"1H-indazole-3-carboxamide compounds as glycogen synthase kinase 3 beta inhibitors"

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FIELD OF THE INVENTION

The present invention relates to 1H-indazole-3-carboxamide compounds acting as glycogen synthase kinase 3 beta (GSK-3β) inhibitors and to their use in the treatment of GSK-3β-related disorders such as (i) insulin-resistance disorders; (ii) neurodegenerative diseases; (iii) mood disorders; (iv) schizophrenic disorders; (v) cancerous disorders; (vi) inflammation, (vii) substance abuse disorders; (viii) epilepsies; and (ix) neuropathic pain.

STATE OF THE ART

Protein kinases constitute a large family of structurally related enzymes, which transfer phosphate groups from high-energy donor molecules (such as adenosine triphosphate, ATP) to specific substrates, usually proteins. After phosphorylation, the substrate undergoes to a functional change, by which kinases can modulate various biological functions.

In general, protein kinases can be divided in several groups, according to the substrate that is phosphorylated. For example, serine/threonine kinase phosphorylates the hydroxyl group on the side chain of serine or threonine aminoacid.

Glycogen synthase kinases 3 (GSK-3) are constitutively active multi-functional enzymes, quite recently discovered, belonging to the serine/threonine kinases group.

Human GSK-3 are encoded by two different and independent genes, which leads to GSK-3α and GSK-3β proteins, with molecular weights of about 51 and 47 kDa, respectively. The two isoforms share nearly identical sequences in their kinase domains, while outside of the kinase domain, their sequences differ substantially (*Benedetti et al.,*

Neuroscience Letters, 2004, 368, 123-126). GSK-3α is a multifunctional protein serine kinase and GSK-3β is a serine-threonine kinase.

It has been found that GSK-3β is widely expressed in all tissues, with widespread expression in the adult brain, suggesting a fundamental role in neuronal signaling pathways *(Grimes and Jope, Progress in Neurobiology, 2001, 65, 391-426).* Interest in glycogen synthase kinases 3 arises from its role in various physiological pathways, such as, for example, metabolism, cell cycle, gene expression, embryonic development oncogenesis and neuroprotection (*Geetha et al., British Journal Pharmacology, 2009, 156, 885-898*).

GSK-3β was originally identified for its role in the regulation of glycogen synthase for the conversion of glucose to glycogen *(Embi et al., Eur J Biochem, 1980, 107, 519-527)*. GSK-3β showed a high degree of specificity for glycogen synthase.

Type 2 diabetes was the first disease condition implicated with GSK-3β, due to its negative regulation of several aspects of insulin signaling pathway. In this pathway 3-phosphoinositide-dependent protein kinase 1 (PDK-1) activates PKB, which in turn inactivates GSK-3β. This inactivation of GSK-3β leads to the dephosphorylation and activation of glycogen synthase, which helps glycogen synthesis *(Cohen et al., FEBS Lett., 1997, 410, 3-10)*. Moreover, selective inhibitors of GSK-3β are expected to enhances insulin signaling in prediabetic insulin-resistant rat skeletal muscle, thus making GSK-3β an attractive target for the treatment of skeletal muscle insulin resistance in the pre-diabetic state *(Dokken et al., Am J. Physiol. Endocrinol. Metab., 2005, 288, E1188-E1194).*

GSK-3β was also found to be a potential drug target in others pathological conditions due to insulin-resistance disorders, such as syndrome X, obesity and polycystic ovary syndrome (*Ring DB et al., Diabetes, 2003, 52: 588-595*).

It has been found that GSK-3β is involved in the abnormal phosphorylation of pathological tau in Alzheimer's disease (*Hanger et*

al., Neurosci. Lett., 1992, 147, 58-62; Mazanetz and Fischer, Nat Rev Drug Discov., 2007, 6, 464-479; Hong and Lee, J. Biol. Chem., 1997, 272, 19547-19553). Moreover, it was proved that early activation of GSK-3β, induced by apolipoprotein ApoE4 and β-amyloid, could lead to apoptosis and tau hyperphosphorylation (*Cedazo-Minguez et al., Journal of Neurochemistry, 2003, 87, 1152-1164*). Among other aspect of Alzheimer's disease, it was also reported the relevance of activation of GSK-3β at molecular level (*Hernandez and Avila, FEBS Letters, 2008, 582, 3848-3854*).

Moreover, it was demonstrated that GSK-3β is involved in the genesis and maintenance of neurodegenerative changes associated with Parkinson's disease (*Duka T. et al., The FASEB Journal, 2009; 23, 2820-2830*).

Accordingly to these experimental observations, inhibitors of GSK-3β may find applications in the treatment of the neuropathological consequences and the cognitive and attention deficits associated with tauopathies; Alzheimer's disease; Parkinson's disease; Huntington's disease (the involvement of GSK-3β in such deficits and diseases is disclosed in Meijer L. et al., *TRENDS Pharm Sci*, 2004; 25, 471-480); dementia, such as, but not limited to, vascular dementia, post-traumatic dementia, dementia caused by meningitis and the like; acute stroke; traumatic injuries; cerebrovascular accidents; brain and spinal cord trauma; peripheral neuropathies; retinopathies and glaucoma (the involvement of GSK-3β in such conditions is disclosed in WO 2010/109005).

The treatment of spinal neurodegenerative disorders, like amyotrophic lateral sclerosis, multiple sclerosis, spinal muscular atrophy and neurodegeneration due to spinal cord injury has been also suggested in several studies related to GSK-3β inhibition, such as, for example in Calderó J. et al., "Lithium prevents excitotoxic cell death of motoneurons in organotypic slice cultures of spinal cord", Neuroscience. 2010 Feb 17;165(4):1353-69, Léger B. et al., "Atrogin-1, MuRF1, and FoXO, as well as phosphorylated GSK-3beta and 4E-BP1 are reduced in skeletal

muscle of chronic spinal cord-injured patients", Muscle Nerve, 2009 Jul; 40(1):69-78, and Galimberti D. et al., "GSK3β genetic variability in patients with Multiple Sclerosis", Neurosci Lett. 2011 Jun 15;497(1):46-8.Furthermore, GSK-3β has been linked to the mood disorders, such as bipolar disorders, depression, and schizophrenia.

Inhibition of GSK-3β may be an important therapeutic target of mood stabilizers, and regulation of GSK-3β may be involved in the therapeutic effects of other drugs used in psychiatry. Dysregulated GSK-3β in mood disorder, bipolar disorder, depression and schizophrenia could have multiple effects that could impair neural plasticity, such as modulation of neuronal architecture, neurogenesis, gene expression and the ability of neurons to respond to stressful, potentially lethal conditions (*Jope and Roh, Curr. Drug Targets, 2006, 7, 1421-1434*).

The role of GSK-3β in mood disorder was highlighted by the study of lithium and valproate (*Chen et al., J. Neurochem., 1999, 72, 1327-1330; Klein and Melton, Proc. Natl. Acad. Sci. USA, 1996, 93, 8455-8459*), both of which are GSK-3β inhibitors and are used to treat mood disorders. There are also existing reports from the genetic perspective supporting the role of GSK-3β in the disease physiology of bipolar disorder (*Gould, Expert. Opin. Ther. Targets, 2006, 10, 377-392*).

It was reported a decrease in AKT1 protein levels and its phosphorylation of GSK-3β at Serine-9 in the peripheral lymphocytes and brains of individuals with schizophrenia. Accordingly, this finding supports the proposal that alterations in AKT1-GSK-3β signaling contribute to schizophrenia pathogenesis (*Emamian et al., Nat Genet, 2004, 36, 131-137*).

Additionally, the role of GSK-3β in cancer is a well-accepted phenomenon.

The potential of small molecules that inhibit GSK-3β has been evidenced for some specific cancer treatments (Jia Luo, *Cancer Letters*, 2009, 273, 194-200). GSK-3β expression and activation are associated with prostate cancer progression (Rinnab et al., Neoplasia, 2008, 10,

624-633) and the inhibition of GSK3b was also proposed as specific target for pancreatic cancer (Garcea et al., *Current Cancer Drug Targets*, 2007, 7, 209-215) and ovarian cancer (Qi Cao et al., Cell Research, 2006, 16 671-677). Acute inhibition of GSK-3β in colon-rectal cancer cells activates p53-dependent apoptosis and antagonizes tumor growth (Ghosh et al., Clin Cancer Res 2005, 11, 4580-4588).

The identification of a functional role for GSK-3β in MLL-associated leukaemia suggests that GSK-3β inhibition may be a promising therapy that is selective for transformed cells that are dependent on HOX overexpression (Birch et al., Cancer Cell, 2010, 17, 529-531).

GSK-3β is involved in numerous inflammatory signalling pathways, for example, among others GSK-3β inhibition has been shown to induce secretion of the anti-inflammatory cytokine IL-10. According to this finding, GSK-3β inhibitors could be useful to regulate suppression of inflammation (*G. Klamer et al., Current Medicinal Chemistry, 2010, 17(26), 2873-2281, Wang et al.*, Cytokine, 2010, 53, 130-140).

GSK-3β inhibition has been also shown to attenuate cocaine-induced behaviors in mice. The administration of cocaine in mice pretreated with a GSK-3β inhibitor demonstrated that pharmacological inhibition of GSK3 reduced both the acute behavioral responses to cocaine and the long-term neuroadaptations produced by repeated cocaine (*Cocaine-induced hyperactivity and sensitization are dependent on GSK3, Miller JS et al. Neuropharmacology. 2009 Jun; 56(8):1116-23, Epub 2009 Mar 27*).

The role of GSK-3β in the development of several forms of epilepsies has been demonstrated in several studies, which suggest that inhibition of GSK-3β could be a pathway for the treatment of epilepsy (*Novel glycogen synthase kinase 3 and ubiquitination pathways in progressive myoclonus epilepsy, Lohi H et al., Hum Mol Genet. 2005 Sep 15;14(18):2727-36 and Hyperphosphorylation and aggregation of Tau in laforin-deficient mice, an animal model for Lafora disease, Puri R et al., J Biol Chem. 2009 Aug 21;284(34):22657-63*).

The relationship between GSK-3β inhibition and treatment of neuropathic pain has been demonstrated in Mazzardo-Martins L. et al., “Glycogen synthase kinase 3-specific inhibitor AR-A014418 decreases neuropathic pain in mice: evidence for the mechanisms of action”, Neuroscience. 2012 Dec 13;226, and Xiaoping Gu et al., “The Role of Akt/GSK3β Signaling Pathway in Neuropathic Pain in Mice”, Poster A525, Anesthesiology 2012 October 13-17, 2012 Washington.

A review on GSK-3β, its function, its therapeutic potential and its possible inhibitors is given in "GSK-3β: role in therapeutic landscape and development of modulators" (*S. Phukan et al., British Journal of Pharmacology (2010), 160, 1-19*).

WO 2004/014864 discloses 1H-indazole-3-carboxamide compounds as selective cyclin-dependant kinases (CDK) inhibitors. Such compounds are assumed to be useful in the treatment of cancer, through a mechanism mediated by CDK_2, and neurodegenerative diseases, in particular Alzheimer’s disease, through a mechanism mediated by CDK_5, and as anti-viral and anti-fungine, through a mechanism mediated by CDK_7, CDK_8 and CDK_9.

Cyclin-dependant kinases (CDKs) are serine/threonine kinases, first discovered for their role in regulating the cell cycle. CDKs are also involved in regulating transcription, mRNA processing, and the differentiation of nerve cells. Such kinases activate only after their interaction and binding with regulatory subunits, namely cyclins.

Moreover, 1H-indazole-3-carboxamide compounds were also described as analgesics in the treatment of chronic and neuropathic pain (see, for example, WO 2004/074275 and WO 2004/101548) and as 5-HT_4 receptor antagonists, useful in the treatment of gastrointestinal disorders, central nervous system disorders and cardiovascular disorders (see, for example, WO 1994/10174).

SUMMARY OF THE INVENTION

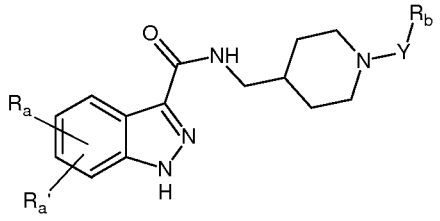
As GSK-3β had been only recently discovered as a pharmacological target, there is a strong need to find compounds that selectively inhibits GSK-3β.

The Applicant has surprisingly found new 1H-indazole-3-carboxamide compounds according to the following formula (I).

The Applicant has also surprisingly found that said new compounds are capable of inhibiting GSK-3β and have very high affinity for GSK-3β, when compared with other kinases. Thus, said compounds are capable of selectively inhibiting GSK-3β.

Accordingly, the compounds according to this invention are useful for the treatment of the pathological conditions arising from the uncontrolled activation and/or over-expression of GSK-3β, selected from the group comprising (i) insulin-resistance disorders, such as type-2 diabetes, syndrome X, obesity and polycystic ovary syndrome; (ii) neurodegenerative diseases, such as Parkinson's disease, Alzheimer's disease, Huntington's disease and spinal neurodegenerative disorders; (iii) mood disorders, such as bipolar disorders and depressive disorders; (iv) schizophrenic disorders; (v) cancerous disorders, such as prostate, pancreatic, ovarian, and colon-rectal cancer and MLL-associated leukaemia; (vi) inflammation; (vii) substance abuse disorders; (viii) epilepsies; and (ix) neuropathic pain.

Then, in a first aspect, the present invention relates to 1H-indazole-3-carboxamide compounds having the following general formula (I):



(I)

wherein

R_a and R_a', equal or different each other, is a hydrogen atom; a halogen atom; a hydroxy group; a C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl and C_1-C_6 alkoxy group, optionally substituted by one or more substituents selected from the group consisting of halogen, hydroxy, -NH_2, and C_1-C_3 alkoxy; a carbocyclic or heterocyclic ring, aliphatic or aromatic, having from 3 to 12 members, optionally substituted by one or more substituents selected from the group consisting of halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, -NR_1R_2, -C(O)OH, -$C(O)OR_1$ and -$C(O)NR_1R_2$;

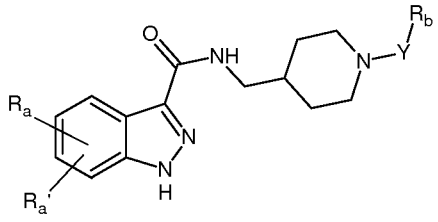
Y is a bond, a C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl group, optionally substituted by one or more substituents selected from the group consisting of halogen, hydroxy, -NH_2, and C_1-C_3 alkoxy;

R_b is a C_1-C_6 alkoxy group; -C(O)OH; -$C(O)OR_1$; -NO_2; -$NHC(O)R_1$;

R_1 and R_2 are independently a hydrogen atom, a C_1-C_4 alkyl group, a C_2-C_4 alkenyl group, a C_2-C_4 alkynyl group, and a phenyl group;

and its salts of addition with pharmaceutically acceptable organic and inorganic acids and bases.

In a second aspect, the present invention relates to the use of 1H-indazole-3-carboxamide compounds having the following general formula (I)



(I)

wherein

R_a and R_a', equal or different each other, is a hydrogen atom; a halogen atom; a hydroxy group; a C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl and C_1-C_6 alkoxy group, optionally substituted by one or more substituents selected from the group consisting of halogen, hydroxy, -NH_2, and C_1-C_3 alkoxy; a carbocyclic or heterocyclic ring, aliphatic or

aromatic, having from 3 to 12 members, optionally substituted by one or more substituents selected from the group consisting of halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, -NR_1R_2, -C(O)OH, -$C(O)OR_1$ and -$C(O)NR_1R_2$;

Y is a bond, a C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl group, optionally substituted by one or more substituents selected from the group consisting of halogen, hydroxy, -NH_2, and C_1-C_3 alkoxy;

R_b is a C_1-C_6 alkoxy group; -C(O)OH; -$C(O)OR_1$; -NO_2; -$NHC(O)R_1$;

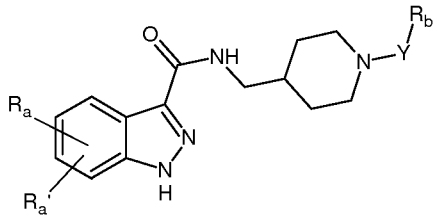
R_1 and R_2 are independently a hydrogen atom, a C_1-C_4 alkyl group, a C_2-C_4 alkenyl group, a C_2-C_4 alkynyl group, and a phenyl group;

and its salts of addition with pharmaceutically acceptable organic and inorganic acids and bases;

for the treatment of a disease arising from the uncontrolled activation and/or over-expression of GSK-3β, selected from the group consisting of (i) insulin-resistance disorders, such as type-2 diabetes, syndrome X, obesity and polycystic ovary syndrome; (ii) neurodegenerative diseases, such as Parkinson's disease, Alzheimer's disease, Huntington's disease and spinal neurodegenerative disorders; (iii) mood disorders, such as bipolar disorders and depressive disorders; (iv) schizophrenic disorders; (v) cancerous disorders, such as prostate, pancreatic, ovarian, and colon-rectal cancer and MLL-associated leukaemia; (vi) inflammation; (vii) substance abuse disorders; (viii) epilepsies; and (ix) neuropathic pain.

