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WO 2015/155549 A1 **WO 2013/192229 A1**
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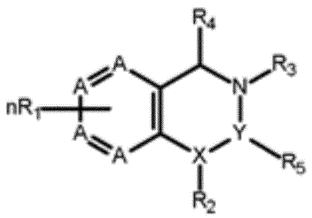
(54) Title of the Invention: **P2X3 receptor antagonists**
Abstract Title: **Pyrido-pyrimidine and pyrido-pyrazine derivatives as P2X3 receptor antagonists**

(57) A compound of Formula (I):



formula I

Or an enantiomer, diastereomer, N-oxide, or pharmaceutically acceptable salt thereof, wherein each A is independently C, N, S or O; X-Y represents in either orientation either N-C or N=C; groups R_3 and R_4, or alternatively R_3 and R_5 are linked to each other to from a five- or six-membered heterocyclic ring containing 2-3 heteroatoms selected from N, O and S, the ring optionally substituted with one or more R_6 with the proviso that the remainder of R_4 or R_5 not linked with R_3 is absent, or is independently selected from doubly-bonded N, O or S; wherein R_1, R_2 and R_3 is as herein defined; and n is 0-3. R_2 is preferably a hydrogen atom or an optionally substituted benzyl group or derivative thereof, in particular 2,5-dimethylbenzyl, 4-methoxybenzyl, 4-methylbenzykm 4-chlorobenzyl or 4-chloro-2,6-difluorobenzyl. The compounds are disclosed to be useful in pharmaceutical compositions, particularly in the treatment of P_2X_3 and $P_2X_{2/3}$ mediated diseases and disorders, or for the treatment of pain; respiratory disorders including asthma and chronic obstructive pulmonary disease (COPD); genitourinary diseases including overactive bladder disorders, urinary incontinence and endometriosis; and cardiovascular disorders including irritable bowel syndrome (IBS), burning mouth syndrome (BMS) and migraines.

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$P2X_3$ RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

[0001] This invention relates to fused heterocyclic derivatives, including 4-imino-1H-pyrido[3,2-d]pyrimidin-2-one and 7H-pyrido[2,3-d]pyridazin-8-imine derivatives, and their use as antagonists of $P2X_3$ and $P2X_{2/3}$ receptor activity, pharmaceutical compositions comprising such compounds, and methods of treatment therewith.

BACKGROUND TO THE INVENTION

[0002] Adenosine-5'-triphosphate (ATP) acts as an extracellular signalling molecule after release from healthy or damaged cells (G. Burnstock, "Discovery of purinergic signalling, the initial resistance and current explosion of interest", *Br. J. Pharmacol.* (2012), No.167, pp.238-55) on two different classes of purinergic receptors: the ionotropic P2X receptors and the G-protein-coupled P2Y receptors.

[0003] P2X receptors are ion channels resulting by seven $P2X_{1-7}$ subunits association as homo- or hetero- trimers (R.A. North, "Molecular physiology of P2X receptors", *Physiol. Rev.* (2002), No.82, pp.1013-67).

[0004] The homo trimer $P2X_3$ receptor and the hetero-trimer $P2X_{2/3}$ receptor are predominantly localized on small- to medium-diameter C- and Aδ-fiber sensory neurons within the dorsal root ganglion and cranial sensory ganglia, and on their peripheral nerve terminals in tissues comprising skin, joints, and viscera. The $P2X_3$ receptor is also present on central projections of sensory neurons within the dorsal horn of the spinal cord and in the brainstem, where it plays a role in augmenting the release of glutamate and substance P. Because of its specific and limited location, the $P2X_3$ receptor subtype thus offers unique opportunity to investigate sensory and nociceptive mechanisms (C. Volontè, G. Burnstock, "$P2X_3$ receptor - a novel 'CASKade' of signalling", *J. Neurochem.* (2013), No.126, pp.1-3).

[0005] The $P2X_3$ receptors is also involved in many conditions where pain symptoms originate from chronic sensitization of peripheral afferent pathways (*e.g.*, overactive bladder, irritable bowel syndrome, chronic itch and cough, airways hyperreactivity).

[0006] The afferent fibres that evoke cough are almost completely confined to the vagus nerve and preclinical studies suggest key roles for both C fibres (chemoreceptors) and Aδ fibres (mechanoreceptors). $P2X_3$ receptors are ATP-gated ion channels selectively localized on populations of primary afferent nerves arising from both cranial and dorsal root ganglia.

[0007] In guinea pigs, vagal C fibres innervating the airways express $P2X_3$ receptors, and can be activated by ATP released into the airways. Moreover, when guinea pigs are exposed to ATP and histamine aerosols, cough responses to tussive stimuli are increased via P2X receptors. The $P2X_3R$ is also involved in many conditions where pain symptoms originate from chronic sensitization of peripheral afferent pathways (*e.g.*, overactive bladder, irritable bowel syndrome, chronic itch and cough, airways hyperreactivity).

[0008] $P2X_3$ ion channel receptors are expressed by a subpopulation of small-diameter primary nociceptors in the trigeminal nervous system and when activated by adenosine triphosphate (ATP) they can evoke a sensation of burning pain. $P2X_3$ receptors, coupled with the transient receptor potential subfamily member V 1 (TRPV1) ion channel, and of nerve growth factor NGF are upregulated in Burning Mouth Syndrome. For this reason, compounds acting on the $P2X_3$ receptors may have a potential role in the treatment of Burning Mouth Syndrome ("Burning Mouth Syndrome: Aetiopathogenesis and Principles of Management", L. Feller, J. Fourie, M. Bouckaert, R. A. G. Khammissa, R. Ballyram, and J. Lemmer, *Pain Research and Management*, Vol.2017, Article ID 1926269, 6 pages).

[0009] Daily systemic injection of an orthosteric $P2X_3$ receptor antagonist attenuated the morphine-induced antinociceptive tolerance to von Frey and thermal stimuli, in comparison with morphine alone, showing that a $P2X_3$ receptor antagonist is able to reverse morphine tolerance and it may be a new therapeutic target in the prevention of tolerance to morphine-induced antinociception ("Blockade and reversal of spinal morphine tolerance by $P2X_3$ receptor antagonist", Ma X and Xu T, Xu H, Jiang W, *Behavioural Pharmacology*, (2015), Vol.26(3), pp.260-267). $P2X_3$ receptor antagonist morphine tolerance attenuation may be attributed to down-regulation of N-methyl-D-aspartate receptor subunits NR1 and NR2B expression in the synaptosomal membrane and inhibition of excitatory amino acids release in morphine-tolerant rats ("Purinergic P2X Receptor Regulates N-Methyl-D-aspartate Receptor Expression and Synaptic Excitatory Amino Acid Concentration in Morphine-tolerant Rats",

Yueh-Hua Tai, Pao-Yun Cheng, Ru-Yin Tsai, Yuh-Fung Chen, Chih-Shung Wong, *Anesthesiology*, (2010), Vol.113(5), pp.1163-75).

[0010] Currently, the carotid body is under consideration as a therapeutic target for hypertension because sympathoexcitatory response is potentiated in hypertensive rats and human. Moreover, the aberrant signalling that contributes to high blood pressure may be normalized by carotid body denervation in rats. $P2X_3$ receptor mRNA expression is upregulated in chemoreceptive petrosal ganglion neurons in hypertensive rats. These neurons generate both tonic drive and hyperreflexia in hypertensive rats, and both phenomena are normalized by $P2X_3$ receptor antagonists. Antagonism of $P2X_3$ receptors also reduces arterial pressure and basal sympathetic activity and normalizes carotid body hyperreflexia in conscious rats with hypertension. The purinergic receptors present in the carotid body can be considered as a potential new target for the control of human hypertension (Wioletta Pijacka, Davi J A Moraes, Laura E K Ratcliffe, Angus K Nightingale, Emma C Hart, Melina P da Silva, Benedito H Machado, Fiona D McBryde, Ana P Abdala, Anthony P Ford & Julian F R Paton).

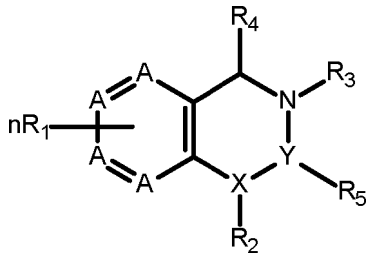
[0011] Endometriosis is a common gynecological disease characterized by the presence of functional endometrium outside the uterine cavity, resulting in dysmenorrhea, dyspareunia, pelvic pain, and infertility, with lack of effective clinical treatment (Strathy JH, Molgaard CA, Coulam CB, Melton LJ 3rd. "Endometriosis and infertility: a laparoscopic study of endometriosis among fertile and infertile women", *Fertility and sterility*, (1982), Vol.38(6), pp.667-72). Endometriosis is considered as a kind of inflammatory and neuropathic pain with increasing evidences indicating the importance of adenosine triphosphate (ATP) and $P2X_3$ receptors in endometriosis pain sensitization and transduction. $P2X_3$ are expressed on endometrial epithelial cells and on endometrial stromal cells. $P2X_3$ are overexpressed in the endometriosis endometrium and endometriotic lesions and both significantly higher as compared with control endometrium, and both positively correlated with pain, and with the severity of pain in women affected with endometriosis. The expression levels of phosphorylated ±ERK (p-ERK), phosphorylated-cAMP-response element binding protein (p-CREB), and $P2X_3$ in endometriotic stromal cells (ESCs) were all significantly increased in comparison to the initial levels after treated with interleukin (IL)-1β or adenosine triphosphate (ATP), respectively, and did not increase after the ESCs were pretreated with $ERK_{1/2}$ inhibitor.

$P2X_3$ receptor may represent a highly innovative target for the non-hormonal treatment of endometriosis ("$P2X_3$ receptor involvement in endometriosis pain via ERK signaling pathway", Shaojie Ding, Libo Zhu, Yonghong Tian, Tianhong Zhu, Xiufeng Huang, Xinmei Zhang; *PLoS ONE*, (2017), Vol.12(9): e0184647).

[0012] Several P2X receptor subtypes, including $P2X_2$, $P2X_3$, $P2X_4$, and $P2X_7$, have been shown to play diverse roles in the pathogenesis of central pain including the mediation of fast transmission in the peripheral nervous system and modulation of neuronal activity in the central nervous system. $P2X_3$ receptors play a significant role in neuropathic and inflammatory pain. Long-lasting allodynia that is produced by intrathecal administration of ATP likely occurs through $P2X_{2/3}$ receptors. Spinal $P2X_2$ and $P2X_3$ receptors have been reported to be involve in neuropathic pain in a mouse model of chronic constriction injury ("Nociceptive transmission and modulation via P2X receptors in central pain syndrome.", Kuan, Y. H., and Shyu, B. C. *Mol. Brain* (2016), Vol.9, pp.58). $P2X_3$ receptors show a combination of fast desensitization onset and slow recovery. $P2X_3$ receptors represent an attractive target for development of new analgesic drugs via promotion of desensitization aimed at suppressing chronic pain, such as: Inflammatory and Neuropathic Pain, Migraine and Trigeminal Pain, and Cancer Pain ("Desensitization properties of $P2X_3$ receptors shaping pain signalling, Rashid Giniatullin and Andrea Nistri", *Front. Cell. Neurosci.*, (2013), Vol.7, pp.245).

SUMMARY OF THE INVENTION

[0013] The invention provides a compound according to general formula I:



formula I

or an enantiomer, diastereomer, N-oxide, or a pharmaceutically acceptable salt or combinations thereof, wherein:

each A independently represents an atom selected from C, N, S or O;

X and Y are selected from C and N atoms, wherein the unit X-Y represents either a N-C group, or a C=N group respectively;

each R_1 independently represents hydrogen, a halogen atom, or an, optionally substituted, hydroxy, carbonyl, carboxyl, amino, amido, C_1-C_6 alkyl or C_1-C_6 alkoxy group, an, optionally substituted, mono-, bi- or tricyclic C_6-C_{14} aryl group or an, optionally substituted, mono-, bi- or tricyclic C_1-C_{13} heterocyclic group containing from 1 to 5 heteroatoms selected from N, O or S;

R_2 represents hydrogen or an, optionally substituted, C_1-C_6 alkyl group, C_1-C_6 alkoxy group, C_4-C_{14} arylalkyl group, C_4-C_{14} heteroarylalkyl group, C_3-C_7 cycloalkyl group, a mono-, bi- or tricyclic C_6-C_{14} aryl group or a mono-, bi- or tricyclic C_1-C_{13} heterocyclic group containing from 1 to 5 heteroatoms selected from N, O or S;

groups R_3 and R_4, or alternatively groups R_3 and R_5, are linked to each other to form a five- or six-membered heterocyclic ring containing from 2 to 3 heteroatoms atoms selected from N, O and S, optionally substituted with one or more groups nR_6, with the proviso that the remainder of R_4 or R_5 not linked with group R_3 to form the heterocyclic ring is absent, or is an atom independently selected from N, O or S which is double-bonded directly to the X-Y containing ring;

each R_6 independently represents hydrogen, a halogen atom selected from F, Cl, Br or I; or an, optionally substituted, carbonyl, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy or C_3-C_7 cycloalkyl group, an, optionally substituted, mono-, bi- or tricyclic C_6-C_{14} aryl group or an, optionally substituted, mono-, bi- or tricyclic C_1-C_{13} heterocyclic group containing from 1 to 5 heteroatoms selected from N, O or S or alternatively, two R_6 groups are linked to each other to form a group of the formula -(Zp)- wherein p is an integer of from 3 to 5 and each Z independently represents an oxygen atom or an optionally substituted methylene group, provided that no two adjacent Y moieties represent oxygen atoms; and

n is an integer independently selected from 0 to 3.

[0014] Preferably, compounds of the invention can be used for the treatment and/or prevention of pain and chronic pain and tolerance to analgesic, respiratory disorders and dysfunctions, and treatment of overactive bladder, bladder pain syndrome, dysuria and in general in genitourinary diseases, cardiovascular disorders and more in general for the potential treatment of visceral organ diseases and disorders characterized by the involvement of $P2X_3$ and $P2X_{2/3}$ receptors.

[0015] Preferably, the optional substituents are independently selected from the group consisting of halogen atoms, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, mercapto, nitro, cyano, oxo, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylsulphonyl, C_1-C_6 alkylcarbonyl, sulphamoyl, C_1-C_6 alkylsulphamoyl, di(C_1-C_6)alkylsulphamoyl, (C_1-C_6)alkoxycarbonyl and (C_1-C_6)alkylcarbonyl(C_1-C_6)alkyl groups, and from groups of the formulae -NR*R*, -C(=O)-NR*R*, -D, -O-D, -C(=O)-D, -(CH_2)q-D, -NR**-D, -C(=O)-NR**-D, -NR**C(=O)-D and -O-C(=O)-D wherein each R* independently represents a hydrogen atom or a C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylcarbonyl, phenyl or benzyl group, R** represents a hydrogen atom or a C_1-C_6 alkyl group, q is an integer from 1 to 6 and D represents a phenyl group or a C_1-C_8 heterocyclic group containing from 1 to 3 heteroatoms selected from N, O and S; a C_1-C_6 cycloalkyl group; each group D being further optionally substituted with from 1 to 3 groups independently selected from halo, hydroxy, cyano, nitro and C_1-C_6 alkyl, preferably wherein the optional substituents are selected from the groups consisting of halogen atoms and C_1-C_6 alkyl groups.

[0016] Preferred compounds of the invention are those in which one of the A groups comprises a heteroatom and the remaining three A groups comprise carbons atoms. A non-limiting example includes the situation where one of the A groups comprises a nitrogen atom, and the remaining three A groups each comprise carbon atoms, such that the heterocyclic ring so-formed is a pyridine ring.

[0017] Preferred compounds of the invention are those in which two of the A groups comprise heteroatoms and the two remaining A groups comprise carbon atoms. Non-limiting examples include the situation where two of the A groups comprise nitrogen atoms, and the remaining two A groups each comprise carbon atoms, such that the heterocyclic ring so-formed is a pyridazine, pyrimidine or pyrazine ring.

[0018] Preferred compounds of the invention are those in which three of the A groups comprise heteroatoms and the remaining A group comprises a carbon atom. Non-limiting examples include the situation where three of the A groups comprise nitrogen atoms, and the remaining A group comprises a carbon atom, such that the heterocyclic ring so-formed is a 1,2,3-triazine or 1,2,4-triazine ring.

[0019] Preferred compounds of the invention are those in which all four of the A groups comprise heteroatoms. A non-limiting example includes the situation where all four of the A groups comprises nitrogen atoms, such that the heterocyclic ring so-formed is a 1,2,3,4-tetrazine ring.

[0020] The skilled person will appreciate that for each of the examples described above, each A group comprising a carbon or other heterocyclic atom, or the heterocyclic ring so-formed, may further comprise one or more hydrogen atoms directly attached to one or more of the ring atoms, and/or n groups of R_1 (as defined above) to satisfy the usual rules relating to atomic bonding and valences.

[0021] The invention also provides for other such combinations of heteroatoms including, but not limited to, heterocyclic rings formed from each A group being independently represented by an atom selected from C, N, S or O, such that the resulting heterocyclic ring so-formed is a piperidine, pyridine, tetrahydropyran, pyran, thiane, thiopyran, morpholine, oxazine, thiomorpholine, thiazine, dioxane, dioxine, dithiane, dithiin, trioxane or trithiane derivative.

[0022] Preferred non-limiting examples include the resulting heterocyclic ring so-formed being a 2H-1,2-oxazine, 4H-1,2-oxazine, 6H-1,2-oxazine, 2H-1,3-oxazine, 4H-1,3-oxazine, 6H-1,3-oxazine, 2H-1,4-oxazine, 4H-1,4-oxazine, thiomorpholine, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,4-dioxane, 1,2-dioxin, 1,4-dioxin, 1,2-dithiane, 1,3-dithiane, 1,4-dithiane, 1,2-dithiin and 1,4-dithiin, 1,2,3-trioxane or 1,2,4-trioxane derivative.

[0023] Preferred compounds of the invention are those in which group X-Y represents a N-C group, such that the six-membered central heterocyclic ring so-formed is a pyrimidine ring.

[0024] Preferred compounds of the invention are those in which group X-Y represents a C=N group, such that the six-membered central heterocyclic ring so-formed is a pyradizine ring.

[0025] Preferred compounds of the invention are those in which group X-Y represents a N-C group, groups R_3 and R_4 are linked to each other to form a five- or six-membered heterocyclic ring containing from 2 to 3 nitrogen heteroatoms atoms, optionally substituted with one or more groups nR_6, as defined above, and R_5 is a carbonyl group.

[0026] Preferred compounds of the invention are those in which group X-Y represents a N-C group, and groups R_3 and R_4 are linked to each other to form a five- or six-membered heterocyclic ring containing from 2 to 3 nitrogen heteroatoms atoms (e.g. 2-imidazoline, imidazole, 1,2,4-triazole or pyrimidine), selected from but not limited to a pyrido[2,3-e]imidazolo[1,2-d]pyrimidine, pyrido[2,3-e]imidazo[1,2-d]pyrimidine, pyrido[2,3-e]1,2,4-triazolo[1,2-d]pyrimidine or 1,4,5,6-tetrahydropyrimido[2,1-f]pyrido[3,2-d]pyrimidine derivative, and R_5 is a carbonyl group.

[0027] Preferred compounds of the invention are those in which group X-Y represents a N-C group, groups R_3 and R_5 are linked to each other to form a five-membered heterocyclic ring containing from 2 to 3 nitrogen heteroatoms atoms, optionally substituted with one or more groups nR_6, as defined above, and R_4 is a carbonyl group.

[0028] Preferred compounds of the invention are those in which group X-Y represents a N-C group, and groups R_3 and R_5 are linked to each other to form a five-membered heterocyclic ring containing from 2 to 3 nitrogen heteroatoms atoms (*e.g.* 1,2,4-triazole), selected from but

not limited to a pyrido[2,3-e]1,2,4-triazolo[2,1-b]pyrimidine derivative, and R_4 is a carbonyl group.

[0029] Preferred compounds of the invention are those in which group X-Y represents a C=N group, groups R_3 and R_4 are linked to each other to form a five- or six-membered heterocyclic ring containing from 2 to 3 nitrogen heteroatoms atoms, optionally substituted with one or more groups nR_6, as defined above, and R_5 is absent.

[0030] Preferred compounds of the invention are those in which group X-Y represents a C=N group, and groups R_3 and R_4 are linked to each other to form a five- or six-membered heterocyclic ring containing from 2 to 3 nitrogen heteroatoms atoms (*e.g.* 1,2,4-triazole), selected from but not limited to a pyrido[3,2-d]1,2,4-triazolo[1,2-d]1,4,5,6-tetrahydropyridazine derivative, and R_5 is a carbonyl group.

[0031] Preferred compounds of the invention are those in which R_1 is selected from the group comprising H, Br, hydroxy, carboxyl, methoxy, methoxyethylamino, 2-hydroxyethylamino, tertiarybutoxycarbonylamino, 2-hydroxyethylaminocarbonyl, an optionally substituted azetidinyl, morpholinyl, oxetanyl, piperazinyl, piperidinyl, pyranyl or pyrrolidinyl moiety or derivative thereof, or an optionally substituted, spiro-fused bi- or tricyclic C_1-C_{13} heterocyclic group containing from 1 to 5 heteroatoms selected from N, O or S.

[0032] Highly preferred compounds of the invention are those in which R_1 is selected from the group comprising 2-oxa-6-azaspiro[3.3]heptan-6-yl, 3-methoxymethylazetidin-1-yl, 3-methoxypyrrolidin-1-yl, 4-acetylpiperazin-1-yl, 4-aminopiperidin-1-yl, 4-hydroxypiperidin-1-yl, 4-hydroxypiperidin-1-yl-carbonyl, 4-methoxypiperidin-1-yl, 4-morpholinyl, dimethylaminopiperidin-1-yl, hydroxymethylpiperidin-1-yl, morpholin-4-ylcarbonyl, tetrahydro-2H-pyran-4-ylamino or tetrahydro-2H-pyran-4-ylaminocarbonyl.

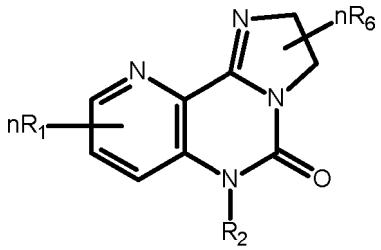
[0033] Preferred compounds of the invention are those in which R_2 is a hydrogen atom or an optionally substituted benzyl group or derivative thereof.

[0034] Highly preferred compounds of the invention are those in which R_2 is a hydrogen atom, or is selected from the group comprising 3,5-dimethoxybenzyl, 4-methoxybenzyl, 4-methylbenzyl, 4-chlorobenzyl or 4-chloro-2,6-difluorobenzyl.

[0035] Preferred compounds of the invention are those in which R_6 is selected from the group comprising phenyl, (1-phenyl)ethyl, 1-ethyl-1H-pyrazol-3-yl, 1-ethyl-1H-pyrazol-5-yl, (tetrahydro-2H-pyran-4-yl)methyl, (tetrahydro-2H-pyran-4-yloxy)methyl, (tetrahydro-2H-pyran-4-yl)ethyl, 3,5-dimethyl-1,2oxazol-4-yl, 2-hydroxypyridin-3-yl, 2-methylpyridin-3-yl, morpholin-4-yl-carbonyl, pyridin-3-yl-methyl, oxo, methyl, ethyl, iso-propyl, tertiary-butyl, methylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, 2,2,2-trifluoroethyl, methoxymethyl, methoxyethyl, (propan-2-yloxy)methyl, tertiary-butoxymethyl, prop-1-en-2-yl, propan-2-yl-acetamide, cyclopropyl, cyclobutyl, cyclohexyl, 1-methylcyclopropyl.

[0036] Preferred compounds of the invention are those in which -(Zp)- represents a group selected from $-O-(CH_2)_2-O-$, $-O-(CH_2)_3-O-$, $-O-(CH_2)_2-$, $-O-(CH_2)_3-$, $-CH_2-O-CH_2-$ or $-(CH_2)_2-O-(CH_2)_2$.

[0037] Preferred compounds of the invention are those in which one of the A groups is a nitrogen atom and the three remaining A groups are carbon atoms, the X-Y unit is a N-C group, groups R_3 and R_4 are linked to each other to form a five-membered heterocyclic ring containing 2 nitrogen heteroatoms atoms and R_5 is an oxygen atom double-bonded directly to the X-Y containing ring (carbonyl group), such that the compound so formed is a pyrido[2,3-e]imidazolo[1,2-d]pyrimidine derivative and has a structure in accordance with formula 1a below:

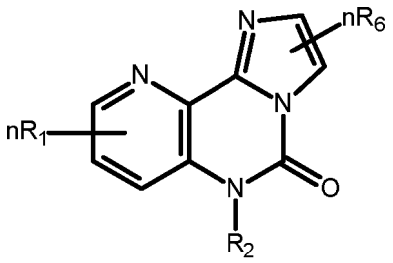


formula 1a

wherein groups R_1, R_2, R_6 and n are as defined for formula I above.

[0038] Preferred compounds of the invention are those in which one of the A groups is a nitrogen atom and the three remaining A groups are carbon atoms, the X-Y unit is a N-C group, groups R_3 and R_4 are linked to each other to form a five-membered heterocyclic ring containing 2 nitrogen heteroatoms atoms and R_5 is an oxygen atom double-bonded directly to the X-Y

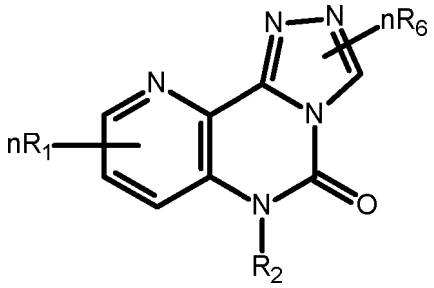
containing ring (carbonyl group), such that the compound so formed is a pyrido[2,3-e]imidazo[1,2-d]pyrimidine derivative and has a structure in accordance with formula 1b below:



formula 1b

wherein groups R_1, R_2, R_6 and n are as defined for formula I above.

[0039] Preferred compounds of the invention are those in which one of the A groups is a nitrogen atom and the three remaining A groups are carbon atoms, the X-Y unit is a N-C group, groups R_3 and R_4 are linked to each other to form a five-membered heterocyclic ring containing 3 nitrogen heteroatoms atoms and R_5 is an oxygen atom double-bonded directly to the X-Y containing ring (carbonyl group), such that the compound so formed is a pyrido[2,3-e]1,2,4-triazolo[1,2-d]pyrimidine derivative and has a structure in accordance with formula 1c below:

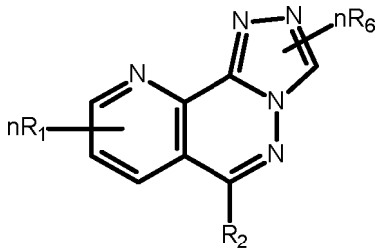


formula 1c

wherein groups R_1, R_2, R_6 and n are as defined for formula I above.

[0040] Preferred compounds of the invention are those in which one of the A groups is a nitrogen atom and the three remaining A groups are carbon atoms, the X-Y unit is a N=C

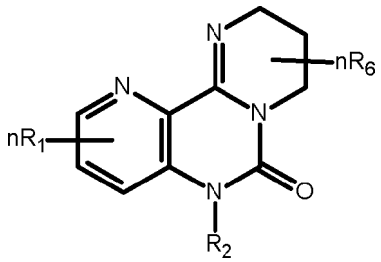
group, groups R_3 and R_4 are linked to each other to form a five-membered heterocyclic ring containing 3 nitrogen heteroatoms atoms and R_5 is an oxygen atom double-bonded directly to the X-Y containing ring (carbonyl group), such that the compound so formed is a pyrido[3,2-d]1,2,4-triazolo[1,2-d]1,4,5,6-tetrahydropyridazine derivative and has a structure in accordance with formula 1d below:



formula 1d

wherein groups R_1, R_2, R_6 and n are as defined for formula I above.

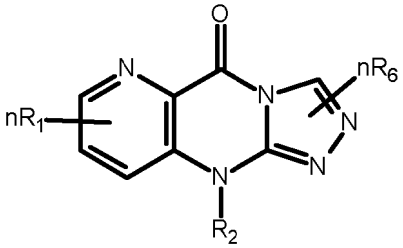
[0041] Preferred compounds of the invention are those in which one of the A groups is a nitrogen atom and the three remaining A groups are carbon atoms, the X-Y unit is a N-C group, groups R_3 and R_4 are linked to each other to form a six-membered heterocyclic ring containing 2 nitrogen heteroatoms atoms and R_5 is an oxygen atom double-bonded directly to the X-Y containing ring (carbonyl group), such that the compound so formed is a 1,4,5,6-tetrahydropyrimido[2,1-f]pyrido[3,2-d]pyrimidine derivative and has a structure in accordance with formula 1e below:



formula 1e

wherein groups R_1, R_2, R_6 and n are as defined for formula I above.

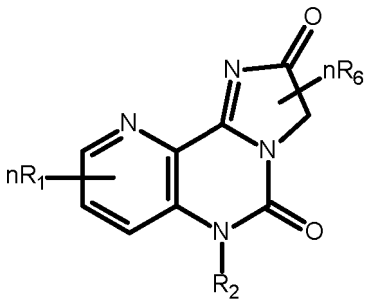
[0042] Preferred compounds of the invention are those in which one of the A groups is a nitrogen atom and the three remaining A groups are carbon atoms, the X-Y unit is a N-C group, groups R_3 and R_5 are linked to each other to form a five-membered heterocyclic ring containing 3 nitrogen heteroatoms atoms and R_4 is an oxygen atom double-bonded directly to the X-Y containing ring (carbonyl group), such that the compound so formed is a pyrido[2,3-e]1,2,4-triazolo[2,1-b]pyrimidine derivative and has a structure in accordance with formula 1f below:



formula 1f

wherein groups R_1, R_2, R_6 and n are as defined for formula I above.

