the synthesis of the compounds of the formula (I) are per se well-known to the skilled person and can be carried out under standard conditions according to or analogously to procedures described in the literature, for example in Houben-Weyl, Methoden der Organischen Chemie (Methods of Organic Chemistry), Thieme-Verlag, Stuttgart, or Organic Reactions, John Wiley & Sons, New York.

It may be noted that, during or after the process, some intermediates compounds or some compounds of formula (I) may be transformed to obtain some (or other) compounds of formula (I) and for that, to obtain products or other products of formula (I), these products may be subjected if desired, and necessary, to one or more of the following conversion reactions, in any order:

a) a reaction for esterification of an acid function,

b) a reaction for saponification of an ester function to an acid function,

c) a reaction for oxidation of an alkylthio group to the corresponding sulfoxide or sulfone group,

d) a reaction for conversion of a ketone function to an oxime function,

e) a reaction for reducing a free or esterified carboxyl function to an alcohol function,

f) a reaction for conversion of an alkoxy function to a hydroxyl function, or alternatively of a hydroxyl function to an alkoxy function,

g) a reaction for oxidation of an alcohol function to an aldehyde, acid or ketone function,

h) a reaction for conversion of a nitrile radical to a tetrazolyl,

i) a reaction for reduction of nitro compounds to amino compounds,

j) a reaction for removal of the protecting groups that may be borne by the protected reactive functions,

k) a reaction for salification with a mineral or organic acid or with a base to obtain the corresponding salt,

l) a reaction for resolution of the racemic forms to resolved products,

said products of formula (I) thus obtained being in any possible racemic, enantiomeric or diastereoisomeric isomer form.

It may be noted that such reactions for converting substituents into other substituents may also be performed on the starting materials, and also on the intermediates as defined above before continuing the synthesis according to the reactions indicated in the process described above.

The various reactive functions that may be borne by certain compounds of the reactions defined above may, if necessary, be protected: these are, for example, hydroxyl, acyl, free carboxyl or amino and monoalkylamino radicals, which may be protected with the appropriate protecting groups.

The following nonexhaustive list of examples of protection of reactive functions may be mentioned:
- the hydroxyl groups may be protected, for example, with alkyl radicals such as tert-butyl, trimethylsilyl, tert-butyldimethylsilyl, methoxymethyl, tetrahydropyranyl, benzyl or acetyl,
- the amino groups may be protected, for example, with acetyl, trityl, benzyl, tert-butoxycarbonyl, benzyloxycarbonyl, phthalimido radicals or other radicals known in peptide chemistry,
- the acyl groups such as the formyl group may be protected, for example, in the form of cyclic or noncyclic ketals or thioketals such as dimethyl or diethylketal or ethylene dioxyketal, or diethylthioketal or ethylenedithioketal,
- the acid functions of the products described above may be, if desired, amidated with a primary or secondary amine, for example in methylene chloride in the presence, for example, of 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride at room temperature,
- the acid functions may be protected, for example, in the form of esters formed with readily cleavable esters such as benzyl esters or tert-butyl esters, or esters known in peptide chemistry.

These reactions a) to k) indicated above may be performed, for example, as indicated below.

a) The products described above may, if desired, undergo, on the possible carboxyl functions, esterification reactions that may be performed according to the usual methods known to those skilled in the art.

b) The possible conversions of ester functions into an acid function of the products described above may be, if desired, performed under the usual conditions known to those skilled in the art, especially by acid or alkaline hydrolysis, for example with sodium hydroxide or potassium hydroxide in alcoholic medium such as, for

example, in methanol, or alternatively with hydrochloric acid or sulfuric acid.

c) The possible alkylthio groups in the products described above, in which the alkyl radical is optionally substituted with one or more halogen atoms, especially fluorine, may, if desired, be converted into the corresponding sulfoxide or sulfone functions under the usual conditions known to those skilled in the art such as, for example, with peracids such as, for example, peracetic acid or meta-chloroperbenzoic acid, or alternatively with ozone, oxone or sodium periodate in a solvent such as, for example, methylene chloride or dioxane at room temperature.

The production of the sulfoxide function may be promoted with an equimolar mixture of the product containing an alkylthio group and the reagent such as, especially, a peracid.

The production of the sulfone function may be promoted with a mixture of the product containing an alkylthio group with an excess of the reagent such as, especially, a peracid.

d) The reaction for conversion of a ketone function into an oxime may be performed under the usual conditions known to those skilled in the art, such as, especially, a reaction in the presence of an optionally O-substituted hydroxylamine in an alcohol such as, for example, ethanol, at room temperature or with heating.

e) The possible free or esterified carboxyl functions of the products described above may be, if desired, reduced to an alcohol function by the methods known to those skilled in the art: the possible esterified carboxyl functions may be, if desired, reduced to an alcohol function by the methods known to those skilled in the art and especially with lithium aluminum hydride in a solvent such as, for example, tetrahydrofuran or dioxane or ethyl ether.

The possible free carboxyl functions of the products described above may be, if desired, reduced to an alcohol function especially with boron hydride.

f) The possible alkoxy functions such as, especially, methoxy, in the products described above, may be, if desired, converted into a hydroxyl function under the usual conditions known to those skilled in the art, for example with boron tribromide in a solvent such as, for example, methylene chloride, with pyridine hydrobromide or hydrochloride or with hydrobromic acid or hydrochloric acid in water or trifluoroacetic acid at reflux.

g) The possible alcohol functions of the products described above may be, if desired, converted into an aldehyde or acid function by oxidation under the usual conditions known to those skilled in the art, such as, for example, by the action of manganese oxide to obtain the aldehydes, or of Jones' reagent to access the acids.

h) The possible nitrile functions of the products described above may be, if desired, converted into tetrazolyl under the usual conditions known to those skilled in the art, such as, for example, by cycloaddition of a metal azide such as, for example, sodium azide or a trialkyltin azide on the nitrile function, as indicated in the method described in the article referenced as follows:

J. Organometallic Chemistry., 33, 337 (1971) KOZIMA S. et al.

It may be noted that the reaction for conversion of a carbamate into urea and especially of a sulfonylcarbamate into sulfonylurea may be performed, for example, at the reflux point of a solvent such as, for example, toluene, in the presence of the appropriate amine.

It is understood that the reactions described above may be performed as indicated or alternatively, where appropriate, according to other common methods known to those skilled in the art.

i) The removal of protecting groups such as, for example, those indicated above may be performed under the usual conditions known to those skilled in the art, especially via an acid hydrolysis performed with an acid such as hydrochloric acid, benzenesulfonic acid or para-toluenesulfonic acid, formic acid or trifluoroacetic acid, or alternatively via a catalytic hydrogenation.
The phthalimido group may be removed with hydrazine.
A list of various protecting groups that may be used will be found, for example, in patent BF 2 499 995.

j) The products described above may, if desired, be subjected to salification reactions, for example with a mineral or organic acid or with a mineral or organic base according to the usual methods known to those skilled in the art.

k) The possible optically active forms of the products described above may be prepared by resolving the racemic mixtures according to the usual methods known to those skilled in the art.

The possible reactive functions are hydroxyl or amino functions. Usual protecting groups are used to protect these functions. Examples that may be mentioned include the following protecting groups for the amino radical: tert-butyl, tert-amyl, trichloroacetyl, chloroacetyl, benzhydryl, trityl, formyl, benzyloxycarbonyl.
Protecting groups for the hydroxyl radical that may be mentioned include radicals such as formyl, chloroacetyl, tetrahydropyranyl, trimethylsilyl and tert-butyldimethylsilyl.

It is clearly understood that the above list is not limiting and that other protecting groups, which are known, for example, in peptide chemistry, may be used. A list of such protecting groups is found, for example, in French patent 2 499 995, the content of which is incorporated herein by reference.

The possible reactions for removal of the protecting groups are performed as indicated in said patent 2 499 995. The preferred method of removal is acid hydrolysis with acids chosen from hydrochloric acid, benzenesulfonic acid or para-toluenesulfonic acid, formic acid or trifluoroacetic acid. Hydrochloric acid is preferred.

The possible reaction for hydrolysis of the >C=NH group to a ketone group is also preferably performed using an acid such as aqueous hydrochloric acid, for example at reflux.

An example of removal of the tert-butyldimethylsilyl group using hydrochloric acid is given below in the examples.

- The possible esterification of a free OH radical is performed under standard conditions. An acid or a functional derivative, for example an anhydride such as acetic anhydride in the presence of a base such as pyridine, may be used, for example.

The possible esterification or salification of a COOH group is performed under the standard conditions known to those skilled in the art.

- The possible amidation of a COOH radical is performed under standard conditions. A primary or secondary amine may be used on a functional derivative of the acid, for example a symmetrical or mixed anhydride.

The products of formula (I) according to the present invention may be prepared by application or adaptation of known methods and especially of the methods described in the literature such as, for example, those described by R.C. Larock in: Comprehensive Organic Transformations, VCH publishers, 1989.

In the reactions described below, it may be necessary to protect reactive functional groups such as, for example, hydroxyl, amino, imino, thio or carboxyl groups, when these groups are desired in the final product but when

their participation is not desired in the reactions for synthesizing the products of formula (I). Conventional protecting groups may be used in accordance with the usual standard practices, for instance those described, for example, by T.W. Greene and P.G.M. Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991.

The heterocyclic amino compounds of the general formula 1 are in some cases commercially available or are described in the literature or can be obtained from derivatives disclosed in the literature by transformations known to a person skilled in the art. The precursors 4 can be obtained for example by reductive amination of aldehydes of the general formula OHC-A''-B'-Y_2', which are commercially available or are prepared by conventional processes, with amino acid derivatives or amino nitriles of the general formula 7.

The products of the present invention are endowed with advantageous pharmacological properties: it has been found that they especially have inhibitory properties on protein kinases

Among these protein kinases, mention is made especially of IGF1R.

Mention is also made of FAK. Mention is also made of AKT.

These properties thus make products of general formula (I) of the present invention usable as medicinal products for treating malignant tumours.

The products of formula (I) may also be used in the veterinary field.

A subject of the invention is thus the use, as medicinal products, of the pharmaceutically acceptable products of

general formula (I).

A subject of the invention is particularly the use, as medicinal products, of the products, the names of which are given hereinbelow:

- 3-(5-Isopropyl-thiazol-2-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl-imidazolidine-2,4- dione
- 3-(5-tert-Butyl-2H-pyrazol-3-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl-imidazolidine-2,4- dione
- 3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl- imidazolidine-2,4-dione
- 3-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl- imidazolidine-2,4-dione
- 5,5-Dimethyl-3-(2-oxo-4-trifluoromethyl-2H-1-benzopyran-7-yl)-1-pyridin-4-ylmethyl-imidazolidine-2,4-dione trifluoroacetate
- 3-(2,2-Dimethyl-4-oxo-4H-1,3-benzodioxin-7-yl)-5,5-dimethyl-1-pyridin-4-ylmethyl-imidazolidine-2,4-dione trifluoroacetate
- 3-(1-Acetyl-2,3-dihydro-1H-indol-5-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl-imidazolidine- 2,4-dione

the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, and also the pharmaceutically acceptable addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

A subject of the invention is particularly the use, as medicinal products, of the products, the names of which

are given hereinbelow:

- 3-(5-Isopropyl-thiazol-2-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl-imidazolidine-2,4- dione

- 3-(5-tert-Butyl-2H-pyrazol-3-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl-imidazolidine-2,4- dione

- 3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl- imidazolidine-2,4-dione

- 3-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl- imidazolidine-2,4-dione

the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, and also the pharmaceutically acceptable addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

The products may be administered via the parenteral, buccal, perlingual, rectal or topical route.

A subject of the invention is also pharmaceutical compositions, characterized in that they contain, as active principle, at least one of the medicinal products of general formula (I).

These compositions may be in the form of injectable solutions or suspensions, tablets, coated tablets, capsules, syrups, suppositories, creams, ointments and lotions. These pharmaceutical forms are prepared according to the usual methods. The active principle may be incorporated into excipients usually used in these compositions, such as aqueous or nonaqueous vehicles, talc, gum arabic, lactose, starch, magnesium stearate,

cocoa butter, fatty substances of animal or plant origin, paraffin derivatives, glycols, various wetting, dispersing or emulsifying agents, and preserving agents.

The usual dose, which varies according to the individual treated and the complaint under consideration, may be, for example, from 10 mg to 500 mg per day orally in man.

The present invention thus relates to the use of products of formula (I) as defined above or of pharmaceutically acceptable salts of said products of formula (I) for the preparation of medicinal products for inhibiting the activity of protein kinases and especially of a protein kinase.

The present invention thus relates to the use of products of formula (I) as defined above or of pharmaceutically acceptable salts of said products of formula (I) in which the protein kinase is a protein tyrosine kinase.

The present invention thus relates to the use of products of formula (I) as defined above or of pharmaceutically acceptable salts of said products of formula (I) in which the protein kinase is chosen from the following group: IGF1, Raf, EGF, PDGF, VEGF, Tie2, KDR, Flt1-3, FAK, Src, Abl, cKit, cdk1-9, Aurora1-2, cdc7, Akt, Pdk, S6K, Jnk, IR, FLK-1, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, PLK, Pyk2, CDK7, CDK2 et EGFR.

Such protein kinase is chosen more especially from the following group: IGF1, cdc7, Aurora1-2, Src, Jnk, FAK, KDR, IR, Tie2, CDK7, CDK2 et EGFR.

The present invention thus relates particularly to the use of products of formula (I) as defined above or of pharmaceutically acceptable salts of said products of formula (I) in which the protein kinase is IGF1R.

The present invention also relates to the use of products of formula (I) as defined above or of pharmaceutically

acceptable salts of said products of formula (I) in which the protein kinase is FAK.

The present invention also relates to the use of products of formula (I) as defined above or of pharmaceutically acceptable salts of said products of formula (I) in which the protein kinase is AKT.

The present invention also relates to the use of products of formula (I) as defined above or of pharmaceutically acceptable salts of said products of formula (I) in which the protein kinase is in a cell culture, and also to this use in a mammal.

The present invention thus relates to the use of products of formula (I) as defined above or of pharmaceutically acceptable salts of said products of formula (I) for the preparation of a medicinal product for preventing or treating a disease characterized by deregulation of the activity of a protein kinase and especially such a disease in a mammal.

The present invention relates to the use of products of formula (I) as defined above or of pharmaceutically acceptable salts of said products of formula (I) for the preparation of a medicinal product for preventing or treating a disease belonging to the following group: disorders of blood vessel proliferation, fibrotic disorders, disorders of mesangial cell proliferation, acromegaly, metabolic disorders, allergies, asthma, Crohn's disease, thrombosis, diseases of the nervous system, retinopathy, psoriasis, rheumatoid arthritis, diabetes, muscle degeneration, aging, age related macula degeneration, oncology diseases and cancer.

The present invention thus relates to the use of products of formula (I) as defined above or of pharmaceutically acceptable salts of said products of formula (I) for the

preparation of a medicinal product for treating oncology diseases.

The present invention relates particularly to the use of products of formula (I) as defined above or of pharmaceutically acceptable salts of said products of formula (I) for the preparation of a medicinal product for treating cancers.

Among these cancers, the present invention is most particularly of interest in the treatment of solid tumours and the treatment of cancers that are resistant to cytotoxic agents.

Among these cancers, the present invention relates most particularly to the treatment of breast cancer, stomach cancer, cancer of the colon, lung cancer, cancer of the ovaries, cancer of the uterus, brain cancer, cancer of the kidney, cancer of the larynx, cancer of the lymphatic system, cancer of the thyroid, cancer of the urogenital tract, cancer of the tract including the seminal vesicle and prostate, bone cancer, cancer of the pancreas and melanomas.

The present invention is even more particularly of interest in treating breast cancer, cancer of the colon and lung cancer.

The present invention also relates to the use of products of formula (I) as defined above or of pharmaceutically acceptable salts of said products of formula (I) for the preparation of a medicinal product for cancer chemotherapy.

As medicinal products according to the present invention for cancer chemotherapy, the products of formula (I) according to the present invention may be used alone or in combination with chemotherapy or radiotherapy or alternatively in combination with other therapeutic agents.

The present invention thus relates especially to the pharmaceutical compositions as defined above, also containing active principles of other chemotherapy medicinal products for combating cancer.

Such therapeutic agents may be commonly used antitumour agents.

As examples of known inhibitors of protein kinases, mention may be made especially of butyrolactone, flavopiridol, 2-(2-hydroxyethylamino)-6-benzylamino-9-methylpurine, olomucine, Glivec and Iressa.