In a further aspect, the present invention relates to a method of treatment of a pathological state arising from the uncontrolled activation and/or over-expression of GSK-3β, selected from the group consisting of (i) insulin-resistance disorders, such as type-2 diabetes, syndrome X, obesity and polycystic ovary syndrome; (ii) neurodegenerative diseases, such as Parkinson's disease, Alzheimer's disease, Huntington's disease and spinal neurodegenerative disorders; (iii) mood disorders, such as bipolar disorders and depressive disorders; (iv) schizophrenic disorders; (v) cancerous disorders, such as prostate,

pancreatic, ovarian, and colon-rectal cancer and MLL-associated leukaemia; (vi) inflammation; (vii) substance abuse disorders; (viii) epilepsies; and (ix) neuropathic pain by the administration to a human being in need thereof of an effective amount of a 1H-indazole-3-carboxamide having the following general formula (I)



(I)

wherein

R_a and R_a', equal or different each other, is a hydrogen atom; a halogen atom; a hydroxy group; a C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl and C_1-C_6 alkoxy group, optionally substituted by one or more substituents selected from the group consisting of halogen, hydroxy, -NH_2, and C_1-C_3 alkoxy; a carbocyclic or heterocyclic ring, aliphatic or aromatic, having from 3 to 12 members, optionally substituted by one or more substituents selected from the group consisting of halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, -NR_1R_2, -C(O)OH, -$C(O)OR_1$ and -$C(O)NR_1R_2$;

Y is a bond, a C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl group, optionally substituted by one or more substituents selected from the group consisting of halogen, hydroxy, -NH_2, and C_1-C_3 alkoxy;

R_b is a C_1-C_6 alkoxy group; -C(O)OH; -$C(O)OR_1$; -NO_2; -$NHC(O)R_1$;

R_1 and R_2 are independently a hydrogen atom, a C_1-C_4 alkyl group, a C_2-C_4 alkenyl group, a C_2-C_4 alkynyl group, and a phenyl group;

and its salts of addition with pharmaceutically acceptable organic and inorganic acids and bases.

The present invention also includes the prodrugs, stereoisomers, and enantiomers of the compounds of formula (I) described above.

DETAILED DESCRIPTION OF THE INVENTION

Throughout the present description and the following claims, "C_{1-6} alkyl" is intended to indicate linear or branched alkyl groups having from 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, sec-pentyl, 3-pentyl, iso-pentyl, neo-pentyl, n-hexyl, sec-hexyl and neo-hexyl.

Throughout the present description and the following claims, "C_{1-4} alkyl" is intended to indicate linear or branched alkyl groups having from 1 to 4 carbon atoms, such as methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

Throughout the present description and the following claims, "C_{1-3} alkyl" is intended to indicate linear or branched alkyl groups having from 1 to 3 carbon atoms, such as methyl, ethyl, propyl and isopropyl.

Throughout the present description and the following claims, "C_{2-6} alkenyl" is intended to indicate linear or branched alkyl groups having from 2 to 6 carbon atoms and at least one double bond, such as ethenyl (vinyl), 1-propenyl, 2-propenyl (allyl), isopropenyl, butenyl, pentenyl and hexenyl.

Throughout the present description and the following claims, "C_{2-4} alkenyl" is intended to indicate linear or branched alkyl groups having from 2 to 4 carbon atoms and at least one double bond, such as ethenyl (vinyl), 1-propenyl, 2-propenyl (allyl), isopropenyl and butenyl.

Throughout the present description and the following claims, "C_{2-6} alkynyl" is intended to indicate linear or branched alkyl groups having from 2 to 6 carbon atoms and at least one triple bond, such as ethynyl, 1-propynyl, 2-propynyl (propargyl), butynyl, pentynyl and hexynyl.

Throughout the present description and the following claims, "C_{2-4} alkynyl" is intended to indicate linear or branched alkyl groups having from 2 to 4 carbon atoms and at least one triple bond, such as ethynyl, 1-propynyl, 2-propynyl (propargyl) and butynyl.

Throughout the present description and the following claims, "C_{1-6} alkoxy" is intended to indicate linear or branched alkoxy groups having from 1 to 6 carbon atoms, such as methoxy, ethoxy, n-propoxy, iso-

propoxy, n-butoxy, tert-butoxy, n-penthoxy, sec-penthoxy, isopenthoxy and n-esiloxy.

Throughout the present description and the following claims, "C_{1-3} alkoxy" is intended to indicate linear or branched alkoxy groups having from 1 to 3 carbon atoms, such as methoxy, ethoxy, n-propoxy and iso-propoxy.

According to a preferred embodiment of the invention, the meanings of R_a, R_a', R_b and Y of the formula (I) above are described here in below.

Preferably, R_a and R_a', equal or different each other, is a hydrogen atom; a halogen atom, selected from chlorine, bromine and iodine; a hydroxy group; a C_1-C_6 alkyl, and C_1-C_6 alkoxy group, optionally substituted by one or more substituents selected from the group consisting of halogen, hydroxy, -NH_2, or C_1-C_3 alkoxy; a carbocyclic or heterocyclic ring, aliphatic or aromatic, having from 4 to 10 members, optionally substituted by one or more substituents selected from the group consisting of halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, -NR_1R_2, -C(O)OH, -C(O)OR_1 and -C(O)NR_1R_2.

More preferably, R_a and R_a', equal or different each other, is a halogen atom, selected from chlorine and bromine; a hydroxy group; a C_1-C_6 alkyl group; a C_1-C_6 alkoxy group; or a carbocyclic or heterocyclic ring, aliphatic or aromatic, having from 5 to 6 members, optionally substituted by one or more substituents, selected from the group consisting of halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, -NR_1R_2 and -C(O)OH.

Advantageously, said carbocyclic or heterocyclic ring, aliphatic or aromatic, having 5 or 6 members is selected from phenyl, pyridine, pyrimidine, pyrazine, pyridazine, pyrrole, furan, thiophene, oxazole, isoxazole, thiazole, isothiazole, 2H-pyran, cyclohexyl, cyclopenthyl piperidine, piperazine.

Even more preferably, R_a and R_a', equal or different each other, is a bromine atom, a hydroxy group; a C_1-C_3 alkoxy group; or an aromatic carbocyclic or heterocyclic ring, having 6 members, optionally

substituted by one or two substituents selected from the group consisting of halogen, hydroxy, C_1-C_3 alkyl, C_1-C_3 alkoxy, -NR_1R_2 and –C(O)OH.

In a preferred embodiment, said carbocyclic or heterocyclic ring, aliphatic or aromatic, having 6 members is selected from phenyl, pyridine, pyrimidine, pyrazine, pyridazine, 2H-pyran, cyclohexyl, piperidine, piperazine.

In an even more preferred embodiment, said carbocyclic or heterocyclic ring, aliphatic or aromatic, having 6 members is selected from phenyl, pyridine, pyrimidine, 2H-pyran, cyclohexyl.

In an even more preferred embodiment, said carbocyclic or heterocyclic ring, aliphatic or aromatic, having 5 members is selected from oxazole and isoxazole.

Preferably, Y is a bond, C_1-C_6 alkyl group, optionally substituted by one or more substituents selected from the group consisting of halogen, hydroxy, -NH_2, and C_1-C_3 alkoxy.

More preferably, Y is a C_1-C_6 alkyl group.

Even more preferably, Y is a C_1-C_3 alkyl group.

Preferably, R_b is a C_1-C_6 alkoxy group; -C(O)OH; -$C(O)OR_1$ or -$NHCOR_1$.

More preferably, R_b is a C_1-C_6 alkoxy group or -C(O)OH.

Even more preferably, R_b is a C_1-C_3 alkoxy group or -C(O)OH.

Preferably, R_1 and R_2 are independently a hydrogen atom, a C_1-C_4 alkyl group, or a phenyl group.

More preferably, R_1 and R_2 are independently a C_1-C_3 alkyl group.

Even more preferably, R_1 and R_2 are both a methyl group.

The compounds according to the present invention are preferably employed as salts with pharmaceutically acceptable organic and inorganic acids or bases.

Preferably, the pharmaceutically acceptable organic acids are selected from the group consisting of oxalic, maleic, methanesulphonic, paratoluenesulphonic, succinic, citric, malic, tartaric and lactic acid.

Preferably, the pharmaceutically acceptable organic bases are selected from the group consisting of tromethamine, lysine, arginine, glycine, alanine and ethanolamine.

Preferably, the pharmaceutically acceptable inorganic acids are selected from the group consisting of hydrochloric, hydrobromic, phosphoric and sulphuric acid.

Preferably, the pharmaceutically acceptable inorganic bases are selected from the group consisting of hydroxide or carbonate of alkaline or alkaline-earth metals, such as sodium, potassium and calcium.

The present invention also includes the prodrugs, stereoisomers, and enantiomers of the compounds of formula (I) described above.

As used herein the term "prodrug" refers to an agent, which is converted into the parent drug in vivo by some physiological chemical process (e.g., a prodrug on being brought to the physiological pH is converted to the desired drug form). Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmacological compositions over the parent drug. An example, without limitation, of a prodrug would be a compound of the present invention wherein it is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is not beneficial, but then it is metabolically hydrolyzed to the carboxylic acid once inside the cell where water solubility is beneficial.

Prodrugs have many useful properties. For example, a prodrug may be more water-soluble than the ultimate drug, thereby facilitating intravenous administration of the drug. A prodrug may also have a higher level of oral bioavailability than the ultimate drug. After

administration, the prodrug is enzymatically or chemically cleaved to deliver the ultimate drug in the blood or tissue.

Ester prodrugs of the compounds disclosed herein are specifically contemplated. An ester may be formed from a carboxylic acid functional group linked to a compound of formula (I) above by reaction with an alcohol or phenol. Alternatively, an ester may be formed from a hydroxyl functional group linked to a compound of formula (I) above by reaction with a carboxylic acid or an amino acid. While not intending to be limiting, an ester may be an alkyl ester, an aryl ester, or a heteroaryl ester. The term alkyl has the meaning generally understood by those skilled in the art and refers to linear, branched, or cyclic alkyl moieties. C_{1-6}alkyl esters are particularly useful, where alkyl part of the ester has from 1 to 6 carbon atoms and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, t-butyl, pentyl isomers, hexyl isomers, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and combinations thereof having from 1-6 carbon atoms.

The compounds of the present invention according to formula (I) above can be used for the treatment of a pathological state arising from the uncontrolled activation and/or overexpression of GSK-3β, selected from the group consisting of (i) insulin-resistance disorders; (ii) neurodegenerative diseases; (iii) mood disorders; (iv) schizophrenic disorders; (v) cancerous disorders; (vi) inflammation; (vii) substance abuse disorders; (viii) epilepsies; and (ix) neuropathic pain.

Advantageously, insulin-resistance disorders are type-2 diabetes, syndrome X, obesity and polycystic ovary syndrome.

Advantageously, acute and chronic neurodegenerative diseases are Parkinson's disease, Alzheimer's disease, Huntington's disease and spinal neurodegenerative disorders.

Preferably, spinal neurodegenerative disorders are amyotrophic lateral sclerosis, multiple sclerosis, spinal muscular atrophy and neurodegeneration due to spinal cord injury.

Advantageously, mood disorders are bipolar disorders and depressive disorders.

Preferably, bipolar disorders are bipolar I, bipolar II, cyclothymia and bipolar disorder not otherwise specified (BD-NOS),

Preferably, depressive disorders are major depressive disorder (MDD), atypical depression (AD), melancholic depression, psychotic major depression (PMD), catatonic depression, postpartum depression (PPD), seasonal affective disorder (SAD), dysthymia, and depressive disorder not otherwise specified (DD-NOS)

Advantageously, schizophrenic disorders are paranoid schizophrenia, disorganized schizophrenia, catatonic schizophrenia, simple schizophrenia, residual schizophrenia, and undifferentiated schizophrenia.

Advantageously, cancerous disorders are prostate, pancreatic, ovarian, and colon-rectal cancer and MLL-associated leukaemia.

Advantageously, substance abuse disorders are abuse disorders due to psychostimulants.

Typically, the 1H-indazole-3-carboxamide compounds according to formula (I) useful in this invention are administered in the form of a pharmaceutical composition.

Accordingly, a further aspect of the present invention relates to a pharmaceutical composition comprising at least one compound of formula (I) as described above and at least one inert pharmaceutically acceptable excipient.

Preferably, the pharmaceutical composition of the present invention is prepared in suitable dosage forms comprising an effective amount of at least one compound of formula (I) as described above, a salt thereof with a pharmaceutically acceptable organic or inorganic acid or base, or a prodrug thereof, and at least one inert pharmaceutically acceptable excipient.

Examples of suitable dosage forms are tablets, capsules, coated tablets, granules, solutions and syrups for oral administration; solutions, pomade and ointment for topical administration; medicated patches for transdermal administration; suppositories for rectal administration and injectable sterile solutions.

Other suitable dosage forms are those with sustained release and those based on liposomes for oral, injectable or transdermal administration.

The dosage forms can also contain other traditional ingredients such as: preservatives, stabilizers, surfactants, buffers, salts for regulating osmotic pressure, emulsifiers, sweeteners, colorants, flavourings and the like.

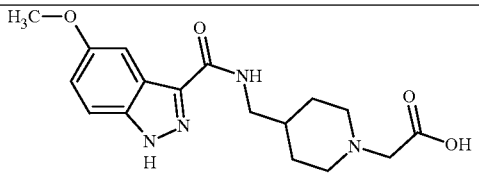
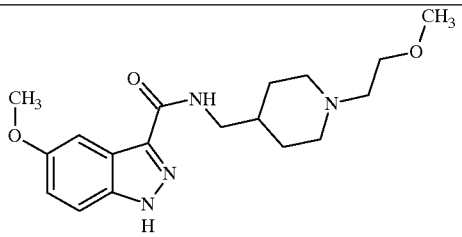
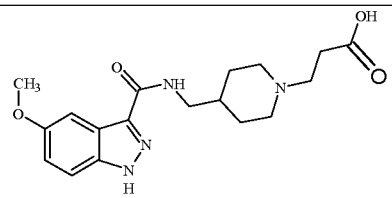
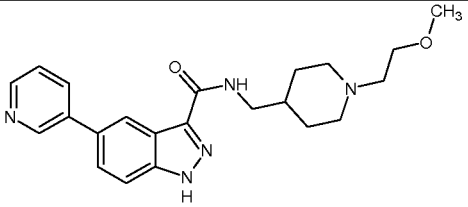
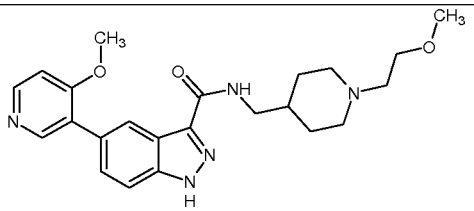
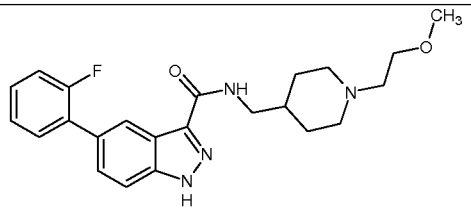
The amount of the 1H-indazole-3-carboxamide according to formula (I) or of the pharmaceutically acceptable salt of acid addition thereof in the pharmaceutical composition of the present invention can vary over a wide range depending on known factors, for example, the type of pathology, the severity of the disease, the patient's body weight, the dosage form, the chosen route of administration, the number of administrations per day and the efficacy of the selected 1H-indazole-3-carboxamide compound according to formula (I). However, a person skilled in the art can determine the optimum amount in easily and routinely manner.

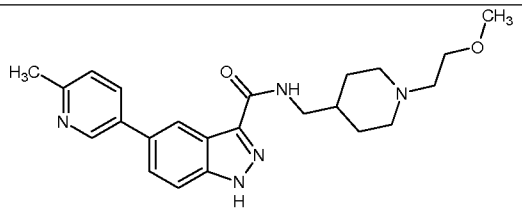
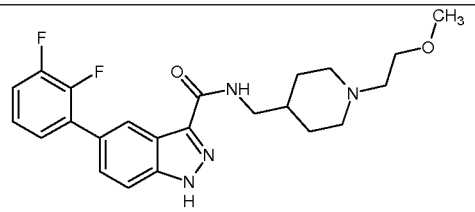
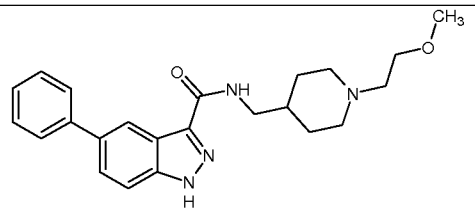
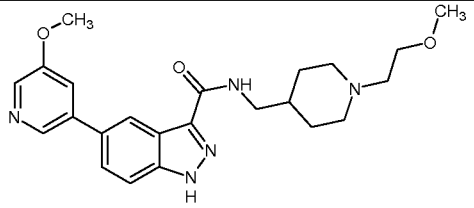
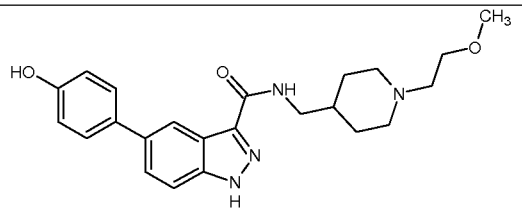
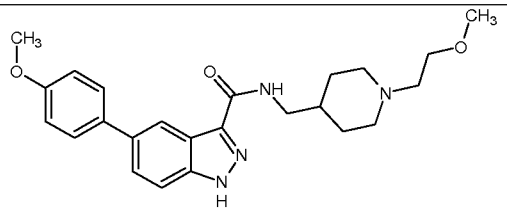
Typically, the amount of compound of formula (I) or of the pharmaceutically acceptable salt of acid addition thereof in the pharmaceutical composition of the present invention will be such as to ensure a level of administration from 0.0001 to 100 mg/kg/day. Preferably, the level of administration is from 0.001 to 50 mg/kg/day, and even more preferably from 0.01 to 10 mg/kg/day.