[0043] Preferred compounds of the invention are those in which one of the A groups is a nitrogen atom and the three remaining A groups are carbon atoms, the X-Y unit is a N-C group, groups R_3 and R_4 are linked to each other to form a five-membered heterocyclic ring containing 2 nitrogen heteroatoms atoms, R_5 is an oxygen atom double-bonded directly to the X-Y containing ring (carbonyl group) and at least one group nR_6 is an oxygen atom double-bonded directly to the R_3/R_4 linked five-membered heterocyclic (imidazoline) ring, such that the compound so formed is a pyrido[2,3-e]imidazo[1,2-d]pyrimidine dione derivative and has a structure in accordance with formula 1g below:

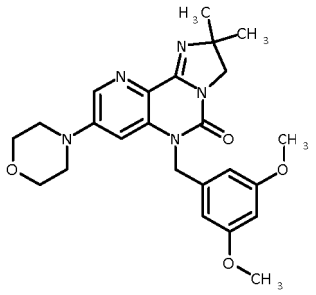
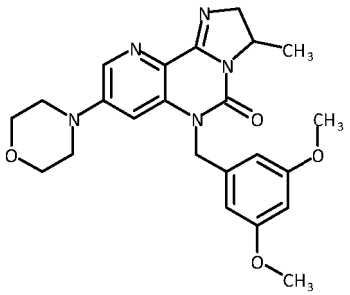
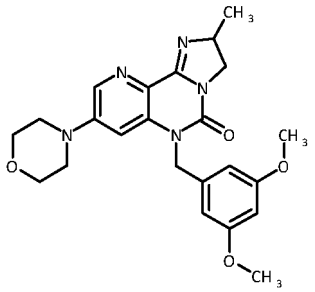


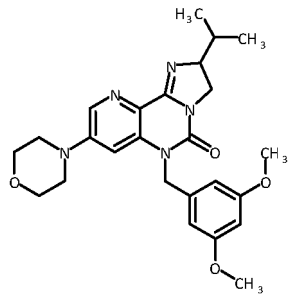
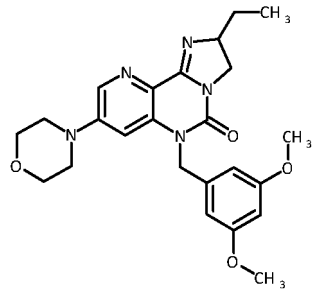
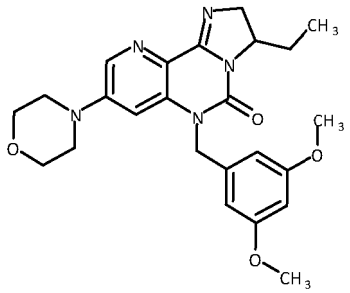
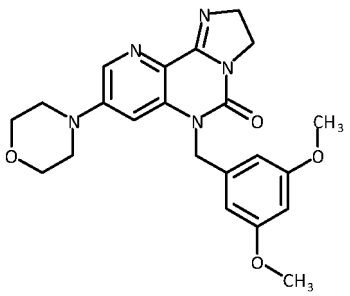
formula 1g

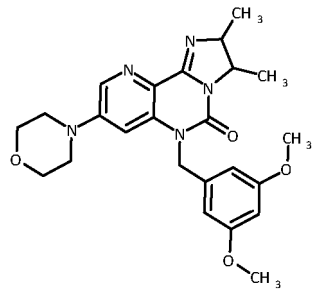
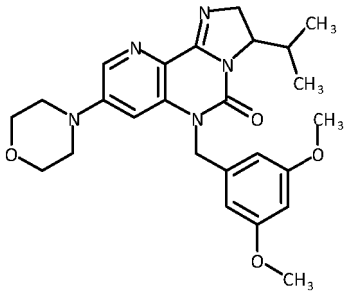
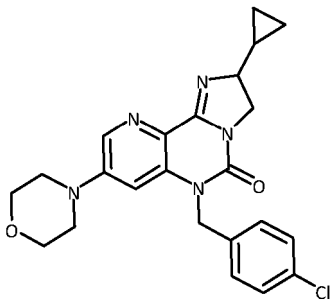
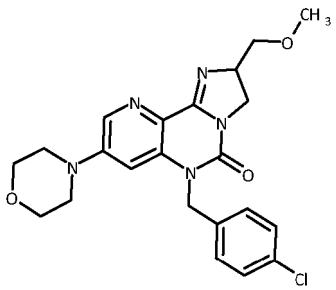
wherein groups R_1, R_2, R_6 and n are as defined for formula I above.

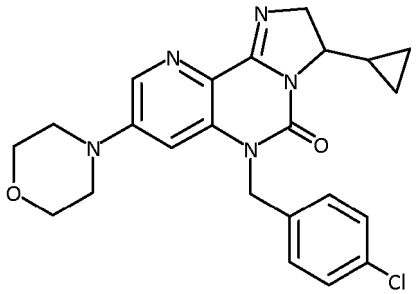
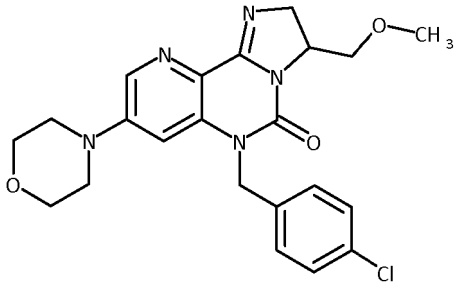
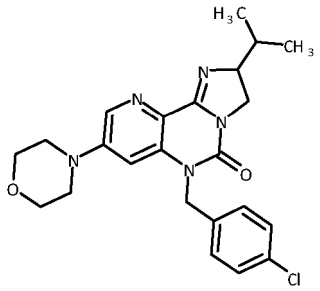
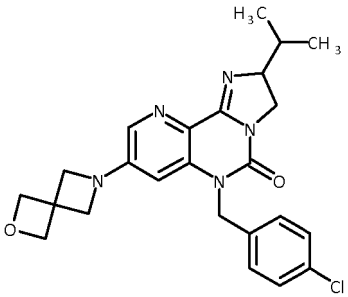
[0044] Preferred compounds according to the invention are compounds or an enantiomer, diastereomer, N-oxide, or a pharmaceutically acceptable salt or combinations thereof, is provided according to general formula 1a selected from the compounds in Table 1 below:

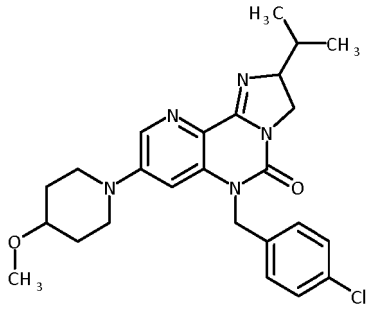
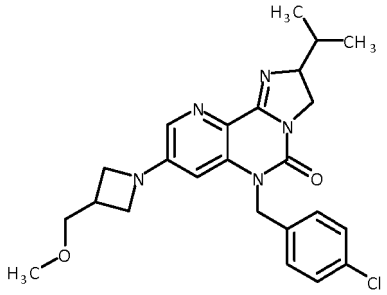
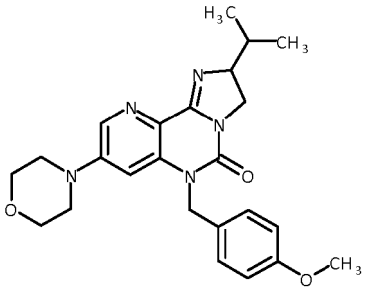
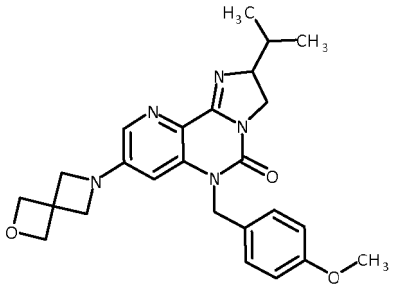
Table 1: Selected compounds of the invention according to formula 1a and 1g.

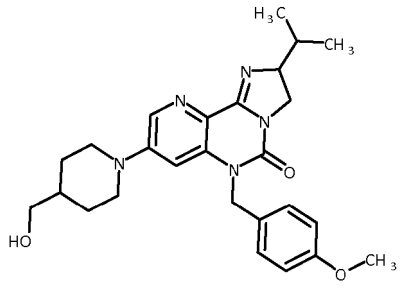
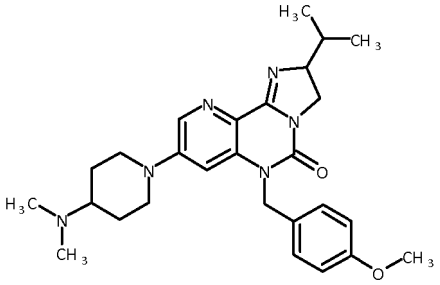
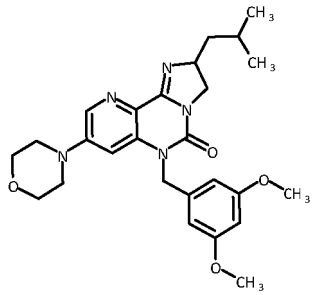
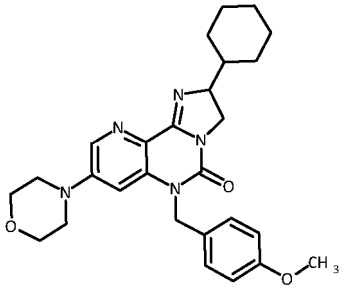
Example	Structure	Name
1		6-(3,5-dimethoxybenzyl)-2,2-dimethyl-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
2		6-(3,5-dimethoxybenzyl)-3-methyl-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
3		6-(3,5-dimethoxybenzyl)-2-methyl-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one

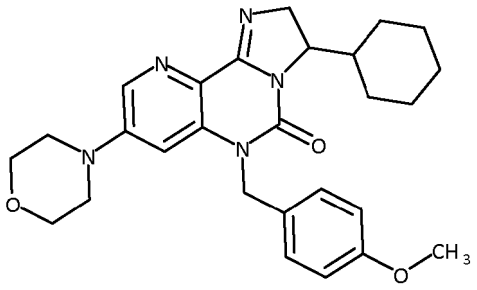
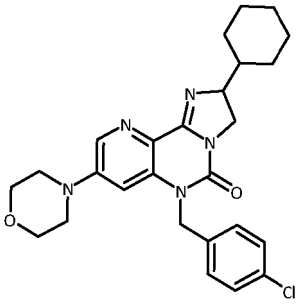
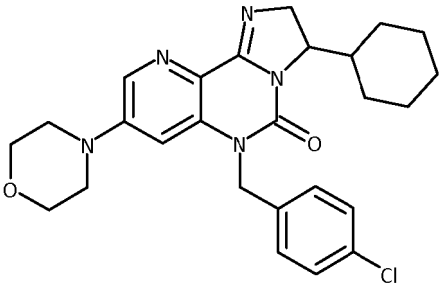
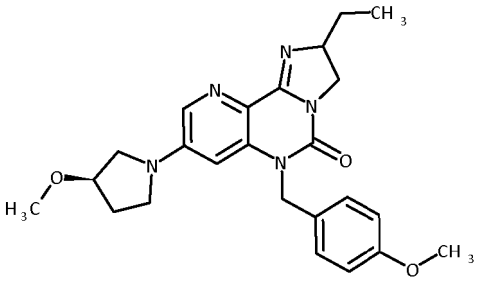
Example	Structure	Name
4		6-(3,5-dimethoxybenzyl)-8-(morpholin-4-yl)-2-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
5		6-(3,5-dimethoxybenzyl)-2-ethyl-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
6		6-(3,5-dimethoxybenzyl)-3-ethyl-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
7		6-(3,5-dimethoxybenzyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one

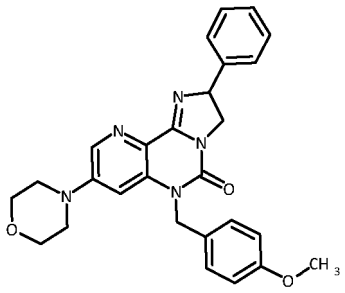
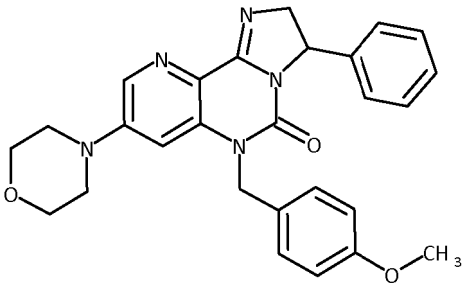
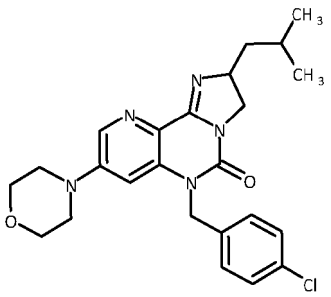
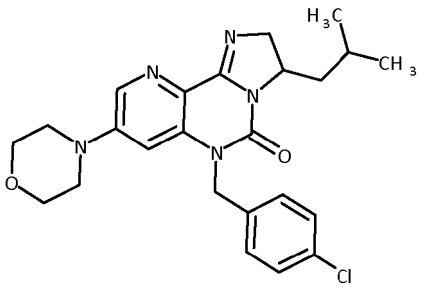
Example	Structure	Name
8		6-(3,5-dimethoxybenzyl)-2,3-dimethyl-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
9		6-(3,5-dimethoxybenzyl)-8-(morpholin-4-yl)-3-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
10		6-(4-chlorobenzyl)-2-cyclopropyl-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
11		6-(4-chlorobenzyl)-2-(methoxymethyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one

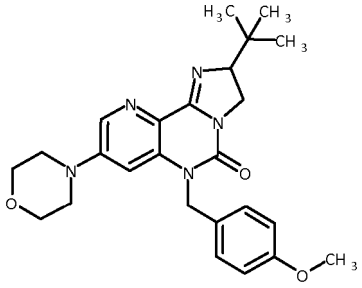
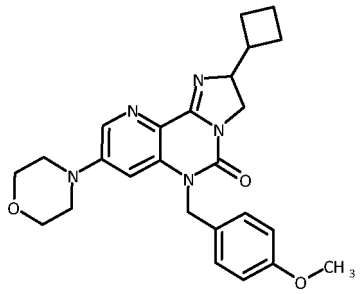
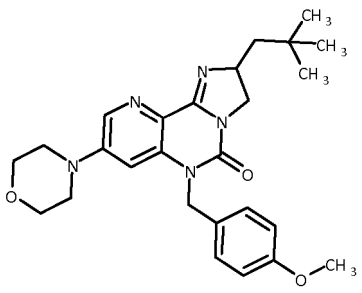
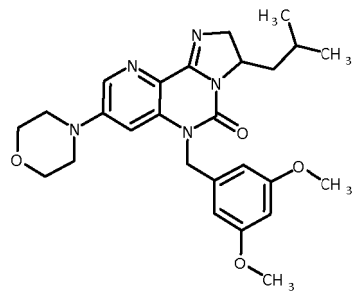
Example	Structure	Name
12		6-(4-chlorobenzyl)-3-cyclopropyl-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
13		6-(4-chlorobenzyl)-3-(methoxymethyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
14		6-(4-chlorobenzyl)-8-(morpholin-4-yl)-2-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
15		6-(4-chlorobenzyl)-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-2-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one

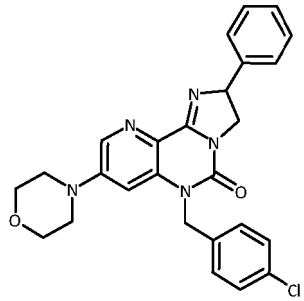
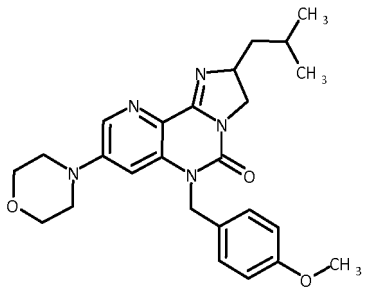
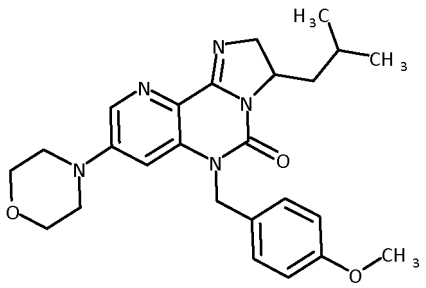
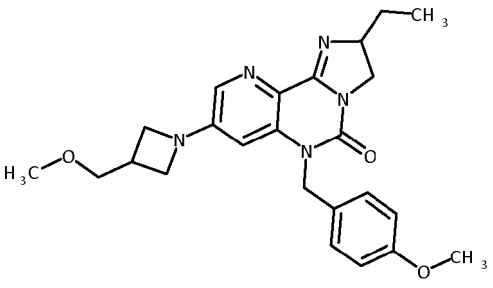
Example	Structure	Name
16		6-(4-chlorobenzyl)-8-(4-methoxypiperidin-1-yl)-2-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
17		6-(4-chlorobenzyl)-8-[3-(methoxymethyl)azetidin-1-yl]-2-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
18		6-(4-methoxybenzyl)-8-(morpholin-4-yl)-2-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
19		6-(4-methoxybenzyl)-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-2-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one

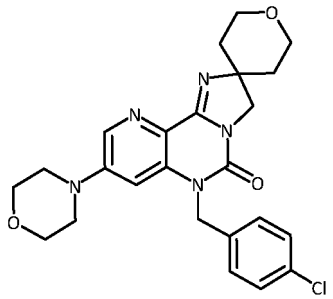
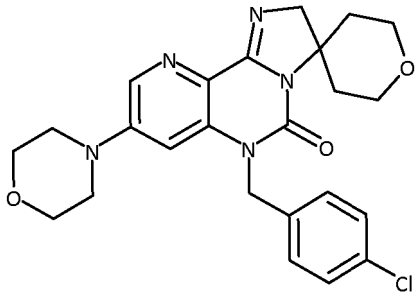
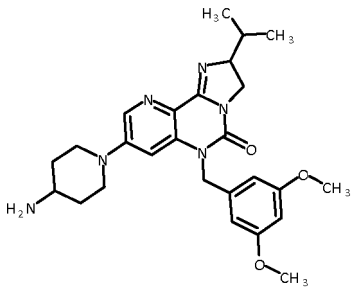
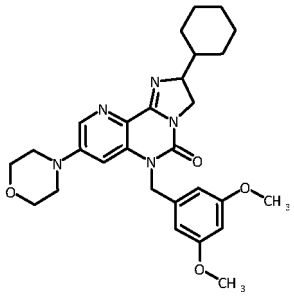
Example	Structure	Name
20		8-[4-(hydroxymethyl)piperidin-1-yl]-6-(4-methoxybenzyl)-2-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
21		8-[4-(dimethylamino)piperidin-1-yl]-6-(4-methoxybenzyl)-2-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
22		6-(3,5-dimethoxybenzyl)-2-(2-methylpropyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
23		2-cyclohexyl-6-(4-methoxybenzyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one

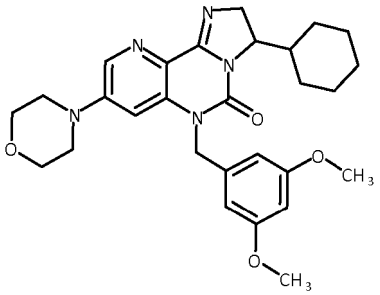
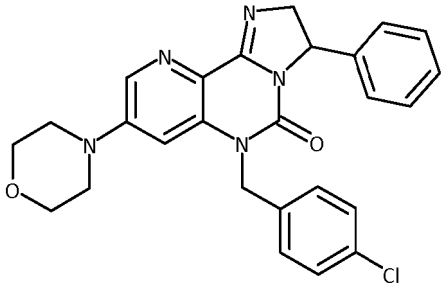
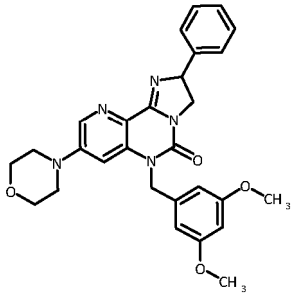
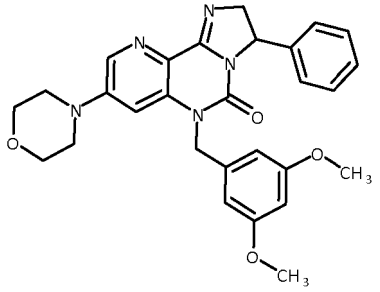
Example	Structure	Name
24		3-cyclohexyl-6-(4-methoxybenzyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
25		6-(4-chlorobenzyl)-2-cyclohexyl-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
26		6-(4-chlorobenzyl)-3-cyclohexyl-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
27		2-ethyl-6-(4-methoxybenzyl)-8-[(3R)-3-methoxypyrrolidin-1-yl]-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one

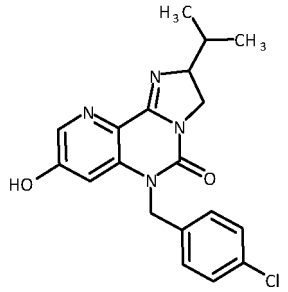
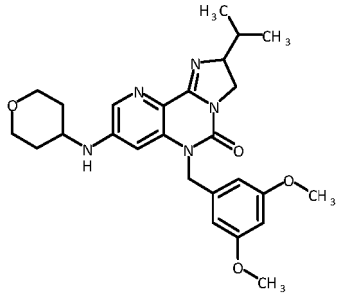
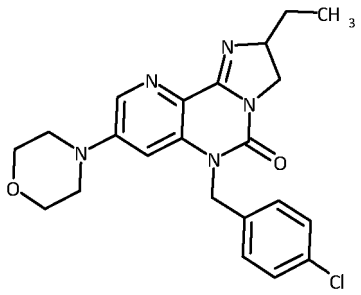
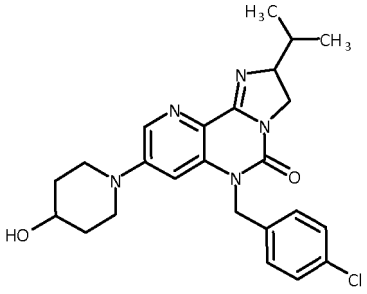
Example	Structure	Name
28		6-(4-methoxybenzyl)-8-(morpholin-4-yl)-2-phenyl-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
29		6-(4-methoxybenzyl)-8-(morpholin-4-yl)-3-phenyl-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
30		6-(4-chlorobenzyl)-2-(2-methylpropyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
31		6-(4-chlorobenzyl)-3-(2-methylpropyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one

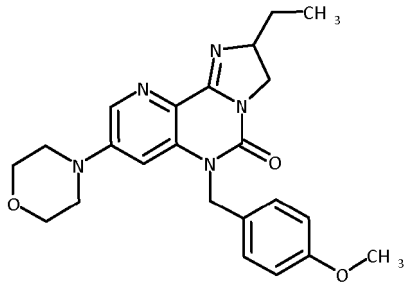
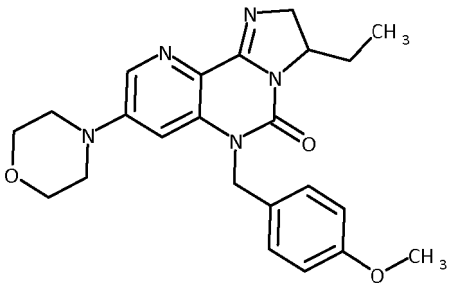
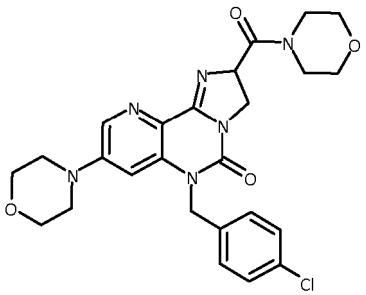
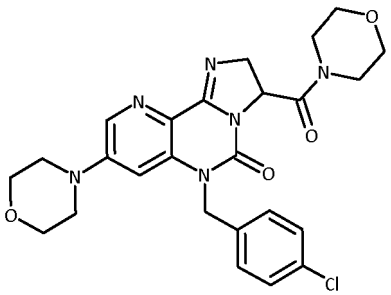
Example	Structure	Name
32		2-tert-butyl-6-(4-methoxybenzyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
33		2-cyclobutyl-6-(4-methoxybenzyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
34		2-(2,2-dimethylpropyl)-6-(4-methoxybenzyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
35		6-(3,5-dimethoxybenzyl)-3-(2-methylpropyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one

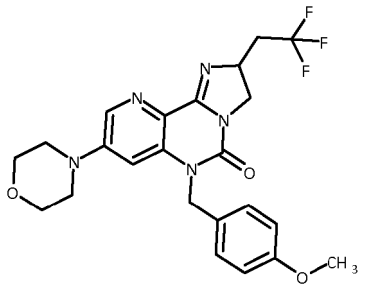
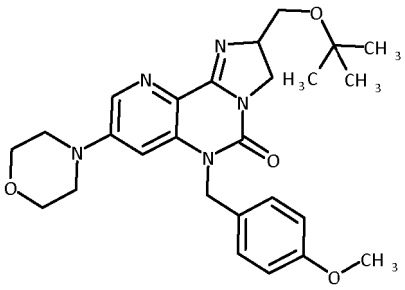
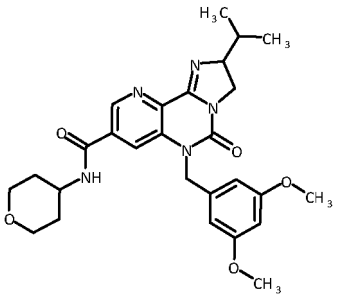
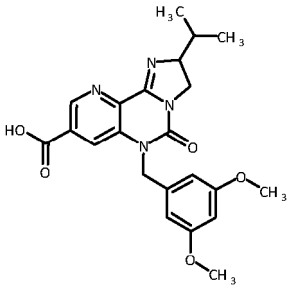
Example	Structure	Name
36		6-(4-chlorobenzyl)-8-(morpholin-4-yl)-2-phenyl-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
37		6-(4-methoxybenzyl)-2-(2-methylpropyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
38		6-(4-methoxybenzyl)-3-(2-methylpropyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
39		2-ethyl-6-(4-methoxybenzyl)-8-[3-(methoxymethyl)azetidin-1-yl]-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one

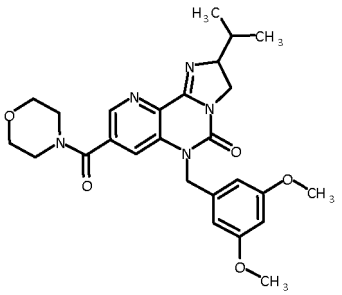
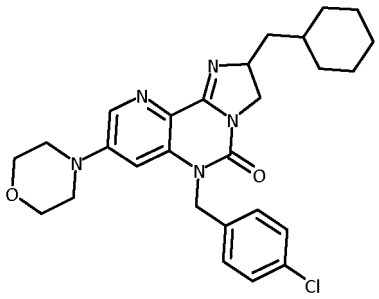
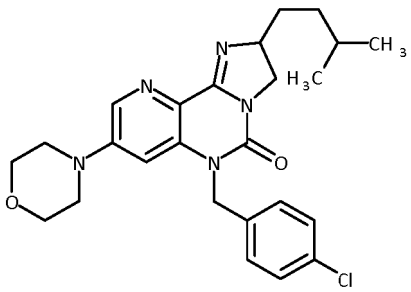
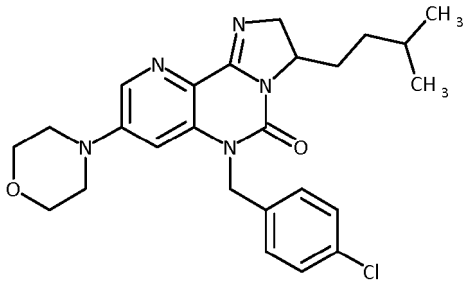
Example	Structure	Name
40		6-(4-chlorobenzyl)-8-(morpholin-4-yl)-2',3',5',6'-tetrahydrospiro[imidazo[1,2-c]pyrido[2,3-e]pyrimidine-2,4'-pyran]-5(6H)-one
41		6-(4-chlorobenzyl)-8-(morpholin-4-yl)-2,2',3',5',6,6'-hexahydro-5H-spiro[imidazo[1,2-c]pyrido[2,3-e]pyrimidine-3,4'-pyran]-5-one
42		8-(4-aminopiperidin-1-yl)-6-(3,5-dimethoxybenzyl)-2-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
43		2-cyclohexyl-6-(3,5-dimethoxybenzyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one

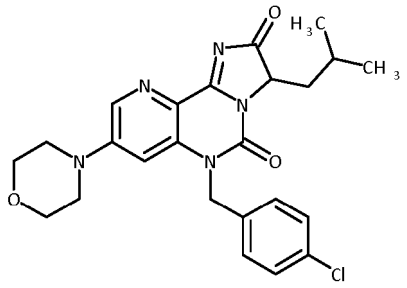
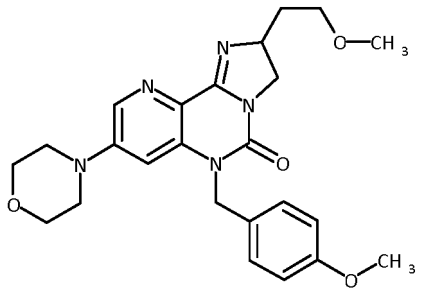
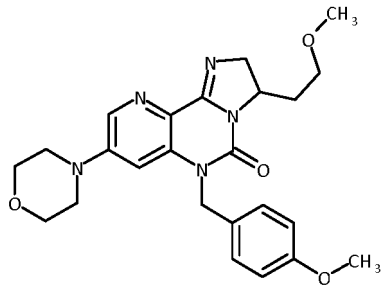
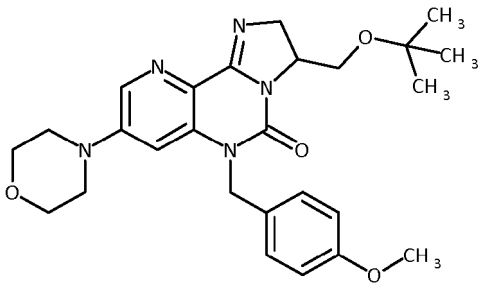
Example	Structure	Name
44		3-cyclohexyl-6-(3,5-dimethoxybenzyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
45		6-(4-chlorobenzyl)-8-(morpholin-4-yl)-3-phenyl-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
46		6-(3,5-dimethoxybenzyl)-8-(morpholin-4-yl)-2-phenyl-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
47		6-(3,5-dimethoxybenzyl)-8-(morpholin-4-yl)-3-phenyl-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one

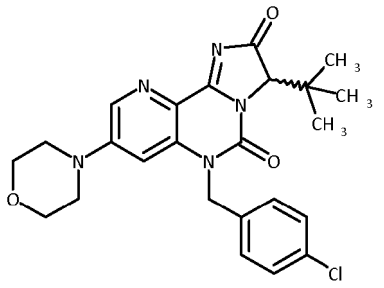
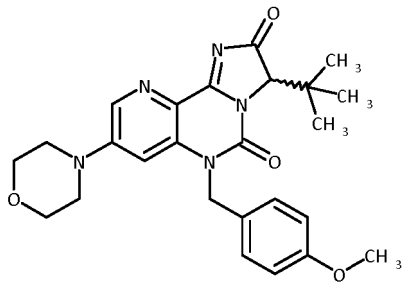
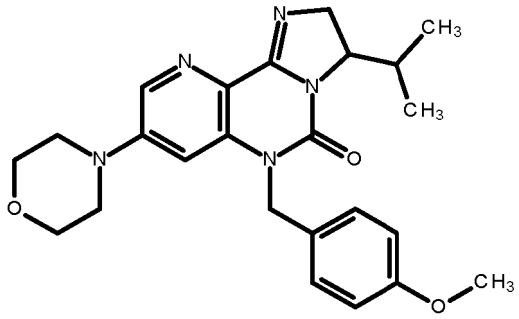
Example	Structure	Name
48		6-(4-chlorobenzyl)-8-hydroxy-2-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
49		6-(3,5-dimethoxybenzyl)-2-(propan-2-yl)-8-(tetrahydro-2H-pyran-4-ylamino)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
50		6-(4-chlorobenzyl)-2-ethyl-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
51		6-(4-chlorobenzyl)-8-(4-hydroxypiperidin-1-yl)-2-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one

Example	Structure	Name
52		2-ethyl-6-(4-methoxybenzyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
53		3-ethyl-6-(4-methoxybenzyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
54		6-(4-chlorobenzyl)-8-(morpholin-4-yl)-2-(morpholin-4-ylcarbonyl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
55		6-(4-chlorobenzyl)-8-(morpholin-4-yl)-3-(morpholin-4-ylcarbonyl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one

Example	Structure	Name
56		6-(4-methoxybenzyl)-8-(morpholin-4-yl)-2-(2,2,2-trifluoroethyl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
57		2-(tert-butoxymethyl)-6-(4-methoxybenzyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
58		6-(3,5-dimethoxybenzyl)-5-oxo-2-(propan-2-yl)-N-(tetrahydro-2H-pyran-4-yl)-2,3,5,6-tetrahydroimidazo[1,2-c]pyrido[2,3-e]pyrimidine-8-carboxamide
59		6-(3,5-dimethoxybenzyl)-5-oxo-2-(propan-2-yl)-2,3,5,6-tetrahydroimidazo[1,2-c]pyrido[2,3-e]pyrimidine-8-carboxylic acid

