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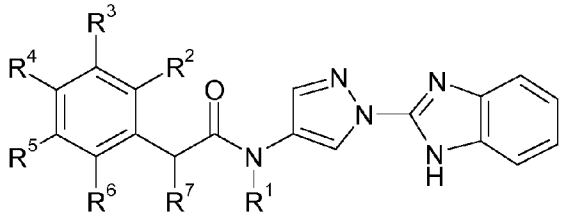
(54) Title: SUBSTITUTED 2-(1H-PYRAZOL-1-YL)-1H-BENZIMIDAZOLE COMPOUNDS



(I)

(57) Abstract: The present invention relates to substituted 2-(1H-pyrazol-1-yl)-1H-benzimidazole compounds of general formula (I); in which R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are as defined herein, to methods of preparing said compounds, to intermediate compounds useful for preparing said compounds, to pharmaceutical compositions and combinations comprising said compounds and to the use of said compounds for manufacturing a pharmaceutical composition for the treatment or prophylaxis of a disease, in particular of neoplasms, as a sole agent or in combination with other active ingredients.

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SUBSTITUTED 2-(1H-PYRAZOL-1-YL)-1H-BENZIMIDAZOLE COMPOUNDS

The present invention relates to substituted 2-(1H-pyrazol-1-yl)-1H-benzimidazole compounds of general formula **(I)** as described and defined herein, to methods of preparing said compounds, to intermediate compounds useful for preparing said compounds, to pharmaceutical compositions and combinations comprising said compounds and to the use of said compounds for manufacturing a pharmaceutical composition for the treatment or prophylaxis of a disease, in particular of neoplasms, as a sole agent or in combination with other active ingredients.

BACKGROUND OF THE INVENTION

Cancer is the leading cause of death in developed countries and the second leading cause of death in developing countries. Deaths from cancer worldwide are projected to continue rising, with an estimated 12 million deaths in 2030. While substantial progress has been made in developing effective therapies, there is a strong need for additional therapeutic modalities that target cancer and related diseases.

The complexity of cancer disease arises after a selection process for cells with acquired functional capabilities to enhance survival and/or resistance towards apoptosis and a limitless proliferative potential. Due to lagging (neo-) vascularization unrestrained growth of cancer cells leads to tumor regions with suboptimal nutrient and oxygen supply. As distance from supplying blood vessels increases, oxygen and nutrient concentrations decrease and cancer cells react by expression of hypoxia and low-nutrition responsive pathways to promote cell survival in an unfavorable metabolic microenvironment. Indeed, cancer cells in undervascularized tumor regions are considered more resistant to radiation and cytostatic chemotherapy and to contribute to repopulation of the tumor after therapy (*Minchinton IA, Tannock IF. Drug penetration in solid tumours. Nature Reviews Cancer 6, 583-592 (August 2006)*). Therefore, substances that target cancer cells in poorly vascularized tumor regions or that target cancer cells which underwent metabolic remodeling or adjustment to an unfavorable metabolic microenvironment (*Villalba M, Chemical Metabolic Inhibitors for the Treatment of Blood-Borne Cancers. Anti-Cancer Agents in Medicinal Chemistry, 2014, 14, 223-232*) have the potential to enhance cytostatic- or radiation-based (chemo)therapy of solid tumors and haematological malignancies.

The objective of the present invention is to provide compounds which can be used for cancer therapy, in particular compounds that target cancer cells including cancer stem(-like) cells in hypoxic or nutrient-deprived tumor regions or which underwent metabolic adjustments to an unfavorable environment.

WO2014/100735 discloses N-(1-phenyl-1H-pyrazol-4-yl)-amides that act as antagonists of the CCR1 receptor.

WO2012/064715 discloses N-(1-phenyl-1H-pyrazol-5-yl)-amides as HSF activating compounds.

EP2133331A1 discloses 2-phenyl-N-(1-phenyl-1H-pyrazol-3-yl)acetamides for the treatment or prevention of a disease associated with abnormal serum uric acid level.

WO03/037274 discloses N-(1-phenyl-1H-pyrazol-4-yl)-amides as sodium channel inhibitors.

WO2012/080729 disclosed inter alia N-(1-phenyl-1H-pyrazol-5-yl)-amides as casein kinase 1 delta inhibitors.

However, the state of the art described above does not describe the specific substituted 2-(1H-pyrazol-1-yl)-1H-benzimidazole compounds of general formula **(I)** of the present invention as defined herein, or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same, as described and defined herein, and as hereinafter referred to as "compounds of the present invention", or their pharmacological activity.

DESCRIPTION of the INVENTION

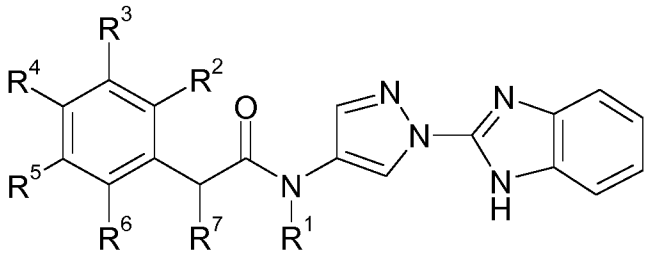
It has now been found, and this constitutes the basis of the present invention, that said compounds of the present invention have surprising and advantageous properties.

In particular, said compounds of the present invention are suitable to treat cancer. The compounds of the present invention have surprisingly been found to effectively reduce tumor cell viability in nutrient deprived regions. In particular, said compounds of the present invention have been found to effectively kill cancer cells in inner tumor spheroid regions.

Said compounds of the present invention may therefore be used for the treatment or prophylaxis of diseases of uncontrolled cell growth, proliferation and/or survival, undesirable cellular immune responses, or undesirable cellular inflammatory responses or diseases which

are accompanied with uncontrolled cell growth, proliferation and/or survival, undesirable cellular immune responses, or undesirable cellular inflammatory responses, for example, haematological tumours, solid tumours, and/or metastases thereof, e.g. leukaemias and myelodysplastic syndrome, malignant lymphomas including angioimmunoblastic T-cell lymphomas, head and neck tumours including brain tumours and brain metastases (e.g. anaplastic astrocytoma, diffuse astrocytoma, glioblastoma, oligodendroglioma, secondary glioblastoma multiforme), tumours of the thorax including non-small cell and small cell lung tumours, gastrointestinal tumours including cholangiocarcinoma, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas including chondrosarcomas, and/or metastases thereof.

In accordance with a first aspect, the present invention covers compounds of general formula **(I)** :



(I) ,

in which :

R^1 represents a hydrogen atom or a methyl group;

R^2 represents a fluorine atom or a group selected from :
methyl, ethyl, C_1-C_2-haloalkyl and (trifluoromethyl)sulfanyl;
and R^3, R^4, R^5 and R^6 each represent a hydrogen atom;

or

R^3 represents a halogen atom or a group selected from :
cyano, methyl, ethyl, C_1-C_2-haloalkyl and (trifluoromethyl)sulfanyl;
and R^2, R^4, R^5 and R^6 each represent a hydrogen atom;

or

R^4 represents a halogen atom, or a group selected from :
cyano, difluoromethoxy and (trifluoromethyl)sulfanyl;
and R^2, R^3, R^5 and R^6 each represent a hydrogen atom;

or

R^2 represents a halogen atom or a group selected from :
methyl, ethyl, C_1-C_2-haloalkyl, and (trifluoromethyl)sulfanyl;
and R^3 represents a halogen atom or a group selected from :
cyano, methyl, ethyl, C_1-C_2-haloalkyl and (trifluoromethyl)sulfanyl;
and R^4, R^5 and R^6 each represent a hydrogen atom;

or

R^2 represents a fluorine atom or a group selected from :
methyl, ethyl, C_1-C_2-haloalkyl and (trifluoromethyl)sulfanyl;
and R^4 represents a halogen atom or a group selected from :
cyano, difluoromethoxy and (trifluoromethyl)sulfanyl;
and R^3, R^5 and R^6 each represent a hydrogen atom;

or

R^2 represents a fluorine atom or a group selected from :
methyl, ethyl, C_1-C_2-haloalkyl and (trifluoromethyl)sulfanyl;
and R^5 represents a halogen atom or a group selected from :
cyano, methyl, ethyl, C_1-C_2-haloalkyl and (trifluoromethyl)sulfanyl;
and R^3, R^4 and R^6 each represent a hydrogen atom;

or

R^3 represents a halogenatom or a group selected from :
cyano, methyl, ethyl, C_1-C_2-haloalkyl and (trifluoromethyl)sulfanyl;
and R^4 represents a halogen atom, or a group selected from :
cyano, difluoromethoxy and (trifluoromethyl)sulfanyl;
and R^2, R^5 and R^6 each represent a hydrogen atom;

or

R^3 and R^5 represent, independently of each other, a halogen atom or a group selected from :
cyano, difluoromethyl and (trifluoromethyl)sulfanyl;
and R^2, R^4 and R^6 each represent a hydrogen atom;

or

R^2, R^3, R^4, R^5 and R^6 each represent a hydrogen atom;

R^7 represents a hydrogen atom;

or

R^2 and R^6 represent, independently of each other, a fluorine or a chlorine atom;

and R^3, R^4 and R^5 each represent a hydrogen atom;

and R^7 represents a methyl group;

or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

The term "substituted" means that one or more hydrogens on the designated atom or group are replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded. Combinations of substituents and/or variables are permissible.

The term "comprising" when used in the specification includes "consisting of".

If it is referred to "as mentioned herein" within the description it is referred to any of the disclosures made within the specification in any of the preceding pages.

The terms as mentioned in the present text have preferably the following meanings:

The term "halogen atom", "halo-" or "Hal-" is to be understood as meaning a fluorine, chlorine, bromine or iodine atom.

The term "C_1-C_2-haloalkyl" means a monovalent hydrocarbon group having 1 or 2 carbon atoms, in which one or more of the hydrogen atoms are replaced, identically or differently, with a halogen atom. Particularly, said halogen atom is fluorine. Said C_1-C_2-haloalkyl group is, for example, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, or pentafluoroethyl.

The term "C_1-C_2", as used throughout this text, *e.g.* in the context of the definition of "C_1-C_2-haloalkyl", means an alkyl group having a finite number of carbon atoms of 1 to 2, *i.e.* 1 or 2 carbon atoms.

The compounds of general formula **(I)** may exist as isotopic variants. The invention therefore includes one or more isotopic variant(s) of the compounds of general formula **(I)**, particularly deuterium-containing compounds of general formula **(I)**.

The term "Isotopic variant" of a compound or a reagent is defined as a compound exhibiting an unnatural proportion of one or more of the isotopes that constitute such a compound.

The term "Isotopic variant of the compound of general formula **(I)**" is defined as a compound of general formula **(I)** exhibiting an unnatural proportion of one or more of the isotopes that constitute such a compound.

The expression "unnatural proportion" is to be understood as meaning a proportion of such isotope which is higher than its natural abundance. The natural abundances of isotopes to be applied in this context are described in "Isotopic Compositions of the Elements 1997", Pure Appl. Chem., 70(1), 217-235, 1998.

Examples of such isotopes include stable and radioactive isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, bromine and iodine, such as ^{2}H (deuterium), ^{3}H (tritium), ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{33}S, ^{34}S, ^{35}S, ^{36}S, ^{18}F, ^{36}Cl, ^{82}Br, ^{123}I, ^{124}I, ^{125}I, ^{129}I and ^{131}I, respectively.

With respect to the treatment and/or prophylaxis of the disorders specified herein the isotopic variant(s) of the compounds of general formula **(I)** preferably contain deuterium ("deuterium-containing compounds of general formula **(I)**"). Isotopic variants of the compounds of general formula **(I)** in which one or more radioactive isotopes, such as ^{3}H or ^{14}C, are incorporated are useful e.g. in drug and/or substrate tissue distribution studies. These isotopes are particularly preferred for the ease of their incorporation and detectability. Positron emitting isotopes such as ^{18}F or ^{11}C may be incorporated into a compound of general formula **(I)**. These isotopic variants of the compounds of general formula **(I)** are useful for in vivo imaging applications. Deuterium-containing and ^{13}C-containing compounds of general formula **(I)** can be used in mass spectrometry analyses (H. J. Leis et al., Curr. Org. Chem., 1998, 2, 131) in the context of preclinical or clinical studies.

Isotopic variants of the compounds of general formula **(I)** can generally be prepared by methods known to a person skilled in the art, such as those described in the schemes and/or examples herein, by substituting a reagent for an isotopic variant of said reagent, preferably for a deuterium-containing reagent. Depending on the desired sites of deuteration, in some cases deuterium from D_2O can be incorporated either directly into the compounds or into reagents that are useful for synthesizing such compounds (Esaki et al., Tetrahedron, 2006, 62, 10954; Esaki et al., Chem. Eur. J., 2007, 13, 4052). Deuterium gas is also a useful reagent for incorporating deuterium into molecules. Catalytic deuteration of olefinic bonds (H. J. Leis et al., Curr. Org. Chem., 1998, 2, 131; J. R. Morandi et al., J. Org. Chem., 1969, 34 (6), 1889) and acetylenic bonds (N. H. Khan, J. Am. Chem. Soc., 1952, 74 (12), 3018; S. Chandrasekhar et al., Tetrahedron, 2011, 52, 3865) is a rapid route for incorporation of deuterium. Metal catalysts (i.e. Pd, Pt, and Rh) in the presence of deuterium gas can be used to directly exchange deuterium for hydrogen in functional groups containing hydrocarbons (J. G. Atkinson et al., US Patent 3966781). A variety of deuterated reagents and synthetic building blocks are commercially available from companies such as for example C/D/N Isotopes, Quebec, Canada; Cambridge Isotope Laboratories Inc., Andover, MA, USA; and CombiPhos Catalysts, Inc., Princeton, NJ, USA. Further information on the state of the art with respect to deuterium-hydrogen exchange is given for example in Hanzlik et al., J. Org. Chem. 55, 3992-3997, 1990; R. P. Hanzlik et al., Biochem. Biophys. Res. Commun. 160, 844, 1989; P. J. Reider et al., J. Org. Chem. 52, 3326-3334, 1987; M. Jarman et al., Carcinogenesis 16(4), 683-688, 1993; J. Atzrodt et al., Angew. Chem., Int. Ed. 2007, 46, 7744; K. Matoishi et al., J. Chem. Soc, Chem. Commun. 2000, 1519–1520; K. Kassahun et al., WO2012/112363.

The term "deuterium-containing compound of general formula **(I)**" is defined as a compound of general formula **(I)**, in which one or more hydrogen atom(s) is/are replaced by one or more deuterium atom(s) and in which the abundance of deuterium at each deuterated position of the compound of general formula **(I)** is higher than the natural abundance of deuterium, which is about 0.015%. Particularly, in a deuterium-containing compound of general formula **(I)** the abundance of deuterium at each deuterated position of the compound of general formula **(I)** is higher than 10%, 20%, 30%, 40%, 50%, 60%, 70% or 80%, preferably higher than 90%, 95%, 96% or 97%, even more preferably higher than 98% or 99% at said position(s). It is understood that the abundance of deuterium at each deuterated position is independent of the abundance of deuterium at other deuterated position(s).

The selective incorporation of one or more deuterium atom(s) into a compound of general formula **(I)** may alter the physicochemical properties (such as for example acidity [A.

Streitwieser et al., *J. Am. Chem. Soc.*, 1963, 85, 2759; C. L. Perrin, et al., *J. Am. Chem. Soc.*, 2007, 129, 4490], basicity [C. L. Perrin, et al., J. Am. Chem. Soc., 2003, 125, 15008; C. L. Perrin in Advances in Physical Organic Chemistry, 44, 144; C. L. Perrin et al., J. Am. Chem. Soc., 2005, 127, 9641], lipophilicity [B. Testa et al., Int. J. Pharm., 1984, 19(3), 271]) and/or the metabolic profile of the molecule and may result in changes in the ratio of parent compound to metabolites or in the amounts of metabolites formed. Such changes may result in certain therapeutic advantages and hence may be preferred in some circumstances. Reduced rates of metabolism and metabolic switching, where the ratio of metabolites is changed, have been reported (D. J. Kushner et al., Can. J. Physiol. Pharmacol., 1999, 77, 79; A. E. Mutlib et al., Toxicol. Appl. Pharmacol., 2000, 169, 102). These changes in the exposure to parent drug and metabolites can have important consequences with respect to the pharmacodynamics, tolerability and efficacy of a deuterium-containing compound of general formula **(I)**. In some cases deuterium substitution reduces or eliminates the formation of an undesired or toxic metabolite and enhances the formation of a desired metabolite (e.g. Nevirapine: A. M. Sharma et al., Chem. Res.Toxicol., 2013, 26, 410; Uetrecht et al., Chemical Research in Toxicology, 2008, 21, 9, 1862; Efavirenz: A. E. Mutlib et al., Toxicol. Appl. Pharmacol., 2000, 169, 102). In other cases the major effect of deuteration is to reduce the rate of systemic clearance. As a result, the biological half-life of the compound is increased. The potential clinical benefits would include the ability to maintain similar systemic exposure with decreased peak levels and increased trough levels. This could result in lower side effects and enhanced efficacy, depending on the particular compound's pharmacokinetic/ pharmacodynamic relationship. Indiplon (A. J. Morales et al., Abstract 285, The 15th North American Meeting of the International Society of Xenobiotics, San Diego, CA, October 12-16, 2008), ML-337 (C. J. Wenthur et al., J. Med. Chem., 2013, 56, 5208), and Odanacatib (K. Kassahun et al., WO2012/112363) are examples for this deuterium effect. Still other cases have been reported in which reduced rates of metabolism result in an increase in exposure of the drug without changing the rate of systemic clearance (e.g. Rofecoxib: F. Schneider et al., Arzneim. Forsch. Drug. Res., 2006, 56, 295; Telaprevir: F. Maltais et al., J. Med. Chem., 2009, 52, 7993). Deuterated drugs showing this effect may have reduced dosing requirements (e.g. lower number of doses or lower dosage to achieve the desired effect) and/or may produce lower metabolite loads.

A compound of general formula **(I)** may have multiple potential sites of attack for metabolism. To optimize the above-described effects on physicochemical properties and metabolic profile, deuterium-containing compounds of general formula **(I)** having a certain pattern of one or

more deuterium-hydrogen exchange(s) can be selected. Particularly, the deuterium atom(s) of deuterium- containing compound(s) of general formula **(I)** is/are attached to a carbon atom and/or is/are located at those positions of the compound of general formula **(I)**, which are sites of attack for metabolizing enzymes such as e.g. cytochrome P_{450}.

In another embodiment the present invention concerns a deuterium-containing compound of general formula **(I)** having 1, 2, 3 or 4 deuterium atoms, particularly with 1, 2 or 3 deuterium atoms.

In another embodiment the present invention concerns a deuterium-containing compound of general formula **(I)**, comprising one or more CD_3 groups.

Where the plural form of the word compounds, salts, polymorphs, hydrates, solvates and the like, is used herein, this is taken to mean also a single compound, salt, polymorph, isomer, hydrate, solvate or the like.

By "stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The compounds of this invention optionally contain one or more asymmetric centre, depending upon the location and nature of the various substituents desired. Asymmetric carbon atoms are present in the (R) or (S) configuration, resulting in racemic mixtures in the case of a single asymmetric centre, and diastereomeric mixtures in the case of multiple asymmetric centres. In certain instances, asymmetry may also be present due to restricted rotation about a given bond, for example, the central bond adjoining two substituted aromatic rings of the specified compounds.

Preferred compounds are those which produce the more desirable biological activity. Separated, pure or partially purified isomers and stereoisomers or racemic or diastereomeric mixtures of the compounds of this invention are also included within the scope of the present invention. The purification and the separation of such materials can be accomplished by standard techniques known in the art.

The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using an optically active acid or base or formation of covalent diastereomers. Examples of appropriate acids are tartaric, diacetyltartaric, ditoluoyltartaric and camphorsulfonic acid. Mixtures of diastereoisomers can be separated into their individual diastereomers on the basis of their physical and/or chemical differences by methods known in the art, for example, by chromatography or fractional crystallisation. The optically active bases or acids are then liberated from the separated diastereomeric salts. A different process for separation of optical isomers involves the use of chiral chromatography (*e.g.*, chiral HPLC columns), with or without conventional derivatisation, optimally chosen to maximise the separation of the enantiomers. Suitable chiral HPLC columns are manufactured by Daicel, *e.g.*, Chiracel OD and Chiracel OJ among many others, all routinely selectable. Enzymatic separations, with or without derivatisation, are also useful. The optically active compounds of this invention can likewise be obtained by chiral syntheses utilizing optically active starting materials.

In order to limit different types of isomers from each other reference is made to IUPAC Rules Section E (Pure Appl Chem 45, 11-30, 1976).

The present invention includes all possible stereoisomers of the compounds of the present invention as single stereoisomers, or as any mixture of said stereoisomers, *e.g.* R- or S- isomers, in any ratio. Isolation of a single stereoisomer, *e.g.* a single enantiomer or a single diastereomer, of a compound of the present invention is achieved by any suitable state of the art method, such as chromatography, especially chiral chromatography, for example.

Further, the compounds of the present invention can exist as N-oxides, which are defined in that at least one nitrogen of the compounds of the present invention is oxidised. The present invention includes all such possible N-oxides.

The present invention also relates to useful forms of the compounds as disclosed herein, such as metabolites, hydrates, solvates, prodrugs, salts, in particular pharmaceutically acceptable salts, and co-precipitates.

The compounds of the present invention can exist as a hydrate, or as a solvate, wherein the compounds of the present invention contain polar solvents, in particular water, methanol or ethanol for example as structural element of the crystal lattice of the compounds. The amount of polar solvents, in particular water, may exist in a stoichiometric or non-stoichiometric ratio. In the case of stoichiometric solvates, *e.g.* a hydrate, hemi-, (semi-), mono-, sesqui-, di-, tri-, tetra-, penta- *etc*. solvates or hydrates, respectively, are possible. The present invention includes all such hydrates or solvates.

Further, the compounds of the present invention can exist in free form, *e.g.* as a free base, or as a free acid, or as a zwitterion, or can exist in the form of a salt. Said salt may be any salt, either an organic or inorganic addition salt, particularly any pharmaceutically acceptable organic or inorganic addition salt, customarily used in pharmacy.

The term "pharmaceutically acceptable salt" refers to a relatively non-toxic, inorganic or organic acid addition salt of a compound of the present invention. For example, see S. M. Berge, *et al*. "Pharmaceutical Salts," J. Pharm. Sci. **1977**, 66, 1-19.

A suitable pharmaceutically acceptable salt of the compounds of the present invention may be, for example, an acid-addition salt of a compound of the present invention bearing a nitrogen atom, in a chain or in a ring, for example, which is sufficiently basic, such as an acid-addition salt with an inorganic acid, such as hydrochloric, hydrobromic, hydroiodic, sulfuric, bisulfuric, phosphoric, or nitric acid, for example, or with an organic acid, such as formic, acetic, acetoacetic, pyruvic, trifluoroacetic, propionic, butyric, hexanoic, heptanoic, undecanoic, lauric, benzoic, salicylic, 2-(4-hydroxybenzoyl)-benzoic, camphoric, cinnamic, cyclopentanepropionic, digluconic, 3-hydroxy-2-naphthoic, nicotinic, pamoic, pectinic, persulfuric, 3-phenylpropionic, picric, pivalic, 2-hydroxyethanesulfonate, itaconic, sulfamic, trifluoromethanesulfonic, dodecylsulfuric, ethansulfonic, benzenesulfonic, para-toluenesulfonic, methansulfonic, 2-naphthalenesulfonic, naphthalinedisulfonic, camphorsulfonic acid, citric, tartaric, stearic, lactic, oxalic, malonic, succinic, malic, adipic, alginic, maleic, fumaric, D-gluconic, mandelic, ascorbic, glucoheptanoic, glycerophosphoric, aspartic, sulfosalicylic, hemisulfuric, or thiocyanic acid, for example.

Further, another suitably pharmaceutically acceptable salt of a compound of the present invention which is sufficiently acidic, is an alkali metal salt, for example a sodium or potassium

salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically acceptable cation, for example a salt with N-methyl-glucamine, dimethyl-glucamine, ethyl-glucamine, lysine, dicyclohexylamine, 1,6-hexadiamine, ethanolamine, glucosamine, sarcosine, serinol, tris-hydroxy-methyl-aminomethane, aminopropandiol, sovak-base, 1-amino-2,3,4-butantriol. Additionally, basic nitrogen containing groups may be quaternised with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides ; dialkyl sulfates like dimethyl, diethyl, and dibutyl sulfate ; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and strearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

Those skilled in the art will further recognise that acid addition salts of the claimed compounds may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts of acidic compounds of the invention are prepared by reacting the compounds of the invention with the appropriate base via a variety of known methods.
The present invention includes all possible salts of the compounds of the present invention as single salts, or as any mixture of said salts, in any ratio.

In the present text, in particular in the Experimental Section, for the synthesis of intermediates and of examples of the present invention, when a compound is mentioned as a salt form with the corresponding base or acid, the exact stoichiometric composition of said salt form, as obtained by the respective preparation and/or purification process, is, in most cases, unknown.