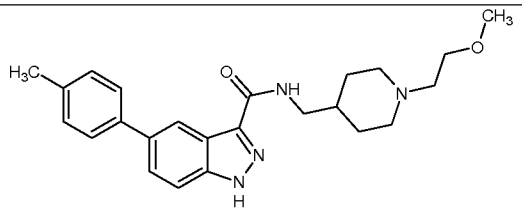
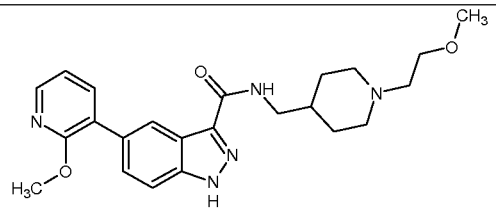
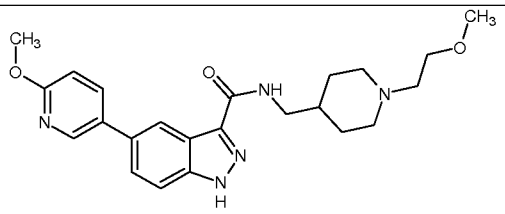
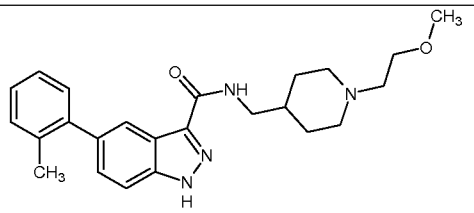
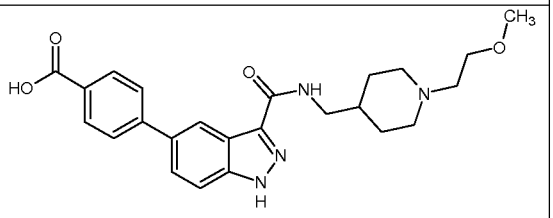
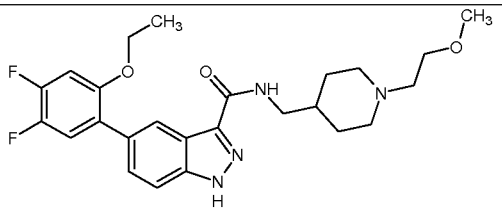
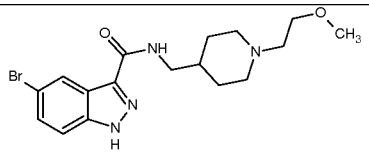
The dosage forms of the pharmaceutical composition of the present invention can be prepared by techniques that are familiar to a pharmaceutical chemist, and comprise mixing, granulation, compression, dissolution, sterilization and the like.

Non-limiting examples of compounds of formula (I) according to the present invention are those of the following table 1.

Table 1

	IUPAC name	Structure
1	[4-({[(5-methoxy-1H-indazol-3-yl)-carbonyl]amino}methyl)piperidin-1-yl]acetic acid	
2	5-methoxy-N-{[1-(2-methoxyethyl)-piperidin-4-yl]methyl}-1H-indazole-3-carboxamide	
3	[4-({[(5-methoxy-1H-indazol-3-yl)-carbonyl]amino}methyl)piperidin-1-yl]propionic acid	
4	N-{[1-(2-methoxyethyl)piperidin-4-yl]methyl}-5-(pyridin-3-yl)-1H-indazole-3-carboxamide	
5	N-{[1-(2-methoxyethyl)piperidin-4-yl]methyl}-5-(4-methoxypyridin-3-yl)-1H-indazole-3-carboxamide	
6	5-(2-fluorophenyl)-N-{[1-(2-methoxyethyl)piperidin-4-yl]methyl}-1H-indazole-3-carboxamide	

	IUPAC name	Structure
7	N-{[1-(2-methoxyethyl)piperidin-4-yl]methyl}-5-(6-methylpyridin-3-yl)-1H-indazole-3-carboxamide	
8	5-(2,3-difluorophenyl)-N-{[1-(2-methoxyethyl)piperidin-4-yl]methyl}-1H-indazole-3-carboxamide	
9	N-{[1-(2-methoxyethyl)piperidin-4-yl]methyl}-5-phenyl-1H-indazole-3-carboxamide	
10	N-{[1-(2-methoxyethyl)piperidin-4-yl]methyl}-5-(5-methylpyridin-3-yl)-1H-indazole-3-carboxamide	
11	5-(4-hydroxyphenyl)-N-{[1-(2-methoxyethyl)piperidin-4-yl]methyl}-1H-indazole-3-carboxamide	
12	N-{[1-(2-methoxyethyl)piperidin-4-yl]methyl}-5-(4-methoxyphenyl)-1H-indazole-3-carboxamide	

	IUPAC name	Structure
13	N-{[1-(2-methoxyethyl)piperidin-4-yl]methyl}-5-(4-methylphenyl)-1H-indazole-3-carboxamide	
14	N-{[1-(2-methoxyethyl)piperidin-4-yl]methyl}-5-(2-methoxypyridin-3-yl)-1H-indazole-3-carboxamide	
15	N-{[1-(2-methoxyethyl)piperidin-4-yl]methyl}-5-(6-methoxypyridin-3-yl)-1H-indazole-3-carboxamide	
16	N-{[1-(2-methoxyethyl)piperidin-4-yl]methyl}-5-(2-methylphenyl)-1H-indazole-3-carboxamide	
17	4-[3-({[1-(2-methoxyethyl)piperidin-4-yl]methyl}carbamoyl)-1H-indazol-5-yl]benzoic acid	
18	5-(2-ethoxy-4,5-difluorophenyl)-N-{[1-(2-methoxyethyl)piperidin-4-yl]methyl}-1H-indazole-3-carboxamide	
19	5-bromo-N-{[1-(2-methoxyethyl)piperidine-4-yl]methyl}-1H-indazole-3-	

	IUPAC name	Structure
	carboxamide	

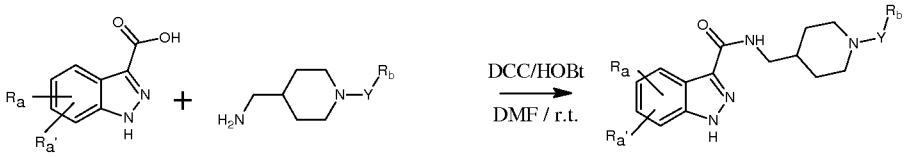
EXPERIMENTAL PART

^{1}H-NMR spectroscopy: internal standard = Tetramethylsilane; DMSO-d_6 = deuterated dimethyl sulfoxide; (s) = singlet; (d) = doublet; (t) = triplet; (br) = broad; (dd) = double doublet; (dt) = double triplet; (ddd) = double double doublet ;(dtd) = double triple doublet; (m) = multiplet; J = coupling constant; δ = chemical shift (in ppm).

Preparation of compounds of formula (I)

Compounds of formula (I) can be obtained by methods known to persons skilled in the art, for example by the following methods A to D.

Method A



(i) (ii) (I)

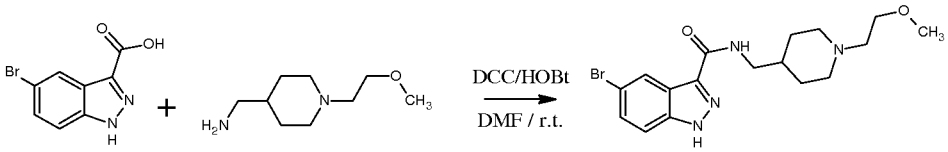
1-Hydroxybenzotriazole (HOBt, 7.40 g, 54.8 mmoles) and N,N'-dicyclohexylcarbodiimide (DCC, 11 g, 53.3 mmoles) were added to a solution of a convenient substituted 1H-indazole-3-carboxylic acid (compound i, 12 g, 49.8 mmoles) in DMF (200 ml) at 0°C. After 1 hour, a solution of a convenient 1-substituted [piperidin-4-yl]methanamine (compound ii, 10 g, 58.1 mmoles) in DMF (100 ml) was added at the same temperature. The mixture was stirred at 0 °C for 2 hours then it was left to reach room temperature during the night. The mixture was diluted with AcOEt then the solid was removed by filtration. The solution was extracted three times with hydrochloridric acid (HCl) 2N. The pH of the acid phase was increased (about 13) with 5N NaOH and solution

was extracted three times with dichloromethane (DCM). The organic phase was dried with anhydrous Na_2SO_4.

The solvent was filtered, evaporated under reduced pressure and the residue was adequately purified.

For example, compound (19) can be prepared according to method A as described below.

Compound (19)



(iii) (iv) (19)

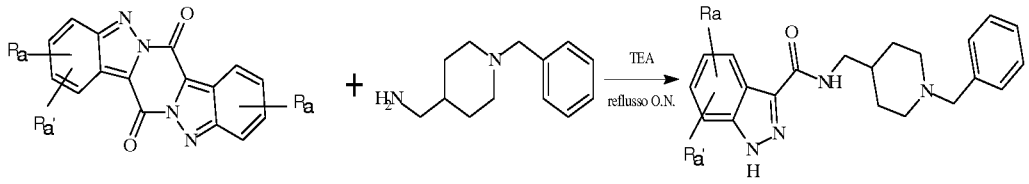
1-Hydroxybenzotriazole (HOBt, 7.40 g, 54.8 mmoles) and N,N'-dicyclohexylcarbodiimide (DCC, 11 g, 53.3 mmoles) were added to a solution of 5-bromo-1H-indazole-3-carboxylic acid (compound iii, 12 g, 49.8 mmoles) in DMF (200 ml) at 0°C. After 1 hour, a solution of 1-[1-(2-methoxyethyl)piperidin-4-yl]methanamine (compound iv, 10 g, 58.1 mmoles) in DMF (100 ml) was added at the same temperature. The mixture was stirred at 0 °C for 2 hours then it was left to reach room temperature during the night. The mixture was diluted with AcOEt then the solid was removed by filtration. The solution was extracted three times with 2N HCl. The pH of the acid phase was increased (about 13) with 5N NaOH and solution was extracted three times with DCM. The organic phase was dried with anhydrous Na_2SO_4.

The solvent was filtered, evaporated under reduced pressure and the residue was purified by flash chromatography (SiO_2, $CHCl_3$/MeOH=85/15).

Compound (19) thus obtained was purified as disclosed in Table 2, obtaining 9.5 g of solid.

Method B

First step:

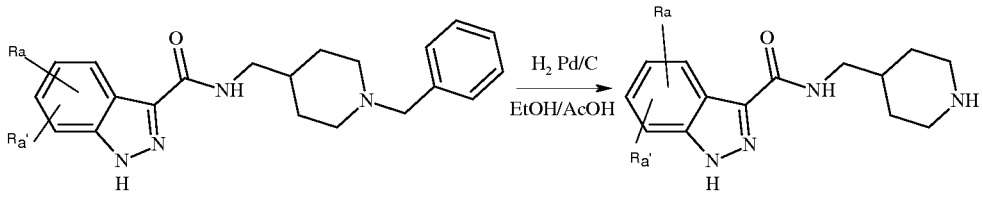


(v) (vi) (vii)

To a suspension of a convenient compound (v) (2.13 g; 0.0061 moles) in toluene (50 ml) was added drop wise a solution of 1-(1-benzylpiperidin-4-yl)methanamine (compound vi; 2,52 g; 0.012 moles), prepared as described in WO 94/10174, and triethylamine (TEA; 3.2 ml; 0.023 moles) in toluene (10 ml). The reaction mixture was refluxed for 12 hours, and then filtered. Solvent was removed by evaporation under reduced pressure and residue was taken up with ethyl acetate. The organic phase was transferred into a separated funnel, washed with saturated $NaHCO_3$ solution and water, separated out and dried over Na_2SO_4.

The product obtained (vii) was adequately crystallized.

Second step:



(vii) (viii)

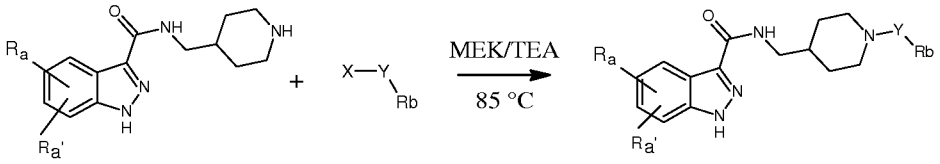
A solution of a convenient N-[(1-benzylpiperidin-4-yl)methyl]-1H-indazole-3-carboxamide (compound vii; 0.506 g; 1.34 mmol) in absolute ethanol (8 ml) and glacial acetic acid (0.8 ml) was hydrogenated in a micro reactor continuous flow system (H-Cube) using CartCart Pd/C 10% as cartridge. Key parameters of H-Cube were set as follow: temperature 80°; pressure 10 bar; flow 1 ml/minute.

After three hours, the solution was concentrated by reduced pressure, diluted with water and transferred into a separating funnel. The aqueous phase was then washed with ethyl acetate, made alkaline

with 1N NaOH and extracted with ethyl acetate. The organic layers were collected, dried over Na_2SO_4 and solvent was removed by evaporation under reduced pressure.

The solid thus obtained was dried in a stove under vacuum to give 0.27 g of the desired substituted N-(piperidin-4-ylmethyl)-1H-indazole-3-carboxamide (viii), which was used without any further purification.

Third step:

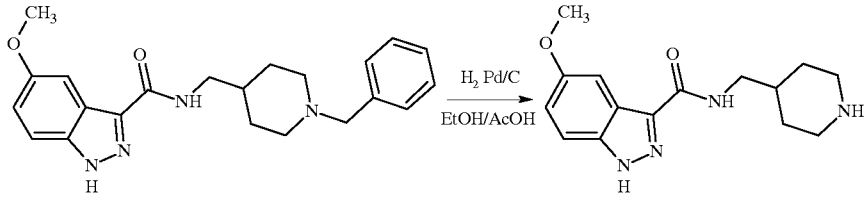


(viii) (ix) (I)

To a solution of (viii) (0.75 mmol; 215 mg) in methyl-ethyl-ketone (MEK; 9 ml) stirred at 85°C, the convenient halogenated compound (ix; 1.05 Eq) and triethylamine (TEA; 210 µl; 2 Eq) were added drop wise. The reaction mixture was refluxed for 8 hours, then cooled and diluted with ethyl acetate. The organic layer was washed with a saturated NH_4Cl solution and water. The organic phase was separated out and dried over Na_2SO_4.

The solvent was removed by evaporating under reduced pressure, and the product (I) was purified as described below.

For example, compound (2) can be prepared according to method B as described below:



(x) (xi)

A solution of N-[(1-benzylpiperidin-4-yl)methyl]-5-methoxy-1H-indazole-3-carboxamide (compound x; 0.506 g; 1.34 mmol) in absolute

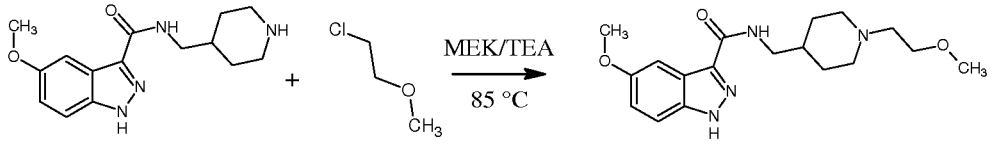
ethanol (8 ml) and glacial acetic acid (0.8 ml) was hydrogenated in a micro reactor continuous flow system (H-Cube) using CartCart Pd/C 10% as cartridge. Key parameters of H-Cube were set as follow: temperature 80°; pressure 10 bar; flow 1 ml/minute.

After three hours, the solution was concentrated by reduced pressure, diluted with water and transferred into a separating funnel. The aqueous phase was then washed with ethyl acetate, made alkaline with 1N NaOH and extracted with ethyl acetate. The organic layers were collected, dried over Na_2SO_4 and solvent was removed by evaporation under reduced pressure.

The solid thus obtained was dried in a stove under vacuum to give 0.27 of the desired 5-methoxy-N-(piperidin-4-ylmethyl)-1H-indazole-3-carboxamide (xi), which was used without any further purification.

^{1}H NMR (DMSO-d_6 - 300 MHz): δ 13.43 (br. s., 1H), 8.27 (t, *J* = 6.13 Hz, 1H), 7.56 (d, *J* = 2.01 Hz, 1H), 7.51 (dd, *J* = 0.55, 8.96 Hz, 1H), 7.06 (dd, *J* = 2.47, 9.06 Hz, 1H), 6.81 (br. s., 1H), 3.81 (s, 3H), 3.19 (t, *J* = 6.22 Hz, 2H), 3.04 (d, *J* = 5.12 Hz, 2H), 2.93 (s, 3H), 2.85 (d, *J* = 11.34 Hz, 2H), 2.38 (t, *J* = 6.77 Hz, 2H), 1.91 (t, *J* = 10.61 Hz, 2H), 1.45 - 1.72 (m, 3H), 1.04 - 1.34 (m, 2H).

[M.M.+H$^+$] calculated 289.1665; [M.M.+H$^+$] found 289.1648.



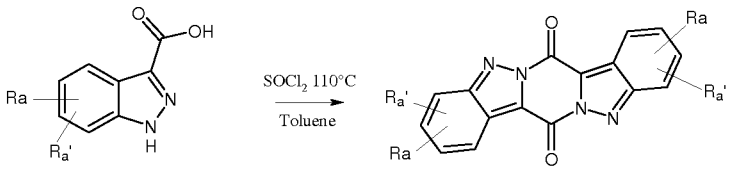
(xi) (xii) (2)

To a solution of (xi) (0.75 mmol; 215 mg) in methyl-ethyl-ketone (MEK; 9 ml) stirred at 85°C, 1-chloro-2-methoxy-ethane (xii; 1.05 Eq) and triethylamine (TEA; 210 µl; 2 Eq) were added drop wise. The reaction mixture was refluxed for 8 hours, then cooled and diluted with ethyl acetate. The organic layer was washed with a saturated NH_4Cl solution and water. The organic phase was separated out and dried over Na_2SO_4.

The solvent was removed by evaporating under reduced pressure, and compound (2) was purified as described below in Table 2.

Method C

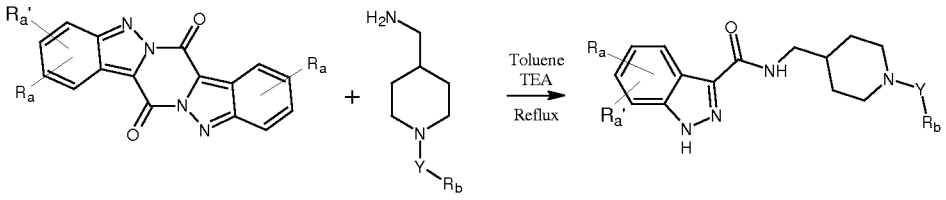
First step:



(i) (xiii)

Thionyl chloride ($SOCl_2$; 9,3 ml; 0.128 moles) was added to a suspension of a convenient substituted 1H-indazole-3-carboxylic acid (compound i; 2,36 g; 0.0123 moles) in toluene (77 ml), and the reaction mixture was refluxed for 4 hours. The solvent was removed by evaporation under reduced pressure and the residue was taken up twice in toluene to give 2.13 g of the desired product (xiii) 2,10-substituted 7H,14H-pyrazino[1,2-b:4,5-b']di-indazole-7,14-dione.

