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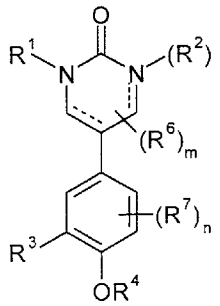
(54) **Title**: PYRIMIDINONE DERIVATIES FOR USE AS MEDICAMENTS



(I)

(57) **Abstract**: There is provided compounds of formula (I). wherein the dotted lines, R^1, R^2, R3, R^4, R^6, R^7, m and n have meanings given in the description, and pharmaceutically acceptable derivatives thereof, which compounds are useful as inhibitors of PDE7 and, particularly, PDE4, and therefore of use e.g. in the treatment of diseases and conditions associated with inflammation.

PYRIMIDINONE DERIVATIVES FOR USE AS MEDICAMENTS

Field of the Invention

The present invention is directed to substituted pyrimidinone and/or tetrahydropyrimidinone compounds and their uses as therapeutic agents, especially PDE4 inhibitors.

Background of the Invention

The Inflammatory Response (Inflammation)

Inflammation is an essential localized host response to invading microorganisms or tissue injury which involves cells of the immune system. The classic signs of inflammation include redness (erythema), swelling (edema), pain and increased heat production (pyrema) at the site of injury. The inflammatory response allows the body to specifically recognize and eliminate an invading organism and/or repair tissue injury. Many of the acute changes at the site of inflammation are either directly or indirectly attributable to the massive influx of leukocytes (e.g., neutrophils, eosinophils, lymphocytes, monocytes) which is intrinsic to this response. Leukocytic infiltration and accumulation in tissue results in their activation and subsequent release of inflammatory mediators such as LTB_4, prostaglandins, TNF-α, IL-1β, IL-8, IL-5, IL-6, histamine, proteases and reactive oxygen species for example.

Normal inflammation is a highly regulated process that is tightly controlled at several levels for each of the cell types involved in the response. For example, expression of the pro-inflammatory cytokine TNF-α is controlled at the level of gene expression, translation, post-translational modification and release of the mature form from the cell membrane. Many of the proteins up-regulated during inflammation are controlled by the transcription factor, NF-κB. Pro-inflammatory responses are normally countered by endogenous anti-inflammatory mechanisms such as generation of IL-10 or IL-4. A characteristic of a normal inflammatory response is that it is temporary in nature and is followed by a resolution phase which brings the state of the tissue back to its prior condition. The resolution phase is thought to involve up-regulation of anti-inflammatory mechanisms, such as IL-10, as well as down-regulation of the proinflammatory processes.

Inflammatory Disease

Inflammatory disease occurs when an inflammatory response is initiated that is inappropriate and/or does not resolve in the normal manner but rather persists and results in a chronic inflammatory state. Inflammatory disease may be systemic (e.g. lupus) or localized to particular tissues or organs and exerts an enormous personal and economic burden on society. Examples of some of the most common and problematic inflammatory diseases are rheumatoid arthritis, inflammatory bowel disease, psoriasis, asthma, chronic obstructive pulmonary disease, emphysema, colitis and ischemia-reperfusion injury.

A common underlying theme in inflammatory disease is a perturbation of the cellular immune response that results in recognition of host proteins (antigens) as foreign. Thus the inflammatory response becomes misdirected at host tissues with effector cells targeting specific organs or tissues often resulting in irreversible damage. The self-recognition aspect of auto-immune disease is often reflected by the clonal expansion of T-cell subsets characterized by a particular T-cell receptor (TCR) subtype in the disease state. Often inflammatory disease is also characterized by an imbalance in the levels of T-helper (Th) subsets (i.e., Th1 cells vs. Th2 cells).

Therapeutic strategies aimed at curing inflammatory diseases usually fall into one of two categories: (a) down-modulation of processes that are up-regulated in the disease state or (b) up-regulation of anti-inflammatory pathways in the affected cells or tissues. Most regimes currently employed in the clinic fall into the first category. Some examples of which are corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs).

Many of the tissue, cellular and biochemical processes which are perturbed in inflammatory disease have been elucidated and this has allowed the development of experimental models or assays to mimic the disease state. These in-vitro assays enable selection and screening of compounds with a high probability of therapeutic efficacy in the relevant inflammatory disease. Thus, currently employed assays used to model the importance of the activated leukocytes in the development of acute inflammation and maintenance of the chronic inflammatory state are assays monitoring leukocyte chemotaxis and cellular degranulation and cytokine synthesis and reactive oxygen species (ROS) production assays in vitro. Since a result of acute or chronic neutrophil activation is release of ROS with resultant tissue damage, an assay for scavengers of ROS allows detection of compounds with potential therapeutic efficacy.

Cellular assays to detect inhibitors of TNF-α release from stimulated macrophage or monocytic cells are an important component of an in vitro model for inflammation as this cytokine is upregulated and has been shown to contribute to the pathology in many inflammatory diseases. Since elevated cAMP in affected cells has been shown to modulate or dampen the inflammatory response, monitoring cellular cyclic AMP (cAMP) levels, and the activity of pathways controlling cAMP levels allows for the detection of potential anti-inflammatory compounds. Assays may include monitoring the level of cAMP itself, phosphodiesterase activity, or changes in cAMP response element (CRE)-luciferase activity.

Cyclic Nucleotide Messengers and Phosphodiesterases

The cyclic nucleotides, cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), play a key role in regulating cell function and phosphodiesterases (PDEs) provide the main route for the degradation of cyclic nucleotides. cAMP is now known to control the functional and genomic responses for a variety of cellular functions triggered by a wide array of receptors (Beavo, J.A. and Brunton, L.L., *Nat. Rev. Mol. Cell Biol.*, 3, 710-718 (2002)). Local control of cAMP signalling is affected by a complex pattern of localized synthesis, by adenylate cyclise (AC), and by phosphodiesterase (PDE)-mediated enzymatic degradation.

The PDEs are a family of enzymes that catalyze the hydrolysis of 3',5'-cyclic nucleotides to 5' nucleoside monophosphates, including the conversion of cAMP to AMP and cGMP to GMP. PDE enzymes are collectively grouped as a superfamily of eleven different, but homologous, gene-families with a highly conserved catalytic domain (Soderling, S.H. and Beavo, J.A., Curr. Opin. Cell Biol., 12, 174-179 (2000)). At present twenty-one different mammalian PDE genes have been identified. Many of these genes are expressed in multiple isoforms either by differing initiation sequences or splicing patterns. Differentiation of the enzymes can be achieved on the basis of substrate specificity, kinetic properties and sensitivity to regulatory molecules. PDEs in families 5, 6 and 9 specifically catalyze the hydrolysis of cGMP while PDEs 4, 7 and 8 are specific for cAMP. Enzymes belonging to the other PDE families (1, 2, 3, 10 and 11) catalyze the hydrolysis of both cAMP and cGMP with differing kinetics. Different PDE isozymes can have specific tissue, cellular and subcellular distributions and more than one type of PDE is usually present in any given cell. The types of PDEs expressed in a cell, together with

their relative proportions and subcellular localization, control the cyclic nucleotide phenotype of that cell.

The PDE4 enzyme is responsible for selective, high affinity hydrolytic degradation of the second messenger cAMP, has a low Michaelis constant and is sensitive to inhibition by rolipram. The PDE4 enzyme family consists of four genes, which produce 4 isoforms of the PDE4 enzyme (PDE4A, PDE4B, PDE4C, and PDE4D) (Wang et al., "Expression, Purification, and Characterization of human cAMP Specific Phosphodiesterase (PDE4) Subtypes A, B, C, and D, Biochem", *Biophys. Res. Comm.*, 234, 320-324 (1997)). Moreover, various splice variants of each PDE4 isoform have been identified and play a role in the compartmentalized cAMP signalling in cells (Houslay, M.D., Schafer, P., and Zhang, K.Y., *Drug Discov. Today*, 15;10(22):1503-19 (2005)). Recently, a number of selective PDE4 inhibitors have been discovered to have beneficial pharmacological effects resulting from PDE4 inhibition as shown in a variety of disease models (Torphy et al., Environ. Health Perspect., 102 Suppl. 10, 79-84, 1994; Duplantier et al., J. Med. Chem., 39 120-125 (1996); Schneider et al., Pharmacol. Biochem. Behav., 50, 211-217 (1995); Banner and Page, Br. J. Pharmacol., 114, 93-98 (1995); Barnette et al., J. Pharmacol. Exp. Ther., 273, 674-679 (1995); Wright et al., "Differential in vivo and in vitro bronchorelaxant activities of CP-80633, a selective phosphodiesterase 4 inhibitor," *Can. J. Physiol. Pharmacol.*, 75, 1001-1008 (1997); Manabe et al., "Anti-inflammatory and bronchodilator properties of KF19514, a phosphodiesterase 4 and 1 inhibitor," *Eur. J. Pharmacol.*, 332, 97-107 (1997); and Ukita et al., "Novel, potent, and selective phosphodiesterase-4 inhibitors as antiasthmatic agents: synthesis and biological activities of a series of 1-pyridylnaphthalene derivatives," *J. Med. Chem.*, 42, 1088-1099 (1999)). Therefore, considerable interest exists in the discovery of additional selective inhibitors of PDE4.

Regulation of cAMP activity is important in many biological processes, including inflammation, depression and cognitive function. Chronic inflammation is a multitude of heterogeneous diseases characterized in part by activation of multiple inflammatory cells, particularly cells of lymphoid lineage (including T lymphocytes) and myeloid lineage (including granulocytes, macrophages, and monocytes). Activation of these inflammatory cells results in production and release of proinflammatory mediators, including cytokines and chemokines, such as tumor necrosis factor (TNF) and interleukin-1 (IL-1). Discovery of a molecule that suppresses or inhibits such cellular activation and proinflammatory mediator release would be useful in the therapeutic treatment of inflammatory diseases. Elevated cAMP levels suppress inflammatory cell activation. Increased cAMP levels

associated with PDE4 inhibition has therefore become a valid potential therapeutic approach to control inflammatory responses and disorders (Beavo et al., "Cyclic Nucleotide Phosphodiesterases: Structure, Regulation and Drug Action," Wiley and Sons, Chichester, pp. 3-14 (1990); Torphy et al., *Drug News and Perspectives*, 6, pp. 203-214 (1993); Giembycz et al., *Clin. Exp. Allergy*, 22, pp. 337-344 (1992); and Sanz, M.J., Cortijo, J., Morcillo, E.J., *Pharmacol Ther.* 106(3):269-97 (2005)).

PDE4 inhibitors have recently shown clinical utility in mitigating the effects of the chronic pulmonary inflammatory diseases of asthma and chronic obstructive pulmonary disease (COPD). Roflumilast, a selective PDE4 inhibitor, demonstrated improvements in measures of airway function (forced expiratory volume in 1 second; FEV1, and peak expiratory flow; PEF) in mild asthmatics in a recently published clinical trial of 12 weeks duration (Bateman et al., Ann. Allergy Asthma Immunol., 96(5): 679-86 (2006)). A separate study with roflumilast also demonstrated improvements in airway hyper-responsiveness (AHR) to direct histamine provocation in a similar group of mild asthmatics in response to allergen challenge (Louw et al., Respiration, Sept. 5 2006). Recently published results of a long term (6 month) study of cilomilast treatment in patients with COPD indicated that treatment with a selective PDE4 inhibitor arrested airway function (FEV1) decline in these patients and positively affected their quality of life as measured by the St. Georges Respiratory Questionnaire (Rennard et al., *Chest*, 129(1) 65-66 (2006)).

The clinical usefulness of PDE4 inhibition has also been demonstrated in disorders of the central nervous system. PDE4 inhibition by rolipram improves cognitive function in rodents and was developed as an antidepressant in humans. cAMP acts as a second messenger for neurotransmitters, and thus mediates their cellular responses. The therapeutic effects of PDE4 inhibitors in cognition and depression likely originate from enhancement of the cAMP-dependent cellular responses.

The listing or discussion of an apparently prior-published document in this specification should not necessarily be taken as an acknowledgement that the document is part of the state of the art or is common general knowledge.

International patent application WO 2007/081570 discloses various compounds that may be useful in the treatment of cholesterol-related diseases. However, there is no disclosure that such compounds may be useful as phosphodiesterase 4 inhibitors, and

therefore in the treatment of inflammation. Further, there is no specific disclosure of substituted pyrimidinones and tetrahydropyrimidinones.

International patent application WO 2006/124874 discloses a broad range of *inter alia* heterocyclic compounds that may be of use as inhibitors of B-Raf, and therefore of use in the treatment of cancer. There is no specific disclosure in that document of substituted pyrimidinones and tetrahydropyrimidinones.

US patents/applications US 6,162,927, US 2002/0055457, US 7,208,517 and US 2007/0203124, international patent applications WO 2002/11713, WO 2002/011713, WO 99/006397, WO 96/006095, WO 97/030045, WO 02/017912, WO 2005/115389 and WO 95/028926 and European patent EP 299 549 all disclose various compounds, including heterocycles, which may be useful as medicaments. However, there is no disclosure in any of these documents of substituted pyrimidinones and/or tetrahydropyrimidinones.

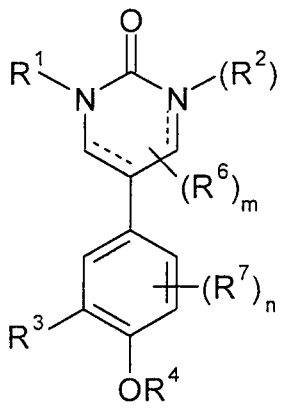
Further, US patent applications US 2003/0186943 and US 2004/0224316 and international patent applications WO 00/14083, WO 2004/031149, WO 2007/137181, WO 2004/091609 and WO 2004/016227 disclose *inter alia* piperidinones that may be useful in the treatment of inflammation-based diseases. However, these documents do not disclose substituted pyrimidinones and/or tetrahydropyrimidinones.

International patent application WO 01/68600 discloses various compounds, including pyrrolidinones and tetrahydropyrimidinoes, which may be useful in the treatment of inflammation-based diseases. However, there is no disclosure of pyrimidinones and tetrahydropyrimidinones substituted (*via* a linker) with certain heteroaryl or heterocycloalkyl groups.

International patent application WO 2007/110793 discloses various compounds, including piperidinones that may be useful as PDE inhibitors. However, there is no disclosure in that document of pyrimidinones.

Disclosure of the Invention

According to the invention, there is now provided a compound of formula (I),



I

wherein:

the dotted lines each independently represent an optional bond (and when the dotted line between the carbon and nitrogen is present, then R^2 is absent, and when the dotted line between the carbon and nitrogen is absent, then R^2 is present);

m represents 0, 1, 2, 3, 4 or 5;

n represents 0, 1, 2 or 3;

at least one of R^1 and, if present, R^2 represents $-A^1-T^z-B^1$ and the other (if present) represents R^5;

R^3 represents hydrogen, $-OR^{4a}$, C_{1-12} alkyl (optionally substituted by one or more substituents selected from =O and X^1) or $-B^2$;

R^4 and R^{4a} independently represent hydrogen, C_{1-12} alkyl (optionally substituted by one or more substituents selected from =O and X^2) or $-B^3$;

R^5 represents hydrogen, C_{1-12} alkyl (optionally substituted by one or more substituents selected from =O and X^3) or $-B^{3a}$;

each R^6 and each R^7 independently represent X^4, C_{1-12} alkyl (optionally substituted by one or more substituents selected from =O and X^5) or $-B^4$; or

any two R^6 groups may be linked together to form a further ring, which is formed either by the two relevant groups being linked together by a direct bond or C_{1-5} alkylene;

A^1 represents C_{1-12} alkylene (optionally substituted by one or more substituents selected from =O and X^6);

T^z represents a direct bond, $-N(R^{w1})-$ or $-C(O)N(R^{w2})-$;

R^{w1} and R^{w2} independently represent hydrogen, C_{1-12} alkyl (optionally substituted by one or more substituents selected from X^7) or $-B^5$;

B^1 represents:
1) a monocyclic 5-membered heteroaryl group;
2) a polycyclic heteroaryl group;
3) a polycyclic aryl group; or
4) a heterocycloalkyl group,
all four of which are optionally and independently substituted with one or more substituents selected from X^8 and, in the case of heterocycloalkyl or any non-aromatic rings of a polycyclic aryl or heteroaryl group, =O;

B^2, B^3 and B^{3a} independently represent aryl (optionally substituted by one or more substituents selected from X^9), heterocycloalkyl (optionally substituted by one or more substituents selected from =O and X^{10}) or heteroaryl (optionally substituted by one or more substituents selected from X^{11});

B^4 and B^5 independently represent heterocycloalkyl (optionally substituted by one or more substituents selected from =O and X^{12});

X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, X^{10} X^{11} and X^{12} independently represent B^6, halo, -CN, $-NO_2$, $-Si(R^{8a})_3$, $-OR^{9a}$, $-OC(O)-R^{9b}$, $-N(R^{9c})R^{9d}$, $-C(O)R^{9e}$, $-C(O)OR^{9f}$, $-C(O)N(R^{9g})R^{9h}$, $-N(R^{9i})C(O)OR^{8b}$, $-N(R^{9j})C(O)R^{8c}$, $-N(R^{9k})S(O)_tR^{8d}$, $-S(O)_tOR^{8e}$, $-S(O)_pR^{8f}$, $-S(O)_tN(R^{9m})R^{9n}$, $-N(R^{9p})C(O)N(R^{9q})R^{9r}$, $-N(R^{9s})S(O)_tOR^{8g}$, $-OC(O)N(R^{9t})R^{9u}$ and/or $-OS(O)_tR^{8h}$;

R^{8a}, R^{8b}, R^{8d}, R^{8f}, R^{8g} and R^{8h} independently represent C_{1-12} alkyl optionally substituted by one or more substituents selected from =O and E^1;

R^{8c}, R^{8e}, R^{9a}, R^{9b}, R^{9c}, R^{9d}, R^{9e}, R^{9f}, R^{9g}, R^{9h}, R^{9i}, R^{9j}, R^{9k}, R^{9m}, R^{9n}, R^{9p}, R^{9q}, R^{9r}, R^{9s}, R^{9t} and R^{9u} independently represent hydrogen or C_{1-12} alkyl optionally substituted by one or more substituents selected from =O and E^2; or

any pair of R^{9c} and R^{9d}, R^{9g} and R^{9h}, R^{9m} and R^{9n}, R^{9q} and R^{9r}, and R^{9t} and R^{9u} may be linked together with the nitrogen atom to which they are attached to form a 3- to 8-membered ring, optionally containing one or more (e.g. one or two) unsaturations (e.g. double bonds), optionally containing one or two (e.g. one) further heteroatoms (preferably selected from nitrogen and oxygen), and which ring is optionally substituted by one or more substituents selected from =O, halo and C_{1-6} alkyl optionally substituted by one or more halo atoms;

B^6 represents C_{1-12} alkyl, heterocycloalkyl (which latter two groups are optionally substituted by one or substituents selected from =O and E^3), aryl or heteroaryl (which latter two groups are optionally substituted by one or substituents selected from E^4);

t represents, at each occurrence when used herein, 1 or 2;

p represents 0, 1 or 2;

E^1, E^2, E^3 and E^4 independently represent halo, -CN, $-NO_2$, $-OR^{10a}$, $-OC(O)-R^{10b}$, $-N(R^{10c})R^{10d}$, $-C(O)R^{10e}$, $-C(O)OR^{10f}$, $-C(O)N(R^{10g})R^{10h}$, $-N(R^{10i})C(O)OR^{11a}$, $-N(R^{10j})C(O)R^{11b}$, $-N(R^{10k})S(O)_{t1}R^{11c}$, $-S(O)_{t1}OR^{11d}$, $-S(O)_{p1}R^{11e}$, $-S(O)_{t1}N(R^{10m})R^{10n}$, $-N(R^{10p})C(O)N(R^{10q})R^{10r}$, $-N(R^{10s})S(O)_{t1}OR^{11f}$, $-OC(O)N(R^{10t})R^{10u}$, $-OS(O)_{t1}R^{11g}$ and/or $-Si(R^{11h})_3$;

R^{10a}, R^{10b}, R^{10c}, R^{10d}, R^{10e}, R^{10f}, R^{10g}, R^{10h}, R^{10i}, R^{10j}, R^{10k}, R^{10m}, R^{10n}, R^{10p}, R^{10q}, R^{10r}, R^{10s}, R^{10t} R^{10u}, R^{11b} and R^{11d} independently represent hydrogen or C_{1-3} alkyl optionally substituted by one or more halo atoms;

R^{11a}, R^{11c}, R^{11e}, R^{11f}, R^{11g} and R^{11h} independently represent C_{1-3} alkyl optionally substituted by one or more halo atoms;

t1 represents, at each occurrence when used herein, 1 or 2;

p1 represents 0, 1 or 2,

or a pharmaceutically acceptable salt thereof,

which compounds are hereinafter referred to as the "compounds of the invention".

Pharmaceutically-acceptable salts include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound of formula I with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. *in vacuo*, by freeze-drying or by filtration). Salts may also be prepared by exchanging a counter-ion of a compound of the invention in the form of a salt with another counter-ion, for example using a suitable ion exchange resin.

Compounds of the invention may contain double bonds and may thus exist as *E* (*entgegen*) and *Z* (*zusammen*) geometric isomers about each individual double bond. All such isomers and mixtures thereof are included within the scope of the invention.

Compounds of the invention may also exhibit tautomerism. All tautomeric forms and mixtures thereof are included within the scope of the invention.

Compounds of the invention may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation (i.e. a 'chiral pool' method), by reaction of the appropriate starting material with a 'chiral auxiliary' which can subsequently be removed at a suitable stage, by derivatisation (i.e. a resolution, including a dynamic resolution), for example with a homochiral acid followed by separation of the diastereomeric derivatives by conventional means such as chromatography, or by reaction with an appropriate chiral reagent or chiral catalyst all under conditions known to the skilled person. All stereoisomers and mixtures thereof are included within the scope of the invention.

Unless otherwise specified, C_{1-q} alkyl, and C_{1-q} alkylene, groups (where q is the upper limit of the range), defined herein may be straight-chain or, when there is a sufficient number (i.e. a minimum of two or three, as appropriate) of carbon atoms, be branched-

chain, and/or cyclic (so forming, in the case of alkyl, a C_{3-q} cycloalkyl group or, in the case of alkylene, a C_{3-q} cycloalkylene group). Further, when there is a sufficient number (i.e. a minimum of four) of carbon atoms, such groups may also be part cyclic. Further, unless otherwise specified, such alkyl groups may also be saturated or, when there is a sufficient number (i.e. a minimum of two) of carbon atoms and unless otherwise specified, be unsaturated (forming, for example, in the case of alkyl, a C_{2-q} alkenyl or a C_{2-q} alkynyl group or, in the case of alkylene, a C_{2-q} alkenylene or a C_{2-q} alkynylene group). In the case of alkylene groups, it is preferred that they are acyclic and/or straight-chain, but may be saturated or unsaturated.

The term "halo", when used herein, includes fluoro, chloro, bromo and iodo.

