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(54) Title: NOVEL PKC INHIBITORS

(57) Abstract: The present invention relates to new kinase inhibitors, more specifically PKC θ inhibitors, compositions, in particular pharmaceuticals, comprising such inhibitors, and to uses of such inhibitors in the treatment and prophylaxis of disease. In particular, the present invention relates to new PKC θ inhibitors compositions, in particular pharmaceuticals, comprising such inhibitors, and to uses of such inhibitors in the treatment and prophylaxis of disease. In addition, the invention relates to methods of treatment and use of said compounds in the manufacture of a medicament for the application to a number of therapeutic indications including autoimmune and inflammatory diseases.



Novel PKC inhibitors

Field of the invention

The present invention relates to new kinase inhibitors, more specifically Protein Kinase C
5 thêta (PKC θ) inhibitors, compositions, in particular pharmaceuticals, comprising such
inhibitors, and to uses of such inhibitors in the treatment and prophylaxis of disease. In
particular, the present invention relates to new PKC thêta inhibitors, compositions, in
particular pharmaceuticals, comprising such inhibitors, and to uses of such inhibitors in
the treatment and prophylaxis of disease.

Background of the invention

The protein kinase C (PKC) family is a family of lipid-activated serine/threonine kinases.
PKC enzymes are key intracellular mediators of signal transduction pathways and are
implicated in various cell functions throughout the body. They are involved in controlling
15 the function of other proteins through the phosphorylation of hydroxyl groups on serine
and threonine amino acid residues on these proteins. PKC family members are
expressed in a wide range of tissues and cell types; precise mechanisms control their
structure, function, and subcellular localization.

Several PKC isozymes, encoded by different genes but sharing high sequence and
20 structure homology, exist. The PKC isozymes are classified according to the Ca^{2+} and/or
diacylglycerol (DAG) signals needed for their activation. The conventional PKCs (cPKCs)
require Ca^{2+} and DAG for activation; the cPKC subfamily includes PKC α , PKC β , and
PKC γ . The novel PKCs (nPKCs) require DAG, but not Ca^{2+} for their activation; the nPKC
subfamily includes PKC δ , PKC ϵ , PKC η , and PKC θ . The atypical PKCs (aPKCs) do not
25 require DAG or Ca^{2+} for their activation; the aPKC subfamily includes PKC ζ and PKC ι/λ .

PKCs are structurally closely related. All isozymes have a regulatory and a catalytic
domain connected by a hinge region. The catalytic domain is highly conserved in all
isozymes and includes the substrate- and the ATP-binding domains. The regulatory
domain is structurally more divergent amongst isozymes and controls the activation of the
30 enzyme. The regulatory domain contains an autoinhibitory pseudosubstrate domain and
two discrete membrane-targeting domains, termed C1 and C2. cPKCs contain a C1
domain that functions as a DAG-binding motif, and a C2 domain that binds anionic
phospholipids in a Ca^{2+} -dependent manner. nPKCs do also contain a C1 and a C2
domain, but their C2 domain lacks Ca^{2+} -binding properties, which largely underlies their

distinct pharmacology compared to cPKCs. Also aPKCs do have a Ca^{2+} -insensitive C2 domain, but besides contain an atypical C1 domain which does not bind DAG. Primed PKCs are activated to phosphorylate their substrates when their regulatory domains engage the appropriate combination of signals (DAG, Ca^{2+} , and phospholipids in the case of cPKCs).

PKC θ belongs to the nPKC subfamily, and is expressed mainly in T-cells, muscle cells, and platelets. PKC θ is highly homologous to the other nPKCs. PKC δ is the isozyme with the closest homology to PKC θ , i.e., they have 76% identity in their catalytic domains and only one amino acid difference in their ATP-binding pockets. Hence, the discovery of inhibitors that are highly selective for PKC θ over the other nPKCs is a challenge.

PKC θ plays a key role in T-cell activation and survival. It has been well established that T-cells play an important role in regulating the immune response. Compared to other PKC isozymes expressed in T-cells, PKC θ displays some unique properties. PKC θ is the only PKC isozyme that is translocated to the immunological synapse, which is the site of contact in the plasma membrane between the antigen-specific T-cell and the antigen-presenting cell. More in particular, PKC θ is translocated to the so-called central supramolecular activation complex area of the synapse where it co-localizes with the T-cell receptor (TCR). At this site, PKC θ integrates TCR and CD28 signals. Localization of PKC θ to the immunological synapse is highly related to T-cell activation. Moreover, PKC θ has an essential role in the survival of activated T-cells. Mutation of the PKC θ gene leads to defective T-cell activation and aberrant expression of apoptosis-related proteins, resulting in poor T-cell survival. Three transcription factors, nuclear factor κB (NF- κB), activator protein-1 (AP-1), and nuclear factor of T-cells (NFAT), are targets of PKC θ in TCR/CD28 co-stimulated cells. These transcription factors are essential for activation of the interleukin-2 (IL-2) promoter and subsequent IL-2 production. Hence, PKC θ activates T-cell cytokine production, especially that of IL-2. Via moesin phosphorylation, PKC θ may be involved in remodeling of the actin cytoskeleton as well.

Experiments with PKC θ -knock-out mice demonstrated a differential requirement for PKC θ in different immune responses. PKC θ plays a critical role in responses mediated by Th2 and Th17 CD4 $^{+}$ T helper cells, while its role in responses mediated by Th1 CD4 $^{+}$ T helper cells and by CD8 $^{+}$ cytotoxic T-cells is less critical. Th1 and CD8 $^{+}$ responses are induced upon bacterial and viral infection, while allergic and anti-helminth responses are driven by Th2, and autoimmune disease models are Th17 mediated. It is presumed that strong activation by pathogens or alternative pathways of T-cell activation can overcome the defects in PKC θ -mediated signals regarding responses mediated by Th1 and CD8 $^{+}$ cytotoxic T-cells. Also, innate immunity signals provided by microorganisms have the

ability to overcome the requirement for PKC θ in antiviral and antibacterial immunity. However, PKC θ -deficient mice showed resistance to the development of several T-cell mediated diseases, including arthritis, asthma, multiple sclerosis, inflammatory bowel disease, cerebral malaria, graft-versus-host disease, or transplant rejection.

5 PKC θ inhibitors could be of interest for the treatment of diseases related to inflammation and immunity, including autoimmunity. More in particular for the treatment of diseases related to inflammation and immunity, without compromising the ability of patients to mount antiviral responses. Because of its restricted expression and important role in inflammation, PKC θ is a potential therapeutic target for multiple lung disorders involving
10 inflammation and immunity, such as Asthma or chronic obstructive pulmonary disease (COPD). In addition, given the often abundant expression of PKC θ in transformed T-cells (leukemias and lymphomas) and gastrointestinal stromal tumors, PKC θ inhibitors might facilitate the elimination of malignant T-cells by promoting their apoptosis, and hence could be of interest for the treatment of hematological malignancies and gastrointestinal
15 stromal tumors.

In skeletal muscle, PKC θ signaling is required for myoblast fusion to form muscle fibers. In PKC θ knockout mice and in muscle-specific PKC θ -dominant negative mutant mouse models, delayed body and muscle fiber growth during the first weeks of post-natal life was observed. Also myofiber formation during muscle regeneration after freeze injury was
20 impaired in PKC θ -mutant mice. In addition, PKC θ activation in muscle has been shown to be associated with insulin resistance. As well, the insulin receptor substrate (IRS1), an adaptor protein that links the insulin receptor to its downstream effectors, is a potential substrate for PKC θ . Suppression of PKC θ activity was also found to greatly reduce palmitate-induced phosphorylation of phosphoinositide-dependent protein kinase 1
25 (PDK1), a master kinase in the regulation of various downstream events such as insulin-stimulated glucose uptake and protein synthesis. Originally it was reported that PKC θ -knock-out mice are protected from fat-induced insulin resistance in their muscle tissue, but a later study found that PKC θ -deficient mice on a high-fat diet develop severe insulin resistance. It will be appreciated that although the preclinical results are disparate,
30 inhibitors of PKC θ could be of interest for treating type II diabetes.

In platelets, PKC θ plays an important role in platelet functional responses downstream of the glycoprotein VI and by G-protein-coupled protease-activated receptors. Murine platelets lacking PKC θ showed impaired platelet aggregation and secretion. This was also the case in human platelets treated with a PKC θ -selective antagonistic peptide.
35 PKC θ -deficient mice exhibited impaired hemostasis and prolonged bleeding following vascular injury.

While PKC θ inhibition appears tolerated, the high sequence homology between the different members of the PKC family significantly complicates the development of isozyme-selective PKC inhibitors. Even though inhibition of multiple PKCs has sometimes been proposed as an interesting approach for the treatment of airway diseases such as asthma or chronic obstructive pulmonary disease (COPD), this situation is problematic in view of the multiple roles that are performed by PKCs in various tissues. As an example, inhibition of the closely related PKC δ could result in increased proliferation of B-cells and in increased production of inflammatory cytokines, thereby causing increased susceptibility to autoimmune disease. Hence, significant systemic exposure to non-selective PKC θ inhibitors should be avoided, if not required by the pathology to be treated.

Local application is a first possibility to reduce systemic exposure to a drug compound, by directly delivering the drug compound to the intended site of action and possibly reducing the quantity of drug compound that is required in order to observe a clinically significant effect. Despite the fact that direct local application is preferred in medical practice, there can still be concerns regarding drug levels reached into the systemic circulation. For example, the treatment of airway diseases by local delivery by for instance inhalation, poses the risk of systemic exposure due to large amounts entering the GI tract and/or systemic absorption through the lungs. For the treatment of eye diseases by local delivery, also significant amounts of compound can enter the GI tract and/or systemic circulation due to the low permeability of the cornea, low capacity for fluid, efficient drainage and presence of blood vessels in the eyelids. Also for dermal applications, local injections and implantable medical devices, there is a severe risk of leakage into the systemic circulation. Therefore, in addition to the physical local application, it is preferable that the compounds display additional chemical or biological properties that will minimize systemic exposure.

Soft drugs are biologically active compounds that are inactivated once they enter the systemic circulation. This inactivation involves the controlled conversion of said soft drug into a predictable metabolite displaying markedly reduced functional activity or, preferably, negligible functional activity. Inactivation can be achieved in the liver, but the preferred inactivation should occur in the blood. These compounds, once applied locally to the target tissue / organ exert their desired effect locally. When they leak out of this target tissue / organ into the systemic circulation, they are very rapidly inactivated. Thus, soft

drugs of choice are sufficiently stable in the target tissue / organ to exert the desired biological effect, but are rapidly degraded in the blood to biologically inactive compounds. In addition, it is highly preferable that the soft drugs of choice have retention at their biological target. This property will limit the number of daily applications and is highly
5 desired to reduce the total load of drug and metabolites and in addition will significantly increase the patient compliance. In view of the potential of non-selective PKC inhibitors for generating undesirable side effects, it will be appreciated that soft drug approaches represent an attractive way of generating PKC θ inhibitors with improved properties; in particular PKC θ inhibitors associated with reduced systemic exposure and therefore lower
10 potential for undesirable side effects.

Although soft drugs represent a potentially attractive approach for the inhibition of PKC θ and the treatment of PKC θ -associated diseases or conditions, the design and optimization of such compounds is however not trivial. Successful soft drugs have to
15 retain strong on-target potency and functional efficacy. Additionally, successful soft drugs should display good stability at the intended site of action (eg eye or lung), so that a pharmacologically relevant concentration of the drug can be reached and maintained for a prolonged period of time (typically several hours) at this intended site of action. Furthermore, successful soft drugs should be rapidly degraded once they enter systemic
20 circulation, so that systemic exposure and the undesired side effects associated with systemic exposure are avoided. As a result, the design and optimization of molecules successfully combining all of these aspects represents a significant technical problem.

In conclusion, there is a continuing need to design and develop soft PKC θ inhibitors for
25 the treatment of a wide range of disease states. The compounds described herein are soft PKC θ inhibitors and solve the technical problem of successfully combining strong on-target and functional efficacy, good stability in target organs (such as, but not limited to, eye or lung) and rapid conversion in blood towards a predictable species. The compounds described herein and pharmaceutically acceptable compositions thereof are useful for
30 treating or lessening the severity of a variety of disorders or conditions associated with PKC θ activation.

More specifically, the compounds of the invention are preferably used in the prevention and/or treatment of at least one disease or disorder, in which PKCs are involved, more
35 specifically PKC θ , such as immunological disorders and inflammatory diseases which can

be treated via local application of a drug compound including, but not limited to inflammatory eye diseases such as, but not limited to uveitis, conjunctivitis, contact allergy, retinopathy or post-trauma/post-surgery/post-laser treatment complications including corneal transplant rejection; inflammatory airway diseases; rheumatoid arthritis, skin diseases such as but not limited to contact dermatitis and psoriasis, organ and bone marrow transplant rejection or allergy, intestinal inflammatory diseases such as but not limited to ulcerative colitis, inflammatory bowel disease and Crohn's disease.

SUMMARY OF THE INVENTION

We have surprisingly found that the compounds described herein act as inhibitors of PKC, in particular as soft PKC θ inhibitors. Compared to art known PKC θ inhibitors, such as for example described in WO2004/067516, WO2006/014482, WO2006/105023, and WO2007/076247, the compounds of the present invention differ in that they are very rapidly converted into predictable, functionally inactive compounds when entering systemic circulation, yet retain good stability in target organs. Compound inactivation can occur in the liver, but is preferentially achieved in the blood flow, through blood enzymes, for example by carboxylic ester hydrolases (EC 3.1.1) such as Cholinesterase or Paraoxonase 1 (PON1) or by plasma proteins displaying pseudoesterase activity such as Human serum albumin. The compounds of the present invention therefore solve the technical problem of successfully combining on-target potency (inhibitory activity against PKC θ) and functional efficacy, good stability in target organs and rapid conversion in blood towards a predictable, species. As a result, the compounds of the invention can achieve a desired pharmacological effect through inhibition of PKC θ at the intended site of action (eg eye or lung), while avoiding a systemic inhibition of PKC θ and/or other PKCs, that would create potential for side effects.

Carboxylic ester hydrolases (EC 3.1.1) represent a large group of enzymes involved in the degradation of carboxylic esters into alcohols and carboxylic acids. As such, enzymes displaying this catalytic activity are of potential interest for the design of soft kinase inhibitors. EC 3.1.1 includes the following sub-classes: EC 3.1.1.1 carboxylesterase, EC 3.1.1.2 arylesterase, EC 3.1.1.3 triacylglycerol lipase, EC 3.1.1.4 phospholipase A2, EC 3.1.1.5 lysophospholipase, EC 3.1.1.6 acetylcholinesterase, EC 3.1.1.7 acetylcholinesterase, EC 3.1.1.8 cholinesterase, EC 3.1.1.10 tropinesterase, EC 3.1.1.11 pectinesterase, EC 3.1.1.13 sterol esterase, EC 3.1.1.14 chlorophyllase, EC 3.1.1.15 L-arabinonolactonase,

EC 3.1.1.17 gluconolactonase, EC 3.1.1.19 uronolactonase, EC 3.1.1.20 tannase, EC 3.1.1.21 retinyl-palmitate esterase, EC 3.1.1.22 hydroxybutyrate-dimer hydrolase, EC 3.1.1.23 acylglycerol lipase, EC 3.1.1.24 3-oxoadipate enol-lactonase, EC 3.1.1.25 1,4-lactonase, EC 3.1.1.26 galactolipase, EC 3.1.1.27 4-pyridoxolactonase, EC 3.1.1.28
5 acylcarnitine hydrolase, EC 3.1.1.29 aminoacyl-tRNA hydrolase, EC 3.1.1.30 D-arabinonolactonase, EC 3.1.1.31 6-phosphogluconolactonase, EC 3.1.1.32 phospholipase A1, EC 3.1.1.33 6-acetylglucose deacetylase, EC 3.1.1.34 lipoprotein lipase, EC 3.1.1.35 dihydrocoumarin hydrolase, EC 3.1.1.36 limonin-D-ring-lactonase, EC 3.1.1.37 steroid-lactonase, EC 3.1.1.38 triacetate-lactonase, EC 3.1.1.39 actinomycin lactonase, EC
10 3.1.1.40 orsellinate-depside hydrolase, EC 3.1.1.41 cephalosporin-C deacetylase, EC 3.1.1.42 chlorogenate hydrolase, EC 3.1.1.43 α -amino-acid esterase, EC 3.1.1.44 4-methyloxaloacetate esterase, EC 3.1.1.45 carboxymethylenebutenolidase, EC 3.1.1.46 deoxylimonate A-ring-lactonase, EC 3.1.1.47 1-alkyl-2-acetyl-glycerophosphocholine esterase, EC 3.1.1.48 fusarinine-C ornithinesterase, EC 3.1.1.49 sinapine esterase, EC
15 3.1.1.50 wax-ester hydrolase, EC 3.1.1.51 phorbol-diester hydrolase, EC 3.1.1.52 phosphatidylinositol deacylase, EC 3.1.1.53 sialate O-acetyl-esterase, EC 3.1.1.54 acetoxylbutynylbithiophene deacetylase, EC 3.1.1.55 acetylsalicylate deacetylase, EC 3.1.1.56 methylumbelliferyl-acetate deacetylase, EC 3.1.1.57 2-pyrone-4,6-dicarboxylate lactonase, EC 3.1.1.58 N-acetylgalactosaminoglycan deacetylase, EC 3.1.1.59 juvenile-hormone esterase, EC 3.1.1.60 bis(2-ethylhexyl)phthalate esterase, EC 3.1.1.61 protein-glutamate methylesterase, EC 3.1.1.63 11-cis-retinyl-palmitate hydrolase, EC 3.1.1.64 all-trans-retinyl-palmitate hydrolase, EC 3.1.1.65 L-rhamnono-1,4-lactonase, EC 3.1.1.66 5-(3,4-diacetoxybut-1-ynyl)-2,2'-bithiophene deacetylase, EC 3.1.1.67 fatty-acyl-ethyl-ester synthase, EC 3.1.1.68 xylono-1,4-lactonase, EC 3.1.1.70 cetraxate benzylesterase, EC
25 3.1.1.71 acetylalkylglycerol acetylhydrolase, EC 3.1.1.72 acetylxyloxy-esterase, EC 3.1.1.73 feruloyl esterase, EC 3.1.1.74 cutinase, EC 3.1.1.75 poly(3-hydroxybutyrate) depolymerase, EC 3.1.1.76 poly(3-hydroxyoctanoate) depolymerase, EC 3.1.1.77 acyloxyacyl hydrolase, EC 3.1.1.78 polyneuridine-aldehyde esterase, EC 3.1.1.79 hormone-sensitive lipase, EC 3.1.1.80 acetylajmaline esterase, EC 3.1.1.81 quorum-quenching N-acyl-homoserine lactonase, EC 3.1.1.82 pheophorbide, EC 3.1.1.83
30 monoterpene ϵ -lactone hydrolase, EC 3.1.1.84 cocaine esterase, EC 3.1.1.85 mannosylglycerate hydrolases.

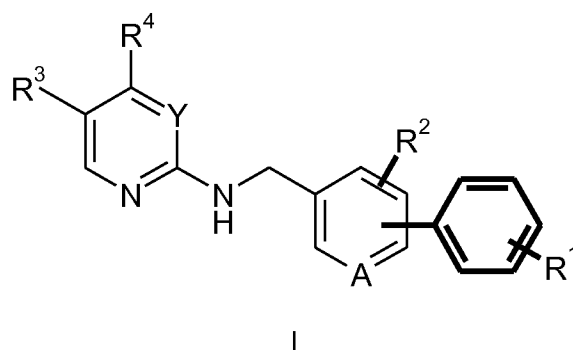
An example of carboxylic ester hydrolase is PON1. PON1 is a Ca^{2+} dependent serum
35 class A esterase, which is synthesized in the liver and secreted in the blood, where it associates exclusively with high-density lipoproteins (HDLs). Furthermore, it is able to

cleave a unique subset of substrates including organophosphates, arylesters, lactones and cyclic carbonates. Therefore, the R¹ substituent of the compounds of the present invention, generally represented by formula I hereinbelow, can be selected to comprise a substituent selected from the group of arylesters, lactones and cyclic carbonates, more specifically from arylesters and lactones.

Human serum albumin (HSA) is a major component of blood plasma, accounting for approximately 60% of all plasma proteins. HSA has been found to catalyze the hydrolysis of various compounds such as aspirin, cinnamoylimidazole, p-nitrophenyl acetate, organophosphate insecticides, fatty acid esters or nicotinic esters. HSA displays multiple nonspecific catalytic sites in addition to its primary reactive site. The catalytic efficiency of these sites is however low, and HSA has often been described not as a true esterase, but as a pseudoesterase. In spite of its low catalytic efficiency, HSA can still play a significant role in the metabolism of drug-like compounds, because of its high concentration in plasma.

Unless a context dictates otherwise, asterisks are used herein to indicate the point at which a mono- or bivalent radical depicted is connected to the structure to which it relates and of which the radical forms part.

Viewed from a first aspect, the invention provides a compound of Formula I or a stereoisomer, tautomer, racemic, salt, hydrate, or solvate thereof,



Wherein

Y is -N- or -CH-;

A is -N- or -CH-;

R¹ is selected from the group consisting of

- a) $-(CH_2)_m-C(=O)-OR^{11}$
 b) $-(CH_2)_m-C(=O)-NH-R^{12}$
 c) $-(CH_2)_m-NH-C(=O)-R^{12}$
 d) $-(CH_2)_m-X-R^{12}$
 e) $(CH_2)_m-C(=O)-R^{12}$

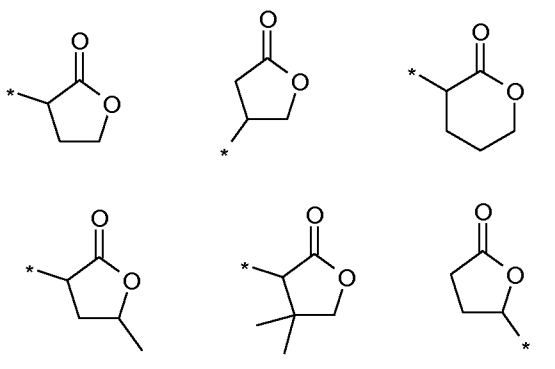
Wherein

m is an integer selected from 0 to 3;

R^{11} is selected from the group comprising optionally substituted C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{1-8} alkoxyalkyl, alkylcycloalkyl, heterocyclyl, aryl, Het^1 , and heteroaryl;

Wherein

Het^1 is selected from the group consisting of



R^{12} is an optionally substituted Het^1 or R^{12} is selected from the group consisting of C_{1-8} alkyl, C_{3-8} cycloalkyl, heterocyclyl, alkylheterocyclyl, aryl and heteroaryl; wherein said C_{1-8} alkyl, C_{3-8} cycloalkyl, heterocyclyl, alkylheterocyclyl, aryl and heteroaryl is substituted with:

- one or more substituents independently selected from the group consisting of Het^1 ; $-O-Het^1$; $-NH-Het^1$, $-S-Het^1$, and $-(CH_2)_n-C(=O)-OR^{11}$; and
- optionally one or more substituents independently selected from the group consisting of halo, hydroxyl, carbonyl, nitro, amino, oxime, imino, azido, hydrazino, cyano, aryl, heteroaryl, cycloalkyl, heterocyclyl, acyl, alkylamino, alkoxy, thiol, alkylthio, acylamino, alkyl

esters, carbamate, thioamido, urea, aminocarbonyl, alkyl, alkenyl, alkynyl, cycloalkylalkyl, $-\text{SO}_2\text{NH}_2$, aralkyl, haloalkyl, haloalkoxy, alkylaminocarbonyl, heteroarylalkyl, alkylsulfonamide, alkylcarbonylaminoalkyl, aryloxy, alkylcarbonyl, acyl, arylcarbonyl, aminocarbonyl, alkylsulfoxide, $-\text{SO}_2\text{R}^a$, carboxyl, and the like; wherein R^a is alkyl or cycloalkyl;

Wherein

n is an integer from 0 to 3;

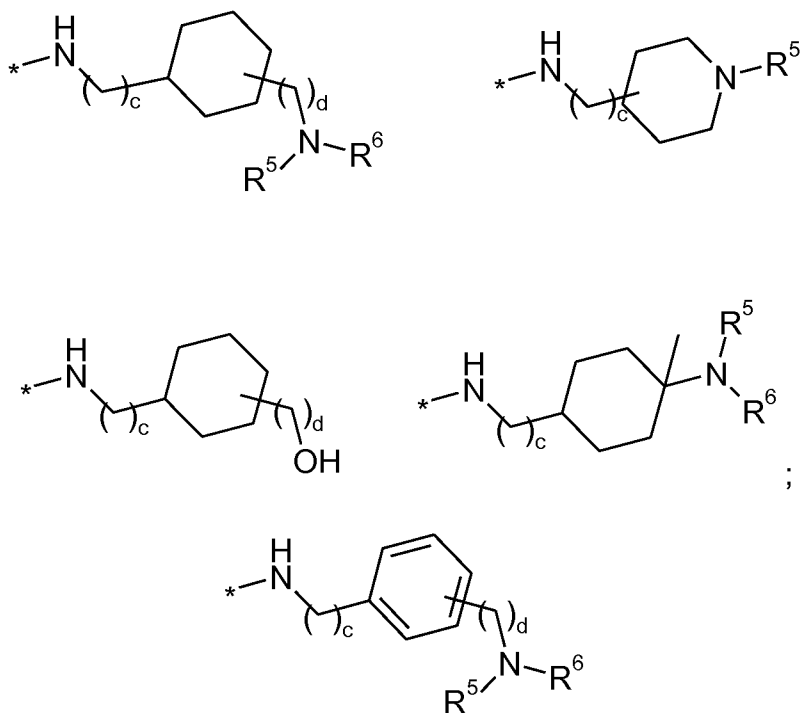
Het^1 and R^{11} are as defined hereinbefore;

10 X is $-\text{NH}-$, $-\text{CH}_2-$, $-\text{O}-$ or $-\text{S}-$;

R^2 is hydrogen or C_{1-4} alkyl;

R^3 is selected from the group consisting of hydrogen, nitro, halo, haloalkyl, cyano or $-\text{C}(=\text{O})\text{NH}_2$;

R^4 is selected from the following groups:



Wherein

20 c and d are each independently an integer from 0 to 3; and

R^5 and R^6 are each independently selected from the group consisting of hydrogen and optionally substituted C_{1-6} alkyl; or

R⁵ and R⁶ together with the nitrogen atom to which they are attached form a heterocycle optionally substituted with C₁₋₆alkyl.

