AMINOINDAZOLE DERIVATIVES ACTIVE AS KINASE INHIBITORS, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

The present invention relates to aminoindazole derivatives active as kinase inhibitors and, more in particular, it relates to 3-amino-indazole 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 3-aminoindazole derivatives, hereinafter shortly referred to as indazole derivatives or indazoles, 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 indazoles 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 indazoles 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.

Several indazoles and aminoindazoles are known in the art as synthetic or chemical intermediates, as polymer stabilizers, as therapeutic agents and even as protein kinase inhibitors.

As an example, some alkylamino-indazoles are disclosed in US 28939 (reissue of US 3,133,081) by Smithkline Co., as endowed with muscle relaxant and analgesic activity; among them are 3-methylamino-5-trifluoromethyl-indazole and 3-diethylamino-5-trifluoromethyl-indazole.

Cyclic N,N'-urea derivatives bearing 3-aminoindazole groups are disclosed in Bioorg. Med. Chem. Lett. (1998), 8(7), 715-720 as HIV protease inhibitors.

Diaryl-urea derivatives useful in the treatment of diseases other than cancer are disclosed as p38 kinase inhibitors in WO 99/32111 by Bayer Co.; among the compounds specifically exemplified therein is N-[4-[(pyridyl-4-yl)oxy]phenyl]-N'-[6-chloro-(indazol-3-yl)]-urea.

Imidazopyridine derivatives further substituted by aryl moieties, e.g. by indazolyl-aminocarbonyl-phenyl, are disclosed as platelet-activating factor (PAF) antagonists in WO 91/17162 by Pfizer Ltd.

Indazole compounds further substituted in position 3 by groups other than amino or derivatives thereof are disclosed in WO 01/02369 by Agouron Pharmaceuticals Inc., as possessing protein kinase inhibitory activity.

Mercapto-cyanoacryloylamino- or alkylthio-cyanoacryloyl-amino-heterocycles are discloses as being useful in the treatment of disorders associated with increased cell growth in US 5,714,514 by Hoechst.

1-Acylamino-3-(N-arylsulfonyl-N-alkoxyamino)-2-hydroxy-propane derivatives, wherein the aryl moiety also comprises indazole groups, are disclosed as HIV aspartyl protease inhibitors in WO 99/65870 by Vertex Pharmaceuticals Inc.

Some other specific indazole derivatives are known as therapeutic agents: in particular, 3-[3-(morpholin-4-yl)propionylamino]-indazole, 3-(N,N,-diethylamino)-propylamino-5-methoxy-indazole, 3-[(3-methyl)morpholin-4-yl]-propylamino-5-methoxy-indazole 3-(N,N,-diethylamino)-propylamino-5-methyl-indazole and 3-[(3-methyl)morpholin-4-yl]-propylamino-5-methyl-indazole are disclosed as possessing analgesic and anti-inflammatory activity [see US 4,751,302 and JP-A-60061569 by Asahi Chemical Industry]; 3-[(2-hydroxyphenyl)carbonylamino]-indazole is disclosed as antimicrobial agent [see Pharmazie (1990), 45(6), 441-2].

Several other indazoles, mainly disclosed as chemical intermediates or for purposes other than therapeutic, e.g. polymer stabilizers, bleaching agents, dyes and the like, are known in the art.

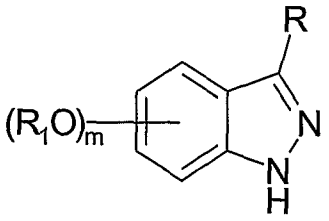
Among them are: 3-(ethoxycarbonylamino)-indazole [see Chemical Abstracts 92(1980):215400]; 3-acetylamino-indazole and 3-benzoylamino-indazole [see J. Org. Chem.(1996), 61(24), 8397-8401]; 3-butyrylamino-indazole, 3-[(4-chlorophenyl)carbonylamino]-indazole, 3-[(4-methyl-phenyl)carbonylamino]indazole and 3-[(3,3-diphenyl)propionylamino]indazole [see Acta Chim. Hung. (1990), 127(6), 795-802]; 3-[(3,5-dimethyl-isoxazol-4-yl)carbonylamino]-indazole [see J. Heterocyl. Chem. (1974), 11(4), 623-6]; 3-[(4-nitrophenyl)carbonylamino]-indazole and 3-(phenylacetylamino)-indazole [see J. Chem. Soc., Perkin Trans. 1 (1982), (3), 759-66]; 3-[(2-aminophenyl)carbonylamino]-indazole and 3-[(2-nitrophenyl)carbonylamino]-indazole [Heterocyles (1996), 43(11), 2385-2396]; 3-[(4-chloro-2-nitrophenyl)carbonyl-amino]-indazole, 3-[(2-amino-4-chlorophenyl)carbonylamino]-indazole, 3-[(2-amino-5-chlorophenyl)carbonylamino]-indazole and 3-[(3-chloro-6-nitrophenyl)carbonylamino]-indazole [see Arch. Pharm. (1999), 332 (9), 317-320]; 3-(acetylamino)-5-amino-indazole [see US 3,316,207 by Farbwerke Hoechst A.G.]; 3-dimethylamino-5-trfifluoromethyl-indazole [see DE-A-2458965 by Bayer A.G.]; 3-phenylamino-6-methyl-indazole, 3-phenylamino-, 3-(4-chloro)phenylamino-, 3-(4-methyl)phenylamino-, 3-(3-methyl)phenylamino- and 3-(4-aminosulfonyl)phenylamino-5-methyl-indazole [see Chemical Abstracts 78(1973):136158]; 3-[(1-hydroxy-2-methyl)-2-propyl]amino-6,7-dimethoxy-indazole [see US 4,864,032 by Ortho Pharmaceutical Co.].

In addition, 3-phthalimido-indazole and 4-chloro-3-phthalimido-indazole are disclosed as synthetic intermediates in the preparation of pharmaceuticals having analgesic and anti-inflammatory activity, in US 4,751,302 by Asahi Chemical Industry Co.

Sulfonylaminoindazoles and, more particularly, long chain alkyloxyphenylsulfonylamino-indazoles are disclosed as cyan dye forming compounds in JP-A-08022109, by Heisei.

Broad classes of pyrazole compounds useful as protein kinase inhibitors are also disclosed by Vertex Pharmaceuticals Inc. in a variety of patent applications such as WO 02/62789, WO 02/59112, WO 02/59111, WO 02/57259, WO 02/50066, WO 02/50065, WO 02/22608, WO 02/22607, WO 02/22606, WO 02/22605, WO 02/22604, WO 02/22603 and WO 02/22601.

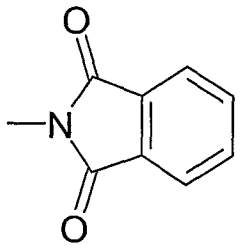
Accordingly, the present invention provides a method for treating diseases caused by and/or associated with an altered protein kinase activity, by administering to a mammal in need thereof an effective amount of an aminoindazole represented by formula (I)



(I)

wherein

R is selected from the group consisting of -NHR', -NR'R", -NHCOR', -NHCONHR', -NHCONR'R", $-NHSO_2R'$ or -NHCOOR', wherein R' and R" are, each independently, a group optionally further substituted selected from straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or alkynyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 or 6 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur; or R is a phthalimido group of formula (II) below



(II)

any R_1, if present, is in position 5 or 6 of the indazole ring and represents a group, optionally further substituted, as set forth above for R' or R";

m is 0 or 1;

or a pharmaceutically acceptable salt thereof.

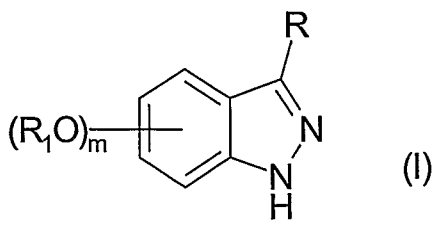
In a preferred embodiment of the method described above, the disease caused by and/or associated with an altered protein kinase activity is selected from the group consisting of cancer, cell proliferative disorders, Alzheimer's disease, viral infections, auto-immune diseases and neurodegenerative disorders.

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.

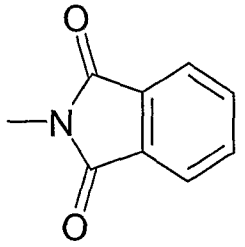
The present invention further provides an aminoindazole derivative represented by formula (I)



(I)

wherein

R is selected from the group consisting of -NHR', -NR'R", -NHCOR', -NHCONHR', -NHCONR'R", $-NHSO_2R'$ or -NHCOOR', wherein R' and R" are, each independently, a group optionally further substituted selected from straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or alkynyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 or 6 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur; or R is a phthalimido group of formula (II) below



(II)

any R_1, if present, is in position 5 or 6 of the indazole ring and represents a group, optionally further substituted, as set forth above for R' or R";

m is 0 or 1;

or a pharmaceutically acceptable salt thereof;

with the provisos that:

a) when R is -NHCOR' and m is 0, then R' is other than methyl, n-propyl, benzyl, 2,2-diphenylethyl, 3,5-dimethyl-isoxazol-4-yl, 2-(morpholin-4-yl)ethyl, or phenyl optionally substituted by chloro, hydroxy, methyl, nitro or amino;

b) when the indazole is substituted in position 5 or 6 by a methoxy group, then R is other than 3-(N,N-diethylamino)propylamino, 3-[(3-methyl)morpholin-4-yl]propylamino or 1-hydroxy-2-methyl-2-propylamino;

c) the compound 3-phthalimido-indazole 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.

In the present description, unless otherwise indicated, 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 straight or branched C_2-C_6 alkenyl or alkynyl we intend an unsaturated hydrocarbon chain having a double or triple bond such as, for instance, vinyl, ethynyl, 1-propenyl, allyl, 1- or 2-propynyl, 1-, 2- or 3-butenyl, 1-, 2- or 3-butynyl, pentenyl, pentynyl, hexenyl, hexynyl 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 or linked to each other 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, tetrazolyl, tetrazolylphenyl, pyrrolidinyl-tetrazolyl, 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 or 6 membered heterocyclyl, hence encompassing aromatic heterocyclic groups also referred to as aryl groups, we further intend a saturated or partially unsaturated 5 or 6 membered carbocycle wherein one or more carbon atoms are replaced by 1 to 3 heteroatoms such as nitrogen, oxygen and sulfur.

Examples of 5 or 6 membered heterocyclyl groups, optionally benzocondensed or further substituted, are 1,3-dioxolane, pyran, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazoline, piperidine, piperazine, morpholine, tetrahydrofuran, and the like.

According to the above meanings provided to R_1, R' and, R", 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 groups 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 halogen atom we intend a fluorine, chlorine, bromine or iodine atom.

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.

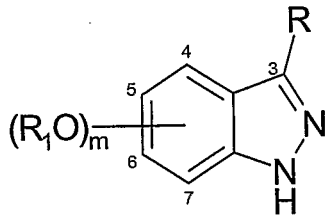
From all of the above, it is clear to the skilled man that any group which name has been identified as a composite name such as, for instance, cycloalkylalkyl, arylalkyl, heterocyclylalkyl, alkoxy, alkylthio, aryloxy, arylalkoxy, heterocyclyloxy, heterocyclylalkoxy, alkylcarbonyloxy and the like, have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

As an example, the term heterocyclyl-alkyl stands for an alkyl group being further substituted by a heterocyclyl group, as above defined.

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.

From all of the above it is clear to the skilled man that, within the compounds of formula (I), when m is 0 there are no $-OR_1$ groups, hence no R_1 groups attached to the indazole skeleton through the oxygen atom. In such a case, therefore, the positions 5 or 6 according to the numbering system reported below, are unsubstituted (or hydrogen substituted).



(I)

On the other hand, when m is 1, one $-OR_1$ group (hence R_1) is present in any one of the positions 5 or 6 of the indazole ring.

A first class of preferred compounds of the invention is represented by the compounds of formula (I) wherein R is a group -NHR' or -NR'R" and R', R", R_1 and m are as above defined.

More preferred, within this class, are the compounds wherein m is 1 and R_1 is in any one of the positions 5 or 6 of the indazole ring.

Even more preferred are the compounds wherein R_1, R' and R" are selected, each independently, from C_2-C_6 alkenyl, C_3-C_6 alkynyl, aryl, aryl C_1-C_6 alkyl, 5 or 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur.

Another class of preferred compounds of the invention is represented by the compounds of formula (I) wherein R is a group -NHCOR' and R', R_1 and m are as above defined.

More preferred, within this class, are the compounds wherein m is 1 and R_1 is in any one of the positions 5 or 6 of the indazole ring.

Even more preferred are the compounds wherein R_1 and R' are selected, each independently, from 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 or 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen, sulfur.

Another class of preferred compounds of the invention is represented by the compounds of formula (I) wherein R is a group -NHCONHR' or -NHCONR'R", and R', R", R_1 and m are as above defined.

More preferred, within this class, are the compounds wherein m is 1 and R_1 is in any one of the positions 5 or 6 of the indazole ring.

Even more preferred are the compounds wherein R_1, R' and R" are selected, each independently, from 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 or 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen and sulfur.

Another class of preferred compounds of the invention is represented by the compounds of formula (I) wherein R is a group -$NHSO_2$R' and R', R_1 and m are as above defined.

More preferred, within this class, are the compounds wherein m is 1 and R_1 is in any one of the positions 5 or 6 of the indazole ring.

Even more preferred are the compounds wherein R_1 and R' are selected, each independently, from 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 or 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen, sulfur.

Another class of preferred compounds of the invention is represented by the compounds of formula (I) wherein R is a group -NHCOOR' and R', R_1 and m are as above defined.

More preferred, within this class, are the compounds wherein m is 1 and R_1 is in any one of the positions 5 or 6 of the indazole ring.

Even more preferred are the compounds wherein R_1 and R' are selected, each independently, from 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 or 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen, sulfur.

Another class of preferred compounds of the invention is represented by the compounds of formula (I) wherein R is a phthalimido group of formula (II) and R_1 and m are as above defined.

More preferred, within this class, are the compounds wherein m is 1 and R_1 is in any one of the positions 5 or 6 of the indazole ring.

Even more preferred are the compounds wherein R_1 is selected from C_2-C_6 alkenyl, C_3-C_6 alkynyl, aryl, aryl C_1-C_6 alkyl, 5 or 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur.

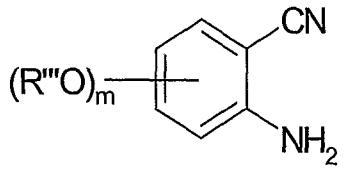
Specific examples of compounds of formula (I), optionally in the form of pharmaceutically acceptable salts, are reported in the experimental section.

As set forth above, it is a further object of the present invention a process for preparing the aminoindazole derivatives of formula (I).

Therefore, the compounds of formula (I) and the pharmaceutically acceptable salts thereof wherein R is as

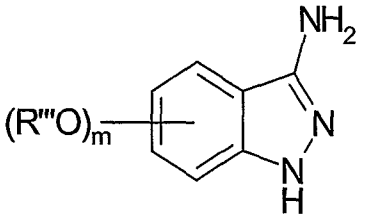
above defined but other than a phthalimido group of formula (II), may be obtained by a process comprising:

a) reacting under acidic conditions a 2-amino-benzonitrile derivative of formula (III)



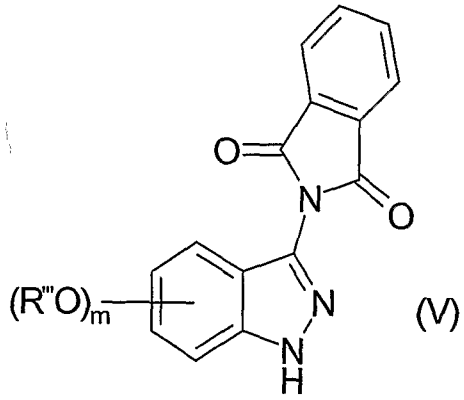
(III)

wherein m is as above defined and, if present, R''' is a methyl or benzyl group; with sodium nitrite in the presence of stannous chloride, so as to obtain a compound of formula (IV)



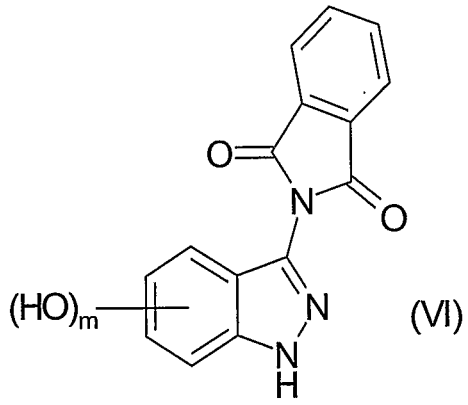
(IV)

b) reacting the compound of formula (IV) with phthalic anhydride so as to obtain a compound of formula (V)



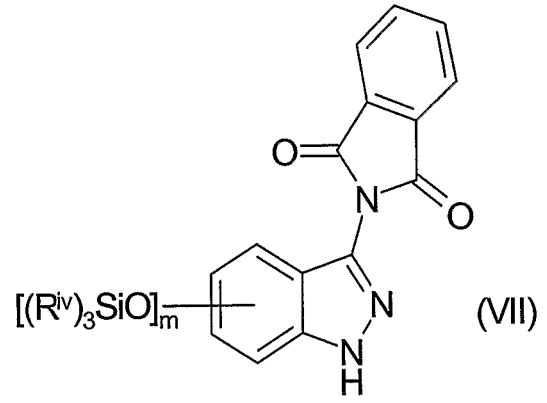
(V)

c) reacting the compound of formula (V) with a suitable ether cleaving agent so as to obtain the corresponding hydroxy derivative of formula (VI)



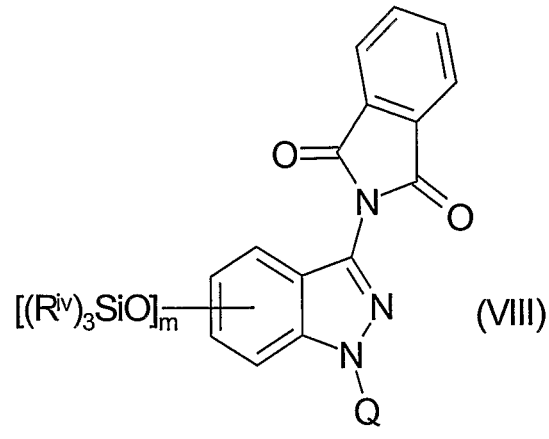
(VI)

d) reacting the compound of formula (VI) with a suitable silylating agent $(R^{iv})_3SiZ$ wherein each R^{iv} is, the same or different, a straight or branched C_1-C_4 alkyl group, and Z is a halogen atom, so as to obtain a compound of formula (VII)



(VII)

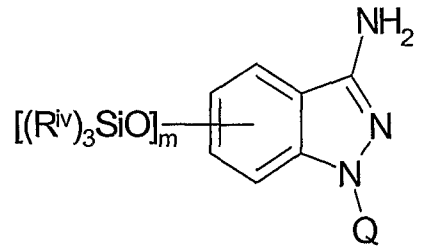
e) reacting the compound of formula (VII) with a suitable indazole nitrogen protecting agent or, alternatively, supporting it onto a suitable polymeric resin so as to obtain a compound of formula (VIII)



(VIII)

wherein Q is the above protecting group or represents the supporting resin;

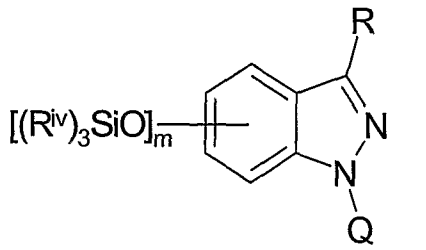
f) reacting the compound of formula (VIII) with hydrazine monohydrate so as to get the compound of formula (IX)



(IX)

and reacting the compound of formula (IX) according to any one of the following steps g.1) or g.2);

g.1) with a suitable reagent of formula R'-Z (X), R'-COZ (XI), R'-NCO (XII), R'-SO_2Z (XIII) or R'OCOZ (XIV), wherein R' is as above defined and Z represents a halogen atom or a suitable leaving group, so as to get the corresponding compound of formula (XV)



(XV)

wherein R is a group -NHR', -NHCOR', -NHCONHR', -$NHSO_2$R' or -NHCOOR' and, if desired, reacting the compounds having R as a -NHR' or -NHCONHR' group with a compound of formula

R"Z (XVI)

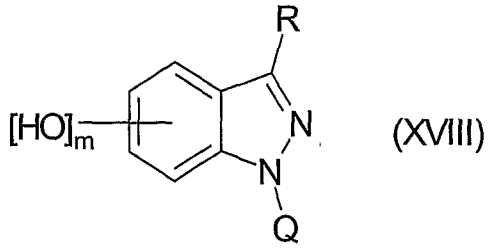
wherein R" and Z are as above defined, so as to get the compounds of formula (XV) wherein R is a group -NR'R" or -NHCONR'R";

g.2) with a compound of formula (XVII)

R'R"NH (XVII)

wherein R' and R" are as above defined, in the presence of 4-nitrophenyl chloroformate, so as to obtain the corresponding compound of formula (XV) wherein R is a group -NHCONR'R";

h) reacting any of the above compounds of formula (XV) with tetrabutylammonium fluoride so as to get the compound of formula (XVIII)

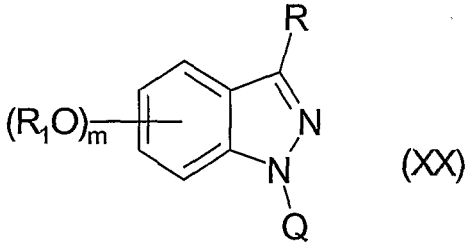


(XVIII)

i) reacting the compound of formula (XVIII) with a derivative of formula

$$R_1\text{-}Z \quad (XIX)$$

wherein R_1 is as above defined and Z is a halogen atom, a suitable leaving group or hydroxy, so as to obtain the compound of formula (XX)



(XX)

j) deprotecting the compound of formula (XX) or, alternatively, cleaving the polymeric resin so as to get the desired compound of formula (I) and, whenever desired, converting it into another compound of formula (I) and/or into a pharmaceutically acceptable salt thereof.

From all of the above, 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 (III), preferably 2-amino-4-methoxy-benzonitrile or 2-amino-5-benzyloxy-benzonitrile, is reacted with sodium nitrite. The diazonium salt is reduced in the presence of stannous chloride under acidic conditions, e.g. hydrochloric acid or sulfuric acid.
The reaction may be carried out in a mixture of water and a suitable solvent such as, for instance, methanol, ethanol and the like, at a temperature ranging from about 0°C to about 10°C.
The reaction may be performed by adding the sodium nitrite to a solution of the compound of formula (III) in concentrated hydrochloric acid, whereas stirring is maintained for a time of about 1 hour to 3 hours.
Then the suspension can be transferred dropwise into a solution of stannous chloride in concentrated hydrochloric acid and cooled at about 0°C, whereas stirring is maintained for a suitable time, for instance from about 4 hours to about 6 hours.

As per step b) of the process, the compound of formula (IV) is reacted with phthalic anhydride according to conventional methods for preparing phthalimido derivatives.
The reaction may be carried out in a variety of solvents including chloroform, acetonitrile, dioxane, tetrahydrofuran, dimethylformamide, dimethyl acetamide and the like; preferably with acetonitrile. In this respect, the phthalic anhydride is added to a solution of the compound of formula (V). The temperature is then brought to a suitable value, for instance from about 70°to about 100°C; preferably at 80°C. Stirring is carried out for a suitable time varying from about 1 hour to about 4 hours.

According to step c) of the process, the compound of formula (V) is converted into the corresponding hydroxy derivative through reaction with a suitable ether cleaving agent such as, for instance, pyridinium hydrochloride salt, iodotrimethylsilane or boron tribromide. The reaction may be carried out in neat pyridinium chloride or, with the other reagents, in dichloromethane or chloroform. Preferably, neat pyridinium chloride is used.
In this respect, the mixture of pyridinium chloride and of the compound of formula (V) is brought to a suitable temperature of from about 180°C to about 200°C whereas stirring is carried out for a time varying from about 1 hour to about 3 hours.

According to step d) of the process, the compound of formula (VI) is reacted with a silyl derivative, preferably tert-butyl-dimethyl-silyl chloride (TBDMSCl), so as to get the corresponding silyl ether derivative. The reaction may be carried out in presence of a suitable base such as, for instance, 1,5-diazabiciclo[4.3.0]non-5-ene (DBN) or, more preferably, 1,8-diazabiciclo[5.4.0]undec-7-ene (DBU).
In this respect, tert-butyl-dimethyl-silyl chloride (TBDMSCl) is added to a solution of the compound of formula (VI). The reaction may be carried out in a variety of solvents such as dichloromethane, acetonitrile, dimethylformamide and the like; dichloromethane being preferred. The temperature may vary from about 20°to about 40°C whilst stirring is maintained for a time of about 1 hour to 4 hours.

According to step e) of the process, the indazole derivative of formula (VII) thus obtained is either protected at the indazole nitrogen atom or, alternatively, is supported onto a suitable polymeric resin.
The reaction of protection may be carried out according to conventional methods well known in the art, for instance by

using suitable nitrogen protecting groups such as, for instance, tert-butoxy-carbonyl (BOC) group.

At this same position, in the alternative, the indazole of formula (VII) may be conveniently anchored to an inert polymeric support such as, for instance, the 2-chloro-trityl chloride resin, the trityl chloride resin, the p-nitrophenyl carbonate Wang resin or the bromo-4-methoxyphenyl)methyl polystyrene, which are all conventionally known in this field.

Clearly, this same option is particularly advantageous for preparing the compounds of formula (I) under solid-phase-synthesis (SPS) conditions, which are typically adopted when preparing libraries of compounds according to combinatorial chemistry techniques, for instance as reported below.

The reaction with the resin is carried out in the presence of a slight excess of a suitable base, for instance an amine, e.g. diisopropylethylamine (DIPEA), triethylamine (TEA), 1,8-diazabiciclo[5.4.0]undec-7-ene (DBU) or 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diaza-phosphorine, in a suitable solvent, for instance dichloromethane, chloroform, tetrahydrofuran, dimethylformamide, dimethylacetamide and the like.

Preferably, the reaction is carried out in dichloromethane at a temperature of about 20°C.

The reaction may be performed by adding to a suspension of the resin, the base and the compound of formula (VII), and by stirring at a temperature of about 20°C for a suitable time, for instance up to 24 hours.

According to step f) of the process, the derivative of formula (VIII) is treated with hydrazine monohydrate so as to cleave the phthalimido group.

The reaction is preferably carried out by using a large excess, for instance up to 10 equivalents, of hydrazine hydrate or monohydrate, in the presence of suitable

solvents such as, for instance, halogenated hydrocarbons, lower alcohols and admixtures thereof.
Preferred solvents are dichloromethane, ethanol and admixtures thereof.
The reaction may be carried out by adding hydrazine to a solution of the compound of formula (VIII) and by stirring for a suitable time at the temperature ranging from about 20°to about 45°C. Preferably, the reaction mixture is maintained under stirring at about 40°C for about 16 hours.

According to any one of steps g.1) or g.2) of the process, the amino derivative of formula (IX) is reacted with a suitable reagent of formula from (X) to (XIV), or with a compound of formula (XVII), according to well-known methods.
Typically, the compound of formula (IX) may be reacted with: a compound of formula (X) so as to get the corresponding -NHR' derivative wherein R' is as above defined; a compound of formula (XI) to get the corresponding -NHCOR' acyl derivative; a compound of formula (XII) to get the corresponding -NHCONHR' ureido derivative; a compound of formula (XIII) to get the corresponding $-NHSO_2R'$ derivative; a compound of formula (XIV) to get the corresponding -NHCOOR' derivative.
Alternatively, the compound of formula (IX) may be reacted with a compound of formula R'R"NH (XVII), in the presence of 4-nitrophenyl chloroformate to get the corresponding ureido -NHCONR'R" derivative.
Any one of the above reactions is carried out according to conventional methods normally used in the preparation of functionalized amino derivatives, by starting from the corresponding amine.
Preferably, within the compounds of formula (X), Z represents a suitable leaving group, for instance, iodine bromine or boronic acid; within the compounds of formula

(XI) (XIII) or (XIV), Z represents a halogen atom and, even more preferably, a chlorine atom.

In addition to the above, it is clear to the skilled man that, whenever desired, any of the above compounds of formula (XV) thus prepared and wherein R represents a group -NHR' or -NHCONHR' may be further converted into the corresponding derivative having R as a -NR'R" or -NHCONR'R" group, respectively.

Also these reactions are performed according to conventional methods by reacting the proper intermediate compound of formula (XV) with a suitable derivative of formula (XVI).

In this respect, the compound of formula (IX) is dissolved in a suitable solvent such as dichloromethane, dimethylformamide, tetrahydrofuran, dioxane or the like, and a suitable base such as triethylamine, diisopropylethylamine, sodium carbonate or the like is added. The compound of general formula (XI), (XIII) or (XIV) is then added and the mixture stirred for a time of about 2 hours to about 15 hours, at a temperature ranging from about 20°C to about 80°C. When using an isocyanate of general formula (XII), the reaction conditions are the same as above except that the base may not be required. In all of these reactions, a suitable catalyst such as dimethylamino pyridine may be optionally used.

Substantially analogous procedures may be applied when the compound of formula (XII) is reacted with a compound of formula (X) to give the corresponding functionalized amino derivative of formula (XIV), according to well known methods.

As an example, the compound of formula (IX) may be reacted with a derivative of formula (X) wherein Z is halogen, for instance iodine or bromine, and R' is an arylalkyl group such as, for instance, a benzyl group, by working according to conventional methods.

On the other side, the compound of formula (IX) may be reacted with a derivative of formula (X) wherein Z is a bromine atom and R' is an aryl group, in presence of a palladium catalyst such as, for instance, tris(dibenzylideneacetone)dipalladium, palladium acetate or 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium, by adding a suitable base, for instance potassium tert-butoxide, cesium carbonate or the like, and a palladium ligand such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, tri-o-tolylphosphine, tri-n-butylphosphine, tri-t-butylphosphine and the like, so as to obtain the corresponding derivative of formula (XV).

In this respect, the compound of formula (IX) is suspended in a suitable anhydrous solvent such as toluene, N-methyl-2-pyrrolidone, dimethoxyethane, dioxane and the like, and the compound of formula (X), the catalyst, the base and the ligand are added therein. The suspension is then brought to a suitable temperature varying from about 50°C to about 100°C whereas stirring is maintained for a time of about 8 hours to 5 hours. The reaction is carried out under inert atmosphere.

According to step h) of the process, the compound of formula (XV) is then reacted with tetrabutylammonium fluoride so as to get the corresponding hydroxy derivative of formula (XVIII). The compound (XV) may be thus suspended in an anhydrous solvent such as dioxane, tetrahydrofuran or the like, and the solution of tetrabutylammoniun fluoride in the suitable solvent is added. The solution is stirred for about 2 hours to about 16 hours, at a temperature ranging from about 20°C to about 50°C.

The product of formula (XVIII) thus obtained may be further reacted according to step i) of the process, with a suitable derivative of formula (XIX).

More in particular, the reaction with a compound of formula (XIX) wherein Z is a halogen atom such as bromine or chlorine or a suitable leaving group, is carried out in the presence of a base such as, for instance, sodium hydroxide, sodium hydride, 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diaza-phosphorine or more preferably cesium carbonate, so as to get the corresponding ether derivative of formula (XX).

In this respect, the compound of formula (XVIII) is suspended in a suitable solvent such as dimethylacetamide, tetrahydrofuran, dioxane or more preferably dimethylformamide, and the base is added.

The mixture is stirred for about 5 hours to about 36 hours at a temperature ranging from about 20°C to about 80°C.

Alternatively, these same compounds of formula (XX) may be obtained by reacting the derivative of formula (XVIII) with a compound of formula (XIX) wherein Z is hydroxy, under Mitsunobu operative conditions, e.g. in the presence of triphenylphosphine and diisopropyl azodicarboxylate.

In this respect, triphenylphosphine, diisopropyl azodicarboxylate and the compound of general formula (XIX) are dissolved in a suitable solvent such as tetrahydrofuran, dioxane or the like, and the solution is transferred into the mixture of the compound of formula (XVIII) being dissolved in a suitable solvent such as tetrahydrofuran, dioxane or the like, in the presence of a suitable base such as triethylamine or diisopropylethylamine. The mixture is stirred for a time varying from about 2 hours to about 15 hours, at a temperature ranging from 0°C to 20°C.

Finally, according to step j) of the process, the compound of formula (XX) is deprotected at the indazole nitrogen atom by working, according to conventional method, in acidic conditions. The compound of formula (XX) is suspended in a suitable solvent such as methyl alcohol,

ethyl alcohol or the like, and a concentrated solution of hydrochloric acid is added. The mixture is stirred for a suitable time of about 5 hours to about 15 hours at a temperature ranging from about 20°C to about 40°C; preferably at about 20°C. Alternatively, this same intermediate compound of formula (XX) is cleaved from the resin to which it is supported.
Resin cleavage may be carried out, for instance, in the presence of trifluoroacetic acid so as to yield the desired compound of formula (I). The resin is suspended in a solution of 5-95% of trifluoroacetic acid in dichloromethane and the mixture is stirred at about 20°C for a time varying from about 5 minutes to about 3 hours.