The products of formula (I) according to the present invention may thus also be advantageously used in combination with antiproliferative agents: as examples of such antiproliferative agents, but without, however, being limited to this list, mention may be made of aromatase inhibitors, antiestrogens, the topoisomerase I inhibitors, the topoisomerase II inhibitors, microtubule-active agents, alkylating agents, histone deacetylase inhibitors, farnesyl transferase inhibitors, COX-2 inhibitors, MMP inhibitors, mTOR inhibitors, antineoplastic antimetabolites, platinum compounds, compounds that reduce the activity of protein kinases and also anti-angiogenic compounds, gonadorelin agonists, antiandrogens, bengamides, biphosphonates and trastuzumab.

Examples that may thus be mentioned include anti-microtubule agents, for instance taxoids, vinca alkaloids, alkylating agents such as cyclophosphamide, DNA-intercalating agents, for instance cis-platinum, agents that are interactive on topoisomerase, for instance camptothecin and derivatives, anthracyclines, for instance adriamycin, antimetabolites, for instance 5-fluorouracil and derivatives, and the like.

The present invention thus relates to products of formula (I) as protein kinase inhibitors, said products of formula (I) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts of said products of formula (I) with pharmaceutically acceptable mineral and organic acids or with pharmaceutically acceptable mineral and organic bases, and also the prodrugs thereof.

The present invention relates particularly to products of formula (I) as defined above as IGF1R inhibitors.

The present invention also relates to products of formula (I) as defined above as FAK inhibitors.

The present invention also relates to products of formula (I) as defined above as AKT inhibitors.

The present invention relates more particularly to the products of formula (IA) as defined above as IGF1R inhibitors.

The examples whose preparation follows are thus products of formula (I) as defined above and illustrate the present invention without, however, limiting it.

Example 1 : 5-Isopropyl-3-(4-phenyl-thiazol-2-yl)-1-pyridin-4-ylmethyl-imidazolidine-2,4- dione

550 mg (2,8mmol) diphosgene in 20ml 1,2-dichlorethane were treated at -20°C with a solution of 198mg (1,1mmol) 2-amino-4-phenylthiazole in 20 ml 1,2-dichlorethane. The mixture was allowed to come to room temperature and then was refuxed for 5h. The solvent was evaporated and the residual oil was taken up in 40ml THF. 250mg (2.25mmol) 3-methyl-2-[(pyridin-4-ylmethyl)-amino]-butyric acid methyl ester in 20 ml THF were added and the mixture was refluxed for 10h. The solvent was evaporated and the residue purified by preparative HPLC (C18 reverse phase

column, elution with a water/acetonitrile gradient with 0.1% trifluoracetic acid). Lyophilization of the selected fractions yielded 48 mg of the desired compound.

MS(ES+): m/e = 393

HPLC Retention time [min] = 1.54

Example 2 : 5-Isopropyl-3-(5-phenyl-pyridin-2-yl)-1-pyridin-4-ylmethyl-imidazolidine-2,4- dione

This product was prepared according to the procedure described for example 1 using 1.1g (5.6mmol) diphosgene, 383mg (2.25mmol) 5-phenyl-pyridin-2-ylamine and 500mg (2.25mmol) 3-methyl-2-[(pyridin-4-ylmethyl)-amino]-butyric acid methyl ester. Yield: 46mg

MS(ES+): m/e = 387

HPLC Retention time [min] = 1.43

Example 3 : 5-Isopropyl-3-(2-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-6-yl)-1-pyridin-4-ylmethyl-imidazolidine-2,4-dione trifluoroacetate

This product was prepared according to the procedure described for example 1 using 757mg (4.5mmol) 2-amino-6-fluorobenzothiazole, 1.3g (6.6mmol) diphosgene, 500mg (2.57mmol) 6-amino-2-methyl-2H-1,4-benzothiazin-3-(4H)-one, 571mg (2.57mmol) 3-methyl-2-[(pyridin-4-ylmethyl)-amino]-butyric acid methyl ester and dioxane instead of THF . Yield: 675mg

MS(ES+): m/e = 411

HPLC Retention time [min] = 1.49

Example 4 : 5-Isopropyl-3-(1-methyl-1H-indazol-5-yl)-1-pyridin-4-ylmethyl-imidazolidine-2,4-dione; compound with trifluoro-acetic acid

616mg (3.8mmol) carbonyldiimidazole and 31 mg (0.45mmol) imidazole in 8ml THF were treated at 0°C with 462.1mg

(3.14mmol) 1-methyl-1H-indazol-6-ylamine in 10 ml THF and stirred for 1h. 500mg (2.25mmol) 3-methyl-2-[(pyridin-4-ylmethyl)-amino]-butyric acid methyl ester were added and the mixture was stirred under reflux for 3h. After standing over night, the mixture was filtered, the solvent was evaporated and the residue purified by preparative HPLC (C18 reverse phase column, elution with a water/acetonitrile gradient with 0.1% trifluoracetic acid). Lyophilization of the selected fractions yielded 135mg of the desired compound.

MS(ES+): m/e = 364

HPLC Retention time [min] = 1.10

Example 5 - 5-Isopropyl-1-pyridin-4-ylmethyl-3-quinolin-2-yl-imidazolidine-2,4-dione; compound with trifluoro-acetic acid

This product was prepared according to the procedure described for example 4 using 31 mg (0.45mmol) Imidazol 988 mg (3.82mmole) carbonyldiimidazole, 454mg (3.15 mmole) 2-aminoquinoline and 500mg (2.249mmol) 3-methyl-2-[(pyridin-4-ylmethyl)-amino]-butyric acid methyl ester.

Yield: 660 mg

MS(ES+): m/e = 361

HPLC Retention time [min] = 1.21

Example 6 : 5-Isopropyl-1-pyridin-4-ylmethyl-3-(2-trifluoromethyl-3H-benzoimidazol-5-yl)- imidazolidine-2,4-dione trifluoroacetate

This product was prepared according to the procedure described for example 4 using 616mg (3.8mmol) carbonyldiimidazole

31mg (0.45mmol) imidazole, 632 mg (3.14mmol) 5-amino-2-(trifluormethyl)-benzimidazole, 500mg (2.25mmol) 3-

methyl-2-[(pyridin-4-ylmethyl)-amino]-butyric acid methyl ester. Yield:380mg
MS(ES+): m/e = 418
HPLC Retention time [min] = 1.14

Example 7 : 3-(5-Bromo-pyridin-2-yl)-5,5-dimethyl-1-pyridin-4-ylmethyl-imidazolidine-2,4-dione; compound with trifluoro-acetic acid
This product was prepared according to the procedure described for example 4 using 4.0g (24.5mmol) carbonyldiimidazole 0.44g (6.5mmol) imidazole, 3.5g (20.2mmol) 2-amino-5-bromopyridine and 3.0g (14.4mmol) 2-methyl-2-[(pyridin-4-ylmethyl)-amino]-propionic acid methyl ester. Yield: 900 mg
MS(ES+): m/e = 375
HPLC Retention time [min] = 0.96

Example 8 : 5,5-Dimethyl-3-(4-phenyl-thiazol-2-yl)-1-pyridin-4-ylmethyl-imidazolidine-2,4-dione; compound with trifluoro-acetic acid
This product was prepared according to the procedure described for example 4 using 778mg (4.8mmol) carbonyldiimidazole 73mg (1.08mmol) imidazole, 592mg (3.36mmol) 2-amino-4-phenylthiazole and 489mg (2.35mmol) 2-methyl-2-[(pyridin-4-ylmethyl)-amino]-propionic acid methyl ester. Yield: 1000 mg
MS(ES+): m/e = 379
HPLC Retention time [min] = 1.37

Example 9 : 5,5-Dimethyl-3-(2-oxo-4-trifluoromethyl-2H-1-benzopyran-7-yl)-1-pyridin-4-ylmethyl-imidazolidine-2,4-dione trifluoroacetate

5,1 g (25 mmol) 2-methyl-2-[(pyridin-4-ylmethyl)-amino]-propionic acid methyl ester were dissolved in 102 ml tetrahydrofurane and treated at 0°C with 4.46 g (27.5 mmol) carbonyldiimidazole. The mixture was stirred for 15 min at 0°C and 1h at RT. A 2ml aliquot of this solution was given to 115mg (0.5mmol) 7-amino-4-trifluoromethylcoumarine, dissolved in 1 ml DMF, and stirred at 50 °C for 15 h. Then the reaction mixture was filtered and the sovent was evapotated. The residue was taken up in 20 ml ethylacetate and washed with 20 ml 5% NaHCO3 solution and 20 ml 5% NaCl solution. The phases were separated, the organic phase dried of Chromabond XTR and the solvent evaporated. The raw product was purified by preparative HPLC (C18 reverse phase column, elution with a water/acetonitrile gradient with 0.1% trifluoracetic acid) Yield: 7.7 mg

MS(ES+): m/e = 432

HPLC Retention time [min] = 1.45

Example 10 : 5,5-Dimethyl-3-[5-(propane-1-sulfonyl)-1H-benzimidazol-2-yl]-1-pyridin-4-ylmethyl-imidazolidine-2,4-dione trifluoroacetate

This product was prepared according to the procedure described for example 9 using 120mg 2-amino-5-N-propylsulphonylbenzimidazole

Yield : 43.5mg

MS(ES+): m/e = 441.15

HPLC Retention time [min] = 0.96

Example 11 : 5,5-Dimethyl-3-(5-phenoxy-1H-benzimidazol-2-yl)-1-pyridin-4-ylmethyl-imidazolidine-2,4-dione trifluoroacetate

This product was prepared according to the procedure described for example 9 using 113mg 5-phenoxy-1h-benzoimidazol-2-ylamine. Yield : 30.1mg
MS(ES+): m/e = 427.16
HPLC Retention time [min] = 1.31

Example 12 : 5,5-Dimethyl-1-pyridin-4-ylmethyl-3-quinolin-3-yl-imidazolidine-2,4-dione trifluoroacetate
This product was prepared according to the procedure described for example 9 using 72mg 3-aminoquinoline. Yield : 32.2mg
MS(ES+): m/e = 346.14
HPLC Retention time [min] = 0.96

Example 13 : 3-[5-(2-Chloro-6-fluoro-benzylsulfanyl)-2H-1,2,4-triazol-3-yl]-5,5-dimethyl-1-pyridin-4-ylmethyl-imidazolidine-2,4-dione trifluoroacetate
This product was prepared according to the procedure described for example 9 using 129mg 3-[(2-chloro-6-fluorobenzyl)sulfanyl]-1h-1,2,4-triazol-5-amine
Yield : 37.4mg
MS(ES+): m/e = 460.09
HPLC Retention time [min] = 1.24

Example 14 : 5,5-Dimethyl-3-(5-morpholin-4-yl-4H-1,2,4-triazol-3-yl)-1-pyridin-4-ylmethyl-imidazolidine-2,4-dione trifluoroacetate
This product was prepared according to the procedure described for example 9 using 84.6mg 3-amino-5-morpholino-1,2,4-triazole. Yield : 50.8mg
MS(ES+): m/e = 371.17

1H-NMR (500 MHz, DMSO/TMS): d = 8.70 (d, 2H); 7.55 (d, 2H); 4.20 (d, 2H); 3.65 (m, 4H); 3.22 (m, 4H); 1.58 (s, 6 H)

Example 15 : 5,5-Dimethyl-3-(5-morpholin-4-yl-1,3,4-oxadiazol-2-yl)-1-pyridin-4-ylmethyl-imidazolidine-2,4-dione trifluoroacetate

This product was prepared according to the procedure described for example 9 using 84.1mg 5-morpholin-4-yl-1,3,4-oxadiazol-2-ylamine. Yield : 13.3mg

MS(ES+): m/e = 372.16

HPLC Retention time [min] = 0.75

Example 16 : 3-(2,2-Dimethyl-4-oxo-4H-1,3-benzodioxin-7-yl)-5,5-dimethyl-1-pyridin-4-ylmethyl-imidazolidine-2,4-dione trifluoroacetate

This product was prepared according to the procedure described for example 9 using 96.6mg 7-amino-2,2-dimethyl-benzo[1,3]dioxin-4-one. Yield : 33mg

MS(ES+): m/e = 395

HPLC Retention time [min] = 1.15

Example 17 : 5,5-Dimethyl-3-(4-methyl-thiazol-2-yl)-1-quinolin-4-ylmethyl-imidazolidine-2,4- dione

To a solution of 344 mg di-imidazol-1-yl-methanone and 18 mg imidazole in 6 ml tetrahydrofuran a solution of 300 mg 2-amino-4-methyl-thiazole in 1 ml tetrahydrofuran was slowly added at 0°C. After stirring at 0°C for 1 hour 320mg 2-methyl-2-[(quinolin-4-ylmethyl)-amino]-propionic acid methyl ester were added and the reaction mixture was allowed to warm up to room temperature. After 2 hours stirring at room temperature the solution was heated for 1 hour at 70°C. After cooling to room temperature the

solvent of the mixture was removed under reduced pressure and the residue was purified by preparative HPLC (C18 reverse phase column, elution with a water/ acetonitrile gradient with 0.1% trifluoroacetic acid). Lyophilization of the solution yielded a white solid

Yield: 575 mg.

MS(ES+): m/e = 367

1H-NMR (500 MHz, DMSO/TMS): d = 9.03 (d, 1H), 8.38 (d, 1H); 8.18 (d, 1H); 7.97 (t, 1H); 7.89 (d, 1H); 7.84 (t, 1H); 7.32 (s, 1H); 5.26 (s, 2H); 2.38 (s, 3H); 1.50 (s, 6 H)

Example 18 : 5,5-Dimethyl-1-quinolin-4-ylmethyl-3-(4-trifluoromethyl-thiazol-2-yl)-imidazolidine-2,4- dione

This compound was prepared in analogy to example 17 by using 300 mg of the corresponding heteroarylamine instead of 2-amino-4-methyl-thiazole. Yield : 45mg

MS(ES+): m/e = 421

1H-NMR (500 MHz, DMSO/TMS): d = 8.97 (d, 1H), 8.42 (s, 1H); 8.34 (d, 1H); 8.15 (d, 1H); 7.93 (t, 1H); 7.87 (d, 1H); 7.81 (t, 1H); 5.26 (s, 2H); 1.50 (s, 6 H)

Example 19 : 3-(4-tert-Butyl-thiazol-2-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl-imidazolidine-2,4- dione

This compound was prepared in analogy to example 17 by using 300 mg of the corresponding heteroarylamine instead of 2-amino-4-methyl-thiazole. Yield : 246mg

MS(ES+): m/e = 409

1H-NMR (500 MHz, DMSO/TMS): d = 8.97 (d, 1H), 8.33 (d, 1H); 8.15 (d, 1H); 7.93 (t, 1H); 7.85 (d, 1H); 7.81 (t, 1H); 7.28 (s, 1H); 5.23 (s, 2H); 1.48 (s, 6H); 1.30 (s, 9H)

Example 20 : 5,5-Dimethyl-3-(5-methyl-thiazol-2-yl)-1-quinolin-4-ylmethyl-imidazolidine-2,4- dione

This compound was prepared in analogy to example 17 by using 300 mg of the corresponding heteroarylamine instead of 2-amino-4-methyl-thiazole. Yield : 195mg

MS(ES+): m/e = 367

1H-NMR (500 MHz, DMSO/TMS): d = 8.99 (d, 1H), 8.35 (d, 1H); 8.16 (d, 1H); 7.95 (t, 1H); 7.83 (m, 2H); 7.48 (s, 1H); 5.25 (s, 2H); 2.48 (s, 3H); 1.50 (s, 6H)

Example 21 : 3-(5-Isopropyl-thiazol-2-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl-imidazolidine-2,4- dione

This compound was prepared in analogy to example 17 by using 300 mg of the corresponding heteroarylamine instead of 2-amino-4-methyl-thiazole. 2-Amino-isopropyl-1,3-thiazole was prepared according to a procedure published by Paolo Pevarello et al. , US Patent Application 2003134836.