Second step:

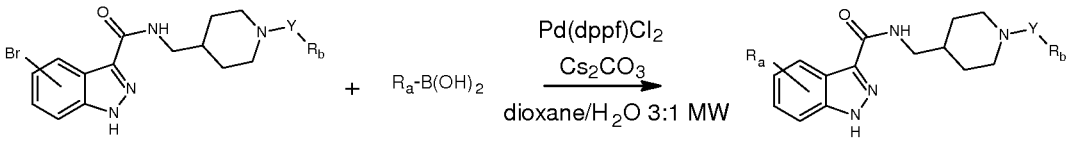


(xiii) (ii) (I)

To a suspension of (xiii) (5,2 mmol) in toluene (40 ml), a solution of the convenient amine (ii; 2,1 Eq) and triethylamine (TEA; 3,6 Eq; 2.6 ml) was added drop wise. The mixture reaction was refluxed for 8 hours, then cooled and stirred in 2N HCl (20 ml) for 8 hours. The suspension was transferred in a separating funnel and aqueous phase was separating out and made alkaline with 1N NaOH.

The solvent was removed by evaporating under reduced pressure, and the product (I) was purified as described below.

Method D



(xiv) (xv) (I)

A solution of product (xiv), a conveniently substituted arylboronic acid (compound xv), [1,1′-bis(diphenylphosphino)ferrocene]-dichloro-palladium(II) [$Pd(dppf)Cl_2$], caesium carbonate in 1,4-dioxane and water (ratio 3:1) was subjected to microwave irradiation.

Program was set as follows:

- 3'; T_1=160°C, T_2=130°C; max power 300W
- 45'; T_1=160°C, T_2=130°C; max power 300W
- 5' ; T_1=20°C, T_2=15°C.

After one cycle of microwave irradiation, solvents were removed by evaporating under reduce pressure and the reaction mixture was diluted with a solution of chloroform and methanol in a 2:1 ratio and filtered.

Products (I) thus obtained were purified as described below.

Purification methods

Compounds of formula (I), obtained according to one of the previously disclosed methods A to D, can be purified with one of the following techniques (a) - (c).

(a) Flash chromatography on silica gel.

Flash chromatography was carried out with a Biotage Flash Master Personal system on 20-45 μM silica cartridge or Grace Reveleris flash chromatography system with 40 μM silica cartridge.

Flow = 60 ml/min.

The solvents used as eluents are methanol and chloroform.

(b) Crystallization

A different crystallization solvent was used depending on the compound to be purified. The solvents are shown in the following Table 2.

(c) Preparative LC/MS system.

LC/MS system consisted of a Waters 2767 Sample manager, a Waters 2478 dual λ absorbance detector and a Waters Micromass ZQ single quadrupole mass spectrometer with an electrospray ionization (ESI) source. The column used was a X-Bridge Prep C18 5 μm with 19x10mm (Waters) pre-column. Fraction collection was available from the system software MassLynx™ v. 4.1. Detection wavelength was set to 230 nm and temperature to 25°C.

The sample was dissolved (50 mg/ml) in DMSO/CH_3CN in 1:1 ratio. The mobile phase was:

channel A = CH_3CN + 0.1% formic acid (Eluent A)

channel B = H_2O + 0.1% formic acid (Eluent B)

flow = 40 ml/min

gradient = minimum and maximum percentage of eluent A reached in 15 minutes are showed in following Table 2.

The following Table 2 shows both the preparation and the purification method for each compound of formula (I) as listed in Table 1 and the monoisotopic mass for each compound.

Table 2

N°	Preparation method	Purification method	Parameters or solvent used for the purification	MM founded $[M+H^+]$	MM calculated $[M+H^+]$
1	B	(b)	AcOEt	347.1677	347.1729
2	B	(b)	EtOH/AcOEt	347.2080	347.2083
3	B	(b)	EtOH abs/AcOEt	361.1856	361.1876
4	D	(c)	2 – 40	394.2241	394.2238
5	D	(c)	2 – 40	424.2350	424.2343
6	D	(c)	10 – 45	411.2196	411.2191

N°	Preparation method	Purification method	Parameters or solvent used for the purification	MM founded [M+H$^+$]	MM calculated [M+H$^+$]
7	D	(c)	2 –27	408.2397	408.2394
8	D	(c)	15 – 50	429.2105	429.2097
9	D	(c)	10 – 45	393.2290	393.2285
10	D	(c)	10 – 45	424.2350	424.2343
11	D	(c)	10 – 34	409.2247	409.2234
12	D	(c)	15 – 43	423.2400	423.2391
13	D	(c)	20 – 55	407.2449	407.2442
14	D	(c)	10 – 34	424.2340	424.2343
15	D	(c)	10 – 34	424.2343	424.2343
16	D	(c)	20-55	407.2453	407.2447
17	D	(c)	10-34	437.2190	437.2189
18	D	(c)	20-55	473.2360	473.2364
19	A	(b)	THF/H_2O	395.1064	395.1077

MM : monoisotopic mass

AcOEt : ethyl acetate

EtOH: ethanol

EtOH abs : absolute ethanol

THF: tetrahydrofurane

H_2O: water

Table 3

N°	1H-NMR peaks
1	DMSO-d6; δ 13.95 (br. s., 2H), 8.24 (t, J = 6.06 Hz, 1H), 7.38 - 7.62 (m, 2H), 6.86 - 7.13 (m, 1H), 3.81 (s, 3H), 3.18 (t, J = 6.16 Hz, 2H), 2.94 (d, J = 11.10 Hz, 2H), 2.74 (s, 2H), 1.99 (t, J = 10.90 Hz, 2H), 1.45 - 1.66 (m, 3H), 1.11 - 1.35 (m, 2H)
2	DMSO-d6; δ 13.41 (br. s., 1H), 8.25 (t, J = 6.07 Hz, 1H), 7.56 (d, J = 2.50 Hz, 1H), 7.51 (d, J = 9.06 Hz, 1H), 7.06 (dd, J = 2.50, 9.05 Hz, 1H), 3.81 (s, 3H), 3.41 (t, J = 5.97 Hz, 2H), 3.23 (s, 3H), 3.19 (t, J = 6.26 Hz, 2H), 2.85 (d, J = 11.56 Hz, 2H), 2.43 (t, J = 5.97 Hz, 2H), 1.79 - 2.06 (m, 2H), 1.48 - 1.73 (m, 3H), 0.99 - 1.39 (m, 2H)
3	DMSO-d6; δ 8.24 (t, J=6.04 Hz, 1H), 7.46-7.61 (m, 2H), 7.03 (dd, J=2.60, 8.70 Hz, 1H), 3.81 (s, 3H), 3.18 (t, J=6.31 Hz, 2H), 2.83 (d, J=11.25 Hz, 2H), 2.40-2.48 (m, 2H), 2.05-2.16 (m, 2H), 1.78-1.94 (m, 2H), 1.49-1.68 (m, 3H), 1.12-1.29 (m, 2H)
4	DMSO-d_6; δ 13.71 (br. s., 1H), 8.90 (dd, *J*=0.82, 2.47 Hz, 1H), 8.58 (dd, *J*=1.56, 4.67 Hz, 1H), 8.42-8.44 (m, 1H), 8.40 (t, *J*=6.00 Hz, 1H), 8.09 (ddd, *J*=1.65, 2.42, 8.00 Hz, 1H), 7.70-7.81 (m, 2H), 7.51 (ddd, *J*=0.82, 4.76, 7.96 Hz, 1H), 3.37-3.44

	(m, 2H), 3.14-3.24 (m, *J*=5.90, 5.90 Hz, 5H), 2.84 (d, *J*=11.53 Hz, 2H), 2.43 (t, *J*=6.04 Hz, 2H), 1.82-1.99 (m, 2H), 1.47-1.74 (m, 3H), 1.09-1.29 (m, 2H)
5	DMSO-d_6; δ 13.66 (br. s., 1H), 8.47 (d, *J*=5.85 Hz, 1H), 8.33-8.42 (m, 2H), 8.24 (dd, *J*=0.91, 1.65 Hz, 1H), 7.66 (dd, *J*=0.91, 8.60 Hz, 1H), 7.53 (dd, *J*=1.65, 8.60 Hz, 1H), 7.19 (d, *J*=5.67 Hz, 1H), 3.48 (s, 3H), 3.38-3.45 (m, 2H), 3.15-3.25 (m, 5H), 2.88 (d, *J*=11.34 Hz, 2H), 2.48 (t, *J*=6.00 Hz, 2H), 1.98 (t, *J*=10.89 Hz, 2H), 1.47-1.73 (m, 3H), 1.09-1.31 (m, 2H)
6	DMSO-d_6; δ 13.55 (s, 1H), 8.25-8.40 (m, 2H), 7.70 (dd, *J*=0.73, 8.78 Hz, 1H), 7.50-7.63 (m, 2H), 7.38-7.49 (m, 1H), 7.28-7.38 (m, 2H), 3.40 (t, *J*=5.95 Hz, 2H), 3.12-3.25 (m, *J*=6.60 Hz, 5H), 2.84 (d, *J*=11.34 Hz, 2H), 2.42 (t, *J*=6.04 Hz, 2H), 1.82-1.99 (m, 2H), 1.46-1.72 (m, 3H), 1.06-1.28 (m, 2H)

7	DMSO-d_6; δ 13.68 (br. s., 1H), 8.77 (d, *J*=1.83 Hz, 1H), 8.32-8.43 (m, 2H), 7.98 (dd, *J*=2.47, 7.96 Hz, 1H), 7.73 (d, *J*=1.28 Hz, 2H), 7.37 (d, *J*=8.05 Hz, 1H), 3.41 (t, *J*=5.95 Hz, 2H), 3.23 (s, 5H), 2.85 (d, *J*=11.34 Hz, 2H), 2.53 (s, 3H), 2.43 (t, *J*=5.95 Hz, 2H), 1.79-2.01 (m, 2H), 1.44-1.74 (m, 3H), 1.07- 1.33 (m, 2H)
8	DMSO-d_6; δ 13.09 (s, 1H), 8.23-8.42 (m, 2H), 7.72 (dd, *J*=0.82, 8.69 Hz, 1H), 7.55 (td, *J*=1.76, 8.74 Hz, 1H), 7.24-7.49 (m, 3H), 3.40 (t, *J*=6.04 Hz, 2H), 3.22 (s, 3H), 3.18 (d, *J*=6.40 Hz, 2H), 2.84 (d, *J*=11.53 Hz, 2H), 2.42 (t, *J*=5.95 Hz, 2H), 1.82-2.02 (m, 2H), 1.41-1.71 (m, 3H), 1.06-1.31 (m, 2H)
9	DMSO-d_6; δ 13.65 (br. s., 1H), 8.40 (t, *J*=1.28 Hz, 1H), 8.36 (t, *J*=6.13 Hz, 1H), 7.65-7.75 (m, 4H), 7.44-7.53 (m, 2H), 7.32-7.41 (m, 1H), 3.40 (t, *J*=6.04 Hz, 2H), 3.12-3.27 (m, *J*=6.00, 6.00 Hz, 5H), 2.84 (d, *J*=11.34 Hz, 2H), 2.42 (t, *J*=6.04 Hz, 2H), 1.83-1.97 (m, 2H), 1.49-1.71 (m, 3H), 1.09-1.31 (m, 2H)
10	DMSO-d_6; δ 13.71 (br. s., 1H), 8.49 (d, *J*=1.65 Hz, 1H), 8.43 (dd, *J*=0.91, 1.65 Hz, 1H), 8.40 (t, *J*=6.13 Hz, 1H), 8.30 (d, *J*=2.74 Hz, 1H), 7.78 (dd, *J*=1.60, 8.70 Hz, 1H), 7.73 (dd, *J*=0.90, 8.70 Hz, 1H), 7.62 (dd, *J*=1.83, 2.74 Hz, 1H), 3.94 (s, 3H), 3.40 (t, *J*=6.04 Hz, 2H), 3.10-3.26 (m, 5H), 2.84 (d, *J*=11.53 Hz, 2H), 2.43 (t, *J*=5.95 Hz, 2H), 1.82-2.00 (m, 2H), 1.44-1.73 (m, 3H), 1.05-1.31 (m, 2H)
11	DMSO-d6; δ 13.53 (br. s., 1H), 9.52 (br. s., 1H), 8.32 (t, J=6.13 Hz, 1H), 8.29 (t, J=1.28 Hz, 1H), 7.63 (d, J=1.28 Hz, 2H), 7.49 (d, J=8.78 Hz, 2H), 6.87 (d, J=8.60 Hz, 2H), 3.40 (t, J=5.95 Hz, 2H), 3.22 (s, 3H), 3.15-3.21 (m, 2H), 2.84 (d, J=11.53 Hz, 2H), 2.42 (t, J=5.95 Hz, 2H), 1.91 (t, J=10.61 Hz, 2H), 1.43-1.72 (m, 3H), 1.03-1.33 (m, 2H)
12	DMSO-d6; δ 13.20 (s, 1H), 8.18-8.40 (m, 2H), 7.49-7.73 (m, 4H), 6.88-7.10 (m, 2H), 3.81 (s, 3H), 3.40 (t, J=5.95 Hz, 2H), 3.22 (s, 5H), 2.84 (d, J=11.34 Hz, 2H), 2.42 (t, J=5.95 Hz, 2H), 1.79-2.01 (m, 2H), 1.43-1.74 (m, 3H), 1.09- 1.29 (m, 2H)
13	DMSO-d6; δ 13.62 (br. s., 1H), 8.29-8.41 (m, 2H), 7.63-7.74 (m, 2H), 7.57 (d, J=8.05 Hz, 2H), 7.29 (d, J=7.87 Hz, 2H), 3.40 (t, J=5.95 Hz, 2H), 3.22 (s, 5H), 2.84 (d, J=11.34 Hz, 2H), 2.42 (t, J=5.95 Hz, 2H), 2.36 (s, 3H), 1.80- 2.02 (m, 2H), 1.43-1.70 (m, 3H), 1.05-1.31 (m, 2H)
14	DMSO-d6; δ 8.24-8.38 (m, 2H), 8.18 (dd, J=1.83, 4.94 Hz, 1H), 7.76 (dd, J=1.83, 7.32 Hz, 1H), 7.62-7.69 (m, 1H), 7.46-7.58 (m, 1H), 7.11 (dd, J=4.94, 7.14 Hz, 1H), 3.89 (s, 3H), 3.40 (t, J=5.95 Hz, 2H), 3.22 (s, 5H), 2.84 (d, J=11.53 Hz, 2H), 2.42 (t, J=6.04 Hz, 2H), 1.82-1.97 (m, 2H), 1.47- 1.72 (m, 3H), 1.06-1.29 (m, 2H)
15	DMSO-d6; δ 13.36 (s, 1H), 8.47 (dd, J=0.73, 2.56 Hz, 1H), 8.26-8.37 (m, 2H), 8.01 (dd, J=2.60, 8.60 Hz, 1H), 7.70 (dd, J=1.00, 8.80 Hz, 1H), 7.65 (dd, J=1.80, 8.80 Hz, 1H), 6.93 (dd, J=0.73, 8.60 Hz, 1H), 3.91 (s, 3H), 3.40 (t, J=6.04 Hz, 2H), 3.22 (s, 5H), 2.84 (d, J=11.34 Hz, 2H), 2.42 (t, J=6.04 Hz, 2H), 1.80-2.01 (m, 2H), 1.47-1.74 (m, 3H), 1.02-1.35 (m, 2H)
16	DMSO-d6; δ 13.59 (s, 1H), 8.34 (t, J=6.13 Hz, 1H), 8.06 (dd, J=1.56, 0.82 Hz, 1H), 7.65 (dd, J=0.73, 8.60 Hz, 1H), 7.39 (dd, J=1.65, 8.60 Hz, 1H), 7.35-7.20 (m, 1H), 3.40 (t, J=5.95 Hz, 2H), 3.22 (s, 5H), 2.84 (d, J=11.53 Hz, 2H), 2.42 (t J=6.04 Hz, 2H), 2.23 (s, 3H), 1.90 (t, J=10.61 Hz, 2H), 1.50-1.70 (m, 3H), 1.10-1.30 (m, 2H)

17	DMSO-d6; δ 13.72 (br.s, 1H), 8.49-8.29 (m, 1H), 8.33 (t, J=6.04 Hz, 1H), 7.83-8.03 (m, 2H), 7.78-7.62 (m, 2H), 7.51-7.61 (m, 2H), 3.41 (t, J=6.04 Hz, 2H), 3.22 (s, 5H), 2.84 (d, J=11.34 Hz, 2H), 2.43 (t J=5.95 Hz, 2H), 1.91 (t, J=10.70 Hz, 2H), 1.71-1.53 (m, 3H), 1.31-1.11 (m, 2H)
18	DMSO-d6; δ 13.56 (s, 1H), 8.36-8.16 (m, 2H), 7.72-7.52 (m, 1H), 7.50 (dd, J=8.78,1.65 Hz 1H), 7.41 (dd J=11.53, 9.33 Hz, 1H), 7.25 (dd J=12.99, 7.14 Hz, 1H), 4.05 (q, J=6.95 Hz, 2H), 3.40 (t, J=5095 Hz, 2H), 3.29-3.09 (m, 5H), 2.83 (d J=11.34 Hz, 2H), 2.42 (t, J=5.95 Hz, 2H), 2.00-1.80 (m, 2H), 1.70-1.50 (m, 3H), 1.24 (s, 5H)
19	DMSO-d_6; δ 13.74 (br. s., 1H), 8.42 (t, J=6.07 Hz, 1H), 8.31 (dd, J=1.83, 0.67 Hz, 1H), 7.61 (dd, J=8.70, 0.70 Hz, 1H), 7.53 (dd, J=8.70, 1.70 Hz, 1H), 3.41 (t, J=5.97 Hz, 2H), 3.22 (s, 3H), 3.13-3.21 (m, 2H), 2.78-2.94 (m, 2H), 2.30-2.47 (m, 2H), 1.82-2.09 (m, 2H), 1.39-1.77 (m, 3H), 1.08-1.30 (m, 2H)

DMSO: dimethyl sulfoxide

The compounds 20 to 44 were prepared as described hereinbelow.