From all of the above, it is clear to the skilled man that the compounds of formula (I) wherein R_1 and m are as above defined and R is a phthalimido group of formula (II), and the pharmaceutically acceptable salts thereof, may be prepared according to an analogous process by reacting the compound of formula (VIII) as per steps h), i) and j) of the process, so as to get the desired derivative of formula (I) bearing a phthalimido group (II) in place of the R group.

Preferably, when preparing the compounds of formula (I) wherein R is a sulfonamido ($-NHSO_2R'$) group, the above synthetic pathway can be conveniently modified by changing the order of the deprotection steps.
More in particular, the compounds of formula (I) wherein R is a $-NHSO_2R'$ group may be preferably prepared by reacting the intermediate derivatives of formula (VIII), being obtained according to step (e) of the process, with tetrabutylammonium fluoride as per step (h) of the process, so as to obtain the compounds of formula (XVIII) wherein R is a phthalimido group.

The thus obtained compounds of formula (XVIII) are then reacted with a derivative of formula (XIX) according to step (i) of the process, so as to get the compounds of formula (XX) wherein R is a phthalimido group.

The above compounds of formula (XX) are then reacted with hydrazine monohydrate, according to step (f) of the process, so as to obtain the compounds of formula (XX) wherein R is $-NH_2$.

Finally, the above compounds of formula (XX) are then reacted with a suitable derivative of formula (XIII), as per step (g.1) of the process, so as to get the corresponding sulphonamido derivatives of formula (XX) wherein R represents the given $-NHSO_2R'$ group, which are further deprotected or cleaved from the resin according to step (j) of the process.

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, the reagents 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 (III) are known or easily prepared according to known methods. As an example, 2-amino-4-methoxy-benzonitrile may be prepared by working as described in EP-A-257583 in the name of Shionogi & Co; 2-

amino-5-benzyloxy-benzonitrile may be prepared as described in J. Heterocycl. Chem. (1972), 9(4), 759-73.

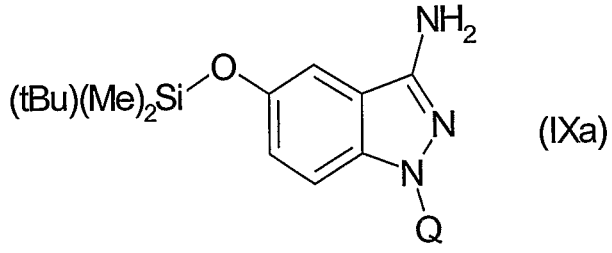
If not commercially available per se, all of the compounds of formula (X), (XI), (XII), (XIII), (XIV), (XVI), (XVII) and (XIX) are known or easily prepared according to well-known methods.

Likewise, any reagent of the present process comprising the silyl derivative $(R^{iv})_3SiZ$ as well as the polymeric resin are commercially available or readily preparable from commercially available sources.

As formerly indicated, the compounds of formula (I) of the invention were conveniently prepared according to combinatorial chemistry techniques widely known in the art, by accomplishing the aforementioned reactions between the several intermediates in a serial manner and by working under SPS conditions.

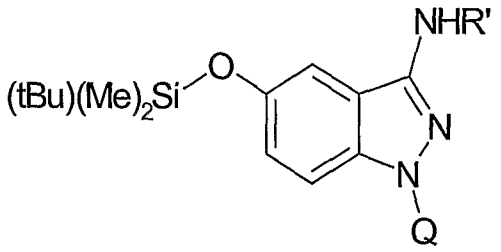
All of the preferred compounds of the invention, whenever appropriate in the form of pharmaceutically acceptable salts, are herewith conveniently indicated and defined as products by process, that is as products of formula (I) which are obtainable, for instance through a given process.

Therefore, herewith provided are novel compounds of the invention and the pharmaceutically acceptable salts thereof which are obtainable, for instance through a combinatorial chemistry technique as per the above process, by first reacting the compound of formula (IXa)



(IXa)

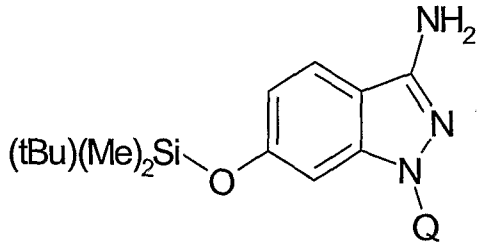
with each one of the compounds of formula (X), as set forth in table I, so as to obtain a plurality of compounds of formula (XVa)



(XVa)

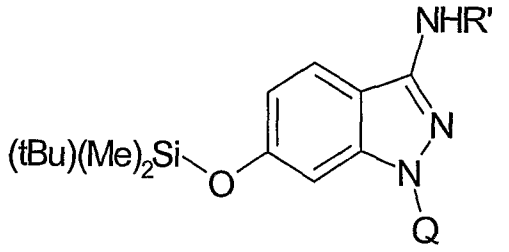
by then reacting each of the derivatives of formula (XVa) with tetrabutylammonium fluoride, as per step h) of the process, and then with each one of the derivatives of formula (XIX), as set forth in tables II or III, and by subsequently operating as per step j) of the process.

Also provided are novel compounds of the invention and the pharmaceutically acceptable salts thereof which are obtainable, for instance through a combinatorial chemistry technique as per the above process, by first reacting the compound of formula (IXb)



(IXb)

with each one of the compounds of formula (X), as set forth in table I, so as to obtain a plurality of compounds of formula (XVa)

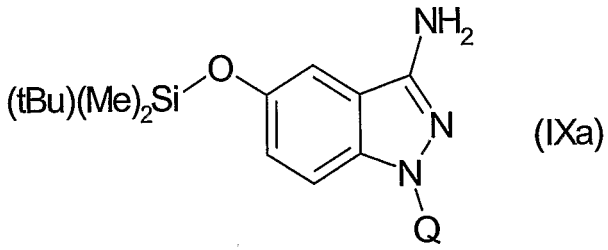


(XVb)

by then reacting each of the derivatives of formula (XVb) with tetrabutylammonium fluoride, as per step h) of the process, and then with each one of the derivatives of

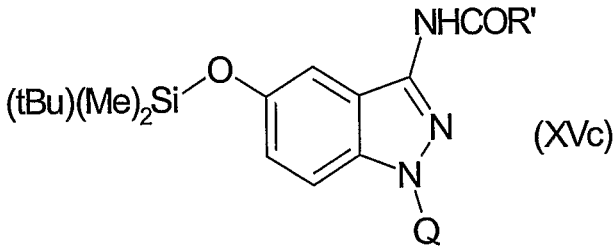
formula (XIX), as set forth in tables II or III, and by subsequently operating as per step j) of the process.

Also, provided are novel compounds of the invention and the pharmaceutically acceptable salts thereof which are obtainable, for instance through a combinatorial chemistry technique as per the above process, by first reacting the compound of formula (IXa)



(IXa)

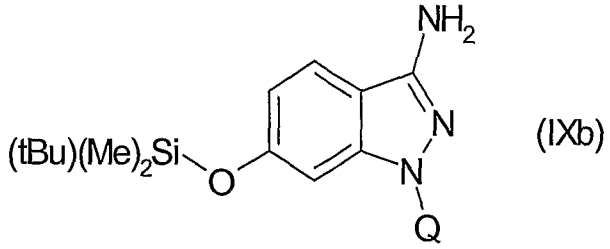
with each one of the compounds of formula (XI), as set forth in table IV, so as to obtain a plurality of compounds of formula (XVc)



(XVc)

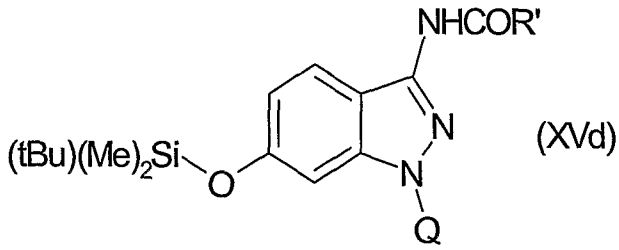
by then reacting each of the derivatives of formula (XVc) with tetrabutylammonium fluoride, as per step h) of the process, and then each one of the derivatives of formula (XIX), as set forth in tables II or III, and by subsequently operating as per step j) of the process.

Also provided are novel compounds of the invention and the pharmaceutically acceptable salts thereof which are obtainable, for instance through a combinatorial chemistry technique as per the above process, by first reacting the compound of formula (IXb)



(IXb)

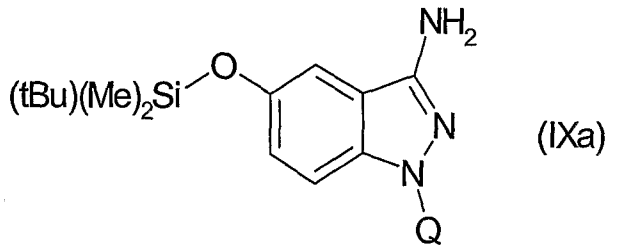
with each one of the compounds of formula (XI), as set forth in table IV, so as to obtain a plurality of compounds of formula (XVd)



(XVd)

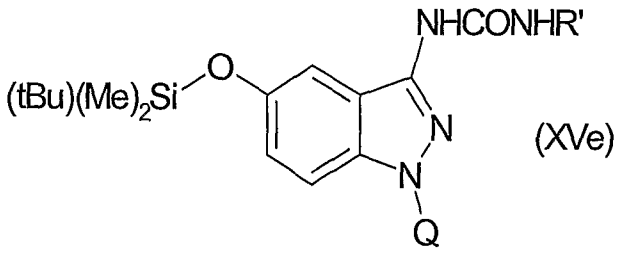
by then reacting each of the derivatives of formula (XVd) with tetrabutylammonium fluoride, as per step h) of the process, and then with each one of the derivatives of formula (XIX), as set forth in tables II and III, and by subsequently operating as per step j) of the process

Also provided are novel compounds of the invention and the pharmaceutically acceptable salts thereof which are obtainable, for instance through a combinatorial chemistry technique as per the above process, by first reacting the compound of formula (IXa)



(IXa)

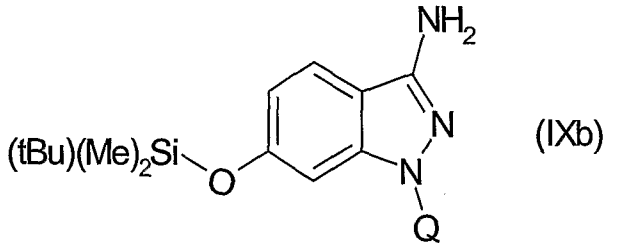
with each one of the compounds of formula (XII), as set forth in table V, so as to obtain a plurality of compounds of formula (XVe)



(XVe)

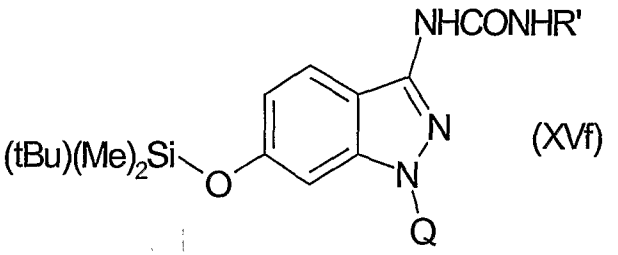
by then reacting each of the derivatives of formula (XVe) with tetrabutylammonium fluoride, as per step h) of the process, and then with each one of the derivatives of formula (XIX), as set forth in tables II or III, and by subsequently operating as per step j) of the process.

Also provided are novel compounds of the invention and the pharmaceutically acceptable salts thereof which are obtainable, for instance through a combinatorial chemistry technique as per the above process, by first reacting the compound of formula (IXb)



(IXb)

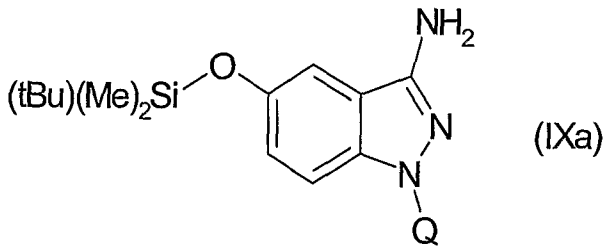
with each one of the compounds of formula (XII), as set forth in table V, so as to obtain a plurality of compounds of formula (XVf)



(XVf)

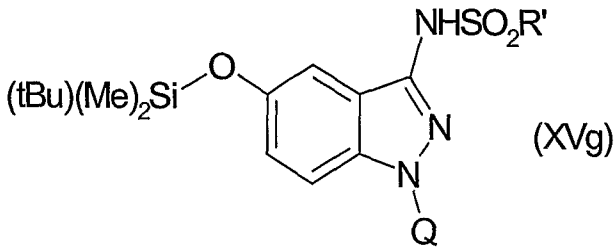
by then reacting each of the derivatives of formula (XVf) with tetrabutylammonium fluoride, as per step h) of the process, and then with each one of the derivatives of formula (XIX), as set forth in tables II or III, and by subsequently operating as per step j) of the process.

Also provided are novel compounds of the invention and the pharmaceutically acceptable salts thereof which are obtainable, for instance through a combinatorial chemistry technique as per the above process, by first reacting the compound of formula (IXa)



(IXa)

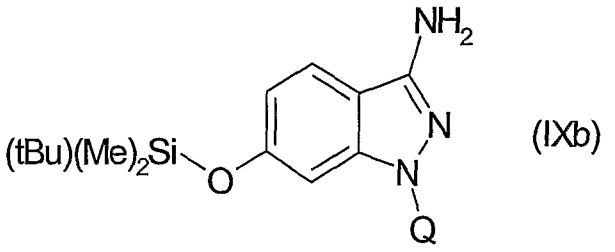
with each one of the compounds of formula (XIII), as set forth in table VI, so as to obtain a plurality of compounds of formula (XVg)



(XVg)

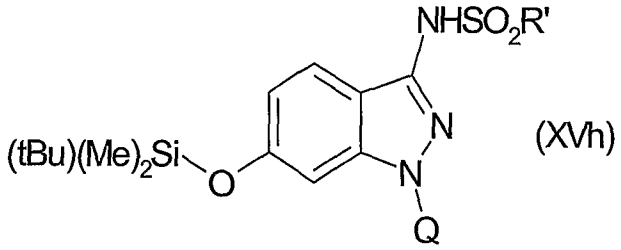
by then reacting each of the derivatives of formula (XVg) with tetrabutylammonium fluoride, as per step h) of the process, and then with each one of the derivatives of formula (XIX), as set forth in tables II or III, and by subsequently operating as per step j) of the process.

Also provided are novel compounds of the invention and the pharmaceutically acceptable salts thereof which are obtainable, for instance through a combinatorial chemistry technique as per the above process, by first reacting the compound of formula (IXb)



(IXb)

with each one of the compounds of formula (XIII), as set forth in table VI, so as to obtain a plurality of compounds of formula (XVh)



(XVh)

by then reacting each of the derivatives of formula (XVh) with tetrabutylammonium fluoride, as per step h) of the process, and then with each one of the derivatives of formula (XIX), as set forth in tables II or III, and by subsequently operating as per step j) of the process.

Table I

Compounds of formula R'-Z (X)

1.	(1-bromoethyl)benzene
2.	alpha-bromo-m-xylene
3.	cinnamyl bromide
4.	3,4-(ethylenedioxy)phenacyl bromide
5.	2-bromo-1-(4-chlorophenyl)-2-phenylethan-1-one
6.	2-benzoyl-2-bromoacetanilide
7.	alpha-bromo-4-(1-pyrrolidino)acetophenone
8.	ethyl 2-bromobutyrate

Table II

Compounds of formula R_1-Z (XIX) wherein Z is bromine

1.	2-bromo-2-phenylacetophenone
2.	benzyl bromide
3.	2-methylbenzyl bromide
4.	alpha-bromo-m-xylene
5.	2-bromo-2',5'-dimethoxyacetophenone
6.	4-methoxyphenacyl bromide
7.	2-bromo-4'-phenylacetophenone
8.	1-bromopinacolone
9.	propargyl bromide
10.	1-bromo-3-methyl-2-butene
11.	allyl bromide
12.	cinnamyl bromide
13.	2-fluorobenzyl bromide

14.	2-fluorobenzyl bromide
15.	2,6-difluorobenzyl bromide
16.	2-chlorobenzyl bromide
17.	4-chlorophenacyl bromide
18.	2-cyanobenzyl bromide
19.	4-nitrobenzyl bromide
20.	methyl 2-bromobutyrate
21.	3,5-difluorobenzyl bromide
22.	2,4-bis(trifluoromethyl)benzyl bromide
23.	2-bromo-n-phenylpropionamide
24.	methyl alpha-bromophenylacetate
25.	2-(trifluoromethyl)benzyl bromide
26.	3-bromocyclohexene
27.	1-bromo-2-fluoroethane
28.	1-bromo-3-fluoropropane
29.	3,4-dichlorobenzyl bromide
30.	3,4-dichlorobenzyl bromide
31.	2-(bromomethyl)anthraquinone
32.	4-bromo-2-fluorobenzyl bromide
33.	4-fluoro-2-(trifluoromethyl)benzyl bromide
34.	2,3,6-trifluorobenzyl bromide
35.	2,4,5-trifluorobenzyl bromide
36.	3-(trifluoromethoxy)benzyl bromide
37.	4-(trifluoromethyl)phenacyl bromide
38.	3-(bromomethyl)-5-chlorobenzo[b]thiophene
39.	2-(difluoromethoxy)benzyl bromide
40.	1-bromo-2-butyne
41.	1-bromo-2-pentyne
42.	(+/-)-3-bromo-1-phenyl-2-pyrrolidinone
43.	alpha-bromo-4-(1-pyrrolidino)acetophenone
44.	benzyl 2-bromoethyl ether
45.	3,5-dimethoxybenzyl bromide
46.	4-(bromomethyl)-3,5-dimethylisoxazole

Table III

Compounds of formula R_1-Z (XIX) wherein Z is hydroxy

1.	3-methylbenzyl alcohol
2.	cyclopentanol
3.	3-methoxybenzyl alcohol
4.	methanol
5.	4-fluoro-1-butanol
6.	4-phenyl-2-butanol
7.	3-dimethylamino-1-propanol

8.	(2-hydroxyethyl)cyclopropane
9.	cyclopentanemethanol
10.	1,2,3,6-tetrahydrobenzylalcohol
11.	2-(3-thienyl)ethanol
12.	6-methyl-2-heptanol
13.	1-methyl-2-pyrrolidineethanol
14.	2-methyl-1-propanol
15.	1-(2-hydroxyethyl)pyrrolidine
16.	5-benzyloxy-1-pentanol
17.	1-hexanol
18.	4-methyl-5-thiazoleethanol
19.	3-butyn-1-ol
20.	n-(2-hydroxyethyl)piperidine
21.	tetrahydrofurfuryl alcohol
22.	4'-(2-hydroxyethoxy)acetanilide

Table IV

Compounds of formula R'COZ (XI)

1.	benzoyl chloride
2.	1,3-benzodioxole-5-carbonyl chloride
3.	1-naphthoyl chloride
4.	2-furoyl chloride
5.	4-dimethylamino-benzoyl chloride
6.	4-(trifluoromethyl)benzoyl chloride
7.	3,5-dichlorobenzoyl chloride
8.	benzyloxyacetyl chloride
9.	4-tert-butylbenzoyl chloride
10.	3,4-dimethoxybenzoyl chloride
11.	2-fluorobenzoyl chloride
12.	4-(trifluoromethoxy)benzoyl chloride
13.	1-acetylisonipecotoyl chloride
14.	2-phenoxypropionyl chloride
15.	4-tert-butylphenoxyacetyl chloride
16.	methoxyacetyl chloride
17.	hippuryl acid chloride
18.	4-bromobenzoyl chloride
19.	4-fluorobenzoyl chloride
20.	4-n-butoxybenzoyl chloride
21.	3-chloro-4-fluorobenzoyl chloride
22.	2-ethoxy-1-naphthoyl chloride
23.	3-chlorothiophene-2-carbonyl chloride
24.	3,5-dimethylisoxasole-4-carbonyl chloride
25.	4-ethylbenzoyl chloride
26.	2-n-propyl-n-valeroyl chloride
27.	3,5-dimethoxybenzoyl chloride

28.	(s)-N-tosyl-phenylalanyl chloride
29.	m-anisoyl chloride
30.	benzoyl chloride
31.	cyclopropanecarbonyl chloride
32.	phenylacetyl chloride
33.	3-chlorobenzoyl chloride
34.	4-methoxyphenylacetyl chloride
35.	hydrocinnamoyl chloride
36.	4-tert-butylphenoxyacetyl chloride
37.	4-tert-butylphenoxyacetyl chloride
38.	4-methoxyphenylacetyl chloride

Table V

Compounds of formula R'-NCO (XII)

1.	3-methoxyphenyl isocyanate
2.	p-tolyl isocyanate
3.	3-chlorophenyl isocyanate
4.	4-biphenylyl isocyanate
5.	4-acetylphenyl isocyanate
6.	benzoyl isocyanate
7.	isopropyl isocyanate
8.	2,4-dimethylphenyl isocyanate
9.	2-(difluoromethoxy)phenyl isocyanate
10.	4-fluorobenzyl isocyanate
11.	n-butyl isocyanate
12.	2,3,4-trifluorophenyl isocyanate
13.	3,5-dimethoxyphenyl isocyanate
14.	2-(methylthio)phenyl isocyanate
15.	3-(trifluoromethyl)phenyl isocyanate
16.	2-fluorophenyl isocyanate
17.	2-phenyl ethylisocyanate
18.	4-methoxyphenyl isocyanate
19.	3,4-(methylenedioxy)phenyl isocyanate
20.	3-carbomethoxyphenyl isocyanate
21.	phenyl isocyanate
22.	benzyl isocyanate
23.	isopropyl isocyanate

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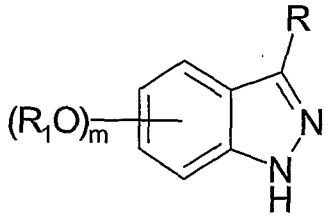
Table VI

Compounds of formula R'-SO_2Z (XIII)

1.	4-isopropylbenzenesulphonyl chloride
2.	2-thiophenesulfonyl chloride
3.	3-(trifluoromethyl)benzenesulfonyl chloride

4.	4-n-propylbenzenesulfonyl chloride
5.	4-(trifluoromethoxy)benzenesulphonyl chloride
6.	2,4-difluorobenzenesulphonyl chloride
7.	1-butanesulfonyl chloride
8.	3-chloro-2-methylbenzenesulfonyl chloride
9.	3-methoxybenzenesulphonyl chloride
10.	3,4-dichlorobenzenesulfonyl chloride
11.	3-methylbenzenesulfonyl chloride
12.	3,5-dimethylisoxazole-4-sulfonyl chloride
13.	4-chloro-2,5-dimethylbenzenesulphonyl chloride
14.	5-(tert-butyl)-2-methylfuran-3-carbonyl chloride
15.	3,4-dimethoxybenzenesulfonyl chloride
16.	2-naphthalenesulfonyl chloride
17.	8-quinolinesulfonyl chloride
18.	3,4-difluorobenzenesulphonyl chloride
19.	4-tert-butylbenzenesulfonyl chloride
20.	4-chlorobenzenesulfonyl chloride
21.	3-methylbenzenesulfonyl chloride
22.	N-acetylsulfanilyl chloride

Accordingly, it is a further object of the present invention a library of two or more aminoindazole derivatives represented by formula (I)

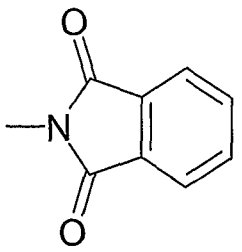


(I)

wherein

R is selected from the group consisting of -NHR', -NR'R", -NHCOR', -NHCONHR', -NHCONR'R", -NHSO$_2$R' or -NHCOOR', wherein R' and R" are, each independently, a group optionally further substituted selected from straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or alkynyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 or 6 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen,

oxygen or sulfur; or R is a phthalimido group of formula (II) below



(II)

any R_1, if present, is in position 5 or 6 of the indazole ring and represents a group, optionally further substituted, as set forth above for R' or R";

m is 0 or 1;

or a pharmaceutically acceptable salt thereof.

From all of the above, it is clear to the skilled man that once a library of indazole 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 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 cdk/cyclin inhibitors and the potency of selected compounds was determined through a method of assay based on the use of the SPA technology (Amersham Pharmacia Biotech).

The assay consists of the transfer of radioactivity labelled phosphate moiety by the kinase to a biotinylated substrate. The resulting 33P-labelled biotinylated product is allowed to bind to streptavidin-coated SPA beads (biotin capacity 130pmol/mg), and light emitted was measured in a scintillation counter.

Inhibition assay of cdk2/Cyclin A activity

Kinase reaction: 4 μM in house biotinylated histone H1 (Sigma # H-5505) substrate, 10 μM ATP (0.1 microCi $P^{33}\gamma$-ATP), 4.2 ng Cyclin A/CDK2 complex, inhibitor in a final volume of 30 μl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) were added to each well of a 96 U bottom. After 30 min at r.t. incubation, reaction was stopped by 100 μl PBS + 32 mM EDTA + 0.1% Triton X-100 + 500 μM ATP, containing 1 mg SPA beads. Then a volume of 110 μl is transferred to Optiplate.

After 20 min. incubation for substrate capture, 100 μl 5M CsCl were added to allow statification of beads to the top of the plate and let stand 4 hours before radioactivity counting in the Top-Count instrument

IC50 determination: inhibitors were tested at different concentrations ranging from 0.0015 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:

Experimental method: Reaction was carried out in buffer (10 mM Tris, pH 7.5, 10 mM $MgCl_2$, 0.2 mg/ml BSA, 7.5 mM DTT) containing 3.7 nM enzyme, histone and ATP (constant ratio of cold/labeled ATP 1/3000). Reaction was stopped with EDTA and the substrate captured on phosphomembrane (Multiscreen 96 well plates from Millipore). After extensive washing, the multiscreen plates are read on a top counter. Control (time zero) for each ATP and histone concentrations was measured.

Experimental design: Reaction velocities are measured at different four ATP, substrate (histone) and inhibitor concentrations. An 80-point concentration matrix was designed around the respective ATP and substrate Km values, and the inhibitor IC50 values (0.3, 1, 3, 9 fold the Km or IC50 values). A preliminary time course experiment in the absence of inhibitor and at the different ATP and substrate concentrations allow the selection of a single endpoint time (10 min) in the linear range of the reaction for the Ki determination experiment.

Kinetic parameter estimates: Kinetic parameters were estimated by simultaneous nonlinear least-square regression using [Eq.1] (competitive inhibitor respect to ATP, random mechanism) using the complete data set (80 points):

$$v = \frac{Vm \bullet A \bullet B}{\alpha \bullet Ka \bullet Kb + \alpha \bullet Ka \bullet B + a \bullet Kb \bullet A + A \bullet B + \alpha \bullet \frac{Ka}{Ki} \bullet I \bullet (Kb + \frac{B}{\beta})} \qquad \text{[Eq.1]}$$

where A=[ATP], B=[Substrate], I=[inhibitor], Vm= maximum velocity, Ka, Kb, Ki the dissociation constants of ATP, substrate and inhibitor respectively. α and β the cooperativity factor between substrate and ATP binding and substrate and inhibitor binding respectively.

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, cdk5/p25, cdk4/ cyclin D1), and also for specificity on MAPK, PKA, EGFR, IGF1-R, and Aurora-2.

Inhibition assay of cdk2/Cyclin E activity

Kinase reaction: 10 μM in house biotinylated histone H1 (Sigma # H-5505) substrate, 30 μM ATP (0.3 microCi $P^{33}\gamma$-ATP), 4 ng GST-Cyclin E/CDK2 complex, inhibitor in a final volume of 30 μl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) were added to each well of a 96 U bottom. After 60 min at r.t. incubation, reaction was stopped by 100 μl PBS + 32 mM EDTA + 0.1% Triton X-100 + 500 μM ATP, containing 1 mg SPA beads. Then a volume of 110 μl is transferred to Optiplate.

After 20 min. incubation for substrate capture, 100 μl 5M CsCl were added to allow statification of beads to the top of the plate and let stand 4 hours before radioactivity counting in the Top-Count instrument

IC50 determination: see above

Inhibition assay of cdk1/Cyclin B1 activity

Kinase reaction: 4 μM in house biotinylated histone H1 (Sigma # H-5505) substrate, 20 μM ATP (0.2 microCi $P^{33}\gamma$-ATP), 3 ng Cyclin B/CDK1 complex, inhibitor in a final volume of 30 μl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) were added to each well of a 96 U bottom. After 20 min at r.t. incubation, reaction was stopped by 100 μl PBS + 32 mM EDTA + 0.1% Triton X-100 + 500 μM ATP, containing 1 mg SPA beads. Then a volume of 110 μl is transferred to Optiplate.

After 20 min. incubation for substrate capture, 100 µl 5M CsCl were added to allow statification of beads to the top of the Optiplate and let stand 4 hours before radioactivity counting in the Top-Count instrument.

IC50 determination: see above

Inhibition assay of cdk5/p25 activity

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

Kinase reaction: 10 µM biotinylated histone H1 (Sigma # H-5505) substrate, 30 µM ATP (0.3 microCi $P^{33}\gamma$-ATP), 15 ng CDK5/p25 complex, inhibitor in a final volume of 30 µl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) were added to each well of a 96 U bottom. After 30 min at r.t. incubation, reaction was stopped by 100 µl PBS + 32 mM EDTA + 0.1% Triton X-100 + 500 µM ATP, containing 1 mg SPA beads. Then a volume of 110 µl is transferred to Optiplate.

After 20 min. incubation for substrate capture, 100 µl 5M CsCl were added to allow statification of beads to the top of the plate and let stand 4 hours before radioactivity counting in the Top-Count instrument.

IC50 determination: see above

Inhibition assay of 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.

IC50 determination: see above

Inhibition assay of MAPK activity

Kinase reaction: 10 µM in house biotinylated MBP (Sigma # M-1891) substrate, 15 µM ATP (0.15 microCi $P^{33}\gamma$-ATP), 30 ng GST-MAPK (Upstate Biothecnology # 14-173), inhibitor in a final volume of 30 µl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) were added to each well of a 96 U bottom. After 30 min at r.t. incubation, reaction was stopped by 100 µl PBS + 32 mM EDTA + 0.1% Triton X-100 + 500 µM ATP, containing 1 mg SPA beads. Then a volume of 110 µl is transferred to Optiplate.

After 20 min. incubation for substrate capture, 100 µl 5M CsCl were added to allow statification of beads to the top of the Optiplate and let stand 4 hours before radioactivity counting in the Top-Count instrument.

IC50 determination: see above

Inhibition assay of PKA activity

Kinase reaction: 10 µM in house biotinylated histone H1 (Sigma # H-5505) substrate, 10 µM ATP (0.2 microM $P^{33}\gamma$-ATP), 0.45 U PKA (Sigma # 2645), inhibitor in a final volume of 30 µl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) were added to each well of a 96 U bottom.

After 90 min at r.t. incubation, reaction was stopped by 100 µl PBS + 32 mM EDTA + 0.1% Triton X-100 + 500 µM ATP, containing 1 mg SPA beads. Then a volume of 110 µl is transferred to Optiplate.

After 20 min. incubation for substrate capture, 100 µl 5M CsCl were added to allow statification of beads to the top of the Optiplate and let stand 4 hours before radioactivity counting in the Top-Count instrument.

IC50 determination: see above

Inhibition assay of EGFR activity

Kinase reaction: 10 µM in house biotinylated MBP (Sigma # M-1891) substrate, 2 µM ATP (0.04 microCi $P^{33}\gamma$-ATP), 36 ng insect cell expressed GST-EGFR, inhibitor in a final volume of 30 µl buffer (Hepes 50 mM pH 7.5, $MgCl_2$ 3 mM, $MnCl_2$ 3 mM, DTT 1 mM, $NaVO_3$ 3µM, + 0.2 mg/ml BSA) were added to each well of a 96 U bottom. After 20 min at r.t. incubation, reaction was stopped by 100 µl PBS + 32 mM EDTA + 0.1% Triton X-100 + 500 µM ATP, containing 1 mg SPA beads. Then a volume of 110 µl is transferred to Optiplate.

After 20 min. incubation for substrate capture, 100 µl 5M CsCl were added to allow statification of beads to the top of the Optiplate and let stand 4 hours before radioactivity counting in the Top-Count instrument.

IC50 determination: see above

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 ATP, 1 microCi ^{33}P-ATP, and 22.5 ng GST-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 20 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.

Inhibition assay of Aurora-2 activity

Kinase reaction: 8 µM biotinylated peptide (4 repeats of LRRWSLG), 10 µM ATP (0.5 uCi P^{33}g-ATP), 15 ng Aurora2, inhibitor in a final volume of 30 µl buffer (HEPES 50 mM pH 7.0, $MgCl_2$ 10 mM, 1 mM DTT, 0.2 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 5 M were added to each well and let stand 4 hour before radioactivity was counted in the Top-Count instrument.

IC50 determination: see above

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).

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 are herewith intended to better illustrate the present invention without posing any limitation to it.

General Methods

Flash Chromatography was performed on silica gel (Merck grade 9395, 60A). The high pressure liquid chromatography retention times (HPLC: R_T values) were determined by:

Method 1:

Instrumentation: Waters 2790 HPLC system equipped with a 996 Waters PDA detector and Micromass mod. ZQ single quadrupole mass spectrometer, equipped with an electrospray (ESI) ion source.