Heterocycloalkyl groups that may be mentioned include non-aromatic monocyclic, bicyclic and tricyclic (e.g. monocyclic or bicyclic) heterocycloalkyl groups (which groups may further be bridged) in which at least one (e.g. one to four) of the atoms in the ring system is other than carbon (i.e. a heteroatom), and in which the total number of atoms in the ring system is between three and twelve (e.g. between five and ten). Further, such heterocycloalkyl groups may be saturated or unsaturated containing one or more double and/or triple bonds, forming for example a C_{2-q} heterocycloalkenyl (where q is the upper limit of the range) or a C_{7-q} heterocycloalkynyl group. C_{2-q} heterocycloalkyl groups that may be mentioned include 7-azabicyclo-[2.2.1]heptanyl, 6-azabicyclo[3.1.1]heptanyl, 6-azabicyclo[3.2.1]-octanyl, 8-azabicyclo[3.2.1]octanyl, aziridinyl, azetidinyl, dihydropyranyl, dihydropyridyl, dihydropyrrolyl (including 2,5-dihydropyrrolyl), dioxolanyl (including 1,3-dioxolanyl), dioxanyl (including 1,3-dioxanyl and 1,4-dioxanyl), dithianyl (including 1,4-dithianyl), dithiolanyl (including 1,3-dithiolanyl), imidazolidinyl, imidazolinyl, morpholinyl, 7-oxabicyclo[2.2.1]heptanyl, 6-oxabicyclo[3.2.1]-octanyl, oxetanyl, oxiranyl, piperazinyl, piperidinyl, pyranyl, pyrazolidinyl, pyrrolidinonyl, pyrrolidinyl, pyrrolinyl, quinuclidinyl, sulfolanyl, 3-sulfolenyl, tetrahydropyranyl, tetrahydrofuranyl, tetrahydropyridyl (such as 1,2,3,4-tetrahydropyridyl and 1,2,3,6-tetrahydropyridyl), thietanyl, thiiranyl, thiolanyl, thiomorpholinyl, trithianyl (including 1,3,5-trithianyl), tropanyl and the like. Substituents on heterocycloalkyl groups may, where appropriate, be located on any atom in the ring system including a heteroatom. Further, in the case where the substituent is another cyclic compound, then the cyclic compound may be attached through a single atom on the heterocycloalkyl group, forming a so-called "spiro"-compound. The point of attachment of heterocycloalkyl groups may be *via* any atom in the ring system including (where appropriate) a heteroatom (such as a nitrogen atom), or an atom on any fused carbocyclic ring that may be present as part of the ring

system. Heterocycloalkyl groups may also be in the *N*- or *S*- oxidised form. Most preferably, heterocycloalkyl groups that may be mentioned include 5- or 6-membered monocyclic heterocycloalkyl groups.

For the avoidance of doubt, the term "bicyclic" (e.g. when employed in the context of heterocycloalkyl groups) refers to groups in which the second ring of a two-ring system is formed between two adjacent atoms of the first ring. Bicyclic also includes bridged bicyclic groups. The term "bridged" (e.g. when employed in the context of heterocycloalkyl groups) refers to monocyclic or bicyclic groups in which two non-adjacent atoms are linked by either an alkylene or heteroalkylene chain (as appropriate).

Aryl groups that may be mentioned include C_{6-14} (such as C_{6-13} (e.g. C_{6-10})) aryl groups. Such groups may be polycyclic (e.g. monocyclic or bicyclic) and have between 6 and 14 ring carbon atoms, in which at least one ring is aromatic. C_{6-14} aryl groups include phenyl, naphthyl and the like, such as 1,2,3,4-tetrahydronaphthyl, indanyl, indenyl and fluorenyl. The point of attachment of aryl groups may be *via* any atom of the ring system. However, when aryl groups are bicyclic or tricyclic, they are linked to the rest of the molecule *via* an aromatic ring.

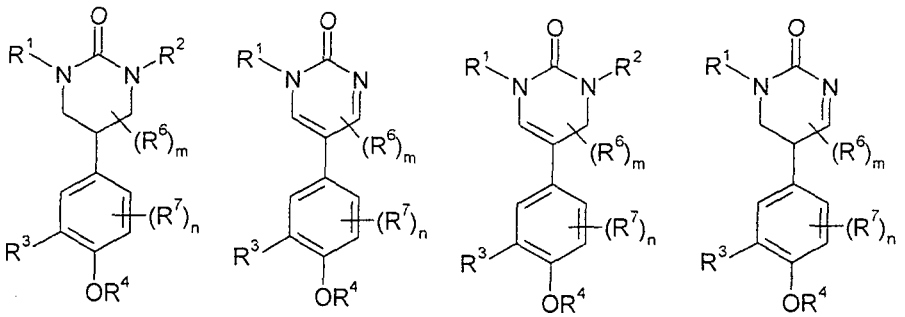
Heteroaryl groups that may be mentioned include those which have between 5 and 14 (e.g. 10) members. Such groups may be monocyclic, bicyclic or tricyclic, provided that at least one of the rings is aromatic and wherein at least one (e.g. one to four) of the atoms in the ring system is other than carbon (i.e. a heteroatom). Heteroaryl groups that may be mentioned include acridinyl, benzimidazolyl, benzodioxanyl, benzodioxepinyl, benzodioxolyl (including 1,3-benzodioxolyl), benzofuranyl, benzofurazanyl, benzothiazolyl, benzoxadiazolyl (including 2,1,3-benzoxadiazolyl), benzoxazinyl (including 3,4-dihydro-2*H*-1,4-benzoxazinyl), benzoxazolyl, benzomorpholinyl, benzoselenadiazolyl (including 2,1,3-benzoselenadiazolyl), benzothiadiazolyl (including 2,1,3-benzothiadiazolyl), benzothienyl, carbazolyl, chromanyl, cinnolinyl, furanyl, imidazolyl, imidazopyridyl (including imidazo[4,5-*b*]pyridyl, imidazo[5,4-*b*]pyridyl and imidazo[1,2-*a*]pyridyl), indazolyl, indolinyl, indolyl, isobenzofuranyl, isochromanyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiaziolyl, isothiochromanyl, isoxazolyl, naphthyridinyl (including 1,6-naphthyridinyl or, preferably, 1,5-naphthyridinyl and 1,8-naphthyridinyl), oxadiazolyl (including 1,3,4-oxadiazolyl), oxazolyl, phenazinyl, phenothiazinyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinolizinyl, quinoxalinyl, tetrahydroisoquinolinyl (including 1,2,3,4-tetrahydroisoquinolinyl and 5,6,7,8-tetrahydroisoquinolinyl),

tetrahydroquinolinyl (including 1,2,3,4-tetrahydroquinolinyl and 5,6,7,8-tetrahydroquinolinyl), tetrazolyl, thiadiazolyl (including 1,3,4-thiadiazolyl), thiazolyl, oxazolopyridyl (including oxazolo[4,5-*b*]pyridyl, oxazolo[5,4-*b*]pyridyl and, in particular, oxazolo[4,5-*c*]pyridyl and oxazolo[5,4-*c*]pyridyl), thiazolopyridyl (including thiazolo[4,5-*b*]pyridyl, thiazolo[5,4-*b*]pyridyl and, in particular, thiazolo[4,5-*c*]pyridyl and thiazolo[5,4-*c*]pyridyl), thiochromanyl, thienyl, triazolyl (including 1,2,3-triazolyl and 1,2,4-triazolyl) and the like. Substituents on heteroaryl groups may, where appropriate, be located on any atom in the ring system including a heteroatom. The point of attachment of heteroaryl groups may be *via* any atom in the ring system including (where appropriate) a heteroatom (such as a nitrogen atom), or an atom on any fused carbocyclic ring that may be present as part of the ring system. However, when heteroaryl groups are polycyclic, they are preferably linked to the rest of the molecule *via* an aromatic ring. Heteroaryl groups may also be in the *N*- or *S*- oxidised form.

Heteroatoms that may be mentioned include phosphorus, silicon, boron, tellurium, selenium and, preferably, oxygen, nitrogen and sulphur.

For the avoidance of doubt, in cases in which the identity of two or more substituents in a compound of the invention may be the same, the actual identities of the respective substituents are not in any way interdependent. For example, in the situation in which B^2 and B^3 both represent an aryl group optionally substituted as hereinbefore defined, the aryl groups in question may be the same or different. Similarly, when groups are substituted by more than one substituent as defined herein, the identities of those individual substituents are not to be regarded as being interdependent. For example, when X^1 represents two optional substituents, the identities of the two X^1 groups are not to be regarded as being interdependent. Likewise, when B^2 represents e.g. an aryl group substituted by one or more (e.g. two) X^9 groups, the identities of the two X^9 groups are not to be regarded as being interdependent.

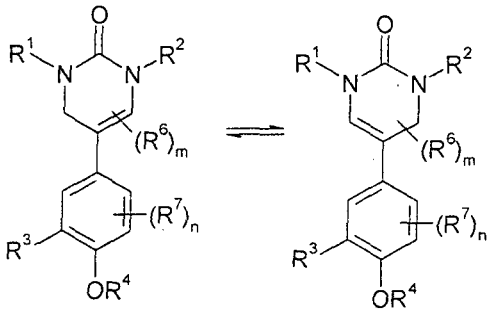
For the avoidance of doubt, where it is stated that the dotted lines may each independently represent an optional bond, we mean that when the optional bond is present (together with the existing bond represented by an unbroken line) so forming a carbon-nitrogen double bond or carbon-carbon double bond (as appropriate). Similarly, where the optional bond represented by the dotted line is absent, only a single bond between the relevant carbon-nitrogen and carbon-carbon bond (represented by the unbroken line) is present. Hence, the following compounds of formula I are included:



Ia Ib Ic Id

For the avoidance of doubt, where the dotted line between carbon and the nitrogen to which R^2 is bound represents a bond (so forming a double bond between carbon and the nitrogen to which R^2 is bound), then R^2 is absent. Similarly, where the dotted line between carbon and the nitrogen to which R^2 is bound does not represent a bond (thus resulting in a single bond between carbon and the nitrogen to which R^2 is bound), then R^2 is present.

Particularly preferred compounds of formula I, include those of formula Ic depicted above, i.e. the following compounds in which the dotted line that is not attached to a nitrogen atom represents a double bond:



which the skilled person will appreciate may be depicted as either one of the above two compounds (in view of the fact that it is specified herein that either one of R^1 and, when present, R^2 may represent certain/the same integers).

For the avoidance of doubt, $-(R^7)_n$, represents between one and three optional (i.e. R^7 may not be present) substituents (as n may be 0, 1, 2 or 3), which may be attached to any one of the three free positions of the requisite benzene ring of the compound of formula I (to which $-(R^7)_n$ is bound). Similarly, $-(R^6)_m$ represents between one and five optional (i.e. R^6 may not be present) substituents, which may be attached to any one of the free positions of the ring to which $-(R^6)_m$ ring is attached, as permitted by the standard valencies of the relevant atoms in the rings.

For the avoidance of doubt, when a term such as "*X^1 to X^{12}*" is employed herein, this will be understood by the skilled person to mean X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, X^{10}, X^{11} and X^{12} inclusively.

Compounds of the invention that may be mentioned include those in which:
R^{8e} represents C_{1-12} alkyl optionally substituted by one or more substituents selected from =O and E^1;
R^{11d} represents C_{1-3} alkyl optionally substituted by one or more halo atoms;
when an alkyl group mentioned herein is substituted with halo, then that halo group is preferably fluoro;
C_{1-12} alkyl groups mentioned herein are more preferably C_{1-6} alkyl groups.

Other compounds of the invention that may be mentioned include those in which:
there is a maximum of one R^6 group (i.e. m represents 0 or 1) present;
there are not two R^6 groups attached to the same carbon atom (of the requisite pyrimidinone ring of formula I);
any two R^6 groups present on the same carbon atom are not linked together;
any two R^6 groups are not linked together; and/or
m represents 0 (i.e. there are no R^6 substituents present).

It is stated above that compounds of the invention that may be mentioned include those in which there are not two R^6 groups attached to the same carbon atom and any two R^6 groups present on the same carbon atom are not linked together; hence, in this instance there is no tetra-substituted carbon atom in the main pyrimidinone ring of the compound of formula I.

Preferred compounds of the invention that may be mentioned include those in which:
the dotted lines either both represent bonds or, more preferably, are both not present (in another preferred embodiment, one double bond is present between two carbon atoms of the requisite pyrimidinone ring of the compound of formula I);
when B^1 represents a polycyclic aryl group, then it is preferably bicyclic (e.g. a naphthyl or tetrahydronaphthyl group), in which the point of attachment (to the T^z moiety) may be *via* an aromatic or non-aromatic ring;
when B^1 represents a polycyclic (e.g. bicyclic) heteroaryl group, the ring attached to the T^z group is a six-membered or, more preferably, five-membered heterocycloalkyl or heteroaryl ring of the polycycle;

B^1 preferably represents a monocyclic 5-membered heteroaryl group; a polycyclic (e.g. bicyclic) heteroaryl group; or a heterocycloalkyl group, all of which are optionally substituted as defined herein;

when R^3 is $-OR^{4a}$, at least one of $-R^4$ and $-R^{4a}$ is other than acyclic C_{1-12} alkyl (e.g. methyl);

when R^3 is $-OR^{4a}$, at least one of $-R^4$ and $-R^{4a}$ is cycloalkyl or heterocycloalkyl as defined herein;

when R^3 is $-OR^{4a}$, at least one of $-R^4$ and $-R^{4a}$ (e.g. R^{4a}) is other than acyclic C_{1-12} alkyl (for example, R^{4a} is cycloalkyl or heterocycloalkyl as defined herein) and the other (e.g. R^4) represents acyclic C_{1-12} (e.g. C_{1-6}) alkyl.

Preferred compounds of the invention include those in which:

m represents 3, preferably, 2, or, more preferably, 0 or 1;

n represents 2 or, preferably, 0 or 1;

R^1 represents $-A^1-T^z-B^1$;

R^3 represents hydrogen, C_{1-12} alkyl (optionally substituted by one or more substituents selected from =O and X^1) or, preferably, $-OR^{4a}$;

R^4 and R^{4a} independently represent C_{1-12} alkyl (optionally substituted by one or more substituents selected from =O and X^2) or $-B^3$;

when R^4 and R^{4a} independently represent C_{1-12} alkyl, then they may represent acyclic C_{1-6} alkyl or, preferably, a C_{3-8} (e.g. C_{5-6}) cycloalkyl group (both of which may be optionally substituted as defined herein);

for instance, certain compounds of formula I in which one of R^4 and R^{4a} is acyclic (e.g. acyclic C_{1-6} alkyl as defined herein) and the other is acyclic (e.g. acyclic C_{1-6} alkyl as defined herein) or, preferably, cyclic (e.g. a C_{3-8} (e.g. C_{5-6}) cycloalkyl group), i.e. most preferably, one of R^4 and R^{4a} is acyclic and the other is preferably cyclic;

R^{4a} more preferably represents a 5- or 6-membered (e.g. 5-membered) heterocycloalkyl group (e.g. in which the heterocycloalkyl group contains two or preferably one heteroatom, preferably selected from nitrogen or, especially oxygen) or, R^{4a} more preferably represents C_{3-8} cycloalkyl (e.g. C_{5-6} cycloalkyl), which heterocycloalkyl and cycloalkyl groups are optionally substituted as hereinbefore defined, but which are preferably unsubstituted;

R^4 more preferably represents C_{1-12} alkyl, such as acyclic C_{1-6} alkyl (e.g. C_{1-3} alkyl, scuh as methyl), which group may be substituted as defined herein, but is preferably unsubstituted;

R^5 represents C_{1-6} (e.g. C_{1-3}) alkyl (optionally substituted by one or more substituents selected from =O and X^3) or, preferably, hydrogen;

each R^6 and each R^7 independently represent X^4 or C_{1-6} (e.g. C_{1-3}) alkyl (optionally substituted by one or more substituents selected from =O and X^5);

any two R^6 groups are not linked together;

A^1 represents C_{1-6} (e.g. C_{1-3}) alkylene (e.g. methylene) (optionally substituted by one or more substituents selected from =O and X^6; but preferably unsubstituted);

R^{w1} and R^{w2} independently represent C_{1-3} alkyl (e.g. methyl) or, preferably, hydrogen;

B^1 represents a 5-membered heteroaryl group or, preferably, a polycyclic (e.g. bicyclic) heteroaryl group (both of which are) optionally substituted with one or more substituents selected from X^8;

when B^1 represents a 5-membered heteroaryl group, then it preferably contains one or two heteroatoms, preferably selected from nitrogen, oxygen and sulfur (more preferably, it contains at least one nitrogen heteroatom and preferably another one heteroatom, i.e. two heteroatoms in total);

when B^1 represents a 5-membered heteroaryl group, then it may be unsubstituted, but is preferably substituted by one or more (e.g. one or two) X^8 substituents (e.g. e.g. halo (e.g. F or Cl), C_{1-3} alkyl (e.g. CH_3 or CF_3) or $-OR^{9e}$ (e.g. OCH_3 or OCF_3), or, more preferably, the X^8 substituents are e.g. halo or C_{1-3} alkyl, e.g. chloro or methyl);

when B^1 represents a polycyclic (e.g. bicyclic) heteroaryl group, then the point of attachment of that polycyclic heteroaryl group to the T^z group is *via* a heterocyclic (e.g. heteroaromatic) ring of that polycyclic group (most preferably the point of attachment is *via* a 5-membered heteroaromatic ring);

B^2, B^3, B^{3a} independently represent phenyl (optionally substituted by one or more substituents selected from X^9), a 5- or 6-membered heterocycloalkyl group (optionally substituted by one or more substituents selected from =O and X^{10}) or a 5- or 6-membered heteroaryl group (optionally substituted by one or more substituents selected from X^{11});

when B^2, B^3 and B^{3a} represent a 5- or 6-membered heterocycloalkyl or heteroaryl group, then, in each case, the heteroatom(s) is/are preferably selected from oxygen and nitrogen (further, in the case where B^2, B^3 and B^{3a} represent heteroaryl, then the heteroatom(s) may also be selected from sulfur);

when B^2, B^3 and B^{3a} represent a 5- or 6-membered heterocycloalkyl or heteroaryl group, then those groups contain two or, preferably, one heteroatom(s);

B^4 and B^5 independently represent a 5- or 6-membered heterocycloalkyl group (optionally substituted by one or more substituents selected from =O and X^{12});

when B^4 and B^5 represent a 5- or 6-membered heterocycloalkyl group, then the heteroatom(s) is/are preferably selected from oxygen and nitrogen;

when B^4 and B^5 represent a 5- or 6-membered heterocycloalkyl group, then those groups contain two or, preferably, one heteroatom(s);

B^3 represents a five-membered heteroaryl or heterocycloalkyl group, in which the heteroatom is preferably oxygen (so forming, e.g. a furanyl or tetrahydrofuranyl group);

X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, X^{10}, X^{11} and X^{12} independently represent B^6, preferably, $-C(O)OR^{9f}$, $-S(O)_tN(R^{9m})R^{9n}$, $-N(R^{9k})S(O)_tR^{8d}$ and/or, more preferably, -CN, $-NO_2$, halo (e.g. fluoro), $-OR^{9a}$, $-N(R^{9c})R^{9d}$, $-C(O)N(R^{9g})R^{9h}$ and/or $-N(R^{9j})C(O)R^{8c}$;

X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, X^{10}, X^{11} and X^{12} (especially X^8) independently represents, at each occurrence when used herein, B^6, -CN, $-NO_2$, halo (e.g. fluoro), $-OR^{9a}$, $-N(R^{9c})R^{9d}$, $-C(O)N(R^{9g})R^{9h}$ and/or $-N(R^{9j})C(O)R^{8c}$;

R^{8a}, R^{8b}, R^{8d}, R^{8e}, R^{8f}, R^{8g} and R^{8h} independently represent C_{1-6} (e.g. C_{1-3}) alkyl optionally substituted by one or more substituents selected from E^1;

R^{8c}, R^{9a}, R^{9b}, R^{9c}, R^{9d}, R^{9e}, R^{9f}, R^{9g}, R^{9h}, R^{9i}, R^{9j}, R^{9k}, R^{9m}, R^{9n}, R^{9p}, R^{9q}, R^{9r}, R^{9s}, R^{9t} and R^{9u} independently represent hydrogen or C_{1-6} (e.g. C_{1-4} or, preferably, C_{1-3}) alkyl (e.g. *t*-butyl or, preferably, methyl) optionally substituted by one or more substituents selected from E^2; or

any pair of R^{9c} and R^{9d}, R^{9g} and R^{9h}, R^{9m} and R^{9n}, R^{9q} and R^{9r}, and R^{9t} and R^{9u} may be linked together with the nitrogen atom to which they are attached to form a 5- or 6-membered ring, optionally containing one or two double bonds, optionally containing one further nitrogen or oxygen heteroatom, and which ring is optionally substituted by one or more substituents selected from fluoro, =O and C_{1-3} alkyl optionally substituted by one or more fluoro atoms (more preferably, any R^9 pair are not linked together);

B^6 represents (acyclic or, e.g. preferably, cyclic) C_{3-8} alkyl, 5- or 6-membered heterocycloalkyl (both of which are optionally substituted by one or more E^3 substituents), preferably, heteroaryl or, more preferably, aryl (e.g. phenyl), which latter two groups are optionally substituted by one or more E^4 substituents;

E^1, E^2, E^3 and E^4 independently represent $-N(R^{10k})S(O)_{t1}R^{11c}$, $-S(O)_{t1}N(R^{10m})R^{10n}$, preferably, $-NO_2$, $-C(O)OR^{10f}$, or, more preferably, halo, -CN, $-OR^{10a}$, $-N(R^{10c})R^{10d}$, $-C(O)N(R^{10g})R^{10h}$ and/or $-N(R^{10j})C(O)R^{11b}$ (particularly preferred groups, e.g. E^2 groups, include $-C(O)N(R^{10g})R^{10h}$);

R^{10a}, R^{10b}, R^{10c}, R^{10d}, R^{10e}, R^{10f}, R^{10g}, R^{10h}, R^{10i}, R^{10j}, R^{10k}, R^{10m}, R^{10n}, R^{10p}, R^{10q}, R^{10r}, R^{10s}, R^{10t}, R^{10u} and R^{11b} independently represent hydrogen, $-CH_3$ or $-CF_3$ (e.g. R^{10g} and R^{10h} independently represent hydrogen);

R^{11a}, R^{11c}, R^{11d}, R^{11e}, R^{11f}, R^{11g} and R^{11h} independently represent $-CH_3$ or $-CF_3$.

When B^1 represents a monocyclic 5-membered heteroaryl group, preferred groups include represents pyrazolyl, thiazolyl, furanyl, imidazolyl and oxazolyl. Particularly preferred groups are 1,3-dimethyl-pyrazol-5-yl and 2-chloro-thiazol-5-yl.

