

Carboxamide compounds and their use as calpain inhibitors V

Description

5 The present invention relates to novel carboxamide compounds and their use for the manufacture of a medicament. The carboxamide compounds are inhibitors of calpain (calcium dependant cysteine proteases). The invention therefore also relates to the use of these carboxamide compounds for treating a disorder associated with an elevated calpain activity.

10

Calpains are intracellular, proteolytic enzymes from the cysteine protease group and are found in many cells. The enzyme calpain is activated by elevated calcium concentration, with a distinction being made between calpain I or μ -calpain, which is activated by μ -molar concentrations of calcium ions, and calpain II or m-calpain, which
15 is activated by m-molar concentrations of calcium ions. Currently, further calpain isoenzymes are also postulated (M.E. Saez et al.; Drug Discovery Today **2006**, *11* (19/20), pp. 917-923; Goll et al., Physiol. Rev. **2003**, 83, oo. 731-801; K. Suzuki et al., Biol. Chem. Hoppe-Seyler, **1995**, 376 (9), pp.523-9).

20 Calpains play an important role in various physiological processes. These processes include the cleavage of different regulatory proteins such as protein kinase C, cytoskeletal proteins such as MAP 2 and spectrin, and muscle proteins, protein degradation in rheumatoid arthritis, proteins in the activation of platelets, neuropeptide metabolism, proteins in mitosis, and others which are listed in: M.J.Barrett et al., Life
25 Sci. **1991**, 48, pp.1659-69; K. Wang et al., Trends in Pharmacol.Sci. **1994**, 15, pp. 412-419.

Elevated calpain levels have been measured in various pathophysiological processes, for example: ischemias of the heart (e.g. myocardial infarction), the kidney, the lung, the
30 liver or the central nervous system (e.g. stroke), inflammations, muscular dystrophies, cataracts of the eyes, diabetes, HIV disorders, injuries to the central nervous system (e.g. brain trauma), Alzheimer's, Huntington's, Parkinson's diseases, multiple sclerosis etc. (see K.K. Wang, above) and infectious diseases such as malaria (IM Medana et al.,

Neuropath and Appl. Neurobiol. **2007**, 33, pp.179-192). It is assumed that there is a connection between these diseases and generally or persistently elevated intracellular calcium levels. This results in calcium-dependent processes becoming hyperactivated and no longer being subject to normal physiological control. A corresponding
5 hyperactivation of calpains can also trigger pathophysiological processes.

For this reason, it was postulated that inhibitors of calpain could be of use for treating these diseases. This postulate was confirmed by a variety of investigations. Thus, Seung-Chyul Hong et al., *Stroke* **1994**, 25 (3), pp. 663-669, and R. T. Bartus et al.,
10 *Neurological Res.* **1995**, 17, pp. 249-258, have demonstrated that calpain inhibitors have a neuroprotective effect in acute neurodegenerative impairments or ischemias such as occur after cerebral stroke. K. E. Saatman et al., *Proc. Natl. Acad. Sci. USA*, **1996**, 93, pp. 3428-3433 describe that following experimental brain trauma, calpain inhibitors also improved recovery from the memory performance deficits and neuromotor
15 impairments. C. L. Edelstein et al., *Proc. Natl. Acad. Sci. USA*, **1995**, 92, pp. 7662-6, found that calpain inhibitors have a protective effect on hypoxia-damaged kidneys. Yoshida, Ken Ischi et al., *Jap. Circ. J.* **1995**, 59 (1), pp. 40-48, pointed out that calpain inhibitors had favorable effects following cardiac damage which was produced by ischemia or reperfusion. The calpain inhibitor BDA-410 delayed the progression of
20 malaria infection in a mouse model of malaria pathogenesis as shown by X. Li et al., *Mol. Biochem. Parasitol.* **2007**, 155 (1), pp 26-32.

More recent studies have shown in calpastatin transgenic animals that the expression of the natural inhibitor of calpain significantly attenuates the pathophysiological effects of
25 activated calpain in experimental glomerulonephritis shown by J. Peltier et al., *J A, Soc Nephrol.* **2006**, 17, pp. 3415-3423, in cardiovascular remodeling in angiotensin II-induced hypertension, in impaired synaptic transmission in slow-channel congenital myasthenic syndrome shown by Groshong JS et al., *J Clin Invest.* **2007**, 117 (10), pp 2903-2912, in excitotoxic DNA fragmentation via mitochondrial pathways shown by J
30 Takano et al., *J Biol Chem.* **2005**, 280 (16) pp. 16175-16184, and in necrotic processes in dystrophic muscles shown by M J Spencer et al., *Hum Mol Gen*, **2002**, 11(21), pp 2645-2655.

It has been shown in recent years that both the function and the metabolism of a number of important proteins involved in the development of Alzheimer's disease are modulated by calpain. Various external influences such as, for example, excitotoxins, oxidative stress or else the action of amyloid protein lead to hyperactivation of calpain in the nerve cell, causing, as cascade, a dysregulation of the CNS-specific kinase cdk5 and subsequently a hyperphosphorylation of the so-called tau protein. Whereas the actual task of the tau protein consists of stabilizing the microtubules and thus the cytoskeleton, phosphorylated tau is no longer able to fulfil this function; the cytoskeleton collapses, axonal transport of matter is impaired and thus eventually the nerve cell degenerates (G. Patrick et al., *Nature* **1999**, *402*, pp. 615-622; E. A. Monaco et al.; *Curr. Alzheimer Res.* **2004**, *1 (1)*, pp. 33-38). Accumulation of phosphorylated tau additionally leads to the formation of so-called neurofibrillary tangles (NFTs) which, together with the well-known amyloid plaques, represent a pathological hallmark of Alzheimer's disease. Similar changes in the tau protein, generally referred to important feature of as tauopathies are also observed in other (neuro)degenerative disorders such as, for example, following stroke, inflammations of the brain, Parkinsonism, in normal-pressure hydrocephalus and Creutzfeldt-Jakob disease.

The involvement of calpain in neurodegenerative processes has been demonstrated in transgenic mice with the aid of calpastatin, a specific and natural inhibitor of calpains (Higuchi et al.; *J. Biol. Chem.* **2005**, *280 (15)*, pp. 15229-15237). It was possible with the aid of a calpain inhibitor to reduce markedly the clinical signs of acute autoimmune encephalomyelitis in a mouse model of multiple sclerosis (F. Mokhtarian et al.; *J. Neuroimmunology* **2006**, Vol. 180, pp. 135-146). It has further been shown that calpain inhibitors on the one hand block the A β -induced degeneration of neurons (Park et al.; *J. Neurosci.* **2005**, *25*, pp. 5365-5375), and in addition reduce the release of the β -amyloid precursor protein (β APP) (J. Higaki et al., *Neuron*, **1995**, *14*, pp. 651-659). With this background, calpain inhibitors having sufficient CNS availability represent a novel therapeutic principle for the treatment of neurodegenerative disorders in general and in particular also of Alzheimer's disease.

The release of interleukin-1 α is likewise inhibited by calpain inhibitors (N. Watanabe et al., *Cytokine* **1994**, *6(6)*, pp. 597-601). It has additionally been found that calpain

inhibitors show cytotoxic effects on tumor cells (E. Shiba et al. 20th Meeting Int. Ass. Breast Cancer Res., Sendai Jp, **1994**, 25.-28.Sept., Int. J. Oncol. S(Suppl.), **1994**, 381).

- The involvement of calpain in HIV disorders has only recently been shown. Thus, it has
5 been demonstrated that the HIV-induced neurotoxicity is mediated by calpain
(O'Donnell et al.; J. Neurosci. **2006**, 26 (3), pp. 981-990). Calpain involvement in the
replication of the HIV virus has also been shown (Teranishi et al.; Biochem. Biophys.
Res. Comm. **2003**, 303 (3), pp. 940-946).
- 10 Recent investigations indicate that calpain plays a part in so-called nociception, the
perception of pain. Calpain inhibitors showed a distinctly beneficial effect in various
preclinically relevant models of pain, e.g. in the thermally induced hyperalgesia in rats
(Kunz et al.; Pain **2004**, 110, pp.409-418), in Taxol-induced neuropathy (Wang et al.;
Brain **2004**, 127, pp.671-679) and in acute and chronic inflammatory processes
15 (Cuzzocrea et al.; American Journal of Pathology **2000**, 157 (6), pp. 2065-2079).

- The involvement of calpain in the development of kidney diseases, such as chronic
kidney diseases, e.g. diabetic nephropathy, has also been shown recently. Thus, it has
been demonstrated by Y. Shi et al. in animal models that the natural calpain inhibitor
20 calpastatin is down regulated during renal ischemia reperfusion (Am. J. Physiol. Renal
Physiol. **2000**, 279, pp. 509-517). Furthermore, A. Dnyanmote et al., Toxicology and
Applied Pharmacology **2006**, 215, pp.146-157, have shown that inhibition of calpain via
overexpression of calpastatin reduces the progression of DCVC-induced renal injury in
a model of acute renal failure. In addition, Peltier et al. have demonstrated that calpain
25 activation and secretion promotes glomerular injury in experimental glomerulonephritis
(J. Am. Soc. Nephrol. **2006**, 17, pp. 3415-3423). It has also been shown that calpain
inhibitors reduce renal dysfunction and injury caused by renal ischemia-reperfusion and
thus may be useful in enhancing the tolerance of the kidney against renal injury
associated with aortovascular surgery or renal transplantation (P. Chatterjee et al.,
30 Biochem. Pharmacol. **2005**, 7, pp. 1121-1131).

Calpain has also been identified as a central mediator essential for parasitic activity.
Parasites like Plasmodium falciparum and Toxoplasma gondii exploit host cell calpains

to facilitate escape from the intracellular parasitophorous vacuole and/or host plasma membrane. Inhibition of calpain-1 in hypotonically lysed and resealed erythrocytes prevented the escape of *P. falciparum* parasites, which was restored by adding purified calpain-1. Similarly, efficient egress of *T. gondii* from mammalian fibroblasts was
5 blocked by either small interfering RNA-mediated suppression or genetic deletion of calpain activity and could be restored by genetic complementation (D. Greenbaum et al., *Science* 324, 794 (2009). Because parasites that fail to escape from their host cells are unable to proliferate, suggesting a strategy for anti-parasitic therapeutics.

Pharmacological inhibition of calpain has been shown to exert anti-malarial activity,
10 and hence presents a novel strategy for anti-parasitic strategy such as diseases caused by protest infections like malaria or toxoplasmosis (Li et al., *Mol Biochem Parasitol.* 2007; 155(1): 26–32; Jung et al. *Archives of Pharmacal Research* (2009), 32(6), 899-906 , Chandramohanadas et al. *Science* (2009), 324, 794).

15 Further possible applications of calpain inhibitors are detailed in: M.Pietsch et al. *Current Topics in Medicinal Chemistry*, 2010, 10, 270-293; M.E. Saez et al.; *Drug Discovery Today* **2006**, 11 (19/20), pp. 917-923; N. O. Carragher, *Curr. Pharm. Design* **2006**, 12, pp. 615-638; K. K. Wang et al.; *Drugs of the Future* **1998**, 23 (7), pp. 741-749; and *Trends in Pharmacol.Sci.* **1994**, 15, pp. 412-419.

20 A comprehensive review of calpain inhibitors reported in the literature is given in: Donkor et al, *Expert Opin. Ther. Patents* **2011**, 21 (5). pp.601-636.

With the calpain inhibitors described to date a general distinction is made between
25 irreversible and reversible inhibitors, and peptide and non-peptide inhibitors.

Irreversible inhibitors are usually alkylating substances. They have the disadvantage that they firstly react unselectively and/or are unstable in the body. Thus, corresponding inhibitors often show unwanted side effects such as toxicity, and application thereof is
30 therefore markedly restricted. The irreversible inhibitors include for example epoxides such as E64, α -halo ketones, and disulfides.

A large number of known reversible calpain inhibitors are peptide aldehydes which are

derived in particular from di- or tripeptides such as, for example, Z-Val-Phe-H (MDL 28170). Derivatives and prodrugs structurally derived from aldehydes are also described, especially corresponding acetals and hemiacetals (e.g. hydroxytetrahydrofurans, hydroxyoxazolindines, hydroxymorpholines and the like), but also imines or hydrazones. However, under physiological conditions, peptide aldehydes and related compounds usually have the disadvantage that, owing to their reactivity, they are frequently unstable, are rapidly metabolized and are prone to unspecific reactions which may likewise cause toxic effects (J. A. Fehrentz and B. Castro, *Synthesis* **1983**, pp. 676-78).

10

In recent years, a number of non-peptide carboxamides having a β -keto function in the amine moiety and inhibiting calpain have been described. Thus, WO 98/16512 describes 3-amino-2-oxo carboxylic acid derivatives whose amino group is amidated with a 4-piperidinecarboxylic acid compound. WO 99/17775 describes similar compounds which are amidated with a quinolinecarboxylic acid. WO 98/25883, WO 98/25899 and WO 99/54294 describe 3-amino-2-oxo carboxylic acid derivatives whose amino group is amidated with a substituted benzoic acid. WO 99/61423 describes 3-amino-2-oxo carboxylic acid derivatives whose amino group is amidated with an aromatic carboxylic acid carrying a tetrahydroquinoline/isoquinoline and 2,3-dihydroindole/isoindole residue. Similar compounds in which the aromatic carboxylic acid residue carries a heterocyloalkyl radical or (hetero)aryl radical which is optionally connected via a linker are described in WO 99/54320, WO 99/54310, WO 99/54304 and WO 99/54305. Likewise, WO 08/080969 describes nicotinamides of 3-amino-2-oxo carboxylic acid derivatives that in position 2 of the pyridine ring are linked to a substituted pyrazole via a nitrogen atom. WO 03/080182 describes the use of the aforementioned amides for the treatment of pulmonary diseases. The nonpeptide calpain inhibitors mentioned therein also have a number of disadvantages, in particular a low or absent selectivity in respect of related cysteine proteases, such as various cathepsins, likewise possibly leading to unwanted side effects.

30

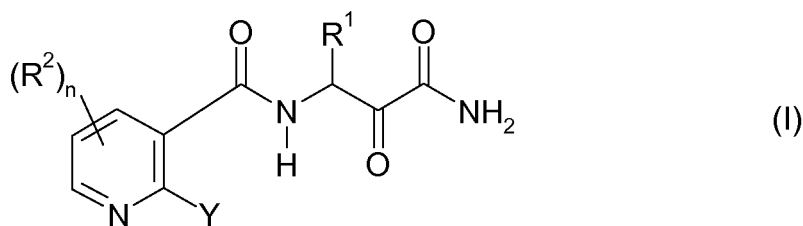
WO 07/016589 and WO 08/106130 describe 2-oxo carboxylic acid derivatives carrying a *N*-acylated 2-pyrrolidinecarboxylamido group in the 3-position. Also disclosed is their use for treating hepatitis C virus infections.

Carboxamides comprising an α -ketoamide moiety in the amine component, in particular those described in WO 08/080969, have been demonstrated to be highly effective and selective calpain inhibitors. However, as found out by the inventors of the present invention, in some cases they have limited cytosolic stability, namely in humans, possibly resulting in their premature clearance from the cytosol. As a consequence, the pharmacokinetics of these compounds may be insufficient.

The cytosolic degradation of said carboxamide compounds having an α -ketoamide moiety is believed to be mainly caused by metabolic reduction of the carbonyl function in the α -position. Carbonyl reduction is an important step in Phase I metabolism of carbonyl-containing drugs by converting aldehyde, ketone or quinone moieties to alcohols to facilitate the elimination by Phase II conjugation or direct excretion (M.J.C. Rosemond and J.S. Walsh: "Human carbonyl reduction pathways and a strategy for their study in vitro", Drug Metabolism Reviews, **2004**, 36, 335-361). Human carbonyl-reducing activities are ubiquitous, found in many tissues including liver, lung, brain, heart, kidney, and blood. Multiple human carbonyl-reducing enzymes have been characterized, including medium-chain (MDR), and short-chain (SDR) dehydrogenases/reductases, aldo-keto reductases (AKR), and quinone reductases (QR), most of these are present in liver cytosols, except for some SDR family present in liver microsomes and mitochondria as described in F. Hoffmann and E. Maser: "Carbonyl reductases and pluripotent hydroxysteroid dehydrogenases of the shortchain dehydrogenases/reductases superfamily", Drug Metabolism Reviews **2007**, 39, 87-144.

The present invention is thus based on the object of providing compounds which inhibit calpain with high affinity and selectivity. The compounds are further intended to display enhanced cytosolic stability in human cells, such as hepatocytes, and in consequence improved pharmacokinetics.

This object and further objects are achieved by the carboxamide compounds of the general formula I described below, the tautomers, the hydrates, the pharmaceutically suitable salts and the prodrugs thereof:



in which

- 5 R^1 is C_1 - C_{10} -alkyl, C_2 - C_{10} -alkenyl, C_2 - C_{10} -alkynyl, where the last 3 radicals mentioned may be partly or completely halogenated and/or have 1, 2 or 3 substituents R^{1a} ,
 C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl- C_1 - C_4 -alkyl, where a CH_2 group in the cycloalkyl moiety of the last two radicals mentioned may be replaced by O,
 10 NH, or S, or two adjacent C atoms may form a double bond, where the cycloalkyl moiety may further have 1, 2, 3 or 4 radicals R^{1b} ,
 aryl, hetaryl, aryl- C_1 - C_6 -alkyl, aryl- C_2 - C_6 -alkenyl, hetaryl- C_1 - C_4 -alkyl or hetaryl- C_2 - C_6 -alkenyl, where aryl and hetaryl in the last 6 radicals mentioned may be unsubstituted or may carry 1, 2, 3 or 4 identical or
 15 different radicals R^{1c} ; where

- R^{1a} is selected independently of one another from the group consisting of
 OH, SH, COOH, CN, OCH_2COOH , C_1 - C_6 -alkoxy, C_1 - C_6 -haloalkoxy,
 C_3 - C_7 -cycloalkyloxy, C_1 - C_6 -alkylthio, C_1 - C_6 -haloalkylthio, $COOR^{a1}$,
 20 $CONR^{a2}R^{a3}$, $SO_2NR^{a2}R^{a3}$, $-NR^{a2}-SO_2-R^{a4}$, $NR^{a2}-CO-R^{a5}$, SO_2-R^{a4} and $NR^{a6}R^{a7}$;

- R^{1b} is selected independently of one another from the group consisting of
 OH, SH, COOH, CN, OCH_2COOH , halogen, phenyl which optionally
 25 has 1, 2 or 3 substituents R^{1d} ,
 C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -alkylthio, where the alkyl moieties in the last 3 substituents mentioned may be partly or completely halogenated and/or have 1, 2 or 3 substituents R^{1a} ,
 $COOR^{b1}$, $CONR^{b2}R^{b3}$, $SO_2NR^{b2}R^{b3}$, $NR^{b2}-SO_2-R^{b4}$, $NR^{b2}-CO-R^{b5}$,

$\text{SO}_2\text{-R}^{\text{b4}}$ and $\text{NR}^{\text{b6}}\text{R}^{\text{b7}}$,

in addition two R^{1b} radicals may together form a $\text{C}_1\text{-C}_4$ -alkylene group, or 2 R^{1b} radicals bonded to adjacent C atoms of cycloalkyl may form together with the carbon atoms to which they are bonded also a benzene ring,

R^{1c} is selected independently of one another from the group consisting of OH, SH, halogen, NO_2 , NH_2 , CN, COOH, OCH_2COOH , $\text{C}_1\text{-C}_6$ -alkyl, $\text{C}_1\text{-C}_6$ -alkoxy, $\text{C}_1\text{-C}_6$ -alkoxy- $\text{C}_1\text{-C}_4$ -alkyl, $\text{C}_1\text{-C}_6$ -alkylthio, where the alkyl moieties in the last 4 substituents mentioned may be partly or completely halogenated and/or have 1, 2 or 3 substituents R^{1a} , $\text{C}_3\text{-C}_7$ -cycloalkyl, $\text{C}_3\text{-C}_7$ -cycloalkyl- $\text{C}_1\text{-C}_4$ -alkyl, $\text{C}_3\text{-C}_7$ -cycloalkyloxy, where the cycloalkyl moiety of the last three radicals mentioned may have 1, 2, 3 or 4 R^{1b} radicals,

aryl, hetaryl, O-aryl, O- CH_2 -aryl, where the last three radicals mentioned are unsubstituted in the aryl moiety or may carry 1, 2, 3 or 4 R^{1d} radicals,

COOR^{c1} , $\text{CONR}^{\text{c2}}\text{R}^{\text{c3}}$, $\text{SO}_2\text{NR}^{\text{c2}}\text{R}^{\text{c3}}$, $\text{NR}^{\text{c2}}\text{-SO}_2\text{-R}^{\text{c4}}$, $\text{NR}^{\text{c2}}\text{-CO-R}^{\text{c5}}$, $\text{SO}_2\text{-R}^{\text{c4}}$,

$\text{-(CH}_2\text{)}_p\text{-NR}^{\text{c6}}\text{R}^{\text{c7}}$ with $p = 0, 1, 2, 3, 4, 5$ or 6 and

$\text{O-(CH}_2\text{)}_q\text{-NR}^{\text{c6}}\text{R}^{\text{c7}}$ with $q = 2, 3, 4, 5$ or 6; where

or two radicals R^{1b} or two radicals R^{1c} bonded to adjacent C atoms form together with the C atoms to which they are bonded a 4, 5, 6 or 7-membered, optionally substituted carbocycle or an optionally substituted heterocycle which has 1, 2 or 3 different or identical heteroatoms from the group of O, N and S as ring members;

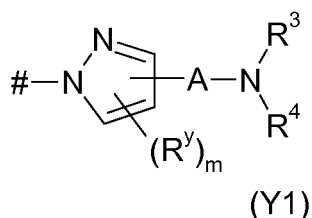
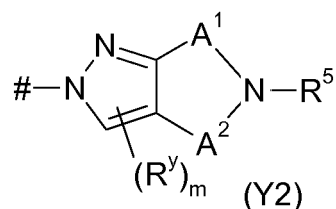
R^{1d} is selected from the group consisting of halogen, OH, SH, NO_2 , COOH, C(O)NH_2 , CHO, CN, NH_2 , OCH_2COOH , $\text{C}_1\text{-C}_6$ -alkyl, $\text{C}_1\text{-C}_6$ -haloalkyl, $\text{C}_1\text{-C}_6$ -alkoxy, $\text{C}_1\text{-C}_6$ -haloalkoxy, $\text{C}_1\text{-C}_6$ -alkylthio, $\text{C}_1\text{-C}_6$ -haloalkylthio, $\text{CO-C}_1\text{-C}_6$ -alkyl, $\text{CO-O-C}_1\text{-C}_6$ -alkyl, $\text{NH-C}_1\text{-C}_6$ -alkyl, NHCHO , $\text{NH-C(O)C}_1\text{-C}_6$ -alkyl, and $\text{SO}_2\text{-C}_1\text{-C}_6$ -alkyl;

R^2 is selected from the group consisting of halogen, NH_2 , CN , CF_3 , CHF_2 , CH_2F , $O-CF_3$, $O-CHF_2$, $O-CH_2F$, $COOH$, OCH_2COOH , C_1-C_2 -alkyl, C_1-C_2 -alkoxy, C_1-C_2 -alkoxy- C_1-C_2 -alkyl, C_1-C_2 -alkylthio and CH_2NRR' , where

R and R' are selected independently of one another from the group consisting of hydrogen and C_1-C_4 -alkyl;

n is 0, 1 or 2;

Y is a radical of the formulae Y1 or Y2



where # indicates the point of attachment of Y to the pyridine ring;

A is $(CH_2)_p$ with p being 1, 2, 3 or 4, where one or two hydrogen atoms may be replaced by a radical R^6 , where A is attached to the 3- or 4-position of the pyrazole radical;

A^1 is $(CH_2)_q$ with q being 0, 1, 2 or 3, where one or two hydrogen atoms may be replaced by halogen or C_1-C_4 -alkyl;

A^2 is $(CH_2)_r$ with r being 0, 1, 2 or 3, where one or two hydrogen atoms may be replaced by halogen or C_1-C_4 -alkyl;

provided that $r + q$ is 2, 3, 4, 5 or 6;

m is 0 or 1;

- 5 R^y is selected from the group consisting of halogen, NH_2 , CN , CF_3 , CHF_2 , CH_2F , $O-CF_3$, $O-CHF_2$, $O-CH_2F$, $COOH$, OCH_2COOH , C_1 - C_2 -alkyl, C_1 - C_2 -alkoxy, C_1 - C_2 -alkoxy- C_1 - C_2 -alkyl and C_1 - C_2 -alkylthio;
- 10 R^3 is selected from the group consisting of hydrogen, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_1 - C_6 -alkyl which has 1, 2 or 3 substituents R^{3a} , C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl- C_1 - C_4 -alkyl, where the cycloalkyl moiety of the last 2 radicals mentioned may have 1, 2, 3 or 4 radicals R^{3b} , C_2 - C_6 -alkenyl or C_2 - C_6 -alkynyl, where alkenyl and alkynyl, in the last 2 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{3a} , phenyl or phenyl- C_1 - C_4 -alkyl, where phenyl in the last 2 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{3c} , and a radical $C(=O)R^{3d}$;
- 15 R^{3a} is selected from the group consisting of OH , SH , CN , C_1 - C_6 -alkoxy, C_1 - C_6 -haloalkoxy, C_3 - C_7 -cycloalkyloxy, C_1 - C_6 -alkylthio, C_1 - C_6 -haloalkylthio, $COOR^{a1}$, $CONR^{a2}R^{a3}$, $SO_2NR^{a2}R^{a3}$, $-NR^{a2}-SO_2-R^{a4}$, $NR^{a2}-CO-R^{a5}$, SO_2-R^{a4} and $NR^{a6}R^{a7}$,
- 20 R^{3b} is selected from the group consisting of OH , SH , CN , halogen, C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -alkylthio, where the alkyl moieties in the last 3 substituents mentioned may be partly or completely halogenated and/or have 1, 2 or 3 substituents R^{3a} , phenyl which optionally has 1, 2 or 3 substituents R^{3c} ,
- 25 $COOR^{b1}$, $CONR^{b2}R^{b3}$, $SO_2NR^{b2}R^{b3}$, $NR^{b2}-SO_2-R^{b4}$, $NR^{b2}-CO-R^{b5}$, SO_2-R^{b4} and $NR^{b6}R^{b7}$, or two R^{3b} radicals may together also form a C_1 - C_4 -alkylene group, or 2 R^{3b} radicals bonded to adjacent C atoms of cycloalkyl may form together with the carbon atoms to which they are bonded also a
- 30 benzene ring,
- R^{3c} is selected from the group consisting of halogen, OH , SH , NO_2 , $C(O)NH_2$, CHO , CN , NH_2 , C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -haloalkoxy, C_1 - C_6 -alkylthio, C_1 - C_6 -haloalkylthio, CO -