Chromatographic condition: RP18 Waters X Terra (4,6 x 50 mm, 3.5 µm) column; 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 minutes. 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 at 254 nm. Mass are given as m/z ratio.

Method 2:

Instrumentation: Waters 2790 Alliance with thermostated autosampler; UV detector with dual wavelength 2487; Satin Interface; Divert valve LabPro, Mass spectrometer Waters ZQ single quadrupole with ESI interface; Antek chemoluminescens nitrogen detector (CLND) 8060.

Chromatographic condition: Zorbax SB C8 (4.6 x 50mm; 5 µm) column; Mobile Phase A was 0.01% formic acid in acetonitrile and Mobile Phase B was 0.01% formic acid in Methanol. Gradient from 0 to 95% B in 10 minutes, hold 95% for 2 minutes. UV detection at 220 nm. Flow rate 1 ml/min. Injection volume 10 µl. Full scan, mass range from 120-1000 amu. Capillary voltage 2.8 KV; source temperature 115°C cone was 32 V.

Retention times (HPLC r.t.) are given in minutes at 220 nm or at 254 nm. Mass are given as m/z ratio.

Method 3:

Instrumentation: HP1100 HPLC binary pump; Gilson 215 autosampler, HP1100 single wavelength UV detector, a Sedex

75c evaporative light scattering (ELS) detector (Sedere, France); and a PE/Sciex API-2000 mass spectrometer

Chromatographic condition: YMC ODS-AQ 4.6 x 50mm, 5µm S5 columns; with HPLC mobile phases consisting of 0.5% formic acid in HPLC grade water (A) and 0.5% formic acid in HPLC grade acetonitrile (B). The HPLC gradient shown in the table was performed with 5µL injections for each sample. UV detection at 220 nm.

LC/MS/UV/ELS Gradient			
Time (min)	Flow (mL/min)	% A	% B
0.00	2.0	98	2
2.58	2.0	2	98
3.08	2.0	2	98
3.13	2.0	0	100
3.28	2.0	0	100
3.33	2.0	98	2
4.00	2.0	98	2

The Turbo IonSpray source was employed with an ion spray voltage of 5kV, a temperature of 475°C, and orifice and ring voltages of 10V and 250V respectively. Positive ions were scanned in Q1 from 160 to 800 amu.

When necessary, the compounds have been purified by preparative HPLC on a Waters Symmetry C18 (19 x 50 mm, 5µm) column using a waters preparative HPLC 600 equipped with a 996 Waters PDA detector and a Micromass mod. ZMD single quadrupole mass spectrometer, electron spray ionization, 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/min.

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

As formerly indicated, several compounds of formula (I) of the invention have been synthesized in parallel, according to combinatorial chemistry techniques.

In this respect, some compounds thus prepared have been conveniently and unambiguously identified, as per the coding system of tables from IX to XVI, together with HPLC retention time (methods 1 to 3) and mass.

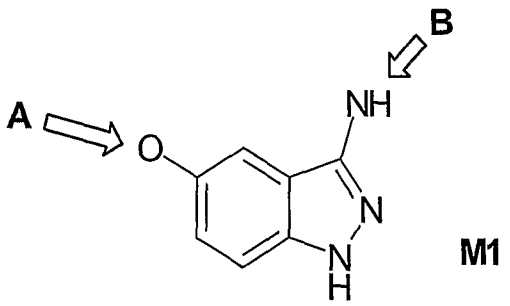
Each code, which identifies a single specific compound of formula (I), consists of three units A-M-B.

A represents any substituent R_1- [see formula (I)] and is attached to the rest of the indazole moiety through the oxygen atom so as to get indazole derivatives being substituted in position 5 (A-M1-B) or in position 6 (A-M2-B); each A radical (substituent) is represented in the following table VII.

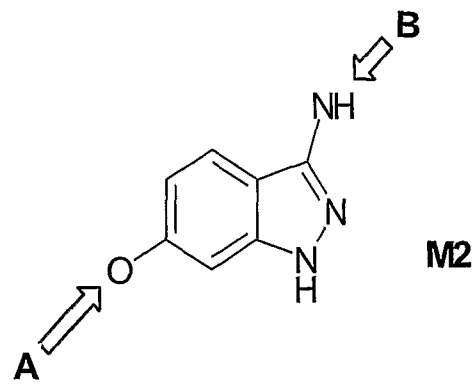
Together with the -NH- group in position 3 of the indazole moiety to which it is attached, B-NH- represents the R group of formula (I); each B radical (substituent) is represented in the following table VIII.

M refers to the central core of the divalent 3-amino-indazole moiety having the -O- group in position 5 or 6 and is substituted by groups A and B.

In particular, M may vary from M1 or M2 as per the formulae below, each identifying a compound being substituted by A-O- groups in position 5 (M1) or in position 6 (M2)



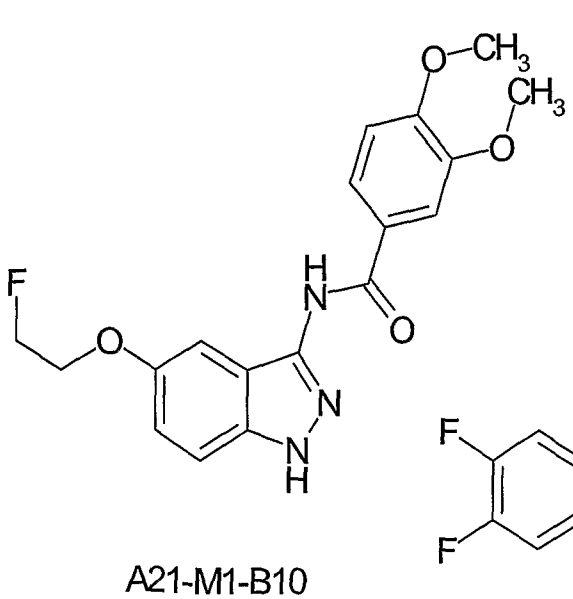
M1



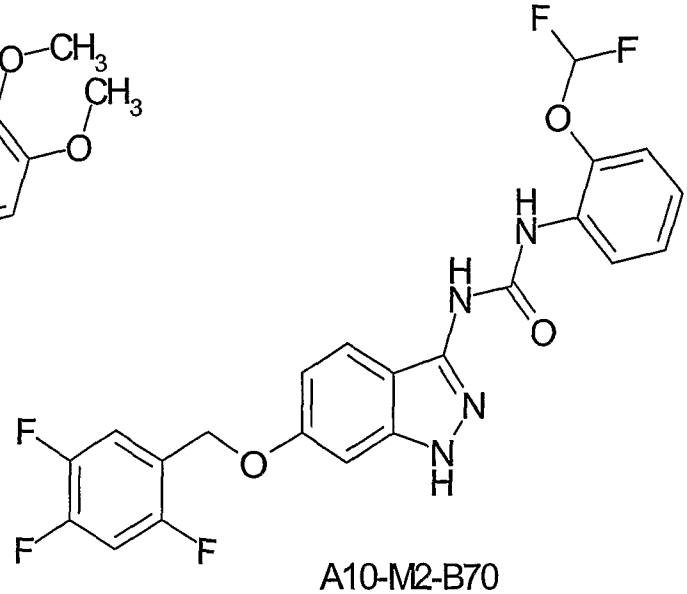
M2

For ease of reference, each A or B groups of tables VII and VIII has been identified with the proper chemical formula also indicating the point of attachment with the rest of the molecule M.

Just as an example, the compound A21-M1-B10 of table XI (see example 11, entry 429) represents an indazole M1 being substituted in position 5 (through the oxygen atom) by the group A21 and in position 3 (through the -NH- group) by the group B10; likewise, the compound A10-M2-B70 of table XII (see example 12, entry 281) represents an indazole M2 being substituted in position 6 (through the oxygen atom) by the group A10 and in position 3 (through the -NH- group) by the group B70:

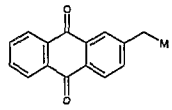
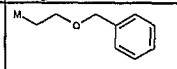
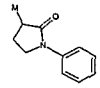
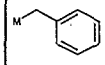
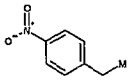
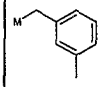
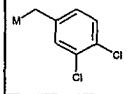
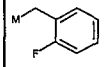
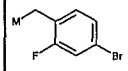
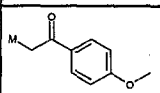
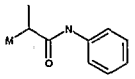
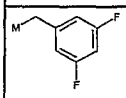
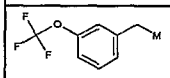
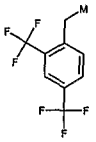
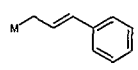
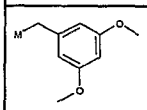
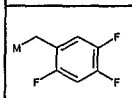
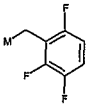
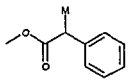
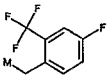
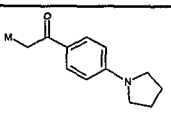
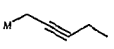


A21-M1-B10



A10-M2-B70

Table VII - A groups

Fragment	Code	Fragment	Code	Fragment	Code
	A00		A13		A27
	A01		A14		A29
	A02		A15		A30
	A03		A16		A31
	A04		A17		A32
	A05		A18		A33
	A06		A20		A35
	A07		A21		A36
	A08		A22		A37
	A09		A23		A38
	A10		A24		A39
	A11		A25		A40
	A12		A26		

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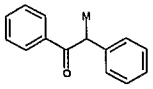
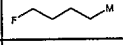
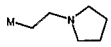
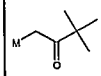
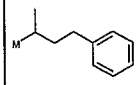
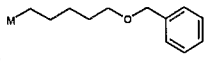
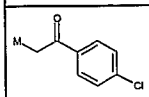
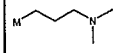
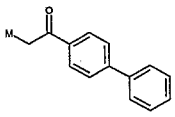
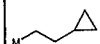
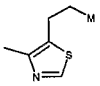
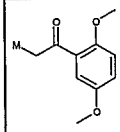
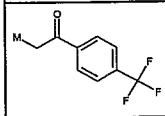
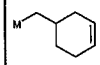
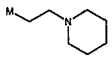
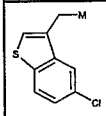
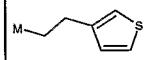
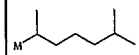
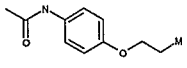
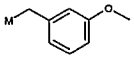
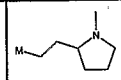
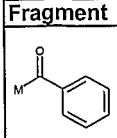
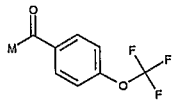
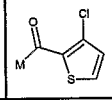
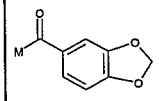
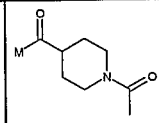
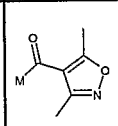
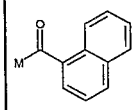
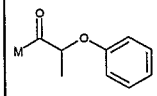
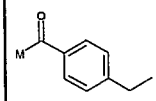
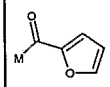
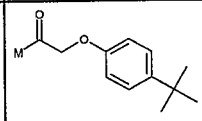
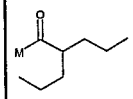
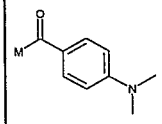
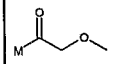
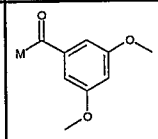
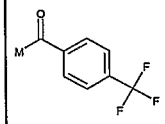
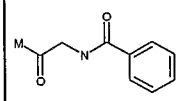
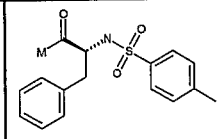
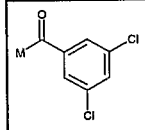
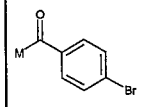
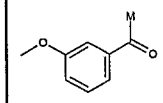
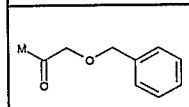
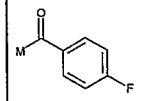
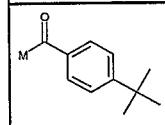
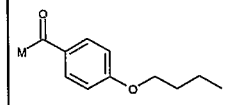
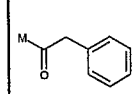
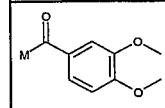
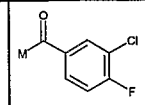
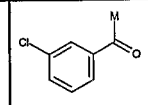
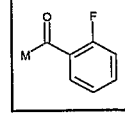
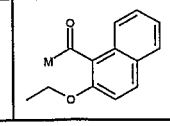
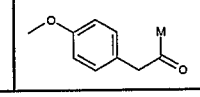
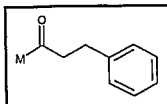
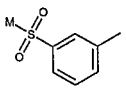
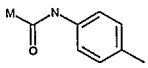
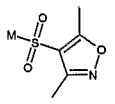
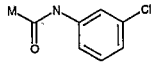
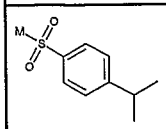
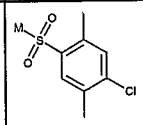
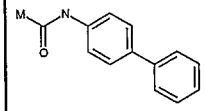
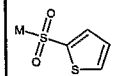
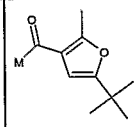
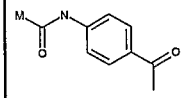
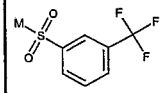
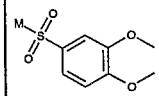
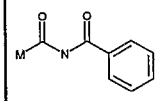
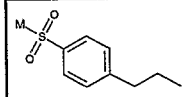
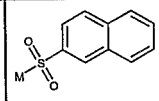
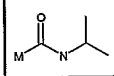
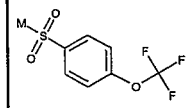
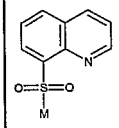
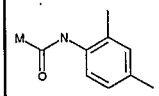
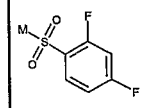
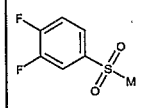
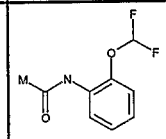
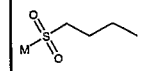
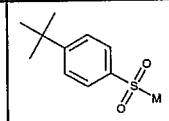
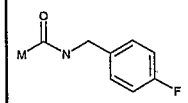
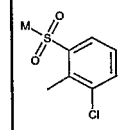
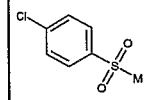
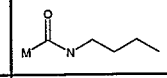
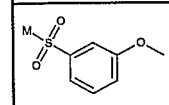
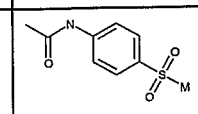
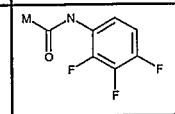
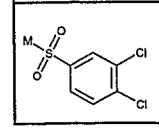
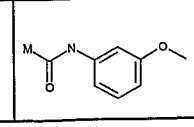
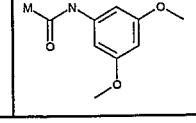
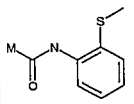
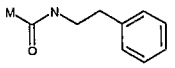
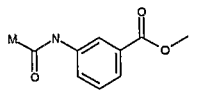
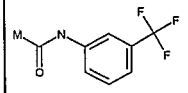
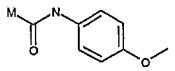
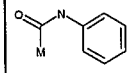
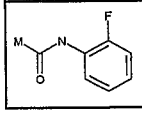
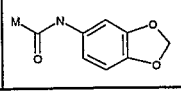
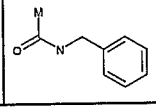
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	A44		A55		A66
	A45		A56		A67
	A46		A57		A68
	A47		A58		A69
	A48		A59		A70
	A50		A60		A71
	A51		A61		
	A52		A62		

Table VIII - B groups

Fragment	Code	Fragment	Code	Fragment	Code
	B01		B12		B23
	B02		B13		B24
	B03		B14		B25
	B04		B15		B26
	B05		B16		B27
	B06		B17		B28
	B07		B18		B29
	B08		B19		B31
	B09		B20		B32
	B10		B21		B33
	B11		B22		B35

	B36		B50		B63
			B51		B64
	B40		B52		B65
	B41		B53		B66
	B42		B54		B67
	B43		B55		B68
	B44		B56		B69
	B45		B57		B70
	B46		B58		B71
	B47		B59		B72
	B48		B61		B73
	B49		B62		B74

	B75		B78		B81
	B76		B79		B82
	B77		B80		B83

Example 1

6-Methoxy-1H-indazol-3-amine

To an ice-cooled suspension of 66.35 g (0.448 mol) of 2-amino-4-methoxybenzonitrile in 530 ml of concentrated HCl, a solution of 37.07 g (0.537 mol) of sodium nitrite in 55 ml of water was added dropwise. After 1.5 hours the cold suspension was added dropwise to a preformed solution of 679.25 g (3.58 mol) of stannous chloride in 530 ml of concentrated hydrochloric acid (HCl), at 5°C. After 3 hours the cold suspension was filtered and the moist solid was treated with 1.7 l of boiling water for 30 min. The hot cloudy solution was clarified by filtration through a cloth filter. The liquors were ice-cooled and treated dropwise with 0.8 l of 17% NaOH. The solid was filtered off and dried under vacuum at 50°C: 67.2 g of product were obtained as light brown solid. Yield = 91.9%. mp =195-197°C dec. HPLC r.t. 1.9 $[M+H]^+$ = 164

H^1NMR (DMSO-d_6), diagnostic signals (ppm): 3.74 (s, 3H), 5.17 (broad s, 2H), 6.5 (dd, 1H), 6.6 (d, 1H), 7.5 (d, 2H), 11.07 (s, 1H).

Example 2

2-({6-methoxy}-1H-indazol-3-yl)-1H-isoindole-1,3(2H)-dione

20 g (0.122 mol) of 6-methoxy-1H-indazol-3-amine, 20 g (0.135 mol) of phthalic anhydride and 140 mg (1.22 mmol) of

4-dimethylaminopyridine were refluxed in 0.4 l of acetonitrile for 2.5 hours. The mixture was cooled to 5°C and filtered obtaining a first crop of product (24.2 g). The mother liquors were concentated under vacuum and treated with 70 ml of tert-buthyl methyl ether (MTBE): a second crop of product (5.8 g) was obtained by filtration. Then, a total of 30.0 g of product as a yellow solid were obtained. Yield = 83.6%. mp = 193-195°C

HPLC r.t. 4.7 $[M+H]^+$ = 294 $[2M+H]^+$ = 587 $[3M+H]^+$ = 880

H^1NMR (DMSO-d_6), diagnostic signals (ppm): 3.84 (s, 3H), 6.78 (dd, 1H), 6.96 (d, 1H), 7.55 (dd, 1H), 7.91-8.1 (m, 4H), 13.14 (s, 1H).

Example 3

2-({6-hydroxy}-1H-indazol-3-yl)-1H-isoindole-1,3(2H)-dione

A mixture of 24.2 g (82.5 mmol) of 2-({6-methoxy}-1H-indazol-3-yl)-1H-isoindole-1,3(2H)-dione and 73.4 g (0.635 mol) of piridine hydrochloride was heated at 200°C for 4 hours. The resulting brown solution was cooled to 140°C and slowly poured in a well stirred mixture of 250 ml of 0.2 N HCl and 350 ml of ethyl acetate. The organic layer was separated and the aqueous layer was salted (45 g of NaCl) and extracted twice with 350 ml of ethyl acetate. Organic extracts were dried over sodium sulfate and concentrated under vacuum to small volume. The precipitate was filtered off and dried: 15.89 g of product as yellow solid were obtained. Yield = 68.9%. mp = 265-270°C dec.

HPLC r.t. 3.7 $[M+H]^+$ = 280 $[2M+H]^+$ = 559 $[3M+H]^+$ = 838

H^1NMR (DMSO-d_6), diagnostic signals (ppm): 6.65 (dd, 1H), 6.8 (s, 1H), 7.44 (d, 1H), 7.97 (m, 4H), 9.73 (broad s, 1H) 12.86 (s, 1H).

Example 4

2-(6-{[tert-butyl(dimethyl)silyl]oxy}-1H-indazol-3-yl)-1H-isoindole-1,3(2H)-dione

To a suspension of 15.03 g (53.82 mmmol) of 2-({6-hydroxy}-1H-indazol-3-yl)-1H-isoindole-1,3(2H)-dione in 150 ml of dichloromethane, a solution of 20.19 g (0.134 mol) of TBDMS chloride in 75 ml of dichloromethane was added. The resulting mixture was treated dropwise with 12.06 ml (80.73 mmol) of 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature, obtaining a clear solution. After 3 hours the reaction mixture was poured in 250 ml of 0.5 N HCl. The aqueous layer was separated and extracted with 120 ml of dichloromethane. Organic extracts were dried over sodium sulfate and the solvent evaporated under vacuum. The moist raw product was stirred in 50 ml of ethyl acetate at 50°C. Then, about one half of the solvent was evaporated under vacuum and the mixture was treated dropwise with 100 ml of cyclohexane. The product was isolated by suction as light yellow solid (15.04 g). Yield = 71.0%. mp = 207-209°C. HPLC r.t. 7.6 $[M+H]^+$ = 394 $[2M+H]^+$ = 787

H^1NMR (DMSO-d_6), diagnostic signals (ppm): 0.21 (s, 6H), 0.98 (s, 9H), 6.71 (dd, 1H), 6.91 (d, 1H), 7.54 (d, 1H), 7.93 (m, 2H), 8.1 (m, 2H).

Example 5

5-benzyloxy-1H-indazol-3-amine

To an ice-cooled suspension of 63.27 g (0.282 mol) of 2-amino-5-(benzyloxy)benzonitrile in 500 ml of concentrated hydrochloric acid, a solution of 23.32 g (0.338 mol) of sodium nitrite in 75 ml of water was added dropwise. After 2 hours the cold suspension was added dropwise to a preformed solution of 509.25 g (2.26 mol) of stannous chloride in 380 ml of concentrated HCl, at 2°C. After 3 hours the cold suspension was filtered and the moist solid was treated with 1.8 l of boiling water and 300 ml of ethanol 95° for 30 min. The hot cloudy solution was clarified by filtration through a cloth filter. The liquors were concentrated to eliminate ethanol and treated dropwise

with 0.35 l of 35% NaOH at 4°C. The solid was filtered off and dried under vacuum at 50°C: 73.82 g of product were obtained as light brown solid. mp =193-195°C HPLC r.t. 4.7 $[M]^+$ = 240 $[2M+H]^+$ = 479

H^1NMR (DMSO-d_6), diagnostic signals (ppm): 5.03 (s, 2H), 5.16 (broad s, 1H), 6.96 (d, 1H), 7.13 (d, 1H), 7.26 (d, 1H), 7.27-7.49(m, 5H).

Example 6

2-[5-(benzyloxy)-1H-indazol-3-yl]-1H-isoindole-1,3(2H)-dione

73.82 g of 5-benzyloxy-1H-indazol-3-amine were treated under stirring with 3 l of acetonitrile. The liquor was decantated and the residue was treated with a mixture of 0.5 l of methanol and 0.5 l of ethyl acetate, under stirring. The remaining solid was filtered off (11.05 g of tin salts) and the liquor was evaporated to dryness under vacuum. The residue was dissolved in the former liquor and the solvent was removed under vacuum to a final volume of about 1 l. To this solution, 45.97 g (0.31 mol) of phthalic anhydride and 345 mg (2.82 mmol) of 4-dimethylamino pyridine were added. The mixture was refluxed for 2 hours, then, it was concentrated under vacuum to obtain a first crop of product (70.11 g). The mother liquors were concentated to dryness and the residue was treated with 30 ml of ethyl acetate and 100 ml of tert butyl methyl ether (MTBE): a second crop of product (9.75 g) was obtained by filtration. Then a total of 79.86 g of product as yellow solid were obtained. Yield = 76.6 % over two steps. mp = 190-192°C HPLC r.t. 6.5 min. $[M+H]^+$ = 370 $[2M+H]^+$ = 739

H^1NMR (DMSO-d_6), diagnostic signals (ppm): 5 (s, 2H), 7.14 (d, 1H), 7.3-7.47 (m, 5H), 7.52 (d, 2H), 8,(m, 4H), 13.27 (s, 1H).

Example 7

2-(5-hydroxy-1H-indazol-3-yl)-1H-isoindole-1,3(2H)-dione

A mixture of 46.14 g (0.125 mol) of 2-[5-(benzyloxy)-1H-indazol-3-yl]-1H-isoindole-1,3(2H)-dione and 143.35 g (1.24 mol) of piridine hydrochloride was heated at 180°C for 1.5 hours. The resulting brown solution was cooled to 120°C and slowly poured in a well stirred mixture of 800 ml of 0.5 N HCl. The precipitate was filtered off and dried: 32.26 g of product as yellow solid were obtained. Yield = 92.4%. mp >270°C HPLC r.t. 3.2 $[M+H]^+$ = 280 $[2M+H]^+$ = 559 H^1NMR (DMSO-d_6), diagnostic signals (ppm): 6.8 (s, 1H), 6.98 (d, 1H), 7.42 (d, 1H), 8 (m, 4H), 9.2 (s, 1H) 13.12 (s, 1H).

Example 8

2-[5-(tert-Butyl-dimethyl-silanyloxy)-1H-indazol-3-yl]-isoindole-1,3-dione

To a suspension of 32.26 g (0.115 mol) of 2-(5-hydroxy-1H-indazol-3-yl)-1H-isoindole-1,3(2H)-dione in 320 ml of dichloromethane, a solution of 43.54 g (0.288 mol) of TBDMS chloride in 150 ml of dichloromethane was added. The resulting mixture was treated dropwise with 35.5 ml (0.23 mol) of 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature, obtaining a clear solution. After 3 hours the reaction mixture was poured in 300 ml of a solution 0.1 N of hydrochloric acid. The aqueous layer was separated and extracted with 200 ml of dichloromethane. Organic extracts were dried over sodium sulfate and the solvent evaporated under vacuum. The raw product was purified by flash chromatography over silica gel eluiting with dichloromethane-cyclohexane-ethyl acetate (4:4:2). 36.03 g of product as white solid were obtained. Yield = 79.2%. mp = 225-228°C. HPLC r.t. 8.3 $[M+H]^+$ = 394 $[2M+H]^+$ = 787

H^1NMR (DMSO-d_6), diagnostic signals (ppm): 0.15 (s, 6H), 0.93 (s, 9H), 6.98 (dd, 1H), 7.07 (s, 1H), 7.49 (d, 1H), 7.96 (m, 4H), 13.25 (s, 1H).

Example 9

N-(6-hydroxy-1H-indazol-3-yl)benzamide

500 mg of Novabiochem trityl resin (declared substitution 1.27 mmol/g, 0.64 mmol) were suspended in dichloromethane and 374 mg of 2-[6-(tert-butyl-dimethyl-silanyloxy)-1H-indazol-3-yl]-isoindole-1,3-dione (0.9 mmol) and 367 µl of 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (1.3 mmol) were added. The suspension was stirred for 16 hours and then the resin was filtered and washed with dichloromethane, methanol, dimethylformamide, methanol and dichloromethane again. The resin was then dried under vacuum.

The identity of the resin and the yield of the loading step were checked by cleavage of the loaded product:

40 mg of resin were suspended in 1 ml of dichloromethane and 150 µl trifluoroacetic acid were added. After 2 hours the resin was drained and washed twice with 1 ml of dichloromethane; the collected solutions were dried and 13.8 mg of titled compound recovered. Calculated loading 0.85 mmol/g, HPLC r.t. Method 1: 7.64 [M+H]+= 394.

The resin obtained from the first step (500 mg, ~0.425 mmol) was suspended in 5 ml of mixture of dichloromethane and methanol 1:1 and 500 µl of hydrazine monohydrate were added. The suspension was heated to 45°C. Heating and stirring were continued overnight, and then the mixture was cooled down to room temperature. The resin was filtered and washed with a mixture of methanol and water 1:1, methanol, dimethylformamide, and methanol again before drying under vacuum.

The identity of the resin was checked by cleavage. The reaction was performed as described above.
Cleaved product: 6-{[tert-butyl(dimethyl)silyl]oxy}-1H-indazol-3-amine: HPLC r.t. Method 1: 5.99 [M+H]+= 264; [M-H]-= 262

A sample of the resin obtained from the second step (100 mg, 0.08 mmol) was suspended in 2.5 ml of dichloromethane; N,N'-diisoproylethylamine (131 µl, ~10 eq) and benzoyl chloride (30 µl, ~3eq) were added. Stirring at room temperature was maintained for 20 hours, the resin was filtered and washed with dichloromethane, methanol, dimethylformamide, methanol and dichloromethane again before drying under vacuum.
The identity of the resin was checked by cleavage of the loaded product. The reaction was performed as previously described.
Cleaved product: N-(6-{[tert-butyl(dimethyl)silyl]oxy}-1H-indazol-3-yl)benzamide HPLC r.t. Method 1: 7.47 [M+H]+= 368 [M-H]-= 366

The resin obtained from the previous step (100 mg, 0.08 mmol) was suspended in 3 ml of tetrahydrofuran anhydrous and 120 µl of a solution 1 M of tetrabutylammonium fluoride in tetrahydrofuran (~1.5 eq) were added. The suspension was stirred overnight then the resin was filtered and washed with dichloromethane, methanol, dimethylformamide, methanol and dichloromethane.

100 mg of resin were suspended in 3 ml of dichloromethane and 450 µl of trifluoroacetic acid were added. After 2 hours the resin was drained and washed twice with 1 ml of dichloromethane; the collected solutions were dried and the title compound recovered.

N-(6-hydroxy-1H-indazol-3-yl)benzamide HPLC Method 1 r.t. 3.5 [M+H]+= 253.99 [M-H]-= 252.

By proceeding in a manner similar to that of Example 9, 2-(6-{[tert-butyl(dimethyl)silyl]oxy}-1H-indazol-3-yl)-1H-isoindole-1,3(2H)-dione and 2-[5-(tert-Butyl-dimethyl-silanyloxy)-1H-indazol-3-yl]-isoindole-1,3-dione were supported on the resin and then, by following the described synthetic scheme, the products below were synthesized.

N-(5-Hydroxy-indazol-3-yl)-benzamide.: HPLC Method 1 r.t. 3.08 [M+H]+= 253.99

2-(4-tert-butylphenoxy)-N-(5-hydroxy-2H-indazol-3-yl)acetamide HPLC Method 1 r.t. 5.38 [M+H]+= 340.2

N-(5-hydroxy-2H-indazol-3-yl)-2-(4-methoxyphenyl)acetamide HPLC Method 1 r.t. 3.35 [M+H]+= 298.1

N-(6-hydroxy-2H-indazol-3-yl)-3-phenylpropanamide HPLC Method 1 r.t. 3.94 [M+H]+= 282.1

N-(6-hydroxy-2H-indazol-3-yl)cyclopropanecarboxamide HPLC Method 1 r.t. 2.36 [M+H]+= 218.1

By proceeding in the same way (example 9), 7 products were synthesized in parallel and coded in table IX, as formerly indicated; related HPLC retention time and the experimentally found [M+H]+ are reported.

Table IX

Entry	Compound	HPLC method	r.t. (min)	[M+H]+
1	A00-M1-B36	1	3.68	282.1
2	A00-M1-B31	1	2	218.1
3	A00-M1-B33	1	4.05	288
4	A00-M2-B68	1	3.08	235.1
5	A00-M2-B15	1	5.52	340.2
6	A00-M2-B35	1	3.62	298.1
7	A00-M2-B33	1	4.38	288

Example 10

N-Butyl-N'-(6-hydroxy-1H-indazol-3-yl)urea

500 mg of Novabiochem trityl resin (declared substitution 1.27 mmol/g, 0.64 mmol) were suspended in dichloromethane and 374 mg of 2-[6-(tert-butyl-dimethyl-silanyloxy)-1H-indazol-3-yl]-isoindole-1,3-dione (0.9 mmol) and 367 µl of 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (1.3 mmol) were added. The suspension was stirred for 16 hours and then the resin was filtered and washed with dichloromethane, methanol, dimethylformamide, methanol and dichloromethane again. The resin was then dried under vacuum.

The identity of the resin and the yield of the loading step were checked by cleavage of the loaded product:

40 mg of resin were suspended in 1 ml of dichloromethane and 150 µl trifluoroacetic acid were added. After 2 hours the resin was drained and washed twice with 1 ml of dichloromethane; the collected solutions were dried and 13.8 mg of titled compound recovered. Calculated loading 0.85 mmol/g, HPLC r.t. Method 1: 7.64 [M+H]+= 394.

The resin obtained from the first step (500 mg, ~0.425 mmol) was suspended in 5 ml of a mixture of dichloromethane and methanol 1:1 and 500 µl of hydrazine monohydrate were added. The suspension was heated to 45°C. Heating and stirring were continued overnight, and then the mixture was cooled down to room temperature. The resin was filtered and washed with a mixture of methanol and water 1:1, methanol, dimethylformamide, and methanol again.

The identity of the resin was checked by cleavage. The reaction was performed as described above.