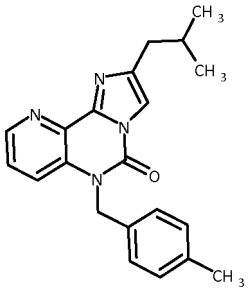
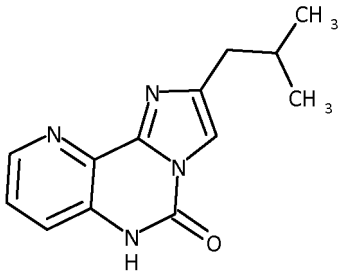
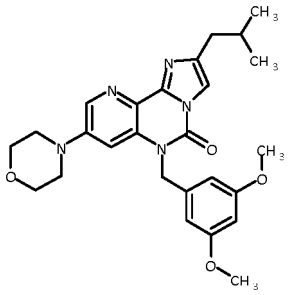
Example	Structure	Name
60		6-(3,5-dimethoxybenzyl)-8-(morpholin-4-ylcarbonyl)-2-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
61		6-(4-chlorobenzyl)-2-(cyclohexylmethyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
62		6-(4-chlorobenzyl)-2-(3-methylbutyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
63		6-(4-chlorobenzyl)-3-(3-methylbutyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one

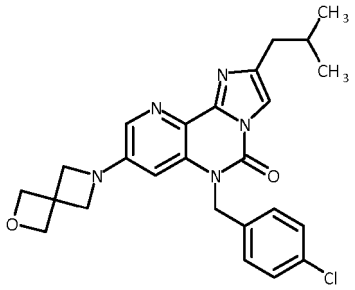
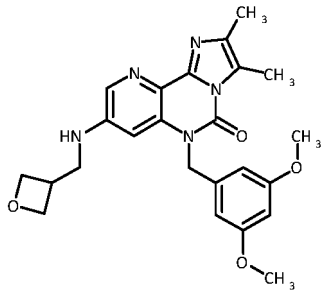
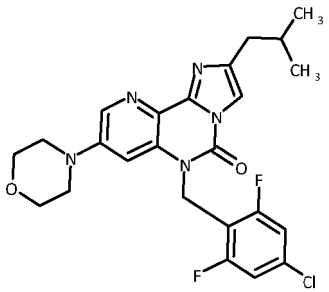
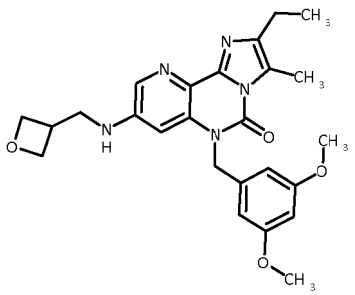
Example	Structure	Name
64		6-(4-chlorobenzyl)-3-(2-methylpropyl)-8-(morpholin-4-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidine-2,5(3H,6H)-dione
65		6-(4-methoxybenzyl)-2-(2-methoxyethyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
66		6-(4-methoxybenzyl)-3-(2-methoxyethyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one
67		3-(tert-butoxymethyl)-6-(4-methoxybenzyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one

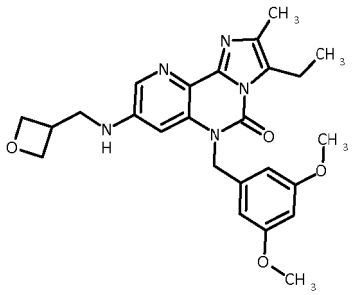
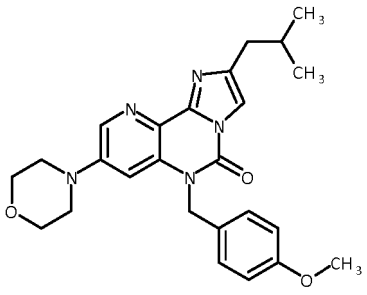
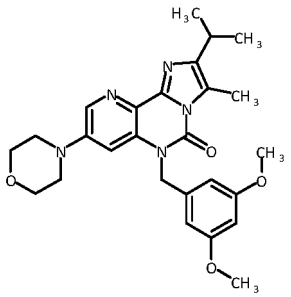
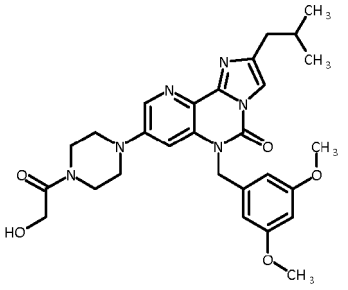
Example	Structure	Name
68		5-tert-butyl-8-[(4-chlorophenyl)methyl]-11-morpholino-3,6,8,13-tetrazatricyclo[7.4.0.02,6]trideca-1(13),2,9,11-tetraene-4,7-dione
69		5-tert-butyl-8-[(4-methoxyphenyl)methyl]-11-morpholino-3,6,8,13-tetrazatricyclo[7.4.0.02,6]trideca-1(13),2,9,11-tetraene-4,7-dione
162		5-isopropyl-8-[(4-methoxyphenyl)methyl]-11-morpholino-3,6,8,13-tetrazatricyclo[7.4.0.02,6]trideca-1(9),2,10,12-tetraen-7-one

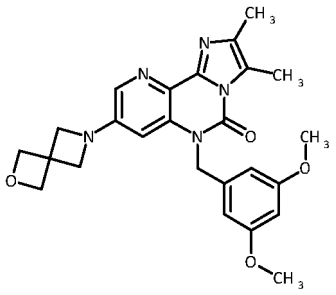
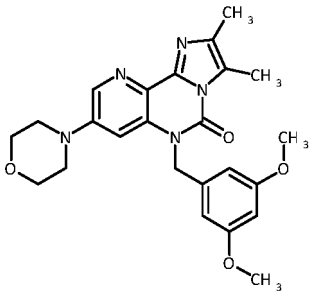
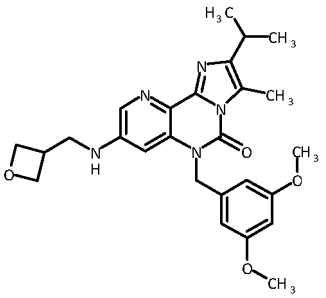
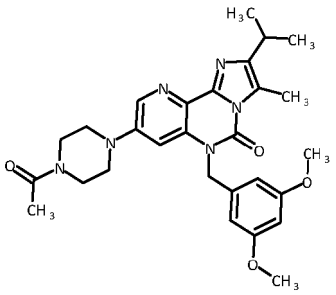
[0045] Preferred compounds according to the invention are compounds or an enantiomer, diastereomer, N-oxide, or a pharmaceutically acceptable salt or combinations thereof, is provided according to general formula 1b or 1c selected from the compounds in Table 2 below:

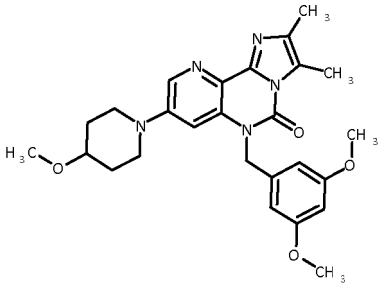
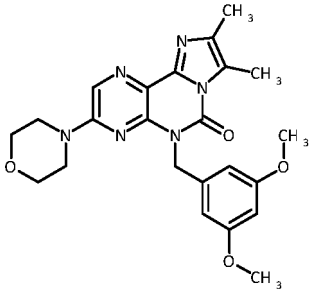
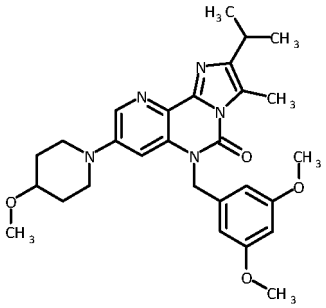
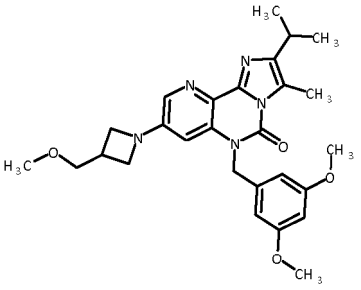
Table 2: Selected compounds of the invention according to formula 1b and 1c.

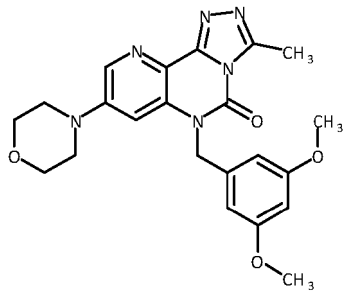
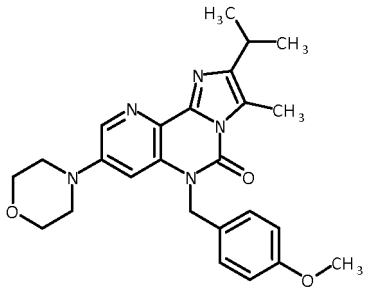
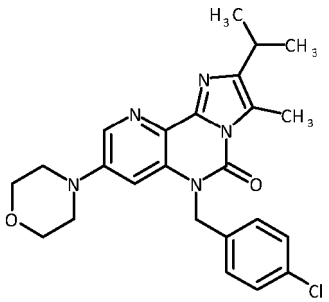
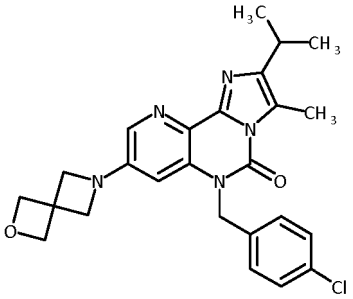
Example	Structure	Name
70		6-[(4-methylphenyl)methyl]-2-(2-methylpropyl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one
71		2-(2-methylpropyl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one
72		6-[(3,5-dimethoxyphenyl)methyl]-2-(2-methylpropyl)-8-(morpholin-4-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one

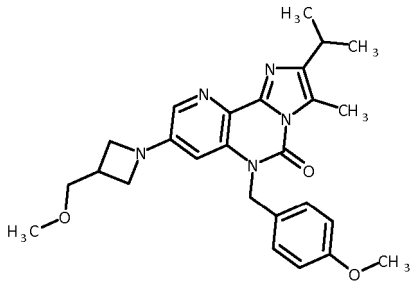
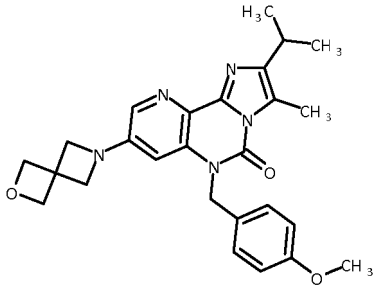
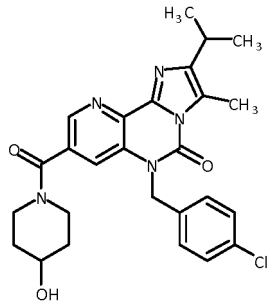
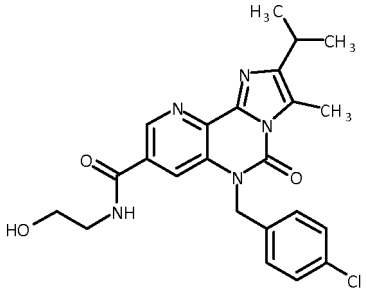
Example	Structure	Name
73		6-[(4-chlorophenyl)methyl]-2-(2-methylpropyl)-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one
74		6-[(3,5-dimethoxyphenyl)methyl]-2,3-dimethyl-8-{[(oxetan-3-yl)methyl]amino}imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one
75		6-[(4-chloro-2,6-difluorophenyl)methyl]-2-(2-methylpropyl)-8-(morpholin-4-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one
76		6-[(3,5-dimethoxyphenyl)methyl]-2-ethyl-3-methyl-8-{[(oxetan-3-yl)methyl]amino}imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one

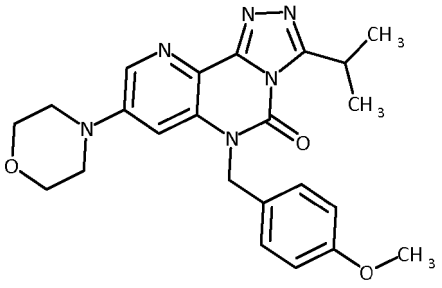
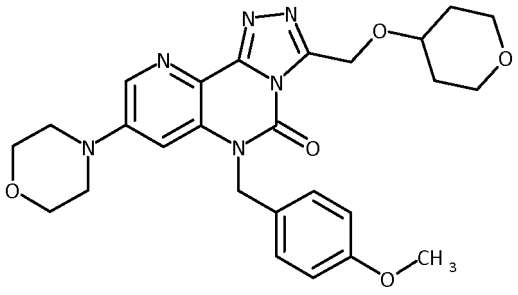
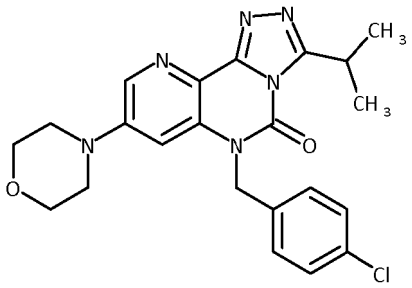
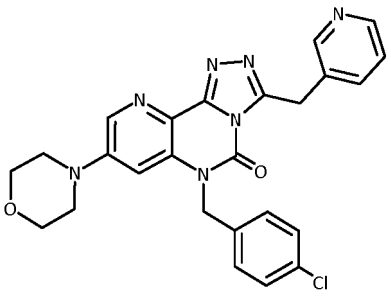
Example	Structure	Name
77		6-[(3,5-dimethoxyphenyl)methyl]-3-ethyl-2-methyl-8-{[(oxetan-3-yl)methyl]amino}imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one
78		6-(4-methoxybenzyl)-2-(2-methylpropyl)-8-(morpholin-4-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one
79		6-(3,5-dimethoxybenzyl)-3-methyl-8-(morpholin-4-yl)-2-(propan-2-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one
80		6-(3,5-dimethoxybenzyl)-8-[4-(hydroxyacetyl)piperazin-1-yl]-2-(2-methylpropyl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one

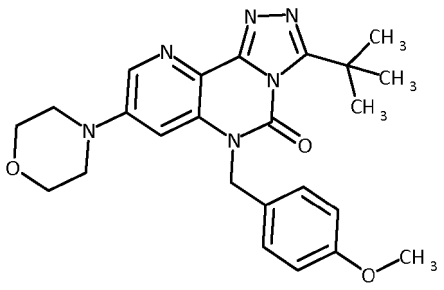
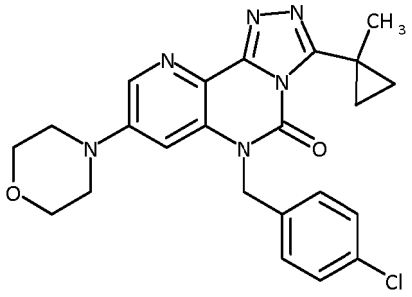
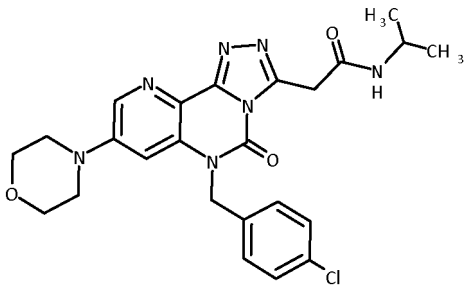
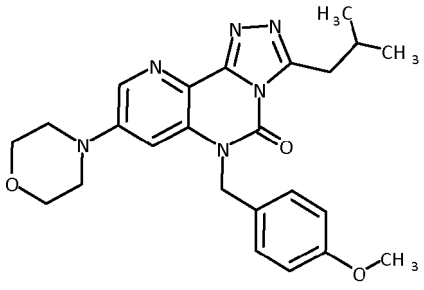
Example	Structure	Name
81		6-(3,5-dimethoxybenzyl)-2,3-dimethyl-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one
82		6-(3,5-dimethoxybenzyl)-2,3-dimethyl-8-(morpholin-4-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one
83		6-(3,5-dimethoxybenzyl)-3-methyl-8-[(oxetan-3-ylmethyl)amino]-2-(propan-2-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one
84		8-(4-acetylpiperazin-1-yl)-6-(3,5-dimethoxybenzyl)-3-methyl-2-(propan-2-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one

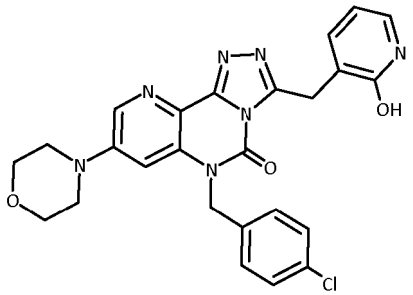
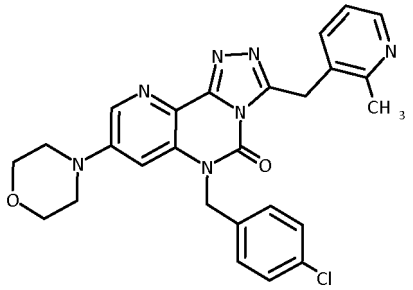
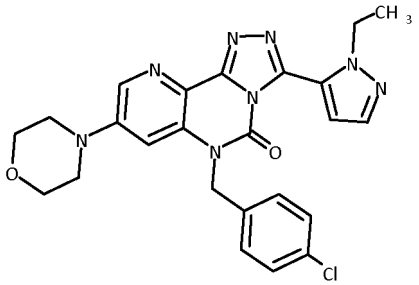
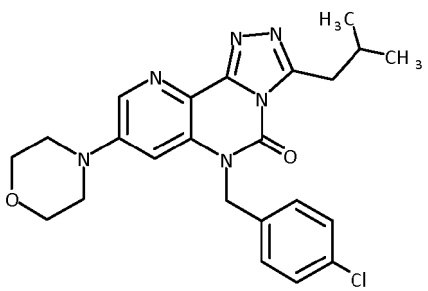
Example	Structure	Name
85		6-(3,5-dimethoxybenzyl)-8-(4-methoxypiperidin-1-yl)-2,3-dimethylimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one
86		5-(3,5-dimethoxybenzyl)-8,9-dimethyl-3-(morpholin-4-yl)imidazo[1,2-c]pteridin-6(5H)-one
87		6-(3,5-dimethoxybenzyl)-8-(4-methoxypiperidin-1-yl)-3-methyl-2-(propan-2-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one
88		6-(3,5-dimethoxybenzyl)-8-[3-(methoxymethyl)azetidin-1-yl]-3-methyl-2-(propan-2-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one

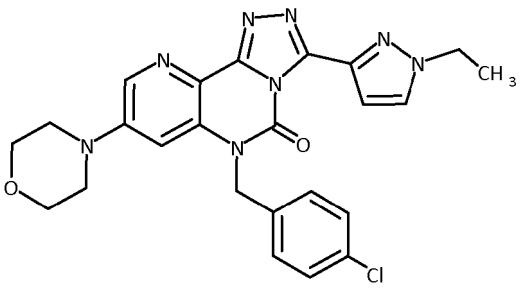
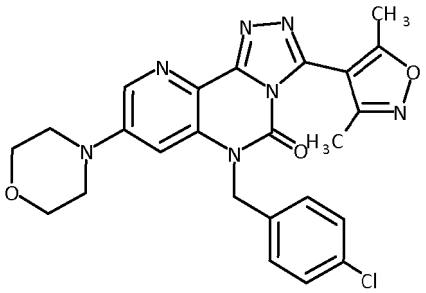
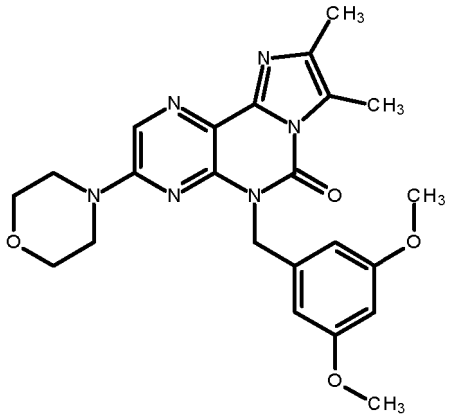
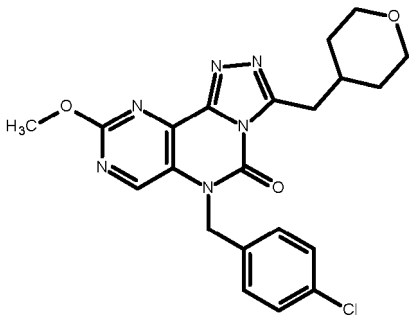
Example	Structure	Name
89		6-(3,5-dimethoxybenzyl)-3-methyl-8-(morpholin-4-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one
90		6-(4-methoxybenzyl)-3-methyl-8-(morpholin-4-yl)-2-(propan-2-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one
91		6-(4-chlorobenzyl)-3-methyl-8-(morpholin-4-yl)-2-(propan-2-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one
92		6-(4-chlorobenzyl)-3-methyl-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-2-(propan-2-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one

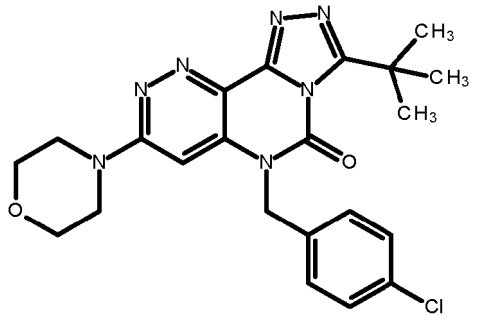
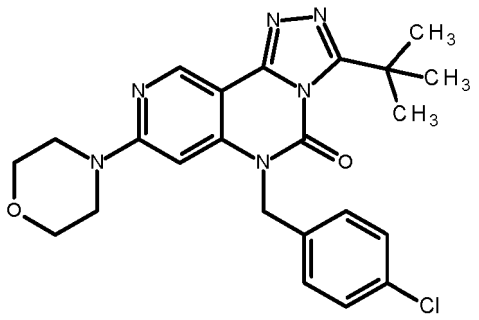
Example	Structure	Name
93		6-(4-methoxybenzyl)-8-[3-(methoxymethyl)azetidin-1-yl]-3-methyl-2-(propan-2-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one
94		6-(4-methoxybenzyl)-3-methyl-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-2-(propan-2-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one
95		6-(4-chlorobenzyl)-8-[(4-hydroxypiperidin-1-yl)carbonyl]-3-methyl-2-(propan-2-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one
96		6-(4-chlorobenzyl)-N-(2-hydroxyethyl)-3-methyl-5-oxo-2-(propan-2-yl)-5,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidine-8-carboxamide

Example	Structure	Name
97		6-(4-methoxybenzyl)-8-(morpholin-4-yl)-3-(propan-2-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one
98		6-(4-methoxybenzyl)-8-(morpholin-4-yl)-3-[(tetrahydro-2H-pyran-4-yloxy)methyl]pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one
99		6-(4-chlorobenzyl)-8-(morpholin-4-yl)-3-(propan-2-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one
100		6-(4-chlorobenzyl)-8-(morpholin-4-yl)-3-(pyridin-3-ylmethyl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one

Example	Structure	Name
101		3-tert-butyl-6-(4-methoxybenzyl)-8-(morpholin-4-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one
102		6-(4-chlorobenzyl)-3-(1-methylcyclopropyl)-8-(morpholin-4-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one
103		2-[6-(4-chlorobenzyl)-8-(morpholin-4-yl)-5-oxo-5,6-dihydropyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-3-yl]-N-(propan-2-yl)acetamide
104		6-(4-methoxybenzyl)-3-(2-methylpropyl)-8-(morpholin-4-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one

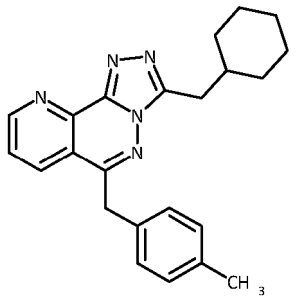
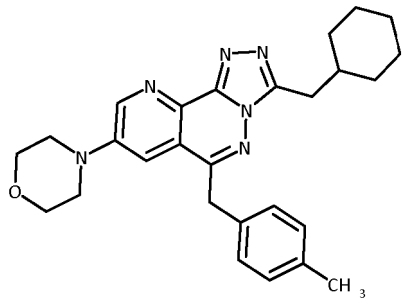
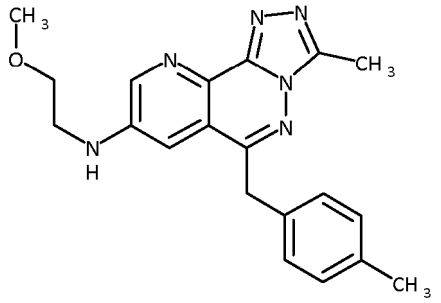
Example	Structure	Name
105		6-(4-chlorobenzyl)-3-[(2-hydroxypyridin-3-yl)methyl]-8-(morpholin-4-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one
106		6-(4-chlorobenzyl)-3-[(2-methylpyridin-3-yl)methyl]-8-(morpholin-4-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one
107		6-(4-chlorobenzyl)-3-(1-ethyl-1H-pyrazol-5-yl)-8-(morpholin-4-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one
108		6-(4-chlorobenzyl)-3-(2-methylpropyl)-8-(morpholin-4-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one

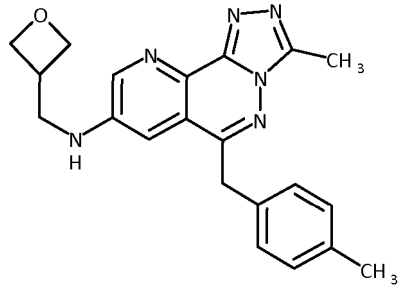
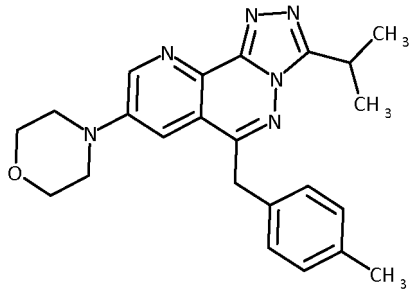
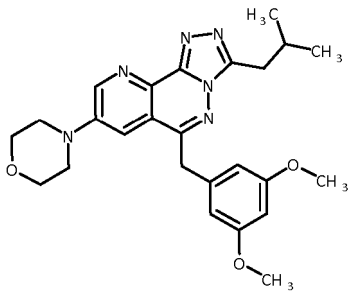
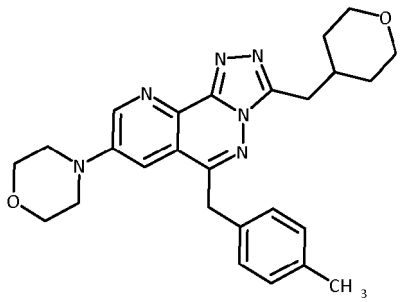
Example	Structure	Name
109		6-(4-chlorobenzyl)-3-(1-ethyl-1H-pyrazol-3-yl)-8-(morpholin-4-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one
110		6-(4-chlorobenzyl)-3-(3,5-dimethyl-1,2-oxazol-4-yl)-8-(morpholin-4-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one
158		6-(3,5-dimethoxybenzyl)-2,3-dimethyl-8-(morpholin-4-yl)imidazo[1,2-c]pyrazino[2,3-e]pyrimidin-5(6H)-one
159		6-(4-chlorobenzyl)-9-methoxy-3-(tetrahydro-2H-pyran-4-ylmethyl)pyrimido[6,5-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one

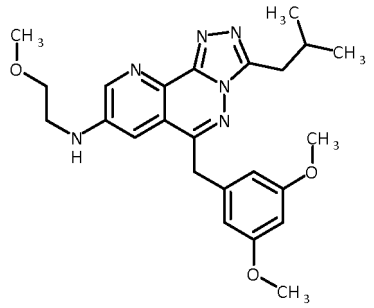
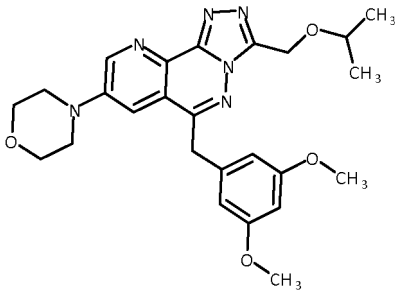
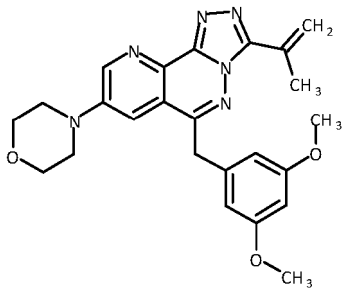
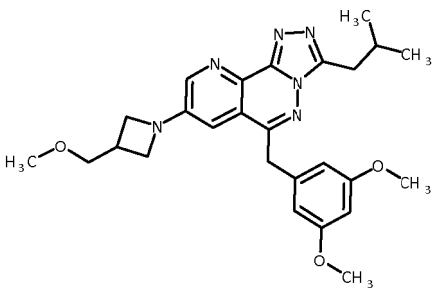
Example	Structure	Name
160		3-tert-butyl-6-(4-chlorobenzyl)-8-(morpholin-4-yl)pyridazo[6,5-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one
161		6-(4-chlorobenzyl)-3-[(2-methylpyridin-3-yl)methyl]-8-(morpholin-4-yl)pyrido[3,4-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one

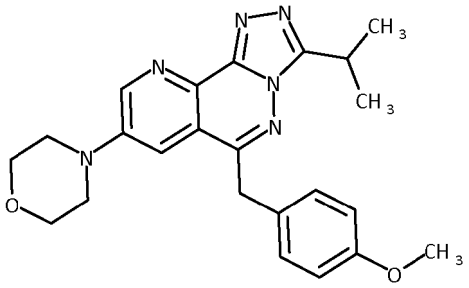
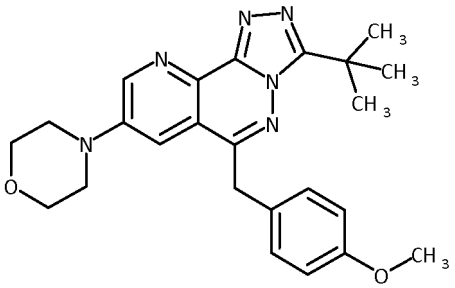
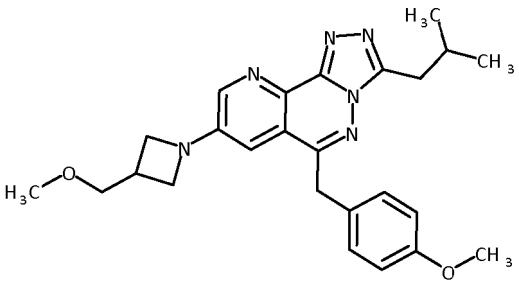
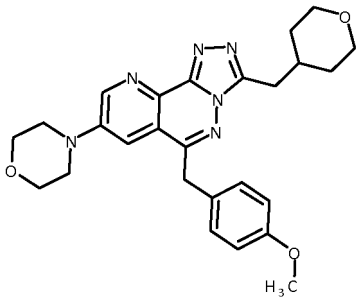
[0046] Preferred compounds according to the invention are compounds or an enantiomer, diastereomer, N-oxide, or a pharmaceutically acceptable salt or combinations thereof, is provided according to general formula 1d selected from the compounds in Table 3 below:

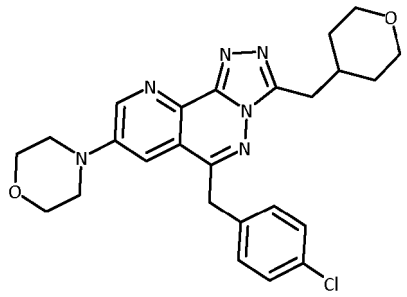
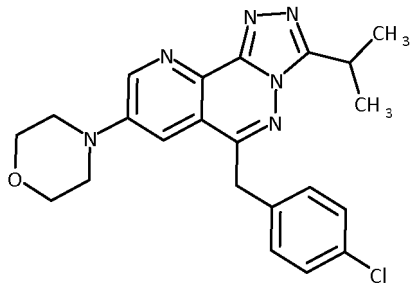
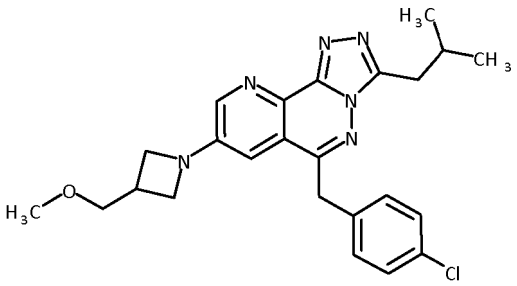
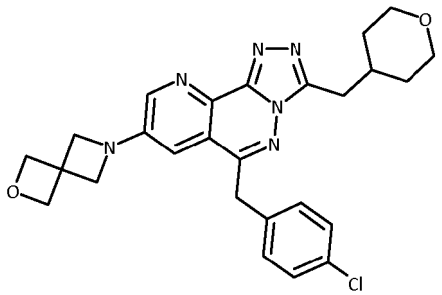
Table 3: Selected compounds of the invention according to formula 1d.

