SPOOR & FISHER

FORM P.8
(To be lodged in duplicate)

REPUBLIC OF SOUTH AFRICA
PATENTS ACT, 1978

PUBLICATION PARTICULARS AND ABSTRACT

(Section 32(3)(a) – Regulation 22(1)(g) and 31)

OFFICIAL APPLICATION NO.		LODGING DATE	ACCEPTANCE DATE
21	01 2004/1316	22 30 JUL 2002	43 10·3·05

18·2·05

INTERNATIONAL CLASSIFICATION		NOT FOR PUBLICATION
51	C07D	CLASSIFIED BY: WIPO

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EARLIEST PRIORITY CLAIMED

COUNTRY		NUMBER		DATE	
33	US	31	09/922,729	32	7 AUG 2001

TITLE OF INVENTION

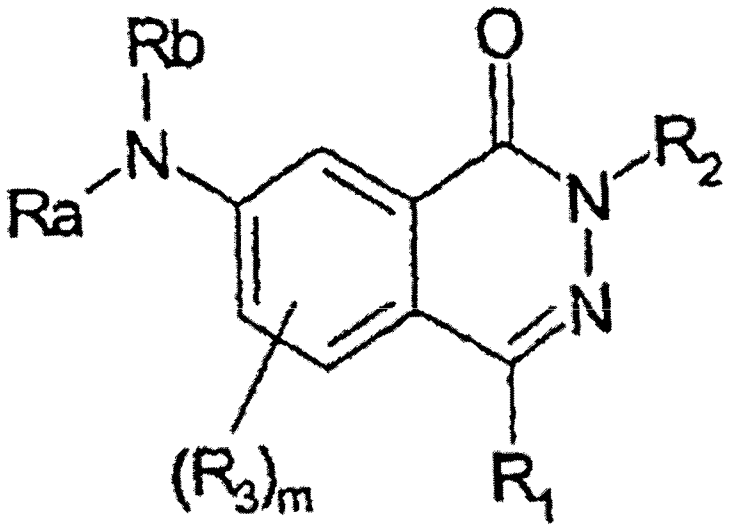
54	AMINO-PHTHALAZINONE DERIVATIVES ACTIVE AS KINASE INHIBITORS, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

57	ABSTRACT (NOT MORE THAT 150 WORDS)	NUMBER OF SHEETS	106

If no classification is finished, Form P.9 should accompany this form.
The figure of the drawing to which the abstract refers is attached.

ABSTRACT

Compounds which are amino-phthalazinone derivatives according to formula 1 and pharmaceutically acceptable salts thereof, togetherwith pharmaceutical compositions comprising them are disclosed; these compounds or compostions are useful in the treatment of diseases caused by and/or associated with an altered protein kinase activity such as cancer, cell proliferative disorders, Alzheimer'sdisease, viral infections, autoimmune diseases and neurodegenerative disorders.



(I)

AMINO-PHTHALAZINONE DERIVATIVES ACTIVE AS KINASE INHIBITORS, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

The present invention relates to amino-phthalazinone derivatives active as kinase inhibitors and, more in particular, it relates to 7-amino-phthalazin-1-one derivatives, to a process for their preparation, to pharmaceutical compositions comprising them and to their use as therapeutic agents, particularly in the treatment of diseases linked to disregulated protein kinases.

The malfunctioning of protein kinases (PKs) is the hallmark of numerous diseases. A large share of the oncogenes and proto-oncogenes involved in human cancers code for PKs. The enhanced activities of PKs are also implicated in many non-malignant diseases, such as benign prostate hyperplasia, familial adenomatosis, polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis.

PKs are also implicated in inflammatory conditions and in the multiplication of viruses and parasites. PKs may also play a major role in the pathogenesis and development of neurodegenerative disorders.

For a general reference to PKs malfunctioning or disregulation see, for instance, Current Opinion in Chemical Biology 1999, 3, 459 - 465.

It is an object of the invention to provide compounds which are useful in therapy as agents against a host of diseases caused by and/or associated to a disregulated protein kinase activity.

It is another object to provide compounds which are endowed with multiple protein kinase inhibiting activity.

The present inventors have now discovered that some 7-amino-phthalazin-1-one derivatives, hereinafter shortly referred to as amino-phthalazinone derivatives or amino-phthalazinones, are endowed with multiple protein kinase inhibiting activity and are thus useful in therapy in the treatment of diseases associated with disregulated protein kinases.

More specifically, the amino-phthalazinones of this invention are useful in the treatment of a variety of cancers including, but not limited to: carcinoma such as bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma; hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocitic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoxanthoma, thyroid follicular cancer and Kaposi's sarcoma.

Due to the key role of PKs in the regulation of cellular proliferation, these amino-phthalazinones are also useful in the treatment of a variety of cell proliferative disorders such as, for instance, benign prostate hyperplasia, familial adenomatosis, polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis,

arthritis glomerulonephritis and post-surgical stenosis and restenosis.

The compounds of the invention can be useful in the treatment of Alzheimer's disease, as suggested by the fact that cdk5 is involved in the phosphorylation of tau protein (*J. Biochem.*, 117, 741-749, 1995).

The compounds of this invention, as modulators of apoptosis, may also be useful in the treatment of cancer, viral infections, prevention of AIDS development in HIV-infected individuals, autoimmune diseases and neurodegenerative disorders.

The compounds of this invention may be useful in inhibiting tumor angiogenesis and metastasis.

The compounds of the invention are useful as cyclin dependent kinase (cdk) inhibitors and also as inhibitors of other protein kinases such as, for instance, protein kinase C in different isoforms, Met, PAK-4, PAK-5, ZC-1, STLK-2, DDR-2, Aurora 1, Aurora 2, Bub-1, PLK, Chk1, Chk2, HER2, raf1, MEK1, MAPK, EGF-R, PDGF-R, FGF-R, IGF-R, VEGF-R, PI3K, weel kinase, Src, Abl, Akt, ILK, MK-2, IKK-2, Cdc7, Nek, and thus be effective in the treatment of diseases associated with other protein kinases.

Some amino-phthalazinone and amino-phthalazinedione derivatives are known in the art, as chemical intermediates, as therapeutic agents and even as protein kinase inhibitors.

As an example, the compounds N-[3-[2,4-bis(1,1-dimethylpropyl)phenoxy]propyl]-N'-(3,4-dihydro-4-oxo-6-phthalazinyl)-urea and 2-[2,4-bis(1,1-dimethylpropyl)phenoxy]-N-(3,4-dihydro-4-oxo-6-phthalazinyl)-butanamide are disclosed as heat development image forming agents, in JP-A-09061961 by Heisei.

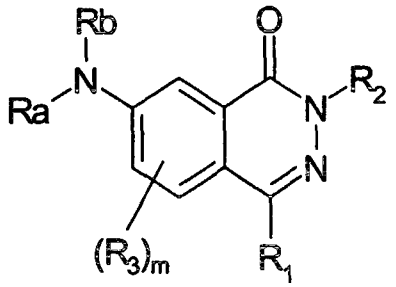
The compound N-[3,4-dihydro-3-[4-[4-(1-naphthalenyl)-1-piperazinyl]butyl]-4-oxo-6-phthalazinyl]-acetamide is

disclosed in JP-A-10287658 by Heisei, as a serotoninergic/dopaminergic agent.

The compounds N-[3,4-dihydro-4-oxo-1-(4-pyridinylmethyl)-6-phthalazinyl]-acetamide and N-[3,4-dihydro-4-oxo-1-(4-pyridinylmethyl)-6-phthalazinyl]-2,2,2-trifluoro-acetamide are disclosed in WO 98/35958 by Novartis, as synthetic intermediates for the preparation of anilino-phthalazines, as VEGF receptor tyrosine kinase inhibitors.

In addition to the above, phthalazinedione or phthalazinone derivatives bearing substituted amino groups in both positions 6 and 7 of the ring such as, for instance, 7-(cyclohexylamino)-6-phenylamino-1(2H)-phthalazinone and 6,7-bis(phenylamino)-1(2H)-phthalazinone, are disclosed in EP-A-600831 by Ciba-Geigy as protein kinase inhibitors.

Accordingly, the present invention provides a method for treating diseases caused by and/or associated with an altered protein kinase activity, by administering to a mammal in need thereof an effective amount of an amino-phthalazinone derivative represented by formula (I):



(I)

wherein

Ra and Rb are, each independently, a hydrogen atom or a group, optionally further substituted, selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur; or one of Ra or Rb is hydrogen or an optionally substituted straight or branched C_1-C_6 alkyl group, and the other is a group selected from -COR', -CONHR', -COOR' or

$-SO_2R'$, wherein R' is hydrogen or an optionally substituted group selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl, as set forth above;

R_1 is a group of formula $-CHR_4R_5$ wherein R_4 and R_5 are, each independently, hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur; or R_1 is a group of formula -NHR', -NR'COR", -NR'CONHR" or $-NR'SO_2R"$, wherein R' has the above reported meanings other than hydrogen, and R" is hydrogen or has the meanings set forth above for R';

R_2 is a hydrogen atom or it is a group, optionally further substituted, selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur;

any R_3, being placed in one or more of the free positions 5, 6 and 8 of the phthalazinone ring are, independently from each other, halogen, nitro, carboxy, cyano or a group optionally further substituted selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur; or R_3 is a group selected from -COR', -CONHR', $-SO_2R'$, -NR'R", -NR'COR", -NR'CONHR' or $-NR'SO_2R"$, wherein R' and R" are, the same or different, hydrogen or a group as set forth above;

m is 0 or an integer from 1 to 3;

or a pharmaceutically acceptable salt thereof.

In a preferred embodiment of the method described above, the disease caused by and/or associated with an altered

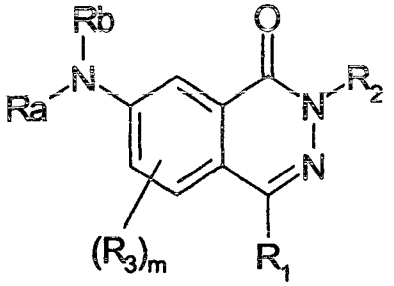
protein kinase activity is selected from the group consisting of cancer, cell proliferative disorders, Alzheimer's disease, viral infections, auto-immune diseases and neurodegenerative disorders.

Specific types of cancer that may be treated include carcinoma, squamous cell carcinoma, hematopoietic tumors of myeloid or lymphoid lineage, tumors of mesenchymal origin, tumors of the central and peripheral nervous system, melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoxanthoma, thyroid follicular cancer and Kaposi's sarcoma.

In another preferred embodiment of the method described above, the cell proliferative disorder is selected from the group consisting of benign prostate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis.

In addition, the method object of the present invention, also provides tumor angiogenesis and metastasis inhibition.

The present invention further provides an amino-phthalazinone derivative represented by formula (I)



(I)

wherein

Ra and Rb are, each independently, a hydrogen atom or a group, optionally further substituted, selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from

1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur; or one of Ra or Rb is hydrogen or an optionally substituted straight or branched C_1-C_6 alkyl group, and the other is a group selected from -COR', -CONHR', -COOR' or -SO_2R', wherein R' is hydrogen or an optionally substituted group selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl, as set forth above;

R_1 is a group of formula -CHR_4R_5 wherein R_4 and R_5 are, each independently, hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur; or R_1 is a group of formula -NHR', -NR'COR", -NR'CONHR" or -NR'SO_2R", wherein R' has the above reported meanings other than hydrogen, and R" is hydrogen or has the meanings set forth above for R';

R_2 is a hydrogen atom or it is a group, optionally further substituted, selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur;

any R_3, being placed in one or more of the free positions 5, 6 and 8 of the phthalazinone ring are, independently from each other, halogen, nitro, carboxy, cyano or a group optionally further substituted selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur; or R_3 is a group selected from -COR', -CONHR', -SO_2R', -NR'R", -NR'COR", -NR'CONHR' or -NR'SO_2R", wherein R' and R" are, the same or different, hydrogen or a group as set forth above;

m is 0 or an integer from 1 to 3;

or a pharmaceutically acceptable salt thereof;
the compounds N-[3,4-dihydro-4-oxo-1-(4-pyridinylmethyl)-6-phthalazinyl]-acetamide and N-[3,4-dihydro-4-oxo-1-(4-pyridinylmethyl)-6-phthalazinyl]-2,2,2-trifluoro-acetamide, being excluded.

The compounds of formula (I), object of the present invention, may have asymmetric carbon atoms and may therefore exist either as racemic admixtures or as individual optical isomers.
Accordingly, all the possible isomers and their admixtures and of both the metabolites and the pharmaceutically acceptable bio-precursors (otherwise referred to as pro-drugs) of the compounds of formula (I), as well as any therapeutic method of treatment comprising them, are also within the scope of the present invention.

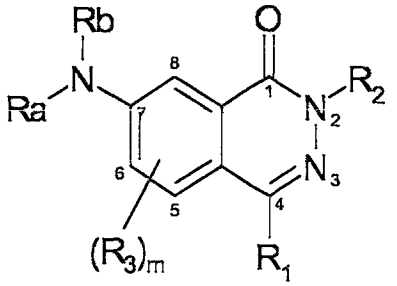
As used herein, unless otherwise specified, with the term halogen atom we intend a chlorine, bromine, fluorine or iodine atom.
With the term straight or branched C_1-C_6 alkyl we intend a group such as, for instance, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl and the like.
With the term C_3-C_6 cycloalkyl we intend a group such as, for instance, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.
With the term aryl we intend a mono-, bi- or poly- either carbocyclic as well as heterocyclic hydrocarbon with from 1 to 4 ring moieties, either fused to each other or linked by single bonds, wherein at least one of the carbocyclic or heterocyclic rings is aromatic.
Non limiting examples of aryl groups are, for instance, phenyl, indanyl, biphenyl, α- or β-naphthyl, fluorenyl, 9,10-dihydroanthracenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, imidazolyl, imidazopyridyl, 1,2-

methylenedioxyphenyl, thiazolyl, isothiazolyl, pyrrolyl, pyrrolyl-phenyl, furyl, phenyl-furyl, benzotetrahydrofuranyl, oxazolyl, isoxazolyl, pyrazolyl, chromenyl, thienyl, benzothienyl, isoindolinyl, benzoimidazolyl, isoindolinyl-phenyl, quinolinyl, isoquinolinyl, 2,6-diphenyl-pyridyl, quinoxalinyl, pyrazinyl, phenyl-quinolinyl, benzofurazanyl, 1,2,3-triazolyl, 1-phenyl-1,2,3-triazolyl, and the like.

With the term 5 to 7 membered heterocyclyl, hence encompassing aromatic heterocyclic groups also referred to as aryl groups, we further intend a saturated or partially unsaturated 5 to 7 membered carbocycle wherein one or more carbon atoms are replaced by 1 to 3 heteroatoms such as nitrogen, oxygen and sulfur.

Besides the above heteroaryl groups, additional examples of 5 to 7 membered heterocyclyl groups, optionally benzocondensed or further substituted, are 1,3-dioxolane, pyran, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazoline, piperidine, piperazine, morpholine, tetrahydrofuran, azepine, diazepine and the like.

According to the present formula (I), it is clear to the skilled man that when m is 0 there are no R_3 groups or, in other words, the positions 5, 6 and 8 of the phthalazinone ring, as per the numbering system below, are unsubstituted or hydrogen substituted



(I)

Likewise, when m is 1 or 2, one or two R_3 substituents, the same or different from each other, are present in one or two of the positions 5, 6 or 8; finally, when m is 3, all

of the available 5, 6 and 8 positions are occupied by R_3 groups, the same or different, as above indicated.

According to the above meanings provided to Ra, Rb, R', R", R_2, R_3, R_4 and R_5 substituents, any of the above groups may be further optionally substituted in any of the free positions by one or more groups, for instance 1 to 6 groups, selected from: halogen, nitro, oxo groups (=O), carboxy, cyano, alkyl, perfluorinated alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, amino groups and derivatives thereof such as, for instance, alkylamino, dialkylamino, arylamino, diarylamino, ureido, alkylureido or arylureido; carbonylamino groups and derivatives thereof such as, for instance, formylamino, alkylcarbonylamino, alkenylcarbonylamino, arylcarbonylamino, alkoxycarbonylamino; hydroxy groups and derivatives thereof such as, for instance, alkoxy, aryloxy, alkylcarbonyloxy, arylcarbonyloxy, cycloalkenyloxy or alkylideneaminooxy; carbonyl groups and derivatives thereof such as, for instance, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, cycloalkyloxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl; sulfurated derivatives such as, for instance, alkylthio, arylthio, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, arylsulfonyloxy, aminosulfonyl, alkylaminosulfonyl or dialkylaminosulfonyl.

In their turn, whenever appropriate, each of the above substituents may be further substituted by one or more of the aforementioned groups.

Among these latter groups and unless otherwise specified in the present description, with the term perfluorinated alkyl we intend a straight or branched C_1-C_6 alkyl group as above defined, wherein more than one hydrogen atom are replaced by fluorine atoms. Example of perfluorinated alkyl groups are, for instance, trifluoromethyl, 2,2,2-trifluoroethyl,

1,2-difluoroethyl, 1,1,1,3,3,3-hexafluoropropyl-2-yl and the like.

With the term alkenyl or alkynyl we intend a straight or branched C_2-C_6 alkenyl or alkynyl group such as, for instance, vinyl, allyl, isopropenyl, 1-, 2- or 3-butenyl, isobutylenyl, hexenyl, ethynyl, 1- or 2-propynyl, butynyl and the like.

From all of the above, it is clear to the skilled man that any group which name has been identified as a composite name such as, for instance, cycloalkylalkyl, arylalkyl, heterocyclylalkyl, alkoxy, alkylthio, aryloxy, arylalkoxy, heterocyclyloxy, heterocyclylalkoxy, alkylcarbonyloxy and the like, has to be intended as conventionally construed from the parts to which it derives.

As an example, the term heterocyclyl-alkoxy stands for an alkoxy (e.g. alkyl-oxy) group further substituted by a heterocyclyl group.

Pharmaceutically acceptable salts of the compounds of formula (I) are the acid addition salts with inorganic or organic, e.g. nitric, hydrochloric, hydrobromic, sulfuric, perchloric, phosphoric, acetic, trifluoroacetic, propionic, glycolic, lactic, oxalic, malonic, malic, maleic, tartaric, citric, benzoic, cinnamic, mandelic, methanesulfonic, isethionic and salicylic acid, as well as the salts with inorganic or organic bases, e.g. alkali or alkaline-earth metals, especially sodium, potassium, calcium or magnesium hydroxides, carbonates or bicarbonates, acyclic or cyclic amines, preferably methylamine, ethylamine, diethylamine, triethylamine or piperidine.

A first class of preferred compounds of the invention is represented by the compounds of formula (I) wherein one of Ra or Rb is a hydrogen atom or an optionally substituted straight or branched C_1-C_6 alkyl group and the other is a group -COR' wherein R' is an optionally substituted group

selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl, as set forth above, and R_1, R_2, R_3 and m are as above defined.

More preferred, within this class, are the compounds of formula (I) wherein R_1 is a group $-CHR_4R_5$ wherein R_4 and R_5 are as above defined, R_2 is hydrogen and m is 0.

Another class of preferred compounds of the invention is represented by the compounds of formula (I) wherein one of Ra or Rb is a hydrogen atom or an optionally substituted straight or branched C_1-C_6 alkyl group and the other is a group -CONHR' wherein R' is a hydrogen atom or an optionally substituted group selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl, as set forth above, and R_1, R_2, R_3 and m are as above defined.

More preferred, within this class, are the compounds of formula (I) wherein R_1 is a group $-CHR_4R_5$ wherein R_4 and R_5 are as above defined, R_2 is hydrogen and m is 0.

Another class of preferred compounds of the invention is represented by the compounds of formula (I) wherein one of Ra or Rb is a hydrogen atom or an optionally substituted straight or branched C_1-C_6 alkyl group and the other is a group -COOR' wherein R' is a hydrogen atom or an optionally substituted group selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl, as set forth above, and R_1, R_2, R_3 and m are as above defined.

More preferred, within this class, are the compounds of formula (I) wherein R_1 is a group $-CHR_4R_5$ wherein R_4 and R_5 are as above defined, R_2 is hydrogen and m is 0.

Another class of preferred compounds of the invention is represented by the compounds of formula (I) wherein one of Ra or Rb is a hydrogen atom or an optionally substituted

straight or branched C_1-C_6 alkyl group and the other is a group $-SO_2R'$ wherein R' is an optionally substituted group selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl, as set forth above, and R_1, R_2, R_3 and m are as above defined.

More preferred, within this class, are the compounds of formula (I) wherein R_1 is a group $-CHR_4R_5$ wherein R_4 and R_5 are as above defined, R_2 is hydrogen and m is 0.