Cleaved product: 6-{[tert-butyl(dimethyl)silyl]oxy}-1H-indazol-3-amine: HPLC r.t. Method 1: 5.99 [M+H]+= 264; [M-H]-= 262

A sample of the resin obtained from the second step (100 mg, 0.08 mmol) was suspended in 2 ml of dimethylformamide; N-butyl isocyanate (28 µl ~5 eq) was added. The suspension was heated to 50°C. Stirring and heating was maintained for 60 hours, then the suspension was cooled down to room temperature. The resin was filtered and washed with dichloromethane, methanol, dimethylformamide, methanol and dichloromethane, before drying under vacuum.

100 mg of resin were then suspended in 3 ml of dichloromethane and 450 µl trifluoroacetic acid were added. After 2 hours the resin was drained and washed twice with 1 ml of dichloromethane; the collected solutions were dried and the title compound recovered.

1-butyl-3-(6-hydroxy-1H-indazol-3-yl)-urea HPLC Method 1 r.t. 3.87 [M+H]+= 249 [M-H]-= 247.

By proceeding in a manner similar to that of Example 10, 2-(6-{[tert-butyl(dimethyl)silyl]oxy}-1H-indazol-3-yl)-1H-isoindole-1,3(2H)-dione and 2-[5-(tert-Butyl-dimethyl-silanyloxy)-1H-indazol-3-yl]-isoindole-1,3-dione were supported on the resin and then, by following the described synthetic scheme, the products below were synthesized.

1-butyl-3-(5-hydroxy-1H-indazol-3-yl)-urea HPLC Method 1 r.t. 3.65 [M+H]+= 249 [M-H]-= 247

N-benzyl-N'-(5-hydroxy-2H-indazol-3-yl)urea HPLC Method 1 r.t.: 4 [M+H]+= 283.1

N-(5-hydroxy-2H-indazol-3-yl)-N'-isopropylurea HPLC Method 1 r.t.: 2.92 [M+H]+= 235.1

N-(6-hydroxy-2H-indazol-3-yl)-N'-phenylurea HPLC Method 1 r.t.: 4.4 [M+H]+= 269.1

By proceeding in the same way (example 10), 13 products were synthesized in parallel and coded in table X, as

formerly indicated; related HPLC retention time and the experimentally found [M+H]+ are reported.

Table X

Entry	Compound	HPLC method	r.t. (min)	[M+H]+
1	A00-M1-B68	3	1.39	235.1
2	A00-M1-B63	3	1.89	283.1
3	A00-M1-B78	3	1.85	297.1
4	A00-M1-B79	3	1.71	299.1
5	A00-M1-B62	3	1.77	299.1
6	A00-M1-B64	3	2.01	303.1
7	A00-M1-B66	3	1.65	311.1
8	A00-M1-B17	3	1.33	311.1
9	A00-M1-B74	3	1.83	329.1
10	A00-M1-B76	3	2.12	337.1
11	A00-M1-B65	3	2.27	345.1
12	A00-M2-B83	1	4.15	283.1
13	A00-M1-B82	1	4.15	269.1

Example 11

N-(6-Benzyloxy-1H-indazol-3-yl)-benzamide

500 mg of Novabiochem trityl resin (declared substitution 1.27 mmol/g, 0.64 mmol) were suspended in dichloromethane and 374 mg of 2-[6-(tert-butyl-dimethyl-silanyloxy)-1H-indazol-3-yl]-isoindole-1,3-dione (0.9 mmol) and 367 µl of 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (1.3 mmol) were added. The suspension was stirred for 16 hours and then the resin was filtered and washed with dichloromethane, methanol, dimethylformamide, methanol and dichloromethane again. The resin was then dried under vacuum.

The identity of the resin and the yield of the loading step were checked by cleavage of the loaded product:

40 mg of resin were suspended in 1 ml of dichloromethane and 150 µl trifluoroacetic acid were added. After 2 hours the resin was drained and washed twice with 1 ml of dichloromethane; the collected solutions were dried and 13.8 mg of titled compound recovered. Calculated loading 0.85 mmol/g, HPLC r.t. Method 1: 7.64 [M+H]+= 394.

The resin obtained from the first step (500 mg, ~0.425 mmol) was suspended in 5 ml of a mixture of dichloromethane and methanol 1:1 and 500 µl of hydrazine monohydrate were added. The suspension was heated to 45°C. Heating and stirring were continued overnight, and then the mixture was cooled down to room temperature. The resin was filtered and washed with a mixture of methanol and water 1:1, methanol, dimethylformamide, and methanol again before drying under vacuum.

The identity of the resin was checked by cleavage. The reaction was performed as described above.

6-{[tert-butyl(dimethyl)silyl]oxy}-1H-indazol-3-amine HPLC r.t. Method 1: 5.99 [M+H]+= 264 [M-H]-= 262

A sample of the resin obtained from the second step (100 mg, 0.08 mmol) was suspended in 2.5 ml of dichloromethane; N,N'-diisoproylethylamine (131 µl, ~10 eq) and benzoyl chloride (30 µl, ~3eq) were added. Stirring at room temperature was maintained for 20 hours, then the resin was filtered and washed with dichloromethane, methanol, dimethylformamide, methanol and dichloromethane again before drying under vacuum.

The identity of the resin was checked by cleavage of the loaded product. The reaction was performed as previously described.

N-(6-{[tert-butyl(dimethyl)silyl]oxy}-1H-indazol-3-yl)benzamide HPLC Method 1 r.t.: 7.47 [M+H]+= 368 [M-H]-= 366

The resin obtained from the third step (100 mg, 0.08 mmol) was suspended in 3 ml of tetrahydrofuran anhydrous and 120 µl of a solution 1 M of tetrabutylammonium fluoride in tetrahydrofuran (~1.5 eq) were added. The suspension was stirred overnight then the resin was filtered and washed

with dichloromethane, methanol, dimethylformamide, methanol and dichloromethane.

The identity of the resin was checked by cleavage of the loaded product. The reaction was performed as previously described.

N-(6-hydroxy-1H-indazol-3-yl)benzamide HPLC Method 1 r.t. 3.5 [M+H]+= 253.99 [M-H]-= 252.

The resin obtained from the fourth step (100 mg, 0.08 mmol) were suspended in 3 ml of 1-methyl-2-pyrrolidinone, then 43 µl of 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (~1.5 eq) and 57 µl of benzyl bromide (~6 eq) were added. The suspension was stirred for 16 hours. The resin was filtered and washed with dichloromethane, methanol, dimethylformamide, methanol and dichloromethane.

100 mg of dry resin were suspended in 3 ml of dichloromethane and 450 µl trifluoroacetic acid were added. After 2 hours the resin was drained and washed twice with 3 ml of dichloromethane; the collected solutions were dried and the desired title compound recovered.

N-(6-Benzyloxy-1H-indazol-3-yl)-benzamide HPLC r.t. Method 1: 6.17 [M+H]+= 344.

By proceeding in a manner similar to that of Example 11, 2-(6-{[tert-butyl(dimethyl)silyl]oxy}-1H-indazol-3-yl)-1H-isoindole-1,3(2H)-dione and 2-[5-(tert-Butyl-dimethyl-silanyloxy)-1H-indazol-3-yl]-isoindole-1,3-dione were supported on the resin and then, by following the described synthetic scheme, the products below were synthesized.

N-(5-benzyloxy-1H-indazol-3-yl)-benzamide HPLC r.t. 6.05 [M+H]+= 344;

Methyl 2-({3-[(3-phenylpropanoyl)amino]-1H-indazol-5-yl}oxy)butanoate HPLC Method 2 r.t. 8.2 [M+H]+= 382.1;

N-{5-[(2-oxo-1-phenylpyrrolidin-3-yl)oxy]-1H-indazol-3-yl}cyclopropanecarboxamide HPLC Method 2 r.t. 7.19 [M+H]+= 377.2;

Methyl 2-({3-[(cyclopropylcarbonyl)amino]-1H-indazol-5-yl}oxy)butanoate HPLC Method 2 r.t. 7.05 [M+H]+= 318.1

methyl 2-[(3-{[(4-methoxyphenyl)acetyl]amino}-1H-indazol-5-yl)oxy]butanoate HPLC Method 2 r.t. 7.78 [M+H]+= 398.2:

N-{6-[(2-methylbenzyl)oxy]-1H-indazol-3-yl}cyclopropanecarboxamide HPLC Method 2 r.t. 8.38 [M+H]+= 322.1;

N-{6-[(2-oxo-1-phenylpyrrolidin-3-yl)oxy]-1H-indazol-3-yl}cyclopropanecarboxamide HPLC Method 2 r.t. 7.41 [M+H]+= 377.2;

Methyl 2-({3-[(cyclopropylcarbonyl)amino]-1H-indazol-6-yl}oxy)butanoate HPLC Method 1 r.t. 4.31 [M+H]+= 318.1;

Methyl 2-({3-[(3-chlorobenzoyl)amino]-1H-indazol-6-yl}oxy)butanoate HPLC Method 1 r.t. 6.02 [M+H]+= 388.1

By proceeding in the same way (example 11), 806 products were synthesized in parallel and coded in table XI, as formerly indicated; related HPLC method and retention time together with experimentally found [M+H]+ are reported.

Table XI

Entry	compound	HPLC Method	r.t. (min)	[M+H]+	Entry	compound	HPLC Method	r.t. (min)	[M+H]+
1	A29-M1-B36	2	8.18	441.2	404	A02-M1-B10	3	2.06	404.2
2	A31-M1-B36	2	8.02	350.2	405	A03-M1-B10	3	2.37	472.1
3	A35-M1-B36	2	8.18	429.2	406	A03-M2-B10	3	2.48	472.1
4	A40-M1-B36	2	8.91	469.2	407	A04-M1-B10	3	2.07	422.1
5	A38-M1-B31	2	8.27	322.1	408	A04-M2-B10	3	2.2	422.1
6	A03-M1-B31	2	8.91	376.1	409	A05-M1-B10	3	2.3	500.1
7	A31-M1-B31	2	6.95	286.1	410	A05-M2-B10	3	2.41	500.1
8	A35-M1-B31	2	7.08	365.2	411	A06-M1-B10	3	1.85	354.1
9	A29-M1-B15	2	9.28	499.2	412	A07-M1-B10	3	2.17	440.1
10	A31-M1-B15	2	9.11	408.2	413	A07-M2-B10	3	2.28	440.1
11	A35-M1-B15	2	9.3	487.2	414	A08-M1-B10	3	2.3	488.1
12	A32-M1-B15	2	9.39	440.2	415	A08-M2-B10	3	2.41	488.1
13	A38-M1-B35	2	8.73	402.2	416	A09-M1-B10	3	2.14	464.2

14	A29-M1-B35	2	7.87	457.2		417	A10-M1-B10	3	2.24	458.1
15	A31-M1-B35	2	7.61	366.2		418	A10-M2-B10	3	2.27	458.1
16	A35-M1-B35	2	7.82	445.2		419	A11-M1-B10	3	2.2	470.1
17	A39-M1-B35	2	8.09	446.2		420	A11-M2-B10	3	2.27	470.1
18	A40-M1-B35	2	8.67	485.2		421	A12-M1-B10	3	2.05	380.2
19	A29-M1-B33	2	8.37	447.1		422	A12-M2-B10	3	2.09	380.2
20	A38-M2-B36	2	9.16	386.2		423	A14-M1-B10	3	2.07	366.1
21	A45-M2-B36	2	9.27	476.2		424	A15-M1-B10	3	2.33	449.1
22	A03-M2-B36	2	9.59	440.1		425	A16-M1-B10	3	2.19	429.1
23	A29-M2-B36	2	8.35	441.2		426	A18-M2-B10	3	2.4	440.1
24	A31-M2-B36	2	8.45	350.2		427	A18-M1-B10	3	2.3	440.1
25	A44-M2-B36	2	8.72	434.1		428	A20-M1-B10	3	2.5	472.1
26	A46-M2-B36	2	8.61	460.2		429	A21-M1-B10	3	1.85	360.1
27	A35-M2-B36	2	8.26	429.2		430	A22-M1-B10	3	2.74	540.1
28	A32-M2-B36	2	8.3	382.2		431	A23-M1-B10	3	2.47	438.1
29	A41-M2-B36	2	8.98	476.2		432	A24-M1-B10	3	2.35	458.1
30	A39-M2-B36	2	8.52	430.2		433	A25-M1-B10	3	2.55	490.1
31	A40-M2-B36	2	9.05	469.2		434	A26-M1-B10	3	2.01	374.1
32	A45-M2-B31	2	8.65	412.2		435	A27-M2-B10	3	2.41	448.2
33	A03-M2-B31	2	9.01	376.1		436	A02-M1-B11	3	2.25	362.1
34	A31-M2-B31	2	7.5	286.1		437	A02-M2-B11	3	2.3	362.1
35	A44-M2-B31	2	7.87	370.1		438	A03-M1-B11	3	2.55	430.0
36	A46-M2-B31	2	7.77	396.1		439	A03-M2-B11	3	2.59	430.0
37	A35-M2-B31	2	7.27	365.2		440	A04-M1-B11	3	2.25	380.1
38	A41-M2-B31	2	8.26	412.2		441	A04-M2-B11	3	2.31	380.1
39	A39-M2-B31	2	7.64	366.1		442	A05-M1-B11	3	2.47	458.0
40	A40-M2-B31	2	8.34	405.2		443	A05-M2-B11	3	2.52	458.0
41	A29-M2-B15	2	9.39	499.2		444	A06-M1-B11	3	2.03	312.1
42	A31-M2-B15	2	8.99	408.2		445	A07-M2-B11	3	2.39	398.1
43	A35-M2-B15	2	9.35	487.2		446	A08-M1-B11	3	2.53	446.1
44	A32-M2-B15	2	9.42	440.2		447	A08-M2-B11	3	2.52	446.1
45	A29-M2-B35	2	8.01	457.2		448	A10-M1-B11	3	2.41	416.1
46	A31-M2-B35	2	8.03	366.2		449	A10-M2-B11	3	2.39	416.1
47	A44-M2-B35	2	8.41	450.1		450	A11-M2-B11	3	2.38	428.1
48	A35-M2-B35	2	7.95	445.2		451	A12-M2-B11	3	2.21	338.1
49	A32-M2-B35	1	5.21	398.2		452	A13-M2-B11	3	2.54	492.1
50	A41-M2-B35	2	8.7	492.2		453	A14-M1-B11	3	2.17	324.1
51	A38-M2-B33	2	9.32	392.1		454	A15-M1-B11	3	2.43	407.1
52	A03-M2-B33	2	9.75	446.0		455	A16-M1-B11	3	2.29	387.1
53	A29-M2-B33	2	8.56	447.1		456	A17-M1-B11	3	2.07	381.1
54	A44-M2-B33	2	8.9	440.0		457	A18-M2-B11	3	2.51	398.1
55	A46-M2-B33	2	8.81	466.1		458	A18-M1-B11	3	2.41	398.1
56	A35-M2-B33	2	8.46	435.1		459	A20-M1-B11	3	2.61	430.1
57	A41-M2-B33	2	9.14	482.1		460	A21-M1-B11	3	1.94	318.1
58	A39-M2-B33	2	8.74	436.1		461	A22-M1-B11	3	2.85	498.1
59	A40-M2-B33	2	9.22	475.1		462	A23-M1-B11	3	2.57	396.1
60	A30-M1-B29	1	6.39	388.2		463	A24-M1-B11	3	2.46	416.1
61	A31-M1-B29	1	4.72	352.2		464	A25-M1-B11	3	2.67	448.1
62	A29-M1-B29	1	5.33	443.2		465	A26-M1-B11	3	2.13	332.1
63	A03-M1-B29	1	7.09	442.1		466	A27-M2-B11	3	2.51	406.1
64	A37-M1-B29	2	7.81	400.2		467	A01-M1-B12	3	2.11	376.1

65	A30-M2-B29	1	6.56	388.2	468	A02-M1-B12	3	2.42	428.1
66	A31-M2-B29	2	8.33	352.2	469	A02-M2-B12	3	2.54	428.1
67	A29-M2-B29	1	5.5	443.2	470	A03-M1-B12	3	2.69	496.0
68	A03-M2-B29	1	7.22	442.1	471	A03-M2-B12	3	2.73	496.0
69	A41-M2-B01	1	6.56	448.2	472	A04-M1-B12	3	2.42	446.1
70	A32-M2-B32	1	5.34	368.2	473	A05-M1-B12	3	2.63	524.0
71	A47-M2-B32	2	8.63	454.1	474	A05-M2-B12	3	2.69	524.0
72	A48-M2-B32	1	7.31	448.1	475	A06-M1-B12	3	2.25	378.1
73	A43-M2-B32	1	5.33	366.2	476	A07-M1-B12	3	2.49	464.1
74	A33-M1-B32	1	5.32	416.2	477	A07-M2-B12	3	2.55	464.1
75	A35-M1-B32	1	5.33	415.2	478	A08-M1-B12	3	2.6	512.1
76	A31-M1-B01	1	4.7	322.1	479	A09-M1-B12	3	2.54	488.1
77	A36-M1-B01	2	7.45	334.1	480	A09-M2-B12	3	2.56	488.1
78	A29-M1-B01	1	5.29	413.2	481	A10-M1-B12	3	2.64	482.1
79	A01-M1-B01	3	1.81	292.1	482	A10-M2-B12	3	2.63	482.1
80	A01-M2-B01	3	1.95	292.1	483	A11-M1-B12	3	2.57	494.1
81	A03-M1-B01	3	2.47	412.1	484	A11-M2-B12	3	2.6	494.1
82	A03-M2-B01	3	2.55	412.1	485	A12-M1-B12	3	2.49	404.1
83	A04-M1-B01	3	2.15	362.1	486	A13-M1-B12	3	2.75	558.1
84	A04-M2-B01	3	2.27	362.1	487	A14-M1-B12	3	2.47	390.1
85	A05-M1-B01	3	2.39	440.0	488	A15-M1-B12	3	2.67	473.1
86	A05-M2-B01	3	2.47	440.0	489	A16-M1-B12	3	2.57	453.1
87	A06-M1-B01	3	1.93	294.1	490	A17-M1-B12	3	2.39	447.1
88	A07-M1-B01	3	2.24	380.1	491	A18-M2-B12	3	2.77	464.1
89	A07-M2-B01	3	2.35	380.1	492	A18-M1-B12	3	2.67	464.1
90	A08-M1-B01	3	2.39	428.1	493	A20-M1-B12	3	2.85	496.1
91	A09-M1-B01	3	2.29	404.2	494	A21-M1-B12	3	2.31	384.1
92	A09-M2-B01	3	2.25	404.2	495	A22-M1-B12	3	3.05	564.1
93	A10-M1-B01	3	2.31	398.1	496	A23-M1-B12	3	2.83	462.1
94	A10-M2-B01	3	2.36	398.1	497	A24-M1-B12	3	2.71	482.1
95	A11-M1-B01	3	2.26	410.1	498	A25-M1-B12	3	2.89	514.1
96	A11-M2-B01	3	2.31	410.1	499	A26-M1-B12	3	2.43	398.1
97	A12-M1-B01	3	2.12	320.1	500	A27-M2-B12	3	2.77	472.1
98	A13-M2-B01	3	2.5	474.1	501	A01-M1-B13	3	1.39	341.2
99	A13-M1-B01	3	2.53	474.1	502	A02-M1-B13	3	1.7	393.2
100	A14-M1-B01	3	2.13	306.1	503	A03-M1-B13	3	2	461.1
101	A15-M1-B01	3	2.39	389.1	504	A12-M1-B13	3	1.67	369.2
102	A16-M1-B01	3	2.26	369.1	505	A13-M1-B13	3	2.08	523.2
103	A17-M1-B01	3	2.04	363.1	506	A14-M1-B13	3	1.7	355.2
104	A18-M2-B01	3	2.45	380.1	507	A18-M2-B13	3	2.07	429.2
105	A18-M1-B01	3	2.37	380.1	508	A20-M1-B13	3	2.29	461.2
106	A20-M1-B01	3	2.58	412.1	509	A22-M1-B13	3	2.5	529.2
107	A21-M1-B01	3	1.9	300.1	510	A27-M2-B13	3	2.06	437.2
108	A22-M1-B01	3	2.81	480.1	511	A01-M1-B14	3	1.95	336.1
109	A23-M1-B01	3	2.53	378.1	512	A01-M2-B14	3	2.04	336.1
110	A24-M1-B01	3	2.42	398.1	513	A02-M1-B14	3	2.27	388.2
111	A25-M1-B01	3	2.63	430.1	514	A03-M1-B14	3	2.57	456.1
112	A26-M1-B01	3	2.07	314.1	515	A03-M2-B14	3	2.61	456.1
113	A27-M2-B01	3	2.47	388.2	516	A04-M1-B14	3	2.28	406.1
114	A01-M1-B02	3	1.82	336.1	517	A04-M2-B14	3	2.38	406.1
115	A01-M2-B02	3	1.97	336.1	518	A05-M1-B14	3	2.51	484.1

116	A02-M1-B02	3	2.14	388.1		519	A05-M2-B14	3	2.57	484.1
117	A02-M2-B02	3	2.26	388.1		520	A06-M1-B14	3	2.07	338.1
118	A03-M1-B02	3	2.44	456.0		521	A07-M1-B14	3	2.43	424.1
119	A04-M1-B02	3	2.14	406.1		522	A07-M2-B14	3	2.45	424.1
120	A04-M2-B02	3	2.27	406.1		523	A08-M1-B14	3	2.49	472.1
121	A05-M1-B02	3	2.36	484.0		524	A08-M2-B14	3	2.55	472.1
122	A05-M2-B02	3	2.46	484.0		525	A09-M1-B14	3	2.41	448.2
123	A06-M1-B02	3	1.92	338.1		526	A09-M2-B14	3	2.41	448.2
124	A07-M1-B02	3	2.29	424.1		527	A10-M1-B14	3	2.51	442.1
125	A07-M2-B02	3	2.35	424.1		528	A10-M2-B14	3	2.51	442.1
126	A08-M1-B02	3	2.35	472.1		529	A11-M1-B14	3	2.46	454.2
127	A08-M2-B02	3	2.46	472.1		530	A11-M2-B14	3	2.47	454.2
128	A09-M1-B02	3	2.2	448.1		531	A12-M2-B14	3	2.35	364.2
129	A09-M2-B02	3	2.25	448.1		532	A13-M1-B14	3	2.64	518.2
130	A10-M1-B02	3	2.3	442.1		533	A14-M1-B14	3	2.27	350.1
131	A11-M1-B02	3	2.25	454.1		534	A15-M1-B14	3	2.51	433.1
132	A11-M2-B02	3	2.3	454.1		535	A16-M1-B14	3	2.39	413.2
133	A12-M1-B02	3	2.1	364.1		536	A17-M1-B14	3	2.19	407.2
134	A13-M2-B02	3	2.48	518.1		537	A18-M2-B14	3	2.59	424.1
135	A13-M1-B02	3	2.49	518.1		538	A18-M1-B14	3	2.5	424.1
136	A14-M1-B02	3	2.11	350.1		539	A20-M1-B14	3	2.7	456.1
137	A15-M1-B02	3	2.39	433.1		540	A21-M1-B14	3	2.09	344.1
138	A16-M1-B02	3	2.26	413.1		541	A22-M1-B14	3	2.93	524.1
139	A17-M1-B02	3	2.06	407.1		542	A23-M1-B14	3	2.66	422.1
140	A18-M2-B02	3	2.47	424.1		543	A24-M1-B14	3	2.54	442.1
141	A18-M1-B02	3	2.37	424.1		544	A25-M1-B14	3	2.75	474.1
142	A20-M1-B02	3	2.56	456.1		545	A26-M1-B14	3	2.24	358.1
143	A21-M1-B02	3	1.93	344.1		546	A27-M2-B14	3	2.57	432.2
144	A22-M1-B02	3	2.79	524.1		547	A01-M1-B15	3	2.32	378.2
145	A23-M1-B02	3	2.53	422.1		548	A01-M2-B15	3	2.43	378.2
146	A24-M1-B02	3	2.41	442.1		549	A02-M1-B15	3	2.61	430.2
147	A25-M1-B02	3	2.61	474.1		550	A02-M2-B15	3	2.65	430.2
148	A26-M1-B02	3	2.1	358.1		551	A03-M1-B15	3	2.85	498.1
149	A27-M2-B02	3	2.48	432.1		552	A04-M1-B15	3	2.61	448.2
150	A01-M1-B03	3	2.01	342.1		553	A04-M2-B15	3	2.65	448.2
151	A01-M2-B03	3	2.13	342.1		554	A05-M1-B15	3	2.79	526.1
152	A02-M1-B03	3	2.32	394.1		555	A05-M2-B15	3	2.84	526.1
153	A02-M2-B03	3	2.42	394.1		556	A06-M1-B15	3	2.45	380.2
154	A03-M1-B03	3	2.61	462.1		557	A07-M1-B15	3	2.67	466.2
155	A04-M1-B03	3	2.32	412.1		558	A08-M1-B15	3	2.76	514.2
156	A04-M2-B03	3	2.43	412.1		559	A08-M2-B15	3	2.81	514.2
157	A05-M1-B03	3	2.54	490.0		560	A09-M1-B15	3	2.73	490.2
158	A06-M1-B03	3	2.13	344.1		561	A09-M2-B15	3	2.72	490.2
159	A06-M2-B03	3	2.24	344.1		562	A10-M1-B15	3	2.81	484.2
160	A07-M1-B03	3	2.4	430.1		563	A11-M1-B15	3	2.75	496.2
161	A07-M2-B03	3	2.5	430.1		564	A11-M2-B15	3	2.75	496.2
162	A08-M1-B03	3	2.52	478.1		565	A12-M1-B15	3	2.67	406.2
163	A08-M2-B03	3	2.61	478.1		566	A12-M2-B15	3	2.67	406.2
164	A09-M1-B03	3	2.36	454.2		567	A13-M2-B15	3	2.92	560.2
165	A09-M2-B03	3	2.41	454.2		568	A13-M1-B15	3	2.93	560.2
166	A10-M1-B03	3	2.46	448.1		569	A20-M1-B15	3	3.05	498.2

167	A11-M1-B03	3	2.4	460.1		570	A02-M1-B16	3	2.1	312.1
168	A11-M2-B03	3	2.46	460.1		571	A05-M1-B16	3	2.37	408.0
169	A12-M1-B03	3	2.29	370.1		572	A06-M1-B16	3	1.74	262.1
170	A12-M2-B03	3	2.37	370.1		573	A08-M1-B16	3	2.41	396.1
171	A14-M1-B03	3	2.34	356.1		574	A11-M1-B16	3	2.21	378.1
172	A15-M1-B03	3	2.57	439.1		575	A14-M1-B16	3	1.72	274.1
173	A16-M1-B03	3	2.46	419.1		576	A15-M1-B16	3	2.11	357.1
174	A17-M1-B03	3	2.26	413.2		577	A16-M1-B16	3	1.95	337.1
175	A18-M2-B03	3	2.65	430.1		578	A17-M1-B16	3	1.67	331.1
176	A18-M1-B03	3	2.55	430.1		579	A18-M1-B16	3	2.06	348.1
177	A20-M1-B03	3	2.75	462.1		580	A04-M1-B16	3	2.11	330.1
178	A21-M1-B03	3	2.17	350.1		581	A20-M1-B16	3	2.3	380.1
179	A22-M1-B03	3	2.97	530.1		582	A21-M1-B16	3	1.47	268.1
180	A23-M1-B03	3	2.71	428.1		583	A22-M1-B16	3	2.58	448.1
181	A24-M1-B03	3	2.59	448.1		584	A23-M1-B16	3	2.22	346.1
182	A25-M1-B03	3	2.8	480.1		585	A24-M1-B16	3	2.11	366.1
183	A26-M1-B03	3	2.29	364.1		586	A25-M1-B16	3	2.37	398.1
184	A27-M2-B03	3	2.66	438.2		587	A26-M1-B16	3	1.71	282.1
185	A01-M1-B04	3	1.62	282.1		588	A15-M1-B17	3	2.23	446.1
186	A01-M2-B04	3	1.76	282.1		589	A16-M1-B17	3	2.09	426.1
187	A02-M1-B04	3	1.99	334.1		590	A17-M1-B17	3	1.86	420.2
188	A02-M2-B04	3	2.11	334.1		591	A18-M1-B17	3	2.17	437.1
189	A03-M1-B04	3	2.32	402.0		592	A20-M1-B17	3	2.39	469.1
190	A03-M2-B04	3	2.41	402.0		593	A21-M1-B17	3	1.73	357.1
191	A04-M1-B04	3	2.01	352.1		594	A22-M1-B17	3	2.63	537.1
192	A04-M2-B04	3	2.13	352.1		595	A23-M1-B17	3	2.33	435.1
193	A05-M1-B04	3	2.24	430.0		596	A24-M1-B17	3	2.24	455.1
194	A05-M2-B04	3	2.34	430.0		597	A25-M1-B17	3	2.43	487.1
195	A06-M1-B04	3	1.75	284.1		598	A26-M1-B17	3	1.88	371.1
196	A06-M2-B04	3	1.89	284.1		599	A02-M1-B18	3	2.62	422.0
197	A07-M1-B04	3	2.1	370.1		600	A05-M1-B18	3	2.87	517.9
198	A07-M2-B04	3	2.21	370.1		601	A06-M1-B18	3	2.39	372.0
199	A08-M1-B04	3	2.25	418.1		602	A08-M1-B18	3	2.86	506.0
200	A08-M2-B04	3	2.35	418.1		603	A10-M1-B18	3	2.72	476.0
201	A09-M1-B04	3	2.08	394.1		604	A11-M1-B18	3	2.65	488.0
202	A09-M2-B04	3	2.1	394.1		605	A12-M1-B18	3	2.51	398.0
203	A10-M1-B04	3	2.19	388.1		606	A14-M1-B18	3	2.37	384.0
204	A11-M1-B04	3	2.14	400.1		607	A15-M1-B18	3	2.61	467.0
205	A11-M2-B04	3	2.17	400.1		608	A16-M1-B18	3	2.49	447.0
206	A12-M1-B04	3	1.98	310.1		609	A17-M1-B18	3	2.29	441.0
207	A13-M2-B04	3	2.35	464.1		610	A18-M1-B18	3	2.61	458.0
208	A13-M1-B04	3	2.39	464.1		611	A04-M1-B18	3	2.63	440.0
209	A14-M1-B04	3	1.94	296.1		612	A20-M1-B18	3	2.79	490.0
210	A15-M1-B04	3	2.25	379.1		613	A21-M1-B18	3	2.18	378.0
211	A16-M1-B04	3	2.11	359.1		614	A22-M1-B18	3	3.01	558.0
212	A17-M1-B04	3	1.87	353.1		615	A23-M1-B18	3	2.77	456.0
213	A18-M2-B04	3	2.31	370.1		616	A24-M1-B18	3	2.63	476.0
214	A18-M1-B04	3	2.22	370.1		617	A25-M1-B18	3	2.83	508.0
215	A20-M1-B04	3	2.43	402.1		618	A26-M1-B18	3	2.34	392.0
216	A21-M1-B04	3	1.69	290.1		619	A02-M1-B19	3	2.45	362.1
217	A22-M1-B04	3	2.69	470.1		620	A05-M1-B19	3	2.7	458.0