Yield: 204 mg

MS(ES+): m/e = 395

1H-NMR (500 MHz, DMSO/TMS): d = 8.97 (d, 1H), 8.33 (d, 1H); 8.15 (d, 1H); 7.92 (t, 1H); 7.78 (m, 2H); 7.52 (s, 1H); 5.23 (s, 2H); 3.26 (m, 1H); 1.48 (s, 6H); 1.30 (d, 6H)

Example 22 : 3-(5-Cyclopropyl-2-methyl-2H-pyrazol-3-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl- imidazolidine-2,4-dione

The following compound was prepared in analogy to example 17 by using 300 mg 5-cyclopropyl-2-methyl-2H-pyrazol-3-ylamine instead of 2-amino-4-methyl-thiazole. The resulting crude product was purified in addition by flash

chromatography on silica gel with a dichloro-methane/ methanol gradient. Yield: 65 mg

MS(ES+): m/e = 390

1H-NMR (500 MHz, DMSO/TMS): d = 8.94 (d, 1H); 8.29 (d, 1H), 8.13 (d, 1H); 7.89 (t, 1H); 7.76 (t, 1H); 7.68 (d, 1H); 6.15 (s, 1H); 5.20 (s, 2H); 3.63 (s, 3H); 1.87 (m, 1H); 1.47 (s, 6H); 0.87 (m, 2 H); 0.65 (m, 2H)

Example 23 - 3-(5-tert-Butyl-2H-pyrazol-3-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl-imidazolidine-2,4- dione

To a solution of 426 mg triphosgene in 2 ml toluene at -20°C 200 mg 5-tert-butyl-2H-pyrazol-3-ylamine in 1 ml toluene were added and the mixture was stirred for 1 hour at room temperature. Afterwards the reaction mixture was heated for 1 hour at 80°C. After removal of the solvent under reduced pressure the residue was dissolved in 2 ml tetrahydrofuran and 371 mg 2-methyl-2-[(quinolin-4-ylmethyl)-amino]-propionic acid methyl ester in 1 ml toluene were added. The resulting solution was stirred for 1 hour at room temperature and then heated for 2 hours at 80°C. After cooling to room temperature the solid that separated was filtered off and the filtrate was purified by preparative HPLC (C18 reverse phase column, elution with a water/ acetonitrile gradient with 0.1% trifluoroacetic acid). Lyophilization of the solution yielded a solid, which was further purified by flash chromatography with a n-heptane/ ethylacetate gradient. The fractions containing the product were evaporated to yield a white solid. Yield: 8 mg

MS(ES+): m/e = 392

1H-NMR (500 MHz, DMSO/TMS): d = 13.80 (s, 1H); 8.89 (d, 1H), 8.27 (d, 1H); 8.09 (d, 1H); 7.83 (t, 1H); 7.72 (t, 1H); 7.55 (d, 1H); 6.13 (s, 1H); 5.13 (s, 2H); 1.41 (s, 6H); 1.30 (s, 9 H)

Example 24 - 3-(1-Acetyl-1H-indol-5-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl-imidazolidine-2,4- dione

a) N-Acetyl-5-nitroindole was prepared according to a procedure published Allan E. Hydorn; J. Org. Chem.; 1967; 32(12); 4100-4101 by using 1 g 5-nitroindole.

b) N-Acetyl-5-aminoindole: A mixture of 840 mg N-acetyl-5-nitroindole, 100 mg of 10% palladium on barium sulphate and 10 ml ethanol was stirred for 2 hours under hydrogen atmosphere. The mixture was filtered through a chem elut cartridge and the compound was eluted with ethanol. After concentration under reduced pressure the residue was purified by preparative HPLC (C18 reverse phase column, elution with a water/ acetonitrile gradient with 0.1% trifluoroacetic acid). Lyophilization of the solution yielded a white solid. Yield: 590 mg MS(ES+): m/e=175

As a side product of the above hydrogenation 160 mg of 1-(5-amino-2,3-dihydro-indol-1-yl)-ethanone were obtained. Yield: 160 mg MS(ES+): m/e=177.

c) The title compound was prepared in analogy to example 17 by using 300 mg N-acetyl-5-aminoindol instead of 2-amino-4-methyl-thiazole. The resulting crude product was purified in addition by flash chromatography on silica gel with a dichloro-methane/ methanol gradient. Yield: 130 mg

MS(ES+): m/e = 427

1H-NMR (500 MHz, DMSO/TMS): d = 8.90 (d, 1H); 8.43 (d, 1H), 8.29 (d, 1H); 8.10 (d, 1H); 7.96 (d, 1H); 7.85 (t,

1H); 7.73 (m, 2H); 7.68 (d, 1H); 7.42 (d, 1H); 6.85 (d, 1H); 5.18 (s, 2H); 2.69 (s, 3H); 1.46 (s, 6 H)

Example 25 - 3-(1-Acetyl-2,3-dihydro-1H-indol-5-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl-imidazolidine- 2,4-dione

a) 1-(5-amino-2,3-dihydro-indol-1-yl)-ethanone was by catalytic reduction of N-acetyl-5-nitroindole as described in example 24.

b) The title compound was prepared in analogy to example 17 by using 160 mg 1-(5-amino-2,3-dihydro-indol-1-yl)-ethanone as starting material. In this case the product was purified in addition by flash chromatography on silica gel with a ethylacetate / ethanol gradient.

Yield: 9 mg

MS(ES+): m/e = 429

1H-NMR (500 MHz, DMSO/TMS): d = 8.88 (d, 1H); 8.25 (d, 1H), 8.10 (m, 2H); 7.83 (t, 1H); 7.70 (t, 1H); 7.60 (d, 1H); 7.33 (s, 1H); 7.23 (d, 1H); 5.13 (s, 2H); 4.15 (t, 2H); 3.19 (t, 2H); 2.18 (s, 3H); 1.43 (s, 6 H)

Example 26 : 3-(1H-Indol-5-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl-imidazolidine-2,4-dione

To a solution of 20 mg 3-(1-acetyl-1H-indol-5-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl-imidazolidine-2,4- dione in 1 ml ethanol 2,6 mg potassium hydroxide were added and the resulting mixture was stirred for 1 hour at room temperature. The product was isolated by filtration, dissolved in 2 ml acetonitrile and 5 ml water and lyophilized to yield a white solid. Yield: 9 mg

MS(ES+): m/e = 385

1H-NMR (500 MHz, DMSO/TMS): d = 11.30 (s, 1H); 8.88 (d, 1H); 8.27 (d, 1H), 8.09 (d, 1H); 7.82 (t, 1H); 7.70 (t,

1H); 7.61 (m, 2H); 7.48 (d, 1H); 7.45 (t, 1H); 7.13 (dd, 1H); 6.51 (s, 1H); 5.15 (s, 2H); 1.44 (s, 6 H)

Example 27 - 3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl-imidazolidine-2,4-dione

1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone was prepared according to a procedure published by Daniel Elbaum et al. Patent Application US 6114365. The title compound was prepared in analogy to example 17 by using 100 mg 1-(6-amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone instead of 2-amino-4-methyl-thiazole. Yield: 28 mg

MS(ES+): m/e = 457

1H-NMR (500 MHz, DMSO/TMS): d = 8.97 (d, 1H); 8.34 (d, 1H), 8.14 (d, 1H); 8.08 (s, 1H); 7.93 (t, 1H); 7.77 (m, 2H); 7.49 (d, 1H); 7.12 (d, 1H); 5.23 (s, 2H); 3.93 (s, 2H); 2.19 (s, 3H); 1.45 (s, 6 H); 1.35 (s, 6H)

Example 28 - 3-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl- imidazolidine-2,4-dione

230 mg 3-(1-acetyl-3,3-dimethyl-2,3-dihydro-1*H*-indol-6-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl-imidazolidine-2,4-dione were dissolved in 5 ml water and 5 ml of an aqueous 2 N solution of hydrochloric acid in a process vial. After sealing with a teflon septum the vial was placed in the microwave cavity and the reaction mixture was stirred for 15 minutes at 120°C by microwave-assisted heating (Emrys Optimizer, Personal Chemistry). The solvent was removed under reduced pressure and the residue purified by preparative HPLC (C18 reverse phase column, elution with a water/ acetonitrile gradient with 0.1%

trifluoroacetic acid). Lyophilization of the solution yielded a white solid.

MS(ES+): m/e = 414

1H-NMR (500 MHz, DMSO/TMS): d = 8.97 (d, 1H); 8.34 (d, 1H), 8.15 (d, 1H); 7.93 (t, 1H); 7.69 (t, 1H); 7.73 (d, 1H); 7.18 (d, 1H); 6.78 (m, 2H); 5.20 (s, 2H); 3.32 (s, 2H); 1.44 (s, 6 H); 1.28 (s, 6H)

LC/UV/MS experiments have been conducted with a Waters 1525 pump, a Waters 2488 UV detector, and a multiplexed ESI-TOF mass spectrometer (Micromass MUX-LCT) using YMC J'sphere H80 (30*2.1 mm, 4u, 80A) columns. UV data have been recorded at 220 nm and at 254 nm. For gradient separation, H2O+0.05% TFA and ACN+ 0.05% TFA are mixed in 95:5 (0 min) to 5:95 (3.4 min) to 5:95 (4.4 min) ratios at a flow rate of 1 ml min-1.

The examples 29 to 70 whose preparation follows are thus products of formula (I) as defined above and illustrate the present invention without, however, limiting it.

Hereafter is described the general procedure for the synthesis of example 29 to 70:

Steps A and B:

5,17 mmol of 1,1'-Carbonyldimidazole and 0,86 mmol of imidazole are dissolved in 10 ml THF and cooled to 0°C. A solution of the aromatic amine (4,31 mmol) in a suitable amount of THF (5 to 10 ml) is added over 15 min. The reaction mixture is allowed to reach RT and stirred for another 2h. Then 4,3 mmol of Net3 and 4,3 mmol of 2-amino-2-methyl-propionic acid methyl ester acid hydrochlorid are added and the resulting mixture is stirred until completion of the reaction. After the evaporation of the solvent the crude product is pure enough for the next step

Step C:

3 mmol of the product of step 2 are dissolved in a mixture of 5 ml dioxane and 5 ml 2N HCl and heated to reflux for 3h. After evaporation of the solvent the resulting material is sufficiently pure for the next step.

Step D:

0,317 mmol of the hydantoine from step C and 0,634 mmol of 2-chloro-4-chloromethyl-pyridine are dissolved in 5 ml of DMF and after the addition of 1,427 mmol of Cs2CO3 the resulting mixture is heated to reflux for 3 h. After evaporation of the solvent the residue is subjected to chromatography on silica gel using a heptane-ethylacete gradient.

Step E:

0,1 mmol of the product of step 4 and 0,15 mmol of any amine, amide or urea is dissolved in 5 ml of dioxane. After the addition of 0,38 mmol of Cs2CO3 and 0,012 mmol Xanthphos and 0,01 mmol Pd(Oac)2 the resulting mixture is heated to 120°C for 4 to 12 h. The reaction is monitored by TLC. After completion of the reaction is mixture is filtered, the solvent evaporated and the residue subjected to chromatography on a HPLC system. Yields are between 9% and 65%

Step F:

0,39 mmol of the product of step 4 and 0,43 mmol of the corresponding acid are dissolved in 5 ml of DMF, 0,09mmol of Pd(PPh3)4 and 0,9 ml of 1N Na2CO3 are added and the

resulting mixture is heated to 100°C until completion of the reaction (monitored by TLC) The solvent is evaporated and the residue subjected to chromatography on a HPLC system. Yields are between 20% and 70%

Example 29

3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-[2-(pyrazin-2-ylamino)-pyridin-4-ylmethyl]-imidazolidine-2,4-dione

Starting from 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone in step A and using steps, B, C, D and E with 2-aminopyrazine

M+H+ measured = 500.24

LC/MS retention time [min] =1.33

Example 30

3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-[2-(pyridin-3-ylamino)-pyridin-4-ylmethyl]-imidazolidine-2,4-dione

Starting from 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone in step A and using steps, B, C, D and E with 3-aminopyridine

M+H+ measured = 499.25

LC/MS retention time [min] =1.36

Example 31

3-(5-tert-Butyl-isoxazol-3-yl)-5,5-dimethyl-1-[2-(pyrazin-2-ylamino)-pyridin-4-ylmethyl]-imidazolidine-2,4-dione

Starting from 5-tert-Butyl-isoxazol-3-ylamine in step A and using steps, B, C, D and E with 2-aminopyrazine

M+H+ measured = 436.22
LC/MS retention time [min] =1.28

Example 32
3-(5-tert-Butyl-isoxazol-3-yl)-5,5-dimethyl-1-[2-(pyridin-4-ylamino)-pyridin-4-ylmethyl]-imidazolidine-2,4-dione
Starting from 5-tert-Butyl-isoxazol-3-ylamine in step A and using steps, B, C, D and E with 4-aminopyridine
M+H+ measured = 435.22
LC/MS retention time [min] =1.34

Example 33
3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-[2-(pyridin-4-ylamino)-pyridin-4-ylmethyl]-imidazolidine-2,4-dione; compound with trifluoro-acetic acid
Starting from 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone in step A and using steps, B, C, D and E with 4-aminopyridine
M+H+ measured = 499.25
LC/MS retention time [min] =1.23

Example 34
3-{4-[3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-2,4-dioxo-imidazolidin-1-ylmethyl]-pyridin-2-yl}-1,1-dimethyl-urea
Starting from 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone in step A and using steps, B, C, D and E with N,N-dimethylurea
M+H+ measured = 493.26
LC/MS retention time [min] =1.26

Example 35

3-{4-[3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-2,4-dioxo- imidazolidin-1-ylmethyl]-pyridin-2-yl}-1,1-dimethyl-urea

Starting from 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone in step A and using steps, B, C, D and E with N,N-dimethylurea

M+H+ measured = 493.26

LC/MS retention time [min] =1.26

Example 36

3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-1-(2-chloro-pyridin-4-ylmethyl)-5,5- dimethyl-imidazolidine-2,4-dione

Starting from 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone in step A and using steps, B, C and D

M+H+ measured = 441.17

LC/MS retention time [min] =1.95

Example 37

3-(5-tert-Butyl-isoxazol-3-yl)-5,5-dimethyl-1-[2-(pyridin-3-ylamino)-pyridin-4- ylmethyl]-imidazolidine-2,4-dione

Starting from 5-tert-Butyl-isoxazol-3-ylamine in step A and using steps, B, C,D and E with 3-aminopyridine

M+H+ measured = 435.22

LC/MS retention time [min] =1.34

Example 38

3-(2-Acetyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-5,5-dimethyl-1-[2-(pyridin-4-ylamino)-pyridin-4-ylmethyl]-imidazolidine-2,4-dione

Starting from 1-(7-Amino-4,4-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone in step A and using steps, B, C, D and E with 4-aminopyridine

M+H+ measured = 513.26

LC/MS retention time [min] =1.22

Example 39

N-{4-[3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-2,4-dioxo-imidazolidin-1-ylmethyl]-pyridin-2-yl}-3-methoxy-benzamide

Starting from 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone in step A and using steps, B, C, D and E with 3-methoxybenzamide

M+H+ measured = 556.26

LC/MS retention time [min] =1.52

Example 40

N-{4-[3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-2,4-dioxo-imidazolidin-1-ylmethyl]-pyridin-2-yl}-4-methoxy-benzamide

Starting from 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone in step A and using steps, B, C, D and E with 4-methoxybenzamide

M+H+ measured = 556.26

LC/MS retention time [min] =1.47

Example 41

3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-1-[2-(2,6-dimethoxy-pyrimidin-4- ylamino)-pyridin-4-ylmethyl]-5,5-dimethyl-imidazolidine-2,4-dione

Starting from 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone in step A and using steps, B, C, D and E with 2,6-Dimethoxy-pyrimidin-4-ylamine

M+H+ measured = 560.26

LC/MS retention time [min] =1.21

Example 42

N-{4-[3-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-2,4-dioxo-imidazolidin- 1-ylmethyl]-pyridin-2-yl}-4-methoxy-benzamide

50 mg of example 40 are dissolved in 5 ml of ethanol and 5 ml of HCl conc. Are added. The resulting mixture is heated to 50°C and stirred for 4 hours. The solvent is evaporated in vacuo and the product collected.