Another class of preferred compounds of the invention is represented by the compounds of formula (I) wherein Ra and Rb are both hydrogen atoms and R_1, R_2, R_3 and m are as above defined.

More preferred, within this class, are the compounds of formula (I) wherein R_1 is a group $-CHR_4R_5$ wherein R_4 and R_5 are as above defined, R_2 is hydrogen and m is 0.

Another class of preferred compounds of the invention is represented by the compounds of formula (I) wherein one of Ra or Rb is a hydrogen atom or an optionally substituted straight or branched C_1-C_6 alkyl and the other is a group, optionally further substituted, selected from alkyl, cycloalkylalkyl, arylalkyl or heterocyclylalkyl as set forth above, and R_1, R_2, R_3 and m are as above defined.

More preferred, within this class, are the compounds of formula (I) wherein R_1 is a group $-CHR_4R_5$ wherein R_4 and R_5 are as above defined, R_2 is hydrogen and m is 0.

Specific examples of preferred compounds of formula (I) of the invention, optionally in the form of pharmaceutically acceptable salts, are:

1. 4-(4-Oxo-6-propionylamino-3,4-dihydro-phthalazin-1-ylmethyl)-benzoic acid methyl ester;
2. 4-[4-Oxo-6-(4-trifluoromethyl-benzoylamino)-3,4-dihydro-phthalazin-1-ylmethyl]-benzoic acid methyl ester;

3. 4-{6-[(Furan-2-carbonyl)-amino]-4-oxo-3,4-dihydro-phthalazin-1-ylmethyl}-benzoic acid methyl ester;
4. 4-[6-(3,4-Dimethoxy-benzoylamino)-4-oxo-3,4-dihydro-phthalazin-1-ylmethyl]-benzoic acid methyl ester;
5. 4-[6-(3-Cyclopentyl-propionylamino)-4-oxo-3,4-dihydro-phthalazin-1-ylmethyl]-benzoic acid methyl ester;
6. 4-[4-Oxo-6-(2-propyl-pentanoylamino)-3,4-dihydro-phthalazin-1-ylmethyl]-benzoic acid methyl ester;
7. 4-{4-Oxo-6-[3-(3-trifluoromethyl-phenyl)-ureido]-3,4-dihydro-phthalazin-1-ylmethyl}-benzoic acid methyl ester;
8. 4-{6-[3-(3-Methoxy-phenyl)-ureido]-4-oxo-3,4-dihydro-phthalazin-1-ylmethyl}-benzoic acid methyl ester;
9. 4-[4-Oxo-6-(3-p-tolyl-ureido)-3,4-dihydro-phthalazin-1-ylmethyl]-benzoic acid methyl ester;
10. 4-{6-[3-(2,4-Difluoro-phenyl)-ureido]-4-oxo-3,4-dihydro-phthalazin-1-ylmethyl}-benzoic acid methyl ester;
11. 4-{6-[3-(3,4-Dichloro-phenyl)-ureido]-4-oxo-3,4-dihydro-phthalazin-1-ylmethyl}-benzoic acid methyl ester;
12. 4-[4-Oxo-6-(3-pyridin-3-yl-ureido)-3,4-dihydro-phthalazin-1-ylmethyl]-benzoic acid methyl ester;
13. 4-(6-Amino-4-oxo-3,4-dihydro-phthalazin-1-ylmethyl)-benzoic acid methyl ester;
14. N-[1-(4-Chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-propionamide;
15. N-[1-(4-Chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide;
16. Furan-2-carboxylic acid [1-(4-chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;
17. N-[1-(4-Chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3,4-dimethoxy-benzamide;
18. N-[1-(4-Chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide;
19. 2-Propyl-pentanoic acid [1-(4-chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;
20. 1-[1-(4-Chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea;

21. 1-[1-(4-Chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-methoxy-phenyl)-urea;
22. 1-[1-(4-Chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea;
23. 1-[1-(4-Chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea;
24. 1-[1-(4-Chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3,4-dichloro-phenyl)-urea;
25. 1-[1-(4-Chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-pyridin-3-yl-urea;
26. 7-Amino-4-(4-chloro-3-fluoro-benzyl)-2H-phthalazin-1-one;
27. N-{1-[(E)-3-(4-Nitro-phenyl)-allyl]-4-oxo-3,4-dihydro-phthalazin-6-yl}-propionamide;
28. N-{1-[(E)-3-(4-Nitro-phenyl)-allyl]-4-oxo-3,4-dihydro-phthalazin-6-yl}- 4-trifluoromethyl-benzamide;
29. Furan-2-carboxylic acid {1-[(E)-3-(4-nitro-phenyl)-allyl]-4-oxo-3,4-dihydro-phthalazin-6-yl}-amide;
30. N-{1-[(E)-3-(4-Nitro-phenyl)-allyl]-4-oxo-3,4-dihydro-phthalazin-6-yl}-3,4-dimethoxy-benzamide;
31. N-{1-[(E)-3-(4-Nitro-phenyl)-allyl]-4-oxo-3,4-dihydro-phthalazin-6-yl}-3-cyclopentyl-propionamide;
32. 2-Propyl-pentanoic acid {1-[(E)-3-(4-nitro-phenyl)-allyl]-4-oxo-3,4-dihydro-phthalazin-6-yl}-amide;
33. 1-{1-[(E)-3-(4-Nitro-phenyl)-allyl]-4-oxo-3,4-dihydro-phthalazin-6-yl}-3-(3-trifluoromethyl-phenyl)-urea;
34. 1-{1-[(E)-3-(4-Nitro-phenyl)-allyl]-4-oxo-3,4-dihydro-phthalazin-6-yl}-(3-methoxy-phenyl)-urea;
35. 1-{1-[(E)-3-(4-Nitro-phenyl)-allyl]-4-oxo-3,4-dihydro-phthalazin-6-yl}-3-p-tolyl-urea;
36. 1-{1-[(E)-3-(4-Nitro-phenyl)-allyl]-4-oxo-3,4-dihydro-phthalazin-6-yl}-3-(2,4-difluoro-phenyl)-urea;
37. 1-{1-[(E)-3-(4-Nitro-phenyl)-allyl]-4-oxo-3,4-dihydro-phthalazin-6-yl}-3-(3,4-dichloro-phenyl)-urea;
38. 1-{1-[(E)-3-(4-Nitro-phenyl)-allyl]-4-oxo-3,4-dihydro-phthalazin-6-yl}-3-pyridin-3-yl-urea;

39. 7-Amino-4-[(E)-3-(4-nitro-phenyl)-allyl]-2H-phthalazin-1-one;

40. N-(4-Oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-propionamide;

41. N-(4-Oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-4-trifluoromethyl-benzamide;

42. Furan-2-carboxylic acid (4-oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-amide;

43. N-(4-Oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3,4-dimethoxy-benzamide;

44. N-(4-Oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-cyclopentyl-propionamide;

45. 2-Propyl-pentanoic acid (4-oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-amide;

46. 1-(4-Oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-(3-trifluoromethyl-phenyl)-urea;

47. 1-(4-Oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-(3-methoxy-phenyl)-urea;

48. 1-(4-Oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-p-tolyl-urea;

49. 1-(4-Oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-(2,4-difluoro-phenyl)-urea;

50. 1-(4-Oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-(3,4-dichloro-phenyl)-urea;

51. 1-(4-Oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-pyridin-3-yl-urea;

52. 7-Amino-4-thiophen-3-ylmethyl-2H-phthalazin-1-one;

53. N-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-propionamide;

54. N-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide;

55. Furan-2-carboxylic acid [1-(3-methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;

56. N-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3,4-dimethoxy-benzamide;

57. N-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide;

58. 2-Propyl-pentanoic acid [1-(3-methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;

59. 1-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea;

60. 1-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-(3-methoxy-phenyl)-urea;

61. 1-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea;

62. 1-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea;

63. 1-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3,4-dichloro-phenyl)-urea;

64. 1-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-pyridin-3-yl-urea;

65. 7-Amino-4-(3-methoxy-benzyl)-2H-phthalazin-1-one;

66. N-(4-Oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-propionamide;

67. N-(4-Oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-4-trifluoromethyl-benzamide;

68. Furan-2-carboxylic acid (4-oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-amide;

69. N-(4-Oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-3,4-dimethoxy-benzamide;

70. N-(4-Oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-3-cyclopentyl-propionamide;

71. 2-Propyl-pentanoic acid (4-oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-amide;

72. 1-(4-Oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-3-(3-trifluoromethyl-phenyl)-urea;

73. 1-(4-Oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-(3-methoxy-phenyl)-urea;

74. 1-(4-Oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-3-p-tolyl-urea;

75. 1-(4-Oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-3-(2,4-difluoro-phenyl)-urea;

76. 1-(4-Oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-3-(3,4-dichloro-phenyl)-urea;

77. 1-(4-Oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-3-pyridin-3-yl-urea;

78. 7-Amino-4-propyl-2H-phthalazin-1-one;

79. N-[1-(3,3-Dimethyl-butyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-propionamide;

80. N-[1-(3,3-Dimethyl-butyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide;

81. Furan-2-carboxylic acid [1-(3,3-dimethyl-butyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;

82. N-[1-(3,3-Dimethyl-butyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3,4-dimethoxy-benzamide;

83. N-[1-(3,3-Dimethyl-butyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide;

84. 2-Propyl-pentanoic acid [1-(3,3-dimethyl-butyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;

85. 1-[1-(3,3-Dimethyl-butyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea;

86. 1-[1-(3,3-Dimethyl-butyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-(3-methoxy-phenyl)-urea;

87. 1-[1-(3,3-Dimethyl-butyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea;

88. 1-[1-(3,3-Dimethyl-butyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea;

89. 1-[1-(3,3-Dimethyl-butyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3,4-dichloro-phenyl)-urea;

90. 1-[1-(3,3-Dimethyl-butyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-pyridin-3-yl-urea;

91. 7-Amino-4-(3,3-dimethyl-butyl)-2H-phthalazin-1-one;

92. N-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-propionamide;

93. N-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide;

94. Furan-2-carboxylic acid [4-oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-amide;

95. N-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-3,4-dimethoxy-benzamide;

96. N-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide;

97. 2-Propyl-pentanoic acid [4-oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-amide;

98. 1-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea;

99. 1-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-(3-methoxy-phenyl)-urea;

100. 1-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea;

101. 1-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea;

102. 1-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-3-(3,4-dichloro-phenyl)-urea;

103. 1-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-3-pyridin-3-yl-urea;

104. 7-Amino-4-(3-phenyl-propyl)-2H-phthalazin-1-one;

105. N-(4-Oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-propionamide;

106. N-(4-Oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-4-trifluoromethyl-benzamide;

107. Furan-2-carboxylic acid (4-oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-amide;

108. N-(4-Oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-succinamic acid ethyl ester;

109. N-(4-Oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-cyclopentyl-propionamide;

110. 2-Propyl-pentanoic acid (4-oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-amide;

111. 1-(4-Oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-(3-trifluoromethyl-phenyl)-urea;

112. 1-(3-Methoxy-phenyl)-3-(4-oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-urea;

113. 1-(4-Oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-p-tolyl-urea;

114. 1-(2,4-Difluoro-phenyl)-3-(4-oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-urea;

115. 1-(3,4-Dichloro-phenyl)-3-(4-oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-urea;

116. 1-(4-Oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-pyridin-3-yl-urea;

117. 7-Amino-4-pyridin-3-ylmethyl-2H-phthalazin-1-one

118. N-(4-Oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-benzamide;

119. N-[1-(4-Chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-propionamide;

120. N-[1-(4-Chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide;

121. Furan-2-carboxylic acid [1-(4-chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;

122. N-[1-(4-Chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-succinamic acid ethyl ester;

123. N-[1-(4-Chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide;

124. 2-Propyl-pentanoic acid [1-(4-chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;

125. 1-[1-(4-Chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea;

126. 1-[1-(4-Chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-methoxy-phenyl)-urea;

127. 1-[1-(4-Chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea;

128. 1-[1-(4-Chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea;

129. 1-[1-(4-Chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3,4-dichloro-phenyl)-urea;

130. 1-[1-(4-Chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-pyridin-3-yl-urea;

131. 7-Amino-4-(4-Chloro-benzyl)-2H-phthalazin-1-one;

132. N-[1-(4-Cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-propionamide;

133. N-[1-(4-Cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide;

134. Furan-2-carboxylic acid [1-(4-cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;

135. N-[1-(4-Cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-succinamic acid ethyl ester;

136. N-[1-(4-Cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide;

137. 2-Propyl-pentanoic acid [1-(4-cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;

138. 1-[1-(4-Cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea;

139. 1-[1-(4-Cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-methoxy-phenyl)-urea;

140. 1-[1-(4-Cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea;

141. 1-[1-(4-Cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea;

142. 1-[1-(4-Cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3,4-dichloro-phenyl)-urea;

143. 1-[1-(4-Cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-pyridin-3-yl-urea;

144. 7-Amino-4-(4-Cyano-benzyl)-2H-phthalazin-1-one;

145. N-[1-(3-Fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-propionamide;

146. N-[1-(3-Fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide;

147. Furan-2-carboxylic acid [1-(3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;

148. N-[1-(3-Fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-succinamic acid ethyl ester;

149. N-[1-(3-Fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide;

150. 2-Propyl-pentanoic acid [1-(3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;

151. 1-[1-(3-Fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea;

152. 1-[1-(3-Fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-methoxy-phenyl)-urea;

153. 1-[1-(3-Fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea;

154. 1-[1-(3-Fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea;

155. 1-[1-(3-Fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3,4-dichloro-phenyl)-urea;

156. 1-[1-(3-Fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-pyridin-3-yl-urea;

157. 7-Amino-4-(3-Fluoro-benzyl)-2H-phthalazin-1-one;

158. N-[1-(3-Methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-propionamide;

159. N-[1-(3-Methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide;

160. Furan-2-carboxylic acid [1-(3-methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;

161. N-[1-(3-Methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-succinamic acid ethyl ester;

162. N-[1-(3-Methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide;

163. 2-Propyl-pentanoic acid [1-(3-methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;

164. 1-[1-(3-Methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea;

165. 1-[1-(3-Methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-methoxy-phenyl)-urea;

166. 1-[1-(3-Methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea;

167. 1-[1-(3-Methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea;

168. 1-[1-(3-Methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3,4-dichloro-phenyl)-urea;

169. 1-[1-(3-Methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-pyridin-3-yl-urea;

170. 7-Amino-4-(3-Methyl-benzyl)-2H-phthalazin-1-one;

171. N-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-propionamide;

172. N-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide;

173. Furan-2-carboxylic acid [1-(2,4-dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;

174. N-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-succinamic acid ethyl ester;

175. N-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide;

176. 2-Propyl-pentanoic acid [1-(2,4-dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;

177. 1-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea;

178. 1-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-methoxy-phenyl)-urea;

179. 1-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea;

180. 1-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea;

181. 1-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3,4-dichloro-phenyl)-urea;

182. 1-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-pyridin-3-yl-urea;

183. 7-Amino-4-(2,4-dichloro-benzyl)-2H-phthalazin-1-one;

184. N-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-propionamide;

185. N-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-4-trifluoromethyl-benzamide;

186. Furan-2-carboxylic acid (4-oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-amide;

187. N-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-succinamic acid ethyl ester;

188. N-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-cyclopentyl-propionamide;

189. 2-Propyl-pentanoic acid (4-oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-amide;

190. 1-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-(3-trifluoromethyl-phenyl)-urea;

191. 1-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-(3-methoxy-phenyl)-urea;

192. 1-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-p-tolyl-urea;

193. 1-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-(2,4-difluoro-phenyl)-urea;

194. 1-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-(3,4-dichloro-phenyl)-urea;

195. 1-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-pyridin-3-yl-urea;

196. 7-Amino-4-quinolin-3-ylmethyl-2H-phthalazin-1-one;

197. N-[4-Oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-propionamide;

198. N-[4-Oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide;

199. Furan-2-carboxylic acid [4-oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-amide;

200. N-[4-Oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-succinamic acid ethyl ester;

201. N-[4-Oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide;

202. 2-Propyl-pentanoic acid [4-oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-amide;

203. 1-[4-Oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea;

204. 1-[4-Oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-3-(3-methoxy-phenyl)-urea;

205. 1-[4-Oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea;

206. 1-[4-Oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea;

207. 1-[4-Oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-3-(3,4-dichloro-phenyl)-urea;

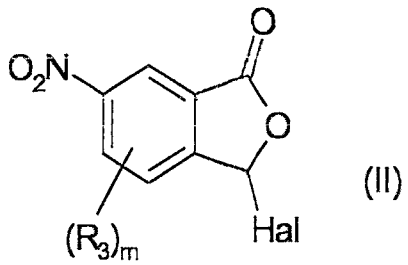
208. 1-[4-Oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-3-pyridin-3-yl-urea;

209. 7-Amino-4-(2-trifluoromethyl-benzyl)-2H-phthalazin-1-one.

As set forth above, the process for preparing the amino-phthalazinone derivatives of formula (I) represents a further object of the present invention.

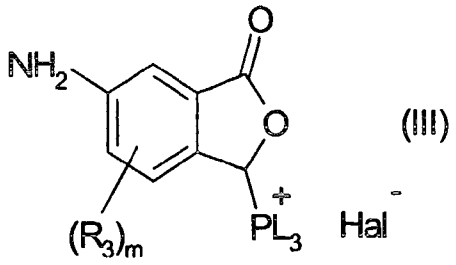
The compounds of formula (I) and the pharmaceutically acceptable salts thereof, may be thus obtained by a process comprising:

a) reacting a compound of formula (II)



(II)

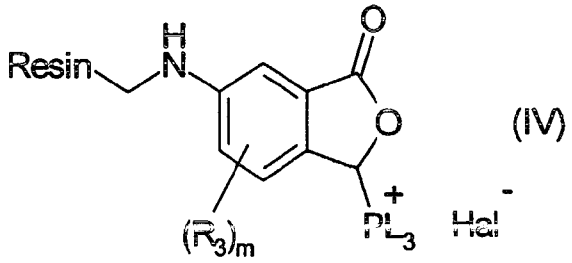
wherein R_3 and m have the above reported meanings and Hal represents a halogen atom, with a suitable phosphine derivative (PL_3), under optional reductive conditions, so as to obtain a compound of formula (III)



(III)

wherein P is a phosphorous atom and L are the phosphine ligands;

b) reacting the compound of formula (III) with an aldehydic Resin-CHO, in the presence of a suitable reducing agent, so as to obtain a resin supported compound of formula (IV)



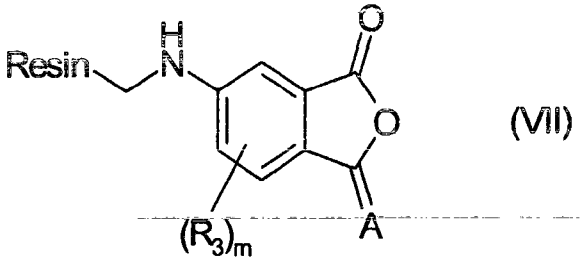
(IV)

wherein R_3, m, P, L, Hal and the Resin are as above defined;

c) reacting the compound of formula (IV) with a carbonyl derivative of formula (V) or a nitroso derivative of formula (VI)

R_4-CO-R_5 (V) R'-NO (VI)

wherein R_4, R_5 and R' are as above defined; so as to obtain the compound of formula (VII)



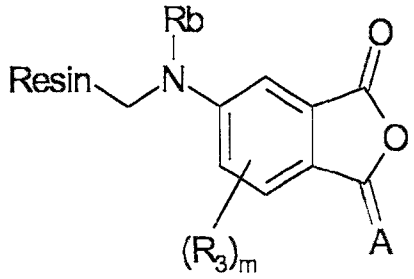
(VII)

wherein A is a group $=CR_4R_5$ or =NR', respectively; and optionally reacting the compound of formula (VII) according to any one of the alternative steps d.1) or d.2) below

d.1) with one of the derivatives of formula (VIII), (IX), (X) or (XI), under optional basic conditions,

R'COZ (VIII), R'NCO (IX), R'OCOZ (X), $R'SO_2Z$ (XI)

wherein Z is a halogen atom or a suitable leaving group and R' is as above defined, so as to obtain the compound of formula (XII)



(XII)

wherein Rb is -COR', -CONHR', -COOR' or $-SO_2R'$, respectively; or

d.2) with a compound of formula (XIII)

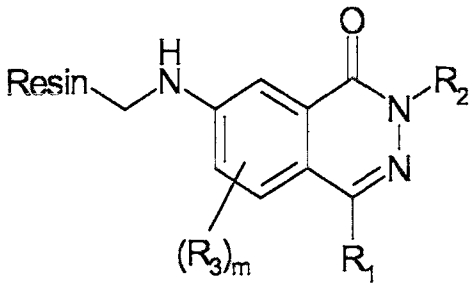
Rb-Z (XIII)

wherein Z is a halogen atom and Rb is alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl as above defined, so as to obtain the corresponding compound of the above formula (XII);

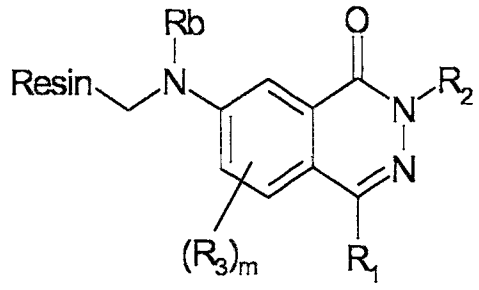
e) reacting the thus obtained compounds of formula (VII) or (XII) with a hydrazine derivative of formula (XIV)

R_2-NH-NH_2 (XIV)

wherein R_2 is as above defined, so as to obtain the compounds of formula (XV) or (XVI), respectively



(XV)



(XVI)

wherein Rb, R_2, R_3, m and the Resin are as above defined and R_1 is a group of formula $-CHR_4R_5$ or -NHR' wherein R_4, R_5 and R' are as above defined;

f) reacting the compounds of formula (XV) or (XVI) under acidic conditions so as to obtain the compound of formula (I) and, whenever desired, converting it into another compound of formula (I) and/or into a pharmaceutically acceptable salt thereof.