Unless specified otherwise, suffixes to chemical names or structural formulae such as "hydrochloride", "trifluoroacetate", "sodium salt", or "x HCl", "x CF_3COOH", "x Na^+", for example, are to be understood as not a stoichiometric specification, but solely as a salt form.

This applies analogously to cases in which synthesis intermediates or example compounds or salts thereof have been obtained, by the preparation and/or purification processes described, as solvates, such as hydrates with (if defined) unknown stoichiometric composition.

As used herein, the term *"in vivo* hydrolysable ester" is understood as meaning an *in vivo* hydrolysable ester of a compound of the present invention containing a carboxy or hydroxy

group, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include for example alkyl, cycloalkyl and optionally substituted phenylalkyl, in particular benzyl esters, C_1-C_6 alkoxymethyl esters, *e.g.* methoxymethyl, C_1-C_6 alkanoyloxymethyl esters, *e.g.* pivaloyloxymethyl, phthalidyl esters, C_3-C_8 cycloalkoxy-carbonyloxy-C_1-C_6 alkyl esters, *e.g.* 1-cyclohexylcarbonyloxyethyl ; 1,3-dioxolen-2-onylmethyl esters, *e.g.* 5-methyl-1,3-dioxolen-2-onylmethyl ; and C_1-C_6-alkoxycarbonyloxyethyl esters, *e.g.* 1-methoxycarbonyloxyethyl, and may be formed at any carboxy group in the compounds of this invention.

An *in vivo* hydrolysable ester of a compound of the present invention containing a hydroxy group includes inorganic esters such as phosphate esters and [alpha]-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of [alpha]-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. The present invention covers all such esters.

Furthermore, the present invention includes all possible crystalline forms, or polymorphs, of the compounds of the present invention, either as single polymorph, or as a mixture of more than one polymorph, in any ratio.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^1 represents a hydrogen atom or a methyl group;

R^2 represents a fluorine atom or a group selected from :
methyl, ethyl and C_1-C_2-haloalkyl;
and R^3, R^4, R^5 and R^6 each represent a hydrogen atom;

or

R^3 represents a halogen atom or a group selected from :
cyano, methyl, ethyl and C_1-C_2-haloalkyl;
and R^2, R^4, R^5 and R^6 each represent a hydrogen atom;

or

R^4 represents a halogen atom, or a group selected from :
cyano and difluoromethoxy;
and R^2, R^3, R^5 and R^6 each represent a hydrogen atom;

or

R^2 represents a halogen atom or a group selected from :
methyl, ethyl and C_1-C_2-haloalkyl;
and R^3 represents a halogen atom or a group selected from :
cyano, methyl, ethyl and C_1-C_2-haloalkyl;
and R^4, R^5 and R^6 each represent a hydrogen atom;

or

R^2 represents a fluorine atom or a group selected from :
methyl, ethyl and C_1-C_2-haloalkyl;
and R^4 represents a halogen atom or a group selected from :
cyano and difluoromethoxy;
and R^3, R^5 and R^6 each represent a hydrogen atom;

or

R^2 represents a fluorine atom or a group selected from :
methyl, ethyl and C_1-C_2-haloalkyl;
and R^5 represents a halogen atom or a group selected from :
cyano, methyl, ethyl and C_1-C_2-haloalkyl;
and R^3, R^4 and R^6 each represent a hydrogen atom;

or

R^3 represents a halogen atom or a group selected from :
cyano, methyl, ethyl and C_1-C_2-haloalkyl;
and R^4 represents a halogen atom, or a group selected from :
cyano and difluoromethoxy;
and R^2, R^5 and R^6 each represent a hydrogen atom;

or

R^3 and R^5 represent, independently of each other, a halogen atom or a group selected from :
cyano and difluoromethyl;
and R^2, R^4 and R^6 each represent a hydrogen atom;
or
R^2, R^3, R^4, R^5 and R^6 each represent a hydrogen atom;

R^7 represents a hydrogen atom;

or
R^2 and R^6 represent, independently of each other, a fluorine or a chlorine atom;
and R^3, R^4 and R^5 each represent a hydrogen atom;
and R^7 represents a methyl group;

or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^1 represents a hydrogen atom or a methyl group;

R^2 represents a fluorine atom or a group selected from :
methyl, difluoromethyl and trifluoromethyl;
and R^3, R^4, R^5 and R^6 each represent a hydrogen atom;
or
R^3 represents a fluorine or a chlorine atom, or a group selected from :
cyano, methyl, difluoromethyl and trifluoromethyl;
and R^2, R^4, R^5 and R^6 each represent a hydrogen atom;
or
R^4 represents a fluorine or a chlorine atom, or a group selected from :
cyano and difluoromethoxy;
and R^2, R^3, R^5 and R^6 each represent a hydrogen atom;
or
R^2 represents a fluorine or a chlorine atom, or a group selected from :
methyl, difluoromethyl and trifluoromethyl;

and R^3 represents a fluorine or a chlorine atom, or a group selected from : cyano, methyl, difluoromethyl and trifluoromethyl;
and R^4, R^5 and R^6 each represent a hydrogen atom;

or

R^2 represents a fluorine atom or a group selected from : methyl, difluoromethyl and trifluoromethyl;
and R^4 represents a fluorine or a chlorine atom, or a group selected from : cyano and difluoromethoxy;
and R^3, R^5 and R^6 each represent a hydrogen atom;

or

R^2 represents a fluorine atom or a group selected from : methyl, difluoromethyl and trifluoromethyl;
and R^5 represents a fluorine or a chlorine atom, or a group selected from : cyano, methyl, difluoromethyl and trifluoromethyl;
and R^3, R^4 and R^6 each represent a hydrogen atom;

or

R^3 represents a fluorine or a chlorine atom, or a group selected from : cyano, methyl, difluoromethyl and trifluoromethyl;
and R^4 represents a fluorine or a chlorine atom, or a group selected from : cyano and difluoromethoxy;
and R^2, R^5 and R^6 each represent a hydrogen atom;

or

R^3 and R^5 represent, independently of each other, a fluorine or a chlorine atom, or a group selected from : cyano and difluoromethyl;
and R^2, R^4 and R^6 each represent a hydrogen atom;

or

R^2, R^3, R^4, R^5 and R^6 each represent a hydrogen atom;

R^7 represents a hydrogen atom;

or

R^2 and R^6 represent, independently of each other, a fluorine or a chlorine atom;

and R^3, R^4 and R^5 each represent a hydrogen atom;

and R^7 represents a methyl group;

or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^1 represents a hydrogen atom or a methyl group;

R^2 represents a fluorine atom or a group selected from :
methyl, difluoromethyl and trifluoromethyl;
and R^3, R^4, R^5 and R^6 each represent a hydrogen atom;

or

R^3 represents a fluorine or a chlorine atom, or a group selected from :
cyano, methyl, difluoromethyl and trifluoromethyl;
and R^2, R^4, R^5 and R^6 each represent a hydrogen atom;

or

R^4 represents a fluorine or a chlorine atom, or a group selected from :
cyano and difluoromethoxy;
and R^2, R^3, R^5 and R^6 each represent a hydrogen atom;

or

R^2 represents a fluorine or a chlorine atom, or a trifluoromethyl group;
and R^3 represents a fluorine atom;
and R^4, R^5 and R^6 each represent a hydrogen atom;

or

R^2 and R^4 each represent a fluorine atom;
and R^3, R^5 and R^6 each represent a hydrogen atom;

or

R^2 and R^5 each represent a fluorine atom;
and R^3, R^4 and R^6 each represent a hydrogen atom;

or

R^3 and R^4 each represent a fluorine atom;

and R^2, R^5 and R^6 each represent a hydrogen atom;

or

R^3 and R^5 represent, independently of each other, a fluorine or a chlorine atom;

and R^2, R^4 and R^6 each represent a hydrogen atom;

or

R^2, R^3, R^4, R^5 and R^6 each represent a hydrogen atom;

R^7 represents a hydrogen atom;

or

R^2 and R^6 each represent a fluorine atom;

and R^3, R^4 and R^5 each represent a hydrogen atom;

and R^7 represents a methyl group;

or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^1 represents a hydrogen atom or a methyl group;

R^2 represents a fluorine atom or a group selected from :

methyl, ethyl, C_1-C_2-haloalkyl and (trifluoromethyl)sulfanyl;

R^3, R^4, R^5 and R^6 each represent a hydrogen atom; and

R^7 represents a hydrogen atom;

or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^1 represents a hydrogen atom or a methyl group;

R^3 represents a halogen atom or a group selected from :

cyano, methyl, ethyl, C_1-C_2-haloalkyl and (trifluoromethyl)sulfanyl;

R^2, R^4, R^5 and R^6 each represent a hydrogen atom; and

R^7 represents a hydrogen atom;

or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^1 represents a hydrogen atom or a methyl group;

R^4 represents a halogen atom, or a group selected from :

cyano, difluoromethoxy and (trifluoromethyl)sulfanyl;

R^2, R^3, R^5 and R^6 each represent a hydrogen atom; and

R^7 represents a hydrogen atom;

or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^1 represents a hydrogen atom or a methyl group;

R^2 represents a halogen atom or a group selected from :

methyl, ethyl, C_1-C_2-haloalkyl, and (trifluoromethyl)sulfanyl;

R^3 represents a halogen atom or a group selected from :

cyano, methyl, ethyl, C_1-C_2-haloalkyl and (trifluoromethyl)sulfanyl;

R^4, R^5 and R^6 each represent a hydrogen atom; and

R^7 represents a hydrogen atom;

or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^1 represents a hydrogen atom or a methyl group;

R^2 represents a fluorine atom or a group selected from :

methyl, ethyl, C_1-C_2-haloalkyl and (trifluoromethyl)sulfanyl;

R^4 represents a halogen atom or a group selected from :

cyano, difluoromethoxy and (trifluoromethyl)sulfanyl;

R^3, R^5 and R^6 each represent a hydrogen atom; and

R^7 represents a hydrogen atom;

or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^1 represents a hydrogen atom or a methyl group;

R^2 represents a fluorine atom or a group selected from :

methyl, ethyl, C_1-C_2-haloalkyl and (trifluoromethyl)sulfanyl;

R^5 represents a halogen atom or a group selected from :

cyano, methyl, ethyl, C_1-C_2-haloalkyl and (trifluoromethyl)sulfanyl;

R^3, R^4 and R^6 each represent a hydrogen atom; and

R^7 represents a hydrogen atom;

or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^1 represents a hydrogen atom or a methyl group;

R^3 represents a halogenatom or a group selected from :

cyano, methyl, ethyl, C_1-C_2-haloalkyl and (trifluoromethyl)sulfanyl;

R^4 represents a halogen atom, or a group selected from :

cyano, difluoromethoxy and (trifluoromethyl)sulfanyl;

R^2, R^5 and R^6 each represent a hydrogen atom; and

R^7 represents a hydrogen atom;

or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^1 represents a hydrogen atom or a methyl group;

R^3 and R^5 represent, independently of each other, a halogen atom or a group selected from :

cyano, difluoromethyl and (trifluoromethyl)sulfanyl;

R^2, R^4 and R^6 each represent a hydrogen atom; and

R^7 represents a hydrogen atom;

or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^1 represents a hydrogen atom or a methyl group;

R^2, R^3, R^4, R^5 and R^6 each represent a hydrogen atom; and

R^7 represents a hydrogen atom;

or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^1 represents a hydrogen atom or a methyl group;

R^2 and R^6 represent, independently of each other, a fluorine or a chlorine atom;

R^3, R^4 and R^5 each represent a hydrogen atom; and

R^7 represents a methyl group;

or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^1 represents a hydrogen atom or a methyl group.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^1 represents a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^1 represents a methyl group.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^7 represents a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^2 represents a fluorine atom or a group selected from methyl, ethyl, C_1-C_2-haloalkyl and (trifluoromethyl)sulfanyl;

and R^3, R^4, R^5 and R^6 each represent a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^2 represents a fluorine atom or a group selected from methyl, difluoromethyl and trifluoromethyl;

and R^3, R^4, R^5 and R^6 each represent a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^3 represents a halogen atom or a group selected from cyano, methyl, ethyl, C_1-C_2-haloalkyl and (trifluoromethyl)sulfanyl;

and R^2, R^4, R^5 and R^6 each represent a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^3 represents a halogen atom or a group selected from cyano, methyl, ethyl and C_1-C_2-haloalkyl;

and R^2, R^4, R^5 and R^6 each represent a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^3 represents a fluorine or a chlorine atom, or a group selected from cyano, methyl, difluoromethyl and trifluoromethyl;

and R^2, R^4, R^5 and R^6 each represent a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^4 represents a halogen atom, or a group selected from cyano, difluoromethoxy and (trifluoromethyl)sulfanyl;

and R^2, R^3, R^5 and R^6 each represent a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^4 represents a halogen atom, or a group selected from cyano and difluoromethoxy;

and R^2, R^3, R^5 and R^6 each represent a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^2 represents a halogen atom or a group selected from methyl, ethyl, C_1-C_2-haloalkyl, and (trifluoromethyl)sulfanyl;

and R^3 represents a halogen atom or a group selected from cyano, methyl, ethyl, C_1-C_2-haloalkyl and (trifluoromethyl)sulfanyl;

and R^4, R^5 and R^6 each represent a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^2 represents a halogen atom or a group selected from methyl, ethyl and C_1-C_2-haloalkyl;

and R^3 represents a halogen atom or a group selected from cyano, methyl, ethyl and C_1-C_2-haloalkyl;

and R^4, R^5 and R^6 each represent a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^2 represents a fluorine or a chlorine atom, or a group selected from methyl, difluoromethyl and trifluoromethyl;

and R^3 represents a fluorine or a chlorine atom, or a group selected from cyano, methyl, difluoromethyl and trifluoromethyl;

and R^4, R^5 and R^6 each represent a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^2 represents a fluorine or a chlorine atom, or a trifluoromethyl group;

and R^3 represents a fluorine atom;

and R^4, R^5 and R^6 each represent a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^2 represents a fluorine atom or a group selected from methyl, ethyl, C_1-C_2-haloalkyl and (trifluoromethyl)sulfanyl;

and R^4 represents a halogen atom or a group selected from cyano, difluoromethoxy and (trifluoromethyl)sulfanyl;
and R^3, R^5 and R^6 each represent a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :
R^2 represents a fluorine atom or a group selected from methyl, ethyl and C_1-C_2-haloalkyl;
and R^4 represents a halogen atom or a group selected from cyano and difluoromethoxy;
and R^3, R^5 and R^6 each represent a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :
R^2 represents a fluorine atom or a group selected from methyl, difluoromethyl and trifluoromethyl;
and R^4 represents a fluorine or a chlorine atom, or a group selected from cyano and difluoromethoxy;
and R^3, R^5 and R^6 each represent a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :
R^2 and R^4 each represent a fluorine atom;
and R^3, R^5 and R^6 each represent a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :
R^2 represents a fluorine atom or a group selected from methyl, ethyl, C_1-C_2-haloalkyl and (trifluoromethyl)sulfanyl;
and R^5 represents a halogen atom or a group selected from cyano, methyl, ethyl, C_1-C_2-haloalkyl and (trifluoromethyl)sulfanyl;
and R^3, R^4 and R^6 each represent a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^2 represents a fluorine atom or a group selected from methyl, ethyl and C_1-C_2-haloalkyl;
and R^5 represents a halogen atom or a group selected from cyano, methyl, ethyl and C_1-C_2-haloalkyl;
and R^3, R^4 and R^6 each represent a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :
R^2 represents a fluorine atom or a group selected from methyl, difluoromethyl and trifluoromethyl;
and R^5 represents a fluorine or a chlorine atom, or a group selected from cyano, methyl, difluoromethyl and trifluoromethyl;
and R^3, R^4 and R^6 each represent a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :
R^2 and R^5 each represent a fluorine atom;
and R^3, R^4 and R^6 each represent a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :
R^3 represents a halogen atom or a group selected from cyano, methyl, ethyl and C_1-C_2-haloalkyl;
and R^4 represents a halogen atom, or a group selected from cyano and difluoromethoxy;
and R^2, R^5 and R^6 each represent a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :
R^3 represents a fluorine or a chlorine atom, or a group selected from cyano, methyl, difluoromethyl and trifluoromethyl;
and R^4 represents a fluorine or a chlorine atom, or a group selected from cyano and difluoromethoxy;
and R^2, R^5 and R^6 each represent a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^3 and R^4 each represent a fluorine atom;

and R^2, R^5 and R^6 each represent a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^3 and R^5 represent, independently of each other, a halogen atom or a group selected from cyano, difluoromethyl and (trifluoromethyl)sulfanyl;

and R^2, R^4 and R^6 each represent a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^3 and R^5 represent, independently of each other, a halogen atom or a group selected from cyano and difluoromethyl;

and R^2, R^4 and R^6 each represent a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^3 and R^5 represent, independently of each other, a fluorine or a chlorine atom, or a group selected from cyano and difluoromethyl;

and R^2, R^4 and R^6 each represent a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which R^3 and R^5 represent, independently of each other, a fluorine or a chlorine atom;

and R^2, R^4 and R^6 each represent a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^2, R^3, R^4, R^5 and R^6 each represent a hydrogen atom.

In another preferred embodiment, the present invention relates to compounds of general formula **(I)**, *supra*, in which :

R^2 and R^6 represent, independently of each other, a fluorine or a chlorine atom;

and R^3, R^4 and R^5 each represent a hydrogen atom;

and R^7 represents a methyl group.

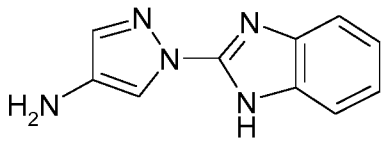
It is to be understood that the present invention relates also to any combination of the preferred embodiments described above.

More particularly still, the present invention covers compounds of general formula **(I)** which are disclosed in the Example section of this text, *infra*.

In accordance with another aspect, the present invention covers methods of preparing compounds of the present invention, said methods comprising the steps as described in the Experimental Section herein.

In accordance with a further aspect, the present invention covers intermediate compounds which are useful for the preparation of the compounds of general formula **(I)**, *supra*.

In accordance with a further aspect, the present invention covers the use of the intermediate compound **(VII)** :



(VII)

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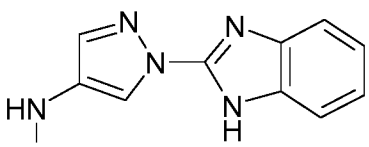
and salts thereof, such as for example salts with hydrochloric acid, for the preparation of a compound of general formula **(I)** as defined *supra*.

In accordance with a further aspect, the present invention covers the use of the intermediate compound **(XI)** :

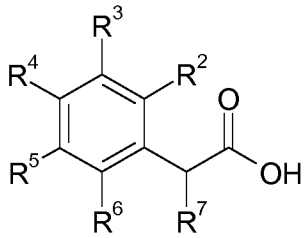


(XI)

,

and salts thereof, such as for example salts with hydrochloric acid, for the preparation of a compound of general formula **(I)** as defined *supra*.

In accordance with a further aspect, the present invention covers the use of the intermediate compounds of general formula **(VIII)** :



(VIII)

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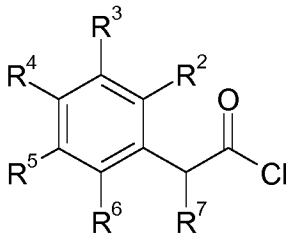
in which R^2, R^3, R^4, R^5, R^6 and R^7 are as defined for the compounds of general formula **(I)** *supra*, for the preparation of a compound of general formula **(I)** as defined *supra*.

In accordance with yet another aspect, the present invention covers the use of the intermediate compounds of general formula **(IX)** :



(IX)

,

in which R^2, R^3, R^4, R^5, R^6 and R^7 are as defined for the compounds of general formula **(I)** *supra*, for the preparation of a compound of general formula **(I)** as defined *supra*.

In accordance with a further aspect, the present invention relates to compounds of general formula **(I)**, as decribed *supra*, or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, for use in the treatment or prophylaxis of a disease.

In accordance with a further aspect, the present invention relates to a pharmaceutical composition comprising a compound of general formula **(I)**, as decribed *supra*, or a

stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, and a pharmaceutically acceptable diluent or carrier.

Particularly, the pharmaceutical combination comprises:

- one or more first active ingredients selected from a compound of general formula **(I)** as decribed *supra*, and
- one or more second active ingredients selected from chemotherapeutic anti-cancer agents (see below).

In accordance with a further aspect, the present invention relates to use of a compound of general formula **(I)**, as described *supra*, or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, for the prophylaxis or treatment of a disease.

In accordance with a further aspect, the present invention relates to use of a compound of general formula **(I)**, as described *supra*, or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, for the preparation of a medicament for the prophylaxis or treatment of a disease.

The disease as mentioned before is in particular a disease of uncontrolled cell growth, proliferation and/or survival, an undesirable cellular immune response, or an undesirable cellular inflammatory response, particularly in which the disease of uncontrolled cell growth, proliferation and/or survival, undesirable cellular immune response, or undesirable cellular inflammatory response is a haematological tumour, a solid tumour and/or metastases thereof, e.g. leukaemias and myelodysplastic syndrome, malignant lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the thorax including non-small cell and small cell lung tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

EXPERIMENTAL SECTION

^{1}H-NMR data are listed in the form of ^{1}H-NMR peaklists. For each signal peak the δ value in ppm is given, followed by the signal intensity, reported in round brackets. The δ value-signal intensity pairs from different peaks are separated by commas. Therefore, a peaklist is described by the general form: δ_1 (intensity$_1$), δ_2 (intensity$_2$), ... , δ_i (intensity$_i$), ... , δ_n (intensity$_n$).

The intensity of a sharp signal correlates with the height (in cm) of the signal in a printed NMR spectrum. When compared with other signals, this data can be correlated to the real ratios of the signal intensities. In the case of broad signals, more than one peak, or the center of the signal along with their relative intensity, compared to the most intense signal displayed in the spectrum, are shown. A ^{1}H-NMR peaklist is similar to a classical ^{1}H-NMR readout, and thus usually contains all the peaks listed in a classical NMR interpretation. Moreover, similar to classical ^{1}H-NMR printouts, peaklists can show solvent signals, signals derived from stereoisomers of target compounds (also the subject of the invention), and/or peaks of impurities. The peaks of stereoisomers, and/or peaks of impurities are typically displayed with a lower intensity compared to the peaks of the target compounds (e.g., with a purity of >90%). Such stereoisomers and/or impurities may be typical for the particular manufacturing process, and therefore their peaks may help to identify the reproduction of our manufacturing process on the basis of "by-product fingerprints". An expert who calculates the peaks of the target compounds by known methods (MestReC, ACD simulation, or by use of empirically evaluated expectation values), can isolate the peaks of target compounds as required, optionally using additional intensity filters. Such an operation would be similar to peak-picking in classical ^{1}H-NMR interpretation. A detailed description of the reporting of NMR data in the form of peaklists can be found in the publication "Citation of NMR Peaklist Data within Patent Applications" (cf. Research Disclosure Database Number 605005, 2014, 01 Aug 2014, or http://www.researchdisclosure.com/searching-disclosures). In the peak picking routine, as described in the Research Disclosure Database Number 605005, the parameter "MinimumHeight" can be adjusted between 1% and 4%. Depending on the chemical structure and/or depending on the concentration of the measured compound it may be reasonable to set the parameter "MinimumHeight" <1%.

Chemical names were generated using the ICS naming tool of ACD labs. In some cases generally accepted names of commercially available reagents were used in place of ICS naming tool generated names.

Table 1: Abbreviations

Abbreviation	**Meaning**
DAD	Diode Array Detector
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
ELSD	Evaporative Light Scattering Detector
ESI	electrospray ionisation
h	hour
HPLC, LC	high performance liquid chromatography
m/z	mass-to-charge ratio (in mass spectrum)
min	minute
MPLC	medium pressure liquid chromatography
MS	mass spectroscopy
NMR	nuclear magnetic resonance
pos	positive
ppm	chemical shift δ in parts per million
R_t	retention time
THF	tetrahydrofuran

Other abbreviations have their meanings customary per se to the skilled person.

The various aspects of the invention described in this application are illustrated by the following examples which are not meant to limit the invention in any way.

