

2-pyridone derivatives as neutrophil elastase inhibitors and their use.

Field of the Invention

5 This invention relates to novel 2-pyridone derivatives, processes for their preparation, pharmaceutical compositions comprising them, and their use in therapy.

Background of the Invention

10 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
15 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 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
20 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
25 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).

30 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 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).

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).

NE has been also shown to play a role in the pathogenesis of pulmonary fibrosis.

- 5 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
- 10 mice are resistant to bleomycin-induced pulmonary fibrosis (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,
- 15 *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).

- Acute lung injury caused by endotoxin in experimental animals is associated with elevated
- 20 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-
- 25 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).

- 30 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).

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).

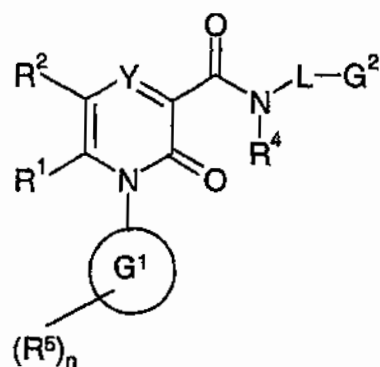
Thus, human NE is known as one of the most destructive serine proteases and has been implicated in a variety of inflammatory diseases. The important endogenous inhibitor of human NE is α_1 -antitrypsin. The imbalance between human NE and antiprotease is believed to give rise to an excess of human NE 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.

WO 02/053543 discloses pyridone derivatives having affinity for cannabinoid 2-type receptor.

The present invention discloses novel 2-pyridione derivatives that are inhibitors of human neutrophil elastase and homologous serine proteases such as proteinase 3 and pancreatic elastase, and are thereby useful in therapy.

5 Disclosure of the Invention

The present invention provides a compound of formula (I)



(I)

wherein:

Y represents CR^3 or N ;

R^1 represents H or $C1$ to 6 alkyl;

R^2 represents:

i) CN , NO_2 , OH , OSO_2R^{47} , $O-C2$ to 6 alkanoyl, CO_2R^{47} , CHO or $C2$ to 6 alkanoyl; or

ii) $C1$ to 6 alkoxy optionally substituted by OH , $C1$ to 6 alkoxy, CN , $NR^{54}R^{55}$, $CONR^{54}R^{55}$, $OCOR^{47}$ or one or more F atoms; or

- iii) C3 to 6 saturated or partially unsaturated cycloalkyl optionally further substituted by C1 to 6 alkyl; or
- iv) C4 to 7 saturated or partially unsaturated heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, S(O)_m and NR⁶² optionally further substituted by C1 to 6 alkyl; or
- v) CONR^{48, 49}R⁴⁹, CONR⁵⁰NR^{48, 49}, C(=NOR⁵²)R⁵³, C(=NH)NHOR⁵² or NR^{48, 49}R⁴⁹; or
- vi) C2 to 6 alkenyl or C2 to 6 alkynyl; said alkenyl or alkynyl group being optionally further substituted by C1 to 6 alkoxy or phenyl or a five- or six-membered heteroaromatic ring containing 1 to 3 heteroatoms independently selected from O, S and N; said phenyl or heteroaromatic ring being optionally further substituted by halogen, CN, C1 to 6 alkyl or C1 to 6 alkoxy; or
- vii) C1 to 6 alkyl substituted by one or more F atoms; or
- viii) C1 to 6 alkyl substituted by one or more groups selected from halogen, OH, oxo, azido, NR^{48, 49}R⁴⁹, C1 to 6 alkoxy and C1 to 6 alkoxy substituted by one or more F atoms; or
- ix) C1 to 6 alkyl substituted by phenyl or a five- or six-membered heteroaromatic ring containing 1 to 3 heteroatoms independently selected from O, S and N; said phenyl or heteroaromatic ring being optionally further substituted by halogen, CN, C1 to 6 alkyl or C1 to 6 alkoxy;

R⁴⁸ and R⁴⁹ independently represent H, OH, C1 to 6 alkoxy, C3 to 6 cycloalkyl, CHO, C2 to 6 alkanoyl, CO₂R⁵⁰, C(X)NR^{63, 64}R⁶⁴ or C1 to 6 alkyl; said alkyl being optionally further substituted by OH, C1 to 4 alkoxy, C3 to 6 cycloalkyl, CN or phenyl or a five- or six-membered heteroaromatic ring containing 1 to 3 heteroatoms independently selected from O, S and N; said alkanoyl being optionally further substituted by CN;

X represent O or S;

or the group $\text{NR}^{48}\text{R}^{49}$ together represents a saturated or partially unsaturated 5 to 7 membered azacyclic ring optionally incorporating one further heteroatom selected from O, S and NR^{56} ; said azacyclic ring being optionally further substituted by one or more substituents selected from OR^{57} and C1 to 4 alkyl; said alkyl being optionally further substituted by OR^{57} ;

R^3 represents H or F;

G^1 represents phenyl or a five- or six-membered heteroaromatic ring containing 1 to 3 heteroatoms independently selected from O, S and N;

R^5 represents H, halogen, C1 to 6 alkyl, CN, C1 to 6 alkoxy, NO_2 , $\text{NR}^{14}\text{R}^{15}$, C1 to 3 alkyl substituted by one or more F atoms or C1 to 3 alkoxy substituted by one or more F atoms;

R^{14} and R^{15} independently represent H or C1 to 3 alkyl; said alkyl being optionally further substituted by one or more F atoms;

n represents an integer 1, 2 or 3 and when n represents 2 or 3, each R^5 group is selected independently;

R^4 represents H or C1 to 6 alkyl; said alkyl being optionally further substituted by OH or C1 to 6 alkoxy;

or R^4 and L are joined together such that the group $-\text{NR}^4\text{L}$ represents a 5 to 7 membered azacyclic ring optionally incorporating one further heteroatom selected from O, S and NR^{16} ; said ring being optionally further substituted by C1 to 6 alkyl or $\text{NR}^{60}\text{R}^{61}$; said alkyl being optionally further substituted by OH;

L represents a bond, O, NR²⁹ or C1 to 6 alkyl; said alkyl optionally incorporating a heteroatom selected from O, S and NR¹⁶; and said alkyl being optionally further substituted by OH or OMe;

5 G² represents a monocyclic ring system selected from:

- i) phenyl or phenoxy,
- ii) a 5 or 6 membered heteroaromatic ring containing one to three heteroatoms independently selected from O, S and N,
- 10 iii) a C3 to 6 saturated or partially unsaturated cycloalkyl, or
- iv) a C4 to 7 saturated or partially unsaturated heterocyclic ring containing one or two heteroatoms independently selected from O, S(O)_p and NR¹⁷ and optionally further incorporating a carbonyl group; or

15 G² represents a bicyclic ring system in which each of the two rings is independently selected from:

- i) phenyl,
- ii) a 5 or 6 membered heteroaromatic ring containing one to three heteroatoms independently selected from O, S and N,
- 20 iii) a C3 to 6 saturated or partially unsaturated cycloalkyl, or
- iv) a C4 to 7 saturated or partially unsaturated heterocyclic ring containing one or two heteroatoms independently selected from O, S(O)_p and NR¹⁷ and optionally further incorporating a carbonyl group;

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and the two rings are either fused together, or are bonded directly together or are separated by a linker group selected from O, S(O)_q or CH₂,

said monocyclic or bicyclic ring system being optionally further substituted by one to three
30 substituents independently selected from CN, OH, C1 to 6 alkyl, C1 to 6 alkoxy, halogen,

$\text{NR}^{18}\text{R}^{19}$, NO_2 , $\text{OSO}_2\text{R}^{38}$, CO_2R^{20} , $\text{C}(=\text{NH})\text{NH}_2$, $\text{C}(\text{O})\text{NR}^{21}\text{R}^{22}$, $\text{C}(\text{S})\text{NR}^{23}\text{R}^{24}$,
 $\text{SC}(=\text{NH})\text{NH}_2$, $\text{NR}^{31}\text{C}(=\text{NH})\text{NH}_2$, $\text{S}(\text{O})_s\text{R}^{25}$, $\text{SO}_2\text{NR}^{26}\text{R}^{27}$, C1 to 3 alkoxy substituted by
 one or more F atoms and C1 to 3 alkyl substituted by SO_2R^{39} or by one or more F atoms;
 or

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when L does not represent an bond, G^2 may also represent H;

at each occurrence, m, p, q, s and t independently represent an integer 0, 1 or 2;

10 R^{18} and R^{19} independently represent H, C1 to 6 alkyl, formyl, C2 to 6 alkanoyl, $\text{S}(\text{O})_t\text{R}^{32}$
 or $\text{SO}_2\text{NR}^{33}\text{R}^{34}$; said alkyl group being optionally further substituted by halogen, CN, C1
 to 4 alkoxy or $\text{CONR}^{41}\text{R}^{42}$;

15 R^{25} represents H, C1 to 6 alkyl or C3 to 6 cycloalkyl; said alkyl group being optionally
 further substituted by one or more substituents selected independently from OH, CN,
 $\text{CONR}^{35}\text{R}^{36}$, CO_2R^{37} , OCOR^{40} , C3 to 6 cycloalkyl, a C4 to 7 saturated heterocyclic ring
 containing one or two heteroatoms independently selected from O, $\text{S}(\text{O})_p$ and NR^{43} and
 phenyl or a 5 or 6 membered heteroaromatic ring containing one to three heteroatoms
 independently selected from O, S and N; said aromatic ring being optionally further
 20 substituted by one or more substituents selected independently from halogen, CN, C1 to 4
 alkyl, C1 to 4 alkoxy, OH, $\text{CONR}^{44}\text{R}^{45}$, CO_2R^{46} , $\text{S}(\text{O})_s\text{R}^{65}$ and NHCOCH_3 ;

R^{32} represents H, C1 to 6 alkyl or C3 to 6 cycloalkyl;

25 R^{16} , R^{17} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{26} , R^{27} , R^{29} , R^{31} , R^{33} , R^{34} , R^{35} , R^{36} , R^{37} , R^{38} ,
 R^{39} , R^{40} , R^{41} , R^{42} , R^{43} , R^{44} , R^{45} , R^{46} , R^{47} , R^{50} , R^{52} , R^{53} , R^{54} , R^{55} , R^{56} , R^{57} , R^{60} ,
 R^{61} , R^{62} , R^{63} , R^{64} and R^{65} independently represent H or C1 to 6 alkyl;

and pharmaceutically acceptable salts thereof.

The compounds of formula (I) may exist in enantiomeric and/or tautomeric forms. It is to be understood that all enantiomers, diastereomers, racemates, tautomers and mixtures
5 thereof are included within the scope of the invention.

Unless otherwise indicated, the term "C1 to 6 alkyl" referred to herein denotes a straight or branched chain alkyl group having from 1 to 6 carbon atoms. Examples of such groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, pentyl and hexyl. The
10 terms "C1 to 3 alkyl" and "C1 to 4 alkyl" are to be interpreted analogously.

Examples of "C1 to 3 alkyl substituted by one or more F atoms" include fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 1,1-difluoroethyl, pentafluoroethyl and 3,3,3-trifluoropropyl.

Unless otherwise indicated, the term "C1 to 6 alkoxy" referred to herein denotes an oxygen substituent bonded to a straight or branched chain alkyl group having from 1 to 6 carbon atoms. Examples of such groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy and s-butoxy. The terms "C1 to 3 alkoxy" and "C1 to 4 alkoxy" are to
20 be interpreted analogously.

Examples of "C1 to 6 alkoxy substituted by one or more F atoms" include fluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy and 3,3,3-trifluoropropoxy.

Unless otherwise indicated, the term "C2 to 6 alkanoyl" referred to herein denotes a
25 straight or branched chain alkyl group having from 1 to 5 carbon atoms bonded to the molecule via a carbonyl group. Examples of such groups include acetyl, propionyl and pivaloyl.

Unless otherwise indicated, the term "halogen" referred to herein denotes fluorine,
30 chlorine, bromine and iodine.

Examples of a five or six membered heteroaromatic ring containing 1 to 3 heteroatoms independently selected from O, S and N include furan, thiophene, pyrrole, oxazole, oxadiazole, isoxazole, imidazole, thiazole, triazole, thiadiazole, pyridine, pyrimidine and pyrazine.

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Unless otherwise indicated, the term "C3 to 6 saturated or partially unsaturated cycloalkyl" referred to herein denotes a 3 to 6 membered non-aromatic carbocyclic ring optionally incorporating one or more double bonds. Examples include cyclopropyl, cyclopentyl, cyclopentenyl, cyclohexyl and cyclohexenyl. The term "five- or six-membered saturated or
10 partially unsaturated cycloalkyl ring" is to be interpreted analogously.

Unless otherwise indicated, the term "C4 to 7 saturated or partially unsaturated heterocyclic ring containing one or two heteroatoms independently selected from O, S(O)_p and NR¹⁷ and optionally further incorporating a carbonyl group" referred to herein denotes
15 a 4 to 7 membered non-aromatic heterocyclic ring optionally incorporating one or more double bonds and optionally incorporating a carbonyl group. Examples include tetrahydrofuran, thiolane 1,1-dioxide, tetrahydropyran, 4-oxo-4H-pyran, pyrrolidine, pyrroline, imidazolidine, 1,3-dioxolane, piperidine, piperazine, morpholine, perhydroazepine, pyrrolidone and piperidone. The terms "five- or six-membered saturated
20 or partially unsaturated heterocyclic ring containing one heteroatom selected from O, S and NR¹³," and "C4 to 7 saturated or partially unsaturated heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, S(O)_m and NR⁶²," are to be interpreted analogously.

25 Examples of a "5 to 7 membered azacyclic ring optionally incorporating one further heteroatom selected from O, S and NR¹⁶," include pyrrolidine, piperidine, morpholine, thiomorpholine and piperazine.

In the definition of L, "C1 to 6 alkyl; said alkyl optionally incorporating a heteroatom
30 selected from O, S and NR¹⁶," embraces a straight or branched chain arrangement of 1 to 6

carbon atoms in which any two carbon atoms are optionally separated by O, S or NR¹⁶.

The definition thus includes, for example, methylene, ethylene, propylene, hexamethylene, ethylethylene, $-\text{CH}_2\text{CH}_2\text{O}-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{O}-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{S}-$ and $-\text{CH}_2\text{CH}_2\text{NR}^{16}-$.

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Examples of bicyclic ring systems in which the two rings are either fused together, or are bonded directly together or are separated by a linker group selected from O, S(O)_q or CH₂ include biphenyl, thienylphenyl, pyrazolylphenyl, phenoxyphenyl, phenylcyclopropyl, naphthyl, indanyl, quinolyl, tetrahydroquinolyl, benzofuranyl, indolyl, isoindolyl, indolinyl, benzofuranyl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, purinyl, isoquinolyl, chromanyl, indenyl, quinazolyl, quinoxalyl, chromanyl, isochromanyl, 3H-indolyl, 1H-indazolyl, quinuclidyl, tetrahydronaphthyl, dihydrobenzofuranyl, morpholine-4-ylphenyl, 1,3-benzodioxolyl, 1,1-dioxido-2,3-dihydro-1-benzothienyl, 2,3-dihydro-1,4-benzodioxinyl, 1,3-benzodioxinyl and 3,4-dihydro-isochromenyl.

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In one embodiment, Y in formula (I) represents CR³. In another embodiment, Y represents N.

In one embodiment, R¹ in formula (I) represents C1 to 6 alkyl. In another embodiment, R¹ represents CH₃.

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In one embodiment R² in formula (I) represents CONR^{48, 49}. In another embodiment, R² represents C1 to 6 alkoxy or C1 to 6 alkoxy substituted by OH, C1 to 6 alkoxy, or by one or more F atoms. In yet another embodiment, R² represents C1 to 6 alkyl substituted by one or more F atoms or C1 to 6 alkyl substituted by OH, NR^{48, 49}, C1 to 6 alkoxy or C1 to 6 alkoxy substituted by one or more F atoms.

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In one embodiment, R³ in formula (I) represents H.

In one embodiment, G^1 in formula (I) represents phenyl or pyridyl. In another embodiment, G^1 in formula (I) represents phenyl.

- 5 In one embodiment, R^5 in formula (I) represents halogen, C1 to 6 alkyl, CN or C1 to 3 alkyl substituted by one or more F atoms. In another embodiment, R^5 in formula (I) represents Cl, CH_3 , CN or CF_3 .

In one embodiment, n represents the integer 1.

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In another embodiment, G^1 in formula (I) represents phenyl, R^5 represents CF_3 and n represents the integer 1.

In one embodiment, R^4 represents H.

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In one embodiment, L represents C1 to 6 alkyl (C1 to 6 alkylidene). In another embodiment, L represents $-CH_2-$. In another embodiment, L represents NR^{29} and R^{29} represents H.

- 20 In one embodiment, G^2 represents an optionally substituted monocyclic ring system selected from:

- i) phenyl,
- ii) a 5 or 6 membered heteroaromatic ring containing one to three heteroatoms
25 independently selected from O, S and N,
- iii) a C3 to 6 saturated or partially unsaturated cycloalkyl, or
- iv) a C4 to 7 saturated or partially unsaturated heterocyclic ring containing one or two
heteroatoms independently selected from O, $S(O)_p$ and NR^{17} and optionally further
incorporating a carbonyl group.

In another embodiment, G^2 represents optionally substituted phenyl. In another embodiment, G^2 represents phenyl substituted by OSO_2R^{38} , $S(O)_sR^{25}$, $SO_2NR^{26}R^{27}$, $NR^{18}R^{19}$ (wherein at least one of R^{18} and R^{19} represents $S(O)_tR^{32}$ or $SO_2NR^{33}R^{34}$) or C1 to 3 alkyl substituted by SO_2R^{39} . In another embodiment, G^2 represents phenyl substituted by $S(O)_sR^{25}$ and R^{25} represents C1 to 6 alkyl or C3 to 6 cycloalkyl and s represents the integer 2.

In another embodiment, G^2 represents an optionally substituted bicyclic ring system in which each of the two rings is independently selected from:

- i) phenyl,
- ii) a 5 or 6 membered heteroaromatic ring containing one to three heteroatoms independently selected from O, S and N,
- iii) a C3 to 6 saturated or partially unsaturated cycloalkyl, or
- iv) a C4 to 7 saturated or partially unsaturated heterocyclic ring containing one or two heteroatoms independently selected from O, $S(O)_p$ and NR^{17} and optionally further incorporating a carbonyl group;

and the two rings are either fused together, or are bonded directly together or are separated by a linker group selected from O, $S(O)_q$ or CH_2 .

In one embodiment, Y in formula (I) represents CR^3 and R^3 represents H; R^1 represents C1 to 6 alkyl; R^2 represents $CONR^{48}R^{49}$ or optionally substituted C1 to 6 alkoxy or substituted C1 to 6 alkyl; G^1 represents phenyl; R^5 represents halogen, C1 to 6 alkyl, CN or C1 to 3 alkyl substituted by one or more F atoms; R^4 represents H; L represents C1 to 6 alkyl; and G^2 represents an optionally substituted monocyclic ring system selected from:

- i) phenyl,
- ii) a 5 or 6 membered heteroaromatic ring containing one to three heteroatoms independently selected from O, S and N,
- iii) a C3 to 6 saturated or partially unsaturated cycloalkyl, or
- iv) a C4 to 7 saturated or partially unsaturated heterocyclic ring containing one or two heteroatoms independently selected from O, S(O)_p and NR¹⁷ and optionally further incorporating a carbonyl group.

In one embodiment, Y in formula (I) represents CR³ and R³ represents H; R¹ represents C1 to 6 alkyl; R² represents CONR^{48, 49} or optionally substituted C1 to 6 alkoxy or substituted C1 to 6 alkyl; G¹ represents phenyl; R⁵ represents halogen, C1 to 6 alkyl, CN or C1 to 3 alkyl substituted by one or more F atoms; R⁴ represents H; L represents C1 to 6 alkyl; and G² represents phenyl substituted by OSO₂R³⁸, S(O)_sR²⁵, SO₂NR^{26, 27}, NR^{18, 19} (wherein at least one of R¹⁸ and R¹⁹ represents S(O)_tR³² or SO₂NR^{33, 34}) or C1 to 3 alkyl substituted by SO₂R³⁹.

In one embodiment, Y in formula (I) represents CR³ and R³ represents H; R¹ represents methyl; R² represents CONR^{48, 49} or optionally substituted C1 to 6 alkoxy or substituted C1 to 6 alkyl; G¹ represents phenyl; R⁵ represents Cl, CH₃, CN or CF₃; R⁴ represents H; L represents C1 to 6 alkyl; and G² represents phenyl substituted by OSO₂R³⁸, S(O)_sR²⁵, SO₂NR^{26, 27}, NR^{18, 19} (wherein at least one of R¹⁸ and R¹⁹ represents S(O)_tR³² or SO₂NR^{33, 34}) or C1 to 3 alkyl substituted by SO₂R³⁹.

In one embodiment, Y in formula (I) represents CR³ and R³ represents H; R¹ represents methyl; R² represents CONR^{48, 49}; G¹ represents phenyl; R⁵ represents Cl, CH₃, CN or CF₃; R⁴ represents H; L represents C1 to 3 alkyl; and G² represents phenyl substituted by

$S(O)_sR^{25}$ and R^{25} represents C1 to 6 alkyl or C3 to 6 cycloalkyl and s represents the integer 2.

In one embodiment, Y in formula (I) represents CR^3 and R^3 represents H; R^1 represents methyl; R^2 represents optionally substituted C1 to 6 alkoxy; G^1 represents phenyl; R^5 represents Cl, CH_3 , CN or CF_3 ; R^4 represents H; L represents C1 to 3 alkyl; and G^2 represents phenyl substituted by $S(O)_sR^{25}$ and R^{25} represents C1 to 6 alkyl or C3 to 6 cycloalkyl and s represents the integer 2.

In one embodiment, Y in formula (I) represents CR^3 and R^3 represents H; R^1 represents methyl; R^2 represents substituted C1 to 6 alkyl; G^1 represents phenyl; R^5 represents Cl, CH_3 , CN or CF_3 ; R^4 represents H; L represents C1 to 3 alkyl; and G^2 represents phenyl substituted by $S(O)_sR^{25}$ and R^{25} represents C1 to 6 alkyl or C3 to 6 cycloalkyl and s represents the integer 2.

