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(54) **2-PYRIDONE DERIVATIVES FOR THE TREATMENT OF DISEASE OR CONDITION IN WHICH INHIBITION OF NEUTROPHIL ELASTASE ACTIVITY IS BENEFICIAL.**

2-PYRIDONDERIVATE ZUR BEHANDLUNG VON KRANKHEITEN ODER LEIDEN, BEI DENEN EINE INHIBIERUNG DER AKTIVITÄT DER NEUTROPHILEN ELASTASE VON NUTZEN IST

DÉRIVÉS DE 2-PYRIDONE DESTINÉS AU TRAITEMENT D'UNE MALADIE OU D'UN ÉTAT DANS LEQUEL L'INHIBITION DE L'ÉLASTASE NEUTROPHILE HUMAINE A UN EFFET BÉNÉFIQUE

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(56) References cited:
EP-A1- 1 300 396 **WO-A1-2004/043924**
WO-A1-2005/021509 **WO-A1-2005/026123**
WO-A1-2005/026124 **WO-A1-2005/080372**
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DescriptionField of the Invention

5 **[0001]** The present invention relates to 2-pyridone derivatives, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

Background of the Invention

10 **[0002]** Elastases are possibly the most destructive enzymes in the body, having the ability to degrade virtually all connective tissue components. The uncontrolled proteolytic degradation by elastases has been implicated in a number of pathological conditions. Human neutrophil elastase (hNE), a member of the chymotrypsin superfamily of serine proteases is a 33-KDa enzyme stored in the azurophilic granules of the neutrophils. In neutrophils the concentration of NE exceeded 5 mM and its total cellular amount has been estimated to be up to 3 pg. Upon activation, NE is rapidly released
15 from the granules into the extracellular space with some portion remaining bound to neutrophil plasma membrane (See Kawabat et al. 2002, Eur. J. Pharmacol. 451, 1-10). The main intracellular physiological function of NE is degradation of foreign organic molecules phagocytosed by neutrophils, whereas the main target for extracellular elastase is elastin (Janoff and Scherer, 1968, J. Exp. Med. 128, 1137-1155). NE is unique, as compared to other proteases (for example, proteinase 3) in that it has the ability to degrade almost all extracellular matrix and key plasma proteins (See Kawabat et al., 2002, Eur. J. Pharmacol. 451, 1-10). It degrades a wide range of extracellular matrix proteins such as elastin, Type 3 and type 4 collagens, laminin, fibronectin, cytokines, etc. (Ohbayashi, H., 2002, Expert Opin. Investig. Drugs, 11, 965-980). NE is a major common mediator of many pathological changes seen in chronic lung disease including epithelial damage (Stockley, R.A. 1994, Am. J. Resp. Crit. Care Med. 150, 109-113).

25 **[0003]** The destructive role of NE was solidified almost 40 years ago when Laurell and Eriksson reported an association of chronic airflow obstruction and emphysema with deficiency of serum α_1 -antitrypsin (Laurell and Eriksson, 1963, Scand. J. Clin. Invest. 15, 132-140). Subsequently it was determined that α_1 -antitrypsin is the most important endogenous inhibitor of human NE. The imbalance between human NE and endogenous antiprotease is believed to cause excess human NE in pulmonary tissues which is considered as a major pathogenic factor in chronic obstructive pulmonary disease (COPD). The excessive human NE shows a prominent destructive profile and actively takes part in destroying
30 the normal pulmonary structures, followed by the irreversible enlargement of the respiratory airspaces, as seen mainly in emphysema. There is an increase in neutrophil recruitment into the lungs which is associated with increased lung elastase burden and emphysema in α_1 -proteinase inhibitor-deficient mice (Cavarra et al., 1996, Lab. Invest. 75, 273-280). Individuals with higher levels of the NE- α_1 protease inhibitor complex in bronchoalveolar lavage fluid show significantly accelerated decline in lung functions compared to those with lower levels (Betsuyaku et al. 2000, Respiration, 67, 261-267). Instillation of human NE via the trachea in rats causes lung haemorrhage, neutrophil accumulation during acute phase and emphysematous changes during chronic phase (Karaki et al., 2002, Am. J. Resp. Crit. Care Med., 166, 496-500). Studies have shown that the acute phase of pulmonary emphysema and pulmonary haemorrhage caused by NE in hamsters can be inhibited by pre-treatment with inhibitors of NE (Fujie et al., 1999, Inflamm. Res. 48, 160-167).

35 **[0004]** Neutrophil-predominant airway inflammation and mucus obstruction of the airways are major pathologic features of COPD, including cystic fibrosis and chronic bronchitis. NE impairs mucin production, leading to mucus obstruction of the airways. NE is reported to increase the expression of major respiratory mucin gene, MUC5AC (Fischer, B.M & Voynow, 2002, Am. J. Respir. Cell Biol., 26,447-452). Aerosol administration of NE to guinea pigs produces extensive epithelial damage within 20 minutes of contact (Suzuki et al., 1996, Am. J. Resp. Crit. Care Med., 153, 1405-1411). Furthermore NE reduces the ciliary beat frequency of human respiratory epithelium *in vitro* (Smallman et al., 1984, Thorax, 39, 663-667) which is consistent with the reduced mucociliary clearance that is seen in COPD patients (Currie et al., 1984, Thorax, 42, 126-130). The instillation of NE into the airways leads to mucus gland hyperplasia in hamsters (Lucey et al., 1985, Am. Resp. Crit. Care Med., 132, 362-366). A role for NE is also implicated in mucus hypersecretion in asthma. In an allergen sensitised guinea pig acute asthma model an inhibitor of NE prevented goblet cell degranulation and mucus hypersecretion (Nadel et al., 1999, Eur. Resp. J., 13, 190-196).

40 **[0005]** NE has been also shown to play a role in the pathogenesis of pulmonary fibrosis. NE: α_1 -protenase inhibitor complex is increased in serum of patients with pulmonary fibrosis, which correlates with the clinical parameters in these patients (Yamanouchi et al., 1998, Eur. Resp. J. 11, 120-125). In a murine model of human pulmonary fibrosis, a NE inhibitor reduced bleomycin-induced pulmonary fibrosis (Taooka et al., 1997, Am. J. Resp. Crit. Care Med., 156, 260-265). Furthermore investigators have shown that NE deficient mice are resistant to bleomycin-induced pulmonary fibrosis
45 (Dunsmore et al., 2001, Chest, 120, 35S-36S). Plasma NE level was found to be elevated in patients who progressed to ARDS implicating the importance of NE in early ARDS disease pathogenesis. (Donnelly et al., 1995, Am. J. Res. Crit. Care Med., 151,428-1433). The antiproteases and NE complexed with antiprotease are increased in lung cancer area (Marchandise et al., 1989, Eur. Resp. J. 2, 623-629). Recent studies have shown that polymorphism in the promoter

region of the NE gene are associated with lung cancer development (Taniguchi et al., 2002, Clin. Cancer Res., 8, 1115-1120).

[0006] Acute lung injury caused by endotoxin in experimental animals is associated with elevated levels of NE (Kawabata, et al., 1999, Am. J. Resp. Crit. Care, 161, 2013-2018). Acute lung inflammation caused by intratracheal injection of lipopolysaccharide in mice has been shown to elevate the NE activity in bronchoalveolar lavage fluid which is significantly inhibited by a NE inhibitor (Fujie et al., 1999, Eur. J. Pharmacol., 374, 117-125; Yasui, et al., 1995, Eur. Resp. J., 8, 1293-1299). NE also plays an important role in the neutrophil-induced increase of pulmonary microvascular permeability observed in a model of acute lung injury caused by tumour necrosis factor α (TNF α) and phorbol myristate acetate (PMA) in isolated perfused rabbit lungs (Miyazaki et al., 1998, Am. J. Respir. Crit. Care Med., 157, 89-94).

[0007] A role for NE has also been suggested in monocrotaline-induced pulmonary vascular wall thickening and cardiac hypertrophy (Molteni et al., 1989, Biochemical Pharmacol. 38, 2411-2419). Serine elastase inhibitor reverses the monocrotaline-induced pulmonary hypertension and remodelling in rat pulmonary arteries (Cowan et al., 2000, Nature Medicine, 6, 698-702). Recent studies have shown that serine elastase, that is, NE or vascular elastase are important in cigarette smoke-induced muscularisation of small pulmonary arteries in guinea pigs (Wright et al., 2002, Am. J. Respir. Crit. Care Med., 166, 954-960).

[0008] NE plays a key role in experimental cerebral ischemic damage (Shimakura et al., 2000, Brain Research, 858, 55-60), ischemia-reperfusion lung injury (Kishima et al., 1998, Ann. Thorac. Surg. 65, 913-918) and myocardial ischemia in rat heart (Tiefenbacher et al., 1997, Eur. J. Physiol., 433, 563-570). Human NE levels in plasma are significantly increased above normal in inflammatory bowel diseases, for example, Crohn's disease and ulcerative colitis (Adeyemi et al., 1985, Gut, 26, 1306-1311). In addition NE has also been assumed to be involved in the pathogenesis of rheumatoid arthritis (Adeyemi et al., 1986, Rheumatol. Int., 6, 57). The development of collagen induced arthritis in mice is suppressed by a NE inhibitor (Kakimoto et al., 1995, Cellular Immunol. 165, 26-32).

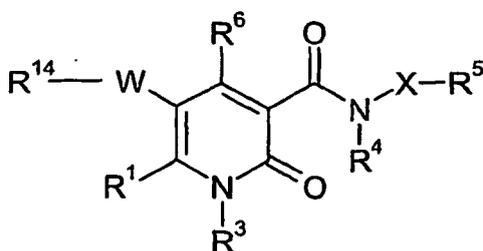
[0009] Thus, human NE is known as one of the most destructive serine proteases and has been implicated in a variety of inflammatory diseases. The important endogenous inhibitor of human NE is α_1 -antitrypsin. The imbalance between human NE and antiprotease is believed to give rise to an excess of human NE resulting in uncontrolled tissue destruction. The protease/ antiprotease balance may be upset by a decreased availability of α_1 -antitrypsin either through inactivation by oxidants such as cigarette smoke, or as a result of genetic inability to produce sufficient serum levels. Human NE has been implicated in the promotion or exacerbation of a number of diseases such as pulmonary emphysema, pulmonary fibrosis, adult respiratory distress syndrome (ARDS), ischemia reperfusion injury, rheumatoid arthritis and pulmonary hypertension.

[0010] WO 2005/026123, WO 2005/026124, WO2005/080372, WO2004/043924, WO 2004/020410 and EP 1 300 396 A1 disclose certain 2-pyridone derivatives as human neutrophil elastase inhibitors. WO2006/098683 and WO2006/098684 both published after the priority date of the present application, also disclose certain 2-pyridone derivatives as human neutrophil elastase inhibitors.

[0011] WO 2005021509 discloses certain quinoline derivatives as human neutrophil elastase inhibitors.

Disclosure of the Invention

[0012] In accordance with the present invention, there is therefore provided a compound of formula (I)



(I)

wherein

R¹ represents hydrogen or C₁-C₆ alkyl;

W represents a 5-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen, oxygen

and sulphur, wherein at least one of the ring carbon atoms may be optionally replaced by a carbonyl group; and wherein the heterocyclic ring is optionally substituted by at least one substituent selected from halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN, OH, NO₂, C₁-C₃ alkyl substituted by one or more F atoms, C₁-C₃ alkoxy substituted by one or more F atoms, NR¹⁰R¹¹, C=CR¹⁵, CONR¹⁶R¹⁷, CHO, C₂-C₄ alkanoyl, S(O)_xR¹⁸ and OSO₂R¹⁹;

R¹⁴ represents phenyl or a 6-membered heteroaromatic ring comprising 1 to 3 ring nitrogen atoms; said ring being optionally substituted with at least one substituent selected from halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN, OH, NO₂, C₁-C₃ alkyl substituted by one or more F atoms, C₁-C₃ alkoxy substituted by one or more F atoms, NR¹²R¹³, C≡CR³⁰, CONR³¹R³², CHO, C₂-C₄ alkanoyl, S(O)_pR³³ and OSO₂R³⁴;

R¹⁰, R¹¹, R¹² and R¹³ independently represent H, C₁-C₆ alkyl, formyl or C₂-C₆ alkanoyl; or the group **NR¹⁰R¹¹** or **-NR¹²R¹³** together represents a 5 to 7 membered azacyclic ring optionally incorporating one further heteroatom selected from O, S and NR²⁶;

R¹⁵ and R³⁰ independently represent H, C₁-C₃ alkyl or Si(CH₃)₃;

R¹⁸, R¹⁹, R³³ and R³⁴ independently represent H or C₁-C₃ alkyl; said alkyl being optionally substituted by one or more F atoms;

R⁶ represents H or F;

R³ represents phenyl or a five- or six-membered heteroaromatic ring containing 1 to 3 heteroatoms independently selected from O, S and N; said ring being optionally substituted with at least one substituent selected from halogen, C₁-C₆ alkyl, cyano, C₁-C₆ alkoxy, nitro, methylcarbonyl, NR³⁵R³⁶, C₁-C₃ alkyl substituted by one or more F atoms or C₁-C₃ alkoxy substituted by one or more F atoms;

R³⁵ and R³⁶ independently represent H or C₁-C₃ alkyl; said alkyl being optionally further substituted by one or more F atoms;

R⁴ represents hydrogen or C₁-C₆ alkyl optionally substituted with at least one substituent selected from fluoro, hydroxyl and C₁-C₆ alkoxy;

X represents a single bond, O, NR²⁴ or a group -C₁-C₆ alkylene-Y-, wherein Y represents a single bond, oxygen atom, NR²⁴ or S(O)_w; and said alkylene being optionally further substituted by OH, halogen, CN, NR³⁷R³⁸, C₁-C₃ alkoxy, CONR³⁹R⁴⁰, CO₂R⁶⁶, SO₂R⁴¹ and SO₂NR⁴²R⁴³;

or **R⁴ and X** are joined together such that the group **-NR⁴X** together represents a 5 to 7 membered azacyclic ring optionally incorporating one further heteroatom selected from O, S and NR⁴⁴; said ring being optionally substituted by C₁-C₆ alkyl or NR⁴⁵R⁴⁶; said alkyl being optionally further substituted by OH;

either **R⁵** represents a monocyclic ring system selected from

i) phenoxy,

ii) phenyl,

iii) a 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur,

iv) a saturated or partially unsaturated C₃-C₆ cycloalkyl ring, or

v) a saturated or partially unsaturated 4- to 7-membered heterocyclic ring comprising at least one ring heteroatom selected from oxygen, S(O)_r and NR²⁰, wherein at least one of the ring carbon atoms may be optionally replaced by a carbonyl group,

or **R⁵** represents a bicyclic ring system in which the two rings are independently selected from the monocyclic ring systems defined in ii), iii), iv) and v) above, wherein the two rings are either fused together, bonded directly to one another or are separated from one another by a linker group selected from oxygen, S(O)_t or C₁-C₆ alkylene optionally comprising one or more internal or terminal heteroatoms selected from oxygen, sulphur and NR²⁷ and being optionally substituted by at least one substituent selected from hydroxyl, oxo and C₁-C₆ alkoxy,

the monocyclic or bicyclic ring system being optionally substituted by at least one substituent selected from oxygen, CN, OH, C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, NR⁴⁷R⁴⁸, NO₂, OSO₂R⁴⁹, CO₂R⁵⁰, C(=NH)NH₂, C(O)NR⁵¹R⁵², C(S)NR⁵³R⁵⁴, SC(=NH)NH₂, NR⁵⁵C(=NH)NH₂, S(O)_vR²¹, SO₂NR⁵⁶R⁷, C₁-C₃ alkoxy substituted by one or more F atoms and C₁-C₃ alkyl substituted by SO₂R⁵⁸ or by one or more F atoms; said C₁-C₆ alkyl being optionally further substituted with at least one substituent selected from cyano, hydroxyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio and -C(O)ONR²²R²³;

or **R⁵** may also represent H;

R²⁰ represents hydrogen, C₁-C₆ alkyl, C₁-C₆ alkylcarbonyl or C₁-C₆ alkoxy carbonyl;

R²¹ represents hydrogen, C₁-C₆ alkyl or C₃-C₈ cycloalkyl; said alkyl or cycloalkyl group being optionally further substituted by one or more substituents selected independently from OH, CN, C₁-C₃ alkoxy and CONR⁵⁹R⁶⁰;

R³⁷ and R³⁸ independently represent H, C₁-C₆ alkyl, formyl or C₂-C₆ alkanoyl;

R⁴⁷ and R⁴⁸ independently represent H, C₁-C₆ alkyl, formyl, C₂-C₆ alkanoyl, S(O)_qR⁶¹ or SO₂NR⁶²R⁶³; said alkyl group being optionally further substituted by halogen, CN, C₁-C₄ alkoxy or CONR⁶⁴R⁶⁵;

R⁴¹ and R⁶¹ independently represent H, C₁-C₆ alkyl or C₃-C₆ cycloalkyl;

p is 0, 1 or 2;

q is 0, 1 or 2;

r is 0, 1 or 2;

t is 0, 1 or 2;

w is 0, 1 or 2;

x is 0, 1 or 2;

v is 0, 1 or 2;

R¹⁶, R¹⁷, R²², R²³, R²⁴, R²⁶, R²⁷, R³¹, R³², R³⁹, R⁴⁰, R⁴², R⁴³, R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁹, R⁵⁰, R⁵¹, R⁵², R⁵³, R⁵⁴, R⁵⁵, R⁵⁶, R⁵⁷, R⁵⁸, R⁵⁹, R⁶⁰, R⁶², R⁶³, R⁶⁴, R⁶⁵ and R⁶⁶ each independently represent hydrogen or C₁-C₆ alkyl;

or a pharmaceutically acceptable salt thereof.

[0013] In the context of the present specification, unless otherwise stated, an alkyl, alkenyl or alkynyl substituent group or an alkyl moiety in a substituent group may be linear or branched. Similarly, an alkylene group may be linear or branched.

[0014] In the definition of W, the 5-membered heterocyclic ring system may have alicyclic or aromatic properties and may thus be a saturated ring system or a partially unsaturated ring system or a fully unsaturated ring system.

[0015] R¹ represents hydrogen or C₁-C₆ alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl).

[0016] In one embodiment of the invention, R¹ represents a C₁-C₄ or C₁-C₂ alkyl group, in particular a methyl group.