The above process is an analogy process which can be carried out according to well known methods.

It is clear to the person skilled in the art that if a compound of formula (I), prepared according to the above process, is obtained as an admixture of isomers, their separation into the single isomers of formula (I), carried out according to conventional techniques, is still within the scope of the present invention.

Likewise, the conversion into the free compound (I) of a corresponding salt thereof, according to well-known procedures in the art, is still within the scope of the invention.

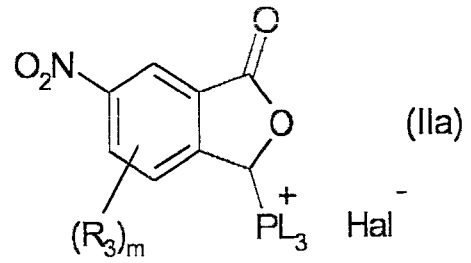
According to step a) of the process, a compound of formula (II) wherein Hal represents a halogen atom, preferably bromine, is reacted with a suitable phosphine derivative PL_3 such as, for instance, triphenylphosphine, tri-n-butylphoshine, tri-t-butylphosphine or 1,4-bis(diphenylphosphino)butane.

Preferably, the phosphine derivative is triphenylphosphine PPh_3.

The reaction may be carried out in a variety of solvents for instance comprising ethyl acetate, ethyl propionate and the like, dimethylformammide, dimethylacetammide and the like, dichloromethane chloroform and the like, acetone, or acetonitrile; preferred is the use of ethyl propionate. The temperature may vary from about 20°C to about 100°C.

The reaction may be performed by adding the phosphine to a solution of the compound of formula (II) or by adding a solution of (II) to the phosphine.

When using triphenylphosphine, the compound of formula (II) is directly converted into the corresponding derivative of formula (III) bearing the amino group in place of the original nitro group. Alternatively, when using PL_3 reagents other than triphenylphosphine, the compound of formula (II) may be first converted into an intermediate derivative of formula (IIa)



(IIa)

wherein R_3, m, P and L are as above defined, which has to be properly reduced to the compound of formula (III).

The reductive conditions to be employed are those conventionally used for reducing aromatic nitro derivatives to amino derivatives and comprise the use of chemical reducing agents such as, for instance, tin dichloride, iron and acetic acid, zinc and hydrochloric acid, or titanium trichloride.

Alternatively, the reductive step may occur under catalytic hydrogenation conditions in the presence of suitable catalysts, typically platinum, palladium or palladium on charcoal.

Preferably, the compound of formula (II) is conveniently converted into the compound of formula (III) by using triphenylphosphine.

According to step b) of the process, the compound of formula (III) is reacted, in the presence of a reducing agent such as, for instance, a pyridine-borane complex, sodium cyanoboron hydride, sodium triacetoxy boron hydride,

dimethylsufide borane and the like, with a suitable aldehydic RCHO resin, for instance a polystirene or polyethyleneglycol resin.

Preferably, the resin is a 4-(4-formyl-3-methoxyphenoxy)butyryl aminomethylated resin or 4-(4-formyl-3-methoxyphenoxy)butyryl (NOVAGEL™).

The reaction is carried out in the presence of a suitable solvent, preferably dichloromethane, 2,2,2-trifluoroethanol and acetic acid, by adding an excess of the reducing agent, optionally dissolved into the same solvent, directly to the mixture of resin and of the compound of formula (III), and by stirring at a temperature ranging from about 0°C to about 40°C for a suitable time. As an example, the reaction may be carried at about 20°C for about 15 hours.

According to step c) of the process, the compound of formula (IV) is then reacted with a compound of formula (V) or, alternatively, of formula (VI), so as to obtain the corresponding derivative of formula (VII).

The reaction is carried out in the presence of a suitable base, for instance triethylamine, diisopropylethylamine, piperidine, sodium carbonate, cesium carbonate, potassium t-butoxide, sodium methoxide, diazabicycloundecene, potassium hydroxide and the like, optionally in the presence of a suitable phase-transfer catalyst.

The compound of formula (V) or, alternatively, of formula (VI), is added to a suspension of the compound of formula (IV) in a suitable solvent such as dichloromethane, dimethyl formammide, tetrahydrofuran or the like. The temperature is then brought to a suitable value, for instance from about -70°C to about 40°C according to the electrophile (V) or (VI), and the base is added. Stirring is carried on for a suitable time, for instance from about 2 to about 15 hours.

The product of formula (VII) thus obtained may be further reacted according to any one of the alternative steps d.1) or d.2), or directly processed according to step e).

According to step d.1) of the process, in particular, the compound of formula (VII) is reacted with a carboxylic acid derivative of formula (VIII), with an isocyanate of formula (IX), with a chloroformate derivative of formula (X) or with a sulphonyl derivative of formula (XI), so as to obtain the corresponding compound of formula (XII) wherein Rb is a group of formula -COR', -CONHR', -COOR' or $-SO_2R'$, respectively.

When using a compound of formula (VIII), (X) or (XI), Z is preferably a halogen atom and, even more preferably, a chlorine atom. In this instance, the compound of formula (VII) is suspended into a suitable solvent such as dichloromethane, dimethylformammide, tetrahydrofuran, dioxane or the like, and a suitable base is then added, for instance triethylamine, diisopropylethylamine, sodium carbonate or the like. The electrophile of general formula (VIII), (X), or (XI) is then added and the mixture stirred for about 2 to about 15 hours, at a temperature ranging from about 20°C to about 80°C. When using an isocyanate of general formula (IX), the reaction conditions are the same as above reported except that the base may not be required. In the latter case a catalyst such as dimethylamino pyridine may be optionally used.

Substantially analogous considerations apply when considering step d.2) of the process wherein the compound of formula (VII) is further converted into the corresponding functionalized amino derivative of formula (XII), according to well known methods.

As an example, the compound of formula (VII) may be reacted with a derivative of formula (XIII) wherein Z is halogen, for instance bromine, and Rb is an arylalkyl group such as,

for instance, the benzyl group, by working according to conventional methods.

According to step e) of the process, the compound of formula (VII) obtained from step c) or, alternatively, the compound of formula (XII) obtained from any one of steps d.1) or d.2), is reacted with hydrazine or a hydrazine derivative of formula (XIV) so as to obtain the corresponding compounds of formula (XV) or (XVI).
The compound of formula (XII) is suspended in a suitable solvent, preferably dimethylformammide, in the presence of hydrazine hydrate or another hydrazine of general formula (XIV) and stirred at a suitable temperature, for instance at 20°C, for about 2 to about 20 hours.

According to step f) of the process, the compounds of formula (XV) or (XVI) are reacted under acidic conditions, preferably in the presence of trifluoroacetic acid, so as to yield the desired compound of formula (I). Compounds of formula (XV) or (XVI) may be thus suspended in a solution of 5-95% trifluoroacetic acid in dichloromethane and the mixture stirred at a temperture ranging from about 20°C to refluxing temperature, for a time varying from about 5 minutes to about 3 hours.

From the above, it is clear to the skilled man that by carrying out the above resin cleavage from the compound of formula (XV), the corresponding derivative having both Ra and Rb as hydrogen atoms will be obtained.
Likewise, when starting from the compound of formula (XVI), the corresponding derivative of formula (I) having one of Ra or Rb, e.g. Ra, as a hydrogen atom and the other, e.g. Rb, as a group as defined under steps d.1) or d.2), will be obtained.
In addition, it is clear to the skilled man that, if desired, any of the above compounds of formula (I) may be

further converted by working according to conventional methods into other compounds of formula (I), as set forth in step f).

As an example, the compounds of formula (I) wherein both Ra and Rb are other than hydrogen atoms may be prepared according to well-known methods by reacting any compound of formula (I) having one of Ra or Rb as a hydrogen atom, into another compound of formula (I) having this same hydrogen atom being replaced by a suitable group.

When preparing the compounds of formula (I) according to any variant of the process, which are all to be intended as within the scope of the present invention, optional functional groups within both the starting materials or the intermediates thereof, which could give rise to unwanted side reactions, need to be properly protected according to conventional techniques.

Likewise, the conversion of these latter into the free deprotected compounds may be carried out according to known procedures.

Pharmaceutically acceptable salts of the compounds of formula (I) or, alternatively, their free compounds from the salts thereof, my be all obtained according to conventional methods.

The compounds of formula (II) are known or easily prepared according to known methods [see, for a reference, *J. Org. Chem.* (1985), *50*, 4120-4125; *J. Chem. Soc.* (1961), 5275-5284].

Alternatively, the compounds of formula (II) wherein Hal represents a bromine atom, may be prepared as reported in the working examples, that is by reacting commercially available 6-nitro-phthalide under brominating conditions, for instance with bromine in the presence of aqueous hydrogen peroxide, in a suitable solvent such as dichloromethane, dichloromethane/water or hexane/water

admixtures, at a temperature varying from about 20°C to reflux.

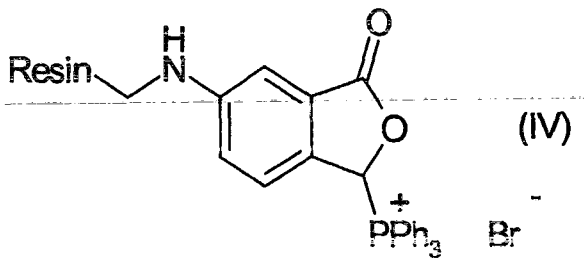
The compounds of formula (V), (VI), (VIII), (IX), (X), (XI), (XIII) and (XIV) are known or easily prepared according to well-known methods.

Likewise, the aldehydic resin R-CHO, the phosphine derivative PL_3 and any other suitable reagent of the process, are known compounds which are commercially available or easily prepared according to known methods.

The compounds of formula (I) of the invention were advantageously prepared according to combinatorial chemistry techniques widely known in the art, by accomplishing the aforementioned reactions between the several intermediates in a serial manner.

Therefore, all of the preferred compounds of the invention, whenever appropriate in the form of pharmaceutically acceptable salts, are herewith conveniently indicated and defined as products by process, that is as products of formula (I) which are obtainable, for instance through a defined process.

Therefore, herewith provided is any specific compound of formula (I) which is obtainable, for instance through a combinatorial chemistry technique according to the process of the invention, by first reacting the compound of formula (IV)

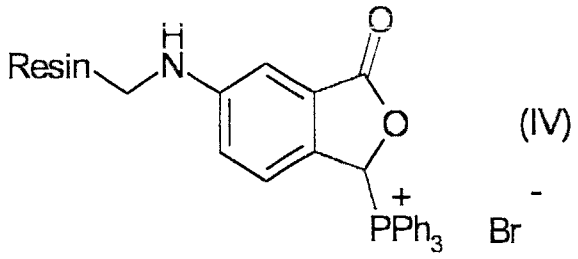


(IV)

with each one of the aldehyde derivatives of formula (V), as set forth in *table I*; by reacting any of the resultant

compounds of formula (VII) with each one of the acyl chloride derivatives of formula (VIII), as set forth in *table II*; by reacting any of the resultant compounds of formula (XII) with hydrazine; and by working according to step f) of the process.

Also provided is any specific compound of formula (I) which is obtainable, for instance through a combinatorial chemistry technique according to the process of the invention, by first reacting the compound of formula (IV)



with each one of the aldehyde derivatives of formula (V), as set forth in *table I*; by reacting any of the resultant compounds of formula (VII) with each one of the isocyanate derivatives of formula (IX), as set forth in *table III*; by reacting any of the resultant compounds of formula (XII) with hydrazine; and by working according to step f) of the process.

Table I

Aldehyde derivatives of formula (V) R_4-CO-R_5 (R_5=H)

1.	3,5-diiodo-4-hydroxybenzaldehyde
2.	3-iodobenzaldehyde
3.	3,5-dibromobenzaldehyde
4.	4-bromothiophene-2-carboxaldehyde
5.	2-naphthaldehyde
6.	n-ethyl-carbazole-3-aldehyde
7.	4-chloro-1-methylpyrazole-3-carboxaldehyde
8.	(3-formyl-1-phenyl-1h-pyrazol-5-yl)methyl acetate
9.	1-acetyl-3-indolecarboxaldehyde
10.	methyl 4-formyl-1-methylpyrrole-2-carboxylate
11.	3,5-di-tert-butyl-4-hydroxybenzaldehyde
12.	5-(methylthio)-2-thiophenecarboxaldehyde
13.	4-(methylthio)benzaldehyde

14.	3-nitro-4-(2-pyridylthio)benzaldehyde
15.	5-methyl-2-thiophenecarboxaldehyde
16.	3-acetoxybenzaldehyde
17.	3,4-dimethylbenzaldehyde
18.	4-pyridinecarboxaldehyde n-oxide
19.	4-fluoro-3-methylbenzaldehyde
20.	2,6-dichloroisonicotinaldehyde
21.	5-(2,4-difluorophenyl)-2-furaldehyde
22.	2-(4-bromobenzoyl)-1-benzofuran-5-carbaldehyde
23.	2-benzoyl-1-benzofuran-5-carbaldehyde
24.	2-butyl-4-formylimidazole
25.	5-benzyloxy-1h-pyrrolo[2,3-c]pyridine-3-carboxaldehyde
26.	6-methyl-2-pyridinecarboxaldehyde
27.	4-[4-(tert-butyl)thiazol-2-yl]benzaldehyde
28.	5-formyl-2,4-dimethoxy-pyrimidine
29.	2-[(4-chlorobenzyl)thio]pyrimidine-4-carbaldehyde
30.	3-fluoro-2-hydroxybenzaldehyde
31.	3-hydroxybenzaldehyde
32.	3-carboxybenzaldehyde
33.	4-vinylbenzaldehyde
34.	5-(2,5-dichlorophenyl)-2-furaldehyde
35.	2-fluoro-5-nitrobenzaldehyde
36.	5-(4-nitrophenyl)-2-furaldehyde
37.	4-dimethylaminobenzaldehyde
38.	4-[3-(dimethylamino)propoxy]benzaldehyde
39.	4-n-butylbenzaldehyde
40.	4-(4-benzylpiperazino)benzaldehyde
41.	2,2'-bithiophene-5-carboxaldehyde
42.	4-[4-(1-adamantyl)-1,3-thiazol-2-yl]benzaldehyde
43.	4-formyl-trans-stilbene
44.	6-chloroimidazo[2,1-b][1,3]thiazole-5-carbaldehyde
45.	4-(phenylethynyl)benzaldehyde
46.	3,3'-(4-formylphenylimino)dipropionitrile
47.	6-formyl-2-(methylthio)nicotinonitrile
48.	4-cyanobenzaldehyde
49.	3-[(4-formylphenoxy)methyl]thiophene-2-carbonitrile
50.	2-(3-formyl-1h-indol-1-yl)benzonitrile
51.	2-formyl-6-methoxyphenyl 2,6-difluorobenzoate
52.	tert-butyl 4-formyl-2-methoxyphenyl carbonate
53.	4-(difluoromethoxy)benzaldehyde
54.	2-[1-methyl-5-(trifluoromethyl)pyrazol-3-yl]thiophene-5-carboxaldehyde
55.	5-(3-trifluoromethylphenyl)furan-2-carboxaldehyde
56.	2,3-difluoro-4-methylbenzaldehyde
57.	3-chloro-5-(trifluoromethyl)pyridine-2-carboxaldehyde

58.	4-(trifluoromethoxy)benzaldehyde
59.	3-[(2,4-difluorophenyl)thio]-5-(trifluoromethyl)pyridine-2-carbaldehyde
60.	3,5-bis(trifluoromethyl)benzaldehyde
61.	2,3,5,6-tetrafluorobenzaldehyde
62.	4-(methylsulfonyl)benzaldehyde
63.	1-[(4-methylphenyl)sulfonyl]-1h-indole-3-carbaldehyde
64.	4-formyl-2-methoxyphenyl 2,4,5-trichlorobenzenesulfonate
65.	4-formylphenyl 2,3,4,5,6-pentamethylbenzenesulfonate
66.	3-(4-formylphenyl)-2-(pyridin-2-ylsulfonyl)acrylonitrile
67.	4-acetamidobenzaldehyde
68.	4-[[5-chloro-2-oxopyrimidin-1(2h)-yl]methoxy]benzaldehyde
69.	4-(5-formyl-2-furyl)benzene-1-sulfonamide
70.	3-Benzo[1,3]dioxol-5-yl-2-methyl-propionaldehyde
71.	3-(phenylthio)butyraldehyde
72.	3-chloro-4,4,4-trifluoro-2-phenylbutanal
73.	2-cyano-2-phenylacetaldehyde
74.	3-methoxyphenylacetaldehyde
75.	pyridine-3-carboxaldehide
76.	4-chlorobenzaldehyde
77.	4-cyanobenzaldehyde
78.	3-fluorobenzaldehyde
79.	m-tolualdehyde
80.	2,4-dichlorobenzaldehyde
81.	quinoline-3-carboxaldehyde
82.	2-(trifluoromethyl)benzaldehyde
83.	methyl 4-formylbenzoate
84.	4-chloro-3-fluorobenzaldehyde
85.	4-nitrocinnamaldehyde
86.	3-thiophenecarboxaldehyde
87.	3-methoxybenzaldehyde
88.	propionaldehyde
89.	3,3-dimethylbutyraldehyde
90.	3-phenylpropionaldehyde

Table II

Acyl chloride derivatives of formula (VIII) R'COZ (Z=Cl)

1.	3,5-bis(trifluoromethyl)benzoyl chloride
2.	benzoyl chloride
3.	2-bromobenzoyl chloride
4.	2-fluorobenzoyl chloride
5.	2,4-difluorobenzoyl chloride
6.	2,6-difluorobenzoyl chloride

7.	2-chlorobenzoyl chloride
8.	2,4-dichlorobenzoyl chloride
9.	2-methoxybenzoyl chloride
10.	2-(trifluoromethyl)benzoyl chloride
11.	o-toluoyl chloride
12.	3-bromobenzoyl chloride
13.	3-fluorobenzoyl chloride
14.	3-chlorobenzoyl chloride
15.	3,4-dichlorobenzoyl chloride
16.	m-anisoyl chloride
17.	3,4-dimethoxybenzoyl chloride
18.	3,4,5-trimethoxybenzoyl chloride
19.	3,5-dimethoxybenzoyl chloride
20.	3-(trifluoromethyl)benzoyl chloride
21.	m-toluoyl chloride
22.	4-bromobenzoyl chloride
23.	4-fluorobenzoyl chloride
24.	4-chlorobenzoyl chloride
25.	p-anisoyl chloride
26.	4-ethoxybenzoyl chloride
27.	4-n-butoxybenzoyl chloride
28.	4-biphenylcarbonyl chloride
29.	4-(trifluoromethyl)benzoyl chloride
30.	4-tert-butylbenzoyl chloride
31.	p-toluoyl chloride
32.	4-ethylbenzoyl chloride
33.	4-n-propylbenzoyl chloride
34.	4-n-butylbenzoyl chloride
35.	pivaloyl chloride
36.	isobutyryl chloride
37.	2-ethylhexanoyl chloride
38.	acetyl chloride
39.	phenoxyacetyl chloride
40.	4-chlorophenoxyacetyl chloride
41.	methoxyacetyl chloride
42.	phenylacetyl chloride
43.	tert-butylacetyl chloride
44.	isovaleryl chloride
45.	propionyl chloride
46.	hydrocinnamoyl chloride
47.	butyryl chloride
48.	pentanoyl chloride
49.	4-iodobenzoyl chloride
50.	cyclopropanecarbonyl chloride
51.	cyclobutanecarbonyl chloride
52.	cyclopentanecarbonyl chloride
53.	3-cyclopentylpropionyl chloride
54.	cyclohexanecarbonyl chloride
55.	4-cyanobenzoyl chloride
56.	2-furoyl chloride
57.	1-naphthoyl chloride