As can be seen from this definition, and in particular from the definition of R₁, all
5 compounds of formula I display at least one ester, or cyclic ester (lactone)

Viewed from a further aspect, the invention provides the use of a compound of the invention, or a composition comprising such a compound, for inhibiting the activity of at least one kinase, in vitro or in vivo.

10

Viewed from a further aspect, the invention provides the use of a compound of the invention, or a composition comprising such a compound, for inhibiting the activity of at least one protein kinase C, for example novel PKCs isoforms, more specifically PKC θ .

Viewed from a further aspect, the invention provides the use of a compound of the
15 invention, or a composition comprising such a compound, for treating a disease or a disorder associated with the activation of T-cells in a patient; such use comprising administering to the patient a therapeutically effective amount of a compound of the present invention as described above.

20 Viewed from a further aspect, the invention provides a pharmaceutical and/or veterinary composition comprising a compound of the invention.

Viewed from a still further aspect, the invention provides a compound of the invention for use as a medicine; in particular a human or veterinary medicine.

25

Viewed from a still further aspect, the invention provides the use of a compound of the invention in the preparation of a medicament for the prevention and/or treatment of immunological disorders and/or inflammatory diseases which can be treated via local application of a drug compound including, but not limited to inflammatory eye diseases
30 such as, but not limited to uveitis, conjunctivitis, contact allergy, retinopathy or post-trauma/post-surgery/post-laser treatment complications including corneal transplant rejection; inflammatory airway diseases; rheumatoid arthritis, skin diseases such as but not limited to contact dermatitis and psoriasis, organ and bone marrow transplant rejection

or allergy, intestinal inflammatory diseases such as but not limited to ulcerative colitis, inflammatory bowel disease and Crohn's disease.

BRIEF DESCRIPTION OF THE DRAWINGS

5 With specific reference now to the figures, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of the different embodiments of the present invention only. They are presented in the cause of providing what is believed to be the most useful and readily description of the principles and conceptual aspects of the invention. In this regard no attempt is made to show structural details of the invention
10 in more detail than is necessary for a fundamental understanding of the invention. The description taken with the drawings making apparent to those skilled in the art how the several forms of the invention may be embodied in practice.

Figure 1: Dose response curves for selected compounds of the invention: IC₅₀ values are
15 plotted in function of compound dose. Circles: Cpd 1. Squares: Cpd 2. Stars: Cpd 4. Diamonds: Cpd 6

Figure 2: Stability of selected compounds in human plasma. Black bars: % remaining after 10 minutes; dark grey bars: % remaining after 60 minutes; white bars: % remaining after 100 minutes.

20 **Figure 3:** Stability of selected compounds on human lung S9 fraction.

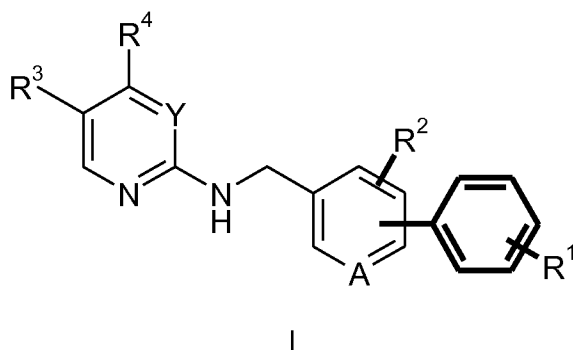
DETAILED DESCRIPTION OF THE INVENTION

The present invention will now be further described. In the following passages, different aspects of the invention are defined in more detail. Each aspect so defined may be
25 combined with any other aspect or aspects unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or advantageous may be combined with any other feature or features indicated as being preferred or advantageous.

Unless a context dictates otherwise, asterisks are used herein to indicate the point at
30 which a mono- or bivalent radical depicted is connected to the structure to which it relates and of which the radical forms part.

Undefined (racemic) asymmetric centers that may be present in the compounds of the present invention are interchangeably indicated by drawing a wavy bonds or a straight bond in order to visualize the undefined steric character of the bond.

- 5 As already mentioned hereinbefore, in a first aspect the present invention provides compounds of Formula I



- 10 wherein X, R¹, R², R³ and R⁴ are as defined hereinbefore, including the stereo-isomeric forms, solvates, and pharmaceutically acceptable addition salts thereof.

When describing the compounds of the invention, the terms used are to be construed in accordance with the following definitions, unless a context dictates otherwise:

- 15 The term "alkyl" by itself or as part of another substituent refers to a fully saturated hydrocarbon of Formula C_xH_{2x+1} wherein x is a number greater than or equal to 1. Generally, alkyl groups of this invention comprise from 1 to 20 carbon atoms. Alkyl groups may be linear or branched and may be substituted as indicated herein. When a subscript is used herein following a carbon atom, the subscript refers to the number of carbon
- 20 atoms that the named group may contain. Thus, for example, C₁₋₄alkyl means an alkyl of one to four carbon atoms. Examples of alkyl groups are methyl, ethyl, n-propyl, i-propyl, butyl, and its isomers (e.g. n-butyl, i-butyl and t-butyl); pentyl and its isomers, hexyl and its isomers, heptyl and its isomers, octyl and its isomers, nonyl and its isomers; decyl and its isomers. C₁-C₆ alkyl includes all linear, branched, or cyclic alkyl groups with between 1
- 25 and 6 carbon atoms, and thus includes methyl, ethyl, n-propyl, i-propyl, butyl and its isomers (e.g. n-butyl, i-butyl and t-butyl); pentyl and its isomers, hexyl and its isomers, cyclopentyl, 2-, 3-, or 4-methylcyclopentyl, cyclopentylmethylene, and cyclohexyl.

- The term "optionally substituted alkyl" refers to an alkyl group optionally substituted with one or more substituents (for example 1 to 4 substituents, for example 1, 2, 3, or 4
- 30 substituents or 1 to 2 substituents) at any available point of attachment. Non-limiting

examples of such substituents include halo, hydroxyl, carbonyl, nitro, amino, oxime, imino, azido, hydrazino, cyano, aryl, heteroaryl, cycloalkyl, heterocyclyl, acyl, alkylamino, alkoxy, thiol, alkylthio, carboxylic acid, acylamino, alkyl esters, carbamate, thioamido, urea, sulfonamido and the like.

- 5 The term "alkenyl", as used herein, unless otherwise indicated, means straight-chain, cyclic, or branched-chain hydrocarbon radicals containing at least one carbon-carbon double bond. Examples of alkenyl radicals include ethenyl, E- and Z-propenyl, isopropenyl, E- and Z-butenyl, E- and Z-isobutenyl, E- and Z-pentenyl, E- and Z-hexenyl, E,E-, E,Z-, Z,E-, Z,Z-hexadienyl, and the like. An optionally substituted alkenyl refers to an
- 10 alkenyl having optionally one or more substituents (for example 1, 2, 3 or 4), selected from those defined above for substituted alkyl.

The term "alkynyl", as used herein, unless otherwise indicated, means straight-chain or branched-chain hydrocarbon radicals containing at least one carbon-carbon triple bond. Examples of alkynyl radicals include ethynyl, E- and Z-propynyl, isopropynyl, E- and Z-

15 butynyl, E- and Z-isobutynyl, E- and Z-pentynyl, E, Z-hexynyl, and the like. An optionally substituted alkynyl refers to an alkynyl having optionally one or more substituents (for example 1, 2, 3 or 4), selected from those defined above for substituted alkyl.

The term "cycloalkyl" by itself or as part of another substituent is a cyclic alkyl group, that is to say, a monovalent, saturated, or unsaturated hydrocarbyl group having 1, 2, or 3

20 cyclic structure. Cycloalkyl includes all saturated or partially saturated (containing 1 or 2 double bonds) hydrocarbon groups containing 1 to 3 rings, including monocyclic, bicyclic, or polycyclic alkyl groups. Cycloalkyl groups may comprise 3 or more carbon atoms in the ring and generally, according to this invention comprise from 3 to 15 atoms. The further rings of multi-ring cycloalkyls may be either fused, bridged and/or joined through one or

25 more spiro atoms. Cycloalkyl groups may also be considered to be a subset of homocyclic rings discussed hereinafter. Examples of cycloalkyl groups include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, adamantanyl, bicyclo(2.2.1)heptanyl and cyclodecyl with cyclopropyl, cyclopentyl, cyclohexyl, adamantanyl, and bicyclo(2.2.1)heptanyl being particularly preferred. An

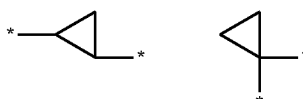
30 "optionally substituted cycloalkyl" refers to a cycloalkyl having optionally one or more substituents (for example 1 to 3 substituents, for example 1, 2, 3 or 4 substituents), selected from those defined above for substituted alkyl. When the suffix "ene" is used in conjunction with a cyclic group, hereinafter also referred to as "Cycloalkylene", this is intended to mean the cyclic group as defined herein having two single bonds as points of

35 attachment to other groups. Cycloalkylene groups of this invention preferably comprise the same number of carbon atoms as their cycloalkyl radical counterparts.

Where alkyl groups as defined are divalent, i.e., with two single bonds for attachment to two other groups, they are termed "alkylene" groups. Non-limiting examples of alkylene groups includes methylene, ethylene, methylenemethylene, trimethylene, propylene, tetramethylene, ethylethylene, 1,2-dimethylethylene, pentamethylene and hexamethylene.

5 Similarly, where alkenyl groups as defined above and alkynyl groups as defined above, respectively, are divalent radicals having single bonds for attachment to two other groups, they are termed "alkenylene" and "alkynylene" respectively.

Generally, alkylene groups of this invention preferably comprise the same number of carbon atoms as their alkyl counterparts. Where an alkylene or cycloalkylene biradical is present, connectivity to the molecular structure of which it forms part may be through a common carbon atom or different carbon atom, preferably a common carbon atom. To illustrate this applying the asterisk nomenclature of this invention, a C₃ alkylene group may be for example *-CH₂CH₂CH₂-, *-CH(-CH₂CH₃)-, or *-CH₂CH(-CH₃)-. Likewise a C₃ cycloalkylene group may be



15 Where a cycloalkylene group is present, this is preferably a C₃-C₆ cycloalkylene group, more preferably a C₃ cycloalkylene (i.e. cyclopropylene group) wherein its connectivity to the structure of which it forms part is through a common carbon atom. Cycloalkylene and alkylene biradicals in compounds of the invention may be, but preferably are not, substituted.

20 The terms "heterocyclyl" or "heterocyclo" as used herein by itself or as part of another group refer to non-aromatic, fully saturated or partially unsaturated cyclic groups (for example, 3 to 13 member monocyclic, 7 to 17 member bicyclic, or 10 to 20 member tricyclic ring systems, or containing a total of 3 to 10 ring atoms) which have at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3 or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom of the ring or ring system, where valence allows. The rings of multi-ring heterocycles may be fused, bridged and/or joined through one or more spiro atoms. An optionally substituted heterocyclic (such as an optionally substituted Het¹) refers to a heterocyclic having optionally one or more substituents (for example 1 to 4 substituents, or for example 1, 2, 3 or 4; in particular 1), selected from those defined for substituted aryl.

Exemplary heterocyclic groups include piperidinyl, azetidiny, imidazoliny, imidazolidiny, isoxazoliny, oxazolidiny, isoxazolidiny, thiazolidiny, isothiazolidiny, piperidyl, succinimidyl, 3H-indolyl, isoindoliny, chromenyl, isochromanyl, xanthenyl, 2H-pyrrolyl, 1-pyrroliny, 2-pyrroliny, 3-pyrroliny, pyrrolidiny, 4H-quinoliziny, 4aH-carbazolyl, 2-oxopiperaziny, piperaziny, homopiperaziny, 2-pyrazoliny, 3-pyrazoliny, pyranly, dihydro-2H-pyranly, 4H-pyranly, 3,4-dihydro-2H-pyranly, phthalaziny, oxetanyl, thietanyl, 3-dioxolanyl, 1,3-dioxanyl, 2,5-dioximidazolidiny, 2,2,4-piperidonyl, 2-oxopiperidiny, 2-oxopyrrolodiny, 2-oxoazepiny, indoliny, tetrahydropyranly, tetrahydrofuranyl, tetrahydrothienyl, tetrahydroquinoliny, tetrahydroisoquinoliny, thiomorpholiny, thiomorpholiny sulfoxide, thiomorpholiny sulfone, 1,3-dioxolanyl, 1,4-oxathianly, 1,4-dithianly, 1,3,5-trioxanyl, 6H-1,2,5-thiadiaziny, 2H-1,5,2-dithiaziny, 2H-oxociny, 1H-pyrroliziny, tetrahydro-1,1-dioxothienyl, N-formylpiperaziny, and morpholiny.

The term "aryl" as used herein refers to a polyunsaturated, aromatic hydrocarbyl group having a single ring (i.e. phenyl) or multiple aromatic rings fused together (e.g. naphthalene or anthracene) or linked covalently, typically containing 6 to 10 atoms; wherein at least one ring is aromatic. The aromatic ring may optionally include one to three additional rings (either cycloalkyl, heterocyclyl, or heteroaryl) fused thereto. Aryl is also intended to include the partially hydrogenated derivatives of the carbocyclic systems enumerated herein. Non-limiting examples of aryl comprise phenyl, biphenylly, biphenylenyl, 5- or 6-tetraliny, 1-, 2-, 3-, 4-, 5-, 6-, 7-, or 8-azulenyl, 1- or 2-naphthyl, 1-, 2-, or 3-indenyl, 1-, 2-, or 9-anthryl, 1- 2-, 3-, 4-, or 5-acenaphtylenyl, 3-, 4-, or 5-acenaphtenyl, 1-, 2-, 3-, 4-, or 10-phenanthryl, 1- or 2-pentalenyl, 1, 2-, 3-, or 4-fluorenyl, 4- or 5-indanyl, 5-, 6-, 7-, or 8-tetrahydronaphthyl, 1,2,3,4-tetrahydronaphthyl, 1,4-dihydronaphthyl, dibenzo[a,d]cylcoheptenyl, and 1-, 2-, 3-, 4-, or 5-pyrenyl.

The aryl ring can optionally be substituted by one or more substituents. An "optionally substituted aryl" refers to an aryl having optionally one or more substituents (for example 1 to 5 substituents, for example 1, 2, 3 or 4) at any available point of attachment. Non-limiting examples of such substituents are selected from halogen, hydroxyl, oxo, nitro, amino, hydrazine, aminocarbonyl, azido, cyano, alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, alkylamino, alkoxy, -SO₂-NH₂, aryl, heteroaryl, aralkyl, haloalkyl, haloalkoxy, alkoxycarbonyl, alkylaminocarbonyl, heteroarylalkyl, alkylsulfonamide, heterocyclyl, alkylcarbonylaminoalkyl, aryloxy, alkylcarbonyl, acyl, arylcarbonyl, aminocarbonyl, alkylsulfoxide, -SO₂R^a, alkylthio, carboxyl, and the like, wherein R^a is alkyl or cycloalkyl.

Where a carbon atom in an aryl group is replaced with a heteroatom, the resultant ring is referred to herein as a heteroaryl ring.

The term "heteroaryl" as used herein by itself or as part of another group refers but is not limited to 5 to 12 carbon-atom aromatic rings or ring systems containing 1 to 3 rings which are fused together or linked covalently, typically containing 5 to 8 atoms; at least one of which is aromatic in which one or more carbon atoms in one or more of these rings can be replaced by oxygen, nitrogen or sulfur atoms where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. Such rings may be fused to an aryl, cycloalkyl, heteroaryl or heterocyclyl ring. Non-limiting examples of such heteroaryl, include: pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, oxatriazolyl, thiatriazolyl, pyridinyl, pyrimidyl, pyrazinyl, pyridazinyl, oxazinyl, dioxinyl, thiazinyl, triazinyl, imidazo[2,1-b][1,3]thiazolyl, thieno[3,2-b]furanyl, thieno[3,2-b]thiophenyl, thieno[2,3-d][1,3]thiazolyl, thieno[2,3-d]imidazolyl, tetrazolo[1,5-a]pyridinyl, indolyl, indoliziny, isoindolyl, benzofuranyl, benzopyranyl, 1(4H)-benzopyranyl, 1(2H)-benzopyranyl, 3,4-dihydro-1(2H)-benzopyranyl, 3,4-dihydro-1(2H)-benzopyranyl, isobenzofuranyl, benzothiophenyl, isobenzothiophenyl, indazolyl, benzimidazolyl, 1,3-benzoxazolyl, 1,2-benzisoxazolyl, 2,1-benzisoxazolyl, 1,3-benzothiazolyl, 1,2-benzoisothiazolyl, 2,1-benzoisothiazolyl, benzotriazolyl, 1,2,3-benzoxadiazolyl, 2,1,3-benzoxadiazolyl, 1,2,3-benzothiadiazolyl, 2,1,3-benzothiadiazolyl, thienopyridinyl, purinyl, imidazo[1,2-a]pyridinyl, 6-oxo-pyridazin-1(6H)-yl, 2-oxopyridin-1(2H)-yl, 6-oxo-pyridazin-1(6H)-yl, 2-oxopyridin-1(2H)-yl, 1,3-benzodioxolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl, 7-azaindolyl, 6-azaindolyl, 5-azaindolyl, 4-azaindolyl.

The term "pyrrolyl" (also called azolyl) as used herein includes pyrrol-1-yl, pyrrol-2-yl and pyrrol-3-yl. The term "furanyl" (also called "furyl") as used herein includes furan-2-yl and furan-3-yl (also called furan-2-yl and furan-3-yl). The term "thiophenyl" (also called "thienyl") as used herein includes thiophen-2-yl and thiophen-3-yl (also called thien-2-yl and thien-3-yl). The term "pyrazolyl" (also called 1H-pyrazolyl and 1,2-diazolyl) as used herein includes pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl and pyrazol-5-yl. The term "imidazolyl" as used herein includes imidazol-1-yl, imidazol-2-yl, imidazol-4-yl and imidazol-5-yl. The term "oxazolyl" (also called 1,3-oxazolyl) as used herein includes oxazol-2-yl; oxazol-4-yl and oxazol-5-yl. The term "isoxazolyl" (also called 1,2-oxazolyl), as used herein includes isoxazol-3-yl, isoxazol-4-yl, and isoxazol-5-yl. The term "thiazolyl" (also called 1,3-thiazolyl), as used herein includes thiazol-2-yl, thiazol-4-yl and thiazol-5-yl (also called 2-thiazolyl, 4-thiazolyl and 5-thiazolyl). The term "isothiazolyl" (also called 1,2-thiazolyl) as used herein includes isothiazol-3-yl, isothiazol-4-yl, and isothiazol-5-yl. The term "triazolyl" as used herein includes 1H-triazolyl and 4H-1,2,4-triazolyl, "1H-triazolyl" includes 1H-1,2,3-triazol-1-yl, 1H-1,2,3-triazol-4-yl, 1H-1,2,3-triazol-5-yl, 1H-1,2,4-triazol-