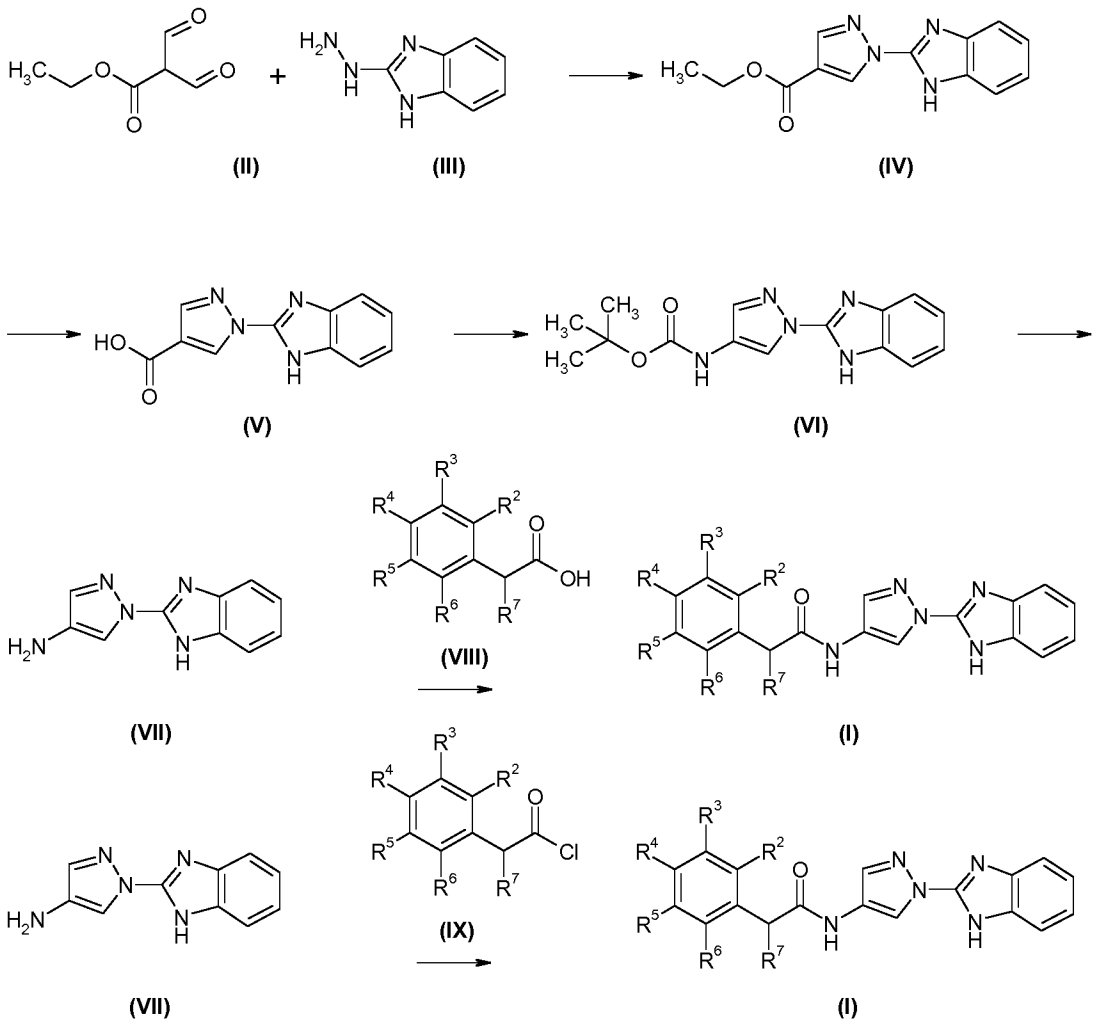
Syntheses of Compounds (Overview)

The following schemes and general procedures illustrate general synthetic routes to the compounds of general formula **(I)** of the invention and are not intended to be limiting. It is obvious to the person skilled in the art that the order of transformations as exemplified in Schemes 1, 2 and 3 can be modified in various ways. The order of transformations exemplified in Schemes 1, 2 and 3 is therefore not intended to be limiting. In addition, interconversion of substituents, for example of residues R^1, R^2, R^3, R^4, R^5, R^6 and R^7 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups,

halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example *T.W. Greene and P.G.M. Wuts*, *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999).

Specific examples are described in the subsequent paragraphs. Further, it is possible that two or more successive steps may be performed without work-up being performed between said steps, e.g. in a "one-pot" reaction, as it is well-known to a person skilled in the art.

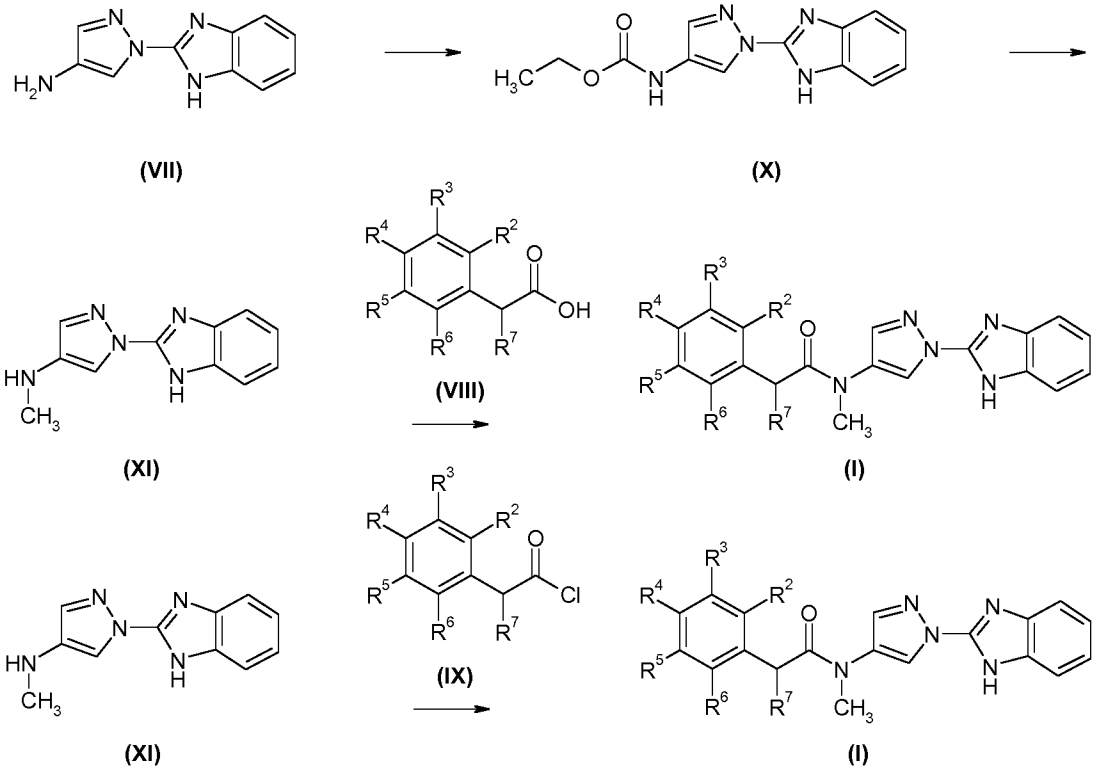
Scheme 1:



Scheme 1: Preparation of compounds of the formula **(I)**, in which R^1 represents a hydrogen atom, starting from 2-hydrazinyl-1H-benzimidazole **(III)**

Scheme 1 outlines the preparation of compounds of the formula **(I)**, in which R^1 represents a hydrogen atom and R^2, R^3, R^4, R^5, R^6 and R^7 are as defined *supra*, starting from 2-hydrazinyl-1H-benzimidazole **(III)**, which can be converted into the ethyl pyrazole-carboxylate **(IV)** by treatment with ethyl 2-formyl-3-oxopropanoate. 2-Hydrazinyl-1H-benzimidazole **(III)** is well known to the person skilled in the art (CAS Registry Number 15108-18-6) and is commercially available. Said ethyl pyrazole-carboxylate **(IV)** can be subsequently converted into pyrazole-carboxylic acid **(V)**, e.g. by hydrolysis with lithium hydroxide or other methods known to the person skilled in the art. Said pyrazole-carboxylic acid **(V)** can be subsequently converted into tert-butyl pyrazol-carbamate **(VI)** via a Curtius rearrangement, e.g. using diphenyl phosphorazidate as reagent. Said tert-butyl pyrazole-carbamate **(VI)** can be subsequently converted into pyrazole-amine **(VII)** or a respective salt thereof, e.g. by hydrolysis with hydrogen chloride or other methods known to the person skilled in the art. Said pyrazole-amine **(VII)** or a respective salt thereof, which is for example a salt with hydrochloric acid, is then elaborated into compounds of the general formula **(I)**. This can be accomplished directly, by reacting the compound **(VII)** or a respective salt thereof, with a carboxylic acid of general formula **(VIII)** in an amide coupling reaction, for example in the presence of a tertiary aliphatic amine, such as N,N-diisopropylethylamine, and propane phosphonic acid anhydride (also known as T3P), in a suitable solvent such as N,N-dimethylformamide. Alternatively other coupling reagents, which are well known to the person skilled in the art, such as for example HATU, can be used. Carboxylic acids of general formula **(VIII)** are well known to the person skilled in the art, and are often commercially available. Alternatively, the amide coupling reaction can be performed by reaction of compound **(VII)** or a respective salt thereof, with an acid chloride of general formula **(IX)**. Methods for the preparation of acid chlorides of general formula **(IX)** from carboxylic acid are well known to the person skilled in the art. Often the acid chloride of general formula **(IX)** is commercially available.

Scheme 2:

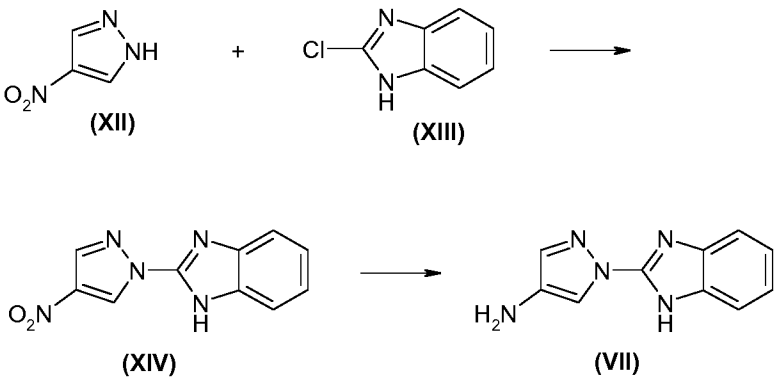


Scheme 2: Preparation of compounds of the formula **(I)**, in which R^1 represents a methyl group, starting from pyrazole-amine **(VII)** or a salt thereof

Scheme 2 outlines the preparation of compounds of the formula **(I)**, in which R^1 is a methyl group and R^2, R^3, R^4, R^5, R^6 and R^7 are as defined *supra*, starting from pyrazole-amine **(VII)** or a respective salt thereof, which can be converted into the ethyl pyrazole-carbamate **(X)** by treatment with ethyl chloroformate. Said ethyl pyrazole-carbamate **(X)** can be subsequently converted into N-methyl-pyrazole-amine **(XI)**, e.g. by reduction with lithium aluminium hydride or other methods known to the person skilled in the art. Said N-methyl-pyrazole-amine **(XI)** or a respective salt thereof, which is for example a salt with hydrochloric acid, is then elaborated into compounds of the general formula **(I)**. This can be accomplished directly by reacting compound **(XI)** or a respective salt thereof, with a carboxylic acid of general formula **(VIII)** in an amide coupling reaction, for example in the presence of a tertiary aliphatic amine, such as N,N-diisopropylethylamine, and propane phosphonic acid anhydride (also known as T3P), in a suitable solvent such as N,N-dimethylformamide. Alternatively other coupling reagents, which are well known to the person skilled in the art, such as for example HATU, can be used. Carboxylic acids of general formula **(VIII)** are well known to the person skilled in the art, and are often commercially available.

Alternatively, the amide coupling reaction can be performed by reaction of compound **(XI)** or a respective salt thereof, with an acid chloride of general formula **(IX)**. Methods for the preparation of acid chlorides of general formula **(IX)** from carboxylic acids are well known to the person skilled in the art. Often the acid chloride of general formula **(IX)** is commercially available.

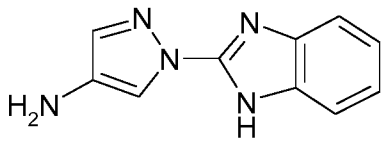
Scheme 3:



Scheme 3: Alternative preparation of compound **(VII)**

Scheme 3 outlines an alternative method for preparation of compound **(VII)**. 4-Nitro-1H-pyrazole **(XII)** (CAS Registry Number 2075-46-9) can be converted into 2-(4-nitro-1H-pyrazol-1-yl)-1H-benzimidazole **(XIV)** by coupling of **(XII)** with 2-chloro-1H-benzimidazole **(XIII)** (CAS Registry Number 4857-06-1) in the presence of a suitable base, such as for example N,N-diisopropylethylamine, in a suitable solvent, such as for example sulfolane.

In accordance with another aspect, the present invention also relates to a method of preparing a compound of general formula **(I)** as defined *supra*, said method comprising the step of allowing a compound of formula **(VII)** :

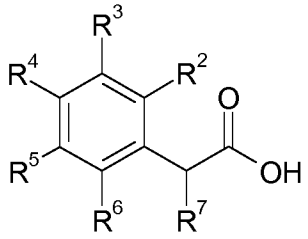


(VII)

,

or a salt thereof, such as for example a salt with hydrochloric acid,

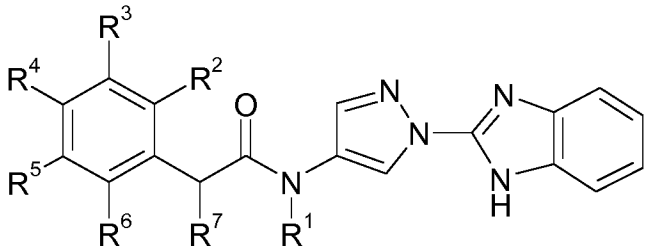
to react with a compound of general formula **(VIII)** :



(VIII)

,

in which R^2, R^3, R^4, R^5, R^6 and R^7 are as defined for the compounds of general formula **(I)** *supra*, in the presence of a tertiary aliphatic amine, such as N,N-diisopropylethylamine, and propane phosphonic acid anhydride, thereby giving a compound of general formula **(I)** :

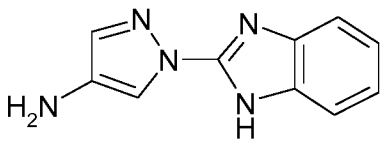


(I)

,

in which R^2, R^3, R^4, R^5, R^6 and R^7 are as defined *supra*., and R^1 represents a hydrogen atom.

In accordance with another aspect, the present invention also relates to a method of preparing a compound of general formula **(I)** as defined *supra*, said method comprising the step of allowing a compound of formula **(VII)** :

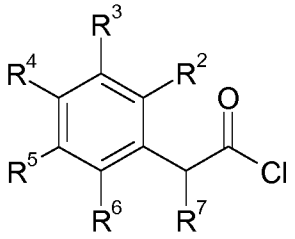


(VII)

,

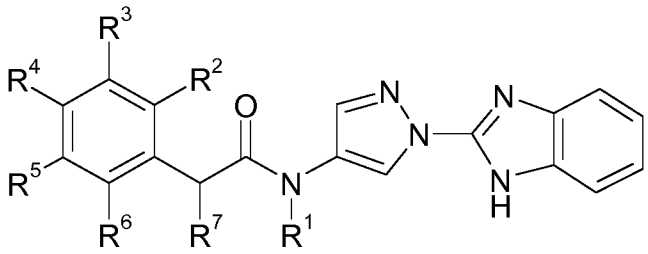
or a salt thereof, such as for example a salt with hydrochloric acid,

to react with a compound of general formula **(IX)** :



(IX) ,

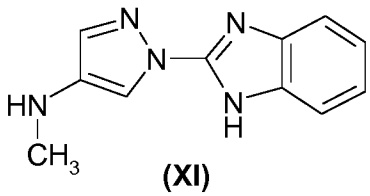
in which R^2, R^3, R^4, R^5, R^6 and R^7 are as defined for the compounds of general formula **(I)** *supra*, thereby giving a compound of general formula **(I)** :



(I) ,

in which R^2, R^3, R^4, R^5, R^6 and R^7 are as *supra*., and R^1 represents a hydrogen atom.

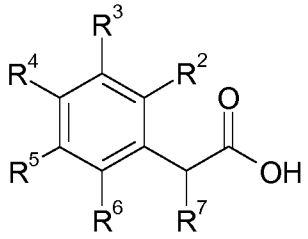
In accordance with another aspect, the present invention also relates to a method of preparing a compound of general formula **(I)** as defined *supra*, said method comprising the step of allowing a compound of general formula **(XI)** :



(XI) ,

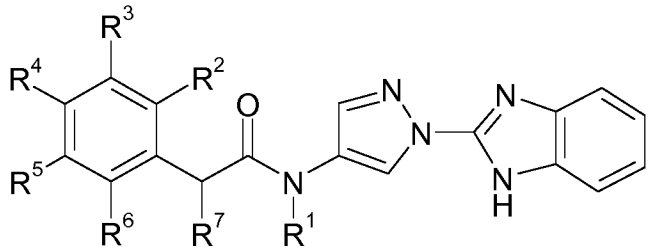
or a salt thereof, such as for example a salt with hydrochloric acid,

to react with a compound of general formula **(VIII)** :



(VIII) ,

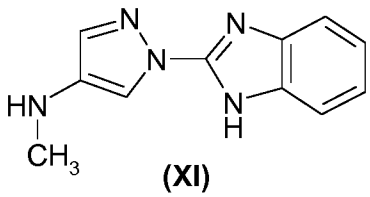
in which R^2, R^3, R^4, R^5 and R^6 are as defined for the compounds of general formula **(I)** *supra*, and R^7 represents a hydrogen atom, in the presence of a tertiary aliphatic amine, such as N,N-diisopropylethylamine, and propane phosphonic acid anhydride, thereby giving a compound of general formula **(I)** :



(I) ,

in which R^2, R^3, R^4, R^5 and R^6 are as *supra*, and R^1 represents a methyl group, and R^7 represents a hydrogen atom.

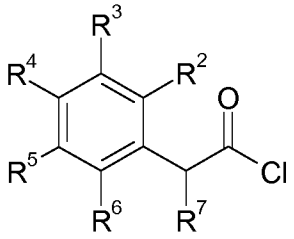
In accordance with another aspect, the present invention also relates to a method of preparing a compound of general formula **(I)** as defined *supra*, said method comprising the step of allowing a compound of general formula **(XI)** :



(XI) ,

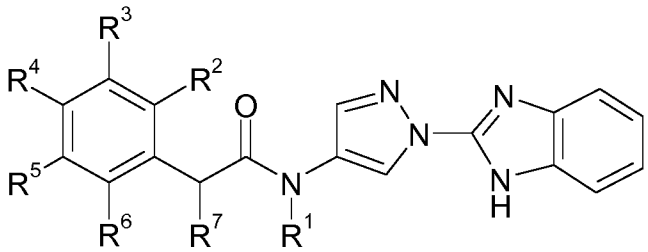
or a salt thereof, such as for example a salt with hydrochloric acid,

to react with a compound of general formula **(IX)** :



(IX) ,

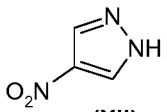
in which R^2, R^3, R^4, R^5 and R^6 are as defined for the compounds of general formula **(I)** *supra*, and R^7 represents a hydrogen atom, thereby giving a compound of general formula **(I)** :



(I) ,

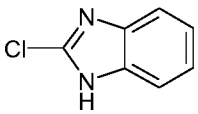
in which R^2, R^3, R^4, R^5 and R^6 are as defined *supra*., and R^1 represents a methyl group, and R^7 represents a hydrogen atom.

In accordance with another aspect, the present invention also relates to a method of preparing a compound of general formula **(I)** as defined *supra*, said method comprising the step of allowing the compound of formula **(XII)** :



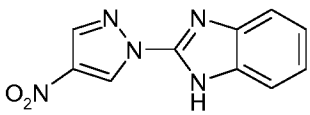
(XII)

to react with the compound of formula **(XIII)** :



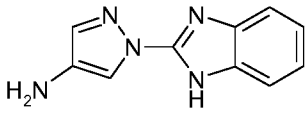
(XIII)

thereby giving the compound of formula **(XIV)** :



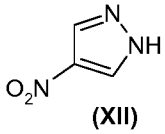
(XIV) .

In accordance with another aspect, the present invention also relates to a method of preparing the compound of formula **(VII)**,



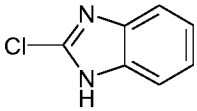
(VII)

said method comprising the step of allowing the compound of formula **(XII)** :



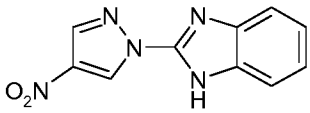
(XII)

to react with the compound of formula **(XIII)** :



(XIII)

thereby giving the compound of formula **(XIV)** :



(XIV)

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General part

All reagents, for which the synthesis is not described in the experimental part, are either commercially available, or are known compounds or may be formed from known compounds by known methods by a person skilled in the art.

The compounds and intermediates produced according to the methods of the invention may require purification. Purification of organic compounds is well known to the person skilled in the art and there may be several ways of purifying the same compound. In some cases, no purification may be necessary. In some cases, the compounds may be purified by crystallization. In some cases, impurities may be digested using a suitable solvent. In some

cases, the compounds may be purified by chromatography, particularly flash column chromatography, using for example prepacked silica gel cartridges, e.g. Biotage SNAP cartidges KP-Sil® or KP-NH® in combination with a Biotage autopurifier system (SP4® or Isolera Four®) and eluents such as gradients of hexane/ethyl acetate or dichloromethane/methanol. In some cases, the compounds may be purified by preparative HPLC using for example a Waters autopurifier equipped with a diode array detector and/or on-line electrospray ionization mass spectrometer in combination with a suitable prepacked reverse phase column and eluents such as gradients of water and acetonitrile which may contain additives such as trifluoroacetic acid, formic acid or aqueous ammonia.

In some cases, purification methods as described above can provide those compounds of the present invention which possess a sufficiently basic or acidic functionality in the form of a salt, such as, in the case of a compound of the present invention which is sufficiently basic, a trifluoroacetate or formate salt for example, or, in the case of a compound of the present invention which is sufficiently acidic, an ammonium salt for example. A salt of this type can either be transformed into its free base or free acid form, respectively, by various methods known to the persion skilled in the art, or be used as salts in subsequent biological assays. It is to be understood that the specific form (e.g. salt, free base etc.) of a compound of the present invention as isolated and as described herein is not necessarily the only form in which said compound can be applied to a biological assay in order to quantify the specific biological activity.

Methods:

Method 1:

Instrument: Waters Autopurificationsystem SQD; column: Waters XBrigde C18 5µ 100x30mm; water + 0.1% vol. formic acid (99%) / acetonitrile gradient; temperature: room temperature; injection: 2500 µL; DAD scan: 210-400 nm.

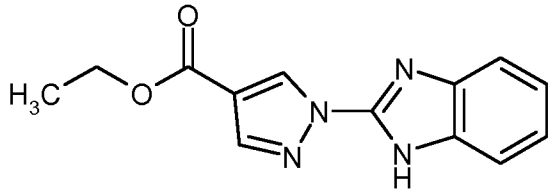
Method 2:

Instrument: Waters Acquity UPLC-MS SQD; column: Acquity UPLC BEH C18 1.7 µ 50x2.1mm; Eluent A: water + 0.1% vol. formic acid (99%), Eluent B: acetonitrile; gradient: 0-1.6 min 1-99% B, 1.6-2.0 min 99% B; rate 0.8 mL/min; temperature: 60 °C; DAD scan: 210-400 nm; ELSD.

Intermediates

Intermediate 1

ethyl 1-(1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylate



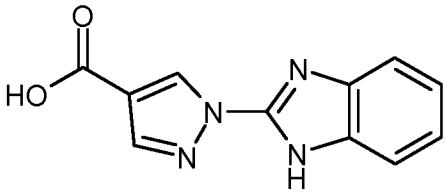
2-Hydrazinyl-1H-benzimidazole (20.0 g, 128 mmol) was provided in a mixture of THF/ethanol (600 mL, 2:1). Ethyl 2-formyl-3-oxopropanoate (16 mL, 130 mmol) was added, and the mixture was stirred at 80 °C for 1.5 h. After cooling down to room temperature, the precipitate was collected by filtration, was washed with hexane and was dried under reduced pressure. 27.2 g (83% of theory) of the title compound were obtained.

LC-MS (method 2): R_t = 1.00 min; MS (ESIpos): m/z = 257 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 1.300 (7.55), 1.318 (16.00), 1.335 (7.71), 2.523 (0.99), 4.266 (2.38), 4.284 (7.27), 4.302 (7.16), 4.319 (2.28), 7.220 (0.90), 7.230 (5.07), 7.238 (4.79), 7.245 (4.99), 7.253 (5.56), 7.264 (1.01), 7.549 (2.98), 7.558 (3.14), 7.565 (3.02), 7.573 (2.54), 8.345 (8.73), 8.973 (9.08).

Intermediate 2

1-(1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid



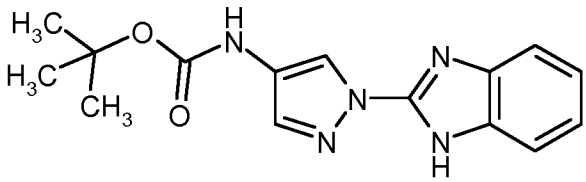
The compound of intermediate 1 (27.2 g, 106 mmol) was provided in 1,4-dioxane (260 mL). Lithium hydroxide (7.63 g, 318 mmol) and water (84 mL) were added, and the mixture was stirred at room temperature over night. The mixture was diluted with water and a 2N aqueous hydrogen chloride solution was added till a pH of 1.5 to 2 was reached. The precipitate was collected by filtration, was washed with water and was dried under reduced pressure. 23.9 g (99% of theory) of the title compound were obtained.