C₁-C₆-alkyl, CO-O-C₁-C₆-alkyl, NH-C₁-C₆-alkyl, NH-C(O)C₁-C₆-alkyl, and SO₂-C₁-C₆-alkyl;

R^{3d} is selected from the group consisting of C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkyl which has 1, 2 or 3 substituents R^{3a},

5 C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₄-alkyl, where the cycloalkyl moiety of the last 2 radicals mentioned is unsubstituted or may have 1, 2, 3 or 4 radicals R^{3b}, phenyl which optionally has 1, 2 or 3 substituents R^{3c},

10 R⁴ is selected from the group consisting of hydrogen, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkyl which has 1, 2 or 3 substituents R^{4a}, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₄-alkyl, where the cycloalkyl moiety of the last 2 radicals mentioned may have 1, 2, 3 or 4 radicals R^{4b}, C₂-C₆-alkenyl or C₂-C₆-alkynyl, where alkenyl and alkynyl, in the last 2
15 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{4a}, phenyl and phenyl-C₁-C₄-alkyl, where phenyl in the last 2 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{4c}, where R^{4a} is as defined for R^{3a}, R^{4b} is as defined for R^{3b}, and R^{4c} is as defined for R^{3c},

20 or the moiety NR³R⁴ in formula Y1 is a saturated, N-bound 4-, 5-, 6-, or 7-membered heteromonocyclic or 7-, 8-, 9-, or 10-membered heterobicyclic radical, where said heteromonocyclic and the heterobicyclic radical, in addition to the nitrogen atom, may have 1 or 2 further heteroatoms or
25 heteroatom moieties as ring members, which are selected from O, S, S(O), S(O)₂ and NR^{4d}, where said heteromonocyclic radical may carry a fused benzene ring and where said heteromonocyclic and the heterobicyclic radical are unsubstituted or may be substituted by 1, 2, 3 or 4 radicals R^{4e};

30 R^{4d} is selected from the group consisting of hydrogen, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkyl which has 1, 2 or 3 substituents R^{4a}, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₄-alkyl, where the cycloalkyl moiety of the last 2 radicals mentioned is unsubstituted or may have 1,

2, 3 or 4 radicals R^{4b} ,

phenyl and phenyl- C_1 - C_4 -alkyl where the phenyl ring of the last 2 radicals mentioned is unsubstituted or may have 1, 2 or 3 substituents R^{4c} ,

5

R^{4e} is selected from the group consisting of halogen, OH, SH, NO_2 , $C(O)NH_2$, CHO, CN, NH_2 , C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -haloalkoxy, C_1 - C_6 -alkylthio, C_1 - C_6 -haloalkylthio, $COOR^{b1}$, $CONR^{b2}R^{b3}$, $SO_2NR^{b2}R^{b3}$, $NR^{b2}-SO_2-R^{b4}$, $NR^{b2}-CO-R^{b5}$, SO_2-R^{b4} , and phenyl which optionally has 1, 2 or 3 substituents R^{4c} ;

10

R^5 has one of the meanings given for R^3 or is a radical $COOR^{b1}$;

R^6 if present, is selected from halogen or C_1 - C_4 -alkyl, or

15

R^6 together with R^4 forms a bivalent radical $(CH_2)_s$ with s being 1, 2 or 3, where one or two hydrogen atoms may be replaced by halogen or C_1 - C_4 -alkyl;

and where

20

R^{a1} , R^{b1} and R^{c1} are independently of one another selected from the group consisting of C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_1 - C_6 -alkyl which has 1, 2 or 3 substituents R^{1a} , or C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl- C_1 - C_4 -alkyl, C_3 - C_7 -heterocycloalkyl- C_1 - C_4 -alkyl, C_1 - C_6 -alkoxy- C_1 - C_4 -alkyl, aryl, aryl- C_1 - C_4 -alkyl, hetaryl and hetaryl- C_1 - C_4 -alkyl, where aryl and hetaryl in the last 4 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{1d} ,

25

R^{a2} , R^{b2} and R^{c2} are independently of one another selected from the group consisting of H, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_1 - C_6 -alkyl which has 1, 2 or 3 substituents R^{1a} , or C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl- C_1 - C_4 -alkyl, C_3 - C_7 -heterocycloalkyl- C_1 - C_4 -alkyl, C_1 - C_6 -alkoxy- C_1 - C_4 -alkyl, aryl, aryl- C_1 - C_4 -alkyl, hetaryl and hetaryl- C_1 - C_4 -alkyl,

30

where aryl and hetaryl in the last 4 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{1d} ,

5 R^{a3} , R^{b3} and R^{c3} are independently of one another selected from the group consisting of H, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_1 - C_6 -alkyl which has 1, 2 or 3 substituents R^{1a} , or C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl- C_1 - C_4 -alkyl, C_3 - C_7 -heterocycloalkyl- C_1 - C_4 -alkyl, C_1 - C_6 -alkoxy- C_1 - C_4 -alkyl, aryl, aryl- C_1 - C_4 -alkyl, hetaryl and hetaryl- C_1 - C_4 -alkyl, where aryl and hetaryl in the last 4 radicals mentioned are unsubstituted or
10 have 1, 2 or 3 substituents R^{1d} , or the two radicals R^{a2} and R^{a3} , or R^{b2} and R^{b3} or R^{c2} and R^{c3} form together with the N atom a 3 to 7-membered, optionally substituted nitrogen heterocycle which may optionally have 1, 2 or 3 further different or identical heteroatoms from the group of O, N, S as ring members,

15

R^{a4} , R^{b4} and R^{c4} are independently of one another selected from the group consisting of C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_1 - C_6 -alkyl which has 1, 2 or 3 substituents R^{1a} , or C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl- C_1 - C_4 -alkyl, C_3 - C_7 -heterocycloalkyl- C_1 - C_4 -alkyl, C_1 - C_6 -alkoxy- C_1 - C_4 -alkyl, aryl, aryl- C_1 - C_4 -alkyl, hetaryl and hetaryl- C_1 - C_4 -alkyl, where
20 aryl and hetaryl in the last 4 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{1d} , and

25 R^{a5} , R^{b5} and R^{c5} have independently of one another the meanings mentioned for R^{a1} , R^{b1} and R^{c1} ;

30 R^{a6} , R^{b6} and R^{c6} are independently of one another selected from the group consisting of H, C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -haloalkyl, C_1 - C_6 -alkyl which has 1, 2 or 3 substituents R^{1a} , or C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl- C_1 - C_4 -alkyl, C_3 - C_7 -heterocycloalkyl- C_1 - C_4 -alkyl, C_1 - C_6 -alkoxy- C_1 - C_4 -alkyl, CO- C_1 - C_6 -alkyl, CO-O- C_1 - C_6 -alkyl, SO₂- C_1 - C_6 -alkyl, aryl, hetaryl, O-aryl, OCH₂-aryl, aryl- C_1 - C_4 -alkyl, hetaryl- C_1 - C_4 -alkyl, CO-aryl, CO-hetaryl, CO-(aryl- C_1 - C_4 -alkyl), CO-

(hetaryl-C₁-C₄-alkyl), CO-O-aryl, CO-O-hetaryl, CO-O-(aryl-C₁-C₄-alkyl), CO-O-(hetaryl-C₁-C₄-alkyl), SO₂-aryl, SO₂-hetaryl, SO₂-(aryl-C₁-C₄-alkyl) and SO₂-(hetaryl-C₁-C₄-alkyl), where aryl and hetaryl in the last 18 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{1d}, and

5

R^{a7}, R^{b7} and R^{c7} are independently of one another selected from the group consisting of H, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkyl which has 1, 2 or 3 substituents R^{1a}, or C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₄-alkyl, C₃-C₇-heterocycloalkyl-C₁-C₄-alkyl, C₁-C₆-alkoxy-C₁-C₄-alkyl, aryl, aryl-C₁-C₄-alkyl, hetaryl and hetaryl-C₁-C₄-alkyl, where aryl and hetaryl in the last 4 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{1d}, or the two radicals R^{a6} and R^{a7}, or R^{b6} and R^{b7} or R^{c6} and R^{c7} form together with the N atom a 3 to 7-membered, optionally substituted nitrogen heterocycle which may optionally have 1, 2 or 3 further different or identical heteroatoms from the group of O, N and S as ring members.

10

15

The present invention therefore relates to the carboxamide compounds of the general formula I, their tautomers, the hydrates thereof, the pharmaceutically suitable salts of the carboxamide compounds I, the prodrugs of I and the pharmaceutically suitable salts of the prodrugs, tautomers or hydrates of I.

20

The carboxamide compounds of the invention of the formula I, their salts, their prodrugs, their hydrates and their tautomers effectively inhibit calpain even at low concentrations. They are additionally distinguished by a high selectivity in relation to the inhibition of the calpain compared with other cysteine proteases, such as cathepsin B, cathepsin K, cathepsin L and cathepsin S, and by their improved stability against cytosolic degradation.

25

The carboxamide compounds of the invention of the formula I, their salts, their prodrugs, their hydrates and their tautomers are therefore particularly suitable for treating disorders and conditions in creatures, especially human creatures, which are associated with an elevated calpain activity.

30

The invention therefore also relates to the use of carboxamide compounds of the formula I, their tautomers, their hydrates and their pharmaceutically suitable salts for the manufacture of a medicament, in particular of a medicament which is suitable for the treatment of a disorder or a condition which is associated with an elevated calpain activity.

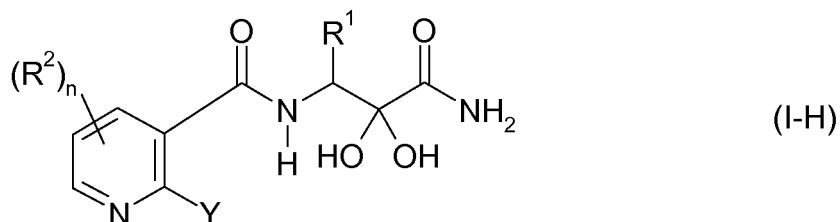
The invention further relates to a medicament, in particular a medicament which is suitable for the treatment of a disorder or a condition which is associated with an elevated calpain activity. The medicament comprises at least one carboxamide compound of the formula I, as described herein, the tautomer, the hydrate or a prodrug of compound I, or a pharmaceutically suitable salt of compound I or of the tautomer, the hydrate or a prodrug of I.

This carboxamide compound, its salts, prodrugs, hydrates and tautomers like the compounds of formula I effectively inhibit calpain even at low concentrations. They are additionally distinguished by a high selectivity in relation to the inhibition of the calpain compared with other cysteine proteases, such as cathepsin B, cathepsin K, cathepsin L and cathepsin S, and by their improved stability against cytosolic degradation.

Therefore, these carboxamide compounds are particularly suitable for treating disorders and conditions in creatures, especially human creatures, which are associated with an elevated calpain activity. The invention therefore also relates to the use of these carboxamide compounds, their tautomers, their hydrates and their pharmaceutically suitable salts for the manufacture of a medicament, in particular of a medicament which is suitable for the treatment of a disorder or a condition which is associated with an elevated calpain activity as described herein for the compounds of formula I. As regards the tautomers, the hydrates, the pharmaceutically suitable salts or the prodrugs reference is made to the compounds of formula I.

The carboxamide compounds of the formula I may be present in the form of the α -ketoamide, as shown in the formula I. Alternatively they may also be present in the form of a hydrate, i.e. the keto group in the α -position relative to the carbamoyl moiety CONH₂ in the amine component is transformed into two geminal hydroxy groups, as

shown in the formula I-H below. R^1 , R^2 , Y and n in formula I-H have the
aforementioned meanings.

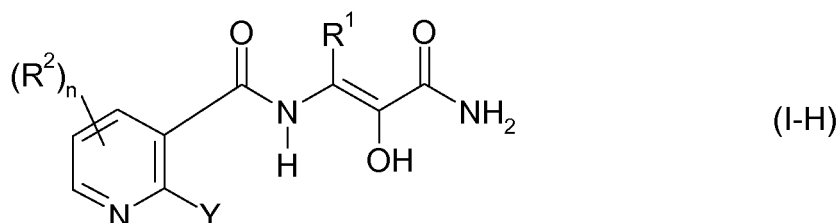


In the presence of water, especially under physiological conditions, usually both the α -
5 ketoamide form and the hydrate form are present in a mixture.

Where only the α -ketoamide form is indicated in the following formulae and
descriptions, it is intended to include also the hydrate and mixtures thereof with the α -
ketoamide form unless indicated otherwise. Hydrates and α -ketoamide forms are
10 equally suitable as calpain inhibitors.

The carboxamide compounds of the invention of the formula I are also able to form
tautomers which are equally suitable as calpain inhibitors. Particular examples of
tautomers to be mentioned are the compounds of the formula I-T:

15



R^1 , R^2 , Y and n in formula I-T have the aforementioned meanings.

20 The carboxamide compounds of the invention of the formula I can also form
hemiacetals, hemiketals, acetals or ketals with alkanols. These compounds are equally
suitable as calpain inhibitors as they are prodrugs of the compounds I. Accordingly,
compounds where one or both of the geminal hydroxy groups shown in formula I-H are
a radical derived from an alkanol, and especially C_1 - C_6 -alkoxy, can also be used
25 according to the invention.

The term prodrug, as used herein and in the claims refers to a compound which is transformed under metabolic conditions into a compound of the formula I. Apart from the aforementioned hemiacetals, hemiketals, acetals and ketals prodrugs of the compounds I include the compounds of the formula I, wherein the oxygen atom of the keto group in α -position to the carbamoyl moiety CONH_2 is replaced with a group O-Alk-O, S-Alk-O or S-Alk-S, where Alk is linear C_2 - C_5 -alkandiyl, which may be unsubstituted or substituted with 1, 2, 3 or 4 radicals selected from C_1 - C_4 -alkyl or halogen, examples for such groups including $\text{O}(\text{CH}_2)_2\text{O}$, $\text{O}(\text{CH}_2)_5\text{O}$, $\text{O}(\text{CH}_2)_4\text{O}$, $\text{S}(\text{CH}_2)_2\text{O}$, $\text{S}(\text{CH}_2)_5\text{O}$, $\text{S}(\text{CH}_2)_4\text{O}$, etc. Further prodrugs or the compounds I include the compounds of the formula I, wherein the keto group in α -position to the carbamoyl moiety CONH_2 is replaced with a group $\text{C}=\text{NR}^\alpha$, where R^α is selected from H, C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, C_2 - C_6 -alkenyl, C_3 - C_6 -cycloalkyl, C_3 - C_6 -cycloalkyl- C_1 - C_4 -alkyl, C_2 - C_6 -alkenyloxy, C_3 - C_6 -cycloalkyloxy, C_3 - C_6 -cycloalkyl- C_1 - C_4 -alkyloxy. Under metabolic conditions, the aforementioned prodrugs are transformed into the corresponding α -ketoamide compounds of the formula I or into the corresponding hydrates of formula I-H. Therefore, said prodrugs and their pharmaceutically acceptable salts are also part of the invention.

It is equally possible to use pharmaceutically suitable salts of the carboxamide compounds of the formula I, of their tautomers, their hydrates or of their prodrugs, especially acid addition salts with physiologically tolerated organic or inorganic acids. Examples of suitable physiologically tolerated organic and inorganic acids are hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, organic sulfonic acids having 1 to 12 carbon atoms, e.g. C_1 - C_4 -alkylsulfonic acids such as methanesulfonic acid, cycloaliphatic sulfonic acids such as S-(+)-10-camphorsulfonic acids, and aromatic sulfonic acids such as benzenesulfonic acid and toluenesulfonic acid, di- and tricarboxylic acids and hydroxy carboxylic acids having 2 to 10 carbon atoms, such as oxalic acid, malonic acid, maleic acid, fumaric acid, mucic acid, lactic acid, tartaric acid, citric acid, glycolic acid and adipic acid, as well as *cis*- and *trans*-cinnamic acid, furan-2-carboxylic acid and benzoic acid. Further suitable acids are described in Fortschritte der Arzneimittelforschung, Volume 10, pages 224 et seq., Birkhäuser Verlag, Basel and Stuttgart, 1966. The physiologically tolerated salts of the compounds of the formula I may be in the form of mono-, di-, tri- or tetrasalts, meaning

that they may comprise 1, 2, 3 or 4 of the aforementioned acid molecules per molecule of the formula I. The acid molecules may be present in their acidic form or as anion.

The compounds of the invention may be in the form of a mixture of diastereomers, or of
5 a mixture of diastereomers in which one of the two diastereomers is enriched, or of essentially diastereomerically pure compounds (diastereomeric excess $de > 90\%$). The compounds are preferably in the form of essentially diastereomerically pure compounds (diastereomeric excess $de > 90\%$). The compounds I of the invention may furthermore be in the form of a mixture of enantiomers (for example as racemate), of a mixture of
10 enantiomers in which one of the two enantiomers is enriched, or essentially in enantiomerically pure compounds (enantiomeric excess $ee > 90\%$). However, the compounds of the invention are frequently prone to racemization in relation to the stereochemistry of the carbon atom which carries the radical R^1 , so that mixtures are frequently obtained in relation to this carbon atom, or compounds which exhibit a
15 uniform stereochemistry in relation to this C atom form mixtures under physiological conditions. However, in relation to other stereocenters and the occurrence, associated therewith, of enantiomers and diastereomers, it is preferred to employ the compounds enantiomerically pure or diastereomerically pure.

20 In the context of the present description, unless stated otherwise, the terms "alkyl", "alkoxy", "alkylthio", "haloalkyl", "haloalkoxy", "haloalkylthio", "alkenyl", "alkynyl", "alkylene" and radicals derived therefrom always include both unbranched and branched "alkyl", "alkoxy", "alkylthio", "haloalkyl", "haloalkoxy", "haloalkylthio", "alkenyl", "alkynyl" and "alkylene", respectively.

25 The prefix C_n-C_m - indicates the respective number of carbons in the hydrocarbon unit. Unless indicated otherwise, halogenated substituents preferably have one to five identical or different halogen atoms, especially fluorine atoms or chlorine atoms. C_0 -Alkylene or $(CH_2)_0$ or similar expressions in the context of the description designate,
30 unless indicated otherwise, a single bond.

The term "halogen" designates in each case, fluorine, bromine, chlorine or iodine, specifically fluorine, chlorine or bromine.

Examples of other meanings are:

Alkyl, and the alkyl moieties for example in alkoxy, alkylthio, arylalkyl, hetarylalkyl,
5 cycloalkylalkyl or alkoxyalkyl: saturated, straight-chain or branched hydrocarbon
radicals having one or more C atoms, e.g. 1 to 4, 1 to 6 or 1 to 10 carbon atoms, e.g. C₁-
C₆-alkyl such as methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl (sec.-
butyl), 2-methylpropyl (isobutyl), 1,1-dimethylethyl (tert.-butyl), pentyl, 1-methylbutyl,
2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1,1-
10 dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl,
4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-
dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-
trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl.
In one embodiment of the invention, alkyl stands for small alkyl groups such as C₁-C₄-
15 alkyl. In another embodiment of the invention, alkyl stands for larger alkyl groups such
as C₅-C₁₀-alkyl.

Haloalkyl: an alkyl radical having ordinarily 1 to 6 or 1 to 4 C atoms as mentioned
above, whose hydrogen atoms are partly or completely replaced by halogen atoms such
20 as fluorine, chlorine, bromine and/or iodine, e.g. chloromethyl, dichloromethyl,
trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chlorofluoromethyl,
dichlorofluoromethyl, chlorodifluoromethyl, 2-fluoroethyl, 2-chloroethyl, 2-
bromoethyl, 2-iodoethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-chloro-2-fluoroethyl,
2-chloro-2,2-difluoroethyl, 2,2-dichloro-2-fluoroethyl, 2,2,2-trichloroethyl,
25 pentafluoroethyl, 2-fluoropropyl, 3-fluoropropyl, 2,2-difluoropropyl, 2,3-
difluoropropyl, 2-chloropropyl, 3-chloropropyl, 2,3-dichloropropyl, 2-bromopropyl, 3-
bromopropyl, 3,3,3-trifluoropropyl, 3,3,3-trichloropropyl, 2,2,3,3,3-pentafluoropropyl,
heptafluoropropyl, 1-(fluoromethyl)-2-fluoroethyl, 1-(chloromethyl)-2-chloroethyl, 1-
(bromomethyl)-2-bromoethyl, 4-fluorobutyl, 4-chlorobutyl, 4-bromobutyl and
30 nonafluorobutyl.

Cycloalkyl, and the cycloalkyl moieties for example in cycloalkoxy or cycloalkyl-C₁-
C₆-alkyl: monocyclic, saturated hydrocarbon groups having three or more C atoms, e.g.

3, 4, 5, 6 or 7 carbon ring members, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

Alkenyl, and alkenyl moieties for example in aryl-(C₂-C₆)-alkenyl: monounsaturated, straight-chain or branched hydrocarbon radicals having two or more C atoms, e.g. 2 to 4, 2 to 6 or 2 to 10 carbon atoms and one double bond in any position, e.g. C₂-C₆-alkenyl such as ethenyl, 1-propenyl, 2-propenyl, 1-methylethenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-methyl-1-propenyl, 2-methyl-1-propenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-methyl-1-butenyl, 2-methyl-1-butenyl, 3-methyl-1-butenyl, 1-methyl-2-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 1-methyl-3-butenyl, 2-methyl-3-butenyl, 3-methyl-3-butenyl, 1,1-dimethyl-2-propenyl, 1,2-dimethyl-1-propenyl, 1,2-dimethyl-2-propenyl, 1-ethyl-1-propenyl, 1-ethyl-2-propenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-methyl-1-pentenyl, 2-methyl-1-pentenyl, 3-methyl-1-pentenyl, 4-methyl-1-pentenyl, 1-methyl-2-pentenyl, 2-methyl-2-pentenyl, 3-methyl-2-pentenyl, 4-methyl-2-pentenyl, 1-methyl-3-pentenyl, 2-methyl-3-pentenyl, 3-methyl-3-pentenyl, 4-methyl-3-pentenyl, 1-methyl-4-pentenyl, 2-methyl-4-pentenyl, 3-methyl-4-pentenyl, 4-methyl-4-pentenyl, 1,1-dimethyl-2-butenyl, 1,1-dimethyl-3-butenyl, 1,2-dimethyl-1-butenyl, 1,2-dimethyl-2-butenyl, 1,2-dimethyl-3-butenyl, 1,3-dimethyl-1-butenyl, 1,3-dimethyl-2-butenyl, 1,3-dimethyl-3-butenyl, 2,2-dimethyl-3-butenyl, 2,3-dimethyl-1-butenyl, 2,3-dimethyl-2-butenyl, 2,3-dimethyl-3-butenyl, 3,3-dimethyl-1-butenyl, 3,3-dimethyl-2-butenyl, 1-ethyl-1-butenyl, 1-ethyl-2-butenyl, 1-ethyl-3-butenyl, 2-ethyl-1-butenyl, 2-ethyl-2-butenyl, 2-ethyl-3-butenyl, 1,1,2-trimethyl-2-propenyl, 1-ethyl-1-methyl-2-propenyl, 1-ethyl-2-methyl-1-propenyl, 1-ethyl-2-methyl-2-propenyl.

25

Alkynyl: straight-chain or branched hydrocarbon groups having two or more C atoms, e.g. 2 to 4, 2 to 6 or 2 to 10 carbon atoms and one or two triple bonds in any position but nonadjacent, e.g. C₂-C₆-alkynyl such as ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-methyl-2-propynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-methyl-2-butyne, 1-methyl-3-butyne, 2-methyl-3-butyne, 3-methyl-1-butyne, 1,1-dimethyl-2-propynyl, 1-ethyl-2-propynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-methyl-2-pentynyl, 1-methyl-3-pentynyl, 1-methyl-4-pentynyl, 2-methyl-3-pentynyl, 2-methyl-4-pentynyl, 3-methyl-1-pentynyl, 3-methyl-4-

30

pentynyl, 4-methyl-1-pentynyl, 4-methyl-2-pentynyl, 1,1-dimethyl-2-butynyl, 1,1-dimethyl-3-butynyl, 1,2-dimethyl-3-butynyl, 2,2-dimethyl-3-butynyl, 3,3-dimethyl-1-butynyl, 1-ethyl-2-butynyl, 1-ethyl-3-butynyl, 2-ethyl-3-butynyl, 1-ethyl-1-methyl-2-propynyl.