[0017] W represents a 5-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, wherein at least one of the ring carbon atoms may be optionally replaced by a carbonyl group; and wherein the heterocyclic ring is optionally substituted by at least one substituent selected from halogen (e.g. fluorine, chlorine, bromine or iodine), C₁-C₄ alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert-butyl), C₁-C₄ alkoxy (e.g. methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy or tert-butoxy), cyano, OH, NO₂, C₁-C₃ alkyl substituted by one or more F atoms (e.g. CH₂F, CHF₂, CF₃, CH₂CH₂F, CH₂CF₃, CF₂CF₃, CH(CF₃)₂ and CH₂CH₂CF₃), C₁-C₃ alkoxy substituted by one or more F atoms (e.g.

OCH₂F, OCHF₂, OCF₃, OCH₂CH₂F, OCH₂CF₃, OCF₂CF₃, OCH(CF₃)₂ and OCH₂CH₂CF₃), NR¹⁰R¹¹, C≡CR¹⁵-C(O)NR¹⁶R¹⁷, CHO, C₂-C₄ alkanoyl (e.g. methylcarbonyl (acetyl), ethylcarbonyl, n-propylcarbonyl or isopropylcarbonyl), -S(O)_xR¹⁸, and OSO₂R¹⁹.

[0019] In one embodiment, the group R¹⁴ and the 2-pyridone ring are bonded to the 5-membered ring W in a 1,2-relationship.

[0020] In one embodiment, W represents a 5-membered heteroaromatic ring, especially an unsubstituted 5-membered heteroaromatic ring.

[0021] Examples of 5-membered heterocyclic ring systems that may be used, which may be saturated or partially unsaturated or fully unsaturated include any one of pyrrolidinyl, tetrahydrofuranyl, pyrroline, imidazolidinyl, imidazolyl, pyrazolidinyl, pyrazolyl, pyrrolidinonyl, imidazolidinonyl, oxazolyl, pyrazolyl, thiazolidinyl, thienyl, isoxazolyl, isothiazolyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, imidazolyl, furazanyl, triazolyl and tetrazolyl.

[0022] Preferred ring systems for group W include pyrazolyl, thiazolyl, oxazolyl and imidazolyl.

[0023] In one embodiment, W represents pyrazolyl, triazolyl, thiazolyl, oxazolyl or imidazolyl.

[0024] R¹⁴ represents phenyl or a 6-membered heteroaromatic ring comprising 1 to 3 (e.g. one, two or three) ring nitrogen atoms; said ring being optionally substituted with at least one (e.g. one, two, three or four) substituent selected from halogen (e.g. fluorine, chlorine, bromine or iodine), C₁-C₄ alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert-butyl), C₁-C₄ alkoxy (e.g. methoxy, methoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy or tert-butoxy), CN, OH, NO₂, C₁-C₃ alkyl substituted by one or more F atoms (e.g. CH₂F, CHF₂, CF₃, CH₂CH₂F, CH₂CF₃, CF₂CF₃, CH(CF₃)₂ and CH₂CH₂CF₃), C₁-C₃ alkoxy substituted by one or more F atoms (e.g. OCH₂F, OCHF₂, OCF₃, OCH₂CH₂F, OCH₂CF₃, OCF₂CF₃, OCH(CF₃)₂ and OCH₂CH₂CF₃), NR¹²R¹³, C≡CR³⁰, CONR³¹R³², CHO, C₂-C₄ alkanoyl (e.g. methylcarbonyl (acetyl), ethylcarbonyl, n-propylcarbonyl or isopropylcarbonyl), S(O)_pR³³ and OSO₂R³⁴.

[0025] Examples of a 6-membered heteroaromatic ring comprising 1 to 3 ring nitrogen atoms include pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl and triazinyl. A preferred ring system is pyridinyl.

[0026] In one embodiment, one substituent on the aromatic ring of group R¹⁴ should be in the 4- (para) position relative to group W.

[0027] In one embodiment of the invention, R¹⁴ represents phenyl or a 6-membered heteroaromatic ring comprising 1 to 3 ring nitrogen atoms; said ring being optionally substituted with at least one substituent selected from F, Cl, CN and CF₃.

[0028] In an embodiment of the invention, R¹⁴ represents phenyl or pyridinyl; said ring being optionally substituted with at least one substituent selected from F, Cl, CN and CF₃.

[0029] In an embodiment of the invention, R¹⁴ represents a phenyl or pyridinyl group optionally substituted with one or two substituents independently selected from F, Cl, CN and CF₃.

[0030] In an embodiment of the invention, R¹⁴ represents phenyl or pyridinyl; said ring being 4-(para) substituted with F, Cl or CN and optionally further substituted.

[0031] In an embodiment of the invention, R¹⁴ represents phenyl or pyridinyl; said ring being 4-(para) substituted with F, Cl or CN.

[0032] In one embodiment, R⁶ represents H.

[0033] R³ represents phenyl or a five- or six-membered heteroaromatic ring containing 1 to 3 (e.g. one, two or three) heteroatoms independently selected from O, S and N; said ring being optionally substituted with at least one (e.g. one, two, three or four) substituent selected from halogen (e.g. fluorine, chlorine; bromine or iodine), C₁-C₆ alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), cyano, C₁-C₆ alkoxy (e.g. methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, n-pentoxy or n-hexoxy), nitro, methylcarbonyl, NR³⁵R³⁶, C₁-C₃ alkyl substituted by one or more F atoms (e.g. CH₂F, CHF₂, CF₃, CH₂CH₂F, CH₂CF₃, CF₂CF₃, CH(CF₃)₂ and CH₂CH₂CF₃) and C₁-C₃ alkoxy substituted with one or more F atoms (e.g. OCH₂F, OCHF₂, OCF₃, OCH₂CH₂F, OCH₂CF₃, OCF₂CF₃, OCH(CF₃)₂ and OCH₂CH₂CF₃).

[0034] In one embodiment, R³ represents a phenyl or pyridinyl ring substituted with at least one substituent (e.g. one, two or three substituents) independently selected from halogen, cyano, nitro, methyl, trifluoromethyl and methylcarbonyl.

[0035] In one embodiment, R³ represents a phenyl group substituted with one or two substituents independently selected from fluorine, chlorine, cyano, nitro and trifluoromethyl.

[0036] In another embodiment, R³ represents a phenyl group substituted with one or two substituents independently selected from fluorine, chlorine and trifluoromethyl.

[0037] In still another embodiment, R³ represents a phenyl group substituted with a trifluoromethyl substituent (preferably in the meta position).

[0038] In still another embodiment, R³ represents a phenyl group substituted in the meta position with Br, Cl, CF₃ or CN.

[0039] R⁴ represents hydrogen or C₁-C₆ alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted with at least one substituent (e.g. one or two substituents) independently selected from fluoro, hydroxyl and C₁-C₆ alkoxy (e.g. methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, n-pentoxy or n-hexoxy).

[0040] In one embodiment, R⁴ represents hydrogen or C₁-C₄ alkyl optionally substituted with one or two substituents independently selected from hydroxyl and C₁-C₄ alkoxy.

[0041] In another embodiment, R⁴ represents hydrogen.

[0042] In one embodiment of the invention, X represents a single bond or a group -C₁-C₆ alkylene-Y-, wherein Y represents a single bond, oxygen atom, NR²⁴ or S(O)_w; said alkylene being optionally further substituted by OH, halogen, CN, NR³⁷R³⁸, C₁-C₃ alkoxy, CONR³⁹R⁴⁰, CO₂R⁶⁶, SO₂R⁴¹ and SO₂NR⁴²R⁴³.

[0043] In one embodiment of the invention, X represents a single bond or a group -C₁-C₆ alkylene-Y-, wherein Y represents a single bond, oxygen atom, NR²⁴ or S(O)_w; said alkylene being optionally further substituted by OH halogen, CN, NR³⁷R³⁸, C₁-C₃ alkoxy, CONR³⁹R⁴⁰, SO₂R⁴¹ and SO₂NR⁴²R⁴³.

[0044] In an embodiment of the invention, X represents a group -C₁-C₆ alkylene-Y- and Y represents a single bond and the alkylene moiety is a linear or branched C₁-C₆ or C₁-C₄ or C₁-C₂ alkylene, optionally substituted by OH, halogen, CN, CO₂R⁶⁶ or C₁-C₃ alkoxy.

[0045] In an embodiment of the invention, X represents a group -C₁-C₆ alkylene-Y- and Y represents a single bond and the alkylene moiety is a linear or branched C₁-C₆ or C₁-C₄ or C₁-C₂ alkylene, optionally substituted by OH, halogen, CN or C₁-C₃ alkoxy.

[0046] In another embodiment of the invention, X represents unsubstituted C₁-C₂ alkylene, particularly methylene.

[0047] In another embodiment of the invention, X represents a single bond.

[0048] In one embodiment of the invention, R⁴ and X are joined together such that the group -NR⁴⁴X together represents a 5 to 7 membered azacyclic ring optionally incorporating one further heteroatom selected from O, S and NR⁴⁴; said ring being optionally substituted by C₁-C₆ alkyl or NR⁴⁵R⁴⁶; said alkyl being optionally further substituted by OH. Examples of a 5 to 7 membered azacyclic ring optionally incorporating one further heteroatom selected from O, S and NR⁴⁴ include pyrrolidine, piperidine, piperazine, morpholine and perhydroazepine.

[0049] R⁵ represents a monocyclic ring system selected from

i) phenoxy,

ii) phenyl,

iii) a 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms) independently selected from nitrogen, oxygen and sulphur,

iv) a saturated or partially unsaturated C₃-C₆ cycloalkyl ring, or

v) a saturated or partially unsaturated 4- to 7-membered heterocyclic ring comprising at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms) independently selected from oxygen, S(O)_r and NR²⁰, wherein at least one of the ring carbon atoms may be optionally replaced by a carbonyl group,

or R⁵ represents a bicyclic ring system in which the two rings are independently selected from the monocyclic ring systems defined in ii), iii), iv) and v) above, wherein the two rings are either fused together, bonded directly to one

another or are separated from one another by a linker group selected from oxygen, S(O)_t or C₁-C₆ alkylene optionally comprising one or more (e.g. one or two) internal or terminal heteroatoms selected from oxygen, sulphur and NR²⁷ and being optionally substituted by at least one substituent (e.g. one or two substituents) independently selected from hydroxyl, oxo and C₁-C₆ alkoxy (e.g. methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, n-pentoxy or n-hexoxy);

the monocyclic or bicyclic ring system being optionally substituted (on a ring atom) by at least one substituent (e.g. one, two or three substituents) independently selected from oxygen (e.g. to form an N-oxide), CN, OH, C₁-C₆ alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C₁-C₆ alkoxy (e.g. methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, n-pentoxy or n-hexoxy), halogen (e.g. fluorine, chlorine, bromine or iodine), NR⁴⁷R⁴⁸, NO₂, OSO₂R⁴⁹, CO₂R⁵⁰, C(=NH)NH₂, C(O)NR⁵¹R⁵², C(S)NR⁵³R⁵⁴, SC(=NH)NH₂, NR⁵⁵C(=NH)NH₂, -S(O)_vR²¹, SO₂NR⁵⁶R⁵⁷, C₁-C₃ alkoxy substituted by one or more F atoms (e.g. OCH₂F, OCHF₂, OCF₃, OCH₂CH₂F, OCH₂CF₃, OCF₂CF₃, OCH(CF₃)₂ and OCH₂CH₂CF₃) and C₁-C₃ alkyl substituted by SO₂R⁵⁸ or by one or more F atoms (e.g. CH₂SO₂R⁵⁸, CH₂CH₂SO₂R⁵⁸, CH(SO₂R⁵⁸)CH₃, CH₂F, CHF₂, CF₃, CH₂CH₂F, CH₂CF₃, CF₂CF₃, CH(CF₃)₂ and CH₂CH₂CF₃); said C₁-C₆ alkyl being optionally further substituted with at least one substituent selected from cyano, hydroxyl, C₁-C₆ alkoxy (e.g. methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, n-pentoxy or n-hexoxy), C₁-C₆ alkylthio (e.g. methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, tert-butylthio, n-pentylthio or n-hexylthio) and -C(O)NR²²R²³; or R⁵ may also represent hydrogen.

[0050] Examples of a 5- or 6-membered heteroaromatic ring include furanyl, thienyl, pyrrolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyrimidinyl and pyrazinyl. Preferred heteroaromatic rings include isoxazolyl, pyridinyl, imidazolyl and triazolyl.

[0051] Unless otherwise indicated, a "saturated or partially unsaturated C₃-C₆ cycloalkyl ring" denotes a 3- to 6-membered non-aromatic cycloalkyl ring optionally incorporating one or more double bonds, examples of which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentenyl and cyclohexenyl. A preferred cycloalkyl ring is cyclopropyl.

[0052] Unless otherwise indicated, a "saturated or partially unsaturated 4- to 7-membered heterocyclic ring" as specified above denotes a 4- to 7-membered non-aromatic heterocyclic ring optionally incorporating one or more double bonds and optionally incorporating a carbonyl group, examples of which include tetrahydrofuranyl, tetramethylenesulfonyl, tetrahydropyranyl, 4-oxo-4H-pyranyl (4H-pyran-4-onyl), pyrrolidinyl, 3-pyrrolinyl, imidazolidinyl, 1,3-dioxolanyl (1,3-dioxacyclopentanyl), piperidinyl, piperazinyl, morpholinyl, perhydroazepinyl (hexamethylene iminyl), pyrrolidonyl and piperidonyl. A preferred saturated or partially unsaturated 4- to 7-membered heterocyclic ring is pyrrolidonyl.

[0053] Examples of bicyclic ring systems in which the two rings are either fused together, bonded directly to one another or are separated from one another by a linker group include biphenyl, thienylphenyl, pyrazolylphenyl, phenoxypheyl, phenylcyclopropyl, naphthyl, indanyl, quinolyl, tetrahydroquinolyl, benzofuranyl, indolyl, isoindolyl, indolinyl, benzofuranyl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, purinyl, isoquinolyl, chromanyl, indenyl, quinazolyl, quinoxalyl, chromanyl, isocromanyl, 3H-indolyl, 1H-indazolyl, quinuclidyl, tetrahydronaphthyl, dihydrobenzofuranyl, morpholine-4-ylphenyl, 1,3-benzodioxolyl, 2,3-dihydro-1,4-benzodioxinyl, 1,3-benzodioxinyl and 3,4-dihydro-isochromenyl.

[0054] In an embodiment of the invention, R⁵ represents a substituted monocyclic ring system as defined above.

[0055] In another embodiment of the invention, R⁵ represents a substituted bicyclic ring system as defined above.

[0056] In another embodiment of the invention, R⁵ represents H.

[0057] In a further embodiment of the invention, R⁵ represents a monocyclic ring system selected from

i) phenoxy,

ii) phenyl,

iii) a 5- or 6-membered heteroaromatic ring comprising one or two ring heteroatoms independently selected from nitrogen, oxygen and sulphur,

iv) a saturated or partially unsaturated C₃-C₆ cycloalkyl ring, or

v) a saturated or partially unsaturated 4- to 7-membered heterocyclic ring comprising one or two ring heteroatoms independently selected from oxygen, S(O)_r and NR²⁰, wherein at least one of the ring carbon atoms may be optionally replaced by a carbonyl group;

or R⁵ represents a bicyclic ring system in which the two rings are independently selected from the monocyclic ring systems defined in ii), iii), iv) and v) above, wherein the two rings are either fused together, bonded directly to one another or are separated from one another by a linker group selected from oxygen, methylene and S(O)_t; the monocyclic or bicyclic ring system being substituted by one or two substituents independently selected from OH, -S(O)_vR²¹ and C₁-C₄ alkyl.

[0058] In a still further embodiment of the invention, R⁵ represents a monocyclic ring system selected from phenyl or a 5- or 6-membered heteroaromatic ring comprising one or two ring heteroatoms independently selected from nitrogen

and oxygen, the monocyclic ring system being substituted by one or two substituents independently selected from OH, $-S(O)_vR^{21}$ and C_1-C_4 alkyl.

[0059] In a still further embodiment of the invention, R^5 represents phenyl or pyridinyl substituted by $-S(O)_vR^{21}$ wherein v represents the integer 2.

[0060] In a still further embodiment of the invention, R^5 represents phenyl substituted by one or two substituents independently selected from OH, $-S(O)_vR^{21}$ and C_1-C_4 alkyl.

[0061] In a still further embodiment of the invention, R^5 represents H.

[0062] In a still further embodiment of the invention, R^5 represents an unsubstituted C_3-C_6 cycloalkyl ring, particularly cyclopropyl.

[0063] In one embodiment, x is 2.

[0064] In one embodiment, p is 2.

[0065] In one embodiment, R^{10} and R^{11} independently represent H, C_1-C_3 alkyl or C_2-C_3 alkylcarbonyl.

[0066] In one embodiment, R^{12} and R^{13} independently represent H, C_1-C_3 alkyl or C_2-C_3 alkylcarbonyl.

[0067] In a further embodiment, R^{20} represents hydrogen, methyl, ethyl, methylcarbonyl, (acetyl), ethylcarbonyl, methoxycarbonyl or ethoxycarbonyl.

[0068] In one embodiment, v is 2.

[0069] R^{21} represents hydrogen, C_1-C_6 alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) or C_3-C_8 cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl); said alkyl or cycloalkyl group being optionally further substituted by one or more substituents selected independently from OH, CN, C_1-C_3 alkoxy and $CONR^{59}R^{60}$.

[0070] In an embodiment according to the invention, R^{21} represents C_1-C_4 alkyl or C_3-C_6 cycloalkyl.

[0071] In another embodiment, R^{21} represents C_1-C_3 alkyl (particularly methyl, ethyl or isopropyl) or cyclopropyl.

[0072] In another embodiment, R^{41} represents C_1-C_3 alkyl (particularly methyl, ethyl or isopropyl) or cyclopropyl.

[0073] In an embodiment of the invention, R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{30} , R^{33} , R^{34} , R^{35} , R^{36} , R^{37} , R^{38} , R^{47} , R^{48} , R^{61} , R^{22} , R^{23} , R^{24} , R^{26} , R^{27} , R^{31} , R^{32} , R^{39} , R^{40} , R^{42} , R^{43} , R^{44} , R^{45} , R^{46} , R^{49} , R^{50} , R^{51} , R^{52} , R^{53} , R^{54} , R^{55} , R^{56} , R^{57} , R^{58} , R^{59} , R^{60} , R^{62} , R^{63} , R^{64} , R^{65} and R^{66} each independently represent hydrogen or C_1-C_3 alkyl, particularly methyl, ethyl, 1-propyl or 2-propyl.