1-yl, 1H-1,2,4-triazol-3-yl and 1H-1,2,4-triazol-5-yl. "4H-1,2,4-triazolyl" includes 4H-1,2,4-triazol-4-yl, and 4H-1,2,4-triazol-3-yl. The term "oxadiazolyl" as used herein includes 1,2,3-oxadiazol-4-yl, 1,2,3-oxadiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,2,5-oxadiazol-3-yl and 1,3,4-oxadiazol-2-yl. The term "thiadiazolyl" as used herein includes 1,2,3-thiadiazol-4-yl, 1,2,3-thiadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 1,2,5-thiadiazol-3-yl (also called furazan-3-yl) and 1,3,4-thiadiazol-2-yl. The term "tetrazolyl" as used herein includes 1H-tetrazol-1-yl, 1H-tetrazol-5-yl, 2H-tetrazol-2-yl, and 2H-tetrazol-5-yl. The term "oxatriazolyl" as used herein includes 1,2,3,4-oxatriazol-5-yl and 1,2,3,5-oxatriazol-4-yl. The term "thiatriazolyl" as used herein includes 1,2,3,4-thiatriazol-5-yl and 1,2,3,5-thiatriazol-4-yl. The term "pyridinyl" (also called "pyridyl") as used herein includes pyridin-2-yl, pyridin-3-yl and pyridin-4-yl (also called 2-pyridyl, 3-pyridyl and 4-pyridyl). The term "pyrimidyl" as used herein includes pyrimid-2-yl, pyrimid-4-yl, pyrimid-5-yl and pyrimid-6-yl. The term "pyrazinyl" as used herein includes pyrazin-2-yl and pyrazin-3-yl. The term "pyridazinyl" as used herein includes pyridazin-3-yl and pyridazin-4-yl. The term "oxazinyl" (also called "1,4-oxazinyl") as used herein includes 1,4-oxazin-4-yl and 1,4-oxazin-5-yl. The term "dioxinyl" (also called "1,4-dioxinyl") as used herein includes 1,4-dioxin-2-yl and 1,4-dioxin-3-yl. The term "thiazinyl" (also called "1,4-thiazinyl") as used herein includes 1,4-thiazin-2-yl, 1,4-thiazin-3-yl, 1,4-thiazin-4-yl, 1,4-thiazin-5-yl and 1,4-thiazin-6-yl. The term "triazinyl" as used herein includes 1,3,5-triazin-2-yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, 1,2,4-triazin-6-yl, 1,2,3-triazin-4-yl and 1,2,3-triazin-5-yl. The term "imidazo[2,1-b][1,3]thiazolyl" as used herein includes imidazo[2,1-b][1,3]thiazol-2-yl, imidazo[2,1-b][1,3]thiazol-3-yl, imidazo[2,1-b][1,3]thiazol-5-yl and imidazo[2,1-b][1,3]thiazol-6-yl. The term "thieno[3,2-b]furanyl" as used herein includes thieno[3,2-b]furan-2-yl, thieno[3,2-b]furan-3-yl, thieno[3,2-b]furan-4-yl, and thieno[3,2-b]furan-5-yl. The term "thieno[3,2-b]thiophenyl" as used herein includes thieno[3,2-b]thien-2-yl, thieno[3,2-b]thien-3-yl, thieno[3,2-b]thien-5-yl and thieno[3,2-b]thien-6-yl. The term "thieno[2,3-d][1,3]thiazolyl" as used herein includes thieno[2,3-d][1,3]thiazol-2-yl, thieno[2,3-d][1,3]thiazol-5-yl and thieno[2,3-d][1,3]thiazol-6-yl. The term "thieno[2,3-d]imidazolyl" as used herein includes thieno[2,3-d]imidazol-2-yl, thieno[2,3-d]imidazol-4-yl and thieno[2,3-d]imidazol-5-yl. The term "tetrazolo[1,5-a]pyridinyl" as used herein includes tetrazolo[1,5-a]pyridine-5-yl, tetrazolo[1,5-a]pyridine-6-yl, tetrazolo[1,5-a]pyridine-7-yl, and tetrazolo[1,5-a]pyridine-8-yl. The term "indolyl" as used herein includes indol-1-yl, indol-2-yl, indol-3-yl, indol-4-yl, indol-5-yl, indol-6-yl and indol-7-yl. The term "indolizinyl" as used herein includes indolizin-1-yl, indolizin-2-yl, indolizin-3-yl, indolizin-5-yl, indolizin-6-yl, indolizin-7-yl, and indolizin-8-yl. The term "isoindolyl" as used herein includes isoindol-1-yl, isoindol-2-yl, isoindol-3-yl, isoindol-4-yl, isoindol-5-yl, isoindol-6-yl and isoindol-7-yl. The

term "benzofuranyl" (also called benzo[b]furanyl) as used herein includes benzofuran-2-yl, benzofuran-3-yl, benzofuran-4-yl, benzofuran-5-yl, benzofuran-6-yl and benzofuran-7-yl. The term "isobenzofuranyl" (also called benzo[c]furanyl) as used herein includes isobenzofuran-1-yl, isobenzofuran-3-yl, isobenzofuran-4-yl, isobenzofuran-5-yl, isobenzofuran-6-yl and isobenzofuran-7-yl. The term "benzothiophenyl" (also called benzo[b]thienyl) as used herein includes 2-benzo[b]thiophenyl, 3-benzo[b]thiophenyl, 4-benzo[b]thiophenyl, 5-benzo[b]thiophenyl, 6-benzo[b]thiophenyl and 7-benzo[b]thiophenyl (also called benzothien-2-yl, benzothien-3-yl, benzothien-4-yl, benzothien-5-yl, benzothien-6-yl and benzothien-7-yl). The term "isobenzothiophenyl" (also called benzo[c]thienyl) as used herein includes isobenzothien-1-yl, isobenzothien-3-yl, isobenzothien-4-yl, isobenzothien-5-yl, isobenzothien-6-yl and isobenzothien-7-yl. The term "indazolyl" (also called 1H-indazolyl or 2-azaindolyl) as used herein includes 1H-indazol-1-yl, 1H-indazol-3-yl, 1H-indazol-4-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 1H-indazol-7-yl, 2H-indazol-2-yl, 2H-indazol-3-yl, 2H-indazol-4-yl, 2H-indazol-5-yl, 2H-indazol-6-yl, and 2H-indazol-7-yl. The term "benzimidazolyl" as used herein includes benzimidazol-1-yl, benzimidazol-2-yl, benzimidazol-4-yl, benzimidazol-5-yl, benzimidazol-6-yl and benzimidazol-7-yl. The term "1,3-benzoxazolyl" as used herein includes 1,3-benzoxazol-2-yl, 1,3-benzoxazol-4-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl and 1,3-benzoxazol-7-yl. The term "1,2-benzisoxazolyl" as used herein includes 1,2-benzisoxazol-3-yl, 1,2-benzisoxazol-4-yl, 1,2-benzisoxazol-5-yl, 1,2-benzisoxazol-6-yl and 1,2-benzisoxazol-7-yl. The term "2,1-benzisoxazolyl" as used herein includes 2,1-benzisoxazol-3-yl, 2,1-benzisoxazol-4-yl, 2,1-benzisoxazol-5-yl, 2,1-benzisoxazol-6-yl and 2,1-benzisoxazol-7-yl. The term "1,3-benzothiazolyl" as used herein includes 1,3-benzothiazol-2-yl, 1,3-benzothiazol-4-yl, 1,3-benzothiazol-5-yl, 1,3-benzothiazol-6-yl and 1,3-benzothiazol-7-yl. The term "1,2-benzisothiazolyl" as used herein includes 1,2-benzisothiazol-3-yl, 1,2-benzisothiazol-4-yl, 1,2-benzisothiazol-5-yl, 1,2-benzisothiazol-6-yl and 1,2-benzisothiazol-7-yl. The term "2,1-benzisothiazolyl" as used herein includes 2,1-benzisothiazol-3-yl, 2,1-benzisothiazol-4-yl, 2,1-benzisothiazol-5-yl, 2,1-benzisothiazol-6-yl and 2,1-benzisothiazol-7-yl. The term "benzotriazolyl" as used herein includes benzotriazol-1-yl, benzotriazol-4-yl, benzotriazol-5-yl, benzotriazol-6-yl and benzotriazol-7-yl. The term "1,2,3-benzoxadiazolyl" as used herein includes 1,2,3-benzoxadiazol-4-yl, 1,2,3-benzoxadiazol-5-yl, 1,2,3-benzoxadiazol-6-yl and 1,2,3-benzoxadiazol-7-yl. The term "2,1,3-benzoxadiazolyl" as used herein includes 2,1,3-benzoxadiazol-4-yl, 2,1,3-benzoxadiazol-5-yl, 2,1,3-benzoxadiazol-6-yl and 2,1,3-benzoxadiazol-7-yl. The term "1,2,3-benzothiadiazolyl" as used herein includes 1,2,3-benzothiadiazol-4-yl, 1,2,3-benzothiadiazol-5-yl, 1,2,3-benzothiadiazol-6-yl and 1,2,3-benzothiadiazol-7-yl. The term

“2,1,3-benzothiadiazolyl” as used herein includes 2,1,3-benzothiadiazol-4-yl, 2,1,3-benzothiadiazol-5-yl, 2,1,3-benzothiadiazol-6-yl and 2,1,3-benzothiadiazol-7-yl. The term “thienopyridinyl” as used herein includes thieno[2,3-b]pyridinyl, thieno[2,3-c]pyridinyl, thieno[3,2-c]pyridinyl and thieno[3,2-b]pyridinyl. The term “purinyl” as used herein includes purin-2-yl, purin-6-yl, purin-7-yl and purin-8-yl. The term “imidazo[1,2-a]pyridinyl”, as used herein includes imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-3-yl, imidazo[1,2-a]pyridin-4-yl, imidazo[1,2-a]pyridin-5-yl, imidazo[1,2-a]pyridin-6-yl and imidazo[1,2-a]pyridin-7-yl. The term “1,3-benzodioxolyl”, as used herein includes 1,3-benzodioxol-4-yl, 1,3-benzodioxol-5-yl, 1,3-benzodioxol-6-yl, and 1,3-benzodioxol-7-yl. The term “quinolinyl” as used herein includes quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-5-yl, quinolin-6-yl, quinolin-7-yl and quinolin-8-yl. The term “isoquinolinyl” as used herein includes isoquinolin-1-yl, isoquinolin-3-yl, isoquinolin-4-yl, isoquinolin-5-yl, isoquinolin-6-yl, isoquinolin-7-yl and isoquinolin-8-yl. The term “cinnolinyl” as used herein includes cinnolin-3-yl, cinnolin-4-yl, cinnolin-5-yl, cinnolin-6-yl, cinnolin-7-yl and cinnolin-8-yl. The term “quinazolinyl” as used herein includes quinazolin-2-yl, quinazolin-4-yl, quinazolin-5-yl, quinazolin-6-yl, quinazolin-7-yl and quinazolin-8-yl. The term “quinoxaliny”. as used herein includes quinoxalin-2-yl, quinoxalin-5-yl, and quinoxalin-6-yl. The term “7-azaindolyl” as used herein refers to 1H-Pyrrolo[2,3-b]pyridinyl and includes 7-azaindol-1-yl, 7-azaindol-2-yl, 7-azaindol-3-yl, 7-azaindol-4-yl, 7-azaindol-5-yl, 7-azaindol-6-yl. The term “6-azaindolyl” as used herein refers to 1H-Pyrrolo[2,3-c]pyridinyl and includes 6-azaindol-1-yl, 6-azaindol-2-yl, 6-azaindol-3-yl, 6-azaindol-4-yl, 6-azaindol-5-yl, 6-azaindol-7-yl. The term “5-azaindolyl” as used herein refers to 1H-Pyrrolo[3,2-c]pyridinyl and includes 5-azaindol-1-yl, 5-azaindol-2-yl, 5-azaindol-3-yl, 5-azaindol-4-yl, 5-azaindol-6-yl, 5-azaindol-7-yl. The term “4-azaindolyl” as used herein refers to 1H-Pyrrolo[3,2-b]pyridinyl and includes 4-azaindol-1-yl, 4-azaindol-2-yl, 4-azaindol-3-yl, 4-azaindol-5-yl, 4-azaindol-6-yl, 4-azaindol-7-yl.

For example, non-limiting examples of heteroaryl can be 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isothiazolyl, 2-, 4- or 5-thiazolyl, 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3-, -4- or -5-yl, 1H-tetrazol-1-, or -5-yl, 2H-tetrazol-2-, or -5-yl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazol-4- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,5-thiadiazol-3- or -4-yl, 1,3,4-thiadiazolyl, 1- or 5-tetrazolyl, 2-, 3- or 4-pyridyl, 3- or 4-pyridazinyl, 2-, 4-, 5- or 6-pyrimidyl, 2-, 3-, 4-, 5- 6-2H-thiopyranyl, 2-, 3- or 4-4H-thiopyranyl, 4-azaindol-1-, 2-, 3-, 5-, or 7-yl, 5-azaindol-1-, or 2-, 3-, 4-, 6-, or 7-yl, 6-azaindol-1-, 2-, 3-, 4-, 5-, or 7-yl, 7-azaindol-1-, 2-, 3-, 4-, 5-, or 6-yl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 1-, 3-, 4- or 5-isobenzofuryl, 2-, 3-, 4-, 5-, 6- or 7-

benzothienyl, 1-, 3-, 4- or 5-isobenzothienyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 2- or 3-pyrazinyl, 1,4-oxazin-2- or -3-yl, 1,4-dioxin-2- or -3-yl, 1,4-thiazin-2- or -3-yl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazin-2-, -4- or -6-yl, thieno[2,3-b]furan-2-, -3-, -4-, or -5-yl, benzimidazol-1-yl, -2-yl, -4-yl, -5-yl, -6-yl, or -7-yl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisothiazolyl, 1,3-benzothiazol-2-yl, -4-yl, -5-yl, -6-yl or -7-yl, 1,3-benzodioxol-4-yl, -5-yl, -6-yl, or -7-yl, benzotriazol-1-yl, -4-yl, -5-yl, -6-yl or -7-yl, 2-thianthrenyl, 3-, 4- or 5-isobenzofuranyl, 1-, 2-, 3-, 4- or 9-xanthenyl, 1-, 2-, 3- or 4-phenoxathiinyl, 2-, 3-pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-indoliziny, 2-, 3-, 4- or 5-isindolyl, 1H-indazol-1-yl, 3-yl, -4-yl, -5-yl, -6-yl, or -7-yl, 2H-indazol-2-yl, 3-yl, -4-yl, -5-yl, -6-yl, or -7-yl, imidazo[2,1-b][1,3]thiazol-2-yl, imidazo[2,1-b][1,3]thiazol-3-yl, imidazo[2,1-b][1,3]thiazol-5-yl or imidazo[2,1-b][1,3]thiazol-6-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-3-yl, imidazo[1,2-a]pyridin-4-yl, imidazo[1,2-a]pyridin-5-yl, imidazo[1,2-a]pyridin-6-yl or imidazo[1,2-a]pyridin-7-yl, tetrazolo[1,5-a]pyridine-5-yl, tetrazolo[1,5-a]pyridine-6-yl, tetrazolo[1,5-a]pyridine-7-yl, or tetrazolo[1,5-a]pyridine-8-yl, 2-, 6-, 7- or 8-purinyl, 4-, 5- or 6-phthalazinyl, 2-, 3- or 4-naphthyridinyl, 2-, 5- or 6-quinoxaliny, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, 1-, 2-, 3- or 4-quinoliziny, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinoliny(quinolyl), 2-, 4-, 5-, 6-, 7- or 8-quinazolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinoliny(isoquinolyl), 3-, 4-, 5-, 6-, 7- or 8-cinnoliny, 2-, 4-, 6- or 7-pteridinyl, 1-, 2-, 3-, 4- or 9-carbazolyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-carboliny, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9- or 10-phenanthridinyl, 1-, 2-, 3- or 4-acridinyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-perimidinyl, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9- or 10-(1,7)phenanthroliny, 1- or 2-phenazinyl, 1-, 2-, 3-, 4-, or 10-phenothiazinyl, 3- or 4-furazanyl, 1-, 2-, 3-, 4-, or 10-phenoxazinyl, or additionally substituted derivatives thereof.

An "optionally substituted heteroaryl" refers to a heteroaryl having optionally one or more substituents (for example 1 to 4 substituents, for example 1, 2, 3 or 4), selected from those defined above for substituted aryl.

The term "oxo" as used herein refers to the group =O.

The term "alkoxy" or "alkyloxy" as used herein refers to a radical having the Formula -OR^b wherein R^b is alkyl. Preferably, alkoxy is C₁-C₁₀ alkoxy, C₁-C₆ alkoxy, or C₁-C₄ alkoxy. Non-limiting examples of suitable alkoxy include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy and hexyloxy. Where the oxygen atom in an alkoxy group is substituted with sulfur, the resultant radical is referred to as thioalkoxy. "Haloalkoxy" is an alkoxy group wherein one or more hydrogen atoms in the alkyl group are substituted with halogen. Non-limiting examples of suitable haloalkoxy include fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, 1,1,2,2-tetrafluoroethoxy, 2-fluoroethoxy, 2-chloroethoxy, 2,2-difluoroethoxy, 2,2,2-trichloroethoxy;

trichloromethoxy, 2-bromoethoxy, pentafluoroethyl, 3,3,3-trichloropropoxy, 4,4,4-trichlorobutoxy.

The term "aryloxy" as used herein denotes a group -O-aryl, wherein aryl is as defined above.

- 5 The term "arylcarbonyl" or "aroyl" as used herein denotes a group -C(O)-aryl, wherein aryl is as defined above.

The term "cycloalkylalkyl" by itself or as part of another substituent refers to a group having one of the aforementioned cycloalkyl groups attached to one of the aforementioned alkyl chains. Examples of such cycloalkylalkyl radicals include
 10 cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 1-cyclopentylethyl, 1-cyclohexylethyl, 2-cyclopentylethyl, 2-cyclohexylethyl, cyclobutylpropyl, cyclopentylpropyl, 3-cyclopentylbutyl, cyclohexylbutyl and the like.

The term "heterocyclalkyl" by itself or as part of another substituents refers to a group having one of the aforementioned heterocyclalkyl group attached to one of the
 15 aforementioned alkyl group, i.e., to a group $-R^d-R^c$ wherein R^d is alkylene or alkylene substituted by alkyl group and R^c is a heterocyclalkyl group.

The term "carboxy" or "carboxyl" or "hydroxycarbonyl" by itself or as part of another substituent refers to the group $-CO_2H$. Thus, a carboxyalkyl is an alkyl group as defined above having at least one substituent that is $-CO_2H$.

- 20 The term "alkoxycarbonyl" by itself or as part of another substituent refers to a carboxy group linked to an alkyl radical i.e. to form $-C(=O)OR^e$, wherein R^e is as defined above for alkyl.

The term "alkylcarbonyloxy" by itself or as part of another substituent refers to a $-O-C(=O)R^e$ wherein R^e is as defined above for alkyl.

- 25 The term "alkylcarbonylamino" by itself or as part of another substituent refers to an group of Formula $-NH(C=O)R$ or $-NR'(C=O)R$, wherein R and R' are each independently alkyl or substituted alkyl.

The term "thiocarbonyl" by itself or as part of another substituent refers to the group $-C(=S)-$.

- 30 The term "alkoxy" by itself or as part of another substituent refers to a group consisting of an oxygen atom attached to one optionally substituted straight or branched alkyl group, cycloalkyl group, aralkyl, or cycloalkylalkyl group. Non-limiting examples of suitable alkoxy group include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, hexanoxy, and the like.

The term "halo" or "halogen" as a group or part of a group is generic for fluoro, chloro, bromo, or iodo.

The term "haloalkyl" alone or in combination, refers to an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen as defined above. Non-limiting examples of such haloalkyl radicals include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl, and the like.

The term "haloaryl" alone or in combination, refers to an aryl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen as defined above.

The term "haloalkoxy" alone or in combination refers to a group of Formula -O-alkyl wherein the alkyl group is substituted by 1, 2, or 3 halogen atoms. For example, "haloalkoxy" includes -OCF₃, -OCHF₂, -OCH₂F, -O-CF₂-CF₃, -O-CH₂-CF₃, -O-CH₂-CHF₂, and -O-CH₂-CH₂F.

Whenever the term "substituted" is used in the present invention, it is meant to indicate that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group, provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a chemically stable compound, i.e. a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into a therapeutic agent.

Where groups may be optionally substituted, such groups may be substituted once or more, and preferably once, twice or thrice. Substituents may be selected from, for example, the group comprising halogen, hydroxyl, oxo, nitro, amido, carboxy, amino, cyano haloalkoxy, and haloalkyl.

As used herein the terms such as "alkyl, aryl, or cycloalkyl, each being optionally substituted with" or "alkyl, aryl, or cycloalkyl, optionally substituted with" refers to optionally substituted alkyl, optionally substituted aryl and optionally substituted cycloalkyl.

As described herein, some of the compounds of the invention may contain one or more asymmetric carbon atoms that serve as a chiral center, which may lead to different optical forms (e.g. enantiomers or diastereoisomers). The invention comprises all such optical forms in all possible configurations, as well as mixtures thereof.

More generally, from the above, it will be clear to the skilled person that the compounds of the invention may exist in the form of different isomers and/or tautomers, including but not limited to geometrical isomers, conformational isomers, E/Z-isomers, stereochemical

isomers (i.e. enantiomers and diastereoisomers) and isomers that correspond to the presence of the same substituents on different positions of the rings present in the compounds of the invention. All such possible isomers, tautomers and mixtures thereof are included within the scope of the invention.

5

Whenever used in the present invention the term "compounds of the invention" or a similar term is meant to include the compounds of general Formula I and any subgroup thereof. This term also refers to the compounds as depicted in Table 1, their derivatives, *N*-oxides, salts, solvates, hydrates, stereoisomeric forms, racemic mixtures, tautomeric forms,
 10 optical isomers, analogues, pro-drugs, esters, and metabolites, as well as their quaternized nitrogen analogues. The *N*-oxide forms of said compounds are meant to comprise compounds wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide.

As used in the specification and the appended claims, the singular forms "a", "an", and
 15 "the" include plural referents unless the context clearly dictates otherwise. By way of example, "a compound" means one compound or more than one compound.

The terms described above and others used in the specification are well understood to those in the art.

20 In a further embodiment, the invention provides compounds of formula I wherein

Y is -N- or -CH-; in particular -N-;

A is -N- or -CH-; in particular -CH-;

R¹ is selected from the group consisting of

- 25 a) $-(CH_2)_m-C(=O)-OR^{11}$;
 b) $-(CH_2)_m-C(=O)-NH-R^{12}$;

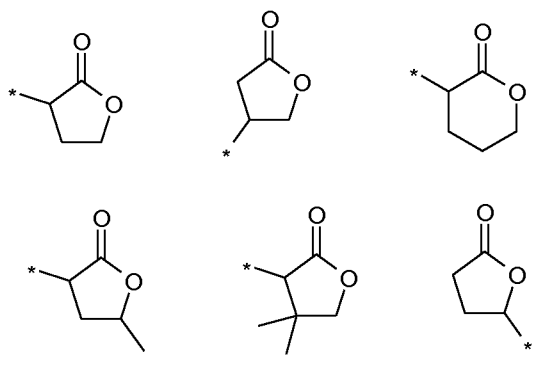
Wherein

m is an integer selected from 0 to 3;

R¹¹ is selected from the group comprising optionally substituted C₁₋₈alkyl, C₃₋₈cycloalkyl, C₁₋₈alkoxyalkyl, alkylcycloalkyl, heterocyclyl, aryl, Het¹, and
 30 heteroaryl;

Wherein

Het¹ is selected from the group consisting of



R¹² is an optionally substituted Het¹ or R¹² is selected from the group consisting of C₁₋₈alkyl, C₃₋₈cycloalkyl, heterocyclyl, alkylheterocyclyl, aryl and heteroaryl; wherein said C₁₋₈alkyl, C₃₋₈cycloalkyl, heterocyclyl, alkylheterocyclyl, aryl and heteroaryl is substituted with:

- one or more substituents independently selected from the group consisting of Het¹; -O-Het¹; -NH-Het¹, -S-Het¹, and -(CH₂)_n-C(=O)-OR¹¹; and
- optionally one or more substituents independently selected from the group consisting of halo, hydroxyl, carbonyl, nitro, amino, oxime, imino, azido, hydrazino, cyano, aryl, heteroaryl, cycloalkyl, heterocyclyl, acyl, alkylamino, alkoxy, thiol, alkylthio, acylamino, alkyl esters, carbamate, thioamido, urea, aminocarbonyl, alkyl, alkenyl, alkynyl, cycloalkylalkyl, -SO₂-NH₂, aralkyl, haloalkyl, haloalkoxy, alkylaminocarbonyl, heteroarylalkyl, alkylsulfonamide, alkylcarbonylaminoalkyl, aryloxy, alkylcarbonyl, acyl, arylcarbonyl, aminocarbonyl, alkylsulfoxide, -SO₂R^a, carboxyl, and the like; wherein R^a is alkyl or cycloalkyl;

Wherein

n is an integer from 0 to 3;

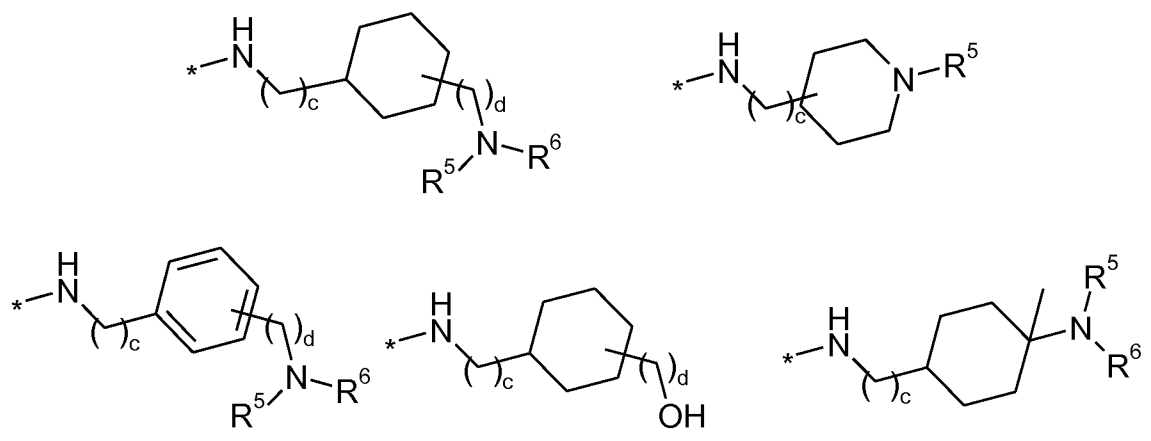
Het¹ and R¹¹ are as defined hereinbefore;

X is -NH-, -CH₂-, -O-, or -S-;

R² is hydrogen or C₁₋₄alkyl;

R³ is selected from the group consisting of hydrogen, nitro, halo, haloalkyl, cyano or -C(=O)NH₂; and

R⁴ is selected from the following groups:



Wherein

- 5 c and d are each independently an integer from 0 to 3; and
- R^5 and R^6 are each independently selected from the group consisting of hydrogen and optionally substituted C_{1-6} alkyl; or
- R^5 and R^6 together with the nitrogen atom to which they are attached form a heterocycle optionally substituted with C_{1-6} alkyl.