5

Alkoxy or alkoxy moieties for example in alkoxyalkyl:

Alkyl as defined above having preferably 1 to 6 or 1 to 4 C atoms, which is linked via an O atom: e.g. methoxy, ethoxy, n-propoxy, 1-methylethoxy, butoxy, 1-methylpropoxy, 2-methylpropoxy or 1,1-dimethylethoxy, pentoxy, 1-methylbutoxy, 2-methylbutoxy, 3-methylbutoxy, 1,1-dimethylpropoxy, 1,2-dimethylpropoxy, 2,2-dimethylpropoxy, 1-ethylpropoxy, hexoxy, 1-methylpentoxy, 2-methylpentoxy, 3-methylpentoxy, 4-methylpentoxy, 1,1-dimethylbutoxy, 1,2-dimethylbutoxy, 1,3-dimethylbutoxy, 2,2-dimethylbutoxy, 2,3-dimethylbutoxy, 3,3-dimethylbutoxy, 1-ethylbutoxy, 2-ethylbutoxy, 1,1,2-trimethylpropoxy, 1,2,2-trimethylpropoxy, 1-ethyl-1-methylpropoxy or 1-ethyl-2-methylpropoxy.

15

Haloalkoxy: alkoxy as described above, in which the hydrogen atoms of these groups are partly or completely replaced by halogen atoms, i.e. for example C₁-C₆-haloalkoxy, such as chloromethoxy, dichloromethoxy, trichloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chlorofluoromethoxy, dichlorofluoromethoxy, chlorodifluoromethoxy, 2-fluoroethoxy, 2-chloroethoxy, 2-bromoethoxy, 2-iodoethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, 2-chloro-2-fluoroethoxy, 2-chloro-2,2-difluoroethoxy, 2,2-dichloro-2-fluoroethoxy, 2,2,2-trichloroethoxy, pentafluoroethoxy, 2-fluoropropoxy, 3-fluoropropoxy, 2,2-difluoropropoxy, 2,3-difluoropropoxy, 2-chloropropoxy, 3-chloropropoxy, 2,3-dichloropropoxy, 2-bromopropoxy, 3-bromopropoxy, 3,3,3-trifluoropropoxy, 3,3,3-trichloropropoxy, 2,2,3,3,3-pentafluoropropoxy, heptafluoropropoxy, 1-(fluoromethyl)-2-fluoroethoxy, 1-(chloromethyl)-2-chloroethoxy, 1-(bromomethyl)-2-bromoethoxy, 4-fluorobutoxy, 4-chlorobutoxy, 4-bromobutoxy, nonafluorobutoxy, 5-fluoro-1-pentoxy, 5-chloro-1-pentoxy, 5-bromo-1-pentoxy, 5-iodo-1-pentoxy, 5,5,5-trichloro-1-pentoxy, undecafluoropentoxy, 6-fluoro-1-hexoxy, 6-chloro-1-hexoxy, 6-bromo-1-hexoxy, 6-iodo-1-hexoxy, 6,6,6-trichloro-1-hexoxy or dodecafluorohexoxy, specifically chloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2-fluoroethoxy, 2-chloroethoxy or 2,2,2-

30

trifluoroethoxy.

Alkoxyalkyl: an alkyl radical ordinarily having 1 to 4 C atoms, in which one hydrogen atom is replaced by an alkoxy radical ordinarily having 1 to 6 or 1 to 4 C atoms.

- 5 Examples thereof are $\text{CH}_2\text{-OCH}_3$, $\text{CH}_2\text{-OC}_2\text{H}_5$, n-propoxymethyl, $\text{CH}_2\text{-OCH}(\text{CH}_3)_2$, n-butoxymethyl, (1-methylpropoxy)methyl, (2-methylpropoxy)methyl, $\text{CH}_2\text{-OC}(\text{CH}_3)_3$, 2-(methoxy)ethyl, 2-(ethoxy)ethyl, 2-(n-propoxy)ethyl, 2-(1-methylethoxy)ethyl, 2-(n-butoxy)ethyl, 2-(1-methylpropoxy)ethyl, 2-(2-methylpropoxy)ethyl, 2-(1,1-dimethylethoxy)ethyl, 2-(methoxy)propyl, 2-(ethoxy)propyl, 2-(n-propoxy)propyl, 2-(1-methylethoxy)propyl, 2-(n-butoxy)propyl, 2-(1-methylpropoxy)propyl, 2-(2-methylpropoxy)propyl, 2-(1,1-dimethylethoxy)propyl, 3-(methoxy)propyl, 3-(ethoxy)propyl, 3-(n-propoxy)propyl, 3-(1-methylethoxy)propyl, 3-(n-butoxy)propyl, 3-(1-methylpropoxy)propyl, 3-(2-methylpropoxy)propyl, 3-(1,1-dimethylethoxy)propyl, 2-(methoxy)butyl, 2-(ethoxy)butyl, 2-(n-propoxy)butyl, 2-(1-methylethoxy)butyl, 2-(n-butoxy)butyl, 2-(1-methylpropoxy)butyl, 2-(2-methylpropoxy)butyl, 2-(1,1-dimethylethoxy)butyl, 3-(methoxy)butyl, 3-(ethoxy)butyl, 3-(n-propoxy)butyl, 3-(1-methylethoxy)butyl, 3-(n-butoxy)butyl, 3-(1-methylpropoxy)butyl, 3-(2-methylpropoxy)butyl, 3-(1,1-dimethylethoxy)butyl, 4-(methoxy)butyl, 4-(ethoxy)butyl, 4-(n-propoxy)butyl, 4-(1-methylethoxy)butyl, 4-(n-butoxy)butyl, 4-(1-methylpropoxy)butyl, 4-(2-methylpropoxy)butyl, 4-(1,1-dimethylethoxy)butyl, etc.
- 10
15
20

Alkylthio: alkyl as defined above preferably having 1 to 6 or 1 to 4 C atoms, which is linked via an S atom, e.g. methylthio, ethylthio, n-propylthio and the like.

25

- Haloalkylthio: haloalkyl as defined above preferably having 1 to 6 or 1 to 4 C atoms, which is linked via an S atom, e.g. fluoromethylthio, difluoromethylthio, trifluoromethylthio, 2-fluoroethylthio, 2,2-difluoroethylthio, 2,2,2-trifluoroethylthio, pentafluoroethylthio, 2-fluoropropylthio, 3-fluoropropylthio, 2,2-difluoropropylthio, 2,3-difluoropropylthio, and heptafluoropropylthio.
- 30

Aryl: a mono-, bi- or tricyclic aromatic hydrocarbon radical such as phenyl or naphthyl, especially phenyl.

Heterocyclyl: a heterocyclic radical which may be saturated or partly unsaturated or aromatic and which ordinarily has 3, 4, 5, 6, 7 or 8 ring atoms, where ordinarily 1, 2, 3 or 4, in particular 1, 2 or 3, of the ring atoms are heteroatoms such as N, S or O, besides
5 carbon atoms as ring members.

Examples of saturated heterocycles are in particular:

Heterocycloalkyl: i.e. a saturated heterocyclic radical which ordinarily has 3, 4, 5, 6 or 7
10 ring atoms, where ordinarily 1, 2 or 3 of the ring atoms are heteroatoms such as N, S or O, besides carbon atoms as ring members. These include for example:

C-bonded, 3-4-membered saturated rings such as
2-oxiranyl, 2-oxetanyl, 3-oxetanyl, 2-aziridinyl, 3-thiethanyl, 1-azetidinyl,
15 2-azetidinyl.

C-bonded, 5-membered saturated rings such as
tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-
3-yl, tetrahydropyrrol-2-yl, tetrahydropyrrol-3-yl, tetrahydropyrazol-3-yl,
20 tetrahydropyrazol-4-yl, tetrahydroisoxazol-3-yl, tetrahydroisoxazol-4-yl,
tetrahydroisoxazol-5-yl, 1,2-oxathiolan-3-yl, 1,2-oxathiolan-4-yl, 1,2-oxathiolan-
5-yl, tetrahydroisothiazol-3-yl, tetrahydroisothiazol-4-yl, tetrahydroisothiazol-5-
yl, 1,2-dithiolan-3-yl, 1,2-dithiolan-4-yl, tetrahydroimidazol-2-yl,
tetrahydroimidazol-4-yl, tetrahydrooxazol-2-yl, tetrahydrooxazol-4-yl,
25 tetrahydrooxazol-5-yl, tetrahydrothiazol-2-yl, tetrahydrothiazol-4-yl,
tetrahydrothiazol-5-yl, 1,3-dioxolan-2-yl, 1,3-dioxolan-4-yl, 1,3-oxathiolan-2-yl,
1,3-oxathiolan-4-yl, 1,3-oxathiolan-5-yl, 1,3-dithiolan-2-yl, 1,3-dithiolan-4-yl,
1,3,2-dioxathiolan-4-yl.

30 C-bonded, 6-membered saturated rings such as:
tetrahydropyran-2-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, piperidin-2-yl,
piperidin-3-yl, piperidin-4-yl, tetrahydrothiopyran-2-yl, tetrahydrothiopyran-3-yl,
tetrahydrothiopyran-4-yl, 1,3-dioxan-2-yl, 1,3-dioxan-4-yl, 1,3-dioxan-5-yl,

1,4-dioxan-2-yl, 1,3-dithian-2-yl, 1,3-dithian-4-yl, 1,3-dithian-5-yl, 1,4-dithian-2-yl, 1,3-oxathian-2-yl, 1,3-oxathian-4-yl, 1,3-oxathian-5-yl, 1,3-oxathian-6-yl, 1,4-oxathian-2-yl, 1,4-oxathian-3-yl, 1,2-dithian-3-yl, 1,2-dithian-4-yl, hexahydropyrimidin-2-yl, hexahydropyrimidin-4-yl, hexahydropyrimidin-5-yl, hexahydropyrazin-2-yl, hexahydropyridazin-3-yl, hexahydropyridazin-4-yl, tetrahydro-1,3-oxazin-2-yl, tetrahydro-1,3-oxazin-4-yl, tetrahydro-1,3-oxazin-5-yl, tetrahydro-1,3-oxazin-6-yl, tetrahydro-1,3-thiazin-2-yl, tetrahydro-1,3-thiazin-4-yl, tetrahydro-1,3-thiazin-5-yl, tetrahydro-1,3-thiazin-6-yl, tetrahydro-1,4-thiazin-2-yl, tetrahydro-1,4-thiazin-3-yl, tetrahydro-1,4-oxazin-2-yl, tetrahydro-1,4-oxazin-3-yl, tetrahydro-1,2-oxazin-3-yl, tetrahydro-1,2-oxazin-4-yl, tetrahydro-1,2-oxazin-5-yl, tetrahydro-1,2-oxazin-6-yl.

N-bonded, 5-membered saturated rings such as:

tetrahydropyrrol-1-yl, tetrahydropyrazol-1-yl, tetrahydroisoxazol-2-yl, tetrahydroisothiazol-2-yl, tetrahydroimidazol-1-yl, tetrahydrooxazol-3-yl, tetrahydrothiazol-3-yl.

N-bonded, 6-membered saturated rings such as:

piperidin-1-yl, hexahydropyrimidin-1-yl, hexahydropyrazin-1-yl, hexahydropyridazin-1-yl, tetrahydro-1,3-oxazin-3-yl, tetrahydro-1,3-thiazin-3-yl, tetrahydro-1,4-thiazin-4-yl, tetrahydro-1,4-oxazin-4-yl, tetrahydro-1,2-oxazin-2-yl.

Unsaturated heterocyclic radicals which ordinarily have 4, 5, 6 or 7 ring atoms, where ordinarily 1, 2 or 3 of the ring atoms are heteroatoms such as N, S or O, besides carbon atoms as ring members. These include for example:

C-bonded, 5-membered, partially unsaturated rings such as:

2,3-dihydrofuran-2-yl, 2,3-dihydrofuran-3-yl, 2,5-dihydrofuran-2-yl, 2,5-dihydrofuran-3-yl, 4,5-dihydrofuran-2-yl, 4,5-dihydrofuran-3-yl, 2,3-dihydrothien-2-yl, 2,3-dihydrothien-3-yl, 2,5-dihydrothien-2-yl, 2,5-dihydrothien-3-yl, 4,5-dihydrothien-2-yl, 4,5-dihydrothien-3-yl, 2,3-dihydro-1H-pyrrol-2-yl, 2,3-dihydro-1H-pyrrol-3-yl, 2,5-dihydro-1H-pyrrol-2-yl, 2,5-dihydro-1H-pyrrol-3-yl, 4,5-dihydro-1H-pyrrol-2-yl, 4,5-dihydro-1H-pyrrol-3-yl, 3,4-dihydro-2H-pyrrol-2-yl, 3,4-

5 dihydro-2H-pyrrol-3-yl, 3,4-dihydro-5H-pyrrol-2-yl, 3,4-dihydro-5H-pyrrol-3-yl,
4,5-dihydro-1H-pyrazol-3-yl, 4,5-dihydro-1H-pyrazol-4-yl, 4,5-dihydro-1H-
pyrazol-5-yl, 2,5-dihydro-1H-pyrazol-3-yl, 2,5-dihydro-1H-pyrazol-4-yl, 2,5-
dihydro-1H-pyrazol-5-yl, 4,5-dihydroisoxazol-3-yl, 4,5-dihydroisoxazol-4-yl, 4,5-
dihydroisoxazol-5-yl, 2,5-dihydroisoxazol-3-yl, 2,5-dihydroisoxazol-4-yl, 2,5-
dihydroisoxazol-5-yl, 2,3-dihydroisoxazol-3-yl, 2,3-dihydroisoxazol-4-yl, 2,3-
dihydroisoxazol-5-yl, 4,5-dihydroisothiazol-3-yl, 4,5-dihydroisothiazol-4-yl, 4,5-
dihydroisothiazol-5-yl, 2,5-dihydroisothiazol-3-yl, 2,5-dihydroisothiazol-4-yl,
2,5-dihydroisothiazol-5-yl, 2,3-dihydroisothiazol-3-yl, 2,3-dihydroisothiazol-4-yl,
10 2,3-dihydroisothiazol-5-yl, 4,5-dihydro-1H-imidazol-2-yl, 4,5-dihydro-1H-
imidazol-4-yl, 4,5-dihydro-1H-imidazol-5-yl, 2,5-dihydro-1H-imidazol-2-yl, 2,5-
dihydro-1H-imidazol-4-yl, 2,5-dihydro-1H-imidazol-5-yl, 2,3-dihydro-1H-
imidazol-2-yl, 2,3-dihydro-1H-imidazol-4-yl, 4,5-dihydrooxazol-2-yl, 4,5-
dihydrooxazol-4-yl, 4,5-dihydrooxazol-5-yl, 2,5-dihydrooxazol-2-yl, 2,5-
dihydrooxazol-4-yl, 2,5-dihydrooxazol-5-yl, 2,3-dihydrooxazol-2-yl, 2,3-
dihydrooxazol-4-yl, 2,3-dihydrooxazol-5-yl, 4,5-dihydrothiazol-2-yl, 4,5-
dihydrothiazol-4-yl, 4,5-dihydrothiazol-5-yl, 2,5-dihydrothiazol-2-yl, 2,5-
dihydrothiazol-4-yl, 2,5-dihydrothiazol-5-yl, 2,3-dihydrothiazol-2-yl, 2,3-
dihydrothiazol-4-yl, 2,3-dihydrothiazol-5-yl, 1,3-dioxol-2-yl, 1,3-dioxol-4-yl, 1,3-
20 dithiol-2-yl, 1,3-dithiol-4-yl, 1,3-oxathiol-2-yl, 1,3-oxathiol-4-yl, 1,3-oxathiol-5-
yl.

C-bonded, 6-membered, partially unsaturated rings such as:

25 2H-3,4-dihydropyran-6-yl, 2H-3,4-dihydropyran-5-yl, 2H-3,4-dihydropyran-4-yl,
2H-3,4-dihydropyran-3-yl, 2H-3,4-dihydropyran-2-yl, 2H-3,4-dihydrothiopyran-
6-yl, 2H-3,4-dihydrothiopyran-5-yl, 2H-3,4-dihydrothiopyran-4-yl, 2H-3,4-
dihydrothiopyran-3-yl, 2H-3,4-dihydrothiopyran-2-yl, 1,2,3,4-tetrahydropyridin-
6-yl, 1,2,3,4-tetrahydropyridin-5-yl, 1,2,3,4-tetrahydropyridin-4-yl, 1,2,3,4-tetra-
hydropyridin-3-yl, 1,2,3,4-tetrahydropyridin-2-yl, 2H-5,6-dihydropyran-2-yl, 2H-
30 5,6-dihydropyran-3-yl, 2H-5,6-dihydropyran-4-yl, 2H-5,6-dihydropyran-5-yl, 2H-
5,6-dihydropyran-6-yl, 2H-5,6-dihydrothiopyran-2-yl, 2H-5,6-dihydrothiopyran-
3-yl, 2H-5,6-dihydrothiopyran-4-yl, 2H-5,6-dihydrothiopyran-5-yl, 2H-5,6-
dihydrothiopyran-6-yl, 1,2,5,6-tetrahydropyridin-2-yl, 1,2,5,6-tetrahydropyridin-

3-yl, 1,2,5,6-tetrahydropyridin-4-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,5,6-tetrahydropyridin-6-yl, 2,3,4,5-tetrahydropyridin-2-yl, 2,3,4,5-tetrahydropyridin-3-yl, 2,3,4,5-tetrahydropyridin-4-yl, 2,3,4,5-tetrahydropyridin-5-yl, 2,3,4,5-tetrahydropyridin-6-yl, 4H-pyran-2-yl, 4H-pyran-3-yl, 4H-pyran-4-yl, 4H-thiopyran-2-yl, 4H-thiopyran-3-yl, 4H-thiopyran-4-yl, 1,4-dihydropyridin-2-yl, 1,4-dihydropyridin-3-yl, 1,4-dihydropyridin-4-yl, 2H-pyran-2-yl, 2H-pyran-3-yl, 2H-pyran-4-yl, 2H-pyran-5-yl, 2H-pyran-6-yl, 2H-thiopyran-2-yl, 2H-thiopyran-3-yl, 2H-thiopyran-4-yl, 2H-thiopyran-5-yl, 2H-thiopyran-6-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 3,4-dihydropyridin-2-yl, 3,4-dihydropyridin-3-yl, 3,4-dihydropyridin-4-yl, 3,4-dihydropyridin-5-yl, 3,4-dihydropyridin-6-yl, 2,5-dihydropyridin-2-yl, 2,5-dihydropyridin-3-yl, 2,5-dihydropyridin-4-yl, 2,5-dihydropyridin-5-yl, 2,5-dihydropyridin-6-yl, 2,3-dihydropyridin-2-yl, 2,3-dihydropyridin-3-yl, 2,3-dihydropyridin-4-yl, 2,3-dihydropyridin-5-yl, 2,3-dihydropyridin-6-yl, 2H-5,6-dihydro-1,2-oxazin-3-yl, 2H-5,6-dihydro-1,2-oxazin-4-yl, 2H-5,6-dihydro-1,2-oxazin-5-yl, 2H-5,6-dihydro-1,2-oxazin-6-yl, 2H-5,6-dihydro-1,2-thiazin-3-yl, 2H-5,6-dihydro-1,2-thiazin-4-yl, 2H-5,6-dihydro-1,2-thiazin-5-yl, 2H-5,6-dihydro-1,2-thiazin-6-yl, 4H-5,6-dihydro-1,2-oxazin-3-yl, 4H-5,6-dihydro-1,2-oxazin-4-yl, 4H-5,6-dihydro-1,2-oxazin-5-yl, 4H-5,6-dihydro-1,2-oxazin-6-yl, 4H-5,6-dihydro-1,2-thiazin-3-yl, 4H-5,6-dihydro-1,2-thiazin-4-yl, 4H-5,6-dihydro-1,2-thiazin-5-yl, 4H-5,6-dihydro-1,2-thiazin-6-yl, 2H-3,6-dihydro-1,2-oxazin-3-yl, 2H-3,6-dihydro-1,2-oxazin-4-yl, 2H-3,6-dihydro-1,2-oxazin-5-yl, 2H-3,6-dihydro-1,2-oxazin-6-yl, 2H-3,6-dihydro-1,2-thiazin-3-yl, 2H-3,6-dihydro-1,2-thiazin-4-yl, 2H-3,6-dihydro-1,2-thiazin-5-yl, 2H-3,6-dihydro-1,2-thiazin-6-yl, 2H-3,4-dihydro-1,2-oxazin-3-yl, 2H-3,4-dihydro-1,2-oxazin-4-yl, 2H-3,4-dihydro-1,2-oxazin-5-yl, 2H-3,4-dihydro-1,2-oxazin-6-yl, 2H-3,4-dihydro-1,2-thiazin-3-yl, 2H-3,4-dihydro-1,2-thiazin-4-yl, 2H-3,4-dihydro-1,2-thiazin-5-yl, 2H-3,4-dihydro-1,2-thiazin-6-yl, 2,3,4,5-tetrahydropyridazin-3-yl, 2,3,4,5-tetrahydropyridazin-4-yl, 2,3,4,5-tetrahydropyridazin-5-yl, 2,3,4,5-tetrahydropyridazin-6-yl, 3,4,5,6-tetrahydropyridazin-3-yl, 3,4,5,6-tetrahydropyridazin-4-yl, 1,2,5,6-tetrahydropyridazin-3-yl, 1,2,5,6-tetrahydropyridazin-4-yl, 1,2,5,6-tetrahydropyridazin-5-yl, 1,2,5,6-tetrahydropyridazin-6-yl, 1,2,3,6-

5 tetrahydropyridazin-3-yl, 1,2,3,6-tetrahydropyridazin-4-yl, 4H-5,6-dihydro-1,3-oxazin-2-yl, 4H-5,6-dihydro-1,3-oxazin-4-yl, 4H-5,6-dihydro-1,3-oxazin-5-yl, 4H-5,6-dihydro-1,3-oxazin-6-yl, 4H-5,6-dihydro-1,3-thiazin-2-yl, 4H-5,6-dihydro-1,3-thiazin-4-yl, 4H-5,6-dihydro-1,3-thiazin-5-yl, 4H-5,6-dihydro-1,3-thiazin-6-yl, 3,4,5,6-tetrahydropyrimidin-2-yl, 3,4,5,6-tetrahydropyrimidin-4-yl, 3,4,5,6-tetrahydropyrimidin-5-yl, 3,4,5,6-tetrahydropyrimidin-6-yl, 1,2,3,4-tetrahydropyrazin-2-yl, 1,2,3,4-tetrahydropyrazin-5-yl, 1,2,3,4-tetrahydropyrimidin-2-yl, 1,2,3,4-tetrahydropyrimidin-4-yl, 1,2,3,4-tetrahydropyrimidin-5-yl, 1,2,3,4-tetrahydropyrimidin-6-yl, 2,3-dihydro-1,4-thiazin-2-yl, 2,3-dihydro-1,4-thiazin-3-yl, 2,3-dihydro-1,4-thiazin-5-yl, 2,3-dihydro-1,4-thiazin-6-yl, 2H-1,3-oxazin-2-yl, 2H-1,3-oxazin-4-yl, 2H-1,3-oxazin-5-yl, 2H-1,3-oxazin-6-yl, 2H-1,3-thiazin-2-yl, 2H-1,3-thiazin-4-yl, 2H-1,3-thiazin-5-yl, 2H-1,3-thiazin-6-yl, 4H-1,3-oxazin-2-yl, 4H-1,3-oxazin-4-yl, 4H-1,3-oxazin-5-yl, 4H-1,3-oxazin-6-yl, 4H-1,3-thiazin-2-yl, 4H-1,3-thiazin-4-yl, 4H-1,3-thiazin-5-yl, 4H-1,3-thiazin-6-yl, 6H-1,3-oxazin-2-yl, 6H-1,3-oxazin-4-yl, 6H-1,3-oxazin-5-yl, 6H-1,3-oxazin-6-yl, 6H-1,3-thiazin-2-yl, 6H-1,3-oxazin-4-yl, 6H-1,3-oxazin-5-yl, 6H-1,3-thiazin-6-yl, 2H-1,4-oxazin-2-yl, 2H-1,4-oxazin-3-yl, 2H-1,4-oxazin-5-yl, 2H-1,4-oxazin-6-yl, 2H-1,4-thiazin-2-yl, 2H-1,4-thiazin-3-yl, 2H-1,4-thiazin-5-yl, 2H-1,4-thiazin-6-yl, 4H-1,4-oxazin-2-yl, 4H-1,4-oxazin-3-yl, 4H-1,4-thiazin-2-yl, 4H-1,4-thiazin-3-yl, 1,4-dihydropyridazin-3-yl, 1,4-dihydropyridazin-4-yl, 1,4-dihydropyridazin-5-yl, 1,4-dihydropyridazin-6-yl, 1,4-dihydropyrazin-2-yl, 1,2-dihydropyrazin-2-yl, 1,2-dihydropyrazin-3-yl, 1,2-dihydropyrazin-5-yl, 1,2-dihydropyrazin-6-yl, 1,4-dihydropyrimidin-2-yl, 1,4-dihydropyrimidin-4-yl, 1,4-dihydropyrimidin-5-yl, 1,4-dihydropyrimidin-6-yl, 3,4-dihydropyrimidin-2-yl, 3,4-dihydropyrimidin-4-yl, 3,4-dihydropyrimidin-5-yl or 3,4-dihydropyrimidin-6-yl.

N-bonded, 5-membered, partially unsaturated rings such as:

30 2,3-dihydro-1H-pyrrol-1-yl, 2,5-dihydro-1H-pyrrol-1-yl, 4,5-dihydro-1H-pyrazol-1-yl, 2,5-dihydro-1H-pyrazol-1-yl, 2,3-dihydro-1H-pyrazol-1-yl, 2,5-dihydroisoxazol-2-yl, 2,3-dihydroisoxazol-2-yl, 2,5-dihydroisothiazol-2-yl, 2,3-dihydroisoxazol-2-yl, 4,5-dihydro-1H-imidazol-1-yl, 2,5-dihydro-1H-imidazol-1-yl, 2,3-dihydro-1H-imidazol-1-yl, 2,3-dihydrooxazol-3-yl, 2,3-dihydrothiazol-3-

yl.