[0074] In an embodiment of the invention, R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{30} , R^{33} , R^{34} , R^{35} , R^{36} , R^{37} , R^{38} , R^{47} , R^{48} , R^{61} , R^{22} , R^{23} , R^{24} , R^{26} , R^{27} , R^{31} , R^{32} , R^{39} , R^{40} , R^{42} , R^{43} , R^{44} , R^{45} , R^{46} , R^{49} , R^{50} , R^{51} , R^{52} , R^{53} , R^{54} , R^{55} , R^{56} , R^{57} , R^{55} , R^{59} , R^{60} , R^{62} , R^{63} , R^{64} , R^{65} and R^{66} each independently represent hydrogen or methyl.

[0075] In an embodiment of the invention, R^{66} represents hydrogen.

[0076] In an embodiment of the invention,

R^1 represents methyl;

W represents a 5-membered heteroaromatic ring, and the group R^{14} and the 2-pyridone ring are bonded to the 5-membered ring W in a 1,2-relationship;

R^{14} represents phenyl or pyridinyl; said ring being optionally substituted with at least one substituent selected from F, Cl, CN and CF_3 ;

R^6 represents H;

R^3 represents a phenyl group substituted with one or two substituents independently selected from fluorine, chlorine, cyano, nitro or trifluoromethyl;

R^4 represents hydrogen;

X represents unsubstituted C_1-C_2 alkylene, particularly methylene; and

R^5 represents phenyl substituted by one or two substituents independently selected from OH, $-S(O)_vR^{21}$ and C_1-C_4 alkyl wherein v represents the integer 2.

[0077] In an embodiment of the invention,

R^1 represents methyl;

W represents a 5-membered heteroaromatic ring, and the group R^{14} and the 2-pyridone ring are bonded to the 5-membered ring W in a 1,2-relationship;

R^{14} represents phenyl or pyridinyl; said ring being optionally substituted with at least one substituent selected from F, Cl, CN and CF_3 ;

R^6 represents H;

R^3 represents a phenyl group substituted with one or two substituents independently selected from fluorine, chlorine, cyano, nitro or trifluoromethyl;

R^4 represents hydrogen;

X represents unsubstituted C_1-C_2 alkylene, particularly methylene; and

R^5 represents H.

[0078] In an embodiment of the invention,

R^1 represents methyl;

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W represents a 5-membered heteroaromatic ring, and the group R^{14} and the 2-pyridone ring are bonded to the 5-membered ring **W** in a 1,2-relationship;

R^{14} represents phenyl or pyridinyl; said ring being 4- (para) substituted with F, Cl or CN;

R^6 represents H;

5 R^3 represents a phenyl group substituted in the meta position with Br, Cl, CF_3 or CN;

R^4 represents hydrogen;

X represents a linear or branched C_1 - C_4 alkylene, optionally substituted by OH, halogen, CN, CO_2R^{66} or C_1 - C_3 alkoxy; and

R^5 represents H.

10 **[0079]** Examples of compounds of the invention include:

5-[1-(4-cyanophenyl)-1*H*-pyrazol-5-yl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

15 5-[1-(4-cyanophenyl)-1*H*-pyrazol-5-yl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[2-amino-5-(4-chlorophenyl)-1,3-thiazol-4-yl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[4-(4-chlorophenyl)-1,3-oxazol-5-yl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

20 5-[2-amino-5-(4-cyanophenyl)-1,3-thiazol-4-yl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

1-(3-chloro-4-fluorophenyl)-5-[1-(4-cyanophenyl)-1*H*-pyrazol-5-yl]-*N*,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxamide;

25 5-[2-(4-chloro-phenyl)-2*H*-pyrazol-3-yl]-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid methylamide;

5-[2-(4-fluoro-phenyl)-2*H* pyrazol-3-yl]-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid methylamide;

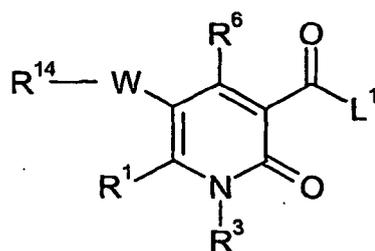
5-[3-(4-cyano-phenyl)-3*H*-[1,2,3]triazol-4-yl]-6-methyl-2-oxo-1-(3-trifluoromethylphenyl)-1,2-dihydro-pyridine-3-carboxylic acid methylamide; and

30 5-[1-(4-cyanophenyl)-1*H*-1,2,4-triazol-5-yl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

and pharmaceutically acceptable salts of any one thereof.

35 **[0080]** The present invention further provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined above which comprises,

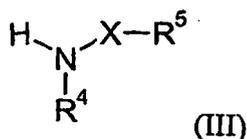
(a) reacting a compound of formula (II)



(II)

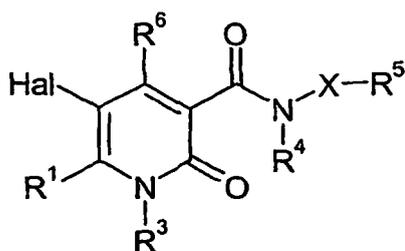
wherein L^1 represents a leaving group (such as halogen or hydroxyl) and R^1 , R^3 , R^6 , R^{14} and **W** are as defined in formula (I),

55 with a compound of formula



wherein X, R⁴ and R⁵ are as defined in formula (I); or

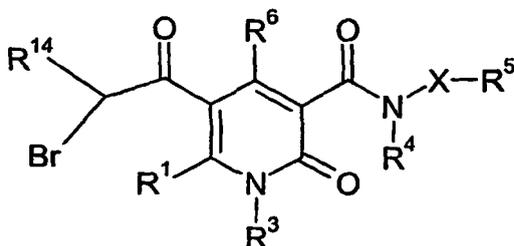
(b) reacting a compound of formula (IV)



(IV)

wherein Hal represents a halogen atom and X, R¹, R³, R⁴, R⁵ and R⁶ are as defined in formula (I), with a nucleophile R¹⁴-W-M wherein R¹⁴ and W are as defined in formula (I) and M represents an organo-tin or organo boronic acid group; or

(c) when W represents thiazolyl or oxazolyl, reacting a compound of formula (V)



(V)

wherein X, R¹, R³, R⁴, R⁵, R⁶ and R¹⁴ are as defined in formula (I), with thiourea or formamide respectively; and optionally after (a), (b) or (c) carrying out one or more of the following:

- converting the compound obtained to a further compound of the invention
- forming a pharmaceutically acceptable salt of the compound.

[0081] In process (a), the reaction may conveniently be carried out in an organic solvent such as dichloromethane or N-methylpyrrolidinone at a temperature, for example, in the range from 0 °C to the boiling point of the solvent. If necessary or desired, a base and/or a coupling reagent such as HATU (O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate), HOAT (1-Hydroxy-7-azabenzotriazole), HOBT (1-Hydroxybenzotriazole hydrate) or DIEA (N,N-Diisopropylethylamine) may be added.

[0082] In process (b), the reaction may conveniently be carried out in an organic solvent such as DMF, NMP or toluene or a mixture thereof at elevated temperature (i.e. above ambient temperature, 20°C), for example, in the range from 50 °C to 150 °C and in the presence of a suitable transition metal catalyst such as bis(tri-t-butylphosphine)palladium. If

necessary or desired, a base such as potassium carbonate may be added.

[0083] In process (c), the reaction may conveniently be carried out by heating together the two starting materials in a suitable organic solvent such as acetonitrile at a temperature, for example, in the range from 50 °C to 150 °C.

[0084] Specific processes for the preparation of compounds of Formula (I) are disclosed within the Examples section of the present specification. Such processes form an aspect of the present invention.

[0085] The necessary starting materials are either commercially available, are known in the literature or may be prepared using known techniques. Specific processes for the preparation of certain key starting materials are disclosed within the Examples section of the present specification and such processes form an aspect of the present invention.

[0086] Certain intermediates of formulae (II), (IV) and (V) are novel. Such novel intermediates form another aspect of the invention.

[0087] Compounds of formula (I) can be converted into further compounds of formula (I) using standard procedures.

[0088] It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) may involve, at an appropriate stage, the addition and/or removal of one or more protecting groups.

[0089] The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 3rd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1999).

[0090] The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, tartrate, lactate, citrate, pyruvate, succinate, oxalate, methanesulphonate or *p*-toluenesulphonate.

[0091] Compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses the use of all geometric and optical isomers (including atropisomers) of the compounds of formula (I) and mixtures thereof including racemates. The use of tautomers and mixtures thereof also form an aspect of the present invention. Enantiomerically pure forms are particularly desired.

[0092] The compounds of formula (I) and their pharmaceutically acceptable salts have activity as pharmaceuticals, in particular as modulators of serine proteases such as proteinase 3 and pancreatic elastase and, especially, human neutrophil elastase, and may therefore be beneficial in the treatment or prophylaxis of inflammatory diseases and conditions.

[0093] The compounds of formula (I) and their pharmaceutically acceptable salts can be used in the treatment of diseases of the respiratory tract such as obstructive diseases of the airways including: asthma, including bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus.

[0094] The compounds of formula (I) and their pharmaceutically acceptable salts can also be used in the treatment of diseases of bone and joints such as arthritides associated with or including osteoarthritis/osteoarthritis, both primary and secondary to, for example, congenital hip dysplasia; cervical and lumbar spondylitis, and low back and neck pain; rheumatoid arthritis and Still's disease; seronegative spondyloarthropathies including ankylosing spondylitis, psoriatic arthritis, reactive arthritis and undifferentiated spondyloarthropathy; septic arthritis and other infection-related arthropathies and bone disorders such as tuberculosis, including Potts' disease and Poncet's syndrome; acute and chronic crystal-induced synovitis including urate gout, calcium pyrophosphate deposition disease, and calcium apatite related tendon, bursal and synovial inflammation; Behcet's disease; primary and secondary Sjogren's syndrome; systemic sclerosis and limited scleroderma; systemic lupus erythematosus, mixed connective tissue disease, and undifferentiated connective tissue disease; inflammatory myopathies including dermatomyositis and polymyositis; polymyalgia rheumatica; juvenile arthritis including idiopathic inflammatory arthritides of whatever joint distribution and associated syndromes, and rheumatic fever and its systemic complications; vasculitides including giant cell arteritis, Takayasu's arteritis, Churg-Strauss syndrome, polyarteritis nodosa, microscopic polyarteritis, and vasculitides associated with viral infection, hypersensitivity reactions, cryoglobulins, and paraproteins; low back pain; Familial Mediterranean fever, Muckle-Wells syndrome, and Familial Hibernian Fever, Kikuchi disease; drug-induced arthralgias, tendonitis, and myopathies.

[0095] The compounds of formula (I) and their pharmaceutically acceptable salts can also be used in the treatment

of pain and connective tissue remodelling of musculoskeletal disorders due to injury [for example, sports injury] or disease: arthritides (for example rheumatoid arthritis, osteoarthritis, gout or crystal arthropathy), other joint disease (such as intervertebral disc degeneration or temporomandibular joint degeneration), bone remodelling disease (such as osteoporosis, Paget's disease or osteonecrosis), polycondritis, scleroderma, mixed connective tissue disorder, spondyloarthropathies or periodontal disease (such as periodontitis).

[0096] The compounds of formula (I) and their pharmaceutically acceptable salts can also be used in the treatment of diseases of skin such as psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis; cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions.

[0097] The compounds of formula (I) and their pharmaceutically acceptable salts can also be used in the treatment of diseases of the eye such as blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune; degenerative or inflammatory disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; infections including viral, fungal, and bacterial.

[0098] The compounds of formula (I) and their pharmaceutically acceptable salts can also be used in the treatment of diseases of the gastrointestinal tract such as glossitis, gingivitis, periodontitis; oesophagitis, including reflux; eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, colitis including ulcerative colitis, proctitis, pruritis ani; coeliac disease, irritable bowel syndrome, non-inflammatory diarrhoea, and food-related allergies which may have effects remote from the gut (for example, migraine, rhinitis or eczema).

[0099] The compounds of formula (I) and their pharmaceutically acceptable salts can also be used in the treatment of diseases of the cardiovascular system such as atherosclerosis, affecting the coronary and peripheral circulation; pericarditis; myocarditis, inflammatory and autoimmune cardiomyopathies including myocardial sarcoid; ischaemic reperfusion injuries; endocarditis, valvulitis, and aortitis including infective (for example syphilitic); vasculitides; disorders of the proximal and peripheral veins including phlebitis and thrombosis, including deep vein thrombosis and complications of varicose veins.

[0100] The compounds of formula (I) and their pharmaceutically acceptable salts can also be used in oncology such as in the treatment of common cancers including prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes.

[0101] In particular, the compounds of formula (I) and their pharmaceutically acceptable salts may be used in the treatment of adult respiratory distress syndrome (ARDS), cystic fibrosis, pulmonary emphysema, bronchitis including chronic bronchitis, bronchiectasis, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, asthma including refractive asthma, rhinitis, psoriasis, ischemia-reperfusion injury, rheumatoid arthritis, osteoarthritis, systemic inflammatory response syndrome (SIRS), chronic wound, cancer, atherosclerosis, peptic ulcers, Crohn's disease, ulcerative colitis and gastric mucosal injury.

[0102] More particularly, the compounds of formula (I) and their pharmaceutically acceptable salts may be used in the treatment of chronic obstructive pulmonary disease (COPD), asthma and rhinitis.

[0103] Even more particularly, the compounds of formula (I) and their pharmaceutically acceptable salts may be used in the treatment of chronic obstructive pulmonary disease (COPD).

[0104] Thus, the present invention provides a compound of formula (I) or a pharmaceutically-acceptable salt thereof as hereinbefore defined for use in therapy.

[0105] In a further aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined in the manufacture of a medicament for use in therapy.

[0106] In a further aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of neutrophil elastase activity is beneficial.

[0107] In a further aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined in the manufacture of a medicament for use in the treatment of an inflammatory disease or condition.

[0108] In a further aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined in the manufacture of a medicament for use in treating adult respiratory distress syndrome (ARDS), cystic fibrosis, pulmonary emphysema, bronchitis including chronic bronchitis, bronchiectasis, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, asthma including refractive asthma, rhinitis, psoriasis, ischemia-reperfusion injury, rheumatoid arthritis, osteoarthritis, systemic inflammatory response syndrome

(SIRS), chronic wound, cancer, atherosclerosis, peptic ulcers, Crohn's disease, ulcerative colitis or gastric mucosal injury.

[0109] In a further aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined in the manufacture of a medicament for use in treating chronic obstructive pulmonary disease (COPD).

[0110] In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

[0111] Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

[0112] The invention also discloses a method of treating, or reducing the risk of, a disease or condition in which inhibition of neutrophil elastase activity is beneficial which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined.

[0113] The invention still further discloses a method of treating, or reducing the risk of, an inflammatory disease or condition which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined.

[0114] The invention still further discloses a method of treating, or reducing the risk of, adult respiratory distress syndrome (ARDS), cystic fibrosis, pulmonary emphysema, bronchitis including chronic bronchitis, bronchiectasis, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, asthma including refractive asthma, rhinitis, psoriasis, ischemia-reperfusion injury, rheumatoid arthritis, osteoarthritis, systemic inflammatory response syndrome (SIRS), chronic wound, cancer, atherosclerosis, peptic ulcers, Crohn's disease, ulcerative colitis or gastric mucosal injury which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined.

[0115] The invention still further discloses a method of treating, or reducing the risk of, chronic obstructive pulmonary disease (COPD) which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined.

[0116] For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. The daily dosage of the compound of the invention may be in the range from 0.05 mg/kg to 100 mg/kg.

[0117] The compounds of formula (I) and pharmaceutically acceptable salts thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988.

[0118] Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

[0119] The present invention also provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

[0120] The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

[0121] The pharmaceutical compositions may be administered topically (e.g. to the skin or to the lung and/or airways) in the form, e.g., of creams, solutions, suspensions, heptafluoroalkane (HFA) aerosols and dry powder formulations, for example, formulations in the inhaler device known as the Turbuhaler®; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules; or by parenteral administration in the form of solutions or suspensions; or by subcutaneous administration; or by rectal administration in the form of suppositories; or transdermally.

[0122] Dry powder formulations and pressurized HFA aerosols of the compounds of the invention may be administered by oral or nasal inhalation. For inhalation, the compound is desirably finely divided. The finely divided compound preferably has a mass median diameter of less than 10 μm , and may be suspended in a propellant mixture with the assistance of a dispersant, such as a C₈-C₂₀ fatty acid or salt thereof, (for example, oleic acid), a bile salt, a phospholipid, an alkyl saccharide, a perfluorinated or polyethoxylated surfactant, or other pharmaceutically acceptable dispersant.

[0123] The compounds of the invention may also be administered by means of a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler.

[0124] One possibility is to mix the finely divided compound of the invention with a carrier substance, for example, a

mono-, di- or polysaccharide, a sugar alcohol, or another polyol. Suitable carriers are sugars, for example, lactose, glucose, raffinose, melezitose, lactitol, maltitol, trehalose, sucrose, mannitol; and starch. Alternatively the finely divided compound may be coated by another substance. The powder mixture may also be dispensed into hard gelatine capsules, each containing the desired dose of the active compound.

[0125] Another possibility is to process the finely divided powder into spheres which break up during the inhalation procedure. This spheronized powder may be filled into the drug reservoir of a multidose inhaler, for example, that known as the Turbuhaler® in which a dosing unit meters the desired dose which is then inhaled by the patient. With this system the active ingredient, with or without a carrier substance, is delivered to the patient.

[0126] For oral administration the compound of the invention may be admixed with an adjuvant or a carrier, for example, lactose, saccharose, sorbitol, mannitol; a starch, for example, potato starch, com starch or amylopectin; a cellulose derivative; a binder, for example, gelatine or polyvinylpyrrolidone; and/or a lubricant, for example, magnesium stearate, calcium stearate, polyethylene glycol, a wax, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain, for example, gum arabic, gelatine, talcum and titanium dioxide. Alternatively, the tablet may be coated with a suitable polymer dissolved in a readily volatile organic solvent.

[0127] For the preparation of soft gelatine capsules, the compound of the invention may be admixed with, for example, a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the compound using either the above-mentioned excipients for tablets. Also liquid or semisolid formulations of the compound of the invention may be filled into hard gelatine capsules.

[0128] Liquid preparations for oral application may be in the form of syrups or suspensions, for example, solutions containing the compound of the invention, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and/or carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

[0129] The compounds of the invention may also be administered in conjunction with other compounds used for the treatment of the above conditions.

[0130] Thus, the invention further relates to combination therapies wherein a compound of the invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition or formulation comprising a compound of the invention, is administered concurrently or sequentially or as a combined preparation with another therapeutic agent or agents, for the treatment of one or more of the conditions listed.