58.	2-naphthoyl chloride
59.	thiophene-2-carbonyl chloride
60.	thiophene-2-acetyl chloride
61.	(3,4-dimethoxyphenyl)acetyl chloride
62.	3,5-dichlorobenzoyl chloride
63.	2,5-difluorobenzoyl chloride
64.	3,4-difluorobenzoyl chloride
65.	9-fluorenone-4-carbonyl chloride
66.	3,5-difluorobenzoyl chloride
67.	benzyloxyacetyl chloride
68.	3-cyanobenzoyl chloride
69.	(2,5-dimethoxyphenyl)acetyl chloride
70.	3-methoxyphenylacetyl chloride
71.	nicotinoyl chloride hydrochloride
72.	isonicotinoyl chloride hydrochloride
73.	2,4,6-trimethylbenzoyl chloride
74.	diphenylacetyl chloride
75.	2-methylvaleryl chloride
76.	3,4-methylenedioxybenzoyl chloride
77.	2,4-dimethoxybenzoyl chloride
78.	2-phenoxypropionyl chloride
79.	2-phenylbutyryl chloride
80.	2-ethylbutyryl chloride
81.	2,3-dichlorobenzoyl chloride
82.	4-chlorophenylacetyl chloride
83.	dl-2-methylbutyryl chloride
84.	2,3-difluorobenzoyl chloride
85.	1-(4-chlorophenyl)-1-cyclopentanecarbonyl-chloride
86.	2-ethoxy-1-naphthoyl chloride
87.	benzo[b]thiophene-2-carbonyl chloride
88.	4-(trifluoromethoxy)benzoyl chloride
89.	2-(trifluoromethoxy)benzoyl chloride
90.	3-chlorobenzo[b]thiophene-2-carbonyl chloride
91.	2-fluoro-3-(trifluoromethyl)benzoyl chloride
92.	2-fluoro-4-(trifluoromethyl)benzoyl chloride
93.	2-fluoro-5-(trifluoromethyl)benzoyl chloride
94.	3-fluoro-5-(trifluoromethyl)benzoyl chloride
95.	4-fluoro-2-(trifluoromethyl)benzoyl chloride
96.	4-fluoro-3-(trifluoromethyl)benzoyl chloride
97.	2-fluoro-6-(trifluoromethyl)benzoyl chloride
98.	2,3,6-trifluorobenzoyl chloride
99.	2,4,5-trifluorobenzoyl chloride
100	3-(trifluoromethoxy)benzoyl chloride
101	isoxazole-5-carbonyl chloride
102	2,4,6-trifluorobenzoyl chloride
103	2,5-bis(trifluoromethyl)benzoyl chloride
104	2,3,4-trifluorobenzoyl chloride
105	2,4,6-trichlorobenzoyl chloride
106	2,4-dichloro-5-fluorobenzoyl chloride
107	4-methoxyphenylacetyl chloride

108	5-fluoro-2-(trifluoromethyl)benzoyl chloride
109	2-chloro-6-fluorobenzoyl chloride
110	2-bromo-5-methoxybenzoyl chloride
111	cyclopentylacetyl chloride
112	3-chloro-4-fluorobenzoyl chloride
113	3-fluoro-4-(trifluoromethyl)benzoyl chloride
114	4-fluorophenylacetyl chloride
115	4-tert-butylphenoxyacetyl chloride
116	7-Imidazol-1-yl-5,6-dihydro-naphthalene-2-carbonyl chloride
117	4-Imidazol-1-ylmethyl-benzoyl chloride
118	4-bromo-3-methylbenzoyl chloride

Table III

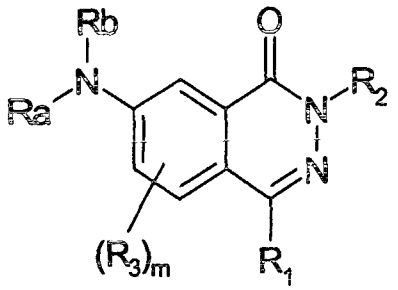
Isocyanate derivatives of formula (IX) R'NCO

1.	phenyl isocyanate
2.	2-bromophenyl isocyanate
3.	2-fluorophenyl isocyanate
4.	2,4-difluorophenyl isocyanate
5.	2,6-difluorophenyl isocyanate
6.	2-chlorophenyl isocyanate
7.	2,3-dichlorophenyl isocyanate
8.	2,4-dichlorophenyl isocyanate
9.	2,5-dichlorophenyl isocyanate
10.	2,6-dichlorophenyl isocyanate
11.	2-methoxyphenyl isocyanate
12.	2,4-dimethoxyphenyl isocyanate
13.	2,5-dimethoxyphenyl isocyanate
14.	2-ethoxyphenyl isocyanate
15.	2-(trifluoromethyl)phenyl isocyanate
16.	o-tolyl isocyanate
17.	2,6-dimethylphenyl isocyanate
18.	2-ethylphenyl isocyanate
19.	3-bromophenyl isocyanate
20.	3-fluorophenyl isocyanate
21.	3-chlorophenyl isocyanate
22.	3,4-dichlorophenyl isocyanate
23.	3-methoxyphenyl isocyanate
24.	3-(trifluoromethyl)phenyl isocyanate
25.	m-tolyl isocyanate
26.	4-bromophenyl isocyanate
27.	4-fluorophenyl isocyanate
28.	4-chlorophenyl isocyanate
29.	4-methoxyphenyl isocyanate
30.	4-(trifluoromethyl)phenyl isocyanate
31.	p-tolyl isocyanate
32.	benzoyl isocyanate
33.	1-naphthyl isocyanate
34.	Benzyl isocyanate
35.	3,5-bis(trifluoromethyl)phenyl isocyanate

36.	2,5-difluorophenyl isocyanate
37.	2,4,5-trichlorophenyl isocyanate
38.	2,4,6-trichlorophenyl isocyanate
39.	2-isopropylphenyl isocyanate
40.	2,3-dimethylphenyl isocyanate
41.	4-methoxy-2-methylphenyl isocyanate
42.	2,4-dimethylphenyl isocyanate
43.	2,5-dimethylphenyl isocyanate
44.	2-ethyl-6-methylphenyl isocyanate
45.	3-cyanophenyl isocyanate
46.	5-chloro-2,4-dimethoxyphenyl isocyanate
47.	3-chloro-4-methylphenyl isocyanate
48.	3,5-dichlorophenyl isocyanate
49.	5-chloro-2-methoxyphenyl isocyanate
50.	3,4,5-trimethoxyphenyl isocyanate
51.	3,5-dimethoxyphenyl isocyanate
52.	3-(methylthio)phenyl isocyanate
53.	3-acetylphenyl isocyanate
54.	3,4-dimethylphenyl isocyanate
55.	3,5-dimethylphenyl isocyanate
56.	2-methoxy-5-methylphenyl isocyanate
57.	3-ethylphenyl isocyanate
58.	4-bromo-2-(trifluoromethyl)phenyl isocyanate
59.	4-chloro-2-(trifluoromethyl)phenyl isocyanate
60.	4-chloro-3-(trifluoromethyl)phenyl isocyanate
61.	4-iodophenyl isocyanate
62.	4-phenoxyphenyl isocyanate
63.	4-ethoxyphenyl isocyanate
64.	4-acetylphenyl isocyanate
65.	4-isopropylphenyl isocyanate
66.	4-ethylphenyl isocyanate
67.	4-n-butylphenyl isocyanate
68.	2,4,6-trimethylphenyl isocyanate
69.	2-isopropyl-6-methylphenyl isocyanate
70.	2,6-diethylphenyl isocyanate
71.	5-chloro-2-methylphenyl isocyanate
72.	4-chloro-2-methylphenyl isocyanate
73.	4-(trifluoromethoxy)phenyl isocyanate
74.	2-chloro-5-(trifluoromethyl)phenyl isocyanate
75.	2-chloro-6-methylphenyl isocyanate
76.	2,4,5-trimethylphenyl isocyanate
77.	3-chloro-2-methoxyphenyl isocyanate
78.	3-chloro-2-methylphenyl isocyanate
79.	3-chloro-4-fluorophenyl isocyanate
80.	4-bromo-2-methylphenyl isocyanate
81.	4-bromo-2,6-dimethylphenyl isocyanate
82.	2,6-dibromo-4-fluorophenyl isocyanate
83.	4-butoxyphenyl isocyanate
84.	3-fluoro-4-methylphenyl isocyanate
85.	5-fluoro-2-methylphenyl isocyanate
86.	2-biphenylyl isocyanate

87.	4-biphenylyl isocyanate
88.	2-bromo-4,6-difluorophenyl isocyanate
89.	(r)-(+)-1-phenylethyl isocyanate
90.	1-(1-naphthyl)ethyl isocyanate
91.	(s)-(+)-1-(1-naphthyl) ethyl isocyanate
92.	3,4-difluorophenyl isocyanate
93.	2-(trifluoromethoxy)phenyl isocyanate
94.	4-benzyloxyphenyl isocyanate
95.	4-bromo-2-chlorophenyl isocyanate
96.	4-bromo-2-fluorophenyl isocyanate
97.	2-fluoro-5-methylphenyl isocyanate
98.	2,3,4-trifluorophenyl isocyanate
99.	2-(difluoromethoxy)phenyl isocyanate
100.	4-(difluoromethoxy)phenyl isocyanate
101.	2-methylbenzyl isocyanate
102.	2-chlorobenzyl isocyanate
103.	4-fluorobenzyl isocyanate
104.	4-methoxybenzyl isocyanate
105.	2,6-difluorobenzoyl isocyanate
106.	4-fluorobenzoyl isocyanate
107.	2-fluoro-3-(trifluoromethyl)phenyl isocyanate
108.	2-fluoro-5-(trifluoromethyl)phenyl isocyanate
109.	2-fluoro-6-(trifluoromethyl)phenyl isocyanate
110.	4-fluoro-2-(trifluoromethyl)phenyl isocyanate
111.	2-(tert-butyl)phenyl isocyanate
112.	3-pyridyl isocyanate

Accordingly, it is a further object of the present invention a library of two or more amino-phthalazinone derivatives of formula (I)



(I)

wherein

Ra and Rb are, each independently, a hydrogen atom or a group, optionally further substituted, selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or

sulfur; or one of Ra or Rb is hydrogen or an optionally substituted straight or branched C_1-C_6 alkyl group, and the other is a group selected from -COR', -CONHR', -COOR' or $-SO_2R'$, wherein R' is hydrogen or an optionally substituted group selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl, as set forth above;

R_1 is a group of formula $-CHR_4R_5$ wherein R_4 and R_5 are, each independently, hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur; or R_1 is a group of formula -NHR', -NR'COR", -NR'CONHR" or $-NR'SO_2R"$, wherein R' has the above reported meanings other than hydrogen, and R" is hydrogen or has the meanings set forth above for R';

R_2 is a hydrogen atom or it is a group, optionally further substituted, selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur;

any R_3, being placed in one or more of the free positions 5, 6 and 8 of the phthalazinone ring are, independently from each other, halogen, nitro, carboxy, cyano or a group optionally further substituted selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur; or R_3 is a group selected from -COR', -CONHR', $-SO_2R'$, -NR'R", -NR'COR", -NR'CONHR' or $-NR'SO_2R"$, wherein R' and R" are, the same or different, hydrogen or a group as set forth above;

m is 0 or an integer from 1 to 3;

or a pharmaceutically acceptable salt thereof.

From all of the above, it is clear to the skilled man that once a library of aminophtalazinone derivatives is thus prepared, for instance consisting of a few thousands of compounds of formula (I), the said library can be very advantageously used for screening towards given target kinases, as formerly reported.

See, for a general reference to libraries of compounds and uses thereof as tools for screening biological activities, J. Med. Chem. 1999, 42, 2373-2382; and Bioorg. Med. Chem. Lett. 10 (2000), 223-226.

Pharmacology

The compounds of formula (I) are active as protein kinase inhibitors and are therefore useful, for instance, to restrict the unregulated proliferation of tumor cells.

In therapy, they may be used in the treatment of various tumors such as, for instance, carcinomas, e.g. mammary carcinoma, lung carcinoma, bladder carcinoma, colon carcinoma, ovary and endometrial tumors, sarcomas, e.g. soft tissue and bone sarcomas, and the hematological malignancies such as, e.g., leukemias.

In addition, the compounds of formula (I) are also useful in the treatment of other cell proliferative disorders such as psoriasis, vascular smooth cell proliferation associated with atherosclerosis and post-surgical stenosis and restenosis and in the treatment of Alzheimer's disease.

The inhibiting activity of putative protein kinase inhibitors and the potency of selected compounds was determined through a method of assay based on the use of the MultiScreen-PH 96 well plate (Millipore), in which a phosphocellulose filter paper was placed at each well bottom allowing binding of positive charged substrate after a washing/filtration step.

When a radioactivity labeled phosphate moiety was transferred by the ser/threo kinase to the filter-bound

histone, light emitted was measured in a scintillation counter.

Inhibition assay of cdk2/Cyclin A activity

Kinase reaction: 1.5 µM histone H1 substrate, 25 µM ATP (0.2 uCi P33γ-ATP), 30 ng of baculovirus co-expressed cdk2/Cyclin A, 10 µM inhibitor in a final volume of 100 µl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, 7.5 mM DTT) were added to each well of a 96 U bottom well plate. After 10 min at 37 °C incubation, reaction was stopped by 20 µl EDTA 120 mM.

Capture: 100 µl were transferred from each well to MultiScreen plate, to allow substrate binding to phosphocellulose filter. Plates were then washed 3 times with 150 µl/well PBS Ca++/Mg++ free and filtered by MultiScreen filtration system.

Detection: filters were allowed to dry at 37°C, then 100 µl/well scintillant were added and 33P labeled histone H1 was detected by radioactivity counting in the Top-Count instrument.

Results: data were analyzed and expressed as % inhibition referred to total activity of enzyme (=100%).

All compounds showing inhibition $\geq$ 50 % were further analyzed in order to study and define potency (IC50) as well as the kinetic-profile of inhibitor through Ki calculation.

IC50 determination: the protocol used was the same described above, where inhibitors were tested at different concentrations ranging from 0.0045 to 10 µM. Experimental data were analyzed by the computer program GraphPad Prizm using the four parameter logistic equation:

y = bottom+(top-bottom)/(1+10^((LogIC50-x)*slope))

where x is the logarithm of the inhibitor concentration, y is the response; y starts at bottom and goes to top with a sigmoid shape.

Ki calculation: either the concentration of ATP and histone H1 substrate were varied: 4, 8, 12, 24, 48 μM for ATP (containing proportionally diluted $P^{33}\gamma$-ATP) and 0.4, 0.8, 1.2, 2.4, 4.8 μM for histone were used in absence and presence of two different, properly chosen inhibitor concentrations.

Experimental data were analyzed by the computer program "SigmaPlot" for Ki determination, using a random bireactant system equation:

$$v = \frac{Vmax \frac{(A)(B)}{aKAKB}}{1 + \frac{(A)}{KA} + \frac{(B)}{KB} + \frac{(A)(B)}{aKAKB}}$$

where A=ATP and B=histone H1.

In addition the selected compounds have been characterized on a panel of ser/threo kinases strictly related to cell cycle (cdk2/cyclin E, cdk1/cyclin B1, cdk4/Cyclin D1), and also for specificity on MAPK, PKA, EGFR, IGF1-R, Cdc7/dbf4 and aurora-2.

Inhibition assay of cdk2/Cyclin E activity

Kinase reaction: 1.5 μM histone H1 (Sigma # H-5505) substrate, 25 μM ATP (0.2 μCi $P^{33}\gamma$-ATP), 15 ng of baculovirus co-expressed cdk2/GST-Cyclin E, suitable concentrations of inhibitor in a final volume of 100 μl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, 7.5 mM DTT+ 0.2mg/ml BSA) were added to each well of a 96 U bottom well plate. After 10 min at 37 °C incubation, reaction was stopped by 20 μl EDTA 120 mM.

Capture: 100 μl were transferred from each well to MultiScreen plate, to allow substrate binding to

phosphocellulose filter. Plates were then washed 3 times with 150 µl/well PBS Ca^{++}/Mg^{++} free and filtered by MultiScreen filtration system.

Detection: filters were allowed to dry at 37°C, then 100 µl/well scintillant were added and ^{33}P labeled histone H1 was detected by radioactivity counting in the Top-Count instrument.

Inhibition assay of cdk1/Cyclin B1 activity

Kinase reaction: 1.5 µM histone H1 (Sigma # H-5505) substrate, 25 µM ATP (0.2 µCi $P^{33}\gamma$-ATP), 30 ng of baculovirus co-expressed cdk1/Cyclin B1, suitable concentrations of inhibitor in a final volume of 100 µl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, 7.5 mM DTT+ 0.2mg/ml BSA) were added to each well of a 96 U bottom well plate. After 10 min at 37 °C incubation, reaction was stopped by 20 µl EDTA 120 mM.

Capture: 100 µl were transferred from each well to MultiScreen plate, to allow substrate binding to phosphocellulose filter. Plates were then washed 3 times with 150 µl/well PBS Ca^{++}/Mg^{++} free and filtered by MultiScreen filtration system.

Detection: filters were allowed to dry at 37°C, then 100 µl/well scintillant were added and ^{33}P labeled histone H1 was detected by radioactivity counting in the Top-Count instrument.

Inhibition assay cdk4/Cyclin D1 activity

Kinase reaction: 0,4 uM µM mouse GST-Rb(769-921) (# sc-4112 from Santa Cruz) substrate, 10 µM ATP (0.5 µCi $P^{33}\gamma$-ATP), 100 ng of baculovirus expressed GST-cdk4/GST-Cyclin D1, suitable concentrations of inhibitor in a final volume of 50 µl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, 7.5 mM DTT+ 0.2mg/ml BSA) were added to each well of a 96 U bottom

well plate. After 40 min at 37 °C incubation, reaction was stopped by 20 µl EDTA 120 mM.

Capture: 60 µl were transferred from each well to MultiScreen plate, to allow substrate binding to phosphocellulose filter. Plates were then washed 3 times with 150 µl/well PBS Ca^{++}/Mg^{++} free and filtered by MultiScreen filtration system.

Detection: filters were allowed to dry at 37°C, then 100 µl/well scintillant were added and ^{33}P labeled Rb fragment was detected by radioactivity counting in the Top-Count instrument.

Inhibition assay of MAPK activity

Kinase reaction: 10 µM MBP (Sigma # M-1891) substrate, 25 µM ATP (0.2 µCi $P^{33}\gamma$-ATP), 25 ng of bacterially expressed GST-MAPK (Upstate Biotechnology # 14-173), suitable concentrations of inhibitor in a final volume of 100 µl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, 7.5 mM DTT + 0.1 mg/ml BSA) were added to each well of a 96 U bottom well plate. After 15 min at 37 °C incubation, reaction was stopped by 20 µl EDTA 120 mM.

Capture: 100 µl were transferred from each well to MultiScreen plate, to allow substrate binding to phosphocellulose filter. Plates were then washed 3 times with 150 µl/well PBS Ca^{++}/Mg^{++} free and filtered by MultiScreen filtration system.

Detection: filters were allowed to dry at 37°C, then 100 µl/well scintillant were added and ^{33}P labeled MBP was detected by radioactivity counting in the Top-Count instrument.

Inhibition assay of PKA activity

Kinase reaction: 10 µM histone H1 (Sigma # H-5505) substrate, 10 µM ATP (0.2 µCi $P^{33}\gamma$-ATP), 1U of bovine heart PKA (Sigma # 2645), suitable concentrations of inhibitor in a final volume of 100 µl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, 7.5 mM DTT+ 0.2mg/ml BSA) were added to each well of a 96 U bottom well plate. After 5 min at 37 °C incubation, reaction was stopped by 20 µl EDTA 120 mM.

Capture: 100 µl were transferred from each well to MultiScreen plate, to allow substrate binding to phosphocellulose filter. Plates were then washed 3 times with 150 µl/well PBS Ca^{++}/Mg^{++} free and filtered by MultiScreen filtration system.

Detection: filters were allowed to dry at 37°C, then 100 µl/well scintillant were added and ^{33}P labeled histone H1 was detected by radioactivity counting in the Top-Count instrument.