LC-MS (method 2): R_t = 0.76 min; MS (ESIpos): m/z = 229 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 2.523 (0.71), 3.563 (2.26), 7.217 (1.32), 7.228 (6.55), 7.236 (6.60), 7.243 (6.91), 7.251 (7.25), 7.261 (1.54), 7.508 (1.03), 7.614 (1.03), 8.280 (16.00), 8.892 (15.96), 13.319 (0.84).

Intermediate 3

tert-butyl [1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]carbamate



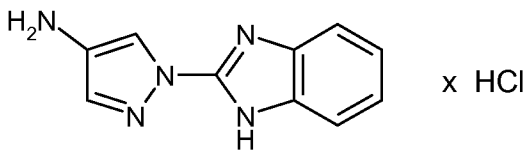
Diphenyl phosphorazidate (45 mL, 210 mmol) was provided in tert-butanol (400 mL). The compound of intermediate 2 (23.9 g, 105 mmol) and triethylamine (58 mL, 420 mmol) were added, and the mixture was stirred at 90 °C for 3 days. Water was added and the mixture was extracted with dichloromethane. The organic phase was dried over sodium sulfate, filtered and concentrated. Purification by MPLC (Biotage Isolera; silica gel; hexane / ethyl acetate gradient) yielded 16.3 g (49% of theory) of the title compound.

LC-MS (method 2): R_t = 1.04 min; MS (ESIpos): m/z = 300 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 1.484 (16.00), 1.986 (0.64), 2.083 (1.33), 7.152 (0.46), 7.162 (2.83), 7.170 (2.54), 7.177 (2.64), 7.185 (2.99), 7.195 (0.52), 7.478 (0.73), 7.824 (1.73), 8.373 (1.68), 9.606 (1.32).

Intermediate 4

1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-amine hydrochloride (1:1)



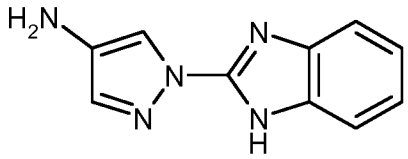
The compound of intermediate 3 (16.3 g, 52.8 mmol) was provided in 1,4-dioxane (1 L). A solution of hydrogen chloride in 1,4-dioxane (145 mL, 4.0 M, 580 mmol) was added, and the mixture was stirred at 65 °C over night. The precipitate was collected by filtration, was washed with 1,4-dioxane and was dried under reduced pressure at 50 °C. 12.4 g (98% of theory) of the title compound were obtained.

LC-MS (method 2): R_t = 0.57 min; MS (ESIpos): m/z = 200 $[M+H–HCl]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 2.523 (0.60), 3.559 (8.34), 7.235 (1.21), 7.239 (1.61), 7.247 (11.08), 7.255 (9.70), 7.262 (9.44), 7.270 (12.32), 7.279 (1.72), 7.282 (1.35), 7.544 (1.37), 7.547 (1.78), 7.556 (12.22), 7.564 (10.15), 7.571 (10.68), 7.579 (10.98), 7.587 (1.32), 7.591 (1.00), 8.099 (14.31), 8.777 (16.00).

Intermediate 5

1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-amine



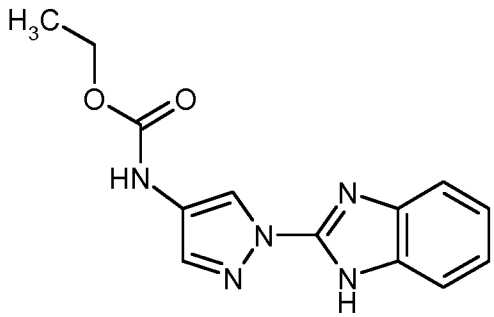
The compound of intermediate 4 (500 mg, 2.12 mmol) was triturated with a mixture of dichloromethane/isopropanol (150 mL, 4:1) and a saturated aqueous sodium bicarbonate solution (70 mL), and the mixture was stirred at room temperature for 30 min. The phases were separated and the organic phase was dried over sodium sulfate, filtered and concentrated. 255 mg (57% of theory) of the title compound were obtained.

LC-MS (method 2): R_t = 0.57 min; MS (ESIpos): m/z = 200 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 1.026 (11.34), 1.035 (1.02), 1.042 (10.96), 1.052 (1.27), 1.070 (0.65), 1.243 (0.47), 1.484 (0.52), 2.322 (0.43), 2.327 (0.62), 2.331 (0.45), 2.523 (1.72), 2.665 (0.44), 2.669 (0.63), 2.673 (0.46), 3.644 (0.41), 3.775 (0.40), 4.348 (1.24), 4.358 (1.27), 4.443 (12.40), 7.112 (1.75), 7.122 (11.63), 7.130 (10.82), 7.137 (11.62), 7.145 (13.27), 7.155 (2.46), 7.372 (0.87), 7.389 (1.00), 7.405 (0.90), 7.425 (0.81), 7.431 (0.96), 7.443 (14.67), 7.445 (16.00), 7.488 (1.06), 7.514 (0.85), 7.728 (13.81), 7.730 (13.92), 12.762 (2.38).

Intermediate 6

ethyl [1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]carbamate



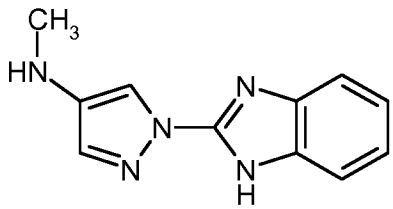
The compound of intermediate 5 (250 mg, 1.25 mmol) was provided in dichloromethane (5 mL) under an argon atmosphere. Potassium carbonate (347 mg, 2.51 mmol), water (5 mL), tetra-n-butylammonium iodide (2.32 mg, 6.27 µmol) and ethyl chloroformate (120 µL, 1.3 mmol) were added at 0 °C, and the mixture was stirred at room temperature for 4 h. Ethyl chloroformate (60 µL, 0.63 mmol) was added, and the mixture was stirred at room temperature for 2 h. The phases were separated and the aqueous phase was extracted twice with a mixture of dichloromethane/isopropanol (4:1). The combined organic phases were dried over sodium sulfate, filtered and concentrated. Purification by HPLC (chromatorex C18, mobile phase: acetonitrile/water + 0.1% formic acid) yielded 152 mg (45% of theory) of the title compound.

LC-MS (method 2): R_t = 0.88 min; MS (ESIpos): m/z = 272 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 1.232 (8.06), 1.250 (16.00), 1.268 (8.39), 2.323 (0.76), 2.327 (1.05), 2.331 (0.76), 2.523 (2.83), 2.665 (0.79), 2.669 (1.07), 2.674 (0.72), 3.645 (0.46), 4.129 (2.53), 4.146 (7.25), 4.164 (7.28), 4.182 (2.66), 7.158 (1.79), 7.168 (10.20), 7.176 (9.90), 7.183 (10.24), 7.191 (11.35), 7.202 (2.19), 7.423 (1.66), 7.559 (1.68), 7.826 (8.17), 8.404 (7.37), 9.847 (6.03), 13.048 (4.69).

Intermediate 7

1-(1H-benzimidazol-2-yl)-N-methyl-1H-pyrazol-4-amine



Lithium aluminium hydride (31.5 mg, 829 µmol) was provided in THF (3 mL). A solution of the compound of intermediate 6 (150 mg, 553 µmol) in THF (1.5 mL) was added dropwise at 0 °C, and the mixture was stirred under reflux for 2 h. Lithium aluminium hydride (15.7 mg, 415 µmol) in THF (1 mL) was added, and the mixture was stirred under reflux for 2 h. Sodium sulfate decahydrate (340 mg, 1.06 mmol) was added, and the mixture was stirred at room temperature for 1 h. After filtration, concentration of the remaining solution yielded 113 mg (77% of theory) of the title compound.

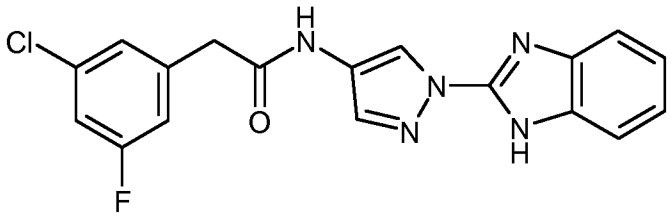
LC-MS (method 2): R_t = 0.65 min; MS (ESIpos): m/z = 214 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 1.227 (2.06), 1.234 (1.44), 1.245 (3.43), 1.263 (1.78), 1.353 (4.83), 1.408 (1.01), 1.417 (1.36), 1.424 (3.84), 1.431 (1.44), 1.439 (1.11), 1.559 (0.64), 1.574 (0.41), 1.740 (4.46), 1.747 (4.21), 1.752 (2.81), 1.756 (13.27), 1.766 (4.01), 1.773 (4.15), 1.778 (0.89), 2.084 (1.45), 2.181 (0.64), 2.322 (0.80), 2.327 (1.16), 2.331 (0.85), 2.523 (2.87), 2.655 (13.58), 2.667 (13.79), 2.719 (0.64), 2.729 (4.31), 2.805 (0.47), 2.821 (2.52), 2.888 (5.33), 3.095 (0.76), 3.182 (0.50), 3.282 (0.76), 3.331 (1.78), 3.345 (1.34), 3.362 (1.88), 3.372 (1.94), 3.378 (3.55), 3.385 (1.88), 3.388 (1.75), 3.394 (1.63), 3.430 (1.12), 3.446 (1.69), 3.462 (0.93), 3.571 (0.45), 3.582 (4.56), 3.592 (3.90), 3.599 (10.40), 3.605 (3.67), 3.609 (2.79), 3.613 (2.85), 3.615 (4.54), 3.619 (0.91), 4.114 (0.50), 4.132 (1.42), 4.150 (1.45), 4.167 (0.56), 4.442 (0.50), 4.879 (1.78), 4.892 (1.80), 6.869 (0.45), 6.945 (1.16), 6.969 (1.24), 7.043 (0.72), 7.050 (0.72), 7.057 (1.57), 7.068 (9.56), 7.076 (8.69), 7.083 (8.57), 7.091 (10.34), 7.101 (1.45), 7.168 (0.50), 7.177 (0.47), 7.183 (0.45), 7.192 (0.54), 7.349 (0.76), 7.360 (2.09), 7.369 (1.90), 7.375 (1.84), 7.383 (1.96), 7.390 (1.63), 7.393 (1.94), 7.401 (12.06), 7.410 (9.89), 7.417 (9.52), 7.424 (10.03), 7.433 (1.40), 7.436 (1.14), 7.453 (13.50), 7.454 (13.81), 7.673 (1.18), 7.731 (0.41), 7.733 (0.45), 7.752 (14.91), 7.755 (16.00), 7.762 (0.97), 7.772 (0.50), 7.951 (0.68), 7.995 (0.78), 8.203 (0.66), 8.247 (0.66), 8.367 (1.42), 8.628 (0.68), 9.681 (0.78).

Examples:

Example 1

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(3-chloro-5-fluorophenyl)acetamide



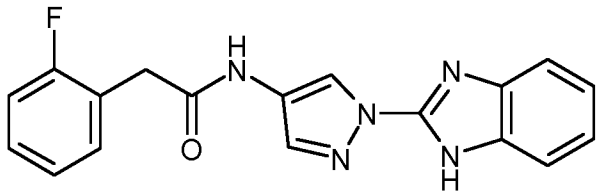
The compound of intermediate 4 (4.00 g, 17.0 mmol) was provided in DMF (70 mL). N,N-diisopropylethylamine (12 mL, 68 mmol), (3-chloro-5-fluorophenyl)acetic acid (3.52 g, 18.7 mmol) and propane phosphonic acid anhydride (T3P, 12 mL, 50% in DMF, 20 mmol) were added, and the mixture was stirred at room temperature for 30 min. After concentration, the remaining material was dissolved in ethanol (50 mL), then water (400 mL) was added and the mixture was stirred for 30 min. The precipitate was collected by filtration, was washed with a mixture of ethanol/water (1:1) and was dried under reduced pressure. Purification by MPLC (Biotage Isolera; silica gel; hexane / ethyl acetate gradient) yielded 4.66 g (74% of theory) of the title compound.

LC-MS (method 2): R_t = 1.11 min; MS (ESIpos): m/z = 370 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 1.172 (0.58), 1.904 (0.42), 1.986 (0.97), 2.523 (1.59), 3.742 (16.00), 7.160 (1.07), 7.170 (6.55), 7.178 (5.99), 7.186 (7.71), 7.193 (9.50), 7.203 (1.84), 7.210 (1.96), 7.215 (2.50), 7.220 (2.12), 7.287 (3.06), 7.293 (5.86), 7.296 (3.80), 7.326 (2.00), 7.332 (2.90), 7.337 (1.71), 7.348 (2.03), 7.353 (2.92), 7.359 (1.72), 7.500 (1.43), 7.950 (10.91), 8.646 (10.87), 10.598 (6.73), 13.052 (0.83).

Example 2

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(2-fluorophenyl)acetamide



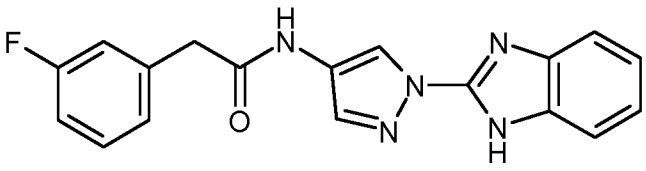
(2-Fluorophenyl)acetic acid (54.5 mg, 354 µmol) was provided in DMF (1.5 mL). N,N-diisopropylethylamine (250 µL, 1.4 mmol), the compound of intermediate 4 (100 mg, 424 µmol) and propane phosphonic acid anhydride (T3P, 250 µL, 50% in DMF, 420 µmol) were added, and the mixture was stirred at room temperature over night. After filtration, purification by HPLC (method 1) yielded 78.6 mg (64% of theory) of the title compound.

LC-MS (method 2): R_t = 0.98 min; MS (ESIpos): m/z = 336 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 2.083 (16.00), 2.479 (0.45), 2.523 (1.61), 3.747 (7.27), 3.750 (7.41), 7.155 (0.75), 7.165 (5.24), 7.173 (5.16), 7.180 (4.73), 7.188 (5.95), 7.194 (2.55), 7.201 (2.33), 7.204 (1.70), 7.216 (1.70), 7.219 (1.21), 7.305 (0.67), 7.310 (0.84), 7.319 (0.82), 7.323 (1.43), 7.329 (1.16), 7.337 (0.83), 7.344 (1.23), 7.349 (0.56), 7.358 (0.50), 7.362 (0.50), 7.390 (1.14), 7.394 (1.05), 7.409 (1.97), 7.414 (1.82), 7.428 (0.99), 7.433 (0.89), 7.489 (1.46), 7.944 (6.73), 8.634 (7.18), 10.611 (4.15).

Example 3

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(3-fluorophenyl)acetamide



The compound of intermediate 4 (4.00 g, 17.0 mmol) was provided in DMF (70 mL). N,N-diisopropylethylamine (12 mL, 68 mmol), (3-fluorophenyl)acetic acid (2.88 g, 18.7 mmol) and propane phosphonic acid anhydride (T3P, 12 mL, 50% in DMF, 20 mmol) were added, and the mixture was stirred at room temperature for 30 min. After concentration, the remaining material was dissolved in ethanol (50 mL), then water (400 mL) was added and the mixture was stirred for 30 min. The precipitate was collected by filtration, was washed with a mixture of ethanol/water (1:1) and was dried under reduced pressure. The remaining material was

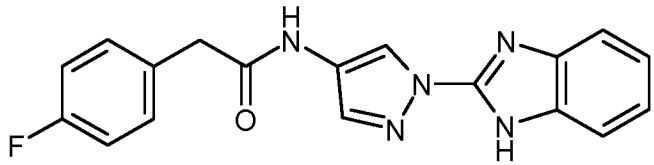
triturated with a mixture of hexane/ethanol (60 mL, 5:1) and stirred for 15 min. The precipitate was collected by filtration, was washed with hexane and was dried under reduced pressure. Purification by MPLC (Biotage Isolera; silica gel; hexane / ethyl acetate gradient) yielded 3.00 g (52% of theory) of the title compound.

LC-MS (method 2): R_t = 1.02 min; MS (ESIpos): m/z = 336 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 2.327 (0.53), 2.331 (0.41), 2.523 (1.63), 2.669 (0.56), 2.673 (0.43), 3.707 (16.00), 7.071 (0.83), 7.076 (1.16), 7.080 (1.12), 7.094 (1.99), 7.101 (2.32), 7.117 (1.19), 7.121 (1.23), 7.124 (1.30), 7.157 (1.38), 7.167 (10.95), 7.176 (6.97), 7.183 (8.03), 7.190 (10.47), 7.200 (2.59), 7.354 (1.30), 7.371 (2.35), 7.375 (2.97), 7.391 (2.76), 7.395 (1.81), 7.410 (1.32), 7.497 (1.97), 7.942 (11.10), 8.648 (10.76), 10.575 (6.39), 13.043 (0.88).

Example 4

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(4-fluorophenyl)acetamide



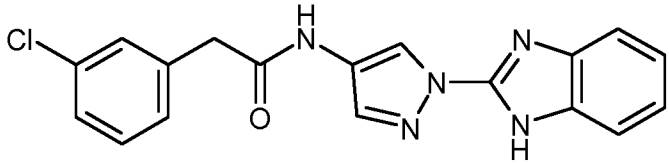
(4-Fluorophenyl)acetic acid (54.5 mg, 354 µmol) was provided in DMF (1.5 mL). N,N-diisopropylethylamine (250 µL, 1.4 mmol), the compound of intermediate 4 (100 mg, 424 µmol) and propane phosphonic acid anhydride (T3P, 250 µL, 50% in DMF, 420 µmol) were added, and the mixture was stirred at room temperature over night. After filtration, purification by HPLC (method 1) yielded 81.2 mg (68% of theory) of the title compound.

LC-MS (method 2): R_t = 1.00 min; MS (ESIpos): m/z = 336 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 1.898 (0.41), 2.083 (3.00), 2.322 (0.51), 2.327 (0.76), 2.331 (0.55), 2.523 (4.70), 2.539 (2.19), 2.544 (1.94), 2.665 (0.60), 2.669 (0.82), 2.673 (0.58), 3.664 (15.60), 7.135 (0.55), 7.143 (5.26), 7.148 (1.89), 7.156 (1.98), 7.159 (2.88), 7.165 (16.00), 7.174 (7.89), 7.181 (9.24), 7.188 (11.24), 7.200 (2.01), 7.344 (0.70), 7.352 (5.32), 7.358 (2.39), 7.366 (5.97), 7.374 (5.23), 7.382 (2.13), 7.388 (4.56), 7.396 (0.76), 7.490 (1.96), 7.935 (11.06), 7.945 (0.53), 8.634 (0.42), 8.643 (11.65), 10.564 (6.91), 13.041 (1.18).

Example 5

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(3-chlorophenyl)acetamide



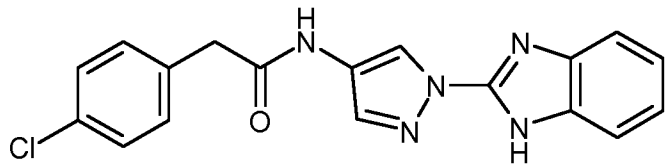
(3-Chlorophenyl)acetic acid (60.3 mg, 354 µmol) was provided in DMF (1.5 mL). N,N-diisopropylethylamine (250 µL, 1.4 mmol), the compound of intermediate 4 (100 mg, 424 µmol) and propane phosphonic acid anhydride (T3P, 250 µL, 50% in DMF, 420 µmol) were added, and the mixture was stirred at room temperature over night. After filtration, purification by HPLC (method 1) yielded 119 mg (96% of theory) of the title compound.

LC-MS (method 2): R_t = 1.07 min; MS (ESIpos): m/z = 352 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 1.902 (0.50), 2.083 (2.35), 2.327 (0.55), 2.523 (3.34), 2.546 (1.33), 2.665 (0.41), 2.669 (0.58), 2.673 (0.41), 3.701 (16.00), 7.158 (1.20), 7.169 (7.37), 7.176 (6.41), 7.184 (6.74), 7.191 (8.29), 7.202 (1.68), 7.289 (1.56), 7.293 (2.83), 7.297 (1.77), 7.306 (2.31), 7.311 (4.68), 7.315 (3.14), 7.320 (1.37), 7.324 (2.10), 7.329 (1.70), 7.339 (3.81), 7.344 (6.22), 7.349 (3.22), 7.358 (6.41), 7.376 (5.00), 7.396 (1.92), 7.416 (3.64), 7.421 (6.36), 7.426 (3.54), 7.495 (1.67), 7.945 (11.04), 8.647 (11.84), 10.601 (6.42), 13.022 (0.84).

Example 6

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(4-chlorophenyl)acetamide



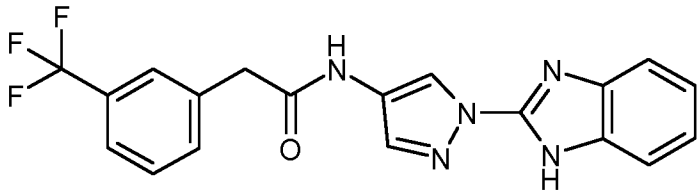
(4-Chlorophenyl)acetic acid (60.3 mg, 354 µmol) was provided in DMF (1.5 mL). N,N-diisopropylethylamine (250 µL, 1.4 mmol), the compound of intermediate 4 (100 mg, 424 µmol) and propane phosphonic acid anhydride (T3P, 250 µL, 50% in DMF, 420 µmol) were added, and the mixture was stirred at room temperature over night. After filtration, purification by HPLC (method 1) yielded 111 mg (88% of theory) of the title compound.

LC-MS (method 2): R_t = 1.07 min; MS (ESIpos): m/z = 352 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 2.083 (6.93), 2.327 (0.60), 2.332 (0.45), 2.475 (0.85), 2.480 (1.25), 2.523 (2.12), 2.665 (0.43), 2.669 (0.60), 2.673 (0.44), 3.677 (14.61), 7.157 (1.05), 7.167 (6.45), 7.176 (6.17), 7.183 (6.41), 7.191 (7.43), 7.201 (1.50), 7.348 (4.71), 7.354 (2.06), 7.363 (2.75), 7.369 (13.21), 7.388 (2.82), 7.393 (16.00), 7.399 (3.49), 7.409 (2.32), 7.414 (5.48), 7.420 (1.00), 7.495 (1.36), 7.936 (10.03), 7.946 (0.49), 8.644 (10.83), 10.587 (5.58), 13.002 (0.60).

Example 7

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-[3-(trifluoromethyl)phenyl]acetamide



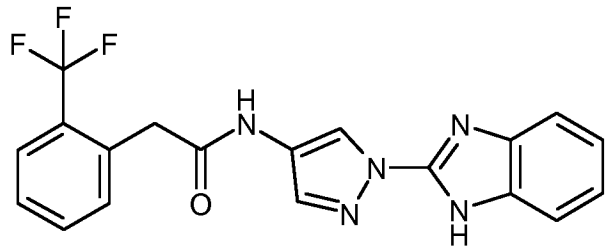
[3-(Trifluoromethyl)phenyl]acetic acid (72.2 mg, 354 µmol) was provided in DMF (1.5 mL). N,N-diisopropylethylamine (250 µL, 1.4 mmol), the compound of intermediate 4 (100 mg, 424 µmol) and propane phosphonic acid anhydride (T3P, 250 µL, 50% in DMF, 420 µmol) were added, and the mixture was stirred at room temperature over night. After filtration, purification by HPLC (method 1) yielded 107 mg (79% of theory) of the title compound.

LC-MS (method 2): R_t = 1.14 min; MS (ESIpos): m/z = 386 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 2.083 (6.32), 2.322 (0.49), 2.327 (0.68), 2.332 (0.52), 2.523 (2.51), 2.535 (0.58), 2.664 (0.48), 2.669 (0.66), 2.673 (0.50), 3.814 (16.00), 7.157 (1.13), 7.167 (6.71), 7.175 (6.23), 7.182 (6.51), 7.190 (7.64), 7.200 (1.49), 7.495 (1.89), 7.566 (1.37), 7.585 (3.20), 7.603 (4.26), 7.630 (4.28), 7.635 (6.24), 7.641 (4.48), 7.651 (2.67), 7.658 (2.74), 7.662 (1.61), 7.715 (5.54), 7.951 (11.51), 8.646 (11.99), 10.649 (7.02), 13.043 (0.62).