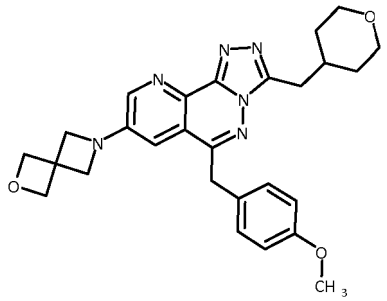
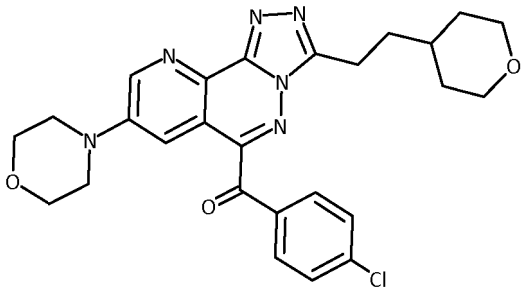
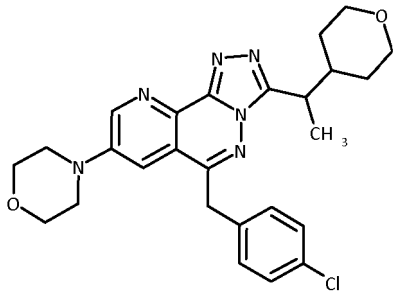
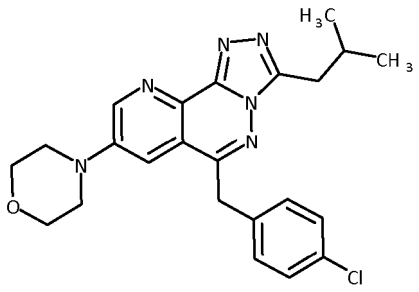
Example	Structure	Name
111		3-(cyclohexylmethyl)-6-[(4-methylphenyl)methyl]pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine
112		3-(cyclohexylmethyl)-6-(4-methylbenzyl)-8-(morpholin-4-yl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine
113		N-(2-methoxyethyl)-3-methyl-6-(4-methylbenzyl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazin-8-amine

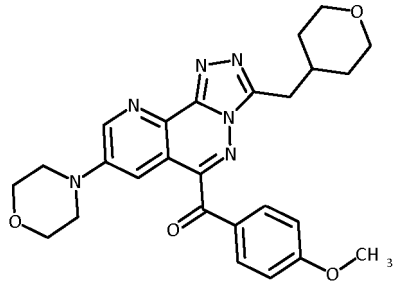
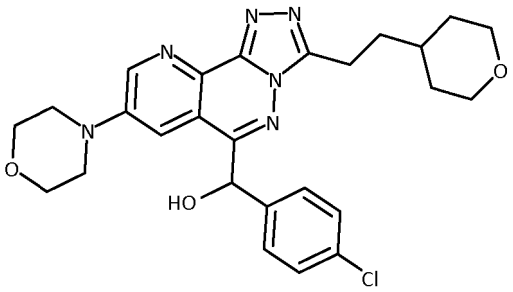
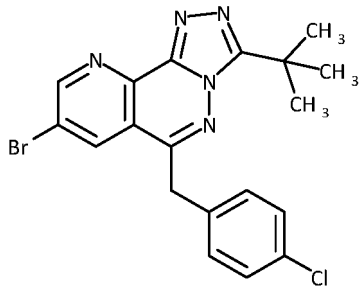
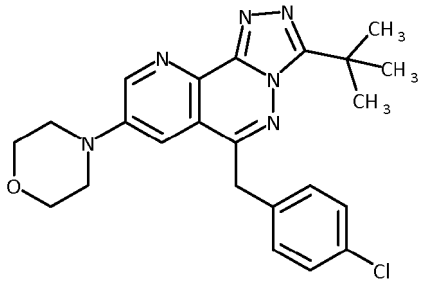
Example	Structure	Name
114		3-methyl-6-(4-methylbenzyl)-N-(oxetan-3-ylmethyl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazin-8-amine
115		6-(4-methylbenzyl)-8-(morpholin-4-yl)-3-(propan-2-yl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine
116		6-(3,5-dimethoxybenzyl)-3-(2-methylpropyl)-8-(morpholin-4-yl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine
117		6-(4-methylbenzyl)-8-(morpholin-4-yl)-3-(tetrahydro-2H-pyran-4-ylmethyl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine

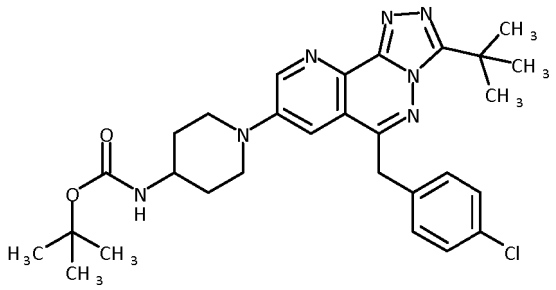
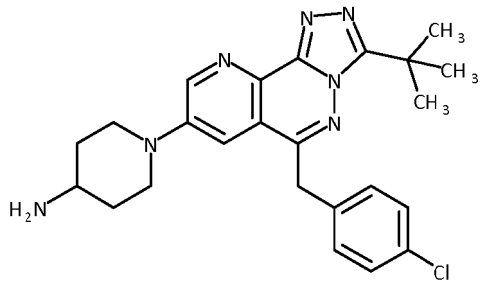
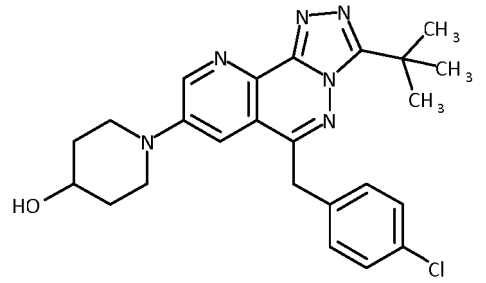
Example	Structure	Name
118		6-(3,5-dimethoxybenzyl)-N-(2-methoxyethyl)-3-(2-methylpropyl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazin-8-amine
119		6-(3,5-dimethoxybenzyl)-8-(morpholin-4-yl)-3-[(propan-2-yloxy)methyl]pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine
120		6-(3,5-dimethoxybenzyl)-8-(morpholin-4-yl)-3-(prop-1-en-2-yl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine
121		6-(3,5-dimethoxybenzyl)-8-[3-(methoxymethyl)azetidin-1-yl]-3-(2-methylpropyl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine

Example	Structure	Name
122		6-(4-methoxybenzyl)-8-(morpholin-4-yl)-3-(propan-2-yl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine
123		3-tert-butyl-6-(4-methoxybenzyl)-8-(morpholin-4-yl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine
124		6-(4-methoxybenzyl)-8-[3-(methoxymethyl)azetidin-1-yl]-3-(2-methylpropyl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine
125		6-(4-methoxybenzyl)-8-(morpholin-4-yl)-3-(tetrahydro-2H-pyran-4-ylmethyl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine

Example	Structure	Name
126		6-(4-chlorobenzyl)-8-(morpholin-4-yl)-3-(tetrahydro-2H-pyran-4-ylmethyl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine
127		6-(4-chlorobenzyl)-8-(morpholin-4-yl)-3-(propan-2-yl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine
128		6-(4-chlorobenzyl)-8-[3-(methoxymethyl)azetidin-1-yl]-3-(2-methylpropyl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine
129		6-(4-chlorobenzyl)-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-3-(tetrahydro-2H-pyran-4-ylmethyl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine

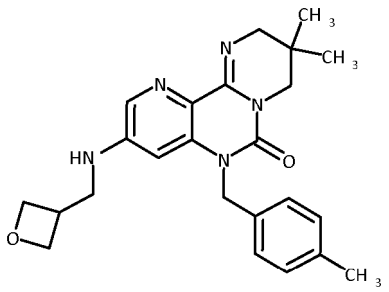
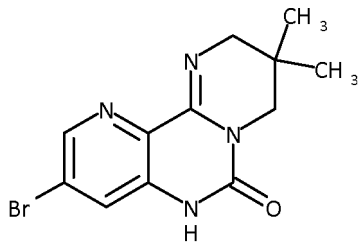
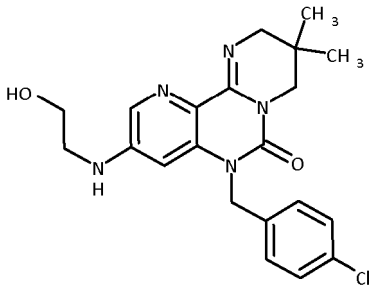
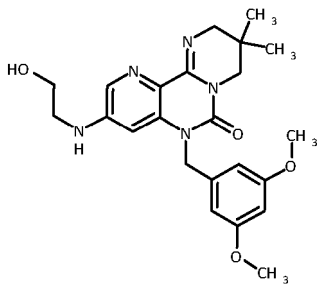
Example	Structure	Name
130		6-(4-methoxybenzyl)-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-3-(tetrahydro-2H-pyran-4-ylmethyl)pyrido[2,3-d][1,2,4]triazolo[4,4-b]pyridazine
131		(4-chlorophenyl){8-(morpholin-4-yl)-3-[2-(tetrahydro-2H-pyran-4-yl)ethyl]pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazin-6-yl}methanone
132		6-(4-chlorobenzyl)-8-(morpholin-4-yl)-3-[1-(tetrahydro-2H-pyran-4-yl)ethyl]pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine
133		6-(4-chlorobenzyl)-3-(2-methylpropyl)-8-(morpholin-4-yl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine

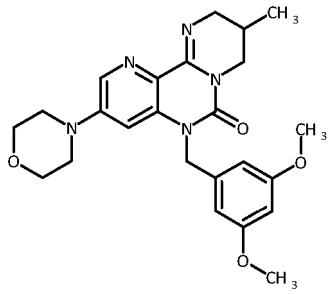
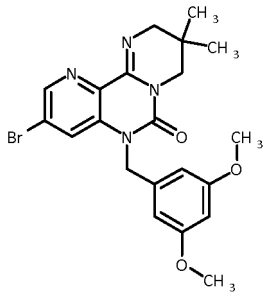
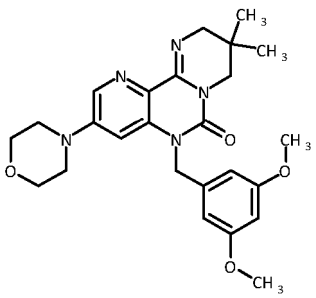
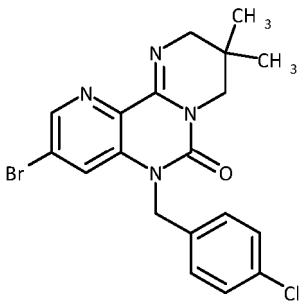
Example	Structure	Name
134		(4-methoxyphenyl)[8-(morpholin-4-yl)-3-(tetrahydro-2H-pyran-4-ylmethyl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazin-6-yl]methanone
135		(4-chlorophenyl){8-(morpholin-4-yl)-3-[2-(tetrahydro-2H-pyran-4-yl)ethyl]pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazin-6-yl}methanol
136		8-bromo-3-tert-butyl-6-(4-chlorobenzyl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine
137		3-tert-butyl-6-(4-chlorobenzyl)-8-(morpholin-4-yl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine

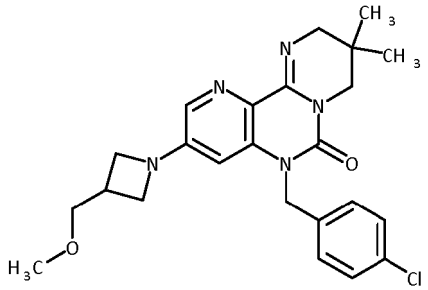
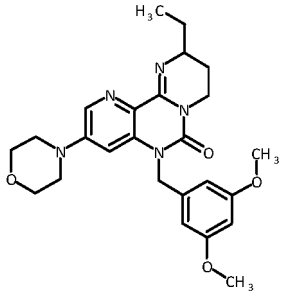
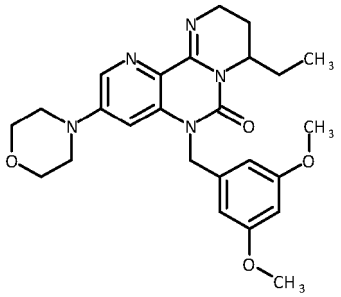
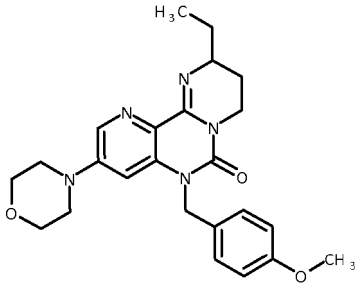
Example	Structure	Name
138		tert-butyl N-[1-[5-tert-butyl-8-[(4-chlorophenyl)methyl]-3,4,6,7,13-pentazatricyclo[7.4.0.02,6]trideca-1(9),2,4,7,10,12-hexaen-11-yl]-4-piperidyl]carbamate
139		1-[5-tert-butyl-8-[(4-chlorophenyl)methyl]-3,4,6,7,13-pentazatricyclo[7.4.0.02,6]trideca-1(9),2,4,7,10,12-hexaen-11-yl]piperidin-4-amine
140		1-[5-tert-butyl-8-[(4-chlorophenyl)methyl]-3,4,6,7,13-pentazatricyclo[7.4.0.02,6]trideca-1(9),2,4,7,10,12-hexaen-11-yl]piperidin-4-ol

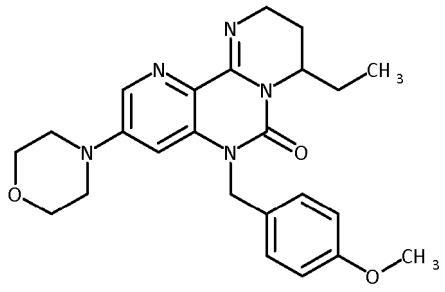
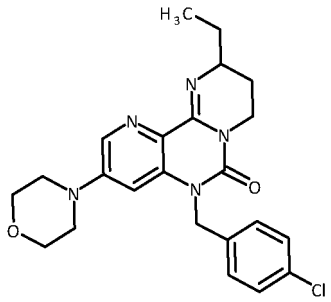
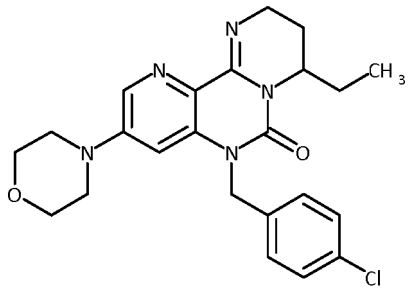
[0047] Preferred compounds according to the invention are compounds or an enantiomer, diastereomer, N-oxide, or a pharmaceutically acceptable salt or combinations thereof, is provided according to general formula 1e selected from the compounds in Table 4 below:

Table 4: Selected compounds of the invention according to formula 1e.

Example	Structure	Name
141		9,9-dimethyl-5-[(4-methylphenyl)methyl]-3-{[(oxetan-3-yl)methyl]amino}-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one
142		3-bromo-9,9-dimethyl-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one
143		5-(4-chlorobenzyl)-3-[(2-hydroxyethyl)amino]-9,9-dimethyl-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one
144		5-(3,5-dimethoxybenzyl)-3-[(2-hydroxyethyl)amino]-9,9-dimethyl-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one

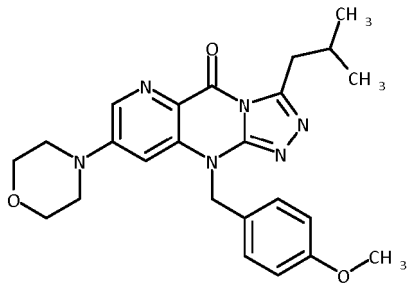
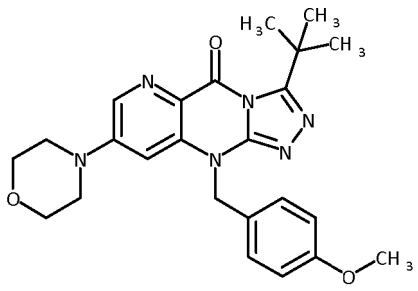
Example	Structure	Name
145		5-(3,5-dimethoxybenzyl)-9-methyl-3-(morpholin-4-yl)-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one
146		3-bromo-5-(3,5-dimethoxybenzyl)-9,9-dimethyl-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one
147		5-(3,5-dimethoxybenzyl)-9,9-dimethyl-3-(morpholin-4-yl)-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one
148		3-bromo-5-(4-chlorobenzyl)-9,9-dimethyl-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one

Example	Structure	Name
149		5-(4-chlorobenzyl)-3-[3-(methoxymethyl)azetidin-1-yl]-9,9-dimethyl-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one
150		5-(3,5-dimethoxybenzyl)-10-ethyl-3-(morpholin-4-yl)-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one
151		5-(3,5-dimethoxybenzyl)-8-ethyl-3-(morpholin-4-yl)-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one
152		10-ethyl-5-(4-methoxybenzyl)-3-(morpholin-4-yl)-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one

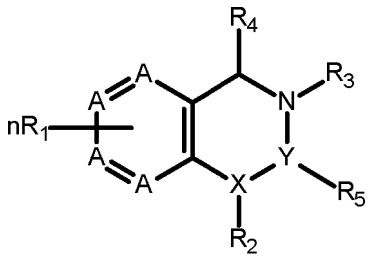
Example	Structure	Name
153		8-ethyl-5-(4-methoxybenzyl)-3-(morpholin-4-yl)-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one
154		5-(4-chlorobenzyl)-10-ethyl-3-(morpholin-4-yl)-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one
155		5-(4-chlorobenzyl)-8-ethyl-3-(morpholin-4-yl)-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one

[0048] Preferred compounds according to the invention are compounds or an enantiomer, diastereomer, N-oxide, or a pharmaceutically acceptable salt or combinations thereof, is provided according to general formula 1f selected from the compounds in Table 5 below:

Table 5: Selected compounds of the invention according to formula 1f.

Example	Structure	Name
156		6-isobutyl-2-[(4-methoxyphenyl)methyl]-12-morpholino-2,4,5,7,10-pentazatricyclo[7.4.0.03,7]trideca-1(13),3,5,9,11-pentaen-8-one
157		6-tert-butyl-2-[(4-methoxyphenyl)methyl]-12-morpholino-2,4,5,7,10-pentazatricyclo[7.4.0.03,7]trideca-1(13),3,5,9,11-pentaen-8-one

[0049] The invention also provides for a pharmaceutical composition comprising a compound of formula I:

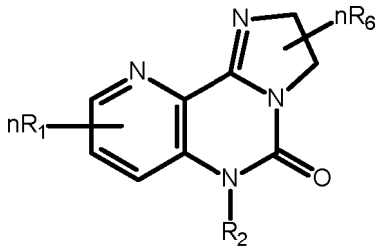


formula I

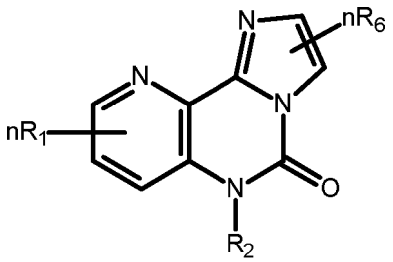
or an enantiomer, diastereomer, N-oxide, or a pharmaceutically acceptable salt or combinations thereof, and a pharmaceutically acceptable carrier, wherein A, X, Y, R_1 through R_6 and n have the meanings ascribed to them above, for use in the treatment and/or prevention of pain, chronic pain and tolerance to analgesic, respiratory disorders and dysfunctions,

overactive bladder, bladder pain syndrome, dysuria and in general in genitourinary diseases, cardiovascular disorders and more in general for the potential treatment of visceral organ diseases and disorders characterized by the involvement of P_2X_3 and $P_2X_{2/3}$.

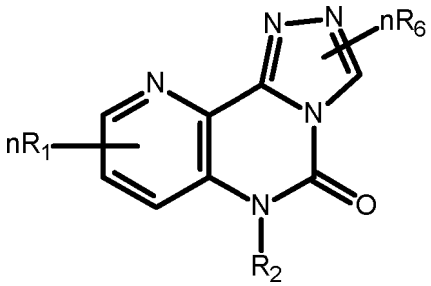
[0050] The invention also provides for a pharmaceutical composition comprising a compound of any of formulae 1a to 1g:



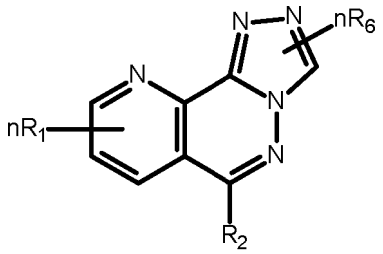
formula 1a



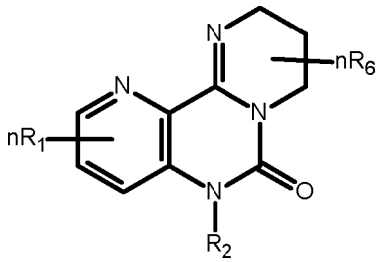
formula 1b



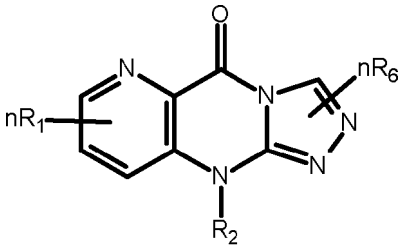
formula 1c



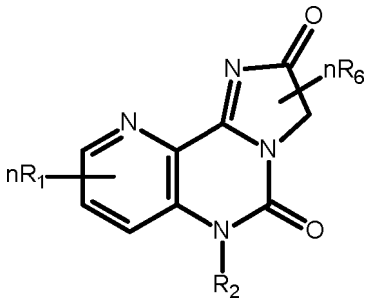
formula 1d



formula 1e



formula 1f



formula 1g

or an enantiomer, diastereomer, N-oxide, or a pharmaceutically acceptable salt or combinations thereof, and a pharmaceutically acceptable carrier, wherein A, X, Y, R_1 through R_6 and n have the meanings ascribed to them above, for use in the treatment and/or prevention of pain, chronic pain and tolerance to analgesic, respiratory disorders and dysfunctions, genitourinary diseases and cardiovascular disorders, in general, for the potential treatment of visceral organ diseases and disorders characterized by the involvement of P_2X_3 and $P_2X_{2/3}$.

[0051] The invention also provides for compounds according to any of formula I or formulae 1a to 1g shown above, which is used in the treatment and/or prevention of, dysfunction including without any limitation involving ATP release, and in general, for the potential treatment of sensory and visceral organ diseases and disorders characterized by the involvement of $P2X_3$ and $P2X_{2/3}$ receptors; for the treatment and/or prevention of pain, chronic pain and cancer pain, addiction and tolerance to analgesic; for the treatment of asthma, cough, COPD and refractory chronic cough and in general of respiratory disorders and dysfunctions; for the treatment of overactive bladder, urinary incontinence, bladder pain syndrome, dysuria and endometriosis and in general in genitourinary diseases; for treatment of cardiovascular disorders, irritable bowel syndrome (IBS), Burning Mouth Syndrome (BMS) migraine and itch.

Terms and Definitions Used

[0052] Except where stated otherwise, the following definitions apply throughout the present specification and claims. These definitions apply regardless of whether a term is used by itself or in combination with other terms. For example, the definition of "alkyl" applies not only to alkyl groups *per se*, but also to the alkyl portions of alkoxy, alkylamino, alkylthio or alkylcarbonyl groups *etc*. Furthermore, all ranges described for a chemical group, for example "from 1 to 13 carbon atoms" or "C_1-C_6 alkyl" include all combinations and sub-combinations of ranges and specific numbers of carbon atoms therein.

[0053] The skilled person will be aware that groups A, X, Y, R_1 to R_6 and n all have the meanings given to them as described herein. For example, "groups X and Y are selected from C and N atoms, wherein the unit X-Y represents either a N-C group, or a C=N group respectively.

[0054] "Alkyl" means a straight chain or branched chain aliphatic hydrocarbon group having from 1 to 20 carbon atoms in the chain. Preferred alkyl groups have from 1 to 12 carbon atoms in the chain. More preferred alkyl groups have from 1 to 6 carbon atoms in the chain. "Lower alkyl" means an alkyl group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. Examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl, sec-butyl, n-butyl, and t-butyl.

[0055] "Alkenyl" means a straight chain or branched chain aliphatic hydrocarbon group having at least one carbon-carbon double bond and having from 2 to 15 carbon atoms in the chain. Preferred alkenyl groups have from 2 to 12 carbon atoms in the chain. More preferred alkenyl groups have from 2 to 6 carbon atoms in the chain. "Lower alkenyl" means an alkenyl group having 2 to about 6 carbon atoms in the chain, which may be straight or branched. Examples of suitable alkenyl groups include ethenyl, propenyl, isopropenyl, n-butenyl, 1-hexenyl and 3-methylbut-2-enyl.

[0056] "Alkynyl" means a straight chain or branched chain aliphatic hydrocarbon group having at least one carbon-carbon triple bond and having from 2 to 15 carbon atoms in the chain. Preferred alkynyl groups have from 2 to 12 carbon atoms in the chain. More preferred alkynyl groups have from 2 to 6 carbon atoms in the chain. "Lower alkynyl" means an alkynyl group having 2 to about 6 carbon atoms in the chain, which may be straight or branched. Examples of suitable alkynyl groups include ethynyl, propynyl and 2-butynyl.

[0057] "Mono-, bi-, or tricyclic heterocyclic" means an aromatic or non-aromatic saturated mono- bi- or tricyclic ring system having from 2 to 14 ring carbon atoms, and containing from 1 to 5 ring atoms selected from N, O and S, alone or in combination. Bi- and tricyclic heterocyclic groups are fused at 2 or 4 points or joined at one point *via* a bond or a heteroatom linker (O, S, NH, or N(C_1-C_6 alkyl). The "mono- bi- or tricyclic heterocyclic" can be optionally substituted on the ring by replacing an available hydrogen on the ring by one or more substituents which may be the same or different. The nitrogen or sulphur atom of the heterocyclic can be optionally oxidized to the corresponding N-oxide, S-oxide or S-dioxide. Examples of suitable heterocyclics include furanyl, imidazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrrolyl, pyridyl, pyrimidyl, pyridazinyl, thiazolyl, triazolyl, tetrazolyl, thienyl, carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, benzotriazolyl,

benzothiazolyl, benzooxazolyl, benzimidazolyl, isoquinolinyl, isoindolyl, acridinyl and benzoisoxazolyl, aziridinyl, piperidinyl, pyrrolidinyl, piperazinyl, tetrahydropyranyl, tetrahydrofuranyl, tetrahydrothiophenyl, morpholinyl and thiomorpholinyl.

[0058] Heterocyclics with aromatic characteristics may be referred to as heteroaryls or heteroaromatics. Examples of suitable heteroaromatics include furanyl, imidazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrrolyl, pyridyl, pyrimidyl, pyridazinyl, thiazolyl, triazolyl, tetrazolyl, thienyl, carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, benzotriazolyl, benzothiazolyl, benzooxazolyl, benzimidazolyl, isoquinolinyl, isoindolyl, acridinyl, benzoisoxazolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, 3-phenylpyridine, 3-cyclohexylpyridine, 3-(pyridin-3-yl) morpholine, 3-phenylisoxazole and 2-(piperidin-1-yl)pyrimidine.

[0059] "Mono-, bi- or tricyclic aryl" means an aromatic monocyclic, bicyclic or tricyclic ring system comprising 6 to 14 carbon atoms. Bi- and tricyclic aryl groups are fused at 2 or 4 points or joined at one point *via* a bond or a heteroatom linker (O, S, NH, or N(C_1-C_6 alkyl) (*e.g.*, biphenyl, 1-phenylnapthyl). The aryl group can be optionally substituted on the ring with one or more substituents, preferably 1 to 6 substituents, which may be the same or different. Examples of suitable aryl groups include phenyl and naphthyl.

[0060] "Cycloalkyl" means a monocyclic or bicyclic carbon ring system having from 3 to 14 carbon atoms, preferably from 3 to 6 carbon atoms. The cycloalkyl can be optionally substituted on the ring by replacing an available hydrogen on the ring by one or more substituents which may be the same or different. Examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl and cycloheptyl. Examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl and adamantyl.

[0061] "Cycloalkenyl" has a meaning corresponding to that of cycloalkyl, but with one or two double bonds within the ring (*e.g.*, cyclohexenyl, cyclohexadiene).

[0062] "Amines" are derivatives of ammonia, wherein one or more hydrogen atoms have been replaced by a substituent such as an alkyl or aryl group. These may respectively be called alkylamines and arylamines; amines in which both types of substituent are attached to one nitrogen atom may be called alkylarylamines.

[0063] Amines can be further organized into four sub-categories. Primary amines arise when one of the three hydrogen atoms in ammonia is replaced by an alkyl or aromatic group (an N-alkylamino or N-arylamino respectively). Examples of suitable primary alkyl amines include methylamine or ethanolamine, or aniline (phenylamine) as an example of an aromatic amine. Secondary amines have two organic substituents (independently alkyl or aryl groups) bound to the nitrogen atom together with one hydrogen (or no hydrogen if one of the substituent bonds is double). Examples of suitable secondary amines include dimethylamine and methylethanolamine, while an example of an aromatic amine would be diphenylamine. Such compounds may also be referred to as "N,N-dialkylamino", "N,N-diarylamino" or "N,N-alkylarylamino" groups depending on the nature of the substituents. A secondary amine substituted by an alkoxy group, as defined herein, would be termed an "N-alkyl-N-alkoxyamino" compound for example. In tertiary amines, all three hydrogen atoms are replaced by organic substituents, such as trimethylamine. The final sub-category is cyclic amines which are either secondary or tertiary amines. Examples of suitable cyclic amines include the 3-member ring aziridine and the six-membered ring piperidine. N-methylpiperidine and N-phenylpiperidine are suitable examples of cyclic tertiary amines.

[0064] "Amides" are compounds with a nitrogen atom attached to a carbonyl group, thus having the structure R–CO–NR'R'', with groups R' and R'' being independently selected from alkyl or aromatic groups as defined herein. For example, when R' is hydrogen and R'' is a 3-pyridyl group, the resulting amide has a 3-pyridylamino substituent. Alternatively, when R' is hydrogen and R'' is a cyclopentyl group, the resulting amide has a cyclopentylamino substituent.

[0065] "Halogen", "halide" or "halo" means fluorine, chlorine, bromine or iodine. Preferred halogens are fluorine, chlorine or bromine, and most preferred are fluorine and chlorine.

[0066] The term "acyl", whether used alone, or within a term such as "acylamino", denotes a radical provided by the residue after removal of hydroxyl from an organic acid. The term "acylamino" refers to an amino radical substituted with an acyl group. An example of an "acylamino" radical is $CH_3C(=O)$-NH- where the amine may be further substituted with alkyl, aryl or aralkyl groups.