[0131] In particular, for the treatment of the inflammatory diseases such as (but not restricted to) rheumatoid arthritis, osteoarthritis, asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD), psoriasis, and inflammatory bowel disease, the compounds of the invention may be combined with agents listed below.

[0132] Non-steroidal anti-inflammatory agents (hereinafter NSAIDs) including non-selective cyclo-oxygenase COX-1 / COX-2 inhibitors whether applied topically or systemically (such as piroxicam, diclofenac, propionic acids such as naproxen, flurbiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, azapropazone, pyrazolones such as phenylbutazone, salicylates such as aspirin); selective COX-2 inhibitors (such as meloxicam, celecoxib, rofecoxib, valdecoxib, lumarocoxib, parecoxib and etoricoxib); cyclo-oxygenase inhibiting nitric oxide donors (CINODs); glucocorticosteroids (whether administered by topical, oral, intramuscular, intravenous, or intra-articular routes); methotrexate; leflunomide; hydroxychloroquine; d-penicillamine; auranofin or other parenteral or oral gold preparations; analgesics; diacerein; intra-articular therapies such as hyaluronic acid derivatives; and nutritional supplements such as glucosamine.

[0133] The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with a cytokine or agonist or antagonist of cytokine function, (including agents which act on cytokine signalling pathways such as modulators of the SOCS system) including alpha-, beta-, and gamma-interferons; insulin-like growth factor type I (IGF-1); interleukins (IL) including IL1 to 23, and interleukin antagonists or inhibitors such as anakinra; tumour necrosis factor alpha (TNF- α) inhibitors such as anti-TNF monoclonal antibodies (for example infliximab; adalimumab, and CDP-870) and TNF receptor antagonists including immunoglobulin molecules (such as etanercept) and low-molecular-weight agents such as pentoxifylline

[0134] In addition the invention relates to a combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with a monoclonal antibody targeting B-Lymphocytes (such as CD20 (rituximab), MRA-all16R and T-Lymphocytes, CTLA4-Ig, HuMax II-15).

[0135] The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with a modulator of chemokine receptor function such as an antagonist of CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX₃CR1 for the C-X₃-C family.

[0136] The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with an inhibitor of matrix metalloprotease (MMPs), i.e., the stromelysins, the collagenases, and the gelatinases, as well as aggrecanase; especially collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3

(MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11) and MMP-9 and MMP-12, including agents such as doxycycline.

5 [0137] The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist such as; zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; a N-(5-substituted)-thiophene-2-alkylsulfonamide; 2,6-di-tert-butylphenolhydrazones; a methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; a pyridinyl-substituted 2-cyanonaphthalene compound such as L-739,010; a 2-cyanoquinoline compound such as L-746,530; or an indole or quinoline compound such as MK-591, MK-886, and BAY x 1005.

10 [0138] The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a receptor antagonist for leukotrienes (LT) B₄, LTC₄, LTD₄, and LTE₄. selected from the group consisting of the phenothiazin-3-1s such as L-651,392; amidino compounds such as CGS-25019c; benzoxalamines such as ontazolast; benzenecarboximidamides such as BIIL 284/260; and compounds such as zafirlukast, ablu-
15 kast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195.

[0139] The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a phosphodiesterase (PDE) inhibitor such as a methylxanthanine including theophylline and aminophylline; a selective PDE isoenzyme inhibitor including a PDE4 inhibitor an inhibitor of the isoform PDE4D, or an inhibitor of PDE5.

20 [0140] The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a histamine type 1 receptor antagonist such as cetirizine, loratadine, desloratadine, fex-
ofenadine, acrivastine, terfenadine, astemizole, azelastine, levocabastine, chlorpheniramine, promethazine, cyclizine, or mizolastine; applied orally, topically or parenterally.

[0141] The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a proton pump inhibitor (such as omeprazole) or a gastroprotective histamine type 2 receptor
25 antagonist.

[0142] The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an antagonist of the histamine type 4 receptor.

30 [0143] The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an alpha-1/alpha-2 adrenoceptor agonist vasoconstrictor sympathomimetic agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, ephedrine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, tramazoline hydrochloride or ethylnorepinephrine hydrochloride.

[0144] The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an anticholinergic agents including muscarinic receptor (M₁, M₂, and M₃) antagonist such
35 as atropine, hyoscine, glycopyrrrolate, ipratropium bromide, tiotropium bromide, oxitropium bromide, pirenzepine or telenzepine.

[0145] The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a beta-adrenoceptor agonist (including beta receptor subtypes 1-4) such as isoprenaline, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, or pirbuterol, or a chiral enantiomer
40 thereof.

[0146] The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a chromone, such as sodium cromoglycate or nedocromil sodium.

[0147] The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with a glucocorticoid, such as flunisolide, triamcinolone acetonide, beclomethasone dipropionate,
45 budesonide, fluticasone propionate, ciclesonide or mometasone furoate.

[0148] The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with an agent that modulates a nuclear hormone receptor such as PPARs.

[0149] The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with an immunoglobulin (Ig) or Ig preparation or an antagonist or antibody modulating
50 Ig function such as anti-IgE (for example omalizumab).

[0150] The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and another systemic or topically-applied anti-inflammatory agent, such as thalidomide or a derivative thereof, a retinoid, dithranol or calcipotriol.

55 [0151] The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and combinations of aminosalicylates and sulfapyridine such as sulfasalazine, mesalazine, balsalazide, and olsalazine; and immunomodulatory agents such as the thiopurines, and corticosteroids such as budesonide.

[0152] The present invention further relates to the combination of a compound of the invention, or a pharmaceutically

acceptable salt thereof, together with an antibacterial agent such as a penicillin derivative, a tetracycline, a macrolide, a beta-lactam, a fluoroquinolone, metronidazole, an inhaled aminoglycoside; an antiviral agent including acyclovir, famciclovir, valaciclovir, ganciclovir, cidofovir, amantadine, rimantadine, ribavirin, zanamavir and oseltamavir; a protease inhibitor such as indinavir, nelfinavir, ritonavir, and saquinavir, a nucleoside reverse transcriptase inhibitor such as didanosine, lamivudine, stavudine, zalcitabine or zidovudine; or a non-nucleoside reverse transcriptase inhibitor such as nevirapine or efavirenz.

[0153] The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a cardiovascular agent such as a calcium channel blocker, a beta-adrenoceptor blocker, an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin-2 receptor antagonist; a lipid lowering agent such as a statin or a fibrate; a modulator of blood cell morphology such as pentoxifylline; thrombolytic, or an anticoagulant such as a platelet aggregation inhibitor.

[0154] The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a CNS agent such as an antidepressant (such as sertraline), an anti-Parkinsonian drug (such as deprenyl, L-dopa, ropinirole, pramipexole, a MAOB inhibitor such as selegine and rasagiline, a comP inhibitor such as tasmar, an A-2 inhibitor, a dopamine reuptake inhibitor, an NMDA antagonist, a nicotine agonist, a dopamine agonist or an inhibitor of neuronal nitric oxide synthase), or an anti-Alzheimer's drug such as donepezil, rivastigmine, tacrine, a COX-2 inhibitor, propentofylline or metrifonate.

[0155] The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an agent for the treatment of acute or chronic pain, such as a centrally or peripherally-acting analgesic (for example an opioid or derivative thereof), carbamazepine, phenytoin, sodium valproate, amitriptyline or other anti-depressant agent-s, paracetamol, or a non-steroidal anti-inflammatory agent.

[0156] The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with a parenterally or topically-applied (including inhaled) local anaesthetic agent such as lignocaine or a derivative thereof.

[0157] A compound of the present invention, or a pharmaceutically acceptable salt thereof, can also be used in combination with an anti-osteoporosis agent including a hormonal agent such as raloxifene, or a bisphosphonate such as alendronate.

[0158] The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with a: (i) tryptase inhibitor; (ii) platelet activating factor (PAF) antagonist; (iii) interleukin converting enzyme (ICE) inhibitor; (iv) IMPDH inhibitor; (v) adhesion molecule inhibitors including VLA-4 antagonist; (vi) cathepsin; (vii) kinase inhibitor such as an inhibitor of tyrosine kinase (such as Btk, Itk, Jak3 or MAP, for example Gefitinib or Imatinib mesylate), a serine / threonine kinase (such as an inhibitor of a MAP kinase such as p38, JNK, protein kinase A, B or C, or IKK), or a kinase involved in cell cycle regulation (such as a cyclin dependent kinase); (viii) glucose-6 phosphate dehydrogenase inhibitor; (ix) kinin-B.sub1. - or B.sub2. -receptor antagonist; (x) anti-gout agent, for example colchicine; (xi) xanthine oxidase inhibitor, for example allopurinol; (xii) uricosuric agent, for example probenecid, sulfipyrazone or benzbromarone; (xiii) growth hormone secretagogue; (xiv) transforming growth factor (THF β); (xv) platelet-derived growth factor (PDGF); (xvi) fibroblast growth factor for example basic fibroblast growth factor (bFGF); (xvii) granulocyte macrophage colony stimulating factor (GM-CSF); (xviii) capsaicin cream; (xix) tachykinin NK.sub1. or NK.sub3. receptor antagonist such as NKP-608C, SB-233412 (talnetant) or D-4418; (xx) elastase inhibitor such as UT-77 or ZD-0892; (xxi) TNF-alpha converting enzyme inhibitor (TACE); (xxii) induced nitric oxide synthase (iNOS) inhibitor; (xxiii) chemoattractant receptor-homologous molecule expressed on TH2 cells, (such as a CRTH2 antagonist); (xxiv) inhibitor of P38; (xxv) agent modulating the function of Toll-like receptors (TLR), (xxvi) agent modulating the activity of purinergic receptors such as P2X7; or (xxvii) inhibitor of transcription factor activation such as NF κ B, API, or STATS.

[0159] A compound of the invention, or a pharmaceutically acceptable salt thereof, can also be used in combination with an existing therapeutic agent for the treatment of cancer, for example suitable agents include:

- (i) an antiproliferative/antineoplastic drug or a combination thereof, as used in medical oncology, such as an alkylating agent (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan or a nitrosourea); an antimetabolite (for example an antifolate such as a fluoropyrimidine like 5-fluorouracil or tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine or paclitaxel); an antitumour antibiotic (for example an anthracycline such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin or mithramycin); an antimetotic agent (for example a vinca alkaloid such as vincristine, vinblastine, vindesine or vinorelbine, or a taxoid such as taxol or taxotere); or a topoisomerase inhibitor (for example an epipodophyllotoxin such as etoposide, teniposide, amsacrine, topotecan or a camptothecin);
- (ii) a cytostatic agent such as an antioestrogen (for example tamoxifen, toremifene, raloxifene, droloxifene or iodoxifene), an oestrogen receptor down regulator (for example fulvestrant), an antiandrogen (for example bicalutamide, flutamide, nilutamide or cyproterone acetate), a LHRH antagonist or LHRH agonist (for example goserelin, leuprorelin or buserelin), a progestogen (for example megestrol acetate), an aromatase inhibitor (for example as anastrozole,

letrozole, vorazole or exemestane) or an inhibitor of 5 α -reductase such as finasteride;

(iii) an agent which inhibits cancer cell invasion (for example a metalloproteinase inhibitor like marimastat or an inhibitor of urokinase plasminogen activator receptor function);

5 (iv) an inhibitor of growth factor function, for example: a growth factor antibody (for example the anti-erbB2 antibody trastuzumab, or the anti-erbB1 antibody cetuximab [C225]), a farnesyl transferase inhibitor, a tyrosine kinase inhibitor or a serine/threonine kinase inhibitor, an inhibitor of the epidermal growth factor family (for example an EGFR family tyrosine kinase inhibitor such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) or 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), an inhibitor of the platelet-derived growth factor family, or an inhibitor of the hepatocyte growth factor family;

10 (v) an antiangiogenic agent such as one which inhibits the effects of vascular endothelial growth factor (for example the anti-vascular endothelial cell growth factor antibody bevacizumab, a compound disclosed in WO 97/22596, WO 97/30035, WO 97/32856 or WO 98/13354), or a compound that works by another mechanism (for example linomide, an inhibitor of integrin $\alpha v \beta 3$ function or an angiostatin);

15 (vi) a vascular damaging agent such as combretastatin A4, or a compound disclosed in WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 or WO 02/08213;

(vii) an agent used in antisense therapy, for example one directed to one of the targets listed above, such as ISIS 2503, an anti-ras antisense;

20 (viii) an agent used in a gene therapy approach, for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; or

25 (ix) an agent used in an immunotherapeutic approach, for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

30 **[0160]** In particular the compounds of the invention may be administered in conjunction with a second active ingredient which is selected from:

a) a PDE4 inhibitor including an inhibitor of the isoform PDE4D;

b) a β -adrenoceptor agonist such as metaproterenol, isoproterenol, isoprenaline, albuterol, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, pirbuterol or indacaterol;

35 c) a muscarinic receptor antagonist (for example a M1, M2 or M3 antagonist, such as a selective M3 antagonist) such as ipratropium bromide, tiotropium bromide, oxitropium bromide, pirenzepine or telenzepine;

d) a modulator of chemokine receptor function (such as a CCR1 or CCR8 receptor antagonist);

e) an inhibitor of kinase function;

f) a non-steroidal glucocorticoid receptor agonist;

40 g) a steroidal glucocorticoid receptor agonist; and

h) a protease inhibitor (such as a MMP12 or MMP9 inhibitor);

[0161] The present invention will now be further explained by reference to the following illustrative examples.

45 General Methods

[0162] ^1H NMR and ^{13}C NMR spectra were recorded on a Varian *Inova* 400 MHz or a Varian *Mercury-VX* 300 MHz instrument. The central peaks of chloroform-*d* (δ_{H} 7.27 ppm), dimethylsulfoxide-*d*₆ (δ_{H} 2.50 ppm), acetonitrile-*d*₃ (δ_{H} 1.95 ppm) or methanol-*d*₄ (δ_{H} 3.31 ppm) were used as internal references. Column chromatography was carried out using silica gel (0.040-0.063 mm, Merck). Unless stated otherwise, starting materials were commercially available. All solvents and commercial reagents were of laboratory grade and were used as received.

[0163] The following method was used for LC/MS analysis:

Instrument Agilent 1100; Column Waters Symmetry 2.1 x 30 mm; Mass APCI; Flow rate 0.7 ml/min; Wavelength 254 nm; Solvent A: water +0.1% TFA; Solvent B: acetonitrile + 0.1% TFA; Gradient 15-95%/B 8 min, 95% B 1 min.

55 **[0164]** Analytical chromatography was run on a Symmetry C₁₈-column, 2.1 x 30 mm with 3.5 μm particle size, with acetonitrile/water/0.1% trifluoroacetic acid as mobile phase in a gradient from 5% to 95% acetonitrile over 8 minutes at a flow of 0.7 ml/min.

[0165] The abbreviations or terms used in the examples have the following meanings:

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HATU: O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
 HOAT: 1-Hydroxy-7-azabenzotriazole
 NMP: 1-N-Methyl-2-pyrrolidinone
 THF: Tetrahydrofuran
 5 DCM: Dichloromethane
 DIEA: N,N-Diisopropylethylamine
 DME: 1,2-Dimethoxyethane
 EtOAc: Ethyl acetate
 DMSO: Dimethyl sulphoxide
 10 SM: Starting material
 Ex: Example
 Aq: Aqueous
 RT: Room temperature

15 Example 1

5-[1-(4-Cyanophenyl)-1H-pyrazol-5-yl]-N,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

20 **[0166]** Argon was bubbled through 5-iodo-N,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (SM2, 200 mg, 0.46 mmol) and [1-(4-cyanophenyl)-1H pyrazol-5-yl]boronic acid (SM3, 150 mg, 0.70 mmol) in DME (10 ml) and 2M Na₂CO₃ (5 ml) for 10 min. Palladium-tri-tert-butylphosphine (25 mg, 0.049 mmol) was added and the mixture was stirred under argon at 82 °C for 2h. More SM3 (150 mg, 0.70 mmol) and palladium-tri-tert-butylphosphine (10 mg, 0.019 mmol) were added and the mixture was stirred for a further 2h under the same conditions. The reaction mixture was then cooled to RT, diluted with ethyl acetate (150 ml) and washed with brine (3 x 100 ml). The organic phase was dried (Na₂SO₄), filtered and evaporated. The residue was purified by HPLC on a Kromasil C-18 column using a gradient of acetonitrile/water. Freeze-drying of the mixture afforded the title compound (80 mg).

25 ¹H NMR (399.99 MHz, DMSO-D₆) δ 9.18 (q, *J* = 4.78 Hz, 1H), 8.05 (s, 1H), 7.96 - 7.64 (m, 9H), 6.72 (d, *J* = 1.76 Hz, 1H), 2.76 (d, *J* = 4.77 Hz, 3H), 1.76 (s, 3H);

30 APCI-MS *m/z*: 478.3 [MH⁺].

Example 2

35 **[0167]** The following compound was synthesised in an analogous manner to Example 1.

Ex	Compound	¹ HNMR	<i>m/z</i>	SM
2	5-[1-(4-Cyanophenyl)-1H-pyrazol-5-yl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	9.81 (1, <i>J</i> = 6.01 Hz, 1H), 8.10 (s, 1H), 7.96 - 7.70 (m, 9H), 7.67 (d, <i>J</i> = 8.67 Hz, 2H), 7.52 (d, <i>J</i> = 8.31 Hz, 2H), 6.73 (d, <i>J</i> = 2.77 Hz, 1H), 4.55 (d, <i>J</i> = 6.01 Hz, 2H), 3.17 (s, 3H), 1.76 (s, 3H).	632.2	SM1 SM3

45 Example 3

5-[2-Amino-5-(4-chlorophenyl)-1,3-thiazol-4-yl]-N,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

50 **[0168]** Thiourea (8.5 mg, 0.11 mmol) was added to 5-[bromo(4-chlorophenyl)acetyl]-N,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (SM4, 30 mg, 55 μmol) in acetonitrile (1 ml) and the mixture was heated in a microwave oven to 120 °C for 10 min. The crude product was purified on an Xterra C8 column using a gradient of acetonitrile/water. Freeze drying of the mixture afforded the title compound (10 mg, 35%).

55 ¹H NMR (400 MHz, DMSO-D₆) δ 9.27 (d, *J* = 4.8 Hz, 1H), 8.27 (s, 1H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.81 (t, *J* = 7.6 Hz, 3H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 4H), 7.32 (s, 3H), 7.25 (d, *J* = 8.5 Hz, 2H), 2.77 (d, *J* = 4.6 Hz, 3H), 1.67 (s, 3H);

APCI-MS *m/z*: 519.0 [MH⁺].