N-bonded, 6-membered, partially unsaturated rings such as:

1,2,3,4-tetrahydropyridin-1-yl, 1,2,5,6-tetrahydropyridin-1-yl, 1,4-dihydropyridin-
5 1-yl, 1,2-dihydropyridin-1-yl, 2H-5,6-dihydro-1,2-oxazin-2-yl, 2H-5,6-dihydro-
1,2-thiazin-2-yl, 2H-3,6-dihydro-1,2-oxazin-2-yl, 2H-3,6-dihydro-1,2-thiazin-2-
yl, 2H-3,4-dihydro-1,2-oxazin-2-yl, 2H-3,4-dihydro-1,2-thiazin-2-yl, 2,3,4,5-
tetrahydropyridazin-2-yl, 1,2,5,6-tetrahydropyridazin-1-yl, 1,2,5,6-
tetrahydropyridazin-2-yl, 1,2,3,6-tetrahydropyridazin-1-yl, 3,4,5,6-
10 tetrahydropyrimidin-3-yl, 1,2,3,4-tetrahydropyrazin-1-yl, 1,2,3,4-
tetrahydropyrimidin-1-yl, 1,2,3,4-tetrahydropyrimidin-3-yl, 2,3-dihydro-1,4-
thiazin-4-yl, 2H-1,2-oxazin-2-yl, 2H-1,2-thiazin-2-yl, 4H-1,4-oxazin-4-yl, 4H-
1,4-thiazin-4-yl, 1,4-dihydropyridazin-1-yl, 1,4-dihydropyrazin-1-yl, 1,2-
dihydropyrazin-1-yl, 1,4-dihydropyrimidin-1-yl or 3,4-dihydropyrimidin-3-yl.

15

Hetaryl: a 5- or 6-membered aromatic heterocyclic radical which ordinarily has 1, 2, 3
or 4 nitrogen atoms or a heteroatom selected from oxygen and sulfur and, if appropriate,
1, 2 or 3 nitrogen atoms as ring members besides carbon atoms as ring members: for
example

20

C-bonded, 5-membered heteroaromatic radicals having 1, 2, 3 or 4 nitrogen atoms
or a heteroatom selected from oxygen and sulfur and, if appropriate, having 1, 2
or 3 nitrogen atoms as ring members, such as:

2-furyl, 3-furyl, 2-thienyl, 3-thienyl, pyrrol-2-yl, pyrrol-3-yl, pyrazol-3-yl,
25 pyrazol-4-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, isothiazol-3-yl,
isothiazol-4-yl, isothiazol-5-yl, imidazol-2-yl, imidazol-4-yl, oxazol-2-yl, oxazol-
4-yl, oxazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, 1,2,3-oxadiazol-4-yl,
1,2,3-oxadiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-
2-yl, 1,2,3-thiadiazol-4-yl, 1,2,3-thiadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-
30 thiadiazol-5-yl, 1,3,4-thiadiazolyl-2-yl, 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl,
tetrazol-5-yl.

C-bonded, 6-membered heteroaromatic radicals having 1, 2, 3 or 4 nitrogen atoms

as ring members, such as:

pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridazin-3-yl, pyridazin-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrazin-2-yl, 1,3,5-triazin-2-yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, 1,2,4-triazin-6-yl, 1,2,4,5-tetrazin-3-yl.

5

N-bonded, 5-membered heteroaromatic radicals having 1, 2, 3 or 4 nitrogen atoms as ring members, such as:

pyrrol-1-yl, pyrazol-1-yl, imidazol-1-yl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, tetrazol-1-yl.

10

Heterocyclyl also includes bicyclic heterocycles which have one of the aforementioned 5- or 6-membered heterocyclic rings and a further saturated, unsaturated or aromatic carbocycle fused thereto, for example a benzene, cyclohexane, cyclohexene or cyclohexadiene ring, or a further 5- or 6-membered heterocyclic ring fused thereto,

15 where the latter may likewise be saturated, unsaturated or aromatic. These bicyclic heterocycles include for example quinolinyl, isoquinolinyl, indolyl, indolizynyl, isoindolyl, indazolyl, benzofuryl, benzothienyl, benzo[b]thiazolyl, benzoxazolyl, benzthiazolyl, benzimidazolyl and 3,5,6,7-tetrahydro-indazolyl. Examples of 5- to 6-membered non-aromatic heterocyclic radicals comprising a fused benzene ring include
20 dihydroindolyl, dihydroindolizynyl, dihydroisoindolyl, dihydroquinolinyl, dihydroisoquinolinyl, chromenyl and chromanyl.

Arylalkyl: an aryl radical as defined above which is linked via an alkylene group, in particular via a methylene, 1,1-ethylene or 1,2-ethylene group, e.g. benzyl, 1-phenyl-ethyl and 2-phenylethyl (= phenethyl).
25

Arylalkenyl: an aryl radical as defined above, which is linked via an alkenylene group, in particular via a 1,1-ethenyl, 1,2-ethenyl or 1,3-propenyl group, e.g. 2-phenylethen-1-yl and 1-phenylethen-1-yl.

30

Cycloalkoxy: a cycloalkyl radical as defined above which is linked via an oxygen atom, e.g. cyclopropyloxy, cyclobutyloxy, cyclopentyloxy or cyclohexyloxy.

Cycloalkylalkyl: a cycloalkyl radical as defined above which is linked via an alkylene group, in particular via a methylene, 1,1-ethylene or 1,2-ethylene group, e.g. cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl or cyclohexylmethyl.

- 5 Heterocyclylalkyl and hetarylalkyl: a heterocyclyl or hetaryl radical as defined above which is linked via an alkylene group, in particular via a methylene, 1,1-ethylene or 1,2-ethylene group.

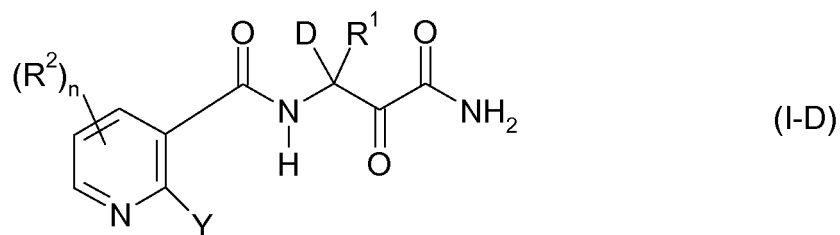
The expression "optionally substituted" means in the context of the present invention
10 that the respective moiety is substituted or has 1, 2 or 3, in particular 1, substituents which are selected from halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, OH, SH, CN, CF₃, O-CF₃, COOH, O-CH₂-COOH, C₁-C₆-alkoxy, C₁-C₄-haloalkoxy, C₁-C₆-alkylthio, C₃-C₇-cycloalkyl, COO-C₁-C₆-alkyl, CONH₂, CONH-C₁-C₆-alkyl, SO₂NH-C₁-C₆-alkyl, CON-(C₁-C₆-alkyl)₂, SO₂N-(C₁-C₆-alkyl)₂, NH-SO₂-C₁-C₆-alkyl, NH-CO-C₁-C₆-alkyl, SO₂-
15 C₁-C₆-alkyl, O-phenyl, O-CH₂-phenyl, CONH-phenyl, SO₂NH-phenyl, CONH-hetaryl, SO₂NH-hetaryl, SO₂-phenyl, NH-SO₂-phenyl, NH-CO-phenyl, NH-SO₂-hetaryl and NH-CO-hetaryl, where phenyl and hetaryl in the last 11 radicals mentioned are unsubstituted or may have 1, 2 or 3 substituents which are selected from halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy and C₁-C₄-haloalkoxy.

20

According to a particular embodiment of the invention the compounds of the formula I are predominately in the S-configuration at the carbon atom carrying the radical R¹, and according to a particular preferred embodiment the compounds I are completely S-configured at said position.

25

According to one aspect of the invention the hydrogen atom linked to the carbon atom carrying the radical R¹ of a compound I is replaced by a deuterium atom, as shown in formula I-D below. R¹, R², Y and n in formula I-D have the aforementioned meanings, and where R¹, R², Y and n alone or in combination, have in particular the preferred or
30 special meanings given below.



The degree of deuteration at said position usually exceeds 80%, preferably exceeds 90% and in particular exceeds 95%. The deuterated diastereomers of formula I-D often show a markedly higher stability against racematisation than their counterparts of formula I, probably due to a kinetic isotope effect (see F. Maltais et al. J. Med. Chem, DOI 10.1021/jm901023f). Thus, it is generally possible to stabilize the S-configuration at the carbon atom carrying radical R^1 of compounds I according to the aforementioned preferred embodiments of the invention, by introducing a deuterium at that carbon atom.

In relation to their use as calpain inhibitors, the variables n , m , Y , R^1 , R^2 and R^y preferably have the following meanings, where these represent, both considered on their own and in combination with at least one other or all, special embodiments of the compounds of the formula I:

R^1 is C_1 - C_{10} -alkyl, preferably C_3 - C_8 -alkyl, which may be partly or completely halogenated and/or have 1, 2 or 3 substituents R^{1a} , in particular is unsubstituted C_1 - C_{10} -alkyl, specifically unsubstituted C_3 - C_8 -alkyl,

C_3 - C_7 -cycloalkyl- C_1 - C_4 -alkyl, where the cycloalkyl moiety may have 1, 2, 3 or 4 radicals R^{1b} , in particular C_3 - C_7 -cycloalkylmethyl, 1-(C_3 - C_7 -cycloalkyl)ethyl or 2-(C_3 - C_7 -cycloalkyl)ethyl, specifically cyclohexylmethyl, or

phenyl- C_1 - C_4 -alkyl or hetaryl- C_1 - C_4 -alkyl, in particular benzyl, 1-phenylethyl, 2-phenylethyl, hetarylmethyl, 1-hetarylethyl, 2-hetarylethyl, such as thienylmethyl, pyridinylmethyl, where phenyl and hetaryl in the last radicals mentioned may be unsubstituted or carry 1, 2, 3 or 4 identical or different radicals R^{1c} .

More preferably R^1 is C_1 - C_{10} -alkyl, preferably C_3 - C_8 -alkyl, which may be partly or completely halogenated and/or have 1, 2 or 3 substituents R^{1a} as defined herein, where R^{1a} is in particular selected from C_1 - C_4 -alkoxy and C_1 - C_4 -haloalkoxy; C_3 - C_7 -cycloalkyl-methyl, where the cycloalkyl moiety may have 1, 2, 3 or 4 radicals R^{1b} , as defined herein, where R^{1b} is in particular selected from halogen, C_1 - C_3 -alkyl, C_1 - C_4 -haloalkyl, C_1 - C_4 -alkoxy or C_1 - C_4 -haloalkoxy; or benzyl or hetaryl-methyl, where phenyl and hetaryl in the last 2 radicals mentioned may be unsubstituted or carry 1, 2, 3 or 4 identical or different radicals R^{1c} as defined herein, where R^{1c} is in particular selected from halogen, specifically fluorine and chlorine, C_1 - C_4 -alkyl, C_1 - C_4 -haloalkyl, C_1 - C_4 -alkoxy, C_1 - C_4 -haloalkoxy and $(CH_2)_pNR^{c6}R^{c7}$, where p is 0 or 1 and R^{c6} and R^{c7} are as defined above, and in particular are selected from hydrogen and C_1 - C_4 -alkyl or $NR^{c6}R^{c7}$ together form a saturated N-bound heterocycle such as 4-morpholinyl, 1-pyrrolidinyl, 1-piperidinyl or 1-piperazinyl or 4-methylpiperazin-1-yl.

In particular, R^1 is benzyl, where the phenyl group of benzyl may be unsubstituted or carry 1 or 2 identical or different radicals R^{1c} as defined herein, where R^{1c} is in particular selected from halogen, specifically fluorine and chlorine, C_1 - C_4 -alkyl, C_1 - C_4 -haloalkyl, C_1 - C_4 -alkoxy, C_1 - C_4 -haloalkoxy and $(CH_2)_pNR^{c6}R^{c7}$, where p is 0 or 1 and R^{c6} and R^{c7} are as defined above, and in particular are selected from hydrogen and C_1 - C_4 -alkyl or $NR^{c6}R^{c7}$ together form a saturated N-bound heterocycle such as 4-morpholinyl, 1-pyrrolidinyl, 1-piperidinyl or 1-piperazinyl or 4-methylpiperazin-1-yl and where R^{1c} is especially selected from fluorine, chlorine, methyl, methoxy, CF_3 , CHF_2 , CH_2F , $O-CF_3$, $O-CHF_2$ and $O-CH_2F$.

In this connection, R^{1a} , R^{1b} and R^{1c} where present have the aforementioned meanings. In particular:

- R^{1a} is C_1 - C_4 -alkoxy or C_1 - C_4 -haloalkoxy;
- R^{1b} is halogen, C_1 - C_4 -alkyl, C_1 - C_4 -haloalkyl, C_1 - C_4 -alkoxy or C_1 - C_4 -haloalkoxy; and
- R^{1c} is halogen, C_1 - C_4 -alkyl, OH, SH, CN, C_1 - C_4 -haloalkyl, C_1 - C_4 -haloalkoxy, COOH, $O-CH_2-COOH$, C_1 - C_6 -alkoxy, C_1 - C_6 -alkylthio, C_3 - C_7 -cycloalkyl, COO- C_1 - C_6 -alkyl, $CONH_2$, $CONH-C_1$ - C_6 -alkyl, SO_2NH-C_1 - C_6 -alkyl, CON-

- (C₁-C₆-alkyl)₂, SO₂N-(C₁-C₆-alkyl)₂, NH-SO₂-C₁-C₆-alkyl, NH-CO-C₁-C₆-alkyl, SO₂-C₁-C₆-alkyl, O-phenyl, O-CH₂-phenyl, CONH-phenyl, SO₂NH-phenyl, CONH-hetaryl, SO₂NH-hetaryl, SO₂-phenyl, NH-SO₂-phenyl, NH-CO-phenyl, NH-SO₂-hetaryl, NH-CO-hetaryl where phenyl and hetaryl in the last 11 radicals mentioned are unsubstituted or may have 1, 2 or 3 substituents which are selected from halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy and C₁-C₄-haloalkoxy,
- 5
10
15
20
25
30
- (CH₂)_p-NR^{c6}R^{c7} with p = 0, 1, 2, 3, 4, 5 or 6, in particular 0, and -O-(CH₂)_q-NR^{c6}R^{c7} with q = 2, 3, 4, 5 or 6, in particular 2, where R^{c6}, R^{c7} are independently of one another hydrogen or C₁-C₆-alkyl, or together with the nitrogen atom to which they are bonded, are a morpholine, piperidine, pyrrolidine, azetidine or piperazine residue, where the last 5 radicals mentioned are unsubstituted or may carry 1, 2, 3 or 4 radicals selected from C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy or C₁-C₄-haloalkoxy.
- R^{1c} is in particular selected from halogen, C₁-C₄-alkyl, C₁-C₄-alkoxy, CF₃, CHF₂, CH₂F, O-CHF₂, O-CH₂F, O-CF₃ and -(CH₂)_p-NR^{c6}R^{c7} with p = 0, 1 or 2, where
- R^{c6} is selected from the group consisting of H and C₁-C₄-alkyl and . R^{c7} is selected from the group consisting of H and C₁-C₄-alkyl or the two radicals R^{c6} and R^{c7} form together with the N atom a 5, 6 or 7-membered, saturated nitrogen heterocycle which may optionally have further different or identical heteroatom from the group of O, N and S as ring member and where the nitrogen heterocycle is unsubstituted or carries 1, 2 or 3 substituents selected from C₁-C₄-alkyl.
- R^{1c} is particularly preferred halogen, specifically fluorine and chlorine, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy and (CH₂)_pNR^{c6}R^{c7}, where p is 0 or 1 and R^{c6} and R^{c7} are as defined above, and in particular are selected from hydrogen and C₁-C₄-alkyl or NR^{c6}R^{c7} together form a saturated N-bound heterocycle such as 4-morpholinyl, 1-pyrrolidinyl, 1-piperidinyl or 1-piperazinyl or 4-methylpiperazin-1-yl and where R^{1c} is especially selected from halogen, C₁-C₄-alkyl, such as methyl,

CF₃, CHF₂, CH₂F, C₁-C₄-alkoxy, such as methoxy, O-CF₃, O-CHF₂ and O-CH₂F.

5 R¹ is in particular benzyl, which may be unsubstituted or carry 1 or 2 identical or different radicals R^{1c}, where the radicals R^{1c} are as defined above and in particular selected from halogen, C₁-C₂-alkyl and C₁-C₂-alkoxy.

n is preferably 0 or 1 and specifically 0.

10 Depending on its occurrence, R² is in particular halogen, specifically fluorine or chlorine, CN, CF₃, CHF₂, CH₂F, C₁-C₂-alkyl or C₁-C₂-alkoxy. In particular, R², if present, is fluorine, chlorine, methyl, ethyl or methoxy, and specifically fluorine or methyl.

15 m is preferably 0.

Depending on its occurrence, R^y is in particular halogen, specifically fluorine or chlorine, CN, CF₃, CHF₂, CH₂F, C₁-C₂-alkyl or C₁-C₂-alkoxy. In particular, R^y, if present, is fluorine, chlorine, methyl, ethyl or methoxy, and specifically fluorine or
20 methyl.

A first group of embodiments of the invention relates to compounds of the formula I, wherein Y is a radical of the formula Y1.

25 Amongst the compounds of the formula I, wherein Y is a radical of the formula Y1, a particular group of embodiments relates to compounds, where the moiety A-NR³R⁴ in formula Y1 is located in the 3-position of the pyrazole ring.

Amongst the compounds of the formula I, wherein Y is a radical of the formula Y1,
30 another particular group of embodiments relates to compounds, where the moiety A-NR³R⁴ in formula Y1 is located in the 4-position of the pyrazole ring.

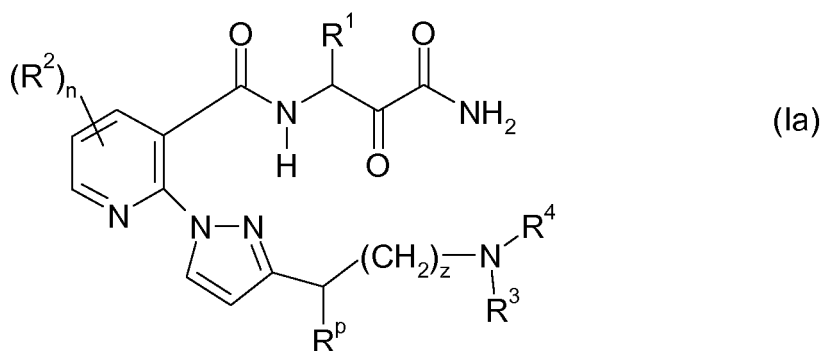
In the compounds of the formula I, where Y is a radical Y1, the variables A, R³ and R⁴

preferably have the following meanings, where these represent, both considered on their own and in combination with at least one other or all, special embodiments of the compounds of the formula I.

- 5 A is a bivalent radical of the formula $\text{CH-R}^p(\text{CH}_2)_z$, where the carbon atom which carries R^p is bound to the pyrazole ring, where z is 0, 1 or 2 and where R^p is hydrogen or has one of the meanings given for R^6 , or R^p together with R^4 forms a bivalent radical of the formula $(\text{CH}_2)_s$ with s being 1, 2 or 3. In particular z is 0, 1 or 2, R^p is hydrogen or methyl, or R^p together with R^4 forms a bivalent radical of the formula $(\text{CH}_2)_s$ with s being 1, 2 or 3.

A particular group of the compounds of formula I, where Y is $Y1$ and where A is a bivalent radical of the formula $\text{CH-R}^p(\text{CH}_2)_z$ and where the carbon atom which carries R^p is bound to the pyrazole ring, where z is 0, 1 or 2, where R^p is hydrogen or has one of the meanings given for R^6 , and where R^p is in particular hydrogen, methyl or ethyl, especially hydrogen.

A special group of the compounds of formula I, where Y is $Y1$ and where A is a bivalent radical of the formula $\text{CH-R}^p(\text{CH}_2)_z$ and where the carbon atom which carries R^p is bound to the pyrazole ring, are the compounds of the formula Ia, the tautomers thereof, the hydrates thereof, the prodrugs thereof and the pharmaceutically suitable salts thereof:



25

where R^1 , R^2 , R^3 , R^4 and n are as defined herein,

R^p is hydrogen, methyl or ethyl, or

- R^p together with R^4 forms a bivalent radical of the formula $(CH_2)_s$ with s being 1, 2 or 3, and
 z is 0, 1 or 2.
- 5 In the compounds of the formulae I and Ia, where Y is Y1, the variables R^3 and R^4 preferably have the following meanings, where these represent, both considered on their own and in combination with at least one other or all, special embodiments of the compounds of the formulae I and Ia:
- 10 R^3 is preferably C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl- C_1 - C_4 -alkyl, where the cycloalkyl moiety of the last 2 radicals mentioned may have 1, 2, 3 or 4 radicals R^{3b} ,
 phenyl or phenyl- C_1 - C_4 -alkyl, where phenyl in the last 2 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{3c} , where
 15 R^{3b} and R^{3c} are as defined above.

In this connection, R^{3b} and R^{3c} where present have the aforementioned meanings.
 In particular:

- 20 R^{3b} is selected from the group consisting of halogen, C_1 - C_6 -alkyl, which may be partly or completely halogenated,
 phenyl which optionally has 1, 2 or 3 substituents R^{3c} ,
 R^{3b} is in particular fluorine or methyl;
- R^{3c} is selected from halogen, OH, SH, NO_2 , $C(O)NH_2$, CHO, CN, NH_2 , C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -haloalkoxy, C_1 - C_6 -alkylthio,
 25 C_1 - C_6 -haloalkylthio, CO- C_1 - C_6 -alkyl, CO-O- C_1 - C_6 -alkyl, NH- C_1 - C_6 -alkyl, NH-C(O)- C_1 - C_6 -alkyl, and SO_2 - C_1 - C_6 -alkyl;
 R^{3c} is in particular selected from halogen, CN, C_1 - C_4 -alkyl, C_1 - C_2 -fluoroalkyl, C_1 - C_2 -alkoxy and C_1 - C_2 -fluoroalkoxy.
- 30 R^3 is in particular C_1 - C_6 -alkyl, C_1 - C_4 -fluoroalkyl, C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl- C_1 -alkyl, where the cycloalkyl moiety of the last 2 radicals mentioned may have 1, 2, 3 or 4 radicals R^{3b} , which are in particular selected from the group

consisting of fluorine or methyl;
phenyl or benzyl, where phenyl in the last 2 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{3c} , where
 R^{3b} and R^{3c} are as defined above.

5

R^4 is preferably hydrogen, C_1 - C_6 -alkyl or C_1 - C_6 -haloalkyl, in particular hydrogen or C_1 - C_4 -alkyl.

In the moiety of the formula Y1, the moiety NR^3R^4 may also form a saturated, N-bound
10 4-, 5-, 6-, or 7-membered heteromonocyclic or 7-, 8-, 9-, or 10-membered heterobicyclic radical as defined above. In particular, the moiety NR^3R^4 is a saturated, N-bound 4-, 5-, 6-, or 7-membered heteromonocyclic or 7-, 8-, 9-, or 10-membered heterobicyclic radical, where said heteromonocyclic and the heterobicyclic radical, in addition to the nitrogen atom, may have 1 further heteroatom or heteroatom moiety as
15 ring member, which are selected from O, S, $S(O)_2$ and NR^{4d} , where said heteromonocyclic radical may carry a fused benzene ring and where said heteromonocyclic and the heterobicyclic radical are unsubstituted or may be substituted by 1, 2, 3 or 4 radicals R^{4e} , where R^{4d} and R^{4e} are as defined above and where

20 R^{4d} is selected from the group consisting of hydrogen, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_1 - C_6 -alkyl which has 1, 2 or 3 substituents R^{4a} , C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl- C_1 - C_4 -alkyl, where the cycloalkyl moiety of the last 2 radicals mentioned is unsubstituted or may have 1, 2, 3 or 4 radicals R^{4b} , phenyl and benzyl where the phenyl ring of the last 2 radicals mentioned is
25 unsubstituted or may have 1, 2 or 3 substituents R^{4c} ;

In this connection, R^{4d} and R^{4e} where present have the aforementioned meanings.
In particular:

30 R^{4d} is selected from the group consisting of hydrogen, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_1 - C_6 -alkyl which has 1, 2 or 3 substituents R^{4a} , C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl- C_1 - C_4 -alkyl, where the cycloalkyl moiety of the last 2 radicals mentioned is unsubstituted or may have 1, 2, 3

or 4 radicals R^{4b} ,

phenyl and benzyl where the phenyl ring of the last 2 radicals mentioned is unsubstituted or may have 1, 2 or 3 substituents R^{4c} ;

- 5 R^{4e} is selected from the group consisting of halogen, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -haloalkoxy, C_1 - C_6 -alkylthio, C_1 - C_6 -haloalkylthio and phenyl.