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In one embodiment, Y in formula (I) represents CR^3 or N; R^1 represents H or C1 to 6 alkyl; R^2 represents CN, NO_2 , OH, CO_2R^{47} , CHO, C2 to 6 alkanoyl, C1 to 6 alkoxy, C1 to 6 alkoxy substituted by one or more F atoms, C3 to 6 saturated or partially unsaturated cycloalkyl, C4 to 7 saturated or partially unsaturated heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, $S(O)_m$ and NR^{62} , $CONR^{48}R^{49}$, $CONR^{50}NHR^{51}$, $C(=NOR^{52})R^{53}$, $NR^{58}R^{59}$, C2 to 6 alkenyl or C2 to 6 alkynyl; said alkenyl or alkynyl group being optionally further substituted by C1 to 6 alkoxy or phenyl or a five- or six-membered heteroaromatic ring containing 1 to 3 heteroatoms independently selected from O, S and N; said phenyl or heteroaromatic ring being optionally further substituted by halogen, CN, C1 to 6 alkyl or C1 to 6 alkoxy; or R^2 represents C1 to 6 alkyl substituted by one or more F atoms; or C1 to 6 alkyl substituted by OH, $NR^{58}R^{59}$, C1 to 6 alkoxy or C1 to 6 alkoxy substituted by one or more F atoms; or C1

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to 6 alkyl substituted by phenyl or a five- or six-membered heteroaromatic ring containing 1 to 3 heteroatoms independently selected from O, S and N; said phenyl or heteroaromatic ring being optionally further substituted by halogen, CN, C1 to 6 alkyl or C1 to 6 alkoxy; R^{48} represents H, OH, C1 to 6 alkoxy or C1 to 6 alkyl; said alkyl being optionally further substituted by OH, C1 to 4 alkoxy or $NR^{54}R^{55}$; R^{49} represents H or C1 to 6 alkyl; said alkyl being optionally further substituted by OH, C1 to 4 alkoxy or $NR^{54}R^{55}$; or the group $NR^{48}R^{49}$ together represents a 5 to 7 membered azacyclic ring optionally incorporating one further heteroatom selected from O, S and NR^{56} ; said azacyclic ring being optionally further substituted by OR^{57} or C1 to 4 alkyl; said alkyl being optionally further substituted by OR^{57} ; R^{58} and R^{59} independently represent H, C1 to 6 alkyl, $NR^{60}R^{61}$ or $CONR^{63}R^{64}$; or the group $NR^{58}R^{59}$ together represents a 5 to 7 membered azacyclic ring optionally incorporating one further heteroatom selected from O, S and NR^{56} ; said azacyclic ring being optionally further substituted by OR^{57} or C1 to 4 alkyl; said alkyl being optionally further substituted by OR^{57} ; R^{51} represents C2 to 4 alkanoyl optionally further substituted by CN, or R^{51} represents $C(X)NH_2$ wherein X represents O or S; R^3 represents H or F; G^1 represents phenyl or a five- or six-membered heteroaromatic ring containing 1 to 3 heteroatoms independently selected from O, S and N; R^5 represents H, halogen, C1 to 6 alkyl, CN, C1 to 6 alkoxy, NO_2 , $NR^{14}R^{15}$, C1 to 3 alkyl substituted by one or more F atoms or C1 to 3 alkoxy substituted by one or more F atoms; R^{14} and R^{15} independently represent H or C1 to 3 alkyl; said alkyl being optionally further substituted by one or more F atoms; n represents an integer 1, 2 or 3 and when n represents 2 or 3, each R^5 group is selected independently; R^4 represents H or C1 to 6 alkyl; said alkyl being optionally further substituted by OH or C1 to 6 alkoxy; or R^4 and L are joined together such that the group $-NR^4L$ represents a 5 to 7 membered azacyclic ring optionally incorporating one further heteroatom selected from O, S and NR^{16} ; L represents a bond, O,

NR²⁹ or C1 to 6 alkyl; said alkyl optionally incorporating a heteroatom selected from O, S and NR¹⁶; and said alkyl being optionally further substituted by OH or OMe; G² represents a monocyclic ring system selected from:

- i) phenyl or phenoxy,
- 5 ii) a 5 or 6 membered heteroaromatic ring containing one to three heteroatoms independently selected from O, S and N,
- iii) a C3 to 6 saturated or partially unsaturated cycloalkyl, or
- iv) a C4 to 7 saturated or partially unsaturated heterocyclic ring containing one or two heteroatoms independently selected from O, S(O)_p and NR¹⁷ and optionally further
- 10 incorporating a carbonyl group; or

G² represents a bicyclic ring system in which each of the two rings is independently selected from:

- i) phenyl,
- 15 ii) a 5 or 6 membered heteroaromatic ring containing one to three heteroatoms independently selected from O, S and N,
- iii) a C3 to 6 saturated or partially unsaturated cycloalkyl, or
- iv) a C4 to 7 saturated or partially unsaturated heterocyclic ring containing one or two heteroatoms independently selected from O, S(O)_p and NR¹⁷ and optionally further incorporating a carbonyl group;

- 20 and the two rings are either fused together, or are bonded directly together or are separated by a linker group selected from O, S(O)_q or CH₂; said monocyclic or bicyclic ring system being optionally further substituted by one to three substituents independently selected from CN, OH, C1 to 6 alkyl, C1 to 6 alkoxy, halogen, NR¹⁸, R¹⁹, NO₂, OSO₂R³⁸, CO₂R²⁰, C(=NH)NH₂, C(O)NR²¹, R²², C(S)NR²³, R²⁴, SC(=NH)NH₂, NR³¹C(=NH)NH₂, S(O)_sR²⁵, SO₂NR²⁶, R²⁷, C1 to 3 alkoxy substituted by one or more F atoms and C1 to 3 alkyl
- 25 substituted by SO₂R³⁹ or by one or more F atoms; or when L does not represent an bond, G² may also represent H; m, p, q, s and t independently represent an integer 0, 1 or 2; R¹⁸ and R¹⁹ independently represent H, C1 to 6 alkyl, formyl, C2 to 6 alkanoyl, S(O)_tR³² or

$\text{SO}_2\text{NR}^{33}\text{R}^{34}$; said alkyl group being optionally further substituted by halogen, CN, C1 to 4 alkoxy or $\text{CONR}^{41}\text{R}^{42}$; R^{25} represents H, C1 to 6 alkyl or C3 to 6 cycloalkyl; said alkyl group being optionally further substituted by one or more substituents selected independently from OH, CN, $\text{CONR}^{35}\text{R}^{36}$, CO_2R^{37} , OCOR^{40} , C3 to 6 cycloalkyl, a C4 to 7 saturated heterocyclic ring containing one or two heteroatoms independently selected from O, S(O)_p and NR^{43} and phenyl or a 5 or 6 membered heteroaromatic ring containing one to three heteroatoms independently selected from O, S and N; said aromatic ring being optionally further substituted by one or more substituents selected independently from halogen, CN, C1 to 4 alkyl, C1 to 4 alkoxy, OH, $\text{CONR}^{44}\text{R}^{45}$, CO_2R^{46} , $\text{S(O)}_s\text{R}^{65}$ and NHCOCH_3 ; R^{32} represents H, C1 to 6 alkyl or C3 to 6 cycloalkyl; and $\text{R}^{16}, \text{R}^{17}, \text{R}^{20}, \text{R}^{21}, \text{R}^{22}, \text{R}^{23}, \text{R}^{24}, \text{R}^{26}, \text{R}^{27}, \text{R}^{29}, \text{R}^{31}, \text{R}^{33}, \text{R}^{34}, \text{R}^{35}, \text{R}^{36}, \text{R}^{37}, \text{R}^{38}, \text{R}^{39}, \text{R}^{40}, \text{R}^{41}, \text{R}^{42}, \text{R}^{43}, \text{R}^{44}, \text{R}^{45}, \text{R}^{46}, \text{R}^{47}, \text{R}^{50}, \text{R}^{52}, \text{R}^{53}, \text{R}^{54}, \text{R}^{55}, \text{R}^{56}, \text{R}^{57}, \text{R}^{60}, \text{R}^{61}, \text{R}^{62}, \text{R}^{63}, \text{R}^{64}$ and R^{65} independently represent H or C1 to 6 alkyl;

In another aspect, the invention specifically provides any compound as described in the Examples herein, or the free base thereof or a pharmaceutically acceptable salt thereof.

Particular compounds include:

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

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

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

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

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

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

- 6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-5-(pyridin-3-ylethynyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-5-(2-pyridin-3-ylethyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 5 6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-5-vinyl-1,2-dihydropyridine-3-carboxamide;
- ethyl 2-methyl-5-([4-(methylsulfonyl)benzyl]amino)carbonyl)-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridine-3-carboxylate;
- 5-(4-methanesulfonyl-benzylcarbonyl)-2-methyl-6-oxo-1-(3-trifluoromethyl-phenyl)-1,6-dihydro-pyridine-3-carboxylic acid;
- 10 6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3,5-dicarboxylic acid 5-dimethylamide 3-(4-methanesulfonyl-benzylamide);
- 6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3,5-dicarboxylic acid 5-amide 3-(4-methanesulfonyl-benzylamide);
- 15 6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3,5-dicarboxylic acid 3-(4-methanesulfonyl-benzylamide) 5-methylamide;
- 6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3,5-dicarboxylic acid 5-[(2-hydroxy-ethyl)-methyl-amide] 3-(4-methanesulfonyl-benzylamide);
- 6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3,5-dicarboxylic acid 3-(4-methanesulfonyl-benzylamide) 5-(methyl-propyl-amide);
- 20 6-methyl-2-oxo-5-(pyrrolidine-1-carbonyl)-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3,5-dicarboxylic acid 3-(4-methanesulfonyl-benzylamide);
- 6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3,5-dicarboxylic acid 5-[(2-dimethylamino-ethyl)-methyl-amide] 3-(4-methanesulfonyl-benzylamide);
- 25 5-((2*R*)-2-hydroxymethyl-pyrrolidine-1-carbonyl)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 3-(4-methanesulfonyl-benzylamide);
- 5-(3-hydroxy-pyrrolidine-1-carbonyl)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3,5-dicarboxylic acid 3-(4-methanesulfonyl-benzylamide);
- N^3 -[(1,1-dioxido-2,3-dihydro-1-benzothien-5-yl)methyl]- $N^5,N^5,6$ -trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- 30 5-(N^1 -acetyl-hydrazinocarbonyl)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide;

- 5-[N¹-(2-cyano-acetyl)-hydrazinocarbonyl]-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide;
- 5-[[2-(aminocarbonothioyl)hydrazino]carbonyl]-6-methyl-N-[4-(methylsulfonyl) benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 5 5-hydrazinocarbonyl-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide;
- 5-({2-[(ethylamino)carbonyl]hydrazino}carbonyl)-6-methyl-N-[4-(methylsulfonyl) benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 5-({2-[(N,N-dimethylamino)carbonyl]hydrazino}carbonyl)-6-methyl-N-[4-(methylsulfonyl) benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 10 5-(3,3-dimethyl-ureido)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide;
- 6-methyl-5-(3-methyl-ureido)-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide;
- 15 6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-5-ureido-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide;
- 5-amino-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide;
- 20 6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-5-propionyl-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 5-formyl-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-5-(3-oxobutyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 25 5-acetyl-N-[4-(isopropylsulfonyl)benzyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 5-acetyl-1-(3-cyano-phenyl)-6-methyl-2-oxo-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide;
- 30 5-acetyl-1-(3-chloro-phenyl)-6-methyl-2-oxo-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide;

- 5-acetyl-6-methyl-2-oxo-1-m-tolyl-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide;
- 5-(1-hydroxyethyl)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 5 5-(1-azidoethyl)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 6-methyl-N-[4-(methylsulfonyl)benzyl]-5-(1-morpholin-4-ylethyl)-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 5-(1-hydroxypropyl)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 10 5-(1-hydroxyethyl)-N-[4-(isopropylsulfonyl)benzyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- N-[4-(cyclopropylsulfonyl)benzyl]-5-formyl-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 15 5-[(E)-(methoxyimino)methyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 5-(hydroxymethyl)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 5-[(dimethylamino)methyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 20 6-methyl-5-[(methylamino)methyl]-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 6-methyl-N-[4-(methylsulfonyl)benzyl]-5-(morpholin-4-ylmethyl)-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 25 5-[[2-furylmethyl]amino]methyl-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 5-[(cyclopropylamino)methyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 5-[[2-hydroxypropyl]amino]methyl-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 30 5-[(cyclopentylamino)methyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

- 5-[[2-hydroxyethyl)(methyl)amino]methyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-5-(pyrrolidin-1-yl)methyl]-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 5 5-[[methoxy(methyl)amino]methyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
5-[[cyanomethyl)amino]methyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
5-[[cyclopropylmethyl)amino]methyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 10 5-[(3-hydroxypyrrolidin-1-yl)methyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
5-(2-hydroxyethoxy)-N-[4-(isopropylsulfonyl)benzyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 15 2-methyl-5-([4-(methylsulfonyl)benzyl]amino)carbonyl)-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridin-3-yl acetate;
5-methoxy-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
5-(3-methoxypropoxy)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 20 2-methyl-5-([4-(methylsulfonyl)benzyl]amino)carbonyl)-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridin-3-yl methanesulfonate;
5-ethoxy-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 25 5-(2-hydroxyethoxy)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
5-(cyanomethoxy)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 30 2-([2-methyl-5-([4-(methylsulfonyl)benzyl]amino)carbonyl)-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridin-3-yl)oxyethyl acetate;
5-[2-(dimethylamino)-2-oxoethoxy]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

- 5-(2-aminoethoxy)-*N*-[4-(isopropylsulfonyl)benzyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 5-(acetyl-amino)-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 5 *N*-[4-(isopropylsulfonyl)benzyl]-6-methyl-5-[3-(methylamino)propoxy]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 5-(1-methoxyethyl)-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 5-(2-bromo-1-methoxyethyl)-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 10 5-(1-isopropoxyethyl)-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 5-(*N*¹-isobutyryl-hydrazinocarbonyl)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide;
- 15 *N*⁵-methoxy-6-methyl-*N*³-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- N*⁵-methoxy-*N*⁵,6-dimethyl-*N*³-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- 5-[(2,5-dimethyl-2,5-dihydro-1H-pyrrol-1-yl)carbonyl]-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-
- 20 carboxamide;
- 6-methyl-*N*³-[4-(methylsulfonyl)benzyl]-2-oxo-*N*⁵-pyrrolidin-1-yl-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- 6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-5-(piperidin-1-ylcarbonyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 25 6-methyl-*N*³-[4-(methylsulfonyl)benzyl]-*N*⁵-morpholin-4-yl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- 6-methyl-5-[(4-methylpiperidin-1-yl)carbonyl]-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 30 6-methyl-*N*³-[4-(methylsulfonyl)benzyl]-2-oxo-*N*⁵-piperidin-1-yl-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;

- N*⁵-(tert-butyl)-*N*⁵,6-dimethyl-*N*³-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- N*⁵-butyl-*N*⁵,6-dimethyl-*N*³-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- 5 *N*⁵-ethyl-*N*⁵-isopropyl-6-methyl-*N*³-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- 5-[*N*¹-(formyl-hydrazinocarbonyl)]-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide;
- N*¹-[5-(4-methanesulfonyl-benzylcarbonyl)-2-methyl-6-oxo-1-(3-trifluoromethyl-phenyl)-1,6-dihydro-pyridine-3-carbonyl]-hydrazinecarboxylic acid ethyl ester;
- 10 5-({2-[(ethylamino)carbonothioyl]hydrazino}carbonyl)-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 5-(isoxazolidin-2-ylcarbonyl)-6-methyl-*N*-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;
- 15 6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3,5-dicarboxylic acid 5-(methoxy-methyl-amide) 3-[4-(propane-2-sulfonyl)-benzylamide];
- 6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3,5-dicarboxylic acid 3-(4-ethanesulfonyl-benzylamide) 5-(methoxy-methyl-amide);
- 20 6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3,5-dicarboxylic acid 3-(4-cyclopropanesulfonyl-benzylamide) 5-(methoxy-methyl-amide);
- 6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3,5-dicarboxylic acid 5-[(2-hydroxy-ethyl)-amide] 3-(4-methanesulfonyl-benzylamide);
- 5-(isoxazolidine-2-carbonyl)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-ethanesulfonyl-benzylamide;
- 25 5-(isoxazolidine-2-carbonyl)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydropyridine-3-carboxylic acid 4-cyclopropanesulfonylbenzylamide;
- 5-(*N*-hydroxycarbamimidoyl)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide;
- 30 *N*³-(cyclohexylmethyl)-*N*⁵,*N*⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;

- N*⁵,*N*⁵,6-trimethyl-2-oxo-*N*³-(pyridin-3-ylmethyl)-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- N*⁵,*N*⁵,6-trimethyl-*N*³-(2-morpholin-4-ylethyl)-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- 5 *N*⁵,*N*⁵,6-trimethyl-*N*³-(3-morpholin-4-ylpropyl)-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- N*³-benzyl-*N*⁵,*N*⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydro-pyridine-3,5-dicarboxamide;
- N*³-[2-(1*H*-indol-3-yl)ethyl]-*N*⁵,*N*⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- 10 *N*⁵,*N*⁵,6-trimethyl-2-oxo-*N*³-(1-phenylethyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- N*⁵,*N*⁵,6-trimethyl-2-oxo-*N*³-(2-phenylethyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- 15 *N*⁵,*N*⁵,6-trimethyl-2-oxo-*N*³-[(2*R*)-2-phenylcyclopropyl]-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- N*³-(2,3-dihydro-1*H*-inden-2-yl)-*N*⁵,*N*⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- N*³-[2-(1,3-benzodioxol-5-yl)ethyl]-*N*⁵,*N*⁵,6-trimethyl-2-oxo-1-[3-(trifluoro-
- 20 methyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- 5-{[4-(2-hydroxyethyl)piperazin-1-yl]carbonyl}-*N*,*N*,2-trimethyl-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridine-3-carboxamide;
- N*³-[(1-ethylpyrrolidin-2-yl)methyl]-*N*⁵,*N*⁵,6-trimethyl-2-oxo-1-[3-(trifluoro-
- methyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- 25 *N*⁵,*N*⁵,6-trimethyl-*N*³-[3-(2-methylpiperidin-1-yl)propyl]-2-oxo-1-[3-(trifluoro-
- methyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- N*⁵,*N*⁵,6-trimethyl-*N*³-(1-naphthylmethyl)-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- N*³-(1,3-benzodioxol-5-ylmethyl)-*N*⁵,*N*⁵,6-trimethyl-2-oxo-1-[3-(trifluoro-methyl)phenyl]-
- 30 1,2-dihydropyridine-3,5-dicarboxamide;
- N*³-(3,4-difluorobenzyl)-*N*⁵,*N*⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;

- N^3 -(2-chloro-4-fluorobenzyl)- $N^5,N^5,6$ -trimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- $N^5,N^5,6$ -trimethyl-2-oxo- N^3 -(2-thienylmethyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- 5 N^3 -(3,4-dichlorobenzyl)- $N^5,N^5,6$ -trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- N^3 -[2-(2,4-dichlorophenyl)ethyl]- $N^5,N^5,6$ -trimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- N^3 -(2-cyclohex-1-en-1-ylethyl)- $N^5,N^5,6$ -trimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- 10 N^3 -[1-(4-chlorophenyl)ethyl]- $N^5,N^5,6$ -trimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- $N^5,N^5,6$ -trimethyl-2-oxo- N^3 -[3-(2-oxopyrrolidin-1-yl)propyl]-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- 15 $N^5,N^5,6$ -trimethyl-2-oxo- N^3 -(pyridin-4-ylmethyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- $N,N,2$ -trimethyl-6-oxo-5-[(4-phenylpiperazin-1-yl)carbonyl]-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridine-3-carboxamide;
- $N,N,2$ -trimethyl-6-oxo-5-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridine-3-carboxamide;
- 20 N^3 -(2,3-dihydro-1-benzofuran-5-ylmethyl)- $N^5,N^5,6$ -trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- methyl 4-[[[5-[(dimethylamino)carbonyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridin-3-yl]carbonyl]amino]methyl]benzoate;
- 25 5-{[3-(dimethylamino)pyrrolidin-1-yl]carbonyl}- $N,N,2$ -trimethyl-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridine-3-carboxamide;
- $N^5,N^5,6$ -trimethyl-2-oxo- N^3 -[2-(2-thienyl)ethyl]-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- $N^5,N^5,6$ -trimethyl-2-oxo- N^3 -(4-phenoxybenzyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- 30 $N^5,N^5,6$ -trimethyl-2-oxo- N^3 -(3-thienylmethyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;

- N^3 -[2-(4-*tert*-butylphenyl)ethyl]- $N^5,N^5,6$ -trimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- N^3 -{2-[4-(aminosulfonyl)phenyl]ethyl}- $N^5,N^5,6$ -trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- 5 $N^5,N^5,6$ -trimethyl-2-oxo- N^3 -[4-(1*H*-pyrazol-1-yl)benzyl]-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- $N^5,N^5,6$ -trimethyl-2-oxo- N^3 -phenoxy-1-[3-(trifluoromethyl)phenyl]-1,2-dihydro-pyridine-3,5-dicarboxamide;
- N^3 -(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)- $N^5,N^5,6$ -trimethyl-2-oxo-1-[3-
- 10 (trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- N^3 -[(6-fluoro-4*H*-1,3-benzodioxin-8-yl)methyl]- $N^5,N^5,6$ -trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- N^3 -(1-benzothien-3-ylmethyl)- $N^5,N^5,6$ -trimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- 15 $N^5,N^5,6$ -trimethyl-2-oxo- N^3 -[2-(tetrahydro-2*H*-pyran-4-yl)ethyl]-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- $N^5,N^5,6$ -trimethyl- N^3 -[(1-methyl-1*H*-pyrazol-4-yl)methyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- $N^5,N^5,6$ -trimethyl-2-oxo- N^3 -[(1-phenyl-1*H*-pyrazol-4-yl)methyl]-1-[3-(trifluoro-
- 20 methyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- N^3 -[(5-methoxy-4-oxo-4*H*-pyran-2-yl)methyl]- $N^5,N^5,6$ -trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- N^3 -(3-azepan-1-ylpropyl)- $N^5,N^5,6$ -trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- 25 N^3 -(4-cyanobenzyl)- $N^5,N^5,6$ -trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- $N^5,N^5,6$ -trimethyl-2-oxo- N^3 -[3-(5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl)propyl]-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- N^3 -{[(2*R*)-1-ethylpyrrolidin-2-yl)methyl]- $N^5,N^5,6$ -trimethyl-2-oxo-1-[3-(trifluoro-
- 30 methyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide;
- 5-cyclopropyl-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

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

5-(4,5-dihydro-oxazol-2-yl)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydropyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide;

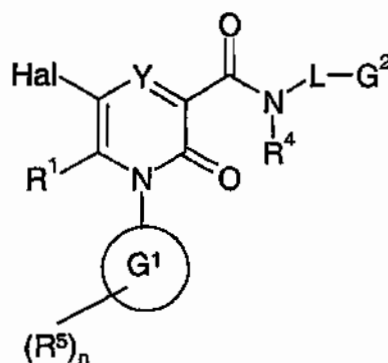
5-cyclopropyl-6-methyl-N-[[5-(methylsulfonyl)pyridin-2-yl]methyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide;

and pharmaceutically acceptable salts thereof.

The present invention includes compounds of formula (I) in the form of salts, in particular acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable although salts of non-pharmaceutically acceptable acids may be of utility in the preparation and purification of the compound in question. Thus, preferred salts include those formed from hydrochloric, hydrobromic, sulphuric, phosphoric, citric, tartaric, lactic, pyruvic, acetic, succinic, fumaric, maleic, methanesulphonic and benzenesulphonic acids.

In a further aspect the invention provides a process for the preparation of a compound of formula (I) which comprises:

a) reacting a compound of formula (II)



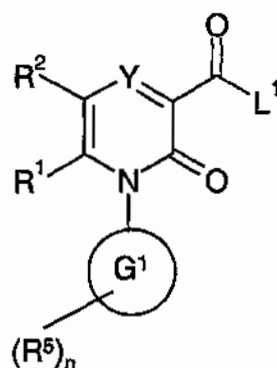
(II)

with a nucleophilic equivalent of R², such as Cu(I)CN, an alkyl vinyl ether, an organo-tin compound, an organo boronic acid, a terminal alkyne or an alcohol and carbon monoxide;

wherein R^1 , R^2 , R^4 , R^5 , Y, G^1 , G^2 , L and n are as defined in formula (I) and Hal represents a halogen atom, preferably bromo or iodo; or

b) reacting a compound of formula (XV)

5

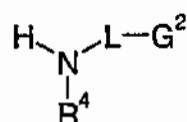


(XV)

wherein R^1 , R^2 , R^5 , n, G^1 and Y are as defined in formula (I) and L^1 represents a leaving group,

with a compound of formula (IX) or a salt thereof

10



(IX)

wherein R^4 , G^2 and L are as defined in formula (I);

15 and where desired or necessary converting the resultant compound of formula (I), or another salt thereof, into a pharmaceutically acceptable salt thereof; or converting one compound of formula (I) into another compound of formula (I); and where desired converting the resultant compound of formula (I) into an optical isomer thereof.

In process (a), the reaction is carried out at a suitable temperature, generally between 50 °C and 150 °C, in a suitable solvent such as toluene or N,N-dimethylformamide in the presence of a transition metal catalyst such as palladium or in the presence of a base such as potassium carbonate.

5

In process (b), the reaction is carried out at a suitable temperature, generally between 0 °C and the boiling point of the solvent, in a suitable solvent such as dichloromethane or N-methylpyrrolidinone. The process is optionally carried out in the presence of a base and/or a coupling reagent such as HATU, HOAT, HOBT or DIEA. Suitable leaving groups L^1 include OH and halogen.

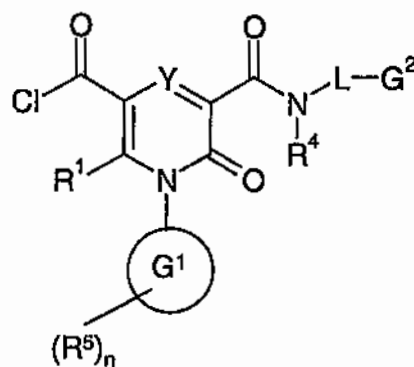
10

The man skilled in the art will readily appreciate that many compounds of formula (I) may also be prepared by processes in which the final step or steps involve functional group interchanges within the substituent R^2 . Some such processes are detailed below. Other specific examples of such processes are described in the Examples section of this specification. All such processes form another aspect of the present invention.

15

Compounds of formula (I) wherein R^2 represents $CONR^{48}R^{49}$ or $CONR^{50}NR^{48}R^{49}$ can be prepared by reacting a compound of formula (III)

20



(III)

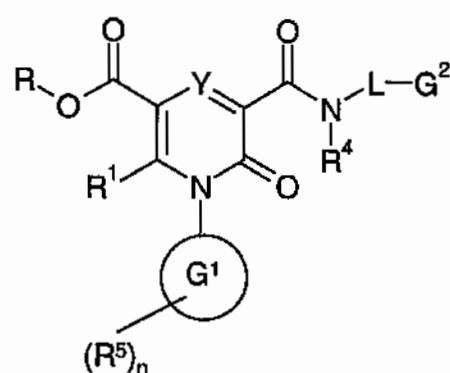
wherein R^1 , R^4 , R^5 , Y , G^1 , G^2 , L and n are as defined in formula (I);

with an amine of the general formula $\text{NHR}^{48}\text{R}^{49}$ or $\text{NHR}^{50}\text{NR}^{48}\text{R}^{49}$.

The process is carried out at a suitable temperature, generally between 0 °C and 50 °C in a suitable solvent such as 1,4-dioxane.

5

Compounds of formula (III) can be prepared by reacting a compound of formula (IV)



(IV)

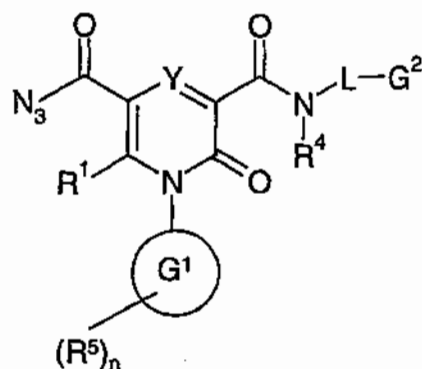
wherein R^1 , R^4 , R^5 , Y , G^1 , G^2 , L and n are as defined in formula (I) and R represents an alkyl group;

10

with an aqueous base such as sodium hydroxide followed by subsequent treatment of the product with a chlorinating agent such as thionyl chloride. The process is carried out at a suitable temperature, generally between 10 °C and 50 °C in a suitable solvent such as tetrahydrofuran or dichloromethane.

15

Compounds of formula (I) wherein R^2 is defined as $\text{NR}^{48}\text{R}^{49}$ can be prepared by reacting a compound of formula (V):



(V)

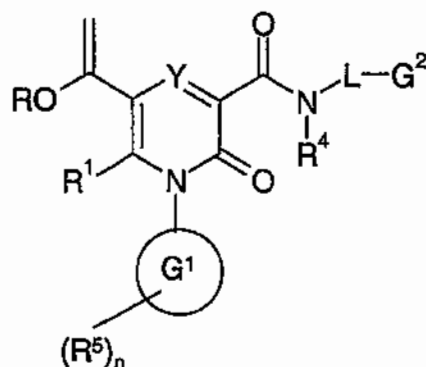
wherein R^1 , R^4 , R^5 , Y , G^1 , G^2 , L and n are as defined in formula (I);

with an aqueous acid or an alkylamine. The process is carried out at a suitable temperature, generally between 50 °C and 150 °C in a suitable solvent such as toluene. The aqueous acid or alkylamine is added after heating for a time period of, typically between 0.5 and 16 hours.