Synthesis of compound 20 - Ethyl [4-({[(5-bromo-6-methoxy-1H-indazol-3-yl) carbonyl]amino} methyl)piperidin-1-yl]acetate

20a) Ethyl [4-(aminomethyl)piperidin-1-yl]acetate

To a stirred solution of N-[phenylmethylidene]-1-(piperidin-4-yl)methanamine (22 g, 0.109 moles (prepared as described in WO2004/101548) in absolute ethanol (150 ml), ethyl bromoacetate (12 mL, 0.109 moles) and potassium carbonate (33 g, 0.24 moles) were added. The solution was heated to reflux for 8 hours, then was cooled and concentrated by evaporating the solvent under reduced pressure. The reaction mixture was diluted with 3N HCl (150 mL) and stirred at room temperature for 2 hours. The acid solution was then washed with ethyl acetate and made alkaline by adding Na_2CO_3. The aqueous phase was extracted with three portions of dichloromethane, which were reunited and dried over Na_2SO_4. The solvent was removed by evaporating under reduced pressure and the resulting product ethyl [4-(aminomethyl)piperidin-1-yl]acetate **20a** was used as such without any further purification.

MS: 201 m/z (M+H+).

1-Hydroxybenzotriazole (HOBt, 2.43 g, 14.2 mmoles) and N,N'-dicyclohexylcarbodiimide (DCC, 2.93 g, 14.2 mmoles) were added to a solution of 5-bromo-6-methoxy-1H-indazole-3-carboxylic acid (3.5 g, 12.9 mmoles) in DMF (40 mL) at 0°C. After 1 hour, a solution of compound **20a** (2.6 g, 12.9 mmoles) in DMF (25 mL) was added at the same temperature. The mixture was stirred at 0°C for 2 hours then was left to reach room temperature during the night. The mixture was diluted with EtOAc and the solid was removed by filtration. The solution was extracted three times with hydrochloric acid (HCl) 2N. The pH of the acid phase was increased (about 13) with 5N NaOH and the solution was extracted three times with dichloromethane (DCM). The organic phase was dried over anhydrous Na_2SO_4 and the solvent was filtered and evaporated under reduced pressure providing 1.6 g (3.5 mmoles, 27% yield) of ethyl [4-({[(5-bromo-6-methoxy-1H-indazol-3-yl)carbonyl]amino}methyl)piperidin-1-yl]acetate (compound 20).

^{1}H NMR (300MHz, DMSO-d6) δ = 13.46 (br. s., 1H), 8.35 (t, J=6.2 Hz, 1H), 8.30 (s, 1H), 7.12 (s, 1H), 4.07 (q, J=7.3 Hz, 2H), 3.93 (s, 3H), 3.16 (s, 4H), 2.81 (d, J=11.0 Hz, 2H), 2.19 - 2.03 (m, 2H), 1.70 - 1.44 (m, 3H), 1.31 - 1.04 (m, 5H)

MS: 453 m/z $(M+H)^+$.

Synthesis of compound 21 - {4-[({[6-methoxy-5-(pyridin-3-yl)-1H-indazol-3-yl]carbonyl}amino)methyl]piperidin-1-yl}acetic acid formiate hydrate

A solution of compound **20** (200 mg, 0.44 mmoles), pyridin-3-ylboronic acid (217 mg, 1.77 mmoles), [1,1'-bis(diphenylphosphino)ferrocene]-dichloro-palladium(II) [Pd(dppf)Cl_2] (81 mg, 0.11 mmoles) and caesium carbonate (575 mg, 1.76 mmoles) in 1,4-dioxane and water (ratio 3:1, 8 mL) was subjected to microwave irradiation as follows:

Time period = 3'; T_1=160°C, T_2=130°C; max power 300W

Time period = 45'; T_1=160°C, T_2=130°C; max power 300W

Time period = 5' ; T_1=20°C, T_2=15°C.

After one cycle of microwave irradiation, solvents were removed by evaporating under reduce pressure and the reaction mixture was diluted with a solution of methanol (20 mL), filtered over Celite and dried under vacuum. The crude product was filtered on a silica cartridge and washed with chloroform and methanol in a 1:1 ratio. The resulting solid was dissolved in DMSO and purified via preparative HPLC (channel A = CH_3CN + 0.1% formic acid; channel B = H_2O + 0.1% formic acid: flow = 40 ml/min; gradient = 2% - 40% of eluent A in 15 minutes), providing {4-[({[6-methoxy-5-(pyridin-3-yl)-1H-indazol-3-yl]carbonyl}amino)methyl] piperidin-1-yl}acetic acid formate hydrate **21** (67 mg, 36% yield).

^{1}H NMR (300MHz, DMSO-d6) δ = 13.44 (br. s., 1H), 8.66 (dd, J=0.9, 2.4 Hz, 1H), 8.54 (dd, J=1.8, 4.8 Hz, 1H), 8.42 (t, J=6.2 Hz, 1H), 8.01 (s, 1H), 7.91 - 7.85 (m, 1H), 7.45 (ddd, J=0.9, 4.8, 7.8 Hz, 1H), 7.13 (s, 1H), 3.86 (s, 3H), 3.41 (br. s., 1H), 3.30 - 3.00 (m, 6H), 2.54 (s, 2H), 1.73 (d, J=11.0 Hz, 3H), 1.52 - 1.28 (m, 2H)

MS: 424 m/z $(M+H)^+$.

Synthesis of compound 22 - {4-[({[6-methoxy-5-(5-methoxy pyridin-3-yl)-1H-indazol-3-yl]carbonyl}amino)methyl]piperidin-1-yl} acetic acid hydrate

{4-[({[6-methoxy-5-(5-methoxypyridin-3-yl)-1H-indazol-3-yl]carbonyl} amino)methyl]-piperidin-1-yl}acetic acid hydrate **22** was prepared, according to the procedure described for compound **21,** starting from (5-methoxypyridin-3-yl)boronic acid and using the following preparative HPLC parameters for the purification: channel A = CH_3CN + 0.1% formic acid; channel B = H_2O + 0.1% formic acid: flow = 40 ml/min; gradient = 10% - 45% of eluent A in 15 minutes. Yield: 33 mg, 17%.

^{1}H NMR (300MHz, DMSO-d6) δ = 13.46 (br. s., 1H), 8.42 (t, J=6.0 Hz, 1H), 8.26 (dd, J=2.0, 6.8 Hz, 2H), 8.02 (s, 1H), 7.43 (dd, J=1.6, 2.7 Hz, 1H), 7.13 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.98 (br. s., 1H), 3.30 -

3.01 (m, 6H), 2.66 - 2.53 (m, 2H), 1.73 (d, J=10.6 Hz, 3H), 1.40 (q, J=11.6 Hz, 2H)

MS: 454 m/z $(M+H)^+$.

Synthesis of compound 23 - {4-[({[5-(2,3-difluorophenyl)-6-methoxy-1H-indazol-3-yl]carbonyl}amino)methyl]piperidin-1-yl} acetic acid hydrate

{4-[({[5-(2,3-difluorophenyl)-6-methoxy-1H-indazol-3-yl]carbonyl} amino)methyl]piperidin-1-yl}acetic acid hydrate **23** was prepared, according to the procedure described for compound **21,** starting from (2,3-difluorophenyl)boronic acid and using the following preparative HPLC parameters for the purification: channel A = CH_3CN + 0.1% formic acid; channel B = H_2O + 0.1% formic acid: flow = 40 ml/min; gradient = 15% - 50% of eluent A in 15 minutes. Yield: 48 mg, 24%.

^1H NMR (300MHz, DMSO-d6) δ = 13.50 (br. s., 1H), 8.42 (t, J=6.0 Hz, 1H), 7.97 (s, 1H), 7.53 - 7.36 (m, 1H), 7.33 - 7.16 (m, 2H), 7.13 (s, 1H), 4.13 (br. s., 1H), 3.84 (s, 3H), 3.30 - 3.08 (m, 6H), 2.65 - 2.53 (m, 2H), 1.72 (d, J=11.0 Hz, 3H), 1.40 (q, J=11.7 Hz, 2H)

MS: 459 m/z $(M+H)^+$.

Synthesis of compound 24 - 4-[4-({[(5-methoxy-1H-indazol-3-yl)carbonyl]amino}methyl)piperidin-1-yl]butanoic acid

24a) Tert-butyl 4-({[(5-methoxy-1H-indazol-3-yl)carbonyl] amino} methyl)piperidine-1-carboxylate

Tert-butyl4-({[(5-methoxy-1H-indazol-3-yl)carbonyl]amino}methyl) piperidine-1-carboxylate **24a** was prepared, according to the procedure described for compound **20,** from 5-methoxy-1H-indazole-3-carboxylic acid and tert-butyl 4-(aminomethyl)piperidine-1-carboxylate. Yield: 35.2 g, 96%.

MS: 389 m/z $(M+H)^+$.

24b)5-Methoxy-N-(piperidin-4-ylmethyl)-1H-indazole-3-carboxamide hydrochloride

2 M HCl in Et_2O (1.8 L) was added to a solution of compound **24a** (92.8 g, 0.24 moles) in MeOH (500 mL). The mixture was stirred for 3 hours at room temperature then the resulting solid was filtered and dried to give 5-methoxy-N-(piperidin-4-ylmethyl)-1H-indazole-3-carboxamide hydrochloride **24b** (61.1 g, 89% yield).

MS: 289 m/z $(M+H)^+$.

24c) Ethyl 4-[4-({[(5-methoxy-1H-indazol-3-yl)carbonyl]amino} methyl) piperidin-1-yl]butanoate

A mixture of compound **24b** (8 g, 24.6 mmoles) and potassium carbonate (17 g, 123 mmoles) in acetone (250 mL) was refluxed for 1 hour, then ethyl 4-chlorobutanoate (3.62 mL, 25.9 mmoles) was added dropwise. The mixture was refluxed overnight then was cooled and filtered. The resulting solid was dried and purified via preparative HPLC (channel A = CH_3CN + 0.1% formic acid; channel B = H_2O + 0.1% formic acid: flow = 40 ml/min; gradient = 10% - 45% of eluent A in 15 minutes) providing 0.9 g (9% yield) of ethyl 4-[4-({[(5-methoxy-1H-indazol-3-yl)carbonyl]amino}methyl)piperidin-1-yl]butanoate **24c**.

MS: 403 m/z $(M+H)^+$.

To a solution of compound **24c** (744 mg, 1.85 mmoles) in MeOH (10 mL) aqueous NaOH (1 M, 3.7 mL) was added. The solution was refluxed overnight then the organic solvent was removed under vacuum, the residue was diluted with H_2O and the pH was adjusted to 5 by adding 1 M HCl. The mixture was kept at 4°C overnight then the resulting solid was filtered, washed with fresh water and dried under vacuum to give 4-[4-({[(5-methoxy-1H-indazol-3-yl)carbonyl]amino} methyl)piperidin-1-yl]butanoic acid **24** (72 mg, 10% yield).

^1H NMR (300MHz, DMSO-d6) δ = 13.54 (br. s., 1H), 11.25 (br. s., 1H), 8.46 (t, J=6.1 Hz, 1H), 7.55 (d, J=2.3 Hz, 1H), 7.52 (d, J=8.9 Hz, 1H), 7.05 (dd, J=2.3, 8.9 Hz, 1H), 3.80 (s, 3H), 3.37 (d, J=12.2 Hz, 2H),

3.23 (t, J=6.1 Hz, 2H), 3.00 - 2.89 (m, 2H), 2.81 (t, J=11.4 Hz, 2H), 2.32 (t, J=7.1 Hz, 2H), 2.01 - 1.70 (m, 5H), 1.64 - 1.41 (m, 2H)

MS: 375 m/z $(M+H)^+$.

Synthesis of compound 25 - {4-[({[5-(Pyrimidin-5-yl)-1H-indazol-3-yl]carbonyl}amino)methyl]piperidin-1-yl} acetic acid hydrate

25a) Tert-butyl 4-({[(5-bromo-1H-indazol-3-yl)carbonyl]amino} methyl)piperidine-1-carboxylate

Tert-butyl4-({[(5-bromo-1H-indazol-3-yl)carbonyl]amino}methyl) piperidine-1-carboxylate **25a** was prepared, according to the procedure described for compound **20,** from 5-bromo-1H-indazole-3-carboxylic acid and tert-butyl 4-(aminomethyl)piperidine-1-carboxylate. Yield: 40.6 g, 87%

MS: 437 m/z $(M+H)^+$.

25b) 5-Bromo-N-(piperidin-4-ylmethyl)-1H-indazole-3-carbox-amide hydrochloride

5-Bromo-N-(piperidin-4-ylmethyl)-1H-indazole-3-carboxamide hydrochloride **25b** was prepared, according to the procedure described for compound **24b,** starting from compound **25a**. Yield: 23.8 g, 76%.

MS: 337 m/z $(M+H)^+$.

25c) Ethyl [4-({[(5-bromo-1H-indazol-3-yl)carbonyl]amino} methyl) piperidin-1-yl]acetate

A mixture of compound **25b** (2 g, 5.4 mmoles) and potassium carbonate (2.3 g, 16.6 mmoles) in DMF (45 mL) was stirred for 1 hour at 70°C. A solution of ethyl bromoacetate (0.89 mL, 8 mmoles) in DMF (5 mL) was added dropwise. After 3 hours at 70°C the reaction mixture was cooled, diluted with water and extracted three times with EtOAc. The reunited organic phases were dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified via flash

chromatography (silica, $CHCl_3$:MeOH 95:5) providing 710 mg (31% yield) of ethyl [4-({[(5-bromo-1H-indazol-3-yl)carbonyl]amino}methyl) piperidin-1-yl]acetate **25c**.

^{1}H NMR (300MHz, DMSO-d6) δ = 13.74 (s, 1H), 8.43 (t, J=6.0 Hz, 1H), 8.32 (dd, J=0.6, 1.9 Hz, 1H), 7.61 (dd, J=0.6, 8.9 Hz, 1H), 7.53 (dd, J=1.9, 8.9 Hz, 1H), 4.07 (q, J=7.1 Hz, 2H), 3.20 (t, J=6.4 Hz, 2H), 3.17 (s, 2H), 2.81 (d, J=11.2 Hz, 2H), 2.22 - 2.03 (m, 2H), 1.72 - 1.46 (m, 3H), 1.31 - 1.08 (m, 5H).

MS: 423 m/z $(M+H)^+$.

4-[({[5-(Pyrimidin-5-yl)-1H-indazol-3-yl]carbonyl}amino)methyl] piperidin-1-yl}acetic acid hydrate **25** was prepared, according to the procedure described for compound **21,** from compound **25c** and pyrimidin-5-ylboronic acid. The product was purified by crystallization in MeOH. Yield: 43 mg, 18%.

^{1}H NMR (300MHz, DMSO-d6) δ = 13.90 (br. s., 1H), 9.20 (s, 1H), 9.15 (s, 2H), 8.54 (t, J=6.0 Hz, 1H), 8.48 (s, 1H), 8.00 - 7.56 (m, 2H), 4.63 (br. s., 1H), 3.45 - 3.01 (m, 6H), 2.60 (t, J=11.3 Hz, 2H), 1.76 (d, J=11.3 Hz, 3H), 1.44 (q, J=11.3 Hz, 2H)

MS: 395 m/z $(M+H)^+$.

Synthesis of compound 26 - {4-[({[5-(3,5-Dimethylisoxazol-4-yl)-1H-indazol-3-yl]carbonyl}amino)methyl]piperidin-1-yl} acetic acid hydrate

{4-[({[5-(3,5-Dimethylisoxazol-4-yl)-1H-indazol-3-yl]carbonyl}amino) methyl]piperidin-1-yl}acetic acid hydrate **26** was prepared, according to the procedure described for compound **21,** from compound **25c** and (3,5-dimethylisoxazol-4-yl)boronic acid. The product was purified by crystallization in MeOH. Yield: 55 mg, 23%.

^{1}H NMR (300MHz, DMSO-d6) δ = 13.84 (br. s., 1H), 8.50 (t, J=5.9 Hz, 1H), 8.10 (s, 1H), 7.72 (d, J=8.6 Hz, 1H), 7.40 (dd, J=1.5, 8.8 Hz,

1H), 4.10 (br. s., 1H), 3.36 - 3.03 (m, 6H), 2.60 (t, J=11.2 Hz, 2H), 2.41 (s, 3H), 2.22 (s, 3H), 1.75 (d, J=11.2 Hz, 3H), 1.42 (q, J=11.4 Hz, 2H)

MS: 412 m/z $(M+H)^+$.

Synthesis of compound 27 - {4-[({[5-(2,3-dichlorophenyl)-1H-indazol-3-yl]carbonyl}amino)methyl]piperidin-1-yl} acetic acid hydrate

{4-[({[5-(2,3-Dichlorophenyl)-1H-indazol-3-yl]carbonyl}amino)methyl] piperidin-1-yl}acetic acid hydrate **27** was prepared, according to the procedure described for compound **21,** from compound **25c** and (2,3-dichlorophenyl)boronic acid and using the following preparative HPLC parameters for the purification: channel A = CH_3CN + 0.1% formic acid; channel B = H_2O + 0.1% formic acid: flow = 40 ml/min; gradient = 20% - 55% of eluent A in 15 minutes. Yield: 42 mg, 15%.

^1H NMR (300MHz, DMSO-d6) δ = 13.81 (br. s., 1H), 8.50 (t, J=6.0 Hz, 1H), 8.17 (dd, J=0.9, 1.6 Hz, 1H), 7.78 - 7.60 (m, 2H), 7.54 - 7.34 (m, 3H), 4.08 (br. s., 1H), 3.38 - 2.96 (m, 6H), 2.58 (t, J=11.0 Hz, 2H), 1.74 (d, J=11.0 Hz, 3H), 1.42 (q, J=11.6 Hz, 2H)

MS: 461 m/z $(M+H)^+$.