10 In this connection, R^{4a} , R^{4b} and R^{4c} where present have the aforementioned meanings. In particular:

R^{4a} is selected from the group consisting of halogen and C_1 - C_4 -alkoxy, in particular fluorine, methoxy or ethoxy;

15 R^{4b} is selected from the group consisting of halogen, C_1 - C_6 -alkyl, which may be partly or completely halogenated, phenyl which optionally has 1, 2 or 3 substituents R^{3c} , R^{4b} is in particular fluorine or methyl;

20 R^{4c} is selected from halogen, OH, SH, NO_2 , $C(O)NH_2$, CHO, CN, NH_2 , C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -haloalkoxy, C_1 - C_6 -alkylthio, C_1 - C_6 -haloalkylthio, CO- C_1 - C_6 -alkyl, CO-O- C_1 - C_6 -alkyl, NH- C_1 - C_6 -alkyl, NH-C(O) C_1 - C_6 -alkyl, and SO_2 - C_1 - C_6 -alkyl; R^{4c} is in particular selected from halogen, CN, C_1 - C_4 -alkyl, C_1 - C_2 -fluoroalkyl, C_1 - C_2 -alkoxy and C_1 - C_2 -fluoroalkoxy.

25 Particular examples of the moiety NR^3R^4 include, but are not limited to the following radicals:

4-morpholinyl, 4-thiomorpholinyl, 1,1-dioxothiomorpholin-4-yl, 2,6-dimethylmorpholin-4-yl, 2-phenylmorpholin-4-yl, 1-azetidiny, 1-azepanyl, 1-pyrrolidinyl, 3-phenylpyrrolidin-1-yl, 1-piperidinyl, 4-methylpiperidin-1-yl, 4-phenylpiperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-(trifluoromethyl)piperidin-1-yl, 4-(tert.-butyl)piperidin-1-yl, 4-methylpiperazin-1-yl, 4-ethylpiperazin-1-yl, 4-propylpiperazin-1-yl, 4-cyclopropylmethylpiperazin-1-yl, 4-cyclopropylpiperazin-1-yl, 4-phenylpiperazin-1-yl, dimethylamino, diethylamino, diisopropylamino,

30

N-phenylamino, N-methyl-N-phenylamino, N-methyl-N-isopropylamino, N-cyclopropyl-N-methylamino, N-cyclopropyl-N-phenylamino, N-cyclopropyl-N-benzylamino, N-cyclohexyl-N-methylamino, N-benzyl-N-methylamino, N-cyclohexylmethyl-N-methylamino, N-(4-trifluoromethylcyclohexyl)methyl-N-methylamino, 3,4-dihydro-2H-1,4-benzoxazin-4-yl, cis-octahydrobenzo-[1,4]oxazin-4-yl, trans-octahydrobenzo[1,4]oxazin-4-yl, 5,5-difluoroocta-hydrocyclopenta[c]pyrrol-2-yl, hexahydrofuro[3,4-c]pyrrol-5-yl, 2,3-dihydroindol-1-yl, 2-oxa-7-azaspiro[3.5]nonane-7-yl, 2,3-dihydro-1H-isoindole-2-yl, 5-trifluoromethyl-2,3-dihydro-1H-isoindole-2-yl, 4-trifluoro-2,3-dihydro-1H-isoindole-2-yl, 2,3-dihydroisoindole-1-one-2-yl, 1,2,3,4-tetrahydroisoquinoline-2-yl, 3-azabicyclo[3.2.0]heptane-3-yl and 6-(4-fluorophenyl)-3-azabicyclo[3.2.0]heptane-3-yl.

A further group of embodiments of the present invention relate to compounds of the formula I, where Y is a radical Y¹, R^p together with R⁴ forms a bivalent radical of the formula (CH₂)_s with s being 1, 2 or 3. In this group of embodiments, n, R¹, R² and R³ are as defined above. In this group of embodiments, R³ has in particular the following meanings:

R³ is preferably C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₄-alkyl, where the cycloalkyl moiety of the last 2 radicals mentioned may have 1, 2, 3 or 4 radicals R^{3b}, phenyl or phenyl-C₁-C₄-alkyl, where phenyl in the last 2 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{3c}, where R^{3b} and R^{3c} are as defined above.

In this connection, R^{3b} and R^{3c} where present have the aforementioned meanings. In particular:

R^{3b} is selected from the group consisting of halogen, C₁-C₆-alkyl, which may be partly or completely halogenated, phenyl which optionally has 1, 2 or 3 substituents R^{3c}, R^{3b} is in particular fluorine or methyl; R^{3c} is selected from halogen, OH, SH, NO₂, C(O)NH₂, CHO, CN, NH₂, C₁-C₆-

alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkoxy, C₁-C₆-haloalkoxy, C₁-C₆-alkylthio, C₁-C₆-haloalkylthio, CO-C₁-C₆-alkyl, CO-O-C₁-C₆-alkyl, NH-C₁-C₆-alkyl, NH-C(O)C₁-C₆-alkyl, and SO₂-C₁-C₆-alkyl;

5 R^{3c} is in particular selected from halogen, CN, C₁-C₄-alkyl, C₁-C₂-fluoroalkyl, C₁-C₂-alkoxy and C₁-C₂-fluoroalkoxy.

10 In this group of embodiments, R³ is especially selected from the group consisting of C₁-C₆-alkyl, C₁-C₄-fluoroalkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-alkyl, where the cycloalkyl moiety of the last 2 radicals mentioned may have 1, 2, 3 or 4 radicals R^{3b}, which are in particular selected from the group consisting of fluorine or methyl, phenyl or benzyl, where phenyl in the last 2 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{3c}, where R^{3b} and R^{3c} are as defined above.

15 In this group of embodiments, particular examples of the moiety A-NR³R⁴ include, but are not limited to the following radicals: azetidin-3-yl, pyrrolidin-3-yl, 1-methylpyrrolidin-3-yl, piperidin-3-yl, 1-methylpiperidin-3-yl, piperidin-4-yl, 1-methylpiperidin-4-yl, 1-ethylpiperidin-4-yl, 1-propylpiperidin-4-yl, 1-cyclopropylpiperidin-4-yl, and 1-benzylpiperidin-4-yl.

20 A second group of embodiments of the invention relates to compounds of the formula I, where Y is a radical of the formula Y2.

25 In the compounds of the formulae I, where Y is Y2, the variables A¹, A² and R⁵ preferably have the following meanings, where these represent, both considered on their own and in combination with at least one other or all, special embodiments of the compounds of the formulae I and Ib:

A¹ is preferably a single bond, CH₂ or CH₂CH₂.

30 A² is preferably CH₂, CH₂CH₂ or CH₂CH₂CH₂.

R⁵ is preferably C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₄-alkyl, where the cycloalkyl moiety of the last 2 radicals mentioned may

have 1, 2, 3 or 4 radicals R^{3b} ,
 a radical $C(=O)R^{3d}$, a radical $COOR^{b1}$,
 phenyl or phenyl- C_1 - C_4 -alkyl, where phenyl in the last 2 radicals mentioned are
 unsubstituted or have 1, 2 or 3 substituents R^{3c} , where
 5 R^{b1} , R^{3b} , R^{3c} and R^{3d} are as defined above.

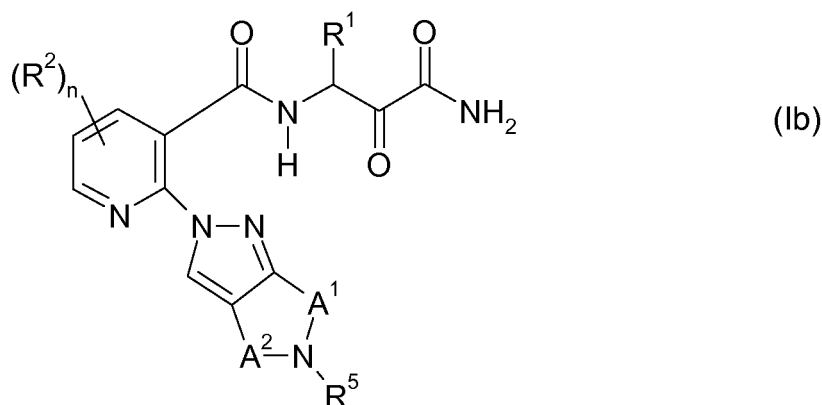
In this context, R^{b1} , R^{3b} , R^{3c} and R^{3d} where present have the aforementioned
 meanings. In particular:

- 10 R^{3b} is selected from the group consisting of halogen, C_1 - C_6 -alkyl, which may be
 partly or completely halogenated,
 phenyl which optionally has 1, 2 or 3 substituents R^{3c} ,
 R^{3b} is in particular fluorine or methyl;
- 15 R^{3c} is selected from halogen, OH, SH, NO_2 , $C(O)NH_2$, CHO, CN, NH_2 , C_1 - C_6 -
 alkyl, C_1 - C_6 -haloalkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -haloalkoxy, C_1 - C_6 -alkylthio,
 C_1 - C_6 -haloalkylthio, CO- C_1 - C_6 -alkyl, CO-O- C_1 - C_6 -alkyl, NH- C_1 - C_6 -alkyl,
 NH-C(O) C_1 - C_6 -alkyl, and SO_2 - C_1 - C_6 -alkyl;
 R^{3c} is in particular selected from halogen, CN, C_1 - C_4 -alkyl, C_1 - C_2 -
 fluoroalkyl, C_1 - C_2 -alkoxy and C_1 - C_2 -fluoroalkoxy;
- 20 R^{b1} is selected from the group consisting of C_1 - C_6 -alkyl, C_3 - C_7 -cycloalkyl, C_3 -
 C_7 -cycloalkyl- C_1 - C_4 -alkyl, phenyl and phenyl- C_1 - C_4 -alkyl, where phenyl in
 the last 2 radicals mentioned is unsubstituted or has 1, 2 or 3 substituents
 R^{1d} , which are selected from the group consisting of halogen, C_1 - C_6 -alkyl,
 C_1 - C_6 -alkoxy and C_1 - C_6 -haloalkyl. R^{1b} is in particular C_1 - C_6 -alkyl.
- 25 R^5 is in particular C_1 - C_6 -alkyl, C_1 - C_4 -fluoroalkyl, C_3 - C_7 -cycloalkyl, C_3 - C_7 -
 cycloalkyl- C_1 -alkyl, where the cycloalkyl moiety of the last 2 radicals mentioned
 may have 1, 2, 3 or 4 radicals R^{3b} , which are in particular selected from the group
 consisting of fluorine or methyl;
- 30 phenyl or benzyl, where phenyl in the last 2 radicals mentioned are unsubstituted
 or have 1, 2 or 3 substituents R^{3c} , where
 R^{3b} and R^{3c} are as defined above.

Particular examples of the moiety Y2 include, but are not limited to the following radicals:

- 4,5,6,7-tetrahydropyrazolo[3,4-c]pyridin-2-yl, 6-(C₁-C₄-alkyl)-4,5,6,7-tetrahydropyrazolo[3,4-c]pyridin-2-yl, 6-(tert.-butoxycarbonyl)-4,5,6,7-tetrahydropyrazolo[3,4-c]pyridin-2-yl, 6-benzyl-4,5,6,7-tetrahydropyrazolo[3,4-c]pyridin-2-yl, 6-cyclopropylmethyl-4,5,6,7-tetrahydropyrazolo[3,4-c]pyridin-2-yl, 4,5,6,7-tetrahydropyrazolo[4,3-c]pyridin-2-yl, 5-(C₁-C₄-alkyl)-4,5,6,7-tetrahydropyrazolo[4,3-c]pyridin-2-yl, 5-(tert.-butoxycarbonyl)-4,5,6,7-tetrahydropyrazolo[4,3-c]pyridin-2-yl, 5-benzyl-4,5,6,7-tetrahydropyrazolo[4,3-c]pyridin-2-yl, 5-cyclopropylmethyl-4,5,6,7-tetrahydropyrazolo[4,3-c]pyridin-2-yl, 2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-2-yl, 5-(C₁-C₄-alkyl)-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-2-yl, 5-benzyl-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-2-yl, 5-(tert.-butoxycarbonyl)-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-2-yl, 4,5,6,7-tetrahydropyrazolo[4,3-c]pyridin-2-yl, 5-(C₁-C₄-alkyl)-4,5,6,7-tetrahydropyrazolo[4,3-b]pyridin-2-yl, 5-(tert.-butoxycarbonyl)-4,5,6,7-tetrahydropyrazolo[4,3-b]pyridin-2-yl, 5-benzyl-4,5,6,7-tetrahydropyrazolo[4,3-b]pyridin-2-yl and 5-cyclopropylmethyl-4,5,6,7-tetrahydropyrazolo[4,3-b]pyridin-2-yl.

A special group of the compounds of formula I, where Y is Y2 are the compounds of the formula Ib, the tautomers thereof, the hydrates thereof, the prodrugs thereof and the pharmaceutically suitable salts thereof:



where R¹, R², R⁵ and n are as defined above and where

A¹ is (CH₂)_q with q being 0, 1 or 2;

25 A² is (CH₂)_r with r being 1, 2 or 3; and

where q + r is 1, 2 or 3.

If not stated otherwise, the radicals R^{1d} , R^{a1} , R^{b1} , R^{c1} , R^{a2} , R^{b2} , R^{c2} , R^{a3} , R^{b3} , R^{c3} , R^{a4} , R^{b4} , R^{c4} , R^{a5} , R^{b5} , R^{c5} , R^{a6} , R^{b6} , R^{c6} , R^{a7} , R^{b7} and R^{c7} have, unless otherwise indicated, independently of one another preferably one of the following meanings:

5

R^{1d} : halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy or C₁-C₄-haloalkoxy.

10

R^{a1} , R^{b1} , R^{c1} independently of one another: hydrogen, C₁-C₆-alkyl, C₁-C₆-haloalkyl, phenyl, benzyl, hetaryl or hetarylmethyl, where phenyl and hetaryl in the last 4 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents which are selected from halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy and C₁-C₄-haloalkoxy.

15

R^{a2} , R^{b2} , R^{c2} independently of one another: hydrogen, C₁-C₆-alkyl, phenyl, benzyl, hetaryl or hetarylmethyl, where phenyl and hetaryl in the last 4 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents which are selected from halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy and C₁-C₄-haloalkoxy.

20

R^{a3} , R^{b3} , R^{c3} independently of one another: hydrogen or C₁-C₆-alkyl, or R^{a2} with R^{a3} (and likewise R^{b2} with R^{b3} and R^{c2} with R^{c3}) together with the nitrogen atom to which they are bonded are a morpholine, piperidine, pyrrolidine, azetidine or piperazine residue, where the last 5 radicals mentioned are unsubstituted or may carry 1, 2, 3 or 4 radicals selected from C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy and C₁-C₄-haloalkoxy.

25

R^{a4} , R^{b4} , R^{c4} independently of one another: C₁-C₆-alkyl, phenyl, benzyl, hetaryl or hetarylmethyl, where phenyl and hetaryl in the last 4 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents which are selected from halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy and C₁-C₄-haloalkoxy.

30

R^{a5} , R^{b5} , R^{c5} independently of one another: hydrogen, C₁-C₆-alkyl, phenyl, benzyl, hetaryl or hetarylmethyl, where phenyl and hetaryl in the last 4 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents which are selected from halogen, C₁-C₄-

alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy and C₁-C₄-haloalkoxy.

R^{a6}, R^{b6}, R^{c6} independently of one another: hydrogen, C₁-C₆-alkyl, phenyl, benzyl, hetaryl or hetarylmethyl, where phenyl and hetaryl in the last 4 radicals mentioned are
5 unsubstituted or have 1, 2 or 3 substituents which are selected from halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy and C₁-C₄-haloalkoxy.

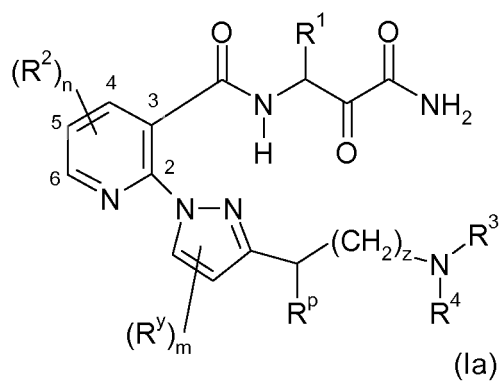
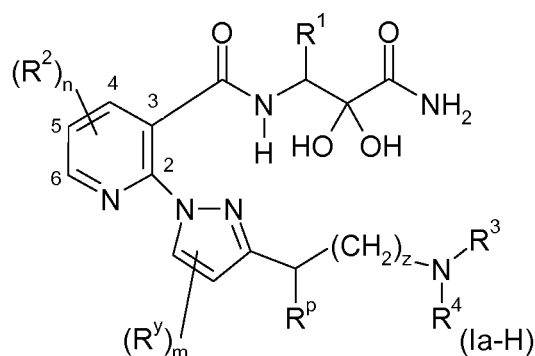
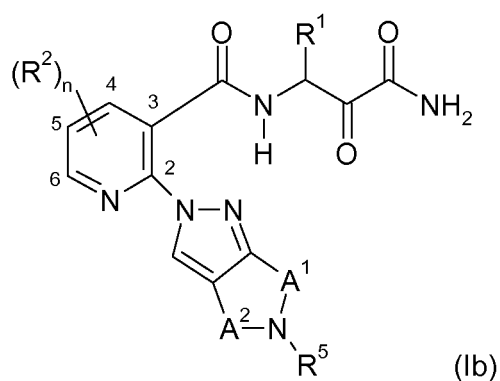
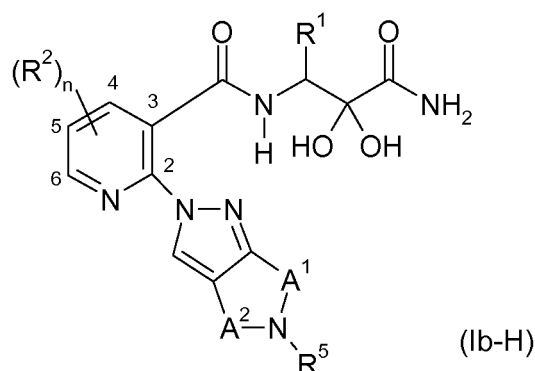
R^{a7}, R^{b7}, R^{c7} independently of one another: hydrogen or C₁-C₆-alkyl,
10 or R^{a6} with R^{a7} (and likewise R^{b6} with R^{b7} and R^{c6} with R^{c7}) together with the nitrogen atom to which they are bonded are a morpholine, piperidine, pyrrolidine, azetidine or piperazine residue, where the last 5 radicals mentioned are unsubstituted or may carry 1, 2, 3 or 4 radicals selected from C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy and C₁-C₄-haloalkoxy.

15

The compounds of the general formulae Ia and Ia-H, Ib and Ib-H which are indicated in Tables 1 to 12 below, and their tautomers, prodrugs and pharmaceutically acceptable salts, represent per se preferred embodiments of the present invention.

20 The meanings for R¹, CH-R^p(CH₂)_z and NR³R⁴ indicated in Table A below represent embodiments of the invention which are likewise preferred independently of one another and especially in combination.

The meanings for R¹, A¹, A² and R⁵ indicated in Table B below represent embodiments
25 of the invention which are likewise preferred independently of one another and especially in combination.



5 Table 1

Compounds of the formulae Ia and Ia-H in which $n = 0$, i.e. $(R^2)_n$ is absent, $m = 0$, i.e. $(R^y)_m$ is absent, and the combination of R^1 and $CH-R^p(CH_2)_z$ and NR^3R^4 for a compound in each case corresponds to one line of Table A.

10 Table 2

Compounds of the formulae Ia and Ia-H in which $n = 1$, $(R^2)_n$ is 4-fluoro, $m = 0$, i.e. $(R^y)_m$ is absent, and the combination of R^1 and $CH-R^p(CH_2)_z$ and NR^3R^4 for a compound in each case corresponds to one line of Table A.

15 Table 3

Compounds of the formulae Ia and Ia-H in which $n = 1$, $(R^2)_n$ is 5-cyano, $m = 0$, i.e. $(R^y)_m$ is absent, and the combination of R^1 and $CH-R^p(CH_2)_z$ and NR^3R^4 for a compound in each case corresponds to one line of Table A.

Table 4

Compounds of the formulae Ia and Ia-H in which $n = 1$, $(R^2)_n$ is 5-fluoro, $m = 0$, i.e. $(R^y)_m$ is absent, and the combination of R^1 and $CH-R^p(CH_2)_z$ and NR^3R^4 for a

5 compound in each case corresponds to one line of Table A.

Table 5

Compounds of the formulae Ia and Ia-H in which $n = 1$, $(R^2)_n$ is 5-chloro, $m = 0$, i.e. $(R^y)_m$ is absent, and the combination of R^1 and $CH-R^p(CH_2)_z$ and NR^3R^4 for a

10 compound in each case corresponds to one line of Table A.

Table 6

Compounds of the formulae Ia and Ia-H in which $n = 1$, $(R^2)_n$ is 6-fluoro, $m = 0$, i.e. $(R^y)_m$ is absent, and the combination of R^1 and $CH-R^p(CH_2)_z$ and NR^3R^4 for a

15 compound in each case corresponds to one line of Table A.

Table 7

Compounds of the formulae Ib and Ib-H in which $n = 0$, i.e. $(R^2)_n$ is absent and the combination of R^1 , A^1 , A^2 and R^5 for a compound in each case corresponds to one line

20 of Table B.

Table 8

Compounds of the formulae Ib and Ib-H in which $n = 1$, $(R^2)_n$ is 4-fluoro and the combination of R^1 , A^1 , A^2 and R^5 for a compound in each case corresponds to one line

25 of Table B.

Table 9

Compounds of the formulae Ib and Ib-H in which $n = 1$, $(R^2)_n$ is 5-cyano and the combination of R^1 , A^1 , A^2 and R^5 for a compound in each case corresponds to one line

30 of Table B.

Table 10

Compounds of the formulae Ib and Ib-H in which $n = 1$, $(R^2)_n$ is 5-fluoro and the

combination of R^1 , A^1 , A^2 and R^5 for a compound in each case corresponds to one line of Table B.

Table 11

- 5 Compounds of the formulae Ib and Ib-H in which $n = 1$, $(R^2)_n$ is 5-chloro and the combination of R^1 , A^1 , A^2 and R^5 for a compound in each case corresponds to one line of Table B.

Table 12

- 10 Compounds of the formulae Ib and Ib-H in which $n = 1$, $(R^2)_n$ is 6-fluoro and the combination of R^1 , A^1 , A^2 and R^5 for a compound in each case corresponds to one line of Table B.