Compounds of formula (V) can be prepared by reacting a compound of formula (IV) wherein R is hydrogen with diphenylphosphoryl azide. The process is carried out at a suitable temperature, generally between 0 °C and 50 °C in a suitable solvent such as dichloromethane.

Compounds of formula (IV) can be prepared by reacting a compound of formula (II) with carbon monoxide in the presence of an alcohol such as methanol or ethanol. The process is carried out at a suitable temperature, generally between 50 °C and 150 °C in a suitable solvent in a suitable solvent such as methanol or ethanol in a carbon monoxide atmosphere at elevated pressure, generally between 2 and 10 atmospheres. The reaction is performed in the presence of a transition metal catalyst such as palladium.

Compounds of formula (I) wherein R^2 is C2 to 6 alkanoyl can be prepared by reacting a compound of formula (VI):



(VI)

wherein R^1 , R^4 , R^5 , Y , G^1 , G^2 , L and n are as defined in formula (I) and R is an alkyl group;
with an aqueous base.

5

The process is carried out at a suitable temperature, generally between 10 °C and 50 °C in a suitable solvent such as *N,N*-dimethylformamide.

Compounds of formula (VI) can be prepared by reacting a compound of formula (II) with
an alkyl vinyl ether. The process is carried out at a suitable temperature, generally between
50 °C and 150 °C in a suitable solvent such as toluene or *N,N*-dimethylformamide in the
presence of a transition metal catalyst such as palladium.

Compounds of formula (I) wherein R^2 is $C(=NOR^{52})R^{53}$ can be prepared by reacting a
compound of formula (I) wherein R^2 is C2 to 6 alkanoyl with an alkoxyamine or
hydroxylamine. The process is carried out at a suitable temperature, generally between 50
°C and 150 °C in a suitable solvent such as or *N,N*-dimethylformamide.

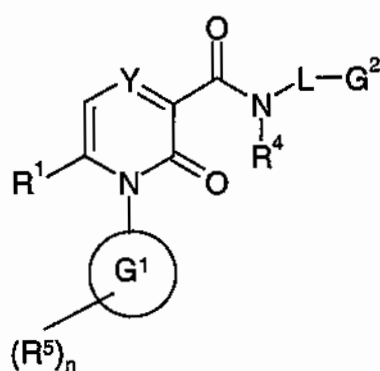
Compounds of formula (I) wherein R^2 is CN can be prepared by reacting a compound of
formula (II) with copper(I) cyanide. The process is carried out at a suitable temperature,
generally between 100 °C and 150 °C in a suitable solvent in a suitable solvent such as 1-
methyl-2-pyrrolidone.

20

Compounds of formula (I) wherein R^2 is NO_2 can be prepared by reacting a compound of formula (VII) with a nitrating agent such as nitric acid. The process is carried out at a suitable temperature, generally between 10 °C and 50 °C in a suitable solvent in a suitable solvent such as acetic anhydride.

5

Compounds of formula (II) can be prepared by reacting a compound of formula (VII)



(VII)

10 wherein R^1 , R^4 , R^5 , Y, G^1 , G^2 , L and n are as defined in formula (I);

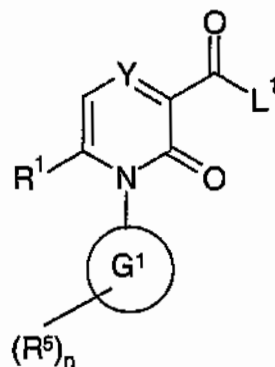
with a halogenating agent, such as N-iodosuccinimide in the presence of a strong acid such as trifluoromethanesulfonic acid.

The process is carried out at a suitable temperature, generally between 0 °C and 50 °C in a suitable solvent such as acetonitrile in the presence of an acid such as trifluoromethanesulfonic acid.

15

Compounds of formula (VII) can be prepared by reacting a compound of formula (VIII)

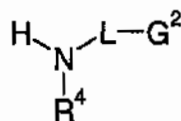
36



(VIII)

wherein R^1 , R^5 , Y , G^1 and n are as defined in formula (I) and L^1 represents a leaving group, with an amine of formula (IX) or a salt thereof

5



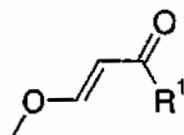
(IX)

wherein R^4 , G^2 and L are as defined in formula (I).

The process is carried out at a suitable temperature, generally between 0 °C and the boiling point of the solvent, in a suitable solvent such as dichloromethane or N-methylpyrrolidinone. The process is optionally carried out in the presence of a base and/or a coupling reagent such as HATU, HOAT, HOBT or DIEA. Suitable leaving groups L^1 include OH and halogen.

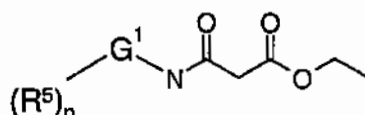
Compounds of formula (VIII) wherein Y is CR^3 , L^1 is OH and R^3 is hydrogen can be prepared by condensing a compound of formula (X)

37



(X)

wherein R^1 is as defined in formula (I), with a compound of formula (XI)



(XI)

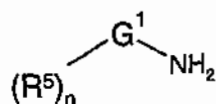
5

wherein G^1 , R^5 and n are as defined in formula (I), in the presence of a suitable base, such as sodium methoxide, in a suitable solvent, such as ethanol, followed by hydrolysis using a suitable base such as sodium hydroxide.

- 10 In general, compounds of formulae (X) and (XI) are either known or may be prepared using methods that will be readily apparent to the man skilled in the art. For example, compounds of formula (X) can be prepared according to the methods of S.M Brombridge et al., *Synthetic Communications*, 1993, 23, 487-494. And compounds of formula (XI) can be prepared according to the methods of Igor V. Ukrainets et al., *Tetrahedron*, 1994, 50,
- 15 10331-10338.

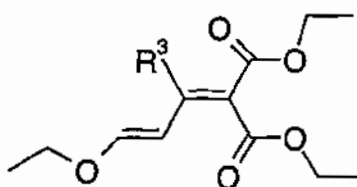
Compounds of formula (VIII) wherein Y is CR^3 , L^1 is OH and R^1 is hydrogen can be prepared by reacting a compound of formula (XII)

38



(XII)

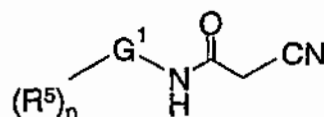
wherein G^1 , R^5 and n are as defined in formula (I), with a compound of formula (XIII)



(XIII)

wherein R^3 is as defined in formula (I), at a suitable temperature, such as 160 °C, followed by base promoted cyclisation and acid hydrolysis. Compounds of formula (XIII) can be prepared according to US 3,838,155.

Compounds of formula (VIII) wherein Y is CR^3 , L^1 is OH , R^1 is methyl and R^3 is hydrogen can be prepared by condensing a compound of formula (XIV)



(XIV)

wherein G^1 , R^5 and n are as defined in formula (I), with 4-methoxy-3-buten-2-one in the presence of a suitable base, such as 1,4-diazabicyclo[2.2.2]octane, at a suitable temperature

in a suitable solvent such as diethyleneglycol monomethyl ether, followed by acid hydrolysis.

Salts of compounds of formula (I) may be formed by reacting the free base or a salt,
5 enantiomer, tautomer or protected derivative thereof, with one or more equivalents of the appropriate acid. The reaction may be carried out in a solvent or medium in which the salt is insoluble, or in a solvent in which the salt is soluble followed by subsequent removal of the solvent *in vacuo* or by freeze drying. Suitable solvents include, for example, water, dioxane, ethanol, 2-propanol, tetrahydrofuran or diethyl ether, or mixtures thereof. The
10 reaction may be a metathetical process or it may be carried out on an ion exchange resin.

Compounds of formula (I) and intermediate compounds thereto may be prepared as such or in protected form. The protection and deprotection of functional groups is, for example, described in 'Protective Groups in Organic Chemistry', edited by J. W. F. McOmie,
15 Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 3rd edition, T. W. Greene & P. G. M. Wuts, Wiley-Interscience (1999).

The compounds of the invention and intermediates may be isolated from their reaction mixtures, and if necessary further purified, by using standard techniques.

20

The compounds of formula (I) may exist in enantiomeric or diastereoisomeric forms or mixtures thereof, all of which are included within the scope of the invention. The various optical isomers may be isolated by separation of a racemic mixture of the compounds using conventional techniques, for example, fractional crystallisation or HPLC. Alternatively, the
25 individual enantiomers may be made by reaction of the appropriate optically active starting materials under reaction conditions that will not cause racemisation.

Intermediate compounds may also exist in enantiomeric forms and may be used as purified enantiomers, diastereomers, racemates or mixtures thereof.

30

According to a further aspect of the invention we provide a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a medicament.

The compounds of formula (I), and their pharmaceutically acceptable salts, are useful because they possess pharmacological activity in animals. The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of human neutrophil elastase and homologous serine proteases such as proteinase 3 and pancreatic elastase, and as such are predicted to be useful in therapy. The compounds of formula (I) are particularly useful as inhibitors of human neutrophil elastase. They may thus be used in the treatment or prophylaxis of inflammatory diseases and conditions.

Examples of these conditions are: adult respiratory distress syndrome (ARDS), cystic fibrosis, pulmonary emphysema, chronic obstructive pulmonary disease (COPD) and ischaemic-reperfusion injury. The compounds of this invention may also be useful in the modulation of endogenous and/or exogenous biological irritants which cause and/or propagate atherosclerosis, diabetes, myocardial infarction; hepatic disorders including but not limited to cirrhosis, systemic lupus erythematosus, inflammatory disease of lymphoid origin, including but not limited to T lymphocytes, B lymphocytes, thymocytes; autoimmune diseases, bone marrow; inflammation of the joint (especially rheumatoid arthritis, osteoarthritis and gout); inflammation of the gastro-intestinal tract (especially inflammatory bowel disease, ulcerative colitis, pancreatitis and gastritis); inflammation of the skin (especially psoriasis, eczema, dermatitis); in tumour metastasis or invasion; in disease associated with uncontrolled degradation of the extracellular matrix such as osteoarthritis; in bone resorptive disease (such as osteoporosis and Paget's disease); diseases associated with aberrant angiogenesis; the enhanced collagen remodelling associated with diabetes, periodontal disease (such as gingivitis), corneal ulceration, ulceration of the skin, post-operative conditions (such as colonic anastomosis) and dermal wound healing; demyelinating diseases of the central and peripheral nervous systems (such as multiple sclerosis); age related illness such as dementia, inflammatory diseases of cardiovascular origins; granulomatous diseases; renal diseases including but not limited to nephritis and polyarteritis; cancer; pulmonary hypertension, ingested poisons, skin contacts, stings, bites; asthma; rhinitis; HIV disease progression; for minimising the effects

of organ rejection in organ transplantation including but not limited to human organs; and replacement therapy of proteinase inhibitors.

Thus, another aspect of the invention provides the use of a compound of formula (I) or a
5 pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of diseases or conditions in which inhibition of neutrophil elastase activity is beneficial; and a method of treating, or reducing the risk of, diseases or conditions in which inhibition of neutrophil elastase activity is beneficial which comprises administering to a person suffering from or at risk of, said disease or condition, a
10 therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the
15 treatment or prophylaxis of inflammatory diseases or conditions; and a method of treating, or reducing the risk of, inflammatory diseases or conditions which comprises administering to a person suffering from or at risk of, said disease or condition, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

20 In particular, the compounds of this invention may be used in the treatment of adult respiratory distress syndrome (ARDS), cystic fibrosis, pulmonary emphysema, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, asthma, rhinitis, ischemia-reperfusion injury, rheumatoid arthritis, osteoarthritis, cancer, atherosclerosis and gastric mucosal injury.

25 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
30 those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

For the above mentioned therapeutic indications, the dose of the compound to be administered will depend on the compound employed, the disease being treated, the mode of administration, the age, weight and sex of the patient. Such factors may be determined
5 by the attending physician. However, in general, satisfactory results are obtained when the compounds are administered to a human at a daily dosage of between 0.1 mg/kg to 100 mg/kg (measured as the active ingredient).

The compounds of formula (I) may be used on their own, or in the form of appropriate
10 pharmaceutical formulations comprising the compound of the invention in combination with a pharmaceutically acceptable diluent, adjuvant or carrier. Particularly preferred are compositions not containing material capable of causing an adverse reaction, for example, an allergic reaction. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Pharmaceuticals - The Science
15 of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988.

According to the invention, there is provided a pharmaceutical formulation comprising preferably less than 95% by weight and more preferably less than 50% by weight of a compound of formula (I) in admixture with a pharmaceutically acceptable diluent or
20 carrier.

We also provide a method of preparation of such pharmaceutical formulations that comprises mixing the ingredients.

25 The compounds may be administered topically, for example, to the lungs and/or the airways, in the form of solutions, suspensions, HFA aerosols or dry powder formulations, for example, formulations in the inhaler device known as the Turbuhaler®; or systemically, for example, by oral administration in the form of tablets, pills, capsules, syrups, powders or granules; or by parenteral administration, for example, in the form of sterile parenteral

solutions or suspensions; or by rectal administration, for example, in the form of suppositories.

Dry powder formulations and pressurized HFA aerosols of the compounds of the invention
5 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 C_8 - C_{20} fatty acid or salt thereof, (for example, oleic acid), a bile salt, a phospholipid, an alkyl saccharide, a perfluorinated or polyethoxylated surfactant, or other
10 pharmaceutically acceptable dispersant.

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.

15

One possibility is to mix the finely divided compound with a carrier substance, for example, a mono-, di- or polysaccharide, a sugar alcohol, or an other 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
20 coated by another substance. The powder mixture may also be dispensed into hard gelatine capsules, each containing the desired dose of the active compound.

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
25 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 compound, with or without a carrier substance, is delivered to the patient.

For oral administration the active compound may be admixed with an adjuvant or a carrier,
30 for example, lactose, saccharose, sorbitol, mannitol; a starch, for example, potato starch,

corn 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
5 coated with a concentrated sugar solution which may contain, for example, gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the tablet may be coated with a suitable polymer dissolved in a readily volatile organic solvent.

For the preparation of soft gelatine capsules, the compound may be admixed with, for
10 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 drug may be filled into hard gelatine capsules.

Liquid preparations for oral application may be in the form of syrups or suspensions, for
15 example, solutions containing the compound, 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.

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

The following Examples are intended to illustrate, but in no way limit the scope of the invention.

General Methods

¹H NMR and ¹³C 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
30 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.

5 The following abbreviations are used:

HBTU O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate;

HATU O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate;

HOBT 1-Hydroxybenzotriazole;

HOAT 1-Hydroxy-7-azabenzotriazole;

10 DIEA N,N-Diisopropylethylamine;

NMP 1-N-Methyl-2-pyrrolidinone;

DME 1,2-Dimethoxyethane;

THF Tetrahydrofuran;

TFA Trifluoroacetic acid;

15 DMF N,N-Dimethylformamide;

DCM Dichloromethane.

The following method was used for LC/MS analysis:

Instrument Agilent 1100; Column Waters Symmetry 2.1 x 30 mm; Mass APCI; Flow rate
20 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.

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
25 from 5% to 95% acetonitrile over 8 minutes at a flow of 0.7 ml/min.

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

30 a) Ethyl 3-oxo-3-{[3-(trifluoromethyl)phenyl]amino}propanoate

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 (approx. 30 minutes) stirring was continued at room temperature 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 the title compound as yellow powder (109 g, 99%).

$^1\text{H NMR}$ (CDCl_3): 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 $[\text{MH}^+]$.

10

b) 6-Methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxylic acid

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 2 h and then cooled. Water (50 ml) and 2M NaOH were added and the mixture was stirred at room temperature 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 3-4, an orange coloured precipitate appeared and was filtered off, washed with water and dried. Recrystallisation twice from heptane/EtOAc (4:1) afforded the title compound (12 g, 58%) as a white powder.

20

$^1\text{H NMR}$ (CDCl_3): 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 $[\text{MH}^+]$.

25

c) 6-Methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

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 1 h, then

4-methylsulphonylbenzyl amine hydrochloride (5.8 g, 26 mmol) was added. After 1 h, 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 citric acid (0.5 M), and stirring was continued for 1h. The precipitate was filtered off, washed with water and dried in vacuum overnight.

5 Recrystallisation from EtOAc gave 8.1 g (70%).

¹H NMR (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⁺].

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

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 room temperature 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 (200 mg).

¹H NMR (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).

20 APCI-MS m/z: 591.0 [MH⁺].

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

A mixture of 5-iodo-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (120 mg, 0.20 mmol) and copper (I) cyanide (66.7 mg, 0.74 mmol) in NMP (2.5 ml) was stirred overnight at 140 °C. The reaction mixture was cooled and partitioned between ethyl acetate and water. The organic layer was dried over sodium sulphate, filtered and concentrated in vacuo. The residue was first purified by preparative HPLC and then by flash chromatography eluting with DCM/methanol (10:0.2) to give the title compound as a white solid (24 mg, 24 %).

^1H NMR (DMSO- d_6): δ 9.55 (1H, t, J 6.1 Hz); 8.49 (1H, s); 7.96 (1H, s); 7.93 (1H, d, J 7.8 Hz); 7.88 - 7.81 (3H, m); 7.77 (1H, d, J 8.0 Hz); 7.52 (2H, d, J 8.4 Hz); 4.56 (2H, d, J 6.2 Hz); 3.16 (3H, s); 2.22 (3H, s).

APCI-MS m/z : 490 [MH^+].

5

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

To a solution of 6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (52 mg, 0.11 mmol) in acetic anhydride (2 ml) was added fuming nitric acid (0.1 ml, 2.1 mmol). The reaction mixture was stirred at room temperature for 40 min. The mixture was partitioned between ethyl acetate and aqueous sodium hydrogen carbonate. The organic layer was washed with water, dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by preparative HPLC to give the title compound as a yellow powder (13 mg, 23%).

15

^1H NMR (CDCl_3): δ 9.47 (1H, t, J 5.6 Hz); 9.31 (1H, s); 7.92 - 7.86 (3H, m); 7.81 (1H, t, J 7.9 Hz); 7.54 - 7.48 (3H, m); 7.44 (1H, d, J 7.9 Hz); 4.69 (2H, dd, J 5.9, 3.9 Hz); 3.03 (3H, s); 2.52 (3H, s).

APCI-MS m/z : 510 [MH^+].

20

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

In a Schlenk vessel equipped with a magnetic stirring bar were placed 5-iodo-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (101.5 mg, 0.17 mmol), bis[1,2-bis(diphenylphosphino)ethane]-palladium (0) (16.5 mg, 18.3 μmol), n-butyl vinyl ether (60 μl , 0.46 mmol), triethylamine (0.5 ml, 3.6 mmol) and DMF (6 ml). The vessel was purged with argon, sealed and heated at 100 $^\circ\text{C}$ overnight. The reaction mixture was cooled and partitioned between ethyl acetate and water. The organic layer was dried over sodium sulphate, filtered and concentrated in

25

vacuo. The residue was purified by preparative HPLC to give the title compound as a white solid (27.3 mg, 28 %).

¹H NMR (CDCl₃): δ 9.96 (1H, t, J 5.8 Hz); 8.64 (1H, s); 7.89 (2H, d, J 8.3 Hz); 7.82 (1H, d, J 8.0 Hz); 7.75 (1H, t, J 7.9 Hz); 7.56 - 7.50 (3H, m); 7.46 (1H, d, J 7.8 Hz); 4.69 (2H, ddd, J 22.1, 15.7, 6.2 Hz); 4.43 (1H, d, J 2.6 Hz); 4.26 (1H, d, J 2.6 Hz); 3.83 (2H, t, J 6.5 Hz); 3.03 (3H, s); 2.11 (3H, s); 1.74 (2H, quintet, J 9.2 Hz); 1.46 (2H, sextet, J 9.1 Hz); 0.98 (3H, t, J 7.4 Hz).

APCI-MS m/z: 563 [MH⁺].

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

To a solution of 5-(1-butoxyvinyl)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (38 mg, 67.5 μmol) in DMF (0.5 ml) was added aqueous hydrochloric acid (2.0M, 50 μl). After 20 min. the solution was neutralized with aqueous sodium hydrogen carbonate. The reaction mixture was purified by preparative HPLC to give the title compound as a white solid (17.6 mg, 51%).

¹H NMR (CDCl₃): δ 9.75 (1H, t, J 5.7 Hz); 9.08 (1H, s); 7.90 (2H, d, J 8.3 Hz); 7.85 (1H, d, J 7.9 Hz); 7.78 (1H, t, J 7.9 Hz); 7.54 (2H, d, J 8.3 Hz); 7.50 (1H, s); 7.42 (1H, d, J 8.0 Hz); 4.70 (2H, t, J 6.0 Hz); 3.03 (3H, s); 2.66 (3H, s); 2.43 (3H, s).

APCI-MS m/z: 507 [MH⁺].

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

25 A mixture of 5-acetyl-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (47.2 mg, 0.09 mmol), methoxylamine hydrochloride (22.9 mg, 0.27 mmol), potassium carbonate (36 mg, 0.26 mmol) and DMF (1 ml) was heated at 100 °C for 1 h. After cooling the reaction mixture was neutralized with aqueous 2.0M hydrochloric acid and purified by preparative HPLC to give the title compound as a white solid (9 mg, 18 %).

¹H NMR (CDCl₃): δ 9.91 (1H, t, J 6.0 Hz); 8.58 (1H, s); 7.88 (2H, d, J 8.3 Hz); 7.82 (1H, d, J 8.3 Hz); 7.75 (1H, t, J 7.9 Hz); 7.54 - 7.49 (3H, m); 7.44 (1H, d, J 7.8 Hz); 4.67 (2H, t, J 5.9 Hz); 3.96 (3H, s); 3.02 (3H, s); 2.20 (3H, s); 2.14 (3H, s).

APCI-MS m/z: 536 [MH⁺].

5

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

A mixture of 5-acetyl-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-

(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (34.7 mg, 68.5 μmol),

10 hydroxylamine hydrochloride (30.3 mg, 0.44 mmol), triethylamine (0.5 ml, 3.6 mmol), tetrahydrofuran (1 ml) and methanol (0.5 ml) was heated at 70 °C for 48 h. The reaction mixture was cooled and concentrated in vacuo. The residue was purified by preparative HPLC to give the title compound as a white solid (8 mg, 22 %).

¹H NMR (CDCl₃): δ 9.92 (1H, t, J 5.6 Hz); 8.59 (1H, s); 7.88 (2H, d, J 8.1 Hz); 7.82 (1H, d, J 7.7 Hz); 7.75 (1H, t, J 7.8 Hz); 7.52 (4H, d, J 4.2 Hz); 7.44 (1H, d, J 7.5 Hz); 4.68 (2H, ddd, J 21.2, 15.3, 6.0 Hz); 3.02 (3H, s); 2.25 (3H, s); 2.12 (3H, s).

APCI-MS m/z: 522 [MH⁺].

Example 7 6-Methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-5-(pyridin-3-ylethynyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

20 A mixture of 5-iodo-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (86.7 mg, 0.15 mmol), copper(I) iodide (3.1 mg, 0.016 mmol), 1,10-phenanthroline monohydrate (5.9 mg, 0.03 mmol), triphenylphosphine (13.8 mg, 0.05 mmol), cesium carbonate (70 mg, 0.22 mmol) tris(dibenzylideneacetone)dipalladium(0) (10 mg, 0.01 mmol),

25 3-(trimethylsilylethynyl)pyridine (38.1 mg, 0.22 mmol) in toluene (15 ml) was heated at 100 °C under argon for 48 h. The reaction mixture was cooled and partitioned between ethyl acetate and water. The organic layer was dried over sodium sulphate, filtered and concentrated in vacuo. The residue was first purified by preparative HPLC on a kromasil

column and then by flash chromatography eluting with DCM/methanol (10:0.25) to give the title compound as a white solid (29.7 mg, 36 %).

^1H NMR (CDCl_3): δ 9.81 (1H, t, J 5.5 Hz); 8.76 (2H, d, J 11.3 Hz); 8.60 (1H, d, J 4.7 Hz); 7.94 - 7.83 (3H, m); 7.83 - 7.75 (2H, m); 7.57 - 7.50 (3H, m); 7.47 (1H, d, J 7.7 Hz); 7.33 (1H, dd, J 7.7, 5.0 Hz); 4.70 (2H, t, J 5.4 Hz); 3.03 (3H, s); 2.35 (3H, s).

APCI-MS m/z : 566 [MH^+].

Example 8 6-Methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-5-(2-pyridin-3-ylethynyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

A suspension of 6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-5-(pyridin-3-ylethynyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (20 mg, 0.035 mmol), 5% palladium on carbon (10 mg) in ethanol (5 ml) and ethyl acetate (5 ml) was stirred vigorously under a hydrogen atmosphere for 48 h. The mixture was filtered through Celite, the filtrate was evaporated to dryness and the residue was purified by preparative HPLC to give the title compound as a white solid (11 mg, 55%).

^1H NMR ($\text{DMSO}-d_6$): δ 9.96 (1H, t, J 6.2 Hz); 8.45 (1H, d, J 1.8 Hz); 8.40 (1H, dd, J 4.8, 1.5 Hz); 8.29 (1H, s); 7.91 - 7.75 (5H, m); 7.72 - 7.60 (2H, m); 7.52 (2H, d, J 8.3 Hz); 7.34 - 7.27 (1H, m); 4.56 (2H, d, J 6.0 Hz); 3.16 (3H, s); 2.88 (4H, s); 1.87 (3H, s).

APCI-MS m/z : 570 [MH^+].

Example 9 6-Methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-5-vinyl-1,2-dihydropyridine-3-carboxamide

A mixture of 5-iodo-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (53 mg, 0.09 mmol), tributyl(vinyl)tin (51 mg, 0.16 mmol), tetrakis(triphenylphosphine)palladium(0) (6.9 mg, 0.006 mmol) in toluene (10 ml) was heated at 100 °C under argon for 12 h. After cooling, the solvent was removed in vacuo and the residue was purified by preparative HPLC to give the title compound as a white solid (18 mg, 41%).