When B^1 represents a polycyclic (e.g. bicyclic) heteroaryl group, preferred groups include optionally substituted (e.g. by X^8) benzoxazolyl (e.g. 2-benzoxazolyl), benzimidazolyl (e.g. 2-benzimidazolyl), benzofuranyl (e.g. 2-benzofuranyl), indolyl (e.g. 3-indolyl), benzothienyl (e.g. 3-benzothienyl), benzothiazolyl (e.g. 2-benzothiazolyl), benzotriazolyl (e.g. benzo-1,2-3-triazol-1-yl) and oxazolopyridinyl (e.g. oxazolo[5,4-b]pyridinyl, oxazolo[5,4-c]pyridinyl, oxazolo[4,5-b]pyridinyl or oxazolo[4,5-c]pyridinyl). Particularly preferred bicyclic heteroaryl groups include benzimidazolyl (e.g. 2-benzimidazolyl) or, preferably, benzoxazolyl (e.g. 2-benzoxazolyl) groups. Particularly preferred groups are 5-fluoro-benzoxazol-2-yl, 1-[-C(O)O*t*-butyl]-benzimidazol-2-yl, 5-methoxy-benzofuran-2-yl, unsubstituted benzimidazol-2-yl, 4-fluoro-benzoxazol-2-yl, 7-fluoro-benzoxazol-2-yl, 6-fluoro-benzoxazol-2-yl, 5-fluoro-benzoxazol-2-yl, 4-cyano-benzoxazol-2-yl and 7-cyano-benzoxazol-2-yl.

Preferred optional substituents on B^1 groups include $-C(O)O-C_{1-4}$ alkyl (e.g. -C(O)O-*t*-butyl); or, preferably, C_{1-4} alkyl (e.g. methyl) optionally substituted by one or more halo atoms (so forming, for example, a difluoromethyl or trifluoromethyl group); halo (e.g. chloro or fluoro); -CN; and $-O-C_{1-4}$ alkyl (e.g. methoxy) optionally substituted by one or more substituents selected from $-C(O)N(R^{18})_2$ (in which R^{18} is preferably hydrogen; so forming, for example an acetamidoxy substituent) or, more preferably, halo (so forming, for example, a difluoromethoxy or trifluoromethoxy group). Particularly preferred such substituents include fluoro atoms. Further, such substituents may, for example, when substituted on a benzimidazolyl (e.g. 2-benzimidazolyl) or benzoxazolyl (e.g. 2-benzoxazolyl) group, be in the 4- to 7- (e.g. 4-, 7- or, preferably, 5-) position.

More preferred compounds of the invention include those in which:

m represents 0;

n represents 0;

the dotted lines both represent bonds (i.e. there are two double bonds in the requisite 6-membered ring of formula I, thereby forming a pyrimidinone), are both not present (i.e. there are only single bonds in the requisite 6-membered ring of formula I, thereby forming a tetrahydropyrimidinone), or, preferably, one of the dotted lines (e.g. the dotted line between two carbon atoms) represents a bond (i.e. such that there is one double

bond present between two carbon atoms in the requisite 6-membered ring of formula I, thereby forming a 2-oxo-2,3-dihydro-pyrimidin-1-yl group);

R^3 represents $-OR^{4a}$;

R^{4a} preferably represents furanyl (e.g. 3-furanyl), tetrahydrofuranyl (e.g. 3-tetrahydrofuranyl) or, more preferably, cyclopentyl;

R^4 represents trifluoromethyl, difluoromethyl or, preferably, methyl;

R^5 represents H;

A^1 represents $-CH_2-$;

T^2 represents a direct bond;

B^1 (preferably unsubstituted or, more preferably, substituted with at least one group selected from X^8) represents pyrazolyl (e.g. 5-pyrazolyl) or, preferably, benzofuranyl (e.g. 3-benzofuranyl or 2-benzofuranyl), benzoxazolyl (e.g. 2-benzoxazolyl), benzimidazolyl (e.g. 2-benzimidazolyl), thienyl (e.g. 2-thienyl), furanyl (e.g. 2-furanyl), imidazolyl (e.g. 2-imidazolyl), oxazolyl (e.g. 2-oxazolyl), thiazolyl (e.g. e.g. 5-thiazolyl or, preferably, 2-thiazolyl), indolyl (e.g. 3-indolyl or 2-indolyl), benzothienyl (e.g. 3-benzothienyl or 2-benzothienyl) or benzotriazolyl (e.g. 1-benzotriazolyl or 2-benzotriazolyl);

X^8 represents C_{1-2} alkyl (e.g. methyl), preferably, $-C(O)O-C_{1-4}$ alkyl (e.g. -C(O)O-*t*-butyl); or, more preferably, $-OCH_3$; halo (e.g. -F and/or -Cl); $-CH_3$; $-NO_2$; -CN; $-CF_3$ and $-O-CH_2-C(=O)-NH_2$.

Particularly preferred compounds of the invention include those in the following list:

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(7-methoxy-2-benzofurylmethyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(7-fluoro-2-benzofurylmethyl)tetrahydropyrimidin-2-one;

1-(2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5,6-dimethyl-2-benzimidazolylmethyl)tetrahydropyrimidin-2-one;

1-(2-benzofurylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(2-thienylmethyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(2-furylmethyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(2-imidazolylmethyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(1-methyl-2-imidazolylmethyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(2-oxazolylmethyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(2-thiazolylmethyl)tetrahydropyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(3-indolylmethyl)tetrahydropyrimidin-2-one;
1-(3-benzothienylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)tetrahydropyrimidin-2-one;
1-(2-benzothiazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)tetrahydropyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5-methyl-2-benzoxazolylmethyl)tetrahydropyrimidin-2-one;
1-(6-chloro-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)tetrahydropyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(4-methyl-2-benzoxazolylmethyl)tetrahydropyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(6-methyl-2-benzoxazolylmethyl)tetrahydropyrimidin-2-one;
1-(1-benzotriazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)tetrahydropyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5-nitro-2-benzoxazolylmethyl)tetrahydropyrimidin-2-one;
1-(5-cyano-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)tetrahydropyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5-fluoro-2-benzoxazolylmethyl)tetrahydropyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5-trifluoromethyl-2-benzoxazolylmethyl)tetrahydropyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(7-methyl-2-benzoxazolylmethyl)tetrahydropyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5-methoxy-2-benzoxazolylmethyl)tetrahydropyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(4-methoxy-2-benzoxazolylmethyl)tetrahydropyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(4-fluoro-2-benzoxazolylmethyl)tetrahydropyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(7-fluoro-2-benzoxazolylmethyl)tetrahydropyrimidin-2-one;
1-(4-cyano-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)tetrahydropyrimidin-2-one;

1-(7-chloro-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)tetrahydropyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(4-trifluoromethyl-2-benzoxazolylmethyl)tetrahydropyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5-methoxy-2-benzofurylmethyl)tetrahydropyrimidin-2-one;
1-(2-benzimidazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)tetrahydropyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(1-methyl-2-benzimidazolylmethyl)tetrahydropyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5,6-dichloro-2-benzimidazolylmethyl)tetrahydropyrimidin-2-one;
1-(4-acetamidoxy-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)tetrahydropyrimidin-2-one;
31(7-acetamidoxy-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)tetrahydropyrimidin-2-one;
1-(4-cyano-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-difluoromethoxyphenyl)tetrahydropyrimidin-2-one;
1-(4-cyano-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-trifluoromethoxyphenyl)tetrahydropyrimidin-2-one;
1-(4-cyano-2-benzoxazolylmethyl)-5-[4-difluoromethoxy-3-(3-tetrahydrofuranyloxy)-phenyl]tetrahydropyrimidin-2-one;
1-(4-cyano-2-benzoxazolylmethyl)-5-[4-methoxy-3-(3-tetrahydrofuranyloxy)phenyl]-tetrahydropyrimidin-2-one;
1-(4-cyano-2-benzoxazolylmethyl)-5-[4-trifluoromethoxy-3-(3-tetrahydrofuranyloxy)-phenyl]tetrahydropyrimidin-2-one.

Further particularly preferred compounds of the invention include those in the following list:

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(7-methoxy-2-benzofurylmethyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(7-fluoro-2-benzofurylmethyl)pyrimidin-2-one;
1-(2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5,6-dimethyl-2-benzimidazolylmethyl)pyrimidin-2-one;
1-(2-benzofurylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(2-thienylmethyl)pyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(2-furylmethyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(2-imidazolylmethyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(1-methyl-2-imidazolylmethyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(2-oxazolylmethyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(2-thiazolylmethyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(3-indolylmethyl)pyrimidin-2-one;
1-(3-benzothienylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)pyrimidin-2-one;
1-(2-benzothiazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5-methyl-2-benzoxazolylmethyl)pyrimidin-2-one;
1-(6-chloro-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(4-methyl-2-benzoxazolylmethyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(6-methyl-2-benzoxazolylmethyl)pyrimidin-2-one;
1-(1-benzotriazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5-nitro-2-benzoxazolylmethyl)pyrimidin-2-one;
1-(5-cyano-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)pyrimidin-2-one
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5-fluoro-2-benzoxazolylmethyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5-trifluoromethyl-2-benzoxazolylmethyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(7-methyl-2-benzoxazolylmethyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5-methoxy-2-benzoxazolylmethyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(4-methoxy-2-benzoxazolylmethyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(4-fluoro-2-benzoxazolylmethyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(7-fluoro-2-benzoxazolylmethyl)pyrimidin-2-one;
1-(4-cyano-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)pyrimidin-2-one
1-(7-chloro-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(4-trifluoromethyl-2-benzoxazolylmethyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5-methoxy-2-benzofurylmethyl)pyrimidin-2-one;
1-(2-benzimidazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)pyrimidin-2-one;

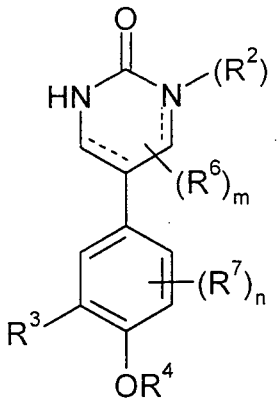
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(1-methyl-2-benzimidazolylmethyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5,6-dichloro-2-benzimidazolylmethyl)pyrimidin-2-one;
1-(4-acetamidoxy-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)pyrimidin-2-one;
1-(7-acetamidoxy-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)pyrimidin-2-one;
1-(4-cyano-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-difluoromethoxyphenyl)pyrimidin-2-one;
1-(4-cyano-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-trifluoromethoxyphenyl)pyrimidin-2-one;
1-(4-cyano-2-benzoxazolylmethyl)-5-[4-difluoromethoxy-3-(3-furanyloxy)phenyl]pyrimidin-2-one;
1-(4-cyano-2-benzoxazolylmethyl)-5-[4-methoxy-3-(3-furanyloxy)phenyl]pyrimidin-2-one;
1-(4-cyano-2-benzoxazolylmethyl)-5-[4-trifluoromethoxy-3-(3-furanyloxy)phenyl]pyrimidin-2-one.

Particularly preferred compounds of the invention include those of the examples described hereinafter.

Compounds of the invention may be made in accordance with techniques that are well known to those skilled in the art, for example as described hereinafter.

According to a further aspect of the invention there is provided a process for the preparation of a compound of formula I which process comprises:

(i) reaction of a compound of formula II,



II

or a protected derivative thereof, wherein R^2, R^3, R^4, R^6, R^7 and the dotted lines are as hereinbefore defined, with a compound of formula IV,

$$B^1\text{—}T^z\text{—}A^1\text{—}L^1 \qquad \text{III}$$

wherein B^1, T^z and A^1 are as hereinbefore defined, and L^1 represents a suitable leaving group, such as a sulfonate group or, more preferably an iodo, bromo or chloro group, in the presence of a base, such as a strong base, for instance an alkali metal-based base such as NaH and/or KO-*tert*-butyl, optionally in the presence of an additive (for example, a sodium or potassium co-ordinating agent, such as a crown ether (e.g. 15-crown-5)), for example in the presence of a suitable solvent, such as a polar aprotic solvent (e.g. tetrahydrofuran or diethyl ether), for example at sub-ambient temperatures (e.g. 0°C to -78°C) under an inert atmosphere. The skilled person will appreciate that the base may need to be added to the compound of formula II before the addition of the compound of formula III. Further, one leaving group may be converted into another leaving group (e.g. into a stronger/better leaving group in the compound of formula III, for instance by iodide exchange, e.g. by adding an iodide source (e.g. KI) to a compound of formula III in which L^1 is chloro, thereby exchanging the chloride with iodide);

(ii) for compounds of formula I in which the dotted lines are not present and R^2 is present and is not H, reaction of a compound of formula I in which the dotted lines are not present and R^2 is H with a compound of formula IV,

$$R^{2a}\text{—}L^2 \qquad \text{IV}$$

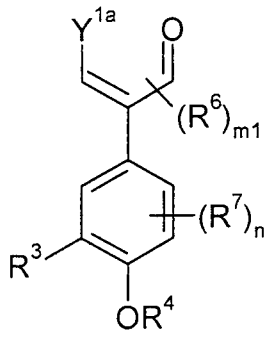
wherein R^{2a} represents R^2 as hereinbefore defined provided that it does not represent H, and L^2 represents a suitable leaving group, such as one hereinbefore defined in respect

of L^1, under suitable conditions, such as those hereinbefore described in respect of process step (i);

(iii) for compounds of formula I in which the dotted lines are not present and R^2 is H, reduction of a compound of formula I in which the dotted lines represent bonds (so forming double bonds in the compound of formula I) or protected derivatives thereof, for example under standard conditions, such as under hydrogenation reaction conditions (e.g. catalytic hydrogenation conditions in the presence of a precious metal catalyst, e.g. Pd/C);

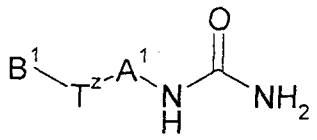
(iv) for compounds of formula I in which one or both of the dotted lines represent bonds (so forming one or two double bonds in the compound of formula I), dehydrogenation or oxidation of a compound of formula I in which one or both of the dotted lines are not present and R^2 is H, or protected derivatives thereof, for example under standard conditions, such as in the presence of a suitable reagent (e.g. DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone)) and/or by heating in the presence of Pd/C;

(v) for compounds of formula I wherein the dotted lines represent bonds, reaction of a compound of formula V,



V

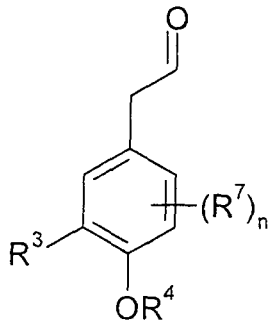
or a protected derivative thereof, wherein R^3, R^4 R^6 R^7 and n are as hereinbefore defined, and m1 is 0, 1 or 2 (the skilled person will appreciate that $-(R^6)_m$ represents two optional R_6 substituents, and that the structure of the compound of formula V dictates that these substituents may only be positioned at the carbonyl carbon and or in the β position relative to the carbonyl carbon) and Y^{1a} is -OH or $-NY^aY^b$, where Y^a and Y^b are independently alkyl (e.g. C_{1-12} alkyl, including cycloalkyl), heterocycloalkyl, aryl and/or heteroaryl, or Y^a and Y^b may be joined to form a ring optionally containing one or more additional heteroatom, with a compound of formula VI,



VI

or a protected derivative thereof, wherein B^1, T^z and A^1 are as hereinbefore defined, under suitable conditions, for example under acid reaction conditions (e.g. in the presence of a hydrogen halide (e.g. HCl) optionally in a suitable solvent, such as an alcoholic solvent, e.g. ethanol);

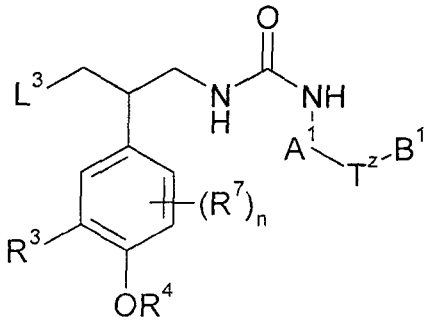
(vi) for compounds of formula I where the dotted lines represent bonds, reaction of a compound of formula VII,



VII

or a protected derivative thereof, wherein R^3, R^4, R^7 and m are as hereinbefore defined, with a compound of formula VI as hereinbefore defined and in the presence of a suitable reagent such as an ester (e.g. C_{1-6} ester) of formic acid (e.g. methyl or ethyl formate) or a suitable equivalent thereof (e.g. triethyl orthoformate) under conditions known to one skilled in the art, such as standard Aldol-type reaction conditions, conditions such as those hereinbefore defined in respect of process step (v) or, when e.g. triethyl formate is employed under acidic reaction conditions;

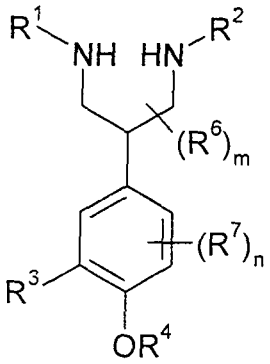
(vii) for compounds of formula I in which the dotted lines do not represent bonds and R^2 is H, intramolecular reaction of a compound of formula VIII,



VIII

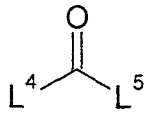
or a protected derivative thereof, wherein L^3 represents a suitable leaving group as hereinbefore defined in respect of L^1, and R^3, R^4, R^7 B^1, T^z, A^1 and n are as hereinbefore defined, under suitable conditions, such as those hereinbefore described in respect of process step (i);

(viii) for compounds of formula I in which the dotted lines do not represent bonds, reaction of a compound of formula IX,



IX

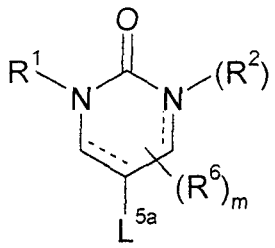
or a protected derivative thereof, where R^1, R^3, R^4, R^6, R^7, m and n are as hereinbefore defined, and R^2 is present and is as hereinbefore defined, with a compound of formula X,



X

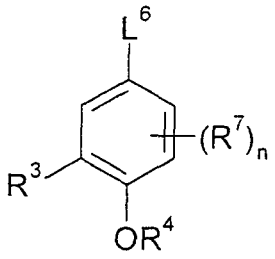
where L^4 and L^5 independently represent a suitable leaving group, such as -O-C_{1-6} alkyl (e.g. -OEt), a heterocycle (e.g. imidazole) wherein the heterocycle is bound to the carbonyl group at the heteroatom (e.g. 1,1'-carbonyldiimidazole) or a chloro group (e.g. phosgene, or a suitable phosgene derivative such as triphosgene), optionally in the presence of a suitable base, such as an amine base (e.g. pyridine), for example optionally in the presence of a suitable solvent, such as a polar aprotic solvent (e.g. toluene, preferably, tetrahydrofuran or diethyl ether);

(ix) for compounds of formula I, reaction of a compound of formula XI,



XI

or a protected derivative thereof, where R^1, R^2, R^6, m and the dotted lines are as hereinbefore defined and L^{5a} represents a suitable leaving group, such as one hereinbefore defined in respect of L^5, e.g. chloro, bromo, iodo, a sulfonate group (e.g. $-OS(O)_2CF_3$, $-OS(O)_2CH_3$, $-OS(O)_2PhMe$ or a nonaflate), $-B(OH)_2$, $-B(OR^{wx})_2$, $-Sn(R^{wx})_3$, diazonium salts, or a similar group known to the skilled person (in which each R^{wx} independently represents a C_{1-6} alkyl group, or, in the case of $-B(OR^{wx})_2$, the respective R^{wx} groups may be linked together to form a 4- to 6-membered cyclic group (such as a 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl group)), and L^{5a} preferably represents $-B(OH)_2$, with a compound of formula XII,

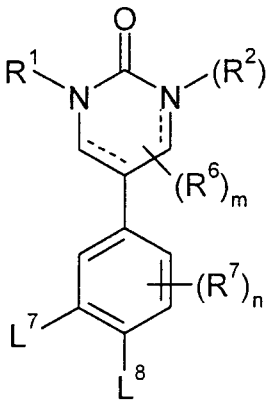


XII

or a protected derivative thereof, where R^3, R^4, R^7 and n are as hereinbefore defined, and L^6 represents a suitable leaving group such as chloro, bromo, iodo, a sulfonate group (e.g. $-OS(O)_2CF_3$, $-OS(O)_2CH_3$, $-OS(O)_2PhMe$ or a nonaflate), $-B(OH)_2$, $-B(OR^{wx})_2$, $-Sn(R^{wx})_3$ or diazonium salts, in which each R^{wx} independently represents a C_{1-6} alkyl group, or, in the case of $-B(OR^{wx})_2$, the respective R^{wx} groups may be linked together to form a 4- to 6-membered cyclic group (such as a 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl group), and L^6 preferably represents bromo (the skilled person will also appreciate that L^5 and L^6 should be mutually compatible, and may also be interchanged), for example, in the presence of a suitable catalyst system, e.g. a metal (or a salt or complex thereof) such as CuI, Pd/C, $PdCl_2$, $Pd(OAc)_2$, $Pd(Ph_3P)_2Cl_2$, $Pd(Ph_3P)_4$, $Pd_2(dba)_3$ or $NiCl_2$ and a ligand such as *t*-Bu_3P, $(C_6H_{11})_3P$, Ph_3P, $AsPh_3$, $P(o\text{-}Tol)_3$, 1,2-bis(diphenylphosphino)ethane, 2,2'-bis(di-*tert*-butylphosphino)-1,1'-biphenyl, 2,2'-bis(diphenylphosphino)-1,1'-bi-naphthyl, 1,1'-bis(diphenylphosphinoferrocene), 1,3-bis(diphenyl-phosphino)propane, xantphos, or a mixture thereof, together with a suitable base such as, Na_2CO_3, K_3PO_4, Cs_2CO_3, NaOH, KOH, K_2CO_3, CsF, Et_3N, $(i\text{-}Pr)_2NEt$, *t*-BuONa or *t*-BuOK (or mixtures thereof) in a suitable solvent such as dioxane, toluene,

ethanol, dimethylformamide, ethylene glycol dimethyl ether, water, dimethylsulfoxide, acetonitrile, dimethylacetamide, *N*-methylpyrrolidinone, tetrahydrofuran or mixtures thereof. The reaction may also be carried out for example at room temperature or above (e.g. at a high temperature such as the reflux temperature of the solvent system) or using microwave irradiation;

(x) compounds of formula I, particularly those in which R^3 represents $-OR^{4a}$ in which R^{4a} is other than hydrogen, reaction of a compound of formula XIII,



XIII

or a protected derivative thereof, wherein R^1, R^2, R^6, R^7, m, n and the dotted lines are as hereinbefore defined and L^7 represents L^x or R^3 as hereinbefore defined, and L^8 represents L^x or $-OR^4$ as hereinbefore defined, and L^x represents a suitable leaving group such as chloro, bromo, iodo, a sulfonate group (e.g. $-OS(O)_2CF_3$, $-OS(O)_2CH_3$, $-OS(O)_2PhMe$ or a nonaflate), $-B(OH)_2$, $-B(OR^n)_2$, $-Sn(R^n)_3$ or diazonium salts, in which each R^n independently represents a C_{1-6} alkyl group with a compound of formula XIV,

$$R^{4x}\text{-OH} \qquad \text{XIV}$$

wherein R^{4x} represents R^4 or R^{4a} as required/appropriate, under suitable conditions, for example optionally in the presence of an appropriate metal catalyst (or a salt or complex thereof) such as Cu, $Cu(OAc)_2$, CuI (or CuI/diamine complex), copper tris(triphenylphosphine)bromide, $Pd(OAc)_2$, $Pd_2(dba)_3$ or $NiCl_2$ and an optional additive such as Ph_3P, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, xantphos, NaI or an appropriate crown ether such as 18-crown-6-benzene, in the presence of an appropriate base such as NaH, Et_3N, pyridine, *N,N'*-dimethylethylenediamine, Na_2CO_3, K_2CO_3, K_3PO_4, Cs_2CO_3, *t*-BuONa or *t*-BuOK (or a mixture thereof, optionally in the presence of 4Å molecular sieves), in a suitable solvent (e.g. dichloromethane, dioxane, toluene, ethanol, isopropanol, dimethylformamide, ethylene glycol, ethylene glycol dimethyl ether, water,