[0067] The term "condensed ring" refers to a polycyclic ring system in a molecule in which two rings share two or more common atoms. Two rings that have only two atoms and one bond in common are said to be ortho-fused, *e.g.* naphthalene. In a polycyclic compound, a ring ortho-fused to different sides of two other rings that are themselves ortho-fused together (*i.e.* there are three common atoms between the first ring and the other two) is said to be ortho- and peri-fused to the other two rings. Phenalene is considered as being composed of three benzene rings, each of which is ortho- and peri-fused to the other two. Fusion nomenclature is concerned with a two-dimensional representation of a polycyclic ring system with the maximum number of non-cumulative double bonds. In addition, this system may be bridged, or involved in assemblies or spiro- systems (see below). For ring systems any ring fused to other rings on all sides must be itself named (i.e. it is not treated as a hole). For nomenclature purposes two rings which have two atoms and one bond in common may be regarded as being derived from the two rings as separate entities. The process of joining rings in this way is termed fusion. Any fusion compound illustrated or described herein, is named in accordance and with reference to "*Nomenclature of fused and bridged fused ring systems*" (IUPAC Recommendations 1998)", IUPAC, *Pure Appl. Chem.*, (1999), Vol.70, pp.143-216.

[0068] A spiro compound has two (or three) rings which have only one atom in common and the two (or three) rings are not linked by a bridge. The rings may form part of other ring systems (fused ring, bridged fused ring, system named by von Baeyer nomenclature, *etc.*). The common atom is known as a spiro atom, and spiro-fusion has also been termed spiro union. Monospiro hydrocarbons with two monocyclic rings are named by the prefix spiro before a von Baeyer descriptor (indicating the numbers of carbon atoms linked to the spiro atom in each ring in ascending order and separated by a full stop) placed in square brackets and then the name of the parent hydrocarbon indicating the total number of skeletal atoms, *e.g.* spiro[4.4]nonane. Monospiro hydrocarbons with two monocyclic rings are numbered consecutively starting in the smaller ring at an atom next to the spiro atom, proceeding around the smaller ring back to the spiro atom and then round the second ring. Heteroatoms are indicated by replacement prefixes and unsaturation is indicated in the usual way by the endings ene, diene, etc. Low locants are allocated for radical positions, or, if the ring system is a substituent, its point of attachment. If there is a choice of numbers the name that gives the

lower locants for spiro atoms is selected. Any spiro compound illustrated or described herein, is named in accordance and with reference to "*Extension and revision of the nomenclature for spiro compounds*" (IUPAC Recommendations 1999)", IUPAC, *Pure Appl. Chem.*, (1999), Vol.71, pp.531.538.

[0069] An asterisk may be used in subgeneric-formulas or groups to indicate the bond which is connected to a parent or core molecule as defined herein.

[0070] The term "treatment" and the like as used herein encompasses eliminating or alleviating symptoms of diseases or disorders and keeping them from worsening (stabilization) and more generally bringing about a desired physiological or pharmacological effect. The term "prevention" and the like as used herein encompasses inhibiting or retarding the manifestation of symptoms of such diseases or disorders or reducing (or increasing as the case may be) or eliminating abnormal values in markers thereof.

Stereochemistry

[0071] Unless specifically indicated, throughout the specification and claims, a given chemical formula or name shall encompass tautomers and all stereo, optical and geometrical isomers (*e.g.* enantiomers, diastereomers, +/-, R/S, E/Z isomers *etc.*) racemic mixtures and racemates thereof. This includes mixtures in different proportions of the separate enantiomers, mixtures of diastereomers, or mixtures of any of the foregoing forms where such isomers and enantiomers exist, as well as salts, including pharmaceutically acceptable salts and solvates thereof such as hydrates, solvates of the free compounds or solvates of a salt of the compound.

Derivatives of Compounds of the Invention

[0072] The invention further encompasses salts, solvates, hydrates, N-oxides, prodrugs and active metabolites of the compounds of formula I.

[0073] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, and commensurate with a reasonable benefit/risk ratio.

[0074] As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. For example, such salts include salts from ammonia, L-arginine, betaine, benethamine, benzathine, calcium hydroxide, choline, deanol, diethanolamine (2,2'-iminobis(ethanol)), diethylamine, 2-(diethylamino)-ethanol, 2-aminoethanol, ethylenediamine, N-ethyl-glucamine, hydrabamine, 1H-imidazole, lysine, magnesium hydroxide, 4-(2-hydroxyethyl)-morpholine, piperazine, potassium hydroxide, 1-(2-hydroxyethyl)-pyrrolidine, sodium hydroxide, triethanolamine (2,2',2''-nitrilotris(ethanol)), tromethamine, zinc hydroxide, acetic acid, 2,2-dichloro-acetic acid, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 2,5-dihydroxybenzoic acid, 4-acetamido-benzoic acid, (+)-camphoric acid, (+)-camphor-10-sulfonic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, decanoic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, ethylenediaminetetraacetic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, D-glucoheptonic acid, D-gluconic acid, D-glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycine, glycolic acid, hexanoic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, DL-lactic acid, lactobionic acid, lauric acid, lysine, maleic acid, (-)-L-malic acid, malonic acid, DL-mandelic acid, methanesulfonic acid, galactaric acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, octanoic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid (embonic acid), phosphoric acid, propionic acid, (-)-L-pyroglutamic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid and undecylenic acid. Further pharmaceutically acceptable salts can be formed with cations from metals such as aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and the like (see Pharmaceutical salts, Berge, S. M. *et al.*, *J. Pharm. Sci.*, (1977), Vol.66, pp.1-19).

[0075] Pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical

methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a sufficient amount of the appropriate base or acid in water or in an organic diluent like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile, or a mixture thereof.

[0076] Salts of other acids than those mentioned above which for example are useful for purifying or isolating the compounds of the present invention (*e.g.* trifluoro acetate salts), also comprise a part of the invention.

[0077] Typically, a pharmaceutically acceptable salt of a compound of formula I may be readily prepared by using a desired acid or base as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. For example, an aqueous solution of an acid such as hydrochloric acid may be added to an aqueous suspension of a compound of formula I and the resulting mixture evaporated to dryness (lyophilized) to obtain the acid addition salt as a solid. Alternatively, a compound of formula I may be dissolved in a suitable solvent, for example an alcohol such as isopropanol, and the acid may be added in the same solvent or another suitable solvent. The resulting acid addition salt may then be precipitated directly, or by addition of a less polar solvent such as diisopropyl ether or hexane, and isolated by filtration.

[0078] The acid addition salts of the compounds of formula I may be prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for purposes of the invention.

[0079] Also included are both total and partial salts, that is to say salts with 1, 2 or 3, preferably 2, equivalents of base per mole of acid of formula I or salts with 1, 2 or 3 equivalents, preferably 1 equivalent, of acid per mole of base of formula I.

[0080] Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are

N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine.

[0081] The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid.

[0082] Compounds of the invention may have both a basic and an acidic centre and may therefore be in the form of zwitterions or internal salts.

[0083] Typically, a pharmaceutically acceptable salt of a compound of formula I may be readily prepared by using a desired acid or base as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. For example, an aqueous solution of an acid such as hydrochloric acid may be added to an aqueous suspension of a compound of formula I and the resulting mixture evaporated to dryness (lyophilized) to obtain the acid addition salt as a solid. Alternatively, a compound of formula I may be dissolved in a suitable solvent, for example an alcohol such as isopropanol, and the acid may be added in the same solvent or another suitable solvent. The resulting acid addition salt may then be precipitated directly, or by addition of a less polar solvent such as diisopropyl ether or hexane, and isolated by filtration.

[0084] Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvates of the compound of the invention are within the scope of the invention. The salts of the compound of formula I may form solvates (*e.g.*, hydrates) and the invention also includes all such solvates. The meaning of the word "solvates" is well known to those skilled in the art as a compound formed by interaction of a solvent and a solute (*i.e.*, solvation). Techniques for the preparation of solvates are well established in the art (see, for example, Brittain. *Polymorphism in Pharmaceutical solids.* Marcel Decker, New York, 1999.).

[0085] The invention also encompasses N-oxides of the compounds of formula I. The term "N-oxide" means that for heterocycles containing an otherwise unsubstituted sp^2 N atom, the

N atom may bear a covalently bound O atom, *i.e.*, -N→O. Examples of such N-oxide substituted heterocycles include pyridyl N-oxides, pyrimidyl N-oxides, pyrazinyl N-oxides and pyrazolyl N-oxides.

[0086] The invention also encompasses prodrugs of the compounds of formula I, *i.e.*, compounds which release an active parent drug according to formula I *in vivo* when administered to a mammalian subject. A prodrug is a pharmacologically active or more typically an inactive compound that is converted into a pharmacologically active agent by a metabolic transformation. Prodrugs of a compound of formula I are prepared by modifying functional groups present in the compound of formula I in such a way that the modifications may be cleaved *in vivo* to release the parent compound. *In vivo*, a prodrug readily undergoes chemical changes under physiological conditions (*e.g.*, are acted on by naturally occurring enzyme(s)) resulting in liberation of the pharmacologically active agent. Prodrugs include compounds of formula I wherein a hydroxy, amino, or carboxy group of a formula I compound is bonded to any group that may be cleaved in vivo to regenerate the free hydroxyl, amino or carboxy group, respectively. Examples of prodrugs include esters (*e.g.*, acetate, formate, and benzoate derivatives) of compounds of formula I or any other derivative which upon being brought to the physiological pH or through enzyme action is converted to the active parent drug. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described in the art (see, for example, Bundgaard. *Design of Prodrugs*. Elsevier, 1985).

[0087] Prodrugs may be administered in the same manner as and in effective amounts analogous to the active ingredient to which they convert or they may be delivered in a reservoir form, *e.g.*, a transdermal patch or other reservoir which is adapted to permit (by provision of an enzyme or other appropriate reagent) conversion of a prodrug to the active ingredient slowly over time, and delivery of the active ingredient to the patient.

[0088] The invention also encompasses metabolites. A "metabolite" of a compound disclosed herein is a derivative of a compound which is formed when the compound is metabolised. The term "active metabolite" refers to a biologically active derivative of a compound which is formed when the compound is metabolized. The term "metabolized" refers to the sum of the processes by which a particular substance is changed in the living body.

In brief, all compounds present in the body are manipulated by enzymes within the body in order to derive energy and/or to remove them from the body. Specific enzymes produce specific structural alterations to the compound. For example, cytochrome P450 catalyses a variety of oxidative and reductive reactions while uridine diphosphate glucuronyltransferases catalyse the transfer of an activated glucuronic-acid molecule to aromatic alcohols, aliphatic alcohols, carboxylic acids, amines and free sulphydryl groups. Further information on metabolism may be obtained from *The Pharmacological Basis of Therapeutics*, 9th Edition, McGraw-Hill (1996), pages 11-17.

[0089] Metabolites of the compounds disclosed herein can be identified either by administration of compounds to a host and analysis of tissue samples from the host, or by incubation of compounds with hepatic cells in vitro and analysis of the resulting compounds. Both methods are well known in the art.

[0090] The term "carrier" refers to a diluent, excipient, and/or vehicle with which an active compound is administered. The pharmaceutical compositions of the invention may contain combinations of more than one carrier. Such pharmaceutical carriers can be sterile liquids, such as water, saline solutions, aqueous dextrose solutions, aqueous glycerol solutions, and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water or aqueous solution saline solutions and aqueous dextrose and glycerol solutions are preferably employed as carriers, particularly for injectable solutions. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin, 18th Edition.

[0091] A "pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes an excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the present application includes both one and more than one such excipient.

[0092] The compounds of the invention may be formulated for administration in any convenient way for use in human or veterinary medicine and the invention therefore includes within its scope pharmaceutical compositions comprising a compound of the invention adapted

for use in human or veterinary medicine. Such compositions may be presented for use in a conventional manner with the aid of one or more suitable carriers. Acceptable carriers for therapeutic use are well-known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co. (A. R. Gennaro edit. 1985). The choice of pharmaceutical carrier can be selected with regard to the intended route of administration and standard pharmaceutical practice. The pharmaceutical compositions may comprise as, in addition to, the carrier any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s), and/or solubilizing agent(s).

Pharmaceutical Compositions Comprising a Compound of Formula I

[0093] While it is possible that a compound I may be administered as the bulk substance, it is preferable to present the active ingredient in a pharmaceutical formulation, *e.g.*, wherein the agent is in admixture with a pharmaceutically acceptable carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

[0094] Accordingly, the invention further provides a pharmaceutical composition comprising a compound of formula I or a solvate, hydrate, isomer (e.g., enantiomer, diastereomer, etc.), N-oxide or pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier. The term "carrier" refers to a diluent, excipient, and/or vehicle with which an active compound is administered.

[0095] A compound of formula I may be used in combination with other therapies and/or active agents. Accordingly, the invention provides, in a further aspect, a pharmaceutical composition comprising a compound of formula I or a solvate, hydrate, isomer (e.g., enantiomer, diastereomer, etc.), N-oxide or pharmaceutically acceptable salt thereof, a second active agent, and a pharmaceutically acceptable carrier.

[0096] The pharmaceutical compositions may comprise as, in addition to, the carrier any suitable binder, lubricant, suspending agent, coating agent and/or solubilizing agent.

[0097] Preservatives, stabilizers, dyes and flavouring agents also may be provided in the pharmaceutical composition. Antioxidants and suspending agents may be also used.

[0098] The compounds of the invention may be reduced to fine particulate form (e.g., milled using known milling procedures such as wet milling) to obtain a particle size

appropriate for tablet formation and for other formulation types. Finely divided (nanoparticulate) preparations of the compounds of the invention may be prepared by processes known in the art, for example see WO02/00196.

Routes of Administration and Unit Dosage Forms

[0099] The routes for administration include oral (*e.g.*, as a tablet, capsule, or as an ingestible solution), topical, mucosal (*e.g.*, as a nasal spray or aerosol for inhalation), nasal, parenteral (*e.g.*, by an injectable form), gastrointestinal, intraspinal, intraperitoneal, intramuscular, intravenous, intrauterine, intraocular, intradermal, intracranial, intrathecal, intratracheal, intravaginal, intracerebroventricular, intracerebral, subcutaneous, ophthalmic (including intravitreal or intracameral), transdermal, rectal, buccal, epidural and sublingual. The compositions of the invention may be especially formulated for any of those administration routes. In preferred embodiments, the pharmaceutical compositions of the invention are formulated in a form that is suitable for oral delivery.

[00100] There may be different composition/formulation requirements depending on the different delivery systems. It is to be understood that not all of the compounds need to be administered by the same route. Likewise, if the composition comprises more than one active component, then those components may be administered by different routes. By way of example, the pharmaceutical composition of the invention may be formulated to be delivered using a mini-pump or by a mucosal route, for example, as a nasal spray or aerosol for inhalation or ingestible solution, or parenterally in which the composition is formulated by an injectable form, for delivery, by, for example, an intravenous, intramuscular or subcutaneous route. Alternatively, the formulation may be designed to be delivered by multiple routes.

[00101] Where the agent is to be delivered mucosally through the gastrointestinal mucosa, it should be able to remain stable during transit though the gastrointestinal tract; for example, it should be resistant to proteolytic degradation, stable at acid pH and resistant to the detergent effects of bile. For example, the compound of Formula I may be coated with an enteric coating layer. The enteric coating layer material may be dispersed or dissolved in either water or in a suitable organic solvent. As enteric coating layer polymers, one or more, separately or in combination, of the following can be used; *e.g.*, solutions or dispersions of methacrylic acid

copolymers, cellulose acetate phthalate, cellulose acetate butyrate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating layer polymer(s). For environmental reasons, an aqueous coating process may be preferred. In such aqueous processes methacrylic acid copolymers are most preferred.

[00102] When appropriate, the pharmaceutical compositions can be administered by inhalation, in the form of a suppository or pessary, topically in the form of a lotion, solution, cream, ointment or dusting powder, by use of a skin patch, orally in the form of tablets containing excipients such as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs, solutions or suspensions containing flavouring or colouring agents, or they can be injected parenterally, for example intravenously, intramuscularly or subcutaneously. For buccal or sublingual administration, the compositions may be administered in the form of tablets or lozenges, which can be formulated in a conventional manner.

[00103] When the composition of the invention is to be administered parenterally, such administration includes one or more of: intravenously, intraarterially, intraperitoneally, intrathecally, intraventricularly, intraurethrally, intrasternally, intracranially, intramuscularly or subcutaneously administering the agent; and/or by using infusion techniques.

[00104] Pharmaceutical compositions of the invention can be administered parenterally, *e.g.*, by infusion or injection. Pharmaceutical compositions suitable for injection or infusion may be in the form of a sterile aqueous solution, a dispersion or a sterile powder that contains the active ingredient, adjusted, if necessary, for preparation of such a sterile solution or dispersion suitable for infusion or injection. This preparation may optionally be encapsulated into liposomes. In all cases, the final preparation must be sterile, liquid, and stable under production and storage conditions. To improve storage stability, such preparations may also contain a preservative to prevent the growth of microorganisms. Prevention of the action of micro-organisms can be achieved by the addition of various antibacterial and antifungal agents, *e.g.*, paraben, chlorobutanol, sodium acetate, sodium lactate, sodium citrate or acsorbic acid. In many cases isotonic substances are recommended, *e.g.*, sugars, buffers and sodium chloride to assure osmotic pressure similar to those of body fluids, particularly blood. Prolonged

absorption of such injectable mixtures can be achieved by introduction of absorption-delaying agents, such as aluminium monostearate or gelatin.

[00105] Dispersions can be prepared in a liquid carrier or intermediate, such as glycerin, liquid polyethylene glycols, triacetin oils, and mixtures thereof. The liquid carrier or intermediate can be a solvent or liquid dispersive medium that contains, for example, water, ethanol, a polyol (*e.g.*, glycerol, propylene glycol or the like), vegetable oils, non-toxic glycerine esters and suitable mixtures thereof. Suitable flowability may be maintained, by generation of liposomes, administration of a suitable particle size in the case of dispersions, or by the addition of surfactants.

[00106] For parenteral administration, the compound is best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

[00107] Sterile injectable solutions can be prepared by mixing a compound of formula I with an appropriate solvent and one or more of the aforementioned carriers, followed by sterile filtering. In the case of sterile powders suitable for use in the preparation of sterile injectable solutions, preferable preparation methods include drying in vacuum and lyophilization, which provide powdery mixtures of the aldosterone receptor antagonists and desired excipients for subsequent preparation of sterile solutions.

[00108] The compounds according to the invention may be formulated for use in human or veterinary medicine by injection (*e.g.*, by intravenous bolus injection or infusion or *via* intramuscular, subcutaneous or intrathecal routes) and may be presented in unit dose form, in ampoules, or other unit-dose containers, or in multi-dose containers, if necessary with an added preservative. The compositions for injection may be in the form of suspensions, solutions, or emulsions, in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing, solubilizing and/or dispersing agents. Alternatively, the active ingredient may be in sterile powder form for reconstitution with a suitable vehicle, *e.g.*, sterile, pyrogen-free water, before use.

[00109] The compounds of the invention can be administered (*e.g.*, orally or topically) in the form of tablets, capsules, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, modified-, sustained-, pulsed-or controlled-release applications.

[00110] The compounds of the invention may also be presented for human or veterinary use in a form suitable for oral or buccal administration, for example in the form of solutions, gels, syrups, mouth washes or suspensions, or a dry powder for constitution with water or other suitable vehicle before use, optionally with flavouring and colouring agents. Solid compositions such as tablets, capsules, lozenges, pastilles, pills, boluses, powder, pastes, granules, bullets or premix preparations may also be used. Solid and liquid compositions for oral use may be prepared according to methods well-known in the art. Such compositions may also contain one or more pharmaceutically acceptable carriers and excipients which may be in solid or liquid form.

[00111] The tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), sodium starch glycolate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia.

[00112] Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

[00113] The compositions may be administered orally, in the form of rapid or controlled release tablets, microparticles, mini tablets, capsules, sachets, and oral solutions or suspensions, or powders for the preparation thereof. In addition to the new solid-state forms of pantoprazole of the invention as the active substance, oral preparations may optionally include various standard pharmaceutical carriers and excipients, such as binders, fillers, buffers, lubricants, glidants, dyes, disintegrants, odourants, sweeteners, surfactants, mold release agents, antiadhesive agents and coatings. Some excipients may have multiple roles in the compositions, *e.g.*, act as both binders and disintegrants.

[00114] Examples of pharmaceutically acceptable disintegrants for oral compositions include starch, pre-gelatinized starch, sodium starch glycolate, sodium carboxymethylcellulose, croscarmellose sodium, microcrystalline cellulose, alginates, resins, surfactants, effervescent compositions, aqueous aluminum silicates and cross-linked polyvinylpyrrolidone.

[00115] Examples of pharmaceutically acceptable binders for oral compositions include acacia; cellulose derivatives, such as methylcellulose, carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose or hydroxyethylcellulose; gelatin, glucose, dextrose, xylitol, polymethacrylates, polyvinylpyrrolidone, sorbitol, starch, pre-gelatinized starch, tragacanth, xanthane resin, alginates, magnesium–aluminum silicate, polyethylene glycol or bentonite.

[00116] Examples of pharmaceutically acceptable fillers for oral compositions include lactose, anhydrolactose, lactose monohydrate, sucrose, dextrose, mannitol, sorbitol, starch, cellulose (particularly microcrystalline cellulose), dihydro- or anhydro-calcium phosphate, calcium carbonate and calcium sulphate.

[00117] Examples of pharmaceutically acceptable lubricants useful in the compositions of the invention include magnesium stearate, talc, polyethylene glycol, polymers of ethylene oxide, sodium lauryl sulphate, magnesium lauryl sulphate, sodium oleate, sodium stearyl fumarate, and colloidal silicon dioxide.

[00118] Examples of suitable pharmaceutically acceptable odourants for the oral compositions include synthetic aromas and natural aromatic oils such as extracts of oils, flowers, fruits (*e.g.*, banana, apple, sour cherry, peach) and combinations thereof, and similar aromas. Their use depends on many factors, the most important being the organoleptic acceptability for the population that will be taking the pharmaceutical compositions.

[00119] Examples of suitable pharmaceutically acceptable dyes for the oral compositions include synthetic and natural dyes such as titanium dioxide, beta-carotene and extracts of grapefruit peel.

[00120] Examples of useful pharmaceutically acceptable coatings for the oral compositions, typically used to facilitate swallowing, modify the release properties, improve the appearance,

and/or mask the taste of the compositions include hydroxypropylmethylcellulose, hydroxypropylcellulose and acrylate-methacrylate copolymers.

[00121] Examples of pharmaceutically acceptable sweeteners for the oral compositions include aspartame, saccharin, saccharin sodium, sodium cyclamate, xylitol, mannitol, sorbitol, lactose and sucrose.

[00122] Examples of pharmaceutically acceptable buffers include citric acid, sodium citrate, sodium bicarbonate, dibasic sodium phosphate, magnesium oxide, calcium carbonate and magnesium hydroxide.

[00123] Examples of pharmaceutically acceptable surfactants include sodium lauryl sulphate and polysorbates.

[00124] Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the agent may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

[00125] The compounds of the invention may also, for example, be formulated as suppositories *e.g.*, containing conventional suppository bases for use in human or veterinary medicine or as pessaries *e.g.*, containing conventional pessary bases.

[00126] The compounds according to the invention may be formulated for topical administration, for use in human and veterinary medicine, in the form of ointments, creams, gels, hydrogels, lotions, solutions, shampoos, powders (including spray or dusting powders), pessaries, tampons, sprays, dips, aerosols, drops (*e.g.*, eye ear or nose drops) or pour-ons.

[00127] For application topically to the skin, the agent of the invention can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol, and water. Such compositions may also contain other pharmaceutically acceptable excipients, such as polymers, oils, liquid carriers,

surfactants, buffers, preservatives, stabilizers, antioxidants, moisturizers, emollients, colourants, and odourants.

[00128] Examples of pharmaceutically acceptable polymers suitable for such topical compositions include acrylic polymers; cellulose derivatives, such as carboxymethylcellulose sodium, methylcellulose or hydroxypropylcellulose; natural polymers, such as alginates, tragacanth, pectin, xanthan and cytosan.

[00129] Examples of suitable pharmaceutically acceptable oils which are so useful include mineral oils, silicone oils, fatty acids, alcohols, and glycols.

[00130] Examples of suitable pharmaceutically acceptable liquid carriers include water, alcohols or glycols such as ethanol, isopropanol, propylene glycol, hexylene glycol, glycerol and polyethylene glycol, or mixtures thereof in which the pseudopolymorph is dissolved or dispersed, optionally with the addition of non-toxic anionic, cationic or non-ionic surfactants, and inorganic or organic buffers.

[00131] Examples of pharmaceutically acceptable preservatives include sodium benzoate, ascorbic acid, esters of p-hydroxybenzoic acid and various antibacterial and antifungal agents such as solvents, for example ethanol, propylene glycol, benzyl alcohol, chlorobutanol, quaternary ammonium salts, and parabens (such as methyl paraben, ethyl paraben and propyl paraben).

[00132] Examples of pharmaceutically acceptable stabilizers and antioxidants include ethylenediaminetetraacetic acid (EDTA), thiourea, tocopherol and butyl hydroxyanisole.

[00133] Examples of pharmaceutically acceptable moisturizers include glycerine, sorbitol, urea and polyethylene glycol.

[00134] Examples of pharmaceutically acceptable emollients include mineral oils, isopropyl myristate, and isopropyl palmitate.

[00135] The compounds may also be dermally or transdermally administered, for example, by use of a skin patch.

[00136] For ophthalmic use, the compounds can be formulated as micronized suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as a benzylalkonium chloride.

[00137] As indicated, the compounds of the invention can be administered intranasally or by inhalation and is conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurized container, pump, spray or nebulizer with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134AT) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA), carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container, pump, spray or nebulizer may contain a solution or suspension of the active compound, *e.g.*, using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, *e.g.*, sorbitan trioleate.

[00138] Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound and a suitable powder base such as lactose or starch.

[00139] For topical administration by inhalation the compounds according to the invention may be delivered for use in human or veterinary medicine *via* a nebulizer.

[00140] The pharmaceutical compositions of the invention may contain from 0.01 to 99% weight per volume of the active material. For topical administration, for example, the composition will generally contain from 0.01-10%, more preferably 0.01-1% of the active material.

[00141] The active agents can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

[00142] The pharmaceutical composition or unit dosage form of the invention may be administered according to a dosage and administration regimen defined by routine testing in the light of the guidelines given above in order to obtain optimal activity while minimizing toxicity or side effects for a particular patient. However, such fine tuning of the therapeutic regimen is routine in the light of the guidelines given herein.

[00143] The dosage of the active agents of the invention may vary according to a variety of factors such as underlying disease conditions, the individual's condition, weight, gender and

age, and the mode of administration. An effective amount for treating a disorder can easily be determined by empirical methods known to those of ordinary skill in the art, for example by establishing a matrix of dosages and frequencies of administration and comparing a group of experimental units or subjects at each point in the matrix. The exact amount to be administered to a patient will vary depending on the state and severity of the disorder and the physical condition of the patient. A measurable amelioration of any symptom or parameter can be determined by a person skilled in the art or reported by the patient to the physician.

[00144] The amount of the agent to be administered can range between about 0.01 and about 25 mg/kg/day, preferably between about 0.1 and about 10 mg/kg/day and most preferably between 0.2 and about 5 mg/kg/day. It will be understood that the pharmaceutical formulations of the invention need not necessarily contain the entire amount of the agent that is effective in treating the disorder, as such effective amounts can be reached by administration of a plurality of doses of such pharmaceutical formulations. In general, an "effective amount" refers to the amount of a pharmaceutical composition administered to improve, inhibit, or ameliorate a disease or disorder or condition of a subject, or a symptom of a disease or disorder, in a clinically relevant manner. Any clinically relevant improvement in the subject is considered sufficient to achieve treatment. Preferably, an amount sufficient to treat is an amount that prevents the occurrence or one or more symptoms of the infection or is an amount that reduces the severity of, or the length of time during which a subject suffers from, or develops, one or more symptoms of the infection relative to a control subject that is not treated with a composition of the invention).

[00145] In a preferred embodiment of the invention, the compounds according to formula I are formulated in capsules or tablets, preferably containing 10 to 200 mg of the compounds of the invention, and are preferably administered to a patient at a total daily dose of 10 to 300 mg, preferably 20 to 150 mg and most preferably about 50 mg.

[00146] A pharmaceutical composition for parenteral administration contains from about 0.01% to about 100% by weight of the active agents of the invention, based upon 100% weight of total pharmaceutical composition.

[00147] Generally, transdermal dosage forms contain from about 0.01% to about 100% by weight of the active agents versus 100% total weight of the dosage form.

[00148] The pharmaceutical composition or unit dosage form may be administered in a single daily dose, or the total daily dosage may be administered in divided doses. In addition, co-administration or sequential administration of another compound for the treatment of the disorder may be desirable. To this purpose, the combined active principles are formulated into a simple dosage unit.

[00149] For combination treatment where the compounds are in separate dosage formulations, the compounds can be administered concurrently, or each can be administered at staggered intervals. Additional compounds may be administered at specific intervals too. The order of administration will depend upon a variety of factors including age, weight, gender and medical condition of the patient; the severity and aetiology of the disorders to be treated, the route of administration, the renal and hepatic function of the patient, the treatment history of the patient, and the responsiveness of the patient. Determination of the order of administration may be fine-tuned and such fine-tuning is routine in the light of the guidelines given herein.

DESCRIPTION OF THE INVENTION

Synthesis

[00150] Compounds of formula I, or indeed those of formulae 1a through 1g, and enantiomers, diastereomers, N-oxides, and pharmaceutically acceptable salts thereof, may be prepared by the general methods outlined hereinafter, said methods constituting a further aspect of the invention.

[00151] The compounds of this invention can be prepared by employing reactions as shown in the following schemes, in addition to other standard manipulations that are known in the literature, exemplified in the experimental section or clear to one skilled in the art. The starting materials which are not described herein are either commercially available or may be prepared by employing reactions described in the literature or are clear to one skilled in the art. The following examples are provided so that the invention might be more fully understood, are illustrative only, and should not be construed as limiting.

[00152] It will be appreciated by those skilled in the art that it may be desirable to use protected derivatives of intermediates used in the preparation of the compounds according to

formula I. Protection and deprotection of functional groups may be performed by methods known in the art (see, for example, Green and Wuts *Protective Groups in Organic Synthesis.* John Wiley and Sons, New York, 1999).