Table A

#	R^1	$CH-R^p(CH_2)_z$	NR^3R^4
1	CH_2-Ph	CH_2	4-morpholinyl
2	CH_2-Ph	CH_2	4-thiomorpholinyl
3	CH_2-Ph	CH_2	1,1-dioxothiomorpholin-4-yl
4	CH_2-Ph	CH_2	2,6-dimethylmorpholin-4-yl
5	CH_2-Ph	CH_2	2-phenylmorpholin-4-yl
6	CH_2-Ph	CH_2	1-azetidiny
7	CH_2-Ph	CH_2	1-pyrrolidinyl
8	CH_2-Ph	CH_2	3-phenylpyrrolidin-1-yl
9	CH_2-Ph	CH_2	1-piperidinyl
10	CH_2-Ph	CH_2	1-azepanyl
11	CH_2-Ph	CH_2	4-methylpiperidin-1-yl
12	CH_2-Ph	CH_2	4-phenylpiperidin-1-yl
13	CH_2-Ph	CH_2	4,4-difluoropiperidin-1-yl
14	CH_2-Ph	CH_2	4-(trifluoromethyl)piperidin-1-yl
15	CH_2-Ph	CH_2	4-(tert.-butyl)piperidin-1-yl
16	CH_2-Ph	CH_2	4-methylpiperazin-1-yl
17	CH_2-Ph	CH_2	4-ethylpiperazin-1-yl

#	R ¹	CH-R ^P (CH ₂) _z	NR ³ R ⁴
18	CH ₂ -Ph	CH ₂	4-propylpiperazin-1-yl
19	CH ₂ -Ph	CH ₂	4-cyclopropylmethylpiperazin-1-yl
20	CH ₂ -Ph	CH ₂	4-cyclopropylpiperazin-1-yl
21	CH ₂ -Ph	CH ₂	4-phenylpiperazin-1-yl
22	CH ₂ -Ph	CH ₂	dimethylamino
23	CH ₂ -Ph	CH ₂	diethylamino
24	CH ₂ -Ph	CH ₂	diisopropylamino
25	CH ₂ -Ph	CH ₂	N-phenylamino
26	CH ₂ -Ph	CH ₂	N-methyl-N-phenylamino
27	CH ₂ -Ph	CH ₂	N-cyclopropyl-N-methylamino
28	CH ₂ -Ph	CH ₂	N-cyclohexyl-N-methylamino
29	CH ₂ -Ph	CH ₂	N-benzyl-N-methylamino
30	CH ₂ -Ph	CH ₂	N-cyclohexylmethyl-N-methylamino
31	CH ₂ -Ph	CH ₂	N-methyl-N-isopropylamino
32	CH ₂ -Ph	CH ₂	N-cyclopropyl-N-phenylamino
33	CH ₂ -Ph	CH ₂	N-cyclopropyl-N-benzylamino
34	CH ₂ -Ph	CH ₂	N-(4-trifluoromethylcyclohexyl)methyl-N-methylamino
35	CH ₂ -Ph	CH ₂	3,4-dihydro-2H-1,4-benzoxazin-4-yl
36	CH ₂ -Ph	CH ₂	cis-octahydrobenzo-[1,4]oxazin-4-yl
37	CH ₂ -Ph	CH ₂	trans-octahydrobenzo[1,4]oxazin-4-yl
38	CH ₂ -Ph	CH ₂	5,5-difluoroocta-hydrocyclopenta[c]pyrrol-2-yl
39	CH ₂ -Ph	CH ₂	hexahydrofuro[3,4-c]pyrrol-5-yl
40	CH ₂ -Ph	CH ₂	2,3-dihydroindol-1-yl
41	CH ₂ -Ph	CH ₂	2-oxa-7-azaspiro[3.5]nonane-7-yl
42	CH ₂ -Ph	CH ₂	2,3-dihydro-1H-isoindole-2-yl
43	CH ₂ -Ph	CH ₂	5-trifluoromethyl-2,3-dihydro-1H-isoindole-2-yl
44	CH ₂ -Ph	CH ₂	4-trifluoro-2,3-dihydro-1H-isoindole-2-yl
45	CH ₂ -Ph	CH ₂	2,3-dihydroisoindole-1-one-2-yl

#	R ¹	CH-R ^P (CH ₂) _z	NR ³ R ⁴
46	CH ₂ -Ph	CH ₂	1,2,3,4-tetrahydroisoquinoline-2-yl
47	CH ₂ -Ph	CH ₂	3-azabicyclo[3.2.0]heptane-3-yl
48	CH ₂ -Ph	CH ₂	6-(4-fluorophenyl)-3-azabicyclo[3.2.0]heptane-3-yl
49	CH ₂ -Ph	CH ₂ CH ₂	4-morpholinyl
50	CH ₂ -Ph	CH ₂ CH ₂	4-thiomorpholinyl
51	CH ₂ -Ph	CH ₂ CH ₂	1,1-dioxothiomorpholin-4-yl
52	CH ₂ -Ph	CH ₂ CH ₂	2,6-dimethylmorpholin-4-yl
53	CH ₂ -Ph	CH ₂ CH ₂	2-phenylmorpholin-4-yl
54	CH ₂ -Ph	CH ₂ CH ₂	1-azetidiny
55	CH ₂ -Ph	CH ₂ CH ₂	1-pyrrolidinyl
56	CH ₂ -Ph	CH ₂ CH ₂	3-phenylpyrrolidin-1-yl
57	CH ₂ -Ph	CH ₂ CH ₂	1-piperidinyl
58	CH ₂ -Ph	CH ₂ CH ₂	1-azepanyl
59	CH ₂ -Ph	CH ₂ CH ₂	4-methylpiperidin-1-yl
60	CH ₂ -Ph	CH ₂ CH ₂	4-phenylpiperidin-1-yl
61	CH ₂ -Ph	CH ₂ CH ₂	4,4-difluoropiperidin-1-yl
62	CH ₂ -Ph	CH ₂ CH ₂	4-(trifluoromethyl)piperidin-1-yl
63	CH ₂ -Ph	CH ₂ CH ₂	4-(tert.-butyl)piperidin-1-yl
64	CH ₂ -Ph	CH ₂ CH ₂	4-methylpiperazin-1-yl
65	CH ₂ -Ph	CH ₂ CH ₂	4-ethylpiperazin-4-yl
66	CH ₂ -Ph	CH ₂ CH ₂	4-propylpiperazin-4-yl
67	CH ₂ -Ph	CH ₂ CH ₂	4-cyclopropylmethylpiperazin-1-yl
68	CH ₂ -Ph	CH ₂ CH ₂	4-cyclopropylpiperazin-1-yl
69	CH ₂ -Ph	CH ₂ CH ₂	4-phenylpiperazin-1-yl
70	CH ₂ -Ph	CH ₂ CH ₂	dimethylamino
71	CH ₂ -Ph	CH ₂ CH ₂	diethylamino
72	CH ₂ -Ph	CH ₂ CH ₂	diisopropylamino
73	CH ₂ -Ph	CH ₂ CH ₂	N-phenylamino
74	CH ₂ -Ph	CH ₂ CH ₂	N-methyl-N-isopropylamino
75	CH ₂ -Ph	CH ₂ CH ₂	N-methyl-N-phenylamino

#	R ¹	CH-R ^P (CH ₂) _z	NR ³ R ⁴
76	CH ₂ -Ph	CH ₂ CH ₂	N-cyclopropyl-N-methylamino
77	CH ₂ -Ph	CH ₂ CH ₂	N-cyclopropyl-N-phenylamino
78	CH ₂ -Ph	CH ₂ CH ₂	N-cyclopropyl-N-benzylamino
79	CH ₂ -Ph	CH ₂ CH ₂	N-cyclohexyl-N-methylamino
80	CH ₂ -Ph	CH ₂ CH ₂	N-benzyl-N-methylamino
81	CH ₂ -Ph	CH ₂ CH ₂	N-cyclohexylmethyl-N-methylamino
82	CH ₂ -Ph	CH ₂ CH ₂	N-(4-trifluoromethylcyclohexyl)methyl-N-methylamino
83	CH ₂ -Ph	CH ₂ CH ₂	3,4-dihydro-2H-1,4-benzoxazin-4-yl
84	CH ₂ -Ph	CH ₂ CH ₂	cis-octahydrobenzo-[1,4]oxazin-4-yl
85	CH ₂ -Ph	CH ₂ CH ₂	trans-octahydrobenzo[1,4]oxazin-4-yl
86	CH ₂ -Ph	CH ₂ CH ₂	5,5-difluoroocta-hydrocyclopenta[c]pyrrol-2-yl
87	CH ₂ -Ph	CH ₂ CH ₂	hexahydrofuro[3,4-c]pyrrol-5-yl
88	CH ₂ -Ph	CH ₂ CH ₂	2,3-dihydroindol-1-yl
89	CH ₂ -Ph	CH ₂ CH ₂	2-oxa-7-azaspiro[3.5]nonane-7-yl
90	CH ₂ -Ph	CH ₂ CH ₂	2,3-dihydro-1H-isoindole-2-yl
91	CH ₂ -Ph	CH ₂ CH ₂	5-trifluoromethyl-2,3-dihydro-1H-isoindole-2-yl
92	CH ₂ -Ph	CH ₂ CH ₂	4-trifluoro-2,3-dihydro-1H-isoindole-2-yl
93	CH ₂ -Ph	CH ₂ CH ₂	2,3-dihydroisoindole-1-one-2-yl
94	CH ₂ -Ph	CH ₂ CH ₂	1,2,3,4-tetrahydroisoquinoline-2-yl
95	CH ₂ -Ph	CH ₂ CH ₂	3-azabicyclo[3.2.0]heptane-3-yl
96	CH ₂ -Ph	CH ₂ CH ₂	6-(4-fluorophenyl)-3-azabicyclo[3.2.0]heptane-3-yl
97	CH ₂ -Ph	azetin-3-yl	
98	CH ₂ -Ph	pyrrolidin-3-yl	
99	CH ₂ -Ph	1-methylpyrrolidin-3-yl	
100	CH ₂ -Ph	piperidin-3-yl	
101	CH ₂ -Ph	1-methylpiperidin-3-yl	
102	CH ₂ -Ph	piperidin-4-yl	

#	R ¹	CH-R ^P (CH ₂) _z	NR ³ R ⁴
103	CH ₂ -Ph		1-methylpiperidin-4-yl
104	CH ₂ -Ph		1-ethylpiperidin-4-yl
105	CH ₂ -Ph		1-propylpiperidin-4-yl
106	CH ₂ -Ph		1-benzylpiperidin-4-yl
107	CH ₂ -Ph		1-cyclopropylpiperidin-4-yl
108	4-Cl-Bz	CH ₂	4-morpholinyl
109	4-Cl-Bz	CH ₂	4-thiomorpholinyl
110	4-Cl-Bz	CH ₂	1,1-dioxothiomorpholin-4-yl
111	4-Cl-Bz	CH ₂	2,6-dimethylmorpholin-4-yl
112	4-Cl-Bz	CH ₂	2-phenylmorpholin-4-yl
113	4-Cl-Bz	CH ₂	1-azetidiny
114	4-Cl-Bz	CH ₂	1-pyrrolidinyl
115	4-Cl-Bz	CH ₂	3-phenylpyrrolidin-1-yl
116	4-Cl-Bz	CH ₂	1-piperidinyl
117	4-Cl-Bz	CH ₂	1-azepanyl
118	4-Cl-Bz	CH ₂	4-methylpiperidin-1-yl
119	4-Cl-Bz	CH ₂	4-phenylpiperidin-1-yl
120	4-Cl-Bz	CH ₂	4,4-difluoropiperidin-1-yl
121	4-Cl-Bz	CH ₂	4-(trifluoromethyl)piperidin-1-yl
122	4-Cl-Bz	CH ₂	4-(tert.-butyl)piperidin-1-yl
123	4-Cl-Bz	CH ₂	4-methylpiperazin-1-yl
124	4-Cl-Bz	CH ₂	4-ethylpiperazin-1-yl
125	4-Cl-Bz	CH ₂	4-propylpiperazin-1-yl
126	4-Cl-Bz	CH ₂	4-cyclopropylmethylpiperazin-1-yl
127	4-Cl-Bz	CH ₂	4-cyclopropylpiperazin-1-yl
128	4-Cl-Bz	CH ₂	4-phenylpiperazin-1-yl
129	4-Cl-Bz	CH ₂	dimethylamino
130	4-Cl-Bz	CH ₂	diethylamino
131	4-Cl-Bz	CH ₂	diisopropylamino
132	4-Cl-Bz	CH ₂	N-phenylamino
133	4-Cl-Bz	CH ₂	N-methyl-N-phenylamino

#	R ¹	CH-R ^p (CH ₂) _z	NR ³ R ⁴
134	4-Cl-Bz	CH ₂	N-cyclopropyl-N-methylamino
135	4-Cl-Bz	CH ₂	N-cyclohexyl-N-methylamino
136	4-Cl-Bz	CH ₂	N-benzyl-N-methylamino
137	4-Cl-Bz	CH ₂	N-cyclohexylmethyl-N-methylamino
138	4-Cl-Bz	CH ₂	N-methyl-N-isopropylamino
139	4-Cl-Bz	CH ₂	N-cyclopropyl-N-phenylamino
140	4-Cl-Bz	CH ₂	N-cyclopropyl-N-benzylamino
141	4-Cl-Bz	CH ₂	N-(4-trifluoromethylcyclohexyl)methyl-N-methylamino
142	4-Cl-Bz	CH ₂	3,4-dihydro-2H-1,4-benzoxazin-4-yl
143	4-Cl-Bz	CH ₂	cis-octahydrobenzo-[1,4]oxazin-4-yl
144	4-Cl-Bz	CH ₂	trans-octahydrobenzo[1,4]oxazin-4-yl
145	4-Cl-Bz	CH ₂	5,5-difluoroocta-hydrocyclopenta[c]pyrrol-2-yl
146	4-Cl-Bz	CH ₂	hexahydrofuro[3,4-c]pyrrol-5-yl
147	4-Cl-Bz	CH ₂	2,3-dihydroindol-1-yl
148	4-Cl-Bz	CH ₂	2-oxa-7-azaspiro[3.5]nonane-7-yl
149	4-Cl-Bz	CH ₂	2,3-dihydro-1H-isoindole-2-yl
150	4-Cl-Bz	CH ₂	5-trifluoromethyl-2,3-dihydro-1H-isoindole-2-yl
151	4-Cl-Bz	CH ₂	4-trifluoro-2,3-dihydro-1H-isoindole-2-yl
152	4-Cl-Bz	CH ₂	2,3-dihydroisoindole-1-one-2-yl
153	4-Cl-Bz	CH ₂	1,2,3,4-tetrahydroisoquinoline-2-yl
154	4-Cl-Bz	CH ₂	3-azabicyclo[3.2.0]heptane-3-yl
155	4-Cl-Bz	CH ₂	6-(4-fluorophenyl)-3-azabicyclo[3.2.0]heptane-3-yl
156	4-Cl-Bz	CH ₂ CH ₂	4-morpholinyl
157	4-Cl-Bz	CH ₂ CH ₂	4-thiomorpholinyl
158	4-Cl-Bz	CH ₂ CH ₂	1,1-dioxothiomorpholin-4-yl
159	4-Cl-Bz	CH ₂ CH ₂	2,6-dimethylmorpholin-4-yl
160	4-Cl-Bz	CH ₂ CH ₂	2-phenylmorpholin-4-yl

#	R ¹	CH-R ^P (CH ₂) _z	NR ³ R ⁴
161	4-Cl-Bz	CH ₂ CH ₂	1-azetidiny1
162	4-Cl-Bz	CH ₂ CH ₂	1-pyrrolidiny1
163	4-Cl-Bz	CH ₂ CH ₂	3-phenylpyrrolidin-1-yl
164	4-Cl-Bz	CH ₂ CH ₂	1-piperidiny1
165	4-Cl-Bz	CH ₂ CH ₂	1-azepany1
166	4-Cl-Bz	CH ₂ CH ₂	4-methylpiperidin-1-yl
167	4-Cl-Bz	CH ₂ CH ₂	4-phenylpiperidin-1-yl
168	4-Cl-Bz	CH ₂ CH ₂	4,4-difluoropiperidin-1-yl
169	4-Cl-Bz	CH ₂ CH ₂	4-(trifluoromethyl)piperidin-1-yl
170	4-Cl-Bz	CH ₂ CH ₂	4-(tert.-butyl)piperidin-1-yl
171	4-Cl-Bz	CH ₂ CH ₂	4-methylpiperazin-1-yl
172	4-Cl-Bz	CH ₂ CH ₂	4-ethylpiperazin-1-yl
173	4-Cl-Bz	CH ₂ CH ₂	4-propylpiperazin-1-yl
174	4-Cl-Bz	CH ₂ CH ₂	4-cyclopropylmethylpiperazin-1-yl
175	4-Cl-Bz	CH ₂ CH ₂	4-cyclopropylpiperazin-1-yl
176	4-Cl-Bz	CH ₂ CH ₂	4-phenylpiperazin-1-yl
177	4-Cl-Bz	CH ₂ CH ₂	dimethylamino
178	4-Cl-Bz	CH ₂ CH ₂	diethylamino
179	4-Cl-Bz	CH ₂ CH ₂	diisopropylamino
180	4-Cl-Bz	CH ₂ CH ₂	N-phenylamino
181	4-Cl-Bz	CH ₂ CH ₂	N-methyl-N-phenylamino
182	4-Cl-Bz	CH ₂ CH ₂	N-cyclopropyl-N-methylamino
183	4-Cl-Bz	CH ₂ CH ₂	N-cyclohexyl-N-methylamino
184	4-Cl-Bz	CH ₂ CH ₂	N-benzyl-N-methylamino
185	4-Cl-Bz	CH ₂ CH ₂	N-cyclohexylmethyl-N-methylamino
186	4-Cl-Bz	CH ₂ CH ₂	N-methyl-N-isopropylamino
187	4-Cl-Bz	CH ₂ CH ₂	N-cyclopropyl-N-phenylamino
188	4-Cl-Bz	CH ₂ CH ₂	N-cyclopropyl-N-benzylamino
189	4-Cl-Bz	CH ₂ CH ₂	N-(4-trifluoromethylcyclohexyl)methyl-N-methylamino
190	4-Cl-Bz	CH ₂ CH ₂	3,4-dihydro-2H-1,4-benzoxazin-4-yl

#	R ¹	CH-R ^P (CH ₂) _z	NR ³ R ⁴
191	4-Cl-Bz	CH ₂ CH ₂	cis-octahydrobenzo-[1,4]oxazin-4-yl
192	4-Cl-Bz	CH ₂ CH ₂	trans-octahydrobenzo[1,4]oxazin-4-yl
193	4-Cl-Bz	CH ₂ CH ₂	5,5-difluoroocta-hydrocyclopenta[c]pyrrol-2-yl
194	4-Cl-Bz	CH ₂ CH ₂	hexahydro furo[3,4-c]pyrrol-5-yl
195	4-Cl-Bz	CH ₂ CH ₂	2,3-dihydroindol-1-yl
196	4-Cl-Bz	CH ₂ CH ₂	2-oxa-7-azaspiro[3.5]nonane-7-yl
197	4-Cl-Bz	CH ₂ CH ₂	2,3-dihydro-1H-isoindole-2-yl
198	4-Cl-Bz	CH ₂ CH ₂	5-trifluoromethyl-2,3-dihydro-1H-isoindole-2-yl
199	4-Cl-Bz	CH ₂ CH ₂	4-trifluoro-2,3-dihydro-1H-isoindole-2-yl
200	4-Cl-Bz	CH ₂ CH ₂	2,3-dihydroisoindole-1-one-2-yl
201	4-Cl-Bz	CH ₂ CH ₂	1,2,3,4-tetrahydroisoquinoline-2-yl
202	4-Cl-Bz	CH ₂ CH ₂	3-azabicyclo[3.2.0]heptane-3-yl
203	4-Cl-Bz	CH ₂ CH ₂	6-(4-fluorophenyl)-3-azabicyclo[3.2.0]heptane-3-yl
204	4-Cl-Bz	azetin-3-yl	
205	4-Cl-Bz	pyrrolidin-3-yl	
206	4-Cl-Bz	1-methylpyrrolidin-3-yl	
207	4-Cl-Bz	piperidin-3-yl	
208	4-Cl-Bz	1-methylpiperidin-3-yl	
209	4-Cl-Bz	piperidin-4-yl	
210	4-Cl-Bz	1-methylpiperidin-4-yl	
211	4-Cl-Bz	1-ethylpiperidin-4-yl	
212	4-Cl-Bz	1-propylpiperidin-4-yl	
213	4-Cl-Bz	1-cyclopropylpiperidin-4-yl	
214	4-Cl-Bz	1-benzylpiperidin-4-yl	
215	4-F-Bz	CH ₂	4-morpholinyl
216	4-F-Bz	CH ₂	4-thiomorpholinyl
217	4-F-Bz	CH ₂	1,1-dioxothiomorpholin-4-yl
218	4-F-Bz	CH ₂	2,6-dimethylmorpholin-4-yl

#	R ¹	CH-R ^P (CH ₂) _z	NR ³ R ⁴
219	4-F-Bz	CH ₂	2-phenylmorpholin-4-yl
220	4-F-Bz	CH ₂	1-azetidiny
221	4-F-Bz	CH ₂	1-pyrrolidiny
222	4-F-Bz	CH ₂	3-phenylpyrrolidin-1-yl
223	4-F-Bz	CH ₂	1-piperidiny
224	4-F-Bz	CH ₂	1-azepanyl
225	4-F-Bz	CH ₂	4-methylpiperidin-1-yl
226	4-F-Bz	CH ₂	4-phenylpiperidin-1-yl
227	4-F-Bz	CH ₂	4,4-difluoropiperidin-1-yl
228	4-F-Bz	CH ₂	4-(trifluoromethyl)piperidin-1-yl
229	4-F-Bz	CH ₂	4-(tert.-butyl)piperidin-1-yl
230	4-F-Bz	CH ₂	4-methylpiperazin-1-yl
231	4-F-Bz	CH ₂	4-ethylpiperazin-1-yl
232	4-F-Bz	CH ₂	4-propylpiperazin-1-yl
233	4-F-Bz	CH ₂	4-cyclopropylmethylpiperazin-1-yl
234	4-F-Bz	CH ₂	4-cyclopropylpiperazin-1-yl
235	4-F-Bz	CH ₂	4-phenylpiperazin-1-yl
236	4-F-Bz	CH ₂	dimethylamino
237	4-F-Bz	CH ₂	diethylamino
238	4-F-Bz	CH ₂	diisopropylamino
239	4-F-Bz	CH ₂	N-phenylamino
240	4-F-Bz	CH ₂	N-methyl-N-phenylamino
241	4-F-Bz	CH ₂	N-cyclopropyl-N-methylamino
242	4-F-Bz	CH ₂	N-cyclohexyl-N-methylamino
243	4-F-Bz	CH ₂	N-benzyl-N-methylamino
244	4-F-Bz	CH ₂	N-cyclohexylmethyl-N-methylamino
245	4-F-Bz	CH ₂	N-methyl-N-isopropylamino
246	4-F-Bz	CH ₂	N-cyclopropyl-N-phenylamino
247	4-F-Bz	CH ₂	N-cyclopropyl-N-benzylamino
248	4-F-Bz	CH ₂	N-(4-trifluoromethylcyclohexyl)methyl-N-methylamino

#	R ¹	CH-R ^p (CH ₂) _z	NR ³ R ⁴
249	4-F-Bz	CH ₂	3,4-dihydro-2H-1,4-benzoxazin-4-yl
250	4-F-Bz	CH ₂	cis-octahydrobenzo-[1,4]oxazin-4-yl
251	4-F-Bz	CH ₂	trans-octahydrobenzo[1,4]oxazin-4-yl
252	4-F-Bz	CH ₂	5,5-difluoroocta- hydrocyclopenta[c]pyrrol-2-yl
253	4-F-Bz	CH ₂	hexahydrofuro[3,4-c]pyrrol-5-yl
254	4-F-Bz	CH ₂	2,3-dihydroindol-1-yl
255	4-F-Bz	CH ₂	2-oxa-7-azaspiro[3.5]nonane-7-yl
256	4-F-Bz	CH ₂	2,3-dihydro-1H-isoindole-2-yl
257	4-F-Bz	CH ₂	5-trifluoromethyl-2,3-dihydro-1H- isoindole-2-yl
258	4-F-Bz	CH ₂	4-trifluoro-2,3-dihydro-1H-isoindole-2-yl
259	4-F-Bz	CH ₂	2,3-dihydroisoindole-1-one-2-yl
260	4-F-Bz	CH ₂	1,2,3,4-tetrahydroisoquinoline-2-yl
261	4-F-Bz	CH ₂	3-azabicyclo[3.2.0]heptane-3-yl
262	4-F-Bz	CH ₂	6-(4-fluorophenyl)-3- azabicyclo[3.2.0]heptane-3-yl
263	4-F-Bz	CH ₂ CH ₂	4-morpholinyl
264	4-F-Bz	CH ₂ CH ₂	4-thiomorpholinyl
265	4-F-Bz	CH ₂ CH ₂	1,1-dioxothiomorpholin-4-yl
266	4-F-Bz	CH ₂ CH ₂	2,6-dimethylmorpholin-4-yl
267	4-F-Bz	CH ₂ CH ₂	2-phenylmorpholin-4-yl
268	4-F-Bz	CH ₂ CH ₂	1-azetidiny
269	4-F-Bz	CH ₂ CH ₂	1-pyrrolidinyl
270	4-F-Bz	CH ₂ CH ₂	3-phenylpyrrolidin-1-yl
271	4-F-Bz	CH ₂ CH ₂	1-piperidinyl
272	4-F-Bz	CH ₂ CH ₂	1-azepanyl
273	4-F-Bz	CH ₂ CH ₂	4-methylpiperidin-1-yl
274	4-F-Bz	CH ₂ CH ₂	4-phenylpiperidin-1-yl
275	4-F-Bz	CH ₂ CH ₂	4,4-difluoropiperidin-1-yl
276	4-F-Bz	CH ₂ CH ₂	4-(trifluoromethyl)piperidin-1-yl

#	R ¹	CH-R ^P (CH ₂) _z	NR ³ R ⁴
277	4-F-Bz	CH ₂ CH ₂	4-(tert.-butyl)piperidin-1-yl
278	4-F-Bz	CH ₂ CH ₂	4-methylpiperazin-1-yl
279	4-F-Bz	CH ₂ CH ₂	4-ethylpiperazin-1-yl
280	4-F-Bz	CH ₂ CH ₂	4-propylpiperazin-1-yl
281	4-F-Bz	CH ₂ CH ₂	4-cyclopropylmethylpiperazin-1-yl
282	4-F-Bz	CH ₂ CH ₂	4-cyclopropylpiperazin-1-yl
283	4-F-Bz	CH ₂ CH ₂	4-phenylpiperazin-1-yl
284	4-F-Bz	CH ₂ CH ₂	dimethylamino
285	4-F-Bz	CH ₂ CH ₂	diethylamino
286	4-F-Bz	CH ₂ CH ₂	diisopropylamino
287	4-F-Bz	CH ₂ CH ₂	N-phenylamino
288	4-F-Bz	CH ₂ CH ₂	N-methyl-N-phenylamino
289	4-F-Bz	CH ₂ CH ₂	N-cyclopropyl-N-methylamino
290	4-F-Bz	CH ₂ CH ₂	N-cyclohexyl-N-methylamino
291	4-F-Bz	CH ₂ CH ₂	N-benzyl-N-methylamino
292	4-F-Bz	CH ₂ CH ₂	N-cyclohexylmethyl-N-methylamino
293	4-F-Bz	CH ₂ CH ₂	N-methyl-N-isopropylamino
294	4-F-Bz	CH ₂ CH ₂	N-cyclopropyl-N-phenylamino
295	4-F-Bz	CH ₂ CH ₂	N-cyclopropyl-N-benzylamino
296	4-F-Bz	CH ₂ CH ₂	N-(4-trifluoromethylcyclohexyl)methyl-N-methylamino
297	4-F-Bz	CH ₂ CH ₂	3,4-dihydro-2H-1,4-benzoxazin-4-yl
298	4-F-Bz	CH ₂ CH ₂	cis-octahydrobenzo-[1,4]oxazin-4-yl
299	4-F-Bz	CH ₂ CH ₂	trans-octahydrobenzo[1,4]oxazin-4-yl
300	4-F-Bz	CH ₂ CH ₂	5,5-difluoroocta-hydrocyclopenta[c]pyrrol-2-yl
301	4-F-Bz	CH ₂ CH ₂	hexahydrofuro[3,4-c]pyrrol-5-yl
302	4-F-Bz	CH ₂ CH ₂	2,3-dihydroindol-1-yl
303	4-F-Bz	CH ₂ CH ₂	2-oxa-7-azaspiro[3.5]nonane-7-yl
304	4-F-Bz	CH ₂ CH ₂	2,3-dihydro-1H-isoindole-2-yl
305	4-F-Bz	CH ₂ CH ₂	5-trifluoromethyl-2,3-dihydro-1H-