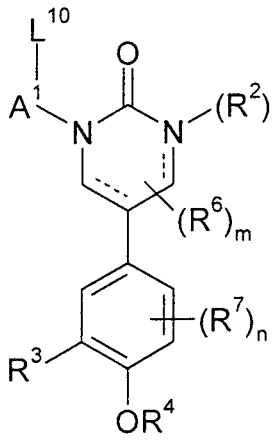
dimethylsulfoxide, acetonitrile, dimethylacetamide, *N*-methylpyrrolidinone, tetrahydrofuran or a mixture thereof) or in the absence of an additional solvent when the reagent may itself act as a solvent (e.g. when $-R^{4x}$ represents R^4 and R^4 represents methyl). This reaction may be carried out at room temperature or above (e.g. at a high temperature, such as the reflux temperature of the solvent system that is employed) or using microwave irradiation;

(xi) for compounds of formula I in which R^3 represents $-OR^{4a}$ in which R^{4a} is other than hydrogen and/or where R^4 is other than hydrogen, reaction of a corresponding compound of formula I in which R^3 represents -OH and/or R^4 represents hydrogen, with a compound of formula XV,

$$R^{4y}\text{-}L^9 \qquad \text{XV}$$

wherein R^{4y} represents R^4 or R^{4a} as required/appropriate, and L^9 represents a suitable leaving group such as one defined hereinbefore in respect of L^1, under suitable reaction conditions, for example such as those hereinbefore described in respect of process step (i);

(xii) for compounds of formula I in which T^z represents $-N(R^{w1})-$, reaction of a compound of formula XVI,



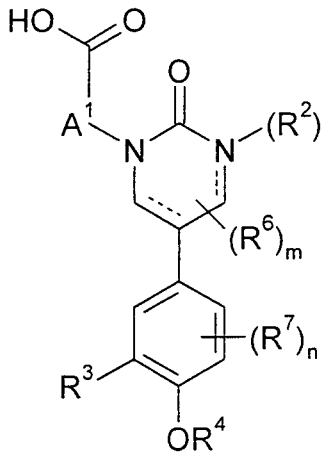
XVI

or a protected derivative thereof, wherein L^{10} represents a suitable leaving group, such as one hereinbefore defined in respect of L^1 and R^2, R^3, R^4, R^6, R^7, m, n and the dotted lines are as hereinbefore defined, with a compound of formula XVII,

$$H\text{-}Z^a \qquad \text{XVII}$$

wherein Z^a represents $-N(R^{w1})-B^1$, and R^{w1} and B^1 are as hereinbefore defined, under suitable conditions, for example those hereinbefore described in respect of process step (i);

(xiii) for compounds of formula I in which T^z represents $-C(O)-N(R^{w2})-$, reaction of a compound of formula XVIII,



XVIII

or a protected derivative thereof (e.g. an ester derivative), wherein the dotted lines, R^2, R^3, R^4, R^5, R^6, R^7, A^1, m, n and the dotted lines are as hereinbefore defined, with a compound of formula XIX,

$$H\text{-}Z^b \qquad \text{XIX}$$

wherein Z^b represents $-N(R^{w2})-B^1$, and R^{w2} and B^1 are as hereinbefore defined, under standard amide coupling reaction conditions, for example in the presence of a suitable coupling reagent (e.g. 1,1'-carbonyldiimidazole, *N,N'*-dicyclohexylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (or hydrochloride thereof), *N,N'*-disuccinimidyl carbonate, benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate, 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, benzotriazol-1-yloxytris-pyrrolidinophosphonium hexafluorophosphate, bromo-tris-pyrrolidinophosponium hexafluorophosphate, 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetra-fluorocarbonate, 1-cyclohexyl-carbodiimide-3-propyloxymethyl polystyrene, *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate and/or *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate), optionally in the presence of a suitable base (e.g. sodium hydride,

sodium bicarbonate, potassium carbonate, pyridine, triethylamine, dimethylaminopyridine, diisopropylamine, sodium hydroxide, potassium *tert*-butoxide and/or lithium diisopropylamide (or variants thereof), an appropriate solvent (e.g. tetrahydrofuran, pyridine, toluene, dichloromethane, chloroform, acetonitrile, dimethylformamide, trifluoromethylbenzene, dioxane or triethylamine) and a further additive (e.g. 1-hydroxybenzotriazole hydrate). Alternatively, the carboxylic acid group of the compound of formula XVIII may be converted under standard conditions to the corresponding acyl chloride (e.g. in the presence of $SOCl_2$ or oxalyl chloride), which acyl chloride is then reacted with a compound of formula XIX, for example under similar conditions to those mentioned above.

Compounds of formula II wherein the dotted lines represent bonds may be prepared by reaction of a compound of formula V, preferably wherein Y^1 represents -OH, with urea under conditions hereinbefore described in respect of process step (v).

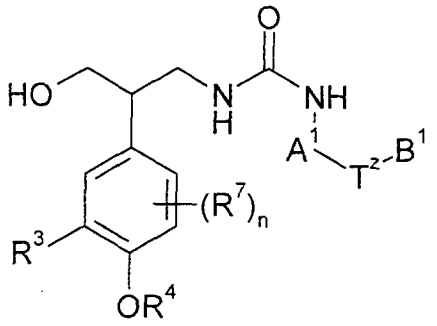
Compounds of formula V in which Y^1 represents -OH may be prepared by hydrolysis of a compound of formula V wherein Y^1 represents $-NY^aY^b$, under conditions known to those skilled in the art, for example in the presence of an aqueous base (e.g. aqueous NaOH) and optionally in the presence of a suitable solvent or solvent mixture (e.g. ethanol and water).

Compounds of formula V in which Y^1 represents -OH may also be prepared by reaction of a compound of formula VII with a suitable ester of formic acid (e.g. methyl or ethyl formate) or the like, for example under reaction conditions known to those skilled in the art, such as those hereinbefore described in respect of preparation of compounds of formula I (process step (v)).

Compounds of formula V, in which Y^1 represents $-NY^aY^b$, wherein Y^a and Y^b are both methyl, may be prepared by reaction of a compound of formula VII with DMF (which, the skilled person will understand, may also be used as a solvent or co-solvent), under conditions known to those skilled in the art, for example in the presence of $POCl_3$ and optionally in the presence of a suitable solvent or solvent mixture.

Compounds of formula VI may be prepared by reaction of urea with a compound of formula III under conditions known to those skilled in the art, for example those described hereinbefore in respect of process step (i).

Compounds of formula VIII wherein L^3 represents an iodo, chloro or, preferably, a bromo group, may be prepared by reaction of a compound of formula XX,



XX

wherein R^3, R^4, R^5, R^7, A^1, T^z, B^1 and n are as hereinbefore defined, with a suitable halogenating agent, for example, where L^3 represents a bromo group, reaction with CBr_4 and PPh_3 in the presence of a suitable solvent (e.g. dichloromethane).

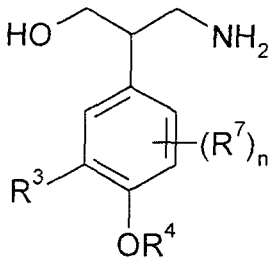
Compounds of formula VIII wherein L^3 represents a sulfonate group may be prepared by reaction of a compound of formula XX as hereinbefore defined, or a suitable protected derivative thereof, with a suitable sulfonyl chloride, for example trifluoromethane sulfonylchloride or *p*-toluene sulfonylchloride, optionally in the presence of a suitable amine base (e.g. pyridine or triethyl amine) and in the presence of a suitable solvent (e.g. dichloromethane).

Compounds of formula XVIII may be prepared by reaction of a compound of formula II as hereinbefore defined, with a compound of formula XXI,

$$L^{11}\text{-}A^1\text{-}C(O)OH \qquad \text{XXI}$$

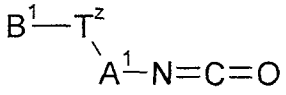
or a protected derivative (e.g. ester) thereof, wherein L^{11} represents a suitable leaving group, for example one hereinbefore defined in respect of L^1 (e.g. bromo) and A^1 is as hereinbefore defined, under standard reaction conditions known to those skilled in the art, for example such as those hereinbefore defined in respect of preparation of compounds of formula I (process step (*i*) above).

Compounds of formula XX may be prepared by reaction of a compound of formula XXII,



XXII

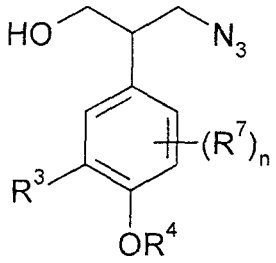
or a protected derivative thereof, with a compound of formula XXIII,



XXIII

wherein R^3, R^4, R^7, A^1, T^z, B^1 and n are as hereinbefore defined, optionally in the presence of a suitable solvent (e.g. tetrahydrofuran) and under conditions known to one skilled in the art.

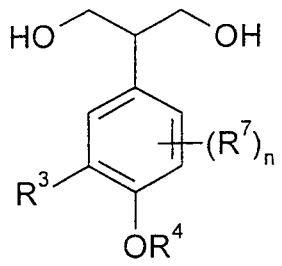
Compounds of formula XXII may be prepared by reduction of a compound of formula XXIV,



XXIV

wherein R^3, R^4, R^7 and n are as hereinbefore described, under conditions known to one skilled in the art, for example by reaction with a suitable reagent, for example a suitable reagent (e.g. triphenylphosphine), optionally in presence of a suitable solvent (e.g. THF).

Compounds of formula XXIV may be prepared by reaction of a compound of formula XXV,



XXV

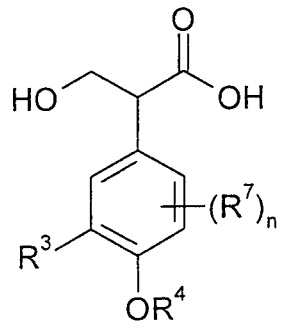
or a suitably protected derivative thereof (e.g. a mono O-protected derivative), wherein R^3, R^4, R^7 and n are as hereinbefore defined, with

A a suitable sulfonating agent (e.g. *p*-toluenesulfonyl chloride), under conditions known to one skilled in the art, for example in the presence of a suitable base (e.g. pyridine), a suitable catalyst (e.g. DMAP) and a suitable solvent (e.g. THF or DCM); followed by

B a suitable source of an azide nucleophile, for example an azide salt (e.g. sodium azide), under conditions known to one skilled in the art, for example in the presence of a suitable solvent (e.g. DMF) and optionally in the presence of a suitable metal ion complexing agent, for example a crown ether (e.g. 15-crown-5).

Compounds of formula XXV may be prepared by reduction of:

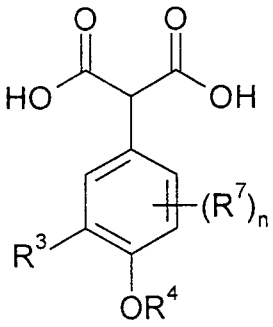
(a) a compound of formula XXVI,



XXVI

; or

(b) a compound of formula XXVIA,



XXVIA

or a suitably protected derivative thereof (e.g. ester), wherein, in both cases, R^3, R^4, R^7 and n are as hereinbefore defined, under conditions known to one skilled in the art, for example in the presence of a suitable reducing agent, such as a suitable borane or complex thereof (e.g. BH_3·THF) and in the presence of a suitable solvent (e.g. THF).

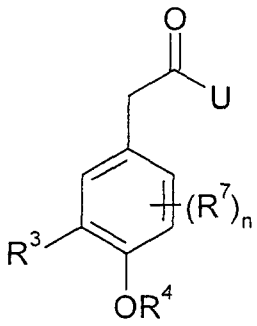
Compounds of formula XXII may also be obtained by reaction of a compound of formula XXVI as hereinbefore defined, or preferably a suitably protected derivative thereof, for example, an ester derivative (e.g. a methyl ester), with:

A a suitable sulfonating agent (e.g. *p*-toluenesulfonyl chloride, so forming a tosylate group; alternatively, the skilled person will appreciate that corresponding compounds in which the tosylate group is replaced with a different leaving group, such as chloro, bromo or iodo, may also be employed), under conditions known to one skilled in the art, for example in the presence of a suitable base (e.g. pyridine), a suitable catalyst (e.g. DMAP) and a suitable solvent (e.g. THF or DCM); followed by

B a suitable source of an azide nucleophile, for example an azide salt (e.g. sodium azide), under conditions known to one skilled in the art, for example in the presence of a suitable solvent (e.g. DMF) and optionally in the presence of a suitable metal ion complexing agent, for example a crown ether (e.g. 15-crown-5); followed by

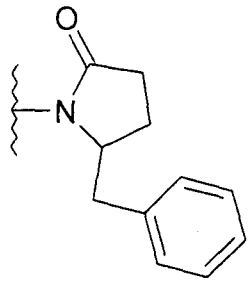
C a suitable reducing agent (e.g. lithium aluminum hydride ($LiAlH_4$)), under conditions known to one skilled in the art, for example in the presence of a suitable solvent (e.g. tetrahydrofuran).

Suitably protected derivatives (e.g. *O*-benzylated derivatives) of compounds of formula XXVI may be prepared by reaction of a compound of formula XXVII,



XXVII

wherein U represents $-OR^u$ or $-N(R^{u1})R^{u2}$, in which R^u, R^{u1} and R^{u2} independently represent hydrogen, C_{1-12} alkyl or aryl (which latter two groups may be optionally substituted by one or more substituents selected from a substituent such as one hereinbefore defined by X^1 and, in the case of C_{1-12} alkyl, =O), or, R^{u1} and R^{u2} may be linked together to form an optionally substituted (e.g. by one or more substituents selected from a substituent such as one hereinbefore defined by X^1, aryl and heteroaryl), and R^3, R^4, R^7 and n are as hereinbefore defined. Preferably R^{u1} and R^{u2} do not represent hydrogen. When R^{u1} and R^{u2} are linked together, they may together form the following group (i.e. U may represent the following group):



or an enantiomer thereof (or another suitable chiral derivative thereof, such as one based on Evans' chiral auxiliary), with formaldehyde, paraformaldehyde or a suitably protected derivative (e.g. an *O*-benzylated derivative) of a compound of formula XXVIII,

$HO\text{-}CH_2\text{-}Cl$ XXVIII

or a derivative thereof, under suitable conditions known to one skilled in the art, for example those hereinbefore defined in respect of process step (i), followed by hydrolysis under suitable conditions as known to one skilled in the art, for example in the presence of an aqueous base such as sodium hydroxide.

Compounds of formula XXVIA may be prepared by reaction of a compound of formula XXVII (as hereinbefore defined) or a compound of formula XXIX (as defined hereinafter) with a compound of formula XXVIIIA,

HO-C(O)-Cl XXVIIIA

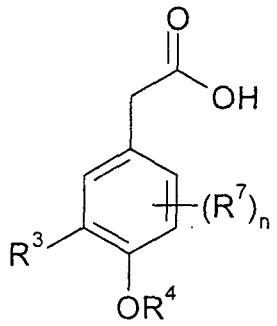
for example under reaction conditions known to those skilled in the art, such as those hereinbefore described in respect of preparation of compounds of formula XXVI.

Alternatively, compounds of formula XXVIA may be prepared by reaction of a compound corresponding to a compound of formula XII but in which L^6 represents a metal-containing group, such as Li, MgBr, ZnCl or the like (which may be prepared by reaction of a corresponding compound of formula XII in which L^6 represents halo, by e.g. lithiation, a Grignard-forming reaction, followed by, if necessary, metal-exchange reactions and the like) with a compound of formula XXVIIIB,

HO-C(O)-C(H)(W^w)-C(O)OH XXVIIIB

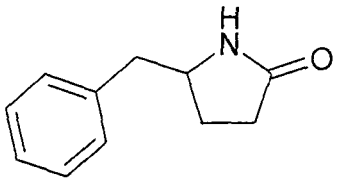
wherein W^w represents a suitable leaving group, such as chloro (or the like), for example under reaction conditions known to those skilled in the art, e.g. such as those catalytic reaction conditions described in respect of preparation of compounds of formula I (process step (ix)).

Compounds of formula XXVII may be prepared by reaction of a compound of formula XXIX,



XXIX

wherein R^3, R^4, R^7 and n are as hereinbefore defined, with a compound of formula XXX,



XXX

under suitable conditions known to one skilled in the art, such as those hereinbefore described in respect of process step (xiii).

Compounds of formulae IV, VII, X, XI, XII, XIII, XV, XVI, XXVIIIA, XXVIIIB, XXIX and XXX (and also others, e.g. certain compounds of formulae VI and IX) may be commercially available, are known in the literature, or may be obtained either by analogy with the processes described herein, or by conventional synthetic procedures, in accordance with standard techniques, from available starting materials using appropriate reagents and reaction conditions. In this respect, the skilled person may refer to *inter alia* "*Comprehensive Organic Synthesis*" by B. M. Trost and I. Fleming, Pergamon Press, 1991.

The substituents either in final compounds of the invention or in relevant intermediates (as appropriate) may be modified one or more times, after or during the processes described above by way of methods that are well known to those skilled in the art. Examples of such methods include substitutions, reductions, oxidations, alkylations, acylations, hydrolyses, esterifications, etherifications, halogenations or nitrations. Such reactions may result in the formation of a symmetric or asymmetric final compound of the invention or intermediate. In this respect, the skilled person may also refer to "*Comprehensive Organic Functional Group Transformations*" by A. R. Katritzky, O. Meth-Cohn and C. W. Rees, Pergamon Press, 1995. Specific transformation steps that may be mentioned include the conversion of one L^6 group (in the compound of formula XII) into another L^6 group (e.g. the conversion of one halo group, such as chloro, into another halo group, such as iodo, for example by reaction in the presence of potassium iodide), or even the conversion of a hydroxy group to a boronic acid group. Other transformation steps include the reduction of a nitro group to an amino group, the hydrolysis of a nitrile group to a carboxylic acid group, and standard nucleophilic aromatic substitution reactions.

As stated herein, the skilled person will also appreciate that chiral groups may be employed in order to obtain optically active compounds of the invention or intermediates thereof. For example, optically active compounds of formula XXVII may be employed (e.g. a variant based on Evan's chiral auxiliary).

It will also be appreciated by those skilled in the art that in the process described below the functional groups of intermediate compounds may need to be protected by suitable protecting groups. Such functional groups include hydroxy, amino, mercapto and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl or diarylalkylsilyl (e.g., t-butyldimethylsilyl, t-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl, benzyl, methyl and the like. Suitable protecting groups for amino, amidino and guanidino include t-butoxycarbonyl, benzyloxycarbonyl, and the like. Suitable protecting groups for mercapto include -C(O)-R" (where R" is alkyl, aryl or aralkyl), p-methoxybenzyl, trityl and the like. Suitable protecting groups for carboxylic acid include alkyl, aryl or aralkyl esters. Further, a carbonyl group may be protected as the silyl enol ether, which may be introduced under standard conditions, and converted back to the enolate (or carbonyl compound) by reaction in the presence of fluoride ions (or a suitable source thereof).

Protecting groups may be added or removed in accordance with standard techniques (for example a methyl protecting group on a hydroxy group may be removed by reaction in the presence of a suitable 'cleaving reagent' such as BBr_3), which are known to one skilled in the art and as described herein. The use of protecting groups is described in detail in Green, T.W. and P.G.M. Wuts, Protective Groups in Organic Synthesis (1999), 3rd Ed., Wiley.

The protecting group may also be a polymer resin such as a Wang resin or a 2-chlorotrityl-chloride resin.

Medical and Pharmaceutical Uses

Compounds of the invention are indicated as pharmaceuticals. According to a further aspect of the invention there is provided a compound of the invention, as hereinbefore defined, for use as a pharmaceutical.

Although compounds of the invention may possess pharmacological activity as such, certain pharmaceutically-acceptable (e.g. "protected") derivatives of compounds of the invention may exist or be prepared which may not possess such activity, but may be administered parenterally or orally and thereafter be metabolised in the body to form compounds of the invention. Such compounds (which may possess some pharmacological activity, provided that such activity is appreciably lower than that of the

"active" compounds to which they are metabolised) may therefore be described as "prodrugs" of compounds of the invention.

By "prodrug of a compound of the invention", we include compounds that form a compound of the invention, in an experimentally-detectable amount, within a predetermined time (e.g. about 1 hour), following oral or parenteral administration. All prodrugs of the compounds of the invention are included within the scope of the invention.

Furthermore, certain compounds of the invention may possess no or minimal pharmacological activity as such, but may be administered parenterally or orally, and thereafter be metabolised in the body to form compounds (e.g. compounds of the invention) that possess pharmacological activity as such. Such compounds (which also includes compounds that may possess some pharmacological activity, but that activity is appreciably lower than that of the "active" compounds of the invention to which they are metabolised), may also be described as "prodrugs".

Thus, the compounds of the invention are useful because they possess pharmacological activity, and/or are metabolised in the body following oral or parenteral administration to form compounds which possess pharmacological activity.

According to a further aspect of the invention there is provided a pharmaceutical composition/formulation including a compound of the invention as hereinbefore defined in admixture with a pharmaceutically acceptable adjuvant, carrier, diluent or excipient.

Depending on e.g. potency and physical characteristics of the compound of the invention (i.e. active ingredient), pharmaceutical formulations that may be mentioned include those in which the active ingredient is present in at least 1% (or at least 10%, at least 30% or at least 50%) by weight. That is, the ratio of active ingredient to the other components (i.e. the addition of adjuvant, diluent and carrier) of the pharmaceutical composition is at least 1:99 (or at least 10:90, at least 30:70 or at least 50:50) by weight.

Such compositions/formulations may be prepared in accordance with standard and/or accepted pharmaceutical practice.

Compounds of the invention will normally be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally, tracheally, bronchially, sublingually, by any other parenteral route or *via* inhalation, in a pharmaceutically acceptable dosage form.

Compounds of the invention may be administered alone, but are preferably administered by way of known pharmaceutical formulations, including tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like.

The invention further provides a process for the preparation of a pharmaceutical composition/formulation, as hereinbefore defined, which process comprises bringing into association a compound of the invention, as hereinbefore defined, or a pharmaceutically acceptable derivative (e.g. salt) thereof, with a pharmaceutically-acceptable adjuvant, carrier, diluent or excipient.

Compounds of the invention may be useful as inhibitors of certain enzymes such as a cyclic AMP phosphodiesterase, a phosphodiesterase 7; a phosphodiesterase 4; a phosphodiesterase 3; or a cyclic GMP phosphodiesterase. In particular, compounds of the invention may be useful as inhibitors of a phosphodiesterase 7 and, particularly, a phosphodiesterase 4.

Accordingly, compounds of the invention may therefore be useful in treating or preventing inflammatory diseases or conditions in a patient. Hence, in another aspect, this invention is directed to methods for treating or preventing an inflammatory disease or condition in a mammal, preferably a human, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of the invention as hereinbefore described.