10

In another embodiment, the invention provides compounds of formula I wherein

Y is $-\text{N}-$ or $-\text{CH}-$; in particular $-\text{N}-$;

A is $-\text{N}-$ or $-\text{CH}-$; in particular $-\text{CH}-$; and

R^1 is selected from the group consisting of

- 15 a) $-(\text{CH}_2)_m-\text{C}(=\text{O})-\text{OR}^{11}$
- b) $-(\text{CH}_2)_m-\text{C}(=\text{O})-\text{NH}-\text{R}^{12}$
- c) $-(\text{CH}_2)_m-\text{NH}-\text{C}(=\text{O})-\text{R}^{12}$
- d) $-(\text{CH}_2)_m-\text{X}-\text{R}^{12}$
- e) $(\text{CH}_2)_m-\text{C}(=\text{O})-\text{R}^{12}$

20

Wherein

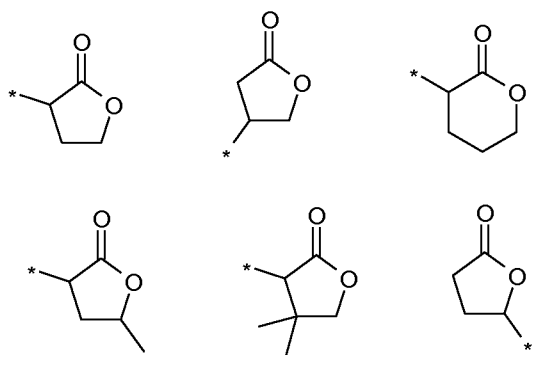
m is an integer selected from 0 to 3;

R^{11} is selected from the group comprising optionally substituted C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{1-8} alkoxyalkyl, alkylcycloalkyl, heterocyclyl, aryl, Het^1 , and heteroaryl;

25

Wherein

Het^1 is selected from the group consisting of



R^{12} is an optionally substituted Het^1 or R^{12} is selected from the group consisting of C_{1-8} alkyl, C_{3-8} cycloalkyl, heterocyclyl, alkylheterocyclyl, aryl and heteroaryl; wherein said C_{1-8} alkyl, C_{3-8} cycloalkyl, heterocyclyl, alkylheterocyclyl, aryl and heteroaryl is substituted with:

- one or more substituents independently selected from the group consisting of Het^1 ; $-O-Het^1$; $-NH-Het^1$, $-S-Het^1$, and $-(CH_2)_n-C(=O)-OR^{11}$; and
- optionally one or more substituents independently selected from the group consisting of halo, hydroxyl, carbonyl, nitro, amino, oxime, imino, azido, hydrazino, cyano, aryl, heteroaryl, cycloalkyl, heterocyclyl, acyl, alkylamino, alkoxy, thiol, alkylthio, acylamino, alkyl esters, carbamate, thioamido, urea, aminocarbonyl, alkyl, alkenyl, alkynyl, cycloalkylalkyl, $-SO_2-NH_2$, aralkyl, haloalkyl, haloalkoxy, alkylaminocarbonyl, heteroarylalkyl, alkylsulfonamide, alkylcarbonylaminoalkyl, aryloxy, alkylcarbonyl, acyl, arylcarbonyl, aminocarbonyl, alkylsulfoxide, $-SO_2R^a$, carboxyl, and the like; wherein R^a is alkyl or cycloalkyl;

Wherein

n is an integer from 0 to 3;

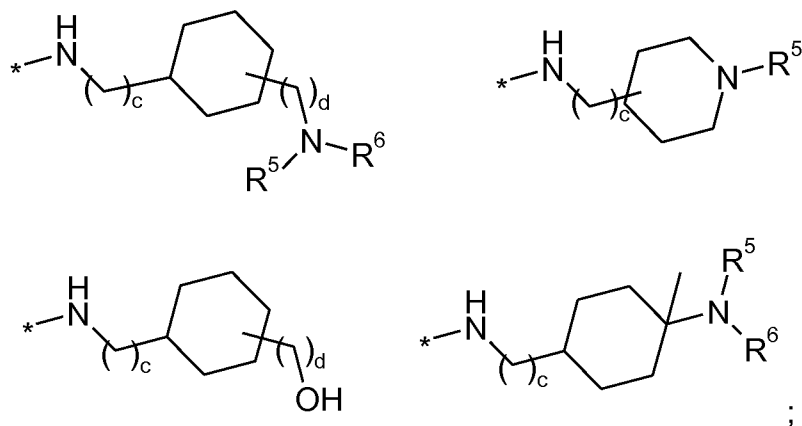
Het^1 and R^{11} are as defined hereinbefore;

X is $-NH-$, $-CH_2-$, $-O-$, or $-S-$;

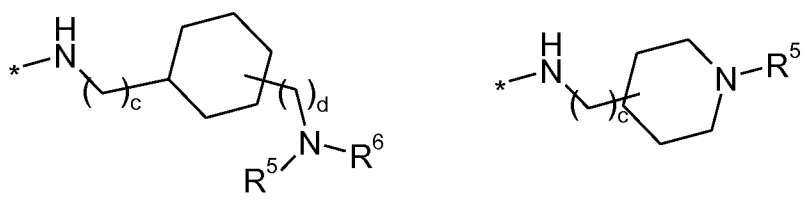
R^2 is hydrogen or C_{1-4} alkyl;

R^3 is selected from the group consisting of hydrogen, nitro, halo, haloalkyl, cyano or $-C(=O)NH_2$; and

R^4 is selected from the following groups:



in particular R^4 is selected from the following groups:



5 Wherein

c and d are each independently an integer from 0 to 3; and

R^5 and R^6 are each independently selected from the group consisting of hydrogen and optionally substituted C_{1-6} alkyl; or

10 R^5 and R^6 together with the nitrogen atom to which they are attached form a heterocycle optionally substituted with C_{1-6} alkyl.

In yet another embodiment, the invention provides compounds of formula I, wherein

Y is -N- or -CH-;

A is -N- or -CH-;

15 R^1 is selected from the group consisting of

- a) $-(CH_2)_m-C(=O)-OR^{11}$
- b) $-(CH_2)_m-C(=O)-NH-R^{12}$
- c) $-(CH_2)_m-NH-C(=O)-R^{12}$
- d) $-(CH_2)_m-X-R^{12}$
- 20 e) $(CH_2)_m-C(=O)-R^{12}$

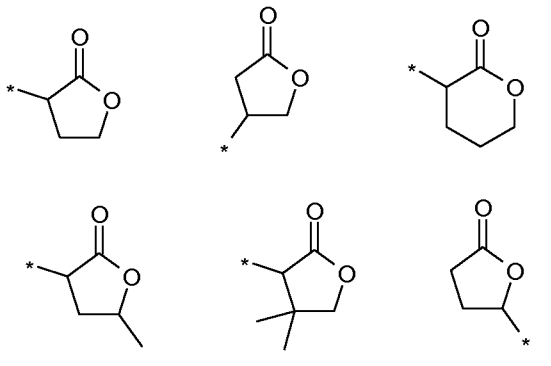
Wherein

m is an integer selected from 0 to 3;

R¹¹ is selected from the group comprising optionally substituted C₁₋₈alkyl, C₃₋₈cycloalkyl, C₁₋₈alkoxyalkyl, alkylcycloalkyl, heterocyclyl, aryl, Het¹, and heteroaryl;

5 Wherein

Het¹ is selected from the group consisting of



10 R¹² is selected from the group consisting of Het¹, or R¹² is selected from the group consisting of C₁₋₈alkyl, C₃₋₈cycloalkyl, heterocyclyl, alkylheterocyclyl, aryl, and heteroaryl; wherein said C₁₋₈alkyl, C₃₋₈cycloalkyl, heterocyclyl, alkylheterocyclyl, aryl, and heteroaryl is substituted with a substituent selected from the group consisting of Het¹, -O-Het¹, -NH-Het¹, -S-Het¹, and -(CH₂)_n-C(=O)-OR¹¹;

15 in particular R¹² is C₁₋₈alkyl substituted with a substituent selected from the group consisting of Het¹, -O-Het¹, -NH-Het¹, -S-Het¹, and -(CH₂)_n-C(=O)-OR¹¹;

more in particular R¹² is C₁₋₈alkyl substituted with a substituent selected from the group consisting of -NH-Het¹, -S-Het¹, and -(CH₂)_n-C(=O)-OR¹¹;

and

20 Wherein

n is an integer from 0 to 3;

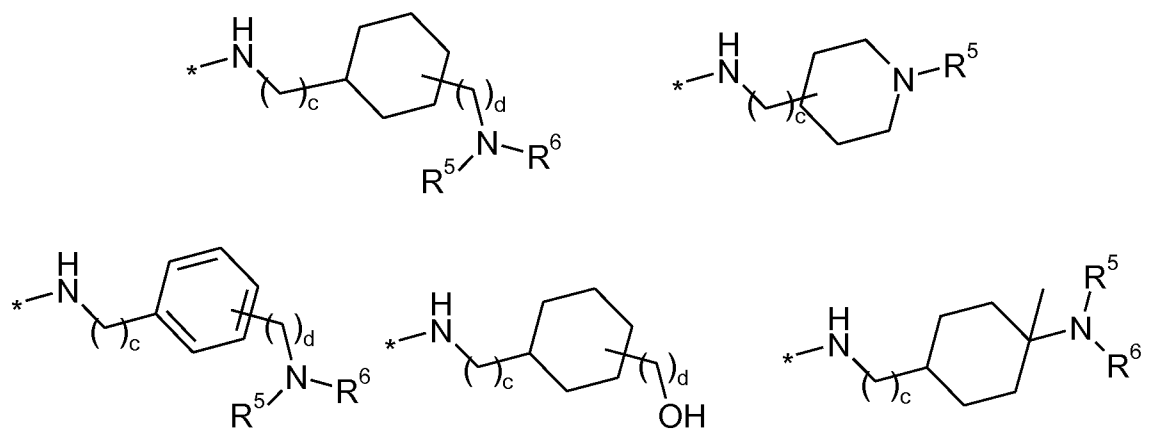
Het¹ and R¹¹ are as defined hereinbefore;

X is -NH-, -CH₂-, -O-, or -S-;

R² is hydrogen or C₁₋₄alkyl;

25 R³ is selected from the group consisting of hydrogen, nitro, halo, haloalkyl, cyano or -C(=O)NH₂; and

R⁴ is selected from the following groups:



Wherein

- 5 c and d are each independently an integer from 0 to 3; and
- R⁵ and R⁶ are each independently selected from the group consisting of hydrogen and optionally substituted C₁₋₆alkyl; or
- R⁵ and R⁶ together with the nitrogen atom to which they are attached form a heterocycle optionally substituted with C₁₋₆alkyl.

10

In a particular embodiment, the present invention provides compounds of formula I, wherein

Y is -N- or -CH-;

15 A is -N- or -CH-;

R¹ is selected from the group consisting of

- a) -(CH₂)_m-C(=O)-OR¹¹
- b) -(CH₂)_m-C(=O)-NH-R¹²
- c) -(CH₂)_m-NH-C(=O)-R¹²
- 20 d) -(CH₂)_m-X-R¹²
- e) (CH₂)_m-C(=O)-R¹²;

in particular R¹ is selected from -(CH₂)_m-C(=O)-OR¹¹ or -(CH₂)_m-C(=O)-NH-R¹²;

Wherein

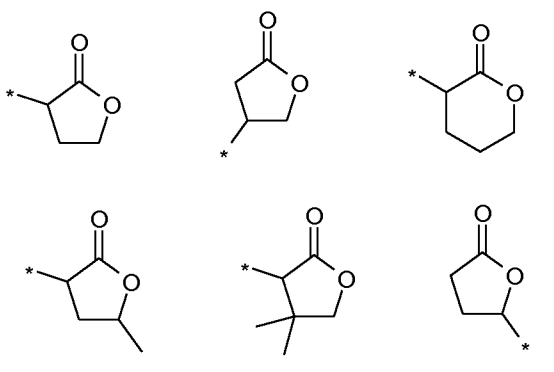
m is an integer selected from 0 to 3; in particular m is 0;

25 R¹¹ is selected from the group comprising optionally substituted C₁₋₈alkyl, C₃₋₈cycloalkyl, C₁₋₈alkoxyalkyl, alkylcycloalkyl, heterocyclyl, aryl, Het¹, and heteroaryl; in

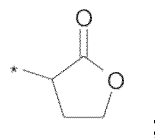
particular from optionally substituted C₁₋₈alkyl and C₃₋₈cycloalkyl; more in particular from C₃₋₈cycloalkyl, C₁₋₈alkyl, C₁₋₈alkyl substituted with hydroxyl, and C₁₋₈alkyl substituted with heterocyclyl;

Wherein

5 Het¹ is selected from the group consisting of



in particular Het¹ is



10 R¹² is an optionally substituted Het¹ or R¹² is selected from the group consisting of C₁₋₈alkyl, C₃₋₈cycloalkyl, heterocyclyl, alkylheterocyclyl, aryl and heteroaryl; in particular C₁₋₈alkyl; wherein said C₁₋₈alkyl, C₃₋₈cycloalkyl, heterocyclyl, alkylheterocyclyl, aryl and heteroaryl is substituted with:

- one or more; in particular one; substituent(s) independently selected from the group consisting of Het¹; -O-Het¹; -NH-Het¹, -S-Het¹, -(CH₂)_n-C(=O)-OR¹¹; in particular from the group consisting of -NH-Het¹, -S-Het¹, and -(CH₂)_n-C(=O)-OR¹¹; and
- optionally one or more substituents independently selected from the group consisting of halo, hydroxyl, carbonyl, nitro, amino, oxime, imino, azido, hydrazino, cyano, aryl, heteroaryl, cycloalkyl, heterocyclyl, acyl, alkylamino, alkoxy, thiol, alkylthio, acylamino, alkyl esters, carbamate, thioamido, urea, aminocarbonyl, alkyl, alkenyl, alkynyl, cycloalkylalkyl, -SO₂-NH₂, aralkyl, haloalkyl, haloalkoxy, alkylaminocarbonyl, heteroarylalkyl, alkylsulfonamide, alkylcarbonylaminoalkyl, aryloxy, alkylcarbonyl, acyl, arylcarbonyl, aminocarbonyl, alkylsulfoxide, -SO₂R^a, carboxyl; wherein R^a is alkyl or cycloalkyl; in particular R¹² is C₁₋₈alkyl substituted with -NH-Het¹, -S-Het¹, or -(CH₂)_n-C(=O)-OR¹¹;

Wherein

n is an integer from 0 to 3; in particular n is 0;

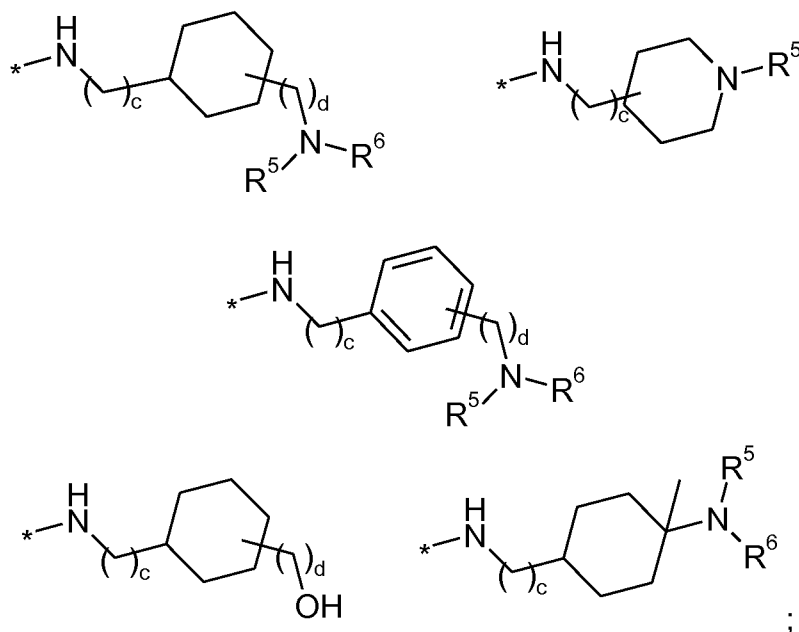
Het¹ and R¹¹ are as defined hereinbefore;

X is -NH-, -CH₂-, -O-, or -S-;

5 R² is hydrogen or C₁₋₄alkyl; in particular R² is methyl;

R³ is selected from the group consisting of hydrogen, nitro, halo, haloalkyl, cyano or -C(=O)NH₂; in particular from nitro and cyano; and

R⁴ is selected from the following groups:



10

10

Wherein

c and d are each independently an integer from 0 to 3; in particular c and d are each independently 0 or 1; and

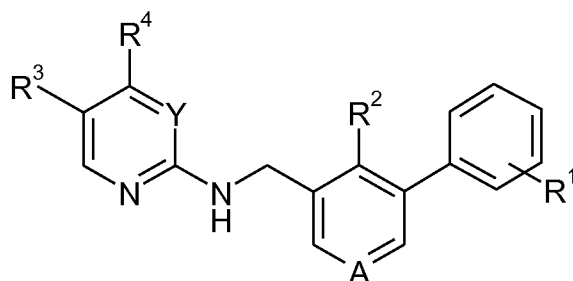
15

R⁵ and R⁶ are each independently selected from the group consisting of hydrogen and optionally substituted C₁₋₆alkyl; in particular from hydrogen and methyl; or

R⁵ and R⁶ together with the nitrogen atom to which they are attached form a heterocycle optionally substituted with C₁₋₆alkyl.

20

In yet another particular embodiment, the present invention provides compounds of Formula II or a stereoisomer, tautomer, racemic, salt, hydrate, or solvate thereof,



II

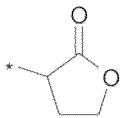
Wherein Y, A, R¹, R², R³, and R⁴ are as defined for any one of the foregoing embodiments of formula I.

5

A further group of interesting compounds provided by the invention, are those compounds of formula I or II as described hereinbefore, wherein one or more of the following restrictions apply:

- Y is -N-;
- A is -CH-;
- R¹ is selected from $-(CH_2)_m-C(=O)-OR^{11}$ and $-(CH_2)_m-C(=O)-NH-R^{12}$;
- R¹ is in the meta position;
- m is an integer from 0 to 2; in particular m is 0 or 1; more in particular m is 0;
- n is an integer from 0 to 2; in particular n is 0 or 1; more in particular n is 0;
- c and d are independently an integer from 0 to 2; in particular c and d are independently 0 or 1;
- R¹¹ is selected from optionally substituted C₁₋₈alkyl and C₃₋₈cycloalkyl; more in particular from C₃₋₈cycloalkyl, C₁₋₈alkyl, C₁₋₈alkyl substituted with hydroxyl, and C₁₋₈alkyl substituted with heterocyclyl;

20

- Het¹ is  ;
- R¹² is an optionally substituted Het¹ or R¹² is selected from the group consisting of C₁₋₈alkyl, C₃₋₈cycloalkyl, heterocyclyl, alkylheterocyclyl, aryl and heteroaryl; in particular C₁₋₈alkyl; wherein said C₁₋₈alkyl, C₃₋₈cycloalkyl, heterocyclyl, alkylheterocyclyl, aryl and heteroaryl is substituted with:

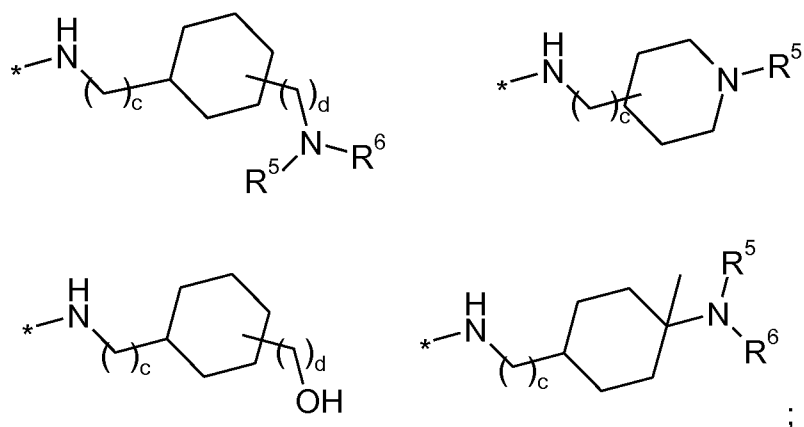
25

- a substituent independently selected from the group consisting of Het¹; -O-Het¹; -NH-Het¹; -S-Het¹; $-(CH_2)_n-C(=O)-OR^{11}$; in particular from the group consisting of -NH-Het¹, -S-Het¹, and $-(CH_2)_n-C(=O)-OR^{11}$; and

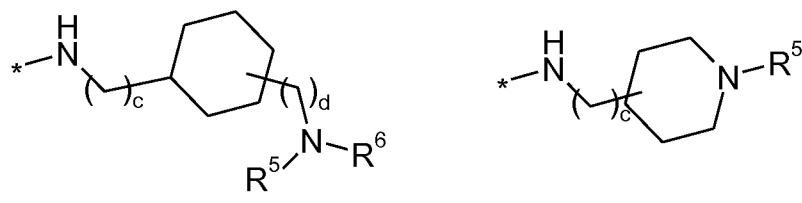
- optionally one or more substituents; in particular optionally one substituent; independently selected from the group consisting of halo, hydroxyl, carbonyl, nitro, amino, oxime, imino, azido, hydrazino, cyano, aryl, heteroaryl, cycloalkyl, heterocyclyl, acyl, alkylamino, alkoxy, thiol, alkylthio, acylamino, alkyl esters, carbamate, thioamido, urea, aminocarbonyl, alkyl, alkenyl, alkynyl, cycloalkylalkyl, $-\text{SO}_2\text{-NH}_2$, aralkyl, haloalkyl, haloalkoxy, alkylaminocarbonyl, heteroarylalkyl, alkylsulfonamide, alkylcarbonylaminoalkyl, aryloxy, alkylcarbonyl, acyl, arylcarbonyl, aminocarbonyl, alkylsulfoxide, $-\text{SO}_2\text{R}^a$, carboxyl; wherein R^a is alkyl or cycloalkyl;

- R^{12} is selected from the group consisting of Het^1 , or R^{12} is selected from the group consisting of C_{1-8} alkyl, C_{3-8} cycloalkyl, heterocyclyl, alkylheterocyclyl, aryl, and heteroaryl; wherein said C_{1-8} alkyl, C_{3-8} cycloalkyl, heterocyclyl, alkylheterocyclyl, aryl, and heteroaryl is substituted with a substituent selected from the group consisting of Het^1 , $-\text{O-Het}^1$, $-\text{NH-Het}^1$, $-\text{S-Het}^1$, and $-(\text{CH}_2)_n\text{-C(=O)-OR}^{11}$; in particular R^{12} is C_{1-8} alkyl substituted with a substituent selected from the group consisting of Het^1 , $-\text{O-Het}^1$, $-\text{NH-Het}^1$, $-\text{S-Het}^1$, and $-(\text{CH}_2)_n\text{-C(=O)-OR}^{11}$; more in particular R^{12} is C_{1-8} alkyl substituted with a substituent selected from the group consisting of $-\text{NH-Het}^1$, $-\text{S-Het}^1$, and $-(\text{CH}_2)_n\text{-C(=O)-OR}^{11}$;

- R^2 is C_{1-4} alkyl; in particular methyl;
- R^3 is nitro or cyano;
- R^4 is selected from the following groups:



- R^4 is selected from the following groups:



- R^5 and R^6 are each independently hydrogen or C_{1-6} alkyl; in particular R^5 and R^6 are each independently hydrogen or methyl.