Examples 4 and 5

[0169] The following compounds were synthesised in an analogous manner to Example 3.

Ex	Compound	¹ HNMR	m/z	SM
4	5-[4-(4-Chlorophenyl)-1,3-oxazol-5-yl]-N,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	¹ H NMR (400 MHz, CDCl ₃) δ 9.32 (s, 1H), 8.61 (s, 1H), 8.02 (d, <i>J</i> = 6.2 Hz, 1H), 7.83 (d, <i>J</i> = 7.6 Hz, 2H), 7.76 (t, <i>J</i> = 7.8 Hz, 2H), 7.55 (s, 1H), 7.48 (d, <i>J</i> = 8.5 Hz, 3H), 7.39 (d, <i>J</i> = 8.5 Hz, 2H), 2.94 (d, <i>J</i> = 5.0 Hz, 3H), 1.99 (s, 3H).	488.0	SM4
5	5-[2-Amino-5-(4-cyanophenyl)-1,3-thiazol-4-yl]-N,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide	¹ H NMR (399.99 MHz, DMSO-D ₆) δ 9.26 (d, <i>J</i> = 4.8 Hz, 1H), 8.27 (s, 1H), 7.85 (m, 3H), 7.75 (d, 2H), 7.69 (d, <i>J</i> = 8.1 Hz, 1H), 7.41 (s, 2H), 2.78 (d, <i>J</i> = 4.8 Hz, 3H), 1.69 (s, 3H).	510.0	

Example 6

[0170] The following compound was synthesised in an analogous manner to Example 1.

1-(3-Chloro-4-fluorophenyl)-5-[1-(4-cyanophenyl)-1H-pyrazol-5-yl]-N,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxamide

[0171] ¹H NMR (300 MHz, DMSO-D₆) δ 9.18 (q, 1H), 8.02 (s, 1H), 7.96-7.90 (m, 3H), 7.78 (dd, 1H), 7.71-7.60 (m, 3H), 7.43 (m, 1H), 6.70 (d, 1H), 2.76 (d, 3H), 1.81 (s, 3H);
APCI-MS ^{m/z}: 462 [MH⁺].

Example 7

5-[2-(4-Chloro-phenyl)-2H-pyrazol-3-yl]-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid methylamide

a) 1-(4-Chloro-phenyl)-5-tributylstannanyl-1H-pyrazole

[0172] 2,2,6,6-Tetramethylpiperidine (TMP, 0.25 g, 1.78 mmol) was dissolved in dry THF (10 ml) in a flask with a magnetic stirrer bar. The flask was flushed with argon and kept under an inert atmosphere. The mixture was cooled to -78 °C, and *n*-BuLi (1.1 ml, 1.6M, 1.78 mmol) was added dropwise during 1 minute. The mixture was stirred for 5 minutes at this temperature, before adding a solution of 1-(4-chloro-phenyl)-1H-pyrazole (0.21 g, 1.1 mmol) in dry THF (2 ml). The solution was added dropwise over 2 minutes, and the obtained solution was stirred at this temperature for 20 minutes, before adding Bu₃SnCl (0.36 g, 1.1 mmol) over 1 minute. The solution was allowed to slowly warm to RT and was then quenched with MeOH (1 ml). The residual mixture was partitioned between EtOAc and water, and the organic phase was dried and concentrated. Purification on silica afforded 0.2 g (40%) of an oil.

¹H NMR (400 MHz, DMSO-D₆) δ 7.77 (d, *J* = 1.8 Hz, 1H), 7.62 (d, *J* = 9.0 Hz, 2H), 7.42 (d, *J* = 9.0 Hz, 2H), 6.54 (d, *J* = 1.8 Hz, 1H), 1.50-0.67 (m, 27H).
APCI-MS ^{m/z}: 468 [MH⁺].

b) 5-[2-(4-Chloro-phenyl)-2H-pyrazol-3-yl]-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid methylamide

[0173] 1-(4-Chloro-phenyl)-5-tributylstannanyl-1H-pyrazole (0.107 g, 0.22 mmol), 5-iodo-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid methylamide (0.05 g, 0.11 mmol), Pd(PBu₃)₂ (10 mg) and DME (2 ml) were placed in a tube for microwave synthesis. The mixture was degassed with argon and heated in a synthesis microwave heater (CEM) at 100 °C (max 150W) for 10 minutes. The solvent was removed in vacuo giving a crude product which was purified on silica and then further purified on preparative HPLC. The pure fractions were freeze-dried giving 10 mg (17%) of the title compound.

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¹H NMR (400 MHz, DMSO-D₆) δ 9.23-9.12 (m, 1H), 8.03 (s, 1H), 7.91 (d, *J*=8.0 Hz, 1H), 7.87-7.80 (m, 3H), 7.69 (d, *J*=8.0 Hz, 1H), 7.53 (d, *J*= 8.8 Hz, 2H), 7.45 (d, *J*= 8.8 Hz, 2H), 6.66 (d, *J*=1.8 Hz, 1H), 2.75 (d, *J*=4.8 Hz, 3H), 1.77 (s, 3H).
APCI-MS *m/z*: 487.0 [MH⁺].

5 **Example 8**

5-[2-(4-Fluoro-phenyl)-2*H*-pyrazol-3-yl]-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid methylamide

10 a) 1-(4-Fluoro-phenyl)-5-tributylstannanyl-1*H*-pyrazole

[0174] The compound was prepared by an analogous procedure to that described in Example 7(a).
APCI-MS *m/z*: 452 [MH⁺].

15 b) 5-[2-(4-Fluoro-phenyl)-2*H*-pyrazol-3-yl]-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid methylamide

[0175] 1-(4-Fluoro-phenyl)-5-tributylstannanyl-1*H*-pyrazole (0.100 g, 0.22 mmol), 5-iodo-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid methylamide (0.05 g, 0.11 mmol), Pd(PBu₃)₂ (10 mg) and DME (2 ml) were placed in a tube for microwave synthesis. The mixture was degassed with argon and heated in a synthesis microwave heater (CEM) at 100 °C (max 150W) for 10 minutes. The solvent was removed in vacuo giving a crude product which was purified on silica and then further purified on preparative HPLC. The pure fractions were freeze-dried giving 10 mg (17%) of the title compound.

¹H NMR (400 MHz, DMSO-D₆) δ 9.22-9.13 (m, 1H), 8.04 (s, 1H), 7.91 (d, *J*=7.7 Hz, 1H), 7.86-7.80 (m, 3H), 7.67 (d, *J*=7.7 Hz, 1H), 7.49-7.42 (m, 2H), 7.30 (t, *J*= 8.8 Hz, 2H), 6.65 (d, *J*=1.8 Hz, 1H), 2.75 (d, *J*=4.8 Hz, 3H), 1.76 (s, 3H).
APCI-MS *m/z*: 471.0 [MH⁺].

Example 9

30 5-[3-(4-Cyano-phenyl)-3*H*-[1,2,3]triazol-4-yl]-6-methyl-2-oxo-1-(3-trifluoromethylphenyl)-12-dihydro-pyridine-3-carboxylic acid methylamide

a) 4-[1,2,3]Triazol-1-yl-benzonitrile

[0176] 4-Fluorobenzonitrile (0.847 g, 7 mmol), 1*H*-[1,2,3]triazole (0.483 g, 7 mmol), Cs₂CO₃ (2.27 g, 7 mmol) and DMF (8 ml) and a magnetic stirrer were placed in a vial. The mixture was heated with stirring for 3h at 80 °C. Extractive work-up (EtOAc/H₂O) and subsequent drying (Na₂SO₄) gave a crude product which was purified on silica giving 0.55 g (46%) of the title compound.

¹H NMR (400 MHz, DMSO-D₆) δ 9.00 (d, *J*=1.2 Hz, 1H), 8.18 (d, *J*=8.8 Hz, 2H), 8.11 (d, *J*=8.8 Hz, 2H), 8.05 (d, *J*=1.2 Hz, 1H).

b) 4-(5-Tributylstannanyl-[1,2,3]triazol-1-yl)-benzonitrile

[0177] 4-[1,2,3]Triazol-1-yl-benzonitrile (0.105 g, 0.6 mmol) and dry THF (6 ml) and a magnetic stirrer were placed in a flask. The flask was flushed with argon and kept under an inert atmosphere and cooled to -78 °C. At this temperature, tert-BuLi (0.36 ml, 1.7M, 0.6 mmol) was added dropwise during 1 to 2 minutes. The mixture was stirred at this temperature for 15 minutes and Bu₃SnCl (0.19 g, 0.6 mmol) was added during 1 minute, and the mixture was then allowed to slowly reach RT. The crude mixture was directly purified on silica (heptane:EtOAc 4:1) giving 0.12 g (43%) of the title stannane.
APCI-MS *m/z*: 460 [MH⁺].

50 c) 5-[3-(4-Cyano-phenyl)-3*H*-[1,2,3]triazol-4-yl]-6-methyl-2-oxo-1-(3-trifluoromethylphenyl)-1,2-dihydro-pyridine-3-carboxylic acid methylamide

[0178] 4-(5-Tributylstannanyl-[1,2,3]triazol-1-yl)-benzonitrile (0.107 g, 0.22 mmol), 5-iodo-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid methylamide (0.05 g, 0.11 mmol), Pd(PBu₃)₂ (10 mg) and DME (2 ml) were placed in a tube for microwave synthesis. The mixture was degassed with argon and heated in a synthesis microwave heater (CEM) at 100°C (max 150W) for 10 minutes. The solvent was removed in vacuo giving a crude product which was purified on silica and then further purified on preparative HPLC. The pure fractions were freeze-dried giving

20 mg (40%) of the title compound.

¹H NMR (400 MHz, DMSO-D₆) δ 9.17-9.09 (m, 1H), 8.12 (s, 1H), 8.09-8.02 (m, 3H), 7.92 (d, *J*=7.8 Hz, 1H), 7.88-7.82 (m, 2H), 7.80 (d, *J*=8.6 Hz, 2H), 7.80 (d, *J*=8.0 Hz, 1H), 2.74 (d, *J*=4.8 Hz, 3H), 1.80 (s, 3H).

APCI-MS *m/z*: 479.0 [MH⁺].

5

Example 10

5-[1-(4-Cyanophenyl)-1H-1,2,4-triazol-5-yl]-N,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

10

[0179] 5-Iodo-N,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (SM2, 0.051 g, 0.117 mmol), 4-(1H-1,2,4-triazol-1-yl)benzotrile (0.020 g, 0.117 mmol), copper(I) iodide (0.044 g, 0.234 mmol), cesium fluoride (0.036 g, 0.234 mmol) and NMP (0.5 ml) were placed in a vial. Argon was bubbled through the stirred mixture for 10 min. Palladium(II) acetate (0.002 g, 0.0089 mmol) was added and the vial was sealed and stirred at 140 °C for 6h. Two more experiments were run the same way and the three reaction mixtures were combined and purified by preparative HPLC to give 0.003 g (2%) of the title compound.

15

¹H NMR (400 MHz, DMSO-D₆) δ 9.16 - 9.09 (m, 1H), 8.42 (s, 1H), 8.16 (s, 1H), 8.01 (d, *J* = 8.7 Hz, 2H), 7.92 (d, *J* = 8.9 Hz, 2H), 7.84 (t, *J* = 7.7 Hz, 1H), 7.80 - 7.74 (m, 3H), 2.75 (d, *J* = 4.7 Hz, 3H), 1.85 (s, 3H).

APCI-MS *m/z*: 479.0 [MH⁺].

20

Preparation of Starting Materials

[0180] The starting materials for the examples above are either commercially available or are readily prepared by standard methods from known materials. For example, the following reactions are illustrations, but not a limitation, of the preparation of some of the starting materials.

25

Starting material SM1

5-Iodo-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

30

[0181] To an ice-cooled solution of 3-(trifluoromethyl)aniline (64.5 g, 0.40 mol) and triethylamine (60 ml) in acetone (700 ml) was added dropwise, ethyl 3-chloro-3-oxopropanoate (63.6 g, 0.42 mol) in acetone (50 ml). After the addition was complete (approx. 30 minutes), stirring was continued at RT overnight. The solvents were removed and water (1200 ml) was added. The resulting precipitate was filtered off, thoroughly washed twice with water and then dried to afford ethyl 3-oxo-3-[[3-(trifluoromethyl)phenyl]amino]propanoate as a yellow powder (109 g, 99%).

35

¹H NMR (399.99 MHz, CDCl₃): δ 9.52 (1H, s); 7.87 (1H, s); 7.78 (1H, d); 7.46 (1H, t); 7.39 (1H, d); 4.29 (2H, q); 3.50 (2H, s); 1.35 (3H, t).

APCI-MS *m/z*: 276.1 [MH⁺].

[0182] To a solution of ethyl 3-oxo-3-[[3-(trifluoromethyl)phenyl]amino]propanoate (19.2 g, 70 mmol) and sodium methoxide (7.6 g, 140 mmol) in EtOH (250 ml) was added 4-methoxybut-3-en-2-one (90%) (7.72 g, 77 mmol). After the addition, the reaction mixture was refluxed for 2h and then cooled. Water (50 ml) and 2M NaOH were added and the mixture was stirred at RT overnight. The organic solvents were removed and the reaction mixture was extracted (washed) with EtOAc. The water phases were acidified with hydrochloric acid to pH 3 to 4, an orange coloured precipitate appeared and was filtered off, washed with water and dried. Recrystallisation twice from heptane/EtOAc (4:1) afforded 6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxylic acid (12 g, 58%) as a white powder.

40

¹H NMR (399.99 MHz, CDCl₃): δ 13.68 (1H, s); 8.54 (1H, d); 7.86 (1H, d); 7.79 (1H, t); 7.55 (1H, brs); 7.48 (1H, d); 6.58 (1H, d); 2.16 (3H, s);

APCI-MS *m/z*: 298.1 [MH⁺].

[0183] A mixture of 6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxylic acid (7.43 g, 25 mmol), HATU (10.5 g, 27.5 mmol), HOAT (3.75 g, 27.5 mmol) and DIEA (14.2 ml, 82.5 mmol) in NMP (65 ml) was reacted for 1h, then 4-methylsulphonylbzyl amine hydrochloride (5.8 g, 26 mmol) was added. After 1h, the reaction mixture was slowly poured into stirred ice water (1 L). A powder was formed and the water mixture was acidified to pH 3 with 0.5M citric acid, and stirring was continued for 1h. The precipitate was filtered off, washed with water and dried in vacuum overnight. Recrystallisation from EtOAc gave 6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (8.1 g, 70%).

45

¹H NMR (399.99 MHz, CDCl₃): δ 10.00 (1H, brt); 8.60 (1H, d); 7.88 (2H, d); 7.83 (1H, d); 7.76 (1H, t); 7.53 (3H, m); 7.46 (1H, d); 6.49 (1H, d); 4.68 (2H, m); 3.03 (3H, s); 2.10 (3H, s);

APCI-MS *m/z*: 465.1 [MH⁺].

50

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[0184] To a solution of 6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (200 mg, 0.43 mmol) in MeCN (1.5 ml) at RT and under argon, was added trifluoromethanesulfonic acid (1 ml) followed by *N*-iodosuccinimide (97 mg, 0.43 mmol). After 45 min, the reaction mixture was diluted with DCM, washed with aqueous NaHCO₃, with aqueous Na₂S₂O₄ and water, dried (Na₂SO₄), and evaporated to give the title compound SM1 (200 mg).

¹H NMR (399.99 MHz, CDCl₃): δ 9.85 (1H, brt); 8.90 (1H, d); 7.88 (2H, d); 7.76 (2H, m); 7.50 (2H, d); 7.48 (1H, s); 7.40 (1H, d); 4.65 (2H, m); 3.03 (3H, s); 2.32 (3H, s); APCI-MS *m/z*: 591.0 [MH⁺].

Starting material SM2

[0185] SM2, 5-iodo-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, was synthesised in an analogous manner to SM1.

Starting material SM3

[1-(4-Cyanophenyl)-1*H*-pyrazol-5-yl]boronic acid

[0186] 4-(1*H*-Pyrazol-1-yl)benzotrile (Eur. J. Org. Chem. 2004, 695-709) (1.5 g, 8.87 mmol) in dry THF (50 ml) under argon was stirred at -78°C whilst lithium diisopropylamide (1.8M solution in THF/hexane/ethyl benzene; 5.2 ml, 9.32 mmol) was added dropwise during 20 min. Stirring and cooling were continued for 1h, triisopropyl borate (8 ml, 34.5 mmol) was added dropwise during 30 min and then the temperature was allowed to rise overnight to RT. The pH of the reaction mixture was adjusted to 5 with 1M HCl and the mixture was then concentrated to a minimum volume and extracted with ethyl acetate (200 ml) and brine (3 x 100 ml). The organic phase was collected, dried (Na₂SO₄), filtered and evaporated to give a brown solid (1.32 g) which was used in the next step without further purification.

APCI-MS *m/z*: 214.1 [MH⁺].

Starting Material SM4

5-[Bromo(4-chlorophenyl)acetyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

[0187] A mixture of 5-iodo-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (139 mg, 0.32 mmol), tetrakis(triphenylphosphine) palladium(0) (1.8 mg, 1.6 μmol), copper(I) iodide (0.6 mg 3.2 μmol), 1-chloro-4-ethynylbenzene (87 mg, 0.638 mmol) and DIEA (64 mg, 0.5 mmol) in acetonitrile (1.5 ml) was heated in a microwave oven to 70°C for 0.5h. After cooling, the reaction mixture was purified by flash chromatography to give 5-[(4-chlorophenyl)ethynyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (111 mg, 78%).

APCI-MS *m/z*: 445.3 [MH⁺].

[0188] 5-[(4-Chlorophenyl)ethynyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (111 mg, 0.25 mmol) was mixed with formic acid (1 ml) and heated in a microwave oven to 120 °C for 1h. The formic acid was evaporated off and the residue was purified on an Xterra C8 column using a gradient of acetonitrile/water. Freeze drying of the mixture afforded 5-[(4-chlorophenyl)acetyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (77 mg, 66%).

¹H NMR (399.99 MHz, DMSO-*D*₆) δ 9.08 (d, *J* = 4.8 Hz, 1H), 8.94 (s, 1H), 7.92 (d, *J* = 9.0 Hz, 2H), 7.83 (t, *J* = 7.8 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 4.38 (s, 2H), 2.81 (d, *J* = 4.8 Hz, 3H), 2.22 (s, 3H);

APCI-MS *m/z*: 463.0 [MH⁺].