The term "inflammation" will be understood by those skilled in the art to include any condition characterised by a localised or a systemic protective response, which may be elicited by physical trauma, infection, chronic diseases, such as those mentioned hereinbefore, and/or chemical and/or physiological reactions to external stimuli (e.g. as part of an allergic response). Any such response, which may serve to destroy, dilute or sequester both the injurious agent and the injured tissue, may be manifest by, for example, heat, swelling, pain, redness, dilation of blood vessels and/or increased blood

flow, invasion of the affected area by white blood cells, loss of function and/or any other symptoms known to be associated with inflammatory conditions.

The term "inflammation" will thus also be understood to include any inflammatory disease, disorder or condition *per se*, any condition that has an inflammatory component associated with it, and/or any condition characterised by inflammation as a symptom, including *inter alia* acute, chronic, ulcerative, specific, allergic and necrotic inflammation, and other forms of inflammation known to those skilled in the art. The term thus also includes, for the purposes of this invention, inflammatory pain and pain generally.

Where a condition has an inflammatory component associated with it, or a condition characterised by inflammation as a symptom, the skilled person will appreciate that compounds of the invention may be useful in the treatment of the inflammatory symptoms and/or the inflammation associated with the condition.

The inflammatory condition or disease may be an autoimmune condition or disease; the inflammatory condition or disease may involve acute or chronic inflammation of bone and/or cartilage compartments of joints; the inflammatory condition or disease may be an arthritis selected from rheumatoid arthritis, gouty arthritis or juvenile rheumatoid arthritis; the inflammatory condition or disease may be a respiratory disorder selected from asthma or a chronic obstructive pulmonary disease (COPD, e.g., emphysema or chronic bronchitis); the condition or disease may be associated with the disregulation of T-cells; the condition or disease may be associated with elevated levels of inflammatory cytokines (e.g., wherein the inflammatory cytokine is IL-2, or wherein the inflammatory cytokine is IFN-γ, or wherein the inflammatory cytokine is TNF-α); the inflammatory condition or disease may be multiple sclerosis; the inflammatory condition or disease may be pulmonary sarcadosis.; the inflammatory condition or disease may be ocular inflammation or allergy; the inflammatory condition or disease may be an inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis); and the inflammatory condition or disease may be an inflammatory cutaneous disease (e.g., psoriasis or dermatitis).

Compounds of the invention may be useful in modulating intracellular cyclic adenosine 5'-monophosphate levels within a mammal, preferably a human. Hence, in another aspect, this invention is directed to methods for modulating intracellular cyclic adenosine 5'-monophosphate levels within a mammal, preferably a human, wherein the method comprises administering to the mammal in need thereof an amount of a compound of the invention (e.g. those hereinbefore defined) or a pharmaceutical formulation/composition

of the invention as hereinbefore described effective to modulate the intracellular cyclic adenosine 5'-monophosphate levels of the mammal. The mammal, preferably a human, may have an inflammatory condition or disease (for example one defined herein).

Compounds of the invention may be useful in treating or preventing a disease or condition in a mammal, preferably a human, where the disease or condition is associated with pathological conditions that are modulated by inhibiting enzymes associated with secondary cellular messengers. Hence, in another aspect, this invention is directed to methods for treating or preventing a disease or condition in a mammal, preferably a human, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of the invention or a pharmaceutical formulation/composition of the invention as hereinbefore described, and the disease or condition is associated with pathological conditions that are modulated by inhibiting enzymes associated with secondary cellular messengers. Such enzymes (that may be inhibited) may be a cyclic AMP phosphodiesterase; a phosphodiesterase 7; a phosphodiesterase 4; a phosphodiesterase 3; or a cyclic GMP phosphodiesterase. Further, more than one type of enzyme may be inhibited, for instance, the enzymes may be both phosphodiesterase 4 and phosphodiesterase 3. In particular, the enzyme that may be inhibited is a phosphodiesterase 7 or, preferably, a phosphodiesterase 4.

Compounds of the invention may be useful in treating or preventing uncontrolled cellular proliferation in a mammal, preferably a human. Hence, in another aspect, this invention is directed to methods for treating or preventing uncontrolled cellular proliferation in a mammal, preferably a human, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount (e.g. an amount effective to treat or prevent uncontrolled cellular) of a compound of the invention or a pharmaceutical formulation/composition of the invention as hereinbefore described. The uncontrolled cellular proliferation may be caused by a cancer selected from leukaemia and solid tumors.

Compounds of the invention may be useful in treating or preventing transplant rejection in a mammal, preferably a human. Hence, in another aspect, this invention is directed to methods for treating or preventing transplant rejection in a mammal, preferably a human, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount (e.g. an amount effective to treat or prevent transplant rejection in the mammal) of a compound of the invention. The rejection may be due to graft versus host disease.

Compounds of the invention may be useful in treating or preventing conditions associated with the central nervous system (CNS) in a mammal, preferably a human. Hence, in another aspect, this invention is directed to methods for treating or preventing conditions associated with the central nervous system in a mammal, preferably a human, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount (e.g. an amount effective to treat or prevent conditions associated with the central nervous system (CNS) in the mammal) of a compound of the invention as described above (e.g. those hereinbefore defined) or a pharmaceutical formulation/composition of the invention as hereinbefore described. The condition associated with the central nervous system (CNS) may be depression.

These and other aspects and embodiments of the present invention will be apparent upon reference to the following detailed description. To this end, various references are set forth herein which describe in more detail certain procedures, compounds and/or formulations/compositions, and are hereby incorporated by reference in their entirety.

In particular, compounds of the invention are inhibitors of PDE7 and, preferably, PDE4.

As used herein, the terms "disease" and "condition" may be used interchangeably or may be different in that the particular malady or condition may not have a known causative agent (so that etiology has not yet been worked out) and it is therefore not yet recognised as a disease but only as an undesirable condition or syndrome, wherein a more-or-less specific set of symptoms have been identified by clinicians.

Thus, the compounds and compositions of the invention may be used to treat inflammation, including both acute and chronic inflammation as well as certain proliferative disorders (cancers). As used herein, inflammation includes, without limitation, ankylosing spondylitis, arthritis (e.g. juvenile arthritis and rheumatoid arthritis), asthma, COPD, chronic bronchitis, respiratory distress syndrome, rhinitis, allergic rhinitis, Crohn's disease, nephritis, eczema, dermatitis (e.g. atopic dermatitis), urticaria, conjunctivitis, ulcerative colitis, rheumatoid arthritis, osteoarthritis, eosinophilic gastrointestinal disorders, vascular disease, diabetes mellitus, fibromyalgia syndrome, gout, inflammations of the brain (including multiple sclerosis, AIDS dementia, Lyme encephalopathy, herpes encephalitis, Creutzfeld-Jakob disease, and cerebral toxoplasmosis), emphysema, inflammatory bowel disease, irritable bowel syndrome, ischemia-reperfusion injury juvenile erythematosus pulmonary sarcoidosis, Kawasaki

disease, osteoarthritis, pelvic inflammatory disease, psoriatic arthritis, psoriasis, tissue/organ transplant, scleroderma, spondyloarthropathies, systemic lupus erythematosus, pulmonary sarcoidosis, ulcerative colitis, viral infections (i.e. inflammation associated with a viral infection) (*e.g.* influenza, common cold, herpes zoster, hepatitis C and AIDS), bacterial infections (i.e. inflammation associated with a bacterial infection), and any other disease with an inflammatory component. As used herein, proliferative disorders includes, without limitation, all cancers, leukemias and solid tumors that are susceptible to undergoing differentiation or apoptosis upon interruption of their cell cycle. As stated herein, the compounds and compositions of the invention may also be useful for treating diseases associated with the central nervous system. Such diseases include cognitive function, Alzheimer's disease and other neurodegenerative disorders, learning and memory disorders.

Compounds of the invention may inhibit disease induction, for example in the models in the biological examples, at doses of less than 500 mg/kg. The Biological Examples below outline some, but not all, of the preclinical models that may be used to support the claims of this patent. For instance, compounds of the examples are tested in the Biological Example 1, and are found to exhibit at least 50% inhibition of PDE4 at a concentration of 10 μM or below (and more preferably at a concentration of 0.3 μM or below).

Compounds of the invention may also be combined with other therapeutic agents that are useful in the treatment of the conditions described herein. For instance, the compounds of the invention may be combined with other compounds that may be useful in the treatment of:

i) an inflammatory disorder;

ii) a disorder in which the modulation of intracellular cyclic adenosine 5'-monophosphate levels within a mammal is desired and/or required, which disorder may be an inflammatory disorder;

iii) a disorder associated with pathological conditions that are modulated by inhibiting enzymes associated with secondary cellular messengers (e.g. a cyclic AMP phosphodiesterase; a phosphodiesterase 4; a phosphodiesterase 3; a cyclic GMP phosphodiesterase; or both phosphodiesterase 4 and phosphodiesterase 3), which disorder may be an inflammatory disorder (it is most preferred that compounds of the invention are combined (an) inhibitor(s) of PDE7 or, in particular, (an) inhibitor(s) of PDE4);

iv) transplant rejection in a mammal;

v) uncontrolled cellular proliferation; and/or

vi) a disorder associated with the central nervous system.

According to a further aspect of the invention, there is provided a combination product comprising:

(A) a compound of the invention as hereinbefore defined; and

(B) another therapeutic agent that is useful in the treatment of i), ii), iii), iv), v) or vi) above (e.g. a therapeutic agent that is useful in the treatment of an inflammatory disorder),

wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent, carrier or excipient.

Such combination products provide for the administration of a compound of the invention in conjunction with the other therapeutic agent, and may thus be presented either as separate formulations, wherein at least one of those formulations comprises a compound of the invention, and at least one comprises the other therapeutic agent, or may be presented (i.e. formulated) as a combined preparation (i.e. presented as a single formulation including a compound of the invention and the other therapeutic agent).

Thus, there is further provided:

(1) a pharmaceutical formulation/composition including a compound of the invention, as hereinbefore defined, another therapeutic agent that is useful in the treatment of i), ii), iii), iv), v) or vi) above (e.g. a therapeutic agent that is useful in the treatment of an inflammatory disorder), and a pharmaceutically-acceptable adjuvant, diluent, carrier or excipient; and

(2) a kit of parts comprising components:

(a) a pharmaceutical formulation/composition including a compound of the invention, as hereinbefore defined, in admixture with a pharmaceutically-acceptable adjuvant, diluent, carrier or excipient; and

(b) a pharmaceutical formulation/composition including another therapeutic agent that is useful in the treatment of i), ii), iii), iv), v) or vi) above (e.g. a therapeutic agent that is useful in the treatment of an inflammatory disorder) in admixture with a pharmaceutically-acceptable adjuvant, diluent, carrier or excipient,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

The invention further provides a process for the preparation of a combination product as hereinbefore defined, which process comprises bringing into association a compound of the invention, as hereinbefore defined, or a pharmaceutically acceptable derivative (e.g. salt) thereof with another therapeutic agent that is useful in the treatment of i), ii), iii), iv), v) or vi) above (e.g. a therapeutic agent that is useful in the treatment of an inflammatory disorder), and at least one pharmaceutically-acceptable adjuvant, diluent, carrier or excipient.

By "bringing into association", we mean that the two components are rendered suitable for administration in conjunction with each other.

Thus, in relation to the process for the preparation of a kit of parts as hereinbefore defined, by bringing the two components "into association with" each other, we include that the two components of the kit of parts may be:
(i) provided as separate formulations (i.e. independently of one another), which are subsequently brought together for use in conjunction with each other in combination therapy; or
(ii) packaged and presented together as separate components of a "combination pack" for use in conjunction with each other in combination therapy.

The compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount, which will vary depending upon a variety of factors including the activity of the specific compound employed; the metabolic stability and length of action of the compound; the age, body weight, general health, sex, and diet of the patient; the mode and time of administration; the rate of excretion; the drug combination; the severity of the particular disease or condition; and the subject undergoing therapy.

The term "effective amount" refers to an amount of a compound, which confers a therapeutic effect on the treated patient. The effect may be objective (i.e. measurable by some test or marker) or subjective (i.e. the subject gives an indication of or feels an effect).

Compounds of the invention may be administered at varying doses. Oral, pulmonary

and topical dosages may range from between about 0.01 mg/kg of body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably about 0.01 to about 10 mg/kg/day, and more preferably about 0.1 to about 5.0 mg/kg/day. For e.g. oral administration, the compositions typically contain between about 0.01 mg to about 500 mg, and preferably between about 1 mg to about 100 mg, of the active ingredient. Intravenously, the most preferred doses will range from about 0.001 to about 10 mg/kg/hour during constant rate infusion. Advantageously, compounds may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. When a pharmaceutical composition containing a compound of the invention is employed, it shall contain an appropriate amount/concentration/ratio of the active ingredient.

The ranges of effective doses provided herein are not intended to be limiting and represent preferred dose ranges. However, the most preferred dosage will be tailored to the individual subject, as is understood and determinable by one skilled in the relevant arts. (see, *e.g.*, Berkow *et al.*, eds., The Merck Manual, 16th edition, Merck and Co., Rahway, N.J., 1992; Goodmanetna., eds.,Goodman and Cilman's The Pharmacological Basis of Therapeutics, 10th edition, Pergamon Press, Inc., Elmsford, N.Y., (2001); Avery's Drug Treatment: Principles and Practice of Clinical Pharmacology and Therapeutics, 3rd edition, ADIS Press, LTD., Williams and Wilkins, Baltimore, MD. (1987), Ebadi, Pharmacology, Little, Brown and Co., Boston, (1985); Osolci al., eds., Remington's Pharmaceutical Sciences, 18th edition, Mack Publishing Co., Easton, PA (1990); Katzung, Basic and Clinical Pharmacology, Appleton and Lange, Norwalk, CT (1992)).

The physician, or the skilled person, will be able to determine the actual dosage and/or route of administration which will be most suitable for an individual patient, which is likely to vary with the route of administration, the type and severity of the condition that is to be treated, as well as the species, age, weight, sex, renal function, hepatic function and response of the particular patient to be treated. The above-mentioned dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Compounds of the invention may have the advantage that they are effective inhibitors (and hence particularly effective in the treatment of the conditions described herein), and

in particular effective PDE inhibitors (such as PDE7 inhibitors and especially effective PDE4 inhibitors).

Compounds of the invention may also have the advantage that they may be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile (e.g. higher oral bioavailability and/or lower clearance) than, and/or have other useful pharmacological, physical, or chemical properties over, compounds known in the prior art, whether for use in the above-stated indications or otherwise.

Biological Examples

In vitro Inhibition of PDE4 phosphodiesterases

PDE4 U937 cytoplasmic extracts are prepared by a modified procedure of the assay described in MacKenzie, S.J. and Houslay, M.D., "Action of rolipram on specific PDE4 cAMP phosphodiesterase isoforms and on the phosphorylation of cAMP-response-element-binding protein (CREB) and p38 mitogen-activated protein (MAP) kinase in U937 monocytic cells", Biochem J. (2000), 347(Pt 2):571-8, by lysis of U937 cells (ATCC: Catalogue No. CRL-159) in M-PER Lysis buffer (Pierce) containing 10% protease inhibitor cocktail (Sigma). The cell lysates are then centrifuged at 30,000 rpm for 15 minutes at 4 °C. The supernatants are aliquoted and stored at –80 °C. PDE4 has been shown to be the predominant cyclic nucleotide phosphodieterase activity in U937 cells.

An alternative source of PDE4 enzymes is from recombinant human PDE4 obtained from baculovirus-SF9 cells expression system. cDNA containing PDE4D1 is cloned into a baculovirus vector, insect cells (SF9) are then infected and cells cultured to express the PDE4 protein. The cells are lysed and used directly in assay or partially purified using standard procedures. The process can be used for other PDE4 and PDE enzymes.

Compounds of the invention are evaluated for inhibitory activity against PDE4 enzymes by the following assay Method A or B.

Method A:

PDE4 assay based on modified procedure of Phosphodiesterase [^{3}H]cAMP SPA Enzyme

Assay (Amersham Biosciences, code TRKQ 7090). In this assay, PDE4 enzymes converts [^{3}H]cAMP to [^{3}H]5'-AMP. The assay is quenched by the addition of SPA yttrium silicate beads which preferentially bind linear nucleotides over cyclic nucleotides in the presence of zinc sulphate. The amount of [^{3}H]5'-AMP formed is proportional to the PDE4 activity, hence PDE4 inhibitors would decrease the amount of [^{3}H]5'-AMP formed. Reactions are performed in duplicate by the addition of 10 µl PDE4 enzyme (U937 lysate or recombinant hPDE4) to 20 µL of assay mix and 20 µL of test compounds in Isoplates (Wallac) for 30 minutes, at 37 °C. The final assay mixture contained: 50 mM Tris (pH 7.5), 8.3 mM $MgCl_2$, 1.7 mM EGTA and [^{3}H]cAMP (0.025 µCi) (Amersham). Assay is terminated by addition 25 µL SPA beads. The plate is sealed, shaken for 1 minute and then allowed to settle 30 minutes and the cpm is determined using a Wallac Micobeta.

Method B:

PDE4 assay based on modified procedure of Thompson and Appleman (Biochemistry (1971); 10; 311-316). In this assay, PDE4 enzymes converts [^{3}H]cAMP to [^{3}H]5'-AMP. The [^{3}H]5'-AMP is then converted to [^{3}H]adenosine and phosphate by nucleotidase. The amount of [^{3}H]adenosine formed is proportional to the PDE4 activity, hence PDE4 inhibitors would decrease the amount of [^{3}H]adenosine formed.

PDE reactions are performed for 30 minutes at 37 °C in 100 µL volumes in 1 µM cAMP, 0.05 µCi [^{3}H]cAMP (Amersham), 0.5 U/mL 5'-nucleotidase (Sigma), 50 mM Tris, 10 mM $MgCl_2$ pH 7.5. Reactions are performed in duplicate. Reactions are terminated by boiling for 2 minutes at 100 °C followed by the addition of 200 µL Dowex 1-8 400 Cl^- anion exchange resin in a ratio of 1 resin:2 methanol:1 H_2O. Samples are mixed by inversion and then allowed to settle for 2-3 hours. An aliquot of 75 µL is transferred to Isoplates (Wallac), 150 µL of scintillation fluid added and the plate sealed and shaken for 30 minutes. The cpm is determined using a Wallac Micobeta.

Compounds of invention are dissolved in 100% DMSO and diluted such that the final DMSO concentration in the assay does not exceed 1% to avoid affecting the PDE4 activity. PDE4 enzyme is added in quantities such that less than 15% of substrate is consumed (linear assay conditions). Test compounds are assayed at 6-8 concentrations ranging from 0.1 nM to 30 µM and IC_{50} values are determined from the concentration curves by nonlinear regression analysis (GraphPad Prism® 4).

Compounds of the invention, when tested in these assays, demonstrate the ability to inhibit PDE4 phosphodiesterase activity.

Measurement of Cyclic AMP PDE7 activity

The PDE7 assay is based on a modified procedure if the phosphodiesterase [^{3}H]cAMP SPA Enzyme Assay (Amersham Biosciences code TRKQ 7090). In this assay, PDE7 enzyme(s) convert [^{3}H]cAMP to [^{3}H]5'-AMP. The assay is quenched by the addition of ice-cold SPA yttrium silicate beads which preferentially binds linear nucleides, eg 5'-AMPover cycling nucleotides in the presence of zinc sulphate. The amount of [^{3}H]5'-AMP formed is proportional to the activity of the PDE7, and hence inhibitors of the enzyme would decrease the amount of [^{3}H]5'-AMP formed.

Reactions are performed in duplicate by the addition of 15 µL of PDE7 (Baculovirus lysate) to 10 µL of assay mix and 25 µL test compounds in 96-well flat-bottom plate for 60 min at ambient temperature. The Assay mixture contains 50 mM Tris (pH 7.5), 8.3 mM $MgCl_2$, 1.7 mM EGTA and [^{3}H]cAMP (0.025 µCi) (Amersham). The assay is terminated by addition 25 µL SPA beads. The plate is sealed, shaken for 1 minute and then allowed to settle for 20 to 45 minutes and the cpm is determined using a Packard Topcount Scintillation counter.

Compounds of the invention may inhibit PDE7, as demonstrated by the above assay.

PBMC cell assay

Peripheral blood mononuclear cells (PBMC) were isolated from healthy volunteers and dissolved in RPMI 1640 to a final cell concentration of $1{,}33x10^6$ cells/mL. 0,2% Fetal bovine serum (FBS) was added to the cell suspension.

1. The PBMC cells in 384 well microtiter plate (100 000 cells/ well) were induced with 2 mg/mL lipopolysaccharide (LPS) giving a final concentration of 10 µg/mL.
2. IC_{50} curves were run in duplicate with 10 different concentrations of compound. 1,5 µL of compound in DMSO were added to each well.
3. The cells were incubated with substance for 18 h at 37 °C and 5% CO_2 in a humidified chamber.
4. Incubation was terminated at -80 °C for at least one hour.
5. 10 µL of assay solution is transferred into a low volume 384-well plate. TNF-α was detected according to Cisbio´s TNF-α HTRF assay (Cisbio, ref no 62TNFPEB). The cell assay was incubated with 5 µL of each HTRF reagent during 3 h. The amount of TNF-α was detected on a Tecan Saphire 2.

6. IC_{50} curves were fitted with GraphPad Prism software.

Examples

Chemicals employed in the synthesis of the compounds in the examples may be commercially available from, *e.g.* Sigma-Aldrich Fine Chemicals or Acros or Int. Alfa Aesar, Menai Organics, Chembrige and Matrix Scientific.

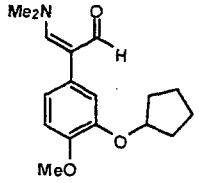
The invention is illustrated by way of the following examples, in which the following abbreviations may be employed:

aq	aqueous
Boc	*tert*-butyloxycarbonyl
conc	concentrated
DCM	dichloromethane
DMSO	dimethylsulphoxide
DMF	*N,N*-dimethylformamide
EtOAc	ethyl acetate
EtOH	ethanol
MeCN	acetonitrile
MeOH	methanol
MS	mass spectrometry
NMR	nuclear magnetic resonance
rt	room temperature
Pd/C	Palladium on activated carbon

Intermediate A

5-(3-Cyclopentyloxy-4-methoxyphenyl)pyrimidin-2-one

(a) 2-(3-Cyclopentyloxy-4-methoxyphenyl)-3-(dimethylamino)acrylaldehyde



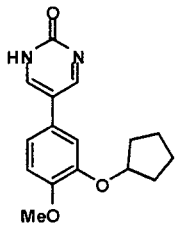
$POCl_3$ (15 g, 9.3 mL, 100 mmol) was added to a solution of 2-(3-cyclopentyloxy-4-methoxyphenyl)acetic acid (10 g, 40 mmol) in DMF (50 mL). The mixture was stirred at 70 °C for 18 h. After cooling to rt the mixture was poured into a stirred aq solution of

K_2CO_3 (2 M, 200 mL, 400 mmol). NaOH (10 g, 250 mmol) was added in portions to the stirred mixture. After the NaOH had dissolved, the mixture was extracted with toluene. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to give the sub-title compound which was used in the next step without further purification.

MS (*m/z*): 290 ($M+H^+$).