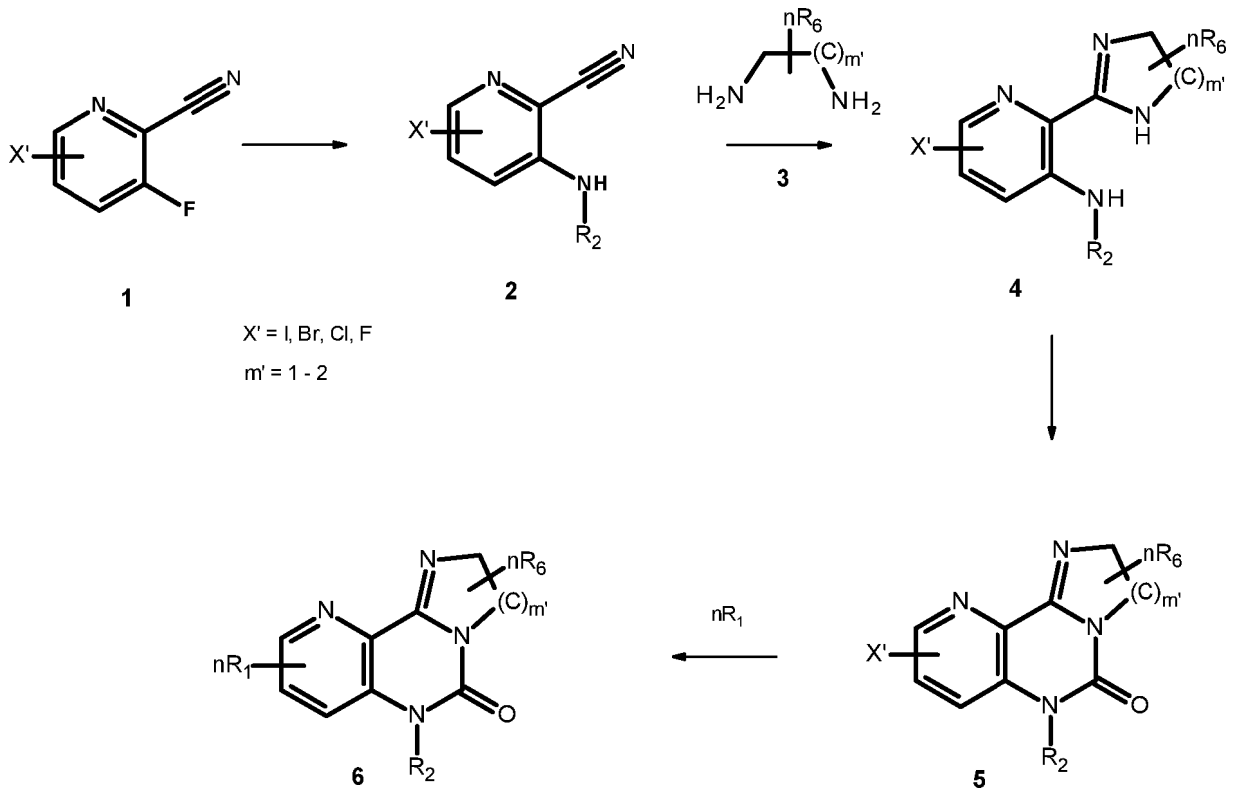
[00153] The abbreviation PG describes a "protecting group" which is introduced to a reactive group before a certain manipulation is carried out, and which is later removed. Examples of PG's for protecting a reactive group include: acetyl-, trifluoracetyl-, benzoyl-, ethoxycarbonyl-, N-tert-butoxycarbonyl- (BOC), N-benzyloxycarbonyl- (Cbz), benzyl-, methoxybenzyl-, 2,4-dimethoxybenzyl- and for amino groups additionally the phthalyl- group for amino-alkylamino or imino groups; N-methoxynethyl- (MOM), N-benzyloxymethyl- (BOM), N-(trimethylsilyl)ethoxymethyl- (SEM), N-tert-butyl-dimethylsiloxymethyl-, N-tert-butyl-dimethylsilyl- (TBDMS), N-triisopropylsilyl- (TIPS), N-benzyl-, N-4-methoxybenzyl (PMB), N-triphenylmethyl- (Tr), N-tert-butoxycarbonyl- (BOC), N-benzyloxycarbonyl- (Cbz) or N-trimethylsilylethylsulfonyl- (SES) for amide groups; methoxy-, benzyloxy-, trimethylsilyl- (TMS), acetyl-, benzoyl-, tert-butyl-, trityl-, benzyl-, or tetrahydropyranyl (THP) groups for hydroxy groups; or trimethylsilyl- (TMS), methyl-ethyl-, tert-butyl-, benzyl-, or tetrahydropyranyl (THP) groups for carboxyl groups.

[00154] The compounds of the invention are generally prepared according to the following different schemes. In some cases, the final product may be further modified, for example by manipulation of substituents. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art. In some cases, the order of carrying out the foregoing reaction schemes may be varied in order to facilitate the reaction or to avoid unwanted reaction products. The following examples are provided so that the invention might be more fully understood. These examples are illustrative only and should not be constructed as limiting the invention in any way.

[00155] As shown in Scheme 1 below, commercially available compounds **1** can be selectively converted by nucleophilic aromatic substitution or alternatively by reductive amination into 3-(R_2-amino)-5-bromopyridine-2-carbonitrile (**2**) by using consolidated methodologies well known to people skilled in the art. In turn **2** is condensed with the requisite diamines (**3**) to obtain 2-(4,5-dihydro-1H-imidazol-2-yl)- or 2-(1,4,5,6-tetrahydropyrimidin-2-

yl) derivatives of R_2-N-5-bromo-pyridin-3-amine N-methyl-pyridin-3-amine (**4**). In the next step compounds **4** are then cyclized by reactant to afford the corresponding compounds **5**, which are finally reacted to produce R_1-substituted intermediates directly to obtain compounds falling under the scope of formula 1a or 1e. This last derivatization procedure can be carried out using standard methods such us *e.g.* Buchwald reactions, acylation reactions, alkylation or any kind of N-derivatization reaction useful to the aim of forming compounds according to formula 1a and 1e, and is very well known to people skilled in the art. The same reaction steps can be rearranged, anticipating or postponing each step in the synthesis without any limitation, *e.g.* the Buchwald reaction can be carried out as a last step, or alternatively as a first step in the entire procedure.

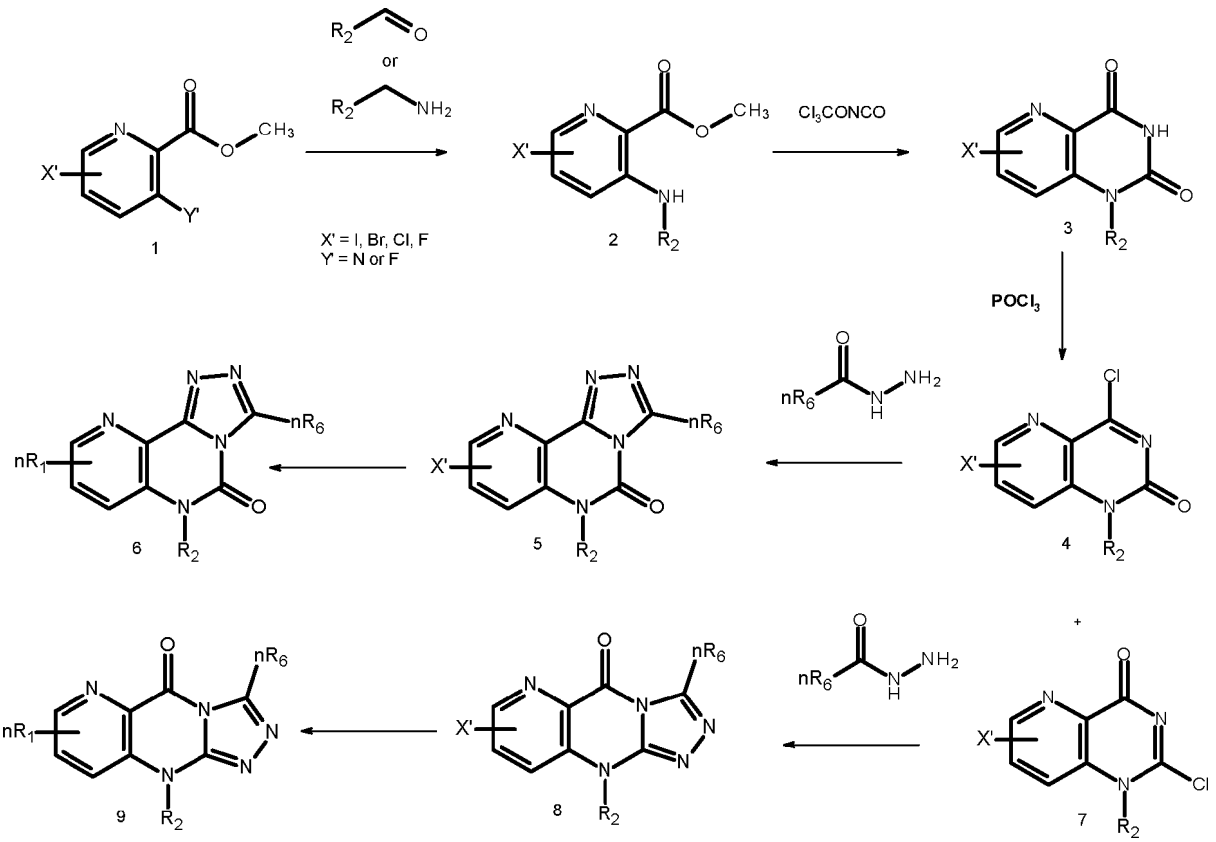
[00156] For Scheme 1 below, the skilled person will appreciate that compounds **4** to **6** illustrate the possibility that the nR_6-substituent containing ring may be a five- or six-membered heterocyclic ring comprising two nitrogen atoms, following the reaction with compound **3**. This arises when integer m' comprises a value of 1 or 2 and provides for group $-(C)_{m'}-$ being a single methylene-bridge carbon atom, or a pair of methylene-bridge carbon atoms in sequence, the heterocyclic ring so-produced being an imidazoline or a pyrimidine derivative respectively. Imidazoline derivatives are illustrated by formula 1a and comprise compounds 1 to 69 as shown in Table 1, and pyrimidine derivatives are illustrated by formula 1e and comprise compounds 141 to 155 as shown in Table 4.



Scheme 1: Production of compounds according to formula 1a and 1e.

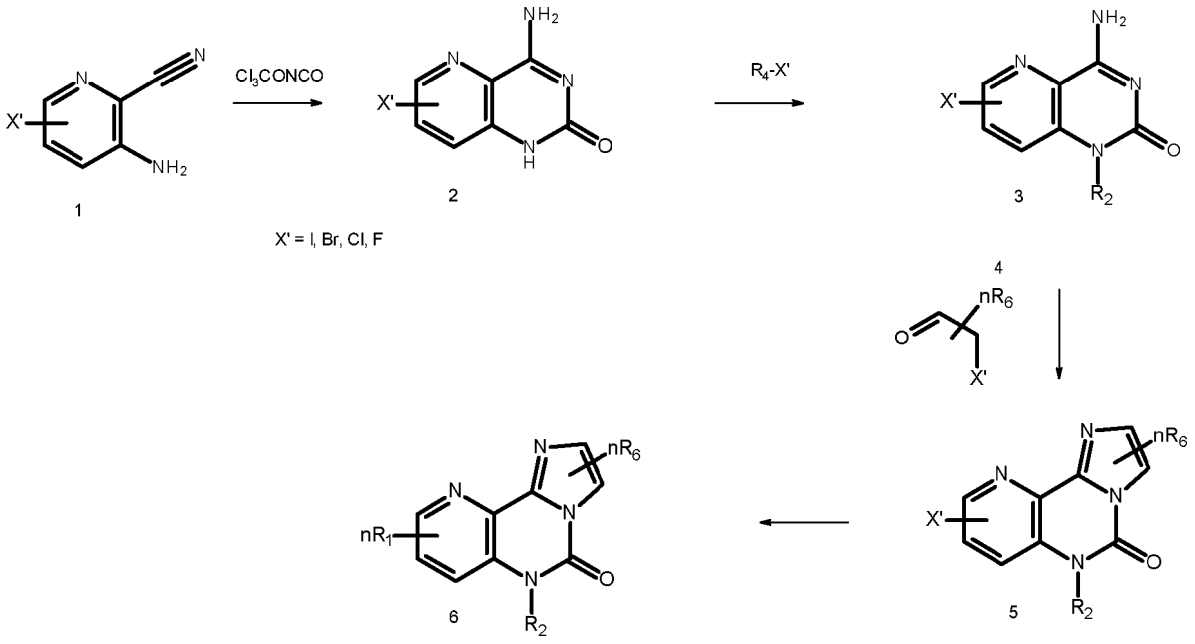
[00157] As shown in Scheme 2 below, commercially available compounds **1** can be converted by nucleophilic aromatic substitution, or alternatively by reductive amination, with the respective amino or aldehyde derivatives into methyl 3-(R_2-amino)-5-halopyridine-2-carboxylate (**2**) by using consolidated methodologies well known to people skilled in the art. In the next step compounds **2** are then cyclized by reactants to afford the corresponding compounds **3**, which are reacted with $POCl_3$ to obtain compounds of formulae **4** and **7**. In turn **4** is cyclized with the requisite hydrazide derivatives to obtain substituted 3,4,6,8,13-pentazatricyclo[7.4.0.02,6]trideca-1(9),2,4,10,12-pentaen-7-one derivatives (**5**). In the last step compounds with the halogen derivative (group X') **5** are finally reacted to produce R_1-substituted intermediates directly to obtain compounds falling under the scope of formula 1c. This last derivatization procedure can be carried out using standard methods such us *e.g.* Buchwald reactions, aromatic nucleophilic reactions, acylation reactions, alkylation or any kind of N-derivatization reaction useful to the aim of forming compounds **6** according to

formula 1c, and is very well known to people skilled in the art. Scheme 2 also shows that compound **7** is cyclized with the requisite hydrazide derivatives to obtain substituted 2,4,5,7,10-pentazatricyclo[7.4.0.03,7]trideca-1(13),3,5,9,11-pentaen-8-one derivatives (**8**). In the last step compounds with the halogen derivative (group X') **8** are finally reacted to produce R_1-substituted intermediates directly to obtain compounds **9** falling under the scope of formula 1f. This last derivatization procedure can be carried out using standard methods such us *e.g.* Buchwald reactions, aromatic nucleophilic reactions, acylation reactions, alkylation or any kind of N-derivatization reaction useful to the aim of forming compounds according to formula 1f, and is very well known to people skilled in the art. The same reaction steps can be rearranged, anticipating or postponing each step in the synthesis without any limitation, *e.g.* the Buchwald reaction can be carried out as a last step, or alternatively as a first step in the entire procedure.



Scheme 2: Production of compounds according to formula 1c and 1f.

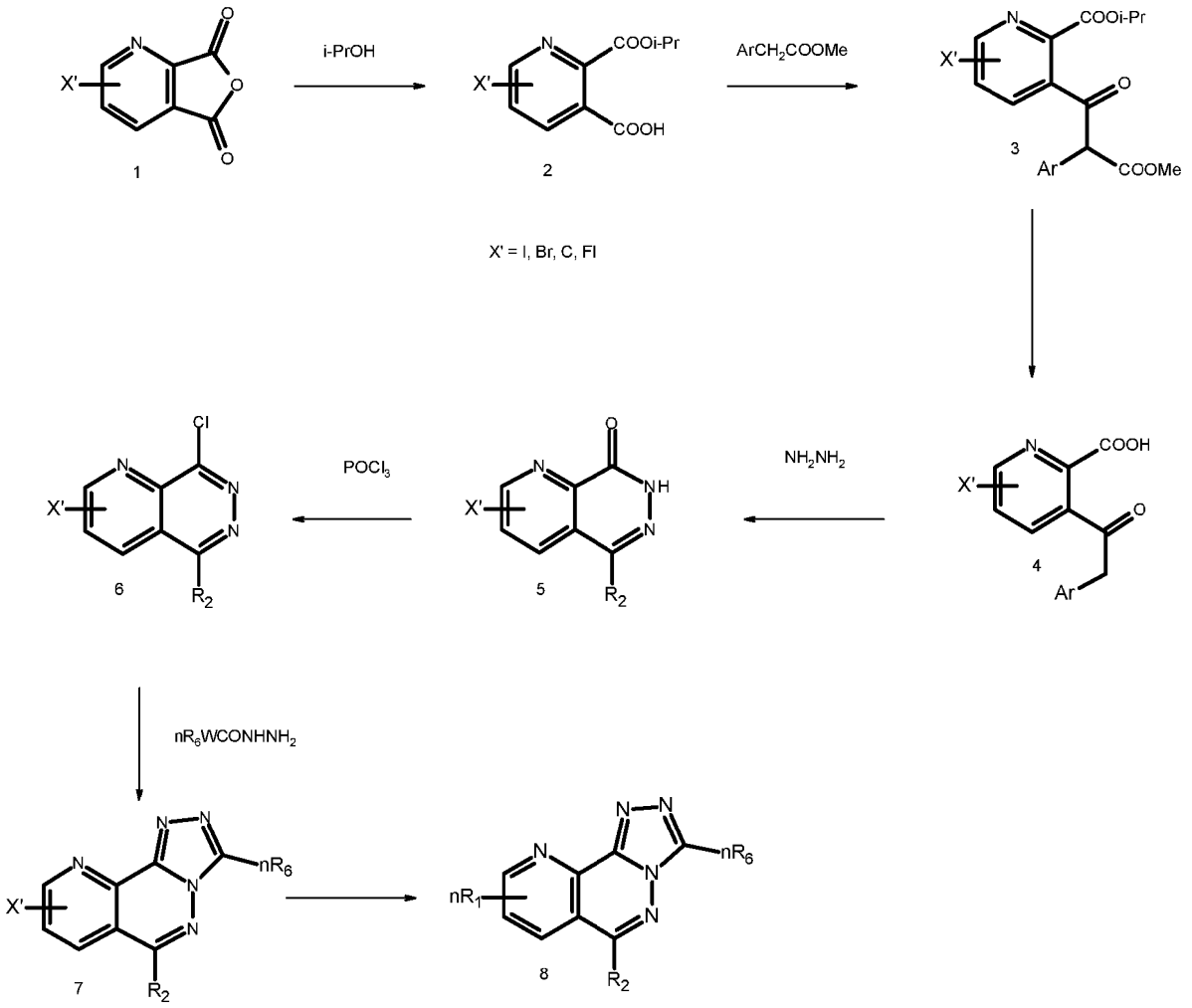
[00158] As shown in Scheme 3 below commercially available compounds **1** can be cyclized by with reactants into 4-amino-6-halo-1H-pyrido[3,2-d]pyrimidin-2-one (**2**). In the next step compounds **2** are then reacted with the reagent to afford the corresponding compounds **3**, which are cyclized with **4** to obtain compounds **5**. In turn **5** are finally reacted to produce R_1-substituted intermediates directly to obtain compounds falling under the scope of formula 1b. This last derivatization procedure can be carried out using standard methods such us *e.g.* Buchwald reactions, aromatic nucleophilic reactions, acylation reactions, alkylation or any kind of N-derivatization reaction useful to the aim of forming compounds according to formula 1b, and is very well known to people skilled in the art. The same reaction steps can be rearranged, anticipating or postponing each step in the synthesis without any limitation, *e.g.* the Buchwald reaction can be carried out as a last step, or alternatively as a first step in the entire procedure.



Scheme 3: Production of compounds according to formula 1b.

[00159] As shown in Scheme 4 below commercially available compound **1** can be reacted with isopropanol to afford 5-bromo-2-isopropoxycarbonyl-pyridine-3-carboxylic acid (**2**). In

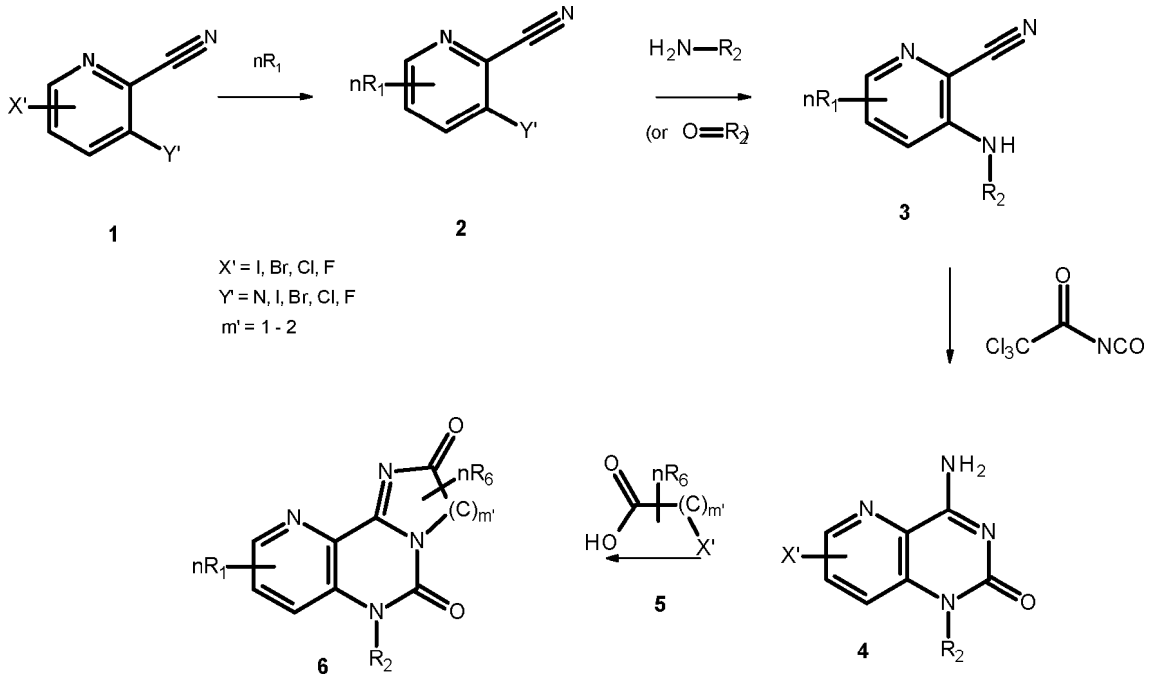
the next step compounds **2** are then reacted with methyl 2-arylacetate to afford the corresponding compounds **3**, which are hydrolysed into **4**. In turn **4** is reacted with hydrazine to obtain compounds **5**. In the next step **5** is reacted with $POCl_3$ to obtain compounds **6**, which are reacted with the requisite hydrazide derivatives affording compounds **7**. Compounds **7** are finally reacted to produce R_1-substituted intermediates directly to obtain compounds falling under the scope of formula 1d. This last derivatization procedure can be carried out using standard methods such us *e.g.* Buchwald reactions, aromatic nucleophilic reactions, acylation reactions, alkylation or any kind of N-derivatization reaction useful to the aim of forming compounds according to formula 1d, and very well known to people skilled in the art. The same reaction steps can be rearranged, anticipating or postponing each step in the synthesis without any limitation, *e.g.* the Buchwald reaction can be carried out as a last step, or alternatively as a first step in the entire procedure.



Scheme 4: Production of compounds according to formula 1d.

[00160] As shown in Scheme 5 below, commercially available compounds **1** can be reacted to produce R_1-substituted intermediates **2** by standard methods such as *e.g.* Buchwald reactions, aromatic nucleophilic reactions, alkylation or any kind of N-derivatization reactions useful to the aim of forming compounds of formula **2,** and very well known to people skilled in the art. The obtained intermediate **2** can be reacted, according Y', by standard methods such as *e.g.* aromatic nucleophilic reactions, reductive amination, Buchwald reactions or any kind of N-derivatization reaction useful to the aim of obtaining the corresponding compounds **3**, which can be cyclized into compounds **4** by reaction with trichloroacetyl isocyanate. In turn compounds **4** are condensed with, commercially available or opportunely synthesized,

intermediates **5** in order to obtain the appropriately substituted 3,6,8,13-tetrazatricyclo[7.4.0.02,6]trideca-1(9),2,10,12-tetraene-4,7-dione derivatives **6**, falling under the scope of formula 1g. The same reaction steps can be rearranged, anticipating or postponing each step in the synthesis without any limitation, *e.g.* the Buchwald reaction can be carried out as a last step, or alternatively as a first step in the entire procedure.



Scheme 5: Production of compounds according to formula 1g.

[00161] The syntheses of other compounds not currently described in this general description are well documented inside the experimental part of this invention which follows.

[00162] The free bases of compounds according to formula I, or indeed those of formulae 1a through 1g, their diastereomers or enantiomers can be converted to the corresponding pharmaceutically acceptable salts under standard conditions well known in the art. For example, the free base is dissolved in a suitable organic solvent, such as methanol, treated with, for example one equivalent of maleic or oxalic acid, one or two equivalents of hydrochloric acid or methanesulphonic acid, and then concentrated under vacuum to provide the corresponding pharmaceutically acceptable salt. The residue can then be purified by

recrystallization from a suitable organic solvent or organic solvent mixture, such as methanol/diethyl ether.

[00163] The N-oxides of compounds according to formula I, or indeed those of formulae 1a through 1g, can be synthesized by simple oxidation procedures well known to those skilled in the art.

Preparation of Compounds of the General Formula I

[00164] Unless otherwise stated, one or more tautomeric forms of compounds of the examples described hereinafter may be prepared in situ and/or isolated. All tautomeric forms of compounds of the examples described hereinafter should be considered to be disclosed.

[00165] The invention is illustrated by way of the following examples, in which the following abbreviations may be employed:

AcOH	acetic acid
MeCN	acetonitrile
Aq.	aqueous
BOC	tert-butyloxycarbonyl
conc.	concentrated
DCM	dichloromethane
DCE	1,2-dichloroethane
DIPEA	N,N-diisopropylethylamine
DMAc	N,N-dimethylacetamide
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
EI	electron ionisation
ESI	electrospray ionisation
EtOAc	ethyl acetate
EtOH	ethanol
HCl	hydrochloric acid
HCOOH	formic acid

MeOH	methanol
MS	mass spectrometry
MW	molecular weight
NaOH	sodium hydroxide
NH_4OH	ammonium hydroxide (30% ammonia in water)
PE	petroleum ether
R_f	retention value (from thin layer chromatography)
RT or r.t.	room temperature
R_t	retention time (from HPLC)
THF	tetrahydrofuran
TEA	triethylamine
TFA	trifluoracetic acid
UPLC	ultra high performance liquid chromatography
UPLC-MS	UPLC coupled with mass spectrometry

[00166] The following examples illustrate methods of making some of the compounds of general formula I as described above. These examples are illustrative only and are not intended to limit the scope of the invention. The reagents and starting materials are readily available to those skilled in the art.

Example 1

[00167] 5-isopropyl-8-[(4-methoxyphenyl)methyl]-11-morpholino-3,6,8,13-tetrazatricyclo[7.4.0.02,6]trideca-1(9),2,10,12-tetraen-7-one (compound 162).

3-fluoro-5-morpholino-pyridine-2-carbonitrile

To a solution of 1.04 g of 3,5-difluoropyridine-2-carbonitrile (7.46 mmol) in DMAC (5 mL) 0.651 mL of morpholine (0.65 g, 7.46 mmol) and 2.08 mL of TEA (1.5097 g, 14.92 mmol) were added in a microwave vial. The mixture was stirred under microwave irradiation at 100°C for 30 min. After cooling at room temperature, water was added to the mixture and a white precipitate was obtained which was washed with water and dried to obtain 1.3 g of 3-fluoro-5-morpholino-pyridine-2-carbonitrile (6.2741 mmol) as a white solid (Yield 84%).

3-[(4-methoxyphenyl)methylamino]-5-morpholino-pyridine-2-carbonitrile

To a solution of 0.5 g of 3-fluoro-5-morpholino-pyridine-2-carbonitrile (2.41 mmol) in DMAC (10 mL) were added 1.886 mL of (4-methoxyphenyl)methanamine (1.98 g, 14.48 mmol) and 0.4 mL of TEA (0.29 g 2.89 mmol). The mixture was stirred at 150°C under MW irradiation for 1h. After cooling at room temperature water was added to the mixture. A white solid was obtained, which was washed with water and dried under vacuum to obtain 550 mg (yield 70%) of 3-[(4-methoxyphenyl)methylamino]-5-morpholino-pyridine-2-carbonitrile, used in the next step without further purification.

2-(4-isopropyl-4,5-dihydro-1H-imidazol-2-yl)-N-[(4-methoxyphenyl)methyl]-5-morpholino-pyridin-3-amine

To a solution of 300 mg of 3-[(4-methoxyphenyl)methylamino]-5-morpholino-pyridine-2-carbonitrile (0.92 mmol) in 5mL of DMAC, were added in a microwave vial 486 mg of 3-methylbutane-1,2-diamine HCl (2.77 mmol) and 0.77 mL of TEA (561 mg, 5.55 mmol). The tube was sealed and the mixture was heated at 160°C for 8h. After cooling at room tempearture, the mixture was diluted in AcOEt and the organic layer was washed with water, brine and dried over Na_2SO_4 anhydrous and evaporated to dryiness to obtain 310 mg of a yellow oil (81%) used in the next step without further purification.

5-isopropyl-8-[(4-methoxyphenyl)methyl]-11-morpholino-3,6,8,13-tetrazatricyclo[7.4.0.02,6]trideca-1(9),2,10,12-tetraen-7-one

To a solution of 300 mg of 2-(4-isopropyl-4,5-dihydro-1H-imidazol-2-yl)-N-[(4-methoxyphenyl)methyl]-5-morpholino-pyridin-3-amine (0.73 mmol) in 8 mL of Acetonitrile, were added in a microwave vial, 142 mg of carbonyldiimidazole (CDI) (0.88 mmol) and 18 mg of DMAP (0.15 mmol). The mixture into the sealed vial was heated under microwave irradiation at 150°C for 90 min. 1.2 equivalents of CDI and 0.2 equivalents of DMAP, were added and the mixture was heated in the same condition for other 90 min. The reaction mixture was poured in water, extracted with AcOEt, dried over Na_2SO_4 anhydrous. The solvent was evaporated to dryness and the crude was purified via automated flash chromatography (Isolera-Dalton): SNAP25 Ultra: eluted with isocratic $CHCl_3$-MeOH 95/5. Two batches of enriched regioisomer were re-purified by SNAP10 Ultra: eluted with AcOEt-MeOH gradient from 5% to 10% to obtain 14 mg of 5-isopropyl-8-[(4-methoxyphenyl)methyl]-11-morpholino-

3,6,8,13-tetrazatricyclo[7.4.0.02,6]trideca-1(9),2,10,12-tetraen-7-one (yield 4.4%) as colorless oil.

UPLC-MS $[M+H]^+ = 436.29$

^1H NMR (400 MHz, METHANOL-d_4) δ ppm 8.23 (d, 1 H), 7.25 (m, 2 H), 6.92 (m, 2 H), 6.80 (d, 1 H), 5.25 (AB quartet, 2 H), 4.54 - 4.69 (m, 1 H), 3.83 - 4.13 (m, 2 H), 3.80 (m, 4 H), 3.78 (s, 3 H), 3.25 - 3.30 (m, 4 H), 2.59 - 2.74 (m, 1 H), 1.00 (d, 3 H), 0.87 (d, 3 H).

[00168] Compounds 1-67 as illustrated in Table 1 were prepared in a similar manner, with the relevant groups/moieties being substituted/selected according to groups A, R_1 through R_6 and n *etc.* of formula 1a respectively.

Example 2

6-[(3,5-dimethoxyphenyl)methyl]-2,3-dimethyl-8-{[(oxetan-3-yl)methyl]amino}imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one (compound 74).

4-amino-7-bromo-1H-pyrido[3,2-d]pyrimidin-2-one

To a solution at 0°C of 1 g of 3-amino-5-bromo-pyridine-2-carbonitrile (5.05 mmol) in 15 mL of THF anhydrous, 0.60 mL of 2,2,2-trichloroacetyl isocyanate (0.95 g, 5.05 mmol) were added dropwise under nitrogen atmosphere. The reaction mixture was stirred at r.t. and followed by TLC top completeness. The reaction was quenched at 0°C with MeOH and the solvents evaporated under reduced pressure. The residue was rinsed with 8 mL of 7M ammonia solution in MeOH (56 mmol) and stirred overnight. The white precipitate was filtered, washed with MeOH and dried in oven at 60°C under vacuum to give 1.13 g of the desired product (yield 93%) as a white solid that was used for the next step without further purification.

4-amino-7-bromo-1-[(3,5-dimethoxyphenyl)methyl]pyrido[3,2-d]pyrimidin-2-one

To a solution of 1g of 4-amino-7-bromo-1H-pyrido[3,2-d]pyrimidin-2-one (4.15 mmol) in 40 mL of DMF anhydrous under N2 atm were added, 182.52 mg of NaH 60% dispersion in oil (4.56 mmol) and the mixture was stirred at r.t. for 30 min. Afterwards, 1.150 g of 1-(bromomethyl)-3,5-dimethoxy-benzene (4.98 mmol) were added and the mixture was stirred at r.t. overnight. The solid formed during the reaction was filtrated and washed with a small portion of DMF and water. The crude was grinded with DCM and the suspension filtrated affording 1.2 g of the desired product (yield 74%) as a pale yellow solid that was used fort the

next step without further purification.