^1H NMR (CDCl_3): δ 9.98 (1H, t, J 5.9 Hz); 8.85 (1H, s); 7.87 (2H, dt, J 8.5, 1.9 Hz); 7.83 - 7.69 (2H, m); 7.54 - 7.47 (3H, m); 7.42 (1H, d, J 7.7 Hz); 6.69 (1H, dd, J 17.2, 11.0 Hz);

5.73 (1H, d, J 17.2 Hz); 5.40 (1H, d, J 11.2 Hz); 4.67 (2H, dd, J 5.9, 3.7 Hz); 3.01 (3H, s); 2.10 (3H, s).

APCI-MS m/z: 491 [MH⁺].

5 **Example 10** Ethyl 2-methyl-5-([4-(methylsulfonyl)benzyl]amino)carbonyl]-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridine-3-carboxylate

In a stainless-steel autoclave (100 ml) were placed 5-iodo-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (108.1 mg, 0.18 mmol), palladium(II) acetate (3.8 mg, 0.02 mmol),
10 triphenylphosphine (10.3 mg, 0.04 mmol), triethylamine (2 ml, 14.4 mmol) and ethanol (6 ml). The reaction mixture was magnetically stirred at 100 °C under a carbon monoxide pressure of 4 atmospheres overnight. After cooling, the solvent was evaporated off and the residue was purified by preparative HPLC to give the title compound as a white solid (77.6 mg, 79 %).

15 ¹H NMR (CDCl₃): δ 9.73 (1H, t, J 5.9 Hz); 9.20 (1H, s); 7.90 (2H, d, J 8.3 Hz); 7.85 (1H, d, J 7.9 Hz); 7.78 (1H, t, J 7.8 Hz); 7.53 (2H, d, J 8.3 Hz); 7.50 (1H, s); 7.42 (1H, d, J 8.0 Hz); 4.69 (2H, t, J 5.9 Hz); 4.38 (2H, q, J 7.2 Hz); 3.03 (3H, s); 2.50 (3H, s); 1.42 (3H, t, J 7.2 Hz).

APCI-MS m/z: 537 [MH⁺].

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Example 11 5-(4-Methanesulfonyl-benzylcarbamoyl)-2-methyl-6-oxo-1-(3-trifluoromethyl-phenyl)-1,6-dihydro-pyridine-3-carboxylic acid

To a solution of ethyl 2-methyl-5-([4-(methylsulfonyl)benzyl]amino)carbonyl]-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridine-3-carboxylate (0.70 g, 1.30 mmol) in THF
25 (10 ml) and water (10 ml) was added 1M NaOH (2 ml, 2 mmol), and the mixture was stirred for 1 h at room temperature, monitoring the progress of the reaction by LC-MS. 20% conversion was observed, and another portion of 1M NaOH (1 ml, 1 mmol) was added, and the reaction was allowed to run for another 1 h. This procedure was repeated until complete conversion of the ester was observed (normally 3-4 hours). The outcome of
30 the reaction is two compounds with the same mass, in a 95:5 proportion. The main product

is the subtitle compound, and the other is a regioisomer. The reaction mixture was evaporated to remove THF, and the residual water solution was acidified and extracted with EtOAc. The organic phase was collected and dried over Na₂SO₄. Filtration and evaporation gave a crude product 0.60 g (90%) as a yellowish solid, which can be used further without purification. A portion was purified by preparative HPLC, ¹H NMR (CDCl₃): δ 9.90 (1H, t, J 6.2 Hz); 9.31 (1H, s); 7.9 (2H, d, J 8.2 Hz); 7.84 (1H, d, J 8.0 Hz); 7.77 (1H, t, J 8.0 Hz); 7.51 (2H, d, J 8.5 Hz); 4.5 (1H, s); 7.41 (1H, d, J 8.0 Hz); 4.92 (1H, bs); 4.78-4.63 (2H, m); 3.01 (3H, s); 2.53 (3H, s). APCI-MS m/z: 509.2 [MH⁺].

10

Example 12 6-Methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3,5-dicarboxylic acid 5-dimethylamide 3-(4-methanesulfonyl-benzylamide)

To 5-(4-methanesulfonyl-benzylcarbamoyl)-2-methyl-6-oxo-1-(3-trifluoromethyl-phenyl)-1,6-dihydro-pyridine-3-carboxylic acid in CH₂Cl₂ (5 ml), SOCl₂ (3 ml) was added, and the flask was sealed and stirred magnetically for 2 h. The crude mixture was evaporated in vacuo giving the intermediate acid chloride as a yellow solid. The solid was dissolved in 1,4-dioxan (5 ml, dried over molecular sieves) and dimethylamine (40% aqueous solution, 0.5 ml) was added quickly. The mixture was stirred for 5 minutes, and LC-MS showed complete formation of the title compound. The mixture was concentrated in vacuo and the residue was purified by preparative HPLC, giving 0.008 g (76%) of the title compound as a white solid after freeze-drying the pure fractions.

¹H NMR (CDCl₃): δ 9.86 (1H, t, J 5.9 Hz); 8.73 (1H, s); 7.89 (2H, d, J 8.3 Hz); 7.84 (1H, d, J 7.8 Hz); 7.77 (1H, t, J 7.8 Hz); 7.52 (2H, d, J 8.4 Hz); 7.51 (1H, s); 7.43 (1H, d, J 7.9 Hz); 6.16 (1H, bs); 4.75-4.63 (2H, m); 3.03 (3H, s); 3.02 (3H, d, J 4.3 Hz); 2.33 (3H, s). APCI-MS m/z: 536.2 [MH⁺].

25

Using the general method of Example 12, the compounds of Examples 13 to 20 and 22 to 25 were prepared.

Example 13 6-Methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3,5-dicarboxylic acid 5-amide 3-(4-methanesulfonyl-benzylamide)

¹H NMR (CDCl₃): δ 9.82 (1H, t, J 5.9 Hz); 8.80 (1H, s); 7.78 (2H, d, J 8.8 Hz); 7.84 (1H, d, J 8.1 Hz); 7.76 (1H, t, J 7.9 Hz); 7.51 (2H, d, J 8.9 Hz); 7.50 (1H, s); 7.42 (1H, d, J 7.8 Hz); 6.15 (1H, bs); 5.75 (1H, bs); 4.73-4.61 (2H, m); 3.02 (3H, s); 2.36 (3H, s).
APCI-MS m/z: 508.2 [MH⁺].

Example 14 6-Methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3,5-dicarboxylic acid 3-(4-methanesulfonyl-benzylamide) 5-methylamide

¹H NMR (CDCl₃): δ 9.90 (1H, t, J 5.9 Hz); 8.54 (1H, s); 7.90 (2H, d, J 8.1 Hz); 7.84 (1H, d, J 7.9 Hz); 7.77 (1H, t, J 7.8 Hz); 7.53 (1H, s); 7.52 (2H, d, J 8.3 Hz); 7.45 (1H, d, J 7.9 Hz); 4.74-4.62 (2H, m); 3.15 (3H, s); 3.07 (3H, s); 3.02 (3H, s); 2.11 (3H, s).
APCI-MS m/z: 522.3 [MH⁺].

Example 15 6-Methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3,5-dicarboxylic acid 5-[(2-hydroxy-ethyl)-methyl-amide] 3-(4-methanesulfonyl-benzylamide)
APCI-MS m/z: 566.2 [MH⁺]. Retention time 1.82 minutes.

Example 16 6-Methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3,5-dicarboxylic acid 3-(4-methanesulfonyl-benzylamide) 5-(methyl-propyl-amide)

¹H NMR (CDCl₃): δ 9.94-9.84 (1H, m); 8.50 (1H, s); 7.88 (2H, d, J 8.6 Hz); 7.83 (1H, d, J 7.9 Hz); 7.76 (1H, t, J 7.9 Hz); 7.52 (1H, s); 7.52 (2H, d, J 8.1 Hz); 7.44 (1H, d, J 7.9 Hz); 4.74-4.62 (2H, m); 3.52 (1.1H, t, J 7.5 Hz, part of rotameric system, rotamer 1); 3.29 (0.9H, t, J 7.5 Hz, part of rotameric system, rotamer 2); 3.10 (1.4H, s, part of rotameric system, rotamer 2); 3.02 (1.6H, s, part of rotameric system, rotamer 1); 3.02 (3H, s); 2.08 (3H, s); 1.75-1.60 (2H, m); 0.99 (1.6H, t, J 7.5 Hz, part of rotameric system, rotamer 1); 0.88 (1.4H, t, J 7.5 Hz, part of rotameric system, rotamer 2).
APCI-MS m/z: 564.3 [MH⁺].

Example 17 6-Methyl-2-oxo-5-(pyrrolidine-1-carbonyl)-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3,5-dicarboxylic acid 3-(4-methanesulfonyl-benzylamide)

¹H NMR (CDCl₃): δ 9.87 (1H, t, J 6.0 Hz); 8.59 (1H, s); 7.88 (2H, d, J 8.2 Hz); 7.82 (1H, d, J 7.9 Hz); 7.75 (1H, t, J 7.9 Hz); 7.54-7.48 (3H, m); 7.44 (1H, d, J 7.6 Hz); 4.73-4.61 (2H, m); 3.66 (2H, t, J 6.7 Hz); 3.46-3.39 (2H, m); 3.02 (3H, s); 2.14 (3H, m); 2.06-1.95 (4H, m).

APCI-MS m/z: 562.5 [MH⁺].

Example 18 6-Methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3,5-dicarboxylic acid 5-[(2-dimethylamino-ethyl)-methyl-amide] 3-(4-methanesulfonyl-benzylamide) trifluoroacetic acid salt

¹H NMR (DMSO-d₆): δ 9.88 (1H, t, J 6.1 Hz); 9.40 (1H, bs); 8.43 (1H, s); 8.00 (1H, s); 7.90 (1H, d, J 7.7 Hz); 7.87 (2H, d, J 8.2 Hz); 7.83-7.76 (2H, m); 7.53 (2H, d, J 8.2 Hz); 4.58 (2H, d, J 5.9 Hz); 4.05-3.70 (2H, m); 3.43-3.31 (2H, m); 3.16 (3H, s); 2.96 (3H, s); 2.89 (3H, s); 2.88 (3H, s); 1.92 (3H, s).

APCI-MS m/z: 593.3 [MH⁺].

Example 19 5-((2R)-2-Hydroxymethyl-pyrrolidine-1-carbonyl)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 3-(4-methanesulfonyl-benzylamide)

¹H NMR (CDCl₃): δ 9.88 (1H, t, J 6.1 Hz); 8.59 (1H, d, J 3.3 Hz); 7.89 (2H, d, J 8.8 Hz); 7.84 (1H, d, J 7.7 Hz); 7.77 (1H, t, J 7.7 Hz); 7.51 (2H, d, J 8.6 Hz); 7.51 (1H, s); 7.44 (1H, d, J 7.8 Hz); 4.70-4.65 (2H, m); 4.44-4.35 (1H, m); 3.91-3.84 (1H, m); 3.74 (1H, p, J 5.7 Hz); 3.55-3.44 (2H, m); 3.02 (3H, s); 2.27-2.17 (1H, m); 2.15 (3H, s); 2.12-1.83 (3H, m); 1.82-1.71 (1H, m).

APCI-MS m/z: 592.4 [MH⁺].

Example 20 5-(3-Hydroxy-pyrrolidine-1-carbonyl)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3,5-dicarboxylic acid 3-(4-methanesulfonyl-benzylamide)

¹H NMR (CDCl₃): δ 9.96-9.89 (1H, m); 8.63-8.56 (1H, m); 7.88 (2H, d, J 8.5 Hz); 7.83 (1H, d, J 8.0 Hz); 7.76 (1H, t, J 7.6 Hz); 7.52 (1H, s); 7.51 (2H, d, J 8.0 Hz); 7.44 (1H, d, J 7.6 Hz); 4.67 (2H, d, J 5.7 Hz); 4.65-4.53 (1H, m); 3.92-3.38 (4H, m); 3.02 (3H, s); 2.19-2.01 (2H, m); 2.14 (3H, s).

5 APCI-MS m/z: 578.3 [MH⁺]. Retention time 1.95 minutes.

Example 21 N³-[(1,1-Dioxido-2,3-dihydro-1-benzothien-5-yl)methyl]-N⁵,N⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

In a stainless-steel autoclave (100 ml) were placed N-[(1,1-dioxido-2,3-dihydro-1-benzothien-5-yl)methyl]-5-iodo-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (66.3 mg, 0.11 mmol), palladium(II)acetate (14.0 mg, 62.4 μmol), triphenylphosphine (25.1 mg, 95.7 μmol), dimethylamine (1.2 g, 27.8 mmol) and ethanol (10 ml). The reaction vessel was cooled to -50 °C, degassed by vacuum/carbon monoxide combined treatment, pressurized at 4 atmospheres with carbon monoxide, and then heated at 100 °C for 6 h. After cooling, the solution was evaporated and the residue was purified by preparative HPLC to give the title compound as a white solid (11 mg, 18%).

¹H NMR (CDCl₃): δ 9.85 (1H, t, J 5.9 Hz); 8.53 (1H, s); 7.84 (1H, d, J 7.7 Hz); 7.77 (1H, t, J 7.9 Hz); 7.68 (1H, d, J 8.0 Hz); 7.52 (1H, s); 7.44 (2H, t, J 8.6 Hz); 7.35 (1H, s); 4.65 (2H, dd, J 5.8, 4.1 Hz); 3.49 (2H, t, J 6.8 Hz); 3.36 (2H, t, J 6.9 Hz); 3.15 (3H, s); 3.07 (3H, s); 2.11 (3H, s).

APCI-MS m/z: 548 [MH⁺].

Example 22 5-(N¹-Acetyl-hydrazinocarbonyl)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide

¹H NMR (DMSO-d₆): δ 10.26 (1H, s); 9.95 (1H, s); 9.79 (1H, t, J 6.0 Hz); 8.50 (1H, s); 7.93 (1H, s); 7.93-7.90 (1H, m); 7.87 (2H, d, J 8.4 Hz); 7.82 (1H, d, J 7.7 Hz); 7.74 (1H, d, J 8.0 Hz); 7.55 (2H, d, J 8.3 Hz); 4.59 (2H, d, J 6.2 Hz); 3.17 (3H, s); 2.18 (3H, s); 1.91 (3H, s).

30 APCI-MS m/z: 565.2 [MH⁺].

Example 23 5-[N¹-(2-Cyano-acetyl)-hydrazinocarbonyl]-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide

¹H NMR (DMSO-d₆): δ 10.55 (1H, s); 10.42 (1H, s); 9.78 (1H, t, J 6.2 Hz); 8.51 (1H, s); 7.94 (1H, s); 7.92 (1H, d, J 8.2 Hz); 7.87 (2H, d, J 8.2 Hz); 7.82 (1H, d, J 7.6 Hz); 7.75 (1H, d, J 7.6 Hz); 7.55 (2H, d, J 8.2 Hz); 4.59 (2H, d, J 6.0 Hz); 3.82 (2H, s); 3.17 (3H, s); 2.18 (3H, s).

APCI-MS m/z: 590.1 [MH⁺].

Example 24 5-[[2-(Aminocarbonothioyl)hydrazino]carbonyl]-6-methyl-N-[4-(methylsulfonyl) benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

¹H NMR (DMSO-d₆): δ 10.31 (1H, s); 9.80 (1H, t, J 6.2 Hz); 9.32 (1H, s); 8.70 (1H, s); 7.92 (1H, d, J 7.8 Hz); 7.91 (1H, bs); 7.90 (1H, bs); 7.86 (2H, d, J 8.3 Hz); 7.83 (1H, d, J 8.3); 7.76 (1H, bs); 7.70 (1H, d, J 7.6 Hz); 7.54 (2H, d, J 8.1 Hz); 4.59 (2H, d, J 6.0 Hz); 3.17 (3H, s); 2.14 (3H, s).

APCI-MS m/z: 582.1 [MH⁺].

Example 25 5-Hydrazinocarbonyl-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide

APCI-MS m/z: 523.2 [MH⁺]. Retention time 1.72 minutes.

Example 26 5-([2-[(Ethylamino)carbonyl]hydrazino]carbonyl)-6-methyl-N-[4-(methylsulfonyl) benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

To 5-hydrazinocarbonyl-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide (0.030 g, 0.057 mmol) in

1,4-dioxan (10 ml) was added ethylisocyanate (0.016 g, 0.23 mmol), and the mixture was stirred at room temperature for 1 h. The mixture was evaporated and the residue was purified on preparative HPLC giving 0.015 g (44%) of the title compound.

¹H NMR (CDCl₃): δ 9.96-9.87 (1H, m); 8.82 (1H, s); 7.88 (1H, d, J 8.2 Hz); 7.84 (2H, d, J 7.9 Hz); 7.83-7.80 (1H, m); 7.77 (1H, t, J 7.9 Hz); 7.52 (1H, s); 7.47 (2H, d, J 8.2 Hz); 7.47-7.41 (1H, m); 4.70-4.55 (2H, m); 3.23 (2H, q, J 6.9 Hz); 3.01 (3H, s); 2.31 (3H, s); 1.11 (3H, t, J 7.1 Hz).

APCI-MS m/z: 594.2 [MH⁺].

Example 27 5-({2-[N,N-Dimethylamino]carbonyl}hydrazino)carbonyl)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

To 5-hydrazinocarbonyl-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydropyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide (0.030 g, 0.057 mmol) in THF (10 ml) was added N,N-dimethylcarbonyl chloride (0.0247 g, 0.23 mmol), and the mixture was stirred at 50 °C for 3 h. The mixture was evaporated and the residue was purified on preparative HPLC giving 0.020 g (60%) of the title compound.

¹H NMR (DMSO-d₆): δ 9.92 (1H, bs); 9.80 (1H, t, J 6.2 Hz); 8.50 (1H, s); 8.48 (1H, s); 7.94-7.89 (2H, m); 7.87 (2H, d, J 8.5 Hz); 7.82 (1H, d, J 8.2 Hz); 7.73 (1H, d, J 7.8 Hz); 7.55 (2H, d, J 8.5 Hz); 4.59 (2H, d, J 6.0 Hz); 3.17 (3H, s); 2.85 (6H, s); 2.19 (3H, s).

APCI-MS m/z: 594.1 [MH⁺].

Example 28 5-(3,3-Dimethyl-ureido)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide

a) 5-(4-Methanesulfonyl-benzylcarbonyl)-2-methyl-6-oxo-1-(3-trifluoromethyl-phenyl)-1,6-dihydro-pyridine-3-carboxylic acid

To 5-(4-methanesulfonyl-benzylcarbonyl)-2-methyl-6-oxo-1-(3-trifluoromethyl-phenyl)-1,6-dihydro-pyridine-3-carboxylic acid (0.055 g, 0.108 mmol) in CH₂Cl₂ (10 ml),

triethylamine (0.020 g, 0.2 mmol) and diphenylphosphoryl azide (0.055 g, 0.2 mmol) were

added, the flask was sealed, and the contents were stirred at room temperature overnight.

The volatiles were removed *in vacuo* and the residue was purified on silica

(heptane:EtOAc 2:1 to 1:1 to 1:2) giving 0.012 g (21 %) of the title compound.

¹H NMR (CDCl₃): δ 9.58 (1H, t, J 5.8 Hz); 9.13 (1H, s); 7.88 (2H, d, J 8.2 Hz); 7.86-7.82
5 (1H, m); 7.77 (1H, t, J 7.9 Hz); 7.51 (2H, d, J 8.7 Hz); 7.49 (1H, s); 7.41 (1H, d, J 7.9 Hz);
4.73-4.61 (2H, m); 3.02 (3H, s); 2.53 (3H, s).

APCI-MS m/z: decomposes.

10 b) 5-(3,3-Dimethyl-ureido)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-
pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide

A mixture of 5-(4-methanesulfonyl-benzylcarbamoyl)-2-methyl-6-oxo-1-(3-
trifluoromethyl-phenyl)-1,6-dihydro-pyridine-3-carbonyl azide

(0.005 g, 0.0094 mmol) and toluene (5 ml) was heated (120 °C) with stirring for 1 h, and
then allowed to cool. The toluene was removed in vacuo and the residue was dissolved in
15 acetonitrile (5 ml), dimethylamine (0.5 ml, 40% in water) was added quickly, and the
resulting mixture was stirred for 5 minutes. Evaporation of the volatiles and purification by
preparative HPLC gave 0.005 g (97%) of the title compound.

¹H NMR (CDCl₃): δ 9.98 (1H, t, J 5.4 Hz); 8.47 (1H, s); 7.87 (2H, d, J 8.6 Hz); 7.80 (1H,
d, J 7.7 Hz); 7.73 (1H, t, J 8.0 Hz); 7.53 (1H, s); 7.50 (2H, d, J 8.3 Hz); 7.46 (1H, d, J 8.0
20 Hz); 6.08 (1H, bs); 4.73-4.60 (2H, m); 3.05 (6H, s); 3.02 (3H, s); 2.02 (3H, s).

APCI-MS m/z: 551.2 [MH⁺].

Following the general method of Example 28, the compounds of Examples 29 and 30 were
prepared:

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Example 29 6-Methyl-5-(3-methyl-ureido)-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-
dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide

¹H NMR (CDCl₃): δ 10.13 (1H, t, J 6.1 Hz); 8.45 (1H, s); 7.87 (2H, d, J 8.1 Hz); 7.81 (1H,
d, J 7.7 Hz); 7.73 (1H, t, J 7.7 Hz); 7.52 (1H, s); 7.49 (2H, d, J 8.2 Hz); 7.45 (1H, d, J 7.4
30 Hz); 6.82 (1H, bs); 4.71-4.58 (2H, m); 3.01 (3H, s); 2.80 (3H, s); 2.06 (3H, s).

APCI-MS m/z : 537.1 $[MH^+]$.

Example 30 6-Methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-5-ureido-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide

1H NMR (DMSO- d_6): δ 9.96 (1H, t, J 6.2 Hz); 8.34 (1H, s); 7.90-7.85 (2H, m); 7.85 (2H, d, J 8.5 Hz); 7.84-7.79 (2H, m); 7.69 (1H, d, J 7.8 Hz); 7.52 (2H, d, J 8.2 Hz); 5.94 (2H, s); 4.58 (2H, d, J 6.2 Hz); 3.15 (3H, s); 1.89 (3H, s).

APCI-MS m/z : 523.1 $[MH^+]$.

Example 31 5-Amino-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide

To a solution of 5-(4-methanesulfonyl-benzylcarbamoyl)-2-methyl-6-oxo-1-(3-trifluoromethyl-phenyl)-1,6-dihydro-pyridine-3-carboxylic acid (0.055 g, 0.108 mmol) in *tert*-butanol (15 ml), triethylamine (0.020 g, 0.2 mmol) and diphenylphosphoryl azide (0.055 g, 0.2 mmol) were added, the flask was equipped with a reflux condenser, and the mixture was heated with stirring at 100 °C overnight. LC-MS showed a complex mixture of products, where one was identified by mass to be the title compound. The compound was isolated by preparative HPLC, and pure fractions were freeze-dried, to give 0.006 g (12%) of a yellow solid.

1H NMR (DMSO- d_6): δ 10.28 (1H, t, J 6.1 Hz); 8.22 (1H, s); 7.86 (2H, d, J 8.2 Hz); 7.85 (1H, s); 7.80 (1H, s); 7.78 (1H, d, J 8.0 Hz); 7.64 (1H, d, J 7.7 Hz); 7.53 (2H, d, J 8.4 Hz); 4.64 (2H, s); 4.57 (2H, d, J 6.2 Hz); 3.17 (3H, s); 1.84 (3H, s).

APCI-MS m/z : 480.1 $[MH^+]$.

Example 32 6-Methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-5-propionyl-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

A solution of 5-iodo-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (1500 mg, 2.5 mmol), bis[1,2-bis(diphenylphosphino)ethane]palladium (230 mg, 0.25 mmol), triethylamine (7.5 ml, 54 mmol) and ethylpropenyl ether (900 μ l, 7.5 mmol) in DMF (45 ml) were heated at

100 °C overnight. After cooling the reaction mixture was poured into water and extracted with ethyl acetate. The extracts were separated and evaporated under reduced pressure. The crude product was dissolved in DMF (25 ml) and 2M HCl (25 ml) and then stirred for 1.5 h. The reaction mixture was then poured into aqueous NaHCO₃ and extracted with ethyl acetate. The extracts were evaporated under reduced pressure and the residue was chromatographed on silica using ethyl acetate/heptane (2/1, 4/1, 10/1) as eluent. Fractions containing the product were combined and evaporated to give 1.3 g (>99%) of the title compound.

¹H NMR (CDCl₃): δ 9.76 (1H, t); 9.06 (1H, s); 7.89 (2H, d); 7.84 (1H, d); 7.76 (1H, t); 7.52 (2H, d); 7.49 (1H, s); 7.40 (1H, d); 4.68 (2H, m); 3.02 (3H, s); 3.00 (2H, q); 2.39 (3H, s); 1.22 (3H, t).

Example 33 5-Formyl-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

The title compound was prepared using a procedure analogous to that described for Example 44.

¹H NMR (CDCl₃): δ 10.06 (1H, s); 9.57 (1H, t, J 5.9 Hz); 9.06 (1H, s); 7.89 (2H, d, J 8.2 Hz); 7.86 (1H, s); 7.79 (1H, t, J 7.9 Hz); 7.52 (3H, d, J 8.2 Hz); 7.43 (1H, d, J 8.2 Hz); 4.69 (2H, m); 3.04 (3H, s); 2.52 (3H, s).

APCI-MS m/z: 493.2 [MH⁺].

Example 34 6-Methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-5-(3-oxobutyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

In a Schlenk vessel equipped with a magnetic stirring bar were placed 5-iodo-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (564.3 mg, 0.96 mmol), bis[1,2-bis(diphenylphosphino)ethane]-palladium (0) (19.9 mg, 0.02 mmol), 3-buten-2-ol (499 mg, 6.9 mmol), triethylamine (1.2 ml, 8.6 mmol) and DMF (6 ml). The vessel was purged with argon, sealed and heated at 105 °C overnight. The reaction mixture was cooled and partitioned between ethyl acetate and water. The organic layer was washed with water, brine, dried over sodium sulfate, filtered

and concentrated in vacuo. The residue was purified by preparative HPLC to give the title compound as a white solid (255 mg, 50 %).