^1H NMR (DMSO-d_6, 400 MHz): δ 8.93 (s, 1H), 7.08 (br. s, 1H), 6.87 (d, 1H), 6.60 (d, 1H), 6.57 (dd, 1H), 4.75-4.79 (m, 1H), 3.73 (s, 3H), 2.80 (br. s, 6H), 1.87-1.77 (m, 2H), 1.75-1.65 (m, 4H), 1.60-1.50 (m, 2H).

(b) 5-(3-Cyclopentyloxy-4-methoxyphenyl)pyrimidin-2-one



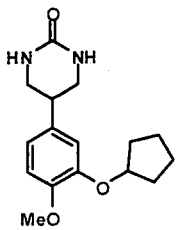
A solution of HCl in EtOH (1.25 M, 48 mL, 60 mmol) was added to a mixture of the 2-(3-cyclopentyloxy-4-methoxyphenyl)-3-(dimethylamino)acrylaldehyde from the previous step, urea (4.8 g, 80 mmol) and EtOH (200 mL). The mixture was stirred at 70 °C for 3 h. After cooling to rt the mixture was concentrated and the product was precipitated by addition of water (~20 mL). Recrystallization from EtOH gave the sub-title compound. Yield 4.3 g (38 % from 2-(3-cyclopentyloxy-4-methoxyphenyl)acetic acid).

MS (*m/z*): 287 ($M+H^+$).

^1H NMR (DMSO-d_6, 400 MHz): δ 12.14 (s, 1H), 8.56 (br. s, 2H), 7.15 (d, 1H), 7.10 (dd, 1H), 6.98 (d, 1H), 4.95-4.90 (m, 1H), 3.75 (s, 3H), 1.95-1.84 (m, 2H), 1.77-1.67 (m, 4H), 1.62-1.52 (m, 2H).

Intermediate B

5-(3-Cyclopentyloxy-4-methoxyphenyl)tetrahydropyrimidin-2-one



A mixture of 5-(3-cyclopentyloxy-4-methoxyphenyl)pyrimidin-2-one (1.97 g, 6.87 mmol), Pd/C (10 %, 500 mg) and EtOH (200 mL) was hydrogenated at ambient temperature and pressure for 2 d. The mixture was filtered through Celite® and concentrated to give the sub-title compound. Yield 1.91 g (96 %).

MS (*m/z*): 291 ($M+H^+$).

^1H NMR ($CDCl_3$, 400 MHz): δ 6.82 (d, 1H), 6.75-6.71 (m, 2H), 5.48 (d, 2H), 4.77-4.72 (m, 1H), 3.82 (s, 3H), 3.47-3.37 (m, 4H), 3.16-3.08 (m, 1H), 1.96-1.78 (m, 6H), 1.66-1.56 (m, 2H).

Intermediate C

5-Fluoro-2-iodomethylbenzoxazole

The title compound was prepared as described in international patent application WO2008/110793, section "Synthetic Preparation of Intermediates of Formula III", Preparation Route 1.

Intermediate D

tert-Butyl 2-iodomethylbenzimidazole-1-carboxylate

The title compound was prepared as described in international patent application WO2008/110793, section "Synthetic Preparation of Intermediates of Formula III", Preparation Route 8.

Intermediate E

2-Bromomethyl-5-methoxybenzofuran

The title compound was prepared as described in international patent application WO2008/110793, section "Synthetic Preparation of Intermediates of Formula III", Preparation Route 11.

Intermediate F

4-Fluoro-2-iodomethylbenzoxazole

The title compound was prepared in accordance with international patent application WO2008/110793, section "Synthetic Preparation of Intermediates of Formula III", Preparation Route 1, from 2-amino-3-fluorophenol.

Intermediate G

7-Fluoro-2-iodomethylbenzoxazole

The title compound was prepared as described in international patent application WO2008/110793, section "Synthetic Preparation of Intermediates of Formula III", Preparation Route 1.

Intermediate H

6-Fluoro-2-iodomethylbenzoxazole

The title compound was prepared in accordance with international patent application WO2008/110793, section "Synthetic Preparation of Intermediates of Formula III", Preparation Route 1, from 2-amino-5-fluorophenol.

Intermediate I

2-(Iodomethyl)benzoxazole-4-carbonitrile

The title compound was prepared as described in international patent application WO2008/110793, section "Synthetic Preparation of Intermediates of Formula III", Preparation Route 5.

Intermediate J

2-(Iodomethyl)benzoxazole-7-carbonitrile

The title compound was prepared in accordance with international patent application WO2008/110793, section "Synthetic Preparation of Intermediates of Formula III", Preparation Route 5, from 2-hydroxybenzonitrile.

Example 1

5-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(5-fluorobenzoxazol-2-ylmethyl)pyrimidin-2-one

NaH (60 % suspention in oil, 20 mg, 0.5 mmol) was added to a solution of Intermediate A (115 mg, 0.4 mmol) in DMF (10 mL) at rt. After stirring for 1 h, Intermediate C (139 mg, 0.5 mmol) was added and the mixture was stirred at rt for 1 h. Ice-cold water was added and the mixture was extracted with DCM. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated. Crystallization of the residue from MeCN gave the sub-title compound. Yield and spectroscopic data are listed in Table 1.

Example 2

5-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(5-fluorobenzoxazol-2-ylmethyl)tetra-hydropyrimidin-2-one

A mixture of the 5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5-fluorobenzoxazol-2-ylmethyl)pyrimidin-2-one (87 mg, 0.2 mmol, see Example 1), Pd/C (10 %, 50 mg) and EtOH (50 mL) was hydrogenated at ambient temperature and pressure for 2 d. The mixture was filtered through Celite and concentrated. Crystallization of the residue gave the title compound. Yield and spectroscopic data are listed in Table 1.

Example 3

tert-Butyl 2-(5-(3-cyclopentyloxy-4-methoxyphenyl)-2-oxopyrimidin-1-ylmethyl)benzimidazole-1-carboxylate

The title compound was prepared in accordance with Example 1 from Intermediates A and D. Yield and spectroscopic data are listed in Table 1.

Example 4

tert-Butyl 2-(5-(3-cyclopentyloxy-4-methoxyphenyl)-2-oxotetrahydropyrimidin-1-ylmethyl)benzimidazole-1-carboxylate

The title compound was prepared in accordance with Example 2 from *tert*-butyl 2-(5-(3-cyclopentyloxy-4-methoxyphenyl)-2-oxopyrimidin-1-ylmethyl)benzimidazole-1-carboxylate (see Example 3). Yield and spectroscopic data are listed in Table 1.

Example 5

5-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(5-methoxybenzofuran-2-ylmethyl)-tetrahydropyrimidin-2-one

The title compound was prepared in accordance with Example 1 from Intermediates B and E. Yield and spectroscopic data are listed in Table 1.

Example 6

1-(Benzimidazol-2-ylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)tetrahydropyrimidin-2-one

Trifluoroacetic acid (1.5 mL) was added to a mixture of *tert*-butyl 2-((5-(3-cyclopentyloxy-4-methoxyphenyl)-2-oxotetrahydropyrimidin-1-yl)methyl)benzimidazole-1-carboxylate (190 mg, 0.37 mmol, see Example 4) and DCM (15 mL) and the mixture was stirred at rt for 4 h. Concentration gave the title compound. Yield and spectroscopic data are listed in Table 1.

Example 7
5-(3-(Cyclopentyloxy)-4-methoxyphenyl)-1-((4-fluorobenzoxazol-2-yl)methyl)pyrimidin-2-one

The title compound was prepared in accordance with Example 1 from Intermediates A and F. Yield and spectroscopic data are listed in Table 1.

Example 8
5-(3-(Cyclopentyloxy)-4-methoxyphenyl)-1-((7-fluorobenzoxazol-2-yl)methyl)pyrimidin-2-one

The title compound was prepared in accordance with Example 1 from Intermediates A and G. Yield and spectroscopic data are listed in Table 1.

Example 9
5-(3-(Cyclopentyloxy)-4-methoxyphenyl)-1-((4-fluorobenzoxazol-2-yl)methyl)-tetrahydropyrimidin-2-one

The title compound was prepared in accordance with Example 2 from 5-(3-(cyclopentyloxy)-4-methoxyphenyl)-1-((4-fluorobenzoxazol-2-yl)methyl)pyrimidin-2-one (see Example 7). Yield and spectroscopic data are listed in Table 1.

Example 10
5-(3-(Cyclopentyloxy)-4-methoxyphenyl)-1-((6-fluorobenzoxazol-2-yl)methyl)pyrimidin-2-one

The title compound was prepared in accordance with Example 1 from Intermediates A and H. Yield and spectroscopic data are listed in Table 1.

Example 11
5-(3-(Cyclopentyloxy)-4-methoxyphenyl)-1-((7-fluorobenzoxazol-2-yl)methyl)-tetrahydropyrimidin-2-one

The title compound was prepared in accordance with Example 2 from 5-(3-(cyclopentyloxy)-4-methoxyphenyl)-1-((7-fluorobenzoxazol-2-yl)methyl)pyrimidin-2-one (see Example 8). Yield and spectroscopic data are listed in Table 1.

Example 12

5-(3-(Cyclopentyloxy)-4-methoxyphenyl)-1-((6-fluorobenzoxazol-2-yl)methyl)-tetrahydropyrimidin-2-one

The title compound was prepared in accordance with Example 2 from 5-(3-(cyclopentyloxy)-4-methoxyphenyl)-1-((6-fluorobenzoxazol-2-yl)methyl)pyrimidin-2-one (see Example 10). Yield and spectroscopic data are listed in Table 1.

Examples 13 and 14

(*R*)- and (*S*)-5-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(5-fluorobenzoxazol-2-yl-methyl)pyrimidin-2-ones

The title compounds where prepared by separation of racemic 5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5-fluorobenzoxazol-2-ylmethylpyrimidin-2-one (see Example 1) using preparative HPLC (column: Phenomenex® Lux 5µ Cellulose-2; eluent: isopropanol:isohexane, 10:90). The compound of Example 13 had lower retention time. The spectroscopic data of the enantiomers are identical to those of the racemate (see Example 1). The absolute configurations were not determined.

Example 15

5-(3-(Cyclopentyloxy)-4-methoxyphenyl)-1-((1,3-dimethylpyrazol-5-yl)methyl)pyrimidin-2-one

KI (1.2 g, 7.2 mmol) was added to a solution of 5-chloromethyl-1,3-dimethylpyrazole (415 mg, 2.9 mmol) in DMF (10 mL) and the mixture was stirred at rt for 30 min. Intermediate A (822 mg, 2.9 mmol) followed by NaH (60 % suspention in oil, 287 mg, 7.2 mmol) were added and the mixture was stirred at rt for 1 h. The mixture was quenched with icecold water (20 mL) and extracted with DCM (3×20 mL). The combined extracts were washed with brine (20 mL), dried over Na_2SO_4 and concentrated. Crystallization from MeCN gave the title compound. Yield and spectroscopic data are listed in Table 1.

Example 16

5-(3-(Cyclopentyloxy)-4-methoxyphenyl)-1-((1,3-dimethylpyrazol-5-yl)methyl)-tetrahydropyrimidin-2-one

The title compound was prepared in accordance with Example 2 from 5-(3-(cyclopentyloxy)-4-methoxyphenyl)-1-((1,3-dimethylpyrazol-5-yl)methyl)pyrimidin-2-one (see Example 15). Yield and spectroscopic data are listed in Table 1.

Example 17

1-((2-Chlorothiazol-5-yl)methyl)-5-(3-(cyclopentyloxy)-4-methoxyphenyl)pyrimidin-2-one

The title compound was prepared in accordance with Example 15 from Intermediate A and 2-chloro-5-(chloromethyl)thiazole. Yield and spectroscopic data are listed in Table 1.

Example 18

2-((5-(3-(Cyclopentyloxy)-4-methoxyphenyl)-2-oxopyrimidin-1-yl)methyl)benzoxazole-4-carbonitrile

The title compound was prepared in accordance with Example 1 from Intermediates A and I. Yield and spectroscopic data are listed in Table 1.

Examples 19 and 20

2-((5-(3-(Cyclopentyloxy)-4-methoxyphenyl)-2-oxo-2,3-dihydropyrimidin-1-yl)-methyl)benzoxazole-4-carbonitrile and 2-((5-(3-(cyclopentyloxy)-4-methoxyphenyl)-2-oxotetrahydropyrimidin-1-yl)methyl)benzoxazole-4-carbonitrile

A mixture of the title compounds was prepared in accordance with Example 2 from 2-((5-(3-(cyclopentyloxy)-4-methoxyphenyl)-2-oxopyrimidin-1-yl)methyl)benzoxazole-4-carbonitrile (see Example 18). The title compounds were obtained by separation using preparative HPLC (column: Agilent® XDB-C18; eluent: MeCN:water gradient, 5:95 – 100:0). Yields and spectroscopic data are listed in Table 1.

Example 21

2-((5-(3-(Cyclopentyloxy)-4-methoxyphenyl)-2-oxopyrimidin-1-yl)methyl)benzoxazole-7-carbonitrile

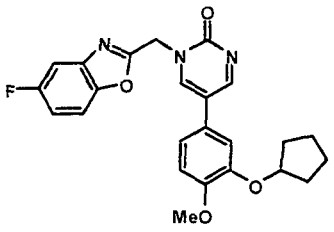
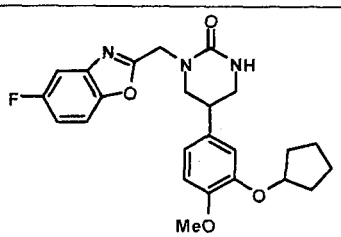
The title compound was prepared in accordance with Example 1 from Intermediates A and J. Yield and spectroscopic data are listed in Table 1.

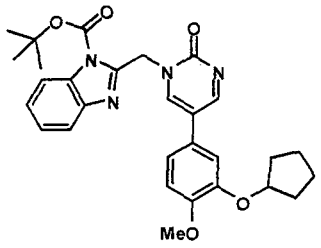
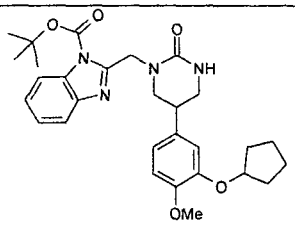
Examples 22 and 23

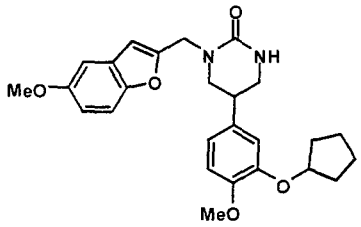
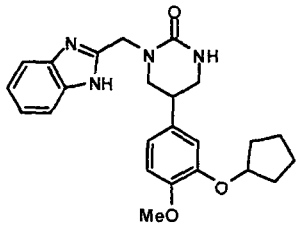
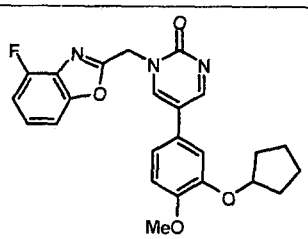
2-((5-(3-(Cyclopentyloxy)-4-methoxyphenyl)-2-oxo-2,3-dihydropyrimidin-1-yl)-methyl)benzoxazole-7-carbonitrile and 2-((5-(3-(cyclopentyloxy)-4-methoxyphenyl)-2-oxotetrahydropyrimidin-1-yl)methyl)benzoxazole-7-carbonitrile

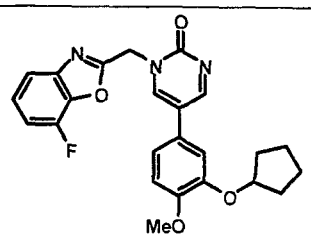
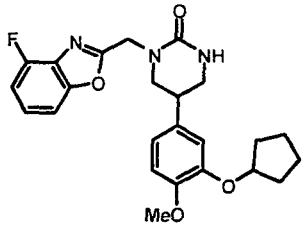
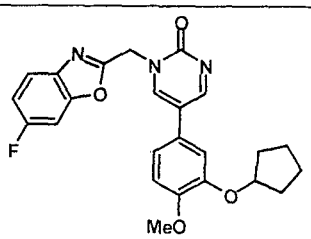
A mixture of the title compounds was prepared in accordance with Example 2 from 2-((5-(3-(cyclopentyloxy)-4-methoxyphenyl)-2-oxopyrimidin-1-yl)methyl)benzoxazole-7-carbonitrile (see Example 21). The title compounds were obtained by separation using preparative HPLC (column: Agilent® XDB-C18; eluent: MeCN:water, gradient 5:95 – 100:0). Yields and spectroscopic data are listed in Table 1.

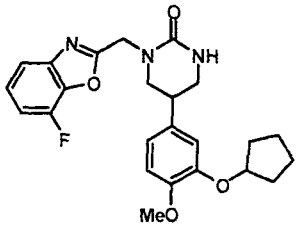
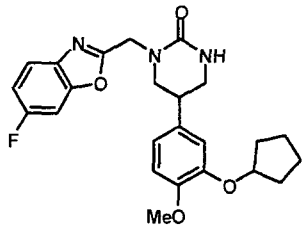
Table 1.

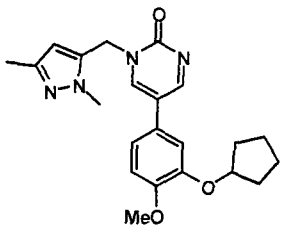
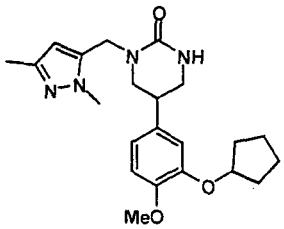
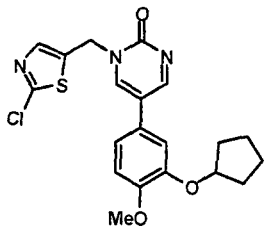
Ex.	**Chemical structure** / **Name** / **NMR**	**MS** (*m/z*)	**Yield** (%)
1		436 ($M+H^+$)	40
	5-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(5-fluorobenzoxazol-2-yl-methyl)pyrimidin-2-one		
	^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.06 (d, 1H), 8.72 (d, 1H), 7.80 (dd, 1H), 7.62 (dd, 1H), 7.27 (ddd, 1H), 7.19 (d, 1H), 7.16 (dd, 1H), 7.04 (d, 1H), 5.48 (s, 2H), 4.94-4.89 (m, 1H), 3.77 (s, 3H), 1.96-1.85 (m, 2H), 1.77-1.67 (m, 4H), 1.62-1.52 (m, 2H)		
2		440 ($M+H^+$)	41
	5-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(5-fluorobenzoxazol-2-yl-methyl)tetrahydropyrimidin-2-one		

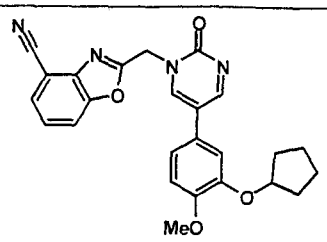
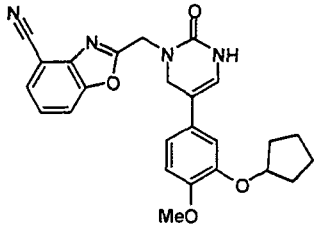
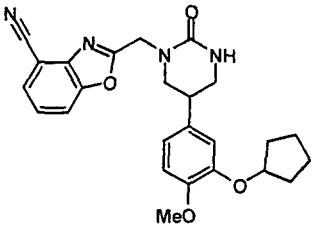
Ex.	Chemical structure / Name / NMR	MS (*m/z*)	Yield (%)
	Name		
	NMR		
	^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.73 (dd, 1H), 7.60 (dd, 1H), 7.24 (ddd, 1H), 6.89 (d, 1H), 6.87 (d, 1H), 6.81 (dd, 1H), 6.70 (d, 1H), 4.82 (d, 1H), 4.79-4.74 (m, 1H), 4.68 (d, 1H), 3.70 (s, 3H), 3.59 (dd, 1H), 3.51 (ddd, 1H), 3.38-3.26 (m, 2H), 3.24-3.16 (m, 1H), 1.90-1.80 (m, 2H), 1.74-1.63 (m, 4H), 1.59-1.50 (m, 2H)		
3		417 (M-Boc+H$^+$)	74
	tert-Butyl 2-(5-(3-cyclopentyloxy-4-methoxyphenyl)-2-oxopyrimidin-1-ylmethyl)benzimidazole-1-carboxylate		
	^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.07 (d, 1H), 8.62 (d, 1H), 7.94 (d, 1H), 7.63 (d, 1H), 7.40 (ddd, 1H), 7.32 (ddd, 1H), 7.19-7.15 (m, 2H), 7.03 (d, 1H), 5.63 (s, 2H), 4.93-4.88 (m, 1H), 3.77 (s, 3H), 1.95-1.85 (m, 2H), 1.77-1.67 (m, 4H), 1.73 (s, 9H), 1.60-1.52 (m, 2H)		
4		421 (M-Boc+H$^+$)	99
	tert-Butyl 2-(5-(3-cyclopentyloxy-4-methoxyphenyl)-2-oxotetrahydro-pyrimidin-1-ylmethyl)benzimidazole-1-carboxylate		
	^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.93-7.89 (m, 1H), 7.71-7.67 (m, 1H), 7.38-7.30 (m, 2H), 6.91 (d, 1H), 6.88 (d, 1H), 6.82 (dd, 1H), 6.57 (d, 1H), 4.93 (d, 1H), 4.88 (d, 1H), 4.81-4.76 (m, 1H), 3.70 (s, 3H), 3.71-3.65 (m, 1H), 3.55-3.49 (m, 1H), 3.41-3.26 (m, 3H), 1.90-1.81 (m, 2H), 1.75-1.64 (m, 4H), 1.67 (s, 9H), 1.59-1.50 (m, 2H)		

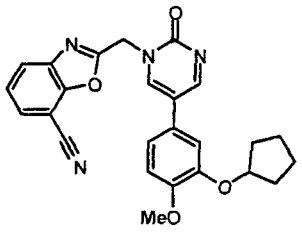
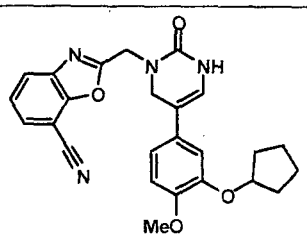
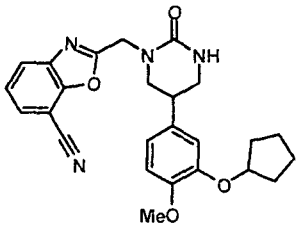
Ex.	Chemical structure / Name / NMR	MS (*m/z*)	Yield (%)
5		451 ($M+H^+$)	14
	5-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(5-methoxybenzofuran-2-yl-methyl)tetrahydropyrimidin-2-one		
	^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.41 (d, 1H), 7.06 (d, 1H), 6.87-6.82 (m, 3H), 6.77 (dd, 1H), 6.63 (s, 1H), 6.58 (d, 1H), 4.75-4.70 (m, 1H), 4.66 (d, 1H), 4.51 (d, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 3.42-3.26 (m, 2H), 3.34-3.28 (m, 1H), 3.27-3.21 (m, 1H), 3.15-3.07 (m, 1H), 1.86-1.77 (m, 2H), 1.73-1.60 (m, 4H), 1.57-1.48 (m, 2H)		
6		421 ($M+H^+$)	99
	1-(Benzimidazol-2-ylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)-tetrahydropyrimidin-2-one		
	^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.82-7.77 (m, 2H), 7.55-7.50 (m, 2H), 6.91 (d, 1H), 6.89 (d, 1H), 8.87 (d, 1H), 6.80 (dd, 1H), 4.90 (d, 1H), 4.86 (d, 1H), 4.79-4.74 (m, 1H), 3.71 (s, 3H), 3.68 (dd, 1H), 3.57 (ddd, 1H), 3.40-3.25 (m, 3H), 1.90-1.80 (m, 2H), 1.75-1.64 (m, 4H), 1.60-1.50 (m, 2H)		
7		436 ($M+H^+$)	50
	5-(3-(Cyclopentyloxy)-4-methoxyphenyl)-1-((4-fluorobenzoxazol-2-yl)-methyl)pyrimidin-2-one		