218	A23-M1-B04	3	2.39	368.1		621	A06-M1-B19	3	2.2	312.1
219	A24-M1-B04	3	2.27	388.1		622	A08-M1-B19	3	2.7	446.1
220	A25-M1-B04	3	2.49	420.1		623	A10-M1-B19	3	2.56	416.1
221	A26-M1-B04	3	1.9	304.1		624	A11-M1-B19	3	2.5	428.1
222	A27-M2-B04	3	2.31	378.1		625	A12-M1-B19	3	2.33	338.1
223	A01-M1-B05	3	1.84	335.1		626	A14-M1-B19	3	2.17	324.1
224	A01-M2-B05	3	2.01	335.1		627	A15-M1-B19	3	2.45	407.1
225	A02-M1-B05	3	2.2	387.2		628	A16-M1-B19	3	2.31	387.1
226	A02-M2-B05	3	2.32	387.2		629	A17-M1-B19	3	2.1	381.1
227	A03-M1-B05	3	2.51	455.1		630	A18-M1-B19	3	2.43	398.1
228	A04-M1-B05	3	2.2	405.2		631	A04-M1-B19	3	2.46	380.1
229	A04-M2-B05	3	2.33	405.2		632	A20-M1-B19	3	2.62	430.1
230	A05-M1-B05	3	2.43	483.1		633	A21-M1-B19	3	1.98	318.1
231	A05-M2-B05	3	2.53	483.1		634	A22-M1-B19	3	2.85	498.1
232	A06-M1-B05	3	1.97	337.2		635	A23-M1-B19	3	2.58	396.1
233	A06-M2-B05	3	2.12	337.2		636	A24-M1-B19	3	2.47	416.1
234	A07-M1-B05	3	2.29	423.2		637	A25-M1-B19	3	2.68	448.1
235	A07-M2-B05	3	2.4	423.2		638	A26-M1-B19	3	2.15	332.1
236	A08-M1-B05	3	2.43	471.2		639	A02-M1-B20	3	2.82	416.2
237	A08-M2-B05	3	2.53	471.2		640	A05-M1-B20	3	3.06	512.1
238	A09-M1-B05	3	2.26	447.2		641	A06-M1-B20	3	2.65	366.2
239	A09-M2-B05	3	2.3	447.2		642	A08-M1-B20	3	3.03	500.2
240	A10-M2-B05	3	2.4	441.1		643	A10-M1-B20	3	2.91	470.2
241	A11-M1-B05	3	2.31	453.2		644	A11-M1-B20	3	2.84	482.2
242	A11-M2-B05	3	2.36	453.2		645	A12-M1-B20	3	2.73	392.2
243	A12-M1-B05	3	2.18	363.2		646	A14-M1-B20	3	2.59	378.2
244	A13-M2-B05	3	2.54	517.2		647	A15-M1-B20	3	2.79	461.2
245	A13-M1-B05	3	2.57	517.2		648	A16-M1-B20	3	2.69	441.2
246	A14-M1-B05	3	2.19	349.2		649	A17-M1-B20	3	2.53	435.2
247	A15-M1-B05	3	2.46	432.2		650	A18-M1-B20	3	2.8	452.2
248	A16-M1-B05	3	2.32	412.2		651	A04-M1-B20	3	2.83	434.2
249	A17-M1-B05	3	2.11	406.2		652	A20-M1-B20	3	2.98	484.2
250	A18-M2-B05	3	2.53	423.2		653	A21-M1-B20	3	2.44	372.2
251	A21-M1-B05	3	1.98	343.1		654	A22-M1-B20	3	3.18	552.2
252	A26-M1-B05	3	2.15	357.2		655	A23-M1-B20	3	2.96	450.2
253	A27-M2-B05	3	2.53	431.2		656	A24-M1-B20	3	2.83	470.2
254	A01-M1-B06	3	2.07	360.1		657	A25-M1-B20	3	3.02	502.2
255	A01-M2-B06	3	2.22	360.1		658	A26-M1-B20	3	2.57	386.2
256	A02-M1-B06	3	2.44	412.1		659	A02-M1-B21	3	2.64	396.1
257	A02-M2-B06	3	2.48	412.1		660	A05-M1-B21	3	2.89	492.0
258	A03-M1-B06	3	2.65	480.0		661	A06-M1-B21	3	2.41	346.1
259	A03-M2-B06	3	2.75	480.0		662	A08-M1-B21	3	2.87	480.1
260	A04-M1-B06	3	2.39	430.1		663	A10-M1-B21	3	2.74	450.1
261	A04-M2-B06	3	2.49	430.1		664	A11-M1-B21	3	2.67	462.1
262	A05-M1-B06	3	2.59	508.0		665	A12-M1-B21	3	2.56	372.1
263	A05-M2-B06	3	2.66	508.0		666	A14-M1-B21	3	2.39	358.1
264	A06-M1-B06	3	2.21	362.1		667	A15-M1-B21	3	2.62	441.1
265	A06-M2-B06	3	2.32	362.1		668	A16-M1-B21	3	2.5	421.1
266	A07-M1-B06	3	2.51	448.1		669	A17-M1-B21	3	2.31	415.1
267	A07-M2-B06	3	2.56	448.1		670	A18-M1-B21	3	2.62	432.1
268	A08-M1-B06	3	2.57	496.1		671	A04-M1-B21	3	2.65	414.1

269	A08-M2-B06	3	2.66	496.1	672	A20-M1-B21	3	2.81	464.1
270	A09-M1-B06	3	2.42	472.1	673	A21-M1-B21	3	2.21	352.1
271	A09-M2-B06	3	2.48	472.1	674	A22-M1-B21	3	3.02	532.1
272	A10-M1-B06	3	2.51	466.1	675	A23-M1-B21	3	2.79	430.0
273	A10-M2-B06	3	2.6	466.1	676	A24-M1-B21	3	2.65	450.1
274	A11-M1-B06	3	2.45	478.1	677	A25-M1-B21	3	2.84	482.1
275	A12-M1-B06	3	2.36	388.1	678	A26-M1-B21	3	2.36	366.1
276	A12-M2-B06	3	2.42	388.1	679	A02-M1-B22	3	2.63	438.2
277	A13-M2-B06	3	2.71	542.1	680	A05-M1-B22	3	2.87	534.1
278	A14-M1-B06	3	2.43	374.1	681	A06-M1-B22	3	2.42	388.2
279	A16-M1-B06	3	2.52	437.1	682	A08-M1-B22	3	2.86	522.2
280	A17-M1-B06	3	2.36	431.1	683	A10-M1-B22	3	2.73	492.1
281	A18-M2-B06	3	2.74	448.1	684	A11-M1-B22	3	2.67	504.2
282	A18-M1-B06	3	2.64	448.1	685	A12-M1-B22	3	2.53	414.2
283	A20-M1-B06	3	2.81	480.1	686	A14-M1-B22	3	2.4	400.2
284	A21-M1-B06	3	2.27	368.1	687	A15-M1-B22	3	2.62	483.2
285	A22-M1-B06	3	3.02	548.1	688	A16-M1-B22	3	2.51	463.2
286	A23-M1-B06	3	2.79	446.1	689	A17-M1-B22	3	2.32	457.2
287	A24-M1-B06	3	2.67	466.1	690	A18-M1-B22	3	2.6	474.2
288	A25-M1-B06	3	2.85	498.1	691	A04-M1-B22	3	2.64	456.2
289	A26-M1-B06	3	2.39	382.1	692	A20-M1-B22	3	2.8	506.2
290	A27-M2-B06	3	2.74	456.1	693	A21-M1-B22	3	2.23	394.1
291	A01-M1-B07	3	2.21	360.0	694	A22-M1-B22	3	3.02	574.1
292	A01-M2-B07	3	2.37	360.0	695	A23-M1-B22	3	2.77	472.1
293	A02-M1-B07	3	2.55	412.1	696	A24-M1-B22	3	2.63	492.1
294	A02-M2-B07	3	2.66	412.1	697	A25-M1-B22	3	2.84	524.2
295	A03-M1-B07	3	2.83	480.0	698	A26-M1-B22	3	2.36	408.2
296	A04-M1-B07	3	2.55	430.0	699	A02-M1-B23	3	2.55	384.0
297	A04-M2-B07	3	2.65	430.0	700	A06-M1-B23	3	2.3	334.0
298	A05-M1-B07	3	2.77	508.0	701	A08-M1-B23	3	2.81	468.0
299	A06-M1-B07	3	2.37	362.0	702	A10-M1-B23	3	2.66	438.0
300	A06-M2-B07	3	2.49	362.0	703	A11-M1-B23	3	2.59	450.0
301	A07-M1-B07	3	2.61	448.0	704	A12-M1-B23	3	2.43	360.0
302	A07-M2-B07	3	2.73	448.0	705	A14-M1-B23	3	2.27	346.0
303	A08-M1-B07	3	2.73	496.0	706	A15-M1-B23	3	2.55	429.0
304	A08-M2-B07	3	2.81	496.0	707	A16-M1-B23	3	2.4	409.0
305	A09-M1-B07	3	2.67	472.1	708	A17-M1-B23	3	2.19	403.1
306	A09-M2-B07	3	2.65	472.1	709	A18-M1-B23	3	2.53	420.0
307	A10-M1-B07	3	2.65	466.0	710	A04-M1-B23	3	2.57	402.0
308	A11-M1-B07	3	2.58	478.0	711	A20-M1-B23	3	2.73	452.0
309	A11-M2-B07	3	2.68	478.0	712	A21-M1-B23	3	2.07	340.0
310	A12-M1-B07	3	2.51	388.1	713	A22-M1-B23	3	2.96	520.0
311	A13-M2-B07	3	2.88	542.1	714	A23-M1-B23	3	2.7	418.0
312	A14-M1-B07	3	2.57	374.0	715	A24-M1-B23	3	2.57	438.0
313	A15-M1-B07	3	2.78	457.0	716	A25-M1-B23	3	2.77	470.0
314	A16-M1-B07	3	2.67	437.0	717	A26-M1-B23	3	2.25	354.0
315	A17-M1-B07	3	2.49	431.1	718	A02-M1-B24	3	2.27	363.1
316	A18-M2-B07	3	2.91	448.0	719	A05-M1-B24	3	2.54	459.0
317	A18-M1-B07	3	2.8	448.0	720	A06-M1-B24	3	1.99	313.1
318	A20-M1-B07	3	2.98	480.0	721	A08-M1-B24	3	2.55	447.1
319	A21-M1-B07	3	2.39	368.0	722	A10-M1-B24	3	2.39	417.1

320	A22-M1-B07	3	3.19	548.0	723	A11-M1-B24	3	2.34	429.1
321	A23-M1-B07	3	2.97	446.0	724	A12-M1-B24	3	2.14	339.1
322	A24-M1-B07	3	2.83	466.0	725	A14-M1-B24	3	1.98	325.1
323	A25-M1-B07	3	3.03	498.0	726	A15-M1-B24	3	2.27	408.1
324	A26-M1-B07	3	2.55	382.0	727	A16-M1-B24	3	2.13	388.1
325	A27-M2-B07	3	2.91	456.1	728	A17-M1-B24	3	1.89	382.1
326	A01-M1-B08	3	1.93	336.1	729	A18-M1-B24	3	2.25	399.1
327	A01-M2-B08	3	2.06	336.1	730	A04-M1-B24	3	2.29	381.1
328	A02-M1-B08	3	2.26	388.2	731	A20-M1-B24	3	2.46	431.1
329	A03-M1-B08	3	2.55	456.1	732	A21-M1-B24	3	1.74	319.1
330	A04-M1-B08	3	2.26	406.1	733	A22-M1-B24	3	2.71	499.1
331	A05-M1-B08	3	2.49	484.1	734	A23-M1-B24	3	2.41	397.1
332	A05-M2-B08	3	2.55	484.1	735	A24-M1-B24	3	2.29	417.1
333	A06-M1-B08	3	2.05	338.1	736	A25-M1-B24	3	2.51	449.1
334	A06-M2-B08	3	2.16	338.1	737	A26-M1-B24	3	1.95	333.1
335	A07-M1-B08	3	2.35	424.1	738	A02-M1-B25	3	2.63	372.2
336	A07-M2-B08	3	2.43	424.1	739	A05-M1-B25	3	2.89	468.1
337	A08-M1-B08	3	2.48	472.1	740	A06-M1-B25	3	2.41	322.1
338	A08-M2-B08	3	2.55	472.1	741	A08-M1-B25	3	2.87	456.1
339	A09-M1-B08	3	2.31	448.2	742	A10-M1-B25	3	2.73	426.1
340	A09-M2-B08	3	2.34	448.2	743	A11-M1-B25	3	2.66	438.2
341	A10-M1-B08	3	2.41	442.1	744	A14-M1-B25	3	2.38	334.1
342	A10-M2-B08	3	2.44	442.1	745	A15-M1-B25	3	2.62	417.1
343	A11-M1-B08	3	2.36	454.2	746	A16-M1-B25	3	2.5	397.2
344	A11-M2-B08	3	2.4	454.2	747	A17-M1-B25	3	2.31	391.2
345	A12-M1-B08	3	2.24	364.2	748	A18-M1-B25	3	2.61	408.1
346	A12-M2-B08	3	2.27	364.2	749	A04-M1-B25	3	2.65	390.2
347	A13-M1-B08	3	2.63	518.2	750	A20-M1-B25	3	2.8	440.2
348	A14-M1-B08	3	2.27	350.1	751	A21-M1-B25	3	2.21	328.1
349	A15-M1-B08	3	2.51	433.1	752	A22-M1-B25	3	3.02	508.1
350	A16-M1-B08	3	2.39	413.2	753	A23-M1-B25	3	2.77	406.1
351	A17-M1-B08	3	2.19	407.2	754	A24-M1-B25	3	2.65	426.1
352	A18-M2-B08	3	2.57	424.1	755	A25-M1-B25	3	2.83	458.1
353	A18-M1-B08	3	2.49	424.1	756	A26-M1-B25	3	2.35	342.2
354	A20-M1-B08	3	2.69	456.1	757	A14-M1-B26	3	3.49	328.2
355	A21-M1-B08	3	2.09	344.1	758	A15-M1-B26	3	3.53	411.2
356	A22-M1-B08	3	2.92	524.1	759	A16-M1-B26	3	3.49	391.2
357	A23-M1-B08	3	2.65	422.1	760	A17-M1-B26	3	3.39	385.2
358	A24-M1-B08	3	2.53	442.1	761	A20-M1-B26	3	3.77	434.2
359	A25-M1-B08	3	2.73	474.1	762	A21-M1-B26	3	3.31	322.2
360	A26-M1-B08	3	2.23	358.1	763	A23-M1-B26	3	3.8	400.2
361	A27-M2-B08	3	2.58	432.2	764	A24-M1-B26	3	3.61	420.2
362	A01-M1-B09	3	2.23	348.2	765	A25-M1-B26	3	3.79	452.2
363	A01-M2-B09	3	2.37	348.2	766	A26-M1-B26	3	3.45	336.2
364	A02-M1-B09	3	2.55	400.2	767	A02-M1-B27	3	2.5	404.2
365	A02-M2-B09	3	2.63	400.2	768	A05-M1-B27	3	2.75	500.1
366	A03-M1-B09	3	2.82	468.1	769	A06-M1-B27	3	2.27	354.1
367	A03-M2-B09	3	2.89	468.1	770	A08-M1-B27	3	2.74	488.1
368	A04-M1-B09	3	2.55	418.2	771	A10-M1-B27	3	2.61	458.1
369	A04-M2-B09	3	2.63	418.2	772	A11-M1-B27	3	2.54	470.1
370	A05-M1-B09	3	2.75	496.1	773	A12-M1-B27	3	2.38	380.2

371	A05-M2-B09	3	2.81	496.1	774	A14-M1-B27	3	2.25	366.1
372	A06-M1-B09	3	2.38	350.2	775	A15-M1-B27	3	2.49	449.1
373	A06-M2-B09	3	2.48	350.2	776	A16-M1-B27	3	2.37	429.1
374	A07-M1-B09	3	2.61	436.2	777	A17-M1-B27	3	2.17	423.2
375	A07-M2-B09	3	2.7	436.2	778	A18-M1-B27	3	2.47	440.1
376	A08-M1-B09	3	2.72	484.2	779	A04-M1-B27	3	2.51	422.1
377	A08-M2-B09	3	2.79	484.2	780	A20-M1-B27	3	2.66	472.1
378	A09-M1-B09	3	2.57	460.2	781	A21-M1-B27	3	2.06	360.1
379	A09-M2-B09	3	2.63	460.2	782	A22-M1-B27	3	2.89	540.1
380	A10-M1-B09	3	2.66	454.2	783	A23-M1-B27	3	2.63	438.1
381	A10-M2-B09	3	2.71	454.2	784	A24-M1-B27	3	2.51	458.1
382	A11-M1-B09	3	2.59	466.2	785	A25-M1-B27	3	2.7	490.4
383	A11-M2-B09	3	2.7	466.2	786	A26-M1-B27	3	2.22	374.4
384	A12-M1-B09	3	2.51	376.2	787	A02-M1-B28	3	2.65	541.2
385	A12-M2-B09	3	2.57	376.2	788	A05-M1-B28	3	2.86	637.1
386	A13-M2-B09	3	2.85	530.2	789	A06-M1-B28	3	2.47	491.2
387	A13-M1-B09	3	2.89	530.2	790	A08-M1-B28	3	2.85	625.2
388	A14-M1-B09	3	2.6	362.2	791	A10-M1-B28	3	2.73	595.2
389	A15-M1-B09	3	2.8	445.2	792	A11-M1-B28	3	2.68	607.2
390	A16-M1-B09	3	2.69	425.2	793	A12-M1-B28	3	2.56	517.2
391	A17-M1-B09	3	2.53	419.2	794	A14-M1-B28	3	2.44	503.2
392	A18-M2-B09	3	2.9	436.2	795	A15-M1-B28	3	2.63	586.2
393	A18-M1-B09	3	2.81	436.2	796	A16-M1-B28	3	2.54	566.2
394	A20-M1-B09	3	2.99	468.2	797	A17-M1-B28	3	2.37	560.2
395	A21-M1-B09	3	2.44	356.2	798	A18-M1-B28	3	2.63	577.2
396	A22-M1-B09	3	3.19	536.2	799	A04-M1-B28	3	2.65	559.2
397	A23-M1-B09	3	2.97	434.2	800	A20-M1-B28	3	2.79	609.2
398	A24-M1-B09	3	2.83	454.2	801	A21-M1-B28	3	2.31	497.2
399	A25-M1-B09	3	3.03	486.2	802	A22-M1-B28	3	3	677.2
400	A26-M1-B09	3	2.59	370.2	803	A23-M1-B28	3	2.76	575.1
401	A27-M2-B09	3	2.9	444.2	804	A24-M1-B28	3	2.65	595.2
402	A01-M1-B10	3	1.73	352.1	805	A25-M1-B28	3	2.83	627.2
403	A01-M2-B10	3	1.88	352.1	806	A26-M1-B28	3	2.42	511.6

Example 12

1-(6-Benzyloxy-1H-indazol-3-yl)-3-butyl-urea

500 mg of Novabiochem trityl resin (declared substitution 1.27 mmol/g, 0.64 mmol) were suspended in dichloromethane and 374 mg of 2-[6-(tert-butyl-dimethyl-silanyloxy)-1H-indazol-3-yl]-isoindole-1,3-dione (0.9 mmol) and 367 µl of 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (1.3 mmol) were added. The suspension was stirred for 16 hours and then the resin was filtered and washed with dichloromethane, methanol,

dimethylformamide, methanol and dichloromethane again. The resin was then dried under vacuum.

The identity of the resin and the yield of the loading step were checked by cleavage of the loaded product:

40 mg of resin were suspended in 1 ml of dichloromethane and 150 µl trifluoroacetic acid were added. After 2 hours the resin was drained and washed twice with 1 ml of dichloromethane; the collected solutions were dried and 13.8 mg of titled compound recovered. Calculated loading 0.85 mmol/g, HPLC r.t. Method 1: 7.64 [M+H]+= 394.

The resin obtained from the first step (300 mg, ~0.25 mmol) was suspended in 5 ml of a mixture of dichloromethane and methanol 1:1 and 400 µl of hydrazine monohydrate were added. The suspension was heated to 45°C. Heating and stirring were continued overnight, and then the mixture was cooled down to room temperature. The resin was filtered and washed with a mixture of methanol and water 1:1, methanol, dimethylformamide, and methanol again, before drying under vacuum.

The identity of the resin was checked by cleavage. The reaction was performed as described above.

Cleaved compound: 6-{[tert-butyl(dimethyl)silyl]oxy}-1H-indazol-3-amine: HPLC r.t. Method 1: 5.99 [M+H]+= 264; [M-H]-= 262

A sample of the resin obtained from the second step (100 mg, 0.08 mmol) was suspended in 2 ml of dimethylformamide; N-butyl isocyanate (28 µl ~5 eq) was added. The suspension was heated to 50°C. Stirring and heating was maintained for 60 hours, then the suspension was cooled down to room temperature. The resin was filtered and washed with dichloromethane, methanol, dimethylformamide, methanol and dichloromethane, before drying under vacuum.

The resin obtained from the third step (100 mg, 0.08 mmol) was suspended in 3 ml of tetrahydrofuran anhydrous and 120 µl of a solution 1 M of tetrabutylammonium fluoride in tetrahydrofuran (~1.5 eq) were added. The suspension was stirred overnight then the resin was filtered and washed with dichloromethane, methanol, dimethylformamide, methanol and dichloromethane.
Cleaved compound: 1-butyl-3-(6-hydroxy-1H-indazol-3-yl)-urea; HPLC Method 1 r.t. 3.87 [M+H]+= 249 [M-H]-= 247.

The resin obtained from the fourth step (100 mg, 0.08 mmol) were suspended in 3 ml of 1-methyl-2-pyrrolidinone, then 43 µl of 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (~1.5 eq) and 57 µl of benzyl bromide (~6 eq) were added. The suspension was stirred for 16 hours. The resin was filtered and washed with dichloromethane, methanol, dimethylformamide, methanol and dichloromethane.

100 mg of dry resin were suspended in 3 ml of dichloromethane and 450 µl trifluoroacetic acid were added. After 2 hours the resin was drained and washed twice with 3 ml of dichloromethane; the collected solutions were dried; the title compound recovered
1-(6-Benzyloxy-1H-indazol-3-yl)-3-butyl-urea: HPLC Method 3 r.t. 2.3 [M+H]+=339.3

By proceeding in a manner similar to that of Example 12, 2-(6-{[tert-butyl(dimethyl)silyl]oxy}-1H-indazol-3-yl)-1H-isoindole-1,3(2H)-dione and 2-[5-(tert-Butyl-dimethyl-silanyloxy)-1H-indazol-3-yl]-isoindole-1,3-dione were supported on the resin and then, by following the described synthetic scheme, the products below were synthesized.
1-(5-Benzyloxy-1H-indazol-3-yl)-3-butyl-urea : HPLC Method 3 r.t. 2.25 [M+H]+=339.3

methyl 2-({3-[(anilinocarbonyl)amino]-1H-indazol-5-yl}oxy)butanoate HPLC r.t. Method 1: 5.88 [M+H]+= 369.1

methyl 2-[(3-{[(benzylamino)carbonyl]amino}-1H-indazol-5-yl)oxy]butanoate HPLC r.t. Method 2: 8.19 [M+H]+= 383.2

N-isopropyl-N'-{5-[(2-oxo-1-phenylpyrrolidin-3-yl)oxy]-1H-indazol-3-yl}urea HPLC r.t. Method 2: 7.84 [M+H]+= 394.2

2-[(3-{[(isopropylamino)carbonyl]amino}-1H-indazol-5-yl)oxy]-N-phenylpropanamide HPLC r.t. Method 2: 7.76 [M+H]+= 382.2

methyl 2-[(3-{[(isopropylamino)carbonyl]amino}-1H-indazol-5-yl)oxy]butanoate HPLC r.t. Method 2: 7.65 [M+H]+= 335.2

N-isopropyl-N'-{6-[(2-oxo-1-phenylpyrrolidin-3-yl)oxy]-1H-indazol-3-yl}urea HPLC r.t. Method 2: 7.89 [M+H]+= 394.2

By proceeding in the same way (example 12), 506 products were synthesized in parallel and coded in table XII, as formerly indicated; related HPLC retention time and the experimentally found [M+H]+ are reported.

Table XII

Entry	Compound	Method HPLC	r.t. (min)	[M+H]+	Entry	Compound	Method HPLC	r.t. (min)	[M+H]+
1	A38-M1-B82	2	9.11	373.2	254	A14-M1-B69	3	2.52	349.2
2	A29-M1-B82	2	8.3	428.2	255	A15-M1-B69	3	2.74	432.2
3	A35-M1-B82	2	8.18	416.2	256	A16-M1-B69	3	2.64	412.2
4	A38-M1-B83	2	9.09	387.2	257	A17-M1-B69	3	2.46	406.2
5	A29-M1-B83	2	8.3	442.2	258	A18-M2-B69	3	2.77	423.2
6	A35-M1-B83	2	8.26	430.2	259	A18-M1-B69	3	2.75	423.2
7	A39-M1-B83	2	8.47	431.2	260	A20-M1-B69	3	2.93	455.2
8	A40-M1-B83	2	9.05	470.2	261	A21-M1-B69	3	2.37	343.1
9	A38-M1-B68	2	8.75	339.2	262	A22-M1-B69	3	3.13	523.1
10	A03-M1-B68	2	9.32	393.1	263	A23-M1-B69	3	2.91	421.1
11	A40-M1-B68	2	8.74	422.2	264	A24-M1-B69	3	2.79	441.1
12	A35-M2-B82	2	8.31	416.2	265	A25-M1-B69	3	2.97	473.2
13	A32-M2-B82	1	6.01	369.1	266	A26-M1-B69	3	2.51	357.2
14	A39-M2-B82	2	8.54	417.1	267	A27-M2-B69	3	2.77	431.2
15	A40-M2-B82	2	9.09	456.2	268	A01-M1-B70	3	2.2	373.1
16	A38-M2-B83	2	9.15	387.2	269	A01-M2-B70	3	2.22	373.1
17	A45-M2-B83	2	9.31	477.2	270	A02-M1-B70	3	2.44	425.1
18	A03-M2-B83	2	9.61	441.1	271	A03-M1-B70	3	2.7	493.1
19	A29-M2-B83	2	8.35	442.2	272	A04-M1-B70	3	2.45	443.1
20	A31-M2-B83	2	8.64	351.2	273	A05-M1-B70	3	2.63	521

21	A44-M2-B83	2	8.77	435.1	274	A05-M2-B70	3	2.61	521
22	A46-M2-B83	2	8.69	461.2	275	A06-M1-B70	3	2.27	375.1
23	A35-M2-B83	2	8.33	430.2	276	A06-M2-B70	3	2.33	375.1
24	A32-M2-B83	1	5.7	383.2	277	A07-M2-B70	3	2.55	461.1
25	A41-M2-B83	2	9.02	477.2	278	A08-M1-B70	3	2.61	509.1
26	A39-M2-B83	2	8.57	431.2	279	A09-M2-B70	3	2.48	485.2
27	A40-M2-B83	2	9.12	470.2	280	A10-M1-B70	3	2.57	479.1
28	A38-M2-B68	2	8.82	339.2	281	A10-M2-B70	3	2.56	479.1
29	A03-M2-B68	2	9.35	393.1	282	A11-M1-B70	3	2.51	491.1
30	A31-M2-B68	2	8.12	303.2	283	A11-M2-B70	3	2.52	491.1
31	A44-M2-B68	2	8.37	387.1	284	A12-M1-B70	3	2.41	401.1
32	A46-M2-B68	2	8.28	413.2	285	A12-M2-B70	3	2.43	401.1
33	A35-M2-B68	2	7.86	382.2	286	A13-M1-B70	3	2.76	555.1
34	A32-M2-B68	1	4.88	335.2	287	A14-M1-B70	3	2.5	387.1
35	A41-M2-B68	2	8.68	429.2	288	A18-M2-B70	3	2.71	461.1
36	A39-M2-B68	2	8.15	383.2	289	A01-M1-B71	3	1.96	339.1
37	A30-M1-B82	1	7.23	373.2	290	A02-M1-B71	3	2.27	391.1
38	A29-M1-B82	1	5.39	337.2	291	A02-M2-B71	3	2.33	391.1
39	A03-M1-B82	1	7.84	427.1	292	A03-M1-B71	3	2.55	459.1
40	A30-M2-B82	1	7.19	373.2	293	A03-M2-B71	3	2.58	459.1
41	A31-M2-B82	2	8.58	337.2	294	A04-M1-B71	3	2.28	409.1
42	A29-M2-B82	2	8.32	428.2	295	A04-M2-B71	3	2.34	409.1
43	A03-M2-B82	2	9.58	427.1	296	A05-M1-B71	3	2.49	487.1
44	A01-M1-B62	3	1.99	337.1	297	A05-M2-B71	3	2.52	487.1
45	A02-M1-B62	3	2.31	389.2	298	A06-M1-B71	3	2.09	341.1
46	A03-M1-B62	3	2.64	457.1	299	A08-M2-B71	3	2.52	475.1
47	A03-M2-B62	3	2.64	457.1	300	A09-M1-B71	3	2.31	451.2
48	A04-M1-B62	3	2.32	407.1	301	A10-M1-B71	3	2.42	445.1
49	A05-M1-B62	3	2.57	485.1	302	A11-M1-B71	3	2.36	457.1
50	A05-M2-B62	3	2.58	485.1	303	A11-M2-B71	3	2.37	457.1
51	A06-M1-B62	3	2.12	339.1	304	A12-M1-B71	3	2.24	367.1
52	A06-M2-B62	3	2.2	339.1	305	A12-M2-B71	3	2.25	367.1
53	A07-M1-B62	3	2.44	425.1	306	A13-M2-B71	3	2.54	521.2
54	A07-M2-B62	3	2.46	425.1	307	A14-M1-B71	3	2.29	353.1
55	A08-M1-B62	3	2.62	473.1	308	A15-M1-B71	3	2.51	436.1
56	A08-M2-B62	3	2.57	473.1	309	A16-M1-B71	3	2.41	416.1
57	A09-M1-B62	3	2.35	449.2	310	A17-M1-B71	3	2.21	410.2
58	A09-M2-B62	3	2.38	449.2	311	A18-M2-B71	3	2.53	427.1
59	A10-M1-B62	3	2.15	443.1	312	A18-M1-B71	3	2.49	427.1
60	A11-M1-B62	3	2.4	455.1	313	A20-M1-B71	3	2.69	459.1
61	A11-M2-B62	3	2.43	455.1	314	A21-M1-B71	3	2.13	347.1
62	A12-M1-B62	3	2.28	365.2	315	A22-M1-B71	3	2.91	527.1
63	A13-M2-B62	3	2.61	519.2	316	A23-M1-B71	3	2.65	425.1
64	A14-M1-B62	3	2.33	351.1	317	A24-M1-B71	3	2.54	445.1
65	A14-M2-B62	3	2.41	351.1	318	A25-M1-B71	3	2.72	477.1
66	A15-M1-B62	3	2.55	434.1	319	A26-M1-B71	3	2.26	361.1
67	A16-M1-B62	3	2.45	414.1	320	A27-M2-B71	3	2.54	435.2
68	A17-M1-B62	3	2.24	408.2	321	A01-M1-B72	3	1.88	287.1
69	A18-M2-B62	3	2.62	425.1	322	A03-M1-B72	3	2.55	407.1
70	A18-M1-B62	3	2.53	425.1	323	A04-M1-B72	3	2.26	357.2
71	A20-M1-B62	3	2.75	457.1	324	A04-M2-B72	3	2.31	357.2

72	A21-M1-B62	3	2.15	345.1	325	A05-M1-B72	3	2.48	435.1
73	A22-M1-B62	3	2.96	525.1	326	A05-M2-B72	3	2.53	435.1
74	A23-M1-B62	3	2.7	423.1	327	A06-M1-B72	3	2.03	289.2
75	A24-M1-B62	3	2.58	443.1	328	A07-M1-B72	3	2.33	375.2
76	A25-M1-B62	3	2.78	475.1	329	A08-M2-B72	3	2.5	423.2
77	A26-M1-B62	3	2.31	359.1	330	A09-M1-B72	3	2.27	399.2
78	A01-M1-B63	3	2.09	321.1	331	A10-M1-B72	3	2.39	393.1
79	A02-M1-B63	3	2.47	373.2	332	A11-M1-B72	3	2.34	405.2
80	A03-M1-B63	3	2.75	441.1	333	A11-M2-B72	3	2.34	405.2
81	A03-M2-B63	3	2.72	441.1	334	A12-M1-B72	3	2.19	315.2
82	A04-M1-B63	3	2.42	391.1	335	A12-M2-B72	3	2.21	315.2
83	A04-M2-B63	3	2.44	391.1	336	A13-M1-B72	3	2.62	469.2
84	A05-M1-B63	3	2.68	469.1	337	A14-M1-B72	3	2.21	301.2
85	A06-M1-B63	3	2.23	323.1	338	A15-M1-B72	3	2.47	384.2
86	A07-M2-B63	3	2.49	409.1	339	A16-M1-B72	3	2.35	364.2
87	A08-M1-B63	3	2.67	457.1	340	A17-M1-B72	3	2.13	358.2
88	A08-M2-B63	3	2.64	457.1	341	A18-M2-B72	3	2.49	375.2
89	A09-M1-B63	3	2.44	433.2	342	A18-M1-B72	3	2.45	375.2
90	A10-M1-B63	3	2.56	427.1	343	A20-M1-B72	3	2.66	407.2
91	A11-M1-B63	3	2.49	439.2	344	A21-M1-B72	3	2.03	295.1
92	A12-M1-B63	3	2.37	349.2	345	A22-M1-B72	3	2.9	475.1
93	A13-M2-B63	3	2.69	503.2	346	A23-M1-B72	3	2.61	373.1
94	A14-M1-B63	3	2.41	335.1	347	A24-M1-B72	3	2.5	393.1
95	A15-M1-B63	3	2.65	418.1	348	A25-M1-B72	3	2.7	425.2
96	A16-M1-B63	3	2.53	398.2	349	A26-M1-B72	3	2.17	309.2
97	A17-M1-B63	3	2.35	392.2	350	A01-M1-B73	3	2.19	361.1
98	A18-M2-B63	3	2.67	409.1	351	A02-M1-B73	3	2.51	413.1
99	A18-M1-B63	3	2.64	409.1	352	A06-M1-B73	3	2.33	363.1
100	A20-M1-B63	3	2.83	441.1	353	A07-M1-B73	3	2.6	449.1
101	A21-M1-B63	3	2.26	329.1	354	A07-M2-B73	3	2.57	449.1
102	A22-M1-B63	3	3.05	509.1	355	A08-M2-B73	3	2.7	497.1
103	A23-M1-B63	3	2.81	407.1	356	A10-M1-B73	3	2.63	467.1
104	A24-M1-B63	3	2.67	427.1	357	A11-M1-B73	3	2.57	479.1
105	A25-M1-B63	3	2.87	459.1	358	A11-M2-B73	3	2.58	479.1
106	A26-M1-B63	3	2.4	343.1	359	A12-M1-B73	3	2.47	389.1
107	A01-M1-B64	3	2.17	341.1	360	A12-M2-B73	3	2.49	389.1
108	A02-M1-B64	3	2.49	393.1	361	A13-M2-B73	3	2.77	543.1
109	A04-M1-B64	3	2.49	411.1	362	A14-M1-B73	3	2.55	375.1
110	A05-M1-B64	3	2.72	489	363	A18-M2-B73	3	2.77	449.1
111	A06-M1-B64	3	2.31	343.1	364	A27-M2-B73	3	2.78	457.1
112	A07-M1-B64	3	2.56	429.1	365	A01-M1-B74	3	2.08	367.1
113	A08-M1-B64	3	2.67	477.1	366	A01-M2-B74	3	2.11	367.1
114	A08-M2-B64	3	2.67	477.1	367	A02-M1-B74	3	2.39	419.2
115	A09-M1-B64	3	2.51	453.1	368	A02-M2-B74	3	2.41	419.2
116	A09-M2-B64	3	2.56	453.1	369	A03-M1-B74	3	2.67	487.1
117	A10-M1-B64	3	2.62	447.1	370	A04-M1-B74	3	2.4	437.2
118	A11-M1-B64	3	2.55	459.1	371	A04-M2-B74	3	2.41	437.2
119	A11-M2-B64	3	2.59	459.1	372	A05-M1-B74	3	2.59	515.1
120	A12-M1-B64	3	2.46	369.1	373	A05-M2-B74	3	2.6	515.1
121	A13-M2-B64	3	2.78	523.1	374	A06-M1-B74	3	2.21	369.1
122	A14-M1-B64	3	2.51	355.1	375	A06-M2-B74	3	2.23	369.1