¹H NMR (CDCl₃): δ 10.05 (1H, t, J 5.8 Hz); 8.49 (1H, s); 7.87 (2H, d, J 8.4 Hz); 7.80 (1H, d, J 7.9 Hz); 7.73 (1H, t, J 7.9 Hz); 7.51 (2H, d, J 8.4 Hz); 7.48 (1H, s); 7.41 (1H, d, J 7.9 Hz); 4.69 (2H, m); 3.01 (3H, s); 2.81 (4H, s); 2.20 (3H, s); 2.10 (3H, s).

APCI-MS m/z: 535.1 [MH⁺].

Example 35 5-Acetyl-N-[4-(isopropylsulfonyl)benzyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

a) N-[4-(Isopropylsulfonyl)benzyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

To a mixture of 6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxylic acid (16.27 g, 54.5 mmol) in DCM was added thionyl chloride (12 ml, 165 mmol) under argon. The colour of the reaction mixture turned black. After 50 minutes stirring at ambient temperature, the solvent was removed by evaporation. The last traces of thionyl chloride were removed by azeotropic evaporation with toluene. To an ice cooled solution of the residue in DCM, was added dropwise a mixture of 1-[4-(isopropylsulfonyl)phenyl] methanamine (11.8 g, 55.4 mmol) and triethylamine (30 ml, 215 mmol) in DCM under vigorous stirring. After the addition, the dark suspension was allowed to warm up to room temperature. After 30 minutes stirring at ambient temperature the reaction mixture was concentrated in vacuo and the residue was partitioned between ethyl acetate and water. The organic layer was washed with water, dried over sodium sulfate, filtered and concentrated in vacuo, giving a dark oil which crystallized on standing. The solid was triturated with ethyl acetate, filtered, washed with ethyl acetate, ether, heptane, and dried under vacuo to give the title compound as a light yellow powder (15.3 g). The filtrates were collected, concentrated and further purified by flash chromatography on silica, eluting with a gradient of tert-butyl methyl ether to 5% methanol in tert-butyl methyl ether to provide an additional 8.78 g of the crude product. The solids were combined to give (24.1 g, 89 %) of the title compound.

¹H NMR (CDCl₃): δ 9.96 (1H, t, *J* 5.5 Hz); 8.57 (1H, d, *J* 7.4 Hz); 7.78 (3H, t, *J* 4.1 Hz); 7.72 (1H, t, *J* 7.9 Hz); 7.52 - 7.45 (3H, m); 7.43 (1H, d, *J* 7.7 Hz); 6.46 (1H, d, *J* 7.6 Hz); 4.67 (2H, ddd, *J* 22.0 15.7 6.2 Hz); 3.13 (1H, septet, *J* 9.8 Hz); 2.07 (3H, s); 1.26 (6H, d, *J* 6.9 Hz).

5 APCI-MS *m/z*: 493.2 [MH⁺].

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

To a stirred solution of N-[4-(isopropylsulfonyl)benzyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (23.98 g, 48.73 mmol) and TFA (90 ml) in DCM (90 ml) was added N-iodosuccinimide (11.03 g, 49.14 mmol). After 2 h the reaction was complete and the solvent was removed by evaporation. To the residue was added ethyl acetate (100 ml) and saturated aqueous sodium hydrogencarbonate solution (60 ml) under stirring. The yellow solid was collected by suction filtration, washed with water, air dried for 30 min, washed again with diethyl ether, heptane and vacuum dried to give the title compound as a light yellow powder (29.67 g, 98 %).

¹H NMR (CDCl₃): δ 9.83 (1H, t, *J* 6.0 Hz); 8.90 (1H, s); 7.83 - 7.76 (3H, m); 7.73 (1H, t, *J* 7.8 Hz); 7.47 (3H, d, *J* 8.0 Hz); 7.39 (1H, d, *J* 7.7 Hz); 4.66 (2H, ddd, *J* 22.3, 15.8 and 6.3 Hz); 3.13 (1H, septet, *J* 9.0 Hz); 2.29 (3H, s); 1.26 (6H, d, *J* 6.9 Hz).

20 APCI-MS *m/z*: 619.1 [MH⁺].

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

A mixture of 5-iodo-N-[4-(isopropylsulfonyl)benzyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (3.55 g, 5.7 mmol), bis[1,2-bis(diphenylphosphino)ethane]-palladium (0) (24.5 mg, 0.03 mmol), *n*-butyl vinyl ether (1.16 g, 11.6 mmol), triethylamine (4 ml, 28.7 mmol) in DMF (14 ml) was stirred at 100 °C under argon for 19 h. The reaction mixture was cooled and concentrated in vacuo. The residue was dissolved in methanol (20 ml) and 2M hydrochloric acid (2 ml) was added.

30 After 1 h stirring at room temperature the mixture was partitioned between ethyl acetate/water and basified with saturated aqueous sodium bicarbonate solution. The water

layer was extracted with ethyl acetate (2 x 50 ml) and DCM (1 x 30 ml). The combined organic layers were washed with water, brine, dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica eluting with tert-butyl methyl ether/methanol (10:0.2) to give the title compound as a light yellow solid (2.5 g, 82%).

^1H NMR (CDCl_3): δ 9.71 (1H, t, J 5.7 Hz); 9.05 (1H, s); 7.85 - 7.78 (3H, m); 7.75 (1H, t, J 7.9 Hz); 7.51 - 7.44 (3H, m); 7.39 (1H, d, J 8.2 Hz); 4.68 (2H, ddd, J 22.4, 15.8 and 6.2 Hz); 3.14 (1H, septet, J 7.7 Hz); 2.63 (3H, s); 2.40 (3H, s); 1.26 (6H, d, J 6.9 Hz).

APCI-MS m/z : 535.2 [MH^+].

10

The compounds of Examples 36 to 38 were prepared using a procedure analogous to that described for Example 4.

Example 36 5-Acetyl-1-(3-cyano-phenyl)-6-methyl-2-oxo-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide

15

^1H NMR (CDCl_3): δ 9.67 (1H, t, J 5.7 Hz); 9.07 (1H, s); 7.90-7.86 (3H, m); 7.76 (1H, t, J=7.9 Hz); 7.53-7.45 (4H, m); 4.74-4.64 (2H, m); 3.02 (3H, s); 2.65 (3H, s); 2.42 (3H, s).
APCI-MS m/z : 464 [MH^+].

Example 37 5-Acetyl-1-(3-chloro-phenyl)-6-methyl-2-oxo-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide

20

^1H NMR (CDCl_3): δ 9.77 (1H, t, J 5.8 Hz); 9.04 (1H, s); 7.89 (2H, d, J 8.3 Hz); 7.56-7.51 (4H, m); 7.22 (1H, s); 7.10-7.08 (1H, m); 4.69 (2H, d, J 6.0 Hz); 3.02 (3H, s); 2.64 (3H, s); 2.44 (3H, s).

25

APCI-MS m/z : 473 [MH^+].

Example 38 5-Acetyl-6-methyl-2-oxo-1-m-tolyl-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide

^1H NMR (CDCl_3): δ 9.89 (1H, t, J 5.5 Hz); 9.04 (1H, s); 7.88 (2H, d, J 8.3 Hz); 7.53-7.47 (3H, m); 7.37-7.35 (1H, m); 6.98-6.96 (2H, m); 4.68 (2H, d, J 6.0 Hz); 3.02 (3H, s); 2.64 (3H, s); 2.44 (3H, s), 2.43 (3H, s).

APCI-MS m/z : 453 [MH^+].

5

Example 39 5-(1-Hydroxyethyl)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

A mixture of 5-acetyl-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (Example 4, 180 mg, 0.35 mmol) and aluminum tri-sec-butoxide (0.2 mg, 0.79 mmol) in anhydrous isopropanol (30 ml) was stirred at 85 °C under a nitrogen atmosphere for 48 h. The reaction mixture was cooled to room temperature, water (0.2 ml) was added and the mixture was then concentrated in vacuo. The residue was purified by preparative HPLC to give the title compound as a white solid (134 mg, 74 %).

^1H NMR (CDCl_3): δ 10.01 (1H, t, J 5.7 Hz); 8.84 (1H, d, J 1.9 Hz); 7.87 (2H, d, J 8.3 Hz); 7.81 (1H, d, J 7.8 Hz); 7.74 (1H, t, J 8.0 Hz); 7.52 (2H, d, J 8.3 Hz); 7.50 (1H, s); 7.42 (1H, d, J 7.9 Hz); 5.03 (1H, dd, J 10.9 1.6 Hz); 4.67 (2H, q, J 6.3 Hz); 3.02 (3H, s); 2.12 (3H, s); 1.91 (1H, t, J 3.9 Hz); 1.58 (3H, dd, J 6.4 2.6 Hz).

APCI-MS m/z : 509.2 [MH^+].

20

Example 40 5-(1-Azidoethyl)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

To a solution of 5-(1-hydroxyethyl)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (29.1 mg, 0.06 mmol) in DCM (1.5 ml) was added thionylchloride (0.15 ml, 2.1 mmol) under an argon atmosphere. After 40 minutes stirring at ambient temperature, the solvent was removed in vacuo. The last traces of thionyl chloride were removed by azeotropic evaporation with toluene. The residue was dissolved in anhydrous DMF (1 ml) and sodium azide (20 mg, 0.3 mmol) was added. After 1 h stirring at room temperature the reaction mixture was diluted with water and purified by preparative HPLC giving the title compound as a white solid (11.5 mg, 37 %).

30

¹H NMR (CDCl₃): δ 9.94 (1H, t, J 5.9 Hz); 8.73 (1H, d, J 2.0 Hz); 7.88 (2H, dt, J 8.4 1.9 Hz); 7.83 (1H, d, J 8.1 Hz); 7.76 (1H, td, J 7.9 3.5 Hz); 7.55 - 7.48 (3H, m); 7.43 (1H, t, J 14.1 Hz); 4.81 - 4.59 (3H, m); 3.02 (3H, s); 2.13 (3H, s); 1.63 (3H, dd, J 6.9 1.6 Hz).
APCI-MS m/z: 534.2 [MH⁺].

5

Example 41 6-Methyl-N-[4-(methylsulfonyl)benzyl]-5-(1-morpholin-4-ylethyl)-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

To a solution of 5-(1-hydroxyethyl)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (15 mg, 0.03 mmol) in DCM
10 (2 ml) was added thionyl chloride (0.5 ml, 6.9 mmol) under an argon atmosphere. After 1 h stirring at ambient temperature, the solvent was removed in vacuo. The last traces of thionyl chloride were removed by azeotropic evaporation with toluene. The residue was dissolved in anhydrous DMF (1 ml) and morpholine (0.3 ml, 3.4 mmol) was added. After 35 minutes stirring at room temperature the reaction mixture was diluted with water and
15 further purified by preparative HPLC giving the title compound as a white solid (4.3 mg, 25 %).

¹H NMR (CDCl₃): δ 10.05 (1H, t, J 5.9 Hz); 8.78 (1H, d, J 1.0 Hz); 7.87 (2H, d, J 8.3 Hz); 7.81 (1H, d, J 7.9 Hz); 7.74 (1H, t, J 8.0 Hz); 7.53 (2H, d, J 8.1 Hz); 7.50 (1H, s); 7.43 (1H, t, J 7.3 Hz); 4.67 (2H, td, J 24.2 5.9 Hz); 3.70 (4H, dd, J 20.6 11.4 Hz); 3.48 (1H, m); 3.02
20 (3H, s); 2.53 (2H, s); 2.43 (2H, m); 2.12 (3H, s); 1.36 (3H, dd, J 6.6 1.3 Hz).
APCI-MS m/z: 578.3 [MH⁺].

Example 42 5-(1-Hydroxypropyl)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

25 The title compound was prepared using a procedure analogous to that described for Example 39.

¹H NMR (CDCl₃): δ 10.01 (1H, t, J 5.9 Hz); 8.79 (1H, d, J 1.7 Hz); 7.87 (2H, d, J 8.3 Hz); 7.81 (2H, d, J 7.9 Hz); 7.74 (2H, t, J 7.8 Hz); 7.52 (2H, d, J 8.3 Hz); 7.49 (1H, s,); 7.42 (1H, d, J = 7.5 Hz); 4.77 - 4.59 (3H, m); 3.01 (3H, s); 2.10 (3H, s); 2.00 (1H, t, J = 4.5 Hz);
30 1.98 - 1.74 (2H, m); 1.01 (3H, td, J 7.4 2.5 Hz).

APCI-MS m/z : 523.2 $[MH^+]$.

Example 43 5-(1-Hydroxyethyl)-N-[4-(isopropylsulfonyl)benzyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

5 The title compound was prepared using a procedure analogous to that described for Example 39.

1H NMR ($CDCl_3$): δ 10.02 (1H, t, J 5.9 Hz); 8.85 (1H, d, J 1.7 Hz); 7.81 (3H, d, J 30.8 Hz); 7.74 (1H, t, J 7.9 Hz); 7.50 (3H, d, J 19.2 Hz); 7.43 (1H, d, J 7.6 Hz); 5.03 (1H, t, J 5.4 Hz); 4.69 (2H, dd, J 29.1 9.7 Hz); 3.15 (1H, quintet, J 6.8 Hz); 2.12 (3H, s); 1.98 (1H, 10 t, J 4.4 Hz); 1.58 (3H, dd, J 6.4 2.2 Hz); 1.28 (6H, d, J 6.9 Hz).

APCI-MS m/z : 578.3 $[MH^+]$.

Example 44 N-[4-(Cyclopropylsulfonyl)benzyl]-5-formyl-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

15 N-[4-(Cyclopropylsulfonyl)benzyl]-5-iodo-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide [2.6 g, 4.2 mmol; prepared by a procedure analogous to that described for Example 35 (b)], tris(dibenzylideneacetone) dipalladium (0) (81.9 mg, 0.09 mmol), triphenylphosphine (263.8 mg, 1.0 mmol) and toluene (28 ml) were added to a 100 ml single-neck round bottomed flask. The flask was fitted with a 30 ml dropping 20 funnel with pressure-equalizer containing tributyltin hydride (2.3 g, 7.8 mmol) and toluene (20ml). The system was thoroughly flushed with carbon monoxide by repeated evacuation and filling and was then pressurized at 2.5 atmospheres carbon monoxide and heated at 95 °C with vigorous stirring. The tributyltin hydride solution was added dropwise over a period of 3 h. After the addition was complete, the reaction mixture was allowed to reach 25 room temperature and then the carbon monoxide was flushed out with argon. The solvent was removed in vacuo and the residue was purified by flash chromatography on silica, eluting with tert-butyl methyl ether/methanol (10:0.2) to give the title compound as a white solid (1.6 g, 73 %).

¹H NMR (CDCl₃): δ 10.06 (1H, s); 9.56 (1H, t, J 5.8 Hz); 9.06 (1H, s); 7.89 - 7.78 (4H, m); 7.54 - 7.47 (3H, m); 7.44 (1H, d, J 7.8 Hz); 4.68 (2H, ddd, J 21.5 15.4 6.2 Hz); 2.51 (3H, s); 2.42 (1H, m); 1.33 (2H, m); 1.01 (2H, m).

APCI-MS m/z: 519.2 [MH⁺].

5

Example 45 5-[(E)-(Methoxyimino)methyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

A mixture of 5-formyl-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (Example 33, 14.7 mg, 0.03 mmol), O-methylhydroxylamine hydrochloride (17.2 mg, 0.21 mmol), potassium acetate (42.7 mg, 0.44 mmol) and water (0.1 ml) in ethanol (1.5 ml) was heated at 60 °C for 2 h. The reaction mixture was cooled, concentrated in vacuo and the residue was purified by preparative HPLC to give the title compound as a white solid (6.2 mg, 39 %).

¹H NMR (DMSO-d₆): δ 9.80 (1H, t, J 6.0 Hz); 8.76 (1H, s); 8.44 (1H, s); 7.95 - 7.79 (5H, m); 7.74 (1H, d, J 8.0 Hz); 7.54 (2H, d, J 8.3 Hz); 4.58 (2H, d, J 6.1 Hz); 3.90 (3H, s); 3.17 (3H, s); 2.10 (3H, s).

APCI-MS m/z: 522.2 [MH⁺].

Example 46 5-(Hydroxymethyl)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

The title compound was prepared using a procedure analogous to that described for Example 39.

¹H NMR (CDCl₃): δ 9.98 (1H, t, J 28.4 Hz); 8.66 (1H, s); 7.87 (2H, d, J 8.3 Hz); 7.82 (1H, d, J 8.0 Hz); 7.75 (1H, t, J 7.9 Hz); 7.51 (3H, d, J 8.4 Hz); 7.43 (1H, d, J 8.1 Hz); 4.67 (4H, m); 3.02 (3H, s); 2.16 (3H, s); 2.01 (1H, t, J 5.3 Hz).

APCI-MS m/z: 495.1 [MH⁺].

Example 47 5-[(Dimethylamino)methyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

30

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

5-(Hydroxymethyl)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (Example 46, 990 mg, 2.0 mmol) was treated with thionyl chloride (476 mg, 4.0 mmol) to give the title compound (1.0 g, 97%).

APCI-MS m/z : 513.2 $[MH]^+$.

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

A solution of 5-(chloromethyl)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (5 mg, 0.097 mmol) and dimethylamine in ethanol (0.5 ml, 33 %) was heated in a microwave for 10 minutes at 50 °C. The mixture was then purified by preparative HPLC to give the title compound as a white solid (4 mg, 79 %).

1H NMR (DMSO- d_6): δ 9.96 (1H, t, J 6.0 Hz); 8.34 (1H, s); 7.90 - 7.85 (4H, m); 7.80 (1H, t, J 7.8 Hz); 7.70 (1H, d, J 8.0 Hz); 7.53 (2H, d, J 8.3 Hz); 4.58 (2H, d, J 6.2 Hz); 3.57 (2H, s); 3.17 (3H, s); 2.18 (6H, s); 2.02 (3H, s).

APCI-MS m/z : 522.1 $[MH]^+$.

20

Example 48 6-Methyl-5-[(methylamino)methyl]-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

The title compound was prepared using a procedure analogous to that described for Example 47.

1H NMR (DMSO- d_6) δ 9.97 (1H, t, J 6.0 Hz); 8.43 (1H, s); 7.94 - 7.85 (4H, m); 7.81 (1H, t, J 7.8 Hz); 7.67 (1H, d, J 7.9 Hz); 7.53 (2H, d, J 8.2 Hz); 4.58 (2H, d, J 6.0 Hz); 3.57 (2H, s); 3.17 (3H, s); 2.30 (3H, s); 2.02 (3H, s).

APCI-MS m/z : 508.1 $[MH]^+$.

25

Example 49 6-Methyl-N-[4-(methylsulfonyl)benzyl]-5-(morpholin-4-ylmethyl)-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

A solution of 5-(chloromethyl)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (Example 47, 8 mg, 0.016 mmol) and morpholine (5.5 mg, 0.062 mmol) in DMF (1 ml) was heated in a microwave oven for 10 minutes at 50 °C. The mixture was then purified by preparative HPLC to give the title compound as a white solid (4 mg, 45 %).

¹H NMR (CDCl₃): δ 10.03 (1H, t,); 8.56 (1H, s,); 7.87 (2H, d, J=8.2 Hz); 7.81 (1H, d, J=7.8 Hz); 7.75 (2H, t, J=7.9 Hz); 7.52 (3H, d, J=8.2 Hz); 4.67 (2H, m); 3.72 (4H, m); 3.37 (2H, m); 3.01 (3H, s,); 2.50 (3H, s); 2.13 (2H, m); 1.57 (2H, s).

APCI-MS m/z: 564.2 [MH⁺].

The compounds of Examples 50 to 59 were prepared using a procedure analogous to that described for Example 49.

Example 50 5-[(2-Furylmethyl)amino]methyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

¹H NMR (DMSO-d₆): δ 9.64 (1H, t, J 6.1 Hz); 8.12 (1H, s); 7.58 - 7.47 (5H, m); 7.35 (1H, d, J 7.7 Hz); 7.24 - 7.20 (3H, m); 6.07 (1H, dd, J 3.1, 1.8 Hz); 5.95 (1H, d, J 3.0 Hz); 4.26 (2H, d, J 6.1 Hz); 3.40 (2H, s); 3.29 (2H, s); 2.85 (3H, s); 1.66 (3H, s).

APCI-MS m/z: 574.2 [MH⁺].

Example 51 5-[(Cyclopropylamino)methyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

¹H NMR (DMSO-d₆): δ 9.97 (1H, t, J 6.0 Hz); 8.43 (1H, s); 7.90 - 7.84 (4H, m); 7.81 (1H, t, J 7.9 Hz); 7.66 (1H, d, J 7.8 Hz); 7.53 (2H, d, J 8.3 Hz); 4.58 (2H, d, J 6.0 Hz); 3.65 (2H, s); 3.17 (3H, s); 2.11 - 2.07 (1H, m); 2.02 (3H, s); 0.38 - 0.35 (2H, m,); 0.26 - 0.23 (2H, m).

APCI-MS m/z: 534.2 [MH⁺].

Example 52 5-[[2-Hydroxypropyl]amino]methyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

¹H NMR (DMSO-d₆): δ 9.97 (1H, t, J 6.1 Hz); 8.45 (1H, s); 7.90 - 7.85 (4H, m); 7.81 (1H, t, J 7.8 Hz); 7.68 (1H, d, J 8.1 Hz); 7.53 (2H, d, J 8.4 Hz); 4.58 (2H, d, J 6.0 Hz); 4.49 (1H, d, J 4.4 Hz); 3.72 - 3.68 (1H, m,); 3.63 (2H, s); 3.17 (3H, s); 2.49 - 2.46 (2H, m); 2.02 (3H, s); 1.05 (3H, d, J 6.2 Hz).

APCI-MS m/z: 552.2 [MH⁺].

Example 53 5-[(Cyclopentylamino)methyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

¹H NMR (DMSO-d₆): δ 9.97 (1H, t, J 6.1 Hz); 8.45 (1H, s); 7.90 - 7.85 (4H, m); 7.81 (1H, t, J 7.9 Hz); 7.67 (1H, d, J 8.0 Hz); 7.53 (2H, d, J 8.3 Hz); 4.58 (2H, d, J 6.0 Hz); 3.57 (2H, s); 3.17 (3H, s); 3.05 (1H, t, J 6.1 Hz); 2.02 (3H, s); 1.77 - 1.70 (2H, m); 1.64 - 1.60 (2H, m); 1.49 - 1.45 (2H, m); 1.39 - 1.33 (2H, m).

APCI-MS m/z: 562.2 [MH⁺].

Example 54 5-[[2-Hydroxyethyl](methyl)amino]methyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

¹H NMR (DMSO-d₆): δ 9.97 (1H, t, J 6.0 Hz); 8.36 (1H, s); 7.89 - 7.85 (4H, m); 7.80 (1H, t, J 8.2 Hz); 7.69 (1H, d, J 8.4 Hz); 7.54 (2H, d, J 8.3 Hz); 4.58 (2H, d, J 6.0 Hz); 4.41 (1H, t, J 5.2 Hz); 3.52 (2H, q, J 5.9 Hz); 3.46 (2H, d, J 30.9 Hz); 3.17 (3H, s); 2.47 (2H, d); 2.18 (3H, s); 2.03 (3H, s).

APCI-MS m/z: 552.2 [MH⁺].

Example 55 6-Methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-5-(pyrrolidin-1-ylmethyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

¹H NMR (DMSO-d₆): δ 9.97 (1H, t, J 6.1 Hz); 8.37 (1H, s); 7.90 - 7.85 (4H, m); 7.80 (1H, t, J 7.8 Hz); 7.70 (1H, d, J 7.9 Hz); 7.53 (2H, d, J 8.4 Hz); 4.57 (2H, d, J 6.1 Hz); 3.51 (2H, s); 3.17 (3H, s); 2.47 - 2.44 (4H, m); 2.03 (3H, s); 1.70 (4H, m).

APCI-MS m/z: 548.2 [MH⁺].

5

Example 56 5-[[Methoxy(methyl)amino]methyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

¹H NMR (DMSO-d₆): δ 9.94 (1H, t, J 6.0 Hz); 8.39 (1H, s); 7.90 - 7.85 (4H, m); 7.81 (1H, t, J 8.1 Hz); 7.69 (1H, d, J 7.9 Hz); 7.54 (2H, d, J 8.4 Hz); 4.58 (2H, d, J 6.0 Hz); 3.72 (2H, s); 3.17 (3H, s); 2.58 (3H, s); 2.04 (3H, s).

APCI-MS m/z: 538.2 [MH⁺].

Example 57 5-[[Cyanomethyl]amino]methyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

¹H NMR (DMSO-d₆): δ 9.78 (1H, t, J 6.2 Hz); 8.25 (1H, s); 7.74 - 7.64 (5H, m); 7.51 (1H, d, J 8.1 Hz); 7.37 (2H, d, J 8.3 Hz); 4.42 (2H, d, J 5.7 Hz); 3.53 (2H, d, J 5.7 Hz); 3.48 (2H, d, J 7.1 Hz); 3.01 (3H, s); 1.87 (3H, s).

APCI-MS m/z: 533.2 [MH⁺].

20

Example 58 5-[[Cyclopropylmethyl]amino]methyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

¹H NMR (DMSO-d₆): δ 9.98 (1H, t, J 6.0 Hz); 8.46 (1H, s); 7.88 (4H, dd, J 10.5, 8.5 Hz); 7.81 (1H, t, J 7.9 Hz); 7.68 (1H, d, J 7.9 Hz); 7.53 (2H, d, J 8.3 Hz); 4.58 (2H, d, J 6.0 Hz); 3.62 (2H, s); 3.17 (3H, s); 2.42 (2H, d, J 6.7 Hz); 2.02 (3H, s); 0.91 (1H, s); 0.43 - 0.38 (2H, m); 0.14 - 0.10 (2H, m).

APCI-MS m/z: 548.2 [MH⁺].