M+H+ measured = 514.25

LC/MS retention time [min] =1.21

Example 43

3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-1-[2-(2,5-dimethyl-2H-pyrazol-3- ylamino)-pyridin-4-ylmethyl]-5,5-dimethyl-imidazolidine-2,4-dione

Starting from 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone in step A and using steps, B, C, D and E with 2,5-Dimethyl-2H-pyrazol-3-ylamine

M+H+ measured = 516.26

LC/MS retention time [min] =1.39

Example 44

N-{4-[3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-2,4-dioxo-imidazolidin-1-ylmethyl]-pyridin-2-yl}-2-methoxy-isonicotinamide

Starting from 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone in step A and using steps, B, C, D and E with 3-methoxybenzamide

M+H+ measured = 557.24

LC/MS retention time [min] =1.76

Example 45

3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-1-[2-(4-methoxy-phenylamino)-pyridin-4-ylmethyl]-5,5-dimethyl-imidazolidine-2,4-dione; compound with trifluoro-acetic acid

Starting from 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone in step A and using steps, B, C, D and E with4-methoxyaniline

M+H+ measured = 528.25

LC/MS retention time [min] =1.57

Example 46

3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-1-[2-(2,6-dimethyl-pyrimidin-4-ylamino)-pyridin-4-ylmethyl]-5,5-dimethyl-imidazolidine-2,4-dione; compound with trifluoro-acetic acid

Starting from 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone in step A and using steps, B, C, D and E with 2,6-Dimethyl-pyrimidin-4-ylamine

M+H+ measured = 528.26

LC/MS retention time [min] =1.39

Example 47

3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-[2-(thiazol-2-ylamino)-pyridin-4-ylmethyl]-imidazolidine-2,4-dione; compound with trifluoro-acetic acid

Starting from 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone in step A and using steps, B, C, D and E with 2-aminothiazole

M+H+ measured = 505.2

LC/MS retention time [min] =1.37

Example 48

3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-[2-(3,4,5-trimethoxy-phenylamino)-pyridin-4-ylmethyl]-imidazolidine-2,4-dione; compound with trifluoro-acetic acid

Starting from 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone in step A and using steps, B, C, D and E with 3,4,5trimethoxyaniline

M+H+ measured = 588.27

LC/MS retention time [min] =1.52

Example 49

4-{4-[3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-2,4-dioxo-imidazolidin-1-ylmethyl]-pyridin-2-yl}-N,N-dimethyl-benzamide; compound with trifluoro-acetic acid

Starting from 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone in step A and using steps, B, C, D and F with 4-(N,N-DIMETHYLAMINOCARBONYL)PHENYLBORONIC ACID

M+H+ measured = 554.27

LC/MS retention time [min] =1.3

Example 50

3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-[2-(pyrimidin-4-ylamino)-pyridin-4-ylmethyl]-imidazolidine-2,4-dione; compound with trifluoro-acetic acid

Starting from 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone in step A and using steps, B, C, D and E with 4-aminopyrimidine

M+H+ measured = 500.24

LC/MS retention time [min] =1.34

Example 51

N-{4-[3-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-2,4-dioxo-imidazolidin- 1-ylmethyl]-pyridin-2-yl}-3-methoxy-benzamide

Starting from example 44 using the same procedure as desribed for example 42

M+H+ measured = 514.24

LC/MS retention time [min] =1.26

Example 52

3-(5-tert-Butyl-[1,3,4]thiadiazol-2-yl)-5,5-dimethyl-1-[2-(pyridin-3-ylamino)-pyridin-4- ylmethyl]-imidazolidine-2,4-dione

Starting from 2-AMINO-5-TERT-BUTYL-1,3,4-THIADIAZOLE in step A and using steps, B, C, D and E with 3-aminopyridine

M+H+ measured = 452.19

LC/MS retention time [min] =1.22

Example 53

3-(5-tert-Butyl-[1,3,4]thiadiazol-2-yl)-1-(2-chloro-pyridin-4-ylmethyl)-5,5-dimethyl- imidazolidine-2,4-dione
Starting from 2-AMINO-5-TERT-BUTYL-1,3,4-THIADIAZOLE in step A and using steps, B, C and D
M+H+ measured = 393.11
LC/MS retention time [min] =1.59

Example 54
3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-[2-(2,2,2-trifluoro- ethylamino)-pyridin-4-ylmethyl]-imidazolidine-2,4-dione; compound with trifluoro-acetic acid
Starting from 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone in step A and using steps, B, C, D and E with 2,2,2-Triflurorethylamine
M+H+ measured = 504.22
LC/MS retention time [min] =1.49

Example 55
3-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-[2-(pyridin-4-ylamino)- pyridin-4-ylmethyl]-imidazolidine-2,4-dione;
Starting from example 33 using the same procedure as desribed for example 42
M+H+ measured = 457.23
LC/MS retention time [min] =1.04

Example 56
3-{4-[3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-2,4-dioxo- imidazolidin-1-ylmethyl]-pyridin-2-ylamino}-benzoic acid ethyl ester; compound with trifluoro-acetic acid

Starting from 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone in step A and using steps, B, C, D and E with ethyl-3-aminobenzoate

M+H+ measured = 570.27

LC/MS retention time [min] =1.42

Example 57

3-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-1-[2-(4-methoxy-phenylamino)-pyridin-4- ylmethyl]-5,5-dimethyl-imidazolidine-2,4-dione

50 mg of example 40 are dissolved in 5 ml of ethanol and 5 ml of HCl conc. Are added. The resulting mixture is heated to 50°C and stirred for 4 hours. The solvent is evaporated in vacuo and the product collected.

M+H+ measured = 486.25

LC/MS retention time [min] =1.24

Example 58

3-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-1-[2-(2,6-dimethyl-pyrimidin-4-ylamino)- pyridin-4-ylmethyl]-5,5-dimethyl-imidazolidine-2,4-dione

Starting from example 46 using the same procedure as desribed for example 42

M+H+ measured = 486.26

LC/MS retention time [min] =1.02

Example 59

3-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-1-[2-(4-methoxy-phenyl)-pyridin-4-ylmethyl]- 5,5-dimethyl-imidazolidine-2,4-dione

Starting from 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone in step A and using steps, B, C, D and F

with 4-methoxyphenyl boronic acid. The resulting 3-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-1-[2-(4-methoxy-phenyl)-pyridin-4-ylmethyl]- 5,5-dimethyl-imidazolidine-2,4-dione is subjected to the same reaction conditions as described in example 42

M+H+ measured = 471.24

LC/MS retention time [min] =1.29

Example 60

4-{4-[3-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-2,4-dioxo-imidazolidin-1- ylmethyl]-pyridin-2-yl}-N,N-dimethyl-benzamide

Starting from 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone in step A and using steps, B, C, D and F with 4-methoxyphenyl boronic acid. The resulting 3-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-1-[2-(4-methoxy-phenyl)-pyridin-4-ylmethyl]- 5,5-dimethyl-imidazolidine-2,4-dione is subjected to the same reaction conditions as described in example 42

M+H+ measured = 512.27

LC/MS retention time [min] =1.09

Example 61

3-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-[2-(thiazol-2-ylamino)- pyridin-4-ylmethyl]-imidazolidine-2,4-dione

Starting from example 47 using the same procedure as desribed for example 42

M+H+ measured = 462.18

LC/MS retention time [min] =1.12

Example 62

3-{4-[3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-2,4-dioxo-imidazolidin-1-ylmethyl]-pyridin-2-ylamino}-N,N-dimethyl-benzamide

Starting from 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone in step A and using steps, B, C, D and E with 3-Amino-N,N-dimethyl-benzamide

M+H+ measured = 569.29

LC/MS retention time [min] =1.26

Example 63

3-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-[2-(pyrazin-2-ylamino)-pyridin-4-ylmethyl]-imidazolidine-2,4-dione

Starting from example 29 using the same procedure as desribed for example 42

M+H+ measured = 458.23

LC/MS retention time [min] =0.95

Example 64

3-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-[2-(pyridin-3-ylamino)-pyridin-4-ylmethyl]-imidazolidine-2,4-dione

Starting from example 30 using the same procedure as desribed for example 42

M+H+ measured = 457.24

LC/MS retention time [min] =1

Example 65

3-{4-[3-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-2,4-dioxo-imidazolidin-1-ylmethyl]-pyridin-2-ylamino}-N,N-dimethyl-benzamide

Starting from example 62 using the same procedure as desribed for example 42

M+H+ measured = 527.28

LC/MS retention time [min] =1.02

Example 66

5,5-Dimethyl-1-[2-(pyrazin-2-ylamino)-pyridin-4-ylmethyl]-3-(1,3,3-trimethyl-2,3-dihydro- 1H-indol-6-yl)-imidazolidine-2,4-dione

Starting from 1,3,3-Trimethyl-2,3-dihydro-1H-indol-6-ylamine in step A and using steps, B, C, D and E with 2-aminopyrazine

M+H+ measured = 472.25

LC/MS retention time [min] =1.26

Example 67

3-{4-[5,5-Dimethyl-2,4-dioxo-3-(1,3,3-trimethyl-2,3-dihydro-1H-indol-6-yl)-imidazolidin- 1-ylmethyl]-pyridin-2-yl}-1,1-dimethyl-urea

Starting from 1,3,3-Trimethyl-2,3-dihydro-1H-indol-6-ylamine in step A and using steps, B, C, D and E with N,N-dimethylurea

M+H+ measured = 465.26

LC/MS retention time [min] =1.29

Example 68

3-{4-[3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-2,4-dioxo- imidazolidin-1-ylmethyl]-pyridin-2-ylamino}-benzoic acid

50 mg of example 56 are dissolved in 5 ml EtOH and treated with 1 ml of 1N NaOH. The resulting mixture is

heated to 50°C for two hours, the solvent is removed in vacuo and the product is collected.
M+H+ measured = 542.24
LC/MS retention time [min] =1.3

Example 69
3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-1-[2-(4-dimethylamino-phenyl)- pyridin-4-ylmethyl]-5,5-dimethyl-imidazolidine-2,4-dione
Starting from 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone in step A and using steps, B, C, D and F with 4-N,N-DIMETHYLAMINOPHENYLBORONIC ACID
M+H+ measured = 526.28
LC/MS retention time [min] =1.4

Example 70
3-{4-[5,5-Dimethyl-2,4-dioxo-3-(1,3,3-trimethyl-2,3-dihydro-1H-indol-6-yl)-imidazolidin- 1-ylmethyl]-pyridin-2-ylamino}-benzoic acid
Starting from 1,3,3-Trimethyl-2,3-dihydro-1H-indol-6-ylamine in step A and using steps, B, C, D and E with Ethyl-3-aminobenzoate. The resulting 3-{4-[5,5-Dimethyl-2,4-dioxo-3-(1,3,3-trimethyl-2,3-dihydro-1H-indol-6-yl)-imidazolidin- 1-ylmethyl]-pyridin-2-ylamino}-benzoic acid ethyl ester is treated as described for example 68 to obtain example 70
M+H+ measured = 514.25
LC/MS retention time [min] =1.39

Example 71a
3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-imidazolidine-2,4- dione

To a solution of 838 mg di-imidazol-1-yl-methanone and 58 mg imidazole in 10 ml tetrahydrofuran a solution of 880 mg 1-(6-amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone in 5 ml tetrahydrofuran was slowly added at 0°C. After stirring at 0°C for 90 minutes 0.60 ml triethylamine and 661 mg 2-amino-2-methyl-propionic acid methyl ester hydrochloride were added and the reaction mixture was allowed to warm up to room temperature. After 2 hours stirring at room temperature the solution was heated for 6 hours at 70°C. After cooling to room temperature the solvent of the mixture was removed under reduced pressure and the residue was purified by flash chromatography on silica gel with a n-heptane/ ethylacetate gradient. The fractions containing the product were combined and evaporated to yield a white solid.

Yield: 920 mg

M+H+ measured = 316

1H-NMR (400 MHz, DMSO/TMS): d = 8.50 (s, 1H); 7.93 (s, 1H); 7.33 (d, 1H); 6.97 (dd, 1H); 3.90 (s, 2H); 2.17 (s, 3H); 1.50 (s, 6H); 1.33 (s, 6H)

Example 71

3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-1-(2-amino-pyridin-4-ylmethyl)-5,5- dimethyl-imidazolidine-2,4-dione

To a suspension of 630 mg diphenylphosphino-polystyrene (resin-bound triphenylphosphine, loading 2.2 mmol/g) and 157 mg (2-amino-pyridin-4-yl)-methanol in 5 ml tetrahydrofuran 301 mg diisopropyl azodicarboxylate were slowly added by a syringe. After 5 minutes of stirring at room temperature a solution of 100 mg 3-(1-acetyl-3,3-

dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-imidazolidine-2,4- dione in 0.5 ml tetrahydrofuran was added. The resulting mixture was stirred for 16 hours. After removing of the solvent under reduced pressure the residue was purified by flash chromatography on silica gel with a dichloro-methane/methanol gradient. The solvent was removed under reduced pressure and the residue was purified in addition by preparative HPLC (C18 reverse phase column, elution with a water/acetonitrile gradient with 0.1% trifluoracetic acid). Lyophilization of the solution yielded a white solid. The product was obtained as its trifluoroacetic salt.
Yield: 3 mg
M+H+ measured = 422
1H-NMR (500 MHz, DMSO/TMS): d = 8.02 (s, 1H); 7.93 (d, 1H); 7.83 (m, 2H); 7.36 (d, 1H); 7.04 (d, 1H); 6.92 (s, 1H); 6.87 (d, 1H); 4.53 (s, 2H); 3.93 (s, 2H); 2.17 (s, 3H); 1.44 (s, 6H); 1.34 (s, 6H)

Example 72a
3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-(2-methylsulfanyl- pyrimidin-4-ylmethyl)-imidazolidine-2,4-dione
To a solution of 50 mg 3-(1-acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-imidazolidine-2,4-dione in 1 ml N,N-dimethylformamide 4 mg sodium hydride were added. After 5 minutes stirring at room temperature 138 mg of a 30% solution of 4-(bromomethyl)-2-(methylthio)pyrimidine were added. The resulting mixture was stirred for 16 hours at room temperature. After removal of the solvent under reduced pressure the residue was purified by flash chromatography on silica gel with a

dichloro-methane/methanol gradient. The fractions containing the product were combined and evaporated to yield a white solid.
Yield: 43 mg
M+H+ measured = 554
1H-NMR (400 MHz, DMSO/TMS): d = 8.58 (d, 1H); 8.00 (s, 1H); 7.35 (d, 1H); 7.26 (d, 1H); 7.02 (d, 1H); 4.54 (s, 2H); 3.91 (s, 2H); 3.28 (s, 3H); 2.15 (s, 3H); 1.43 (s, 6H); 1.33 (s, 6H)

Example 72
3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-1-(2-amino-pyrimidin-4-ylmethyl)- 5,5-dimethyl-imidazolidine-2,4-dione
40 mg 3-(1-acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-(2-methylsulfanyl- pyrimidin-4-ylmethyl)-imidazolidine-2,4-dione were dissolved in 2 ml dichloromethane and 30 mg 3-chloro-perbenzoic acid were added. After stirring at room temperature for 1 hour the reaction mixture was treated with water. The organic layer was dried over anhydrous sodium sulfate. After filtration and concentration of the solvent under reduced pressure the residue was dissolved in a mixture of 1 ml dioxane and 1 ml of an aqueous 30% solution of ammonia in a process vial. After sealing with a teflon septum the vial was placed in the microwave cavity and the reaction mixture was stirred for 30 minutes at 120°C by microwave-assisted heating (Emrys Optimizer, Personal Chemistry) . The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel with a dichloro-methane/methanol gradient. After evaporation of the combined fractions the residue was

dissolved in a mixture of 2 ml acetonitrile and 5 ml water. Lyophilization of the solution yielded a white solid.

Yield: 11.2 mg

M+H+ measured = 423

1H-NMR (400 MHz, DMSO/TMS): d = 8.17 (d, 1H); 8.00 (s, 1H); 7.34 (d, 1H); 7.04 (d, 1H); 6.60 (m, 3H); 4.40 (s, 2H); 3.91 (s, 2H); 2.17 (s, 3H); 1.41 (s, 6H); 1.33 (s, 6H)

Example 73

3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-pyridin-4-ylmethyl- imidazolidine-2,4-dione

A suspension of 100 mg 3-(1-acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-imidazolidine-2,4-dione, 516 mg cesium carbonate and 80 mg 4-bromomethyl-pyridine hydrobromide in 2 ml N,N-dimethylformamide was stirred for 4 hours at 80°C. 250 mg cesium carbonate and 40 mg 4-bromomethyl-pyridine hydrobromide were added and the reaction mixture was stirred for further 2 hours at 80°C. After addition of 150 mg cesium carbonate and 15 mg 4-bromomethyl-pyridine hydrobromide the mixture was stirred once more for 2 hours at 80°C. After cooling to room temperature that separated was filtered off and the filtrate was purified by preparative HPLC (C18 reverse phase column, elution with a water/acetonitrile gradient with 0.1% trifluoracetic acid). Lyophilization of the solution yielded a white solid.