123	A15-M1-B64	3	2.72	438.1		376	A07-M1-B74	3	2.49	455.1
124	A16-M1-B64	3	2.63	418.1		377	A07-M2-B74	3	1.18	455.1
125	A17-M1-B64	3	2.43	412.1		378	A08-M1-B74	3	2.58	503.1
126	A18-M2-B64	3	2.77	429.1		379	A08-M2-B74	3	2.6	503.1
127	A18-M1-B64	3	2.72	429.1		380	A09-M1-B74	3	2.37	479.2
128	A20-M1-B64	3	2.91	461.1		381	A09-M2-B74	3	2.4	479.2
129	A21-M1-B64	3	2.36	349.1		382	A11-M1-B74	3	2.41	485.2
130	A22-M1-B64	3	3.12	529.1		383	A11-M2-B74	3	2.44	485.2
131	A23-M1-B64	3	2.89	427.1		384	A12-M1-B74	3	2.29	395.2
132	A24-M1-B64	3	2.75	447.1		385	A12-M2-B74	3	2.33	395.2
133	A25-M1-B64	3	2.95	479.1		386	A13-M2-B74	3	2.62	549.2
134	A26-M1-B64	3	2.5	363.1		387	A13-M1-B74	3	2.69	549.2
135	A01-M1-B65	3	2.35	383.1		388	A14-M1-B74	3	2.35	381.1
136	A02-M1-B65	3	2.64	435.2		389	A14-M2-B74	3	2.43	381.1
137	A04-M1-B65	3	2.63	453.2		390	A15-M1-B74	3	2.58	464.1
138	A05-M1-B65	3	2.83	531.1		391	A16-M1-B74	3	2.47	444.2
139	A06-M1-B65	3	2.47	385.2		392	A17-M1-B74	3	2.28	438.2
140	A07-M2-B65	3	2.68	471.2		393	A18-M2-B74	3	2.61	455.1
141	A08-M1-B65	3	2.79	519.2		394	A18-M1-B74	3	2.56	455.1
142	A09-M1-B65	3	2.65	495.2		395	A21-M1-B74	3	2.2	375.1
143	A09-M2-B65	3	2.67	495.2		396	A22-M1-B74	3	2.97	555.1
144	A10-M1-B65	3	2.75	489.1		397	A23-M1-B74	3	2.73	453.1
145	A11-M1-B65	3	2.67	501.2		398	A24-M1-B74	3	2.6	473.1
146	A11-M2-B65	3	2.7	501.2		399	A25-M1-B74	3	2.8	505.1
147	A12-M1-B65	3	2.6	411.2		400	A26-M1-B74	3	2.33	389.2
148	A14-M1-B65	3	2.71	397.2		401	A02-M1-B75	3	2.69	405.1
149	A16-M1-B65	3	2.8	460.2		402	A05-M1-B75	3	2.93	501
150	A17-M1-B65	3	2.64	454.2		403	A06-M1-B75	3	2.48	355.1
151	A18-M1-B65	3	2.89	471.2		404	A08-M1-B75	3	2.93	489.1
152	A20-M1-B65	3	3.07	503.2		405	A10-M1-B75	3	2.79	459.1
153	A21-M1-B65	3	2.57	391.1		406	A11-M1-B75	3	2.74	471.1
154	A22-M1-B65	3	3.25	571.1		407	A12-M1-B75	3	2.58	381.1
155	A23-M1-B65	3	3.05	469.1		408	A14-M1-B75	3	2.44	367.1
156	A24-M1-B65	3	2.93	489.1		409	A15-M1-B75	3	2.66	450.1
157	A25-M1-B65	3	3.1	521.2		410	A16-M1-B75	3	2.57	430.1
158	A26-M1-B65	3	2.69	405.2		411	A17-M1-B75	3	2.38	424.1
159	A01-M1-B66	3	1.89	349.1		412	A18-M1-B75	3	2.65	441.1
160	A04-M1-B66	3	2.22	419.1		413	A04-M1-B75	3	2.7	423.1
161	A06-M1-B66	3	2.02	351.1		414	A20-M1-B75	3	2.87	473.1
162	A06-M2-B66	3	2.06	351.1		415	A21-M1-B75	3	2.31	361.1
163	A08-M2-B66	3	2.45	485.1		416	A22-M1-B75	3	3.08	541.1
164	A09-M1-B66	3	2.24	461.2		417	A23-M1-B75	3	2.83	439.1
165	A09-M2-B66	3	2.82	461.2		418	A24-M1-B75	3	2.71	459.1
166	A11-M1-B66	3	2.31	467.1		419	A25-M1-B75	3	2.9	491.1
167	A11-M2-B66	3	2.34	467.1		420	A26-M1-B75	3	2.43	375.1
168	A12-M1-B66	3	2.16	377.2		421	A14-M1-B76	3	2.58	389.1
169	A12-M2-B66	3	2.21	377.2		422	A15-M1-B76	3	2.77	472.1
170	A14-M1-B66	3	2.22	363.1		423	A16-M1-B76	3	2.69	452.1
171	A15-M1-B66	3	2.46	446.1		424	A17-M1-B76	3	2.51	446.1
172	A16-M1-B66	3	2.35	426.1		425	A18-M1-B76	3	2.77	463.1
173	A17-M1-B66	3	2.13	420.2		426	A20-M1-B76	3	2.96	495.1

174	A18-M2-B66	3	2.51	437.1	427	A21-M1-B76	3	2.45	383.1
175	A18-M1-B66	3	2.44	437.1	428	A22-M1-B76	3	3.15	563.1
176	A20-M1-B66	3	2.65	469.1	429	A23-M1-B76	3	2.93	461.1
177	A21-M1-B66	3	2.06	357.1	430	A24-M1-B76	3	2.8	481.1
178	A22-M1-B66	3	2.87	537.1	431	A25-M1-B76	3	2.99	513.1
179	A24-M1-B66	3	2.49	455.1	432	A26-M1-B76	3	2.57	397.1
180	A25-M1-B66	3	2.69	487.1	433	A06-M1-B77	3	2.47	327.1
181	A26-M1-B66	3	2.19	371.1	434	A08-M1-B77	3	2.89	461.1
182	A27-M2-B66	3	2.51	445.2	435	A11-M1-B77	3	2.69	443.1
183	A01-M1-B67	3	1.91	335.1	436	A12-M1-B77	3	2.54	353.1
184	A01-M2-B67	3	2.01	335.1	437	A14-M1-B77	3	2.4	339.1
185	A02-M1-B67	3	2.26	387.1	438	A16-M1-B77	3	2.53	402.1
186	A02-M2-B67	3	2.35	387.1	439	A17-M1-B77	3	2.34	396.1
187	A03-M1-B67	3	2.56	455.1	440	A18-M1-B77	3	2.62	413.1
188	A03-M2-B67	3	2.59	455.1	441	A04-M1-B77	3	2.67	395.1
189	A04-M1-B67	3	2.27	405.1	442	A20-M1-B77	3	2.83	445.1
190	A04-M2-B67	3	2.36	405.1	443	A22-M1-B77	3	3.05	513.1
191	A05-M1-B67	3	2.48	483	444	A23-M1-B77	3	2.79	411.1
192	A06-M1-B67	3	2.05	337.1	445	A24-M1-B77	3	2.66	431.1
193	A06-M2-B67	3	2.16	337.1	446	A25-M1-B77	3	2.86	463.1
194	A08-M2-B67	3	2.55	471.1	447	A26-M1-B77	3	2.39	347.1
195	A09-M1-B67	3	2.3	447.2	448	A02-M1-B78	3	2.55	387.2
196	A09-M2-B67	3	2.34	447.2	449	A05-M1-B78	3	2.79	483.1
197	A10-M1-B67	3	2.4	441.1	450	A06-M1-B78	3	2.35	337.2
198	A11-M1-B67	3	2.35	453.1	451	A08-M1-B78	3	2.79	471.2
199	A11-M2-B67	3	2.4	453.1	452	A10-M1-B78	3	2.67	441.1
200	A12-M1-B67	3	2.21	363.1	453	A11-M1-B78	3	2.63	453.2
201	A12-M2-B67	3	2.27	363.1	454	A12-M1-B78	3	2.45	363.2
202	A13-M2-B67	3	2.59	517.1	455	A14-M1-B78	3	2.33	349.2
203	A14-M1-B67	3	2.27	349.1	456	A16-M1-B78	3	2.45	412.2
204	A15-M1-B67	3	2.51	432.1	457	A17-M1-B78	3	2.27	406.2
205	A16-M1-B67	3	2.38	412.1	458	A18-M1-B78	3	2.53	423.2
206	A17-M1-B67	3	2.18	406.1	459	A04-M1-B78	3	2.57	405.2
207	A18-M2-B67	3	2.54	423.1	460	A20-M1-B78	3	2.73	455.2
208	A18-M1-B67	3	2.49	423.1	461	A21-M1-B78	3	2.2	343.1
209	A20-M1-B67	3	2.7	455.1	462	A22-M1-B78	3	2.95	523.1
210	A21-M1-B67	3	2.07	343.1	463	A23-M1-B78	3	2.69	421.1
211	A22-M1-B67	3	2.93	523.1	464	A24-M1-B78	3	2.57	441.1
212	A23-M1-B67	3	2.66	421.1	465	A25-M1-B78	3	2.77	473.2
213	A24-M1-B67	3	2.53	441.1	466	A26-M1-B78	3	2.32	357.2
214	A25-M1-B67	3	2.74	473.1	467	A05-M1-B79	3	2.76	485.1
215	A26-M1-B67	3	2.22	357.1	468	A06-M1-B79	3	2.28	339.1
216	A27-M2-B67	3	2.54	431.2	469	A08-M1-B79	3	2.76	473.1
217	A01-M1-B68	3	1.79	273.1	470	A12-M1-B79	3	2.4	365.2
218	A02-M1-B68	3	2.1	325.2	471	A14-M1-B79	3	2.27	351.1
219	A03-M1-B68	3	2.48	393.1	472	A17-M1-B79	3	2.2	408.2
220	A04-M1-B68	3	2.11	343.1	473	A04-M1-B79	3	2.53	407.1
221	A04-M2-B68	3	2.15	343.1	474	A20-M1-B79	3	2.69	457.1
222	A05-M1-B68	3	2.4	421.1	475	A22-M1-B79	3	2.91	525.1
223	A06-M1-B68	3	1.87	275.1	476	A23-M1-B79	3	2.65	423.1
224	A11-M1-B68	3	2.22	391.2	477	A24-M1-B79	3	2.53	443.1

225	A13-M1-B68	3	2.51	455.2	478	A25-M1-B79	3	2.73	475.1
226	A14-M1-B68	3	2.04	287.1	479	A26-M1-B79	3	2.24	359.1
227	A15-M1-B68	3	2.35	370.1	480	A05-M1-B80	3	2.75	499
228	A16-M1-B68	3	2.2	350.2	481	A06-M1-B80	3	2.29	353.1
229	A17-M1-B68	3	1.97	344.2	482	A08-M1-B80	3	2.75	487.1
230	A18-M2-B68	3	2.35	361.1	483	A11-M1-B80	3	2.57	469.1
231	A18-M1-B68	3	2.31	361.1	484	A14-M1-B80	3	2.27	365.1
232	A20-M1-B68	3	2.53	393.1	485	A17-M1-B80	3	2.2	422.1
233	A21-M1-B68	3	1.83	281.1	486	A04-M1-B80	3	2.52	421.1
234	A22-M1-B68	3	2.78	461.1	487	A20-M1-B80	3	2.69	471.1
235	A23-M1-B68	3	2.48	359.1	488	A22-M1-B80	3	2.91	539.1
236	A24-M1-B68	3	2.37	379.1	489	A23-M1-B80	3	2.65	437.1
237	A26-M1-B68	3	1.99	295.1	490	A24-M1-B80	3	2.53	457.1
238	A01-M1-B69	3	2.24	335.1	491	A25-M1-B80	3	2.73	489.1
239	A01-M2-B69	3	2.26	335.1	492	A26-M1-B80	3	2.25	373.1
240	A02-M1-B69	3	2.52	387.2	493	A02-M1-B81	3	2.59	417.1
241	A03-M1-B69	3	2.81	455.1	494	A05-M1-B81	3	2.83	513
242	A04-M1-B69	3	2.52	405.2	495	A06-M1-B81	3	2.39	367.1
243	A05-M1-B69	3	2.73	483.1	496	A08-M1-B81	3	2.83	501.1
244	A05-M2-B69	3	2.15	483.1	497	A11-M1-B81	3	2.64	483.1
245	A06-M1-B69	3	2.33	337.2	498	A12-M1-B81	3	2.47	393.1
246	A06-M2-B69	3	2.38	337.2	499	A14-M1-B81	3	2.33	379.1
247	A08-M2-B69	3	2.71	471.2	500	A04-M1-B81	3	2.61	435.1
248	A09-M1-B69	3	2.53	447.2	501	A20-M1-B81	3	2.77	485.1
249	A09-M2-B69	3	2.54	447.2	502	A22-M1-B81	3	2.99	553.1
250	A11-M1-B69	3	2.58	453.2	503	A23-M1-B81	3	2.73	451.1
251	A12-M1-B69	3	2.47	363.2	504	A24-M1-B81	3	2.6	471.1
252	A12-M2-B69	3	2.48	363.2	505	A25-M1-B81	3	2.8	503.1
253	A13-M2-B69	3	2.76	517.2	506	A26-M1-B81	3	2.33	387.1

Example 13

3-methyl-N-{5-[(3-methylbenzyl)oxy]-1H-indazol-3-yl}benzenesulfonamide

500 mg of Novabiochem trityl resin (declared substitution 1.27 mmol/g, 0.64 mmol) were suspended in dichloromethane and 374 mg of 2-[5-(tert-butyl-dimethyl-silanyloxy)-1H-indazol-3-yl]-isoindole-1,3-dione (0.9 mmol) and 367 µl of 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (1.3 mmol) were added. The suspension was stirred for 16 hours and then the resin was filtered and washed with dichloromethane, methanol, dimethylformamide, methanol and dichloromethane again. The resin was then dried under vacuum.

The identity of the resin and the yield of the loading step were checked by cleavage of the loaded product:
40 mg of resin were suspended in 1 ml of dichloromethane and 150 µl trifluoroacetic acid were added. After 2 hours the resin was drained and washed twice with 1 ml of dichloromethane; the collected solutions were dried and 13.8 mg of titled compound recovered. Calculated loading 0.85 mmol/g, HPLC r.t. Method 1: 7.64 [M+H]+= 394.

The resin obtained from the first step (500 mg, ~0.42 mmol) was suspended in 3 ml of tetrahydrofuran anhydrous and 630 µl of a solution 1 M of tetrabutylammonium fluoride in tetrahydrofuran (~1.5 eq) were added. The suspension was stirred overnight then the resin was filtered and washed with dichloromethane, methanol, dimethylformamide, methanol and dichloromethane.
The identity of the resin was checked by cleavage. The reaction was performed as described above.
2-[6-hydroxy-1H-indazol-3-yl]-isoindole-1,3-dione:HPLC r.t. Method 1: 3.9 [M+H]+= 280.

A sample of the resin obtained from the second step (100 mg, ~0.08 mmol) were suspended in 3 ml of 1-methyl-2-pyrrolidinone, then 43 µl of 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (~1.5 eq) and 65 µl of 3-methylbenzylbromide (~6 eq) were added. The suspension was stirred for 16 hours. The resin was filtered and washed with dichloromethane, methanol, dimethylformamide, methanol and dichloromethane.

The resin obtained from the third step (100 mg, ~0.08 mmol) was suspended in 5 ml of a mixture of dichloromethane and methanol 1:1 and 100 µl of hydrazine monohydrate were added. The suspension was heated to 45°C. Heating and stirring were continued overnight, and then the mixture was

cooled down to room temperature. The resin was filtered and washed with a mixture of methanol and water 1:1, methanol, dimethylformamide, and methanol again, before drying under vacuum.

The resin obtained from the fourth step (100 mg, ~0.08 mmol) was suspended in 2.5 ml of dichloromethane and 90 mg of m-toluenesulfonyl chloride (~6eq), 200 µl of N,N'-diisoproylethylamine (~15 eq) and a catalytic amount of 4-dimethylaminopyridine were added. The suspension was left stirring overnight. The resin was filtered and washed with a mixture of methanol and water 1:1, methanol, dimethylformamide, and methanol, and dichloromethane. Before drying under vacuum.

The resin obtained from the fifth step was suspended in 3 ml of tetrahydrofuran anhydrous and 120 µl of a solution 1 M of tetrabutylammonium fluoride in tetrahydrofuran (~1.5 eq) were added. The suspension was stirred overnight then the resin was filtered and washed with dichloromethane, methanol, dimethylformamide, methanol and dichloromethane.

100 mg of dry resin were suspended in 3 ml of dichloromethane and 450 µl trifluoroacetic acid were added. After 2 hours the resin was drained and washed twice with 3 ml of dichloromethane; the collected solutions were dried; the title compound recovered.
3-methyl-N-{5-[(3-methylbenzyl)oxy]-1H-indazol-3-yl}benzenesulfonamide HPLC Method 2 r.t.: 8.79 [M+H]+=408.1

By working in an analogous way (example 13) the following compounds of table XIII were prepared.

Table XIII

Entry	Compound	HPLC method	r.t. (min)	[M+H]+	Entry	Compound	HPLC method	r.t. (min)	[M+H]+
1	A30-M2-B59	1	4.29	427.1	167	A21-M1-B46	3	1.97	315.1
2	A30-M2-B61	2	8.2	450.1	168	A22-M1-B46	3	2.83	495.1
3	A30-M2-B58	1	4.58	449.2	169	A23-M1-B46	3	2.57	393.1
4	A30-M2-B57	1	4.19	429.1	170	A24-M1-B46	3	2.45	413.1
5	A31-M2-B61	2	7.32	414.1	171	A25-M1-B46	3	2.65	445.1
6	A31-M2-B58	1	4.21	413.2	172	A26-M1-B46	3	2.13	329.1
7	A30-M1-B59	1	4.2	427.1	173	A27-M2-B46	3	2.44	403.2
8	A30-M1-B61	2	7.86	450.1	174	A01-M1-B47	3	2.11	375.0
9	A30-M1-B58	1	4.51	449.2	175	A02-M2-B47	3	2.47	427.1
10	A30-M1-B57	1	4.16	429.1	176	A09-M1-B47	3	2.43	487.1
11	A01-M1-B40	3	2.14	369.1	177	A09-M2-B47	3	2.46	487.1
12	A02-M1-B40	3	2.48	421.1	178	A10-M1-B47	3	2.53	481.0
13	A03-M1-B40	3	2.73	489.1	179	A11-M1-B47	3	2.47	493.1
14	A04-M1-B40	3	2.42	439.1	180	A11-M2-B47	3	2.51	493.1
15	A05-M1-B40	3	2.62	517.0	181	A12-M1-B47	3	2.38	403.1
16	A06-M1-B40	3	2.27	371.1	182	A13-M1-B47	3	2.73	557.1
17	A07-M1-B40	3	2.5	457.1	183	A14-M1-B47	3	2.44	389.1
18	A08-M1-B40	3	2.61	505.1	184	A15-M1-B47	3	2.64	472.1
19	A09-M1-B40	3	2.54	481.2	185	A16-M1-B47	3	2.53	452.1
20	A09-M2-B40	3	2.53	481.2	186	A17-M1-B47	3	2.35	446.1
21	A10-M1-B40	3	2.63	475.1	187	A18-M2-B47	3	2.71	463.1
22	A10-M2-B40	3	2.61	475.1	188	A18-M1-B47	3	2.63	463.1
23	A11-M1-B40	3	2.58	487.1	189	A20-M1-B47	3	2.82	495.1
24	A11-M2-B40	3	2.57	487.1	190	A21-M1-B47	3	2.27	383.1
25	A12-M1-B40	3	2.5	397.1	191	A23-M1-B47	3	2.79	461.0
26	A13-M1-B40	3	2.75	551.2	192	A24-M1-B47	3	2.67	481.0
27	A01-M1-B41	3	1.88	333.0	193	A25-M1-B47	3	2.88	513.1
28	A02-M1-B41	3	2.13	385.1	194	A26-M1-B47	3	2.4	397.1
29	A04-M1-B41	3	2.14	403.0	195	A02-M2-B48	3	2.29	409.1
30	A05-M1-B41	3	2.43	481.0	196	A05-M1-B48	3	2.46	505.0
31	A06-M1-B41	3	2	335.0	197	A05-M2-B48	3	2.48	505.0
32	A07-M1-B41	3	2.23	421.0	198	A06-M1-B48	3	2	359.1
33	A08-M1-B41	3	2.35	469.0	199	A08-M1-B48	3	2.48	493.1
34	A09-M1-B41	3	2.29	445.1	200	A10-M1-B48	3	2.34	463.1
35	A10-M1-B41	3	2.37	439.0	201	A11-M1-B48	3	2.3	475.1
36	A10-M2-B41	3	2.35	439.0	202	A11-M2-B48	3	2.33	475.1
37	A11-M1-B41	3	2.33	451.0	203	A12-M1-B48	3	2.18	385.1
38	A12-M2-B41	3	2.18	361.1	204	A13-M2-B48	3	2.51	539.1
39	A14-M1-B41	3	2.13	347.0	205	A13-M1-B48	3	2.55	539.1
40	A15-M1-B41	3	2.37	430.0	206	A14-M1-B48	3	2.21	371.1
41	A16-M1-B41	3	2.25	410.1	207	A15-M1-B48	3	2.45	454.1
42	A17-M1-B41	3	2.03	404.1	208	A16-M1-B48	3	2.32	434.1
43	A18-M1-B41	3	2.35	421.0	209	A17-M1-B48	3	2.12	428.1
44	A21-M1-B41	3	1.91	341.0	210	A18-M2-B48	3	2.5	445.1
45	A23-M1-B41	3	2.51	419.0	211	A18-M1-B48	3	2.41	445.1
46	A24-M1-B41	3	2.39	439.0	212	A21-M1-B48	3	2.01	365.1
47	A25-M1-B41	3	2.59	471.0	213	A22-M1-B48	3	2.83	545.1

48	A26-M1-B41	3	2.07	355.0	214	A23-M1-B48	3	2.57	443.1
49	A01-M1-B42	3	2.15	395.1	215	A24-M1-B48	3	2.46	463.1
50	A02-M1-B42	3	2.36	447.1	216	A25-M1-B48	3	2.67	495.1
51	A03-M1-B42	3	2.69	515.0	217	A26-M1-B48	3	2.17	379.1
52	A04-M1-B42	3	2.35	465.1	218	A27-M2-B48	3	2.47	453.1
53	A05-M1-B42	3	2.55	543.0	219	A09-M1-B49	3	2.58	507.0
54	A06-M1-B42	3	2.19	397.1	220	A02-M1-B50	3	2.5	393.1
55	A07-M1-B42	3	2.49	483.1	221	A05-M1-B50	3	2.73	489.0
56	A08-M1-B42	3	2.6	531.1	222	A06-M1-B50	3	2.27	343.1
57	A09-M1-B42	3	2.49	507.1	223	A08-M1-B50	3	2.74	477.1
58	A10-M1-B42	3	2.57	501.1	224	A10-M1-B50	3	2.6	447.1
59	A11-M1-B42	3	2.51	513.1	225	A11-M1-B50	3	2.55	459.1
60	A11-M2-B42	3	2.51	513.1	226	A12-M1-B50	3	2.4	369.1
61	A12-M1-B42	3	2.43	423.1	227	A14-M1-B50	3	2.25	355.1
62	A12-M2-B42	3	2.41	423.1	228	A15-M1-B50	3	2.5	438.1
63	A01-M1-B43	3	2.16	369.1	229	A16-M1-B50	3	2.38	418.1
64	A02-M1-B43	3	2.45	421.1	230	A18-M1-B50	3	2.47	429.1
65	A03-M1-B43	3	2.75	489.1	231	A04-M1-B50	3	2.49	411.1
66	A04-M1-B43	3	2.44	439.1	232	A20-M1-B50	3	2.67	461.1
67	A05-M1-B43	3	2.68	517.0	233	A21-M1-B50	3	2.11	349.1
68	A06-M1-B43	3	2.34	371.1	234	A22-M1-B50	3	2.88	529.1
69	A07-M1-B43	3	2.51	457.1	235	A23-M1-B50	3	2.62	427.1
70	A08-M1-B43	3	2.62	505.1	236	A24-M1-B50	3	2.51	447.1
71	A09-M1-B43	3	2.56	481.2	237	A25-M1-B50	3	2.71	479.1
72	A09-M2-B43	3	2.55	481.2	238	A26-M1-B50	3	2.21	363.1
73	A10-M1-B43	3	2.64	475.1	239	A02-M1-B51	3	2.42	398.1
74	A10-M2-B43	3	2.63	475.1	240	A05-M1-B51	3	2.67	494.0
75	A11-M1-B43	3	2.59	487.1	241	A06-M1-B51	3	2.18	348.1
76	A11-M2-B43	3	2.58	487.1	242	A08-M1-B51	3	2.68	482.1
77	A14-M1-B43	3	2.51	383.1	243	A10-M1-B51	3	2.53	452.1
78	A15-M1-B43	3	2.7	466.1	244	A11-M1-B51	3	2.49	464.1
79	A16-M1-B43	3	2.59	446.1	245	A12-M1-B51	3	2.32	374.1
80	A17-M1-B43	3	2.42	440.2	246	A14-M1-B51	3	2.17	360.1
81	A18-M2-B43	3	2.76	457.1	247	A15-M1-B51	3	2.42	443.1
82	A18-M1-B43	3	2.68	457.1	248	A16-M1-B51	3	2.3	423.1
83	A20-M1-B43	3	2.87	489.1	249	A17-M1-B51	3	2.11	417.1
84	A21-M1-B43	3	2.35	377.1	250	A18-M1-B51	3	2.4	434.1
85	A23-M1-B43	3	2.83	455.1	251	A04-M1-B51	3	2.43	416.1
86	A24-M1-B43	3	2.72	475.1	252	A20-M1-B51	3	2.6	466.1
87	A25-M1-B43	3	2.9	507.1	253	A21-M1-B51	3	2.01	354.1
88	A26-M1-B43	3	2.47	391.1	254	A22-M1-B51	3	2.82	534.1
89	A27-M2-B43	3	2.73	465.2	255	A23-M1-B51	3	2.55	432.1
90	A01-M1-B44	3	2.19	411.1	256	A24-M1-B51	3	2.43	452.1
91	A03-M1-B44	3	2.65	531.0	257	A25-M1-B51	3	2.64	484.1
92	A04-M1-B44	3	2.39	481.1	258	A26-M1-B51	3	2.13	368.1
93	A05-M1-B44	3	2.57	559.0	259	A02-M1-B52	3	2.77	441.1
94	A06-M1-B44	3	2.24	413.1	260	A05-M1-B52	3	3.01	537.0
95	A07-M1-B44	3	2.52	499.1	261	A06-M1-B52	3	2.59	391.1
96	A09-M1-B44	3	2.53	523.1	262	A08-M1-B52	3	2.99	525.1
97	A10-M1-B44	3	2.57	517.1	263	A10-M1-B52	3	2.86	495.1
98	A11-M1-B44	3	2.55	529.1	264	A11-M1-B52	3	2.79	507.1

99	A11-M2-B44	3	2.53	529.1	265	A12-M1-B52	3	2.69	417.1
100	A12-M1-B44	3	2.47	439.1	266	A14-M1-B52	3	2.56	403.1
101	A12-M2-B44	3	2.45	439.1	267	A16-M1-B52	3	2.65	466.1
102	A14-M1-B44	3	2.47	425.1	268	A17-M1-B52	3	2.47	460.1
103	A15-M1-B44	3	2.65	508.1	269	A04-M1-B52	3	2.77	459.1
104	A16-M1-B44	3	2.55	488.1	270	A20-M1-B52	3	2.93	509.1
105	A17-M1-B44	3	2.39	482.1	271	A21-M1-B52	3	2.4	397.1
106	A18-M2-B44	3	2.71	499.1	272	A22-M1-B52	3	3.13	577.1
107	A18-M1-B44	3	2.63	499.1	273	A23-M1-B52	3	2.89	475.1
108	A20-M1-B44	3	2.81	531.1	274	A24-M1-B52	3	2.77	495.1
109	A21-M1-B44	3	2.31	419.1	275	A25-M1-B52	3	2.97	527.1
110	A23-M1-B44	3	2.78	497.0	276	A26-M1-B52	3	2.52	411.1
111	A24-M1-B44	3	2.67	517.1	277	A02-M1-B53	3	2.9	403.2
112	A25-M1-B44	3	2.85	549.1	278	A05-M1-B53	3	3.15	499.1
113	A26-M1-B44	3	2.43	433.4	279	A06-M1-B53	3	2.69	353.2
114	A27-M2-B44	3	2.69	507.1	280	A08-M1-B53	3	3.11	487.2
115	A02-M1-B45	3	2.3	415.1	281	A10-M1-B53	3	2.99	457.2
116	A03-M1-B45	3	2.59	483.0	282	A11-M1-B53	3	2.93	469.2
117	A05-M1-B45	3	2.49	511.0	283	A12-M1-B53	3	2.81	379.2
118	A06-M1-B45	3	2.04	365.1	284	A14-M1-B53	3	2.66	365.2
119	A07-M1-B45	3	2.37	451.1	285	A16-M1-B53	3	2.75	428.2
120	A09-M1-B45	3	2.37	475.1	286	A17-M1-B53	3	2.58	422.2
121	A10-M1-B45	3	2.45	469.1	287	A18-M1-B53	3	2.87	439.2
122	A10-M2-B45	3	2.43	469.1	288	A04-M1-B53	3	2.91	421.2
123	A11-M1-B45	3	2.4	481.1	289	A20-M1-B53	3	3.07	471.2
124	A11-M2-B45	3	2.39	481.1	290	A21-M1-B53	3	2.49	359.2
125	A12-M2-B45	3	2.28	391.1	291	A22-M1-B53	3	3.27	539.2
126	A13-M2-B45	3	2.56	545.1	292	A23-M1-B53	3	3.05	437.2
127	A13-M1-B45	3	2.57	545.1	293	A24-M1-B53	3	2.9	457.2
128	A14-M1-B45	3	2.25	377.1	294	A25-M1-B53	3	3.09	489.2
129	A15-M1-B45	3	2.47	460.1	295	A26-M1-B53	3	2.62	373.2
130	A16-M1-B45	3	2.35	440.1	296	A02-M1-B54	3	2.33	439.1
131	A17-M1-B45	3	2.15	434.1	297	A06-M1-B54	3	2.09	389.1
132	A18-M2-B45	3	2.52	451.1	298	A08-M1-B54	3	2.61	523.1
133	A18-M1-B45	3	2.45	451.1	299	A10-M1-B54	3	2.45	493.1
134	A20-M1-B45	3	2.64	483.1	300	A11-M1-B54	3	2.41	505.1
135	A21-M1-B45	3	2.05	371.1	301	A12-M1-B54	3	2.24	415.1
136	A23-M1-B45	3	2.6	449.0	302	A14-M1-B54	3	2.09	401.1
137	A24-M1-B45	3	2.49	469.1	303	A17-M1-B54	3	2.05	458.1
138	A25-M1-B45	3	2.68	501.1	304	A18-M1-B54	3	2.32	475.1
139	A26-M1-B45	3	2.21	385.1	305	A04-M1-B54	3	2.33	457.1
140	A27-M2-B45	3	2.49	459.1	306	A20-M1-B54	3	2.51	507.1
141	A01-M1-B46	3	1.87	307.1	307	A22-M1-B54	3	2.74	575.1
142	A02-M1-B46	3	2.25	359.1	308	A23-M1-B54	3	2.45	473.1
143	A02-M2-B46	3	2.26	359.1	309	A24-M1-B54	3	2.36	493.1
144	A03-M1-B46	3	2.49	427.1	310	A25-M1-B54	3	2.56	525.1
145	A03-M2-B46	3	2.52	427.1	311	A26-M1-B54	3	2.04	409.1
146	A04-M1-B46	3	2.2	377.1	312	A02-M1-B55	3	2.59	429.1
147	A05-M1-B46	3	2.41	455.0	313	A06-M1-B55	3	2.39	379.1
148	A05-M2-B46	3	2.46	455.0	314	A08-M1-B55	3	2.83	513.1
149	A06-M1-B46	3	1.99	309.1	315	A10-M1-B55	3	2.69	483.1

150	A07-M1-B46	3	2.28	395.1	316	A11-M1-B55	3	2.64	495.1
151	A08-M1-B46	3	2.41	443.1	317	A12-M1-B55	3	2.51	405.1
152	A08-M2-B46	3	2.46	443.1	318	A14-M1-B55	3	2.39	391.1
153	A09-M1-B46	3	2.25	419.2	319	A04-M1-B55	3	2.59	447.1
154	A09-M2-B46	3	2.26	419.2	320	A20-M1-B55	3	2.75	497.1
155	A10-M1-B46	3	2.34	413.1	321	A21-M1-B55	3	2.23	385.1
156	A11-M1-B46	3	2.3	425.1	322	A22-M1-B55	3	2.96	565.1
157	A11-M2-B46	3	2.32	425.1	323	A23-M1-B55	3	2.71	463.1
158	A12-M1-B46	3	2.17	335.1	324	A24-M1-B55	3	2.6	483.1
159	A13-M2-B46	3	2.49	489.1	325	A25-M1-B55	3	2.79	515.1
160	A13-M1-B46	3	2.55	489.1	326	A26-M1-B55	3	2.35	399.1
161	A14-M1-B46	3	2.17	321.1	327	A20-M1-B56	3	2.61	498.1
162	A15-M1-B46	3	2.42	404.1	328	A23-M1-B56	3	2.57	464.1
163	A16-M1-B46	3	2.3	384.1	329	A24-M1-B56	3	2.46	484.1
164	A17-M1-B46	3	2.09	378.1	330	A25-M1-B56	3	2.66	516.1
165	A18-M2-B46	3	2.47	395.1	331	A26-M1-B56	3	2.15	400.1
166	A18-M1-B46	3	2.4	395.1					

Example 14

4-isopropyl-N-{6-[(3-methylbenzyl)oxy]-1H-indazol-3-yl}benzenesulfonamide

500 mg of Novabiochem trityl resin (declared substitution 1.27 mmol/g, 0.64 mmol) were suspended in dichloromethane and 374 mg of 2-[6-(tert-butyl-dimethyl-silanyloxy)-1H-indazol-3-yl]-isoindole-1,3-dione (0.9 mmol) and 367 µl of 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (1.3 mmol) were added. The suspension was stirred for 16 hours and then the resin was filtered and washed with dichloromethane, methanol, dimethylformamide, methanol and dichloromethane again. The resin was then dried under vacuum.