25

Example 59 5-[(3-Hydroxypyrrolidin-1-yl)methyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

¹H NMR (DMSO-d₆): δ 9.97 (1H, t, J 6.1 Hz); 8.37 (1H, s); 7.90 - 7.85 (4H, m); 7.80 (1H, t, J 7.9 Hz); 7.70 (1H, d, J 7.9 Hz); 7.54 (2H, d, J 8.3 Hz); 4.71 (1H, d, J 4.2 Hz); 4.58 (2H, d, J 6.1 Hz); 4.20 (1H, dt, J 9.7, 3.7 Hz); 3.49 (2H, s); 3.17 (3H, s); 2.79 - 2.74 (1H, m); 2.58 (1H, t, J 7.6 Hz); 2.50 - 2.45 (1H, m); 2.35 - 2.32 (1H, m); 2.03 (3H, s); 2.00 - 1.97 (1H, m); 1.57 - 1.53 (1H, m).

APCI-MS m/z: 564.2 [MH⁺].

Example 60 5-(2-Hydroxyethoxy)-N-[4-(isopropylsulfonyl)benzyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

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

To ice-cooled 35% hydrogen peroxide (11.11 g, 114.4 mmol) was added concentrated sulphuric acid (8.92 g, 91.0 mmol) and 5-acetyl-N-[4-(isopropylsulfonyl)benzyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (Example 35 (c), 2.2 g, 4.1 mmol) in DCM (3 ml). The mixture was stirred vigorously and heated at 45 °C for 1.5 h. The reaction mixture was cooled to room temperature and then added dropwise to an ice cooled mixture of ethyl acetate (100 ml) and saturated aqueous sodium carbonate solution under stirring. The organic layer was collected and the water layer was extracted with ethyl acetate (2 x 60 ml). The combined organic layers were washed with water and brine, dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica eluting with tert-butyl methyl ether/methanol (10:0.2) to give the title compound as a yellow solid (1.1 g, 52 %).

¹H NMR (CDCl₃): δ 10.66 (1H, t, J 6.0 Hz); 8.97 (1H, s); 8.16 (1H, s); 7.81 (3H, m); 7.74 (1H, t, J 7.8 Hz); 7.51 (3H, t, J 4.1 Hz); 7.43 (1H, d, J 7.8 Hz); 4.68 (2H, td, J 9.5 4.5 Hz); 3.16 (1H, quintet, J 6.9 Hz); 2.04 (3H, s); 1.28 (6H, d, J 6.9 Hz).

APCI-MS m/z: 509.1 [MH⁺].

b) 2-({5-({[4-(Isopropylsulfonyl)benzyl]amino}carbonyl)-2-methyl-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridin-3-yl}oxy)ethyl acetate

A mixture of 5-hydroxy-N-[4-(isopropylsulfonyl)benzyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (1.05 g, 2.06 mmol), 2-bromoethyl acetate (1.03 g, 6.17 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.94 g, 6.17 mmol) in anhydrous DMF (2.5 ml) was heated at 80 °C for 25 min under argon. The reaction mixture was cooled and partitioned between ethyl acetate and water. The organic layer was washed with water, dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography eluting with a gradient of tert-butyl methyl ether to 2.5% methanol in tert-butyl methyl ether to provide the title compound as a light green solid (0.87 g, 71%).

¹H NMR (CDCl₃): δ 10.11 (1H, t, J 5.8 Hz); 8.58 (1H, s); 7.79 (3H, d, J 8.4 Hz); 7.73 (1H, t, J 7.9 Hz); 7.48 (3H, d, J 8.2 Hz); 7.41 (1H, d, J 7.9 Hz); 4.67 (2H, ddd, J 21.7, 15.6 and 6.1 Hz); 4.38 (2H, dd, J 5.4 4.0 Hz); 4.21 (2H, dd, J 5.2, 3.7 Hz); 3.13 (1H, septet, J 9.0 Hz); 2.10 (3H, s); 2.04 (3H, s); 1.26 (6H, d, J = 6.9 Hz).

APCI-MS m/z: 595.1 [MH⁺].

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

A mixture of 2-({5-({[4-(isopropylsulfonyl)benzyl]amino}carbonyl)-2-methyl-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridin-3-yl}oxy)ethyl acetate (0.87 g, 1.46 mmol), methanol (5 ml) and 2M sodium hydroxide solution (0.2 ml, 0.4 mmol) was stirred at ambient temperature for 20 min. The solution was acidified with acetic acid, diluted with water and purified by preparative HPLC to give the title compound as a light green solid (0.65 g, 82%).

¹H NMR (CDCl₃): δ 10.13 (1H, t, J 5.7 Hz); 8.59 (1H, s); 7.79 (3H, d, J 8.4 Hz); 7.73 (1H, t, J 7.9 Hz); 7.51 - 7.46 (3H, m); 7.42 (1H, d, J 7.8 Hz); 4.67 (2H, ddd, J 21.7 15.6 6.1 Hz); 4.12 (2H, t, J 4.5 Hz); 3.96 (2H, septet, J 9.6 Hz); 3.14 (1H, septet, J 9.6 Hz); 2.06 (3H, s); 1.83 (1H, t, J 6.0 Hz); 1.26 (6H, d, J 6.9 Hz).

APCI-MS m/z: 553.1 [MH⁺].

Example 61 2-Methyl-5-([4-(methylsulfonyl)benzyl]amino)-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridin-3-yl acetate

The title compound was obtained as a byproduct during the synthesis of 5-hydroxy-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide when the latter compound was prepared by a procedure analogous to that described for Example 60 (a).

¹H NMR (DMSO-d₆): δ 9.93 (1H, t, J 6.1 Hz); 8.33 (1H, s); 7.96 - 7.80 (4H, m); 7.75 (2H, d, J 8.2 Hz); 7.54 (2H, d, J 8.3 Hz); 4.59 (2H, d, J 6.2 Hz); 3.17 (3H, s); 2.32 (3H, s); 1.89 (3H, s).

APCI-MS m/z: 523.3 [MH⁺].

Example 62 5-Methoxy-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

A solution of 5-hydroxy-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (Example 61, 15 mg, 0.031 mmol) and K₂CO₃ (13.8 mg, 0.1 mmol) in acetone (1 ml) was heated to 60 °C. After 15 minutes the mixture was cooled to room temperature, iodomethane (7 mg, 0.050 mmol) was added, and the reaction mixture was heated for an additional 30 minutes at 60 °C. The mixture was then purified by preparative HPLC to give the title compound as a white solid (14 mg, 90 %).

¹H NMR (DMSO-d₆): δ 10.11 (1H, t, J=5.9 Hz); 8.39 (1H, s,); 7.90 - 7.85 (5H, m,); 7.81 (4H, t, J=7.9 Hz); 7.71 (1H, d, J=8.0 Hz); 7.54 (3H, d, J=8.3 Hz); 4.59 (2H, d, J=6.0 Hz); 3.81 (3H, s,); 3.18 (4H, s,); 1.95 (3H, s,).

APCI-MS m/z: 495.5 [MH⁺].

Example 63 5-(3-Methoxypropoxy)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

To a solution of 5-hydroxy-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (Example 61, 10 mg, 0.02 mmol), lithium iodide (2.7 mg, 0.02 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (7 mg, 0.04 mmol) in DMF (1 ml), 1-bromo-3-methoxypropane (6.1 mg, 0.04 mmol) was added,

and the reaction mixture was heated for 60 minutes at 40 °C. The mixture was then purified by preparative HPLC to give the title compound as a white solid (5 mg, 45 %).

¹H NMR (CDCl₃): δ 8.58 (1H, s); 10.2 (1H, t); 7.87 (2H, d, J 8.3 Hz); 7.80 (1H, d); 7.74 (1H, t,); 7.52 (3H, d, J 8.4 Hz); 7.4 (1H, d); 4.67 (2H, t, J 5.6 Hz); 4.10 (2H, t, J 6.3 Hz);
5 3.56 (2H, t, J 6.1 Hz); 3.37 (3H, s); 3.02 (3H, s,); 2.05 (3H, s).

APCI-MS m/z: 553.2 [MH⁺].

Example 64 2-Methyl-5-([4-(methylsulfonyl)benzyl]amino)carbonyl]-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridin-3-yl methanesulfonate

10 To a solution of 5-hydroxy-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (5 mg, 0.01 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (3 mg, 0.02mmol) in DCM (1 ml), 2-chloroethylamine hydrochloride (2.3 mg, 0.02 mmol) was added and the reaction mixture was heated for 60 minutes at 40 °C. The mixture was then purified by preparative HPLC to give the title
15 compound as a white solid (3 mg, 54 %).

¹H NMR (CDCl₃): δ 7.88 (2H, d, J 8.4 Hz); 7.83 (1H, s); 7.77 (1H,); 7.55 - 7.50 (3H, m); 7.48 - 7.43 (1H, m,); 4.67 (2H, t, J 6.3 Hz); 3.33 (3H, s); 3.02 (3H, s); 2.15 (3H, s).
APCI-MS m/z: 559.1 [MH⁺].

20 **Example 65** 5-Ethoxy-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

A mixture of 5-hydroxy-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (Example 61, 40.7 mg, 0.08 mmol), iodoethane (0.4 ml, 5.0 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.6 g, 4.1
25 mmol) in DMF (1.5 ml) was stirred at 85 °C for 30 minutes under argon. The reaction mixture was cooled, diluted with water and purified by preparative HPLC to give the title compound as a white solid (11.5 mg, 26 %).

¹H NMR (CDCl₃): δ 10.19 (1H, t, J 5.8 Hz); 8.57 (1H, s); 7.87 (2H, d, J 8.3 Hz); 7.81 (1H, d, J 8.0 Hz); 7.74 (1H, t, J 7.9 Hz); 7.52 (3H, d, J 8.4 Hz); 7.43 (1H, d, J 7.7 Hz); 4.69
30 (2H, m); 4.09 (2H, q, J 7.0 Hz); 3.01 (3H, s); 2.05 (3H, s); 1.41 (3H, t, J 7.0 Hz).

APCI-MS m/z : 509.0 $[MH^+]$.

Example 66 5-(2-Hydroxyethoxy)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

5 The title compound was obtained by a procedure analogous to that described for Example 60.

1H NMR ($CDCl_3$): δ 10.15 (1H, t, J 5.9 Hz); 8.60 (1H, s); 7.87 (2H, d, J 8.3 Hz); 7.81 (1H, d, J 7.8 Hz); 7.74 (1H, t, J 7.8 Hz); 7.52 (3H, d, J 8.3 Hz); 7.43 (1H, d, J 7.8 Hz); 4.67 (2H, m); 4.13 (2H, t, J 4.5 Hz); 3.98 (2H, q, J 20.3 Hz); 3.02 (3H, s); 2.08 (3H, s); 1.86 (1H, t, J 6.0 Hz).

API-MS m/z : 525.1 $[MH^+]$.

Example 67 5-(Cyanomethoxy)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide trifluoroacetate

15 The title compound was obtained using analogous conditions to those described in Example 65.

1H NMR ($CDCl_3$): δ 10.12 (1H, t, J 5.6 Hz); 8.61 (1H, s); 7.89 (2H, d, J 8.3 Hz); 7.84 (1H, d, J 7.9 Hz); 7.76 (1H, t, J 7.9 Hz); 7.51 (3H, d, J 8.2 Hz); 7.45 (1H, d, J 8.0 Hz); 4.82 (2H, s); 4.69 (2H, ddd, J 21.5 15.4 6.1 Hz); 3.02 (3H, s); 2.14 (3H, s).

20 APCI-MS m/z : 520.0 $[MH^+]$.

Example 68 2-({2-Methyl-5-({[4-(methylsulfonyl)benzyl]amino}carbonyl)-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridin-3-yl}oxy)ethyl acetate

25 The title compound was obtained under similar conditions to those described in Example 60.

1H NMR ($CDCl_3$): δ 10.13 (1H, t, J 5.7 Hz); 8.59 (1H, s); 7.88 (2H, d, J 8.4 Hz); 7.81 (1H, d, J 8.0 Hz); 7.75 (1H, t, J 7.9 Hz); 7.52 (3H, d, J 8.4 Hz); 7.43 (1H, d, J 8.0 Hz); 4.67 (2H, t, J 5.7 Hz); 4.40 (2H, dd, J 5.4 3.9 Hz); 4.22 (2H, dd, J 5.2 3.8 Hz); 3.02 (3H, s); 2.12 (3H, s); 2.05 (3H, s).

30 APCI-MS m/z : 567.2 $[MH^+]$.

Example 69 5-[2-(Dimethylamino)-2-oxoethoxy]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

5

a) tert-Butyl ({2-methyl-5-([4-(methylsulfonyl)benzyl]amino)carbonyl}-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridin-3-yl}oxy)acetate

The title compound was obtained under similar conditions to those described in Example 60.

10 ^1H NMR (CDCl_3): δ 10.15 (1H, t, J 5.9 Hz); 8.51 (1H, s); 7.87 (2H, d, J 8.4 Hz); 7.81 (1H, d, J 8.0 Hz); 7.74 (1H, t, J 7.9 Hz); 7.51 (3H, m); 7.43 (1H, d, J 7.8 Hz); 4.67 (2H, ddd, J 20.6, 15.2 and 5.8 Hz); 4.57 (2H, s); 3.01 (3H, s); 2.14 (3H, s); 1.51 (9H, s).

APCI-MS m/z : 595.3 [MH^+].

15 **b)** ({2-Methyl-5-([4-(methylsulfonyl)benzyl]amino)carbonyl}-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridin-3-yl}oxy)acetic acid

To a solution of tert-butyl ({2-methyl-5-([4-(methylsulfonyl)benzyl]amino)carbonyl}-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridin-3-yl}oxy)acetate (103 mg, 0.17 mmol) in THF (3 ml) and methanol (2 ml) was added 2M aqueous sodium hydroxide solution (0.6 ml, 1.2 mmol). After stirring for 1 h, the reaction mixture was acidified with acetic acid and concentrated in vacuo. The residue was purified by preparative HPLC to give the title compound as a white solid (87.7 mg, 95 %).

20 ^1H NMR (CDCl_3): δ 10.48 (1H, t, J 5.9 Hz); 8.58 (1H, s); 7.87 (2H, d, J 8.4 Hz); 7.82 (1H, d, J 8.1 Hz); 7.75 (1H, t, J 7.9 Hz); 7.51 (3H, d, J 23.6 Hz); 7.44 (1H, d, J 7.9 Hz); 4.78 (2H, s); 4.67 (2H, ddd, J 21.7 15.5 6.1 Hz); 3.02 (3H, s); 2.14 (3H, s).

25 APCI-MS m/z : 539.1 [MH^+].

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

30 A mixture of ({2-methyl-5-([4-(methylsulfonyl)benzyl]amino)carbonyl}-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridin-3-yl}oxy)acetic acid (87.5 mg, 0.16 mmol)

and thionyl chloride (0.6 ml, 8.24 mmol) in DCM (5 ml) was stirred at 35 °C for 30 minutes under an argon atmosphere. The mixture was cooled and concentrated in vacuo. The last traces of thionyl chloride were removed by azeotropic evaporation with toluene. The residue was dissolved in DCM (4 ml) and dimethylamine (0.5 ml) was added. After 30 minutes stirring at ambient temperature the reaction mixture was concentrated and purified by preparative HPLC to give the title compound as a white solid (47.7 mg, 53 %).

^1H NMR (CDCl_3): δ 10.19 (1H, t, J 5.9 Hz); 8.48 (1H, s); 7.87 (2H, d, J 8.3 Hz); 7.80 (1H, d, J 7.9 Hz); 7.73 (1H, t, J 7.8 Hz); 7.51 (3H, d, J 8.1 Hz); 7.44 (1H, d, J 8.3 Hz); 4.81 (2H, s); 4.66 (2H, dd, J 20.7 9.5 Hz); 3.02 (6H, d, J 4.8 Hz); 2.99 (3H, s); 2.16 (3H, s).

APCI-MS m/z : 566.2 [MH^+].

Example 70 5-(2-Aminoethoxy)-N-[4-(isopropylsulfonyl)benzyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

To a solution of 5-hydroxy-6-methyl-N-[4-(isopropylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (Example 60 (a), 25 mg, 0.049 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (15 mg, 0.099 mmol) in NMP (1.5 ml), 2-chloroethylamine hydrochloride (11.5 mg, 0.099 mmol) was added and the reaction mixture was heated in a microwave oven for 10 minutes at 70 °C. The mixture was then purified by preparative HPLC to give the title compound as a white solid (8 mg, 25 %).

^1H NMR ($\text{DMSO}-d_6$): δ 10.11 (1H, t, J=6.1 Hz); 8.38 (1H, s,); 7.90 (2H, d, J=7.8 Hz); 7.83 - 7.78 (3H, m,); 7.72 (1H, d, J=8.0 Hz); 7.54 (2H, d, J=8.3 Hz); 4.61 (2H, d, J=6.2 Hz); 3.93 (2H, t, J=5.6 Hz); 3.42 - 3.31 (2H, m,); 2.86 (2H, t, J=5.6 Hz); 1.97 (3H, s, J=4.6 Hz); 1.14 (3H, s,); 1.12 (3H, s,).

APCI-MS m/z : 552.2 [MH^+].

Example 71 5-(Acetylamino)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

A mixture of 6-methyl-N-[4-(methylsulfonyl)benzyl]-5-nitro-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (Example 2, 15.3 mg, 0.03 mmol) and iron powder (20 mg, 0.36 mmol) in acetic acid (1.5 ml) was stirred at ambient temperature for 1 h. The iron powder was filtered off and the filtrate was concentrated in

vacuo. Acetic anhydride (0.25 ml, 2.6 mmol), DMF (1 ml) and saturated aqueous sodium hydrogencarbonate solution were added to the residue. After stirring the reaction mixture at room temperature for 30 minutes, it was neutralized with aqueous sodium hydroxide solution and purified by preparative HPLC to give the title compound as a white solid (3.5 mg, 22 %).

^1H NMR (CDCl_3): δ 9.94 (1H, t, J 6.0 Hz); 8.47 (1H, s); 7.87 (2H, d, J 8.4 Hz); 7.81 (1H, d, J 7.9 Hz); 7.74 (1H, t, J 7.9 Hz); 7.53 (1H, s); 7.50 (2H, d, J 8.4 Hz); 7.46 (1H, d, J 7.9 Hz); 7.13 (1H, s); 4.68 (2H, m); 3.02 (3H, s); 2.20 (3H, s); 1.99 (3H, s).

APCI-MS m/z : 522.1 $[\text{MH}^+]$.

Example 72 *N*-[4-(Isopropylsulfonyl)benzyl]-6-methyl-5-[3-(methylamino)propoxy]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide.

a) 5-(3-Bromopropoxy)-*N*-[4-(isopropylsulfonyl)benzyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

A solution of 5-hydroxy-*N*-[4-(isopropylsulfonyl)benzyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (500 mg, 0.98 mmol), CsCO_3 (1.28 mg, 3.94 mmol) and 1,3 dibromopropane (795 mg, 3.94 mmol) in DMF (6 ml) was heated to 70 °C for 30 minutes. After cooling the mixture was purified by preparative HPLC to give the title compound as a white solid (100 mg, 16 %).

APCI-MS m/z : 629.2 $[\text{MH}^+]$.

b) *N*-[4-(Isopropylsulfonyl)benzyl]-6-methyl-5-[3-(methylamino)propoxy]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

A solution of 5-(3-bromopropoxy)-*N*-[4-(isopropylsulfonyl)benzyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (30 mg, 0.048 mmol) and methanamine (0.5 ml, 2M in THF) was heated in a microwave oven for 60 minutes at 50 °C. The mixture was then purified by preparative HPLC to give the title compound as a white solid (13 mg, 46%).

^1H NMR (CDCl_3): δ 10.06 (1H, t, J 6.0 Hz); 8.43 (1H, s); 7.68 - 7.66 (3H, m); 7.61 (1H, t, J 7.8); 7.37 (3H, d, J 8.4 Hz); 7.31 (1H, d, J 7.6 Hz); 4.55 (2H, t, J 5.8 Hz); 3.98 (2H, t, J

6.1 Hz); 3.06 - 3.00 (1H, m); 2.75 (2H, t, J 7.0 Hz); 2.40 (3H, s); 1.95 (2H, t); 1.91 (3H, s); 1.15 (3H, s); 1.14 (3H, s).

APCI-MS m/z: 580.2 [MH⁺].

5 **Example 73** 5-(1-Methoxyethyl)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

To a solution of 6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-5-vinyl-1,2-dihydropyridine-3-carboxamide (Example 9, 20.7 mg, 0.04 mmol) in methanol (2 ml) was added concentrated sulphuric acid (0.05 ml). The mixture was stirred at 65 °C overnight and then neutralized with aqueous sodium hydrogencarbonate solution. The reaction mixture was purified by preparative HPLC to give the title compound as white solid (5.9 mg, 27 %).

¹H NMR (CDCl₃): δ 10.01 (1H, t, J 5.8 Hz); 8.72 (1H, s); 7.87 (2H, d, J 8.3 Hz); 7.81 (1H, d, J 7.8 Hz); 7.75 (1H, t, J 7.8 Hz); 7.52 (3H, d, J 28.4 Hz); 7.44 (1H, t, J 6.6 Hz); 4.67 (2H, m); 4.44 (1H, dq, J 0.1 6.3 Hz); 3.29 (3H, d, J 1.0 Hz); 3.01 (3H, s); 2.09 (3H, s); 1.48 (3H, dd, J 6.5 2.1 Hz).

APCI-MS m/z: 523.0 [MH⁺].

20 **Example 74** 5-(2-Bromo-1-methoxyethyl)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

A mixture of 6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-5-vinyl-1,2-dihydropyridine-3-carboxamide (Example 9, 66.9 mg, 0.14 mmol), N-bromosuccinimide (37.7 mg, 0.21 mmol) and dibenzoyl peroxide (7.1 mg, 0.03 mmol) in methanol (2 ml) was stirred at ambient temperature for 1.5 h. The solvent was removed in vacuo and the residue was purified by preparative HPLC to give the title compound as white solid (44 mg, 52 %).

¹H NMR (CDCl₃): δ 9.94 (1H, t, J 5.9 Hz); 8.69 (1H, d, J 0.8 Hz); 7.88 (2H, d, J 8.3 Hz); 7.83 (1H, d, J 8.0 Hz); 7.76 (1H, t, J 7.9 Hz); 7.52 (2H, d, J 8.2 Hz); 7.50 (1H, s); 7.44 (1H, t, J 7.2 Hz); 4.68 (2H, m); 4.54 (1H, t, J 6.7 Hz); 3.67 (1H, m); 3.46 (1H, m); 3.37 (3H, d, J 1.1 Hz); 3.02 (3H, s); 2.13 (3H, s).

APCI-MS m/z: 600.1, 601.1, 602.1, 603.2 [MH⁺].

Example 75 5-(1-Isopropoxyethyl)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

5 The title compound was prepared by a procedure analogous to that described for Example 73.

¹H NMR (CDCl₃): δ 10.02 (1H, t, J 5.8 Hz); 8.76 (1H, s); 7.87 (2H, d, J 8.3 Hz); 7.81 (1H, d, J 7.8 Hz); 7.74 (1H, t, J 7.9 Hz); 7.52 (3H, d, J 25.3 Hz); 7.43 (1H, t, J 6.7 Hz); 4.68 (3H, m); 3.56 (1H, td, J 6.1 3.7 Hz); 3.01 (3H, s); 2.10 (3H, s); 1.44 (3H, dd, J 6.5 and 2.2
10 Hz); 1.18 (6H, dd, J 10.8 and 6.1 Hz).

APCI-MS m/z: 551.2 [MH⁺].

Example 76 5-(N¹-Isobutyryl-hydrazinocarbonyl)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide

15

a) 5-Hydrazinocarbonyl-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide

The compound obtained in Example 11 (0.051 g, 0.14 mmol) in DCM (5 ml) was treated with SOCl₂ (5 ml) and the flask was sealed and stirred magnetically for 2 h, when LC-MS
20 showed that the reaction was complete. The crude mixture was evaporated in vacuo, giving the intermediate acid chloride as a yellow solid. The solid was dissolved in 1,4-dioxane (5 ml, dried over molecular sieves) and hydrazine hydrate (0.05 g, 1.0 mmol) was added. The mixture was stirred for 10 minutes, and LC-MS showed complete formation of the title compound. The mixture was concentrated in vacuo and the residue was purified by
25 preparative HPLC giving the title compound (0.036 g, 70%) as a white solid after freeze-drying the pure fractions.

APCI-MS m/z: 523.2 [MH⁺].

b) 5-(N¹-Isobutyryl-hydrazinocarbonyl)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide

30

The compound obtained in step (a) (0.025 g, 0.047 mmol) in dry THF (10 ml) was stirred and isobutyric anhydride (0.040 g, 0.25 mmol) was added. The obtained mixture was stirred for 15 minutes, and LC-MS showed complete conversion of the starting material to the desired amide. The solvent was evaporated and the residue was purified by preparative HPLC giving the subtitle compound (0.024 g, 85%) as a white powder after freeze-drying the pure fractions.

^1H NMR (DMSO- d_6): δ 10.25 (1H, bs); 9.89 (1H, bs); 9.79 (1H, t, J 6.2 Hz); 8.50 (1H, s); 7.93 (1H, s); 7.94-7.90 (1H, m); 7.87 (2H, d, J 8.5 Hz); 7.84 (1H, t, J 7.7 Hz); 7.74 (1H, d, J 7.7 Hz); 7.55 (2H, d, J 8.3 Hz); 4.63-4.56 (2H, m); 3.18 (3H, s); 2.55-2.49 (1H, p, J 6.8 Hz); 2.18 (3H, s); 1.08 (6H, d, J 6.8 Hz).

APCI-MS m/z : 593.2 [MH^+].

The compounds of Examples 77 to 87 and 91 to 97 were prepared using a procedure analogous to that described for Example 12.

15

Example 77 N^5 -Methoxy-6-methyl- N^3 -[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

^1H NMR (DMSO- d_6): δ 11.74 (1H, bs); 9.79 (1H, t); 8.41 (1H, s); 7.95-7.70 (6H, m); 7.54 (2H, d); 4.58 (2H, d); 3.70 (3H, s); 3.18 (3H, s); 2.13 (3H, s).