[0189] A solution of bromine (30 mg, 19 mmol) in acetic acid - THF was added dropwise to a solution of 5-[(4-chlorophenyl)acetyl]-*N*,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (75 mg, 0.162 mmol). After the addition, stirring was continued at RT overnight. The solvents were removed and the residue was purified on an Xterra C8 column using a gradient of acetonitrile/water. Freeze drying of the mixture afforded the title compound (86 mg, 95%).

¹H NMR (399.988 MHz, CDCl₃) δ 9.06 (m, 2H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.77 (q, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 1.5 Hz, 2H), 7.47 - 7.35 (m, 4H), 6.27 (d, *J* = 3.4 Hz, 1H), 2.96 (d, *J* = 5.0 Hz, 3H), 2.35 (s, 3H);

APCI-MS *m/z*: 540.9 [MH⁺].

Human Neutrophil Elastase Quenched-FRET Assay

[0190] The assay uses Human Neutrophil Elastase (HNE) purified from serum (Calbiochem art. 324681; Ref. Baugh,

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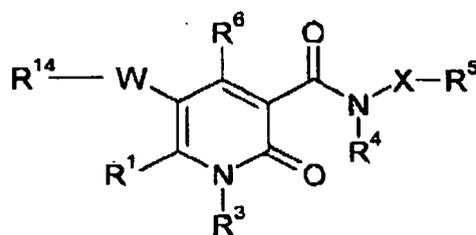
R.J. et al., 1976, *Biochemistry*. 15, 836-841). HNE was stored in 50 mM sodium acetate (NaOAc), 200 mM sodium chloride (NaCl), pH 5.5 with added 30% glycerol at -20°C. The protease substrate used was Elastase Substrate V Fluorogenic, MeOSuc-AAPV-AMC (Calbiochem art. 324740; Ref. Castillo, M.J. et al., 1979, *Anal. Biochem.* 99, 53-64). The substrate was stored in dimethyl sulphoxide (DMSO) at -20°C. The assay additions were as follows: Test compounds and controls were added to black 96-well flat-bottom plates (Greiner 655076), 1 μ L in 100% DMSO, followed by 30 μ L HNE in assay buffer with 0.01% Triton (trade mark) X-100 detergent. The assay buffer constitution was: 100 mM Tris (hydroxymethyl)aminomethane (TRIS) (pH 7.5) and 500 mM NaCl. The enzyme and the compounds were incubated at room temperature for 15 minutes. Then 30 μ L substrate in assay buffer was added. The assay was incubated for 30 minutes at room temperature. The concentrations of HNE enzyme and substrate during the incubation were 1.7 nM and 100 μ M, respectively. The assay was then stopped by adding 60 μ L stop solution (140 mM acetic acid, 200 mM sodium monochloroacetate, 60 mM sodium acetate, pH 4.3). Fluorescence was measured on a Wallac 1420 Victor 2 instrument at settings: Excitation 380 nm, Emission 460 nm. IC₅₀ values were determined using Xlfit curve fitting using model 205.

[0191] When tested in the above screen, the compounds of the Examples gave IC₅₀ values for inhibition of human neutrophil elastase activity of less than 30 μ M (micromolar), indicating that the compounds of the invention are expected to possess useful therapeutic properties. Specimen results are shown in the following Table:

Compound	Inhibition of Human Neutrophil Elastase IC ₅₀ (micromolar, μ M)
Example 1	0.00021
Example 3	0.00026
Example 4	0.0016
Example 5	0.00026
Example 6	0.00093

Claims

1. A compound of formula (I)



(I)

wherein

R¹ represents hydrogen or C₁-C₆ alkyl;

W represents a 5-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, wherein at least one of the ring carbon atoms may be optionally replaced by a carbonyl group; and wherein the heterocyclic ring is optionally substituted by at least one substituent selected from halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN, OH, NO₂, C₁-C₃ alkyl substituted by one or more F atoms, C₁-C₃ alkoxy, substituted by one or more F atoms, NR¹⁰R¹¹, C≡CR¹⁵, CONR¹⁶R¹⁷, CHO, C₂-C₄ alkanoyl, S(O)_xR¹⁸ and OSO₂R¹⁹;

R¹⁴ represents phenyl or a 6-membered heteroaromatic ring comprising 1 to 3 ring nitrogen atoms; said ring being optionally substituted with at least one substituent selected from halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN, OH, NO₂, C₁-C₃ alkyl substituted by one or more F atoms, C₁-C₃ alkoxy substituted by one or more F atoms, NR¹²R¹³, C≡CR³⁰, CONR³¹R³², CHO, C₂-C₄ alkanoyl, S(O)_pR³³ and OSO₂R³⁴;

R¹⁰, R¹¹, R¹² and R¹³ independently represent H, C₁-C₆ alkyl, formyl or C₂-C₆ alkanoyl; or the group **-NR¹⁰R¹¹** or **-NR¹²R¹³** together represents a 5 to 7 membered azacyclic ring optionally incorporating one further heteroatom

selected from O, S and NR²⁶;

R¹⁵ and **R³⁰** independently represent H, C₁-C₃ alkyl or Si(CH₃)₃;

R¹⁸, **R¹⁹**, **R³³** and **R³⁴** independently represents H or C₁-C₃ alkyl; said alkyl being optionally substituted by one or more F atoms;

R⁶ represents H or F;

R³ represents phenyl or a five- or six-membered heteroaromatic ring containing 1 to 3 heteroatoms independently selected from O, S and N; said ring being optionally substituted with at least one substituent selected from halogen, C₁-C₆ alkyl, cyano, C₁-C₆ alkoxy, nitro, methylcarbonyl, NR³⁵R³⁶, C₁-C₃ alkyl substituted by one or more F atoms or C₁-C₃ alkoxy substituted by one or more F atoms;

R³⁵ and **R³⁶** independently represent H or C₁-C₃ alkyl; said alkyl being optionally further substituted by one or more F atoms;

R⁴ represents hydrogen or C₁-C₆ alkyl optionally substituted with at least one substituent selected from fluoro, hydroxyl and C₁-C₆ alkoxy;

X represents a single bond, O, NR²⁴ or a group -C₁-C₆ alkylene-Y-, wherein Y represents a single bond, oxygen atom, NR²⁴ or S(O),; and said alkylene being optionally further substituted by OH, halogen, CN, NR³⁷R³⁸, C₁-C₃ alkoxy, CONR³⁹R⁴⁰, CO₂R⁶⁶, SO₂R⁴¹ and SO₂NR⁴²R⁴³;

or **R⁴** and X are joined together such that the group -**NR⁴X** together represents a 5 to 7 membered azacyclic ring optionally incorporating one further heteroatom selected from O, S and NR⁴⁴; said ring being optionally substituted by C₁-C₆ alkyl or NR⁴⁵R⁴⁶; said alkyl being optionally further substituted by OH;

either **R⁵** represents a monocyclic ring system selected from

i) phenoxy,

ii) phenyl,

iii) a 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur,

iv) a saturated or partially unsaturated C₃-C₆ cycloalkyl ring, or

v) a saturated or partially unsaturated 4- to 7-membered heterocyclic ring comprising at least one ring heteroatom selected from oxygen, S(O)_r and NR²⁰, wherein at least one of the ring carbon atoms may be optionally replaced by a carbonyl group,

or **R⁵** represents a bicyclic ring system in which the two rings are independently selected from the monocyclic ring systems defined in ii), iii), iv) and v) above, wherein the two rings are either fused together, bonded directly to one another or are separated from one another by a linker group selected from oxygen, S(O)_t or C₁-C₆ alkylene optionally comprising one or more internal or terminal heteroatoms selected from oxygen, sulphur and NR²⁷ and being optionally substituted by at least one substituent selected from hydroxyl, oxo and C₁-C₆ alkoxy, the monocyclic or bicyclic ring system being optionally substituted by at least one substituent selected from oxygen, CN, OH, C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, NR⁴⁷R⁴⁸, NO₂, OSO₂R⁴⁹, CO₂R⁵⁰, C(=NH)NH₂, C(O)NR⁵¹R⁵², C(S)NR⁵³R⁵⁴, SC(=NH)NH₂, NR⁵⁵C(=NH)NH₂, S(O)_vR⁷¹, SO₂NR⁵⁶R⁵⁷, C₁-C₃ alkoxy substituted by one or more F atoms and C₁-C₃ alkyl substituted by SO₂R⁵⁸ or by one or more F atoms; said C₁-C₆ alkyl being optionally further substituted with at least one substituent selected from cyano, hydroxyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio and -C(O)NR²²R²³;

or **R⁵** may also represent **H**;

R²⁰ represents hydrogen, C₁-C₆ alkyl, C₁-C₆ alkylcarbonyl or C₁-C₆ alkoxy carbonyl;

R²¹ represents hydrogen, C₁-C₆ alkyl or C₃-C₈ cycloalkyl; said alkyl or cycloalkyl group being optionally further substituted by one or more substituents selected independently from OH, CN, C₁-C₃ alkoxy and CONR⁵⁹R⁶⁰;

R³⁷ and **R³⁸** independently represent H, C₁-C₆ alkyl, formyl or C₂-C₆ alkanoyl;

R⁴⁷ and **R⁴⁸** independently represent H, C₁-C₆ alkyl, formyl, C₂-C₆ alkanoyl, S(O)_qR⁶¹ or SO₂NR⁶²R⁶³; said alkyl group being optionally further substituted by halogen, CN, C₁-C₄ alkoxy or CONR⁶⁴R⁶⁵;

R⁴¹ and **R⁶¹** independently represent H, C₁-C₆ alkyl or C₃-C₆ cycloalkyl;

p is 0, 1 or 2;

q is 0, 1 or 2;

r is 0, 1 or 2;

t is 0, 1 or 2;

w is 0, 1 or 2;

x is 0, 1 or 2;

v is 0, 1 or 2;

R¹⁶, **R¹⁷**, **R²²**, **R²³**, **R²⁴**, **R²⁶**, **R²⁷**, **R³¹**, **R³²**, **R³⁹**, **R⁴⁰**, **R⁴²**, **R⁴³**, **R⁴⁴**, **R⁴⁵**, **R⁴⁶**, **R⁴⁹**, **R⁵⁰**, **R⁵¹**, **R⁵²**, **R⁵³**, **R⁵⁴**, **R⁵⁵**, **R⁵⁶**, **R⁵⁷**, **R⁵⁸**, **R⁵⁹**, **R⁶⁰**, **R⁶²**, **R⁶³**, **R⁶⁴**, **R⁶⁵** and **R⁶⁶** each independently represent hydrogen or C₁-C₆ alkyl; or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1, wherein the group R¹⁴ and the 2-pyridone ring are bonded to the 5-membered ring W in a 1,2-relationship.
3. A compound according to Claim 1 or Claim 2, wherein R³ represents a phenyl group substituted with one or two substituents independently selected from F, Cl, CN, NO₂ and CF₃.
4. A compound according to any one of Claims 1 to 3, wherein R¹⁴ represents a phenyl or pyridinyl group optionally substituted with one or two substituents independently selected from F, Cl, CN and CF₃.
5. A compound according to any one of Claims 1 to 4, wherein R⁵ represents phenyl or pyridinyl, substituted by -S(O)_vR²¹ wherein v represents the integer 2.
6. A compound according to any one of Claims 1 to 5, wherein X represents unsubstituted C₁-C₂ alkylene.
7. A compound according to any one of Claims 1 to 4 or Claim 6, herein R⁵ represents H.
8. A compound of formula (I) as defined in Claim 1 selected from:

5-[1-(4-cyanophenyl)-1H-pyrazol-5-yl]-N,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[1-(4-cyanophenyl)-1H-pyrazol-5-yl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[2-amino-5-(4-chlorophenyl)-1,3-thiazol-4-yl]-N,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[4-(4-chlorophenyl)-1,3-oxazol-5-yl]-N,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

5-[2-amino-5-(4-cyanophenyl)-1,3-thiazol-4-yl]-N,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

1-(3-chloro-4-fluorophenyl)-5-[1-(4-cyanophenyl)-1H-pyrazol-5-yl]-N,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxamide;

5-[2-(4-chloro-phenyl)-2H-pyrazol-3-yl]-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid methylamide;

5-[2-(4-fluoro-phenyl)-2H-pyrazol-3-yl]-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid methylamide;

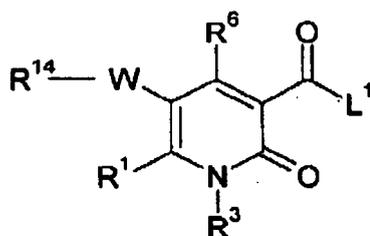
5-[3-(4-cyano-phenyl)-3H-[1,2,3]triazol-4-yl]-6-methyl-2-oxo-1-(3-trifluoromethylphenyl)-1,2-dihydro-pyridine-3-carboxylic acid methylamide; and

5-[1-(4-cyanophenyl)-1H-1,2,4-triazol-5-yl]-N,6-dimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

or a pharmaceutically acceptable salt thereof.

9. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 1 which comprises,

(a) reacting a compound of formula (II)



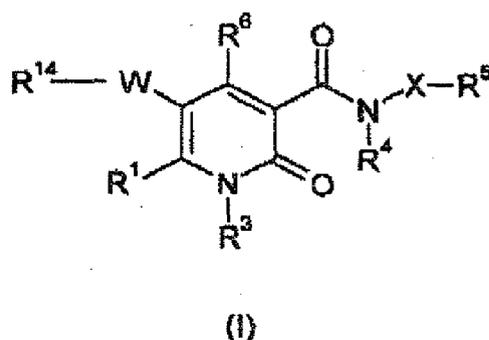
(II)

use in therapy.

13. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 8 in the manufacture of a medicament for the treatment of an inflammatory disease or condition.
14. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 8 in the manufacture of a medicament for use in treating adult respiratory distress syndrome (ARDS), cystic fibrosis, pulmonary emphysema, bronchitis including chronic bronchitis, bronchiectasis, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, asthma including refractive asthma, rhinitis, psoriasis, ischemia-reperfusion injury, rheumatoid arthritis, osteoarthritis, systemic inflammatory response syndrome (SIRS), chronic wound, cancer, atherosclerosis, peptic ulcers, Crohn's disease, ulcerative colitis or gastric mucosal injury.
15. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 8 and another therapeutic agent or agents in the manufacture of a medicament for the treatment of an inflammatory disease, wherein the compound of formula (I) is administered concurrently or sequentially or as a combined preparation with the other therapeutic agent or agents.

Patentansprüche

1. Verbindung der Formel (I)



worin

R¹ für Wasserstoff oder C₁-C₆-Alkyl steht;

W für einen 5-gliedrigen heterocyclischen Ring mit mindestens einem unter Stickstoff, Sauerstoff und Schwefel ausgewählten Ringheteroatom steht, wobei mindestens eines der Ringkohlenstoffatome gegebenenfalls durch eine Carbonylgruppe ersetzt sein kann und der heterocyclische Ring gegebenenfalls durch mindestens einen unter Halogen, C₁-C₄-Alkyl, C₁-C₄-Alkoxy, CN, OH, NO₂, durch ein oder mehrere F-Atome substituiertem C₁-C₃-Alkyl, durch ein oder mehrere F-Atome substituiertem C₁-C₃-Alkoxy, NR¹⁰R¹¹, C=CR¹⁵, CONR¹⁶R¹⁷, CHO, C₂-C₄-Alkanoyl, S(O)_xR¹⁸ und OSO₂R¹⁹ ausgewählten Substituenten substituiert ist;

R¹⁴ für Phenyl oder einen 6-gliedrigen heteroaromatischen Ring mit 1 bis 3 Ringstickstoffatomen steht; wobei der Ring gegebenenfalls durch mindestens einen unter Halogen, C₁-C₄-Alkyl, C₁-C₄-Alkoxy, CN, OH, NO₂, durch ein oder mehrere F-Atome substituiertem C₁-C₃-Alkyl, durch ein oder mehrere F-Atome substituiertem C₁-C₃-Alkoxy, NR¹²R¹³, C=CR³⁰, CONR³¹R³², CHO, C₂-C₄-Alkanoyl, S(O)_xR³³ und OSO₂R³⁴ ausgewählten Substituenten substituiert ist;

R¹⁰, R¹¹, R¹² und R¹³ unabhängig voneinander für H, C₁-C₆-Alkyl, Formyl oder C₂-C₆-Alkanoyl stehen oder die Gruppe -NR¹⁰R¹¹ oder -NR¹²R¹³ zusammen für einen 5- bis 7-gliedrigen azacyclischen Ring steht, der gegebenenfalls ein weiteres unter O, S und NR²⁶ ausgewähltes Heteroatom enthält;

R¹⁵ und R³⁰ unabhängig voneinander für H, C₁-C₃-Alkyl oder Si(CH₃)₃ stehen;

R¹⁸, R¹⁹, R³³ und R³⁴ unabhängig voneinander für H oder C₁-C₃-Alkyl stehen; wobei das Alkyl gegebenenfalls durch ein oder mehrere F-Atome substituiert ist;

R⁶ für H oder F steht;

R³ für Phenyl oder einen fünf- oder sechsgliedrigen heteroaromatischen Ring mit 1 bis 3 unabhängig voneinander unter O, S und N ausgewählten Heteroatomen steht; wobei der Ring gegebenenfalls durch mindestens einen unter

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Halogen, C₁-C₆-Alkyl, Cyano, C₁-C₆-Alkoxy, Nitro, Methylcarbonyl, NR³⁵R³⁶, durch ein oder mehrere F-Atome substituiertem C₁-C₃-Alkyl oder durch ein oder mehrere F-Atome substituiertem C₁-C₃-Alkoxy ausgewählten Substituenten substituiert ist;

R³⁵ und R³⁶ unabhängig voneinander für H oder C₁-C₃-Alkyl stehen; wobei das Alkyl gegebenenfalls durch ein oder mehrere F-Atome substituiert ist;

R⁴ für Wasserstoff oder C₁-C₆-Alkyl, das gegebenenfalls durch mindestens einen unter Fluor, Hydroxyl und C₁-C₆-Alkoxy ausgewählten Substituenten substituiert ist, steht;

X für eine Einfachbindung, O, NR²⁴ oder eine Gruppe -C₁-C₆-Alkylen-Y- steht, wobei Y für eine Einfachbindung, ein Sauerstoffatom, NR²⁴ oder S(O)_w steht und das Alkylen gegebenenfalls weiter durch OH, Halogen, CN, NR³⁷R³⁸, C₁-C₃-Alkoxy, CONR³⁹R⁴⁰, CO₂R⁶⁶, SO₂R⁴¹ und SO₂NR⁴²R⁴³ substituiert ist;

oder R⁴ und X so miteinander verbunden sind, daß die Gruppe -NR⁴X zusammen für einen 5- bis 7-gliedrigen azacyclischen Ring steht, der gegebenenfalls ein weiteres unter O, S und NR⁴⁴ ausgewähltes Heteroatom enthält und gegebenenfalls durch C₁-C₆-Alkyl oder NR⁴⁵R⁴⁶ substituiert ist; wobei das Alkyl gegebenenfalls weiter durch OH substituiert ist;