Ex.	Chemical structure / Name / NMR	MS (*m/z*)	Yield (%)
	Name		
	NMR		
	^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.08 (d, 1H), 8.73 (d, 1H), 7.64 (dd, 1H), 7.45 (td, 1H), 7.27 (ddd, 1H), 7.20 (d, 1H), 7.18 (dd, 1H), 7.05 (d, 1H), 5.51 (s, 2H), 4.95-4.90 (m, 1H), 3.78 (s, 3H), 1.97-1.85 (m, 2H), 1.78-1.67 (m, 4H), 1.62-1.52 (m, 2H)		
8		436 ($M+H^+$)	20
	5-(3-(Cyclopentyloxy)-4-methoxyphenyl)-1-((7-fluorobenzoxazol-2-yl)-methyl)pyrimidin-2-one		
	^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.08 (d, 1H), 8.73 (d, 1H), 7.58 (dd, 1H), 7.43-7.34 (m, 2H), 7.20 (d, 1H), 7.18 (dd, 1H), 7.05 (d, 1H), 5.52 (s, 2H), 4.94-4.89 (m, 1H), 3.78 (s, 3H), 1.97-1.85 (m, 2H), 1.78-1.67 (m, 4H), 1.62-1.52 (m, 2H)		
9		440 ($M+H^+$)	98
	5-(3-(Cyclopentyloxy)-4-methoxyphenyl)-1-((4-fluorobenzoxazol-2-yl)-methyl)tetrahydropyrimidin-2-one		
	^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.57 (dd, 1H), 7.40 (td, 1H), 7.24 (ddd, 1H), 6.90 (d, 1H), 6.86 (d, 1H), 6.81 (dd, 1H) 6.72 (d, 1H), 4.85 (d, 1H), 4.79-4.74 (m, 1H), 4.71 (d, 1H), 3.70 (s, 3H), 3.60 (dd, 1H), 3.53 (ddd, 1H), 3.33 (dd, 1H), 3.31-3.27 (m, 1H), 3.24-3.17 (m, 1H), 1.89-1.80 (m, 2H), 1.74-1.63 (m, 4H), 1.58-1.50 (m, 2H)		
10		436 ($M+H^+$)	32

Ex.	Chemical structure / Name / NMR	MS (*m/z*)	Yield (%)
	Name: 5-(3-(Cyclopentyloxy)-4-methoxyphenyl)-1-((6-fluorobenzoxazol-2-yl)-methyl)pyrimidin-2-one **NMR:** ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.07 (d, 1H), 8.72 (d, 1H), 7.78 (dd, 1H), 7.75 (dd. 1H), 7.27 (dd, 1H), 7.25 (dd, 1H), 7.19 (d, 1H), 7.16 (d, 1H), 7.05 (d, 1H), 5.47 (s, 1H), 4.94-4.90 (m, 1H), 3.78 (s, 1H), 1.96-1.87 (m, 2H), 1.78-1.68 (m, 4H), 1.62-1.53 (m, 2H)		
11		440 ($M+H^+$)	99
	Name: 5-(3-(Cyclopentyloxy)-4-methoxyphenyl)-1-((7-fluorobenzoxazol-2-yl)-methyl)tetrahydropyrimidin-2-one **NMR:** ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.57 (dd, 1H), 7.37 (td, 1H), 7.32 (ddd, 1H), 6.90 (d, 1H), 6.86 (d, 1H), 6.81 (dd, 1H), 6.72 (d, 1H), 4.87 (d, 1H), 4.79-4.74 (m, 1H), 4.72 (d, 1H), 3.70 (s, 3H), 3.60 (dd, 1H), 3.53 (ddd, 1H), 3.38-3.32 (m, 1H), 3.32-3.26 (m, 1H), 3.25-3.17 (m, 1H), 1.90-1.79 (m, 2H), 1.74-1.62 (m, 4H), 1.60-1.50 (m, 2H)		
12		440 ($M+H^+$)	99
	Name: 5-(3-(Cyclopentyloxy)-4-methoxyphenyl)-1-((6-fluorobenzoxazol-2-yl)-methyl)tetrahydropyrimidin-2-one **NMR:** ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.73 (dd, 1H), 7.69 (dd, 1H), 7.23 (ddd, 1H), 6.89 (d, 1H), 6.86 (d, 1H), 6.80 (dd, 1H), 6.70 (d, 1H), 4.83 (d, 1H), 4.79-4.74 (m, 1H), 4.68 (d, 1H), 3.70 (s, 3H), 3.57 (dd, 1H), 3.51 (ddd, 1H), 3.37-3.32 (m, 1H), 3.32-3.26 (m, 1H), 3.23-3.16 (m, 1H), 1.90-1.79 (m, 2H), 1.74-1.63 (m, 4H), 1.59-1.50 (m, 2H)		

Ex.	Chemical structure / Name / NMR	MS (*m/z*)	Yield (%)
15		395 ($M+H^+$)	50
	5-(3-(Cyclopentyloxy)-4-methoxyphenyl)-1-((1,3-dimethylpyrazol-5-yl)-methyl)pyrimidin-2-one		
	^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.95 (d, 1H), 8.56 (d, 1H), 7.14 (d, 1H), 7.12 (dd, 1H), 7.02 (d, 1H), 5.99 (s, 1H), 5.13 (s, 2H), 4.92-4.90 (m, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 2.06 (s, 3H), 1.94-1.86 (m, 2H), 1.76-1.68 (m, 4H), 1.63-1.54 (m, 2H)		
16		399 ($M+H^+$)	99
	5-(3-(Cyclopentyloxy)-4-methoxyphenyl)-1-((1,3-dimethylpyrazol-5-yl)-methyl)tetrahydropyrimidin-2-one		
	^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.85 (d, 1H), 6.84 (d, 1H), 6.76 (dd, 1H), 6.55 (d, 1H), 5.90 (s, 1H), 4.75-4.73 (m, 1H), 4.45 (s, 2H), 3.69 (s, 3H), 3.66 (s, 3H), 3.31-3.19 (m, 4H), 3.09-3.02 (m, 1H), 2.06 (s, 3H), 1.88-1.80 (m, 2H), 1.74-1.62 (m, 4H), 1.59-1.51 (m, 2H)		
17		418 ($M+H^+$)	13
	1-((2-Chlorothiazol-5-yl)methyl)-5-(3-(cyclopentyloxy)-4-methoxy-phenyl)pyrimidin-2-one		
	^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.97 (d, 1H), 8.68 (d, 1H), 7.82 (s, 1H), 7.14 (d, 1H), 7.11 (dd, 1H), 7.02 (d, 1H), 5.26 (s, 2H), 4.93-4.88 (m, 1H), 3.77 (s, 3H), 1.95-1.85 (m, 2H), 1.78-1.68 (m, 4H), 1.63-1.53 (m, 2H)		

Ex.	Chemical structure / Name / NMR	MS (*m/z*)	Yield (%)
18		443 ($M+H^+$)	36
	2-((5-(3-(Cyclopentyloxy)-4-methoxyphenyl)-2-oxopyrimidin-1-yl)-methyl)benzoxazole-4-carbonitrile		
	^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.09 (d, 1H), 8.74 (d, 1H), 8.17 (dd, 1H), 7.92 (dd, 1H), 7.60 (dd, 1H), 7.21 (d, 1H), 7.19 (dd, 1H), 7.05 (d, 1H), 5.57 (s, 2H), 4.95-4.90 (m, 1H), 3.78 (s, 3H), 1.97-1.86 (m, 2H), 1.78-1.67 (m, 4H), 1.63-1.52 (m, 2H)		
19		445 ($M+H^+$)	16
	2-((5-(3-(Cyclopentyloxy)-4-methoxyphenyl)-2-oxo-2,3-dihydro-pyrimidin-1-yl)methyl)benzoxazole-4-carbonitrile		
	^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.76 (d, 1H), 8.15 (dd, 1H), 7.90 (dd, 1H), 7.57 (dd, 1H), 6.89 (d, 1H), 6.87 (d, 1H), 6.76 (dd, 1H), 6.63 (d, 1H), 4.93 (s, 2H), 4.87-4.82 (m, 1H), 4.32 (s, 2H), 3.71 (s, 3H), 1.90-1.80 (m, 2H), 1.75-1.65 (m, 4H), 1.59-1.50 (m, 2H)		
20		447 ($M+H^+$)	21
	2-((5-(3-(Cyclopentyloxy)-4-methoxyphenyl)-2-oxotetrahydropyrimidin-1-yl)methyl)benzoxazole-4-carbonitrile		

Ex.	Chemical structure / Name / NMR	MS (*m/z*)	Yield (%)
	Name		
	NMR		
	^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.11 (dd, 1H), 7.89 (dd, 1H), 7.56 (dd, 1H), 6.89 (d, 1H), 6.87 (d, 1H), 6.83 (dd, 1H), 6.74 (d, 1H), 4.89 (d, 1H), 4.79-4.74 (m, 1H), 4.77 (d, 1H), 3.70 (s, 3H), 3.61 (dd, 1H), 3.55 (ddd, 1H), 3.39-3.31 (m, 1H), 3.31-3.27 (m, 1H), 3.26-3.18 (m, 1H), 1.90-1.80 (m, 2H), 1.74-1.62 (m, 4H), 1.59-1.50 (m, 2H)		
21		443 (M+H$^+$)	99
	2-((5-(3-(Cyclopentyloxy)-4-methoxyphenyl)-2-oxopyrimidin-1-yl)-methyl)benzoxazole-7-carbonitrile		
	^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.08 (d, 1H), 8.73 (d, 1H), 8.12 (dd, 1H), 7.95 (dd, 1H), 7.57 (t, 1H), 7.19 (d, 1H), 7.17 (dd, 1H), 7.05 (d, 1H), 5.57 (s, 2H), 4.94-4.89 (m, 1H), 3.78 (s, 3H), 1.95-1.86 (m, 2H), 1.78-1.67 (m, 4H), 1.62-1.53 (m, 2H)		
22		445 (M+H$^+$)	37
	2-((5-(3-(Cyclopentyloxy)-4-methoxyphenyl)-2-oxo-2,3-dihydro-pyrimidin-1-yl)methyl)benzoxazole-7-carbonitrile		
	^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.75 (d, 1H), 8.12 (dd, 1H), 7.91 (dd, 1H), 7.56 (t, 1H), 6.89 (d, 1H), 6.86 (d, 1H), 6.74 (dd, 1H), 6.63 (d, 1H), 4.93 (s, 2H), 4.87-4.82 (m, 1H), 4.43 (s, 2H), 3.72 (s, 3H), 1.90-1.80 (m, 2H), 1.75-1.65 (m, 4H), 1.58-1.50 (m, 2H)		
23		447 (M+H$^+$)	50

Ex.	Chemical structure	MS (*m/z*)	Yield (%)
	Name		
	NMR		
	2-((5-(3-(Cyclopentyloxy)-4-methoxyphenyl)-2-oxotetrahydropyrimidin-1-yl)methyl)benzoxazole-7-carbonitrile		
	^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.11 (dd, 1H), 7.90 (dd, 1H), 7.55 (t, 1H), 6.89 (d, 1H), 6.87 (d, 1H), 6.82 (dd, 1H), 6.74 (d, 1H), 4.90 (d, 1H), 4.79-4.75 (m, 1H), 4.77 (d, 1H), 3.70 (s, 3H), 3.61 (dd, 1H), 3.55 (ddd, 1H), 3.38-3.31 (m, 1H), 3.31-3.27 (m, 1H), 3.25-3.18 (m, 1H), 1.90-1.80 (m, 2H), 1.74-1.63 (m, 4H), 1.59-1.49 (m, 2H)		

Example 24

The following examples/compounds of the invention are prepared in accordance with the techniques described herein:

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(7-methoxy-2-benzofurylmethyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(7-fluoro-2-benzofurylmethyl)tetrahydropyrimidin-2-one;

1-(2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5,6-dimethyl-2-benzimidazolylmethyl)tetrahydropyrimidin-2-one;

1-(2-benzofurylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(2-thienylmethyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(2-furylmethyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(2-imidazolylmethyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(1-methyl-2-imidazolylmethyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(2-oxazolylmethyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(2-thiazolylmethyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(3-indolylmethyl)tetrahydropyrimidin-2-one;

1-(3-benzothienylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)tetrahydropyrimidin-2-one;

1-(2-benzothiazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5-methyl-2-benzoxazolylmethyl)tetrahydropyrimidin-2-one;

1-(6-chloro-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(4-methyl-2-benzoxazolylmethyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(6-methyl-2-benzoxazolylmethyl)tetrahydropyrimidin-2-one;

1-(1-benzotriazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5-nitro-2-benzoxazolylmethyl)tetrahydropyrimidin-2-one;

1-(5-cyano-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5-fluoro-2-benzoxazolylmethyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5-trifluoromethyl-2-benzoxazolylmethyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(7-methyl-2-benzoxazolylmethyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5-methoxy-2-benzoxazolylmethyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(4-methoxy-2-benzoxazolylmethyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(4-fluoro-2-benzoxazolylmethyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(7-fluoro-2-benzoxazolylmethyl)tetrahydropyrimidin-2-one;

1-(4-cyano-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)tetrahydropyrimidin-2-one;

1-(7-chloro-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(4-trifluoromethyl-2-benzoxazolylmethyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5-methoxy-2-benzofurylmethyl)tetrahydropyrimidin-2-one;

1-(2-benzimidazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(1-methyl-2-benzimidazolylmethyl)tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5,6-dichloro-2-benzimidazolylmethyl)tetrahydropyrimidin-2-one;

1-(4-acetamidoxy-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)tetrahydropyrimidin-2-one;

31(7-acetamidoxy-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)tetrahydropyrimidin-2-one;

1-(4-cyano-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-difluoromethoxyphenyl)tetrahydropyrimidin-2-one;

1-(4-cyano-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-trifluoromethoxyphenyl)tetrahydropyrimidin-2-one;

1-(4-cyano-2-benzoxazolylmethyl)-5-[4-difluoromethoxy-3-(3-tetrahydrofuranyloxy)-phenyl]tetrahydropyrimidin-2-one;

1-(4-cyano-2-benzoxazolylmethyl)-5-[4-methoxy-3-(3-tetrahydrofuranyloxy)phenyl]-tetrahydropyrimidin-2-one;

1-(4-cyano-2-benzoxazolylmethyl)-5-[4-trifluoromethoxy-3-(3-tetrahydrofuranyloxy)-phenyl]tetrahydropyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(7-methoxy-2-benzofurylmethyl)pyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(7-fluoro-2-benzofurylmethyl)pyrimidin-2-one;

1-(2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)pyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5,6-dimethyl-2-benzimidazolylmethyl)pyrimidin-2-one;

1-(2-benzofurylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)pyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(2-thienylmethyl)pyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(2-furylmethyl)pyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(2-imidazolylmethyl)pyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(1-methyl-2-imidazolylmethyl)pyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(2-oxazolylmethyl)pyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(2-thiazolylmethyl)pyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(3-indolylmethyl)pyrimidin-2-one;

1-(3-benzothienylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)pyrimidin-2-one;

1-(2-benzothiazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)pyrimidin-2-one;

5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5-methyl-2-benzoxazolylmethyl)pyrimidin-2-one;

1-(6-chloro-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(4-methyl-2-benzoxazolylmethyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(6-methyl-2-benzoxazolylmethyl)pyrimidin-2-one;
1-(1-benzotriazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5-nitro-2-benzoxazolylmethyl)pyrimidin-2-one;
1-(5-cyano-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)pyrimidin-2-one
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5-fluoro-2-benzoxazolylmethyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5-trifluoromethyl-2-benzoxazolylmethyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(7-methyl-2-benzoxazolylmethyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5-methoxy-2-benzoxazolylmethyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(4-methoxy-2-benzoxazolylmethyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(4-fluoro-2-benzoxazolylmethyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(7-fluoro-2-benzoxazolylmethyl)pyrimidin-2-one;
1-(4-cyano-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)pyrimidin-2-one
1-(7-chloro-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(4-trifluoromethyl-2-benzoxazolylmethyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5-methoxy-2-benzofurylmethyl)pyrimidin-2-one;
1-(2-benzimidazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(1-methyl-2-benzimidazolylmethyl)pyrimidin-2-one;
5-(3-cyclopentyloxy-4-methoxyphenyl)-1-(5,6-dichloro-2-benzimidazolylmethyl)pyrimidin-2-one;
1-(4-acetamidoxy-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)pyrimidin-2-one;
1-(7-acetamidoxy-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-methoxyphenyl)pyrimidin-2-one;
1-(4-cyano-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-difluoromethoxyphenyl)pyrimidin-2-one;

1-(4-cyano-2-benzoxazolylmethyl)-5-(3-cyclopentyloxy-4-trifluoromethoxyphenyl)pyrimidin-2-one;
1-(4-cyano-2-benzoxazolylmethyl)-5-[4-difluoromethoxy-3-(3-furanyloxy)phenyl]pyrimidin-2-one;
1-(4-cyano-2-benzoxazolylmethyl)-5-[4-methoxy-3-(3-furanyloxy)phenyl]pyrimidin-2-one;
1-(4-cyano-2-benzoxazolylmethyl)-5-[4-trifluoromethoxy-3-(3-furanyloxy)phenyl]pyrimidin-2-one.

Example 25

Title compounds of the Examples were tested in a biological test described above (PBMC cell assay) and were found to inhibit PDE-4. Thus, when the total concentration of title compounds in the assay was 10 μM, the following %-inhibition values where obtained:

Example	% inhibition
1	74
2	77
3	82
4	88
5	81

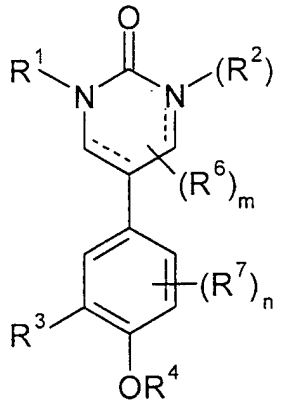
Example 26

Title compounds of the Examples were tested in the biological test described above and were found to inhibit PDE-4. Thus, the following IC_{50} values where obtained:

Example	IC_{50}	Example	IC_{50}
1	3700	13	870
2	540	14	670
3	1600	15	12000
4	530	16	9400
5	160	17	3300
6	520	18	250
7	1300	19	14
8	3200	20	87
9	350	21	160
10	2500	22	12
11	290	23	130
12	1000		

Claims

1. A compound of formula (I),



I

wherein:

the dotted lines each independently represent an optional bond (and when the dotted line between the carbon and nitrogen is present, then R^2 is absent, and when the dotted line between the carbon and nitrogen is absent, then R^2 is present);

m represents 0, 1, 2, 3, 4 or 5;

n represents 0, 1, 2 or 3;

at least one of R^1 and, if present, R^2 represents $-A^1-T^z-B^1$ and the other (if present) represents R^5;

R^3 represents hydrogen, $-OR^{4a}$, C_{1-12} alkyl (optionally substituted by one or more substituents selected from =O and X^1) or $-B^2$;

R^4 and R^{4a} independently represent hydrogen, C_{1-12} alkyl (optionally substituted by one or more substituents selected from =O and X^2) or $-B^3$;

R^5 represents hydrogen, C_{1-12} alkyl (optionally substituted by one or more substituents selected from =O and X^3) or $-B^{3a}$;

each R^6 and each R^7 independently represent X^4, C_{1-12} alkyl (optionally substituted by one or more substituents selected from =O and X^5) or $-B^4$; or

any two R^6 groups may be linked together to form a further ring, which is formed either by the two relevant groups being linked together by a direct bond or C_{1-5} alkylene;

A^1 represents C_{1-12} alkylene (optionally substituted by one or more substituents selected from =O and X^6);

T^z represents a direct bond, $-N(R^{w1})-$ or $-C(O)N(R^{w2})-$;

R^{w1} and R^{w2} independently represent hydrogen, C_{1-12} alkyl (optionally substituted by one or more substituents selected from X^7) or $-B^5$;

B^1 represents:
1) a monocyclic 5-membered heteroaryl group;
2) a polycyclic heteroaryl group;
3) a polycyclic aryl group; or
4) a heterocycloalkyl group,
all four of which are optionally and independently substituted with one or more substituents selected from X^8 and, in the case of heterocycloalkyl or any non-aromatic rings of a polycyclic aryl or heteroaryl group, =O;

B^2, B^3 and B^{3a} independently represent aryl (optionally substituted by one or more substituents selected from X^9), heterocycloalkyl (optionally substituted by one or more substituents selected from =O and X^{10}) or heteroaryl (optionally substituted by one or more substituents selected from X^{11});

B^4 and B^5 independently represent heterocycloalkyl (optionally substituted by one or more substituents selected from =O and X^{12});

X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, X^{10} X^{11} and X^{12} independently represent B^6, halo, -CN, $-NO_2$, $-Si(R^{8a})_3$, $-OR^{9a}$, $-OC(O)-R^{9b}$, $-N(R^{9c})R^{9d}$, $-C(O)R^{9e}$, $-C(O)OR^{9f}$, $-C(O)N(R^{9g})R^{9h}$, $-N(R^{9i})C(O)OR^{8b}$, $-N(R^{9j})C(O)R^{8c}$, $-N(R^{9k})S(O)_tR^{8d}$, $-S(O)_tOR^{8e}$, $-S(O)_pR^{8f}$, $-S(O)_tN(R^{9m})R^{9n}$, $-N(R^{9p})C(O)N(R^{9q})R^{9r}$, $-N(R^{9s})S(O)_tOR^{8g}$, $-OC(O)N(R^{9t})R^{9u}$ and/or $-OS(O)_tR^{8h}$;

R^{8a}, R^{8b}, R^{8d}, R^{8f}, R^{8g} and R^{8h} independently represent C_{1-12} alkyl optionally substituted by one or more substituents selected from =O and E^1;

R^{8c}, R^{8e}, R^{9a}, R^{9b}, R^{9c}, R^{9d}, R^{9e}, R^{9f}, R^{9g}, R^{9h}, R^{9i}, R^{9j}, R^{9k}, R^{9m}, R^{9n}, R^{9p}, R^{9q}, R^{9r}, R^{9s}, R^{9t} and R^{9u} independently represent hydrogen or C_{1-12} alkyl optionally substituted by one or more substituents selected from =O and E^2; or

any pair of R^{9c} and R^{9d}, R^{9g} and R^{9h}, R^{9m} and R^{9n}, R^{9q} and R^{9r}, and R^{9t} and R^{9u} may be linked together with the nitrogen atom to which they are attached to form a 3- to 8-membered ring, optionally containing one or more unsaturations, optionally containing one or two further heteroatoms, and which ring is optionally substituted by one or more substituents selected from =O, halo and C_{1-6} alkyl optionally substituted by one or more halo atoms;

B^6 represents C_{1-12} alkyl, heterocycloalkyl (which latter two groups are optionally substituted by one or substituents selected from =O and E^3), aryl or heteroaryl (which latter two groups are optionally substituted by one or substituents selected from E^4);

t represents, at each occurrence when used herein, 1 or 2;

p represents 0, 1 or 2;

E^1, E^2, E^3 and E^4 independently represent halo, -CN, $-NO_2$, $-OR^{10a}$, $-OC(O)-R^{10b}$, $-N(R^{10c})R^{10d}$, $-C(O)R^{10e}$, $-C(O)OR^{10f}$, $-C(O)N(R^{10g})R^{10h}$, $-N(R^{10i})C(O)OR^{11a}$, $-N(R^{10j})C(O)R^{11b}$, $-N(R^{10k})S(O)_{t1}R^{11c}$, $-S(O)_{t1}OR^{11d}$, $-S(O)_{p1}R^{11e}$, $-S(O)_{t1}N(R^{10m})R^{10n}$, $-N(R^{10p})C(O)N(R^{10q})R^{10r}$, $-N(R^{10s})S(O)_{t1}OR^{11f}$, $-OC(O)N(R^{10t})R^{10u}$, $-OS(O)_{t1}R^{11g}$ and/or $-Si(R^{11h})_3$;

R^{10a}, R^{10b}, R^{10c}, R^{10d}, R^{10e}, R^{10f}, R^{10g}, R^{10h}, R^{10i}, R^{10j}, R^{10k}, R^{10m}, R^{10n}, R^{10p}, R^{10q}, R^{10r}, R^{10s}, R^{10t} R^{10u}, R^{11b} and R^{11d} independently represent hydrogen or C_{1-3} alkyl optionally substituted by one or more halo atoms;

R^{11a}, R^{11c}, R^{11e}, R^{11f}, R^{11g} and R^{11h} independently represent C_{1-3} alkyl optionally substituted by one or more halo atoms;

t1 represents, at each occurrence when used herein, 1 or 2;

p1 represents 0, 1 or 2,

or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in Claim 1, wherein R^1 represents $-A^1-T^z-B^1$.