Example 8

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-[2-(trifluoromethyl)phenyl]acetamide



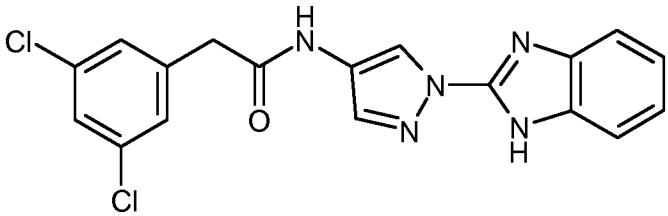
[2-(Trifluoromethyl)phenyl]acetic acid (72.2 mg, 354 µmol) was provided in DMF (1.5 mL). N,N-diisopropylethylamine (250 µL, 1.4 mmol), the compound of intermediate 4 (100 mg, 424 µmol) and propane phosphonic acid anhydride (T3P, 250 µL, 50% in DMF, 420 µmol) were added, and the mixture was stirred at room temperature over night. After filtration, purification by HPLC (method 1) yielded 98.0 mg (68% of theory) of the title compound.

LC-MS (method 2): R_t = 1.10 min; MS (ESIpos): m/z = 386 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 1.904 (0.51), 2.083 (8.56), 2.322 (0.48), 2.327 (0.69), 2.331 (0.51), 2.523 (3.45), 2.664 (0.50), 2.669 (0.69), 2.673 (0.51), 3.933 (12.52), 3.935 (13.23), 3.937 (12.55), 7.157 (1.62), 7.167 (9.57), 7.175 (8.73), 7.182 (9.10), 7.190 (10.87), 7.200 (2.19), 7.488 (3.93), 7.507 (6.45), 7.526 (4.15), 7.549 (4.62), 7.568 (5.91), 7.655 (3.24), 7.674 (4.59), 7.693 (1.86), 7.718 (5.20), 7.721 (4.97), 7.738 (4.43), 7.741 (4.16), 7.947 (15.57), 8.618 (16.00), 10.607 (9.72), 13.009 (0.93).

Example 9

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(3,5-dichlorophenyl)acetamide



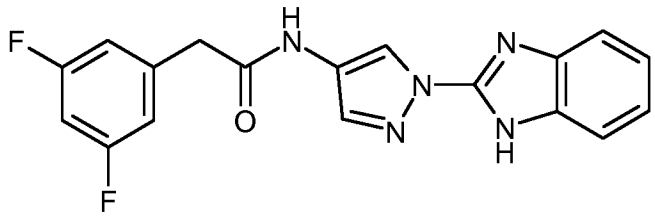
(3,5-Dichlorophenyl)acetic acid (72.5 mg, 354 µmol) was provided in DMF (1.5 mL). N,N-diisopropylethylamine (250 µL, 1.4 mmol), the compound of intermediate 4 (100 mg, 424 µmol) and propane phosphonic acid anhydride (T3P, 250 µL, 50% in DMF, 420 µmol) were added, and the mixture was stirred at room temperature over night. After filtration, purification by HPLC (method 1) yielded 105 mg (76% of theory) of the title compound.

LC-MS (method 2): R_t = 1.20 min; MS (ESIpos): m/z = 386 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 2.327 (0.49), 2.523 (2.01), 2.669 (0.48), 3.739 (13.92), 5.759 (1.65), 7.159 (1.06), 7.169 (7.10), 7.176 (6.42), 7.183 (6.70), 7.192 (8.15), 7.202 (1.58), 7.414 (14.71), 7.419 (16.00), 7.496 (1.94), 7.523 (5.40), 7.528 (8.86), 7.533 (4.20), 7.951 (10.11), 8.644 (10.83), 10.613 (6.27), 13.059 (0.61).

Example 10

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(3,5-difluorophenyl)acetamide



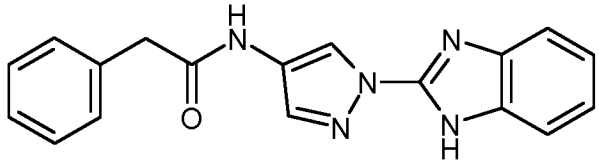
(3,5-Difluorophenyl)acetic acid (60.9 mg, 354 µmol) was provided in DMF (1.5 mL). N,N-diisopropylethylamine (250 µL, 1.4 mmol), the compound of intermediate 4 (100 mg, 424 µmol) and propane phosphonic acid anhydride (T3P, 250 µL, 50% in DMF, 420 µmol) were added, and the mixture was stirred at room temperature over night. After filtration, purification by HPLC (method 1) yielded 75.0 mg (59% of theory) of the title compound.

LC-MS (method 2): R_t = 1.06 min; MS (ESIpos): m/z = 354 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 1.908 (0.52), 2.075 (0.48), 2.083 (0.91), 2.323 (0.48), 2.327 (0.70), 2.332 (0.50), 2.523 (3.56), 2.540 (0.87), 2.665 (0.56), 2.669 (0.78), 2.674 (0.56), 3.741 (16.00), 7.050 (0.60), 7.056 (1.32), 7.066 (5.37), 7.072 (7.93), 7.088 (7.28), 7.094 (6.54), 7.104 (1.57), 7.109 (0.98), 7.117 (1.96), 7.122 (2.97), 7.128 (1.63), 7.140 (3.67), 7.146 (5.92), 7.152 (3.13), 7.164 (2.77), 7.170 (9.82), 7.179 (7.04), 7.186 (7.23), 7.193 (8.80), 7.195 (7.78), 7.206 (1.57), 7.416 (2.66), 7.428 (2.82), 7.435 (2.55), 7.439 (2.38), 7.561 (2.83), 7.572 (2.98), 7.584 (2.62), 7.951 (9.31), 8.651 (14.94), 10.604 (5.49), 13.063 (1.88).

Example 11

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-phenylacetamide



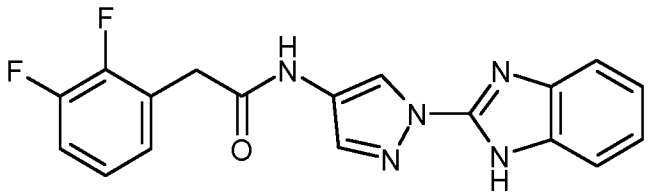
Phenylacetic acid (48.1 mg, 354 µmol) was provided in DMF (1.5 mL). N,N-diisopropylethylamine (250 µL, 1.4 mmol), the compound of intermediate 4 (100 mg, 424 µmol) and propane phosphonic acid anhydride (T3P, 250 µL, 50% in DMF, 420 µmol) were added, and the mixture was stirred at room temperature for 2 h. After filtration, purification by HPLC (method 1) yielded 75.0 mg (65% of theory) of the title compound.

LC-MS (method 2): R_t = 0.99 min; MS (ESIpos): m/z = 318 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 2.083 (12.12), 2.326 (0.41), 2.522 (2.09), 2.668 (0.42), 3.661 (11.47), 7.156 (0.70), 7.166 (4.39), 7.174 (3.77), 7.181 (3.99), 7.189 (4.99), 7.199 (0.98), 7.234 (0.41), 7.242 (0.62), 7.245 (1.06), 7.252 (0.68), 7.256 (1.96), 7.264 (0.96), 7.267 (1.70), 7.270 (1.04), 7.278 (1.21), 7.312 (0.53), 7.315 (0.47), 7.319 (0.40), 7.324 (0.59), 7.334 (13.03), 7.345 (16.00), 7.356 (0.69), 7.495 (0.90), 7.936 (6.43), 8.648 (6.75), 10.577 (3.88).

Example 12

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(2,3-difluorophenyl)acetamide



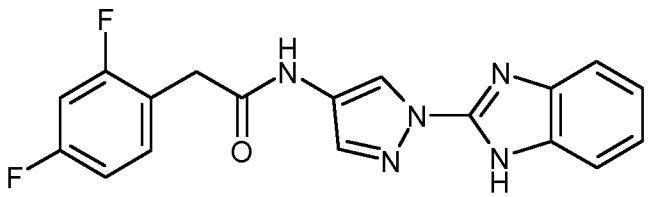
(2,3-Difluorophenyl)acetic acid (60.9 mg, 354 µmol) was provided in DMF (1.5 mL). N,N-diisopropylethylamine (250 µL, 1.4 mmol), the compound of intermediate 4 (100 mg, 424 µmol) and propane phosphonic acid anhydride (T3P, 250 µL, 50% in DMF, 420 µmol) were added, and the mixture was stirred at room temperature for 2 h. After filtration, purification by HPLC (method 1) yielded 74.0 mg (57% of theory) of the title compound.

LC-MS (method 2): R_t = 1.03 min; MS (ESIpos): m/z = 354 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 1.889 (0.57), 2.084 (12.06), 2.318 (0.50), 2.322 (1.04), 2.327 (1.41), 2.331 (1.07), 2.337 (0.52), 2.523 (5.87), 2.539 (1.95), 2.659 (0.54), 2.664 (1.07), 2.669 (1.47), 2.673 (1.11), 2.678 (0.52), 3.820 (14.73), 3.821 (16.00), 3.823 (14.89), 7.153 (1.47), 7.164 (8.02), 7.172 (7.71), 7.179 (8.57), 7.187 (10.79), 7.197 (4.33), 7.200 (2.97), 7.207 (2.95), 7.217 (5.76), 7.222 (4.17), 7.230 (2.38), 7.235 (3.56), 7.253 (1.25), 7.322 (1.11), 7.327 (1.13), 7.341 (2.02), 7.347 (2.36), 7.356 (1.38), 7.362 (1.38), 7.367 (2.54), 7.374 (1.99), 7.388 (1.07), 7.393 (0.97), 7.491 (3.26), 7.947 (13.46), 8.631 (13.67), 10.646 (8.73), 13.058 (0.95).

Example 13

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(2,4-difluorophenyl)acetamide



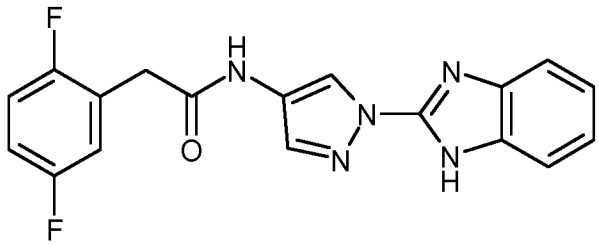
(2,4-Difluorophenyl)acetic acid (60.9 mg, 354 µmol) was provided in DMF (1.5 mL). N,N-diisopropylethylamine (250 µL, 1.4 mmol), the compound of intermediate 4 (100 mg, 424 µmol) and propane phosphonic acid anhydride (T3P, 250 µL, 50% in DMF, 420 µmol) were added, and the mixture was stirred at room temperature for 2 h. After filtration, purification by HPLC (method 1) yielded 88.0 mg (69% of theory) of the title compound.

LC-MS (method 2): R_t = 1.03 min; MS (ESIpos): m/z = 354 $[M+H]^+$

^{1}H-NMR (500 MHz, DMSO-d_6) δ [ppm]: 2.083 (2.29), 2.357 (0.56), 2.361 (0.78), 2.365 (0.59), 2.518 (2.36), 2.522 (1.84), 2.631 (0.63), 2.635 (0.82), 2.639 (0.59), 3.737 (16.00), 7.061 (1.50), 7.066 (1.68), 7.068 (1.54), 7.078 (3.13), 7.080 (3.13), 7.083 (3.42), 7.085 (3.13), 7.096 (1.66), 7.097 (1.54), 7.100 (1.79), 7.102 (1.62), 7.163 (1.41), 7.171 (8.76), 7.177 (8.14), 7.183 (8.30), 7.189 (9.60), 7.197 (1.72), 7.218 (2.16), 7.223 (2.12), 7.238 (3.16), 7.243 (2.99), 7.257 (2.14), 7.263 (2.05), 7.436 (2.10), 7.450 (2.68), 7.454 (4.02), 7.467 (4.39), 7.471 (2.99), 7.484 (2.87), 7.503 (1.33), 7.945 (14.98), 8.629 (15.45), 10.600 (8.69).

Example 14

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(2,5-difluorophenyl)acetamide



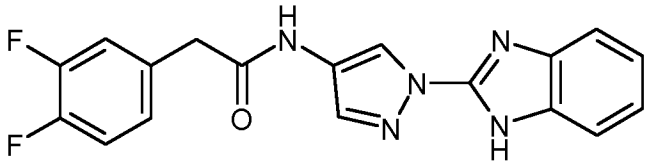
(2,5-Difluorophenyl)acetic acid (60.9 mg, 354 µmol) was provided in DMF (1.5 mL). N,N-diisopropylethylamine (250 µL, 1.4 mmol), the compound of intermediate 4 (100 mg, 424 µmol) and propane phosphonic acid anhydride (T3P, 250 µL, 50% in DMF, 420 µmol) were added, and the mixture was stirred at room temperature for 2 h. After filtration, purification by HPLC (1. method 1, 2. column: chromatorex C18, mobile phase: acetonitrile/water + 0.1% formic acid) yielded 63.0 mg (50% of theory) of the title compound.

LC-MS (method 2): R_t = 1.03 min; MS (ESIpos): m/z = 354 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 2.083 (2.57), 2.523 (1.09), 2.539 (16.00), 3.764 (5.27), 3.767 (5.31), 7.157 (0.90), 7.167 (3.39), 7.175 (3.22), 7.182 (3.28), 7.190 (3.99), 7.200 (1.32), 7.208 (0.60), 7.229 (0.91), 7.241 (0.96), 7.252 (1.40), 7.264 (1.40), 7.275 (1.19), 7.286 (0.96), 7.291 (0.84), 7.298 (1.27), 7.306 (0.71), 7.313 (0.75), 7.321 (0.62), 7.497 (1.01), 7.947 (5.47), 8.631 (5.41), 10.617 (3.27), 13.060 (0.65).

Example 15

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(3,4-difluorophenyl)acetamide



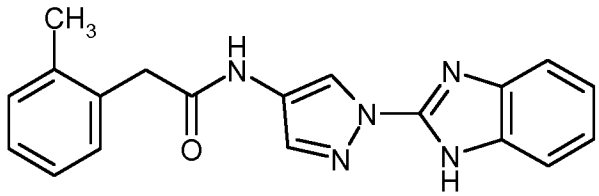
(3,4-Difluorophenyl)acetic acid (60.9 mg, 354 µmol) was provided in DMF (1.5 mL). N,N-diisopropylethylamine (250 µL, 1.4 mmol), the compound of intermediate 4 (100 mg, 424 µmol) and propane phosphonic acid anhydride (T3P, 250 µL, 50% in DMF, 420 µmol) were added, and the mixture was stirred at room temperature for 2 h. After filtration, purification by HPLC (method 1) yielded 95.0 mg (74% of theory) of the title compound.

LC-MS (method 2): R_t = 1.03 min; MS (ESIpos): m/z = 354 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 2.083 (1.94), 2.322 (0.48), 2.326 (0.64), 2.331 (0.49), 2.523 (3.15), 2.664 (0.51), 2.669 (0.68), 2.673 (0.53), 3.696 (16.00), 7.158 (2.82), 7.169 (8.17), 7.177 (8.34), 7.184 (8.68), 7.191 (9.21), 7.202 (1.90), 7.364 (1.75), 7.386 (4.80), 7.392 (2.85), 7.402 (2.47), 7.407 (4.04), 7.413 (5.21), 7.435 (3.24), 7.500 (1.84), 7.942 (11.26), 8.644 (11.50), 10.571 (7.03), 13.040 (1.35).

Example 16

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(2-methylphenyl)acetamide



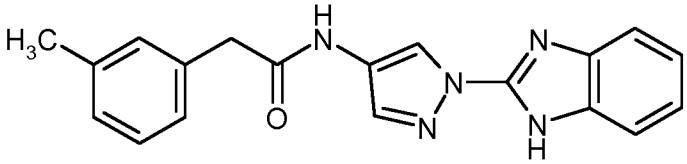
(2-Methylphenyl)acetic acid (53.1 mg, 354 µmol) was provided in DMF (1.5 mL). N,N-diisopropylethylamine (250 µL, 1.4 mmol), the compound of intermediate 4 (100 mg, 424 µmol) and propane phosphonic acid anhydride (T3P, 250 µL, 50% in DMF, 420 µmol) were added, and the mixture was stirred at room temperature for 2 h. After filtration, purification by HPLC (method 1) yielded 70.0 mg (58% of theory) of the title compound.

LC-MS (method 2): R_t = 1.03 min; MS (ESIpos): m/z = 332 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 2.083 (8.03), 2.302 (16.00), 2.523 (0.80), 3.386 (0.73), 3.696 (8.20), 7.145 (1.78), 7.151 (1.50), 7.156 (1.93), 7.162 (2.77), 7.168 (6.56), 7.176 (4.54), 7.179 (4.00), 7.183 (3.68), 7.191 (3.70), 7.201 (0.90), 7.240 (1.42), 7.251 (1.47), 7.256 (0.63), 7.262 (0.97), 7.943 (5.19), 8.646 (5.00), 10.523 (3.19), 13.046 (0.78).

Example 17

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(3-methylphenyl)acetamide



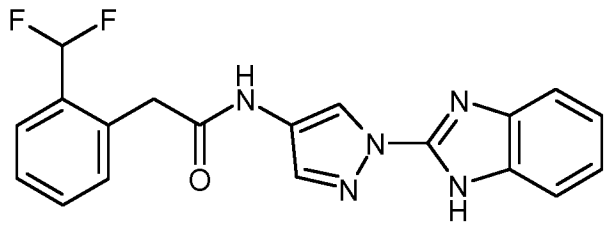
(3-Methylphenyl)acetic acid (53.1 mg, 354 µmol) was provided in DMF (1.5 mL). N,N-diisopropylethylamine (250 µL, 1.4 mmol), the compound of intermediate 4 (100 mg, 424 µmol) and propane phosphonic acid anhydride (T3P, 250 µL, 50% in DMF, 420 µmol) were added, and the mixture was stirred at room temperature for 2 h. After filtration, purification by HPLC (column: chromatorex C18, mobile phase: acetonitrile/water + 0.1% formic acid) yielded 77.0 mg (66% of theory) of the title compound.

LC-MS (method 2): R_t = 1.04 min; MS (ESIpos): m/z = 332 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 2.083 (1.10), 2.298 (16.00), 2.326 (0.42), 2.523 (1.50), 3.612 (8.85), 7.058 (1.34), 7.077 (1.74), 7.115 (1.31), 7.135 (2.03), 7.148 (2.99), 7.157 (1.13), 7.167 (3.79), 7.175 (3.57), 7.182 (3.76), 7.190 (4.33), 7.200 (3.07), 7.219 (3.27), 7.238 (1.26), 7.935 (5.59), 8.647 (6.22), 10.544 (3.82), 13.047 (0.88).

Example 18

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-[2-(difluoromethyl)phenyl]acetamide



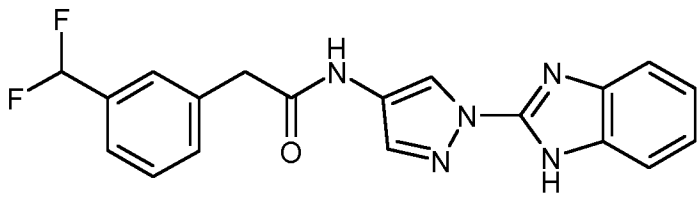
[2-(Difluoromethyl)phenyl]acetic acid (65.8 mg, 354 µmol) was provided in DMF (1.4 mL). N,N-diisopropylethylamine (250 µL, 1.4 mmol), the compound of intermediate 4 (100 mg, 424 µmol) and propane phosphonic acid anhydride (T3P, 250 µL, 50% in DMF, 420 µmol) were added, and the mixture was stirred at room temperature over night. After filtration, purification by HPLC (column: chromatorex C18, mobile phase: acetonitrile/water + 0.1% formic acid) yielded 79.0 mg (60% of theory) of the title compound

LC-MS (method 2): R_t = 1.03 min; MS (ESIpos): m/z = 368 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 0.934 (0.41), 1.898 (0.57), 2.083 (4.72), 2.323 (0.68), 2.327 (0.96), 2.332 (0.68), 2.523 (2.29), 2.665 (0.71), 2.669 (0.96), 2.674 (0.63), 3.299 (1.01), 3.303 (1.20), 3.730 (0.41), 3.889 (16.00), 7.117 (3.39), 7.156 (1.37), 7.166 (7.95), 7.174 (7.48), 7.181 (7.81), 7.190 (8.79), 7.200 (1.72), 7.255 (6.61), 7.392 (3.25), 7.417 (2.13), 7.425 (3.52), 7.431 (4.04), 7.435 (5.13), 7.444 (5.46), 7.448 (4.70), 7.452 (4.75), 7.486 (2.10), 7.504 (4.56), 7.507 (4.78), 7.526 (4.26), 7.541 (1.75), 7.545 (1.69), 7.595 (4.75), 7.613 (3.14), 7.617 (2.95), 7.950 (13.98), 8.634 (14.39), 8.644 (0.49), 10.618 (8.60).

Example 19

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-[3-(difluoromethyl)phenyl]acetamide



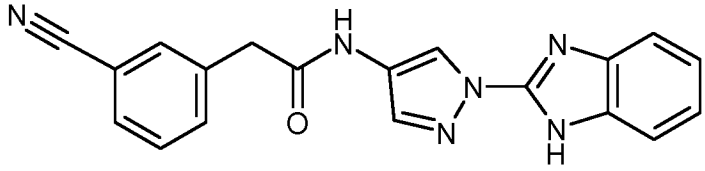
[3-(Difluoromethyl)phenyl]acetic acid (65.8 mg, 354 µmol) was provided in DMF (1.4 mL). N,N-diisopropylethylamine (250 µL, 1.4 mmol), the compound of intermediate 4 (100 mg, 424 µmol) and propane phosphonic acid anhydride (T3P, 250 µL, 50% in DMF, 420 µmol) were added, and the mixture was stirred at room temperature over night. After filtration, purification by HPLC (column: chromatorex C18, mobile phase: acetonitrile/water) yielded 112 mg (84% of theory) of the title compound.

LC-MS (method 2): R_t = 1.08 min; MS (ESIpos): m/z = 368 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 1.905 (0.46), 2.084 (0.95), 2.323 (0.61), 2.327 (0.84), 2.332 (0.60), 2.523 (2.10), 2.665 (0.61), 2.669 (0.84), 2.673 (0.61), 3.700 (0.53), 3.755 (16.00), 6.909 (3.19), 7.048 (6.50), 7.159 (1.09), 7.169 (5.88), 7.176 (5.59), 7.183 (5.99), 7.192 (7.14), 7.202 (1.33), 7.393 (0.49), 7.425 (0.78), 7.452 (1.36), 7.459 (1.82), 7.462 (1.97), 7.476 (5.95), 7.493 (7.06), 7.502 (3.49), 7.509 (6.36), 7.511 (5.42), 7.524 (1.58), 7.531 (1.31), 7.545 (5.84), 7.947 (11.44), 8.649 (11.99), 10.629 (6.86), 13.056 (1.75), 13.058 (1.70).

Example 20

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(3-cyanophenyl)acetamide



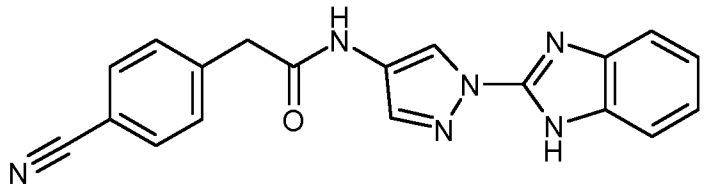
(3-Cyanophenyl)acetic acid (103 mg, 636 µmol) was provided in DMF (2 mL). N,N-diisopropylethylamine (220 µL, 1.3 mmol), the compound of intermediate 4 (100 mg, 424 µmol) and propane phosphonic acid anhydride (T3P, 370 µL, 50% in DMF, 640 µmol) were added, and the mixture was stirred at room temperature over night. After filtration, purification by HPLC (column: chromatorex C18, mobile phase: acetonitrile/water + 0.1% formic acid) yielded 93.0 mg (64% of theory) of the title compound.

LC-MS (method 2): R_t = 0.96 min; MS (ESIpos): m/z = 343 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 0.908 (0.48), 1.137 (0.44), 1.224 (1.19), 1.485 (0.54), 1.907 (1.07), 2.083 (8.50), 2.318 (0.42), 2.322 (0.81), 2.327 (1.13), 2.332 (0.86), 2.523 (2.32), 2.665 (0.86), 2.669 (1.19), 2.674 (0.75), 3.782 (15.71), 7.159 (2.42), 7.169 (12.39), 7.177 (12.32), 7.185 (12.89), 7.192 (13.66), 7.204 (2.63), 7.417 (3.43), 7.433 (3.61), 7.545 (6.73), 7.565 (16.00), 7.584 (10.40), 7.679 (6.96), 7.698 (5.24), 7.744 (10.67), 7.760 (6.35), 7.763 (8.88), 7.803 (13.70), 7.952 (9.07), 8.645 (13.08), 10.635 (5.16), 13.061 (2.80).