Inhibition assay of EGFR activity

Kinase reaction: 25 nM in house biotinylated PolyGluTyr (Sigma # 0275) substrate, 2,5 µM ATP (0.3 µCi $P^{33}\gamma$-ATP), 80 ng baculovirus expressed GST-EGFR, suitable concentrations of inhibitor in a final volume of 100 µl buffer (Hepes 50 mM pH 7,5, $MnCl_2$- $MgCl_2$ 3mM, 1mM DTT + 3 µM NaVO3, 0.1 mg/ml BSA) were added to each well of a 96 U bottom well plate. After 5 min. at 37 °C incubation, reaction was stopped by 20 µl EDTA 120 mM.

Capture: 100 µl were transferred from each well to streptavidin-Flashplate, to allow biotinylated-substrate binding to plate. Plates were then washed 3 times with 150 µl/well PBS Ca^{++}/Mg^{++} free.

Detection: radioactivity counting in the Top-Count instrument.

Inhibition assay of IGF1-R activity

The inhibition assay of IGF1-R activity was performed according to the following protocol.

Kinase reaction: 10 µM biotinylated MBP (Sigma cat. # M-1891) substrate, 0-20 µM inhibitor, 6 µM cold ATP, 2 nM ^{33}P-ATP, and 22.5 ng IGF1-R (pre-incubated for 30 min at room temperature with cold 60 µM cold ATP) in a final volume of 30 µl buffer (50 mM HEPES pH 7.9, 3 mM $MnCl_2$, 1 mM DTT, 3 µM $NaVO_3$) were added to each well of a 96 U bottom well plate. After incubation for 35 min at room temperature, the reaction was stopped by addition of 100 µl PBS buffer containing 32 mM EDTA, 500 µM cold ATP, 0.1% Triton X100 and 10mg/ml streptavidin coated SPA beads. After 15 min incubation, 110 µL of suspension were withdrawn and transferred into 96-well OPTIPLATEs containing 100 µl of 5M CsCl. After 4 hours, the plates were read for 2 min in a Packard TOP-Count radioactivity reader.

Results: Experimental data were analyzed with the program GraphPad Prizm.

In addition, the inhibiting activity of putative protein kinase inhibitors and the potency of selected compounds was also determined through a method of assay based on the use of a SPA (Scintillation Proximity Assay) 96 well plate assay. The assay is based on the ability of streptavidin coated SPA beads to capture a biotinylated peptide derived from a phosphorylation site of histone.

When a radioactivity labeled phosphate moiety was transferred by the ser/threo kinase to the biotinylated histone peptide, light emitted was measured in a scintillation counter.

Inhibition assay of cdk5/p25 activity

The inhibition assay of cdk5/p25 activity was performed according to the following protocol.

Kinase reaction: 1.0 µM biotinylated histone peptide substrate, 0.25 uCi P33g-ATP, 4 nM cdk5/p25 complex, 0-100 µM inhibitor in a final volume of 100 µl buffer (Hepes 20 mM pH 7.5, MgCl2 15 mM, 1 mM DTT) were added to each well of a 96 U bottom well plate. After 20 min at 37 °C incubation, the reaction was stopped by the addition of 500 ug SPA beads in phosphate-buffered saline containing 0.1% Triton X-100, 50 uM ATP and 5 mM EDTA. The beads were allowed to settle, and the radioactivity incorporated in the 33P-labelled peptide was detected in a Top Count scintillation counter.

Results: Data were analyzed and expressed as % Inhibition using the formula:

100X(1 - (Unknown - Bkgd)/(Enz. Control - Bkgd))

IC50 values were calculated using a variation of the four parameter logistics equation:

Y = 100/[1 + 10 ^((LogEC50 - X)*Slope)]

Where X =log(uM) and Y = % Inhibition.

Inhibition assay of Cdc7/dbf4 activity

The inhibition assay of Cdc7/dbf4 activity was performed according to the following protocol.

The Biotin-MCM2 substrate is trans-phosphorylated by the Cdc7/Dbf4 complex in the presence of ATP traced with γ^{33}-ATP. The phosphorylated Biotin-MCM2 substrate is then captured by Streptavidin-coated SPA beads and the extent of phosphorylation evaluated by β counting.

The inhibition assay of Cdc7/dbf4 activity was performed in 96 wells plate according to the following protocol.

To each well of the plate were added :

- 10 µl substrate (biotinylated MCM2, 6 µM final concentration)
- 10 µl enzyme (Cdc7/Dbf4, 12.5 nM final concentration)
- 10 µl test compound (12 increasing concentrations in the nM to µM range to generate a dose-response curve)
- 10 µl of a mixture of cold ATP (10µM final concentration) and radioactive ATP (1/2500 molar ratio with cold ATP) was then used to start the reaction which was allowed to take place at 37°C.

Substrate, enzyme and ATP were diluted in 50 mM HEPES pH 7.9 containing 15 mM $MgCl_2$, 2 mM DTT, 3 µM $NaVO_3$, 2mM glycerophosphate and 0.2mg/ml BSA. The solvent for test compounds also contained 10% DMSO.

After incubation for 20 minutes, the reaction was stopped by adding to each well 100 µl of PBS pH 7.4 containing 50 mM EDTA, 1 mM cold ATP, 0.1% Triton X100 and 10 mg/ml streptavidin coated SPA beads.

After 15 minutes of incubation at room temperature to allow the biotinylated MCM2-streptavidin SPA beads interaction to occur, beads were trapped in a 96 wells filter plate (Unifilter^R GF/B^{TM}) using a Packard Cell Harvester (Filtermate), washed with distilled water and then counted using a Top Count (Packard).

Counts were blank-subtracted and then the experimental data (each point in triplicate) were analyzed for IC50 determination using a non-linear regression analysis (Sigma Plot).

Inhibition assay of aurora-2 activity

The inhibiting activity and the potency of selected compounds was determined through a method of assay based on the use of the streptavidin scintillation proximity assay beads (amershampharmacia biotech) run in a 96 well plates. At the end of the reaction, the biotinylated peptide

substrate was captured with the beads and subsequently allowed to stratify using $CsCl_2$.

When a radioactivity labeled phosphate moiety was transferred by the kinase to the beads-bound peptide, light emitted was measured in a scintillation counter.

The inhibition assay of Aurora-2 activity was performed in 96 wells plate according to the following protocol.

Kinase reaction: 8 µM biotinylated peptide (4 repeats of LRRWSLG), 10 µM ATP (0.5 uCi P^{33}g-ATP), 10 nM Aurora2, 10 µM inhibitor in a final volume of 60 µl buffer (HEPES 50 mM pH 7.0, $MgCl_2$ 10 mM, 1 mM DTT, 0.125 mg/ml BSA, 3µM orthovanadate) were added to each well of a 96 U bottom well plate. After 30 minutes at room temperature incubation, reaction was stopped and biotinylated peptide captured by adding 100 µl of bead suspension.

Stratification: 100 µl of CsCl2 7.5 M were added to each well and let stand one hour before radioactivity was counted in the Top-Count instrument.

Results: data were analyzed and expressed as % inhibition referred to total activity of enzyme (=100%).

All compounds showing inhibition $\geq$ 60 % were further analyzed in order to study the potency of the inhibitor through IC50 calculation.

The protocol used was the same described above, except that serial dilution of the inhibitor was used. Experimental data were fitted by nonlinear regression using the following equation:

$$v = v_0 + \frac{(v_0 - v_b)}{1 + 10^{n(\log IC_{50} - \log[I])}}$$

With v_b as the baseline velocity, v as the observed reaction velocity, v_o as the velocity in the absence of inhibitors, and [I] as the inhibitor concentration.

The compounds of formula (I) of the present invention, suitable for administration to a mammal, e.g. to humans, can be administered by the usual routes and the dosage level depends upon the age, weight, conditions of the patient and the administration route.

For example, a suitable dosage adopted for oral administration of a compound of formula (I) may range from about 10 to about 500 mg pro dose, from 1 to 5 times daily.

The compounds of the invention can be administered in a variety of dosage forms, e.g. orally, in the form of tablets, capsules, sugar or film coated tablets, liquid solutions or suspensions; rectally in the form of suppositories; parenterally, e.g. intramuscularly, or by intravenous and/or intrathecal and/or intraspinal injection or infusion.

In addition, the compounds of the invention can be administered either as single agents or, alternatively, in combination with known anticancer treatments such as radiation therapy or chemotherapy regimen in combination with cytostatic or cytotoxic agents, antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents, immunological agents, interferon-type agents, cyclooxygenase inhibitors (e.g. COX-2 inhibitors), metallomatrixprotease inhibitors, telomerase inhibitors, tyrosine kinase inhibitors, anti-growth factor receptor agents, anti-HER agents, anti-EGFR agents, anti-angiogenesis agents, farnesyl transferase inhibitors, ras raf signal transduction pathway inhibitors, cell cycle inhibitors, other cdks inhibitors, tubulin binding agents, topoisomerase I inhibitors, topoisomerase II inhibitors, and the like.

As an example, the compounds of the invention can be administered in combination with one or more chemotherapeutic agents such as, for instance, exemestane,

formestane, anastrozole, letrozole, fadrozole, taxane, taxane derivatives, encapsulated taxanes, CPT-11, camptothecin derivatives, anthracycline glycosides, e.g., doxorubicin, idarubicin, epirubicin, etoposide, navelbine, vinblastine, carboplatin, cisplatin, estramustine, celecoxib, tamoxifen, raloxifen, Sugen SU-5416, Sugen SU-6668, Herceptin, and the like, optionally within liposomal formulations thereof.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described above and the other pharmaceutically active agent within the approved dosage range.

Compounds of formula (I) may be used sequentially with known anticancer agents when a combination formulation is inappropriate.

The present invention also includes pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable excipient (which can be a carrier or a diluent).

The pharmaceutical compositions containing the compounds of the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form.

For example, the solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, sucrose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic , magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gum, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. a starch, alginic , alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents such as lecithin, polysorbates, laurylsulfates; and, in general,

non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tabletting, sugar-coating, or film-coating processes.

The liquid dispersions for oral administration may be e.g. syrups, emulsions and suspensions.

The syrups may contain as carrier, for example, saccharose or saccharose with glycerin and/or mannitol and/or sorbitol.

The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride. The solutions for intravenous injections or infusions may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions or they may contain as a carrier propylene glycol.

The suppositories may contain together with the active compound a pharmaceutically acceptable carrier, e.g. cocoa butter, polyethylene glycol, a polyoxyethylene sorbitan fatty ester surfactant or lecithin.

The following examples illustrate but do not limit the present invention.

General Methods

Flash chromatografy was performed on silica gel (Merck grade 9385, 60Å). HPLC/MS was performed on a Waters X Terra

RP 18 (4.6 x 50 mm, 3.5 μm) column using a Waters 2790 HPLC system equipped with a 996 Waters PDA detector and a Micromass mod. ZQ single quadrupole mass spectrometer, equipped with an electrospray (ESI) ion source. Mobile phase A was ammonium acetate 5 mM buffer (pH 5.5 with acetic acid / acetonitrile 95:5), and Mobile phase B was H_2O / acetonitrile (5:95). Gradient from 10 to 90% B in 8 minutes, hold 90% B 2 min. UV detection at 220 nm and 254 nm. Flow rate 1 ml/min. Injection volume 10 μl. Full scan, mass range from 100 to 800 amu. Capillary voltage was 2.5 KV; Source temp.was 120°C; Cone was 10 V. Retention Times (HPLC r.t.) are given in minutes at 220 nm or 254 nm. Mass are given as m/z ratio.

When necessary compounds have been purified by Preparative HPLC on a Waters Symmetry C18 (19 x 50 mm, 5um) column using a Waters preparative HPLC 600 equipped with a 996 Waters PDA detector and a Micromass mod. ZMD single quadrupole mass spectrometer, electrospray ionisation, positive mode. Mobile phase A was water 0.01% TFA, and Mobile phase B was acetonitrile. Gradient from 10 to 90%B in 8 min, hold 90%B 2 min. Flow rate 20 ml/m.

^{1}H-NMR spectroscopy was performed on a Mercury VX 400 operating at 400.45 MHz equipped with a 5mm double resonance probe (1H {15N-31P} ID_PFG Varian).

Example 1

6-nitro-3-bromo-3H-isobenzofuran-1-one (II)

To 125 ml of a dichloromethane solution of 6-nitrophtalide (8.0 g, 0.047 mol), bromine (8.25 g, 0.052 mol, 1.15 eq) and hydrogen peroxide (5.07 g of a 35 % solution in water, equivalent to 1.77 of hydrogen peroxide, 0.052 mol, 1,15 eq) were added. The mixture was gently refluxed for 11 hours, then cooled down and concentrated by solvent evaporation. The aqueous layer was separated, and the organic phase washed with water before drying up (Na_2SO_4).

After evaporation of the solvent the crude residue was purified by flash chromatography over silica gel (hexane-ethyl acetate 8-2 to 7-3). 8.18 g of the titled compound were obtained. $[M-1]^-$ = 257; HPLC r.t. 5.37; ^{1}H-NMR ($CDCl_3$), diagnostic signals (ppm): 7.47 (s, 1H), 7.86 (d, 1H), 8.67 (dd, 1H), 8.74 (d, 1H).

Example 2

(5-Amino-3-oxo-1,3-dihydro-isobenzofuran-1-yl)-triphenyl-phosphonium bromide (III)

A solution of 6-nitro-3-bromo-3H-isobenzofuran-1-one (8.7 g, 0.034 mol) in ethyl propionate (464 ml) was heated to 70-75°C, and stirred while 313 ml of an ethyl propionate solution of triphenyl phosphine (36 g, 0.137 mol, 4 eq) were added dropwise over a time of 7 hours. Heating and stirring were continued overnight, and then the mixture was cooled down to room temperature. The precipitate was collected, dried up under vacuum and purified by flash chromatography over silica gel. A gradient of dichloromethane-methanol-acetic acid, from 97-3-0 to 93-5-2 was used as the eluant, to yield 6.2 g of the title compound. $[M]^+$ = 410; HPLC r.t. 4.72; ^{1}H-NMR (DMSO-d_6), diagnostic signals (ppm): 6.01 (br. s, 2H exchangeable with deuterated water), 6.49 (dd, 1H), 6.80 (d, 1H), 6.87 (d, 1H), 7.62-8.00 (m, 15H), 8.17 (s, 1H).

Example 3

(5-{2-Methoxy-4-[3-(4-resin-benzylcarbamoyl)-propoxyl-benzylamino}-3-oxo-1,3-dihydro-isobenzofuran-1-yl)-triphenyl-phosphonium bromide

The compound of example 2 (252 mg, 0.514 mmol) was dissolved in 15.25 ml of a solvent mixture made up of dichloromethane (13.5 ml), trifluoroethanol (1.5 ml) and acetic acid (0.25 ml). *Novabiochem* 4-(4-Formyl-3-methoxyphenoxy)butyryl aminomethylated resin (326 mg, declared substitution 0.94 mmol/g, 0.6 eq.) was poured into

the solution, and the resulting suspension was gently stirred for 9 hours before adding dropwise the pyridine-borane complex (250 µl, ~ 6 mmol, 10 eq.). After 40 hours the resin was filtered, washed with dichloromethane, methanol and again dichloromethane, hence dried under vacuum (518 mg, calculated loading: 0.78 mmol/g; IR: 1787 cm^{-1}, lactone stretching band).

Example 4

4-[3-Methoxy-4-({3-oxo-1-[1-pyridin-3-yl-methylidene]-1,3-dihydro-isobenzofuran-5-ylamino}-methyl)-phenoxy]-N-(4-resin-benzyl)-butyramide

(5-{2-Methoxy-4-[3-(4-resin-benzylcarbamoyl)-propoxy]-benzylamino}-3-oxo-1,3-dihydro-isobenzofuran-1-yl)-triphenyl-phosphonium bromide of example 3 (100 mg, 0.078 meq) was suspended in dried dichloromethane (3 ml); pyridine-3-carboxaldehyde (50 µl, about ~ 6 eq.) was added, followed by TEA (50 µl). Stirring at room temperature was maintained for 20 hours then the resin was filtered and washed with dichloromethane, methanol, and again dichloromethane before drying under vacuum (IR: 1776 cm^{-1}).

Example 5

N-{2-Methoxy-4-[3-(4-resin-benzylcarbamoyl)-propoxy]-benzyl}-N-{3-oxo-1-[1-pyridin-3-yl-methylidene]-1,3-dihydro-isobenzofuran-5-yl}-benzamide

4-[3-Methoxy-4-({3-oxo-1-[1-pyridin-3-yl-methylidene]-1,3-dihydro-isobenzofuran-5-ylamino}-methyl)-phenoxy]-N-(4-resin-benzyl)-butyramide of example 4 was suspended in dried dichloromethane (3 ml); diisopropyl ethylamine (200 µl) and benzoyl chloride (100 µl, ~10 eq.) were added in this order. After stirring at room temperature for 20 hours, the resin was filtered and washed with dichloromethane, methanol, and again dichloromethane before drying under vacuum (IR: 1786 cm^{-1}).

Example 6

4-[3-Methoxy-4-(1-{3-oxo-1-[1-pyridin-3-yl-methylidene]-1,3-dihydro-isobenzofuran-5-yl}-3-p-tolyl-ureidomethyl)-phenoxy]-N-(4-resin-benzyl)-butyramide

4-[3-Methoxy-4-({3-oxo-1-[1-pyridin-3-yl-methylidene]-1,3-dihydro-isobenzofuran-5-ylamino}-methyl)-phenoxy]-N-(4-resin-benzyl)-butyramide of example 4 was suspended in dried dichloromethane (3 ml) and p-toluyl isocyanate (100 µl, ~10 eq.) was added. After stirring at room temperature for 20 hours, the resin was filtered and washed with dichloromethane, methanol, and again dichloromethane before drying under vacuum.

Example 7

N-{2-Methoxy-4-[3-(4-resin-benzylcarbamoyl)-propoxy]-benzyl}-N-(4-oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-benzamide

N-{2-Methoxy-4-[3-(4-resin-benzylcarbamoyl)-propoxy]-benzyl}-N-{3-oxo-1-[1-pyridin-3-yl-methylidene]-1,3-dihydro-isobenzofuran-5-yl}-benzamide of example 5 was suspended in dimethylformammide (3 ml) and aqueous hydrazine (approximately 25 % solution) was added (400 µl, about 40 eq.). After stirring at room temperature for 20 hours, the resin was filtered, washed with dimethylformammide, methanol and dichloromethane before drying under vacuum. (IR: disappearance of lactone stretching band).

Example 8

4-{3-Methoxy-4-[1-(4-oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-p-tolyl-ureidomethyl]-phenoxy}-N-(4-resin-benzyl)-butyramide

4-[3-Methoxy-4-(1-{3-oxo-1-[1-pyridin-3-yl-methylidene]-1,3-dihydro-isobenzofuran-5-yl}-3-p-tolyl-ureidomethyl)-phenoxy]-N-(4-resin-benzyl)-butyramide of example 6 was suspended in dimethylformammide (3 ml) and aqueous

hydrazine (approximately 25 % solution) was added (400 µl, about 40 eq.). After stirring at room temperature for 20 hours, the resin was filtered, washed with dimethylformammide, methanol and dichloromethane before drying under vacuum.

Example 9

N-(4-Oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-benzamide

N-{2-Methoxy-4-[3-(4-resin-benzylcarbamoyl)-propoxy]-benzyl}-N-(4-oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-benzamide of example 7 was suspended in a solution of 20% TFA in DCM (3 ml), and stirred at room temperature for 2 hours. The resin was filtered and the solution collected and dried up yielding 15 mg of title compound. $[M+1]^+$ = 357; HPLC r.t. 4.02; ^{1}H-NMR (DMSO-d6), diagnostic signals (ppm): 4.39 (s, 2H), 7.47-7.62 (m, 3H), 7.93-8.05 (m, 3H), 8.26 (dd, 1H), 8.54 (m, 1H), 8.65 (br. S, 1H), 8.76 (d, 1H), 10.73 (s, 1H, exchangeable with water), 12.45 (s, 1H, exchangeable with water).

Example 10

1-(4-Oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-p-tolyl-urea

4-{3-Methoxy-4-[1-(4-oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-p-tolyl-ureidomethyl]-phenoxy}-N-(4-methyl-benzyl)-butyramide of example 8 was suspended in a solution of 20% TFA in DCM (3 ml), and stirred at room temperature for 2 hours. The resin was filtered and the solution collected and dried up yielding 11 mg of title compound. $[M+1]^+$ = 386; HPLC r.t. 4.72; ^{1}H-NMR (DMSO-d6), diagnostic signals (ppm): 2.23 (s, 3H), 4.26 (s, 2H), 7.10 (d, 2H), 7.29 (m, 1H) 7.33 (d, 2H), 7.64 (m, 1H), 7.83 (dd, 1H), 7.89 (d, 1H), 8.40 (m, 2H), 8.56 (d, 1H), 8.70 (br. S, 1H), 9.22 (br. s, 1H), 12.38 (br. s, 1H).