R⁵ für ein monocyclisches Ringsystem, das unter

i) Phenoxy,

ii) Phenyl,

iii) einem 5- oder 6-gliedrigen heteroaromatischen Ring mit mindestens einem unter Stickstoff, Sauerstoff und Schwefel ausgewählten Ringheteroatom,

iv) einem gesättigten oder teilweise ungesättigten C₃-C₆-Cycloalkylring oder

v) einem gesättigten oder teilweise ungesättigten 4- bis 7-gliedrigen heterocyclischen Ring mit mindestens einem unter Sauerstoff, S(O)_r und NR²⁰ ausgewählten Ringheteroatom, wobei mindestens eines der Ringkohlenstoffatome gegebenenfalls durch eine Carbonylgruppe ersetzt ist,

ausgewählt ist, steht;

oder R⁵ für ein bicyclisches Ringsystem steht, in dem die beiden Ringe unabhängig voneinander unter den oben in ii), iii), iv) und v) definierten monocyclischen Ringsystemen ausgewählt sind, wobei die beiden Ringe entweder miteinander kondensiert sind, direkt aneinander gebunden sind oder über eine unter Sauerstoff, S(O)_t oder C₁-C₆-Alkylen, das gegebenenfalls ein oder mehrere innen- oder endständige, unter Sauerstoff, Schwefel und NR²⁷ ausgewählte Heteroatomen enthält und gegebenenfalls durch mindestens einen unter Hydroxyl, Oxo und C₁-C₆-Alkoxy ausgewählten Substituenten substituiert ist, ausgewählte Linker-Gruppe voneinander getrennt sind,

wobei das monocyclische oder bicyclische Ringsystem gegebenenfalls durch mindestens einen unter Sauerstoff, CN, OH, C₁-C₆-Alkyl, C₁-C₆-Alkoxy, Halogen, NR⁴⁵R⁴⁸, NO₂, OSO₂R⁴⁹, CO₂R⁵⁰, C(=NH)NH₂, C(O)NR⁵¹R⁵², C(S)NR⁵³R⁵⁴, SC(=NH)NH₂, NR⁵⁵C(=NH)NH₂, S(O)_vR²¹, SO₂NR⁵⁶R⁵⁷, durch ein oder mehrere F-Atome substituiertes C₁-C₃-Alkoxy und durch SO₂R⁵⁸ oder ein oder mehrere F-Atome substituiertes C₁-C₃-Alkyl ausgewählten Substituenten substituiert ist; wobei das C₁-C₆-Alkyl gegebenenfalls weiter durch mindestens einen unter Cyano, Hydroxyl, C₁-C₆-Alkoxy, C₁-C₆-Alkylthio und -C(O)NR²²R²³ ausgewählten Substituenten substituiert ist; oder R⁵ auch für H stehen kann;

R²⁰ für Wasserstoff, C₁-C₆-Alkyl, C₁-C₆-Alkylcarbonyl oder C₁-C₆-Alkoxy carbonyl steht;

R²¹ für Wasserstoff, C₁-C₆-Alkyl oder C₃-C₈-Cycloalkyl steht; wobei die Alkyl- oder Cycloalkylgruppe gegebenenfalls weiter durch einen oder mehrere unabhängig voneinander unter OH, CN, C₁-C₃-Alkoxy und CONR⁵⁹R⁶⁰ ausgewählte Substituenten substituiert ist;

R³⁷ und R³⁸ unabhängig voneinander für H, C₁-C₆-Alkyl, Formyl oder C₂-C₆-Alkanoyl stehen;

R⁴⁷ und R⁴⁸ unabhängig voneinander für H, C₁-C₆-Alkyl, Formyl, C₂-C₆-Alkanoyl, S(O)_qR⁶¹ oder SO₂NR⁶²R⁶³ stehen; wobei die Alkylgruppe gegebenenfalls weiter durch Halogen, CN, C₁-C₄-Alkoxy oder CONR⁶⁴R⁶⁵ substituiert ist;

R⁴¹ und R⁶¹ unabhängig voneinander für H, C₁-C₆-Alkyl oder C₃-C₆-Cycloalkyl stehen;

p für 0, 1 oder 2 steht;

q für 0, 1 oder 2 steht;

r für 0, 1 oder 2 steht;

t für 0, 1 oder 2 steht;

w für 0, 1 oder 2 steht;

x für 0, 1 oder 2 steht;

v für 0, 1 oder 2 steht;

R¹⁶, R¹⁷, R²², R²³, R²⁴, R²⁶, R²⁷, R³¹, R³², R³⁹, R⁴⁰, R⁴², R⁴³, R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁹, R⁵⁰, R⁵¹, R⁵², R⁵³, R⁵⁴, R⁵⁵, R⁵⁶, R⁵⁷, R⁵⁸, R⁵⁹, R⁶⁰, R⁶², R⁶³, R⁶⁴, R⁶⁵ und R⁶⁶ jeweils unabhängig voneinander für Wasserstoff oder C₁-C₆-Alkyl stehen;

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oder ein pharmazeutisch annehmbares Salz davon.

2. Verbindung nach Anspruch 1, worin die Gruppe R¹⁴ und der 2-Pyridonring in einer 1,2-Beziehung an den 5-gliedrigen Ring W gebunden sind.

5 3. Verbindung nach Anspruch 1 oder Anspruch 2, worin R³ für eine durch einen oder zwei unabhängig voneinander unter F, Cl, CN, NO₂ und CF₃ ausgewählte Substituenten substituierte Phenylgruppe steht.

10 4. Verbindung nach einem der Ansprüche 1 bis 3, worin R¹⁴ für eine gegebenenfalls durch einen oder zwei unabhängig voneinander unter F, Cl, CN und CF₃ ausgewählte Substituenten substituierte Phenyl- oder Pyridinylgruppe steht.

5. Verbindung nach einem der Ansprüche 1 bis 4, worin R⁵ für Phenyl oder Pyridyl, das durch -S(O)_vR²¹, worin v für die ganze Zahl 2 steht, substituiert ist, steht.

15 6. Verbindung nach einem der Ansprüche 1 bis 5, worin X für unsubstituiertes C₁-C₂-Alkylen steht.

7. Verbindung nach einem der Ansprüche 1 bis 4 oder Anspruch 6, worin R⁵ für H steht.

8. Verbindung der Formel (I) gemäß Anspruch 1, ausgewählt unter:

20 5-[1-(4-Cyanophenyl)-1*H*-pyrazol-5-yl]-N,6-dimethyl-2-oxo-1-[3-(trifluormethyl)phenyl]-1,2-dihydropyridin-3-carboxamid;

5-[1-(4-Cyanophenyl)-1*H*-pyrazol-5-yl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluormethyl)phenyl]-1,2-dihydropyridin-3-carboxamid;

25 5-[2-Amino-5-(4-chlorphenyl)-1,3-thiazol-4-yl]-N,6-dimethyl-2-oxo-1-[3-(trifluormethyl)phenyl]-1,2-dihydropyridin-3-carboxamid;

5-[4-(4-Chlorphenyl)-1,3-oxazol-5-yl]-N,6-dimethyl-2-oxo-1-[3-(trifluormethyl)phenyl]-1,2-dihydropyridin-3-carboxamid;

30 5-[2-Amino-5-(4-cyanophenyl)-1,3-thiazol-4-yl]-N,6-dimethyl-2-oxo-1-[3-(trifluormethyl)phenyl]-1,2-dihydropyridin-3-carboxamid;

1-(3-Chlor-4-fluorphenyl)-5-[1-(4-cyanophenyl)-1*H*-pyrazol-5-yl]-N,6-dimethyl-2-oxo-1,2-dihydropyridin-3-carboxamid;

5-[2-(4-Chlorphenyl)-2*H*-pyrazol-3-yl]-6-methyl-2-oxo-1-[3-(trifluormethyl)phenyl]-1,2-dihydropyridin-3-carbonsäuremethyramid;

35 5-[2-(4-Fluorphenyl)-2*H*-pyrazol-3-yl]-6-methyl-2-oxo-1-[3-(trifluormethyl)phenyl]-1,2-dihydropyridin-3-carbonsäuremethyramid;

5-[3-(4-Cyanophenyl)-3*H*-[1,2,3]triazol-4-yl]-6-methyl-2-oxo-1-[3-(trifluormethyl)phenyl]-1,2-dihydropyridin-3-carbonsäuremethyramid und

40 5-[1-(4-Cyanophenyl)-1*H*-1,2,4-triazol-5-yl]-N,6-dimethyl-2-oxo-1-[3-(trifluormethyl)phenyl]-1,2-dihydropyridin-3-carboxamid;

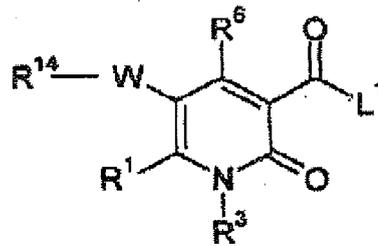
oder ein pharmazeutische annehmbares Salz davon.

9. Verfahren zur Herstellung einer Verbindung der Formel (I) oder eines pharmazeutisch annehmbaren Salzes davon gemäß Anspruch 1, bei dem man

45 (a) eine Verbindung der Formel (II)

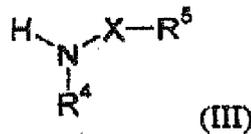
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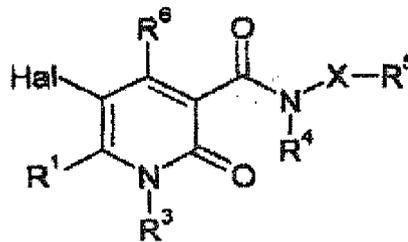
(II)

15 worin L¹ für eine Abgangsgruppe (wie Halogen oder Hydroxyl) steht und R¹, R³, R⁶, R¹⁴ und W wie in Formel (I) definiert sind, mit einer Verbindung der Formel



(III)

30 worin X, R⁴ und R⁵ wie in Formel (I) definiert sind, umgesetzt; oder (b) eine Verbindung der Formel (IV)

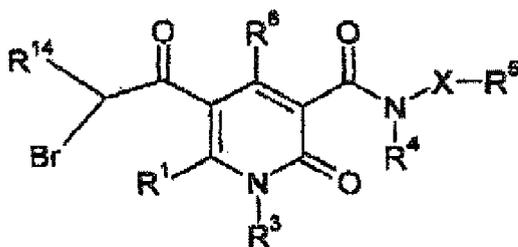


(IV)

45 worin Hal für ein Halogenatom steht und X, R¹, R³, R⁴, R⁵ und R⁶ wie in Formel (I) definiert sind, mit einem Nucleophil R¹⁴-W-M, worin R¹⁴ und W wie in Formel (I) definiert sind und M für eine Organozinn- oder Organoboronsäuregruppe steht, umgesetzt; oder (c) wenn W für Thiazolyl oder Oxazolyl steht, eine Verbindung der Formel (V)

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(I)

15 worin X, R¹, R³, R⁴, R⁵, R⁶ und R¹⁴ wie in Formel (I) definiert sind,

mit Thioharnstoff bzw. Formamid umgesetzt;

und gegebenenfalls nach (a), (b) oder (c) eine oder mehrere der folgenden Operationen durchführt:

- Umwandlung der erhaltenen Verbindung in eine weitere erfindungsgemäße Verbindung
 - Bildung eines pharmazeutisch annehmbaren Salzes der Verbindung.
- 20

10. Pharmazeutische Zusammensetzung, enthaltend eine Verbindung der Formel (I) oder ein pharmazeutisch annehmbares Salz davon gemäß einem der Ansprüche 1 bis 8 zusammen mit einem pharmazeutisch annehmbaren Hilfsstoff, Verdünnungsmittel oder Träger.

25 11. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung gemäß Anspruch 10, bei dem man eine Verbindung der Formel (I) oder ein pharmazeutisch annehmbares Salz davon gemäß einem der Ansprüche 1 bis 8 mit einem pharmazeutisch annehmbaren Hilfsstoff, Verdünnungsmittel oder Träger mischt.

30 12. Verbindung der Formel (I) oder ein pharmazeutisch annehmbares Salz davon gemäß einem der Ansprüche 1 bis 8 zur Verwendung bei der Therapie.

35 13. Verwendung einer Verbindung der Formel (I) oder eines pharmazeutisch annehmbaren Salzes davon gemäß einem der Ansprüche 1 bis 8 bei der Herstellung eines Arzneimittels zur Behandlung einer entzündlichen Erkrankung oder eines entzündlichen Leidens.

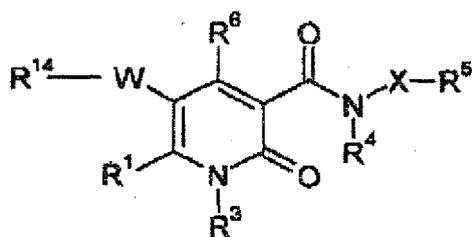
40 14. Verwendung einer Verbindung der Formel (I) oder eines pharmazeutisch annehmbaren Salzes davon gemäß einem der Ansprüche 1 bis 8 bei der Herstellung eines Arzneimittels zur Verwendung bei der Behandlung von akutem Atemnotsyndrom (Adult Respiratory Distress Syndrom, ARDS), zystischer Fibrose, Lungenemphysem, Bronchitis einschließlich chronischer Bronchitis, Bronchiektase, chronisch obstruktiver Lungenerkrankung (Chronic Obstructive Pulmonary Disease, COPD), pulmonaler Hypertonie, Asthma einschließlich refraktärem Asthma, Rhinitis, Psoriasis, Ischämie-Reperfusionverletzung, rheumatoider Arthritis, Osteoarthritis, SIRS (Systemic Inflammatory Response Syndrome), chronischen Wunden, Krebs, Atherosklerose, Ulcus pepticum, Morbus Crohn, Colitis ulcerosa oder Verletzung der Magenschleimhaut.

45 15. Verwendung einer Verbindung der Formel (I) oder eines pharmazeutisch annehmbaren Salzes davon gemäß einem der Ansprüche 1 bis 8 und eines anderen Therapeutikums oder anderer Therapeutika bei der Herstellung eines Arzneimittels zur Behandlung einer entzündlichen Erkrankung, bei der die Verbindung der Formel (I) gleichzeitig oder aufeinanderfolgend oder als Kombinationspräparat mit dem anderen Therapeutikum bzw. den anderen Therapeutika verabreicht wird.

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Revendications

55 1. Composé de formule (I)



(I)

15 dans laquelle

R¹ représente un hydrogène ou un alkyle en C₁-C₆ ;

W représente un cycle hétérocyclique à 5 chaînons comprenant au moins un hétéroatome cyclique choisi parmi l'azote, l'oxygène et le soufre, où au moins un des atomes de carbone cycliques peut être facultativement remplacé par un groupe carbonyle ; et où le cycle hétérocyclique est facultativement substitué par au moins un substituant choisi parmi un halogène, un alkyle en C₁-C₄, un alcoxy en C₁-C₄, CN, OH, NO₂, un alkyle en C₁-C₃ substitué par un ou plusieurs atomes F, un alcoxy en C₁-C₃ substitué par un ou plusieurs atomes F, NR¹⁰R¹¹, C=CR¹⁵, CONR¹⁶R¹⁷, CHO, un alcanoyle en C₂-C₄, S(O)_xR¹⁸ et OSO₂R¹⁹ ;

R¹⁴ représente un phényle ou un cycle hétéroaromatique à 6 chaînons comprenant de 1 à 3 atomes d'azote cycliques ; ledit cycle étant facultativement substitué par au moins un substituant choisi parmi un halogène, un alkyle en C₁-C₄, un alcoxy en C₁-C₄, CN, OH, NO₂, un alkyle en C₁-C₃ substitué par un ou plusieurs atomes F, un alcoxy en C₁-C₃ substitué par un ou plusieurs atomes F, NR¹²R¹³, C=CR³⁰, CONR³¹R³², CHO, un alcanoyle en C₂-C₄, S(O)_pR³³ et OSO₂R³⁴ ;

R¹⁰, R¹¹, R¹² et R¹³ représentent indépendamment H, un alkyle en C₁-C₆, un formyle ou un alcanoyle en C₂-C₆ ; ou le groupe -NR¹⁰R¹¹ ou -NR¹²R¹³ représente conjointement un cycle azacyclique à 5 à 7 chaînons incorporant facultativement un autre hétéroatome choisi parmi O, S et NR²⁶ ;

R¹⁵ et R³⁰ représentent indépendamment H, un alkyle en C₁-C₃ ou Si (CH₃)₃ ;

R¹⁸, R¹⁹, R³³ et R³⁴ représentent indépendamment H ou un alkyle en C₁-C₃ ; ledit alkyle étant facultativement substitué par un ou plusieurs atomes F ;

R⁶ représente H ou F ;

R³ représente un phényle ou un cycle hétéroaromatique à six chaînons contenant de 1 à 3 hétéroatomes indépendamment choisis parmi O, S et N ; ledit cycle étant facultativement substitué par au moins un substituant choisi parmi un halogène, un alkyle en C₁-C₆, un cyano, un alcoxy en C₁-C₆, un nitro, un méthylcarbonyle, NR³⁵R³⁶, un alkyle en C₁-C₃ substitué par un ou plusieurs atomes F ou un alcoxy en C₁-C₃ substitué par un ou plusieurs atomes F ; R³⁵ et R³⁶ représentent indépendamment H ou un alkyle en C₁-C₃ ; ledit alkyle étant facultativement substitué en outre par un ou plusieurs atomes F ;

R⁴ représente un hydrogène ou un alkyle en C₁-C₆ facultativement substitué par au moins un substituant choisi parmi un fluoro, un hydroxyle et un alcoxy en C₁-C₆ ;

X représente une simple liaison, O, NR²⁴ ou un groupe - (alkylène en C₁-C₆)-Y-, où Y représente une simple liaison, un atome d'oxygène, NR²⁴ ou S(O)_w ; et ledit alkylène étant facultativement substitué en outre par OH, un halogène, CN, NR³⁷R³⁸, un alcoxy en C₁-C₃, CONR³⁹R⁴⁰, CO₂R⁶⁶, SO₂R⁴¹ et SO₂NR⁴²R⁴³ ;

ou R⁴ et X sont liés conjointement de sorte que le groupe -NR⁴X représente conjointement un cycle azacyclique à 5 à 7 chaînons incorporant facultativement un hétéroatome supplémentaire choisi parmi O, S et NR⁴⁴ ; ledit cycle étant facultativement substitué par un alkyle en C₁-C₆ ou NR⁴⁵R⁴⁶ ; ledit alkyle étant en outre facultativement substitué par OH ;