Example 21

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(4-cyanophenyl)acetamide



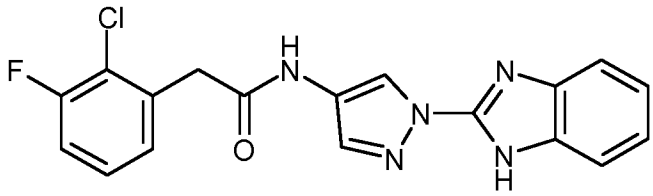
(4-Cyanophenyl)acetic acid (103 mg, 636 µmol) was provided in DMF (2 mL). N,N-diisopropylethylamine (220 µL, 1.3 mmol), the compound of intermediate 4 (100 mg, 424 µmol) and propane phosphonic acid anhydride (T3P, 370 µL, 50% in DMF, 640 µmol) were added, and the mixture was stirred at room temperature over night. After filtration, purification by HPLC (column: chromatorex C18, mobile phase: acetonitrile/water + 0.1% formic acid) yielded 59.8 mg (41% of theory) of the title compound.

LC-MS (method 2): R_t = 0.95 min; MS (ESIpos): m/z = 343 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 0.911 (0.92), 0.929 (0.63), 0.935 (0.55), 0.938 (0.52), 1.227 (1.68), 1.482 (0.84), 1.908 (0.48), 2.083 (4.74), 2.322 (0.48), 2.327 (0.66), 2.331 (0.50), 2.523 (2.32), 2.664 (0.51), 2.669 (0.70), 2.673 (0.55), 2.729 (1.85), 2.887 (2.24), 3.642 (0.54), 3.713 (0.72), 3.848 (0.60), 7.157 (1.38), 7.171 (8.97), 7.183 (7.96), 7.191 (9.85), 7.194 (8.94), 7.206 (1.62), 7.415 (3.80), 7.428 (3.83), 7.439 (3.28), 7.463 (0.52), 7.483 (0.48), 7.536 (10.99), 7.556 (15.48), 7.569 (5.19), 7.581 (3.99), 7.806 (16.00), 7.826 (13.90), 7.945 (10.08), 8.141 (0.70), 8.644 (13.62), 10.647 (5.98), 13.047 (4.34).

Example 22

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(2-chloro-3-fluorophenyl)acetamide



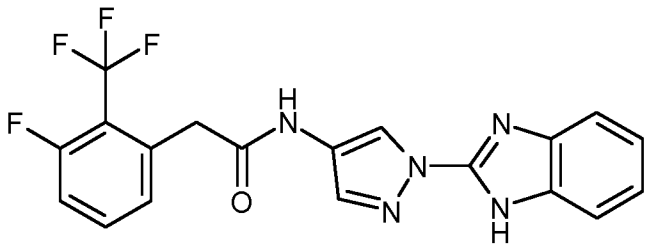
(2-Chloro-3-fluorophenyl)acetic acid (120 mg, 636 µmol) was provided in DMF (2 mL). N,N-diisopropylethylamine (220 µL, 1.3 mmol), the compound of intermediate 4 (100 mg, 424 µmol) and propane phosphonic acid anhydride (T3P, 370 µL, 50% in DMF, 640 µmol) were added, and the mixture was stirred at room temperature over night. After filtration, purification by HPLC (column: chromatorex C18, mobile phase: acetonitrile/water + 0.1% formic acid) yielded 87.5 mg (55% of theory) of the title compound.

LC-MS (method 2): R_t = 1.07 min; MS (ESIpos): m/z = 370 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 2.083 (10.09), 2.523 (0.90), 3.916 (16.00), 7.159 (1.00), 7.169 (5.43), 7.177 (5.31), 7.184 (5.60), 7.192 (6.17), 7.203 (1.25), 7.301 (1.82), 7.307 (2.30), 7.317 (2.44), 7.324 (4.39), 7.330 (1.78), 7.345 (3.91), 7.351 (2.65), 7.359 (3.79), 7.367 (4.03), 7.374 (6.23), 7.380 (1.93), 7.391 (2.37), 7.395 (1.38), 7.397 (1.26), 7.412 (0.97), 7.450 (0.74), 7.513 (0.78), 7.536 (0.80), 7.557 (0.71), 7.953 (10.70), 8.632 (10.67), 10.633 (6.35), 13.050 (1.44), 13.053 (1.42).

Example 23

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-[3-fluoro-2-(trifluoromethyl)phenyl]acetamide



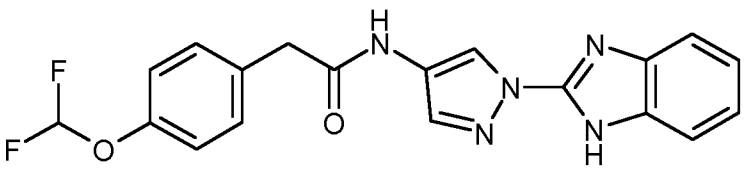
[3-Fluoro-2-(trifluoromethyl)phenyl]acetic acid (141 mg, 636 µmol) was provided in DMF (2 mL). N,N-diisopropylethylamine (220 µL, 1.3 mmol), the compound of intermediate 4 (100 mg, 424 µmol) and propane phosphonic acid anhydride (T3P, 370 µL, 50% in DMF, 640 µmol) were added, and the mixture was stirred at room temperature over night. After filtration, purification by HPLC (column: chromatorex C18, mobile phase: acetonitrile/water + 0.1% formic acid) yielded 75.6 mg (44% of theory) of the title compound.

LC-MS (method 2): R_t = 1.11 min; MS (ESIpos): m/z = 404 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 1.881 (1.22), 2.083 (5.88), 2.322 (0.80), 2.327 (1.14), 2.332 (0.82), 2.523 (2.79), 2.665 (0.84), 2.669 (1.16), 2.673 (0.84), 4.008 (4.06), 4.014 (9.33), 4.021 (9.15), 4.027 (3.77), 7.150 (1.45), 7.160 (8.73), 7.168 (7.77), 7.175 (8.07), 7.183 (9.56), 7.193 (1.75), 7.350 (4.30), 7.370 (4.80), 7.406 (2.27), 7.427 (2.89), 7.435 (2.53), 7.456 (3.05), 7.478 (3.29), 7.481 (3.53), 7.674 (1.71), 7.687 (1.95), 7.694 (3.03), 7.708 (2.91), 7.714 (1.61), 7.728 (1.32), 7.933 (14.90), 8.603 (16.00), 10.589 (9.11).

Example 24

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-[4-(difluoromethoxy)phenyl]acetamide



[4-(Difluoromethoxy)phenyl]acetic acid (129 mg, 636 µmol) was provided in DMF (2 mL). N,N-diisopropylethylamine (220 µL, 1.3 mmol), the compound of intermediate 4 (100 mg, 424 µmol) and propane phosphonic acid anhydride (T3P, 370 µL, 50% in DMF, 640 µmol) were added, and the mixture was stirred at room temperature over night. After filtration, purification by HPLC

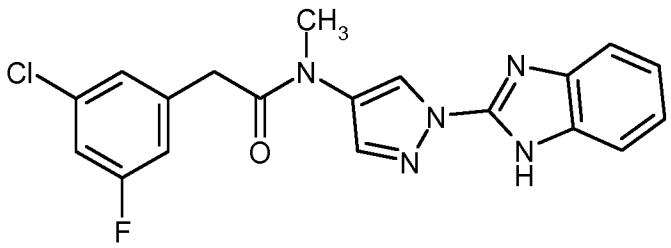
(column: chromatorex C18, mobile phase: acetonitrile/water + 0.1% formic acid) yielded 83.0 mg (50% of theory) of the title compound.

LC-MS (method 2): R_t = 1.07 min; MS (ESIpos): m/z = 384 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 1.900 (0.78), 2.083 (11.56), 2.322 (0.55), 2.327 (0.78), 2.332 (0.57), 2.523 (2.00), 2.665 (0.57), 2.669 (0.78), 2.673 (0.56), 3.670 (16.00), 7.026 (4.72), 7.130 (1.09), 7.138 (8.86), 7.143 (3.05), 7.159 (11.13), 7.167 (8.72), 7.174 (7.03), 7.181 (7.22), 7.190 (8.49), 7.200 (1.73), 7.211 (9.91), 7.367 (1.55), 7.374 (10.82), 7.380 (3.43), 7.390 (3.42), 7.397 (12.78), 7.404 (1.29), 7.495 (1.91), 7.934 (12.06), 8.643 (13.22), 10.587 (7.13), 13.050 (0.82).

Example 25

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(3-chloro-5-fluorophenyl)-N-methylacetamide



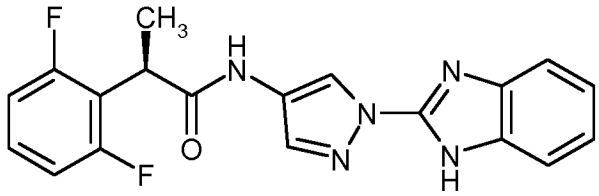
The compound of intermediate 7 (113 mg, 424 µmol) was provided in DMF (1.2 mL). N,N-diisopropylethylamine (260 µL, 1.5 mmol), (3-chloro-5-fluorophenyl)acetic acid (87.9 mg, 466 µmol) and propane phosphonic acid anhydride (T3P, 370 µL, 50% in DMF, 640 µmol) were added, and the mixture was stirred at room temperature for 2 days. After filtration, purification by HPLC (column: chromatorex C18, mobile phase: acetonitrile/water + 0.1% formic acid) yielded 51.6 mg (31% of theory) of the title compound.

LC-MS (method 2): R_t = 1.17 min; MS (ESIpos): m/z = 384 $[M+H]^+$

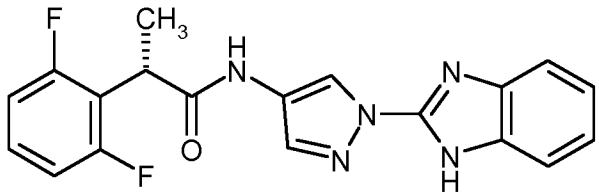
^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 1.231 (1.36), 2.084 (4.19), 2.318 (1.00), 2.323 (2.54), 2.327 (3.72), 2.332 (2.66), 2.337 (1.36), 2.523 (16.00), 2.660 (1.06), 2.665 (2.60), 2.669 (3.72), 2.674 (2.66), 2.679 (1.30), 2.729 (6.91), 2.888 (9.39), 3.202 (14.52), 3.485 (13.82), 3.736 (7.97), 4.054 (7.38), 6.993 (1.54), 6.998 (1.36), 7.019 (1.54), 7.097 (3.42), 7.146 (1.54), 7.169 (2.01), 7.180 (2.95), 7.204 (5.25), 7.226 (3.25), 7.247 (3.72), 7.264 (1.89), 7.269 (1.36), 7.280 (1.18), 7.286 (1.71), 7.292 (1.18), 7.329 (1.54), 7.345 (1.12), 7.352 (1.54), 7.421 (1.18), 7.438 (1.42), 7.459 (1.48), 7.478 (1.24), 7.559 (1.30), 7.580 (1.71), 7.611 (1.18), 7.951 (1.24), 8.093 (5.02), 8.263 (4.78), 8.793 (4.78), 8.854 (5.14), 13.116 (2.13), 13.209 (2.01).

Example 26

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(2,6-difluorophenyl)propanamide



and



2-(2,6-Difluorophenyl)propanoic acid (65.8 mg, 354 µmol) was provided in DMF (1.5 mL). N,N-diisopropylethylamine (250 µL, 1.4 mmol), the compound of intermediate 4 (100 mg, 424 µmol) and propane phosphonic acid anhydride (T3P, 250 µL, 50% in DMF, 420 µmol) were added, and the mixture was stirred at room temperature over night. After filtration, purification by HPLC (column: chromatorex C18, mobile phase: acetonitrile/water + 0.1% formic acid) yielded 21.3 mg (15% of theory) of the title compound.

LC-MS (method 2): R_t = 1.60 min; MS (ESIpos): m/z = 368 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 0.910 (0.65), 0.932 (0.53), 0.949 (0.50), 1.137 (1.38), 1.225 (0.62), 1.227 (0.68), 1.240 (0.53), 1.254 (0.73), 1.271 (0.68), 1.474 (15.68), 1.492 (16.00), 1.895 (0.94), 2.084 (14.47), 2.115 (0.62), 2.318 (0.56), 2.322 (1.26), 2.326 (1.73), 2.332 (1.29), 2.336 (0.59), 2.477 (1.00), 2.523 (7.96), 2.539 (1.73), 2.660 (0.53), 2.664 (1.23), 2.669 (1.73), 2.673 (1.29), 2.678 (0.62), 4.121 (1.20), 4.139 (4.20), 4.157 (4.14), 4.175 (1.20), 7.077 (0.47), 7.081 (0.79), 7.091 (5.28), 7.103 (1.29), 7.112 (11.71), 7.121 (1.29), 7.125 (1.14), 7.133 (6.66), 7.142 (1.14), 7.147 (0.82), 7.155 (1.56), 7.166 (8.90), 7.173 (8.16), 7.180 (8.63), 7.188 (10.28), 7.199 (2.17), 7.352 (1.20), 7.369 (2.70), 7.374 (2.00), 7.385 (1.70), 7.390 (4.34), 7.395 (1.67), 7.406 (2.03), 7.411 (2.35), 7.427 (1.53), 7.447 (0.88), 7.466 (1.17), 7.482 (1.53), 7.563 (0.44), 7.656 (0.47), 7.916 (12.92), 8.646 (14.27), 10.147 (9.31), 13.027 (1.12).

Further, the compounds of formula **(I)** of the present invention can be converted to any salt as described herein, by any method which is known to the person skilled in the art. Similarly, any salt of a compound of formula **(I)** of the present invention can be converted into the free compound, by any method which is known to the person skilled in the art.

Pharmaceutical compositions of the compounds of the invention

This invention also relates to pharmaceutical compositions containing one or more compounds of the present invention. These compositions can be utilised to achieve the desired pharmacological effect by administration to a patient in need thereof. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for the particular condition or disease. Therefore, the present invention includes pharmaceutical compositions that are comprised of a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound, or salt thereof, of the present invention. A pharmaceutically acceptable carrier is preferably a carrier that is relatively non-toxic and innocuous to a patient at concentrations consistent with effective activity of the active ingredient so that any side effects ascribable to the carrier do not vitiate the beneficial effects of the active ingredient. A pharmaceutically effective amount of compound is preferably that amount which produces a result or exerts an influence on the particular condition being treated. The compounds of the present invention can be administered with pharmaceutically-acceptable carriers well known in the art using any effective conventional dosage unit forms, including immediate, slow and timed release preparations, orally, parenterally, topically, nasally, ophthalmically, optically, sublingually, rectally, vaginally, and the like.

For oral administration, the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, troches, lozenges, melts, powders, solutions, suspensions, or emulsions, and may be prepared according to methods known to the art for the manufacture of pharmaceutical compositions. The solid unit dosage forms can be a capsule that can be of the ordinary hard- or soft-shelled gelatine type containing, for example, surfactants, lubricants, and inert fillers such as lactose, sucrose, calcium phosphate, and corn starch.

In another embodiment, the compounds of this invention may be tableted with conventional tablet bases such as lactose, sucrose and cornstarch in combination with binders such as acacia, corn starch or gelatine, disintegrating agents intended to assist the break-up and dissolution of the tablet following administration such as potato starch, alginic acid, corn starch, and guar gum, gum tragacanth, acacia, lubricants intended to improve the flow of tablet granulation and

to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, for example talc, stearic acid, or magnesium, calcium or zinc stearate, dyes, colouring agents, and flavouring agents such as peppermint, oil of wintergreen, or cherry flavouring, intended to enhance the aesthetic qualities of the tablets and make them more acceptable to the patient. Suitable excipients for use in oral liquid dosage forms include dicalcium phosphate and diluents such as water and alcohols, for example, ethanol, benzyl alcohol, and polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent or emulsifying agent. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance tablets, pills or capsules may be coated with shellac, sugar or both.

Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example those sweetening, flavouring and colouring agents described above, may also be present.

The pharmaceutical compositions of this invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil such as liquid paraffin or a mixture of vegetable oils. Suitable emulsifying agents may be (1) naturally occurring gums such as gum acacia and gum tragacanth, (2) naturally occurring phosphatides such as soy bean and lecithin, (3) esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, (4) condensation products of said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil such as, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as, for example, beeswax, hard paraffin, or cetyl alcohol. The suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate ; one or more colouring agents ; one or more flavouring agents ; and one or more sweetening agents such as sucrose or saccharin.

Syrups and elixirs may be formulated with sweetening agents such as, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, and preservative, such as methyl and propyl parabens and flavouring and colouring agents.

The compounds of this invention may also be administered parenterally, that is, subcutaneously, intravenously, intraocularly, intrasynovially, intramuscularly, or interperitoneally, as injectable dosages of the compound in preferably a physiologically acceptable diluent with a pharmaceutical carrier which can be a sterile liquid or mixture of liquids such as water, saline, aqueous dextrose and related sugar solutions, an alcohol such as ethanol, isopropanol, or hexadecyl alcohol, glycols such as propylene glycol or polyethylene glycol, glycerol ketals such as 2,2-dimethyl-1,1-dioxolane-4-methanol, ethers such as poly(ethylene glycol) 400, an oil, a fatty acid, a fatty acid ester or, a fatty acid glyceride, or an acetylated fatty acid glyceride, with or without the addition of a pharmaceutically acceptable surfactant such as a soap or a detergent, suspending agent such as pectin, carbomers, methylcellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agent and other pharmaceutical adjuvants.

Illustrative of oils which can be used in the parenteral formulations of this invention are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, sesame oil, cottonseed oil, corn oil, olive oil, petrolatum and mineral oil. Suitable fatty acids include oleic acid, stearic acid, isostearic acid and myristic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl myristate. Suitable soaps include fatty acid alkali metal, ammonium, and triethanolamine salts and suitable detergents include cationic detergents, for example dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates ; anionic detergents, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates ; non-ionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene-oxypropylene)s or ethylene oxide or propylene oxide copolymers ; and amphoteric detergents, for example, alkyl-beta-aminopropionates, and 2-alkylimidazoline quarternary ammonium salts, as well as mixtures.

The parenteral compositions of this invention will typically contain from about 0.5% to about 25% by weight of the active ingredient in solution. Preservatives and buffers may also be used advantageously. In order to minimise or eliminate irritation at the site of injection, such compositions may contain a non-ionic surfactant having a hydrophile-lipophile balance (HLB) preferably of from about 12 to about 17. The quantity of surfactant in such formulation preferably ranges from about 5% to about 15% by weight. The surfactant can be a single component having the above HLB or can be a mixture of two or more components having the desired HLB.

Illustrative of surfactants used in parenteral formulations are the class of polyethylene sorbitan fatty acid esters, for example, sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

The pharmaceutical compositions may be in the form of sterile injectable aqueous suspensions. Such suspensions may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents such as, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia ; dispersing or wetting agents which may be a naturally occurring phosphatide such as lecithin, a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate, a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadeca-ethyleneoxycetanol, a condensation product of ethylene oxide with a partial ester derived form a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or a condensation product of an ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Diluents and solvents that may be employed are, for example, water, Ringer's solution, isotonic sodium chloride solutions and isotonic glucose solutions. In addition, sterile fixed oils are conventionally employed as solvents or suspending media. For this purpose, any bland, fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can be used in the preparation of injectables.

A composition of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritation excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are, for example, cocoa butter and polyethylene glycol.

Another formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art (see, e.g., US Patent No. 5,023,252, issued June 11, 1991, incorporated herein

by reference). Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Controlled release formulations for parenteral administration include liposomal, polymeric microsphere and polymeric gel formulations that are known in the art.

It may be desirable or necessary to introduce the pharmaceutical composition to the patient via a mechanical delivery device. The construction and use of mechanical delivery devices for the delivery of pharmaceutical agents is well known in the art. Direct techniques for, for example, administering a drug directly to the brain usually involve placement of a drug delivery catheter into the patient's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of agents to specific anatomical regions of the body, is described in US Patent No. 5,011,472, issued April 30, 1991.

The compositions of the invention can also contain other conventional pharmaceutically acceptable compounding ingredients, generally referred to as carriers or diluents, as necessary or desired. Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized.

Such ingredients and procedures include those described in the following references, each of which is incorporated herein by reference: Powell, M.F. *et al.*, "Compendium of Excipients for Parenteral Formulations" PDA Journal of Pharmaceutical Science & Technology **1998**, 52(5), 238-311 ; Strickley, R.G "Parenteral Formulations of Small Molecule Therapeutics Marketed in the United States (1999)-Part-1" PDA Journal of Pharmaceutical Science & Technology **1999**, 53(6), 324-349 ; and Nema, S. *et al.*, "Excipients and Their Use in Injectable Products" PDA Journal of Pharmaceutical Science & Technology **1997**, 51(4), 166-171.

Commonly used pharmaceutical ingredients that can be used as appropriate to formulate the composition for its intended route of administration include:

acidifying agents (examples include but are not limited to acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid) ;

alkalinizing agents (examples include but are not limited to ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, trolamine) ;

adsorbents (examples include but are not limited to powdered cellulose and activated charcoal) ;

aerosol propellants (examples include but are not limited to carbon dioxide, CCl_2F_2, $F_2ClC\text{-}CClF_2$ and $CClF_3$) ;

air displacement agents (examples include but are not limited to nitrogen and argon) ;

antifungal preservatives (examples include but are not limited to benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate) ;

antimicrobial preservatives (examples include but are not limited to benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal) ;

antioxidants (examples include but are not limited to ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite) ;

binding materials (examples include but are not limited to block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones, polysiloxanes and styrene-butadiene copolymers) ;

buffering agents (examples include but are not limited to potassium metaphosphate, dipotassium phosphate, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate)

carrying agents (examples include but are not limited to acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection)

chelating agents (examples include but are not limited to edetate disodium and edetic acid)

colourants (examples include but are not limited to FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red) ;

clarifying agents (examples include but are not limited to bentonite) ;

emulsifying agents (examples include but are not limited to acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyoxyethylene 50 monostearate) ;

encapsulating agents (examples include but are not limited to gelatin and cellulose acetate phthalate)

flavourants (examples include but are not limited to anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin) ;

humectants (examples include but are not limited to glycerol, propylene glycol and sorbitol) ;

levigating agents (examples include but are not limited to mineral oil and glycerin) ;

oils (examples include but are not limited to arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil) ;

ointment bases (examples include but are not limited to lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment) ;

penetration enhancers (transdermal delivery) (examples include but are not limited to monohydroxy or polyhydroxy alcohols, mono- or polyvalent alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas)

plasticizers (examples include but are not limited to diethyl phthalate and glycerol) ;

solvents (examples include but are not limited to ethanol, corn oil, cottonseed oil, glycerol, isopropanol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation) ;

stiffening agents (examples include but are not limited to cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax) ;

suppository bases (examples include but are not limited to cocoa butter and polyethylene glycols (mixtures)) ;

surfactants (examples include but are not limited to benzalkonium chloride, nonoxynol 10, oxtoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan mono-palmitate) ;

suspending agents (examples include but are not limited to agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum) ;

sweetening agents (examples include but are not limited to aspartame, dextrose, glycerol, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose) ;

tablet anti-adherents (examples include but are not limited to magnesium stearate and talc) ;

tablet binders (examples include but are not limited to acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, non-crosslinked polyvinyl pyrrolidone, and pregelatinized starch) ;

tablet and capsule diluents (examples include but are not limited to dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch) ;

tablet coating agents (examples include but are not limited to liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac) ;

tablet direct compression excipients (examples include but are not limited to dibasic calcium phosphate) ;

tablet disintegrants (examples include but are not limited to alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, cross-linked polyvinylpyrrolidone, sodium alginate, sodium starch glycollate and starch) ;

tablet glidants (examples include but are not limited to colloidal silica, corn starch and talc) ;

tablet lubricants (examples include but are not limited to calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate) ;

tablet/capsule opaquants (examples include but are not limited to titanium dioxide) ;

tablet polishing agents (examples include but are not limited to carnuba wax and white wax) ;

thickening agents (examples include but are not limited to beeswax, cetyl alcohol and paraffin) ;

tonicity agents (examples include but are not limited to dextrose and sodium chloride) ;

viscosity increasing agents (examples include but are not limited to alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose, polyvinyl pyrrolidone, sodium alginate and tragacanth) ; and

wetting agents (examples include but are not limited to heptadecaethylene oxycetanol, lecithins, sorbitol monooleate, polyoxyethylene sorbitol monooleate, and polyoxyethylene stearate).

Pharmaceutical compositions according to the present invention can be illustrated as follows:

Sterile IV Solution: A 5 mg/mL solution of the desired compound of this invention can be made using sterile, injectable water, and the pH is adjusted if necessary. The solution is diluted for administration to 1 – 2 mg/mL with sterile 5% dextrose and is administered as an IV infusion over about 60 min.