By working in an analogous way and by reacting the compound of formula (III) with the appropriate aldehyde of formula (V) and then with the proper acyl chloride derivative of formula (VIII) or isocyante of formula (IX), the following compounds were prepared:

7-Amino-4-(4-chloro-benzyl)-2H-phthalazin-1-one $[M+1]^+$ = 286; HPLC r.t. 4.62; ^{1}H-NMR (DMSO-d6), diagnostic signals (ppm): 4.11 (s, 2H), 6.97 (dd, 1H), 7.24-7.32 (m, 5H), 7.56 (d, 1H), 12.05 (s, 1H, exchangeable with deuterated water).

7-Amino-4-(4-methoxy-benzyl)-2H-phthalazin-1-one $[M+1]^+$ = 282; HPLC r.t. 3.83; ^{1}H-NMR (DMSO-d6), diagnostic signals (ppm): 3.68 (s, 3H) 4.04 (s, 2H), 6.10 (s, 2H, exchangeable with deuterated water), 6.82 (d, 2H), 6.97 (dd, 1H), 7.17 (d, 2H), 7.23 (d, 1H), 7.57 (d, 1H).

7-Amino-4-(4-nitro-benzyl)-2H-phthalazin-1-one $[M+1]^+$ = 297; ^{1}H-NMR (DMSO-d6), diagnostic signals (ppm): 4.29 (s, 2H), 6.18 (s, 2H, exchangeable with deuterated water), 7.00 (dd, 1H), 7.26 (d, 1H), 7.57 (m, 3H), 8.14 (d, 2H).

N-(4-Oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-propionamide; [M+H]+ = 309; HPLC r.t. 2.88.

N-(4-Oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-4-trifluoromethyl-benzamide; [M+H]+ = 425; HPLC r.t. 5.1.

Furan-2-carboxylic acid (4-oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-amide; [M+H]+ = 346; HPLC r.t. 3.37.

N-(4-Oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-cyclopentyl-propionamide; [M+H]+ = 377; HPLC r.t. 4.99.

2-Propyl-pentanoic acid (4-oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-amide; [M+H]+ = 379; HPLC r.t. 5.09.

1-(4-Oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-(3-trifluoromethyl-phenyl)-urea; [M+H]+ = 440; HPLC r.t. 5.29.

1-(3-Methoxy-phenyl)-3-(4-oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-urea; [M+H]+ = 402; HPLC r.t. 4.33.

1-(4-Oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-p-tolyl-urea; [M+H]+ = 386; HPLC r.t. 4.62.

1-(2,4-Difluoro-phenyl)-3-(4-oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-urea; [M+H]+ = 408; HPLC r.t. 4.58.

1-(3,4-Dichloro-phenyl)-3-(4-oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-urea; [M+H]+ = 440; HPLC r.t. 5.59.

N-[1-(4-Chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-propionamide; [M+H]+ = 342; HPLC r.t. 5.18.

N-[1-(4-Chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide; [M+H]+ = 458; HPLC r.t. 7.13.

Furan-2-carboxylic acid [1-(4-chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide; [M+H]+ = 380; HPLC r.t. 5.66.

N-[1-(4-Chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide; [M+H]+ = 410; HPLC r.t. 7.22.

2-Propyl-pentanoic acid [1-(4-chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide; [M+H]+ = 412; HPLC r.t. 7.33.

1-[1-(4-Chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea; [M+H]+ = 473; HPLC r.t. 7.26.

1-[1-(4-Chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-methoxy-phenyl)-urea; [M+H]+ = 435; HPLC r.t. 6.43.

1-[1-(4-Chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea; [M+H]+ = 419; HPLC r.t. 6.74.

1-[1-(4-Chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea; [M+H]+ = 441; HPLC r.t. 6.71.

N-[1-(4-Cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-propionamide; [M+H]+ = 333; HPLC r.t. 4.26.

N-[1-(4-Cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide; [M+H]+ = 449; HPLC r.t. 6.3.

Furan-2-carboxylic acid [1-(4-cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide; [M+H]+ = 371; HPLC r.t. 4.72.

N-[1-(4-Cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide; [M+H]+ = 401; HPLC r.t. 6.3.

2-Propyl-pentanoic acid [1-(4-cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide; [M+H]+ = 403; HPLC r.t. 6.42.

1-[1-(4-Cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea; [M+H]+ = 464; HPLC r.t. 6.46; ^{1}H-NMR (DMSO-d6), diagnostic signals (ppm): 4.34 (s, 2H), 7.34 (d, 1H), 7.47-7.55 (m, 3H), 7.59 (d, 1H), 7.73 (d, 2H), 7.80-7-88 (m, 2H), 8.00 (s, 1H), 8.43 (d, 1H), 9.20 (s, 1H), 9.40 (s, 1H), 12.44 (br. s, 1H).

1-[1-(4-Cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-methoxy-phenyl)-urea; [M+H]+ = 426; HPLC r.t. 5.59.

1-[1-(4-Cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea; [M+H]+ = 410; HPLC r.t. 5.89.

1-[1-(4-Cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea; [M+H]+ = 432; HPLC r.t. 6.

N-[1-(3-Fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-propionamide; [M+H]+ = 326; HPLC r.t. 4.69; ^{1}H-NMR (DMSO-d6), diagnostic signals (ppm): 1.08 (t, 3H), 2.35 (q, 2H), 4.24 (s, 2H), 7.00 (m, 1H), 7.11 (m, 2H), 7.29 (m,

1H), 7.90 (d, 1H), 7.95 (dd, 1H), 8.53 (d, 1H), 10.35 (br. s, 1H), 12.42 (br. S, 1H).

N-[1-(3-Fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide; [M+H]+ = 442; HPLC r.t. 6.68.

Furan-2-carboxylic acid [1-(3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide; [M+H]+ = 364; HPLC r.t. 5.16.

N-[1-(3-Fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide; [M+H]+ = 394; HPLC r.t. 6.73.

2-Propyl-pentanoic acid [1-(3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide; [M+H]+ = 396; HPLC r.t. 6.85.

1-[1-(3-Fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea; [M+H]+ = 457; HPLC r.t. 6.86.

1-[1-(3-Fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-methoxy-phenyl)-urea; [M+H]+ = 419; HPLC r.t. 5.98.

N-[1-(3-Methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-propionamide; [M+H]+ = 322; HPLC r.t. 4.92.

N-[1-(3-Methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide; [M+H]+ = 438; HPLC r.t. 6.93.

Furan-2-carboxylic acid [1-(3-methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide; [M+H]+ = 360; HPLC r.t. 5.38.

N-[1-(3-Methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide; [M+H]+ = 390; HPLC r.t. 6.95.

2-Propyl-pentanoic acid [1-(3-methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide; [M+H]+ = 392; HPLC r.t. 7.08.

1-[1-(3-Methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea; [M+H]+ = 453; HPLC r.t. 7.04.

1-[1-(3-Methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-methoxy-phenyl)-urea; [M+H]+ = 415; HPLC r.t. 6.18.

1-[1-(3-Methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea; [M+H]+ = 399; HPLC r.t. 6.48.

1-[1-(3-Methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea; [M+H]+ = 421; HPLC r.t. 6.5.

N-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-propionamide; [M+H]+ = 376; HPLC r.t. 5.83; ^{1}H-NMR (DMSO-d6), diagnostic signals (ppm): 1.09 (t, 3H), 2.37 (q, 2H), 4.33 (s, 2H), 7.30 (d, 1H), 7.32 (dd, 1H), 7.60 (d, 1H), 7.93 (d, 1H), 8.02 (dd, 1H), 8.56 (d, 1H), 10.39 (s, 1H), 12.33 (s, 1H).

N-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide; [M+H]+ = 492; HPLC r.t. 7.68; ^{1}H-NMR (DMSO-d6), diagnostic signals (ppm): 4.37 (s, 2H), 7.30-7.37 (m, 2H), 7.62 (d, 1H), 7.94 (d, 2H), 8.02 (d, 1H), 8.19 (d, 2H), 8.27 (dd, 1H), 8.77 (d, 1H), 10.96 (br. S, 1H), 12.41 (br. S, 1H).

Furan-2-carboxylic acid [1-(2,4-dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide; [M+H]+ = 414; HPLC r.t. 6.26.

N-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-succinamic acid ethyl ester; [M+H]+ = ; HPLC r.t. 6.11.

N-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide; [M+H]+ = 444; HPLC r.t. 7.82; ^{1}H-NMR (DMSO-d6), diagnostic signals (ppm): 1.00-1.85 (m, 11H), 2.37 (t, 2H), 4.33 (s, 2H), 7.30 (d, 1H), 7.32 (dd, 1H), 7.60 (dd, 1H), 7.92 (d, 1H), 8.00 (dd, 1H), 8.56 (dd, 1H), 10.40 (br. S., 1H), 12.33 (br. S., 1H).

2-Propyl-pentanoic acid [1-(2,4-dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide; [M+H]+ = 446; HPLC r.t. 7.94; ^{1}H-NMR (DMSO-d6), diagnostic signals (ppm): 1.00-1.85 (m, 9H), 1.58-1.66 (m, 2H), 2.37 (m, 2H), 4.33 (s, 2H), 7.30 (d, 1H), 7.32 (dd, 1H), 7.60 (d, 1H), 7.92 (d, 1H), 8.00 (dd, 1H), 8.56 (dd, 1H), 10.40 (br. S, 1H), 12.33 (br. S, 1H).

1-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea; [M+H]+ = 507; HPLC r.t. 7.83.

1-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-methoxy-phenyl)-urea; [M+H]+ = 469; HPLC r.t. 7.02; ^{1}H-NMR (DMSO-d6), diagnostic signals (ppm): 3.73 (s, 3H), 4.33 (s, 2H), 6.58 (m, 1H), 6.96 (m, 1H), 7.15-7.22 (m, 2H), 7.28-7.36 (m, 2H), 7.61 (d, 1H), 7.82-7.90 (m, 2H), 8.44 (d, 1H), 8.91 (br. S, 1H), 9.35 (br. S, 1H), 12.31 (br.s, 1H).

1-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea; [M+H]+ = 453; HPLC r.t. 7.35.

1-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea; [M+H]+ = 475; HPLC r.t. 7.38; ^{1}H-NMR (DMSO-d6), diagnostic signals (ppm): 4.33 (s, 2H), 7.06 (m, 1H), 7.25-7.36 (m, 3H), 7.61 (d, 1H), 7.85 (dd, 1H), 7.88 (d, 1H), 8.03 (m, 1H), 8.45 (d, 1H), 8.75 (s, 1H), 9.71 (s, 1H), 12.33 (s, 1H).

N-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-propionamide; [M+H]+ = 359; HPLC r.t. 4.01.

N-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-4-trifluoromethyl-benzamide; [M+H]+ = 475; HPLC r.t. 6; ^{1}H-NMR (DMSO-d6), diagnostic signals (ppm): 4.51 (s, 2H), 7.57 (dt, 1H), 7.69 (dt, 1H) 7.87-8.00 (m, 4H), 8.09 (d, 1H), 8.15-8.20 (m, 3H), 8.23 (dd, 1H), 8.76 (d, 1H), 8.92 (d, 1H), 10.92 (s, 1H), 12.49 (s, 1H).

N-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-succinamic acid ethyl ester; [M+H]+ = 431; HPLC r.t. 4.37.

N-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-cyclopentyl-propionamide; [M+H]+ = 427; HPLC r.t. 5.97.

2-Propyl-pentanoic acid (4-oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-amide; [M+H]+ = 429; HPLC r.t. 6.08. ^{1}H-NMR (DMSO-d6), diagnostic signals (ppm): 0.80-0.88 (m, 6H), 1.18-1.29 (m, 4H), 1.29-1.64 (m, 4H), 2.37-2.48 (m, 1H), 4.48 (s, 2H), 7.55 (m, 1H), 7.70 (m, 1H), 7.88 (dd, 1H), 7.95-8.01 (m, 3H), 8.17 (d, 1H), 8.58 (d, 1H), 8.91 (d, 1H), 10.36 (br. s, 1H), 12.42 (br. S, 1H).

1-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-(3-trifluoromethyl-phenyl)-urea; [M+H]+ = 490; HPLC r.t. 6.16.

1-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-(3-methoxy-phenyl)-urea; [M+H]+ = 452; HPLC r.t. 5.27; ^{1}H-NMR (DMSO-d6), diagnostic signals (ppm): 3.72 (s, 3H), 4.47 (s, 2H), 6.57 (m, 1H), 6.94 (m, 1H), 7.19 (m, 2H), 7.55 (dd, 1H), 7.69 (dd, 1H), 7.81 (dd, 1H), 7.88 (dd, 1H), 7.96 (m, 2H), 8.16 (d, 1H), 8.44 (d, 1H), 8.82 (br. s, 1H), 8.91 (d, 1H), 9.25 (br. s, 1H), 12.40 (br. s, 1H).

1-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-p-tolyl-urea; [M+H]+ = 436; HPLC r.t. 5.56.

1-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-(2,4-difluoro-phenyl)-urea; [M+H]+ = 458; HPLC r.t. 5.55; ^{1}H-NMR (DMSO-d6), diagnostic signals (ppm): 4.48 (s, 2H), 7.05 (m, 1H), 7.30 (m, 1H), 7.54 (dt, 1H), 7.69 (dt, 1H), 7.79 (dd, 1H), 7.87 (d, 1H), 7.95-8.07 (m, 2H), 8.16 (d, 1H), 8.44 (d, 1H), 8.61 (d, 1H), 8.90 (s, 1H), 9.56 (s, 1H) 12.41 (s, 1H).

1-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-(3,4-dichloro-phenyl)-urea; [M+H]+ = 491; HPLC r.t. 6.51.

N-[4-Oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-propionamide; [M+H]+ = 376; HPLC r.t. 5.41.

N-[4-Oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide; [M+H]+ = 492; HPLC r.t. 7.23.

Furan-2-carboxylic acid [4-oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-amide; [M+H]+ = 414; HPLC r.t. 5.82.

N-[4-Oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide; [M+H]+ = 444; HPLC r.t. 7.33.

2-Propyl-pentanoic acid [4-oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-amide; [M+H]+ = 446; HPLC r.t. 7.43.

1-[4-Oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea; [M+H]+ = 507; HPLC r.t. 7.36.

1-[4-Oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea; [M+H]+ = 453; HPLC r.t. 6.88.

1-[4-Oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea; [M+H]+ = 475; HPLC r.t. 6.88.

4-(4-Oxo-6-propionylamino-3,4-dihydro-phthalazin-1-ylmethyl)-benzoic acid methyl ester; [M+H]+ = 366; HPLC r.t. 2.61.

4-[4-Oxo-6-(4-trifluoromethyl-benzoylamino)-3,4-dihydro-phthalazin-1-ylmethyl]-benzoic acid methyl ester; [M+H]+ = 482; HPLC r.t. 6.47.

4-{6-[(Furan-2-carbonyl)-amino]-4-oxo-3,4-dihydro-phthalazin-1-ylmethyl}-benzoic acid methyl ester; [M+H]+ = 404; HPLC r.t. 4.91.

4-[6-(3,4-Dimethoxy-benzoylamino)-4-oxo-3,4-dihydro-phthalazin-1-ylmethyl]-benzoic acid methyl ester; [M+H]+ = 474; HPLC r.t. 5.27.

4-[6-(3-Cyclopentyl-propionylamino)-4-oxo-3,4-dihydro-phthalazin-1-ylmethyl]-benzoic acid methyl ester; [M+H]+ = 434; HPLC r.t. 6.48.

4-[4-Oxo-6-(2-propyl-pentanoylamino)-3,4-dihydro-phthalazin-1-ylmethyl]-benzoic acid methyl ester; [M+H]+ = 436; HPLC r.t. 6.61.

4-{6-[3-(3-Methoxy-phenyl)-ureido]-4-oxo-3,4-dihydro-phthalazin-1-ylmethyl}-benzoic acid methyl ester; [M+H]+ = 459; HPLC r.t. 5.74.

4-[4-Oxo-6-(3-p-tolyl-ureido)-3,4-dihydro-phthalazin-1-ylmethyl]-benzoic acid methyl ester; [M+H]+ = 443; HPLC r.t. 6.03.

4-{6-[3-(2,4-Difluoro-phenyl)-ureido]-4-oxo-3,4-dihydro-phthalazin-1-ylmethyl}-benzoic acid methyl ester; [M+H]+ = 465; HPLC r.t. 6.04.

N-[1-(4-Chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-propionamide; [M+H]+ = 360; HPLC r.t. 4.04.

N-[1-(4-Chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide; [M+H]+ = 476; HPLC r.t. 6.3.

Furan-2-carboxylic acid [1-(4-chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide; [M+H]+ = 398; HPLC r.t. 4.58.

N-[1-(4-Chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3,4-dimethoxy-benzamide; [M+H]+ = 468; HPLC r.t. 4.97.

N-[1-(4-Chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide; [M+H]+ = 428; HPLC r.t. 7.3.

2-Propyl-pentanoic acid [1-(4-chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide; [M+H]+ = 430; HPLC r.t. 7.41.

1-[1-(4-Chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea; [M+H]+ = 491; HPLC r.t. 6.54.

1-[1-(4-Chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea; [M+H]+ = 437; HPLC r.t. 5.91.

N-{1-[(E)-3-(4-Nitro-phenyl)-allyl]-4-oxo-3,4-dihydro-phthalazin-6-yl}-3,4-dimethoxy-benzamide; [M+H]+ = ; HPLC r.t. 4.96.

N-(4-Oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-propionamide; [M+H]+ = 314; HPLC r.t. 4.26.

N-(4-Oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-4-trifluoromethyl-benzamide; [M+H]+ = 430; HPLC r.t. 6.43.

Furan-2-carboxylic acid (4-oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-amide; [M+H]+ = 352; HPLC r.t. 4.76.

N-(4-Oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3,4-dimethoxy-benzamide; [M+H]+ = 422; HPLC r.t. 5.16.

2-Propyl-pentanoic acid (4-oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-amide; [M+H]+ = 384; HPLC r.t. 6.54.

1-(4-Oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-(3-trifluoromethyl-phenyl)-urea; [M+H]+ = 445; HPLC r.t. 6.57.

1-(4-Oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-(3-methoxy-phenyl)-urea; [M+H]+ = 407; HPLC r.t. 5.66.

1-(4-Oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-p-tolyl-urea; [M+H]+ = 391; HPLC r.t. 5.98.

1-(4-Oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-(2,4-difluoro-phenyl)-urea; [M+H]+ = 413; HPLC r.t. 5.96.

N-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-propionamide; [M+H]+ = 338; HPLC r.t. 4.48.

N-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide; [M+H]+ = 454; HPLC r.t. 6.52.

Furan-2-carboxylic acid [1-(3-methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide; [M+H]+ = 376; HPLC r.t. 4.95.

N-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3,4-dimethoxy-benzamide; [M+H]+ = 446; HPLC r.t. 5.32.

N-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide; [M+H]+ = 406; HPLC r.t. 6.53.

2-Propyl-pentanoic acid [1-(3-methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide; [M+H]+ = 408; HPLC r.t. 6.65; ^{1}H-NMR (DMSO-d6), diagnostic signals (ppm): 0.84 (q, 6H), 1.15-1.62 (m, 8H), 2.41 (m, 1H), 3.68 (s, 3H), 4.18 (s, 2H), 6.75 (ddd, 1H), 6.82 (dt, 1H), 6.86 (t, 1H), 7.16 (t, 1H), 7.89 (d, 1H), 7.95 (dd, 1H), 8.55 (d, 1H), 10.34 (s, 1H), 12.41 (s, 1H).

1-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea; [M+H]+ = 469; HPLC r.t. 6.67.

1-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-(3-methoxy-phenyl)-urea; [M+H]+ = 431; HPLC r.t. 5.79.

1-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea; [M+H]+ = 415; HPLC r.t. 6.08.

1-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea; [M+H]+ = 437; HPLC r.t. 6.08.

N-(4-Oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-propionamide; [M+H]+ = 260; HPLC r.t. 3.78.

Furan-2-carboxylic acid (4-oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-amide; [M+H]+ = 298; HPLC r.t. 4.35.

1-(4-Oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-3-p-tolyl-urea; [M+H]+ = ; HPLC r.t. 5.69.

1-(4-Oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-3-(2,4-difluoro-phenyl)-urea; [M+H]+ = 359; HPLC r.t. 5.68.

N-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-propionamide; [M+H]+ = 336; HPLC r.t. 5.35.