#	R ¹	CH-R ^p (CH ₂) _z	NR ³ R ⁴
			isoindole-2-yl
306	4-F-Bz	CH ₂ CH ₂	4-trifluoro-2,3-dihydro-1H-isoindole-2-yl
307	4-F-Bz	CH ₂ CH ₂	2,3-dihydroisoindole-1-one-2-yl
308	4-F-Bz	CH ₂ CH ₂	1,2,3,4-tetrahydroisoquinoline-2-yl
309	4-F-Bz	CH ₂ CH ₂	3-azabicyclo[3.2.0]heptane-3-yl
310	4-F-Bz	CH ₂ CH ₂	6-(4-fluorophenyl)-3-azabicyclo[3.2.0]heptane-3-yl
311	4-F-Bz	azetin-3-yl	
312	4-F-Bz	pyrrolidin-3-yl	
313	4-F-Bz	1-methylpyrrolidin-3-yl	
314	4-F-Bz	piperidin-3-yl	
315	4-F-Bz	1-methylpiperidin-3-yl	
316	4-F-Bz	piperidin-4-yl	
317	4-F-Bz	1-methylpiperidin-4-yl	
318	4-F-Bz	1-ethylpiperidin-4-yl	
319	4-F-Bz	1-propylpiperidin-4-yl	
320	4-F-Bz	1-benzylpiperidin-4-yl	
321	4-F-Bz	1-cyclopropylpiperidin-4-yl	
322	2-F-Bz	CH ₂	4-morpholinyl
323	2-F-Bz	CH ₂	4-thiomorpholinyl
324	2-F-Bz	CH ₂	1,1-dioxothiomorpholin-4-yl
325	2-F-Bz	CH ₂	2,6-dimethylmorpholin-4-yl
326	2-F-Bz	CH ₂	2-phenylmorpholin-4-yl
327	2-F-Bz	CH ₂	1-azetidiny
328	2-F-Bz	CH ₂	1-pyrrolidinyl
329	2-F-Bz	CH ₂	3-phenylpyrrolidin-1-yl
330	2-F-Bz	CH ₂	1-piperidinyl
331	2-F-Bz	CH ₂	1-azepanyl
332	2-F-Bz	CH ₂	4-methylpiperidin-1-yl
333	2-F-Bz	CH ₂	4-phenylpiperidin-1-yl
334	2-F-Bz	CH ₂	4,4-difluoropiperidin-1-yl

#	R ¹	CH-R ^p (CH ₂) _z	NR ³ R ⁴
335	2-F-Bz	CH ₂	4-(trifluoromethyl)piperidin-1-yl
336	2-F-Bz	CH ₂	4-(tert.-butyl)piperidin-1-yl
337	2-F-Bz	CH ₂	4-methylpiperazin-1-yl
338	2-F-Bz	CH ₂	4-ethylpiperazin-1-yl
339	2-F-Bz	CH ₂	4-propylpiperazin-1-yl
340	2-F-Bz	CH ₂	4-cyclopropylmethylpiperazin-1-yl
341	2-F-Bz	CH ₂	4-cyclopropylpiperazin-1-yl
342	2-F-Bz	CH ₂	4-phenylpiperazin-1-yl
343	2-F-Bz	CH ₂	dimethylamino
344	2-F-Bz	CH ₂	diethylamino
345	2-F-Bz	CH ₂	diisopropylamino
346	2-F-Bz	CH ₂	N-phenylamino
347	2-F-Bz	CH ₂	N-methyl-N-phenylamino
348	2-F-Bz	CH ₂	N-cyclopropyl-N-methylamino
349	2-F-Bz	CH ₂	N-cyclohexyl-N-methylamino
350	2-F-Bz	CH ₂	N-benzyl-N-methylamino
351	2-F-Bz	CH ₂	N-cyclohexylmethyl-N-methylamino
352	2-F-Bz	CH ₂	N-methyl-N-isopropylamino
353	2-F-Bz	CH ₂	N-cyclopropyl-N-phenylamino
354	2-F-Bz	CH ₂	N-cyclopropyl-N-benzylamino
355	2-F-Bz	CH ₂	N-(4-trifluoromethylcyclohexyl)methyl-N-methylamino
356	2-F-Bz	CH ₂	3,4-dihydro-2H-1,4-benzoxazin-4-yl
357	2-F-Bz	CH ₂	cis-octahydrobenzo-[1,4]oxazin-4-yl
358	2-F-Bz	CH ₂	trans-octahydrobenzo[1,4]oxazin-4-yl
359	2-F-Bz	CH ₂	5,5-difluoroocta-hydrocyclopenta[c]pyrrol-2-yl
360	2-F-Bz	CH ₂	hexahydro furo[3,4-c]pyrrol-5-yl
361	2-F-Bz	CH ₂	2,3-dihydroindol-1-yl
362	2-F-Bz	CH ₂	2-oxa-7-azaspiro[3.5]nonane-7-yl
363	2-F-Bz	CH ₂	2,3-dihydro-1H-isoindole-2-yl

#	R ¹	CH-R ^P (CH ₂) _z	NR ³ R ⁴
364	2-F-Bz	CH ₂	5-trifluoromethyl-2,3-dihydro-1H-isoindole-2-yl
365	2-F-Bz	CH ₂	4-trifluoro-2,3-dihydro-1H-isoindole-2-yl
366	2-F-Bz	CH ₂	2,3-dihydroisoindole-1-one-2-yl
367	2-F-Bz	CH ₂	1,2,3,4-tetrahydroisoquinoline-2-yl
368	2-F-Bz	CH ₂	3-azabicyclo[3.2.0]heptane-3-yl
369	2-F-Bz	CH ₂	6-(4-fluorophenyl)-3-azabicyclo[3.2.0]heptane-3-yl
370	2-F-Bz	CH ₂ CH ₂	4-morpholinyl
371	2-F-Bz	CH ₂ CH ₂	4-thiomorpholinyl
372	2-F-Bz	CH ₂ CH ₂	1,1-dioxothiomorpholin-4-yl
373	2-F-Bz	CH ₂ CH ₂	2,6-dimethylmorpholin-4-yl
374	2-F-Bz	CH ₂ CH ₂	2-phenylmorpholin-4-yl
375	2-F-Bz	CH ₂ CH ₂	1-azetidiny
376	2-F-Bz	CH ₂ CH ₂	1-pyrrolidinyl
377	2-F-Bz	CH ₂ CH ₂	3-phenylpyrrolidin-1-yl
378	2-F-Bz	CH ₂ CH ₂	1-piperidinyl
379	2-F-Bz	CH ₂ CH ₂	1-azepanyl
380	2-F-Bz	CH ₂ CH ₂	4-methylpiperidin-1-yl
381	2-F-Bz	CH ₂ CH ₂	4-phenylpiperidin-1-yl
382	2-F-Bz	CH ₂ CH ₂	4,4-difluoropiperidin-1-yl
383	2-F-Bz	CH ₂ CH ₂	4-(trifluoromethyl)piperidin-1-yl
384	2-F-Bz	CH ₂ CH ₂	4-(tert.-butyl)piperidin-1-yl
385	2-F-Bz	CH ₂ CH ₂	4-methylpiperazin-1-yl
386	2-F-Bz	CH ₂ CH ₂	4-ethylpiperazin-1-yl
387	2-F-Bz	CH ₂ CH ₂	4-propylpiperazin-1-yl
388	2-F-Bz	CH ₂ CH ₂	4-cyclopropylmethylpiperazin-1-yl
389	2-F-Bz	CH ₂ CH ₂	4-cyclopropylpiperazin-1-yl
390	2-F-Bz	CH ₂ CH ₂	4-phenylpiperazin-1-yl
391	2-F-Bz	CH ₂ CH ₂	dimethylamino
392	2-F-Bz	CH ₂ CH ₂	diethylamino

#	R ¹	CH-R ^p (CH ₂) _z	NR ³ R ⁴
393	2-F-Bz	CH ₂ CH ₂	diisopropylamino
394	2-F-Bz	CH ₂ CH ₂	N-phenylamino
395	2-F-Bz	CH ₂ CH ₂	N-methyl-N-phenylamino
396	2-F-Bz	CH ₂ CH ₂	N-cyclopropyl-N-methylamino
397	2-F-Bz	CH ₂ CH ₂	N-cyclohexyl-N-methylamino
398	2-F-Bz	CH ₂ CH ₂	N-benzyl-N-methylamino
399	2-F-Bz	CH ₂ CH ₂	N-cyclohexylmethyl-N-methylamino
400	2-F-Bz	CH ₂ CH ₂	N-methyl-N-isopropylamino
401	2-F-Bz	CH ₂ CH ₂	N-cyclopropyl-N-phenylamino
402	2-F-Bz	CH ₂ CH ₂	N-cyclopropyl-N-benzylamino
403	2-F-Bz	CH ₂ CH ₂	N-(4-trifluoromethylcyclohexyl)methyl-N-methylamino
404	2-F-Bz	CH ₂ CH ₂	3,4-dihydro-2H-1,4-benzoxazin-4-yl
405	2-F-Bz	CH ₂ CH ₂	cis-octahydrobenzo-[1,4]oxazin-4-yl
406	2-F-Bz	CH ₂ CH ₂	trans-octahydrobenzo[1,4]oxazin-4-yl
407	2-F-Bz	CH ₂ CH ₂	5,5-difluoroocta-hydrocyclopenta[c]pyrrol-2-yl
408	2-F-Bz	CH ₂ CH ₂	hexahydrofuro[3,4-c]pyrrol-5-yl
409	2-F-Bz	CH ₂ CH ₂	2,3-dihydroindol-1-yl
410	2-F-Bz	CH ₂ CH ₂	2-oxa-7-azaspiro[3.5]nonane-7-yl
411	2-F-Bz	CH ₂ CH ₂	2,3-dihydro-1H-isoindole-2-yl
412	2-F-Bz	CH ₂ CH ₂	5-trifluoromethyl-2,3-dihydro-1H-isoindole-2-yl
413	2-F-Bz	CH ₂ CH ₂	4-trifluoro-2,3-dihydro-1H-isoindole-2-yl
414	2-F-Bz	CH ₂ CH ₂	2,3-dihydroisoindole-1-one-2-yl
415	2-F-Bz	CH ₂ CH ₂	1,2,3,4-tetrahydroisoquinoline-2-yl
416	2-F-Bz	CH ₂ CH ₂	3-azabicyclo[3.2.0]heptane-3-yl
417	2-F-Bz	CH ₂ CH ₂	6-(4-fluorophenyl)-3-azabicyclo[3.2.0]heptane-3-yl
418	2-F-Bz	azetin-3-yl	
419	2-F-Bz	pyrrolidin-3-yl	

#	R ¹	CH-R ^p (CH ₂) _z	NR ³ R ⁴
420	2-F-Bz	1-methylpyrrolidin-3-yl	
421	2-F-Bz	piperidin-3-yl	
422	2-F-Bz	1-methylpiperidin-3-yl	
423	2-F-Bz	piperidin-4-yl	
424	2-F-Bz	1-methylpiperidin-4-yl	
425	2-F-Bz	1-ethylpiperidin-4-yl	
426	2-F-Bz	1-propylpiperidin-4-yl	
427	2-F-Bz	1-benzylpiperidin-4-yl	
428	2-F-Bz	1-cyclopropylpiperidin-4-yl	
429	3-F-Bz	CH ₂	4-morpholinyl
430	3-F-Bz	CH ₂	4-thiomorpholinyl
431	3-F-Bz	CH ₂	1,1-dioxothiomorpholin-4-yl
432	3-F-Bz	CH ₂	2,6-dimethylmorpholin-4-yl
433	3-F-Bz	CH ₂	2-phenylmorpholin-4-yl
434	3-F-Bz	CH ₂	1-azetidiny
435	3-F-Bz	CH ₂	1-pyrrolidinyl
436	3-F-Bz	CH ₂	3-phenylpyrrolidin-1-yl
437	3-F-Bz	CH ₂	1-piperidinyl
438	3-F-Bz	CH ₂	1-azepanyl
439	3-F-Bz	CH ₂	4-methylpiperidin-1-yl
440	3-F-Bz	CH ₂	4-phenylpiperidin-1-yl
441	3-F-Bz	CH ₂	4,4-difluoropiperidin-1-yl
442	3-F-Bz	CH ₂	4-(trifluoromethyl)piperidin-1-yl
443	3-F-Bz	CH ₂	4-(tert.-butyl)piperidin-1-yl
444	3-F-Bz	CH ₂	4-methylpiperazin-1-yl
445	3-F-Bz	CH ₂	4-ethylpiperazin-1-yl
446	3-F-Bz	CH ₂	4-propylpiperazin-1-yl
447	3-F-Bz	CH ₂	4-cyclopropylmethylpiperazin-1-yl
448	3-F-Bz	CH ₂	4-cyclopropylpiperazin-1-yl
449	3-F-Bz	CH ₂	4-phenylpiperazin-1-yl
450	3-F-Bz	CH ₂	dimethylamino

#	R ¹	CH-R ^p (CH ₂) _z	NR ³ R ⁴
451	3-F-Bz	CH ₂	diethylamino
452	3-F-Bz	CH ₂	diisopropylamino
453	3-F-Bz	CH ₂	N-phenylamino
454	3-F-Bz	CH ₂	N-methyl-N-phenylamino
455	3-F-Bz	CH ₂	N-cyclopropyl-N-methylamino
456	3-F-Bz	CH ₂	N-cyclohexyl-N-methylamino
457	3-F-Bz	CH ₂	N-benzyl-N-methylamino
458	3-F-Bz	CH ₂	N-cyclohexylmethyl-N-methylamino
459	3-F-Bz	CH ₂	N-methyl-N-isopropylamino
460	3-F-Bz	CH ₂	N-cyclopropyl-N-phenylamino
461	3-F-Bz	CH ₂	N-cyclopropyl-N-benzylamino
462	3-F-Bz	CH ₂	N-(4-trifluoromethylcyclohexyl)methyl-N-methylamino
463	3-F-Bz	CH ₂	3,4-dihydro-2H-1,4-benzoxazin-4-yl
464	3-F-Bz	CH ₂	cis-octahydrobenzo-[1,4]oxazin-4-yl
465	3-F-Bz	CH ₂	trans-octahydrobenzo[1,4]oxazin-4-yl
466	3-F-Bz	CH ₂	5,5-difluoroocta-hydrocyclopenta[c]pyrrol-2-yl
467	3-F-Bz	CH ₂	hexahydrofuro[3,4-c]pyrrol-5-yl
468	3-F-Bz	CH ₂	2,3-dihydroindol-1-yl
469	3-F-Bz	CH ₂	2-oxa-7-azaspiro[3.5]nonane-7-yl
470	3-F-Bz	CH ₂	2,3-dihydro-1H-isoindole-2-yl
471	3-F-Bz	CH ₂	5-trifluoromethyl-2,3-dihydro-1H-isoindole-2-yl
472	3-F-Bz	CH ₂	4-trifluoro-2,3-dihydro-1H-isoindole-2-yl
473	3-F-Bz	CH ₂	2,3-dihydroisoindole-1-one-2-yl
474	3-F-Bz	CH ₂	1,2,3,4-tetrahydroisoquinoline-2-yl
475	3-F-Bz	CH ₂	3-azabicyclo[3.2.0]heptane-3-yl
476	3-F-Bz	CH ₂	6-(4-fluorophenyl)-3-azabicyclo[3.2.0]heptane-3-yl
477	3-F-Bz	CH ₂ CH ₂	4-morpholinyl

#	R ¹	CH-R ^p (CH ₂) _z	NR ³ R ⁴
478	3-F-Bz	CH ₂ CH ₂	4-thiomorpholinyl
479	3-F-Bz	CH ₂ CH ₂	1,1-dioxothiomorpholin-4-yl
480	3-F-Bz	CH ₂ CH ₂	2,6-dimethylmorpholin-4-yl
481	3-F-Bz	CH ₂ CH ₂	2-phenylmorpholin-4-yl
482	3-F-Bz	CH ₂ CH ₂	1-azetidiny
483	3-F-Bz	CH ₂ CH ₂	1-pyrrolidinyl
484	3-F-Bz	CH ₂ CH ₂	3-phenylpyrrolidin-1-yl
485	3-F-Bz	CH ₂ CH ₂	1-piperidinyl
486	3-F-Bz	CH ₂ CH ₂	1-azepanyl
487	3-F-Bz	CH ₂ CH ₂	4-methylpiperidin-1-yl
488	3-F-Bz	CH ₂ CH ₂	4-phenylpiperidin-1-yl
489	3-F-Bz	CH ₂ CH ₂	4,4-difluoropiperidin-1-yl
490	3-F-Bz	CH ₂ CH ₂	4-(trifluoromethyl)piperidin-1-yl
491	3-F-Bz	CH ₂ CH ₂	4-(tert.-butyl)piperidin-1-yl
492	3-F-Bz	CH ₂ CH ₂	4-methylpiperazin-1-yl
493	3-F-Bz	CH ₂ CH ₂	4-ethylpiperazin-1-yl
494	3-F-Bz	CH ₂ CH ₂	4-propylpiperazin-1-yl
495	3-F-Bz	CH ₂ CH ₂	4-cyclopropylmethylpiperazin-1-yl
496	3-F-Bz	CH ₂ CH ₂	4-cyclopropylpiperazin-1-yl
497	3-F-Bz	CH ₂ CH ₂	4-phenylpiperazin-1-yl
498	3-F-Bz	CH ₂ CH ₂	dimethylamino
499	3-F-Bz	CH ₂ CH ₂	diethylamino
500	3-F-Bz	CH ₂ CH ₂	diisopropylamino
501	3-F-Bz	CH ₂ CH ₂	N-phenylamino
502	3-F-Bz	CH ₂ CH ₂	N-methyl-N-phenylamino
503	3-F-Bz	CH ₂ CH ₂	N-cyclopropyl-N-methylamino
504	3-F-Bz	CH ₂ CH ₂	N-cyclohexyl-N-methylamino
505	3-F-Bz	CH ₂ CH ₂	N-benzyl-N-methylamino
506	3-F-Bz	CH ₂ CH ₂	N-cyclohexylmethyl-N-methylamino
507	3-F-Bz	CH ₂ CH ₂	N-methyl-N-isopropylamino
508	3-F-Bz	CH ₂ CH ₂	N-cyclopropyl-N-phenylamino

#	R ¹	CH-R ^p (CH ₂) _z	NR ³ R ⁴
509	3-F-Bz	CH ₂ CH ₂	N-cyclopropyl-N-benzylamino
510	3-F-Bz	CH ₂ CH ₂	N-(4-trifluoromethylcyclohexyl)methyl-N-methylamino
511	3-F-Bz	CH ₂ CH ₂	3,4-dihydro-2H-1,4-benzoxazin-4-yl
512	3-F-Bz	CH ₂ CH ₂	cis-octahydrobenzo-[1,4]oxazin-4-yl
513	3-F-Bz	CH ₂ CH ₂	trans-octahydrobenzo[1,4]oxazin-4-yl
514	3-F-Bz	CH ₂ CH ₂	5,5-difluoroocta-hydrocyclopenta[c]pyrrol-2-yl
515	3-F-Bz	CH ₂ CH ₂	hexahydrofuro[3,4-c]pyrrol-5-yl
516	3-F-Bz	CH ₂ CH ₂	2,3-dihydroindol-1-yl
517	3-F-Bz	CH ₂ CH ₂	2-oxa-7-azaspiro[3.5]nonane-7-yl
518	3-F-Bz	CH ₂ CH ₂	2,3-dihydro-1H-isoindole-2-yl
519	3-F-Bz	CH ₂ CH ₂	5-trifluoromethyl-2,3-dihydro-1H-isoindole-2-yl
520	3-F-Bz	CH ₂ CH ₂	4-trifluoro-2,3-dihydro-1H-isoindole-2-yl
521	3-F-Bz	CH ₂ CH ₂	2,3-dihydroisoindole-1-one-2-yl
522	3-F-Bz	CH ₂ CH ₂	1,2,3,4-tetrahydroisoquinoline-2-yl
523	3-F-Bz	CH ₂ CH ₂	3-azabicyclo[3.2.0]heptane-3-yl
524	3-F-Bz	CH ₂ CH ₂	6-(4-fluorophenyl)-3-azabicyclo[3.2.0]heptane-3-yl
525	3-F-Bz	azetin-3-yl	
526	3-F-Bz	pyrrolidin-3-yl	
527	3-F-Bz	1-methylpyrrolidin-3-yl	
528	3-F-Bz	piperidin-3-yl	
529	3-F-Bz	1-methylpiperidin-3-yl	
530	3-F-Bz	piperidin-4-yl	
531	3-F-Bz	1-methylpiperidin-4-yl	
532	3-F-Bz	1-ethylpiperidin-4-yl	
533	3-F-Bz	1-propylpiperidin-4-yl	
534	3-F-Bz	1-benzylpiperidin-4-yl	
535	3-F-Bz	1-cyclopropylpiperidin-4-yl	

#	R ¹	CH-R ^P (CH ₂) _z	NR ³ R ⁴
536	CH ₂ -c-Hex	CH ₂	4-morpholinyl
537	CH ₂ -c-Hex	CH ₂	4-thiomorpholinyl
538	CH ₂ -c-Hex	CH ₂	1,1-dioxothiomorpholin-4-yl
539	CH ₂ -c-Hex	CH ₂	2,6-dimethylmorpholin-4-yl
540	CH ₂ -c-Hex	CH ₂	2-phenylmorpholin-4-yl
541	CH ₂ -c-Hex	CH ₂	1-azetidiny
542	CH ₂ -c-Hex	CH ₂	1-pyrrolidinyl
543	CH ₂ -c-Hex	CH ₂	3-phenylpyrrolidin-1-yl
544	CH ₂ -c-Hex	CH ₂	1-piperidinyl
545	CH ₂ -c-Hex	CH ₂	1-azepanyl
546	CH ₂ -c-Hex	CH ₂	4-methylpiperidin-1-yl
547	CH ₂ -c-Hex	CH ₂	4-phenylpiperidin-1-yl
548	CH ₂ -c-Hex	CH ₂	4,4-difluoropiperidin-1-yl
549	CH ₂ -c-Hex	CH ₂	4-(trifluoromethyl)piperidin-1-yl
550	CH ₂ -c-Hex	CH ₂	4-(tert.-butyl)piperidin-1-yl
551	CH ₂ -c-Hex	CH ₂	4-methylpiperazin-1-yl
552	CH ₂ -c-Hex	CH ₂	4-ethylpiperazin-1-yl
553	CH ₂ -c-Hex	CH ₂	4-propylpiperazin-1-yl
554	CH ₂ -c-Hex	CH ₂	4-cyclopropylmethylpiperazin-1-yl
555	CH ₂ -c-Hex	CH ₂	4-cyclopropylpiperazin-1-yl
556	CH ₂ -c-Hex	CH ₂	4-phenylpiperazin-1-yl
557	CH ₂ -c-Hex	CH ₂	dimethylamino
558	CH ₂ -c-Hex	CH ₂	diethylamino
559	CH ₂ -c-Hex	CH ₂	diisopropylamino
560	CH ₂ -c-Hex	CH ₂	N-phenylamino
561	CH ₂ -c-Hex	CH ₂	N-methyl-N-phenylamino
562	CH ₂ -c-Hex	CH ₂	N-cyclopropyl-N-methylamino
563	CH ₂ -c-Hex	CH ₂	N-cyclohexyl-N-methylamino
564	CH ₂ -c-Hex	CH ₂	N-benzyl-N-methylamino
565	CH ₂ -c-Hex	CH ₂	N-cyclohexylmethyl-N-methylamino
566	CH ₂ -c-Hex	CH ₂	N-methyl-N-isopropylamino

#	R ¹	CH-R ^P (CH ₂) _z	NR ³ R ⁴
567	CH ₂ -c-Hex	CH ₂	N-cyclopropyl-N-phenylamino
568	CH ₂ -c-Hex	CH ₂	N-cyclopropyl-N-benzylamino
569	CH ₂ -c-Hex	CH ₂	N-(4-trifluoromethylcyclohexyl)methyl-N-methylamino
570	CH ₂ -c-Hex	CH ₂	3,4-dihydro-2H-1,4-benzoxazin-4-yl
571	CH ₂ -c-Hex	CH ₂	cis-octahydrobenzo-[1,4]oxazin-4-yl
572	CH ₂ -c-Hex	CH ₂	trans-octahydrobenzo[1,4]oxazin-4-yl
573	CH ₂ -c-Hex	CH ₂	5,5-difluoroocta-hydrocyclopenta[c]pyrrol-2-yl
574	CH ₂ -c-Hex	CH ₂	hexahydrofuro[3,4-c]pyrrol-5-yl
575	CH ₂ -c-Hex	CH ₂	2,3-dihydroindol-1-yl
576	CH ₂ -c-Hex	CH ₂	2-oxa-7-azaspiro[3.5]nonane-7-yl
577	CH ₂ -c-Hex	CH ₂	2,3-dihydro-1H-isoindole-2-yl
578	CH ₂ -c-Hex	CH ₂	5-trifluoromethyl-2,3-dihydro-1H-isoindole-2-yl
579	CH ₂ -c-Hex	CH ₂	4-trifluoro-2,3-dihydro-1H-isoindole-2-yl
580	CH ₂ -c-Hex	CH ₂	2,3-dihydroisoindole-1-one-2-yl
581	CH ₂ -c-Hex	CH ₂	1,2,3,4-tetrahydroisoquinoline-2-yl
582	CH ₂ -c-Hex	CH ₂	3-azabicyclo[3.2.0]heptane-3-yl
583	CH ₂ -c-Hex	CH ₂	6-(4-fluorophenyl)-3-azabicyclo[3.2.0]heptane-3-yl
584	CH ₂ -c-Hex	CH ₂ CH ₂	4-morpholinyl
585	CH ₂ -c-Hex	CH ₂ CH ₂	4-thiomorpholinyl
586	CH ₂ -c-Hex	CH ₂ CH ₂	1,1-dioxothiomorpholin-4-yl
587	CH ₂ -c-Hex	CH ₂ CH ₂	2,6-dimethylmorpholin-4-yl
588	CH ₂ -c-Hex	CH ₂ CH ₂	2-phenylmorpholin-4-yl
589	CH ₂ -c-Hex	CH ₂ CH ₂	1-azetidiny
590	CH ₂ -c-Hex	CH ₂ CH ₂	1-pyrrolidinyl
591	CH ₂ -c-Hex	CH ₂ CH ₂	3-phenylpyrrolidin-1-yl
592	CH ₂ -c-Hex	CH ₂ CH ₂	1-piperidinyl
593	CH ₂ -c-Hex	CH ₂ CH ₂	1-azepanyl