Lyophilised powder for IV administration: A sterile preparation can be prepared with (i) 100 - 1000 mg of the desired compound of this invention as a lyophilised powder, (ii) 32- 327 mg/mL sodium citrate, and (iii) 300 – 3000 mg Dextran 40. The formulation is reconstituted with sterile, injectable saline or dextrose 5% to a concentration of 10 to 20 mg/mL, which is further diluted with saline or dextrose 5% to 0.2 – 0.4 mg/mL, and is administered either IV bolus or by IV infusion over 15 – 60 min.

Intramuscular suspension: The following solution or suspension can be prepared, for intramuscular injection:

50 mg/mL of the desired, water-insoluble compound of this invention

5 mg/mL sodium carboxymethylcellulose

4 mg/mL TWEEN 80

9 mg/mL sodium chloride

9 mg/mL benzyl alcohol

Hard Shell Capsules: A large number of unit capsules are prepared by filling standard two-piece hard galantine capsules each with 100 mg of powdered active ingredient, 150 mg of lactose, 50 mg of cellulose and 6 mg of magnesium stearate.

Soft Gelatin Capsules: A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into molten gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules are washed and dried. The active ingredient can be dissolved in a mixture of polyethylene glycol, glycerin and sorbitol to prepare a water miscible medicine mix.

Tablets: A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 mg of active ingredient, 0.2 mg. of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8 mg of lactose. Appropriate aqueous and non-aqueous coatings may be applied to increase palatability, improve elegance and stability or delay absorption.

Immediate Release Tablets/Capsules: These are solid oral dosage forms made by conventional and novel processes. These units are taken orally without water for immediate dissolution and delivery of the medication. The active ingredient is mixed in a liquid containing ingredient such as sugar, gelatin, pectin and sweeteners. These liquids are solidified into solid tablets or caplets by freeze drying and solid state extraction techniques. The drug compounds may be compressed with viscoelastic and thermoelastic sugars and polymers or effervescent components to produce porous matrices intended for immediate release, without the need of water.

Combination therapies

The term "combination" in the present invention is used as known to persons skilled in the art and may be present as a fixed combination, a non-fixed combination or kit-of-parts.

A "fixed combination" in the present invention is used as known to persons skilled in the art and is defined as a combination wherein the said first active ingredient and the said second active ingredient are present together in one unit dosage or in a single entity. One example of a "fixed combination" is a pharmaceutical composition wherein the said first active ingredient and the said second active ingredient are present in admixture for simultaneous administration, such as in a formulation. Another example of a "fixed combination" is a pharmaceutical combination wherein the said first active ingredient and the said second active ingredient are present in one unit without being in admixture.

A non-fixed combination or "kit-of-parts" in the present invention is used as known to persons skilled in the art and is defined as a combination wherein the said first active ingredient and the said second active ingredient are present in more than one unit. One example of a non-fixed combination or kit-of-parts is a combination wherein the said first active ingredient and the said second active ingredient are present separately. The components of the non-fixed combination or kit-of-parts may be administered separately, sequentially, simultaneously, concurrently or chronologically staggered.

The compounds of this invention can be administered as the sole pharmaceutical agent or in combination with one or more other pharmaceutical agents where the combination causes no unacceptable adverse effects. The present invention relates also to such combinations. For example, the compounds of this invention can be combined with known chemotherapeutic agents or anti-cancer agents, e.g. anti-hyper-proliferative or other indication agents, and the

like, as well as with admixtures and combinations thereof. Other indication agents include, but are not limited to, anti-angiogenic agents, mitotic inhibitors, alkylating agents, anti-metabolites, DNA-intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzyme inhibitors, toposisomerase inhibitors, biological response modifiers, or anti-hormones.

The term “chemotherapeutic anti-cancer agents”, includes but is not limited to

131I-chTNT, abarelix, abiraterone, aclarubicin, ado-trastuzumab emtansine, afatinib, aflibercept, aldesleukin, alemtuzumab, Alendronic acid, alitretinoin, altretamine, amifostine, aminoglutethimide, Hexyl aminolevulinate, amrubicin, amsacrine, anastrozole, ancestim, anethole dithiolethione, angiotensin II, antithrombin III, aprepitant, arcitumomab, arglabin, arsenic trioxide, asparaginase, axitinib, azacitidine, basiliximab, belotecan, bendamustine, belinostat, bevacizumab, bexarotene, bicalutamide, bisantrene, bleomycin, bortezomib, buserelin, bosutinib, brentuximab vedotin, busulfan, cabazitaxel, cabozantinib, calcium folinate, calcium levofolinate, capecitabine, capromab, carboplatin, carfilzomib, carmofur, carmustine, catumaxomab, celecoxib, celmoleukin, ceritinib, cetuximab, chlorambucil, chlormadinone, chlormethine, cidofovir, cinacalcet, cisplatin, cladribine, clodronic acid, clofarabine, copanlisib, crisantaspase, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, darbepoetin alfa, dabrafenib, dasatinib, daunorubicin, decitabine, degarelix, denileukin diftitox, denosumab, depreotide, deslorelin, dexrazoxane, dibrospidium chloride, dianhydrogalactitol, diclofenac, docetaxel, dolasetron, doxifluridine, doxorubicin, doxorubicin + estrone, dronabinol, eculizumab, edrecolomab, elliptinium acetate, eltrombopag, endostatin, enocitabine, enzalutamide, epirubicin, epitiostanol, epoetin alfa, epoetin beta, epoetin zeta, eptaplatin, eribulin, erlotinib, esomeprazole, estradiol, estramustine, etoposide, everolimus, exemestane, fadrozole, fentanyl, filgrastim, fluoxymesterone, floxuridine, fludarabine, fluorouracil, flutamide, folinic acid, formestane, fosaprepitant, fotemustine, fulvestrant, gadobutrol, gadoteridol, gadoteric acid meglumine, gadoversetamide, gadoxetic acid, gallium nitrate, ganirelix, gefitinib, gemcitabine, gemtuzumab, Glucarpidase, glutoxim, GM-CSF, goserelin, granisetron, granulocyte colony stimulating factor, histamine dihydrochloride, histrelin, hydroxycarbamide, I-125 seeds, lansoprazole, ibandronic acid, ibritumomab tiuxetan, ibrutinib, idarubicin, ifosfamide, imatinib, imiquimod, improsulfan, indisetron, incadronic acid, ingenol mebutate, interferon alfa, interferon beta, interferon gamma, iobitridol, iobenguane (123I), iomeprol, ipilimumab, irinotecan, Itraconazole, ixabepilone, lanreotide, lapatinib, lasocholine, lenalidomide, lenograstim, lentinan, letrozole, leuprorelin, levamisole, levonorgestrel, levothyroxine sodium, lisuride, lobaplatin, lomustine, lonidamine, masoprocol, medroxyprogesterone, megestrol, melarsoprol, melphalan, mepitiostane, mercaptopurine,

mesna, methadone, methotrexate, methoxsalen, methylaminolevulinate, methylprednisolone, methyltestosterone, metirosine, mifamurtide, miltefosine, miriplatin, mitobronitol, mitoguazone, mitolactol, mitomycin, mitotane, mitoxantrone, mogamulizumab, molgramostim, mopidamol, morphine hydrochloride, morphine sulfate, nabilone, nabiximols, nafarelin, naloxone + pentazocine, naltrexone, nartograstim, nedaplatin, nelarabine, neridronic acid, nivolumabpentetreotide, nilotinib, nilutamide, nimorazole, nimotuzumab, nimustine, nitracrine, nivolumab, obinutuzumab, octreotide, ofatumumab, omacetaxine mepesuccinate, omeprazole, ondansetron, oprelvekin, orgotein, orilotimod, oxaliplatin, oxycodone, oxymetholone, ozogamicine, p53 gene therapy, paclitaxel, palifermin, palladium-103 seed, palonosetron, pamidronic acid, panitumumab, pantoprazole, pazopanib, pegaspargase, PEG-epoetin beta (methoxy PEG-epoetin beta), pembrolizumab, pegfilgrastim, peginterferon alfa-2b, pemetrexed, pentazocine, pentostatin, peplomycin, Perflubutane, perfosfamide, Pertuzumab, picibanil, pilocarpine, pirarubicin, pixantrone, plerixafor, plicamycin, poliglusam, polyestradiol phosphate, polyvinylpyrrolidone + sodium hyaluronate, polysaccharide-K, pomalidomide, ponatinib, porfimer sodium, pralatrexate, prednimustine, prednisone, procarbazine, procodazole, propranolol, quinagolide, rabeprazole, racotumomab, radium-223 chloride, radotinib, raloxifene, raltitrexed, ramosetron, ramucirumab, ranimustine, rasburicase, razoxane, refametinib, regorafenib, risedronic acid, rhenium-186 etidronate, rituximab, romidepsin, romiplostim, romurtide, roniciclib, samarium (153Sm) lexidronam, sargramostim, satumomab, secretin, sipuleucel-T, sizofiran, sobuzoxane, sodium glycididazole, sorafenib, stanozolol, streptozocin, sunitinib, talaporfin, tamibarotene, tamoxifen, tapentadol, tasonermin, teceleukin, technetium (99mTc) nofetumomab merpentan, 99mTc-HYNIC-[Tyr3]-octreotide, tegafur, tegafur + gimeracil + oteracil, temoporfin, temozolomide, temsirolimus, teniposide, testosterone, tetrofosmin, thalidomide, thiotepa, thymalfasin, thyrotropin alfa, tioguanine, tocilizumab, topotecan, toremifene, tositumomab, trabectedin, tramadol, trastuzumab, trastuzumab emtansine, treosulfan, tretinoin, trifluridine + tipiracil, trilostane, triptorelin, trametinib, trofosfamide, thrombopoietin, tryptophan, ubenimex, valatinib, valrubicin, vandetanib, vapreotide, vemurafenib, vinblastine, vincristine, vindesine, vinflunine, vinorelbine, vismodegib, vorinostat, vorozole, yttrium-90 glass microspheres, zinostatin, zinostatin stimalamer, zoledronic acid, zorubicin.

The compounds of the invention may also be administered in combination with protein therapeutics. Such protein therapeutics suitable for the treatment of cancer or other angiogenic disorders and for use with the compositions of the invention include, but are not

limited to, an interferon (e.g., interferon .alpha., .beta., or .gamma.) supraagonistic monoclonal antibodies, Tuebingen, TRP-1 protein vaccine, Colostrinin, anti-FAP antibody, YH-16, gemtuzumab, infliximab, cetuximab, trastuzumab, denileukin diftitox, rituximab, thymosin alpha 1, bevacizumab, mecasermin, mecasermin rinfabate, oprelvekin, natalizumab, rhMBL, MFE-CP1 + ZD-2767-P, ABT-828, ErbB2-specific immunotoxin, SGN-35, MT-103, rinfabate, AS-1402, B43-genistein, L-19 based radioimmunotherapeutics, AC-9301, NY-ESO-1 vaccine, IMC-1C11, CT-322, rhCC10, r(m)CRP, MORAb-009, aviscumine, MDX-1307, Her-2 vaccine, APC-8024, NGR-hTNF, rhH1.3, IGN-311, Endostatin, volociximab, PRO-1762, lexatumumab, SGN-40, pertuzumab, EMD-273063, L19-IL-2 fusion protein, PRX-321, CNTO-328, MDX-214, tigapotide, CAT-3888, labetuzumab, alpha-particle-emitting radioisotope-llinked lintuzumab, EM-1421, HyperAcute vaccine, tucotuzumab celmoleukin, galiximab, HPV-16-E7, Javelin - prostate cancer, Javelin - melanoma, NY-ESO-1 vaccine, EGF vaccine, CYT-004-MelQbG10, WT1 peptide, oregovomab, ofatumumab, zalutumumab, cintredekin besudotox, WX-G250, Albuferon, aflibercept, denosumab, vaccine, CTP-37, efungumab, or 131I-chTNT-1/B. Monoclonal antibodies useful as the protein therapeutic include, but are not limited to, muromonab-CD3, abciximab, edrecolomab, daclizumab, gentuzumab, alemtuzumab, ibritumomab, cetuximab, bevicizumab, efalizumab, adalimumab, omalizumab, muromomab-CD3, rituximab, daclizumab, trastuzumab, palivizumab, basiliximab, and infliximab.

A compound of general formula **(I)** as defined herein can optionally be administered in combination with one or more of the following: ARRY-162, ARRY-300, ARRY-704, AS-703026, AZD-5363, AZD-8055, BEZ-235, BGT-226, BKM-120, BYL-719, CAL-101, CC-223, CH-5132799, deforolimus, E-6201, enzastaurin , GDC-0032, GDC-0068, GDC-0623, GDC-0941, GDC-0973, GDC-0980, GSK-2110183, GSK-2126458, GSK-2141795, MK-2206, novolimus, OSI-027, perifosine, PF-04691502, PF-05212384, PX-866, rapamycin, RG-7167, RO-4987655, RO-5126766, selumetinib, TAK-733, trametinib, triciribine, UCN-01, WX-554, XL-147, XL-765, zotarolimus, ZSTK-474.

Generally, the use of cytotoxic and/or cytostatic agents in combination with a compound or composition of the present invention will serve to:

(1) yield better efficacy in reducing the growth of a tumor or even eliminate the tumor as compared to administration of either agent alone,

(2) provide for the administration of lesser amounts of the administered chemo-therapeutic agents,

(3) provide for a chemotherapeutic treatment that is well tolerated in the patient with fewer deleterious pharmacological complications than observed with single agent chemotherapies and certain other combined therapies,

(4) provide for treating a broader spectrum of different cancer types in mammals, especially humans,

(5) provide for a higher response rate among treated patients,

(6) provide for a longer survival time among treated patients compared to standard chemotherapy treatments,

(7) provide a longer time for tumor progression, and/or

(8) yield efficacy and tolerability results at least as good as those of the agents used alone, compared to known instances where other cancer agent combinations produce antagonistic effects.

Methods of Sensitizing Cells to Radiation

In a distinct embodiment of the present invention, a compound of the present invention may be used to sensitize a cell to radiation. That is, treatment of a cell with a compound of the present invention prior to radiation treatment of the cell renders the cell more susceptible to DNA damage and cell death than the cell would be in the absence of any treatment with a compound of the invention. In one aspect, the cell is treated with at least one compound of the invention.

Thus, the present invention also provides a method of killing a cell, wherein a cell is administered one or more compounds of the invention in combination with conventional radiation therapy.

The present invention also provides a method of rendering a cell more susceptible to cell death, wherein the cell is treated with one or more compounds of the invention prior to the treatment of the cell to cause or induce cell death. In one aspect, after the cell is treated with one or more compounds of the invention, the cell is treated with at least one compound, or at least one method, or a combination thereof, in order to cause DNA damage for the purpose of inhibiting the function of the normal cell or killing the cell.

In one embodiment, a cell is killed by treating the cell with at least one DNA damaging agent. That is, after treating a cell with one or more compounds of the invention to sensitize the cell

to cell death, the cell is treated with at least one DNA damaging agent to kill the cell. DNA damaging agents useful in the present invention include, but are not limited to, chemotherapeutic agents (*e.g.*, cisplatinum), ionizing radiation (X-rays, ultraviolet radiation), carcinogenic agents, and mutagenic agents.

In another embodiment, a cell is killed by treating the cell with at least one method to cause or induce DNA damage. Such methods include, but are not limited to, activation of a cell signalling pathway that results in DNA damage when the pathway is activated, inhibiting of a cell signalling pathway that results in DNA damage when the pathway is inhibited, and inducing a biochemical change in a cell, wherein the change results in DNA damage. By way of a non-limiting example, a DNA repair pathway in a cell can be inhibited, thereby preventing the repair of DNA damage and resulting in an abnormal accumulation of DNA damage in a cell.

In one aspect of the invention, a compound of the invention is administered to a cell prior to the radiation or other induction of DNA damage in the cell. In another aspect of the invention, a compound of the invention is administered to a cell concomitantly with the radiation or other induction of DNA damage in the cell. In yet another aspect of the invention, a compound of the invention is administered to a cell immediately after radiation or other induction of DNA damage in the cell has begun.

In another aspect, the cell is in vitro. In another embodiment, the cell is in vivo.

As mentioned supra, the compounds of the present invention have surprisingly been found to effectively reduce tumor cell viability in nutrient deprived regions. In particular, said compounds of the present invention have been found to effectively kill cancer cells in inner tumor spheroid regions and may therefore be used for the treatment or prophylaxis of diseases of uncontrolled cell growth, proliferation and/or survival, undesirable cellular immune responses, or undesirable cellular inflammatory responses, or diseases which are accompanied with uncontrolled cell growth, proliferation and/or survival, undesirable cellular immune responses, or undesirable cellular inflammatory responses, particularly in which the uncontrolled cell growth, proliferation and/or survival, undesirable cellular immune responses, or undesirable cellular inflammatory responses are affected by reduction of tumor cell viability in nutrient deprived regions, such as, for example, haematological tumours, solid tumours, and/or metastases thereof, e.g. leukaemias and myelodysplastic syndrome, malignant lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the thorax including non-small cell and small cell lung tumours, gastrointestinal tumours,

endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

In accordance with another aspect therefore, the present invention covers a compound of general formula **(I)**, or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, as described and defined herein, for use in the treatment or prophylaxis of a disease, as mentioned supra.

Another particular aspect of the present invention is therefore the use of a compound of general formula **(I)**, described *supra*, or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, for the prophylaxis or treatment of a disease.

Another particular aspect of the present invention is therefore the use of a compound of general formula **(I)** described supra for manufacturing a pharmaceutical composition for the treatment or prophylaxis of a disease.

The diseases referred to in the two preceding paragraphs are diseases of uncontrolled cell growth, proliferation and/or survival, undesirable cellular immune responses, or undesirable cellular inflammatory responses, or diseases which are accompanied with uncontrolled cell growth, proliferation and/or survival, undesirable cellular immune responses, or undesirable cellular inflammatory responses, such as, for example, haematological tumours, solid tumours, and/or metastases thereof, e.g. leukaemias and myelodysplastic syndrome, malignant lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the thorax including non-small cell and small cell lung tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

The term “undesirable” within the context of the present invention, in particular in the context of “undesirable cellular immune responses, or undesirable cellular inflammatory responses”, as used herein, is to be understood as meaning a response which is less than, or greater than normal, and which is associated with, responsible for, or results in, the pathology of said diseases.

Preferably, the use is in the treatment or prophylaxis of diseases, wherein the diseases are haemotological tumours, solid tumours and/or metastases thereof.

Method of treating hyper-proliferative disorders

The present invention relates to a method for using the compounds of the present invention and compositions thereof, to treat mammalian hyper-proliferative disorders. Compounds can be utilized to inhibit, block, reduce, decrease, etc., cell proliferation and/or cell division, and/or produce apoptosis. This method comprises administering to a mammal in need thereof, including a human, an amount of a compound of this invention, or a pharmaceutically acceptable salt, isomer, polymorph, metabolite, hydrate, solvate or ester thereof ; etc. which is effective to treat the disorder. Hyperproliferative disorders include but are not limited, e.g., psoriasis, keloids, and other hyperplasias affecting the skin, benign prostate hyperplasia (BPH), solid tumours, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases. Those disorders also include lymphomas, sarcomas, and leukaemias.

Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ.

Examples of cancers of the respiratory tract include, but are not limited to small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

Examples of brain cancers include, but are not limited to brain stem and hypophtalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, anaplastic astrocytoma, diffuse astrocytoma, glioblastoma, oligodendroglioma, secondary glioblastoma multiforme as well as neuroectodermal and pineal tumour.

Tumours of the male reproductive organs include, but are not limited to prostate and testicular cancer. Tumours of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

Tumours of the digestive tract include, but are not limited to anal, colon, colorectal, oesophageal, gallbladder, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.

Tumours of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, urethral and human papillary renal cancers.

Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

Head-and-neck cancers include, but are not limited to laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer and squamous cell. Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Burkitt lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

Sarcomas include, but are not limited to sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma.

Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

These disorders have been well characterized in humans, but also exist with a similar etiology in other mammals, and can be treated by administering pharmaceutical compositions of the present invention.

The term "treating" or "treatment" as stated throughout this document is used conventionally, *e.g.,* the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, improving the condition of, *etc.*, of a disease or disorder, such as a carcinoma.

Methods of treating angiogenic disorders

The present invention also provides methods of treating disorders and diseases associated with excessive and/or abnormal angiogenesis.

Undesirable and ectopic expression of angiogenesis can be deleterious to an organism. A number of pathological conditions are associated with the growth of extraneous blood vessels. These include, e.g., diabetic retinopathy, ischemic retinal-vein occlusion, and retinopathy of prematurity [Aiello et al. New Engl. J. Med. **1994**, 331, 1480 ; Peer et al. Lab. Invest. **1995**, 72, 638], age-related macular degeneration [AMD ; see, Lopez et al. Invest. Opththalmol. Vis. Sci. **1996**, 37, 855], neovascular glaucoma, psoriasis, retrolental fibroplasias, angiofibroma, inflammation, rheumatoid arthritis (RA), restenosis, in-stent restenosis, vascular graft restenosis, etc. In addition, the increased blood supply associated with cancerous and neoplastic tissue, encourages growth, leading to rapid tumour enlargement and metastasis. Moreover, the growth of new blood and lymph vessels in a tumour provides an escape route

for renegade cells, encouraging metastasis and the consequence spread of the cancer. Thus, compounds of the present invention can be utilized to treat and/or prevent any of the aforementioned angiogenesis disorders, e.g., by inhibiting and/or reducing blood vessel formation ; by inhibiting, blocking, reducing, decreasing, etc. endothelial cell proliferation or other types involved in angiogenesis, as well as causing cell death or apoptosis of such cell types.

Dose and administration

Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of hyper-proliferative disorders and angiogenic disorders, by standard toxicity tests and by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the compounds of this invention can readily be determined for treatment of each desired indication. The amount of the active ingredient to be administered in the treatment of one of these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

The total amount of the active ingredient to be administered will generally range from about 0.001 mg/kg to about 200 mg/kg body weight per day, and preferably from about 0.01 mg/kg to about 20 mg/kg body weight per day. Clinically useful dosing schedules will range from one to three times a day dosing to once every four weeks dosing. In addition, "drug holidays" in which a patient is not dosed with a drug for a certain period of time, may be beneficial to the overall balance between pharmacological effect and tolerability. A unit dosage may contain from about 0.5 mg to about 1500 mg of active ingredient, and can be administered one or more times per day or less than once a day. The average daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will

preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The average daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.

Of course the specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific compound employed, the age and general condition of the patient, time of administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of treatment and number of doses of a compound of the present invention or a pharmaceutically acceptable salt or ester or composition thereof can be ascertained by those skilled in the art using conventional treatment tests.

Preferably, the diseases of said method are haematological tumours, solid tumour and/or metastases thereof.

The compounds of the present invention can be used in particular in therapy and prevention, i.e. prophylaxis, of tumour growth and metastases, especially in solid tumours of all indications and stages with or without pre-treatment of the tumour growth.

Methods of testing for a particular pharmacological or pharmaceutical property are well known to persons skilled in the art.

The example testing experiments described herein serve to illustrate the present invention and the invention is not limited to the examples given.

Biological assays:

Examples were tested in selected biological assays one or more times. When tested more than once, data are reported as either average values or as median values, wherein

- the average value, also referred to as the arithmetic mean value, represents the sum of the values obtained divided by the number of times tested, and
- the median value represents the middle number of the group of values when ranked in ascending or descending order. If the number of values in the data set is odd, the median is the middle value. If the number of values in the data set is even, the median is the arithmetic mean of the two middle values.

Examples were synthesized one or more times. When synthesized more than once, data from biological assays represent average values or median values calculated utilizing data sets obtained from testing of one or more synthetic batch.

3D tumor spheroid assay

With three-dimensional growth conditions, multicellular tumor spheroids (MCTS) reproduce several parameters of the tumor microenvironment, including oxygen and nutrient gradients as well as the development of dormant tumor regions and therefore represent a promising model system for discovery of compounds that target tumor cells in stressed, hypoxic or nutrient-depleted regions *(Wenzel CW., 3D high-content screening for the identification of compounds that target cells in dormant tumor spheroid regions. Experimental Cell Research 323, 2014, 131-143)*.

By using automated microscopy and image analysis (high-content analysis) the tumor spheroid assay enables the identification of compounds that induce cell death in inner, nutrient-deprived tumor spheroid core regions, while not affecting well-supplied outer regions with direct access to the culture media, thereby excluding general cytotoxic compounds.

In general tumor spheroids were generated for high-content screening by seeding single cell suspensions of cancer cells into agarose-coated multiwell (e.g. 96 well or 384 well plates) plates (*Friedrich J. Spheroid-based drug screen: considerations and practical approach. Nat. Protoc. 4, 309-324, 2009; Wenzel CW., 3D high-content screening for the identification of compounds that target cells in dormant tumor spheroid regions. Experimental Cell Research 323, 2014, 131-143)* and incubated for 4 days in a humidified incubator (37 °C and 5% CO_2). During this time, the cells form so called tumor spheroids, round cell aggregates with diameters of 400-600 µm. These reproduce several parameters of the metabolic tumor microenvironment and are used to screen for compounds that target cancer cells in nutrient-deprived tumor spheroid regions.