The identity of the resin and the yield of the loading step were checked by cleavage of the loaded product:

40 mg of resin were suspended in 1 ml of dichloromethane and 150 µl trifluoroacetic acid were added. After 2 hours the resin was drained and washed twice with 1 ml of dichloromethane; the collected solutions were dried and 13.8 mg of titled compound recovered. Calculated loading 0.85 mmol/g, HPLC r.t. Method 1: 7.64 [M+H]+= 394.

The resin obtained from the first step (500 mg, ~0.42 mmol) was suspended in 3 ml of tetrahydrofuran anhydrous and 630 µl of a solution 1 M of tetrabutylammonium fluoride in tetrahydrofuran (~1.5 eq) were added. The suspension was stirred overnight then the resin was filtered and washed with dichloromethane, methanol, dimethylformamide, methanol and dichloromethane, before drying under vacuum.
The identity of the resin was checked by cleavage. The reaction was performed as described above.
2-[6-hydroxy-1H-indazol-3-yl]-isoindole-1,3-dione:HPLC r.t. Method 1: 3.9 [M+H]+= 280.

A sample of the resin obtained from the second step (100 mg, ~0.08 mmol) was suspended in 1.5 ml of tetrahydrofuran anhydrous. In a round bottom flask, 209 mg of triphenylphosphine (0.8mmol, ~10eq) were dissolved in 2 ml of tetrahydrofuran anhydrous, then 157 µl of diisopropyl azodicarboxylate (0.8 mmol, ~10eq) and 145 µl of 3-methylbenzyl alcohol (1.2 mmol, ~15eq) were gently added at 0°C. The solution was left shaking 2 h, then it was transferred into the suspension of the resin.
The suspension was stirred overnight then the resin was filtered and washed with dichloromethane, methanol, dimethylformamide, methanol and dichloromethane.
The procedure is repeated twice.

The resin obtained from the third step (100 mg, ~0.08 mmol) was suspended in 5 ml of a mixture of dichloromethane and methanol 1:1 and 100 µl of hydrazine monohydrate were added. The suspension was heated to 45°C. Heating and stirring were continued overnight, and then the mixture was cooled down to room temperature. The resin was filtered and washed with a mixture of methanol and water 1:1, methanol, dimethylformamide, and methanol again, before drying under vacuum.

The resin obtained from the fourth step (100 mg, ~0.08 mmol) was suspended in 2.5 ml of dichloromethane and 111 mg of 4-tert-butylbenzenesulfonyl chloride (~6eq), 200 µl of N,N'-diisoproylethylamine (~15 eq) and a catalytic amount of 4-dimethylaminopyridine were added. The suspension was left stirring overnight. The resin was filtered and washed with a mixture of methanol and water 1:1, methanol, dimethylformamide, and methanol, and dichloromethane. Before drying under vacuum.

The resin obtained from the fifth step was suspended in 3 ml of tetrahydrofuran anhydrous and 120 µl of a solution 1 M of tetrabutylammonium fluoride in tetrahydrofuran (~1.5 eq) were added. The suspension was stirred overnight then the resin was filtered and washed with dichloromethane, methanol, dimethylformamide, methanol and dichloromethane.

100 mg of dry resin were suspended in 3 ml of dichloromethane and 450 µl trifluoroacetic acid were added. After 2 hours the resin was drained and washed twice with 3 ml of dichloromethane; the collected solutions were dried; the title compound recovered.

4-isopropyl-N-{6-[(3-methylbenzyl)oxy]-1H-indazol-3-yl}benzenesulfonamide HPLC Method 3 r.t.2.69, [M+H]+= 436.2

By working in an anlogous way (example 14) the following compounds of table XIV were prepared.

Table XIV

Entry	Compound	HPLC Method	r.t. (min)	[M+H]+		Entry	Compound	HPLC Method	r.t. (min)	[M+H]+
1	A50-M2-B41	3	2.45	364.1		43	A56-M2-B46	3	2.5	338.1
2	A51-M1-B41	3	2.36	416.1		44	A57-M2-B46	3	2.69	352.2
3	A52-M1-B41	3	1.84	310		45	A58-M2-B46	3	2.71	364.2
4	A53-M1-B41	3	2.19	370.1		46	A59-M2-B46	3	2.48	380.1
5	A57-M2-B41	3	2.65	378.1		47	A60-M2-B46	3	2.97	382.2
6	A60-M2-B41	3	2.93	408.1		48	A61-M2-B46	3	1.36	381.2

7	A50-M2-B43	3	2.82	400.2		49	A62-M2-B46	3	2.51	326.1
8	A50-M1-B43	3	2.76	400.2		50	A30-M1-B47	3	2.64	442.1
9	A51-M1-B43	3	2.69	452.2		51	A30-M2-B47	3	2.67	442.1
10	A52-M1-B43	3	2.32	346.1		52	A50-M1-B47	3	2.71	406.1
11	A53-M1-B43	3	2.55	406.2		53	A50-M2-B47	3	2.76	406.1
12	A55-M2-B43	3	1.69	417.2		54	A51-M1-B47	3	2.64	458.1
13	A56-M2-B43	3	2.83	400.2		55	A52-M1-B47	3	2.25	352
14	A57-M2-B43	3	3	414.2		56	A53-M1-B47	3	2.49	412.1
15	A58-M2-B43	3	3.01	426.2		57	A55-M2-B47	3	1.63	423.1
16	A59-M2-B43	3	2.77	442.1		58	A56-M2-B47	3	2.77	406.1
17	A60-M2-B43	3	2.95	444.2		59	A57-M2-B47	3	2.94	420.1
18	A61-M2-B43	3	1.71	443.2		60	A58-M2-B47	3	2.95	432.1
19	A50-M1-B44	3	2.71	442.1		61	A59-M2-B47	3	2.72	448
20	A50-M2-B44	3	2.76	442.1		62	A60-M2-B47	3	3.19	450.2
21	A51-M1-B44	3	2.65	494.1		63	A61-M2-B47	3	1.65	449.1
22	A52-M1-B44	3	2.29	388.1		64	A62-M2-B47	3	2.77	394.1
23	A53-M1-B44	3	2.51	448.1		65	A50-M2-B48	3	2.53	388.1
24	A55-M2-B44	3	1.67	459.1		66	A51-M1-B48	3	2.43	440.1
25	A56-M2-B44	3	2.76	442.1		67	A52-M1-B48	3	1.96	334.1
26	A59-M2-B44	3	2.73	484.1		68	A53-M1-B48	3	2.27	394.1
27	A60-M2-B44	3	3.17	486.2		69	A55-M2-B48	3	1.41	405.2
28	A50-M2-B45	3	2.55	394.1		70	A56-M2-B48	3	2.54	388.1
29	A51-M1-B45	3	2.45	446.1		71	A60-M2-B48	3	2.99	432.2
30	A52-M1-B45	3	2	340		72	A51-M1-B50	3	2.49	424.1
31	A53-M1-B45	3	2.31	400.1		73	A53-M1-B50	3	2.31	378.1
32	A55-M2-B45	3	1.42	411.1		74	A51-M1-B51	3	2.41	429.1
33	A56-M2-B45	3	2.56	394.1		75	A52-M1-B51	3	1.97	323.1
34	A59-M2-B45	3	2.53	436.1		76	A53-M1-B51	3	2.23	383.1
35	A60-M2-B45	3	3	438.2		77	A52-M1-B52	3	2.4	366.1
36	A62-M2-B45	3	2.57	382.1		78	A53-M1-B52	3	2.61	426.1
37	A50-M1-B46	3	2.44	338.1		79	A51-M1-B53	3	2.87	434.2
38	A50-M2-B46	3	2.49	338.1		80	A52-M1-B53	3	2.48	328.2
39	A51-M1-B46	3	2.41	390.1		81	A53-M1-B53	3	2.71	388.2
40	A52-M1-B46	3	1.9	284.1		82	A53-M1-B54	3	2.15	424.1
41	A53-M1-B46	3	2.25	344.1		83	A53-M1-B55	3	2.43	414.1
42	A55-M2-B46	3	1.33	355.2						

Example 15

3-phenyl-N-[5-(2-pyrrolidin-1-ylethoxy)-1H-indazol-3-yl]propanamide

500 mg of Novabiochem trityl resin (declared substitution 1.27 mmol/g, 0.64 mmol) were suspended in dichloromethane and 374 mg of 2-[6-(tert-butyl-dimethyl-silanyloxy)-1H-indazol-3-yl]-isoindole-1,3-dione (0.9 mmol) and 367 µl of 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-

1,3,2-diazaphosphorine (1.3 mmol) were added. The suspension was stirred for 16 hours and then the resin was filtered and washed with dichloromethane, methanol, dimethylformamide, methanol and dichloromethane again. The resin was then dried under vacuum.
The identity of the resin and the yield of the loading step were checked by cleavage of the loaded product:
40 mg of resin were suspended in 1 ml of dichloromethane and 150 µl trifluoroacetic acid were added. After 2 hours the resin was drained and washed twice with 1 ml of dichloromethane; the collected solutions were dried and 13.8 mg of titled compound recovered. Calculated loading 0.85 mmol/g, HPLC r.t. Method 1: 7.64 [M+H]+= 394.

The resin obtained from the first step (500 mg, ~0.425 mmol) was suspended in 5 ml of a mixture of dichloromethane and methanol 1:1 and 500 µl of hydrazine monohydrate were added. The suspension was heated to 45°C. Heating and stirring were continued overnight, and then the mixture was cooled down to room temperature. The resin was filtered and washed with a mixture of methanol and water 1:1, methanol, dimethylformamide, and methanol again before drying under vacuum.
The identity of the resin was checked by cleavage. The reaction was performed as described above.
6-{[tert-butyl(dimethyl)silyl]oxy}-1H-indazol-3-amine HPLC r.t. Method 1: 5.99 [M+H]+= 264 [M-H]-= 262

A sample of the resin obtained from the second step (100 mg, 0.08 mmol) was suspended in 2.5 ml of dichloromethane; N,N'-diisoproylethylamine (131 µl, ~10 eq) and hydrocinnamoyl chloride (35 µl, 0.24 mmol, ~3eq) were added. Stirring at room temperature was maintained for 20 hours, then the resin was filtered and washed with

dichloromethane, methanol, dimethylformamide, methanol and dichloromethane again before drying under vacuum.

The resin obtained from the third step (100 mg, ~0.08 mmol) was suspended in 3 ml of tetrahydrofuran anhydrous and 120 µl of a solution 1 M of tetrabutylammonium fluoride in tetrahydrofuran (~1.5 eq) were added. The suspension was stirred overnight then the resin was filtered and washed with dichloromethane, methanol, dimethylformamide, methanol and dichloromethane, before drying under vacuum.

The resin obtained from the fourth step (100 mg, ~0.08 mmol) was suspended in 1 ml of tetrahydrofuran anhydrous. In a round bottom flask, 209 mg of triphenylphosphine (0.8mmol, ~10eq) were dissolved in 2 ml of tetrahydrofuran anhydrous, then 157 µl of diisopropyl azodicarboxylate (0.8 mmol, ~10eq) and 147 µl of 1-(2-hydroxyethyl)pyrrolidine (1.2 mmol, ~15eq) were gently added at 0°C. The solution was left shaking 2 h, then transferred into the suspension of the resin.
The suspension was stirred overnight then the resin was filtered and washed with dichloromethane, methanol, dimethylformamide, methanol and dichloromethane.
The procedure is repeated twice.

100 mg of dry resin were suspended in 3 ml of dichloromethane and 450 µl trifluoroacetic acid were added. After 2 hours the resin was drained and washed twice with 3 ml of dichloromethane; the collected solutions were dried and the desired title compound recovered.
3-phenyl-N-[5-(2-pyrrolidin-1-ylethoxy)-1H-indazol-3-yl]propanamide HPLC r.t. Method 1: 2.99 [M+H]+= 379.2

By proceeding in a manner similar to that of Example 15, 2-(6-{[tert-butyl(dimethyl)silyl]oxy}-1H-indazol-3-yl)-1H-isoindole-1,3(2H)-dione and 2-[5-(tert-Butyl-dimethyl-silanyloxy)-1H-indazol-3-yl]-isoindole-1,3-dione were supported on the resin, then, by following the described synthetic scheme, the following products were synthesized.

2-(4-tert-butylphenoxy)-N-[5-(2-pyrrolidin-1-ylethoxy)-1H-indazol-3-yl]acetamide HPLC Method 2 r.t. 6.65 [M+H]+= 437.2

2-(4-methoxyphenyl)-N-[5-(2-pyrrolidin-1-ylethoxy)-1H-indazol-3-yl]acetamide HPLC Method 2 r.t. 4.56 [M+H]+= 395.2

By proceeding in the same way of example 15, 195 products of table XV were synthesized in parallel.

Table XV

Entry	Compound	HPLC Method	r.t. (min)	[M+H]+	Entry	Compound	HPLC Method	r.t. (min)	[M+H]+
1	A65-M1-B36	2	9.55	458.2	99	A57-M2-B08	3	2.8	380.2
2	A52-M1-B36	1	4.52	296.1	100	A59-M2-B08	3	2.62	408.1
3	A65-M1-B31	2	8.97	394.2	101	A60-M2-B08	3	3.1	410.2
4	A64-M1-B31	1	1.6	315.2	102	A61-M2-B08	3	1.57	409.2
5	A66-M1-B31	1	6.06	302.2	103	A50-M2-B09	3	2.96	378.2
6	A67-M1-B31	1	3.86	343.1	104	A51-M1-B09	3	2.81	430.2
7	A68-M1-B31	2	6.63	270.1	105	A52-M1-B09	3	2.43	324.2
8	A69-M1-B31	1	1.9	329.2	106	A53-M1-B09	3	2.66	384.2
9	A65-M1-B15	2	10.3	516.3	107	A55-M2-B09	3	1.83	395.2
10	A66-M1-B15	2	10.4	424.3	108	A59-M2-B09	3	2.95	420.2
11	A67-M1-B15	1	6.27	465.2	109	A60-M2-B09	3	3.4	422.3
12	A68-M1-B15	2	9.15	392.2	110	A61-M2-B09	3	1.87	421.3
13	A70-M1-B15	2	9.21	424.2	111	A50-M2-B10	3	2.41	382.2
14	A71-M1-B15	2	8.95	517.2	112	A51-M1-B10	3	2.31	434.2
15	A65-M1-B35	2	9.32	474.2	113	A52-M1-B10	3	1.81	328.1
16	A67-M2-B15	2	9.65	465.2	114	A53-M1-B10	3	2.13	388.2
17	A68-M2-B15	2	9.27	392.2	115	A55-M2-B10	3	1.37	399.2
18	A52-M2-B35	2	7.17	312.1	116	A56-M2-B10	3	2.45	382.2
19	A50-M2-B01	3	2.51	322.1	117	A59-M2-B10	3	2.45	424.1
20	A50-M1-B01	3	2.44	322.1	118	A60-M2-B10	3	2.95	426.2
21	A51-M1-B01	3	2.38	374.1	119	A61-M2-B10	3	1.43	425.2
22	A52-M1-B01	3	1.85	268.1	120	A50-M2-B11	3	2.54	340.1
23	A53-M1-B01	3	2.19	328.1	121	A51-M1-B11	3	2.41	392.1

24	A55-M2-B01	3	1.38	339.2		122	A52-M1-B11	3	1.9	286.1
25	A56-M2-B01	3	2.51	322.1		123	A53-M1-B11	3	2.23	346.1
26	A57-M2-B01	3	2.7	336.2		124	A55-M2-B11	3	1.39	357.2
27	A60-M2-B01	3	3.02	366.2		125	A56-M2-B11	3	2.56	340.1
28	A61-M2-B01	3	1.44	365.2		126	A57-M2-B11	3	2.76	354.2
29	A50-M2-B02	3	2.51	366.1		127	A59-M2-B11	3	2.56	382.1
30	A50-M1-B02	3	2.44	366.1		128	A60-M2-B11	3	3.07	384.2
31	A51-M1-B02	3	2.38	418.1		129	A61-M2-B11	3	1.46	383.2
32	A52-M1-B02	3	1.88	312.1		130	A50-M2-B12	3	2.81	406.1
33	A53-M1-B02	3	2.21	372.1		131	A51-M1-B12	3	2.68	458.1
34	A55-M2-B02	3	1.41	383.2		132	A52-M1-B12	3	2.28	352.1
35	A56-M2-B02	3	2.51	366.1		133	A53-M1-B12	3	2.53	412.1
36	A57-M2-B02	3	2.7	380.2		134	A55-M2-B12	3	1.73	423.2
37	A59-M2-B02	3	2.51	408.1		135	A56-M2-B12	3	2.83	406.1
38	A60-M2-B02	3	3.01	410.2		136	A57-M2-B12	3	3	420.1
39	A61-M2-B02	3	1.46	409.2		137	A58-M2-B12	3	3.01	432.1
40	A62-M2-B02	3	2.51	354.1		138	A59-M2-B12	3	2.81	448.1
41	A50-M2-B03	3	2.71	372.2		139	A60-M2-B12	3	3.27	450.2
42	A50-M1-B03	3	2.65	372.2		140	A61-M2-B12	3	1.77	449.2
43	A51-M1-B03	3	2.56	424.2		141	A50-M2-B13	3	2.05	371.2
44	A52-M1-B03	3	2.13	318.1		142	A55-M2-B13	3	1.09	388.2
45	A53-M1-B03	3	2.39	378.2		143	A56-M2-B13	3	2.09	371.2
46	A55-M2-B03	3	1.58	389.2		144	A59-M2-B13	3	2.1	413.2
47	A57-M2-B03	3	2.89	386.2		145	A50-M2-B14	3	2.63	366.2
48	A58-M2-B03	3	2.89	398.2		146	A51-M1-B14	3	2.51	418.2
49	A61-M2-B03	3	1.63	415.2		147	A52-M1-B14	3	2.04	312.1
50	A50-M2-B04	3	2.33	312.1		148	A53-M1-B14	3	2.37	372.2
51	A51-M1-B04	3	2.23	364.1		149	A55-M2-B14	3	1.51	383.2
52	A52-M1-B04	3	1.62	258.1		150	A56-M2-B14	3	2.63	366.2
53	A53-M1-B04	3	2.03	318.1		151	A57-M2-B14	3	2.81	380.2
54	A55-M2-B04	3	1.21	329.2		152	A59-M2-B14	3	2.6	408.1
55	A56-M2-B04	3	2.33	312.1		153	A60-M2-B14	3	3.08	410.2
56	A57-M2-B04	3	2.53	326.1		154	A62-M2-B14	3	2.65	354.2
57	A59-M2-B04	3	2.35	354.1		155	A51-M1-B16	3	2.07	342.1
58	A60-M2-B04	3	2.87	356.2		156	A52-M1-B16	3	1.38	236.1
59	A61-M2-B04	3	1.27	355.2		157	A53-M1-B16	3	1.82	296.1
60	A62-M2-B04	3	2.33	300.1		158	A51-M1-B17	3	2.18	431.2
61	A50-M2-B05	3	2.57	365.2		159	A52-M1-B17	3	1.65	325.1
62	A51-M1-B05	3	2.43	417.2		160	A53-M1-B17	3	2.05	385.2
63	A52-M1-B05	3	1.92	311.1		161	A51-M1-B18	3	2.6	452.1
64	A53-M1-B05	3	2.26	371.2		162	A52-M1-B18	3	2.15	346
65	A55-M2-B05	3	1.46	382.2		163	A53-M1-B18	3	2.43	406
66	A56-M2-B05	3	2.57	365.2		164	A51-M1-B19	3	2.42	392.1
67	A57-M2-B05	3	2.76	379.2		165	A52-M1-B19	3	1.92	286.1
68	A59-M2-B05	3	2.57	407.1		166	A53-M1-B19	3	2.25	346.1
69	A60-M2-B05	3	3.08	409.3		167	A51-M1-B20	3	2.81	446.2
70	A61-M2-B05	3	1.51	408.2		168	A52-M1-B20	3	2.43	340.2
71	A50-M1-B06	3	2.75	390.1		169	A53-M1-B20	3	2.65	400.2
72	A50-M2-B06	3	2.78	390.1		170	A51-M1-B21	3	2.63	426.1
73	A51-M1-B06	3	2.64	442.1		171	A52-M1-B21	3	2.18	320.1
74	A52-M1-B06	3	2.24	336.1		172	A53-M1-B21	3	2.45	380.1

75	A53-M1-B06	3	2.48	396.1		173	A51-M1-B22	3	2.61	468.2
76	A55-M2-B06	3	1.69	407.2		174	A52-M1-B22	3	2.2	362.1
77	A56-M2-B06	3	2.81	390.1		175	A53-M1-B22	3	2.45	422.2
78	A57-M2-B06	3	2.97	404.2		176	A51-M1-B23	3	2.53	414.1
79	A58-M2-B06	3	2.97	416.2		177	A52-M1-B23	3	2.03	308
80	A59-M2-B06	3	2.78	432.1		178	A53-M1-B23	3	2.35	368.1
81	A61-M2-B06	3	1.73	433.2		179	A51-M1-B24	3	2.25	393.1
82	A50-M2-B07	3	2.98	390.1		180	A52-M1-B24	3	1.67	287.1
83	A51-M1-B07	3	2.8	442.1		181	A53-M1-B24	3	2.05	347.1
84	A52-M1-B07	3	2.39	336		182	A51-M1-B25	3	2.61	402.2
85	A53-M1-B07	3	2.63	396.1		183	A52-M1-B25	3	2.17	296.1
86	A55-M2-B07	3	1.77	407.1		184	A53-M1-B25	3	2.44	356.2
87	A56-M2-B07	3	2.99	390.1		185	A51-M1-B26	3	3.62	396.2
88	A57-M2-B07	3	3.17	404.1		186	A52-M1-B26	3	3.43	290.2
89	A59-M2-B07	3	2.95	432		187	A53-M1-B26	3	3.51	350.2
90	A60-M2-B07	3	3.45	434.1		188	A57-M2-B26	3	2.98	358.2
91	A61-M2-B07	3	1.81	433.1		189	A60-M2-B26	3	3.25	388.3
92	A30-M1-B08	3	2.53	402.2		190	A51-M1-B27	3	2.49	434.2
93	A50-M2-B08	3	2.6	366.2		191	A52-M1-B27	3	2.03	328.1
94	A51-M1-B08	3	2.5	418.2		192	A53-M1-B27	3	2.32	388.2
95	A52-M1-B08	3	2.04	312.1		193	A51-M1-B28	3	2.63	571.2
96	A53-M1-B08	3	2.33	372.2		194	A52-M1-B28	3	2.28	465.2
97	A55-M2-B08	3	1.52	383.2		195	A53-M1-B28	3	2.49	525.2
98	A56-M2-B08	3	2.61	366.2						

Example 16

N-(5-{[5-(benzyloxy)pentyl]oxy}-1H-indazol-3-yl)-N'-isopropylurea

500 mg of Novabiochem trityl resin (declared substitution 1.27 mmol/g, 0.64 mmol) were suspended in dichloromethane and 374 mg of 2-[5-(tert-butyl-dimethyl-silanyloxy)-1H-indazol-3-yl]-isoindole-1,3-dione (0.9 mmol) and 367 µl of 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (1.3 mmol) were added. The suspension was stirred for 16 hours and then the resin was filtered and washed with dichloromethane, methanol, dimethylformamide, methanol and dichloromethane again. The resin was then dried under vacuum.

The identity of the resin and the yield of the loading step were checked by cleavage of the loaded product:

40 mg of resin were suspended in 1 ml of dichloromethane and 150 µl trifluoroacetic acid were added. After 2 hours the resin was drained and washed twice with 1 ml of dichloromethane; the collected solutions were dried and 13.8 mg of titled compound recovered. Calculated loading 0.85 mmol/g, HPLC r.t. Method 1: 7.64 [M+H]+= 394.

The resin obtained from the first step (500 mg, ~0.425 mmol) was suspended in 5 ml of a mixture of dichloromethane and methanol 1:1 and 500 µl of hydrazine monohydrate were added. The suspension was heated to 45°C. Heating and stirring were continued overnight, and then the mixture was cooled down to room temperature. The resin was filtered and washed with a mixture of methanol and water 1:1, methanol, dimethylformamide, and methanol again before drying under vacuum.
The identity of the resin was checked by cleavage. The reaction was performed as described above.
6-{[tert-butyl(dimethyl)silyl]oxy}-1H-indazol-3-amine HPLC r.t. Method 1: 5.99 [M+H]+= 264 [M-H]-= 262

A sample of the resin obtained from the second step (100 mg, 0.08 mmol) was suspended in 2 ml of dimethylformamide; isopropyl isocyanate (39 µl, 0.4mmol, ~5 eq) was added. The suspension was heated to 50°C. Stirring and heating was maintained for 60 hours, then the suspension was cooled down to room temperature. The resin was filtered and washed with dichloromethane, methanol, dimethylformamide, methanol and dichloromethane, before drying under vacuum.

The resin obtained from the third step (100 mg, ~0.08 mmol) was suspended in 3 ml of tetrahydrofuran anhydrous and 120 µl of a solution 1 M of tetrabutylammonium fluoride in tetrahydrofuran (~1.5 eq) were added. The suspension was stirred overnight then the resin was filtered and washed

with dichloromethane, methanol, dimethylformamide, methanol and dichloromethane, before drying under vacuum.

The resin obtained from the fourth step (100 mg, ~0.08 mmol) was suspended in 1 ml of tetrahydrofuran anhydrous. In a round bottom flask, 209 mg of triphenylphosphine (0.8mmol, ~10eq) were dissolved in 2 ml of tetrahydrofuran anhydrous, then 157 µl of diisopropyl azodicarboxylate (0.8 mmol, ~10eq) and 230 µl of 5-benzyloxy-1-pentanol (1.2 mmol, ~15eq) were gently added at 0°C. The solution was left shaking 2 h, then transferred into the suspension of the resin.
The suspension was stirred overnight then the resin was filtered and washed with dichloromethane, methanol, dimethylformamide, methanol and dichloromethane.
The procedure is repeated twice.

100 mg of dry resin were suspended in 3 ml of dichloromethane and 450 µl trifluoroacetic acid were added. After 2 hours the resin was drained and washed twice with 3 ml of dichloromethane; the collected solutions were dried and the desired title compound recovered.
N-(5-{[5-(benzyloxy)pentyl]oxy}-1H-indazol-3-yl)-N'-isopropylurea HPLC Method 1 r.t.6.75 [M+H]+=411.2

By proceeding in a manner similar to that of example 16, 2-(6-{[tert-butyl(dimethyl)silyl]oxy}-1H-indazol-3-yl)-1H-isoindole-1,3(2H)-dione and 2-[5-(tert-Butyl-dimethyl-silanyloxy)-1H-indazol-3-yl]-isoindole-1,3-dione were supported on the resin, then, by following the described synthetic scheme, the following products were synthesized.
N-[5-(but-3-ynyloxy)-1H-indazol-3-yl]-N'-isopropylurea HPLC Method 1 r.t. 4.77 [M+H]+= 287.1
N-benzyl-N'-[5-(2-pyrrolidin-1-ylethoxy)-1H-indazol-3-yl]urea HPLC Method 1 r.t. 3.28 [M+H]+= 380.2

N-isopropyl-N'-{5-[2-(4-methyl-1,3-thiazol-5-yl)ethoxy]-1H-indazol-3-yl}urea HPLC Method 2 r.t. 8.02 [M+H]+= 360.1

By proceeding in the same way of example 16, 95 products of table XVI were synthesized in parallel.

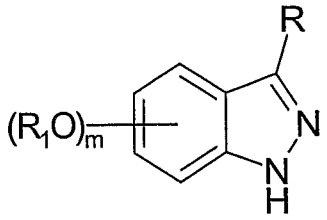
Table XVI

Entry	Compound	Method HPLC	r.t. (min)	[M+H]+	Entry	Compound	Method HPLC	r.t. (min)	[M+H]+
1	A65-M1-B83	1	7.3	459.2	49	A59-M2-B70	3	2.75	445.1
2	A66-M1-B83	1	7.41	367.2	50	A60-M2-B70	3	3.22	447.2
3	A67-M1-B83	2	8.53	408.1	51	A62-M2-B70	3	2.77	391.2
4	A64-M1-B68	1	2.42	332.2	52	A50-M2-B71	3	2.57	369.2
5	A66-M1-B68	1	6.78	319.2	53	A51-M1-B71	3	2.5	421.2
6	A68-M1-B68	1	4.77	287.1	54	A52-M1-B71	3	2.08	315.1
7	A50-M2-B62	3	2.67	367.2	55	A53-M1-B71	3	2.36	375.2
8	A50-M1-B62	3	2.61	367.2	56	A54-M2-B71	3	2.59	433.2
9	A51-M1-B62	3	2.55	419.2	57	A55-M2-B71	3	1.94	386.2
10	A52-M1-B62	3	2.11	313.1	58	A57-M2-B71	3	2.75	383.2
11	A53-M1-B62	3	2.4	373.2	59	A60-M2-B71	3	3.05	413.2
12	A54-M2-B62	3	2.62	431.2	60	A61-M2-B71	3	1.54	412.2
13	A50-M1-B63	3	2.72	351.2	61	A62-M2-B71	3	2.63	357.2
14	A50-M2-B63	3	2.72	351.2	62	A50-M2-B72	3	2.51	317.2
15	A51-M1-B63	3	2.64	403.2	63	A51-M1-B72	3	2.45	369.2
16	A52-M1-B63	3	2.22	297.1	64	A52-M1-B72	3	1.97	263.1
17	A53-M1-B63	3	2.5	357.2	65	A53-M1-B72	3	2.29	323.2
18	A51-M1-B64	3	2.73	423.1	66	A54-M2-B72	3	2.59	381.2
19	A52-M1-B64	3	2.34	317.1	67	A55-M2-B72	3	1.83	334.2
20	A53-M1-B64	3	2.59	377.1	68	A57-M2-B72	3	2.73	331.2
21	A50-M2-B65	3	3.05	413.2	69	A60-M2-B72	3	3.05	361.3
22	A51-M1-B65	3	2.9	465.2	70	A61-M2-B72	3	1.43	360.5
23	A52-M1-B65	3	2.57	359.1	71	A50-M2-B73	3	2.85	391.1
24	A53-M1-B65	3	2.78	419.2	72	A54-M2-B73	3	2.79	455.2
25	A62-M2-B65	3	3.05	401.2	73	A50-M2-B74	3	2.67	397.2
26	A50-M2-B66	3	2.54	379.2	74	A50-M1-B74	3	2.63	397.2
27	A51-M1-B66	3	2.45	431.2	75	A51-M1-B74	3	2.57	449.2
28	A52-M1-B66	3	1.99	325.1	76	A52-M1-B74	3	2.17	343.1
29	A53-M1-B66	3	2.32	385.2	77	A53-M1-B74	3	2.44	403.2
30	A59-M2-B66	3	2.55	421.1	78	A60-M2-B74	3	3.14	441.2
31	A50-M2-B67	3	2.58	365.2	79	A51-M1-B75	3	2.67	435.1
32	A51-M1-B67	3	2.5	417.1	80	A52-M1-B75	3	2.28	329.1
33	A52-M1-B67	3	2.03	311.1	81	A53-M1-B75	3	2.52	389.1
34	A53-M1-B67	3	2.35	371.1	82	A51-M1-B76	3	2.78	457.1
35	A60-M2-B67	3	3.09	409.2	83	A52-M1-B76	3	2.43	351.1
36	A50-M2-B68	3	2.35	303.2	84	A53-M1-B76	3	2.66	411.1
37	A51-M1-B68	3	2.32	355.2	85	A52-M1-B77	3	2.21	301.1
38	A52-M1-B68	3	1.76	249.1	86	A53-M1-B77	3	2.48	361.1

39	A53-M1-B68	3	2.16	309.2		87	A51-M1-B78	3	2.55	417.2
40	A57-M2-B68	3	2.58	317.2		88	A53-M1-B78	3	2.4	371.2
41	A62-M2-B68	3	2.37	291.2		89	A51-M1-B79	3	2.5	419.2
42	A50-M2-B69	3	2.84	365.2		90	A52-M1-B79	3	2.07	313.1
43	A51-M1-B69	3	2.75	417.2		91	A53-M1-B79	3	2.35	373.2
44	A52-M1-B69	3	2.35	311.1		92	A52-M1-B80	3	2.08	327.1
45	A53-M1-B69	3	2.61	371.2		93	A53-M1-B80	3	2.35	387.1
46	A61-M2-B69	3	1.71	408.2		94	A52-M1-B81	3	2.16	341.1
47	A50-M2-B70	3	2.77	403.2		95	A53-M1-B81	3	2.43	401.2
48	A57-M2-B70	3	2.95	417.2						

CLAIMS

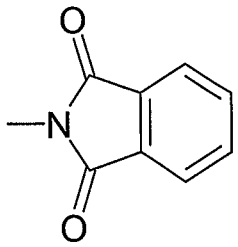
1. A method for treating diseases caused by and/or associated with an altered protein kinase activity which comprises administering to a mammal in need thereof an effective amount of an aminoindazole derivative represented by formula (I)



(I)

wherein

R is selected from the group consisting of -NHR', -NR'R", -NHCOR', -NHCONHR', -NHCONR'R", $-NHSO_2R'$ or -NHCOOR', wherein R' and R" are, each independently, a group optionally further substituted selected from straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or alkynyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 or 6 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur; or R is a phthalimido group of formula (II) below



(II)

any R_1, if present, is in position 5 or 6 of the indazole ring and represents a group, optionally further substituted, as set forth above for R' or R";

m is 0 or 1;

or a pharmaceutically acceptable salt thereof.