N-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide; [M+H]+ = 452; HPLC r.t. 7.26.

Furan-2-carboxylic acid [4-oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-amide; [M+H]+ = 374; HPLC r.t. 5.78.

N-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-3,4-dimethoxy-benzamide; [M+H]+ = 444; HPLC r.t. 6.11.

N-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide; [M+H]+ = 404; HPLC r.t. 7.31.

2-Propyl-pentanoic acid [4-oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-amide; [M+H]+ = 406; HPLC r.t. 7.43.

1-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea; [M+H]+ = 467; HPLC r.t. 7.41.

1-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-(3-methoxy-phenyl)-urea; [M+H]+ = 429; HPLC r.t. 6.56.

1-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea; [M+H]+ = 413; HPLC r.t. 6.88.

1-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea; [M+H]+ = 435; HPLC r.t. 6.88.

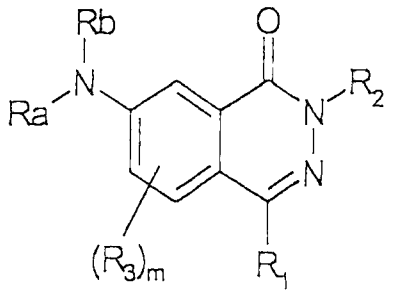
1-[1-(3-Fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea; [M+H]+ = 425; ^{1}H-NMR (DMSO-d6), diagnostic signals (ppm): 4.25 (s, 2H), 6.97-7.08 (m, 2H), 7.09-7.15 (m, 2H), 7.27-7.35 (m, 2H), 7.77 (dd, 1H), 7.86 (d, 1H), 7.98-8.08 (m, 1H), 8.42 (d, 1H), 8.61 (d, 1H), 9.55 (s, 1H), 12.42 (s, 1H).

1-[1-(3-Fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea; [M+H]+ = 403; ^{1}H-NMR (DMSO-d6), diagnostic signals (ppm): 2.23 (s, 3H), 4.24 (s, 2H), 7.00 (m, 1H), 7.05-7.16 (m, 4H), 7.27-7.35 (m, 3H), 7.79 (dd,

1H), 7.84 (d, 1H), 8.39 (d, 1H), 8.70 (br. S, 1H), 9.20 (br. S, 1H), 12. 39 (s, 1H).

CLAIMS

1. Use of amino-phthalazinone derivative represented by formula (I)



(I)

wherein

Ra and Rb are, each independently, a hydrogen atom or a group, optionally further substituted, selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur; or one of Ra or Rb is hydrogen or an optionally substituted straight or branched C_1-C_6 alkyl group, and the other is a group selected from -COR', -CONHR', -COOR' or $-SO_2R'$, wherein R' is hydrogen or an optionally substituted group selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl, as set forth above;

R_1 is a group of formula $-CHR_4R_5$ wherein R_4 and R_5 are, each independently, hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur; or R_1 is a group of formula -NHR',

-NR'COR", -NR'CONHR" or -NR'SO_2R", wherein R' has the above reported meanings other than hydrogen, and R" is hydrogen or has the meanings set forth above for R';

R_2 is a hydrogen atom or it is a group, optionally further substituted, selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur;

any R_3, being placed in one or more of the free positions 5, 6 and 8 of the phthalazinone ring are, independently from each other, halogen, nitro, carboxy, cyano or a group optionally further substituted selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur; or R_3 is a group selected from -COR', -CONHR', -SO_2R', -NR'R", -NR'COR", -NR'CONHR' or -NR'SO_2R", wherein R' and R" are, the same or different, hydrogen or a group as set forth above;

m is 0 or an integer from 1 to 3;

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method for treating diseases caused by and/or associated with an altered protein kinase activity, wherein the method comprises administering to a mammal in need thereof an effective amount of the compound.

2. The use of claim 1 wherein the disease caused by and/or associated with an altered protein kinase activity is a cell proliferative disorder selected from the group consisting of cancer, Alzheimer's disease, viral infections, auto-immune diseases and neurodegenerative disorders.

3. The use of claim 2 wherein the cancer is selected from carcinoma, squamous cell carcinoma, hematopoietic tumors of lymphoid or myeloid lineage, tumors of mesenchymal origin, tumors of the central and peripheral nervous system, melanoma, seminoma, teratocarcinoma,

osteosarcoma, xeroderma pigmentosum, keratocanthoma, thyroid follicular cancer and Kaposi's sarcoma.

4. The use of claim 2 wherein the cell proliferative disorder is selected from benign prostate hyperplasia, familial adenomatosis, polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis.

5. The use of claim 1 wherein the method provides tumor angiogenesis and metastasis inhibition.

6. The use of claim 1 wherein the method further comprises subjecting the mammal in need thereof to a radiation therapy or chemotherapy regimen in combination with at least one cytostatic or cytotoxic agent.

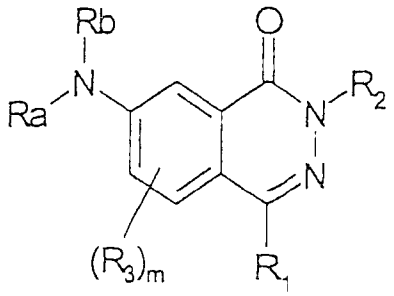
7. The use of claim 1 wherein the mammal in need thereof is a human.

8. The use of claim 1 wherein, within the compounds of formula (I), one of Ra and Rb is a hydrogen atom and the other is a group -COR', -CONHR', -COOR' or $-SO_2R'$, wherein R' is as defined in claim 1.

9. The use of claim 1 wherein, within the compounds of formula (I), one of Ra and Rb is a hydrogen atom and the other is a group -COR', -CONHR', -COOR' or $-SO_2R'$, R_2 is hydrogen, m is 0 and R_1 and R' are as defined in claim 1.

10. The use of a compound as defined in claim 1 in the manufacture of a medicament for use in a method for inhibiting protein kinase activity, wherein the method comprises contacting the said kinase with an effective amount of the compound.

11. An amino-phthalazinone derivative represented by formula (I)



(I)

wherein

Ra and Rb are, each independently, a hydrogen atom or a group, optionally further substituted, selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur; or one of Ra or Rb is hydrogen or an optionally substituted straight or branched C_1-C_6 alkyl group, and the other is a group selected from -COR', -CONHR', -COOR' or $-SO_2R'$, wherein R' is hydrogen or an optionally substituted group selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl, as set forth above;

R_1 is a group of formula $-CHR_4R_5$ wherein R_4 and R_5 are, each independently, hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur; or R_1 is a group of formula $-NHR^1$, -NR'COR", -NR'CONHR" or $-NR'SO_2R"$, wherein R' has the above reported meanings other than hydrogen, and R" is hydrogen or has the meanings set forth above for R';

R_2 is a hydrogen atom or it is a group, optionally further substituted, selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6

alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur;
any R_3, being placed in one or more of the free positions 5, 6 and 8 of the phthalazinone ring are, independently from each other, halogen, nitro, carboxy, cyano or a group optionally further substituted selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur; or R_3 is a group selected from -COR', -CONHR', -SO_2R', -NR'R", -NR'COR", -NR'CONHR' or -NR'SO_2R", wherein R' and R" are, the same or different, hydrogen or a group as set forth above;
m is 0 or an integer from 1 to 3;
or a pharmaceutically acceptable salt thereof;
the compounds N-[3,4-dihydro-4-oxo-1-(4-pyridinylmethyl)-6-phthalazinyl]-acetamide and N-[3,4-dihydro-4-oxo-1-(4-pyridinylmethyl)-6-phthalazinyl]-2,2,2-trifluoro-acetamide, being excluded.

12. A compound of formula (I) according to claim 11 wherein one of Ra or Rb is a hydrogen atom or an optionally substituted straight or branched C_1-C_6 alkyl group and the other is a group -COR' wherein R' is an optionally substituted group selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl, as defined in claim 11, and R_1, R_2, R_3 and m are as defined in claim 11.

13. A compound of formula (I) according to claim 12 wherein R_1 is a group -CHR_4R_5 wherein R_4 and R_5 are as defined in claim 11, R_2 is hydrogen and m is 0.

14. A compound of formula (I) according to claim 11 wherein one of Ra or Rb is a hydrogen atom or an optionally substituted straight or branched C_1-C_6 alkyl group and the

other is a group -CONHR' wherein R' is a hydrogen atom or an optionally substituted group selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl, as defined in claim 11, and R_1, R_2, R_3 and m are as defined in claim 11.

15. A compound of formula (I) according to claim 14 wherein R_1 is a group $-CHR_4R_5$ wherein R_4 and R_5 are as defined in claim 11, R_2 is hydrogen and m is 0.

16. A compound of formula (I) according to claim 11 wherein one of Ra or Rb is a hydrogen atom or an optionally substituted straight or branched C_1-C_6 alkyl group and the other is a group -COOR' wherein R' is a hydrogen atom or an optionally substituted group selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl, as defined in claim 11, and R_1, R_2, R_3 and m are as defined in claim 11.

17. A compound of formula (I) according to claim 16 wherein R_1 is a group $-CHR_4R_5$ wherein R_4 and R_5 are as defined in claim 11, R_2 is hydrogen and m is 0.

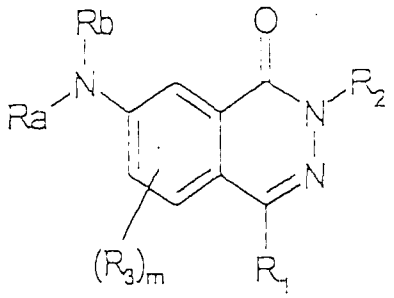
18. A compound of formula (I) according to claim 11 wherein one of Ra or Rb is a hydrogen atom or an optionally substituted straight or branched C_1-C_6 alkyl group and the other is a group $-SO_2R'$ wherein R' is an optionally substituted group selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl, as defined in claim 11, and R_1, R_2, R_3 and m are as defined in claim 11.

19. A compound of formula (I) according to claim 18 wherein R_1 is a group $-CHR_4R_5$ wherein R_4 and R_5 are as defined in claim 11, R_2 is hydrogen and m is 0.

20. A compound of formula (I) according to claim 11 wherein Ra and Rb are both hydrogen atoms and R_1, R_2, R_3 and m are as defined in claim 11.

21. A compound of formula (I) according to claim 20 wherein R_1 is a group $-CHR_4R_5$ wherein R_4 and R_5 are as defined in claim 11, R_2 is hydrogen and m is 0.

22. An amino-phthalazinone derivative represented by formula (I)



(I)

wherein one of Ra or Rb is a hydrogen atom or an optionally substituted straight or branched C_1 - C_6 alkyl and the other is a group, optionally further substituted, selected from alkyl, cycloalkylalkyl, arylalkyl or heterocyclylalkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur;

R_1 is a group of formula $-CHR_4R_5$ wherein R_4 and R_5 are, each independently, hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur; or R_1 is a group of formula -NHR', - NR'COR",- NR'CONHR"or-NR'SO_2R", wherein R' is an optionally substituted group selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl, as set forth above, and R" is hydrogen or has the meanings set forth above for R';

R_2 is a hydrogen atom or it is a group, optionally further substituted, selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur;
any R_3, being placed in one or more of the free positions 5, 6 and 8 of the phthalazinone ring are, independently from each other, halogen, nitro, carboxy, cyano or a group optionally further substituted selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur; or R_3 is a group selected from -COR', -CONHR', -SO_2R', -NR'R", -NR'COR", -NR'CONHR' or -NR'SO_2R", wherein R' and R" are, the same or different, hydrogen or a group as set forth above;
m is 0 or an integer from 1 to 3;
or a pharmaceutically acceptable salt thereof;
the compounds N-[3,4-dihydro-4-oxo-1-(4-pyridinylmethyl)-6-phthalazinyl]-acetamide and N-[3,4-dihydro-4-oxo-1-(4-pyridinylmethyl)-6-phthalazinyl]-2,2,2-trifluoro-acetamide, being excluded.

23. A compound of formula (I) according to claim 22 wherein R_1 is a group -CHR_4R_5 wherein R_4 and R_5 are as above defined, R_2 is hydrogen and m is 0.

24. A compound of formula (I) as defined in claim 11, optionally in the form of a pharmaceutically acceptable salt, selected from:
1. 4-(4-Oxo-6-propionylamino-3,4-dihydro-phthalazin-1-ylmethyl)-benzoic acid methyl ester;

2. 4-[4-Oxo-6-(4-trifluoromethyl-benzoylamino)-3,4-dihydro-phthalazin-1-ylmethyl]-benzoic acid methyl ester;
3. 4-{6-[(Furan-2-carbonyl)-amino]-4-oxo-3,4-dihydro-phthalazin-1-ylmethyl}-benzoic acid methyl ester;
4. 4-[6-(3,4-Dimethoxy-benzoylamino)-4-oxo-3,4-dihydro-phthalazin-1-ylmethyl]-benzoic acid methyl ester;
5. 4-[6-(3-Cyclopentyl-propionylamino)-4-oxo-3,4-dihydro-phthalazin-1-ylmethyl]-benzoic acid methyl ester;
6. 4-[4-Oxo-6-(2-propyl-pentanoylamino)-3,4-dihydro-phthalazin-1-ylmethyl]-benzoic acid methyl ester;

7. 4-{4-Oxo-6-[3-(3-trifluoromethyl-phenyl)-ureido]-3,4-dihydro-phthalazin-1-ylmethyl}-benzoic acid methyl ester;
8. 4-{6-[3-(3-Methoxy-phenyl)-ureido]-4-oxo-3,4-dihydro-phthalazin-1-ylmethyl}-benzoic acid methyl ester;
9. 4-[4-Oxo-6-(3-p-tolyl-ureido)-3,4-dihydro-phthalazin-1-ylmethyl]-benzoic acid methyl ester;
10. 4-{6-[3-(2,4-Difluoro-phenyl)-ureido]-4-oxo-3,4-dihydro-phthalazin-1-ylmethyl}-benzoic acid methyl ester;
11. 4-{6-[3-(3,4-Dichloro-phenyl)-ureido]-4-oxo-3,4-dihydro-phthalazin-1-ylmethyl}-benzoic acid methyl ester;
12. 4-[4-Oxo-6-(3-pyridin-3-yl-ureido)-3,4-dihydro-phthalazin-1-ylmethyl]-benzoic acid methyl ester;
13. 4-(6-Amino-4-oxo-3,4-dihydro-phthalazin-1-ylmethyl)-benzoic acid methyl ester;
14. N-[1-(4-Chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-propionamide;
15. N-[1-(4-Chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide;
16. Furan-2-carboxylic acid [1-(4-chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;
17. N-[1-(4-Chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3,4-dimethoxy-benzamide;
18. N-[1-(4-Chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide;
19. 2-Propyl-pentanoic acid [1-(4-chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;
20. 1-[1-(4-Chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea;
21. 1-[1-(4-Chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-methoxy-phenyl)-urea;
22. 1-[1-(4-Chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea;
23. 1-[1-(4-Chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea;
24. 1-[1-(4-Chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3,4-dichloro-phenyl)-urea;

25. 1-[1-(4-Chloro-3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-pyridin-3-yl-urea;

26. 7-Amino-4-(4-chloro-3-fluoro-benzyl)-2H-phthalazin-1-one;

27. N-{1-[(E)-3-(4-Nitro-phenyl)-allyl]-4-oxo-3,4-dihydro-phthalazin-6-yl}-propionamide;

28. N-{1-[(E)-3-(4-Nitro-phenyl)-allyl]-4-oxo-3,4-dihydro-phthalazin-6-yl}- 4-trifluoromethyl-benzamide;

29. Furan-2-carboxylic acid {1-[(E)-3-(4-nitro-phenyl)-allyl]-4-oxo-3,4-dihydro-phthalazin-6-yl}-amide;

30. N-{1-[(E)-3-(4-Nitro-phenyl)-allyl]-4-oxo-3,4-dihydro-phthalazin-6-yl}-3,4-dimethoxy-benzamide;

31. N-{1-[(E)-3-(4-Nitro-phenyl)-allyl]-4-oxo-3,4-dihydro-phthalazin-6-yl}-3-cyclopentyl-propionamide;

32. 2-Propyl-pentanoic acid {1-[(E)-3-(4-nitro-phenyl)-allyl]-4-oxo-3,4-dihydro-phthalazin-6-yl}-amide;

33. 1-{1-[(E)-3-(4-Nitro-phenyl)-allyl]-4-oxo-3,4-dihydro-phthalazin-6-yl}-3-(3-trifluoromethyl-phenyl)-urea;

34. 1-{1-[(E)-3-(4-Nitro-phenyl)-allyl]-4-oxo-3,4-dihydro-phthalazin-6-yl}-(3-methoxy-phenyl)-urea;

35. 1-{1-[(E)-3-(4-Nitro-phenyl)-allyl]-4-oxo-3,4-dihydro-phthalazin-6-yl}-3-p-tolyl-urea;

36. 1-{1-[(E)-3-(4-Nitro-phenyl)-allyl]-4-oxo-3,4-dihydro-phthalazin-6-yl}-3-(2,4-difluoro-phenyl)-urea;

37. 1-{1-[(E)-3-(4-Nitro-phenyl)-allyl]-4-oxo-3,4-dihydro-phthalazin-6-yl}-3-(3,4-dichloro-phenyl)-urea;

38. 1-{1-[(E)-3-(4-Nitro-phenyl)-allyl]-4-oxo-3,4-dihydro-phthalazin-6-yl}-3-pyridin-3-yl-urea;

39. 7-Amino-4-[(E)-3-(4-nitro-phenyl)-allyl]-2H-phthalazin-1-one;

40. N-(4-Oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-propionamide;

41. N-(4-Oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-4-trifluoromethyl-benzamide;

42. Furan-2-carboxylic acid (4-oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-amide;

43. N-(4-Oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3,4-dimethoxy-benzamide;

44. N-(4-Oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-cyclopentyl-propionamide;

45. 2-Propyl-pentanoic acid (4-oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-amide;

46. 1-(4-Oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-(3-trifluoromethyl-phenyl)-urea;

47. 1-(4-Oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-(3-methoxy-phenyl)-urea;

48. 1-(4-Oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-p-tolyl-urea;

49. 1-(4-Oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-(2,4-difluoro-phenyl)-urea;

50. 1-(4-Oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-(3,4-dichloro-phenyl)-urea;

51. 1-(4-Oxo-1-thiophen-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-pyridin-3-yl-urea;

52. 7-Amino-4-thiophen-3-ylmethyl-2H-phthalazin-1-one;

53. N-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-propionamide;

54. N-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide;

55. Furan-2-carboxylic acid [1-(3-methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;

56. N-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3,4-dimethoxy-benzamide;

57. N-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide;

58. 2-Propyl-pentanoic acid [1-(3-methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;

59. 1-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea;

60. 1-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-(3-methoxy-phenyl)-urea;

61. 1-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea;

62. 1-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea;

63. 1-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3,4-dichloro-phenyl)-urea;

64. 1-[1-(3-Methoxy-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-pyridin-3-yl-urea;

65. 7-Amino-4-(3-methoxy-benzyl)-2H-phthalazin-1-one;

66. N-(4-Oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-propionamide;

67. N-(4-Oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-4-trifluoromethyl-benzamide;

68. Furan-2-carboxylic acid (4-oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-amide;

69. N-(4-Oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-3,4-dimethoxy-benzamide;

70. N-(4-Oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-3-cyclopentyl-propionamide;

71. 2-Propyl-pentanoic acid (4-oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-amide;

72. 1-(4-Oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-3-(3-trifluoromethyl-phenyl)-urea;

73. 1-(4-Oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-(3-methoxy-phenyl)-urea;

74. 1-(4-Oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-3-p-tolyl-urea;

75. 1-(4-Oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-3-(2,4-difluoro-phenyl)-urea;

76. 1-(4-Oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-3-(3,4-dichloro-phenyl)-urea;

77. 1-(4-Oxo-1-propyl-3,4-dihydro-phthalazin-6-yl)-3-pyridin-3-yl-urea;

78. 7-Amino-4-propyl-2H-phthalazin-1-one;