More precisely, for the generation of imaging-compatible 3D tumor spheroids, 10 µL of a heated (e.g. by Microwave) 1.5% w/v agarose (e.g. Agarose NA, Sigma-Aldrich GE17-0554-01)(in DMEM (e.g. Life Technologies 11880-028) without phenol red and without fetal bovine serum (FBS)) solution was dispended by liquid dispensers (e.g. Multidrop Combi, Type 836 and standard tube dispensing cassettes, Thermo Scientific) into sterile 384-well clear bottom imaging plates (e.g. Greiner bio-one, 781090) and let cool for 2 h. To prevent premature gelation of the agarose suspension, the multidrop and dispensing cassette was heated by infrared lamps. For tumor spheroid seeding, a trypsinized (e.g. TrypLE from Life Technologies 12604-013) single cell suspension (of e.g. T47D (ATCC: HTB-133), MCF7 (ATCC: HTB-22), DLD-1 (ATCC: CCL-221), H460 (ATCC: HTB-177)) was seeded into agarose-coated (1.5% w/v) 384-well clear bottom plates in 40 µL RPMI1640 or suitable cell culture medium (e.g. Life Technologies,

11875-093) containing 10% (v/v) FBS (e.g. PAA Laboratories A15-151) supplemented with 1% Penicillin/Streptomycin (e.g. Sigma-Aldrich P0781) (and 0.01 µg/mL insulin for T47D cells (e.g. Life Technologies 12585-014)) using a liquid dispenser (e.g. Multidrop Combi, Type 836 and standard tube dispensing cassettes, Thermo Scientific). Cell lines seeding number was optimized to obtain spheroids with an approximate diameter of 400 µm on day 4 (e.g. typically 2000 cells per well (c/w) for T47D and MCF-7, 5000 c/w for DLD1 and 200 c/w for H-460).

The plates were incubated under standard cell culture conditions at 37 °C and 5% CO_2 in humidified incubators for 4 days to allow formation of reproducible spheroids of defined size and morphology. On day 4 test compounds were added from a 3x stock solution by hand or liquid handling robots (e.g. CyBi-Well with 384-Well pipetting head) in 20 µL suitable cell culture medium (e.g. Life Technologies, 11875-093) containing 10% (v/v) FBS (e.g. PAA Laboratories A15-151) supplemented with 1% Penicillin/Streptomycin (e.g. Sigma-Aldrich P0781) (and 0.01 µg/mL insulin for T47D cells (e.g. Life Technologies 12585-014)) either in single concentration, typically reaching 10 µM endconcentration on the spheroids from a 10 mM Stock solution with DMSO levels never exceeding 1%, or as dilution typically covering a range of 10 µM to 0.51 nM final concentration on the spheroids and subsequently incubated for three days under standard cell culture conditions at 37 °C and 5% CO_2 in humidified incubators.

Prior to imaging, spheroids were stained for 6 h by adding Hoechst 33342 (final 2µg/mL from a 1 mg/mL stock solution, e.g. Life Technologies H-1399) as counterstain for all nuclei and 0.5 µM Sytox Green (as stain for dead cells (e.g. from a 2 mM stock solution, Life Technologies S26926) in 10 µL of a 7x solution in suitable cell culture medium (e.g. Life Technologies, 11875-093) containing 10% (v/v) FBS (e.g. PAA Laboratories A15-151) supplemented with 1% Penicillin/Streptomycin (e.g. Sigma-Aldrich P0781) (and 0.01 µg/mL insulin for T47D cells (e.g. Life Technologies 12585-014)) by liquid dispensers (e.g. Multidrop Combi, Type 836 and standard tube dispensing cassettes, Thermo Scientific).

Subsequently the plates were imaged on automated microscopes at the appropriate wavelengths and filter conditions for Hoechst and Sytox green staining (e.g. Opera confocal spinning disc, Hoechst excitation: 405 nm, emission: 450 nm; Sytox green excitation 488 nm, emission 540-575 nm).

For automated image analysis, the total area of the spheroid was identified by images from the Hoechst staining and subsequently intensity values in the second image (from sytox green staining) were determined as a read-out for the extent of cell death induced by the respective

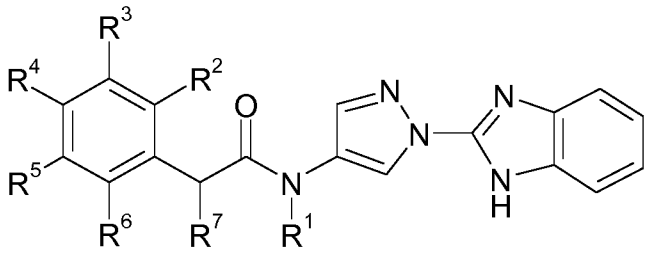
compound (*Wenzel CW., 3D high-content screening for the identification of compounds that target cells in dormant tumor spheroid regions. Experimental Cell Research 323, 2014, 131-143)* (software programs used were e.g. Molecular Devices MetaXpress and Genedata Screener Assay Analyzer and Condoseo).

Table 2: Induction of inner core cell death in 3D tumor spheroids, T47D cells

Example No.	IC_{50} [mol/L]
1	1.0 E-7
2	1.0 E-6
3	9.1 E-8
4	1.2 E-7
5	7.3 E-8
6	4.0 E-7
7	4.9 E-6
8	7.4 E-6
9	7.7 E-8
10	1.1 E-7
11	1.7 E-7
12	1.2 E-6
13	2.2 E-6
14	5.1 E-7
15	1.2 E-6
16	2.8 E-6
17	1.4 E-6
18	8.8 E-7
19	2.1 E-6
20	4.2 E-7
21	1.1 E-6
22	1.5 E-6
23	1.6 E-6
24	3.2 E-6
25	3.3 E-7
26	5.0 E-6

CLAIMS

1. A compound of formula **(I)**



(I) ,

in which :

R^1 represents a hydrogen atom or a methyl group;

R^2 represents a fluorine atom or a group selected from :
methyl, ethyl, C_1-C_2-haloalkyl and (trifluoromethyl)sulfanyl;
and R^3, R^4, R^5 and R^6 each represent a hydrogen atom;
or

R^3 represents a halogen atom or a group selected from :
cyano, methyl, ethyl, C_1-C_2-haloalkyl and (trifluoromethyl)sulfanyl;
and R^2, R^4, R^5 and R^6 each represent a hydrogen atom;
or

R^4 represents a halogen atom, or a group selected from :
cyano, difluoromethoxy and (trifluoromethyl)sulfanyl;
and R^2, R^3, R^5 and R^6 each represent a hydrogen atom;
or

R^2 represents a halogen atom or a group selected from :
methyl, ethyl, C_1-C_2-haloalkyl, and (trifluoromethyl)sulfanyl;
and R^3 represents a halogen atom or a group selected from :
cyano, methyl, ethyl, C_1-C_2-haloalkyl and (trifluoromethyl)sulfanyl;
and R^4, R^5 and R^6 each represent a hydrogen atom;
or

R^2 represents a fluorine atom or a group selected from :
methyl, ethyl, C_1-C_2-haloalkyl and (trifluoromethyl)sulfanyl;
and R^4 represents a halogen atom or a group selected from :
cyano, difluoromethoxy and (trifluoromethyl)sulfanyl;
and R^3, R^5 and R^6 each represent a hydrogen atom;

or

R^2 represents a fluorine atom or a group selected from :
methyl, ethyl, C_1-C_2-haloalkyl and (trifluoromethyl)sulfanyl;
and R^5 represents a halogen atom or a group selected from :
cyano, methyl, ethyl, C_1-C_2-haloalkyl and (trifluoromethyl)sulfanyl;
and R^3, R^4 and R^6 each represent a hydrogen atom;

or

R^3 represents a halogen atom or a group selected from :
cyano, methyl, ethyl, C_1-C_2-haloalkyl and (trifluoromethyl)sulfanyl;
and R^4 represents a halogen atom, or a group selected from :
cyano, difluoromethoxy and (trifluoromethyl)sulfanyl;
and R^2, R^5 and R^6 each represent a hydrogen atom;

or

R^3 and R^5 represent, independently of each other, a halogen atom or a group selected from :
cyano, difluoromethyl and (trifluoromethyl)sulfanyl;
and R^2, R^4 and R^6 each represent a hydrogen atom;

or

R^2, R^3, R^4, R^5 and R^6 each represent a hydrogen atom;

R^7 represents a hydrogen atom;

or

R^2 and R^6 represent, independently of each other, a fluorine or a chlorine atom;
and R^3, R^4 and R^5 each represent a hydrogen atom;
and R^7 represents a methyl group;

or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

2. The compound according to claim 1, wherein :

R^1 represents a hydrogen atom or a methyl group;

R^2 represents a fluorine atom or a group selected from :
methyl, ethyl and C_1-C_2-haloalkyl;
and R^3, R^4, R^5 and R^6 each represent a hydrogen atom;
or
R^3 represents a halogen atom or a group selected from :
cyano, methyl, ethyl and C_1-C_2-haloalkyl;
and R^2, R^4, R^5 and R^6 each represent a hydrogen atom;
or
R^4 represents a halogen atom, or a group selected from :
cyano and difluoromethoxy;
and R^2, R^3, R^5 and R^6 each represent a hydrogen atom;
or
R^2 represents a halogen atom or a group selected from :
methyl, ethyl and C_1-C_2-haloalkyl;
and R^3 represents a halogen atom or a group selected from :
cyano, methyl, ethyl and C_1-C_2-haloalkyl;
and R^4, R^5 and R^6 each represent a hydrogen atom;
or
R^2 represents a fluorine atom or a group selected from :
methyl, ethyl and C_1-C_2-haloalkyl;
and R^4 represents a halogen atom or a group selected from :
cyano and difluoromethoxy;
and R^3, R^5 and R^6 each represent a hydrogen atom;
or
R^2 represents a fluorine atom or a group selected from :
methyl, ethyl and C_1-C_2-haloalkyl;
and R^5 represents a halogen atom or a group selected from :
cyano, methyl, ethyl and C_1-C_2-haloalkyl;
and R^3, R^4 and R^6 each represent a hydrogen atom;
or

R^3 represents a halogen atom or a group selected from :
cyano, methyl, ethyl and C_1-C_2-haloalkyl;
and R^4 represents a halogen atom, or a group selected from :
cyano and difluoromethoxy;
and R^2, R^5 and R^6 each represent a hydrogen atom;

or

R^3 and R^5 represent, independently of each other, a halogen atom or a group selected from :
cyano and difluoromethyl;
and R^2, R^4 and R^6 each represent a hydrogen atom;

or

R^2, R^3, R^4, R^5 and R^6 each represent a hydrogen atom;

R^7 represents a hydrogen atom;

or

R^2 and R^6 represent, independently of each other, a fluorine or a chlorine atom;
and R^3, R^4 and R^5 each represent a hydrogen atom;
and R^7 represents a methyl group;

or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

3. The compound according to claim 1 or 2, wherein :

R^1 represents a hydrogen atom or a methyl group;

R^2 represents a fluorine atom or a group selected from :
methyl, difluoromethyl and trifluoromethyl;
and R^3, R^4, R^5 and R^6 each represent a hydrogen atom;

or

R^3 represents a fluorine or a chlorine atom, or a group selected from :
cyano, methyl, difluoromethyl and trifluoromethyl;
and R^2, R^4, R^5 and R^6 each represent a hydrogen atom;

or

R^4 represents a fluorine or a chlorine atom, or a group selected from :
cyano and difluoromethoxy;
and R^2, R^3, R^5 and R^6 each represent a hydrogen atom;

or

R^2 represents a fluorine or a chlorine atom, or a group selected from :
methyl, difluoromethyl and trifluoromethyl;
and R^3 represents a fluorine or a chlorine atom, or a group selected from :
cyano, methyl, difluoromethyl and trifluoromethyl;
and R^4, R^5 and R^6 each represent a hydrogen atom;

or

R^2 represents a fluorine atom or a group selected from :
methyl, difluoromethyl and trifluoromethyl;
and R^4 represents a fluorine or a chlorine atom, or a group selected from :
cyano and difluoromethoxy;
and R^3, R^5 and R^6 each represent a hydrogen atom;

or

R^2 represents a fluorine atom or a group selected from :
methyl, difluoromethyl and trifluoromethyl;
and R^5 represents a fluorine or a chlorine atom, or a group selected from :
cyano, methyl, difluoromethyl and trifluoromethyl;
and R^3, R^4 and R^6 each represent a hydrogen atom;

or

R^3 represents a fluorine or a chlorine atom, or a group selected from :
cyano, methyl, difluoromethyl and trifluoromethyl;
and R^4 represents a fluorine or a chlorine atom, or a group selected from :
cyano and difluoromethoxy;
and R^2, R^5 and R^6 each represent a hydrogen atom;

or

R^3 and R^5 represent, independently of each other, a fluorine or a chlorine atom, or a group selected from :
cyano and difluoromethyl;
and R^2, R^4 and R^6 each represent a hydrogen atom;

or

R^2, R^3, R^4, R^5 and R^6 each represent a hydrogen atom;

R^7 represents a hydrogen atom;

or

R^2 and R^6 represent, independently of each other, a fluorine or a chlorine atom;
and R^3, R^4 and R^5 each represent a hydrogen atom;
and R^7 represents a methyl group;

or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

4. The compound according to claim 1, 2 or 3, wherein :

R^1 represents a hydrogen atom or a methyl group;

R^2 represents a fluorine atom or a group selected from :
methyl, difluoromethyl and trifluoromethyl;
and R^3, R^4, R^5 and R^6 each represent a hydrogen atom;

or

R^3 represents a fluorine or a chlorine atom, or a group selected from :
cyano, methyl, difluoromethyl and trifluoromethyl;
and R^2, R^4, R^5 and R^6 each represent a hydrogen atom;

or

R^4 represents a fluorine or a chlorine atom, or a group selected from :
cyano and difluoromethoxy;
and R^2, R^3, R^5 and R^6 each represent a hydrogen atom;

or

R^2 represents a fluorine or a chlorine atom, or a trifluoromethyl group;
and R^3 represents a fluorine atom;
and R^4, R^5 and R^6 each represent a hydrogen atom;

or

R^2 and R^4 each represent a fluorine atom;
and R^3, R^5 and R^6 each represent a hydrogen atom;

or

R^2 and R^5 each represent a fluorine atom;

and R^3, R^4 and R^6 each represent a hydrogen atom;

or

R^3 and R^4 each represent a fluorine atom;

and R^2, R^5 and R^6 each represent a hydrogen atom;

or

R^3 and R^5 represent, independently of each other, a fluorine or a chlorine atom;

and R^2, R^4 and R^6 each represent a hydrogen atom;

or

R^2, R^3, R^4, R^5 and R^6 each represent a hydrogen atom;

R^7 represents a hydrogen atom;

or

R^2 and R^6 each represent a fluorine atom;

and R^3, R^4 and R^5 each represent a hydrogen atom;

and R^7 represents a methyl group;

or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

5. The compound according to any one of claims 1 to 4, which is selected from the group consisting of:

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(3-chloro-5-fluorophenyl)acetamide ,

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(2-fluorophenyl)acetamide ,

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(3-fluorophenyl)acetamide ,

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(4-fluorophenyl)acetamide ,

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(3-chlorophenyl)acetamide ,

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(4-chlorophenyl)acetamide ,

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-[3-(trifluoromethyl)phenyl]acetamide ,

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-[2-(trifluoromethyl)phenyl]acetamide ,

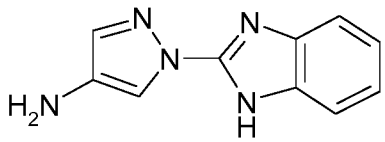
N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(3,5-dichlorophenyl)acetamide ,

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(3,5-difluorophenyl)acetamide ,

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-phenylacetamide ,

N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(2,3-difluorophenyl)acetamide ,
N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(2,4-difluorophenyl)acetamide ,
N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(2,5-difluorophenyl)acetamide ,
N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(3,4-difluorophenyl)acetamide ,
N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(2-methylphenyl)acetamide ,
N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(3-methylphenyl)acetamide ,
N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-[2-(difluoromethyl)phenyl]acetamide ,
N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-[3-(difluoromethyl)phenyl]acetamide ,
N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(3-cyanophenyl)acetamide ,
N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(4-cyanophenyl)acetamide ,
N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(2-chloro-3-fluorophenyl)acetamide ,
N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-[3-fluoro-2-(trifluoromethyl)phenyl]acetamide ,
N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-[4-(difluoromethoxy)phenyl]acetamide ,
N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(3-chloro-5-fluorophenyl)-N-methylacetamide ,
(±)-N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(2,6-difluorophenyl)propanamide ,
(2R)-N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(2,6-difluorophenyl)propanamide , and
(2S)-N-[1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(2,6-difluorophenyl)propanamide ,
or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

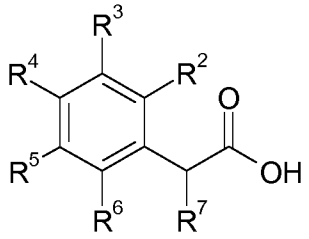
6. A method of preparing a compound of general formula **(I)** according to any one of claims 1 to 5, said method comprising the step of allowing a compound of formula **(VII)** :



(VII) ,

or a salt thereof, such as for example a salt with hydrochloric acid,

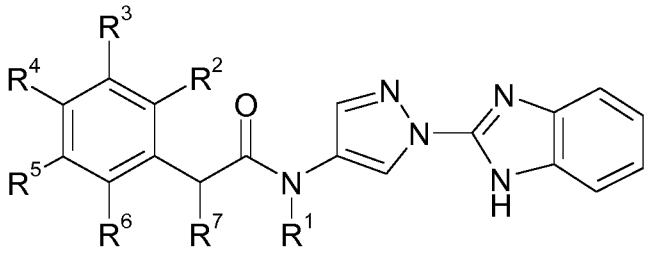
to react with a compound of general formula **(VIII)** :



(VIII) ,

in which R^2, R^3, R^4, R^5, R^6 and R^7 are as defined for the compounds of general formula **(I)** according to any one of claims 1 to 5, in the presence of a tertiary aliphatic amine, such as N,N-diisopropylethylamine, and propane phosphonic acid anhydride,

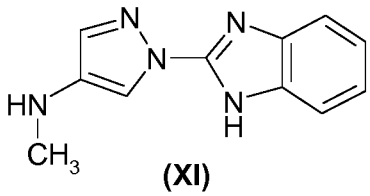
thereby giving a compound of general formula **(I)** :



(I) ,

in which R^2, R^3, R^4, R^5, R^6 and R^7 are as defined for the compounds of general formula **(I)** according to any one of claims 1 to 5, and R^1 represents a hydrogen atom.

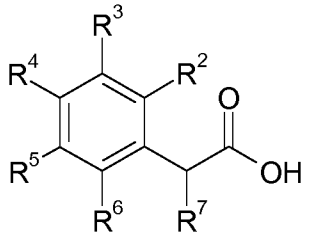
7. A method of preparing a compound of general formula **(I)** according to any one of claims 1 to 5, said method comprising the step of allowing a compound of formula **(XI)** :



(XI) ,

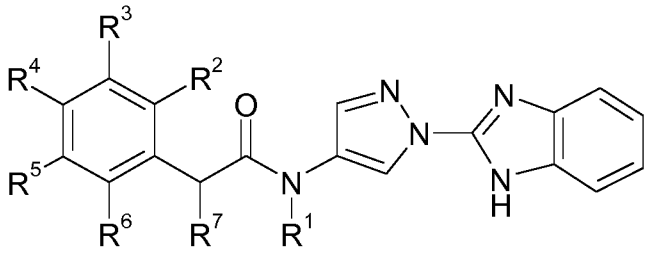
or a salt thereof, such as for example a salt with hydrochloric acid,

to react with a compound of general formula **(VIII)** :



(VIII)

in which R^2, R^3, R^4, R^5 and R^6 are as defined for the compounds of general formula **(I)** according to any one of claims 1 to 5, and R^7 represents a hydrogen atom, in the presence of a tertiary aliphatic amine, such as N,N-diisopropylethylamine, and propane phosphonic acid anhydride, thereby giving a compound of general formula **(I)** :



(I)

in which R^2, R^3, R^4, R^5 and R^6 are as defined for the compounds of general formula **(I)** according to any one of claims 1 to 5, and R^1 represents a methyl group, and R^7 represents a hydrogen atom.

8. A compound of general formula **(I)**, or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, according to any one of claims 1 to 5, for use in the treatment or prophylaxis of a disease.

9. A pharmaceutical composition comprising a compound of general formula **(I)**, or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, according to any one of claims 1 to 5, and a pharmaceutically acceptable diluent or carrier.

10. A pharmaceutical combination comprising :

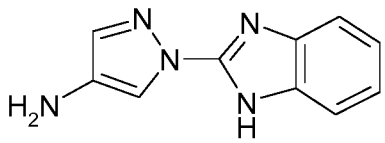
- one or more first active ingredients selected from a compound of general formula **(I)** according to any of claims 1 to 5, and
- one or more second active ingredients selected from chemotherapeutic anti-cancer agents.

11. Use of a compound of general formula **(I)**, or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, according to any one of claims 1 to 5, for the prophylaxis or treatment of a disease.

12. Use of a compound of general formula **(I)**, or a stereoisomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, according to any one of claims 1 to 5, for the preparation of a medicament for the prophylaxis or treatment of a disease.

13. Use according to claim 8, 11 or 12, wherein said disease is a disease of uncontrolled cell growth, proliferation and/or survival, an undesirable cellular immune response, or an undesirable cellular inflammatory response, particularly in which the disease of uncontrolled cell growth, proliferation and/or survival, undesirable cellular immune response, or undesirable cellular inflammatory response is a haematological tumour, a solid tumour and/or metastases thereof, e.g. leukaemias and myelodysplastic syndrome, malignant lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the thorax including non-small cell and small cell lung tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

14. Use of a compound of formula **(VII)** :



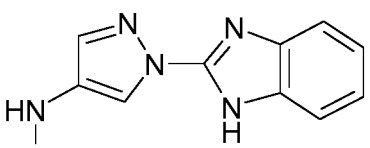
(VII)

,

or a salt thereof, such as for example a salt with hydrochloric acid,

for the preparation of a compound of general formula **(I)** according to any one of claims 1 to 5.

15. Use of a compound of formula **(XI)** :



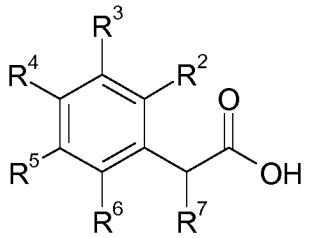
(XI)

,

or a salt thereof, such as for example a salt with hydrochloric acid,

for the preparation of a compound of general formula **(I)** according to any one of claims 1 to 5.

16. Use of a compound of general formula **(XIII)** :



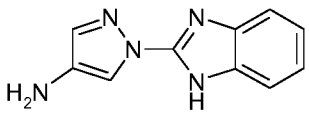
(VIII)

,

in which R^2, R^3, R^4, R^5, R^6 and R^7 are as defined for the compounds of general formula **(I)** according to any one of claims 1 to 5,

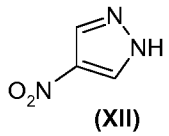
for the preparation of a compound of general formula **(I)** according to any one of claims 1 to 5.

17. Method of preparing the compound of formula **(VII)**,



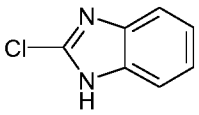
(VII)

said method comprising the step of allowing the compound of formula **(XII)** :



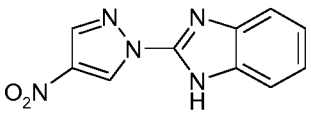
(XII)

to react with the compound of formula **(XIII)** :



(XIII)

thereby giving the compound of formula **(XIV)** :



(XIV)

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/063545

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/04 A61K31/4184 A61P35/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/035065 A1 (AVENTIS PHARMA INC [US]; EDWARDS MICHAEL LOUIS [US]; COX PAUL JOSEPH [) 1 May 2003 (2003-05-01) compound A1-B36 on page 110; claims 1, 4, 202, 227-234, 238	1-17
A	WO 2005/077939 A1 (BASILEA PHARMACEUTICA AG [CH]; EBERLE MARTIN [CH]; BACHMANN FELIX [CH]) 25 August 2005 (2005-08-25) claims 1, 8-13; table 2	1-17
X	US 2014/179733 A1 (CHEN XI [US] ET AL) 26 June 2014 (2014-06-26) cited in the application examples; paragraph [[0227]] - paragraph [[0228]]; claim 1	1-17

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 July 2016	12/08/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sáez Díaz, R

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/063545

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 2005/002552 A2 (ASTEX TECHNOLOGY LTD [GB]; BERDINI VALERIO [GB]; O'BRIEN MICHAEL ALIST) 13 January 2005 (2005-01-13) claims 1, 46, 47; example 8 -----	1-17
A	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 11 November 2011 (2011-11-11), XP002759939, Database accession no. 134436-46-0 1-(1H-benzimidazol-2-yl)-1H-pyrazol-4-amin e -----	14,17

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/063545

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