5 The compounds of the present invention can be prepared according to the reaction schemes provided in the examples hereinafter, but those skilled in the art will appreciate that these are only illustrative for the invention and that the compounds of this invention can be prepared by any of several standard synthetic processes commonly used by those skilled in the art of organic chemistry.

10

In a preferred embodiment, the compounds of the present invention are useful as kinase inhibitors, more in particular for the inhibition of at least one novel PKC, in particular soft PKC θ inhibitors.

15 The present invention provides a compound of the invention, or a composition comprising such a compound for use in the prevention and/or treatment of a disease or a disorder associated with the activation of T-cells in a patient comprising administering to the patient a therapeutically effective amount of a compound of the present invention as described above.

20 In a preferred embodiment, the present invention provides the use of a compound of the invention in the preparation of a medicament for the prevention and/or treatment of immunological disorders and/or inflammatory diseases which can be treated via local application of a drug compound including, but not limited to inflammatory eye diseases such as, but not limited to uveitis, conjunctivitis, contact allergy, retinopathy or post-trauma/post-surgery/post-laser treatment complications including corneal transplant rejection; inflammatory airway diseases; rheumatoid arthritis, skin diseases such as but not limited to contact dermatitis and psoriasis, organ and bone marrow transplant rejection or allergy, intestinal inflammatory diseases such as but not limited to ulcerative colitis, inflammatory bowel disease and Crohn's disease.

30

METHOD OF TREATMENT

The present invention further provides a method for the prevention and/or treatment of at least one disease or disorder associated with the activation of T-cells in a patient comprising administering to the patient a therapeutically effective amount of a compound of the present invention as described above.

5 In a preferred embodiment, the present invention provides the use of a compound of the invention in the preparation of a medicament for the prevention and/or treatment of immunological disorders and/or inflammatory diseases which can be treated via local application of a drug compound including, but not limited to inflammatory eye diseases such as, but not limited to uveitis, conjunctivitis, contact allergy, retinopathy or post-
10 trauma/post-surgery/post-laser treatment complications including corneal transplant rejection; inflammatory airway diseases; rheumatoid arthritis, skin diseases such as but not limited to contact dermatitis and psoriasis, organ and bone marrow transplant rejection or allergy, intestinal inflammatory diseases such as but not limited to ulcerative colitis, inflammatory bowel disease and Crohn's disease..

15 In the invention, particular preference is given to compounds of Formula I or any subgroup thereof that in the inhibition assay for PKC θ described below inhibit PKC θ with an IC₅₀ value of less than 10 μ M, preferably less than 1 μ M.

Said inhibition may be effected *in vitro* and/or *in vivo*, and when effected *in vivo*, is preferably effected in a selective manner, as defined above.

20 The term "PKC θ -mediated condition" or "disease", as used herein, means any disease or other deleterious condition in which PKC θ is known to play a role. The term "PKC θ -mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with a PKC θ inhibitor. Accordingly, another embodiment of the present invention relates to treating or lessening the severity of one or more diseases in
25 which PKC θ is known to play a role.

For pharmaceutical use, the compounds of the invention may be used as a free acid or base, and/or in the form of a pharmaceutically acceptable acid-addition and/or base-addition salt (e.g. obtained with non-toxic organic or inorganic acid or base), in the form of a hydrate, solvate and/or complex, and/or in the form of a pro-drug or pre-drug. As used
30 herein and unless otherwise stated, the term "solvate" includes any combination which may be formed by a compound of this invention with a suitable inorganic solvent (e.g. hydrates) or organic solvent, such as but not limited to alcohols, ketones, esters and the like. Such salts, hydrates, solvates, etc. and the preparation thereof will be clear to the skilled person; reference is for instance made to the salts, hydrates, solvates, etc.
35 described in US-A-6,372,778, US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733.

The pharmaceutically acceptable salts of the compounds according to the invention, i.e. in the form of water-, oil-soluble, or dispersible products, include the conventional non-toxic salts or the quaternary ammonium salts which are formed, e.g., from inorganic or organic acids or bases. Examples of such acid addition salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalene-sulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. In addition, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl-bromides and others. Other pharmaceutically acceptable salts include the sulfate salt ethanolate and sulfate salts.

Generally, for pharmaceutical use, the compounds of the inventions may be formulated as a pharmaceutical preparation or pharmaceutical composition comprising at least one compound of the invention and at least one pharmaceutically acceptable carrier, diluent or excipient and/or adjuvant, and optionally one or more further pharmaceutically active compounds.

By means of non-limiting examples, such a formulation may be in a form suitable for oral administration, for topical administration (including ocular), for administration by inhalation, by a skin patch, by an implant, by a suppository, etc.. Such suitable administration forms – which may be solid, semi-solid or liquid, depending on the manner of administration – as well as methods and carriers, diluents and excipients for use in the preparation thereof, will be clear to the skilled person; reference is again made to for instance US-A-6,372,778, US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733, as well as to the standard handbooks, such as the latest edition of Remington's Pharmaceutical Sciences.

Some preferred, but non-limiting examples of such preparations include tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments, creams, lotions, soft and hard gelatin capsules, suppositories, eye

drops, sterile injectable solutions and sterile packaged powders (which are usually reconstituted prior to use) for administration as a bolus and/or for continuous administration, which may be formulated with carriers, excipients, and diluents that are suitable per se for such formulations, such as lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, polyethylene glycol, cellulose, (sterile) water, methylcellulose, methyl- and propylhydroxybenzoates, talc, magnesium stearate, edible oils, vegetable oils and mineral oils or suitable mixtures thereof. The formulations can optionally contain other pharmaceutically active substances (which may or may not lead to a synergistic effect with the compounds of the invention) and other substances that are commonly used in pharmaceutical formulations, such as lubricating agents, wetting agents, emulsifying and suspending agents, dispersing agents, desintegrants, bulking agents, fillers, preserving agents, sweetening agents, flavoring agents, flow regulators, release agents, etc.. The compositions may also be formulated so as to provide rapid, sustained or delayed release of the active compound(s) contained therein, for example using liposomes or hydrophilic polymeric matrices based on natural gels or synthetic polymers. In order to enhance the solubility and/or the stability of the compounds of a pharmaceutical composition according to the invention, it can be advantageous to employ α -, β - or γ -cyclodextrins or their derivatives. An interesting way of formulating the compounds in combination with a cyclodextrin or a derivative thereof has been described in EP-A-721,331. In particular, the present invention encompasses a pharmaceutical composition comprising an effective amount of a compound according to the invention with a pharmaceutically acceptable cyclodextrin.

In addition, co-solvents such as alcohols may improve the solubility and/or the stability of the compounds. In the preparation of aqueous compositions, addition of salts of the compounds of the invention can be more suitable due to their increased water solubility.

For the treatment of pain, the compounds of the invention may be used locally. For local administration, the compounds may advantageously be used in the form of a spray, ointment or transdermal patch or another suitable form for topical, transdermal and/or intradermal administration.

For ophthalmic application, solutions, gels, tablets and the like are often prepared using a physiological saline solution, gel or excipient as a major vehicle. Ophthalmic formulations should preferably be prepared at a comfortable pH with an appropriate buffer system.

More in particular, the compositions may be formulated in a pharmaceutical formulation comprising a therapeutically effective amount of particles consisting of a solid dispersion

of the compounds of the invention and one or more pharmaceutically acceptable water-soluble polymers.

The term "a solid dispersion" defines a system in a solid state (as opposed to a liquid or gaseous state) comprising at least two components, wherein one component is dispersed more or less evenly throughout the other component or components. When said dispersion of the components is such that the system is chemically and physically uniform or homogenous throughout or consists of one phase as defined in thermodynamics, such a solid dispersion is referred to as "a solid solution". Solid solutions are preferred physical systems because the components therein are usually readily bioavailable to the organisms to which they are administered.

It may further be convenient to formulate the compounds in the form of nanoparticles which have a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than 1000 nm. Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants.

Yet another interesting way of formulating the compounds according to the invention involves a pharmaceutical composition whereby the compounds are incorporated in hydrophilic polymers and applying this mixture as a coat film over many small beads, thus yielding a composition with good bio-availability which can conveniently be manufactured and which is suitable for preparing pharmaceutical dosage forms for oral administration. Materials suitable for use as cores in the beads are manifold, provided that said materials are pharmaceutically acceptable and have appropriate dimensions and firmness. Examples of such materials are polymers, inorganic substances, organic substances, and saccharides and derivatives thereof.

The preparations may be prepared in a manner known per se, which usually involves mixing at least one compound according to the invention with the one or more pharmaceutically acceptable carriers, and, if desired, in combination with other pharmaceutical active compounds, when necessary under aseptic conditions. Reference is again made to US-A-6,372,778, US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733 and the further prior art mentioned above, as well as to the standard handbooks, such as the latest edition of Remington's Pharmaceutical Sciences.

The pharmaceutical preparations of the invention are preferably in a unit dosage form, and may be suitably packaged, for example in a box, blister, vial, bottle, sachet, ampoule

or in any other suitable single-dose or multi-dose holder or container (which may be properly labeled); optionally with one or more leaflets containing product information and/or instructions for use. Generally, such unit dosages will contain between 1 and 1000 mg, and usually between 5 and 500 mg, of the at least one compound of the invention, e.g. about 10, 25, 50, 100, 200, 300 or 400 mg per unit dosage.

The compounds can be administered by a variety of routes including the oral, rectal, ocular, transdermal, subcutaneous, intravenous, intramuscular or intranasal routes, depending mainly on the specific preparation used and the condition to be treated or prevented, and with oral and intravenous administration usually being preferred. The at least one compound of the invention will generally be administered in an "effective amount", by which is meant any amount of a compound of the Formula I, II or III or any subgroup thereof that, upon suitable administration, is sufficient to achieve the desired therapeutic or prophylactic effect in the individual to which it is administered. Usually, depending on the condition to be prevented or treated and the route of administration, such an effective amount will usually be between 0.01 to 1000 mg per kilogram body weight day of the patient per day, more often between 0.1 and 500 mg, such as between 1 and 250 mg, for example about 5, 10, 20, 50, 100, 150, 200 or 250 mg, per kilogram body weight day of the patient per day, which may be administered as a single daily dose, divided over one or more daily doses, or essentially continuously, e.g. using a drip infusion. The amount(s) to be administered, the route of administration and the further treatment regimen may be determined by the treating clinician, depending on factors such as the age, gender and general condition of the patient and the nature and severity of the disease/symptoms to be treated. Reference is again made to US-A-6,372,778, US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733 and the further prior art mentioned above, as well as to the standard handbooks, such as the latest edition of Remington's Pharmaceutical Sciences.

In accordance with the method of the present invention, said pharmaceutical composition can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The present invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

For an oral administration form, the compositions of the present invention can be mixed with suitable additives, such as excipients, stabilizers, or inert diluents, and brought by means of the customary methods into the suitable administration forms, such as tablets, coated tablets, hard capsules, aqueous, alcoholic, or oily solutions. Examples of suitable inert carriers are gum arabic, magnesia, magnesium carbonate, potassium phosphate,

lactose, glucose, or starch, in particular, corn starch. In this case, the preparation can be carried out both as dry and as moist granules. Suitable oily excipients or solvents are vegetable or animal oils, such as sunflower oil or cod liver oil. Suitable solvents for aqueous or alcoholic solutions are water, ethanol, sugar solutions, or mixtures thereof.

5 Polyethylene glycols and polypropylene glycols are also useful as further auxiliaries for other administration forms. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

10 When administered by nasal aerosol or inhalation, these compositions may be prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. Suitable pharmaceutical formulations for
15 administration in the form of aerosols or sprays are, for example, solutions, suspensions or emulsions of the compounds of the invention or their physiologically tolerable salts in a pharmaceutically acceptable solvent, such as ethanol or water, or a mixture of such solvents. If required, the formulation can also additionally contain other pharmaceutical auxiliaries such as surfactants, emulsifiers and stabilizers as well as a propellant.

20 For subcutaneous administration, the compound according to the invention, if desired with the substances customary therefore such as solubilizers, emulsifiers or further auxiliaries are brought into solution, suspension, or emulsion. The compounds of the invention can also be lyophilized and the lyophilizates obtained used, for example, for the production of injection preparations, for instance for intravitreal injections. Suitable solvents are, for
25 example, water, physiological saline solution or alcohols, e.g. ethanol, propanol, glycerol, in addition also sugar solutions such as glucose or mannitol solutions, or alternatively mixtures of the various solvents mentioned. The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic
30 sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

When rectally administered in the form of suppositories, these formulations may be prepared by mixing the compounds according to the invention with a suitable non-irritating
35 excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which

are solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug.

In preferred embodiments, the compounds and compositions of the invention are used locally, for instance topical or in both absorbed and non-adsorbed applications.

- 5 The compositions are of value in the veterinary field, which for the purposes herein not only includes the prevention and/or treatment of diseases in animals, but also – for economically important animals such as cattle, pigs, sheep, chicken, fish, etc. – enhancing the growth and/or weight of the animal and/or the amount and/or the quality of the meat or other products obtained from the animal. Thus, in a further aspect, the
10 invention relates to a composition for veterinary use that contains at least one compound of the invention and at least one suitable carrier (i.e. a carrier suitable for veterinary use). The invention also relates to the use of a compound of the invention in the preparation of such a composition.

- The invention will now be illustrated by means of the following synthetic and biological
15 examples, which do not limit the scope of the invention in any way.

EXAMPLES

A. Physicochemical properties of the compounds

20 **A.1. Compound purity**

Unless indicated otherwise, the purity of the compounds was confirmed by liquid chromatography/mass spectrometry (LC/MS)

A.2. Attribution of the configuration:

- The Cahn-Ingold-Prelog system was used to attribute the absolute configuration of chiral
25 center, in which the four groups on an asymmetric carbon are ranked to a set of sequences rules. Reference is made to Cahn; Ingold; Prelog *Angew. Chem. Int. Ed. Engl.* **1966**, 5, 385-415.

A.3. Stereochemistry:

- It is known by those skilled in the art that specific enantiomers (or diastereoisomers) can
30 be obtained by different methods such as, but not limited to chiral resolution (for example, salts formed with optically active acids or bases may be used to form diastereoisomeric salts that can facilitate the separation of optically active isomers of the compounds of Formula I or any subgroup thereof), asymmetric synthesis or preparative chiral

chromatography (using different column such as Chiralcel OD-H (tris-3,5-dimethylphenylcarbamate, 46 x 250 or 100 x 250 mm, 5 μ m), Chiralcel OJ (tris-methylbenzoate, 46 x 250 or 100 x 250 mm, 5 μ m), Chiralpak AD (tris-3,5-dimethylphenylcarbamate, 46 x 250 mm, 10 μ m) and Chiralpak AS (tris-(S)-1-phenylethylcarbamate, 46 x 250 mm, 10 μ m) from Chiral Technologies Europe (Illkirch, France)). Whenever it is convenient, stereoisomers can be obtained starting from commercial materials with known configuration (such compounds include amino acid for instance).

A.4. Name of the molecules

- 10 The software MDL ISISTM / Draw 2.3 was used to assign the name of the molecules.

B. Compound synthesis

- 15 The compounds of the invention may be prepared by methods well known to those skilled in the art, and as described in the synthetic and experimental procedures shown below.

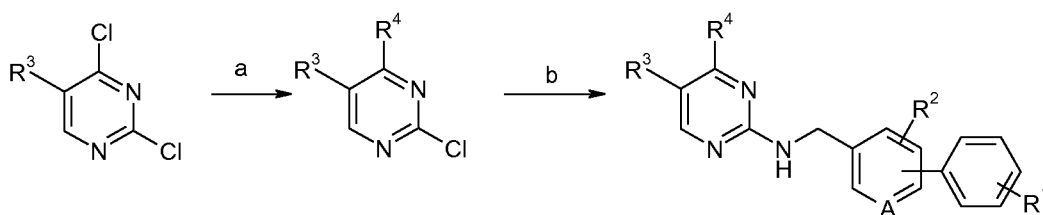
B.1. General synthetic Methods

- 20 The compounds of the invention may be prepared by the following general methods described hereinbelow. Detailed examples in line with these general synthetic methods will be provided in points B2 and B3.

Unless specified otherwise, R¹, R², R³ and R⁴ are as defined above for Formula I.

25

B.1.1: Method A



Step a:

The appropriate 2,4-dichloropyrimidine derivative is reacted with a selected amine R^4 -H and triethylamine or DIEA as base in either THF or EtOH as solvent (0°C to RT) to yield the corresponding mono-substituted chloropyrimidine derivative

Step b:

- 5 The chloropyrimidine derivative is reacted further with a selected amine and triethylamine or DIEA as base, in THF or EtOH as solvent (0°C to 140°C).

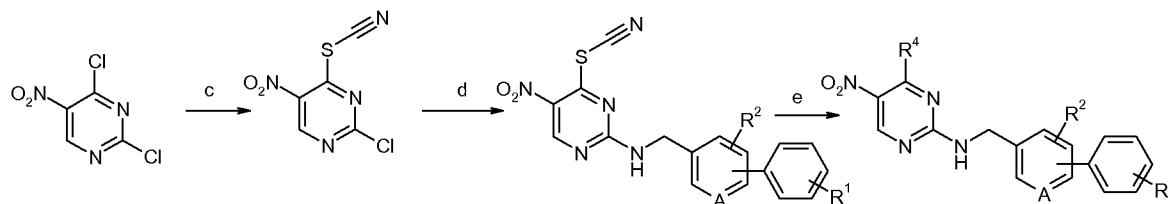
The reactions at step a and step b can also be carried out on commercially available 2,4-dichloropyridines.

10

When a second reactive amine group, is present in the reagent that is coupled to the pyrimidine at step a or step b, the second amine is preferably protected by a suitable group such as Boc-group, which is removed to afford compounds of Formula I.

15 B.1.2: Method B

When R^3 is a nitro group, the compounds of the invention may be prepared by the following alternative method:



Step c:

- 20 A solution of 2,4-dichloro-5-nitropyrimidine in AcOH at 5°C is reacted with potassium thiocyanate to yield 2-chloro-5-nitro-4-thiocyanatopyrimidine

Step d:

A solution of 2-chloro-5-nitro-4-thiocyanatopyrimidine in THF or EtOH is reacted with a selected amine, triethylamine or DIEA as base at 0°C to RT to yield the corresponding substituted intermediate;

25

Step e:

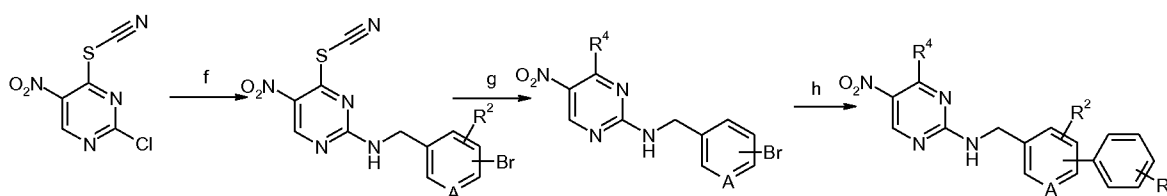
This thiocyanato pyrimidine derivative is reacted with a selected amine R^4 -H and triethylamine or DIEA as base in either THF or EtOH as solvent, to yield the desired compound.

30

When a second reactive amine group is present in the reagent that is coupled to the pyrimidine at step d or step e, the second amine is preferably protected by a suitable group such as Boc-group, which is removed to afford compounds of Formula I.

5 B.1.3: Method C

The thiocyanate intermediate produced at step c can be reacted with a selected bromo benzylamine (e.g. 2-methyl-3-bromo benzylamine) in order to provide an advanced intermediate. The R^4 group is then coupled to the pyridine/pyrimidine. A metal-catalyzed coupling reaction is ultimately used to build the bisaryl structure.



Step f:

A solution of 2-chloro-4-thiocyanato intermediate in THF or EtOH is reacted with a selected bromo-benzylamine (e.g. 2-methyl-3-bromo benzylamine), triethylamine or DIEA as base at 0°C to RT to yield the advanced thiocyanato intermediate.

Step g:

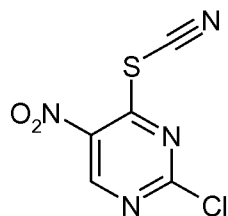
This advanced thiocyanato intermediate is further reacted with a selected amine R^4 -H and triethylamine or DIEA as base in either THF or EtOH as solvent, to yield the desired compound.

Step h:

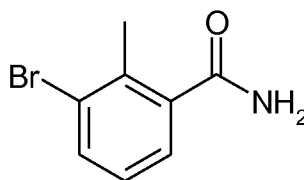
The intermediate resulting from step g is dissolved with a selected boronic acid and Na_2CO_3 in dioxane/ H_2O . A metal catalyst (e.g. $Pd(PPh_3)_4$) is added under inert atmosphere. The reaction mixture is stirred and heated to yield the desired product.

When a second reactive amine group is present in the reagent that is coupled to the pyrimidine at step f or step g, the second amine is preferably protected by a suitable group such as Boc-group, which is removed to afford compounds of Formula I.

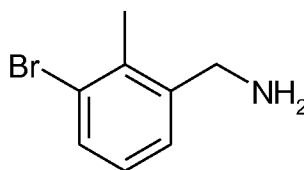
B.2. Intermediates

Intermediate 1: 2-chloro-5-nitro-4-thiocyanato-pyrimidine:

To a solution of 2,4-dichloro-5-nitro-pyrimidine (58.4 g, 300 mmol, 1.0 eq) in AcOH (150 ml) was added potassium thiocyanate (29.1 g, 300 mmol, 1.0 eq) at 5°C and the reaction was stirred for 15 min. The reaction mixture was poured into ice water and the precipitate was filtered to give Intermediate 1 (40 g, 62% yield) as yellow solid.

Intermediate 2: 3-bromo-2-methyl-benzamide:

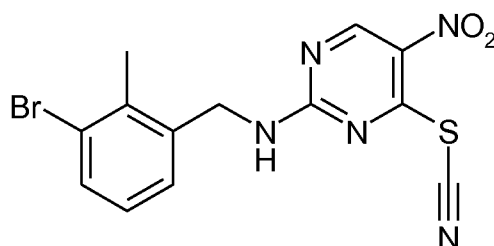
To a solution of 3-bromo-2-methyl-benzoic acid (20 g, 93 mmol, 1.0 eq), NH₄Cl (19.6 g, 364 mmol, 3.9 eq) and DIEA (51.2 ml, 287 mmol, 3.1 eq) in DMF (160 ml) was added EDCI (21.8 g, 114 mmol, 1.22 eq) and HOBt (15.9 g, 117 mmol, 1.25 eq), then stirred at room temperature overnight. The solvent was poured into water (400 ml). The resulting precipitate was filtered, washed with water, and dried under reduced pressure to give intermediate 2 (15 g, 75% yield) as white solid.