Synthesis of compound 28 - {4-[({[5-(3-Fluorophenyl)-1H-indazol-3-yl]carbonyl}amino)methyl]piperidin-1-yl} acetic acid hydrate

{4-[({[5-(3-Fluorophenyl)-1H-indazol-3-yl]carbonyl}amino)methyl] piperidin-1-yl}acetic acid hydrate **28** was prepared, according to the procedure described for compound **21,** from compound **25c** and (3-fluorophenyl)boronic acid and using the following preparative HPLC parameters for the purification: channel A = CH_3CN + 0.1% formic acid; channel B = H_2O + 0.1% formic acid: flow = 40 ml/min; gradient = 15% - 50% of eluent A in 15 minutes. Yield: 87 mg, 36%.

^{1}H NMR (300MHz, DMSO-d6) δ = 13.71 (br. s., 1H), 8.45 (t, J=6.0 Hz, 1H), 8.41 (s, 1H), 7.86 - 7.66 (m, 2H), 7.63 - 7.41 (m, 3H), 7.19 (dddd, J=2.4, 2.6, 6.5, 9.0 Hz, 1H), 4.75 (br. s., 1H), 3.34 - 3.07 (m, 6H), 2.64 - 2.53 (m, 2H), 1.75 (d, J=11.0 Hz, 3H), 1.42 (q, J=11.5 Hz, 2H)

MS: 411 m/z $(M+H)^+$.

Synthesis of compound 29 - {4-[({[5-(2,3-difluorophenyl)-1H-indazol-3-yl]carbonyl}amino)methyl]piperidin-1-yl} acetic acid

{4-[({[5-(2,3-difluorophenyl)-1H-indazol-3-yl]carbonyl}amino)methyl] piperidin-1-yl}acetic acid **29** was prepared, according to the procedure described for compound **21,** starting from compound **25c** and (2,3-difluorophenyl)boronic acid and using the following preparative HPLC parameters for the purification: channel A = CH_3CN + 0.1% formic acid; channel B = H_2O + 0.1% formic acid: flow = 40 ml/min; gradient = 15 to 50 % of eluent A in 15 minutes. Yield: 20 mg, (11.7%).

^{1}H NMR (300 MHz, DMSO-d6) δ = 13.68 (br. s., 1H), 8.51 (t, J=6.1 Hz, 1H), 8.35 (d, J=0.6 Hz, 1H), 7.74 (dd, J=0.7, 8.8 Hz, 1H), 7.61 (td, J=1.7, 8.7 Hz, 1H), 7.51 - 7.25 (m, 3H), 3.33 - 3.10 (m, 6H), 2.64 - 2.53 (m, 2H), 1.74 (d, J=10.5 Hz, 3H), 1.54 - 1.29 (m, 2H)

Synthesis of compound 30 - {4-[({[5-(5-methoxypyridin-3-yl)-1H-indazol-3-yl]carbonyl}amino)methyl]piperidin-1-yl}acetic acid

{4-[({[5-(5-methoxypyridin-3-yl)-1H-indazol-3-yl]carbonyl}amino) methyl]piperidin-1-yl}acetic acid **30** was prepared, according to the procedure described for compound **21,** starting from compound **25c** and (5-methoxypyridin-3-yl)boronic acid and using the following preparative HPLC parameters for the purification: channel A = CH_3CN + 0.1% formic acid; channel B = H_2O + 0.1% formic acid: flow = 40 ml/min; gradient = 2 to 40% of eluent A in 15 minutes. Yield: 47 mg (27.8%).

^{1}H NMR (300 MHz, DMSO-d6) δ = 13.73 (br. s., 1H), 8.54 - 8.49 (m, 1H), 8.48 (d, J=1.6 Hz, 1H), 8.44 - 8.39 (m, 1H), 8.30 (d, J=2.7 Hz,

1H), 7.81 - 7.76 (m, 1H), 7.76 - 7.69 (m, J=0.7 Hz, 1H), 7.61 (dd, J=1.8, 2.7 Hz, 1H), 3.93 (s, 3H), 3.29 - 3.12 (m, 6H), 2.69 - 2.55 (m, 2H), 1.75 (d, J=11.0 Hz, 3H), 1.58 - 1.27 (m, 2H)

Synthesis of compound 31 - [4-({[(5-ethyl-1H-indazol-3-yl)carbonyl]amino}methyl)piperidin-1-yl] acetic acid

A mixture of product **25c** (170 mg, 0.4 mmol), vinyl-boronic acid pinacol ester (0.53 mmol), [1,1′-bis(diphenylphosphino)ferrocene]-dichloro-palladium(II) (50 mg, 0.06 mmol), sodium carbonate saturated solution (1.7 mL) in toluene/ethanol (ratio 1:1, 10 mL) was heated in a microwave oven at 150°C, 500W for 2 h. After filtration over celite, solvents were removed under reduce pressure and the crude product was eluted through a silica gel cartridge with a mixture of chloroform/methanol 1:1 ratio. Solvents were removed under reduced pressure and the resulting crude intermediate was dissolved in ethanol (20 mg/mL) and hydrogenated over a 10% Pd/C cartridge at 30°C, 1 mL/min in a Thales Nano H-CUBE hydrogenetor to obtain [4-({[(5-ethyl-1H-indazol-3-yl)carbonyl]amino}methyl)piperidin-1-yl] acetic acid **31**, purified using the following preparative HPLC parameters: channel A = CH_3CN + 0.1% formic acid; channel B = H_2O + 0.1% formic acid: flow = 40 ml/min; gradient = 10 to 45 % of eluent A in 15 minutes. Yield 170 mg, (41.0 %).

^1H NMR (300 MHz, DMSO-d6) δ = 13.48 (br. s., 1H), 8.38 (t, J=6.1 Hz, 1H), 7.97 (s, 1H), 7.52 (d, J=8.6 Hz, 1H), 7.28 (dd, J=1.6, 8.6 Hz, 1H), 4.38 (br. s., 1H), 3.33 - 3.09 (m, 6H), 2.73 (q, J=7.5 Hz, 2H), 2.65 - 2.53 (m, 2H), 1.83 - 1.60 (m, 3H), 1.54 - 1.31 (m, 2H), 1.23 (t, J=7.5 Hz, 3H)

Synthesis of compound 32 - {4-[({[5-(propan-2-yl)-1H-indazol-3-yl]carbonyl}amino)methyl]piperidin-1-yl}acetic acid

{4-[({[5-(propan-2-yl)-1H-indazol-3-yl]carbonyl}amino)methyl] piperidin-1-yl}acetic acid **32** was prepared, according to the procedure

described for compound **31,** starting from 1-methylethylen-boronic acid pinacol ester. Yield = 33 mg (7.7 %).

^{1}H NMR (300 MHz, DMSO-d6) δ = 13.45 (br. s., 1H), 8.38 (t, J=6.1 Hz, 1H), 8.10 - 7.86 (m, 1H), 7.52 (dd, J=0.5, 8.6 Hz, 1H), 7.32 (dd, J=1.6, 8.8 Hz, 1H), 4.65 (br. s., 1H), 3.29 - 3.13 (m, 6H), 3.02 (quind, J=6.8, 13.7 Hz, 1H), 2.57 (t, J=11.3 Hz, 2H), 1.73 (d, J=10.8 Hz, 3H), 1.55 - 1.32 (m, 2H), 1.26 (d, J=7.0 Hz, 6H)

Synthesis of compound 33 - {4-[({[5-(3,6-dihydro-2H-pyran-4-yl)-1H-indazol-3-yl]carbonyl}amino)methyl]piperidin-1-yl} acetic acid

{4-[({[5-(3,6-dihydro-2H-pyran-4-yl)-1H-indazol-3-yl]carbonyl}amino) methyl]piperidin-1-yl}acetic acid **33** was prepared, according to the procedure described for compound **31** (without the hydrogenation step), starting from 4-methyl-3,6-dihydro-2H-pyranyl-boronic acid pinacol ester. Yield = 150 mg (37.7 %).

^{1}H NMR (300 MHz, DMSO-d6) δ = 13.65 (br. s., 1H), 8.44 (t, J=5.9 Hz, 1H), 8.15 (s, 1H), 7.71 - 7.47 (m, 2H), 6.27 (br. s., 1H), 5.78 - 4.52 (m, 1H), 4.25 (d, J=2.2 Hz, 2H), 3.86 (t, J=5.3 Hz, 2H), 3.34 - 3.05 (m, 6H), 2.68 - 2.54 (m, 4H), 1.74 (d, J=10.9 Hz, 3H), 1.42 (q, J=11.5 Hz, 2H).

Synthesis of compound 34 - [4-({[(5-cyclohexyl-1H-indazol-3-yl)carbonyl]amino}methyl)piperidin-1-yl] acetic acid

[4-({[(5-cyclohexyl-1H-indazol-3-yl)carbonyl]amino}methyl)piperidin-1-yl]acetic acid **34**, was prepared, according to the procedure described for compound **31,** starting from cyclohexenyl-boronic acid pinacol ester. Yield = 158 mg (39.6 %).

^{1}H NMR (300 MHz, DMSO-d6) δ = 13.48 (br. s., 1H), 8.38 (t, J=6.0 Hz, 1H), 7.98 (s, 1H), 7.51 (d, J=8.8 Hz, 1H), 7.30 (dd, J=1.2, 8.7 Hz,

1H), 4.67 (br. s., 1H), 3.24 (d, J=4.8 Hz, 6H), 2.68 - 2.53 (m, 3H), 1.96 - 1.58 (m, 8H), 1.54 - 1.14 (m, 7H)

Synthesis of compound 35 - [4-({[(5-pentyl-1H-indazol-3-yl)carbonyl]amino}methyl)piperidin-1-yl]acetic acid

[4-({[(5-pentyl-1H-indazol-3-yl)carbonyl]amino}methyl)piperidin-1-yl]acetic acid **35** was prepared, according to the procedure described for compound **31,** starting from 5-pentyl-boronic acid pinacol ester. Yield = 176 mg (45.6 %).

^{1}H NMR (300 MHz, DMSO-d6) δ = 13.49 (br. s., 1H), 8.38 (t, J=5.9 Hz, 1H), 7.95 (s, 1H), 7.51 (dd, J=0.7, 8.6 Hz, 1H), 7.25 (dd, J=1.5, 8.8 Hz, 1H), 3.20 (s, 6H), 2.69 (t, J=7.4 Hz, 2H), 2.59 (t, J=11.1 Hz, 2H), 1.86 - 1.15 (m, 11H), 0.93 - 0.77 (m, 3H).

Synthesis of compound 36 - 5-methoxy-N-[(1-{3-[(phenyl carbonyl)amino]propyl}piperidin-4-yl)methyl]-1H-indazole-3-carboxamide

36a) tert-butyl {3-[4-({[(5-methoxy-1H-indazol-3-yl)carbonyl] amino} methyl)piperidin-1-yl]propyl}carbamate

A solution of compound **24b** (1.37g, 4.36mmol) in DMF (45 ml) and triethylamine (1.3ml, 9.5mmol) was stirred at 80 °C for 1h and then was treated with tert-butyl (3-bromopropyl)carbamate (1.7g, 7.1 mmol). The mixture was stirred overnight at the same temperature. The reaction was then cooled to room temperature and the solvent was removed by evaporation at reduced pressure. The crude tert-butyl {3-[4-({[(5-methoxy-1H-indazol-3-yl)carbonyl]amino}methyl)piperidin-1-yl]propyl}-carbamate **36a** was used for the subsequent step without further purifications.

LC-MS: 446.3 $(M+H)^+$.

36b) N-{[1-(3-aminopropyl)piperidin-4-yl]methyl}-5-methoxy-1H-indazole-3-carboxamide

A solution of crude tert-butyl {3-[4-({[(5-methoxy-1H-indazol-3-yl)carbonyl]amino}methyl)piperidin-1-yl]propyl}carbamate **36a** (approx. 1.8 g) in CH_2Cl_2 (15 ml) was treated with trifluoroacetic acid (7 ml) at room temperature overnight. The solution was then poured in water (50 ml) and washed with CH_2Cl_2 (3x 20 ml). The acid phase was basified and concentrated at reduced pressure. The solid residue was extracted with a mixture of CH_3Cl/CH_3OH in 8/2 ratio (3x 20ml) and the solvent evaporated at reduced pressure. The crude N-{[1-(3-aminopropyl)piperidin-4-yl]methyl}-5-methoxy-1H-indazole-3-carboxamide **36b** was used for the next steps without further purifications.

LC-MS: 346.2 $(M+H)^+$.

To a solution of crude N-{[1-(3-aminopropyl)piperidin-4-yl]methyl}-5-methoxy-1H-indazole-3-carboxamide **36b** (approx. 350 mg, 1 mmol) in DMSO (1.5 mL) and CH_2Cl_2 (10 mL) was added benzoyl chloride (71 μl, 0.61 mmol). The solution was then stirred at room temperature for 2h. The mixture was then added to water (20 ml) and extracted with CH_2Cl_2 (3x 10 mL). The combined organic phases was concentrated at reduced pressure and the crude product was purify by flash chromatography on silica gel, using a mixture of $CHCl_3/CH_3OH$ = 9:1 as eluent. 5-methoxy-N-[(1-{3-[(phenylcarbonyl)amino]propyl}piperidin-4-yl) methyl]-1H-indazole-3-carboxamide **36** was obtained (71 mg).

^1H NMR (300 MHz, DMSO-d6) δ = 13.43 (s,1H), 8.59-8.47 (t, J=5.31 Hz, 1H), 8.38-8.24 (t, J=6.04 Hz, 1H), 7.90-7.74 (m, 2H), 7.61-7.35 (m, 5H), 7.10-6.99 (dd, J=9.15, 2.56 Hz, 1H), 3.89-3.69 (s, 3H), 3.39-3.12 (m, 6H), 3.11-2.94 (m, 2H), 2.25-1.89 (m, 2H), 1.83-1.53 (m, 5H), 1.36-1.12 (d, J=11.34 Hz, 2H)

LC-MS: 450.25 (MH+)

Synthesis of compound 37 - N-({1-[3-(butanoylamino) propyl]piperidin-4-yl}methyl)-5-methoxy-1H-indazole-3-carboxamide

N-({1-[3-(butanoylamino)propyl]piperidin-4-yl}methyl)-5-methoxy-1H-indazole-3-carboxamide **37**, was prepared, according to the procedure described for compound **36,** starting from butanoyl chloride. Yield = 75 mg (36.8 %).

^{1}H NMR (300 MHz, DMSO-d6) δ = 13.44 (s,1H), 8.41-8.26 (t, J=6.11 Hz, 1H), 7.89-7.69 (t, J=5.12 Hz, 1H), 7.58-7.54 (d, J=2.31, 1H), 7.53-7.47 (dd, J=8.92, 0.66 Hz, 1H), 7.11-6.96 (dd, J=9.08, 2.48 Hz, 1H), 3.80 (s, 3H), 3.52-2.77 (m, 10H), 2.10-1.92 (t, J=7.27 Hz, 2H), 1.81-1.12 (m, 9H), 0.91-0.77 (t, J=7.27, 3H)

LC-MS: 416.27 (MH+)

Synthesis of compound 38 - N-[(1-{3-[(2E)-but-2-enoylamino] propyl}piperidin-4-yl)methyl]-5-methoxy-1H-indazole-3-carboxamide

N-[(1-{3-[(2E)-but-2-enoylamino]propyl}piperidin-4-yl)methyl]-5-methoxy-1H-indazole-3-carboxamide **38** was prepared, according to the procedure described for compound **36,** starting from (2E)-but-2-enoyl chloride. Yield = 45 mg (51.4 %).

^{1}H NMR (300 MHz, DMSO-d6) δ = 13.44 (s, 1H), 8.45-8.25 (m, 1H), 8.00-7.75 (m, 1H), 7.60-7.53 (d, J=2.40 Hz, 1H), 7.53-7.47 (d, J=8.90 Hz, 1H), 7.09-7.01 (dd, J=2.70, 2.30 Hz, 1H), 6.67-6.50 (m, 1H), 5.75-6.00 (m, 1H), 3.80 (s, 3H), 3.50-1.00 (m, 20H)

LC-MS: 414.25 (M-H+)

Synthesis of compound 39 - 5-methoxy-N-({1-[3-(propanoyl amino)propyl]piperidin-4-yl}methyl)-1H-indazole-3-carboxamide

5-methoxy-N-({1-[3-(propanoylamino)propyl]piperidin-4-yl}methyl)-1H-indazole-3-carboxamide **39**, was prepared, according to the procedure described for compound **36,** starting from propanoyl chloride. Yield = 90 mg (68.8 %).

^{1}H NMR (300 MHz, DMSO-d6) δ = 13.28 (s, 1H), 8.17-8.00 (m, 1H), 7.65-7.55 (m, 1H), 7.58-7.54 (d, J=2.20 Hz, 1H), 7.52-7.45 (d, J=9.20 Hz, 1H), 7.10-7.00 (dd, J=9.15, 2.60 Hz, 1H), 3.81 (s, 3H), 3.30-2.85 (m, 8H), 2.11-2.00 (q, J=7.70 Hz, 2H), 1.80-1.52 (m, 6H), 1.40-1.15 (m, 3H), 1.03-0.95 (t, J=7.70 Hz, 3H)

LC-MS: 402.25 (M-H+)

Synthesis of compound 40 - N-({1-[3-(but-2-ynoylamino) propyl]piperidin-4-yl}methyl)-5-methoxy-1H-indazole-3-carboxamide

N-({1-[3-(but-2-ynoylamino)propyl]piperidin-4-yl}methyl)-5-methoxy-1H-indazole-3-carboxamide **40** was prepared, according to the procedure described for compound **36,** starting from 2-butynoyl chloride. Yield = 17 mg (17.1 %).