Yield: 108.5 mg

M+H+ measured = 407

1H-NMR (500 MHz, DMSO/TMS): d = 8.72 (d, 2H); 8.05 (s, 1H); 7.76 (d, 2H); 7.37 (d, 1H); 7.07 (d,1H); 4.78 (s,

2H); 3.93 (s, 2H); 2.18 (s, 3H); 1.41 (s, 6H); 1.33 (s, 6H)

Example 74

3-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-pyridin-4-ylmethyl- imidazolidine-2,4-dione

45 mg 3-(1-acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-pyridin-4-ylmethyl- imidazolidine-2,4-dione were dissolved in a mixture of 0.5 ml dioxane and 0.5 ml of an aqueous 1 N solution of hydrochloric acid in a process vial. The vial was sealed with a teflon septum and placed in the microwave cavity. The reaction mixture was stirred for 15 minutes at 120°C by microwave-assisted heating (Emrys Optimizer, Personal Chemistry). After removal of the solvent under reduced pressure the residue was purified by preparative HPLC (C18 reverse phase column, elution with a water/acetonitrile gradient with 0.1% trifluoracetic acid). Lyophilization of the combined fractions containing the product yielded a white solid that was treated with an aqueous saturated solution of sodium hydrogen carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate. Filtration and concentration of the solvent under reduced pressure yielded a white solid.
Yield: 58 mg
M+H+ measured = 365
1H-NMR (500 MHz, DMSO/TMS): d = 8.75 (d, 2H); 7.81 (d, 2H); 7.14 (d, 1H); 6.70 (d, 1H); 6.66 (s,1H); 4.80 (s, 2H); 3.29 (s, 2H); 1.40 (s, 6H); 1.26 (s, 6H)

Example 75

1-(2-Amino-pyrimidin-4-ylmethyl)-3-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5- dimethyl-imidazolidine-2,4-dione

The following compounds were prepared in analogy to example A003403576 by using 45 mg 3-(1-acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-1-(2-amino-pyrimidin-4-ylmethyl)- 5,5-dimethyl-imidazolidine-2,4-dione as starting material.

Yield: 30 mg

M+H+ measured = 381

1H-NMR (400 MHz, DMSO/TMS): d = 8.25 (d, 1H); 7.18 (d, 1H); 6.75 (m, 2H); 6.71 (s, 1H); 4.49 (s, 2H); 3.31 (s, 2H); 1.42 (s, 6H); 1.27 (s, 6H)

Example 76a

1,3,3-Trimethyl-6-nitro-2,3-dihydro-1H-indole

To a solution of 400 mg 3,3-dimethyl-6-nitro-2,3-dihydro-1H-indole in 4 ml N,N-dimethylformamide 350 mg potassium tert-butoxide and 443 mg iodomethane were added at 0°C. After stirring for 1 hour the solvent was removed under reduced pressure. The residue was dissolved in a mixture of dichloro-methane and water. The organic layer was dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel with a n-heptane/ethyl acetate gradient. The fractions containing the product were evaporated to yield a white solid.

Yield: 110 mg

M+H+ measured =

1H-NMR (400 MHz, DMSO/TMS): d = 7.50 (d, 1H); 7.23 (m, 2H); 3.20 (s, 2H); 2.80 (s, 3H); 1.27 (s, 6H)

Example 76b

1,3,3-Trimethyl-2,3-dihydro-1H-indol-6-ylamine

A mixture of 100 mg 1,3,3-trimethyl-6-nitro-2,3-dihydro-1H-indole, 15 mg of 10% palladium on carbon and 2 ml methanol was stirred for 1 hour under a hydrogen atmosphere. The mixture was filtered through a chem elut cartridge and the compound was eluted with ethanol. After concentration under reduced pressure the residue was directly subjected to the subsequent reaction without further purification.

Yield: 90 mg

M+H+ measured =

1H-NMR (400 MHz, DMSO/TMS): d = 6.61 (d, 1H); 5.85 (dd, 1H); 5.75 (d, 1H); 4.68 (s, 2H); 2.92 (s, 2H); 2.49 (s, 3H); 1.15 (s, 6H)

Example 76c

3,3-Dimethyl-2,6-dinitro-2,3-dihydro-1,2-benzoisothiazole 1,1-dioxide

A solution of 5 g 3,3-dimethyl-2,3-dihydro-1,2-benzoisothiazole 1,1-dioxide in a mixture of 28 ml sulfuric acid and 2 ml nitric acid was stirred at room temperature. After 48 hours stirring 2 ml nitric acid were added and the solution was stirred for further 2 hours at room temperature. The mixture was added to ice water and the resulting precipitation was collected by filtration and washed with additional water. The residue was coevaporated twice with 50 ml toluene.

Yield: 6.54 g

M+H+ measured = 288

1H-NMR (400 MHz, DMSO/TMS): d = 9.19 (s, 1H); 8.75 (d, 1H); 8.32 (d, 1H); 1.93 (s, 6H)

Example 76d

3,3-Dimethyl-1,1-dioxo-2,3-dihydro-1H-1,2-benzoisothiazol-6-ylamine

A mixture of 7.8 g 3,3-dimethyl-2,6-dinitro-2,3-dihydro-1,2-benzoisothiazole 1,1-dioxide, 1.18 g of 10% palladium on carbon, 60 ml of a 8 N solution of hydrochloric acid in methanol and 240 ml methanol was stirred for 2 hours under a hydrogen atmosphere. Then further 0.5 g of 10% palladium on carbon were added and the suspension was stirred for 16 hours under a hydrogen pressure of 1.5 bar. The mixture was filtered through a chem elut cartridge and the compound was eluted with additional methanol. After concentration under reduced pressure the residue was partitioned between ethyl acetate and a saturated aqueous solution of sodium hydrogen carbonate. The organic layer was dried over sodium sulfate and after filtration the clear solution was evaporated to yield a white solid.

Yield: 2.94 g

M+H+ measured = 212

1H-NMR (400 MHz, DMSO/TMS): d = 7.53 (d, 1H); 7.07 (d, 1H); 6.95 (s, 1H); 6.00 (s, 2H); 1.78 (s, 6H)

Example 76e

3-(3,3-Dimethyl-1,1-dioxo-2,3-dihydro-1H-1,2-benzoisothiazol-6-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl-imidazolidine-2,4-dione

To a solution of 466 mg diphosgene in 5 ml dichloro-ethane at -20°C 200 mg 3,3-dimethyl-1,1-dioxo-2,3-dihydro-1H-1,2-benzoisothiazol-6-ylamine in 2 ml dichloro-ethane were added and the mixture was stirred

for 1 hour at room temperature. Afterwards the reaction mixture was heated for 1 hour at 60°C. After removal of the solvent under reduced pressure the reaction mixture was diluted with dichloro-methane and 10 ml of a saturated aqueous solution of sodium hydrogen carbonate were added. The organic layer was dried over sodium sulfate. After filtration and evaporation the residue was dissolved in 5 ml tetrahydrofuran and 243 mg 2-methyl-2-[(quinolin-4-ylmethyl)-amino]-propionic acid methyl ester in 3 ml tetrahydrofuran were added. The resulting solution was stirred for 2 hours at room temperature. After removal of the solvent under reduced pressure the solid was suspended in 10 ml dichloro-methane. The precipitate was collected by filtration and purified by flash chromatography on silica gel with a dichloro-methane/ methanol gradient. The fractions containing the product were combined and evaporated to yield a white solid.

Yield: 10 mg

M+H+ measured =

1H-NMR (500 MHz, DMSO/TMS): d = 8.87 (d, 1H); 8.39 (s, 1H); 8.27 (d, 1H); 8.18 (d, 1H); 8.13 (d, 1H); 8.08 (d, 1H); 7.83 (t, 1H); 7.68 (m, 2H); 5.16 (s, 2H); 1.93 (s, 6H); 1.48 (s, 6H)

Example 77

5,5-Dimethyl-1-quinolin-4-ylmethyl-3-(1,3,3-trimethyl-2,3-dihydro-1H-indol-6-yl)- imidazolidine-2,4-dione.

The following compound was prepared in analogy to example A003410455 by using 90 mg 1,3,3-trimethyl-2,3-dihydro-1H-indol-6-ylamine as starting material. The purification was performed by using flash chromatography on silica gel

with a n-heptane/ethyl acetate gradient. The fractions containing the product were combined and evaporated to yield a white solid.
Yield: 18 mg
M+H+ measured = 429
1H-NMR (500 MHz, DMSO/TMS): d = 8.88 (d, 1H); 8.25 (d, 1H); 8.09 (d, 1H); 7.82 (t, 1H); 7.70 (t, 1H); 7.56 (d, 1H); 7.09 (d, 1H); 6.65 (dd, 1H); 6.54 (d, 1H); 5.13 (s, 2H); 3.11 (s, 2H); 2.73 (s, 3H); 1.40 (s, 6H); 1.27 (s, 6H)

Example 78a
2-(2,4-Dinitro-phenyl)-2-methyl-propionic acid ethyl ester
A solution of 1 g 2-methyl-2-phenyl-propionic acid ethyl ester in a mixture of 14 ml sulfuric acid and 1 ml nitric acid was stirred at room temperature for 4 hours. The mixture was added to ice water and extracted with ethyl acetate. The organic layer was washed with a satured aqueous solution of sodium hydrogen carbonate and dried over anhydrous sodium sulfate. Filtration and concentration of the solvent under reduced pressure yielded a yellow solid. The residue was purified by flash chromatography on silica gel with a n-heptane/ dichloro-methane gradient. The fractions containing the product were combined and evaporated to yield a yellow solid.
Yield: 560 mg
M+H+ measured =
1H-NMR (400 MHz, DMSO/TMS): d = 8.69 (d, 1H); 8.53 (dd, 1H); 8.10 (d, 1H); 4.02 (q, 2H); 1.65 (s, 6H); 1.12 (t, 3H)

Example 78b

6-Amino-3,3-dimethyl-1,3-dihydro-indol-2-one

A mixture of 560 mg 2-(2,4-dinitro-phenyl)-2-methyl-propionic acid ethyl ester, 31 mg of 10% palladium on carbon and 10 ml methanol was stirred for 2 hours under a hydrogen atmosphere. The mixture was filtered through a chem elut cartridge and the compound was eluted with additional methanol. After concentration under reduced pressure the residue was purified by flash chromatography on silica gel with a dichloro-methane/ methanol gradient. The fractions containing the product were combined and evaporated to yield a white solid.

Yield: 250 mg

M+H+ measured =

1H-NMR (400 MHz, DMSO/TMS): d = 10.00 (s, 1H); 6.85 (d, 1H); 6.12 (m, 2H); 5.01 (s, 2H); 1.15 (s, 6H)

Example 78c

3-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl- imidazolidine-2,4-dione

To a solution of 110 mg di-imidazol-1-yl-methanone and 6 mg imidazole in 2 ml tetrahydrofuran a solution of 100 mg 6-amino-3,3-dimethyl-1,3-dihydro-indol-2-one in 1 ml tetrahydrofuran was slowly added at 0°C. After stirring at 0°C for 30 minutes and 1 hour at room temperature 103 mg 2-methyl-2-[(quinolin-4-ylmethyl)-amino]-propionic acid methyl ester were added and the reaction mixture was allowed to warm up to room temperature. After 16 hours stirring at room temperature the solution was heated for 1 hour at 70°C. After cooling to room temperature the solvent of the mixture was removed under reduced pressure and the residue was purified by preparative HPLC (C18

reverse phase column, elution with a water/ acetonitrile gradient with 0.1% trifluoroacetic acid). Lyophilization of the solution yielded a white solid, that was purified in addition by flash chromatography on silica gel with a dichloro-methane/methanol gradient. The fractions containing the product were combined and evaporated to yield a white solid.
Yield: 7.5 mg
M+H+ measured = 429
1H-NMR (500 MHz, DMSO/TMS): d = 10.50 (s, 1H); 8.87 (d, 1H); 8.25 (d, 1H); 8.09 (d, 1H); 7.82 (t, 1H); 7.70 (t, 1H); 7.63 (d, 1H); 7.42 (d, 1H); 7.07 (d, 1H); 7.01 (s, 1H); 5.14 (s, 2H); 1.43 (s, 6H); 1.29 (s, 6H)

Example 79a
3,3-Dimethyl-6-nitro-2,3-dihydro-1,2-benzoisothiazole 1,1-dioxide
To a solution of 1 g 3,3-dimethyl-2,6-dinitro-2,3-dihydro-1,2-benzo[d]isothiazole 1,1-dioxide in 10 ml sulfuric acid at 0°C 0.41 g anisole were added and the mixture was stirred for 30 minutes at 0°C. Then the reaction mixture was added to ice water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate. After filtration and concentration of the solvent under reduced pressure the residue was purified by flash chromatography on silica gel with a n-heptane/ ethyl acetate gradient. The fractions containing the product were combined and evaporated to yield a yellow solid.
Yield: 0.74 g
M+H+ measured = 243

1H-NMR (400 MHz, DMSO/TMS): d = 8.56 (s, 1H); 8.52 (d, 1H); 8.37 (s, 1H); 8.02 (d, 1H); 1.58 (s, 6H)

Example 79b

2,3,3-Trimethyl-6-nitro-2,3-dihydro-1,2-benzoisothiazole 1,1-dioxide

To a solution of 200 mg 3,3-dimethyl-6-nitro-2,3-dihydro-1,2-benzoisothiazole 1,1-dioxide in 2 ml N,N-dimethylformamide 19.8 mg sodium hydride were added at 0°C. After stirring at 0°C for 10 minutes 176 mg iodomethane were added. The reaction mixture was allowed to warm up to room temperature and stirred for 2 hours. After removal of the solvent under reduced pressure the residue was purified by flash chromatography on silica gel with a n-heptane/ ethyl acetate gradient. Evaporation of the combined fractions yielded a white solid.

Yield: 195 mg

M+H+ measured = 257

1H-NMR (400 MHz, DMSO/TMS): d = 8.70 (s, 1H); 8.58 (dd, 1H); 8.13 (d, 1H); 2.79 (s, 3H); 1.53 (s, 6H)

Example 79c

2,3,3-Trimethyl-1,1-dioxo-2,3-dihydro-1H-1,2-benzoisothiazol-6-ylamine

A mixture of 190 mg 2,3,3-trimethyl-6-nitro-2,3-dihydro-1,2-benzoisothiazole 1,1-dioxide, 24 mg of 10% palladium on carbon and 10 ml methanol was stirred for 1 hour under a hydrogen atmosphere. The mixture was filtered through a chem elut cartridge and the compound was eluted with additional methanol. Concentration of the filtrate under reduced pressure yielded a white solid.

Yield: 160 mg

M+H+ measured = 227

1H-NMR (400 MHz, DMSO/TMS): d = 7.33 (d, 1H); 6.87 (dd, 1H); 6.79 (d, 1H); 5.67 (s, 2H); 2.65 (s, 3H); 1.36 (s, 6H)

Example 79d

5,5-Dimethyl-1-quinolin-4-ylmethyl-3-(2,3,3-trimethyl-1,1-dioxo-2,3-dihydro-1H-1,2-benzoisothiazol-6-yl)-imidazolidine-2,4-dione

To a solution of 142 mg di-imidazol-1-yl-methanone and 8 mg imidazole in 6 ml tetrahydrofuran a solution of 165 mg 2,3,3-trimethyl-1,1-dioxo-2,3-dihydro-1H-1,2-benzoisothiazol-6-ylamine in 1 ml tetrahydrofuran was slowly added at 0°C. After stirring at 0°C for 30 minutes and at room temperature for 1 hour 132 mg 2-methyl-2-[(quinolin-4-ylmethyl)-amino]-propionic acid methyl ester were added and the reaction mixture was stirred for 16 hours at room temperature. Then the solution was heated for 3 hours at 70°C. After cooling to room temperature the solvent of the mixture was removed under reduced pressure and the residue was purified by preparative HPLC (C18 reverse phase column, elution with a water/acetonitrile gradient with 0.1% trifluoroacetic acid). Lyophilization of the solution yielded a white solid that was partitioned between ethyl acetate and a saturated aqueous solution of sodium hydrogen carbonate. The organic layer was dried over sodium sulfate and after filtration the clear solution was evaporated to yield a residue, that was dissolved in a mixture of 10 ml acetonitrile and 5 ml water. Lyophilization yielded a white foam.