Intermediate 3: 3-bromo-2-methyl-benzylamine:

To a solution of intermediate 2 (14 g, 65.7 mmol, 1.0 eq) in THF (150 ml) was added dropwise Me₂S.BH₃ (13.4 ml, 197.1 mmol, 3.0 eq, 94%), and stirred at room temperature for 1 hour, then the reaction mixture was heated to reflux overnight. The reaction mixture was cooled to room temperature, and MeOH was added dropwise until no more air bubbles were formed, 10 min later, 20 ml of 10% aq. HCl was added dropwise, and the

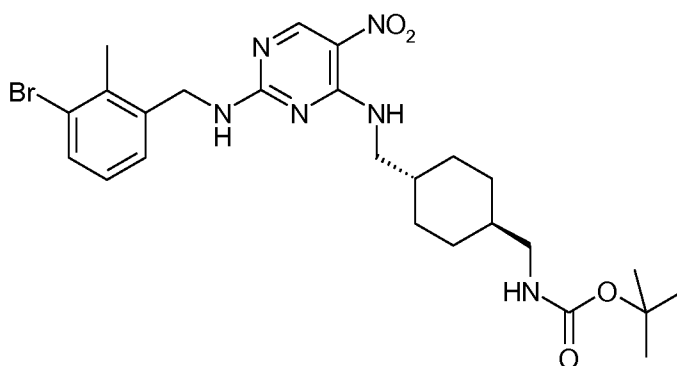
mixture was stirred for 1 hour at room temperature. The solvent was removed by rotavapor and the residue was recrystallized from i-PrOH to give intermediate 3 (10 g, 76.48% yield) as white HCl salt.

5 Intermediate 4: 2-(3-bromo-2-methyl-benzylamino)-4-thiocyanato-5-nitro pyrimidine:



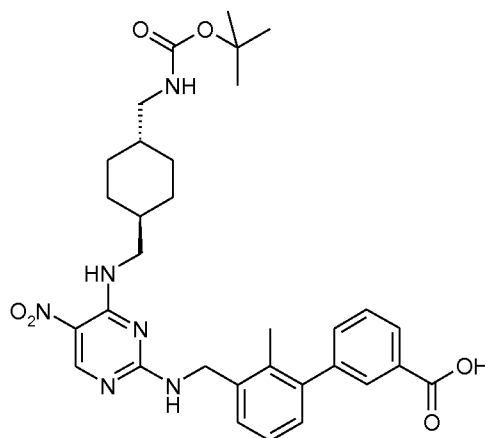
To a solution of Intermediate 1 (12 g, 55.2 mmol, 1.0 eq) in EtOH (110 ml) was added a solution of intermediate 3 hydrochloric acid salt (13 g, 55.2 mmol, 1.0 eq) in EtOH (110 ml). TEA (15.8 ml, 110.4 mmol, 2.0 eq) was added dropwise to the reaction mixture and stirred at room temperature overnight. The resulting precipitate was filtered and dried under high vacuum to give the expected compound (7.5 g, 35.85% yield).

15 Intermediate 5: Tert-butyl N-[[trans-4-[[2-[[3-bromo-2-methylphenyl)methyl]amino]-5-nitropyrimidin-4-yl]amino]methyl] cyclohexyl]methyl]carbamate:



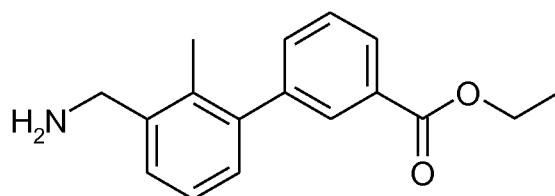
To a solution of the intermediate 4 (7.5 g, 20 mmol, 1.0 eq) in DMF (40 ml) was added a solution of *trans*-(4-aminomethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (9.75 g, 40 mmol, 2.0 eq) in DMF (40 ml). The reaction mixture was stirred at room temperature overnight, then the reaction mixture was poured into water (240 ml), and the resulting precipitate was filtered and dried under high vacuum to give the intermediate 5 (10.0 g, 89.0% yield).

Intermediate 6: 3'-[(4-{[*trans*-4-(*tert*-Butoxycarbonylamino-methyl)-cyclohexylmethyl]-amino}-5-nitro-pyrimidin-2-ylamino)-methyl]-2'-methyl-biphenyl-3-carboxylic acid



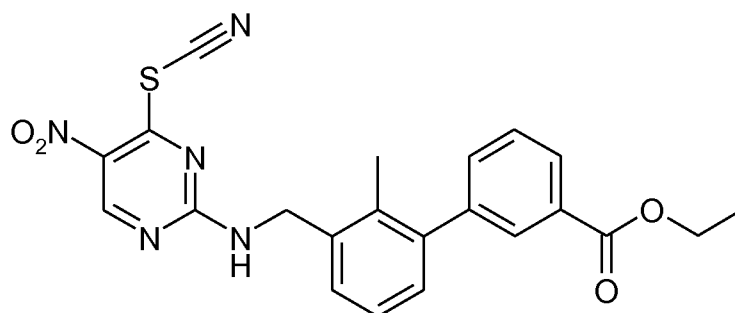
To a solution of intermediate 5 (9.4 g, 16.7 mmol, 1.0 eq), 3-carboxyphenylboronic acid
 5 (5.3 g, 31.7 mmol, 1.9 eq) and Na₂CO₃ (5.3 g, 50.1 mmol, 3.0 eq) in dioxane (167 ml) and H₂O (42 ml) was added Pd(PPh₃)₄ (0.964 g, 0.85 mmol, 0.05 eq) under N₂ protection. The reaction mixture was heated to 100°C with stirring overnight and then cooled to room temperature. The solvent was evaporated by rotavapor. The residue was dissolved in water and treated with 5% aq. HCl solution to pH = 5, the resulting precipitate was filtered
 10 and dried to give Intermediate 6 (8 g, 79% yield) as white solid.

Intermediate 7: Ethyl 3-[3-(aminomethyl)-2-methylphenyl]-benzoate:



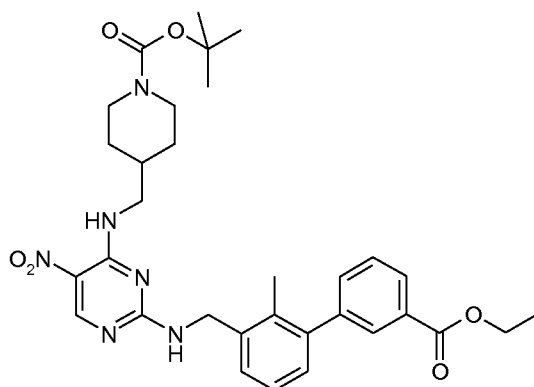
To a solution of intermediate 3 (15 g, 75 mmol, 1.0 eq), 3-(ethoxycarbonyl)phenyl)boronic
 15 acid (21.8 g, 112.5 mmol, 1.5 eq) and Cs₂CO₃ (36.6 g, 112.5 mmol, 1.5 eq) in dioxane (300 ml) was added PdCl₂(dtbpf) (0.964 g, 3.75 mmol, 0.05 eq) under N₂ protection. The reaction mixture was heated to 100 °C with stirring overnight and then cooled to room temperature. The solvent was evaporated by rotavapor and EtOAc (400 ml) was added into the mixture. After washing with H₂O (200 ml x3), drying over MgSO₄, filtration and
 20 evaporation under reduced pressure, the residue was dissolved in EtOAc (300 ml). Then 10% aq. HCl (15 ml) was added dropwise and the resulting precipitate was filtered and dried to give intermediate 7 (12 g, 60% yield) as a white solid.

Intermediate 8: Ethyl 3-[3-({[4-(thiocyanato)-5-nitropyrimidin-2-yl]amino}methyl)-2-methylphenyl]benzoate:



To a solution of intermediate 1 (9.6 g, 44.6 mmol, 1.0 eq) in EtOH (100 ml) was added a solution of intermediate 7 (12 g, 44.6 mmol, 1.0 eq) in EtOH (110 ml). TEA (11.8 ml, 89.2 mmol, 2.0 eq) was added dropwise to the reaction mixture and stirred at room temperature overnight. The resulting precipitate was filtered and dried under high vacuum to give intermediate 8 (11.0 g, 55% yield).

Intermediate 9: Ethyl 3-[3-({[4-({[1-({tert-butoxy}carbonyl)piperidin-4-yl]methyl)amino]-5-nitropyrimidin-2-yl]amino}methyl)-2-methylphenyl]benzoate:



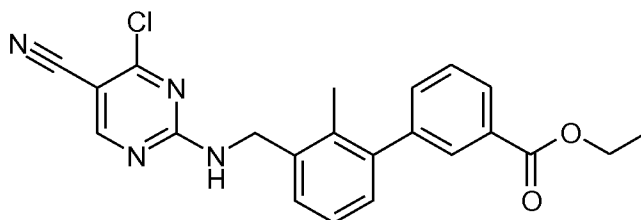
To a solution of intermediate 8 (1.0 g, 2.2 mmol, 1.0 eq) in DMF (10 ml) was added a solution of *tert*-butyl 4-(aminomethyl)piperidine-1-carboxylate (0.94 g, 4.4 mmol, 2.0 eq) in DMF (10 ml). The reaction mixture was stirred at room temperature overnight, then the reaction mixture was poured into water (100 ml), and the resulting precipitate was filtered and washed subsequently with a 1:5 DMF:H₂O mixture (5ml x2): and H₂O (5ml x2), and ultimately dried under high vacuum to give intermediate 9 (1.1 g, 82 % yield).

The following intermediates can be prepared according to an analogous procedure, by reacting intermediate 8 with other commercially available amines as was done for the

synthesis of intermediate 9; the required changes in experimental procedures being straightforward to persons skilled in the art.

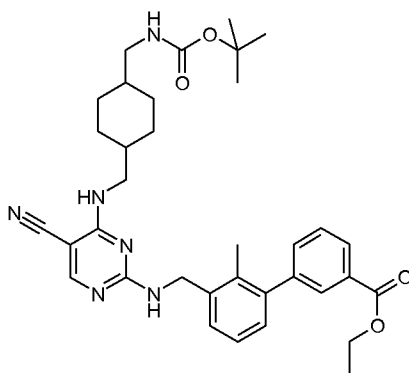
Intermediate structure	Name	IUPAC Name
	Intermediate 10	Ethyl 3-[3-({[4-({1-[(tert-butoxy)carbonyl]piperidin-4-yl}amino)-5-nitropyrimidin-2-yl]amino}methyl)-2-methylphenyl]benzoate
	Intermediate 11	Ethyl 3-(3-({[4-({(4-[(tert-butoxy)carbonyl]amino)cyclohexyl)methyl]amino}-5-nitropyrimidin-2-yl]amino}methyl)-2-methylphenyl)benzoate
	Intermediate 12	Ethyl 3-{3-({[4-[(4-[(tert-butoxy)carbonyl]amino)cyclohexyl]amino]-5-nitropyrimidin-2-yl]amino}methyl)-2-methylphenyl}benzoate
	Intermediate 13	Ethyl 3-(3-({[4-[(4-[(tert-butoxy)carbonyl]amino)methyl]cyclohexyl]amino}-5-nitropyrimidin-2-yl]amino}methyl)-2-methylphenyl)benzoate

5 Intermediate 14: Ethyl 3-[3-({[4-chloro-5-cyanopyrimidin-2-yl]amino}methyl)-2-methylphenyl]benzoate:



2,4-Dichloro-pyrimidine-5-carbonitrile (50 mg, 0.287 mmol, 1.0 eq) was dissolved in DMF (1 ml) and intermediate 7 (77 mg, 0.287 mmol, 1.0 eq) was added to the solution, followed by DIEA (51 μ l, 0.287 mmol, 1.0 eq). The reaction mixture was stirred for 1 hour at room temperature, diluted with EtOAc (50 ml) and washed with water (50 ml x4). The organic
5 fraction was dried over anhydrous Na_2SO_4 , filtrated and concentrated under reduced pressure and purified by preparative HPLC to yield the desired intermediate 14.

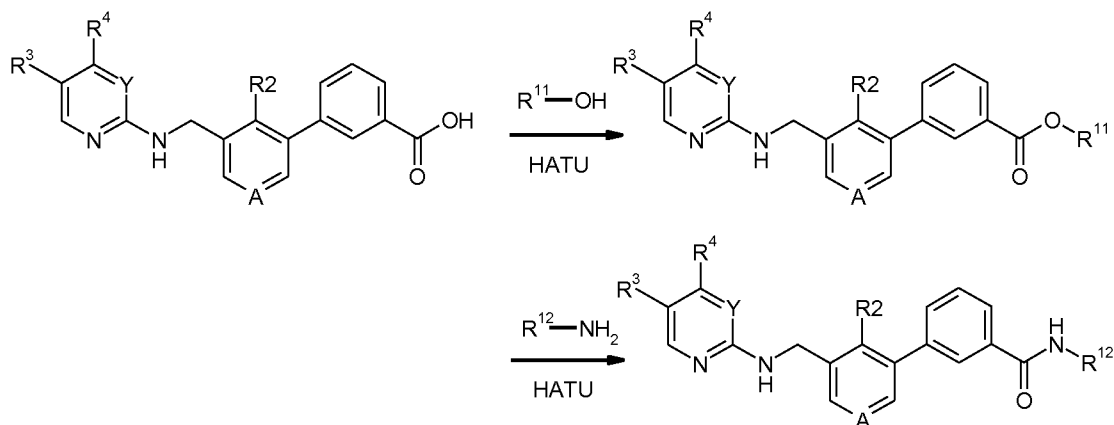
Intermediate 15: Ethyl 3-{3-[(5-cyano-4-[(4-[(tert-butoxycarbonylamino)methyl]cyclohexyl)methyl]amino)pyrimidin-2-yl]amino)methyl]-2-methylphenyl}benzoate:



A solution of intermediate 14 (117 mg, 287 μ mol, 1.0 eq), TEA (30 mg, 297 μ mol, 1.03 eq) and *tert*-butyl N-{[4-(aminomethyl)cyclohexyl]methyl}carbamate (70 mg, 287 μ mol, 1.0 eq) in THF (2 ml) was stirred at 60 $^{\circ}\text{C}$ for 16 hrs. The solvent was removed under reduced pressure and 4N HCl-EtOH (4 ml) was added to the residue. This mixture was stirred at
15 room temperature overnight and the solvent was removed by rotavapor to give the crude product, which was purified by preparative HPLC to give the desired intermediate 15.

B.3. Compounds of the invention

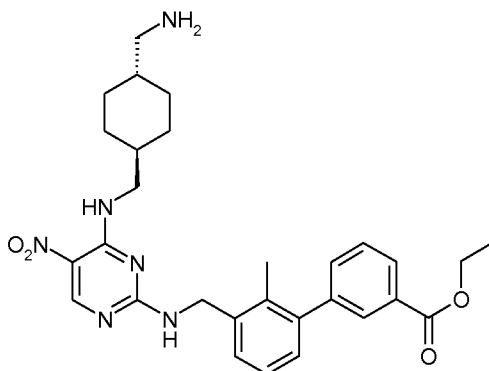
20 Compounds of the invention can be obtained by reacting advanced benzoic acid intermediates such as intermediate 6 with selected alcohols or amines, using an appropriate coupling reagent such as HATU.



Any protecting group(s) remaining after the coupling reaction is/are then removed in order to yield the compounds of the invention.

- 5 A detailed example of such synthesis is hereby provided.

Compound 1: Propyl 3-[3-({[4-({[4-(aminomethyl)cyclohexyl]methyl}amino)-5-nitropyrimidin-2-yl]amino}methyl)-2-methylphenyl]benzoate:



- 10 To a solution of intermediate 6 (242 mg, 0.40 mmol, 1.0 eq), *n*-propanol (39 μ l, 0.52 mmol, 1.3 eq) and triethylamine (229 μ l, 1.60 mmol, 4.0 eq) in DMF (6 ml) was added EDCI (114.6 mg, 0.60 mmol, 1.5 eq) and HOBt (30.4 mg, 0.20 mmol, 0.5 eq) and the reaction mixture was stirred at 30 °C overnight. The solvent was then evaporated under reduced pressure to give the crude Boc-protected intermediate.

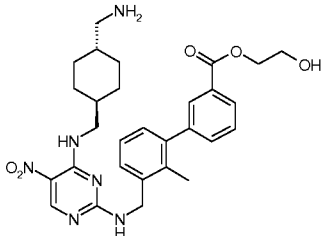
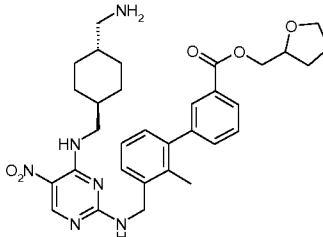
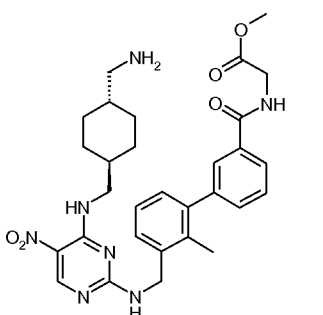
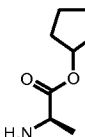
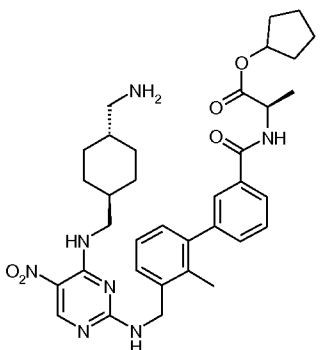
15

This intermediate was dissolved in a 5:1 DCM:TFA mixture (6 ml) and the reaction mixture was stirred at 30 °C for 2 hrs. Then the reaction mixture was concentrated under reduced pressure and the crude product was purified by prep. HPLC to give compound 1 (83 mg, 38% yield)

20

The following compounds of the invention can be prepared according to analogous procedures, by reacting intermediate 6 with appropriate alcohols or amines and removing the tBoc protecting group as for compound 1; the required changes in experimental procedures being straightforward to persons skilled in the art.

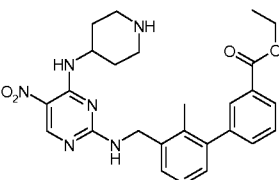
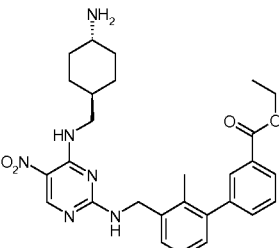
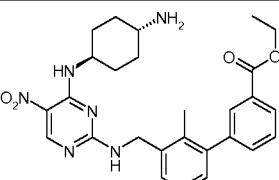
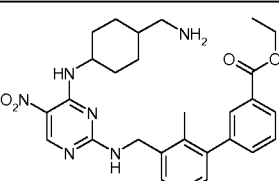
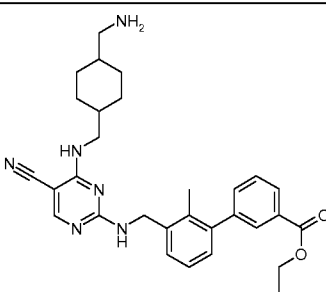
5

Cpd	Interm.	Reagent	Structure	Name
2	6			2-hydroxyethyl 3-[3-({4-({[<i>trans</i> -4-(aminomethyl)cyclohexyl]methyl}amino)-5-nitropyrimidin-2-yl]amino)methyl)-2-methylphenyl]benzoate
3	6			Oxolan-2-ylmethyl 3-[3-({4-({[<i>trans</i> -4-(aminomethyl)cyclohexyl]methyl}amino)-5-nitropyrimidin-2-yl]amino)methyl)-2-methylphenyl]benzoate
4	6			Methyl 2-({3-[2-methyl-3-({5-nitro-4-({[<i>trans</i> -4-(aminomethyl)cyclohexyl]methyl}amino)pyrimidin-2-yl]amino)methyl}phenyl]phenyl}formamido)acetate
5	6			Cyclopentyl (2S)-2-({3-[2-methyl-3-({5-nitro-4-({[<i>trans</i> -4-(aminomethyl)cyclohexyl]methyl}amino)pyrimidin-2-yl]amino)methyl}phenyl]phenyl}formamido)propanoate

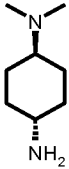
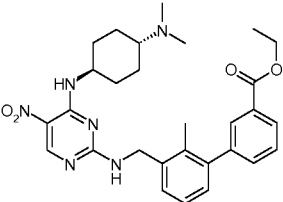
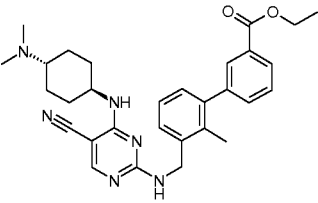
Cpd	Interm.	Reagent	Structure	Name
6	6			3-[2-methyl-3-({[5-nitro-4-({[<i>trans</i> -4-(aminomethyl)cyclohexyl]methyl}amino)pyrimidin-2-yl]amino)methyl]phenyl]-N-{3-[(2-oxooxolan-3-yl)sulfanyl]propyl}benzamide
7	6			3-[2-methyl-3-({[5-nitro-4-({[<i>trans</i> -4-(aminomethyl)cyclohexyl]methyl}amino)pyrimidin-2-yl]amino)methyl]phenyl]-N-{3-[(2-oxooxolan-3-yl)amino]propyl}benzamide

Additional compounds of the invention can be obtained by removing the tBoc protection from intermediates 10, 11, 12, 13 & 15. tBoc deprotection is described hereinabove as part of the synthetic route yielding compound 1. The required changes in experimental
5 procedures are considered straightforward to a person skilled in the art.

Cpd	Interm.	Structure	Name
8	7		Ethyl 3-{2-methyl-3-[(5-nitro-4-[(piperidin-4-ylmethyl)amino]pyrimidin-2-yl)amino)methyl]phenyl}benzoate

Cpd	Interm.	Structure	Name
9	8		Ethyl 3-(2-methyl-3-((5-nitro-4-((piperidin-4-yl)amino)pyrimidin-2-yl)amino)methyl)phenyl)benzoate
10	9		Ethyl 3-(2-methyl-3-((5-nitro-4-((trans-4-aminocyclohexyl)methyl)amino)pyrimidin-2-yl)amino)methyl)phenyl)benzoate
11	10		Ethyl 3-(2-methyl-3-((5-nitro-4-((trans-4-aminocyclohexyl)amino)pyrimidin-2-yl)amino)methyl)phenyl)benzoate
12	11		Ethyl 3-(2-methyl-3-((5-nitro-4-((trans-4-(aminomethyl)cyclohexyl)amino)pyrimidin-2-yl)amino)methyl)phenyl)benzoate
13	15		Ethyl 3-(3-((4-((4-(aminomethyl)cyclohexyl)methyl)amino)-5-cyanopyrimidin-2-yl)amino)methyl)-2-methylphenyl)benzoate

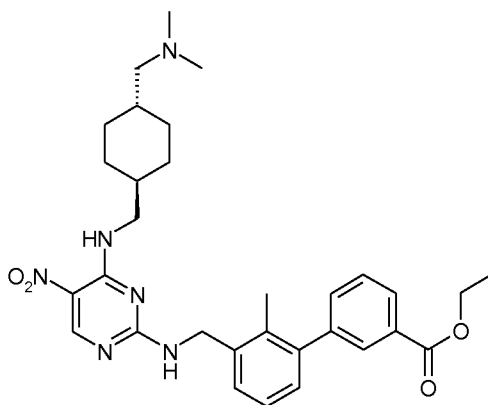
More compounds of the invention can be synthesized by reacting diamines displaying one tertiary amine in their structure; using procedures analogous to the one used for the synthesis of intermediates 9-13 & 15. In such cases, no tBoc-deprotection is required, and the reaction between the selected thiocyanate/chloropyrimidine and diamine directly yields the final compound.

Cpd	Interm.	Reagent	Structure	Name
14	8			Ethyl 3-(2-methyl-3-[[[(5-nitro-4-[[trans-4-dimethylaminocyclohexyl]amino]pyrimidin-2-yl)amino]methyl]phenyl)benzoate
15	14			Ethyl 3-(2-methyl-3-[[[(5-cyano-4-[[trans-4-dimethylaminocyclohexyl]amino]pyrimidin-2-yl)amino]methyl]phenyl)benzoate

Alternatively, compounds of the invention displaying a tertiary amine can also be obtained through reductive amination of advanced intermediates or of other compounds of the invention displaying a primary amine; as described in the following example.