79. N-[1-(3,3-Dimethyl-butyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-propionamide;

80. N-[1-(3,3-Dimethyl-butyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide;
81. Furan-2-carboxylic acid [1-(3,3-dimethyl-butyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;
82. N-[1-(3,3-Dimethyl-butyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3,4-dimethoxy-benzamide;
83. N-[1-(3,3-Dimethyl-butyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide;
84. 2-Propyl-pentanoic acid [1-(3,3-dimethyl-butyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;
85. 1-[1-(3,3-Dimethyl-butyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea;
86. 1-[1-(3,3-Dimethyl-butyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-(3-methoxy-phenyl)-urea;
87. 1-[1-(3,3-Dimethyl-butyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea;
88. 1-[1-(3,3-Dimethyl-butyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea;
89. 1-[1-(3,3-Dimethyl-butyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3,4-dichloro-phenyl)-urea;
90. 1-[1-(3,3-Dimethyl-butyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-pyridin-3-yl-urea;
91. 7-Amino-4-(3,3-dimethyl-butyl)-2H-phthalazin-1-one;
92. N-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-propionamide;
93. N-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide;
94. Furan-2-carboxylic acid [4-oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-amide;
95. N-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-3,4-dimethoxy-benzamide;
96. N-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide;
97. 2-Propyl-pentanoic acid [4-oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-amide;

98. 1-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea;

99. 1-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-(3-methoxy-phenyl)-urea;

100. 1-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea;

101. 1-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea;

102. 1-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-3-(3,4-dichloro-phenyl)-urea;

103. 1-[4-Oxo-1-(3-phenyl-propyl)-3,4-dihydro-phthalazin-6-yl]-3-pyridin-3-yl-urea;

104. 7-Amino-4-(3-phenyl-propyl)-2H-phthalazin-1-one;

105. N-(4-Oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-propionamide;

106. N-(4-Oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-4-trifluoromethyl-benzamide;

107. Furan-2-carboxylic acid (4-oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-amide;

108. N-(4-Oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-succinamic acid ethyl ester;

109. N-(4-Oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-cyclopentyl-propionamide;

110. 2-Propyl-pentanoic acid (4-oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-amide;

111. 1-(4-Oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-(3-trifluoromethyl-phenyl)-urea;

112. 1-(3-Methoxy-phenyl)-3-(4-oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-urea;

113. 1-(4-Oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-p-tolyl-urea;

114. 1-(2,4-Difluoro-phenyl)-3-(4-oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-urea;

115. 1-(3,4-Dichloro-phenyl)-3-(4-oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-urea;

116. 1-(4-Oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-pyridin-3-yl-urea;

117. 7-Amino-4-pyridin-3-ylmethyl-2H-phthalazin-1-one

118. N-(4-Oxo-1-pyridin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-benzamide;

119. N-[1-(4-Chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-propionamide;

120. N-[1-(4-Chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide;

121. Furan-2-carboxylic acid [1-(4-chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;

122. N-[1-(4-Chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-succinamic acid ethyl ester;

123. N-[1-(4-Chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide;

124. 2-Propyl-pentanoic acid [1-(4-chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;

125. 1-[1-(4-Chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea;

126. 1-[1-(4-Chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-methoxy-phenyl)-urea;

127. 1-[1-(4-Chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea;

128. 1-[1-(4-Chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea;

129. 1-[1-(4-Chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3,4-dichloro-phenyl)-urea;

130. 1-[1-(4-Chloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-pyridin-3-yl-urea;

131. 7-Amino-4-(4-Chloro-benzyl)-2H-phthalazin-1-one;

132. N-[1-(4-Cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-propionamide;

133. N-[1-(4-Cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide;

134. Furan-2-carboxylic acid [1-(4-cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;

135. N-[1-(4-Cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-succinamic acid ethyl ester;

136. N-[1-(4-Cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide;

137. 2-Propyl-pentanoic acid [1-(4-cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;

138. 1-[1-(4-Cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea;

139. 1-[1-(4-Cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-methoxy-phenyl)-urea;

140. 1-[1-(4-Cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea;

141. 1-[1-(4-Cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea;

142. 1-[1-(4-Cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3,4-dichloro-phenyl)-urea;

143. 1-[1-(4-Cyano-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-pyridin-3-yl-urea;

144. 7-Amino-4-(4-Cyano-benzyl)-2H-phthalazin-1-one;

145. N-[1-(3-Fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-propionamide;

146. N-[1-(3-Fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide;

147. Furan-2-carboxylic acid [1-(3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;

148. N-[1-(3-Fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-succinamic acid ethyl ester;

149. N-[1-(3-Fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide;

150. 2-Propyl-pentanoic acid [1-(3-fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;

151. 1-[1-(3-Fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea;

152. 1-[1-(3-Fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-methoxy-phenyl)-urea;

153. 1-[1-(3-Fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea;

154. 1-[1-(3-Fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea;

155. 1-[1-(3-Fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3,4-dichloro-phenyl)-urea;

156. 1-[1-(3-Fluoro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-pyridin-3-yl-urea;

157. 7-Amino-4-(3-Fluoro-benzyl)-2H-phthalazin-1-one;

158. N-[1-(3-Methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-propionamide;

159. N-[1-(3-Methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide;

160. Furan-2-carboxylic acid [1-(3-methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;

161. N-[1-(3-Methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-succinamic acid ethyl ester;

162. N-[1-(3-Methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide;

163. 2-Propyl-pentanoic acid [1-(3-methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;

164. 1-[1-(3-Methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea;

165. 1-[1-(3-Methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-methoxy-phenyl)-urea;

166. 1-[1-(3-Methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea;

167. 1-[1-(3-Methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea;

168. 1-[1-(3-Methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3,4-dichloro-phenyl)-urea;

169. 1-[1-(3-Methyl-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-pyridin-3-yl-urea;

170. 7-Amino-4-(3-Methyl-benzyl)-2H-phthalazin-1-one;

171. N-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-propionamide;

172. N-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide;

173. Furan-2-carboxylic acid [1-(2,4-dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;

174. N-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-succinamic acid ethyl ester;

175. N-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide;

176. 2-Propyl-pentanoic acid [1-(2,4-dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-amide;

177. 1-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea;

178. 1-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3-methoxy-phenyl)-urea;

179. 1-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea;

180. 1-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea;

181. 1-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-(3,4-dichloro-phenyl)-urea;

182. 1-[1-(2,4-Dichloro-benzyl)-4-oxo-3,4-dihydro-phthalazin-6-yl]-3-pyridin-3-yl-urea;

183. 7-Amino-4-(2,4-dichloro-benzyl)-2H-phthalazin-1-one;

184. N-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-propionamide;

185. N-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-4-trifluoromethyl-benzamide;

186. Furan-2-carboxylic acid (4-oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-amide;

187. N-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-succinamic acid ethyl ester;

188. N-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-cyclopentyl-propionamide;

189. 2-Propyl-pentancic acid (4-oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-amide;

190. 1-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-(3-trifluoromethyl-phenyl)-urea;

191. 1-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-(3-methoxy-phenyl)-urea;

192. 1-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-p-tolyl-urea;

193. 1-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-(2,4-difluoro-phenyl)-urea;

194. 1-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-(3,4-dichloro-phenyl)-urea;

195. 1-(4-Oxo-1-quinolin-3-ylmethyl-3,4-dihydro-phthalazin-6-yl)-3-pyridin-3-yl-urea;

196. 7-Amino-4-quinolin-3-ylmethyl-2H-phthalazin-1-one;

197. N-[4-Oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-propionamide;

198. N-[4-Oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-4-trifluoromethyl-benzamide;

199. Furan-2-carboxylic acid [4-oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-amide;

200. N-[4-Oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-succinamic acid ethyl ester;

201. N-[4-Oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-3-cyclopentyl-propionamide;

202. 2-Propyl-pentanoic acid [4-oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-amide;

203. 1-[4-Oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-3-(3-trifluoromethyl-phenyl)-urea;

204. 1-[4-Oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-3-(3-methoxy-phenyl)-urea;

205. 1-[4-Oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-3-p-tolyl-urea;

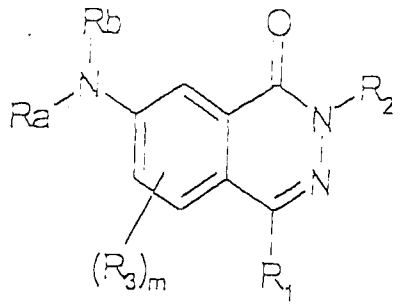
206. 1-[4-Oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-3-(2,4-difluoro-phenyl)-urea;

207. 1-[4-Oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-3-(3,4-dichloro-phenyl)-urea;

208. 1-[4-Oxo-1-(2-trifluoromethyl-benzyl)-3,4-dihydro-phthalazin-6-yl]-3-pyridin-3-yl-urea;

209. 7-Amino-4-(2-trifluoromethyl-benzyl)-2H-phthalazin-1-one.

25. A process for preparing an amino-phthalazinone derivative represented by formula (I)



(I)

wherein

Ra and Rb are, each independently, a hydrogen atom or a group, optionally further substituted, selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur; or one of Ra or Rb is hydrogen or an optionally substituted straight or branched C_1-C_6 alkyl group, and the other is a group selected from -COR', -CONHR', -COOR'or -SO2R', wherein R' is hydrogen or an optionally substituted group selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl, as set forth above;

R_1 is a group of formula-CHR_4R_5 wherein R_4 and R_5 are, each independently, hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl

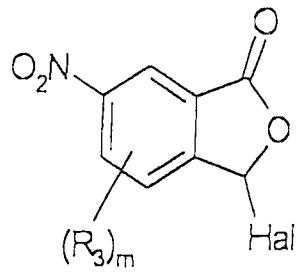
C_1-C_6 alkyl, 5 to 7 membered heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur; or R_1 is a group of formula -NHR', - NR'COR", -NR'CONHR" or -NR'SO_2R", wherein R' has the above reported meanings other than hydrogen, and R" is hydrogen or has the meanings set forth above for R';

R_2 is a hydrogen atom or it is a group, optionally further substituted, selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur;

any R_3, being placed in one or more of the free positions 5, 6 and 8 of the phthalazinone ring are, independently from each other, halogen, nitro, carboxy, cyano or a group optionally further substituted selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur; or R_3 is a group selected from -COR',-CONHR', -SO_2R', -NR'R",-NR'COR", -NR'CONHR'or-NR'SO_2R", wherein R' and R" are, the same or different, hydrogen or a group as set forth above; m is 0 or an integer from 1 to 3; or a pharmaceutically acceptable salt thereof; the compounds N- [3,4-dihydro-4-oxo-1- (4-pyridinylmethyl)-6-phthalazinyl]-acetamide and N- [3, 4-dihydro-4-oxo-1- (4-pyridinylmethyl)-6-phthalazinyl]-2, 2,2-trifluoro-acetamide, being excluded,

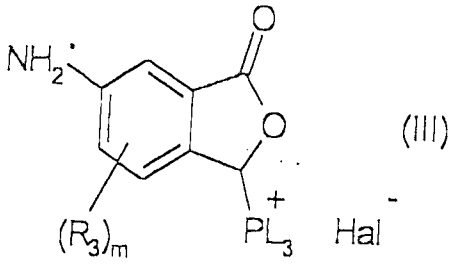
which process comprises:

a) reacting a compound of formula (II)



(II)

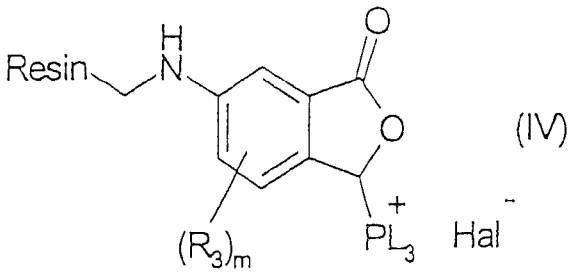
wherein R_3 and m are as above defined and Hal represents a halogen atom, with a suitable phosphine derivative (PL_3), under optional reductive conditions, so as to obtain a compound of formula(III)



(III)

wherein P is a phosphorous atom and L are the phosphine ligands;

b) reacting the compound of formula (III) with an aldehydic Resin-CHO, in the presence of a suitable reducing agent, so as to obtain a resin supported compound of formula (IV)



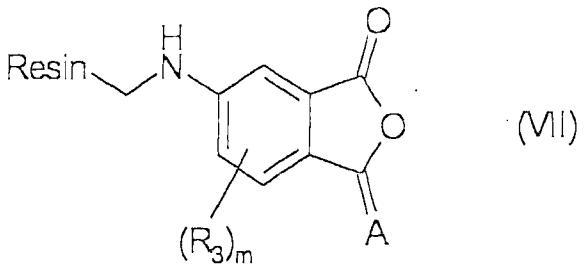
(IV)

wherein R_3, m, P, L, Hal and the Resin are as above defined;

c) reacting the compound of formula (IV) with a carbonyl derivative of formula (V) or a nitroso derivative of formula (VI)

R_4-CO-R_5 (V) R'-NO (VI)

wherein R_4, R_5 and R^1 are as above defined; so as to obtain the compound of formula (VII)



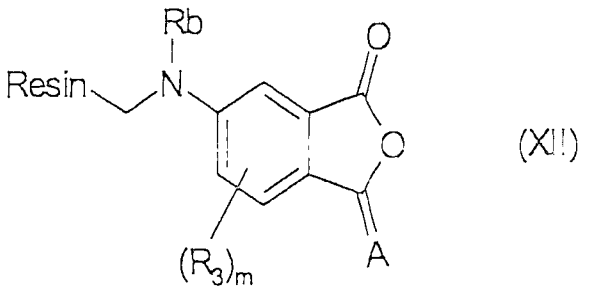
(VII)

wherein A is a group $=CR_4R_5$ or $=NR^1$, respectively; and optionally reacting the compound of formula (VII) according to any one of the alternative steps d.1) or d.2) below

d.1) with one of the derivatives of formula (VIII), (IX), (X) or (XI), under optional basic conditions,

R'COZ (VIII), R'NCO (IX), R'OCOZ (X), $R'SO_2Z$ (XI)

wherein Z is a halogen atom or a suitable leaving group and R^1 is as above defined, so as to obtain the compound of formula (XII)



(XII)

wherein Rb is -COR', -CONHR', -COOR' or $-SO_2R'$, respectively; or

d.2) with a compound of formula (XIII)

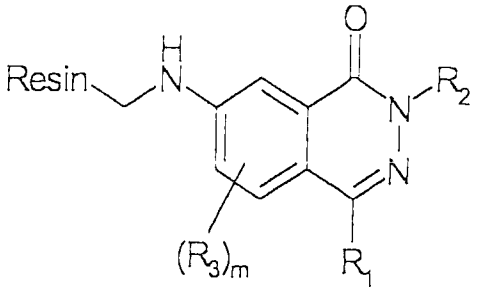
$$Rb\text{-}Z \quad (XIII)$$

wherein Z is a halogen atom and Rb is alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl as above defined, so as to obtain the corresponding compound of the above formula (XII);

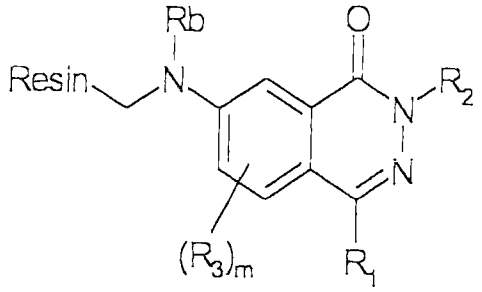
e) reacting the thus obtained compounds of formula (VII) or (XII) with a hydrazine derivative of formula (XIV)

$$R_2\text{-}NH\text{-}NH_2 \quad (XIV)$$

wherein R_2 is as above defined, so as to obtain the compounds of formula (XV) or (XVI), respectively



(XV)



(XVI)

wherein Rb, R_2, R_3, m and the Resin are as above defined and R_1 is a group of formula $-CHR_4R_5$ or -NHR' wherein R_4, R_5 and R' are as above defined;

f) reacting the compounds of formula (XV) or (XVI) under acidic conditions so as to obtain the compound of formula (I) and, whenever desired, converting it into another compound of formula (I) and/or into a pharmaceutically acceptable salt thereof.

26. The process of claim 25 wherein, in step a), the phosphine derivative is triphenylphosphine PPh_3.

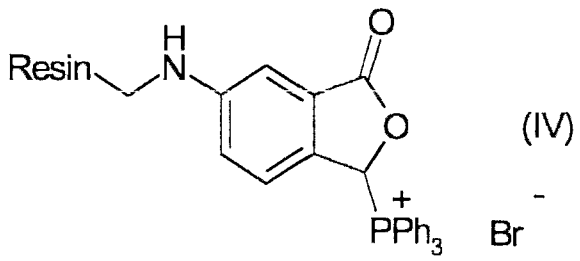
27. The process of claim 25 wherein, in step b), the reducing agent is selected from pyridine-borane complex,

sodium cyanoboron hydride, sodium triacetate boron hydride or dimethylsufide borane.

28. The process of claim 25 wherein, in step d.1), it is used a compound of formula (VIII), (X) or (XI), wherein Z is a chlorine atom.

29. The process of claim 25 wherein, in step f), acidic conditions are reached by using trifluoroacetic acid.

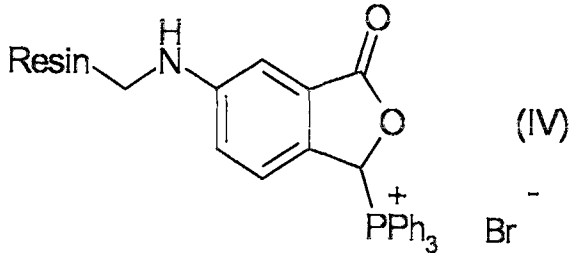
30. Any specific compound of formula (I), as defined in claim 11, which is obtainable, for instance through a combinatorial chemistry technique according to the process as set forth in claim 25, by first reacting the compound of formula (IV)



(IV)

with each one of the aldehyde derivatives of formula (V), as set forth in *table I*; by reacting any of the resultant compounds of formula (VII) with each one of the acyl chloride derivatives of formula (VIII), as set forth in *table II*; by reacting any of the resultant compounds of formula (XII) with hydrazine; and by working according to step f) of the process of claim 25.

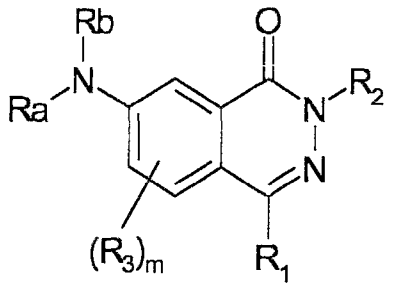
31. Any specific compound of formula (I), as defined in claim 11, which is obtainable, for instance through a combinatorial chemistry technique according to the process as set forth in claim 25, by first reacting the compound of formula (IV)



(IV)

with each one of the aldehyde derivatives of formula (V), as set forth in *table I*; by reacting any of the resultant compounds of formula (VII) with each one of the isocyanate derivatives of formula (IX), as set forth in *table III*; by reacting any of the resultant compounds of formula (XII) with hydrazine; and by working according to step f) of the process of claim 25.

32. A library of two or more amino-phthalazinone derivatives of formula (I)



(I)

wherein

Ra and Rb are, each independently, a hydrogen atom or a group, optionally further substituted, selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur; or one of Ra or Rb is hydrogen or an optionally substituted straight or branched C_1-C_6 alkyl group, and the other is a group selected from -COR', -CONHR', -COOR' or $-SO_2R'$, wherein R' is hydrogen or an optionally substituted group selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl, as set forth above;

R_1 is a group of formula $-CHR_4R_5$ wherein R_4 and R_5 are, each independently, hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur; or R_1 is a group of formula -NHR', -NR'COR", -NR'CONHR" or $-NR'SO_2R"$, wherein R' has the above reported meanings other than hydrogen, and R" is hydrogen or has the meanings set forth above for R';

R_2 is a hydrogen atom or it is a group, optionally further substituted, selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur;

any R_3, being placed in one or more of the free positions 5, 6 and 8 of the phthalazinone ring are, independently from each other, halogen, nitro, carboxy, cyano or a group optionally further substituted selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 to 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur; or R_3 is a group selected from -COR', -CONHR', $-SO_2R'$, -NR'R", -NR'COR", -NR'CONHR' or $-NR'SO_2R"$, wherein R' and R" are, the same or different, hydrogen or a group as set forth above;

m is 0 or an integer from 1 to 3;

or a pharmaceutically acceptable salt thereof.

33. A pharmaceutical composition comprising an effective amount of a compound of formula (I) as defined in claim 11 and, at least, one pharmaceutically acceptable excipient, carrier or diluent.

34. A pharmaceutical composition according to claim 33 further comprising one or more chemotherapeutic agents, as a combined preparation for simultaneous, separate or sequential use in anticancer therapy.

35. A product or kit comprising a compound of claim 11 or a pharmaceutical composition thereof as defined in claim 33, and one or more chemotherapeutic agents, as a combined preparation for simultaneous, separate or sequential use in anticancer therapy.

36. A compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 11, for use as a medicament.

37. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 11, in the manufacture of a medicament for treating diseases caused by and/or associated with an altered protein kinase activity.

38. Use according to claim 37 for treating tumors.