11-bromo-8-[(3,5-dimethoxyphenyl)methyl]-4,5-dimethyl-3,6,8,13-tetrazatricyclo[7.4.0.02,6]trideca-1(9),2,4,10,12-pentaen-7-one

A solution of 700 mg of 4-amino-7-bromo-1-[(3,5-dimethoxyphenyl)methyl]pyrido[3,2-d]pyrimidin-2-one (1.79 mmol) and 0.38 mL of 3-bromobutan-2-one (540 mg, 3.58 mmol, 2 equiv) in 4 mL of DMAc was stirred in MW oven at 160°C for 45 min. The reaction mixture was cooled to r.t., poured into water and extracted with EtOAc. The organic layer was washed with water, dried over Na2SO4 anhydrous, the solvent was evaporated to dryness. The resulting crude was purified via automated flash chromatography (Isolera-Dalton): SNAP 25, eluting with a gradient from EDP/AcOEt from 30% to 100% to obtain 260 mg of the desired product (yield 33%) as a pale yellow solid.

8-[(3,5-dimethoxyphenyl)methyl]-4,5-dimethyl-11-(oxetan-3-ylmethylamino)-3,6,8,13-tetrazatricyclo[7.4.0.02,6]trideca-1(9),2,4,10,12-pentaen-7-one

In a microwave vial 120 mg of 11-bromo-8-[(3,5-dimethoxyphenyl)methyl]-4,5-dimethyl-3,6,8,13-tetrazatricyclo[7.4.0.02,6]trideca-1(9),2,4,10,12-pentaen-7-one (0.27 mmol) and 35.4 mg oxetan-3-ylmethanamine (0.41 mmol) were dissolved in 4mL of 1,4 Dioxane. The solution was purged with N2 and after 5 minutes, 12.15 mg of Palladium(II) Acetate (0.054 mmol), 62.65 mg of Xantphos (0.108 mmol) and 176.4 mg of Cesium Carbonate (0.54 mmol) were added and the mixture was stirred in a microwave oven at 150°C for 1h. The reaction was poured in water extracted with EtOAc. The organic layer was dried over Na2SO4 anhydrous, filtered and evaporated to dryiness. The crude residue was purified by means of Isolera One instrument, cartridge type SNAP10, using a gradient from EtOAc 100% to EtOAc : MeOH 95:5, to obtain 100 mg of the desired product (yield 82%).

UPLC-MS $[M+H]^+ = 450.30$

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.01 (d, 1 H), 6.53 (d, 1 H), 6.26 - 6.46 (m, 3 H), 5.35 (s, 2 H), 4.82 (dd, 2 H), 4.35 (br s, 1 H), 4.39 (dd, 2 H), 3.75 (s, 6 H), 3.28 - 3.46 (m, 2 H), 3.03 - 3.22 (m, 1 H), 2.68 (s, 3 H), 2.34 (s, 3 H).

[00169] Compounds 70-73, 75-96 and 158 as illustrated in Table 2 were prepared in a similar manner, with the relevant groups/moieties being substituted/selected according to groups A, R_1 through R_6 and n *etc.* of formula 1b respectively.

Example 3

[00170] 3-tert-butyl-6-(4-methoxybenzyl)-8-(morpholin-4-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one (compound 101).

methyl 5-bromo-3-[(4-methoxyphenyl)methylamino]pyridine-2-carboxylate

To a solution of methyl 3-fluoro-5-bromo-pyridine-2-carboxylate (3.0 g, 12.819 mmol) and (4-methoxyphenyl)methanamine (2.286 g, 2.171 mL, 16.66 mmol) in 60 ml of ACN, ethyl-diisopropyl-amine (3.313 g, 4.39 mL, 25.639 mmol) was added and the mixture was stirred at reflux for 4 hours. After cooling at room temperature, acetonitrile was removed under vacuum. The crude was dissolved in ethyl acetate. The organic solution was washed with water and brine, dried over Na_2SO_4, filtered and evaporated to dryness. 4.33 g of methyl 5-bromo-3-[(4-methoxyphenyl)methylamino]pyridine-2-carboxylate as white powder was collected and used in the next step without any further purification.

7-bromo-1-[(4-methoxyphenyl)methyl]pyrido[3,2-d]pyrimidine-2,4-dione

To a stirred solution of methyl 5-bromo-3-[(4-methoxyphenyl)methylamino]pyridine-2-carboxylate in 35 ml of DCM, 2,2,2-trichloroacetyl isocyanate (7.12 mmol, 0.847 ml, 1.34 g) was added. The reaction was stirred at room temperature for 18 hours. Then the solvent was evaporated and sodium methanolate (11.8 g, 12.4 ml, 54.4 mmol) was added. The suspension was heated to 60°C for 1 hour. After cooling at room temperature, the mixture was treated with water and glacial acetic acid until complete dissolution (pH = 4-5). The aqueous layer was extracted with dichloromethane (3 times) and the organic phases were dried over Na_2SO_4, filtered and evaporated. 1.96 g of 7-bromo-1-[(4-methoxyphenyl)methyl]pyrido[3,2-d]pyrimidine-2,4-dione was collected and used in the next step without any further purification.

7-bromo-4-chloro-1-[(4-methoxyphenyl)methyl]pyrido[3,2-d]pyrimidin-2-one

Under nitrogen atmosphere, a solution of 7-bromo-1-[(4-methoxyphenyl)methyl]pyrido[3,2-d]pyrimidine-2,4-dione (0.475 g, 1.311 mmol) and ethyl-diisopropyl-amine (0.508 g, 0.673 mL, 3.934 mmol) in $POCl_3$ (16.090 g, 9.63 mL,104.9 mmol) was stirred at 50°C for 3 hours. After cooling at room temperature, the solvent was removed and the residue was diluted with 1,4-dioxane and the mixture evaporated (3 times). 500 mg of 7-bromo-4-chloro-1-[(4-

methoxyphenyl)methyl]pyrido[3,2-d]pyrimidin-2-one as crude dark oil was collected and used in the next step without any further purification.

11-bromo-5-tert-butyl-8-[(4-methoxyphenyl)methyl]-3,4,6,8,13-pentazatricyclo [7.4.0.02,6]trideca-1(13),2,4,9,11-pentaen-7-one

A solution of 7-bromo-4-chloro-1-[(4-methoxyphenyl)methyl]pyrido[3,2-d]pyrimidin-2-one (2.89 g, 7.593 mmol) and 2,2-dimethylpropanidrazide (1.764 g, 15.19 mmol) in 40 ml of 1,4-dioxane was stirred at 90°C for 2 hours. Then water and ethyl acetate were added into. The two phases were separated, the organic layer was dried over Na_2SO_4, filtered and evaporated to dryness. The crude was purified by means of Isolera One, cartridge type SNAP50, using a gradient from petroleum ether : ethyl acetate = 1:1 to petroleum ether : ethyl acetate = 1:9.

1.1 g of the desired product as a light yellow powder was collected.

3-tert-butyl-6-(4-methoxybenzyl)-8-(morpholin-4-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one

In a microwave vial a solution of 11-bromo-5-tert-butyl-8-[(4-methoxyphenyl)methyl]-3,4,6,8,13-pentazatricyclo[7.4.0.02,6]trideca-1(13),2,4,9,11-pentaen-7-one (155 mg, 0.35 mmol) and morpholine (45.80 mg, 45.8 µl, 0.5257 mmol,) in 1,4-Dioxane (2 ml) was purged with nitrogen; after 5 minutes palladium(II) acetate (15.73 mg, 0.07009 mmol), xantphos (81.11 mg, 0.1402 mmol,) and cesium carbonate (228.4 mg, 0.7009 mmol) were added and the mixture was heated in sand bath at 80°C for 4h. After cooling at room temperature, water and ethyl acetate were added, the two liquid phases were separated and the aqueous layer was extracted with ethyl acetate (2x). The combined organic phases were dried over Na_2SO_4, filtered and evaporated. The crude residue was purified by means of a Isolera One, cartridge type SNAP25, using a gradient from ethyl acetate 100% to ethyl acetate : methanol 9:1. The fractions collected were further purified by reverse phase column chromatography eluting with a gradient from aqueous ammonium bicarbonate buffer : acetonitrile 8:2 to 1:1. 15 mg of 3-tert-butyl-6-(4-methoxybenzyl)-8-(morpholin-4-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one as white powder, was collected.

UPLC-MS $[M+H]^+ = 449.26$

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.38 (d, 1 H), 7.34 (m, 2 H), 7.08 (d, 1 H), 6.90 (m, 2 H), 5.45 (s, 2 H), 3.73 - 3.79 (m, 4 H), 3.72 (s, 3 H), 3.31 - 3.34 (m, 4 H), 1.58 (s, 9 H).

[00171] Compounds 89, 97-100, 102-110 and 159-161 as illustrated in Table 2 were prepared in a similar manner, with the relevant groups/moieties being substituted/selected according to groups A, R_1 through R_6 and n *etc.* of formula 1c respectively.

Example 4

4-[5-tert-butyl-8-[(4-chlorophenyl)methyl]-3,4,6,7,13-pentazatricyclo[7.4.0.02,6]trideca-1(9),2,4,7,10,12-hexaen-11-yl]morpholine (compound 137).

5-bromo-2-isopropoxycarbonyl-pyridine-3-carboxylic acid

A suspension of 3-bromofuro[3,4-b]pyridine-5,7-dione (15,2 g, 66,67 mmol) in 150 ml of isopropanol was stirred at RT overnight. A clear brown solution was obtained. The solvent was removed to dryness and the crude was purified by column chromatography eluting with dichloromethane : methanol = 10:1. 13.7 g of the desired compound were obtained. (yield 71%).

Isopropyl 5-bromo-3-[2-(4-chlorophenyl)-3-methoxy-3-oxo-propanoyl]pyridine-2-carboxylate

5-bromo-2-isopropoxycarbonyl-pyridine-3-carboxylic acid (1 g, 3.5 mmol) was mixed with carbodiimidazole (732 mg, 4.5 mmol) and anhydrous DMF (10 ml). The reaction mixture was stirred overnight at 50°C, then it was cooled at rt and methyl 2-(4-chlorophenyl)acetate (628 mg, 3.8 mmol) was added. The mixture was cooled to -40°C and NaH (487 mg, 4.5 mmol, 60% suspended in oil) in four portion was added. It was stirred for 1 hour at -25°C for 1 hour at 0°C and for 2 hours at RT until reaction was completed. The mixture was quenched with 75 ml of water and neutralized with 2M HCl solution. The aqueous layers were extracted with ethyl acetate (3 x 200 ml). The organic phase was washed with water and brine, dried with Na_2SO_4 anhydrous, filtered and concentrated under vacuum, to obtain 2 g of desired product (yield = 66%).

5-bromo-3-[2-(4-chlorophenyl)acetyl]pyridine-2-carboxylic acid

Isopropyl 5-bromo-3-[2-(4-chlorophenyl)-3-methoxy-3-oxo-propanoyl]pyridine-2-carboxylate (1.5 g, 3.45 mmol) was dissolved in dioxane (75 ml) and 6 M HCl (8 ml). The mixture was stirred at 80°C for 2 days. The mixture was concentrated under vacuum and neutralized with sodium acetate. The aqueous phase was extracted with ethyl acetate (3 x 100

ml), organic layers were dried over $MgSO_4$ anhydrous and evaporated to dryness under vacuum. 906 mg of the desired compound were obtained (yield 78%).

3-bromo-5-[(4-chlorophenyl)methyl]-7H-pyrido[2,3-d]pyridazin-8-one

To a solution of 5-bromo-3-[2-(4-chlorophenyl)acetyl]pyridine-2-carboxylic acid (906 mg, 2.7 mmol) in 20 ml of ethanol, hydrazine monohydrate (203 mg, 4.1 mmol) was added. The mixture was stirred at 60°C for 24 hours. Ethanol was evaporated and the crude was diluted with water and extracted with ethyl acetate (3 x 100 ml). The organic layers were washed with brine and dried over $MgSO_4$ anhydrous, filtered and evaporated to dryness. The crude was purified by silica gel column chromatography eluting with ethyl acetate/hexane gradient starting from 0:100 to 100:0. 350 mg of the desired product were obtained.

3-bromo-8-chloro-5-[(4-chlorophenyl)methyl]pyrido[2,3-d]pyridazine

3-bromo-5-[(4-chlorophenyl)methyl]-7H-pyrido[2,3-d]pyridazin-8-one (760 mg, 2.168 mmol) and ethyl-diisopropyl-amine (840.5 mg, 1.11 ml, 6.503 mmol) were placed in a dry flask with POCl3 (26.590 g, 15.9 ml, 173.4 mmol). The mixture was stirred at 50°c for 3 hours. After cooling at room temperature, the solvent was removed and the residue was diluted with 1,4-dioxane and the mixture evaporated (repeated three times). 2.5 g of the desired product as a dark oil were obtained and used in the next step without any further purification.

11-bromo-5-tert-butyl-8-[(4-chlorophenyl)methyl]-3,4,6,7,13-pentazatricyclo[7.4.0.02,6]trideca-1(9),2,4,7,10,12-hexaene

A solution of 3-bromo-8-chloro-5-[(4-chlorophenyl)methyl]pyrido[2,3-d]pyridazine (760 mg, 2.06 mmol) and 2,2-dimethylpropanidrazide (717.7 mg, 6.179 mmol) in 1,4-dioxane (20 ml) was stirred at 60°C for 2 hours, then at room temperature overnight. The solvent was removed under vacuum, water and ethyl acetate were added. The organic layer was separated, dried over Na_2SO_4 anhydrous filtered and evaporated to dryness. The obtained crude was purified by Isolera One, cartridge type SNAP50, eluting in gradient from petroleum ether: ethyl acetate = 1:1 to Ethyl Acetate 100%. Collected fractions gave 560 mg of desired compound as an orange powder.

4-[5-tert-butyl-8-[(4-chlorophenyl)methyl]-3,4,6,7,13-pentazatricyclo[7.4.0.02,6]trideca-1(9),2,4,7,10,12-hexaen-11-yl]morpholine

In a microwave vial a solution of 11-bromo-5-tert-butyl-8-[(4-chlorophenyl)methyl]-

3,4,6,7,13-pentazatricyclo[7.4.0.02,6]trideca-1(9),2,4,7,10,12-hexaene (50 mg, 0.116 mmol) and morpholine (15.17 mg, 0.174 mmol) in 1,4-dioxane (2 ml) was purged with N2; after 5 minutes palladium(II) acetate (5.212 mg, 0.0232 mmol), xantphos (26.87 mg, 0.04644 mmol) and cesium carbonate (75.65 mg, 0.2322 mmol) were added and the mixture was heated in sand bath at 80°C for 2 hours. Then water and ethyl acetate were added, the two liquid phases were separated and the aqueous layer was extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 anhydrous, filtered and evaporated to dryness. The crude residue was purified by means of a Isolera One, cartridge type SNAP10, using a gradient from ethyl acetate : methanol = 100:0 to ethyl acetate : methanol = 80 : 20. Collected fractions gave 24 mg of the desired product as yellow powder which were purified again on a reverse phase column chromatography using a gradient from NH_4HCO_3 buffer : ACN = 7:3 to NH_4HCO_3 buffer : ACN = 3:7 to obtain 11 mg of the final compound. (yield 21%)

UPLC-MS $[M+H]^+ = 437.28$

^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.88 (d, 1 H), 7.32 - 7.39 (m, 3 H), 7.23 (d, 2 H), 4.46 (s, 2 H), 3.89 - 3.98 (m, 4 H), 3.27 - 3.36 (m, 4 H), 1.62 (s, 9 H).

[00172] Compounds 111-136 and 138-140 as illustrated in Table 3 were prepared in a similar manner, with the relevant groups/moieties being substituted/selected according to groups A, R_1 through R_6 and n *etc.* of formula 1d respectively.

Example 5

[00173] 5-(3,5-dimethoxybenzyl)-9,9-dimethyl-3-(morpholin-4-yl)-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one (compound 147).

5-bromo-2-(5,5-dimethyl-4,6-dihydro-1H-pyrimidin-2-yl)pyridin-3-amine

3-amino-5-bromo-pyridine-2-carbonitrile (500 mg, 2.52 mmol), 2,2-dimethylpropane-1,3-diamine (774 mg, 7.57 mmol) and DMAc (5 ml) were placed in a microwave tube. The tube was sealed and the reaction was heated at 160°C in a sand bath and stirred overnight. The reaction was cooled to RT, water was added and a solid precipitate was obtained. The pale yellow solid was filtered, washed with water and dried in oven at 60°C under vacuum to give 700 mg of the desired product (yield 98%) used in the next step without further purification.

12-bromo-5,5-dimethyl-3,7,9,14-tetrazatricyclo[8.4.0.02,7]tetradeca-1(10),2,11,13-tetraen-

8-one

5-bromo-2-(5,5-dimethyl-4,6-dihydro-1H-pyrimidin-2-yl)pyridin-3-amine (700 mg, 2.47 mmol) was dissolved in 15 mL of acetonitrile. After addition of carbonyldiimidazole (481 mg, 2.96 mmol) the resulting mixture was heated to 80°C overnight. The reaction was cooled at RT. A solid precipitate was obtained, filtered and washed with acetonitrile. The 700 mg of crude product (yield 91%), isolated as a yellowish solid, was used in the next step without any further purification.

12-bromo-9-[(3,5-dimethoxyphenyl)methyl]-5,5-dimethyl-3,7,9,14-tetrazatricyclo[8.4.0.02,7] tetradeca-1(10),2,11,13-tetraen-8-one

To a solution of 12-bromo-5,5-dimethyl-3,7,9,14-tetrazatricyclo[8.4.0.02,7] tetradeca-1(10),2,11,13-tetraen-8-one (150 mg, 0.485 mml) in 5 mL of DMF anhydrous, under nitrogen atmosphere, NaH 60% (23.287 mg, 0.5822 mmol) was added and the mixture stirred at Rt for 30 minutes. Afterwards, 1-(bromomethyl)-3,5-dimethoxy-benzene (123.33 mg, 0.5337 mmol) was added and the mixture was stirred at RT overnight. The obtained precipitate was filtrated and washed with a small portion of DMF. Water was added to the filtrate and the resulting solid was obtained. The crude product was grinded with DCM and the suspension filtrated affording the 120 mg of the desired product (yield 54%) as a pale yellow solid that was used in the next step without purification.

9-[(3,5-dimethoxyphenyl)methyl]-5,5-dimethyl-12-morpholino-3,7,9,14-tetrazatricyclo[8.4.0.02,7]tetradeca-1(10),2,11,13-tetraen-8-one

In a microwave vial, to a solution purged with N2 of 12-bromo-9-[(3,5-dimethoxyphenyl)methyl]-5,5-dimethyl-3,7,9,14-tetrazatricyclo[8.4.0.02,7]tetradeca-1(10),2,11,13-tetraen-8-one (120 mg, 0.2613 mmol) and morpholine (34.14 mg, 0.3919 mmol), in 3 ml 1,4-dioxane, after 5 minutes were added palladium(II) acetate (11.73 mg, 0.052 mmol), XantPhos (60.47 mg, 0.10 mmol) and cesium carbonate (170 mg, 0.52 mmol). The mixture was stirred in microwave oven at 150°C for 2 hours, cooled to RT, poured into water and extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4 anhydrous, and the solvent was evaporated to give the crude that was purified via automated flash chromatography (Isolera, SNAP10) eluted with EtOAc/MeOH-NH_3 gradient from 5 to 20%. The desired product (70 mg) was isolated as a pale yellow solid. (Yield = 57%).

UPLC-MS $[M+H]^+$ = 466.32

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.22 (d, 1 H), 6.85 (d, 1 H), 6.49 (d, 2 H), 6.40 (dd, 1 H), 5.25 (s, 2 H), 3.70 - 3.76 (m, 4 H), 3.70 (s, 6 H), 3.62 (s, 2 H), 3.30 - 3.34 (m, 4 H), 3.27 (s, 2 H), 1.01 (s, 6 H).

[00174] Compounds 141-146 and 148-155 as illustrated in Table 4 were prepared in a similar manner, with the relevant groups/moieties being substituted/selected according to groups A, R_1 through R_6 and n *etc.* of formula 1e respectively.

Example 6

[00175] 6-tert-butyl-2-[(4-methoxyphenyl)methyl]-12-morpholino-2,4,5,7,10-pentazatricyclo[7.4.0.03,7]trideca-1(13),3,5,9,11-pentaen-8-one (compound 157).

Following preparation of compound 101 (Example 3), after the final purification a fraction of 12 mg was recovered and after structural analysis it corresponds to the regional isomer of the compound 101 and precisely to the compound 6-tert-butyl-2-[(4-methoxyphenyl)methyl]-12-morpholino-2,4,5,7,10-pentazatricyclo[7.4.0.03,7]trideca-1(13),3,5,9,11-pentaen-8-one.

UPLC-MS $[M+H]^+$ = 449.26

^{1}H NMR (400 MHz, DMSO-d_6) □ ppm 8.44 (d, 1 H), 7.34 (m, 2 H), 7.12 (d, 1 H), 6.89 (m, 2 H), 5.51 (s, 2 H), 3.73 - 3.80 (m, 4 H), 3.72 (s, 3 H), 3.32 - 3.39 (m, 4 H), 1.44 (s, 9 H).

[00176] Compound 156 as illustrated in Table 5 was prepared in a similar manner, with the relevant groups/moieties being substituted/selected according to groups A, R_1 through R_6 and n *etc.* of formula 1f respectively.

Example 7

[00177] 5-tert-butyl-8-[(4-methoxyphenyl)methyl]-11-morpholino-3,6,8,13-tetrazatricyclo[7.4.0.02,6]trideca-1(13),2,9,11-tetraene-4,7-dione (compound 69).

3-fluoro-5-morpholino-pyridine-2-carbonitrile

To a solution of 1.04 g of 3,5-difluoropyridine-2-carbonitrile (7.46 mmol) in DMAC (5 mL) 0.651 mL of morpholine (0.65 g, 7.46 mmol) and 2.08 mL of TEA (1.5097 g, 14.92 mmol) were added in a microwave vial. The mixture was stirred under microwave irradiation at 100°C for 30 min. After cooling at room temperature, water was added to the mixture and a white

precipitate was obtained which was washed with water and dried to obtain 1.3 g of 3-fluoro-5-morpholino-pyridine-2-carbonitrile (6.2741 mmol) as a white solid (yield 84%).

3-[(4-methoxyphenyl)methylamino]-5-morpholino-pyridine-2-carbonitrile

To a solution of 0.5 g of 3-fluoro-5-morpholino-pyridine-2-carbonitrile (2.41 mmol) in DMAC (10 mL) were added 1.886 mL of (4-methoxyphenyl)methanamine (1.98 g, 14.48 mmol) and 0.4 mL of TEA (0.29 g 2.89 mmol). The mixture was stirred at 150°C under MW irradiation for 1h. After cooling at room temperature water was added to the mixture. A white solid was obtained, which was washed with water and dried under vacuum to obtain 550 mg (yield 70%) of 3-[(4-methoxyphenyl)methylamino]-5-morpholino-pyridine-2-carbonitrile, used in the next step without further purification.

4-amino-1-[(4-methoxyphenyl)methyl]-7-morpholino-pyrido[3,2-d]pyrimidin-2-one

To a solution at 0°C of 300 mg of 3-[(4-methoxyphenyl)methylamino]-5-morpholino-pyridine-2-carbonitrile (0.92 mmol) in anhydrous THF (10 mL), 0.11 mL of trichloroacetyl isocyanate (174 mg, 0.92 mmol) were added dropwise under nitrogen atmosphere. The reaction mixture was stirred at r.t. to complete disappearing of intermediate. The reaction mixture was quenched at 0°C with MeOH and the solvents evaporated under reduced pressure. The residue was rinsed with 4 mL 7M ammonia solution in MeOH (28 mmol) and stirred overnight. The white precipitate that was formed was filtered and washed with cold methanol to obtain 180 mg (yield 53%) of 4-amino-1-[(4-methoxyphenyl)methyl]-7-morpholino-pyrido[3,2-d]pyrimidin-2-one which was used in the next step without further purification.

5-tert-butyl-8-[(4-methoxyphenyl)methyl]-11-morpholino-3,6,8,13-tetrazatricyclo[7.4.0.02,6]trideca-1(13),2,9,11-tetraene-4,7-dione

To a solution of 318.5 mg of 2-bromo-3,3-dimethyl-butanoic acid (1.63 mmol) in 3 mL of Toluene, 0.17 mL Oxalyl Chloride (259 mg, 2.04 mmol) and two drops of DMF were added. The solution was stirred at room temperature for 3 hours. The solvent was removed and the residue dissolved in DMA (1 mL) was added to a solution of 150 mg of 4-amino-1-[(4-methoxyphenyl)methyl]-7-morpholino-pyrido[3,2-d]pyrimidin-2-one (0.41 mmol) and 0.748 mL of DIPEA (564 mg, 4.9 mmol). The mixture was heated at 120°C for 3 hours, poured in water and extracted with AcOEt. The organic layer was dried over sodium sulphate anhydrous and the solvent was evaporated to dryness. The crude was purified via automated flash

chromatography (Isolera-Dalton): SNAP10 Cartridge and eluted with EtOAc/Petroleum Ether gradient from10% to 70% to obtain 20 mg of 5-tert-butyl-8-[(4-methoxyphenyl)methyl]-11-morpholino-3,6,8,13-tetrazatricyclo[7.4.0.02,6]trideca-1(13),2,9,11-tetraene-4,7-dione (yield 10%) as a pale yellow solid.

UPLC-MS $[M+H]^+ = 464.29$

^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.41 (d, 1 H), 7.32 (m, 2 H), 6.85 - 6.93 (m, 3 H), 5.30 (s, 2 H), 4.26 (s, 1 H), 3.72 (s, 3 H), 3.68 - 3.77 (m, 4 H), 3.41 - 3.49 (m, 4 H), 1.03 (s, 9 H).

[00178] Compounds 64 and 68 as illustrated in Table 1 were prepared in a similar manner, with the relevant groups/moieties being substituted/selected according to groups A, R_1 through R_6 and n *etc.* of formula 1g respectively.

Biological Assay: Calcium Fluorescence Measurements

[00179] The assay for the human purinergic $P2X_3$ receptor has been adapted to the internal screening instrumentation using the FLEXSTATION as reader and a photoprotein as luminescent readout. The assay consists of CHO-K1 cells recombinantly co-expressing the human P2rx3 receptor and a Ca^{2+} sensitive photoprotein. Cells are maintained in DMEM F-12 (1:1) mixture (LONZA cat. n° BE04-687F/U1) supplemented with 9 mL of 100 mM Sodium Pyruvate (LONZA cat. n° BE13-115E), 29 mL of 7.5% Sodium Bicarbonate (LONZA cat. n°: BE17-613E), 5.5 mL of 1 M Hepes (LONZA cat. n° BE17-737E), 5 mL of 100X Penicillin/Streptomycin (LONZA cat. n° DE17-602E) and 50 mL of Fetal Bovine Serum (Sigma cat. n° F7524), 1 mg/mL G418 (Sigma cat. n° G8168) and 5 µg/ml puromycin (Sigma cat. n° P9620). Standard propagation conditions consist of seeding in a P75 flask twice a week, recovering about 20x106 cells, corresponding to about 80% confluency. Cells were seeded into black-walled clear bottom 96 well plates at a density of 40000 cells/well in a Tyrode's buffer (Standard Tyrode's buffer: in house solution, 130 mM NaCl, 5 mM KCl, 2 mM CaCl2, 5 mM NaHCO3, 1 mM MgCl2, 20 mM HEPES, pH 7.4). After 24 h the culture medium was replaced with 200 µL/well of coelenterazine in Tyrode's buffer (Coelenterazine: from BIOSYNTH (cat. n° C-7001). 10 mM stock solution was prepared in DMSO and glutathione and stored at -20° C). The plates were incubated for 4 hours at 37°C, and injected with 10 µL/well of test compounds at 25X concentration in Tyrode's buffer. After 4 minutes a second

injection of 50 µL/well of 5X α,β-Met-ATP in Tyrode's buffer (α,β-Met-ATP: from Tocris (cat. n° 3209), was dissolved at 100 mM in water and stored in aliquots at -20°C) was performed and the signal of the emitted luminescence was recorded by FLEXSTATION III (Molecular Devices). The tested compounds showed an antagonism versus human $P2X_3$ receptor between 1 nM and 10 µM. Example 101 and Example 102 showed an inhibition of 20.7 and 25.5 nM, respectively.

[00180] Selected antagonists of human $P2X_3$ receptors expressed as IC_{50} (nM) for some of the compounds of interest, prepared according to the invention, are shown below in Tables 6 to 9.

Table 6: Human $P2X_3$ receptor antagonist activity for selected compounds of the invention.

Example	*h*-$P2X_3$ **IC_{50} nM**
1	4294.0
2	1191.0
3	1155.0
4	178.0
5	278.4
6	503.7
7	1643.0
8	636.4
9	74.3
10	241.0
11	357.6
12	427.9
13	1258.0
14	171.9
15	1425.5
16	2233.5
17	690.0

18	300.9
19	5509.5
20	1138.0
21	7193.0
22	142.8
23	506.2
24	515.2
25	388.9
26	468.8
28	375.0
29	367.9
30	350.2
31	228.5
32	123.8
33	219.2
34	408.1
35	793.3
36	245.3
37	677.7
38	2037.5
39	5141.0
40	1047.9
41	3318.5
42	188.6
43	111.8
44	491.0
45	200.5
46	126.8
47	199.0

49	871.7
50	280.1
51	731.0
52	1252.0
53	2068.0
54	1696.0
55	2439.5
56	345.1
57	3285.0
58	9201.0
60	1095.5
61	1076.8
62	720.3
63	298.7
64	108.6
65	1788.5
66	2281.0
67	217.7
68	108.9
69	98.3

Table 7: Human $P2X_3$ receptor antagonist activity for selected compounds of the invention.

Example	*h*-$P2X_3$ **IC_{50} nM**
70	1386.0
72	416.4
73	917.3
74	138.9
75	3506.0

76	381.1
77	238.9
78	631.0
79	53.7
80	1534.0
81	268.6
82	332.4
83	292.5
84	259.1
85	1304.0
87	443.9
88	53.6
89	2442.0
90	574.9
91	332.0
92	507.4
93	801.5
94	1009.0
95	8262.0
96	2985.0
97	393.7
98	897.0
99	121.5
100	153.1
101	20.7
102	25.5
103	810.5
104	734.1
105	655.4

106	40.6
107	1316.7
108	175.4
109	203.4
110	256.6

Table 8: Human $P2X_3$ receptor antagonist activity for selected compounds of the invention.

Example	*h*-$P2X_3$ **IC_{50} nM**
111	1788.0
112	234.4
115	436.6
116	468.6
117	197.4
118	1055.0
119	1214.0
120	543.6
121	1151.0
122	1813.5
123	246.2
124	2817.5
125	538.0
126	20.6
127	147.1
128	575.5
132	19.1
133	216.8
137	82.4
139	442.1

140	221.4

Table 9: Human $P2X_3$ receptor antagonist activity for selected compounds of the invention.

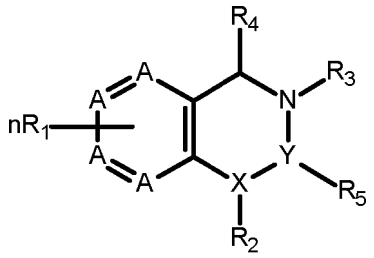
Example	*h*-$P2X_3$ **IC_{50} nM**
143	2255
144	2483
145	1783
147	2441
151	937.7
154	1046.4
155	2170.5
156	607.8

Statistical analysis.