Yield: 27 mg

M+H+ measured = 479

1H-NMR (500 MHz, DMSO/TMS): d = 8.87 (d, 1H); 8.27 (d, 1H); 8.09 (m, 2H); 7.95 (d, 1H); 7.88 (dd, 1H); 7.82 (t, 1H); 7.69 (m, 2H); 5.15 (s, 2H); 2.77 (s, 3H); 1.52 (s, 6H); 1.47 (s, 6H)

Starting materials

Synthesis of 2-chloro-4-chloromethylpyridine: 10g of 2-chloro-4-methylpyridine are dissolved in 50 ml of CH3CN and heated to 85°C. Then a mixture of 32g N-Chlorosuccinimid and 1,6g AIBN is added over a period of 5 minutes. The resulting mixture is refluxed for two hours, then the solvent is removed in vacuo, the residue treated with 100ml of CH2Cl2 and washed with water 2 times. The organic phases are collected, dried over Na2SO4 and the residue obtained after evaporation of the solvent is distilled (80°C, 100 mTorr). Yield 79%

Synthesis of 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone is described in WO 2002066470 and WO 2004014871

Synthesis of 1-(7-Amino-4,4-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone is carried out in analogy to the synthesis of 1-(6-Amino-3,3-dimethyl-2,3-dihydro-indol-1-yl)-ethanone

Example 80: 5-Benzo[b]thiophen-3-ylmethyl-3(1H-indazol-5-yl)-1-pyridin-4-ylmethyl-imidazolidine-2,4-dione

1 g (0.73 mmol) of Rapp Polymer Polystyrene AM RAM resin was treated with 20 ml of 10% piperidine in DMF for 30

minutes to remove Fmoc protecting group and provide the resin bound free amine. The resin was then washed 6 x 8 ml of DMF before treatment with coupling mixture of 0.388 g (0.88 mmol) of Fmoc-D-3-Benzothienylalanine, 0.458 g (0.88 mmol) of pyBOP and 0.305 ml (1.75 mmol) of DIEA and shaken at room temperature for 15 hours. The resin was then washed 4 x 8 ml of DMF and treated with 10 ml of 10% piperidine in DMF for 30 minutes. The resin was washed 4 x 8 ml of DMF, 2 x 10 ml of DCM, 2 x 10 ml of methanol, and allowed to dry in air. The dry resin was washed 3 x 10 ml in mixture of 1:1 tetramethylorthoformate (TMOF) and THF followed by treatment with 0.413 ml (4.38 mmol) of 4-pyridine-carboxaldehyde in 5 ml of 1:1 TMOF in THF and agitated for 15 hours at room temperature. The resin was washed 3 x 8 ml of 1:1 TMOF in THF and treated with 20 ml of previously prepared solution made of 100 ml of 1.0 M $NaCNBH_3$ in THF, 10 ml methanol and 1 ml acetic acid. The resin suspension was agitated at room temperature for 6 hours. The resin was then washed with 1 x 10 ml of methanol, 3 x 10 ml of 30% acetic acid in DMF, 1 x 10 ml of methanol, 3 x 10 ml of DCM, 1 x 10 ml of methanol, 3 x 10 ml of DCM and a final wash with 1 x 10 ml methanol before allowing the resin to dry in air.

In parallel, 0.591 g (4.44 mmol) of 1H-Indazol-5-ylamine was dissolved in 10 ml DCM and treated with 0.775 ml of DIEA, chilled on an ice water bath before treatment with 4 ml of 20% phosgene in Toluene and agitated for 1 hour. The resulting solution was evaporated under reduced pressure to remove volatile components. Then, the residue was dissolved in 15 ml of DCM, 0.636 ml DIEA, and added to the functionalized resin followed by agitation at room temperature for 15 hours. The finished resin was

washed with 1 x 10 ml of DCM, 3 x 10 ml of DMF, 2 x 10 ml of DCM, 2 x 10 ml of methanol, 2 x 10 ml of DCM and 2 x 10 ml of methanol. The resin was dried under vacuum prior to treatment with 6 ml of 95:5 TFA: H2O and agitated for 24 hours. The resin was filtered out and washed with additional 5 ml of TFA: H2O mixture. The combined filtrates were evaporated to dryness under vacuum. The crude residue was purified by preparative HPLC and the final product characterized by LC/MS. Freeze-drying of desired fractions gave 0.022 g of the intended compound.

MS(ES+): m/e = 453

Example 81: PHARMACEUTICAL COMPOSITION

Tablets were prepared corresponding to the following formula:

Product of Example 21..... 0.2 g
Excipient for a finished tablet weighing..... 1 g
(details of the excipient: lactose, talc, starch, magnesium stearate).

Example 82: PHARMACEUTICAL COMPOSITION

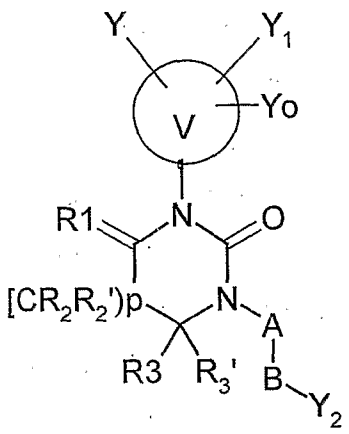
Tablets were prepared corresponding to the following formula:

Product of Example 27..... 0.2 g
Excipient for a finished tablet weighing..... 1 g
(details of the excipient: lactose, talc, starch, magnesium stearate).

Pharmaceutical Compositions: Examples 81 and 82 above illustrate the present invention, it being understood that the same preparations can be made with other preferred products of formula (I) of the present invention, and form part of the present invention.

CLAIMS

1) Products of formula (I):



(I)

in which

V represents an unsaturated or partially or totally saturated monocyclic or bicyclic heterocyclic 5- to 11-membered radical, containing one or more other hetero atoms, which may be identical or different, chosen from O, N, NR4 and S, optionally substituted with one or more substituents, which may be identical or different, chosen from the values of Y and Y1;
the atom S that V can contain, being optionally oxidized by one or two oxygen,

Yo, Y and Y1, which may be identical or different, are such that Yo represents hydrogen or alkyl and one from among Y and Y1 is chosen from OCF3; -O-CF2-CHF2; -O-CHF2; -O-CH2-CF3; -SO2NR5R6; SF5; -S(O)n-alkyl; alkyl containing 1 to 7 carbon atoms optionally substituted with one or more fluorine atoms or cycloalkyl radicals; 3- to 7-membered cycloalkyl optionally substituted with one or more radicals, which may be identical or different, chosen from fluorine atoms and alkyl radicals containing 1 to 3 carbon atoms; alkylamino, optionally

substituted with one or more flourine atoms; dialkylamino, optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and alkoxy radicals and in which the two alkyl residues may optionally form, together with the nitrogen atom to which they are attached, a 4- to 10-membered heterocycle optionally containing one or more other hetero atoms, which may be identical or different, chosen from O, N, NR4 and S and optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and alkyl and alkoxy radicals; phenyl, phenoxy; arylmercapto or heteroarylmercapto, optionally substituted with one or more radicals, which may be identical or different, chosen from fluorine atoms and alkyl and alkoxy radicals;

and the other from among Y and Y1 is chosen from these same values and in addition from the following values: hydrogen; halogen; hydroxyl; oxo; acyl; alkoxy; nitro; CN; NR5R6; optionally substituted alkyl; optionally substituted aryl and heteroaryl; CF3; O-alkenyl; O-alkynyl; O-cycloalkyl; S(O)n-alkenyl; S(O)n-alkynyl; S(O)n-cycloalkyl; free, salified or esterified carboxyl and CONR5R6;

p represents the integers 0, 1 and 2;

R1 represents O or NH;

R2, R2′, R3 and R3′, which may be identical or different, represent hydrogen, halogen; alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl and heteroaryl, all optionally substituted, or alternatively two of the residues R2, R2′, R3 and R3′ form, together with the carbon atom(s) to which they are attached, a carbocyclic

or heterocyclic radical, these radicals being 3- to 10-membered and the heterocyclic radical containing one or more hetero atoms chosen from O, S, N and NR4, all these radicals optionally being substituted;

A represents a single bond; an alkylene radical; an alkenyl radical; alkynyl; CO; SO2; O; NH; NH-alkyl;

B represents a saturated or unsaturated monocyclic or bicyclic heterocyclic radical containing one or more hetero atoms, which may be identical or different, chosen from O, S, N and NR4, optionally substituted with one or more substituents, which may be identical or different, chosen from the values of Y2;

Y2 represents hydrogen; halogen; hydroxyl; cyano; alkyl; alkoxy; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; -O-alkenyl; -O-alkynyl; -O-cycloalkyl; -S(O)n-alkyl; -S(O)n-alkenyl; -S(O)n-alkynyl; S(O)n-cycloalkyl; COOR13; -OCOR13; NR5R6; CONR5R6; S(O)n-NR5R6; -NR10-CO-R13; -NR10-SO2-R13; NH-SO2-NR5R6; -NR10-CO-NR5R6; -NR10-CS-NR5R6 and -NR10-COOR13; all these radicals being optionally substituted;

R4 represents a hydrogen atom or an alkyl, alkenyl, alkynyl, cycloalkyl, alkylCO, alkylSO_2, or aryle radical, all optionally substituted with one or more substituents, which may be identical or different, chosen from halogen atoms; hydroxyl; alkoxy; dialkylamino; aryl and heteroaryl radicals, these last two radicals optionally substituted with one or more substituents, which may be identical or different, chosen from halogen atoms and alkyl and alkoxy radicals;

R5 and R6, which may be identical or different, are chosen from hydrogen; alkyl, alkenyl, alkynyl,

cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl and heteroaryl, all optionally substituted or alternatively R5 and R6 form, with the nitrogen atom to which they are attached, a 3- to 10-membered heterocyclic radical containing one or more hetero atoms chosen from O, S, N and optionally substituted NR4;

all the above alkyl, alkenyl, alkynyl and alkoxy radicals being linear or branched and containing up to 6 carbon atoms;

all the above cycloalkyl and heterocycloalkyl radicals containing up to 7 carbon atoms;

all the above aryl and heteroaryl radicals containing up to 10 carbon atoms;

all the above alkyl, alkenyl, alkynyl and alkoxy radicals cycloalkyl, heterocycloalkyl, aryl and heteroaryl radicals, carbocyclic and heterocyclic radicals, and also the ring formed by R5 and R6 with the atom to which they are attached, being optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms; cyano; hydroxyl; alkoxy; CF3; nitro; aryl, heteroaryl and heterocycloalkyl themselves optionally substituted by one or more radicals chosen among halogen, alkyl, OH or alcoxy; -C(=O)-OR9; -C(=O)-R8; -NR11R12; -C(=O)-NR11R12; -N(R10)-C(=O)-R8; -N(R10)-C(=O)-OR9; N(R10)-C(=O)-NR11R12; -N(R10)-S(O)n-R8; -S(O)n-R8; -N(R10)-S(O)n-NR11R12 and -S(O)n-NR11R12 radicals;

all the above heterocycloalkyl, aryl and heteroaryl radicals being also optionally substituted with one or more radicals chosen from alkyl, phenylalkyl and alkylenedioxy radicals;

all the above cyclic radicals and also the ring formed by

R5 and R6 with the atom to which they are attached being also optionally substituted with one or more radicals chosen from oxo and thioxo;

n represents an integer from 0 to 2,

R8 represents alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl; all these radicals being optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and cyano, hydroxyl, alkoxy, alkyl, CF3, nitro, phenyl and free, salified, esterified or amidated carboxyl radicals;

R9 represents the values of R8 and hydrogen;

R10 represents hydrogen or alkyl;

R11 and R12, which may be identical or different, represent hydrogen; alkyl, cycloalkyl and phenyl optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and cyano, hydroxyl, alkoxy, alkyl, CF3, nitro, phenyl and free, salified, esterified or amidated carboxyl radicals;

or alternatively R11 and R12 form, with the nitrogen atom to which they are attached, a 5- to 7-membered cyclic radical containing one or more hetero atoms chosen from O, S, N and NR14 and preferably a cyclic amine, optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and cyano, hydroxyl, alkoxy, alkyl, CF3, nitro, phenyl, phenylalkyl and free, salified, esterified or amidated carboxyl radicals;

R13, which may be identical to or different from R5 or R6, being chosen from the values of R5 or R6;

the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

2) Products of formula (I) as defined in claim 1 in which

V represents an unsaturated or partially or totally saturated monocyclic or bicyclic heterocyclic 5- to 11-membered radical, containing one or more other hetero atoms, which may be identical or different, chosen from O, N, NR4 and S, optionally substituted with one or more substituents, which may be identical or different, chosen from the values of Y and Y1;

Y and Y1, which may be identical or different, are such that one from among Y and Y1 is chosen from OCF3; -O-CF2-CHF2; -O-CHF2; -O-CH2-CF3; -SO2NR5R6; SF5; -S(O)n-alkyl;

alkyl containing 1 to 7 carbon atoms optionally substituted with one or more fluorine atoms or cycloalkyl radicals; 3- to 7-membered cycloalkyl optionally substituted with one or more radicals, which may be identical or different, chosen from fluorine atoms and alkyl radicals containing 1 to 3 carbon atoms;

alkylamino, optionally substituted with one or more flourine atoms; dialkylamino, optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and alkoxy radicals and in which the two alkyl residues may optionally form, together with the nitrogen atom to which they are attached, a 4- to 10-membered heterocycle optionally containing one or more other hetero atoms, which may be identical or different, chosen from O, N, NR4 and S and

optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and alkyl and alkoxy radicals; phenyl, phenoxy; arylmercapto or heteroarylmercapto, optionally substituted with one or more radicals, which may be identical or different, chosen from fluorine atoms and alkyl and alkoxy radicals;

and the other from among Y and Y1 is chosen from these same values and in addition from the following values: hydrogen; halogen; hydroxyl; oxo; alkoxy; nitro; CN; NR5R6; optionally substituted alkyl; optionally substituted aryl and heteroaryl; CF3; O-alkenyl; O-alkynyl; O-cycloalkyl; S(O)n-alkenyl; S(O)n-alkynyl; S(O)n-cycloalkyl; free, salified or esterified carboxyl and CONR5R6;

p represents the integers 0, 1 and 2;

R1 represents O or NH;

R2, R2′ , R3 and R3′, which may be identical or different, represent hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl and heteroaryl which are optionally substituted, or alternatively two of the residues R2, R2′, R3 and R3′ form, together with the carbon atom(s) to which they are attached, a carbocyclic or heterocyclic radical, these radicals being 3- to 10-membered and the heterocyclic radical containing one or more hetero atoms chosen from O, S, N and NR4, all these radicals optionally being substituted;

A represents a single bond; an alkylene radical; an alkenyl radical; alkynyl; CO; SO2; O; NH; NH-alkyl;

B represents a saturated or unsaturated monocyclic or bicyclic heterocyclic radical containing one or more

hetero atoms, which may be identical or different, chosen from O, S, N and NR4, optionally substituted with one or more substituents, which may be identical or different, chosen from the values of Y2;

Y2 represents hydrogen; halogen; hydroxyl; cyano; alkyl; alkoxy; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; -O-alkenyl; -O-alkynyl; -O-cycloalkyl; -S(O)n-alkyl; -S(O)n-alkenyl; -S(O)n-alkynyl; S(O)n-cycloalkyl; COOR13; -OCOR13; NR5R6; CONR5R6; S(O)n-NR5R6; -NR10-CO-R13; -NR10-SO2-R13; NH-SO2-NR5R6; -NR10-CO-NR5R6; -NR10-CS-NR5R6 and -NR10-COOR13; all these radicals being optionally substituted;

R4 represents a hydrogen atom or an alkyl, alkenyl, alkynyl, cycloalkyl, alkylCO, alkylSO$_2$, or aryle radical, all optionally substituted with one or more substituents, which may be identical or different, chosen from halogen atoms; hydroxyl; alkoxy; dialkylamino; aryl and heteroaryl radicals, these last two radicals optionally substituted with one or more substituents, which may be identical or different, chosen from halogen atoms and alkyl and alkoxy radicals;

R5 and R6, which may be identical or different, are chosen from hydrogen; alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, optionally substituted aryl and heteroaryl; or alternatively R5 and R6 form, with the nitrogen atom to which they are attached, a 3- to 10-membered heterocyclic radical containing one or more hetero atoms chosen from O, S, N and optionally substituted NR4;

all the above alkyl, alkenyl, alkynyl and alkoxy radicals being linear or branched and containing up to 6 carbon

atoms;
all the above cycloalkyl and heterocycloalkyl radicals containing up to 7 carbon atoms;
all the above aryl and heteroaryl radicals containing up to 10 carbon atoms;
all the above alkyl, alkenyl, alkynyl and alkoxy radicals, cycloalkyl, heterocycloalkyl, aryl and heteroaryl radicals, carbocyclic and heterocyclic radicals, and also the ring formed by R5 and R6 with the atom to which they are attached being optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms; cyano; hydroxyl; alkoxy; CF3; nitro; aryl; heteroaryl; -C(=O)-OR9; -C(=O)-R8; -NR11R12; -C(=O)-NR11R12; -N(R10)-C(=O)-R8; -N(R10)-C(=O)-OR9; N(R10)-C(=O)-NR11R12; -N(R10)-S(O)n-R8; -S(O)n-R8; -N(R10)-S(O)n-NR11R12 and -S(O)n-NR11R12 radicals;
all the above aryl and heteroaryl radicals also being optionally substituted with one or more radicals chosen from alkyl, phenylalkyl, alkoxy and alkylenedioxy radicals;all the above cyclic radicals and also the ring formed by R5 and R6 with the atom to which they are attached being also optionally substituted with one or more radicals chosen from oxo and thioxo;
n represents an integer from 0 to 2,
R8 represents alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkyl-alkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl;
all these radicals being optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and cyano, hydroxyl, alkoxy, alkyl, CF3, nitro, phenyl and free, salified, esterified or amidated carboxyl radicals;