2. The method 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 method 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, keratoxanthoma, thyroid follicular cancer and Kaposi's sarcoma.

4. The method of claim 1 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.

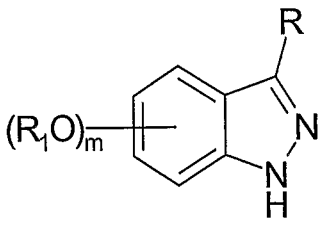
5. The method of claim 1 which provides tumor angiogenesis and metastasis inhibition.

6. The method of claim 1 further comprising 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 method of claim 1 wherein the mammal in need thereof is a human.

8. A method for inhibiting protein kinase activity which comprises contacting the said kinase with an effective amount of a compound of formula (I) as defined in claim 1.

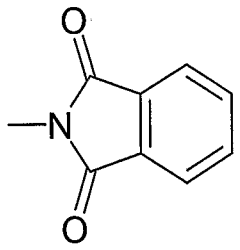
9. An aminoindazole derivative represented by formula (I)



(I)

wherein

R is selected from the group consisting of -NHR', -NR'R", -NHCOR', -NHCONHR', -NHCONR'R", $-NHSO_2R'$ or -NHCOOR', wherein R' and R" are, each independently, a group optionally further substituted selected from straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or alkynyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 or 6 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur; or R is a phthalimido group of formula (II) below



(II)

any R_1, if present, is in position 5 or 6 of the indazole ring and represents a group, optionally further substituted, as set forth above for R' or R";

m is 0 or 1;

or a pharmaceutically acceptable salt thereof;

with the provisos that:

a) when R is -NHCOR' and m is 0, then R' is other than methyl, n-propyl, benzyl, 2,2-diphenylethyl, 3,5-dimethyl-isoxazol-4-yl, 2-(morpholin-4-yl)ethyl, or phenyl optionally substituted by chloro, hydroxy, methyl, nitro or amino;

b) when the indazole is substituted in position 5 or 6 by a methoxy group then R is other than 3-(N,N-diethylamino)propylamino, 3-[(3-methyl)morpholin-4-yl]propylamino or 1-hydroxy-2-methyl-2-propylamino;

c) the compound 3-phthalimido-indazole being excluded.

10. A compound of formula (I) according to claim 9 wherein R is a group -NHR' or -NR'R" and R', R", R_1 and m are as defined in claim 9.

11. A compound of formula (I) according to claim 10 wherein m is 1 and R_1, R' and R" are selected, each independently, from C_2-C_6 alkenyl, C_3-C_6 alkynyl, aryl, aryl C_1-C_6 alkyl, 5 or 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur.

12. A compound of formula (I) according to claim 9 wherein R is a group -NHCOR' and R', R_1 and m are as defined in claim 9.

13. A compound of formula (I) according to claim 12 wherein m is 1 and R_1 and R' are selected, each independently, from 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 or 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen, sulfur.

14. A compound of formula (I) according to claim 9 wherein R is a group -NHCONHR' or -NHCONR'R", and R', R", R_1 and m are as defined in claim 9.

15. A compound of formula (I) according to claim 14 wherein m is 1 and R_1, R' and R" are selected, each independently, from 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 or 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen and sulfur.

16. A compound of formula (I) according to claim 9 wherein R is a group $-NHSO_2R'$ and R', R_1 and m are as defined in claim 9.

17. A compound of formula (I) according to claim 16 wherein m is 1 and R_1 and R' are selected, each independently, from 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 or 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen, sulfur.

18. A compound of formula (I) according to claim 9 wherein R is a group -NHCOOR' and R', R_1 and m are as defined in claim 9.

19. A compound of formula (I) according to claim 18 wherein m is 1 and R_1 and R' are selected, each independently, from 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 or 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen, sulfur.

20. A compound of formula (I) according to claim 9 wherein R is a phthalimido group of formula (II) and R_1 and m are as defined in claim 9.

21. A compound of formula (I) according to claim 20 wherein m is 1 and R_1 is selected from C_2-C_6 alkenyl, C_3-C_6 alkynyl, aryl, aryl C_1-C_6 alkyl, 5 or 7 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur.

22. A compound of formula (I) as defined in claim 9, optionally in the form of a pharmaceutically acceptable salt, selected from the group consisting of:

1) methyl 2-({3-[(anilinocarbonyl)amino]-1H-indazol-5-yl}oxy)butanoate;
2) N-benzyl-N'-[5-(2-pyrrolidin-1-ylethoxy)-1H-indazol-3-yl]urea;
3) methyl 2-[(3-{[(benzylamino)carbonyl]amino}-1H-indazol-5-yl)oxy]butanoate;
4) N-isopropyl-N'-{5-[(2-oxo-1-phenylpyrrolidin-3-yl)oxy]-1H-indazol-3-yl}urea;
5) 2-[(3-{[(isopropylamino)carbonyl]amino}-1H-indazol-5-yl)oxy]-N-phenylpropanamide,
6) methyl 2-[(3-{[(isopropylamino)carbonyl]amino}-1H-indazol-5-yl)oxy]butanoate;
7) N-isopropyl-N'-{5-[2-(4-methyl-1,3-thiazol-5-yl)ethoxy]-1H-indazol-3-yl}urea;
8) N-[5-(but-3-ynyloxy)-1H-indazol-3-yl]-N'-isopropylurea;
9) methyl 2-({3-[(3-phenylpropanoyl)amino]-1H-indazol-5-yl}oxy)butanoate;
10) N-{5-[(2-oxo-1-phenylpyrrolidin-3-yl)oxy]-1H-indazol-3-yl}cyclopropanecarboxamide;
11) methyl 2-({3-[(cyclopropylcarbonyl)amino]-1H-indazol-5-yl}oxy)butanoate;
12) 2-(4-tert-butylphenoxy)-N-[5-(2-pyrrolidin-1-ylethoxy)-1H-indazol-3-yl]acetamide;
13) 2-(4-methoxyphenyl)-N-[5-(2-pyrrolidin-1-ylethoxy)-1H-indazol-3-yl]acetamide;
14) methyl 2-[(3-{[(4-methoxyphenyl)acetyl]amino}-1H-indazol-5-yl)oxy]butanoate;
15) N-isopropyl-N'-{6-[(2-oxo-1-phenylpyrrolidin-3-yl)oxy]-1H-indazol-3-yl}urea;
16) N-{6-[(2-methylbenzyl)oxy]-1H-indazol-3-yl}cyclopropanecarboxamide;
17) N-{6-[(2-oxo-1-phenylpyrrolidin-3-yl)oxy]-1H-indazol-3-yl}cyclopropanecarboxamide;
18) methyl 2-({3-[(cyclopropylcarbonyl)amino]-1H-indazol-6-yl}oxy)butanoate;

19) methyl 2-({3-[(3-chlorobenzoyl)amino]-1H-indazol-6-yl}oxy)butanoate;

20) N-benzyl-N'-(5-hydroxy-2H-indazol-3-yl)urea;

21) N-(5-hydroxy-2H-indazol-3-yl)-N'-isopropylurea;

22) 2-(4-tert-butylphenoxy)-N-(5-hydroxy-2H-indazol-3-yl)acetamide;

23) N-(5-hydroxy-2H-indazol-3-yl)-2-(4-methoxyphenyl)acetamide;

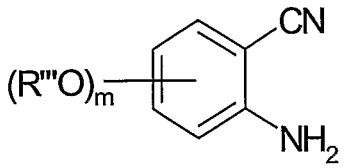
24) N-(6-hydroxy-2H-indazol-3-yl)-N'-phenylurea;

25) N-(6-hydroxy-2H-indazol-3-yl)-3-phenylpropanamide;

26) N-(6-hydroxy-2H-indazol-3-yl)cyclopropanecarboxamide.

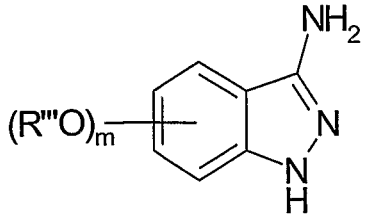
23. A process for preparing the compounds of formula (I) and the pharmaceutically acceptable salts thereof, as defined in claim 9, wherein R is as defined in claim 9 but other than a phthalimido group of formula (II), which process comprises:

a) reacting under acidic conditions a 2-amino-benzonitrile derivative of formula (III)



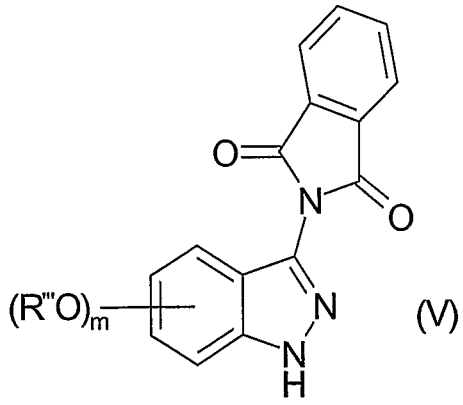
(III)

wherein m is as defined in claim 9 and, if present, R''' is a methyl or benzyl group; with sodium nitrite in the presence of stannous chloride, so as to obtain a compound of formula (IV)



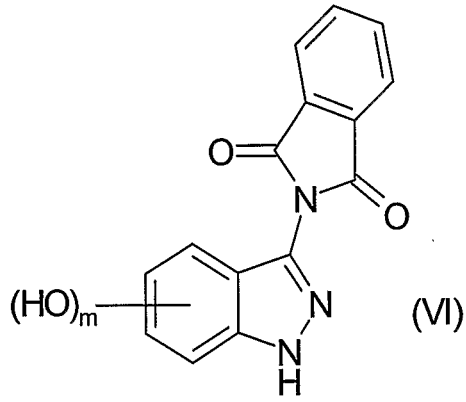
(IV)

b) reacting the compound of formula (IV) with phthalic anhydride so as to obtain a compound of formula (V)



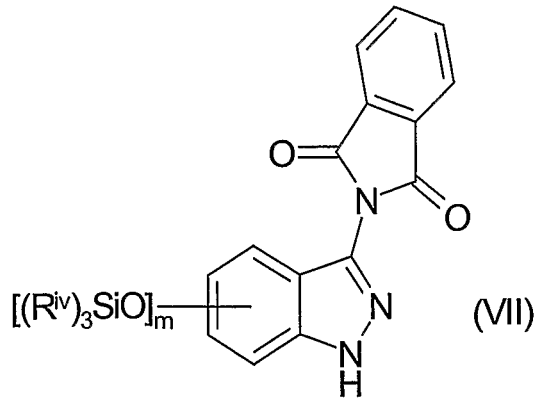
(V)

c) reacting the compound of formula (V) with a suitable ether cleaving agent so as to obtain the corresponding hydroxy derivative of formula (VI)



(VI)

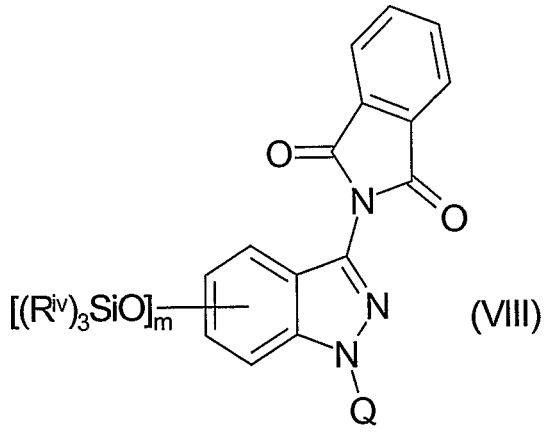
d) reacting the compound of formula (VI) with a suitable silylating agent $(R^{iv})_3SiZ$ wherein each R^{iv} is, the same or different, a straight or branched C_1-C_4 alkyl group, and Z is a halogen atom, so as to obtain a compound of formula (VII)



(VII)

e) reacting the compound of formula (VII) with a suitable indazole nitrogen protecting agent or, alternatively,

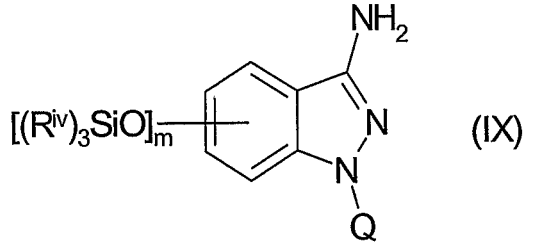
supporting it onto a suitable polymeric resin so as to obtain a compound of formula (VIII)



(VIII)

wherein Q is the above protecting group or represents the supporting resin;

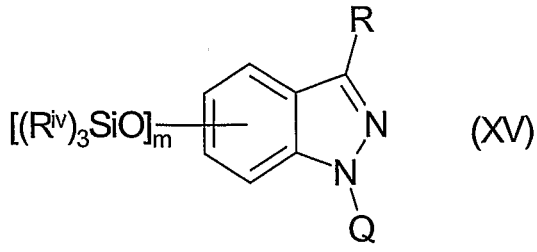
f) reacting the compound of formula (VIII) with hydrazine monohydrate so as to get the compound of formula (IX)



(IX)

and reacting the compound of formula (IX) according to any one of the following steps g.1) or g.2);

g.1) with a suitable reagent of formula R'-Z (X), R'-COZ (XI), R'-NCO (XII), R'-SO_2Z (XIII) or R'OCOZ (XIV), wherein R' is as defined in claim 9 and Z represents a halogen atom or a suitable leaving group, so as to get the corresponding compound of formula (XV)



(XV)

wherein R is a group -NHR', -NHCOR', -NHCONHR', -$NHSO_2$R' or -NHCOOR' and, if desired, reacting the compounds having R as a -NHR' or -NHCONHR' group with a compound of formula

R"Z (XVI)

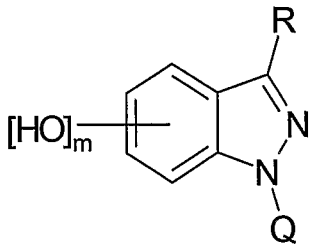
wherein R" is as defined in claim 9 and Z is as above defined, so as to get the compounds of formula (XV) wherein R is a group -NR'R" or -NHCONR'R";

g.2) with a compound of formula (XVII)

R'R"NH (XVII)

wherein R' and R" are as above defined, in the presence of 4-nitrophenyl chloroformate, so as to obtain the corresponding compound of formula (XV) wherein R is a group -NHCONR'R";

h) reacting any of the above compounds of formula (XV) with tetrabutylammonium fluoride so as to get the compound of formula (XVIII)

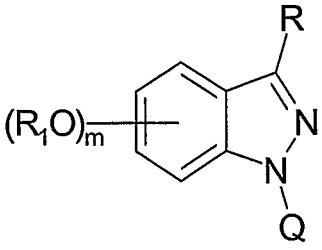


(XVIII)

i) reacting the compound of formula (XVIII) with a derivative of formula

R_1-Z (XIX)

wherein R_1 is as defined in claim 9 and Z is a halogen atom, a suitable leaving group or hydroxy, so as to obtain the compound of formula (XX)



(XX)

j) deprotecting the compound of formula (XX) or, alternatively, cleaving the polymeric resin so as to get the desired compound of formula (I) and, whenever desired, converting it into another compound of formula (I) and/or into a pharmaceutically acceptable salt thereof.

24. The process of claim 23 wherein the compound of formula (III) is 2-amino-4-methoxy-benzonitrile or 2-amino-5-benzyloxy-benzonitrile.

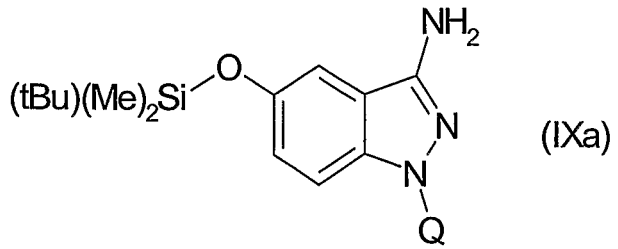
25. The process of claim 23 wherein step a) is carried out in the presence of hydrochloric acid.

26. The process of claim 23 wherein, in step d), the silylating agent is tert-butyl-dimethyl-silyl chloride.

27. The process of claim 23 wherein, in step e), the indazole derivative of formula (VII) is supported onto a chloro-trityl chloride polymeric resin.

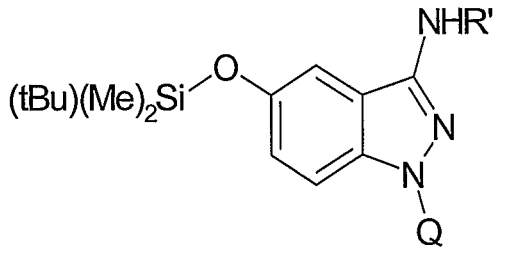
28. A process for preparing the compounds of formula (I) as defined in claim 9 and wherein R is a phthalimido group of formula (II), and the pharmaceutically acceptable salts thereof, which process comprises reacting the compounds of formula (VIII), as defined in claim 23, according to steps h), i) and j) of the process of claim 23.

29. A compound of formula (I) as defined in claim 9, and the pharmaceutically acceptable salts thereof, which are obtainable, for instance through a combinatorial chemistry technique as per the above process of claim 23, by first reacting the compound of formula (IXa)



(IXa)

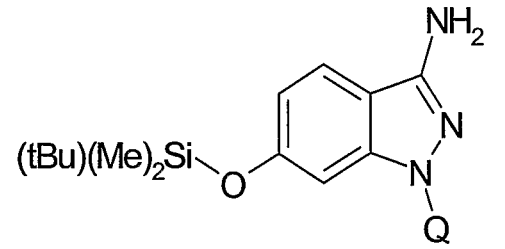
with each one of the compounds of formula (X), as set forth in table I, so as to obtain a plurality of compounds of formula (XVa)



(XVa)

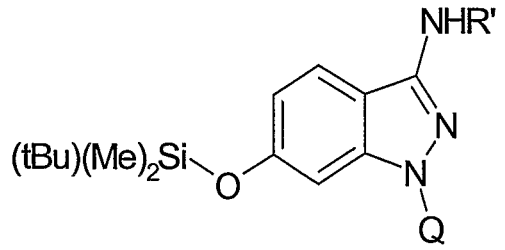
by then reacting each of the derivatives of formula (XVa) with tetrabutylammonium fluoride, as per step h) of the process, and then with each one of the derivatives of formula (XIX), as set forth in tables II or III, and by subsequently operating as per step j) of the process.

30. A compound of formula (I) as defined in claim 9, and the pharmaceutically acceptable salts thereof, which are obtainable, for instance through a combinatorial chemistry technique as per the process of claim 23, by first reacting the compound of formula (IXb)



(IXb)

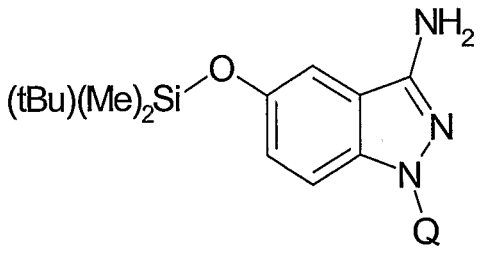
with each one of the compounds of formula (X), as set forth in table I, so as to obtain a plurality of compounds of formula (XVa)



(XVb)

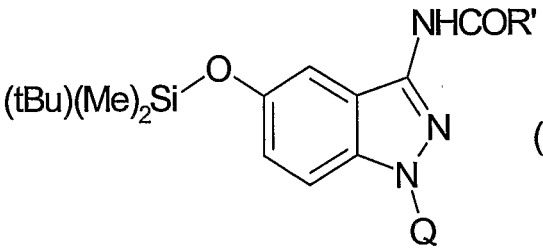
by then reacting each of the derivatives of formula (XVb) with tetrabutylammonium fluoride, as per step h) of the process, and then with each one of the derivatives of formula (XIX), as set forth in tables II or III, and by subsequently operating as per step j) of the process.

31. A compound of formula (I) as defined in claim 9, and the pharmaceutically acceptable salts thereof, which are obtainable, for instance through a combinatorial chemistry technique as per the process of claim 23, by first reacting the compound of formula (IXa)



(IXa)

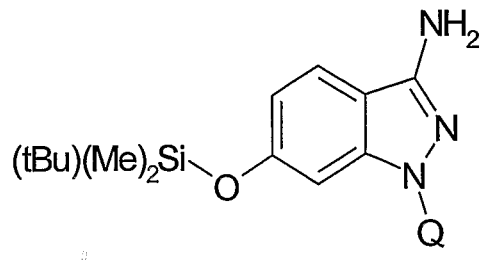
with each one of the compounds of formula (XI), as set forth in table IV, so as to obtain a plurality of compounds of formula (XVc)



(XVc)

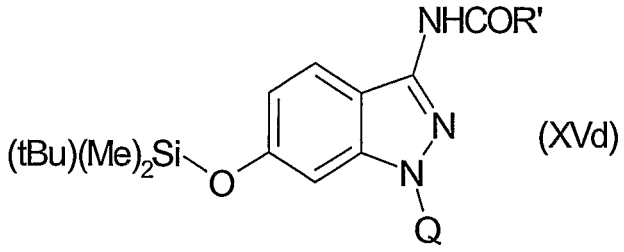
by then reacting each of the derivatives of formula (XVc) with tetrabutylammonium fluoride, as per step h) of the process, and then each one of the derivatives of formula (XIX), as set forth in tables II or III, and by subsequently operating as per step j) of the process.

32. A compound of formula (I) as defined in claim 9, and the pharmaceutically acceptable salts thereof, which are obtainable, for instance through a combinatorial chemistry technique as per the process of claim 23, by first reacting the compound of formula (IXb)



(IXb)

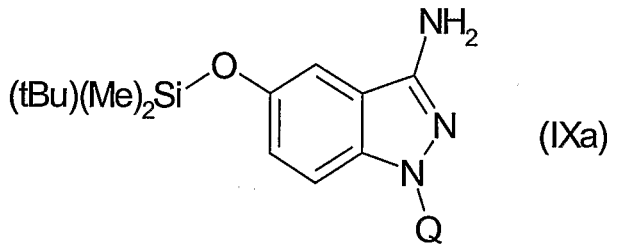
with each one of the compounds of formula (XI), as set forth in table IV, so as to obtain a plurality of compounds of formula (XVd)



(XVd)

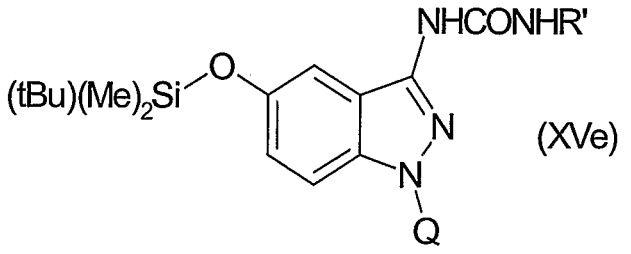
by then reacting each of the derivatives of formula (XVd) with tetrabutylammonium fluoride, as per step h) of the process, and then with each one of the derivatives of formula (XIX), as set forth in tables II or III, and by subsequently operating as per step j) of the process

33. A compound of formula (I) as defined in claim 9, and the pharmaceutically acceptable salts thereof, which are obtainable, for instance through a combinatorial chemistry technique as per the process of claim 23, by first reacting the compound of formula (IXa)



(IXa)

with each one of the compounds of formula (XII), as set forth in table V, so as to obtain a plurality of compounds of formula (XVe)

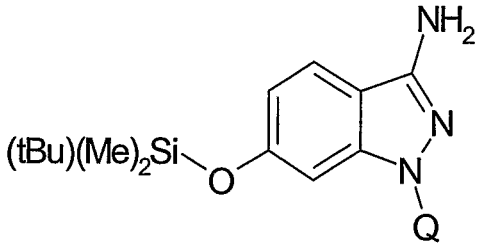


(XVe)

by then reacting each of the derivatives of formula (XVe) with tetrabutylammonium fluoride, as per step h) of the process, and then with each one of the derivatives of

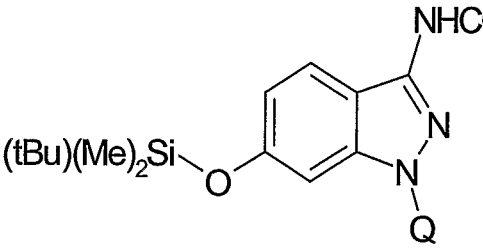
formula (XIX), as set forth in tables II or III, and by subsequently operating as per step j) of the process.

34. A compound of formula (I) as defined in claim 9, and the pharmaceutically acceptable salts thereof, which are obtainable, for instance through a combinatorial chemistry technique as per the process of claim 23, by first reacting the compound of formula (IXb)



(IXb)

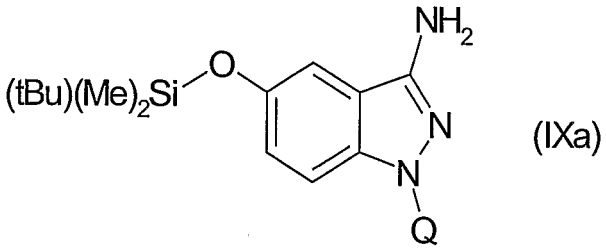
with each one of the compounds of formula (XII), as set forth in table V, so as to obtain a plurality of compounds of formula (XVf)



(XVf)

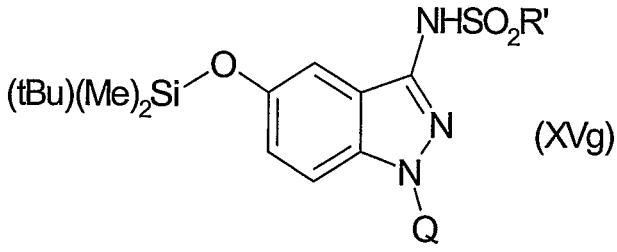
by then reacting each of the derivatives of formula (XVf) with tetrabutylammonium fluoride, as per step h) of the process, and then with each one of the derivatives of formula (XIX), as set forth in tables II or III, and by subsequently operating as per step j) of the process.

35. A compound of formula (I) as defined in claim 9, and the pharmaceutically acceptable salts thereof, which are obtainable, for instance through a combinatorial chemistry technique as per the process of claim 23, by first reacting the compound of formula (IXa)



(IXa)

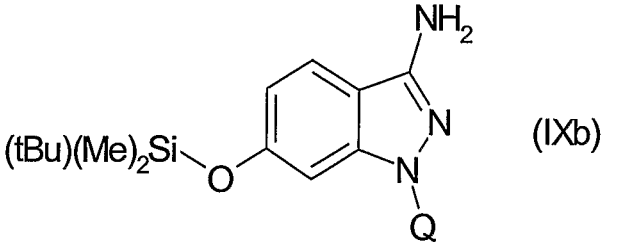
with each one of the compounds of formula (XIII), as set forth in table VI, so as to obtain a plurality of compounds of formula (XVg)



(XVg)

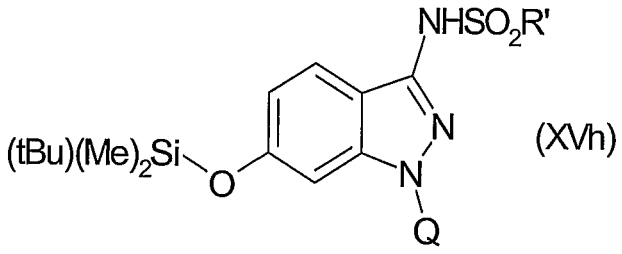
by then reacting each of the derivatives of formula (XVg) with tetrabutylammonium fluoride, as per step h) of the process, and then with each one of the derivatives of formula (XIX), as set forth in tables II or III, and by subsequently operating as per step j) of the process.

36. A compound of formula (I) as defined in claim 9, and the pharmaceutically acceptable salts thereof, which are obtainable, for instance through a combinatorial chemistry technique as per the process of claim 23, by first reacting the compound of formula (IXb)



(IXb)

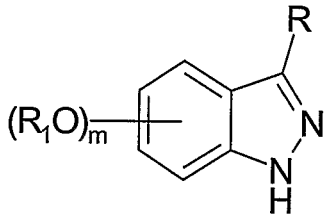
with each one of the compounds of formula (XIII), as set forth in table VI, so as to obtain a plurality of compounds of formula (XVh)



(XVh)

by then reacting each of the derivatives of formula (XVh) with tetrabutylammonium fluoride, as per step h) of the process, and then with each one of the derivatives of formula (XIX), as set forth in tables II or III, and by subsequently operating as per step j) of the process.

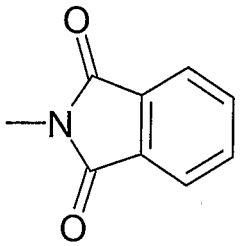
37. A library of two or more aminoindazole derivatives represented by formula (I)



(I)

wherein

R is selected from the group consisting of -NHR', -NR'R", -NHCOR', -NHCONHR', -NHCONR'R", $-NHSO_2R'$ or -NHCOOR', wherein R' and R" are, each independently, a group optionally further substituted selected from straight or branched C_1-C_6 alkyl, C_2-C_6 alkenyl or alkynyl, C_3-C_6 cycloalkyl or cycloalkyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, 5 or 6 membered heterocyclyl or heterocyclyl C_1-C_6 alkyl with from 1 to 3 heteroatoms selected among nitrogen, oxygen or sulfur; or R is a phthalimido group of formula (II) below



(II)

any R_1, if present, is in position 5 or 6 of the indazole ring and represents a group, optionally further substituted, as set forth above for R' or R";
m is 0 or 1;
or a pharmaceutically acceptable salt thereof.

38. A specific compound of formula (I), optionally in the form of a pharmaceutically acceptable salt, as defined in any one of tables from IX to XVI.

39. A pharmaceutical composition comprising an effective amount of an aminoindazole of formula (I) as defined in claim 9 and, at least, one pharmaceutically acceptable excipient, carrier or diluent.

40. A pharmaceutical composition according to claim 39 further comprising one or more chemotherapeutic agents, as a combined preparation for simultaneous, separate or sequential use in anticancer therapy.

41. A product or kit comprising a compound of claim 9 or a pharmaceutical composition thereof as defined in claim 39, and one or more chemotherapeutic agents, as a combined preparation for simultaneous, separate or sequential use in anticancer therapy.

42. A compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 9, for use as a medicament.

43. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 9, in the manufacture of a medicament for treating diseases caused by and/or associated with an altered protein kinase activity.

44. Use according to claim 43 for treating tumors.