5

Compound 16: Propyl 3-[3-({[4-({[4-(dimethylaminomethyl)cyclohexyl]methyl} amino)-5-nitropyrimidin-2-yl]amino}methyl)-2-methylphenyl]benzoate:



To a solution of Intermediate 6 (4.5 g, 7.61 mmol, 1.0 eq) in EtOAc (150 ml) was added 4N HCl-EtOAc (150 ml) and the mixture was stirred at room temperature for 4 hrs. The solvent was removed under reduced pressure to give 3.7 g of crude de-Boc intermediate, which was used directly in the next step without purification.

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To a solution of de-Boc intermediate (0.8 g, 1.58 mmol, 1.0 eq), paraformaldehyde (0.49 g, 15.8 mmol, 10.0 eq), TEA (0.3 g, 3.17 mmol, 2.0 eq) and H₂O (0.5 ml) in MeOH (20 ml) was added NaBH₃CN (0.2 g, 3.17 mmol, 2.0 eq) and the mixture was stirred for 16 hrs at room temperature. The solvent was removed by rotavapor to give the crude product, which was purified by preparative HPLC to the dimethylated intermediate (65 mg).

To a solution of the dimethylated intermediate (45 mg, 84.6 μ mol, 1.0 eq), *n*-PrOH (50.7 mg, 846 μ mol, 10.0 eq) and TEA (25.6 mg, 253.8 μ mol, 3.0 eq) in DMF (1.0 ml) was added EDCI (24.2 mg, 126.9 μ mol, 1.5 eq) and HOBt (312.8 mg, 84.6 μ mol, 1.0 eq) and the reaction mixture was stirred at 30 °C overnight. Then the reaction mixture was concentrated under reduced pressure and the crude product was purified by preparative HPLC to give the final compound 16 (23 mg, 47% yield).

At this stage, it will be appreciated that yet additional compounds of the invention can be obtained from intermediates 7-13 & 15 and commercially available alcohols and amines. In order to produce such compounds, the selected intermediate first undergoes saponification, for instance through reaction with LiOH; such a reaction being straightforward to persons skilled in the art. The resulting intermediate is then coupled with the appropriate alcohol or amine. The tBoc protection is removed as a last synthetic step. Coupling of advanced carboxylic intermediates with selected alcohols or amines and removal of the tBoc protection are described hereinabove as part of the synthetic route yielding compound 1. The required changes in experimental procedures are considered straightforward to a person skilled in the art.

C. In vitro and in vivo assays:

C.1. PKC inhibitory activity screening:

C.1.1. Kinase inhibition (PKC θ):

On-target activity against PKC θ was measured in a biochemical assay, using the following reagents: Base Reaction buffer; 20 mM Hepes (pH 7.5), 10 mM MgCl₂, 1mM EGTA, 0.02% Brij35, 0.02 mg/ml BSA, 0.1 mM Na₃VO₄, 2 mM DTT, 1% DMSO. Required cofactors are added individually to each kinase reaction. The reaction procedure first involved the preparation of a peptide substrate in a freshly prepared reaction buffer. Required cofactors were then added to the substrate solution. PKC θ (1nM final concentration) was then delivered to the substrate solution. After gentle mix, DMSO

solutions of the test compounds were added to the enzyme. Substrate mix ^{33}P -ATP (specific activity 0.01 $\mu\text{Ci}/\mu\text{l}$ final) was then delivered into the reaction mixture to initiate the reaction. The kinase reaction was incubated for 120 min. at room temperature. Reactions were then spotted onto P81 ion exchange paper (Whatman # 3698-915). Filters were washed extensively in 0.1% Phosphoric acid. A radiometric count was then performed and IC_{50} values were subsequently determined.

When evaluated under such conditions, compounds of the invention display IC_{50} values $<10\mu\text{M}$. Preferred compounds display IC_{50} values $<1\mu\text{M}$. Most preferred compounds display IC_{50} values $<0.1\mu\text{M}$. Examples of dose-response curves determined under such conditions are hereby provided in Figure 1 for compounds 1 ($\text{IC}_{50}=296\text{nM}$), 2 ($\text{IC}_{50}=48\text{nM}$), 4 ($\text{IC}_{50}=10\text{nM}$) and 6 ($\text{IC}_{50}=17\text{nM}$). From these examples, it will be appreciated that compounds of the invention display inhibitory activity against PKC θ .

C.2. Pharmacological Characterization:

C.2.1. Stability assay in human and other species plasma:

Compounds are incubated at a concentration of 1 μM in human or animal (ex: rat/mice/rabbit/dog) plasma. Samples are taken at fixed time points and the percentage of remaining compound is determined by LC-MS/MS after protein precipitation.

When evaluated under such conditions, compounds of the invention display a half-life in human plasma that is inferior to 60 minutes. Preferred compounds display a half-life in human plasma that is inferior to 30 minutes. Most preferred compounds display a half-life in human plasma that is inferior to 15 minutes. Example data is hereby provided in the following table and in figure 2 for compounds 1, 2, 3 and 6, which all display a half-life in human plasma that is inferior to 10 minutes. Procaine (unstable reference) and Enalapril (stable reference) are included for comparison. From these examples, it will be appreciated that compounds of the invention display low stability in human plasma and, by extension, low stability in human whole blood.

Compound	% rem. after 10 min (human plasma)	% rem. after 60 min (human plasma)	% rem. after 100 min (human plasma)
Procaine	1	0	0
Enalapril	100	100	95

Cpd1	39	13	9
Cpd2	19	ND	1
Cpd3	11	ND	0
Cpd6	43	ND	19
Cpd8	ND	14	ND
Cpd16	ND	28	ND

ND: Not determined.

C.2.2. Stability towards drug metabolizing enzymes in lung S9:

A 1 μ M solution of the compounds is incubated with a reaction mixture containing lung S9 (from smokers) as well as the cofactors NADPH, UDPGA, PAPS and GSH. Samples are collected at fixed time points. Negative control samples incubated with PKC inhibitors and S9 fraction in the absence of cofactors are run in parallel. By using LC-MS/MS analysis, the percent of compounds remaining at each time point, the metabolic half-life of the compounds (expressed in minutes) and the metabolic half-life of the control compounds are determined.

When evaluated under such conditions, selected compounds of the invention display a half-life in human lung S9 that is superior to 60 minutes. Preferred compounds display a half-life in human lung S9 that is superior to 120 minutes. Most preferred compounds display a half-life in human lung S9 that is superior to 240 minutes. Example data is hereby provided in the following table and in Figure 3 for compound 6, which displays a half-life in human lung S9 that is largely superior to 60 minutes. Ethoxyresorufin (stable reference) is included for comparison. From this example, it will be appreciated that selected compounds of the invention display good stability in human lung S9, and, by extension, in human lung.

Incubation time (min)	Ethoxyresorufin (% rem)	Cpd4 (% rem)	Cpd6 (% rem)
0	100	100	100
10	97	100	100
20	96	99	98

30	92	90	89
60	89	72	84

C.2.3. Stability assay in rabbit aqueous humor:

Compounds are incubated at a concentration of 1 μ M in rabbit aqueous humor (AH). Samples are taken at fixed time points and the percentage of remaining compound is determined by LC-MS/MS after protein precipitation.

When evaluated under such conditions, selected compounds of the invention display a half-life in aqueous humor that is superior to 60 minutes. Preferred compounds display a half-life in aqueous humor that is superior to 120 minutes. Example data is hereby provided for compound 2, which displays a half-life in rabbit aqueous humor that is superior to 60 minutes (estimated half life: 110 min). From this example, it will be appreciated that selected compounds of the invention display good stability in aqueous humor.

Incubation time (min)	% remaining: Cpd2
0	100
30	91
120	46

D. Soft PKC θ inhibitors for local treatment of PKC θ -associated diseases

D.1. Soft PKC θ inhibitor for the local treatment of lung diseases

From the data disclosed in points C.1.1, C.2.1 and C.2.2, it will be appreciated that compounds of the invention such as compound 6 simultaneously display inhibitory activity against PKC θ , good stability in lung and low stability in plasma. Such compounds therefore qualify as soft, locally acting PKC θ inhibitors for the treatment of lung diseases.

5 Such compounds can be locally applied to lung by methods known in the art, such as (but not limited to) aerosols or dry powder inhalers, in order to modulate PKC θ activity in lung during a sustained period of time, typically several hours. Rapid degradation of such compounds in plasma / whole blood will however limit or prevent systemic PKC inhibition following administration.

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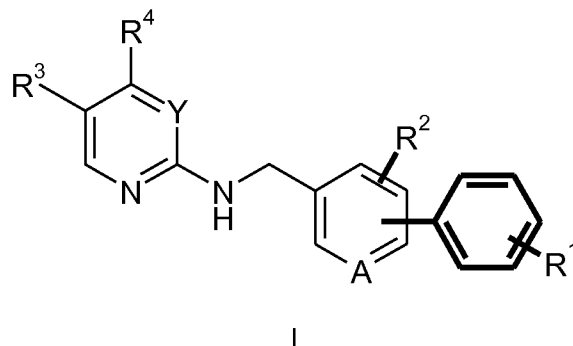
D.2. Soft PKC θ inhibitor for the local treatment of eye diseases

From the data disclosed in points C.1.1, C.2.1 and C.2.3, it will be appreciated that compounds of the invention such as compound 2 simultaneously display inhibitory activity against PKC θ , good stability in aqueous humor and low stability in plasma. Such

15 compounds therefore qualify as soft, locally acting PKC θ inhibitors for the treatment of eye diseases. Such compounds can be locally applied to the eye by methods known in the art, such as (but not limited to) eye drops or intravitreal injections, in order to modulate PKC θ activity in the eye during a sustained period of time. Rapid degradation of such compounds in plasma / whole blood will however limit or prevent systemic PKC inhibition
20 following administration.

CLAIMS

1. A compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, or solvate thereof,



Wherein

Y is -N- or -CH-;

A is -N- or -CH-;

R¹ is selected from the group consisting of

- a) $-(CH_2)_m-C(=O)-OR^{11}$
- b) $-(CH_2)_m-C(=O)-NH-R^{12}$
- c) $-(CH_2)_m-NH-C(=O)-R^{12}$
- d) $-(CH_2)_m-X-R^{12}$
- e) $(CH_2)_m-C(=O)-R^{12}$

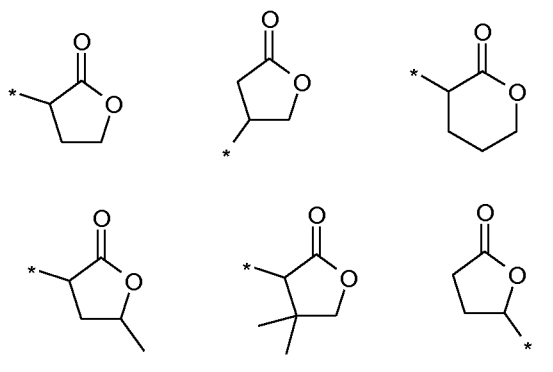
Wherein

m is an integer selected from 0 to 3;

R¹¹ is selected from the group comprising optionally substituted C₁₋₈alkyl, C₃₋₈cycloalkyl, C₁₋₈alkoxyalkyl, alkylcycloalkyl, heterocyclyl, aryl, Het¹, and heteroaryl;

Wherein

Het¹ is selected from the group consisting of



R^{12} is an optionally substituted Het^1 or R^{12} is selected from the group consisting of C_{1-8} alkyl, C_{3-8} cycloalkyl, heterocyclyl, alkylheterocyclyl, aryl and heteroaryl; wherein said C_{1-8} alkyl, C_{3-8} cycloalkyl, heterocyclyl, alkylheterocyclyl, aryl and heteroaryl is substituted with:

- one or more substituents independently selected from the group consisting of Het^1 ; $-O-Het^1$; $-NH-Het^1$, $-S-Het^1$, and $-(CH_2)_n-C(=O)-OR^{11}$; and
- optionally, one or more substituents independently selected from the group consisting of halo, hydroxyl, carbonyl, nitro, amino, oxime, imino, azido, hydrazino, cyano, aryl, heteroaryl, cycloalkyl, heterocyclyl, acyl, alkylamino, alkoxy, thiol, alkylthio, acylamino, alkyl esters, carbamate, thioamido, urea, aminocarbonyl, alkyl, alkenyl, alkynyl, cycloalkylalkyl, $-SO_2-NH_2$, aralkyl, haloalkyl, haloalkoxy, alkylaminocarbonyl, heteroarylalkyl, alkylsulfonamide, alkylcarbonylaminoalkyl, aryloxy, alkylcarbonyl, acyl, arylcarbonyl, aminocarbonyl, alkylsulfoxide, $-SO_2R^a$, carboxyl, and the like; wherein R^a is alkyl or cycloalkyl;

Wherein

n is an integer from 0 to 3;

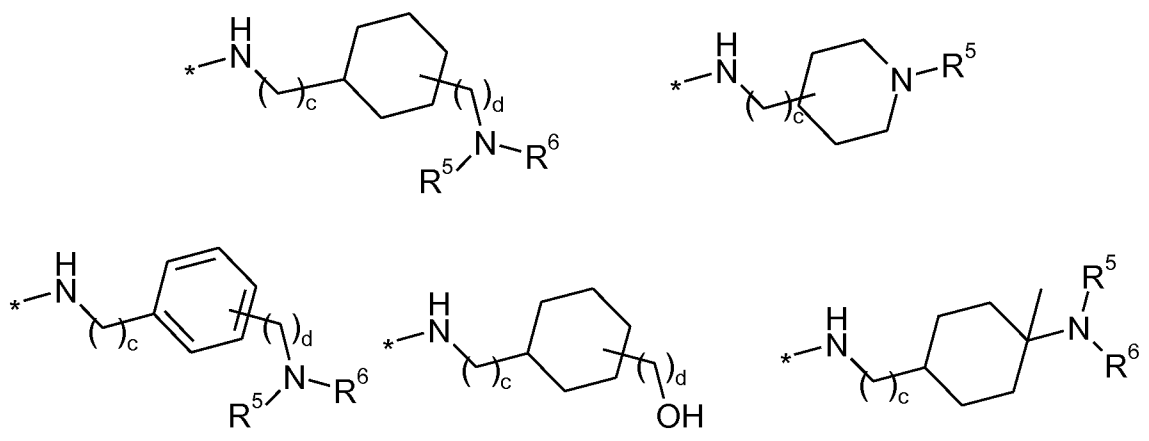
Het^1 and R^{11} are as defined hereinbefore;

X is $-NH-$, $-CH_2-$, $-O-$, or $-S-$;

R^2 is hydrogen or C_{1-4} alkyl;

R^3 is selected from the group consisting of hydrogen, nitro, halo, haloalkyl, cyano or $-C(=O)NH_2$; and

R^4 is selected from the following groups:



Wherein

c and d are each independently an integer from 0 to 3; and

R^5 and R^6 are each independently selected from the group consisting of hydrogen and optionally substituted C_{1-6} alkyl; or

R^5 and R^6 together with the nitrogen atom to which they are attached form a heterocycle optionally substituted with C_{1-6} alkyl.

2. A compound according to claim 1 wherein

Y is -N- or -CH-; in particular -N-;

A is -N- or -CH-; in particular -CH-;

R^1 is selected from the group consisting of

- a) $-(CH_2)_m-C(=O)-OR^{11}$;
- b) $-(CH_2)_m-C(=O)-NH-R^{12}$;

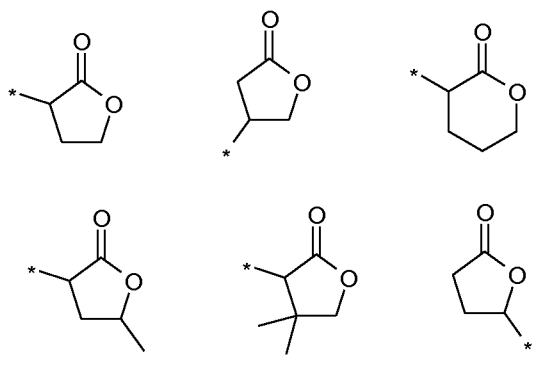
Wherein

m is an integer selected from 0 to 3;

R^{11} is selected from the group comprising optionally substituted C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{1-8} alkoxyalkyl, alkylcycloalkyl, heterocyclyl, aryl, Het^1 , and heteroaryl;

Wherein

Het^1 is selected from the group consisting of



R^{12} is an optionally substituted Het^1 or R^{12} is selected from the group consisting of C_{1-8} alkyl, C_{3-8} cycloalkyl, heterocyclyl, alkylheterocyclyl, aryl and heteroaryl; wherein said C_{1-8} alkyl, C_{3-8} cycloalkyl, heterocyclyl, alkylheterocyclyl, aryl and heteroaryl is substituted with:

- one or more substituents independently selected from the group consisting of Het^1 ; $-O-Het^1$; $-NH-Het^1$, $-S-Het^1$, and $-(CH_2)_n-C(=O)-OR^{11}$; and
- optionally one or more substituents independently selected from the group consisting of halo, hydroxyl, carbonyl, nitro, amino, oxime, imino, azido, hydrazino, cyano, aryl, heteroaryl, cycloalkyl, heterocyclyl, acyl, alkylamino, alkoxy, thiol, alkylthio, acylamino, alkyl esters, carbamate, thioamido, urea, aminocarbonyl, alkyl, alkenyl, alkynyl, cycloalkylalkyl, $-SO_2-NH_2$, aralkyl, haloalkyl, haloalkoxy, alkylaminocarbonyl, heteroarylalkyl, alkylsulfonamide, alkylcarbonylaminoalkyl, aryloxy, alkylcarbonyl, acyl, arylcarbonyl, aminocarbonyl, alkylsulfoxide, $-SO_2R^a$, carboxyl, and the like; wherein R^a is alkyl or cycloalkyl;

Wherein

n is an integer from 0 to 3;

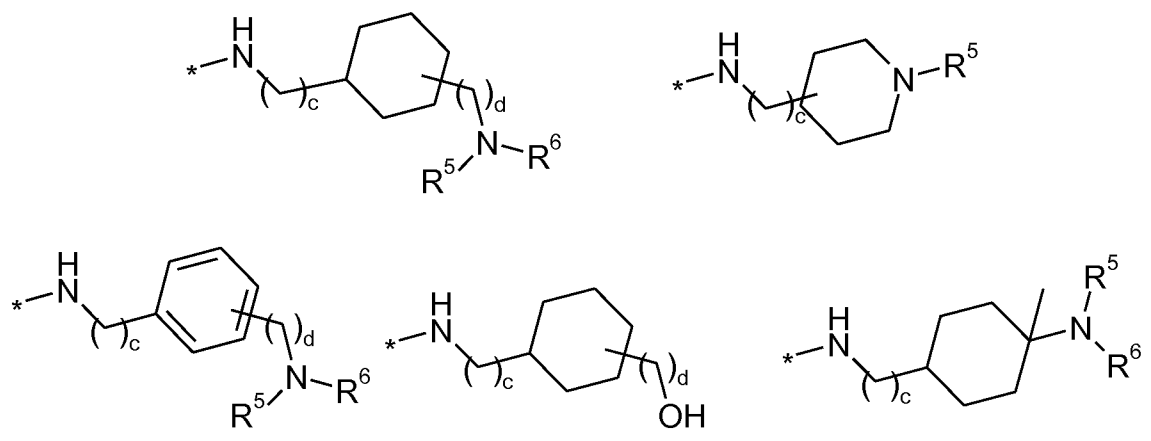
Het^1 and R^{11} are as defined hereinbefore;

X is $-NH-$, $-CH_2-$, $-O-$, or $-S-$;

R^2 is hydrogen or C_{1-4} alkyl;

R^3 is selected from the group consisting of hydrogen, nitro, halo, haloalkyl, cyano or $-C(=O)NH_2$; and

R^4 is selected from the following groups:



Wherein

c and d are each independently an integer from 0 to 3; and

R^5 and R^6 are each independently selected from the group consisting of hydrogen and optionally substituted C_{1-6} alkyl; or

R^5 and R^6 together with the nitrogen atom to which they are attached form a heterocycle optionally substituted with C_{1-6} alkyl.

3. A compound according to claim 1, wherein

Y is -N- or -CH-; in particular -N-;

A is -N- or -CH-; in particular -CH-; and

R^1 is selected from the group consisting of

- $-(CH_2)_m-C(=O)-OR^{11}$
- $-(CH_2)_m-C(=O)-NH-R^{12}$
- $-(CH_2)_m-NH-C(=O)-R^{12}$
- $-(CH_2)_m-X-R^{12}$
- $(CH_2)_m-C(=O)-R^{12}$

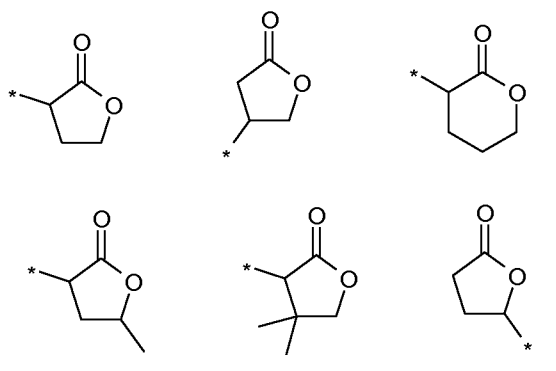
Wherein

m is an integer selected from 0 to 3;

R^{11} is selected from the group comprising optionally substituted C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{1-8} alkoxyalkyl, alkylcycloalkyl, heterocyclyl, aryl, Het^1 , and heteroaryl;

Wherein

Het^1 is selected from the group consisting of



R^{12} is an optionally substituted Het^1 or R^{12} is selected from the group consisting of C_{1-8} alkyl, C_{3-8} cycloalkyl, heterocyclyl, alkylheterocyclyl, aryl and heteroaryl; wherein said C_{1-8} alkyl, C_{3-8} cycloalkyl, heterocyclyl, alkylheterocyclyl, aryl and heteroaryl is substituted with:

- one or more substituents independently selected from the group consisting of Het^1 ; $-O-Het^1$; $-NH-Het^1$, $-S-Het^1$, and $-(CH_2)_n-C(=O)-OR^{11}$; and
- optionally one or more substituents independently selected from the group consisting of halo, hydroxyl, carbonyl, nitro, amino, oxime, imino, azido, hydrazino, cyano, aryl, heteroaryl, cycloalkyl, heterocyclyl, acyl, alkylamino, alkoxy, thiol, alkylthio, acylamino, alkyl esters, carbamate, thioamido, urea, aminocarbonyl, alkyl, alkenyl, alkynyl, cycloalkylalkyl, $-SO_2-NH_2$, aralkyl, haloalkyl, haloalkoxy, alkylaminocarbonyl, heteroarylalkyl, alkylsulfonamide, alkylcarbonylaminoalkyl, aryloxy, alkylcarbonyl, acyl, arylcarbonyl, aminocarbonyl, alkylsulfoxide, $-SO_2R^a$, carboxyl, and the like; wherein R^a is alkyl or cycloalkyl;

Wherein

n is an integer from 0 to 3;

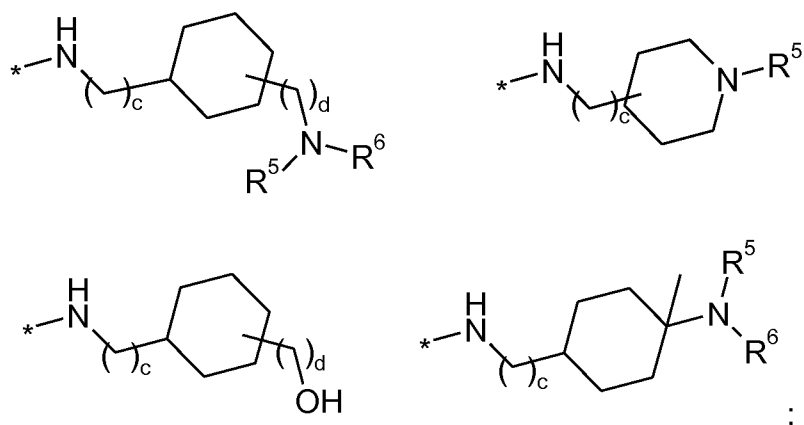
Het^1 and R^{11} are as defined hereinbefore;

X is $-NH-$, $-CH_2-$, $-O-$, or $-S-$;

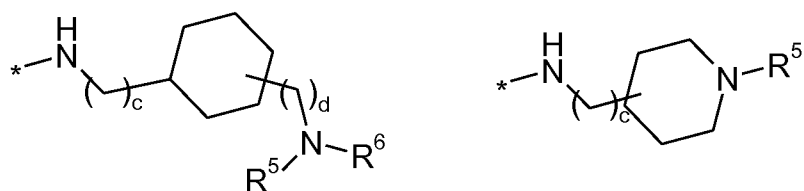
R^2 is hydrogen or C_{1-4} alkyl;

R^3 is selected from the group consisting of hydrogen, nitro, halo, haloalkyl, cyano or $-C(=O)NH_2$; and

R^4 is selected from the following groups:



in particular R^4 is selected from the following groups:



Wherein

c and d are each independently an integer from 0 to 3; and

R^5 and R^6 are each independently selected from the group consisting of hydrogen and optionally substituted C_{1-6} alkyl; or

R^5 and R^6 together with the nitrogen atom to which they are attached form a heterocycle optionally substituted with C_{1-6} alkyl.