APCI-MS m/z : 538.1 [MH^+].

20

Example 78 N^5 -Methoxy- N^5 ,6-dimethyl- N^3 -[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

^1H NMR (DMSO- d_6): δ 9.83 (1H, t); 8.36 (1H, s); 8.01 (1H, bs); 7.94-7.76 (5H, m); 7.54 (2H, d); 4.58 (2H, d); 3.59 (3H, s); 3.28 (3H, s); 3.18 (3H, s); 2.00 (3H, s).

25

APCI-MS m/z : 552.2 [MH^+].

Example 79 5-[(2,5-Dimethyl-2,5-dihydro-1H-pyrrol-1-yl)carbonyl]-6-methyl- N -[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

30

¹H NMR (DMSO-d₆): δ 9.86 (1H, q); 8.29 (0.5H, d); 8.26 (0.5H, s); 8.06 (0.5H, bs); 8.01 (0.5H, bs); 7.95-7.74 (5H, m); 7.55 (2H, d); 5.83 (2H, dt); 4.80 (1H, bt); 4.58 (2H, d); 4.49 (1H, bd); 3.17 (3H, s); 2.03 (1H, d); 1.92 (1H, d); 1.34 (3H, d); 1.08 (2H, d); 1.05 (1H, m).
APCI-MS m/z: 588.2 [MH⁺].

5

Example 80 6-Methyl-N³-[4-(methylsulfonyl)benzyl]-2-oxo-N⁵-pyrrolidin-1-yl-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

¹H NMR (DMSO-d₆): δ 9.84 (2H, bt); 8.43 (1H, s); 7.99-7.78 (5H, m); 7.72 (1H, d); 7.54 (2H, d); 4.58 (2H, d); 3.18 (3H, s); 3.02 (4H, bs); 2.13 (3H, s); 1.80 (4H, bs).

10 APCI-MS m/z: 577.2 [MH⁺].

Example 81 6-Methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-5-(piperidin-1-ylcarbonyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

¹H NMR (DMSO-d₆): δ 9.88 (1H, t); 8.20 (1H, s); 8.03 (1H, d); 7.94-7.74 (5H, m); 7.54 (2H, d); 4.58 (2H, bs); 3.79-3.22 (4H, m); 3.18 (3H, s); 1.93 (3H, s); 1.69-1.36 (6H, m).

15 APCI-MS m/z: 576.2 [MH⁺].

Example 82 6-Methyl-N³-[4-(methylsulfonyl)benzyl]-N⁵-morpholin-4-yl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

20 ¹H NMR (DMSO-d₆): δ 9.82 (1H, t); 9.57 (0.8H, s); 9.22 (0.2H, s); 8.41 (0.8H, s); 8.36 (0.2H, s); 8.00-7.76 (5H, m); 7.72 (1H, d); 7.54 (2H, d); 4.58 (2H, d); 3.66 (4H, m); 3.17 (3H, s); 2.84 (3.2H, m); 2.73 (0.8H, bs); 2.11 (0.8H, s); 2.02 (0.2H, s).

APCI-MS m/z: 593.2 [MH⁺].

25 **Example 83** 6-Methyl-5-[(4-methylpiperidin-1-yl)carbonyl]-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

^1H NMR (DMSO- d_6): δ 9.88 (1H, t); 8.19 (1H, bd); 8.08-7.73 (6H, m); 7.72 (1H, d); 7.54 (2H, d); 4.58 (2H, bs); 4.43 (1H, bs); 3.72 (1H, bs); 3.17 (3H, s); 3.05 (1H, m); 2.76 (1H, m); 1.93 (3H, d); 1.77-1.55 (3H, m); 1.19-0.80 (5H, m).
APCI-MS m/z : 590.2 [MH^+].

5

Example 84 6-Methyl- N^3 -[4-(methylsulfonyl)benzyl]-2-oxo- N^5 -piperidin-1-yl-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

^1H NMR (DMSO- d_6): δ 9.82 (1H, t); 9.64 (0.8H, s); 9.12 (0.2H, s); 8.39 (0.8H, s); 8.35 (0.2H, s); 8.00-7.77 (5H, m); 7.72 (1H, d); 7.54 (2H, d); 4.58 (2H, d); 3.19 (3H, s); 2.84 (3H, m); 2.11 (0.8H, bs); 2.02 (0.2H, s); 1.66-1.53 (4H, m); 1.53-1.32 (3H, m).
APCI-MS m/z : 591.2 [MH^+].

10

Example 85 N^5 -(tert-Butyl)- N^5 ,6-dimethyl- N^3 -[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

^1H NMR (DMSO- d_6): δ 9.88 (1H, t); 8.19 (1H, s); 7.99 (1H, d); 7.91-7.73 (5H, m); 7.54 (2H, d); 4.58 (2H, bs); 3.18 (3H, s); 2.91 (3H, s); 1.95 (3H, s); 1.45 (9H, s).
APCI-MS m/z : 578.2 [MH^+].

15

Example 86 N^5 -Butyl- N^5 ,6-dimethyl- N^3 -[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

^1H NMR (DMSO- d_6): δ 9.88 (1H, t); 8.19 (1H, d); 8.01 (1H, s); 7.95-7.74 (5H, m); 7.54 (2H, d); 4.58 (2H, bs); 3.18 (3H, s); 2.95 (1.2H, s); 2.94 (1.8H, s); 1.92 (1.8H, s); 1.91 (1.2H, s); 1.63-1.40 (2H, m); 1.40-1.10 (2H, m); 0.92 (1.8H, t); 0.83 (1.2H, t).
APCI-MS m/z : 578.2 [MH^+].

20

25

Example 87 N^5 -Ethyl- N^5 -isopropyl-6-methyl- N^3 -[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

¹H NMR (DMSO-d₆): δ 9.90 (1H, t); 8.20 (0.3H, s); 8.15 (0.7H, s); 8.10-7.95 (1H, m); 7.95-7.75 (5H, m); 7.54 (2H, d); 4.58 (2H, bs); 4.02 (1H, bs); 3.36 (2H, bs); 3.18 (3H, s); 1.91 (3H, s); 1.32-0.96 (9H, m).
APCI-MS m/z: 578.2 [MH⁺].

5

The compounds of Examples 88 to 90 were prepared using a procedure analogous to that described for Example 76.

Example 88 5-[N¹-(Formyl-hydrazinocarbonyl)]-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide

10

¹H NMR (DMSO-d₆): δ 10.43 (1H, s); 10.13 (1H, s); 9.79 (1H, t, *J* 6.2 Hz); 8.52 (1H, s); 8.11 (1H, s); 7.93 (1H, s); 7.94-7.89 (1H, s); 7.87 (2H, d, *J* 8.65 Hz); 7.87 (1H, d, *J* 8.21); 7.74 (1H, d, *J* 8.21 Hz); 7.55 (2H, d, *J* 8.21 Hz); 4.63-4.54 (2H, m); 3.17 (3H, s); 2.18 (3H, s).

15

APCI-MS m/z: 551.2 [MH⁺].

Example 89 N¹-[5-(4-Methanesulfonyl-benzylcarbamoyl)-2-methyl-6-oxo-1-(3-trifluoromethyl-phenyl)-1,6-dihydro-pyridine-3-carbonyl]-hydrazinecarboxylic acid ethyl ester

20

¹H NMR (DMSO-d₆): δ 10.23 (1H, s); 9.79 (1H, t, *J* 6.1 Hz); 9.23 (1H, s); 8.47 (1H, s); 7.94 (1H, s); 7.94-7.89 (1H, d, *J* 8.2 Hz); 7.87 (2H, d, *J* 8.4 Hz); 7.82 (1H, d, *J* 7.7 Hz); 7.74 (1H, d, *J* 7.8 Hz); 7.54 (2H, d, *J* 8.4 Hz); 4.65-4.55 (2H, m); 4.14-4.01 (2H, m); 3.17 (3H, s); 2.16 (3H, s); 1.25-1.15 (3H, m).

APCI-MS m/z: 595.2 [MH⁺].

25

Example 90 5-({2-[(Ethylamino)carbonothioyl]hydrazino}carbonyl)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

¹H NMR (DMSO-d₆): δ 10.26 (1H, s); 9.81 (1H, t, *J* 6.0 Hz); 9.23 (1H, s); 8.71 (1H, s); 8.14 (1H, bs); 7.95-7.81 (4H, m); 7.71 (1H, d, *J* 8.0 Hz); 7.55 (2H, d, *J* 8.3 Hz); 4.60 (2H, d, *J* 6.1 Hz); 3.54-3.44 (2H, m); 3.18 (3H, s); 2.16 (3H, s); 1.08 (3H, t, *J* 7.1 Hz)
APCI-MS *m/z*: 610.2 [MH⁺].

5

Example 91 5-(Isoxazolidin-2-ylcarbonyl)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

¹H NMR (DMSO-d₆): δ 9.79 (1H, t); 8.41 (1H, s); 7.99 (1H, s); 7.93-7.74 (5H, m); 7.54 (2H, d); 4.58 (2H, d); 3.96 (2H, t); 3.76 (2H, m); 3.17 (3H, s); 2.31 (2H, p); 2.05 (3H, s).

10 APCI-MS *m/z*: 564.3 [MH⁺].

Example 92 6-Methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3,5-dicarboxylic acid 5-(methoxy-methyl-amide) 3-[4-(propane-2-sulfonyl)-benzylamide]

¹H NMR (CDCl₃): δ 9.87 (1H, bt); 8.67 (1H, s); 7.84-7.74 (4H, m); 7.52-7.49 (3H, bd);
15 7.45-7.43 (1H, bd); 4.74-4.64 (2H, m); 3.62 (3H, s); 3.38 (3H, s); 3.19-3.13 (1H, m); 2.13 (3H, s); 1.28 (6H, d, *J* 6.8 Hz).

APCI-MS *m/z*: 580 [MH⁺].

Example 93 6-Methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3,5-dicarboxylic acid 3-(4-ethanesulfonyl-benzylamide) 5-(methoxy-methyl-amide)

¹H NMR (CDCl₃): δ 9.87 (1H, bt); 8.67 (1H, s); 7.86-7.82 (3H, m); 7.78-7.74 (1H, bt);
20 7.53-7.50 (3H, m); 7.45-7.43 (1H, bd); 4.74-4.64 (2H, m); 3.66 (3H, s); 3.38 (3H, s); 3.09 (2H, q, *J* 7.5 Hz); 2.13 (3H, s); 1.26 (3H, t, *J* 7.5 Hz).

APCI-MS *m/z*: 566 [MH⁺].

25

Example 94 6-Methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3,5-dicarboxylic acid 3-(4-cyclopropanesulfonyl-benzylamide) 5-(methoxy-methyl-amide)

^1H NMR (CDCl_3): δ 9.86 (1H, bt); 8.67 (1H, s); 7.84-7.82 (3H, bd); 7.78-7.74 (1H, bt); 7.51-7.49 (3H, bd); 7.45-7.43 (1H, bd); 4.73-4.63 (2H, m); 3.66 (3H, s); 3.38 (3H, s); 2.46-2.39 (1H, m); 1.35-1.31 (2H, m); 1.04-0.99 (2H, m).

APCI-MS m/z : 578 $[\text{MH}^+]$.

5

Example 95 6-Methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3,5-dicarboxylic acid 5-[(2-hydroxy-ethyl)-amide] 3-(4-methanesulfonyl-benzylamide)

^1H NMR ($\text{DMSO}-d_6$): δ 9.82 (1H, t, J 6.0 Hz); 8.48 (1H, s); 8.48 (1H, t, J 5.6 Hz); 7.93-7.89 (1H, m); 7.90 (1H, s); 7.87 (2H, d, J 8.2 Hz); 7.83 (1H, t, J 7.6 Hz); 7.72 (1H, d, J 7.9 Hz); 7.54 (2H, d, J 8.2 Hz); 4.74 (1H, bs); 4.64-4.54 (2H, m); 3.50 (2H, t, J 6.2 Hz); 3.32-3.25 (2H, m); 3.17 (3H, s); 2.14 (3H, s).

10

APCI-MS m/z : 552.2 $[\text{MH}^+]$.

15

Example 96 5-(Isoxazolidine-2-carbonyl)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-ethanesulfonyl-benzylamide

^1H NMR (CDCl_3): δ 9.83 (1H, bt); 8.70 (1H, s); 7.85-7.81 (3H, m); 7.77-7.73 (1H, bt); 7.53-7.50 (3H, m); 7.45-7.43 (1H, bd); 4.73-4.63 (2H, m); 4.06 (2H, t, J 7.2 Hz); 3.91 (2H, t, J 7.2 Hz); 3.08 (2H, q, J 7.7 Hz); 2.48-2.41 (2H, m); 2.19 (3H, s); 1.26 (3H, t, J 7.7 Hz).

APCI-MS m/z : 579 $[\text{MH}^+]$.

20

Example 97 5-(Isoxazolidine-2-carbonyl)-6-methyl-2-oxo-1-(3-trifluoromethylphenyl)-1,2-dihydropyridine-3-carboxylic acid 4-cyclopropanesulfonylbenzylamide

^1H NMR (CDCl_3): δ 9.81 (1H, bt); 8.70 (1H, s); 7.84-7.81 (3H, m); 7.77-7.73 (1H, bt); 7.52-7.48 (3H, m); 7.45-7.43 (1H, bd); 4.73-4.62 (2H, m); 4.06 (2H, t, J 6.8 Hz); 3.91 (2H, t, J 7.2 Hz); 2.48-2.39 (3H, m); 2.19 (3H, s); 1.35-1.31 (2H, m); 1.04-0.99 (2H, m).

25

APCI-MS m/z : 590 $[\text{MH}^+]$.

Example 98 5-(N-Hydroxycarbamimidoyl)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide

5-Cyano-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide Example 1, 0.040 g, 0.082 mmol), hydroxylamine hydrochloride (0.015 g, 0.209 mmol), NaOAc (0.017 g, 0.209 mmol), ethanol (3 ml), water (0.1 ml) and a magnetic stirrer were placed in a vial. The mixture was heated at 90 °C overnight. LC-MS showed a 50:50 mixture of two components, one of which had the expected MW. The product was isolated by preparative HPLC giving 0.012 g (28%) of the title compound.

¹H NMR (DMSO-d₆): δ 9.85 (1H, t, *J* 6.2 Hz); 9.53 (1H, s); 8.33 (1H, s); 7.91 (1H, d, *J* 7.6 Hz); 7.86 (2H, d, *J* 8.2 Hz); 7.85 (1H, s); 7.83 (1H, t, *J* 7.8 Hz); 7.69 (1H, d, *J* 7.8 Hz); 7.54 (2H, d, *J* 8.3 Hz); 5.88 (2H, bs); 4.64-4.55 (2H, m); 3.17 (3H, s); 2.07 (3H, s).

APCI-MS *m/z*: 523.2 [MH⁺].

Example 99 *N*³-(Cyclohexylmethyl)-*N*⁵,*N*⁶,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

a) Ethyl 6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxylate

A suspension of 6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxylic acid (Example 1 (b), 13.1 g, 43.9 mmol), sodium carbonate (5.2 g, 48.3 mmol) and iodoethane (10.6 g, 67.7 mmol) in NMP (60 ml) was stirred at ambient temperature for 19 h under a nitrogen atmosphere. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was collected, washed with water and brine, dried over sodium sulphate, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica eluting with tert-butyl methyl ether/methanol (10:0.4) to give the title compound as a light brown solid (12.5 g, 87%).

¹H NMR (CDCl₃): δ 8.21 (1H, d, *J* 7.4 Hz); 7.75 (1H, d, *J* 7.8 Hz); 7.68 (1H, t, *J* 7.8 Hz); 7.49 (1H, s); 7.42 (1H, d, *J* 7.8 Hz); 6.25 (1H, d, *J* 7.4 Hz); 4.36 (2H, q, *J* 7.2 Hz); 2.03 (3H, s); 1.37 (3H, t, *J* 7.2 Hz).

APCI-MS *m/z*: 326.1 [MH⁺].

b) Ethyl 5-iodo-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxylate

To a solution ethyl 6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxylate (9.9 g, 30.5 mmol) in CH₂Cl₂ (45 ml) and TFA (38 ml) was added N-iodosuccinimide (6.89 g, 30.6 mmol) under a nitrogen atmosphere. After 19 h stirring at ambient temperature the solvent was concentrated in vacuo. To the residue were added ethyl acetate and saturated aqueous sodium hydrogencarbonate to neutralize the remaining TFA. The organic phase was collected, washed with water and brine, dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica eluting with DCM/methanol (10:0.2) to give the title compound as a yellow solid (11.4 g, 83%).

¹H NMR (CDCl₃): δ 8.52 (1H, s); 7.76 (1H, d, *J* 7.8 Hz); 7.69 (1H, t, *J* 7.9 Hz); 7.46 (1H, s); 7.38 (1H, d, *J* 7.7 Hz); 4.36 (2H, q, *J* 7.1 Hz); 2.26 (3H, s); 1.37 (3H, t, *J* 7.2 Hz).

APCI-MS *m/z*: 452.0 [MH⁺].

c) Ethyl 5-[(dimethylamino)carbonyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxylate

Ethyl 5-iodo-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxylate (2.6 g, 5.76 mmol), palladium(II) acetate (16.4 mg, 0.07 mmol), triphenylphosphine (38.7 mg, 0.15 mmol), anhydrous dimethylamine (5 ml) and anhydrous ethanol (20 ml) were placed in a stainless-steel autoclave (100 ml). The reaction mixture was stirred at 85 °C under a carbon monoxide pressure of 5.5 atmospheres for 2 h. After cooling, excess carbon monoxide was released into a fume hood and the solvent was concentrated in vacuo. The residue was purified by preparative HPLC to give the title compound as a white solid (1.3 g, 58 %).

¹H NMR (CDCl₃): δ 8.16 (1H, s); 7.77 (1H, d, *J* 7.9 Hz); 7.70 (1H, t, *J* 7.8 Hz); 7.49 (1H, s); 7.41 (1H, d, *J* 7.9 Hz); 4.36 (2H, q, *J* 7.1 Hz); 3.09 (6H, d, *J* 30.2 Hz); 2.04 (3H, s); 1.37 (3H, t, *J* 7.2 Hz).

APCI-MS *m/z*: 397.2 [MH⁺].

d) 5-[(Dimethylamino)carbonyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxylic acid

To a solution of ethyl 5-[(dimethylamino)carbonyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxylate (1.28 g, 3.2 mmol) in THF (5 ml) and water (1 ml) was added dropwise 2M sodium hydroxide (1.7 ml, 3.4 mmol) over 1 h. After an additional 2 h stirring at ambient temperature, the solution was acidified to pH 1 and concentrated in vacuo. The residue was purified by preparative HPLC to give the title compound as a white solid (0.92 g, 77 %).

^1H NMR (CDCl_3): δ 8.47 (1H, s); 7.88 (1H, d, J 7.8 Hz); 7.80 (1H, t, J 7.9 Hz); 7.56 (1H, s); 7.48 (1H, d, J 7.9 Hz); 3.12 (6H, d, J 36.0 Hz); 2.15 (3H, s).

APCI-MS m/z : 369.1 $[\text{MH}^+]$.

e) N^3 -(Cyclohexylmethyl)- N^5 , N^5 ,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

A mixture of 5-[(dimethylamino)carbonyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3-carboxylic acid (12 mg, 0.03 mmol), HATU (15 mg, 0.04 mmol), HOAT (7 mg, 0.04 mmol) and DIEA (13 mg, 0.1 mmol) in NMP (160 μl) was added to (cyclohexylmethyl)amine in NMP (135 μl , 0.3M, 0.04 mmol). The reaction mixture was stirred for 17 h at room temperature. The solvent was removed in vacuo, and the residue was dissolved in acetonitrile/water, 50/50, to a total volume of 1.6 ml, and purified using preparative HPLC to give the title compound (8 mg, 58%).

RT (C_{18} , UV 220 nm): 7.3 min.

APCI-MS m/z : 464.2 $[\text{MH}^+]$.

The compounds of Examples 100 to 146 were prepared using a procedure analogous to that described for Example 99.

Example 100 N^5 , N^5 ,6-Trimethyl-2-oxo- N^3 -(pyridin-3-ylmethyl)-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C_{18} , UV 220 nm): 5.0 min.

APCI-MS m/z : 459.2 $[\text{MH}^+]$.

Example 101 *N*⁵,*N*⁵,6-Trimethyl-*N*³-(2-morpholin-4-ylethyl)-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 4.9 min.

APCI-MS m/z: 481.1 [MH⁺].

5

Example 102 *N*⁵,*N*⁵,6-Trimethyl-*N*³-(3-morpholin-4-ylpropyl)-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 5.0 min.

APCI-MS m/z: 495.2 [MH⁺].

10

Example 103 *N*³-Benzyl-*N*⁵,*N*⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydro-pyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 6.8 min.

APCI-MS m/z: 458.2 [MH⁺].

15

Example 104 *N*³-[2-(1*H*-Indol-3-yl)ethyl]-*N*⁵,*N*⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 6.9 min.

APCI-MS m/z: 511.1 [MH⁺].

20

Example 105 *N*⁵,*N*⁵,6-Trimethyl-2-oxo-*N*³-(1-phenylethyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 7.0 min.

APCI-MS m/z: 472.3 [MH⁺].

25

Example 106 *N*⁵,*N*⁵,6-Trimethyl-2-oxo-*N*³-(2-phenylethyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 5.3 min.

APCI-MS m/z: 472.1 [MH⁺].

30

Example 107 *N⁵,N⁵,6*-Trimethyl-2-oxo-*N³*-[(2*R*)-2-phenylcyclopropyl]-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 5.5 min.

APCI-MS *m/z*: 484.1 [MH⁺].

5

Example 108 *N³*-(2,3-Dihydro-1*H*-inden-2-yl)-*N⁵,N⁵,6*-trimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 5.4 min.

APCI-MS *m/z*: 484.1 [MH⁺].

10

Example 109 *N³*-[2-(1,3-Benzodioxol-5-yl)ethyl]-*N⁵,N⁵,6*-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 5.2 min.

APCI-MS *m/z*: 516.2 [MH⁺].

15

Example 110 5-([4-(2-Hydroxyethyl)piperazin-1-yl]carbonyl)-*N,N*,2-trimethyl-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridine-3-carboxamide

RT (C₁₈, UV 220 nm): 3.1 min.

APCI-MS *m/z*: 481.3 [MH⁺].

20

Example 111 *N³*-[(1-Ethylpyrrolidin-2-yl)methyl]-*N⁵,N⁵,6*-trimethyl-2-oxo-1-[3-(trifluoro-methyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 3.5 min.

APCI-MS *m/z*: 479.2 [MH⁺].

25

Example 112 *N⁵,N⁵,6*-Trimethyl-*N³*-[3-(2-methylpiperidin-1-yl)propyl]-2-oxo-1-[3-(trifluoro-methyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 3.7 min.

APCI-MS *m/z*: 507.2 [MH⁺].

30

Example 113 *N*⁵,*N*⁵,6-Trimethyl-*N*³-(1-naphthylmethyl)-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 5.7 min.

APCI-MS m/z: 508.1 [MH⁺].

5

Example 114 *N*³-(1,3-Benzodioxol-5-ylmethyl)-*N*⁵,*N*⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 5.1 min.

APCI-MS m/z: 502.1 [MH⁺].

10

Example 115 *N*³-(3,4-Difluorobenzyl)-*N*⁵,*N*⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 5.4 min.

APCI-MS m/z: 494.2 [MH⁺].

15

Example 116 *N*³-(2-Chloro-4-fluorobenzyl)-*N*⁵,*N*⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 5.6 min.

APCI-MS m/z: 510.1 [MH⁺].

20

Example 117 *N*⁵,*N*⁵,6-Trimethyl-2-oxo-*N*³-(2-thienylmethyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 5.0 min.

APCI-MS m/z: 464.2 [MH⁺].

25

Example 118 *N*³-(3,4-Dichlorobenzyl)-*N*⁵,*N*⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 5.9 min.

APCI-MS m/z: 526.1 [MH⁺].

30

Example 119 *N*³-[2-(2,4-Dichlorophenyl)ethyl]-*N*⁵,*N*⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 6.0 min.

APCI-MS *m/z*: 540.1 [MH⁺].

5

Example 120 *N*³-(2-Cyclohex-1-en-1-ylethyl)-*N*⁵,*N*⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 5.7 min.

APCI-MS *m/z*: 476.2 [MH⁺].

10

Example 121 *N*³-[1-(4-Chlorophenyl)ethyl]-*N*⁵,*N*⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 5.8 min.

APCI-MS *m/z*: 506.2 [MH⁺].

15

Example 122 *N*⁵,*N*⁵,6-Trimethyl-2-oxo-*N*³-[3-(2-oxopyrrolidin-1-yl)propyl]-1-[3-(trifluoro-methyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 4.0 min.

APCI-MS *m/z*: 493.3 [MH⁺].

20

Example 123 *N*⁵,*N*⁵,6-Trimethyl-2-oxo-*N*³-(pyridin-4-ylmethyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 3.3 min.

APCI-MS *m/z*: 459.2 [MH⁺].

25

Example 124 *N,N*,2-Trimethyl-6-oxo-5-[(4-phenylpiperazin-1-yl)carbonyl]-1-[3-(trifluoro-methyl)phenyl]-1,6-dihydropyridine-3-carboxamide

RT (C₁₈, UV 220 nm): 4.1 min.

APCI-MS *m/z*: 513.2 [MH⁺].

30

Example 125 *N,N*,2-Trimethyl-6-oxo-5-[(4-pyridin-2-yl)piperazin-1-yl]carbonyl]-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridine-3-carboxamide

RT (C₁₈, UV 220 nm): 3.2 min.

APCI-MS *m/z*: 514.3 [MH⁺].

5

Example 126 *N*³-(2,3-Dihydro-1-benzofuran-5-ylmethyl)-*N*⁵,*N*⁶-6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 5.1 min.

APCI-MS *m/z*: 500.2 [MH⁺].

10

Example 127 Methyl 4-[[[5-[(dimethylamino)carbonyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridin-3-yl]carbonyl]amino]methyl]benzoate

RT (C₁₈, UV 220 nm): 5.1 min.