R9 represents the values of R8 and hydrogen;

R10 represents hydrogen or alkyl;

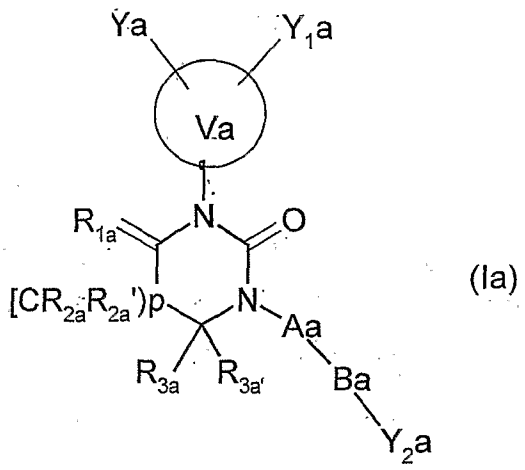
R11 and R12, which may be identical or different, represent hydrogen; alkyl, cycloalkyl and phenyl optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and cyano, hydroxyl, alkoxy, alkyl, CF3, nitro, phenyl and free, salified, esterified or amidated carboxyl radicals;

or alternatively R11 and R12 form, with the nitrogen atom to which they are attached, a 5- to 7-membered cyclic radical containing one or more hetero atoms chosen from O, S, N and NR14 and preferably a cyclic amine, optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and cyano, hydroxyl, alkoxy, alkyl, CF3, nitro, phenyl, phenylalkyl and free, salified, esterified or amidated carboxyl radicals;

R13, which may be identical to or different from R5 or R6, being chosen from the values of R5 or R6;

the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

3) Products of formula (I) as defined in either of the preceding claims, corresponding to formula (Ia):



(Ia)

in which:

p represents an integer from 0 to 2,

Va represents a 5- or 6-membered heteroaryl radical or a 9- to 11-membered fused heterocyclic radical, containing one or more other hetero atoms, which may be identical or different, chosen from O, N, NR4a and S

optionally substituted with one or more substituents, which may be identical or different, chosen from the values of Ya and Y1a;

Ya and Y1a, which may be identical or different, are such that one from among Ya and Y1a is chosen from OCF3; -O-CF2-CHF2; -O-CHF2; -O-CH2-CF3; SO2NR5aR6a; SF5; -S(O)n-alkyl; alkyl containing 1 to 7 carbon atoms optionally substituted with one or more fluorine atoms; 3- to 7-membered cycloalkyl optionally substituted with one or more radicals, which may be identical or different, chosen from fluorine atoms , alkyl radicals containing 1 to 3 carbon atoms, cyclopropyl; alkylamino, optionally substituted with one or more fluorine atoms; dialkylamino, optionally substituted with one or more radicals, which may be identical or different, chosen from fluorine atoms and alkoxy radicals and in which the two alkyl residues may optionally form, together with the

nitrogen atom to which they are attached, a 4- to 10-membered heterocycle optionally containing one or more other hetero atoms, which may be identical or different, chosen from O, N, Nalkyl and S and optionally substituted with one or more radicals, which may be identical or different, chosen from fluorine atoms and alkyl and alkoxy radicals; phenyl, phenoxy;5- to 6-membered phenylmercapto or heteroarylmercapto, optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and alkyl and alkoxy radicals;

and the other from among Ya and Y1a is chosen from these same values and in addition from the following values:

hydrogen; halogen; hydroxyl; oxo; nitro; CN; alkenyl; alkoxy; O-allyl; O-propynyl; O-cycloalkyl; CF3; optionally substituted phenyl and heteroaryl; - S(O)nCF3; SO2CHF2, SO2CF2CF3 S(O)n-allyl; S(O)n-propynyl; S(O)n-cycloalkyl; free, salified or esterified carboxyl; CONR5aR6a;

R1a stands for O;

R2a, R2a', R3a, R3a' represent hydrogen and alkyl, it being understood that two of the substituents R2a, R2a', R3a, R3a' can form, together with the carbon atom to which they are attached, a 3- to 6-membered cycloalkyl or heterocycloalkyl radical containing a nitrogen atom, all these radicals being optionally substituted;

Aa represents a single bond; an alkylene radical; CO; SO2; O; NH; NH-alkyl;

Ba represents pyridyl, pyrimidinyl, quinolyl, azaindolyl, quinazolyl, thiazolyl, imidazolyl, pyrazolyl, furazanyl,

isoxazolyl, morpholinyl, pyrrolidinyl, furyl, piperidyl, thienyl, chromenyl, oxochromenyl, indolyl, pyrrolyl, purinyl, benzoxazinyl, benzimidazolyl, indazolyl and benzofuryl radicals, these radicals being optionally substituted with one or more radicals chosen from the values of Y2a;

Y2a represents hydrogen; halogen; hydroxyl; alkyl; alkoxy; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; O-allyl; O-propynyl; O-cycloalkyl; S(O)n-alkyl; S(O)n-allyl; S(O)n-propynyl; S(O)n-cycloalkyl; COOR9a; OCOR8a; NR5aR6a; CONR5aR6a; S(O)n-R5aR6a; NHCOR8a; -NR10a-CO-NR5aR6a NH-S(O)nR8a; NH-S(O)nCF3; NH-SO2-NR5aR6a, all these radicals being optionally substituted;

R4a represents a hydrogen atom; an alkyl; cycloalkyl; or phenyl, all optionally substituted;

R5a and R6a, which may be identical or different, are chosen from hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, optionally substituted aryl and heteroaryl; or alternatively R5a and R6a form, with the nitrogen atom to which they are attached, a 3- to 10-membered heterocyclic radical containing one or more hetero atoms chosen from O, S, N and optionally substituted NR4a;

all the above alkyl, alkenyl, alkynyl and alkoxy radicals being linear or branched and containing up to 6 carbon atoms;

all the above cycloalkyl and heterocycloalkyl radicals containing up to 7 carbon atoms,

all the above aryl and heteroaryl radicals containing up to 10 carbon atoms;

all the above alkyl, alkenyl, alkynyl, alkoxy,

cycloalkyl, heterocycloalkyl, aryl, heteroaryl, carbocyclic and heterocyclic radicals being optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms; cyano; hydroxyl; alkoxy; CF3; nitro; aryl; heteroaryl; -C(=O)-OR9a; -C(=O)-R8a; -NR11aR12a; -C(=O)-NR11aR12a; -N(R10a)-C(=O)-R8a; -N(R10a)-C(=O)-OR9a; N(R10a)-C(=O)-NR11aR12a; -N(R10a)-S(O)n-R8a; -S(O)n-R8a; -N(R10a)-S(O)n-NR11aR12a and -S(O)n-NR11aR12a radicals;

all the above aryl and heteroaryl radicals also being optionally substituted with one or more radicals chosen from alkyl, phenylalkyl and alkylenedioxy radicals;

n represents an integer from 0 to 2;

R8a represents alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkyl-alkyl, phenyl, phenylalkyl, heteroaryl and heteroarylalkyl; all these radicals being optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and hydroxyl, alkoxy, alkyl, CF3, nitro, phenyl and free, salified, esterified or amidated carboxyl radicals;

R9a represents the values of R8 and hydrogen;

R10a represents hydrogen or alkyl;

R11a and R12a, which may be identical or different, represent hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl and phenylalkyl optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and cyano, hydroxyl, alkoxy, alkyl, CF3, nitro, phenyl and free, salified, esterified or amidated carboxyl radicals;

or alternatively R11a and R12a form, with the nitrogen

atom to which they are attached, a cyclic radical chosen from pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, indolinyl, pyrindolinyl, tetrahydroquinolyl, thiazolidinyl and naphthyridyl; optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and alkyl, phenyl and phenylalkyl radicals;

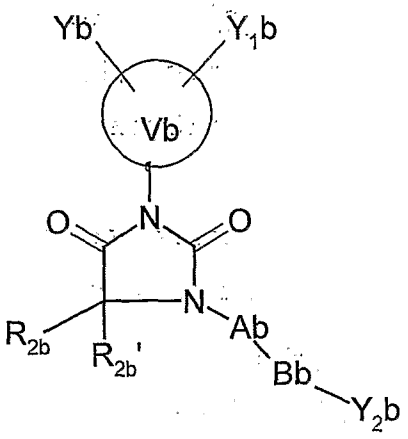
the said products of formula (Ia) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (Ia).

4) Products of formula (I) as defined in either of the preceding claims, such that p represents the integer 0, the other substituents of the said products of formula (I) having the values defined in any one of the preceding claims.

5) Products of formula (I) as defined in any one of the preceding claims, such that p represents the integer 1, the other substituents of the said products of formula (I) having the values defined in any one of the preceding claims.

6) Products of formula (I) as defined in any one of the preceding claims, such that p represents the integer 2, the other substituents of the said products of formula (I) having the values defined in any one of the preceding claims.

7) Products of formula (I) or (Ia) according to the preceding claims, corresponding to formula (Ib):



(Ib)

in which

Vb represents pyridine; pyrimidine; pyrrole; thiophene; thiazole; imidazole; oxazole; pyrazole; isoxaozole; indole; indazole; benzimidazole; benzothiazole; benzoxazole; 2,3-dihydro-1H-indole; 2,3-dihydro-1H-isoindole; 2,3-dihydrobenzothiazole; 1,2,3,4-tetrahydro-quinoline, 1,2,3,4-Tetrahydro-isoquinoline, triazole; oxadiazole; dihydrobenzothiazine; benzodioxinyl; benzopyranyl; quinolyl; optionally substituted with one or more substituents, which may be identical or different, chosen from the values of Yb and Y1b;

Yb and Y1b, which may be identical or different, are such that one from among Yb and Y1b is chosen from OCF3; S(O)nCF3; S(O)nAlk; SO2CHF2; SO2CF2CF3; SO2NR5bR6b; alkyl containing 1 to 6 carbon atoms optionally substituted by one or more F; 3- to 6-membered cycloalkyl optionally substituted with one or more methyl radicals or one or more F; alkylamino; dialkylamino, in which the two alkyl residues may optionally form, together with the nitrogen atom to which they are attached, a 5- or 6-membered heterocycle optionally containing one or more other hetero atoms, which may be identical or different, chosen from O, N, Nalkyl and S and optionally substituted

with one or more radicals, which may be identical or different, chosen from fluorine atoms and alkyl radicals; phenyl, phenoxy; 5- to 6-membered phenylmercapto or heteroarylmercapto, optionally substituted with one or more radicals, which may be identical or different, chosen from halogen atoms and alkyl radicals;

and the other from among Yb and Y1b is chosen from the same values and also from hydrogen; halogen; hydroxyl; oxo; nitro; free or esterified carboxyl; NR5bR6b; optionally substituted alkyl, alkoxy and phenyl; -O-CF2-CHF2; -O-CHF2; -O-CH2-CF3; -S-CF2-CF2-CF3; -S-Alk-O-Alk; -S-Alk-OH; -S-Alk-CN; -S-Alk-heterocycloalkyl; pyrazolyl, pyridyl, morpholino, pyrrolidinyl and piperazinyl optionally substituted with an alkyl, phenyl or phenylalkyl radical;

R2b and R2b' represent hydrogen and alkyl, or two substituents R2b and R2b', can form, together with the carbon atom to which they are attached, a cycloalkyl radical containing from 3 to 6 carbon atoms, or form an azetidinyl, pyrrolidinyl or piperidyl radical.

Ab represents a single bond, an alkylene radical;; O; NH; NH-alkyl;

Bb represents a heterocyclic radical chosen from 3- or 4-pyridyl; pyrimidinyl;; 3- or 4- quinolyl; azaindolyl; quinazolyl;indazolyl; thiazolyl; imidazolyl; pyrazolyl, furazanyl and isoxazolyl radicals; these radicals being optionally substituted with one or more radicals chosen from the values of Yb,

Y2b represents hydrogen; halogen; hydroxyl; alkyl; alkoxy; cycloalkyl; heterocycloalkyl; phenyl; heteroaryl; O-cycloalkyl; S(O)n-alk; S(O)n-cycloalkyl; COOR9; OCOR8;

NR5R6; CONR5R6; S(O)n-R5R6; NHCOR8 -NR10b-CO-NR5bR6b and NH-S(O)nR8; all these radicals being optionally substituted,

R4b represents a hydrogen atom or an alkyl, cycloalkyl or phenyl radical,

R5b and R6b, which may be identical or different, are chosen from hydrogen, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, optionally substituted phenyl and heteroaryl or alternatively R5b and R6b form, with the nitrogen atom to which they are attached, a 3- to 10-membered heterocyclic radical containing one or more hetero atoms chosen from O, S, N and optionally substituted NR4b,

all the above alkyl, alkenyl, alkynyl and alkoxy radicals being linear or branched and containing up to 6 carbon atoms,

all the above cycloalkyl and heterocycloalkyl radicals containing up to 7 carbon atoms,

all the above aryl and heteroaryl radicals containing up to 10 carbon atoms,

all the above radicals being optionally substituted with one or more radicals chosen from halogen, cyano, hydroxyl, alkyl and alkoxy containing 1 to 4 carbon atoms, CF3, nitro, phenyl, carboxyl, free, salified, esterified with an alkyl radical or amidated with a radical NR11bR12b, -C(=O)-R9b, -NR11bR12b or -C(=O)-NR11bR12b,

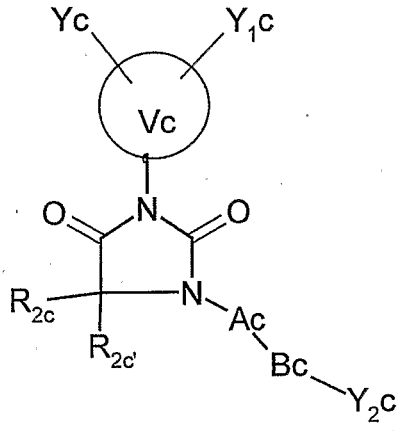
R8b represents alkyl, cycloalkyl, cycloalkylalkyl and phenyl,

R9b, which may be identical to or different from R8b, represents hydrogen and the values of R8b,

R11b and R12b, which may be identical or different, represent hydrogen, alkyl, cycloalkyl and phenyl or alternatively R11b and R12b form, with the nitrogen atom to which they are attached, a pyrolidine, piperidinyl, morpholinyl or a piperazinyl radical optionally substituted with an alkyl, phenyl or phenylalkyl radical;

the said products of formula (Ib) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (Ib).