4. A compounds according to claim 1, wherein

Y is -N- or -CH-;

A is -N- or -CH-;

R^1 is selected from the group consisting of

- a) $-(CH_2)_m-C(=O)-OR^{11}$
- b) $-(CH_2)_m-C(=O)-NH-R^{12}$
- c) $-(CH_2)_m-NH-C(=O)-R^{12}$
- d) $-(CH_2)_m-X-R^{12}$
- e) $(CH_2)_m-C(=O)-R^{12}$

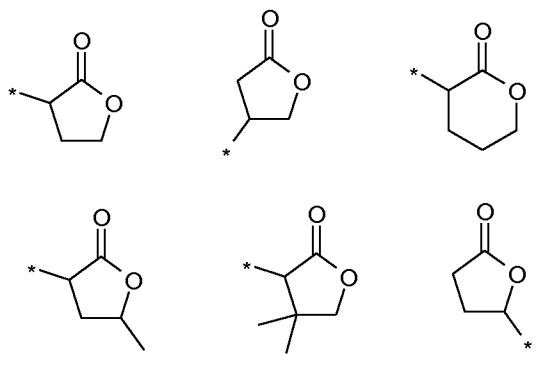
Wherein

m is an integer selected from 0 to 3;

R^{11} is selected from the group comprising optionally substituted C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{1-8} alkoxyalkyl, alkylcycloalkyl, heterocyclyl, aryl, Het^1 , and heteroaryl;

Wherein

Het^1 is selected from the group consisting of



R^{12} is selected from the group consisting of Het^1 , or R^{12} is selected from the group consisting of C_{1-8} alkyl, C_{3-8} cycloalkyl, heterocyclyl, alkylheterocyclyl, aryl, and heteroaryl; wherein said C_{1-8} alkyl, C_{3-8} cycloalkyl, heterocyclyl, alkylheterocyclyl, aryl, and heteroaryl is substituted with a substituent selected from the group consisting of Het^1 ; $-O-Het^1$; $-NH-Het^1$; $-S-Het^1$, and $-(CH_2)_n-C(=O)-OR^{11}$;

in particular R^{12} is C_{1-8} alkyl substituted with a substituent selected from the group consisting of Het^1 ; $-O-Het^1$; $-NH-Het^1$; $-S-Het^1$, and $-(CH_2)_n-C(=O)-OR^{11}$;

more in particular R^{12} is C_{1-8} alkyl substituted with a substituent selected from the group consisting of $-NH-Het^1$, $-S-Het^1$, and $-(CH_2)_n-C(=O)-OR^{11}$;

and

Wherein

n is an integer from 0 to 3;

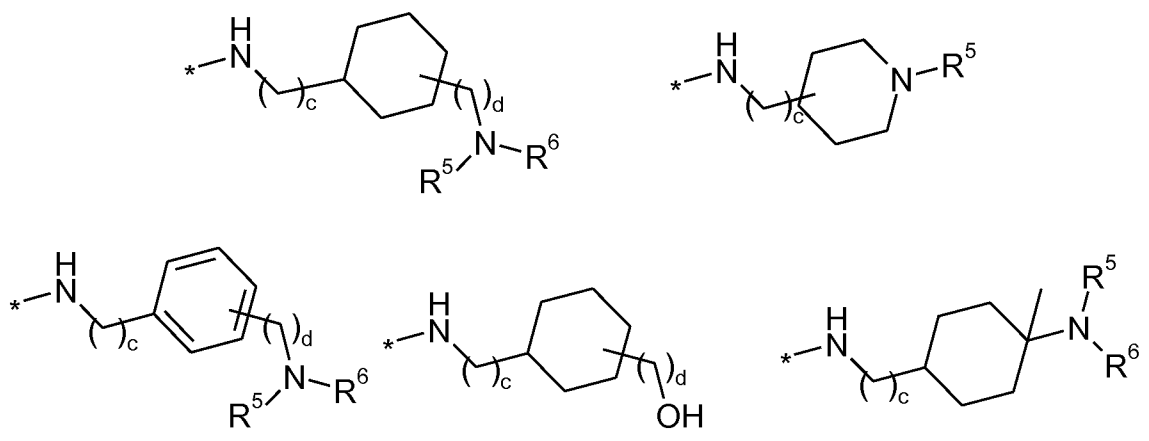
Het^1 and R^{11} are as defined hereinbefore;

X is $-NH-$, $-CH_2-$, $-O-$, or $-S-$;

R^2 is hydrogen or C_{1-4} alkyl;

R^3 is selected from the group consisting of hydrogen, nitro, halo, haloalkyl, cyano or $-C(=O)NH_2$; and

R^4 is selected from the following groups:



Wherein

c and d are each independently an integer from 0 to 3; and

R^5 and R^6 are each independently selected from the group consisting of hydrogen and optionally substituted C_{1-6} alkyl; or

R^5 and R^6 together with the nitrogen atom to which they are attached form a heterocycle optionally substituted with C_{1-6} alkyl.

5. A compound according to claim 1 wherein

Y is -N- or -CH-;

A is -N- or -CH-;

R^1 is selected from the group consisting of

- a) $-(CH_2)_m-C(=O)-OR^{11}$
- b) $-(CH_2)_m-C(=O)-NH-R^{12}$
- c) $-(CH_2)_m-NH-C(=O)-R^{12}$
- d) $-(CH_2)_m-X-R^{12}$
- e) $(CH_2)_m-C(=O)-R^{12}$;

in particular R^1 is selected from $-(CH_2)_m-C(=O)-OR^{11}$ or $-(CH_2)_m-C(=O)-NH-R^{12}$;

Wherein

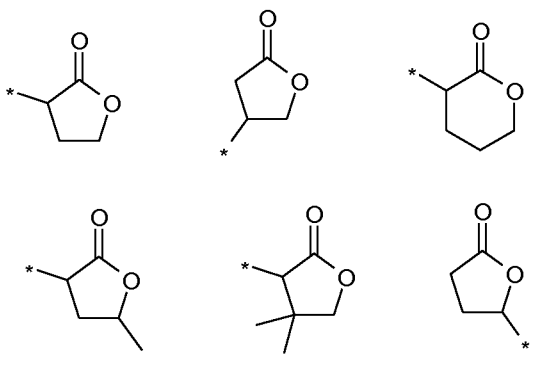
m is an integer selected from 0 to 3; in particular m is 0;

R^{11} is selected from the group comprising optionally substituted C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{1-8} alkoxyalkyl, alkylcycloalkyl, heterocyclyl, aryl, Het^1 , and heteroaryl; in particular from optionally substituted C_{1-8} alkyl and C_{3-8} cycloalkyl; more in particular

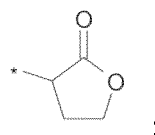
from C₃₋₈cycloalkyl, C₁₋₈alkyl, C₁₋₈alkyl substituted with hydroxyl, and C₁₋₈alkyl substituted with heterocyclyl;

Wherein

Het¹ is selected from the group consisting of



in particular Het¹ is



R¹² is an optionally substituted Het¹ or R¹² is selected from the group consisting of C₁₋₈alkyl, C₃₋₈cycloalkyl, heterocyclyl, alkylheterocyclyl, aryl and heteroaryl; in particular C₁₋₈alkyl; wherein said C₁₋₈alkyl, C₃₋₈cycloalkyl, heterocyclyl, alkylheterocyclyl, aryl and heteroaryl is substituted with:

- one or more; in particular one; substituent(s) independently selected from the group consisting of Het¹; -O-Het¹; -NH-Het¹, -S-Het¹, -(CH₂)_n-C(=O)-OR¹¹; in particular from the group consisting of -NH-Het¹, -S-Het¹, and -(CH₂)_n-C(=O)-OR¹¹; and
- optionally one or more substituents independently selected from the group consisting of halo, hydroxyl, carbonyl, nitro, amino, oxime, imino, azido, hydrazino, cyano, aryl, heteroaryl, cycloalkyl, heterocyclyl, acyl, alkylamino, alkoxy, thiol, alkylthio, acylamino, alkyl esters, carbamate, thioamido, urea, aminocarbonyl, alkyl, alkenyl, alkynyl, cycloalkylalkyl, -SO₂-NH₂, aralkyl, haloalkyl, haloalkoxy, alkylaminocarbonyl, heteroarylalkyl, alkylsulfonamide, alkylcarbonylaminoalkyl, aryloxy, alkylcarbonyl, acyl, arylcarbonyl, aminocarbonyl, alkylsulfoxide, -SO₂R^a, carboxyl; wherein R^a is alkyl or cycloalkyl; in particular R¹² is C₁₋₈alkyl substituted with -NH-Het¹, -S-Het¹, or -(CH₂)_n-C(=O)-OR¹¹;

Wherein

n is an integer from 0 to 3; in particular n is 0;

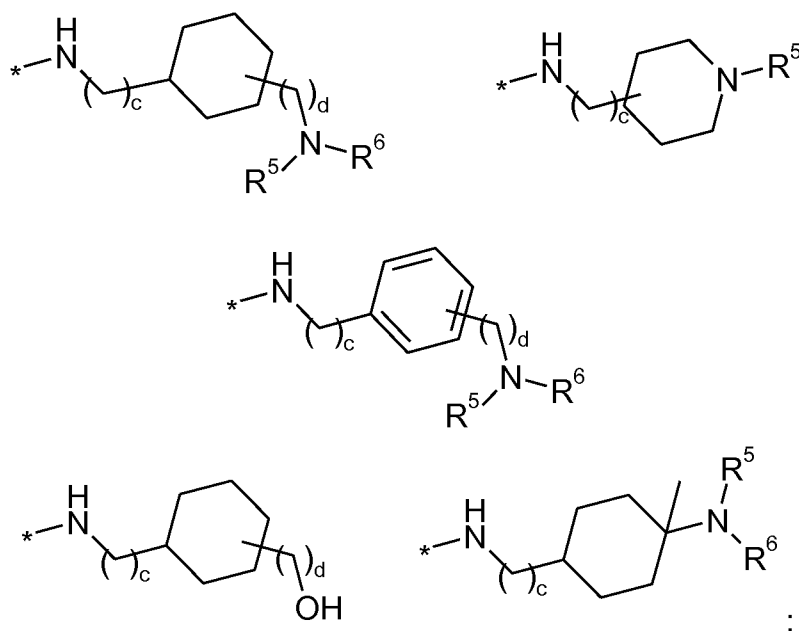
Het¹ and R¹¹ are as defined hereinbefore;

X is -NH-, -CH₂-, -O-, or -S-;

R² is hydrogen or C₁₋₄alkyl; in particular R² is methyl;

R³ is selected from the group consisting of hydrogen, nitro, halo, haloalkyl, cyano or -C(=O)NH₂; in particular from nitro and cyano; and

R⁴ is selected from the following groups:



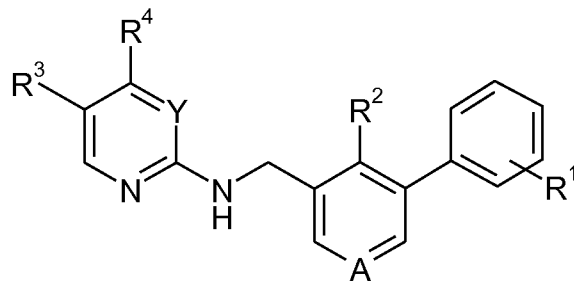
Wherein

c and d are each independently an integer from 0 to 3; in particular c and d are each independently 0 or 1; and

R⁵ and R⁶ are each independently selected from the group consisting of hydrogen and optionally substituted C₁₋₆alkyl; in particular from hydrogen and methyl; or

R⁵ and R⁶ together with the nitrogen atom to which they are attached form a heterocycle optionally substituted with C₁₋₆alkyl.

6. A compound of Formula II or a stereoisomer, tautomer, racemic, salt, hydrate, or solvate thereof,



II

Wherein Y, A, R¹, R², R³, and R⁴ are as defined in any one of claims 1 to 5.

7. A compound as defined in any one of claims 1 to 6 for use as a human or veterinary medicine.
8. A composition comprising a compound as defined in any one of claims 1 to 6, for use as a human or veterinary medicine.
9. Use of a compound as defined in any one of claims 1 to 6 or a composition as defined in claim 8, for inhibiting the activity of a kinase; in particular PKC.
10. Use of a compound as defined in any one of claims 1 to 6 or a composition as defined in claim 8, for inhibiting the activity of a kinase; in particular PKC theta.
11. A compound as defined in any one of claims 1 to 6, or a composition as defined in claim 8, for use in the prevention and/or treatment of at least one disease or disorder, in which PKC theta is involved, such as immunological disorders and inflammatory diseases.
12. A compound as defined in any one of claims 1 to 6, for use in the prevention and/or treatment of immunological disorders and inflammatory diseases such as inflammatory eye diseases; inflammatory airway diseases; rheumatoid arthritis, skin diseases such as contact dermatitis and psoriasis, organ and bone marrow transplant rejection, allergy, intestinal inflammatory diseases such as ulcerative colitis, inflammatory bowel disease and Crohn's disease.

13. A compound as defined in any one of claims 1 to 6, or a composition as defined in claim 8, for use in the prevention and/or treatment of an eye disease, in particular an inflammatory eye disease.
14. A compound as defined in any one of claims 1 to 6, or a composition as defined in claim 8, for use in the prevention and/or treatment of a lung disease, in particular an inflammatory lung disease.

Figure 1:

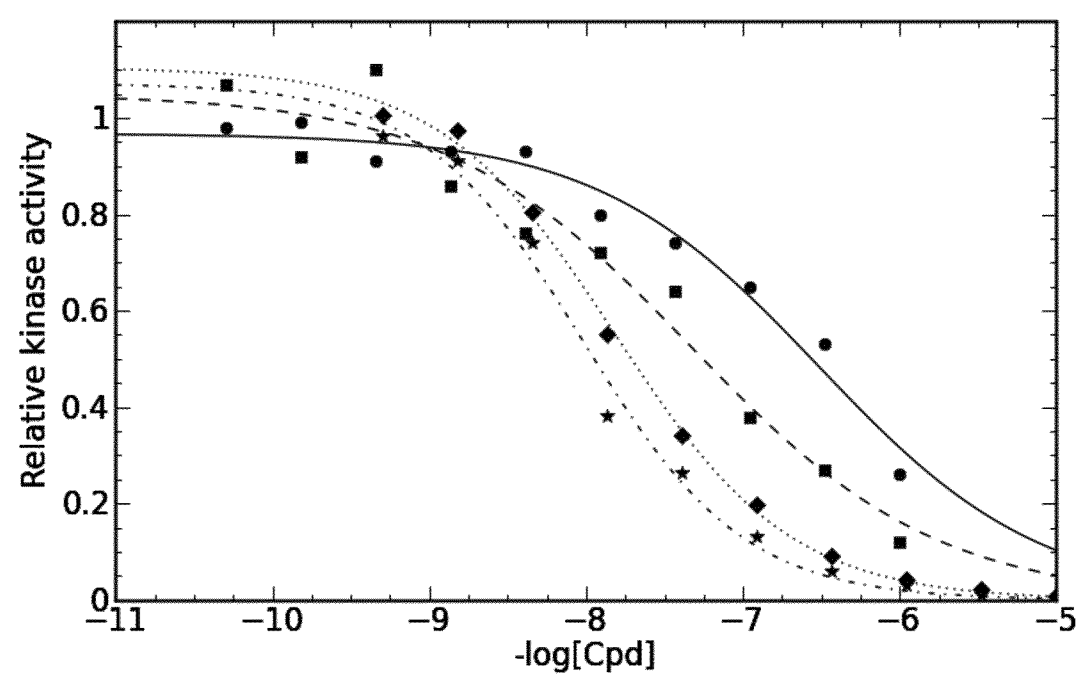


Figure 2:

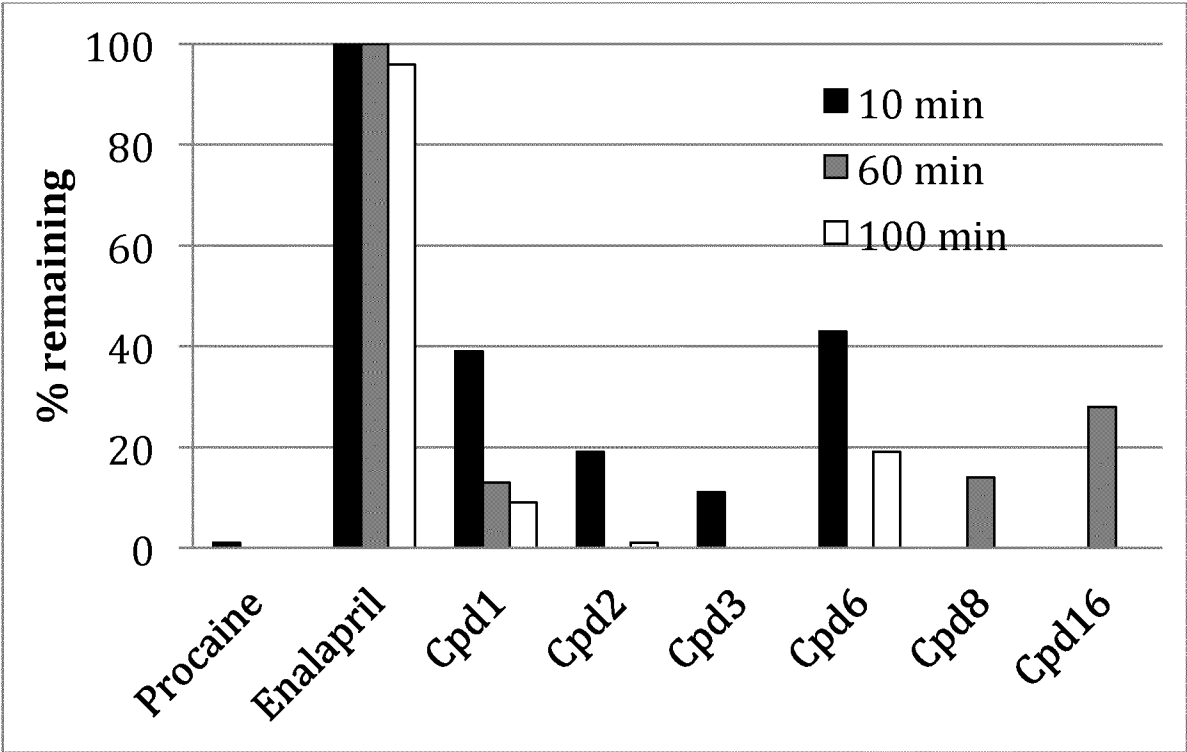
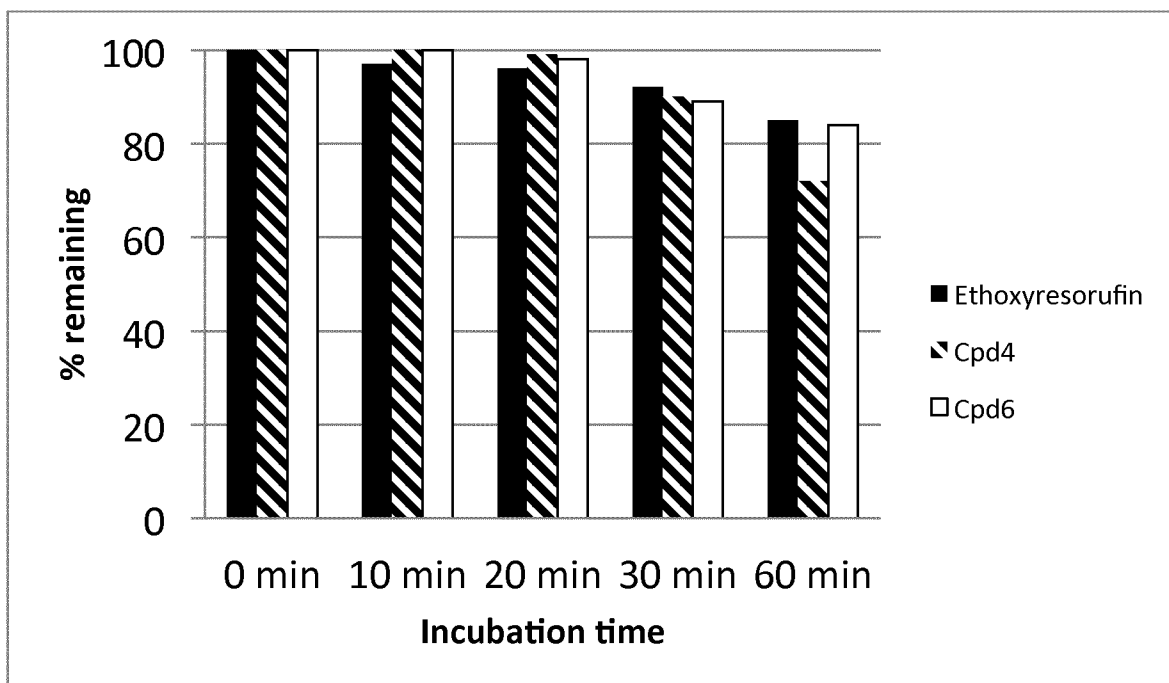


Figure 3:



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/059170

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D239/50 A61K31/505 A61P37/02 C07D405/12 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, WPI Data, 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 2007/076247 A1 (BOEHRINGER INGELHEIM INT GMBH) 5 July 2007 (2007-07-05) cited in the application claim1; Table 1 -----	1-14
X	----- US 2006/217417 A1 (BRUNETTE STEVEN R [US] ET AL BRUNETTE STEVEN RICHARD [US] ET AL) 28 September 2006 (2006-09-28) cited in the application examples;; claim 1 -----	1-14
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "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 9 August 2012		Date of mailing of the international search report 21/08/2012
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Wolf, Claudia

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/059170

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007076247	A1	05-07-2007	CA 2633992 A1 05-07-2007
			EP 1966163 A1 10-09-2008
			JP 2009521488 A 04-06-2009
			US 2008318929 A1 25-12-2008
			WO 2007076247 A1 05-07-2007

US 2006217417	A1	28-09-2006	AT 432260 T 15-06-2009
			CA 2602250 A1 05-10-2006
			EP 1866286 A1 19-12-2007
			ES 2324837 T3 17-08-2009
			JP 2008534597 A 28-08-2008
			US 2006217417 A1 28-09-2006
			WO 2006105023 A1 05-10-2006