APCI-MS *m/z*: 516.2 [MH⁺].

15

Example 128 5-[[3-(Dimethylamino)pyrrolidin-1-yl]carbonyl]-*N,N*,2-trimethyl-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridine-3-carboxamide

RT (C₁₈, UV 220 nm): 3.1 min.

APCI-MS *m/z*: 465.2 [MH⁺].

20

Example 129 *N*⁵,*N*⁶-6-Trimethyl-2-oxo-*N*³-[2-(2-thienyl)ethyl]-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 5.2 min.

APCI-MS *m/z*: 478.1 [MH⁺].

25

Example 130 *N*⁵,*N*⁶-6-Trimethyl-2-oxo-*N*³-(4-phenoxybenzyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 6.0 min.

APCI-MS *m/z*: 550.3 [MH⁺].

30

Example 131 *N*⁵,*N*⁵,6-Trimethyl-2-oxo-*N*³-(3-thienylmethyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide
RT (C₁₈, UV 220 nm): 5.0 min.
APCI-MS *m/z*: 464.2 [MH⁺].

5

Example 132 *N*³-[2-(4-*tert*-Butylphenyl)ethyl]-*N*⁵,*N*⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide
RT (C₁₈, UV 220 nm): 6.3 min.
APCI-MS *m/z*: 528.2 [MH⁺].

10

Example 133 *N*³-[2-[4-(Aminosulfonyl)phenyl]ethyl]-*N*⁵,*N*⁵,6-trimethyl-2-oxo-1-[3-(trifluoro-methyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide
RT (C₁₈, UV 220 nm): 4.4 min.
APCI-MS *m/z*: 551.2 [MH⁺].

15

Example 134 *N*⁵,*N*⁵,6-Trimethyl-2-oxo-*N*³-[4-(1*H*-pyrazol-1-yl)benzyl]-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide
RT (C₁₈, UV 220 nm): 5.0 min.
APCI-MS *m/z*: 524.2 [MH⁺].

20

Example 135 *N*⁵,*N*⁵,6-Trimethyl-2-oxo-*N*³-phenoxy-1-[3-(trifluoromethyl)phenyl]-1,2-dihydro-pyridine-3,5-dicarboxamide
RT (C₁₈, UV 220 nm): 5.1 min.
APCI-MS *m/z*: 460.1 [MH⁺].

25

Example 136 *N*³-(2,3-Dihydro-1,4-benzodioxin-2-ylmethyl)-*N*⁵,*N*⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide
RT (C₁₈, UV 220 nm): 5.4 min.
APCI-MS *m/z*: 516.2 [MH⁺].

30

Example 137 *N*³-[(6-Fluoro-4*H*-1,3-benzodioxin-8-yl)methyl]-*N*⁵,*N*⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 5.2 min.

APCI-MS *m/z*: 534.2 [MH⁺].

5

Example 138 *N*³-(1-Benzothien-3-ylmethyl)-*N*⁵,*N*⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 5.6 min.

APCI-MS *m/z*: 514.1 [MH⁺].

10

Example 139 *N*⁵,*N*⁵,6-Trimethyl-2-oxo-*N*³-[2-(tetrahydro-2*H*-pyran-4-yl)ethyl]-1-[3-(trifluoro-methyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 4.5 min.

APCI-MS *m/z*: 480.2 [MH⁺].

15

Example 140 *N*⁵,*N*⁵,6-Trimethyl-*N*³-[(1-methyl-1*H*-pyrazol-4-yl)methyl]-2-oxo-1-[3-(trifluoro-methyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 4.0 min.

APCI-MS *m/z*: 462.2 [MH⁺].

20

Example 141 *N*⁵,*N*⁵,6-Trimethyl-2-oxo-*N*³-[(1-phenyl-1*H*-pyrazol-4-yl)methyl]-1-[3-(trifluoro-methyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 5.1 min.

APCI-MS *m/z*: 524.2 [MH⁺].

25

Example 142 *N*³-[(5-Methoxy-4-oxo-4*H*-pyran-2-yl)methyl]-*N*⁵,*N*⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 3.9 min.

APCI-MS *m/z*: 506.2 [MH⁺].

30

Example 143 *N*³-(3-Azepan-1-ylpropyl)-*N*⁵,*N*⁶-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 3.7 min.

APCI-MS *m/z*: 507.2 [MH⁺].

5

Example 144 *N*³-(4-Cyanobenzyl)-*N*⁵,*N*⁶-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 5.0 min.

APCI-MS *m/z*: 483.2 [MH⁺].

10

Example 145 *N*⁵,*N*⁶-Trimethyl-2-oxo-*N*³-[3-(5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl)propyl]-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 3.8 min.

APCI-MS *m/z*: 492.2 [MH⁺].

15

Example 146 *N*³-{[(2*R*)-1-Ethylpyrrolidin-2-yl]methyl}-*N*⁵,*N*⁶-trimethyl-2-oxo-1-[3-(trifluoro-methyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide

RT (C₁₈, UV 220 nm): 3.4 min.

APCI-MS *m/z*: 479.2 [MH⁺].

20

Example 147 5-Cyclopropyl-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

A mixture of 5-iodo-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-

(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (Example 1 (d), 120.4 mg,

25 0.20 mmol), cyclopropylboronic acid (48.7 mg, 0.57 mmol), potassium phosphate (195.3 mg, 0.85 mmol), tricyclohexylphosphine (19.9 mg, 0.07 mmol) and palladium acetate (8.5 mg, 0.03 mmol) in toluene (4 ml) and water (0.08 ml) was stirred at 100 °C under an argon atmosphere for 2 h. The reaction mixture was cooled and concentrated in vacuo.

The residue was purified by preparative HPLC to give the title compound as a white solid

30 (36 mg, 35%).

¹H NMR (CDCl₃): δ 10.06 (1H, t, J 5.9 Hz); 8.48 (1H, s); 7.87 (2H, d, J 8.4 Hz); 7.81 (1H, d, J 7.8 Hz); 7.74 (1H, t, J 7.8 Hz); 7.51 (3H, d, J 8.4 Hz); 7.42 (1H, d, J 7.7 Hz); 4.67 (2H, m); 3.01 (3H, s); 2.20 (3H, s); 1.76 (1H, dd, J 13.6 3.0 Hz); 0.99 (2H, m); 0.70 (2H, q, J 5.1 Hz).

5 APCI-MS m/z: 505.1 [MH⁺].

Example 148 6-Methyl-5-(2-methyl-1,3-dioxolan-2-yl)-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

5-Acetyl-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide (Example 4, 55 mg, 0.11 mmol), ethane-1,2-diol (482 mg, 8.7 mmol), toluene-4-sulfonic acid monohydrate (21 mg, 0.11 mmol) and toluene (50 ml) were placed in a round-bottomed flask (100 ml) equipped with a Dean and Stark water separator, reflux condenser and magnetic stirrer. The reaction mixture was heated at reflux for 48 h. After cooling, the mixture was neutralized with aqueous sodium hydrogen carbonate solution and the solvent was removed in vacuo. The residue was purified by preparative HPLC to give the title compound as a white solid (31.5 mg, 52 %).

¹H NMR (CDCl₃): δ 9.99 (1H, t); 8.90 (1H, s); 7.87 (2H, d); 7.81 (1H, d); 7.74 (1H, t); 7.52 (2H, d); 7.50 (1H, s); 7.42 (1H, d); 4.67 (2H, m); 4.07 (2H, m); 3.85 (2H, m); 3.01 (3H, s); 2.23 (3H, s); 1.67 (3H, s).

20 APCI-MS m/z: 551.0 [MH⁺].

Example 149 5-(4,5-Dihydro-oxazol-2-yl)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide

The compound obtained in Example 95 (0.022 g, 0.04 mmol) was dissolved in dry DCM (2 ml). To this solution was added one drop of SOCl₂, and the mixture was allowed to stand for 1 h. LC-MS showed complete consumption of the starting material. Evaporation and subsequent purification on preparative HPLC afforded the title compound 0.004 g (20%) as a white solid after freeze-drying the pure fractions.

¹H NMR (DMSO-d₆): δ 9.74 (1H, t, J 6.1 Hz); 8.78 (1H, s); 7.96 (1H, s); 7.91 (1H, d, J 7.6 Hz); 7.86 (2H, d, J 8.2 Hz); 7.83 (1H, t, J 7.8 Hz); 7.76 (1H, d, J 7.8 Hz); 7.54 (2H, d, J

8.2 Hz); 4.65–4.55 (2H, m); 4.38 (2H, t, J 9.2 Hz); 3.99 (2H, t, J 9.2 Hz); 3.17 (3H, s); 2.40 (3H, s).

APCI-MS m/z : 534.1 $[MH]^+$.

5 **Example 150** 5-Cyclopropyl-6-methyl-N-[[5-(methylsulfonyl)pyridin-2-yl]methyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

a) 5-Cyclopropyl-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxylic acid

10 Ethyl 5-iodo-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxylate (Example 99 (b), 0.77 g, 1.6 mmol), toluene (35 ml), cyclopropyl-boronic acid (0.257 g, 3 mmol), $Pd(OAc)_2$ (0.072 g, 0.35 mmol), $P(c\text{-Hex})_3$ (0.169 g, 0.6 mmol), K_3PO_4 monohydrate (1.6 g, 6.9 mmol), water (0.7 ml) and a magnetic stirrer bar were placed in a pressure safe glass vessel. The vessel was sealed and heated (130 °C) with stirring
15 overnight. LC-MS showed complete formation of the intermediate ethyl ester. The mixture was allowed to cool and the phases were diluted with EtOAc (50 ml) and water (50 ml) and the phases were allowed to separate. The organic phase was washed with water and brine, and further dried with Na_2SO_4 . Filtration and evaporation gave a crude intermediate. This material was dissolved in THF (10 ml) and water (5 ml). To this solution was added
20 NaOH (1M, 3 ml, 3 mmol) and the mixture was stirred for 2 h at 50 °C. The THF was evaporated and the residual aqueous phase was acidified and extracted with EtOAc (2 x 20 ml). The extracts were washed with water and brine and finally dried over Na_2SO_4 . Filtration and evaporation gave the required carboxylic acid (0.19 g, 33%).
APCI-MS m/z : 338.1 $[MH]^+$. Retention time 2.35 minutes.

25

b) 5-(Methylthio)pyridine-2-carbonitrile

5-Bromo-pyridine-2-carbonitrile (2.63 g, 13.7 mmol), sodium methanethiolate (1.44 g, 20.5 mmol), potassium carbonate (3.79 g, 27.4 mmol) in NMP (60 ml) were stirred in a sealed flask overnight. The mixture was partitioned between ethyl acetate and water. The organic
30 phase was washed with water several times, brine and dried over sodium sulphate. The solvent was removed in vacuo to afford the title compound as a yellow solid (2.0 g, 99%).

¹H NMR (CD₃OD): δ 8.54 (1H, d, J 2.3 Hz); 7.83 - 7.71 (2H, m); 2.60 (3H, s).

c) 5-(Methylsulfonyl)pyridine-2-carbonitrile

5-(Methylthio)pyridine-2-carbonitrile (2.0 g, 13.3 mmol) was dissolved in DCM (20 ml) and cooled to -15 °C and 3-chloroperoxybenzoic acid (6.75 g, 27.4 mmol) was added in portions while the temperature was kept between -15 °C to -10 °C. When the addition was complete, the cooling bath was removed and the mixture was stirred at room temperature for 2 h. 2M KOH and DCM were added. The organic phase was separated, washed twice with 2M KOH, water and brine, dried over sodium sulphate and evaporated to afford the title compound as a white solid (2.15 g, 89%).

¹H NMR (CD₃OD): δ 9.22 (1H, d, J 2.3 Hz); 8.54 (1H, dd, J 8.1, 2.3 Hz); 8.13 (1H, d, J 8.3 Hz); 3.27 (3H, s).

d) {[5-(Methylsulfonyl)pyridin-2-yl]methyl}amine hydrochloride

5-(Methylsulfonyl)pyridine-2-carbonitrile (2.15 g, 11.8 mmol) was dissolved in methanol (230 ml). 6M HCl (1 ml) and 10% palladium on carbon (234 mg) were added and the mixture was stirred under an atmospheric pressure of hydrogen overnight. The catalyst was removed by filtration through celite and the solvent was evaporated, water was added and the solution was freeze-dried to afford the title compound as a yellow powder (2.34 g, 89%).

¹H NMR (CD₃OD): δ 9.10 (1H, d, J 2.2 Hz); 8.36 (1H, dd, J 8.2, 2.4 Hz); 7.68 (1H, d, J 8.8 Hz); 4.29 (2H, s); 3.22 (3H, s).

e) 5-Cyclopropyl-6-methyl-N-([5-(methylsulfonyl)pyridin-2-yl]methyl)-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide

5-Cyclopropyl-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxylic acid, {[5-(methylsulfonyl)pyridin-2-yl]methyl}amine hydrochloride, HBTU and DIEA in NMP were reacted together overnight. Purification by HPLC gave the title compound.

¹H NMR (DMSO): δ 10.14 (1H, t, J 5.8 Hz); 8.98 (1H, d, J 2.3 Hz); 8.26 (1H, dd, J 8.2, 2.4 Hz); 8.18 (1H, s); 7.94 - 7.79 (3H, m); 7.74 - 7.68 (1H, m); 7.55 (1H, d, J 8.4 Hz); 4.69 (2H, d, J 5.9 Hz); 3.29 (3H, s); 2.13 (3H, s); 1.90 - 1.78 (1H, m); 0.99 - 0.90 (2H, m); 0.64 - 0.56 (2H, m).

5 APCI-MS m/z : 506.1 [MH^+].

Screen

10

Human Neutrophil Elastase Quenched-FRET Assay

The assay uses Human Neutrophil Elastase (HNE) purified from serum (Calbiochem art. 324681; Ref. Baugh, R.J. et al., 1976, Biochemistry. 15, 836-841). HNE was stored in
15 50 mM NaOAc, 200 mM 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 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%
20 DMSO, followed by 30 μ L HNE in assay buffer with 0.01% TritonX-100. The assay buffer constitution was: 100 mM 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 stopped after 30 minutes incubation at room temperature by adding 60 μ L stop solution (140 mM acetic acid, 200 mM sodium
25 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.

When tested in the above screen, the compounds of the Examples gave IC₅₀ values for
30 inhibition of human neutrophil elastase activity of less than 30 μ M, indicating that the

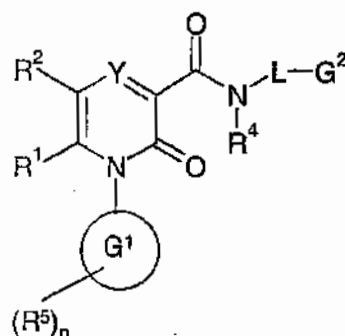
compounds of the invention are expected to possess useful therapeutic properties.

Specimen results are shown in the following Table:

Compound	Inhibition of Human Neutrophil Elastase IC ₅₀ (nM)
Example 8	83
Example 16	48
Example 19	99
Example 58	51
Example 66	22

Claims

1. A compound of formula (I)



(I)

wherein:

Y represents CR³ or N;

R¹ represents H or C1 to 6 alkyl;

R² represents:

i) CN, NO₂, OH, OSO₂R⁴⁷, O-C2 to 6 alkanoyl, CO₂R⁴⁷, CHO or C2 to 6 alkanoyl; or

ii) C1 to 6 alkoxy optionally substituted by OH, C1 to 6 alkoxy, CN, NR^{54, 55}, CONR^{54, 55}, OCOR⁴⁷ or one or more F atoms; or

iii) C3 to 6 saturated or partially unsaturated cycloalkyl optionally further substituted by C1 to 6 alkyl; or

iv) C4 to 7 saturated or partially unsaturated heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, S(O)_m and NR⁶² optionally further substituted by C1 to 6 alkyl; or

v) $\text{CONR}^{48,49}$, $\text{CONR}^{50}\text{NR}^{48,49}$, $\text{C(=NOR}^{52})\text{R}^{53}$, C(=NH)NHOR^{52} or $\text{NR}^{48,49}$;

or

vi) C2 to 6 alkenyl or C2 to 6 alkynyl; said alkenyl or alkynyl group being optionally further substituted by C1 to 6 alkoxy or phenyl or a five- or six-membered heteroaromatic ring containing 1 to 3 heteroatoms independently selected from O, S and N; said phenyl or heteroaromatic ring being optionally further substituted by halogen, CN, C1 to 6 alkyl or C1 to 6 alkoxy; or

vii) C1 to 6 alkyl substituted by one or more F atoms; or

viii) C1 to 6 alkyl substituted by one or more groups selected from halogen, OH, oxo, azido, $\text{NR}^{48,49}$, C1 to 6 alkoxy and C1 to 6 alkoxy substituted by one or more F atoms; or

ix) C1 to 6 alkyl substituted by phenyl or a five- or six-membered heteroaromatic ring containing 1 to 3 heteroatoms independently selected from O, S and N; said phenyl or heteroaromatic ring being optionally further substituted by halogen, CN, C1 to 6 alkyl or C1 to 6 alkoxy;

R^{48} and R^{49} independently represent H, OH, C1 to 6 alkoxy, C3 to 6 cycloalkyl, CHO, C2 to 6 alkanoyl, CO_2R^{50} , $\text{C(X)NR}^{63,64}$ or C1 to 6 alkyl; said alkyl being optionally further substituted by OH, C1 to 4 alkoxy, C3 to 6 cycloalkyl, CN or phenyl or a five- or six-membered heteroaromatic ring containing 1 to 3 heteroatoms independently selected from O, S and N; said alkanoyl being optionally further substituted by CN;

X represent O or S;

or the group $\text{NR}^{48,49}$ together represents a saturated or partially unsaturated 5 to 7 membered azacyclic ring optionally incorporating one further heteroatom selected from O, S and N; said azacyclic ring being optionally further substituted by one or more substituents selected from OR^{57} and C1 to 4 alkyl; said alkyl being optionally further substituted by OR^{57} ;

R^3 represents H or F;

G^1 represents phenyl or a five- or six-membered heteroaromatic ring containing 1 to 3
5 heteroatoms independently selected from O, S and N;

R^5 represents H, halogen, C1 to 6 alkyl, CN, C1 to 6 alkoxy, NO_2 , $NR^{14}R^{15}$, C1 to 3 alkyl
substituted by one or more F atoms or C1 to 3 alkoxy substituted by one or more F atoms;

10 R^{14} and R^{15} independently represent H or C1 to 3 alkyl; said alkyl being optionally further
substituted by one or more F atoms;

n represents an integer 1, 2 or 3 and when n represents 2 or 3, each R^5 group is selected
independently;

15 R^4 represents H or C1 to 6 alkyl; said alkyl being optionally further substituted by OH or
C1 to 6 alkoxy;

or R^4 and L are joined together such that the group $-NR^4L$ represents a 5 to 7 membered
20 azacyclic ring optionally incorporating one further heteroatom selected from O, S and
 NR^{16} ; said ring being optionally further substituted by C1 to 6 alkyl or $NR^{60}R^{61}$; said
alkyl being optionally further substituted by OH;

L represents a bond, O, NR^{29} or C1 to 6 alkyl; said alkyl optionally incorporating a
25 heteroatom selected from O, S and NR^{16} ; and said alkyl being optionally further
substituted by OH or OMe;

G^2 represents a monocyclic ring system selected from:

- i) phenyl or phenoxy,
- ii) a 5 or 6 membered heteroaromatic ring containing one to three heteroatoms independently selected from O, S and N,
- 5 iii) a C3 to 6 saturated or partially unsaturated cycloalkyl, or
- iv) a C4 to 7 saturated or partially unsaturated heterocyclic ring containing one or two heteroatoms independently selected from O, S(O)_p and NR¹⁷ and optionally further incorporating a carbonyl group; or

10 G² represents a bicyclic ring system in which each of the two rings is independently selected from:

- i) phenyl,
- ii) a 5 or 6 membered heteroaromatic ring containing one to three heteroatoms independently selected from O, S and N,
- 15 iii) a C3 to 6 saturated or partially unsaturated cycloalkyl, or
- iv) a C4 to 7 saturated or partially unsaturated heterocyclic ring containing one or two heteroatoms independently selected from O, S(O)_p and NR¹⁷ and optionally further incorporating a carbonyl group;

20

and the two rings are either fused together, or are bonded directly together or are separated by a linker group selected from O, S(O)_q or CH₂,

said monocyclic or bicyclic ring system being optionally further substituted by one to three
 25 substituents independently selected from CN, OH, C1 to 6 alkyl, C1 to 6 alkoxy, halogen, NR^{18, 19}, NO₂, OSO₂R³⁸, CO₂R²⁰, C(=NH)NH₂, C(O)NR^{21, 22}, C(S)NR^{23, 24}, SC(=NH)NH₂, NR³¹C(=NH)NH₂, S(O)_sR²⁵, SO₂NR^{26, 27}, C1 to 3 alkoxy substituted by one or more F atoms and C1 to 3 alkyl substituted by SO₂R³⁹ or by one or more F atoms;
 or

30

when L does not represent a bond, G^2 may also represent H;

at each occurrence, m, p, q, s and t independently represent an integer 0, 1 or 2;

R^{18} and R^{19} independently represent H, C1 to 6 alkyl, formyl, C2 to 6 alkanoyl, $S(O)_tR^{32}$ or $SO_2NR^{33}R^{34}$; said alkyl group being optionally further substituted by halogen, CN, C1 to 4 alkoxy
5 or $CONR^{41}R^{42}$;

R^{25} represents H, C1 to 6 alkyl or C3 to 6 cycloalkyl; said alkyl group being optionally further substituted by one or more substituents selected independently from OH, CN, $CONR^{35}R^{36}$, CO_2R^{37} , $OCOR^{40}$, C3 to 6 cycloalkyl, a C4 to 7 saturated heterocyclic ring containing one or two heteroatoms independently selected from O, $S(O)_p$ and NR^{43} and phenyl or a 5 or 6 membered
10 heteroaromatic ring containing one to three heteroatoms independently selected from O, S and N; said aromatic ring being optionally further substituted by one or more substituents selected independently from halogen, CN, C1 to 4 alkyl, C1 to 4 alkoxy, OH, $CONR^{44}R^{45}$, CO_2R^{46} , $S(O)_sR^{65}$ and $NHCOCH_3$;

R^{32} represents H, C1 to 6 alkyl or C3 to 6 cycloalkyl;

15 R^{16} , R^{17} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{26} , R^{27} , R^{29} , R^{31} , R^{33} , R^{34} , R^{35} , R^{36} , R^{37} , R^{38} , R^{39} , R^{40} , R^{41} , R^{42} , R^{43} , R^{44} , R^{45} , R^{46} , R^{47} , R^{50} , R^{52} , R^{53} , R^{54} , R^{55} , R^{56} , R^{57} , R^{60} , R^{61} , R^{62} , R^{63} , R^{64} and R^{65} independently represent H or C1 to 6 alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound of formula (I), according to Claim 1, wherein Y represents CR^3 .

20 3. A compound of formula (I), according to Claim 1 or Claim 2, wherein G^1 represents phenyl.

4. A compound of formula (I), according to any one of Claims 1 to 3, wherein R^5 represents C1, CH_3 , CN or CF_3 .

25 5. A compound of formula (I), according to any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof, for use as a medicament.

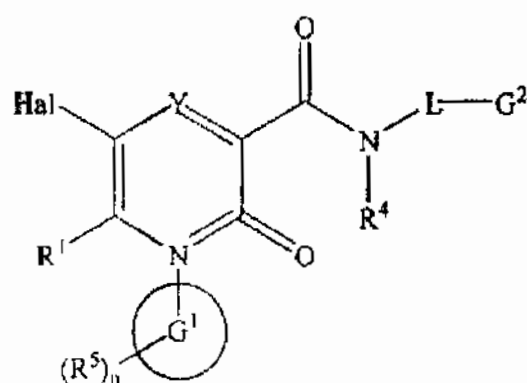
6. A pharmaceutical formulation comprising a compound of formula (I), as defined in any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof, optionally in admixture with a pharmaceutically acceptable diluent or carrier.

7. The use of a compound of formula (I) as defined in any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of human diseases or conditions in which inhibition of neutrophil elastase activity is beneficial.

8. The use of a compound of formula (I) as defined in any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of inflammatory diseases or conditions.

9. A process for the preparation of a compound of formula (I) according to Claim 1, as defined in any one of Claims 1 to 4, or optical isomers, racemates or tautomers thereof or pharmaceutically acceptable salts thereof, which comprises:

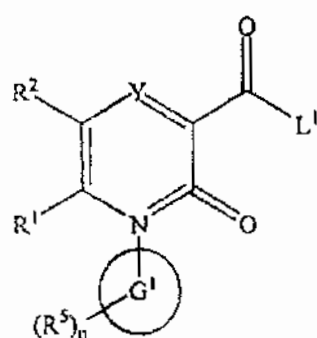
a) reacting a compound of formula (II)



(II)

with a nucleophilic equivalent of R^2 ; wherein R^1 , R^2 , R^4 , R^5 , Y , G^1 , G^2 , L and n are as defined in formula (I) according to Claim 1 and Hal represents a halogen atom; or

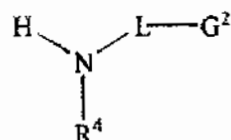
b) reacting a compound of formula (XV)



(XV)

wherein R^1 , R^2 , R^5 , n , G^1 and Y are as defined in formula (I) according to Claim 1 and L^1 represents a leaving group,

with a compound of formula (IX) or a salt thereof



(IX)

wherein R^4 , G^2 and L are as defined in formula (I) according to Claim 1;

and optionally converting the resultant compound of formula (I), or another salt thereof, into a pharmaceutically acceptable salt thereof; or converting one compound of formula (I) into another compound of formula (I); and optionally converting the resultant compound of formula (I) into an optical isomer thereof.

10. A process according to Claim 9 wherein the nucleophilic equivalent of R^2 is selected from the group consisting of $Cu(I)CN$, an alkyl vinyl ether, an organo-tin compound, an organo boronic acid, a terminal alkyne and an alcohol and carbon monoxide.

11. A process according to Claim 9 or 10, wherein Hal represents bromo or iodo.