R⁵ représente un système cyclique monocyclique choisi parmi

i) un phénoxy,

ii) un phényle,

iii) un cycle hétéroaromatique à 5 ou 6 chaînons comprenant au moins un hétéroatome choisi parmi l'azote, l'oxygène et le soufre,

iv) un cycle cycloalkyle en C₃-C₆ saturé ou partiellement insaturé, ou

v) un cycle hétérocyclique à 4 à 7 chaînons saturé ou partiellement insaturé comprenant au moins un hétéroatome cyclique choisi parmi l'oxygène, S(O)_r et NR²⁰, où au moins l'un des atomes de carbone cycliques peut

être facultativement remplacé par un groupe carbonyle,

ou R⁵ représente un système cyclique bicyclique dans lequel les deux cycles sont indépendamment choisis parmi les systèmes cycliques monocycliques définis dans ii), iii), iv) et v) ci-dessus, où les deux cycles sont condensés conjointement, liés directement l'un à l'autre ou sont séparés l'un de l'autre par un groupe lieur choisi parmi un oxygène, S(O)_t ou un alkylène en C₁-C₆ comprenant facultativement un ou plusieurs hétéroatomes internes ou terminaux choisis parmi l'oxygène, le soufre et NR²⁷ et étant facultativement substitués par au moins un substituant choisi parmi un hydroxyle, un oxo et un alcoxy en C₁-C₆,

le système cyclique monocyclique ou bicyclique étant facultativement substitué par au moins un substituant choisi parmi l'oxygène, CN, OH, un alkyle en C₁-C₆, un alcoxy en C₁-C₆, un halogène, NR⁴⁷R⁴⁸, NO₂, OSO₂R⁴⁹, CO₂R⁵⁰, C(=NH)NH₂, C(O)NR⁵¹R⁵², C(S)NR⁵³R⁵⁴, SC(=NH)NH₂, NR⁵⁵C(=NH)NH₂, S(O)_vR²¹, SO₂NR⁵⁶R⁵⁷, un alcoxy en C₁-C₃ substitué par un ou plusieurs atomes F et un alkyle en C₁-C₃ substitué par SO₂R⁵⁸ ou par un ou plusieurs atomes F ; ledit alkyle en C₁-C₆ étant facultativement substitué en outre par au moins un substituant choisi parmi un cyano, un hydroxyle, un alcoxy en C₁-C₆, un alkylthio en C₁-C₆ et -C(O)NR²²R²³;

ou R⁵ peut également représenter H ;

R²⁰ représente un hydrogène, un alkyle en C₁-C₆, un (alkyle en C₁-C₆) carbonyle ou un (alcoxy en C₁-C₆) carbonyle ; R²¹ représente un hydrogène, un alkyle en C₁-C₆ ou un cycloalkyle en C₃-C₈ ; ledit groupe alkyle ou cycloalkyle étant facultativement substitué en outre par un ou plusieurs substituants indépendamment choisis parmi OH, CN, un alcoxy en C₁-C₃ et CONR⁵⁹R⁶⁰ ;

R³⁷ et R³⁸ représentent indépendamment H, un alkyle en C₁-C₆, un formyle ou un alcanoyle en C₂-C₆ ;

R⁴⁷ et R⁴⁸ représentent indépendamment H, un alkyle en C₁-C₆, un formyle, un alcanoyle en C₂-C₆, S(O)_qR⁶¹ ou SO₂NR⁶²R⁶³ ; ledit groupe alkyle étant facultativement substitué en outre par un halogène, CN, un alcoxy en C₁-C₄ ou CONR⁶⁴R⁶⁵ ;

R⁴¹ et R⁶¹ représentent indépendamment H, un alkyle en C₁-C₆ ou un cycloalkyle en C₃-C₆ ;

p est 0, 1 ou 2 ;

q est 0, 1 ou 2 ;

r est 0, 1 ou 2 ;

t est 0, 1 ou 2 ;

w est 0, 1 ou 2 ;

x est 0, 1 ou 2 ;

v est 0, 1 ou 2 ;

R¹⁶, R¹⁷, R²², R²³, R²⁴, R²⁶, R²⁷, R³¹, R³², R³⁹, R⁴⁰, R⁴², R⁴³, R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁹, R⁵⁰, R⁵¹, R⁵², R⁵³, R⁵⁴, R⁵⁵, R⁵⁶, R⁵⁷, R⁵⁸, R⁵⁹, R⁶⁰, R⁶², R⁶³, R⁶⁴, R⁶⁵ et R⁶⁶ représentent chacun indépendamment un hydrogène ou un alkyle en C₁-C₆ ;

ou un sel pharmaceutiquement acceptable de celui-ci.

2. Composé selon la revendication 1, **caractérisé en ce que** le groupe R¹⁴ et le cycle 2-pyridone sont liés au cycle à 5 chaînons W dans une relation 1,2.
3. Composé selon la revendication 1 ou la revendication 2, **caractérisé en ce que** R³ représente un groupe phényle substitué par un ou deux substituants indépendamment choisis parmi F, Cl, CN, NO₂ et CF₃.
4. Composé selon l'une quelconque des revendications 1 à 3, **caractérisé en ce que** R¹⁴ représente un groupe phényle ou pyridinyle facultativement substitué par un ou deux substituants indépendamment choisis parmi F, Cl, CN et CF₃.
5. Composé selon l'une quelconque des revendications 1 à 4, **caractérisé en ce que** R⁵ représente un phényle ou un pyridinyle substitué par - S(O)_vR²¹ où v représente l'entier 2.
6. Composé selon l'une quelconque des revendications 1 à 5, **caractérisé en ce que** X représente un alkylène en C₁-C₂ non substitué.
7. Composé selon l'une quelconque des revendications 1 à 4 ou la revendication 6, **caractérisé en ce que** R⁵ représente H.
8. Composé de formule (I) comme défini dans la revendication 1 choisi parmi :

5-[1-(4-cyanophényl)-1H-pyrazol-5-yl]-N,6-diméthyl-2-oxo-1-[3-(trifluorométhyl)phényl]-1,2-dihydropyridine-3-

carboxamide ;

5-[1-(4-cyanophényl)-1H-pyrazol-5-yl]-6-méthyl-N-[4-(méthylsulfonyl)benzyl]-2-oxo-1-[3-(trifluorométhyl)phényl]-1,2-dihydropyridine-3-carboxamide ;

5-[2-amino-5-(4-chlorophényl)-1,3-thiazol-4-yl]-N,6-diméthyl-2-oxo-1-[3-(trifluorométhyl)phényl]-1,2-dihydropyridine-3-carboxamide ;

5-[4-(4-chlorophényl)-1,3-oxazol-5-yl]-N,6-diméthyl-2-oxo-1-[3-(trifluorométhyl)phényl]-1,2-dihydropyridine-3-carboxamide ;

5-[2-amino-5-(4-cyanophényl)-1,3-thiazol-4-yl]-N,6-diméthyl-2-oxo-1-[3-(trifluorométhyl)phényl]-1,2-dihydropyridine-3-carboxamide ;

1-(3-chloro-4-fluorophényl)-5-[1-(4-cyanophényl)-1H-pyrazol-5-yl]-N,6-diméthyl-2-oxo-1,2-dihydropyridine-3-carboxamide ;

méthylamide d'acide 5-[2-(4-chloro-phényl)-2H-pyrazol-3-yl]-6-méthyl-2-oxo-1-(3-trifluorométhyl-phényl)-1,2-dihydro-pyridine-3-carboxylique ;

méthylamide d'acide 5-[2-(4-fluoro-phényl)-2H-pyrazol-3-yl]-6-méthyl-2-oxo-1-(3-trifluorométhyl-phényl)-1,2-dihydro-pyridine-3-carboxylique ;

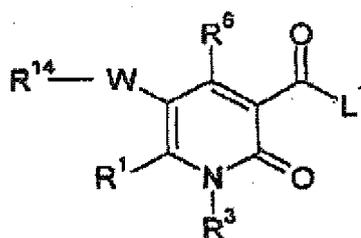
méthylamide d'acide 5-[3-(4-cyano-phényl)-3H-[1,2,3]triazol-4-yl]-6-méthyl-2-oxo-1-(3-trifluorométhyl-phényl)-1,2-dihydro-pyridine-3-carboxylique ; et

5-[1-(4-cyanophényl)-1H-1,2,4-triazol-5-yl]-N,6-diméthyl-2-oxo-1-[3-(trifluorométhyl)phényl]-1,2-dihydropyridine-3-carboxamide ;

ou un sel pharmaceutiquement acceptable de ceux-ci.

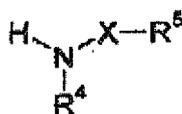
9. Procédé pour la préparation d'un composé de formule (I) ou un sel pharmaceutiquement acceptable de celui-ci comme défini dans la revendication 1 qui comprend,

(a) la réaction d'un composé de formule (II)



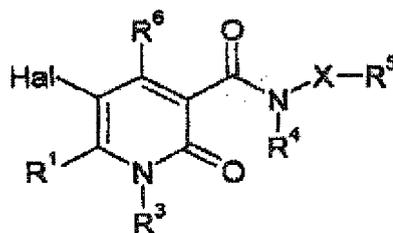
(II)

dans laquelle L¹ représente un groupe partant (tel qu'un halogène ou un hydroxyle) et R¹, R³, R⁶, R¹⁴ et W sont comme défini dans la formule (I), avec un composé de formule



(III)

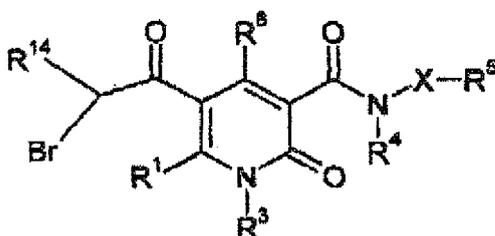
dans laquelle X, R⁴ et R⁵ sont comme défini dans la formule (I) ; ou
(b) réaction d'un composé de formule (IV)



(IV)

15 dans laquelle Hal représente un atome d'halogène et X, R¹, R³, R⁴, R⁵ et R⁶ sont comme défini dans la formule (I), avec un nucléophile R¹⁴-W-M où R¹⁴ et W sont comme défini dans la formule (I) et M représente un groupe organo-étain ou acide organoborique ; ou

(c) lorsque W représente un thiazolylole ou un oxazolylole, la réaction d'un composé de formule (V)



(V)

30 dans laquelle X, R¹, R³, R⁴, R⁵, R⁶ et R¹⁴ sont comme défini dans la formule (I), avec la thiourée ou le formamide, respectivement ;

et facultativement après (a), (b) ou (c) la conduite d'un ou plusieurs des suivants :

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- conversion du composé obtenu en un autre composé de l'invention
 - formation d'un sel pharmaceutiquement acceptable du composé.

40 **10.** Composition pharmaceutique comprenant un composé de formule (I) ou un sel pharmaceutiquement acceptable de celui-ci selon l'une quelconque des revendications 1 à 8 en association avec un adjuvant, diluant ou véhicule pharmaceutiquement acceptable.

45 **11.** Procédé pour la préparation d'une composition pharmaceutique selon la revendication 10 qui comprend le mélange d'un composé de formule (I) ou un sel pharmaceutiquement acceptable de celui-ci selon l'une quelconque des revendications 1 à 8 avec un adjuvant, diluant ou véhicule pharmaceutiquement acceptable.

12. Composé de formule (I) ou sel pharmaceutiquement acceptable de celui-ci selon l'une quelconque des revendications 1 à 8 pour utilisation en thérapie.

50 **13.** Utilisation d'un composé de formule (I) ou un sel pharmaceutiquement acceptable de celui-ci selon l'une quelconque des revendications 1 à 8 dans la fabrication d'un médicament pour le traitement d'une maladie ou pathologie inflammatoire.

55 **14.** Utilisation d'un composé de formule (I) ou un sel pharmaceutiquement acceptable de celui-ci selon l'une quelconque des revendications 1 à 8 dans la fabrication d'un médicament pour utilisation dans le traitement du syndrome de détresse respiratoire de l'adulte (ARDS), la mucoviscidose, l'emphysème pulmonaire, la bronchite comprenant la bronchite chronique, la bronchectasie, la pneumopathie obstructive chronique (COPD), l'hypertension artérielle pulmonaire, l'asthme comprenant l'asthme réfractaire, la rhinite, le psoriasis, une lésion de reperfusion ischémique, la polyarthrite rhumatoïde, l'arthrose, le syndrome de réponse inflammatoire systémique (SIRS), une plaie chronique,

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le cancer, l'athérosclérose, les ulcères gastro-duodénaux, la maladie de Crohn, la recto-colite hémorragique ou une lésion des muqueuses gastriques.

- 5 **15.** Utilisation d'un composé de formule (I) ou un sel pharmaceutiquement acceptable de celui-ci selon l'une quelconque des revendications 1 à 8 et un/des autre(s) agent ou agents thérapeutique(s) dans la fabrication d'un médicament pour le traitement d'une maladie inflammatoire, où le composé de formule (I) est administré simultanément ou séquentiellement ou sous la forme d'une préparation combinée avec le/les autre(s) agent ou agents thérapeutique(s).

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REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO 2005026123 A [0010]
- WO 2005026124 A [0010]
- WO 2005080372 A [0010]
- WO 2004043924 A [0010]
- WO 2004020410 A [0010]
- EP 1300396 A1 [0010]
- WO 2006098683 A [0010]
- WO 2006098684 A [0010]
- WO 2005021509 A [0011]
- WO 9722596 A [0159]
- WO 9730035 A [0159]
- WO 9732856 A [0159]
- WO 9813354 A [0159]
- WO 9902166 A [0159]
- WO 0040529 A [0159]
- WO 0041669 A [0159]
- WO 0192224 A [0159]
- WO 0204434 A [0159]
- WO 0208213 A [0159]

Non-patent literature cited in the description

- **Kawabat et al.** *Eur. J. Pharmacol.*, 2002, vol. 451, 1-10 [0002]
- **Janoff ; Scherer.** *J. Exp. Med.*, 1968, vol. 128, 1137-1155 [0002]
- **Ohbayashi, H.** *Expert Opin. Investig. Drugs*, 2002, vol. 11, 965-980 [0002]
- **Stockley, R.A.** *Am. J. Resp. Crit. Care Med.*, 1994, vol. 150, 109-113 [0002]
- **Laurell ; Eriksson.** *Scand. J. Clin. Invest.*, 1963, vol. 15, 132-140 [0003]
- **Cavarra et al.** *Lab. Invest.*, 1996, vol. 75, 273-280 [0003]
- **Betsuyaku et al.** *Respiration*, 2000, vol. 67, 261-267 [0003]
- **Karaki et al.** *Am. J. Resp. Crit. Care Med.*, 2002, vol. 166, 496-500 [0003]
- **Fujie et al.** *Inflamm. Res.*, 1999, vol. 48, 160-167 [0003]
- **Fischer, B.M ; Voynow.** *Am. J. Respir. Cell Biol.*, 2002, vol. 26, 447-452 [0004]
- **Suzuki et al.** *Am. J. Resp. Crit. Care Med.*, 1996, vol. 153, 1405-1411 [0004]
- **Smallman et al.** *Thorax*, 1984, vol. 39, 663-667 [0004]
- **Currie et al.** *Thorax*, 1984, vol. 42, 126-130 [0004]
- **Lucey et al.** *Am. Resp. Crit. Care Med.*, 1985, vol. 132, 362-366 [0004]
- **Nadel et al.** *Eur. Resp. J.*, 1999, vol. 13, 190-196 [0004]
- **Yamanouchi et al.** *Eur. Resp. J.*, 1998, vol. 11, 120-125 [0005]
- **Taooka et al.** *Am. J. Resp. Crit. Care Med.*, 1997, vol. 156, 260-265 [0005]
- **Dunsmore et al.** *Chest*, 2001, vol. 120, 35S-36S [0005]
- **Donnelly et al.** *Am. J. Res. Crit. Care Med.*, 1995, vol. 151, 428-433 [0005]
- **Marchandise et al.** *Eur. Resp. J.*, 1989, vol. 2, 623-629 [0005]
- **Taniguchi et al.** *Clin. Cancer Res.*, 2002, vol. 8, 1115-1120 [0005]
- **Kawabata et al.** *Am. J. Resp. Crit. Care*, 1999, vol. 161, 2013-2018 [0006]
- **Fujie et al.** *Eur. J. Pharmacol.*, 1999, vol. 374, 117-125 [0006]
- **Yasui et al.** *Eur. Resp. J.*, 1995, vol. 8, 1293-1299 [0006]
- **Miyazaki et al.** *Am. J. Respir. Crit. Care Med.*, 1998, vol. 157, 89-94 [0006]
- **Molteni et al.** *Biochemical Pharmacol.*, 1989, vol. 38, 2411-2419 [0007]
- **Cowan et al.** *Nature Medicine*, 2000, vol. 6, 698-702 [0007]
- **Wright et al.** *Am. J. Respir. Crit. Care Med.*, 2002, vol. 166, 954-960 [0007]
- **Shimakura et al.** *Brain Research*, 2000, vol. 858, 55-60 [0008]
- **Kishima et al.** *Ann. Thorac. Surg.*, 1998, vol. 65, 913-918 [0008]
- **Tiefenbacher et al.** *Eur. J. Physiol.*, 1997, vol. 433, 563-570 [0008]
- **Adeyemi et al.** *Gut*, 1985, vol. 26, 1306-1311 [0008]
- **Adeyemi et al.** *Rheumatol. Int.*, 1986, vol. 6, 57 [0008]
- **Kakimoto et al.** *Cellular Immunol.*, 1995, vol. 165, 26-32 [0008]
- **Protective Groups in Organic Chemistry.** Plenum Press, 1973 [0089]
- **T.W. Greene ; P.G.M. Wuts.** *Protective Groups in Organic Synthesis.* Wiley-Interscience, 1999 [0089]

EP 2 018 375 B1

- **M. E. Aulton.** *Pharmaceuticals - The Science of Dosage Form Designs*, 1988 [0117]
- *Eur. J. Org. Chem.*, 2004, 695-709 [0186]
- **Baugh, R.J. et al.** *Biochemistry*, 1976, vol. 15, 836-841 [0190]
- **Castillo, M.J. et al.** *Anal. Biochem.*, 1979, vol. 99, 53-64 [0190]