3. A compound as claimed in Claim 1 or Claim 2, wherein R^3 represents $-OR^{4a}$.

4. A compound as claimed in any one of the preceding claims, wherein R^4 and R^{4a} independently represent C_{1-12} alkyl (optionally substituted by one or more substituents selected from =O and X^2) or $-B^3$.

5. A compound as claimed in any one of the preceding claims, wherein each R^5 represents C_{1-6} alkyl (optionally substituted by one or more substituents selected from =O and X^3) or hydrogen.

6. A compound as claimed in any one of the preceding claims, wherein each R^6 and each R^7 independently represent X^4 or C_{1-6} alkyl (optionally substituted by one or more substituents selected from =O and X^5).

7. A compound as claimed in any one of the preceding claims, wherein A^1 represents unsubstituted C_{1-6} alkylene.

8. A compound as claimed in any one of the preceding claims, wherein R^{w1} and R^{w2} independently represent hydrogen.

9. A compound as claimed in any one of the preceding claims, wherein B^1 represents a 5-membered heteroaryl group or a bicyclic heteroaryl group optionally substituted with one or more substituents selected from X^8.

10. A compound as claimed in any one of the preceding claims, wherein B^2, B^3, B^{3a} independently represent phenyl (optionally substituted by one or more substituents selected from X^9), a 5- or 6-membered heterocycloalkyl group (optionally substituted by one or more substituents selected from =O and X^{10}) or a 5- or 6-membered heteroaryl group (optionally substituted by one or more substituents selected from X^{11}).

11. A compound as claimed in any one of the preceding claims, wherein B^4 and B^5 independently represent a 5- or 6-membered heterocycloalkyl group (optionally substituted by one or more substituents selected from =O and X^{12}).

12. A compound as claimed in any one of the preceding claims, wherein: X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, X^{10}, X^{11} and X^{12} independently represent B^6, $-C(O)OR^{9f}$, $-S(O)_tN(R^{9m})R^{9n}$, $-N(R^{9k})S(O)_tR^{8d}$, -CN, $-NO_2$, halo, $-OR^{9a}$, $-N(R^{9c})R^{9d}$, $-C(O)N(R^{9g})R^{9h}$ and/or $-N(R^{9j})C(O)R^{8c}$; R^{8a}, R^{8b}, R^{8d}, R^{8e}, R^{8f}, R^{8g} and R^{8h} independently represent C_{1-6} alkyl optionally substituted by one or more substituents selected from E^1; R^{8c}, R^{9a}, R^{9b}, R^{9c}, R^{9d}, R^{9e}, R^{9f}, R^{9g}, R^{9h}, R^{9i}, R^{9j}, R^{9k}, R^{9m}, R^{9n}, R^{9p}, R^{9q}, R^{9r}, R^{9s}, R^{9t} and R^{9u} independently represent hydrogen or C_{1-6} alkyl optionally substituted by one or more substituents selected from E^2; B^6 represents C_{3-8} alkyl, 5- or 6-membered heterocycloalkyl (both of which are optionally substituted by one or more E^3 substituents), heteroaryl or, aryl, which latter two groups are optionally substituted by one or more E^4 substituents; E^1, E^2, E^3 and E^4 independently represent $-N(R^{10k})S(O)_{t1}R^{11c}$, $-S(O)_{t1}N(R^{10m})R^{10n}$, $-NO_2$, $-C(O)OR^{10f}$, halo, -CN, $-OR^{10a}$, $-N(R^{10c})R^{10d}$, $-C(O)N(R^{10g})R^{10h}$ and/or $-N(R^{10j})C(O)R^{11b}$; R^{10a}, R^{10b}, R^{10c}, R^{10d}, R^{10e}, R^{10f}, R^{10g}, R^{10h}, R^{10i}, R^{10j}, R^{10k}, R^{10m}, R^{10n}, R^{10p}, R^{10q}, R^{10r}, R^{10s}, R^{10t}, R^{10u} and R^{11b} independently represent hydrogen, $-CH_3$ or $-CF_3$; and/or R^{11a}, R^{11c}, R^{11d}, R^{11e}, R^{11f}, R^{11g} and R^{11h} independently represent $-CH_3$ or $-CF_3$.

13. A compound of formula I as defined in any one of Claims 1 to 12, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

14. A pharmaceutical formulation including a compound of formula I, as defined in any one of Claims 1 to 12, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent, carrier or excipient.

15. A compound, as defined in any one of Claims 1 to 12, or a pharmaceutically acceptable salt thereof, for use in the treatment of: i) an inflammatory disorder; ii) a disorder in which the modulation of intracellular cyclic adenosine 5'-monophosphate levels within a mammal is desired and/or required, which disorder may be an inflammatory disorder; iii) a disorder associated with pathological conditions that are modulated by inhibiting enzymes associated with secondary cellular messengers; iv) transplant rejection in a mammal; v) uncontrolled cellular proliferation; and/or vi) a disorder associated with the central nervous system.

16. Use of a compound of formula I, as defined in any one of Claims 1 to 12, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a disorder as defined by any of i) to vi) in Claim 15.

17. A compound, as defined in any one of Claims 1 to 12, or a pharmaceutically acceptable salt thereof, for use in the in treatment of a disease/disorder in which the inhibition of a phosphodiesterase is desired and/or required.

18. Use of a compound of formula I, as defined in any one of Claims 1 to 12, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a disease/disorder in which the inhibition of a phosphodiesterase is desired and/or required.

19. A compound or use as claimed in Claim 17 or Claim 18, wherein the phosphodiesterase is PDE7 or PDE4.

20. A compound as claimed in Claim 15, 17 or 19 (as dependent on Claims 15 or 17) or a use as claimed in Claim 16, 18 or 19 (as dependent on Claims 16 or 18), wherein the disorder is inflammation, a proliferative disorder or a disease or pathological condition of the central nervous system.

21. A compound or use as claimed in Claim 20, wherein the disorder is ankylosing spondylitis, arthritis, asthma, chronic obstructive pulmonary disease, chronic bronchitis, respiratory distress syndrome, rhinitis, allergic rhinitis, Crohn's disease, nephritis, eczema, atopic dermatitis, urticaria, conjunctivitis, ulcerative colitis, rheumatoid arthritis, osteoarthritis, eosinophilic gastrointestinal disorders, vascular disease, diabetes mellitus, fibromyalgia syndrome, gout, inflammations of the brain, emphysema, inflammatory bowel disease, irritable bowel syndrome, ischemia-reperfusion injury juvenile erythematosus pulmonary sarcoidosis, Kawasaki disease, osteoarthritis, pelvic inflammatory disease, psoriatic arthritis (psoriasis), rheumatoid arthritis, psoriasis, tissue/organ transplant, scleroderma, spondyloarthropathies, systemic lupus erythematosus, pulmonary sarcoidosis, ulcerative colitis, a viral infection, a bacterial infection, cancer, leukemia, a solid tumor, cognitive function, Alzheimer's disease, a learning and memory disorder, cerebrovascular disease, depression, schizophrenia, Parkinson's disease and/or multiple sclerosis.

22. A method of treatment of a disorder as defined by i) to vi) in Claim 15, which method comprises administration of a therapeutically effective amount of a compound of formula I as defined in any one of Claims 1 to 12, or a pharmaceutically-acceptable salt thereof, to a patient suffering from, or susceptible to, such a condition.

23. A method of treatment of a disease/disorder in which the inhibition of a phosphodiesterase is desired and/or required, which method comprises administration of a therapeutically effective amount of a compound of formula I as defined in any one of Claims 1 to 12, or a pharmaceutically-acceptable salt thereof, to a patient suffering from, or susceptible to, such a condition.

24. A method as claimed in Claim 23, wherein the phosphodiesterase is PDE7 or PDE4.

25. A combination product comprising:

(A) a compound of formula I as defined in any one of Claims 1 to 12, or a pharmaceutically-acceptable salt thereof; and

(B) another therapeutic agent that is useful in the treatment of a disorder as defined by i), ii), iii), iv), v) or vi) in Claim 15,

wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent, carrier or excipient.

26. A combination product as claimed in Claim 25 which comprises a pharmaceutical formulation including a compound of formula I as defined in any one of Claims 1 to 12, or a pharmaceutically-acceptable salt thereof, another therapeutic agent that is useful in the treatment of a disorder as defined by i), ii), iii), iv), v) or vi) in Claim 15, and a pharmaceutically-acceptable adjuvant, diluent, carrier or excipient.

27. A combination product as claimed in Claim 25 which comprises a kit of parts comprising components:

(a) a pharmaceutical formulation including a compound of formula I as defined in any one of Claims 1 to 12, or a pharmaceutically-acceptable salt thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent, carrier or excipient; and

(b) a pharmaceutical formulation including another therapeutic agent that is useful in the treatment of a disorder as defined by i), ii), iii), iv), v) or vi) in Claim 15 in admixture with a pharmaceutically-acceptable adjuvant, diluent, carrier or excipient,

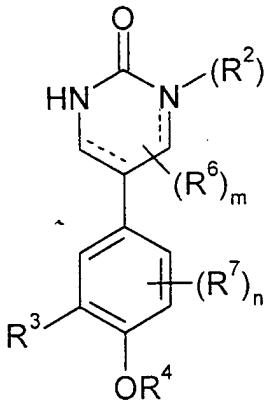
which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

28. A combination product as claimed in any one of Claims 25 to 27, wherein the other therapeutic agent is an inhibitor of a phosphodiesterase.

29. A combination product as claimed in Claim 28, wherein the phosphodiesterase is PDE7 or PDE4.

30. A process for the preparation of a compound of the formula I as defined in Claim 1 which process comprises:

(i) reaction of a compound of formula II,



II

or a protected derivative thereof, wherein R^2, R^3, R^4, R^6, R^7 and the dotted lines are as defined in Claim 1, with a compound of formula IV,

$$B^1—T^z—A^1—L^1 \qquad \text{III}$$

wherein L^1 represents a suitable leaving group and B^1, T^z and A^1 are as defined in Claim 1;

(ii) for compounds of formula I in which the dotted lines are not present and R^2 is present and is not H, reaction of a compound of formula I in which the dotted lines are not present and R^2 is H with a compound of formula IV,

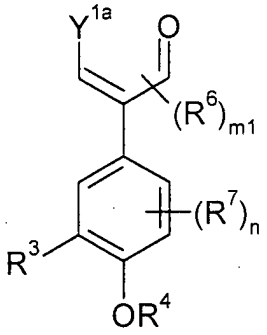
$$R^{2a}—L^2 \qquad \text{IV}$$

wherein R^{2a} represents R^2 as defined in Claim 1 provided that it does not represent H, and L^2 represents a suitable leaving group;

(iii) for compounds of formula I in which the dotted lines are not present and R^2 is H, reduction of a compound of formula I in which the dotted lines represent bonds (so forming double bonds in the compound of formula I) or protected derivatives thereof;

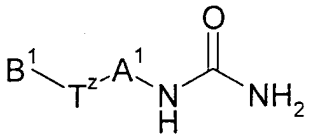
(iv) for compounds of formula I in which one or both of the dotted lines represent bonds (so forming one or two double bonds in the compound of formula I), dehydrogenation or oxidation of a compound of formula I in which one or both of the dotted lines are not present and R^2 is H, or protected derivatives thereof;

(v) for compounds of formula I wherein the dotted lines represent bonds, reaction of a compound of formula V,



V

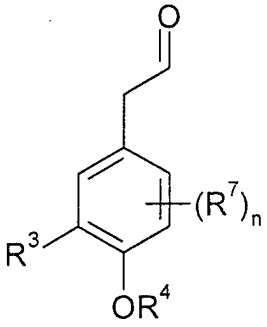
or a protected derivative thereof, wherein R^3, R^4 R^6 R^7 and n are as defined in Claim 1, and m1 is 0, 1 or 2 (the skilled person will appreciate that $-(R^6)_m$ represents two optional R_6 substituents, and that the structure of the compound of formula V dictates that these substituents may only be positioned at the carbonyl carbon and or in the β position relative to the carbonyl carbon) and Y^{1a} is -OH or $-NY^aY^b$, where Y^a and Y^b are independently alkyl, heterocycloalkyl, aryl and/or heteroaryl, or Y^a and Y^b may be joined to form a ring optionally containing one or more additional heteroatom, with a compound of formula VI,



VI

or a protected derivative thereof, wherein B^1, T^Z and A^1 are as defined in Claim 1;

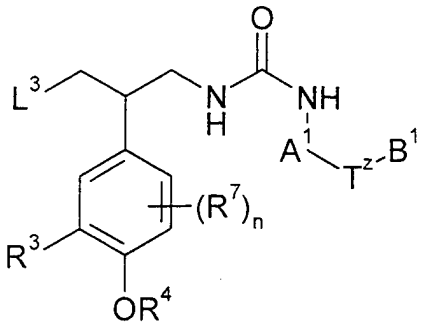
(vi) for compounds of formula I where the dotted lines represent bonds, reaction of a compound of formula VII,



VII

or a protected derivative thereof, wherein R^3, R^4, R^7 and m are as defined in Claim 1, with a compound of formula VI as defined above, in the presence of an ester of formic acid or the like;

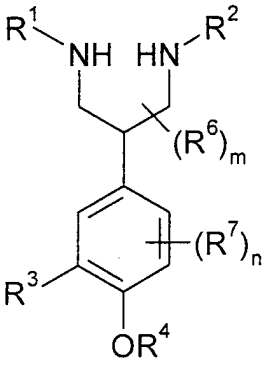
(vii) for compounds of formula I in which the dotted lines do not represent bonds and R^2 is H, intramolecular reaction of a compound of formula VIII,



VIII

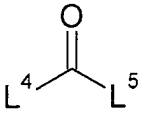
or a protected derivative thereof, wherein L^3 represents a suitable leaving group as defined above in respect of L^1, and R^3, R^4, R^7 B^1, T^z, A^1 and n are as defined in Claim 1;

(viii) for compounds of formula I in which the dotted lines do not represent bonds, reaction of a compound of formula IX,



IX

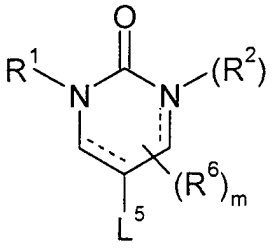
or a protected derivative thereof, wherein R^1, R^2, R^3, R^4, R^6, R^7, m and n are as defined in Claim 1, with a compound of formula X,



X

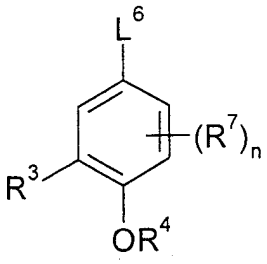
where L^4 and L^5 independently represent a suitable leaving group;

(ix) for compounds of formula I, reaction of a compound of formula XI,



XI

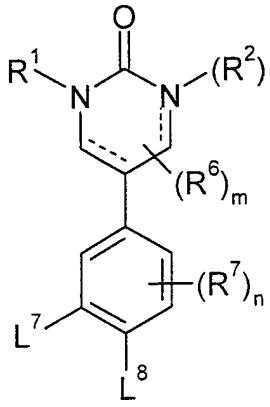
or a protected derivative thereof, where R^1, R^2, R^6, m and the dotted lines are as defined in Claim 1 and L^5 represents a suitable leaving group, with a compound of formula XII,



XII

or a protected derivative thereof, where R^3, R^4, R^7 and n are as defined in Claim 1, and L^6 represents a suitable leaving group;

(x) compounds of formula I, particularly those in which R^3 represents $-OR^{4a}$ in which R^{4a} is other than hydrogen, reaction of a compound of formula XIII,



XIII

or a protected derivative thereof, wherein R^1, R^2, R^6, R^7, m, n and the dotted lines are as defined in Claim 1 and L^7 represents L^x or R^3, L^8 represents L^x or $-OR^4$, and L^x represents a suitable leaving group and R^3 and R^4 are as defined in Claim 1, with a compound of formula XIV,

$$R^{4x}\text{-OH} \qquad \text{XIV}$$

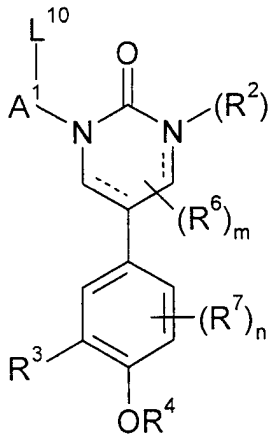
wherein R^{4x} represents R^4 or R^{4a} as defined above (or as defined in Claim 1);

(xi) for compounds of formula I in which R^3 represents $-OR^{4a}$ in which R^{4a} is other than hydrogen and/or where R^4 is other than hydrogen, reaction of a corresponding compound of formula I in which R^3 represents -OH and/or R^4 represents hydrogen, with a compound of formula XV,

$$R^{4y}\text{-}L^9 \qquad \text{XV}$$

wherein R^{4y} represents R^4 or R^{4a} as required/appropriate, and L^9 represents a suitable leaving group, and R^4 and R^{4a} are as defined above (or defined in Claim 1);

(xii) for compounds of formula I in which T^z represents $-N(R^{w1})-$, reaction of a compound of formula XVI,



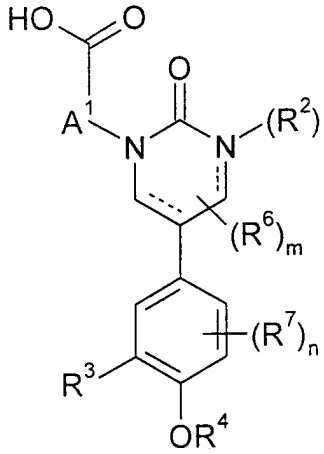
XVI

or a protected derivative thereof, wherein L^{10} represents a suitable leaving group, and R^2, R^3, R^4, R^6, R^7, m, n and the dotted lines are as defined in Claim 1, with a compound of formula XVII,

$$H\text{-}Z^a \qquad \text{XVII}$$

wherein Z^a represents $-N(R^{w1})-B^1$, and R^{w1} and B^1 are as defined in Claim 1;

(xiii) for compounds of formula I in which T^z represents $-C(O)-N(R^{w2})-$, reaction of a compound of formula XVIII,



XVIII

or a protected derivative thereof, wherein the dotted lines, R^2, R^3, R^4, R^5, R^6, R^7, A^1, m, n and the dotted lines are as defined in Claim 1, with a compound of formula XIX,

$$H\text{-}Z^b \qquad \text{XIX}$$

wherein Z^b represents $-N(R^{w2})-B^1$, and R^{w2} and B^1 are as defined in Claim 1,.

31. A process for the preparation of a pharmaceutical formulation as defined in Claim 14, which process comprises bringing into association a compound of formula I, as defined in any one of Claims 1 to 12, or a pharmaceutically acceptable salt thereof with a pharmaceutically-acceptable adjuvant, diluent, carrier or excipient.

32. A process for the preparation of a combination product as defined in any one of Claims 25 to 29, which process comprises bringing into association a compound of formula I, as defined in any one of Claims 1 to 12, or a pharmaceutically acceptable salt thereof with the other therapeutic agent that is useful in the treatment of a disorder as defined by i), ii), iii), iv), v) or vi) in Claim 15, or with an inhibitor of a phosphodiesterase as defined in Claim 28 or Claim 29, and at least one pharmaceutically-acceptable adjuvant, diluent, carrier or excipient.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2009/002169

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/06 C07D405/06 C07D409/06 C07D413/06 C07D417/06

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 814 651 A (DUPLANTIER ALLEN JACOB [US] ET AL) 29 September 1998 (1998-09-29) example 28, column 29	1-32
X	WO 01/55119 A (NEUROCRINE BIOSCIENCES INC [US]; ZHU YUN FEI [US]; CHEN CHEN [US]; TUC) 2 August 2001 (2001-08-02) claim 1 and compounds 9-29 and 9-34 in page 75, 9-42 in p. 76, 9-336 in p. 94 and 9-337 in p. 95	1-32

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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

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

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

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

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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 December 2009	17/12/2009

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2009/002169

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TUCCI F C ET AL: "3-[(2R)-amino-2-phenylethyl]-1-(2,6-difluorobenzyl)-5-(2-fluoro-3-methoxyphenyl)-6-methylpyrimidin-2,4-dione (NBI 42902) as a potent and orally active antagonist of the human gonadotropin-releasing hormone receptor. Design, synthesis, and in vitro and in vivo characterization" JOURNAL OF MEDICINAL CHEMISTRY 20050224 US, vol. 48, no. 4, 24 February 2005 (2005-02-24), pages 1169-1178, XP002559387 ISSN: 0022-2623 compound 19e, page 1171	1-32
P,A	WO 2008/110793 A (BIOLIPOX AB [SE]; PELCMAN BENJAMIN [SE]; KROG-JENSEN CHRISTIAN [SE]; S) 18 September 2008 (2008-09-18) the whole document	1-32

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2009/002169

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		NO 20023525 A	24-07-2002
WO 2008110793 A	18-09-2008	AR 065708 A1	24-06-2009
		CA 2680412 A1	18-09-2008