8) Products of formula (I), (Ia) or (Ib) according to the preceding claims, corresponding to formula (Ic):



(Ic)

in which

Vc represents pyrrole, thiophene, thiazole, pyrazole, , indazole, 2,3-dihydro-1H-indole: benzodioxinyl ; benzopyranyl, optionally substituted with one or more substituents, which may be identical or different, chosen from the values of Yc and Y1c;

Yc and Y1c, which may be identical or different, are such that one from among Yc and Y1c is chosen from OCF3; -S(O)nCF3; S(O)n-Alk;SO2CHF2; SO2CF2CF3; SO2NR5cR6c; alkyl especially such as methyl, ethyl, isopropyl, tert-

butyl, sec-butyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl; cyclopropyl or cyclobutyl especially such as 1-methylcyclopropyl, 2-methylcyclopropyl, 2,2-dimethylcyclopropyl, cyclobutyl, 2,2,3,3-tetrafluorocyclobutyl;

di(C2-C4-alkyl)amino;

piperid-1-yl, thiomorpholin-4-yl, morpholin-4-yl, pyrrolidin-1-yl optionally substituted with one or more radicals chosen from fluorine atoms and alkyl radicals;

phenyl, optionally substituted with one or more halogen atoms, phenoxy, phenyl, optionally substituted with one or more halogen atoms; phenylmercapto, optionally substituted with one or more halogen atoms;

and the other from among Yc and Y1c is chosen from these same values and also from hydrogen; halogen; hydroxyl; oxo; NR5cR6c; optionally substituted alkyl, alkoxy and phenyl; optionally substituted pyrazolyl and pyridyl;

R2 and R2c' represent a hydrogen atom, alkyl of form together with the carbon atom bearing them a 3 to 6 membered cycloalkyl ring;

Ac represents a single bond , -O- or -CH2;

Bc represents a heterocyclic radical chosen from 3- or 4-pyridyl, pyrimidinyl, 3- or 4- quinolyl, azaindolyl and quinazolyl, indazolyl, these radicals being optionally substituted with one or more radicals chosen from the values of Y2c;

Y2c represents hydrogen; halogen; alkyl; cycloalkyl; hydroxyl; alkoxy; NH2; NHalk; N(alk)2; NH-Phenyl-; NH-Heteroaryl; NH-CO-R5c; NH-CO-heteroaryl; NH-CO-NR5cR6c; and phenyl; all the alkyl, alkoxy phenyl and heteroaryl radicals being optionally substituted;

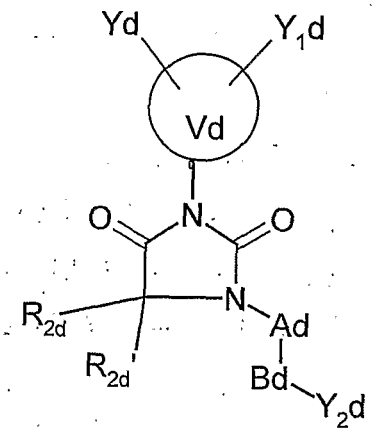
R5c and R6c, which may be identical or different,

represent hydrogen, alkyl, cycloalkyl and phenyl, which are optionally substituted, or alternatively R5c and R6c form, with the nitrogen atom to which they are attached, a cyclic radical chosen from pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, piperazinyl, indolinyl, pyrindolinyl, tetrahydroquinoline and azetidine radicals, all these radicals being optionally substituted with one or more radicals chosen from alkyl, alkoxy and phenyl;

all the above alkyl, alkoxy and phenyl radicals being optionally substituted with one or more radicals chosen from halogen, OH, alk, Oalk, OCF3, S(O)n-CF3, CF3, NH2, NHAlk and N(alk)2; it beeing understood, that all dialkylamino radicals optionally can form a pyrrolidine, piperidine, morpholine or piperazine ring optionally substituted by one or more alkyl;

the said products of formula (Ic) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (Ic).

9) Products of formula (I) as defined in any one of the preceding claims, corresponding to formula (Id):



(Id)

in which

Vd represents pyridine; pyrimidine; pyrrole; thiophene; thiazole; imidazole; oxazole; pyrazole; isoxaozole;; indazole; benzimidazole; benzothiazole; benzoxazole; 2,3-dihydro-1H-indole; 2,3-dihydro-1H-isoindole; 2,3-dihydrobenzothiazole; triazole; oxadiazole; dihydrobenzothiazine; benzodioxinyl; benzopyranyl; quinolyl;

Yd and Y1d, which may be identical or different, are such that one from among Y and Y1 is chosen from alkyl, optionally substituted by one or more fluorine atoms, phenyl, O-phenyl, S(O)n-alkyl, S(O)n-alkylphenyl and morpholino and one or and the other from among Y and Y1 is chosen from these same values and in addition from the following values: F, Cl and Br atoms; hydroxyl; oxo; cyano; free or esterified carboxyl; COCH3; phenyl; O-phenyl; S(O)n alkyl; S(O)n-alkylphenyl and morpholino radicals;

all the alkyl and phenyl radicals being themselves optionally substituted with one or more radicals , which may be identical or different, chosen from halogen atoms and alkyl, alkoxy, OCF3, cyano, amino, alkylamino and dialkylamino radicals, and a phenyl radical, itself optionally substituted with one or more halogen atoms;

R2d and R2d', which may be identical or different, are chosen from hydrogen, methyl, ethyl or form together with the atom bearing thema cyclopropyl or a cyclobutyl ring;

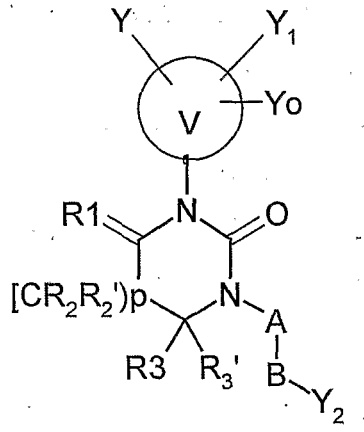
Ad represents a single bond or CH2;

Bd represents a quinolyl or pyridyl radical optionally substituted with one or more radicals Y2d chosen from halogen, -OH, alk, -Oalk, -CO2H, -CO2alk, -NH2, NHalk,

N(alk)2, -CF3, -OCF3 and phenyl,NH-phenyl; NH-heteroaryl NH-CO-phenyl, NH-CO-heteroaryl; NH-CO-NH-alkyl; NH-CO-NH-dialkyl ; NH-CO-NH-phenyl;the alkyl and phenyl radicals being themselves optionally substituted with one or more radicals chosen from halogen atoms and alkyl and alkoxy and dialkylamino radicals; it beeing understood, that all dialkylamino radicals optionally can form a pyrrolidine, piperidine, morpholine or piperazine ring optionally substituted by one or more alkyl;

the said products of formula (Id) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (Id).

10) Products of formula (I) as defined in any one of the preceding claims, in which:



V represents pyridine; pyrimidine; pyrrole; thiophene; thiazole; dithiazole; imidazole; oxazole; isoxazole; pyrazole; isoxaozole; indazole; benzimidazole; benzothiazole; benzoxazole; 2,3-dihydro-1H-indole; 2,3-dihydro-1H-isoindole; 2,3-dihydrobenzothiazole; triazole;

oxadiazole; dihydrobenzothiazine; benzodioxinyl; benzopyranyl; quinolyl; 1,2,3,4 tetrahydroquinolyl;
the atom S that V can contain, being optionally oxidized by one or two oxygen;

Yo, Y and Y1, which may be identical or different, are such that Yo represents hydrogen or alkyl and one from among Y and Y1 is chosen from alkyl optionally substituted by one or more fluorine atoms, phenyl, O-phenyl, S(O)n-alkyl, S(O)n-alkylphenyl and morpholino and the other from among Y and Y1 is chosen from these same values and in addition from the following values: F, Cl and Br atoms; hydroxyl; oxo; cyano; free or esterified carboxyl; COCH3; -alkyl-CO-piperazinyl itself optionally substituted by alkyl; phenyl; O-phenyl; S(O)n-alkyl; S(O)n-alkylphenyl and morpholino radicals;
all the alkyl and phenyl radicals being themselves optionally substituted with one or more radicals , which may be identical or different, chosen from halogen atoms and alkyl, alkoxy, OCF3, cyano, amino, alkylamino and dialkylamino radicals, and a phenyl radical, itself optionally substituted with one or more halogen atoms;

R2 and R2', which may be identical or different, are chosen from hydrogen and alkyl optionally substituted with aryl or heteroaryl themselves optionally substituted by one or more radicals chosen among halogen, alkyl, OH or alcoxy;

A represents CH2;

B represents a quinolyl, pyrimidinyle or pyridyl radical optionally substituted by one or more radicals identical or different chosen among halogen; -NH2; -NH-alkyl and N(alk)2 with alkyl optionally substituted by one or more

halogen; -NH-CO-N(alk)2; phenyl, -NH-phenyl, -NH-heteroaryl, NH heterocycloalkyl, -NH-CO-phenyl and -NH-CO-heteroaryl themselves optionally substituted by one or more radicals identical or different chosen among halogen, alkyl, alcoxy, N(alk)2, CO2H, CO2ethyl and CO-N(alk)2;

the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

11) Products of formula (I) as defined in any one of the preceding claims, in which V is chosen from the values defined in any one of the preceding claims,

R2 and R2', which may be identical or different, are chosen from hydrogen and alkyl;

A represents CH2;

B represents a quinolyl or pyridyl radical;

the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

12) Products of formula (I) as defined in any one of the preceding claims, in which

V represents pyridine; pyrimidine; pyrrole; thiophene; thiazole; imidazole; oxazole; pyrazole; isoxaozole;; indazole; benzimidazole; benzothiazole; benzoxazole; 2,3-dihydro-1H-indole; 2,3-dihydro-1H-isoindole; 2,3-

dihydrobenzothiazole; triazole; oxadiazole; dihydrobenzothiazine; benzodioxinyl; benzopyranyl; quinolyl;

Y and Y1, which may be identical or different, are such that one from among Y and Y1 is chosen from alkyl, optionally substituted by one or more fluorine atoms, phenyl, O-phenyl, S(O)n-alkyl, S(O)n-alkylphenyl and morpholino and one or and the other from among Y and Y1 is chosen from these same values and in addition from the following values: F, Cl and Br atoms; hydroxyl; oxo; cyano; free or esterified carboxyl; COCH3; phenyl; O-phenyl; S(O)n alkyl; S(O)n-alkylphenyl and morpholino radicals;

all the alkyl and phenyl radicals being themselves optionally substituted with one or more radicals , which may be identical or different, chosen from halogen atoms and alkyl, alkoxy, OCF3, cyano, amino, alkylamino and dialkylamino radicals, and a phenyl radical, itself optionally substituted with one or more halogen atoms;

R2 and R2', which may be identical or different, are chosen from hydrogen and alkyl;

A represents CH2;

B represents a quinolyl or pyridyl radical;

the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

13) Products of formula (I) as defined in any one of Claims 1 to 12, the names of which are given hereinbelow:

- 3-(5-Isopropyl-thiazol-2-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl-imidazolidine-2,4- dione

- 3-(5-tert-Butyl-2H-pyrazol-3-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl-imidazolidine-2,4- dione

- 3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl- imidazolidine-2,4-dione

- 3-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl- imidazolidine-2,4-dione

- 5,5-Dimethyl-3-(2-oxo-4-trifluoromethyl-2H-1-benzopyran-7-yl)-1-pyridin-4-ylmethyl-imidazolidine-2,4-dione trifluoroacetate

- 3-(2,2-Dimethyl-4-oxo-4H-1,3-benzodioxin-7-yl)-5,5-dimethyl-1-pyridin-4-ylmethyl-imidazolidine-2,4-dione trifluoroacetate

- 3-(1-Acetyl-2,3-dihydro-1H-indol-5-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl-imidazolidine- 2,4-dione

the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

14) Products of formula (I) as defined in any one of Claims 1 to 12, the names of which are given hereinbelow:

- 3-(5-Isopropyl-thiazol-2-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl-imidazolidine-2,4- dione

- 3-(5-tert-Butyl-2H-pyrazol-3-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl-imidazolidine-2,4- dione

- 3-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl- imidazolidine-2,4-dione

- 3-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-5,5-dimethyl-1-quinolin-4-ylmethyl- imidazolidine-2,4-dione

the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, and also the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

15) As medicinal products, the products of formula (I) as defined in any one of Claims 1 to 14, and also the prodrugs thereof, the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, and also the pharmaceutically acceptable addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

16) As medicinal products, the products of formula (Ia), (Ib), (Ic) or (Id) as defined in the preceding claims, and also the prodrugs thereof, the said products of formula (Ia), (Ib), (Ic) or (Id) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, and also the pharmaceutically acceptable addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (Ia), (Ib), (Ic) or (Id).

17) As medicinal products, the products as defined in Claim 13 or 14 and also the prodrugs thereof, and also

the pharmaceutically acceptable addition salts of these products with mineral and organic acids or with mineral and organic bases.

18) Pharmaceutical compositions containing, as active principle, at least one of the medicinal products as defined in Claims 15 to 17.

19) Pharmaceutical compositions according to Claim 18 characterized in that they are used as medicinal products, in particular for cancer chemotherapy.

20) Pharmaceutical compositions according to Claim 19, also containing active principles of other chemotherapy medicinal products for combating cancer.

21) Use of products of formula (I) as defined in any one of the claims, or of pharmaceutically acceptable salts of the products of formula (I) for the preparation of medicinal products for inhibiting the activity of protein kinases and especially of a protein kinase.

22) Use of products of formula (I) as defined in the preceding claim or of pharmaceutically acceptable salts of the products of formula (I), in which the protein kinase is a protein tyrosine kinase.

23) Use of products of formula (I) as defined in any one of the preceding claims, or of pharmaceutically acceptable salts of the products of formula (I), in which the protein kinase is chosen from the following group:

IGF1, Raf, EGF, PDGF, VEGF, Tie2, KDR, Flt1-3, FAK, Src, Abl, cKit, cdk1-9, Aurora1-2, cdc7, Akt, Pdk, S6K, Jnk, IR, FLK-1, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, PLK, Pyk2, CDK7, CDK2 et EGFR

24) Use of products of formula (I) as defined in any one of the claims, or of pharmaceutically acceptable salts of the products of formula (I), in which the protein kinase is chosen from the following group: IGF1, cdc7, Aurora1-2, Src, Jnk, FAK, KDR, IR, Tie2, CDK7, CDK2 et EGFR.

25) Use of products of formula (I) as defined in any one of the claims, or of pharmaceutically acceptable salts of the products of formula (I), in which the protein kinase is IGF1R.

26) Use of products of formula (I) as defined in any one of the claims, or of pharmaceutically acceptable salts of the products of formula (I), in which the protein kinase is in a cell culture.

27) Use of products of formula (I) as defined in any one of the claims, or of pharmaceutically acceptable salts of the products of formula (I), in which the protein kinase is in a mammal.

28) Use of products of formula (I) as defined in any one of the claims or of pharmaceutically acceptable salts of the products of formula (I), for the preparation of a medicinal product for preventing or treating a disease characterized by deregulation of the activity of a protein kinase.

29) Use of products of formula (I) according to the preceding claim, in which the disease to be prevented or treated is in a mammal.

30) Use of products of formula (I) as defined in any one of the claims or of pharmaceutically acceptable salts of the products of formula (I), for the preparation of a

medicinal product for preventing or treating a disease belonging to the following group: disorders of blood vessel proliferation, fibrotic disorders, disorders of mesangial cell proliferation, acromegaly, metabolic disorders, allergies, asthma, Crohn's disease, thrombosis, diseases of the nervous system, retinopathy, psoriasis, rheumatoid arthritis, diabetes, muscle degeneration, aging, age related macula degeneration, oncology diseases and cancer.

31) Use of products of formula (I) as defined in any one of the claims or of pharmaceutically acceptable salts of said products of formula (I) for the preparation of a medicinal product for treating oncology diseases.

32) Use of products of formula (I) as defined in any one of the claims or of pharmaceutically acceptable salts of said products of formula (I) for the preparation of a medicinal product for treating cancer.

33) Use of products of formula (I) as claimed in the preceding claim, in which the disease to be treated is a cancer of solid tumours.

34) Use of products of formula (I) as claimed in the preceding claim, in which the disease to be treated is a cancer that is resistant to cytotoxic agents.

35) Use of products of formula (I) as defined in any one of the claims, or of pharmaceutically acceptable salts of said products of formula (I), for the preparation of a medicinal product for treating cancers, among which are breast cancer, stomach cancer, cancer of the colon, lung cancer, cancer of the ovaries, cancer of the uterus, brain cancer, cancer of the kidney, cancer of the larynx, cancer of the lymphatic system, cancer of the thyroid, cancer of the urogenital tract, cancer of the tract

including the seminal vesicle and prostate, bone cancer, cancer of the pancreas and melanomas.

36) Use of products of formula (I) as claimed in the preceding claim, in which the disease to be treated is a breast cancer, cancer of the colon or lung cancer.

37) Use of products of formula (I) as defined in any one of the claims or of pharmaceutically acceptable salts of said products of formula (I) for the preparation of a medicinal product for cancer chemotherapy.

38) Use of products of formula (I) as defined in any one of the claims or of pharmaceutically acceptable salts of said products of formula (I) for the preparation of medicinal products for cancer chemotherapy, used alone or in combination.

39) Use of products of formula (I) as defined in any one of the claims or of pharmaceutically acceptable salts of said products of formula (I) for the preparation of medicinal products for use alone or in combination with chemotherapy or radiotherapy or alternatively in combination with other therapeutic agents.

40) Use of products of formula (I) as claimed in the preceding claim, in which the therapeutic agents may be commonly used antitumour agents.

41) Products of formula (I) as defined in any one of the claims, as protein kinase inhibitors, said products of formula (I) being in any possible racemic, enantiomeric or diastereoisomeric isomer form, and also the addition salts of said products of formula (I) with pharmaceutically acceptable mineral and organic acids or with pharmaceutically acceptable mineral and organic bases, and also the prodrugs thereof.

42) Products of formula (I) as defined in any one of the claims, as IGF1R inhibitors.

43) Products of formula (Id) as defined in the claims, as IGF1R inhibitors.