^{1}H NMR (300 MHz, DMSO-d6) δ = 13.34 (s, 1H), 8.52-8.42 (t, J=5.31 Hz, 1H), 8.27-8.18 (t, J=6.04 Hz, 1H), 7.56-7.52 (d, J=2.20 Hz, 1H), 7.52-7.47 (d, J=8.78 Hz, 1H), 7.05-6.99 (dd, J=8.96, 2.38 Hz, 1H), 3.80 (s, 3H), 3.21-3.13 (t, J=6.40 Hz, 2H), 3.11-3.01 (q, J=6.59 Hz, 2H), 2.87-2.75 (d, J=11.34 Hz, 2H), 2.30-2.18 (t, J=6.95 Hz, 2H), 1.94 (s, 3H), 1.88-1.73 (t, J=10.61 Hz, 2H), 1.70-1.45 (m, 5H), 1.30-1.10 (m, 2H)

LC-MS: 412.23 (M-H+)

Synthesis of compound 41 - [4-({[(5-bromo-6-hydroxy-1H-indazol-3-yl)carbonyl]amino}methyl)piperidin-1-yl] acetic acid

To a solution of compound **20** (200mg, 0.44 mmol) in CH_2Cl_2 (15 ml) cooled to -78 °C was slowly added a solution of 1M BBr_3 in CH_2Cl_2 (2.2 ml, 2.2 mmol) (about 1h). The mixture was leaved to reach room temperature and stirred at this temperature for 2 days. The mixture was then poured in a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3x 100ml). The basic phase was acidified with 1N HCl and concentrated at reduced pressure. The residue was then treated with

DMSO (6 ml) and the [4-({[(5-bromo-6-hydroxy-1H-indazol-3-yl)carbonyl]amino}methyl)piperidin-1-yl]acetic acid **41** was purified using the following preparative HPLC parameters: channel A = CH_3CN + 0.1% formic acid; channel B = H_2O + 0.1% formic acid: flow = 40 ml/min; gradient = 10 to 45 % of eluent A in 15 minutes. Yield 36 mg.

^{1}H NMR (300 MHz, DMSO-d6) δ = 13.27 (br. s., 1H), 12.53 - 8.62 (m, 0H), 8.39 (t, J=6.0 Hz, 1H), 8.27 - 8.14 (m, 1H), 7.08 (s, 1H), 6.74 - 3.42 (m, 2H), 3.34 - 3.07 (m, 6H), 2.62 (t, J=11.2 Hz, 2H), 1.74 (d, J=11.0 Hz, 3H), 1.42 (q, J=11.7 Hz, 2H)

Synthesis of compound 42 - [4-({[(5-bromo-6-methoxy-1H-indazol-3-yl)carbonyl]amino}methyl)piperidin-1-yl] acetic acid

[4-({[(5-bromo-6-methoxy-1H-indazol-3-yl)carbonyl]amino}methyl) piperidin-1-yl]acetic acid **42** was obtained by the purification step described in the preparation of compound **41**. Yield 35 mg.

^{1}H NMR (300 MHz, DMSO-d6) δ = 13.66 (br. s., 1H), 8.45 (t, J=6.1 Hz, 1H), 8.30 (s, 1H), 7.15 (s, 1H), 6.80 - 4.69 (m, 1H), 3.93 (s, 3H), 3.33 - 3.10 (m, 6H), 2.64 (t, J=11.2 Hz, 2H), 1.75 (d, J=10.9 Hz, 3H), 1.43 (q, J=11.6 Hz, 2H)

Synthesis of compound 44 - ethyl [4-({[(5-methoxy-1H-indazol-3-yl)carbonyl]amino}methyl)piperidin-1-yl]acetate

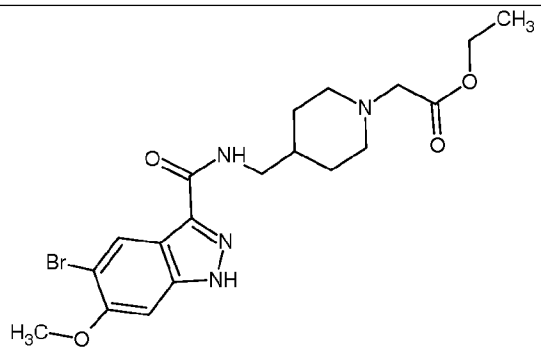
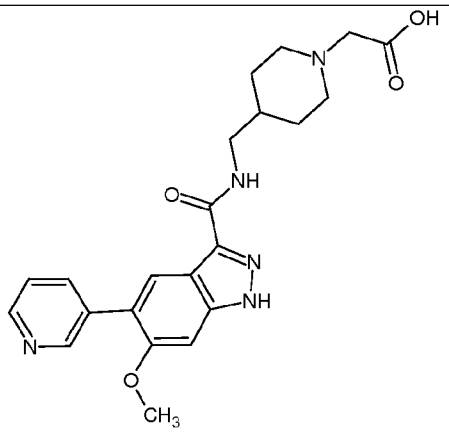
Ethyl[4-({[(5-methoxy-1H-indazol-3-yl)carbonyl]amino}methyl) piperidin-1-yl]acetate was prepared, according to the procedure described for compound **25c,** starting from 5-methoxy-N-(piperidin-4-ylmethyl)-1H-indazole-3-carboxamide hydrochloride **24b** (65 %).

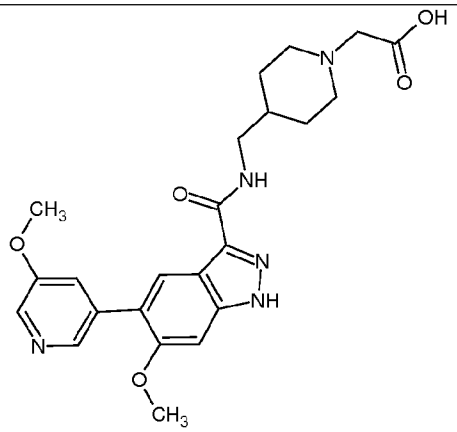
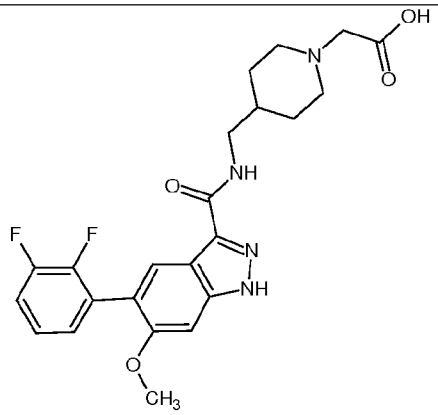
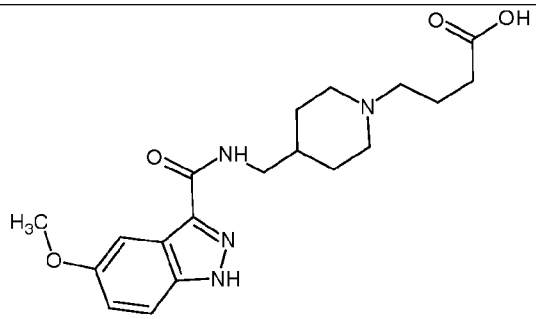
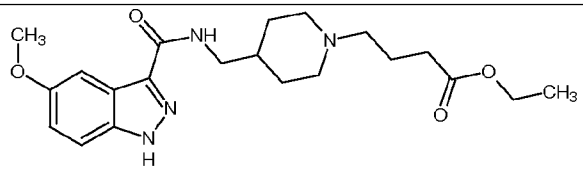
^{1}H NMR (300 MHz, DMSO-d6) δ = 13.54 (s, 1H), 8.30 (t, J=6.06 Hz, 1H), 7.56 (s, 1H), 7.51 (d, J=8.91 Hz, 1H), 7.05 (d, J=8.91 Hz, 1H), 4.00 (q, J=7.13 Hz, 2H), 3.81 (s, 3H), 3.34 (s, 2H), 3.17-3.24 (m, 2H), 2.81-2.95 (m, 4H), 1.50-1.75 (m, 3H), 1.16-1.36 (m, 2H), 1.11 (t, J=7.13 Hz, 3H)

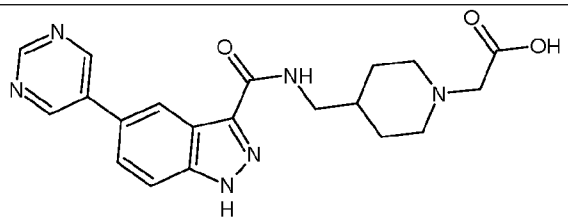
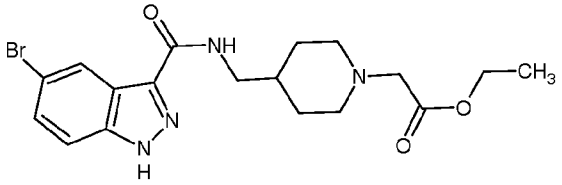
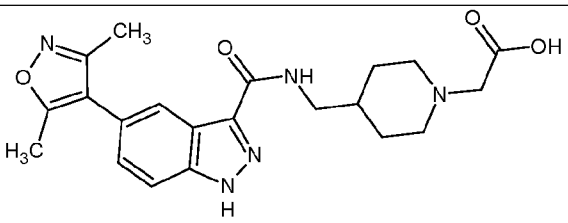
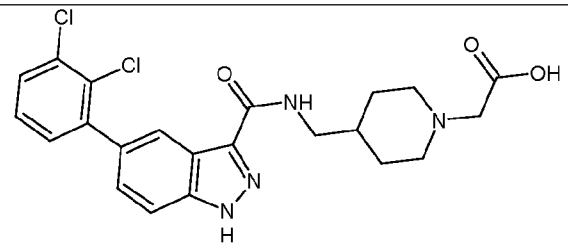
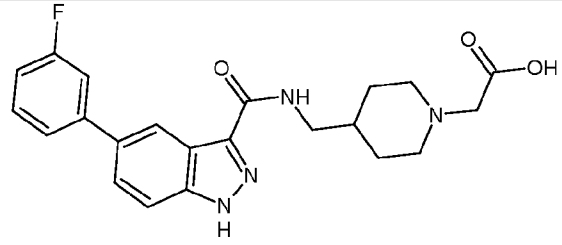
LC-MS: 375.2 (M-H+)

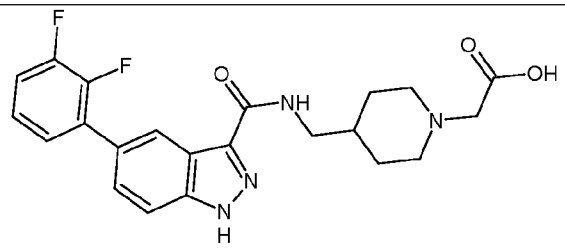
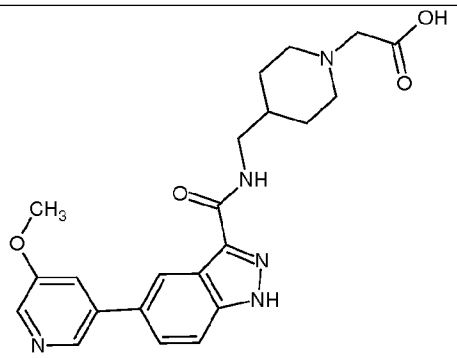
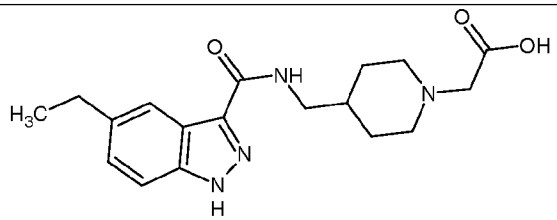
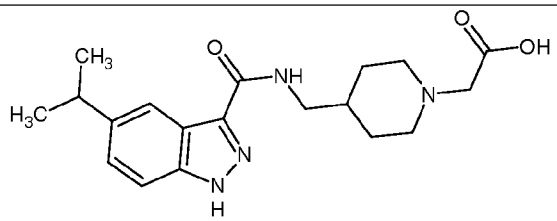
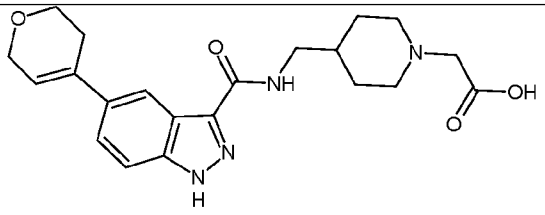
The following Table 1A summarizes the chemical name and structure of the above described compounds 20-44.

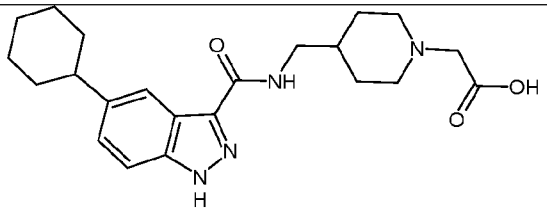
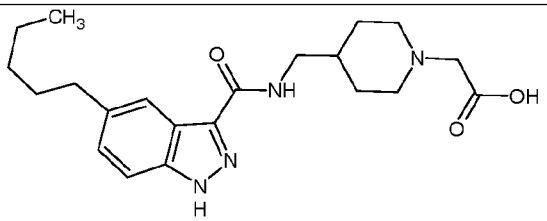
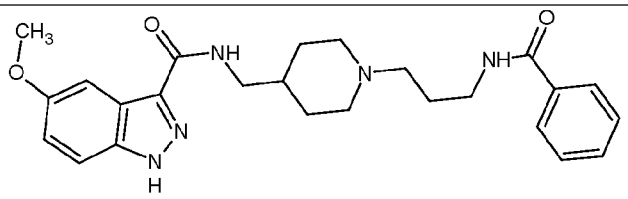
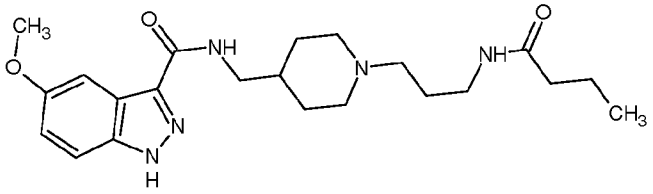
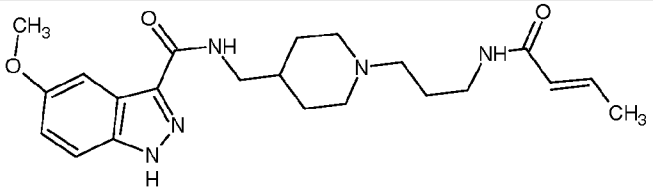
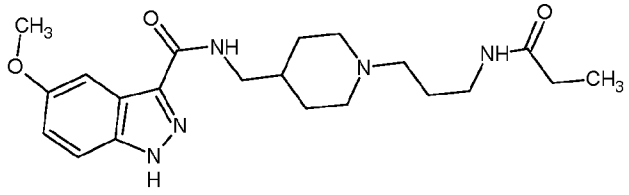
TABLE 1A

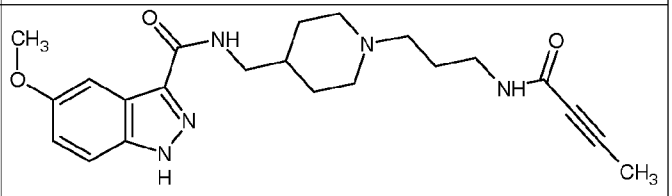
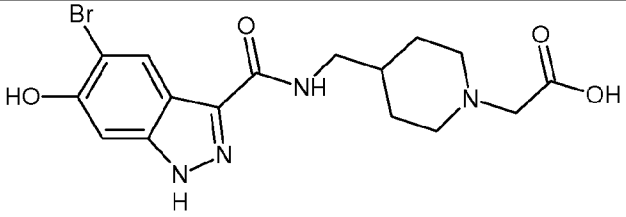
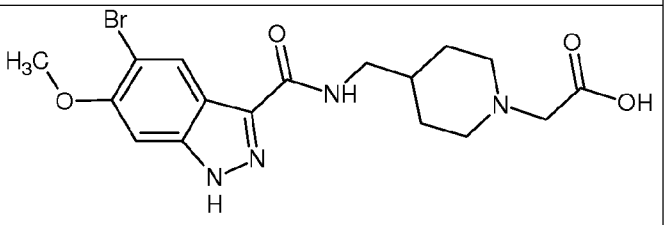
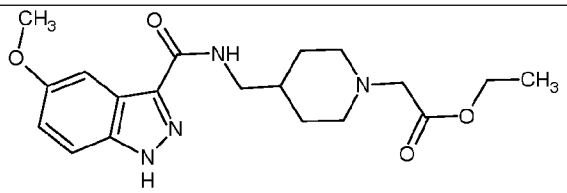
	IUPAC name	Structure
20	Ethyl [4-({[(5-bromo-6-methoxy-1H-indazol-3-yl)carbonyl]amino} methyl)piperidin-1-yl]acetate	
21	{4-[({[6-methoxy-5-(pyridin-3-yl)-1H-indazol-3-yl]carbonyl}amino)methyl] piperidin-1-yl}acetic acid formiate hydrate	

	IUPAC name	Structure
22	{4-[({[6-methoxy-5-(5-methoxypyridin-3-yl)-1H-indazol-3-yl]carbonyl}amino) methyl]piperidin-1-yl}acetic acid hydrate	
23	{4-[({[5-(2,3-difluorophenyl)-6-methoxy-1H-indazol-3-yl]carbonyl}amino) methyl]piperidin-1-yl}acetic acid hydrate	
24	4-[4-({[(5-methoxy-1H-indazol-3-yl) carbonyl]amino}methyl)piperidin-1-yl] butanoic acid	
24c	Ethyl 4-[4-({[(5-methoxy-1H-indazol-3-yl)carbonyl]amino} methyl) piperidin-1-yl]butanoate	

	IUPAC name	Structure
25	{4-[({[5-(Pyrimidin-5-yl)-1H-indazol-3-yl]carbonyl}amino)methyl]piperidin-1-yl}acetic acid hydrate	
25c	Ethyl [4-({[(5-bromo-1H-indazol-3-yl) carbonyl]amino}methyl)piperidin-1-yl] acetate	
26	{4-[({[5-(3,5-Dimethylisoxazol-4-yl)-1H-indazol-3-yl]carbonyl}amino)methyl] piperidin-1-yl}acetic acid hydrate	
27	{4-[({[5-(2,3-dichlorophenyl)-1H-indazol-3-yl]carbonyl}amino)methyl]piperidin-1-yl} acetic acid hydrate	
28	{4-[({[5-(3-fluorophenyl)-1H-indazol-3-yl]carbonyl}amino)methyl]piperidin-1-yl} acetic acid hydrate	

	IUPAC name	Structure
29	{4-[({[5-(2,3-difluorophenyl)-1H-indazol-3-yl]carbonyl}amino)methyl]piperidin-1-yl}acetic acid	
30	{4-[({[5-(5-methoxypyridin-3-yl)-1H-indazol-3-yl]carbonyl}amino) methyl]piperidin-1-yl}acetic acid	
31	[4-({[(5-ethyl-1H-indazol-3-yl)carbonyl]amino}methyl)piperidin-1-yl]acetic acid	
32	{4-[({[5-(propan-2-yl)-1H-indazol-3-yl] carbonyl}amino)methyl]piperidin-1-yl} acetic acid	
33	{4-[({[5-(3,6-dihydro-2H-pyran-4-yl)-1H-indazol-3-yl]carbonyl}amino)methyl] piperidin-1-yl}acetic acid	

	IUPAC name	Structure
34	[4-({[(5-cyclohexyl-1H-indazol-3-yl) carbonyl]amino}methyl)piperidin-1-yl] acetic acid	
35	[4-({[(5-pentyl-1H-indazol-3-yl) carbonyl]amino}methyl)piperidin-1-yl] acetic acid	
36	5-methoxy-N-[(1-{3-[(phenylcarbonyl)amino]propyl}piperidin-4-yl)methyl]-1H-indazole-3-carboxamide	
37	N-({1-[3-(butanoylamino)propyl] piperidin-4-yl}methyl)-5-methoxy-1H-indazole-3-carboxamide	
38	N-[(1-{3-[(2E)-but-2-enoylamino]propyl} piperidin-4-yl)methyl]-5-methoxy-1H-indazole-3-carboxamide	
39	5-methoxy-N-({1-[3-(propanoylamino) propyl]piperidin-4-yl}methyl)-1H-indazole-3-carboxamide	

	IUPAC name	Structure
40	N-({1-[3-(but-2-ynoylamino)propyl] piperidin-4-yl}methyl)-5-methoxy-1H-indazole-3-carboxamide	
41	[4-({[(5-bromo-6-hydroxy-1H-indazol-3-yl)carbonyl]amino}methyl)piperidin-1-yl] acetic acid	
42	[4-({[(5-bromo-6-methoxy-1H-indazol-3-yl)carbonyl]amino}methyl)piperidin-1-yl] acetic acid	
44	ethyl [4-({[(5-methoxy-1H-indazol-3-yl) carbonyl]amino}methyl)piperidin-1-yl] acetate	

Pharmacological properties

The pharmacological properties of the compounds of formula (I) useful in the present invention were evaluated by the methods described in the following sections.