[00181] The inhibition curves of the tested compounds at cloned $P2X_3$ receptor were determined by nonlinear regression analysis using software Prism 4.0 (Graphpad, San Diego, CA). The IC_{50} values and pseudo-Hill slope coefficients were estimated by the program.

CLAIMS:

1. A compound according to formula I:



formula I

or an enantiomer, diastereomer, N-oxide, or a pharmaceutically acceptable salt or combinations thereof, wherein:

each A independently represents an atom selected from C, N, S or O;

X and Y are selected from C and N atoms, wherein the unit X-Y represents either a N-C group, or a C=N group respectively;

each R_1 independently represents hydrogen, a halogen atom, or an, optionally substituted, hydroxy, carbonyl, carboxyl, amino, amido, C_1-C_6 alkyl or C_1-C_6 alkoxy group, an, optionally substituted, mono-, bi- or tricyclic C_6-C_{14} aryl group or an, optionally substituted, mono-, bi- or tricyclic C_1-C_{13} heterocyclic group containing from 1 to 5 heteroatoms selected from N, O or S;

R_2 is absent or represents hydrogen or an, optionally substituted, C_1-C_6 alkyl group, C_1-C_6 alkoxy group, C_4-C_{14} arylalkyl group, C_4-C_{14} heteroarylalkyl group, C_3-C_7 cycloalkyl group, a mono-, bi- or tricyclic C_6-C_{14} aryl group or a mono-, bi- or tricyclic C_1-C_{13} heterocyclic group containing from 1 to 5 heteroatoms selected from N, O or S;

groups R_3 and R_4, or alternatively groups R_3 and R_5, are linked to each other to form a five- or six-membered heterocyclic ring containing from 2 to 3 heteroatoms atoms selected from N, O and S, optionally substituted with one or more groups nR_6, with the proviso that the remainder of R_4 or R_5 not linked with group R_3 to form the heterocyclic ring is absent, or is an atom

independently selected from N, O or S which is double-bonded directly to the X-Y containing ring;

each R_6 independently represents hydrogen, a halogen atom selected from F, Cl, Br or I; or an, optionally substituted, carbonyl, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy or C_3-C_7 cycloalkyl group, an, optionally substituted, mono-, bi- or tricyclic C_6-C_{14} aryl group or an, optionally substituted, mono-, bi- or tricyclic C_1-C_{13} heterocyclic group containing from 1 to 5 heteroatoms selected from N, O or S or alternatively, two R_6 groups are linked to each other to form a group of the formula -(Zp)- wherein p is an integer of from 3 to 5 and each Z independently represents an oxygen atom or an optionally substituted methylene group, provided that no two adjacent Y moieties represent oxygen atoms; and

n is an integer independently selected from 0 to 3.

2. A compound according to claim 1 wherein the optional substituents are independently selected from the group consisting of halogen atoms, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, mercapto, nitro, cyano, oxo, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylsulphonyl, C_1-C_6 alkylcarbonyl, sulphamoyl, C_1-C_6 alkylsulphamoyl, di(C_1-C_6)alkylsulphamoyl, (C_1-C_6)alkoxycarbonyl and (C_1-C_6)alkylcarbonyl(C_1-C_6)alkyl groups, and from groups of the formulae -NR*R*, -C(=O)-NR*R*, -D, -O-D, -C(=O)-D, -(CH_2)q-D, -NR**-D, -C(=O)-NR**-D, -NR**C(=O)-D and -O-C(=O)-D wherein each R* independently represents a hydrogen atom or a C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylcarbonyl, phenyl or benzyl group, R** represents a hydrogen atom or a C_1-C_6 alkyl group, q is an integer from 1 to 6 and D represents a phenyl group or a C_1-C_8 heterocyclic group containing from 1 to 3 heteroatoms selected from N, O and S; a C_1-C_6 cycloalkyl group; each group D being further optionally substituted with from 1 to 3 groups independently selected from halo, hydroxy, cyano, nitro and C_1-C_6 alkyl, preferably wherein the optional substituents are selected from the groups consisting of halogen atoms and C_1-C_6 alkyl groups.

3. A compound according to claim 1 or claim 2, wherein group X-Y represents a N-C group, groups R_3 and R_4 are linked to each other to form a five- or six-membered heterocyclic

ring containing from 2 to 3 nitrogen heteroatoms atoms, optionally substituted with one or more groups nR_6, and R_5 is a carbonyl group.

4. A compound according to claim 1 or claim 2, wherein group X-Y represents a N-C group, groups R_3 and R_5 are linked to each other to form a five-membered heterocyclic ring containing from 2 to 3 nitrogen heteroatoms atoms, optionally substituted with one or more groups nR_6, and R_4 is a carbonyl group.

5. A compound according to claim 1 or claim 2, wherein group X-Y represents a C=N group, groups R_3 and R_4 are linked to each other to form a five- or six-membered heterocyclic ring containing from 2 to 3 nitrogen heteroatoms atoms, optionally substituted with one or more groups nR_6, and R_5 is absent.

6. A compound according to any preceding claim, wherein R_1 is selected from the group comprising H, Br, hydroxy, carboxyl, methoxy, methoxyethylamino, 2-hydroxyethylamino, tertiarybutoxycarbonylamino, 2-hydroxyethylaminocarbonyl, an optionally substituted azetidinyl, morpholinyl, oxetanyl, piperazinyl, piperidinyl, pyranyl or pyrrolidinyl moiety or derivative thereof, or an optionally substituted, spiro-fused bi- or tricyclic C_1-C_{13} heterocyclic group containing from 1 to 5 heteroatoms selected from N, O or S.

7. A compound according to claim 6, wherein R_1 is selected from the group comprising 2-oxa-6-azaspiro[3.3]heptan-6-yl, 3-methoxymethylazetidin-1-yl, 3-methoxypyrrolidin-1-yl, 4-acetylpiperazin-1-yl, 4-aminopiperidin-1-yl, 4-hydroxypiperidin-1-yl, 4-hydroxypiperidin-1-yl-carbonyl, 4-methoxypiperidin-1-yl, 4-morpholinyl, dimethylaminopiperidin-1-yl, hydroxymethylpiperidin-1-yl, morpholin-4-ylcarbonyl, tetrahydro-2H-pyran-4-ylamino or tetrahydro-2H-pyran-4-ylaminocarbonyl.

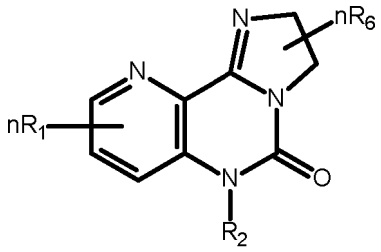
8. A compound according to any preceding claim, wherein R_2 is a hydrogen atom or an optionally substituted benzyl group or derivative thereof.

9. A compound according to claim 8, wherein R_2 is a hydrogen atom, or is selected from the group comprising 3,5-dimethoxybenzyl, 4-methoxybenzyl, 4-methylbenzyl, 4-chlorobenzyl or 4-chloro-2,6-difluorobenzyl.

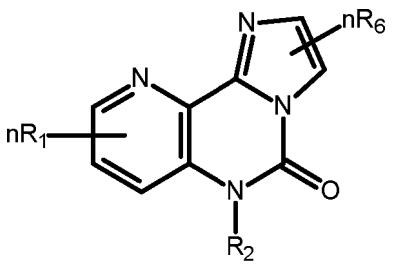
10. A compound according to any preceding claim, wherein R_6 is selected from the group comprising phenyl, (1-phenyl)ethyl, 1-ethyl-1H-pyrazol-3-yl, 1-ethyl-1H-pyrazol-5-yl, (tetrahydro-2H-pyran-4-yl)methyl, (tetrahydro-2H-pyran-4-yloxy)methyl, (tetrahydro-2H-pyran-4-yl)ethyl, 3,5-dimethyl-1,2oxazol-4-yl, 2-hydroxypyridin-3-yl, 2-methylpyridin-3-yl, morpholin-4-yl-carbonyl, pyridin-3-yl-methyl, oxo, methyl, ethyl, iso-propyl, tertiary-butyl, methylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, 2,2,2-trifluoroethyl, methoxymethyl, methoxyethyl, (propan-2-yloxy)methyl, tertiary-butoxymethyl, prop-1-en-2-yl, propan-2-yl-acetamide, cyclopropyl, cyclobutyl, cyclohexyl, 1-methylcyclopropyl.

11. A compound according to claim 1, wherein -(Zp)- represents a group selected from $-O-(CH_2)_2-O-$, $-O-(CH_2)_3-O-$, $-O-(CH_2)_2-$, $-O-(CH_2)_3-$, $-CH_2-O-CH_2-$ or $-(CH_2)_2-O-(CH_2)_2$.

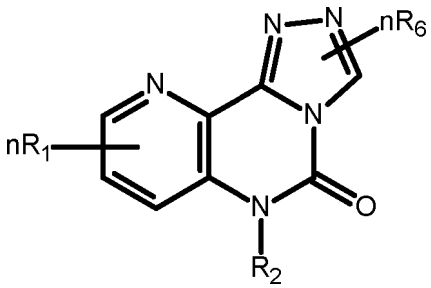
12. A compound according to any preceding claim, wherein the compound has a structure in accordance with one of the following formulae 1a to 1g:



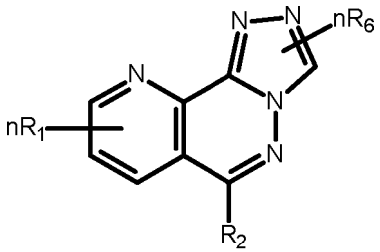
formula 1a;



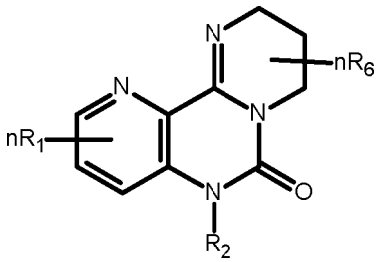
formula 1b;



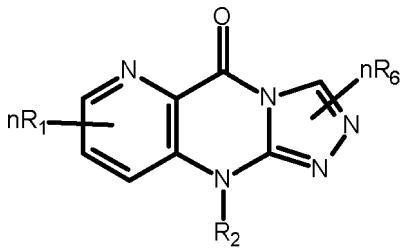
formula 1c;



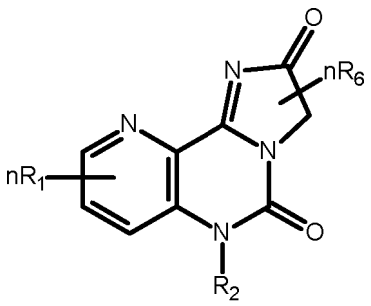
formula 1d;



formula 1e;



formula 1f; or



formula 1g.

wherein groups R_1, R_2, R_6 and n are as defined in claim 1.

13. A compound according to claim 1, the compound being selected from the group consisting of:

6-(3,5-dimethoxybenzyl)-2,2-dimethyl-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;

6-(3,5-dimethoxybenzyl)-3-methyl-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;

6-(3,5-dimethoxybenzyl)-2-methyl-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;

6-(3,5-dimethoxybenzyl)-8-(morpholin-4-yl)-2-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;

6-(3,5-dimethoxybenzyl)-2-ethyl-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;

6-(3,5-dimethoxybenzyl)-3-ethyl-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(3,5-dimethoxybenzyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(3,5-dimethoxybenzyl)-2,3-dimethyl-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(3,5-dimethoxybenzyl)-8-(morpholin-4-yl)-3-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-chlorobenzyl)-2-cyclopropyl-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-chlorobenzyl)-2-(methoxymethyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-chlorobenzyl)-3-cyclopropyl-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-chlorobenzyl)-3-(methoxymethyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-chlorobenzyl)-8-(morpholin-4-yl)-2-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-chlorobenzyl)-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-2-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-chlorobenzyl)-8-(4-methoxypiperidin-1-yl)-2-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-chlorobenzyl)-8-[3-(methoxymethyl)azetidin-1-yl]-2-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-methoxybenzyl)-8-(morpholin-4-yl)-2-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-methoxybenzyl)-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-2-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
8-[4-(hydroxymethyl)piperidin-1-yl]-6-(4-methoxybenzyl)-2-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;

8-[4-(dimethylamino)piperidin-1-yl]-6-(4-methoxybenzyl)-2-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(3,5-dimethoxybenzyl)-2-(2-methylpropyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
2-cyclohexyl-6-(4-methoxybenzyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
3-cyclohexyl-6-(4-methoxybenzyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-chlorobenzyl)-2-cyclohexyl-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-chlorobenzyl)-3-cyclohexyl-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
2-ethyl-6-(4-methoxybenzyl)-8-[(3R)-3-methoxypyrrolidin-1-yl]-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-methoxybenzyl)-8-(morpholin-4-yl)-2-phenyl-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-methoxybenzyl)-8-(morpholin-4-yl)-3-phenyl-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-chlorobenzyl)-2-(2-methylpropyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-chlorobenzyl)-3-(2-methylpropyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
2-tert-butyl-6-(4-methoxybenzyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
2-cyclobutyl-6-(4-methoxybenzyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
2-(2,2-dimethylpropyl)-6-(4-methoxybenzyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(3,5-dimethoxybenzyl)-3-(2-methylpropyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;

6-(4-chlorobenzyl)-8-(morpholin-4-yl)-2-phenyl-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-methoxybenzyl)-2-(2-methylpropyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-methoxybenzyl)-3-(2-methylpropyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
2-ethyl-6-(4-methoxybenzyl)-8-[3-(methoxymethyl)azetidin-1-yl]-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-chlorobenzyl)-8-(morpholin-4-yl)-2',3',5',6'-tetrahydrospiro[imidazo[1,2-c]pyrido[2,3-e]pyrimidine-2,4'-pyran]-5(6H)-one;
6-(4-chlorobenzyl)-8-(morpholin-4-yl)-2,2',3',5',6,6'-hexahydro-5H-spiro[imidazo[1,2-c]pyrido[2,3-e]pyrimidine-3,4'-pyran]-5-one;
8-(4-aminopiperidin-1-yl)-6-(3,5-dimethoxybenzyl)-2-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
2-cyclohexyl-6-(3,5-dimethoxybenzyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
3-cyclohexyl-6-(3,5-dimethoxybenzyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-chlorobenzyl)-8-(morpholin-4-yl)-3-phenyl-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(3,5-dimethoxybenzyl)-8-(morpholin-4-yl)-2-phenyl-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(3,5-dimethoxybenzyl)-8-(morpholin-4-yl)-3-phenyl-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-chlorobenzyl)-8-hydroxy-2-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(3,5-dimethoxybenzyl)-2-(propan-2-yl)-8-(tetrahydro-2H-pyran-4-ylamino)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-chlorobenzyl)-2-ethyl-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;

6-(4-chlorobenzyl)-8-(4-hydroxypiperidin-1-yl)-2-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
2-ethyl-6-(4-methoxybenzyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
3-ethyl-6-(4-methoxybenzyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-chlorobenzyl)-8-(morpholin-4-yl)-2-(morpholin-4-ylcarbonyl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-chlorobenzyl)-8-(morpholin-4-yl)-3-(morpholin-4-ylcarbonyl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-methoxybenzyl)-8-(morpholin-4-yl)-2-(2,2,2-trifluoroethyl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
2-(tert-butoxymethyl)-6-(4-methoxybenzyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(3,5-dimethoxybenzyl)-5-oxo-2-(propan-2-yl)-N-(tetrahydro-2H-pyran-4-yl)-2,3,5,6-tetrahydroimidazo[1,2-c]pyrido[2,3-e]pyrimidine-8-carboxamide;
6-(3,5-dimethoxybenzyl)-5-oxo-2-(propan-2-yl)-2,3,5,6-tetrahydroimidazo[1,2-c]pyrido[2,3-e]pyrimidine-8-carboxylic acid;
6-(3,5-dimethoxybenzyl)-8-(morpholin-4-ylcarbonyl)-2-(propan-2-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-chlorobenzyl)-2-(cyclohexylmethyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-chlorobenzyl)-2-(3-methylbutyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-chlorobenzyl)-3-(3-methylbutyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
6-(4-chlorobenzyl)-3-(2-methylpropyl)-8-(morpholin-4-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidine-2,5(3H,6H)-dione;
6-(4-methoxybenzyl)-2-(2-methoxyethyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;

6-(4-methoxybenzyl)-3-(2-methoxyethyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
3-(tert-butoxymethyl)-6-(4-methoxybenzyl)-8-(morpholin-4-yl)-2,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(3H)-one;
5-tert-butyl-8-[(4-chlorophenyl)methyl]-11-morpholino-3,6,8,13-tetrazatricyclo[7.4.0.02,6]trideca-1(13),2,9,11-tetraene-4,7-dione;
5-tert-butyl-8-[(4-methoxyphenyl)methyl]-11-morpholino-3,6,8,13-tetrazatricyclo[7.4.0.02,6]trideca-1(13),2,9,11-tetraene-4,7-dione;
6-[(4-methylphenyl)methyl]-2-(2-methylpropyl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one;
2-(2-methylpropyl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one;
6-[(3,5-dimethoxyphenyl)methyl]-2-(2-methylpropyl)-8-(morpholin-4-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one;
6-[(4-chlorophenyl)methyl]-2-(2-methylpropyl)-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one;
6-[(3,5-dimethoxyphenyl)methyl]-2,3-dimethyl-8-{[(oxetan-3-yl)methyl]amino}imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one;
6-[(4-chloro-2,6-difluorophenyl)methyl]-2-(2-methylpropyl)-8-(morpholin-4-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one;
6-[(3,5-dimethoxyphenyl)methyl]-2-ethyl-3-methyl-8-{[(oxetan-3-yl)methyl]amino}imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one;
6-[(3,5-dimethoxyphenyl)methyl]-3-ethyl-2-methyl-8-{[(oxetan-3-yl)methyl]amino}imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one;
6-(4-methoxybenzyl)-2-(2-methylpropyl)-8-(morpholin-4-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one;
6-(3,5-dimethoxybenzyl)-3-methyl-8-(morpholin-4-yl)-2-(propan-2-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one;
6-(3,5-dimethoxybenzyl)-8-[4-(hydroxyacetyl)piperazin-1-yl]-2-(2-methylpropyl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one;

6-(3,5-dimethoxybenzyl)-2,3-dimethyl-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one;
6-(3,5-dimethoxybenzyl)-2,3-dimethyl-8-(morpholin-4-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one;
6-(3,5-dimethoxybenzyl)-3-methyl-8-[(oxetan-3-ylmethyl)amino]-2-(propan-2-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one;
8-(4-acetylpiperazin-1-yl)-6-(3,5-dimethoxybenzyl)-3-methyl-2-(propan-2-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one;
6-(3,5-dimethoxybenzyl)-8-(4-methoxypiperidin-1-yl)-2,3-dimethylimidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one;
5-(3,5-dimethoxybenzyl)-8,9-dimethyl-3-(morpholin-4-yl)imidazo[1,2-c]pteridin-6(5H)-one;
6-(3,5-dimethoxybenzyl)-8-(4-methoxypiperidin-1-yl)-3-methyl-2-(propan-2-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one;
6-(3,5-dimethoxybenzyl)-8-[3-(methoxymethyl)azetidin-1-yl]-3-methyl-2-(propan-2-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one;
6-(3,5-dimethoxybenzyl)-3-methyl-8-(morpholin-4-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one;
6-(4-methoxybenzyl)-3-methyl-8-(morpholin-4-yl)-2-(propan-2-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one;
6-(4-chlorobenzyl)-3-methyl-8-(morpholin-4-yl)-2-(propan-2-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one;
6-(4-chlorobenzyl)-3-methyl-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-2-(propan-2-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one;
6-(4-methoxybenzyl)-8-[3-(methoxymethyl)azetidin-1-yl]-3-methyl-2-(propan-2-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one;
6-(4-methoxybenzyl)-3-methyl-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-2-(propan-2-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one;
6-(4-chlorobenzyl)-8-[(4-hydroxypiperidin-1-yl)carbonyl]-3-methyl-2-(propan-2-yl)imidazo[1,2-c]pyrido[2,3-e]pyrimidin-5(6H)-one;

6-(4-chlorobenzyl)-N-(2-hydroxyethyl)-3-methyl-5-oxo-2-(propan-2-yl)-5,6-dihydroimidazo[1,2-c]pyrido[2,3-e]pyrimidine-8-carboxamide;
6-(4-methoxybenzyl)-8-(morpholin-4-yl)-3-(propan-2-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one;
6-(4-methoxybenzyl)-8-(morpholin-4-yl)-3-[(tetrahydro-2H-pyran-4-yloxy)methyl]pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one;
6-(4-chlorobenzyl)-8-(morpholin-4-yl)-3-(propan-2-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one;
6-(4-chlorobenzyl)-8-(morpholin-4-yl)-3-(pyridin-3-ylmethyl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one;
3-tert-butyl-6-(4-methoxybenzyl)-8-(morpholin-4-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one;
6-(4-chlorobenzyl)-3-(1-methylcyclopropyl)-8-(morpholin-4-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one;
2-[6-(4-chlorobenzyl)-8-(morpholin-4-yl)-5-oxo-5,6-dihydropyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-3-yl]-N-(propan-2-yl)acetamide;
6-(4-methoxybenzyl)-3-(2-methylpropyl)-8-(morpholin-4-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one;
6-(4-chlorobenzyl)-3-[(2-hydroxypyridin-3-yl)methyl]-8-(morpholin-4-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one;
6-(4-chlorobenzyl)-3-[(2-methylpyridin-3-yl)methyl]-8-(morpholin-4-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one;
6-(4-chlorobenzyl)-3-(1-ethyl-1H-pyrazol-5-yl)-8-(morpholin-4-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one;
6-(4-chlorobenzyl)-3-(2-methylpropyl)-8-(morpholin-4-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one;
6-(4-chlorobenzyl)-3-(1-ethyl-1H-pyrazol-3-yl)-8-(morpholin-4-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one;
6-(4-chlorobenzyl)-3-(3,5-dimethyl-1,2-oxazol-4-yl)-8-(morpholin-4-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one;

3-(cyclohexylmethyl)-6-[(4-methylphenyl)methyl]pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine;
3-(cyclohexylmethyl)-6-(4-methylbenzyl)-8-(morpholin-4-yl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine;
N-(2-methoxyethyl)-3-methyl-6-(4-methylbenzyl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazin-8-amine;
3-methyl-6-(4-methylbenzyl)-N-(oxetan-3-ylmethyl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazin-8-amine;
6-(4-methylbenzyl)-8-(morpholin-4-yl)-3-(propan-2-yl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine;
6-(3,5-dimethoxybenzyl)-3-(2-methylpropyl)-8-(morpholin-4-yl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine;
6-(4-methylbenzyl)-8-(morpholin-4-yl)-3-(tetrahydro-2H-pyran-4-ylmethyl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine;
6-(3,5-dimethoxybenzyl)-N-(2-methoxyethyl)-3-(2-methylpropyl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazin-8-amine;
6-(3,5-dimethoxybenzyl)-8-(morpholin-4-yl)-3-[(propan-2-yloxy)methyl]pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine;
6-(3,5-dimethoxybenzyl)-8-(morpholin-4-yl)-3-(prop-1-en-2-yl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine;
6-(3,5-dimethoxybenzyl)-8-[3-(methoxymethyl)azetidin-1-yl]-3-(2-methylpropyl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine;
6-(4-methoxybenzyl)-8-(morpholin-4-yl)-3-(propan-2-yl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine;
3-tert-butyl-6-(4-methoxybenzyl)-8-(morpholin-4-yl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine;
6-(4-methoxybenzyl)-8-[3-(methoxymethyl)azetidin-1-yl]-3-(2-methylpropyl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine;
6-(4-methoxybenzyl)-8-(morpholin-4-yl)-3-(tetrahydro-2H-pyran-4-ylmethyl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine;

6-(4-chlorobenzyl)-8-(morpholin-4-yl)-3-(tetrahydro-2H-pyran-4-ylmethyl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine;
6-(4-chlorobenzyl)-8-(morpholin-4-yl)-3-(propan-2-yl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine;
6-(4-chlorobenzyl)-8-[3-(methoxymethyl)azetidin-1-yl]-3-(2-methylpropyl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine;
6-(4-chlorobenzyl)-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-3-(tetrahydro-2H-pyran-4-ylmethyl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine;
6-(4-methoxybenzyl)-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-3-(tetrahydro-2H-pyran-4-ylmethyl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine;
(4-chlorophenyl){8-(morpholin-4-yl)-3-[2-(tetrahydro-2H-pyran-4-yl)ethyl]pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazin-6-yl}methanone;
6-(4-chlorobenzyl)-8-(morpholin-4-yl)-3-[1-(tetrahydro-2H-pyran-4-yl)ethyl]pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine;
6-(4-chlorobenzyl)-3-(2-methylpropyl)-8-(morpholin-4-yl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine;
(4-methoxyphenyl)[8-(morpholin-4-yl)-3-(tetrahydro-2H-pyran-4-ylmethyl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazin-6-yl]methanone;
(4-chlorophenyl){8-(morpholin-4-yl)-3-[2-(tetrahydro-2H-pyran-4-yl)ethyl]pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazin-6-yl}methanol;
8-bromo-3-tert-butyl-6-(4-chlorobenzyl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine;
3-tert-butyl-6-(4-chlorobenzyl)-8-(morpholin-4-yl)pyrido[2,3-d][1,2,4]triazolo[4,3-b]pyridazine;
tert-butyl N-[1-[5-tert-butyl-8-[(4-chlorophenyl)methyl]-3,4,6,7,13-pentazatricyclo[7.4.0.02,6]trideca-1(9),2,4,7,10,12-hexaen-11-yl]-4-piperidyl]carbamate;
1-[5-tert-butyl-8-[(4-chlorophenyl)methyl]-3,4,6,7,13-pentazatricyclo[7.4.0.02,6]trideca-1(9),2,4,7,10,12-hexaen-11-yl]piperidin-4-amine;
1-[5-tert-butyl-8-[(4-chlorophenyl)methyl]-3,4,6,7,13-pentazatricyclo[7.4.0.02,6]trideca-1(9),2,4,7,10,12-hexaen-11-yl]piperidin-4-ol;

9,9-dimethyl-5-[(4-methylphenyl)methyl]-3-{[(oxetan-3-yl)methyl]amino}-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one;
3-bromo-9,9-dimethyl-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one;
5-(4-chlorobenzyl)-3-[(2-hydroxyethyl)amino]-9,9-dimethyl-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one;
5-(3,5-dimethoxybenzyl)-3-[(2-hydroxyethyl)amino]-9,9-dimethyl-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one;
5-(3,5-dimethoxybenzyl)-9-methyl-3-(morpholin-4-yl)-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one;
3-bromo-5-(3,5-dimethoxybenzyl)-9,9-dimethyl-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one;
5-(3,5-dimethoxybenzyl)-9,9-dimethyl-3-(morpholin-4-yl)-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one;
3-bromo-5-(4-chlorobenzyl)-9,9-dimethyl-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one;
5-(4-chlorobenzyl)-3-[3-(methoxymethyl)azetidin-1-yl]-9,9-dimethyl-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one;
5-(3,5-dimethoxybenzyl)-10-ethyl-3-(morpholin-4-yl)-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one;
5-(3,5-dimethoxybenzyl)-8-ethyl-3-(morpholin-4-yl)-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one;
10-ethyl-5-(4-methoxybenzyl)-3-(morpholin-4-yl)-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one;
8-ethyl-5-(4-methoxybenzyl)-3-(morpholin-4-yl)-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one;
5-(4-chlorobenzyl)-10-ethyl-3-(morpholin-4-yl)-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one;
5-(4-chlorobenzyl)-8-ethyl-3-(morpholin-4-yl)-5,8,9,10-tetrahydro-6H-pyrido[2,3-e]pyrimido[1,2-c]pyrimidin-6-one;

6-isobutyl-2-[(4-methoxyphenyl)methyl]-12-morpholino-2,4,5,7,10-pentazatricyclo[7.4.0.03,7]trideca-1(13),3,5,9,11-pentaen-8-one;
6-tert-butyl-2-[(4-methoxyphenyl)methyl]-12-morpholino-2,4,5,7,10-pentazatricyclo[7.4.0.03,7]trideca-1(13),3,5,9,11-pentaen-8-one;
6-(3,5-dimethoxybenzyl)-2,3-dimethyl-8-(morpholin-4-yl)imidazo[1,2-c]pyrazino[2,3-e]pyrimidin-5(6H)-one;
6-(4-chlorobenzyl)-9-methoxy-3-(tetrahydro-2H-pyran-4-ylmethyl)pyrimido[6,5-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one;
3-tert-butyl-6-(4-chlorobenzyl)-8-(morpholin-4-yl)pyridazo[6,5-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one;
6-(4-chlorobenzyl)-3-[(2-methylpyridin-3-yl)methyl]-8-(morpholin-4-yl)pyrido[3,4-e][1,2,4]triazolo[4,3-c]pyrimidin-5(6H)-one; and
5-isopropyl-8-[(4-methoxyphenyl)methyl]-11-morpholino-3,6,8,13-tetrazatricyclo[7.4.0.02,6]trideca-1(9),2,10,12-tetraen-7-one.

14. A pharmaceutical composition comprising a compound according to any one of claims 1 to 12 and a pharmaceutically acceptable carrier or diluent.

15. A compound for use in the treatment or prevention of pain, chronic pain and cancer pain, addiction and tolerance to analgesic, respiratory disorders and dysfunctions selected from asthma, coughs, COPD and refractory chronic cough, genitourinary diseases selected from overactive bladder, urinary incontinence, bladder pain syndrome, dysuria and endometriosis, cardiovascular disorders selected from irritable bowel syndrome (IBS) and Burning Mouth Syndrome (BMS) relating to migraines and itches, visceral organ diseases and disorders characterized by the involvement of P_2X_3 and $P_2X_{2/3}$ comprising administering to a subject in need of treatment an effective amount of a pharmaceutical composition according to claim 14.

Intellectual Property Office

Application No:	GB1811452.0	**Examiner:**	Mr Aaron Butt
Claims searched:	1-15	**Date of search:**	4 February 2019

Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
X	1-3, 6-11, 14-15	WO 2013/192229 A1 (DART NEUROSCIENCE CAYMAN LTD) See whole document, esp. Formula (I), Examples and Page 48, Line 24 to Page 49, Line 6.
X	1-2, 5-12, 14	WO 00/26218 A1 (NEUROGEN CORP) See whole document, esp. Example 15.
X	1-2, 4, 6, 8-11, 14	US 3982000 A (HARDTMANN) See whole document, esp. Example 1 and Claim 1.
X	1-3, 6-11, 14	WO 2017/046603 A1 (REDX PHARMA LTD) See whole document, esp. Formula (I).
X	1-3, 6-11, 14	WO 2015/155549 A1 (REDX PHARMA LTD) See whole document, esp. Formula (I).
X	1-3, 6-11, 14	WO 97/33889 A1 (NEUROGEN CORP) See whole document, esp. Formula I.
X	1-3, 6-11, 14	US 4463007 A (SCHLECKER ET AL) See whole document, esp. Formula I.
X	1-3, 6-11, 14	EP 0053767 A1 (BAYER AG) See whole document, esp. Claim 1.

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC^{X} :

Intellectual Property Office

Worldwide search of patent documents classified in the following areas of the IPC

A61K; C07D

The following online and other databases have been used in the preparation of this search report

EPODOC, WPI, Patent Fulltext, CAS Online, MARPAT

International Classification:

Subclass	Subgroup	Valid From
C07D	0471/14	01/01/2006
A61K	0031/4985	01/01/2006
A61K	0031/5025	01/01/2006
A61K	0031/519	01/01/2006
C07D	0487/14	01/01/2006