Test I - Activity on human GSK-3β (test *in vitro*)

Activity on human GSK-3β was assessed using the following methods (according to Meijer et al., Chem. Biol., 2003-10:1255-1266).

In a first screening assay, compounds were tested in duplicate at a concentration of 10 µM.

Human recombinant enzyme GSK-3β was incubated for 90 minutes at 22°C in the presence of compounds or vehicle in a reaction buffer containing ATP plus 100 nM unphosphorylated specific substrate peptide (Ulight-CFFKNIVTPRTPPPSQGK-amide). Substrate phosphorylation was measured by LANCE technology (PerkinElmer, CT, USA).

The results, reported in the following Table 4, are expressed as a percentage of inhibition of control specific activity obtained in the presence of the test compounds (as % inhibition at 10 μM).

In a second assay, the same compounds were assayed at five concentrations ranging from 100 μM to 10 nM with ten-fold dilutions in duplicate. Compounds 1 to 15 were tested using the same first assay, compounds 16 to 41 were tested in another assay based on the binding and displacement of AlexaFluor® 647 labeled, ATP-competitive Kinase inhibitor scaffold using LanthaScreen™ TR-FRET technology Eu Kinase assay packet according to manufacturer's instruction (Life Technologies, Italy). The results of the two assays are comparable.

The IC_{50} values (concentration causing a half maximal inhibition of control specific activity), reported in table 4, were determined by non-linear regression analysis of the inhibition curves generated with mean replicate values using Hill equation curve fitting.

Table 4

Compound N°	% Inhibition [10 μM]	**IC_{50}** [μM]
1	92	0.67
2	85	0.87
3	94	0.69
4	-	0.03
5	-	0.05
6	-	0.07
7	-	0.06
8	-	0.02

9	-	0.20
10	-	0.03
11	-	0.89
12	-	0.56
13	-	0.56
14	-	1.40
15	-	0.05
16	-	0.58
18	-	1.06
24	-	1.03
25	-	0.22
25b	-	0.53
26	-	0.91
27	-	0.10
28	-	0.11
29	-	0.03
30	-	0.02
31	-	0.96
32	-	3.91
33	-	1.04
34	-	1.07
35	-	2.04
36	-	3.42
37	-	0.97
38	-	0.78
39	-	0.95
40	-	0.88
41	71	-

The results showed that the compounds according to the present invention had good inhibitory activity in this assay: at 10 µM the % of inhibition is greater than 70% and the IC_{50} is obtained with less than 4.00 µM of each compound. Most compounds showed an IC50 value lower than 1.50 µM.

Test II – Selectivity on GSK-3β (test *in vitro*)

(a) Compounds 1 and 2 were tested against a panel of 60 kinases in order to assess their selectivity. The assays were chosen taking into consideration the diversity of assay families.

Tested kinases were representative of following kinase sub-families:

- protein-serine/threonine kinases;
- protein-tyrosine kinases;
- other kinases; and
- atypical kinases.

Human recombinant kinases were incubated in the presence of specific peptide substrates plus ATP for different times (10, 15, 30, 60 or 90 minutes) at 22°C. Phosphorylated substrate was detected by LANCE or HTRF technology (CISBIO, MA, USA). The compounds were tested at 10 µM in duplicate.

The results are expressed as a percentage of inhibition of control specific activity obtained in the presence of the test compounds and are reported in the following Table 5.

Table 5

Kinase Family	Kinase Sub-Family	Assay	% inhibition of control values	
			compound 1	compound 2
Protein-tyrosine kinases	RTK	c-Met kinase (h)	3	0
	RTK	EphA4 kinase (h)	0	0
	RTK	EphB2 kinase (h)	4	7
	RTK	EphB4 kinase (h)	2	17
	RTK	FGFR1 kinase (h)	0	0
	RTK	FGFR4 kinase (h)	0	0
	RTK	IGF1R kinase (h)	0	0
	RTK	IRK (h) (InsR)	0	0
	RTK	Ret kinase (h)	0	0
	RTK	TRKA (h)	1	0
	CTK	Abl kinase (h)	0	0
	CTK	JAK1 (h)	0	0
	CTK	JAK2 (h)	0	0
	CTK	Fyn kinase (h)	0	3
	CTK	Src kinase (h)	1	6
Protein serine/threo	CMGC	GSK3beta (h)	94	90
	CMGC	DYRK1a (h)	76	56

Kinase Family	Kinase Sub-Family	Assay	% inhibition of control values	
			compound 1	compound 2
nine kinases	CMGC	PCTAIRE1 kinase (h)	22	71
	CMGC	CDC2/CDK1 (h) (cycB)	7	0
	CMGC	CDK2 (h) (cycA)	18	11
	CMGC	CDK5 /p35 (h)	19	13
	CMGC	ERK1 (h)	20	15
	CMGC	ERK2 (h) (P42mapk)	58	46
	CMGC	p38alpha kinase (h)	0	0
	CMGC	p38gamma kinase (h)	0	0
	CMGC	p38delta kinase (h)	0	0
	CaMK	CHK1 (h)	5	8
	CaMK	AMPKalpha	16	19
	CaMK	CaMK4 (h)	0	0
	CaMK	DAPK1 (h)	22	12
	CaMK	DCAMKL1 (h)	0	3
	CaMK	Pim2 kinase (h)	3	4
	CaMK	MAPKAPK2 (h)	0	0
	CaMK	MNK2 (h)	0	0
	CaMK	PhKgamma 2 (h)	30	1
	CaMK	Pim1 kinase (h)	0	2
	CaMK	smMLCK (h) (MYLK)	0	8
	AGC	GRK3 /BARK2 (h) (ADRBK2)	0	0
	AGC	Akt1/PKBalpha (h)	0	4
	AGC	MSK1 (h)	7	16
	AGC	PDK1 (h)	6	6
	AGC	RSK2 (h)	0	1
	AGC	PKA (h)	0	2
	AGC	PKCalpha (h)	0	0
	AGC	PKCbeta 1 (h)	0	1
	AGC	PKCgamma (h)	3	0
	CK1	CK1alpha (h)	0	12
	STE	PAK1 (h)	1	0
	STE	HGK (h) (MAP4K4)	8	23
	STE	MEK1/MAP2K1 (h)	24	9
	STE	TAOK2 (TAO1) (h)	3	26
	TKL	DLK1 (h) (MAP3K12)	0	0
	TKL	IRAK4 (h)	0	8
Other kinases	-	IKKalpha (h)	0	0
	-	IKKepsilon (h) (IKBKE)	0	0
	-	MYT1 kinase (h)	0	1
	-	NEK1 (h)	0	0
	-	NEK7 (h)	0	0
	-	AurA/Aur2 kinase (h)	7	1
	-	AurB/Aur1 kinase (h)	0	6
Atypical kinases	-	mTOR kinase (h) (FRAP1)	2	2

Results confirmed that both the tested compounds have an inhibitory activity on GSK-3β and that they have higher affinity to GSK-3β when compared to the other kinases, showing a good selectivity profile.

(b) Compounds 3, 8, 29 and 31 were tested against the same panel of 60 kinases under the same conditions described above for compounds 1 and 2.

The results are expressed as a percent of inhibition of control specific activity obtained in the presence of the test compounds and are reported in the following Table 6.

TABLE 6

Kinase Family	Kinase Sub-Family	Assay	Compound 3	Compound 8	Compound 29	Compound 31
Protein-tyrosine kinases	RTK	c-Met kinase (h)	0	7	--	--
	RTK	EphA4 kinase (h)	0	0	--	--
	RTK	EphB2 kinase (h)	0	2	--	--
	RTK	EphB4 kinase (h)	0	0	--	--
	RTK	FGFR1 kinase (h)	0	8	--	--
	RTK	FGFR4 kinase (h)	0	2	--	--
	RTK	IGF1R kinase (h)	0	3	--	--
	RTK	IRK (h) (InsR)	0	9	0	0
	RTK	Ret kinase (h)	0	0	--	--
	RTK	TRKA (h)	0	14	3	0
	CTK	Abl kinase (h)	0	0	--	--
	CTK	JAK1 (h)	4	7	--	--
	CTK	JAK2 (h)	0	23	--	--
	CTK	Fyn kinase (h)	0	0	--	--
	CTK	Src kinase (h)	0	0	0	9
Protein serine/threonine kinases	CMGC	GSK3beta (h)	89	99	100	89
	CMGC	DYRK1a (h)	51	99	100	77
	CMGC	PCTAIRE1 kinase (h)	0	84	49	27
	CMGC	CDC2/CDK1 (h)	8	80	80	10

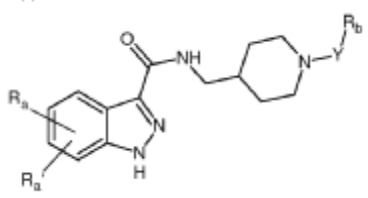
Kinase Family	Kinase Sub-Family	Assay	Compound 3	Compound 8	Compound 29	Compound 31
		(cycB)				
	CMGC	CDK2 (h) (cycA)	21	92	77	35
	CMGC	CDK5 /p35 (h)	9	77	77	16
	CMGC	ERK1 (h)	19	66	61	1
	CMGC	ERK2 (h) (P42mapk)	34	74	67	9
	CMGC	p38alpha kinase (h)	0	1	--	--
	CMGC	p38gamma kinase (h)	--	--	--	--
	CMGC	p38delta kinase (h)	0	18	--	--
	CaMK	CHK1 (h)	0	0	--	--
	CaMK	AMPKalpha	5	68	--	--
	CaMK	CaMK4 (h)	15	4	--	--
	CaMK	DAPK1 (h)	3	47	--	--
	CaMK	DCAMKL1 (h)	0	0	--	--
	CaMK	Pim2 kinase (h)	0	0	--	--
	CaMK	MAPKAPK2 (h)	0	17	--	--
	CaMK	MNK2 (h)	3	4	--	--
	CaMK	PhKgamma 2 (h)	1	0	--	--
	CaMK	Pim1 kinase (h)	12	17	--	--
	CaMK	smMLCK (h) (MYLK)	--	--	17	1
	AGC	GRK3 /BARK2 (h) (ADRBK2)	0	8	--	--
	AGC	Akt1/PKBalpha (h)	0	0	--	--
	AGC	MSK1 (h)	--	--	--	--
	AGC	PDK1 (h)	0	0	--	--
	AGC	RSK2 (h)	4	4	--	--
	AGC	PKA (h)	0	0	--	--
	AGC	PKCalpha (h)	5	19	--	--
	AGC	PKCbeta 1 (h)	0	28	--	--
	AGC	PKCgamma (h)	2	0	--	--
	CK1	CK1alpha (h)	0	6	--	--
	STE	PAK1 (h)	0	3	--	--
	STE	HGK (h) (MAP4K4)	3	72	71	10
	STE	MEK1/MAP2K1 (h)	--	--	75	9

Kinase Family	Kinase Sub-Family	Assay	Compound 3	Compound 8	Compound 29	Compound 31
	STE	TAOK2 (TAO1) (h)	0	79	61	9
	TKL	DLK1 (h) (MAP3K12)	0	58	--	--
	TKL	IRAK4 (h)	0	0	--	--
Other kinases	-	IKKalpha (h)	0	1	--	--
	-	IKKepsilon (h) (IKBKE)	0	3	--	--
	-	MYT1 kinase (h)	2	20	--	--
	-	NEK1 (h)	--	--	9	0
	-	NEK7 (h)	2	0	--	--
	-	AurA/Aur2 kinase (h)	4	10	--	--
	-	AurB/Aur1 kinase (h)	0	0	--	--
Atypical kinases	-	mTOR kinase (h) (FRAP1)	--	--	--	--

Results confirmed that also compounds 3 and 31 had an inhibitory activity on GSK-3β and higher affinity to GSK-3β when compared to all other kinases, showing a good selectivity profile, and that compounds 8 and 29 had an inhibitory activity on GSK-3β and good affinity to GSK-3β when compared to most of other kinases of the same family and to the kinases of different families.

CLAIMS

1. Use of 1 H-indazole-3-carboxamide compounds having the following general formula (I)



(I)

wherein

R_a and R_a', equal or different each other, is a hydrogen atom; a halogen atom; a hydroxy group; a Ci-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl and CrC_6 alkoxy group, optionally substituted by one or more substituents selected from the group consisting of halogen, hydroxy, -NH_2, and CrC_3 alkoxy; a carbocyclic or heterocyclic ring, aliphatic or aromatic, having from 3 to 1 2 members, optionally substituted by one or more substituents selected from the group consisting of halogen, hydroxy, Ci-C_6 alkyl, Ci-C_6 alkoxy, -NR^, - C(0)OH, -C(0)ORi and -C(0)NRi R_2;

Y is a bond, a d-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl group, optionally substituted by one or more substituents selected from the group consisting of halogen, hydroxy, -NH_2, and C_1 -C3 alkoxy;

R_b is a Ci-C_6 alkoxy group; -C(0)OH; -C(0)ORi ; -N0$_2$; -NHC(0)Ri ;

Ri and R_2 are independently a hydrogen atom, a Ci-C_4 alkyl group, a C_2-C_4 alkenyl group, a C_2-C_4 alkynyl group, and a phenyl group; and its salts of addition with pharmaceutically acceptable organic and inorganic acids and bases;

for the manufacture of a medicament for treatment of a disease arising from the uncontrolled activation and/or overexpression of GSK-33, selected from the group consisting of (i) insulin-resistance disorders; (ii) neurodegenerative diseases; (iii) mood disorders; (iv) schizophrenic disorders; (v) cancerous disorders; (vi) inflammation, (vii) substance abuse disorders; (viii) epilepsies; and (ix) neuropathic pain.

2. The use of a 1 H-indazole-3-carboxamide according to claim 1, wherein said insulin-resistance disorders are selected from the group consisting of type-2 diabetes, syndrome X, obesity and polycystic ovary syndrome.

3. The use of a 1 H-indazole-3-carboxamide according to claim 1, wherein said neurodegenerative diseases are selected from the group consisting of Parkinson's disease, Alzheimer's disease, Huntington's disease, and spinal neurodegenerative disorders.

4. The use of a 1 H-indazole-3-carboxamide according to claim 3, wherein said spinal neurodegenerative disorders are selected from the group consisting of amyotrophic lateral sclerosis, multiple sclerosis, spinal muscular atrophy and neurodegeneration due to spinal cord injury.

5. The use of a 1 H-indazole-3-carboxamide according to claim 1, wherein said mood disorders are selected from the group consisting of bipolar disorders and depressive disorders.

6. The use of a 1 H-indazole-3-carboxamide according to claim 5, wherein said bipolar disorders are selected from the group consisting of bipolar I, bipolar II, cyclothymia and bipolar disorder not otherwise specified (BD-NOS).

7. The use of a 1 H-indazole-3-carboxamide according to claim 5, wherein said depressive disorders are selected from the group consisting of major depressive disorder (MDD), atypical depression (AD), melancholic depression, psychotic major depression (PMD), catatonic depression, postpartum depression (PPD), seasonal affective disorder (SAD), dysthymia, and depressive disorder not otherwise specified (DD-NOS).

8. The use of a 1 H-indazole-3-carboxamide according to claim 1, wherein said substance abuse disorders are selected from the group of abuse disorders due to psychostimulants.

9. The use of a 1 H-indazole-3-carboxamide according to claim 1, wherein said schizophrenic disorders are selected from the group consisting of paranoid schizophrenia, disorganized schizophrenia, catatonic schizophrenia, simple schizophrenia, residual schizophrenia, and undifferentiated schizophrenia.

10. The use of a 1 H-indazole-3-carboxamide according to claim 1, wherein said cancerous disorders are selected from the group consisting of prostate, pancreatic, ovarian, and colon-rectal cancer and MLL-associated leukemia.