#	R ¹	CH-R ^P (CH ₂) _z	NR ³ R ⁴
594	CH ₂ -c-Hex	CH ₂ CH ₂	4-methylpiperidin-1-yl
595	CH ₂ -c-Hex	CH ₂ CH ₂	4-phenylpiperidin-1-yl
596	CH ₂ -c-Hex	CH ₂ CH ₂	4,4-difluoropiperidin-1-yl
597	CH ₂ -c-Hex	CH ₂ CH ₂	4-(trifluoromethyl)piperidin-1-yl
598	CH ₂ -c-Hex	CH ₂ CH ₂	4-(tert.-butyl)piperidin-1-yl
599	CH ₂ -c-Hex	CH ₂ CH ₂	4-methylpiperazin-1-yl
600	CH ₂ -c-Hex	CH ₂ CH ₂	4-ethylpiperazin-1-yl
601	CH ₂ -c-Hex	CH ₂ CH ₂	4-propylpiperazin-1-yl
602	CH ₂ -c-Hex	CH ₂ CH ₂	4-cyclopropylmethylpiperazin-1-yl
603	CH ₂ -c-Hex	CH ₂ CH ₂	4-cyclopropylpiperazin-1-yl
604	CH ₂ -c-Hex	CH ₂ CH ₂	4-phenylpiperazin-1-yl
605	CH ₂ -c-Hex	CH ₂ CH ₂	dimethylamino
606	CH ₂ -c-Hex	CH ₂ CH ₂	diethylamino
607	CH ₂ -c-Hex	CH ₂ CH ₂	diisopropylamino
608	CH ₂ -c-Hex	CH ₂ CH ₂	N-phenylamino
609	CH ₂ -c-Hex	CH ₂ CH ₂	N-methyl-N-phenylamino
610	CH ₂ -c-Hex	CH ₂ CH ₂	N-cyclopropyl-N-methylamino
611	CH ₂ -c-Hex	CH ₂ CH ₂	N-cyclohexyl-N-methylamino
612	CH ₂ -c-Hex	CH ₂ CH ₂	N-benzyl-N-methylamino
613	CH ₂ -c-Hex	CH ₂ CH ₂	N-cyclohexylmethyl-N-methylamino
614	CH ₂ -c-Hex	CH ₂ CH ₂	N-methyl-N-isopropylamino
615	CH ₂ -c-Hex	CH ₂ CH ₂	N-cyclopropyl-N-phenylamino
616	CH ₂ -c-Hex	CH ₂ CH ₂	N-cyclopropyl-N-benzylamino
617	CH ₂ -c-Hex	CH ₂ CH ₂	N-(4-trifluoromethylcyclohexyl)methyl-N-methylamino
618	CH ₂ -c-Hex	CH ₂ CH ₂	3,4-dihydro-2H-1,4-benzoxazin-4-yl
619	CH ₂ -c-Hex	CH ₂ CH ₂	cis-octahydrobenzo-[1,4]oxazin-4-yl
620	CH ₂ -c-Hex	CH ₂ CH ₂	trans-octahydrobenzo[1,4]oxazin-4-yl
621	CH ₂ -c-Hex	CH ₂ CH ₂	5,5-difluoroocta-hydrocyclopenta[c]pyrrol-2-yl
622	CH ₂ -c-Hex	CH ₂ CH ₂	hexahydrofuro[3,4-c]pyrrol-5-yl

#	R ¹	CH-R ^p (CH ₂) _z	NR ³ R ⁴
623	CH ₂ -c-Hex	CH ₂ CH ₂	2,3-dihydroindol-1-yl
624	CH ₂ -c-Hex	CH ₂ CH ₂	2-oxa-7-azaspiro[3.5]nonane-7-yl
625	CH ₂ -c-Hex	CH ₂ CH ₂	2,3-dihydro-1H-isoindole-2-yl
626	CH ₂ -c-Hex	CH ₂ CH ₂	5-trifluoromethyl-2,3-dihydro-1H-isoindole-2-yl
627	CH ₂ -c-Hex	CH ₂ CH ₂	4-trifluoro-2,3-dihydro-1H-isoindole-2-yl
628	CH ₂ -c-Hex	CH ₂ CH ₂	2,3-dihydroisoindole-1-one-2-yl
629	CH ₂ -c-Hex	CH ₂ CH ₂	1,2,3,4-tetrahydroisoquinoline-2-yl
630	CH ₂ -c-Hex	CH ₂ CH ₂	3-azabicyclo[3.2.0]heptane-3-yl
631	CH ₂ -c-Hex	CH ₂ CH ₂	6-(4-fluorophenyl)-3-azabicyclo[3.2.0]heptane-3-yl
632	CH ₂ -c-Hex	azetin-3-yl	
633	CH ₂ -c-Hex	pyrrolidin-3-yl	
634	CH ₂ -c-Hex	1-methylpyrrolidin-3-yl	
635	CH ₂ -c-Hex	piperidin-3-yl	
636	CH ₂ -c-Hex	1-methylpiperidin-3-yl	
637	CH ₂ -c-Hex	piperidin-4-yl	
638	CH ₂ -c-Hex	1-methylpiperidin-4-yl	
639	CH ₂ -c-Hex	1-ethylpiperidin-4-yl	
640	CH ₂ -c-Hex	1-propylpiperidin-4-yl	
641	CH ₂ -c-Hex	1-benzylpiperidin-4-yl	
642	CH ₂ -c-Hex	1-cyclopropylpiperidin-4-yl	
643	(CH ₂) ₃ CH ₃	CH ₂	4-morpholinyl
644	(CH ₂) ₃ CH ₃	CH ₂	4-thiomorpholinyl
645	(CH ₂) ₃ CH ₃	CH ₂	1,1-dioxothiomorpholin-4-yl
646	(CH ₂) ₃ CH ₃	CH ₂	2,6-dimethylmorpholin-4-yl
647	(CH ₂) ₃ CH ₃	CH ₂	2-phenylmorpholin-4-yl
648	(CH ₂) ₃ CH ₃	CH ₂	1-azetidiny
649	(CH ₂) ₃ CH ₃	CH ₂	1-pyrrolidinyl
650	(CH ₂) ₃ CH ₃	CH ₂	3-phenylpyrrolidin-1-yl
651	(CH ₂) ₃ CH ₃	CH ₂	1-piperidiny

#	R ¹	CH-R ^P (CH ₂) _z	NR ³ R ⁴
652	(CH ₂) ₃ CH ₃	CH ₂	1-azepanyl
653	(CH ₂) ₃ CH ₃	CH ₂	4-methylpiperidin-1-yl
654	(CH ₂) ₃ CH ₃	CH ₂	4-phenylpiperidin-1-yl
655	(CH ₂) ₃ CH ₃	CH ₂	4,4-difluoropiperidin-1-yl
656	(CH ₂) ₃ CH ₃	CH ₂	4-(trifluoromethyl)piperidin-1-yl
657	(CH ₂) ₃ CH ₃	CH ₂	4-(tert.-butyl)piperidin-1-yl
658	(CH ₂) ₃ CH ₃	CH ₂	4-methylpiperazin-1-yl
659	(CH ₂) ₃ CH ₃	CH ₂	4-ethylpiperazin-1-yl
660	(CH ₂) ₃ CH ₃	CH ₂	4-propylpiperazin-1-yl
661	(CH ₂) ₃ CH ₃	CH ₂	4-cyclopropylmethylpiperazin-1-yl
662	(CH ₂) ₃ CH ₃	CH ₂	4-cyclopropylpiperazin-1-yl
663	(CH ₂) ₃ CH ₃	CH ₂	4-phenylpiperazin-1-yl
664	(CH ₂) ₃ CH ₃	CH ₂	dimethylamino
665	(CH ₂) ₃ CH ₃	CH ₂	diethylamino
666	(CH ₂) ₃ CH ₃	CH ₂	diisopropylamino
667	(CH ₂) ₃ CH ₃	CH ₂	N-phenylamino
668	(CH ₂) ₃ CH ₃	CH ₂	N-methyl-N-phenylamino
669	(CH ₂) ₃ CH ₃	CH ₂	N-cyclopropyl-N-methylamino
670	(CH ₂) ₃ CH ₃	CH ₂	N-cyclohexyl-N-methylamino
671	(CH ₂) ₃ CH ₃	CH ₂	N-benzyl-N-methylamino
672	(CH ₂) ₃ CH ₃	CH ₂	N-cyclohexylmethyl-N-methylamino
673	(CH ₂) ₃ CH ₃	CH ₂	N-methyl-N-isopropylamino
674	(CH ₂) ₃ CH ₃	CH ₂	N-cyclopropyl-N-phenylamino
675	(CH ₂) ₃ CH ₃	CH ₂	N-cyclopropyl-N-benzylamino
676	(CH ₂) ₃ CH ₃	CH ₂	N-(4-trifluoromethylcyclohexyl)methyl-N-methylamino
677	(CH ₂) ₃ CH ₃	CH ₂	3,4-dihydro-2H-1,4-benzoxazin-4-yl
678	(CH ₂) ₃ CH ₃	CH ₂	cis-octahydrobenzo-[1,4]oxazin-4-yl
679	(CH ₂) ₃ CH ₃	CH ₂	trans-octahydrobenzo[1,4]oxazin-4-yl
680	(CH ₂) ₃ CH ₃	CH ₂	5,5-difluoroocta-hydrocyclopenta[c]pyrrol-2-yl

#	R ¹	CH-R ^p (CH ₂) _z	NR ³ R ⁴
681	(CH ₂) ₃ CH ₃	CH ₂	hexahydrofuro[3,4-c]pyrrol-5-yl
682	(CH ₂) ₃ CH ₃	CH ₂	2,3-dihydroindol-1-yl
683	(CH ₂) ₃ CH ₃	CH ₂	2-oxa-7-azaspiro[3.5]nonane-7-yl
684	(CH ₂) ₃ CH ₃	CH ₂	2,3-dihydro-1H-isoindole-2-yl
685	(CH ₂) ₃ CH ₃	CH ₂	5-trifluoromethyl-2,3-dihydro-1H-isoindole-2-yl
686	(CH ₂) ₃ CH ₃	CH ₂	4-trifluoro-2,3-dihydro-1H-isoindole-2-yl
687	(CH ₂) ₃ CH ₃	CH ₂	2,3-dihydroisoindole-1-one-2-yl
688	(CH ₂) ₃ CH ₃	CH ₂	1,2,3,4-tetrahydroisoquinoline-2-yl
689	(CH ₂) ₃ CH ₃	CH ₂	3-azabicyclo[3.2.0]heptane-3-yl
690	(CH ₂) ₃ CH ₃	CH ₂	6-(4-fluorophenyl)-3-azabicyclo[3.2.0]heptane-3-yl
691	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	4-morpholinyl
692	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	4-thiomorpholinyl
693	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	1,1-dioxothiomorpholin-4-yl
694	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	2,6-dimethylmorpholin-4-yl
695	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	2-phenylmorpholin-4-yl
696	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	1-azetidiny
697	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	1-pyrrolidinyl
698	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	3-phenylpyrrolidin-1-yl
699	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	1-piperidinyl
700	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	1-azepanyl
701	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	4-methylpiperidin-1-yl
702	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	4-phenylpiperidin-1-yl
703	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	4,4-difluoropiperidin-1-yl
704	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	4-(trifluoromethyl)piperidin-1-yl
705	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	4-(tert.-butyl)piperidin-1-yl
706	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	4-methylpiperazin-1-yl
707	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	4-ethylpiperazin-1-yl
708	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	4-propylpiperazin-1-yl
709	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	4-cyclopropylmethylpiperazin-1-yl

#	R ¹	CH-R ^p (CH ₂) _z	NR ³ R ⁴
710	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	4-cyclopropylpiperazin-1-yl
711	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	4-phenylpiperazin-1-yl
712	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	dimethylamino
713	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	diethylamino
714	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	diisopropylamino
715	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	N-phenylamino
716	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	N-methyl-N-phenylamino
717	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	N-cyclopropyl-N-methylamino
718	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	N-cyclohexyl-N-methylamino
719	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	N-benzyl-N-methylamino
720	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	N-cyclohexylmethyl-N-methylamino
721	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	N-methyl-N-isopropylamino
722	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	N-cyclopropyl-N-phenylamino
723	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	N-cyclopropyl-N-benzylamino
724	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	N-(4-trifluoromethylcyclohexyl)methyl-N-methylamino
725	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	3,4-dihydro-2H-1,4-benzoxazin-4-yl
726	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	cis-octahydrobenzo-[1,4]oxazin-4-yl
727	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	trans-octahydrobenzo[1,4]oxazin-4-yl
728	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	5,5-difluoroocta-hydrocyclopenta[c]pyrrol-2-yl
729	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	hexahydrofuro[3,4-c]pyrrol-5-yl
730	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	2,3-dihydroindol-1-yl
731	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	2-oxa-7-azaspiro[3.5]nonane-7-yl
732	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	2,3-dihydro-1H-isoindole-2-yl
733	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	5-trifluoromethyl-2,3-dihydro-1H-isoindole-2-yl
734	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	4-trifluoro-2,3-dihydro-1H-isoindole-2-yl
735	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	2,3-dihydroisoindole-1-one-2-yl
736	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	1,2,3,4-tetrahydroisoquinoline-2-yl
737	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	3-azabicyclo[3.2.0]heptane-3-yl

#	R ¹	CH-R ^p (CH ₂) _z	NR ³ R ⁴
738	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	6-(4-fluorophenyl)-3-azabicyclo[3.2.0]heptane-3-yl
739	(CH ₂) ₃ CH ₃		azetin-3-yl
740	(CH ₂) ₃ CH ₃		pyrrolidin-3-yl
741	(CH ₂) ₃ CH ₃		1-methylpyrrolidin-3-yl
742	(CH ₂) ₃ CH ₃		piperidin-3-yl
743	(CH ₂) ₃ CH ₃		1-methylpiperidin-3-yl
744	(CH ₂) ₃ CH ₃		piperidin-4-yl
745	(CH ₂) ₃ CH ₃		1-methylpiperidin-4-yl
746	(CH ₂) ₃ CH ₃		1-ethylpiperidin-4-yl
747	(CH ₂) ₃ CH ₃		1-propylpiperidin-4-yl
748	(CH ₂) ₃ CH ₃		1-benzylpiperidin-4-yl
749	(CH ₂) ₃ CH ₃		1-cyclopropylpiperidin-4-yl

Ph: Phenyl

4-F-Bz: 4-Fluorobenzyl

4-Cl-Bz: 4-Chlorobenzyl

3-F-Bz: 3-Fluorobenzyl

5 2-F-Bz: 2-Fluorobenzyl

c-Hex: Cyclohexyl

Table B

#	R ¹	A ¹	A ²	R ⁵
1	CH ₂ -Ph	CH ₂	CH ₂	H
2	CH ₂ -Ph	CH ₂	CH ₂	CH ₃
3	CH ₂ -Ph	CH ₂	CH ₂	CH ₂ CH ₃
4	CH ₂ -Ph	CH ₂	CH ₂	CH ₂ CH ₂ CH ₃
5	CH ₂ -Ph	CH ₂	CH ₂	isopropyl
6	CH ₂ -Ph	CH ₂	CH ₂	cyclopropyl
7	CH ₂ -Ph	CH ₂	CH ₂	CH ₂ -cyclopropyl
8	CH ₂ -Ph	CH ₂	CH ₂	acetyl
9	CH ₂ -Ph	CH ₂	CH ₂	CO ₂ -t-Bu

#	R ¹	A ¹	A ²	R ⁵
10	CH ₂ -Ph	CH ₂	CH ₂	CH ₂ -Ph
11	CH ₂ -Ph	CH ₂	CH ₂ CH ₂	H
12	CH ₂ -Ph	CH ₂	CH ₂ CH ₂	CH ₃
13	CH ₂ -Ph	CH ₂	CH ₂ CH ₂	CH ₂ CH ₃
14	CH ₂ -Ph	CH ₂	CH ₂ CH ₂	CH ₂ CH ₂ CH ₃
15	CH ₂ -Ph	CH ₂	CH ₂ CH ₂	isopropyl
16	CH ₂ -Ph	CH ₂	CH ₂ CH ₂	cyclopropyl
17	CH ₂ -Ph	CH ₂	CH ₂ CH ₂	CH ₂ -cyclopropyl
18	CH ₂ -Ph	CH ₂	CH ₂ CH ₂	acetyl
19	CH ₂ -Ph	CH ₂	CH ₂ CH ₂	CO ₂ -t-Bu
20	CH ₂ -Ph	CH ₂	CH ₂ CH ₂	CH ₂ -Ph
21	CH ₂ -Ph	-	CH ₂ CH ₂ CH ₂	H
22	CH ₂ -Ph	-	CH ₂ CH ₂ CH ₂	CH ₃
23	CH ₂ -Ph	-	CH ₂ CH ₂ CH ₂	CH ₂ CH ₃
24	CH ₂ -Ph	-	CH ₂ CH ₂ CH ₂	CH ₂ CH ₂ CH ₃
25	CH ₂ -Ph	-	CH ₂ CH ₂ CH ₂	isopropyl
26	CH ₂ -Ph	-	CH ₂ CH ₂ CH ₂	cyclopropyl
27	CH ₂ -Ph	-	CH ₂ CH ₂ CH ₂	CH ₂ -cyclopropyl
28	CH ₂ -Ph	-	CH ₂ CH ₂ CH ₂	acetyl
29	CH ₂ -Ph	-	CH ₂ CH ₂ CH ₂	CO ₂ -t-Bu
30	CH ₂ -Ph	-	CH ₂ CH ₂ CH ₂	CH ₂ -Ph
31	CH ₂ -Ph	CH ₂ CH ₂	CH ₂ CH ₂	H
32	CH ₂ -Ph	CH ₂ CH ₂	CH ₂ CH ₂	CH ₃
33	CH ₂ -Ph	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ CH ₃
34	CH ₂ -Ph	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ CH ₂ CH ₃
35	CH ₂ -Ph	CH ₂ CH ₂	CH ₂ CH ₂	isopropyl
36	CH ₂ -Ph	CH ₂ CH ₂	CH ₂ CH ₂	cyclopropyl
37	CH ₂ -Ph	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ -cyclopropyl
38	CH ₂ -Ph	CH ₂ CH ₂	CH ₂ CH ₂	acetyl
39	CH ₂ -Ph	CH ₂ CH ₂	CH ₂ CH ₂	CO ₂ -t-Bu
40	CH ₂ -Ph	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ -Ph

#	R ¹	A ¹	A ²	R ⁵
41	CH ₂ -Ph	CH ₂ CH ₂	CH ₂	H
42	CH ₂ -Ph	CH ₂ CH ₂	CH ₂	CH ₃
43	CH ₂ -Ph	CH ₂ CH ₂	CH ₂	CH ₂ CH ₃
44	CH ₂ -Ph	CH ₂ CH ₂	CH ₂	CH ₂ CH ₂ CH ₃
45	CH ₂ -Ph	CH ₂ CH ₂	CH ₂	isopropyl
46	CH ₂ -Ph	CH ₂ CH ₂	CH ₂	cyclopropyl
47	CH ₂ -Ph	CH ₂ CH ₂	CH ₂	CH ₂ -cyclopropyl
48	CH ₂ -Ph	CH ₂ CH ₂	CH ₂	acetyl
49	CH ₂ -Ph	CH ₂ CH ₂	CH ₂	CO ₂ -t-Bu
50	CH ₂ -Ph	CH ₂ CH ₂	CH ₂	CH ₂ -Ph
51	CH ₂ -Ph	CH ₂ CH ₂ CH ₂	-	H
52	CH ₂ -Ph	CH ₂ CH ₂ CH ₂	-	CH ₃
53	CH ₂ -Ph	CH ₂ CH ₂ CH ₂	-	CH ₂ CH ₃
54	CH ₂ -Ph	CH ₂ CH ₂ CH ₂	-	CH ₂ CH ₂ CH ₃
55	CH ₂ -Ph	CH ₂ CH ₂ CH ₂	-	isopropyl
56	CH ₂ -Ph	CH ₂ CH ₂ CH ₂	-	cyclopropyl
57	CH ₂ -Ph	CH ₂ CH ₂ CH ₂	-	CH ₂ -cyclopropyl
58	CH ₂ -Ph	CH ₂ CH ₂ CH ₂	-	acetyl
59	CH ₂ -Ph	CH ₂ CH ₂ CH ₂	-	CO ₂ -t-Bu
60	CH ₂ -Ph	CH ₂ CH ₂ CH ₂	-	CH ₂ -Ph
61	4-Cl-Bz	CH ₂	CH ₂	H
62	4-Cl-Bz	CH ₂	CH ₂	CH ₃
63	4-Cl-Bz	CH ₂	CH ₂	CH ₂ CH ₃
64	4-Cl-Bz	CH ₂	CH ₂	CH ₂ CH ₂ CH ₃
65	4-Cl-Bz	CH ₂	CH ₂	isopropyl
66	4-Cl-Bz	CH ₂	CH ₂	cyclopropyl
67	4-Cl-Bz	CH ₂	CH ₂	CH ₂ -cyclopropyl
68	4-Cl-Bz	CH ₂	CH ₂	acetyl
69	4-Cl-Bz	CH ₂	CH ₂	CO ₂ -t-Bu
70	4-Cl-Bz	CH ₂	CH ₂	CH ₂ -Ph
71	4-Cl-Bz	CH ₂	CH ₂ CH ₂	H

#	R ¹	A ¹	A ²	R ⁵
72	4-Cl-Bz	CH ₂	CH ₂ CH ₂	CH ₃
73	4-Cl-Bz	CH ₂	CH ₂ CH ₂	CH ₂ CH ₃
74	4-Cl-Bz	CH ₂	CH ₂ CH ₂	CH ₂ CH ₂ CH ₃
75	4-Cl-Bz	CH ₂	CH ₂ CH ₂	isopropyl
76	4-Cl-Bz	CH ₂	CH ₂ CH ₂	cyclopropyl
77	4-Cl-Bz	CH ₂	CH ₂ CH ₂	CH ₂ -cyclopropyl
78	4-Cl-Bz	CH ₂	CH ₂ CH ₂	acetyl
79	4-Cl-Bz	CH ₂	CH ₂ CH ₂	CO ₂ -t-Bu
80	4-Cl-Bz	CH ₂	CH ₂ CH ₂	CH ₂ -Ph
81	4-Cl-Bz	-	CH ₂ CH ₂ CH ₂	H
82	4-Cl-Bz	-	CH ₂ CH ₂ CH ₂	CH ₃
83	4-Cl-Bz	-	CH ₂ CH ₂ CH ₂	CH ₂ CH ₃
84	4-Cl-Bz	-	CH ₂ CH ₂ CH ₂	CH ₂ CH ₂ CH ₃
85	4-Cl-Bz	-	CH ₂ CH ₂ CH ₂	isopropyl
86	4-Cl-Bz	-	CH ₂ CH ₂ CH ₂	cyclopropyl
87	4-Cl-Bz	-	CH ₂ CH ₂ CH ₂	CH ₂ -cyclopropyl
88	4-Cl-Bz	-	CH ₂ CH ₂ CH ₂	acetyl
89	4-Cl-Bz	-	CH ₂ CH ₂ CH ₂	CO ₂ -t-Bu
90	4-Cl-Bz	-	CH ₂ CH ₂ CH ₂	CH ₂ -Ph
91	4-Cl-Bz	CH ₂ CH ₂	CH ₂ CH ₂	H
92	4-Cl-Bz	CH ₂ CH ₂	CH ₂ CH ₂	CH ₃
93	4-Cl-Bz	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ CH ₃
94	4-Cl-Bz	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ CH ₂ CH ₃
95	4-Cl-Bz	CH ₂ CH ₂	CH ₂ CH ₂	isopropyl
96	4-Cl-Bz	CH ₂ CH ₂	CH ₂ CH ₂	cyclopropyl
97	4-Cl-Bz	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ -cyclopropyl
98	4-Cl-Bz	CH ₂ CH ₂	CH ₂ CH ₂	acetyl
99	4-Cl-Bz	CH ₂ CH ₂	CH ₂ CH ₂	CO ₂ -t-Bu
100	4-Cl-Bz	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ -Ph
101	4-Cl-Bz	CH ₂ CH ₂	CH ₂	H
102	4-Cl-Bz	CH ₂ CH ₂	CH ₂	CH ₃

#	R ¹	A ¹	A ²	R ⁵
103	4-Cl-Bz	CH ₂ CH ₂	CH ₂	CH ₂ CH ₃
104	4-Cl-Bz	CH ₂ CH ₂	CH ₂	CH ₂ CH ₂ CH ₃
105	4-Cl-Bz	CH ₂ CH ₂	CH ₂	isopropyl
106	4-Cl-Bz	CH ₂ CH ₂	CH ₂	cyclopropyl
107	4-Cl-Bz	CH ₂ CH ₂	CH ₂	CH ₂ -cyclopropyl
108	4-Cl-Bz	CH ₂ CH ₂	CH ₂	acetyl
109	4-Cl-Bz	CH ₂ CH ₂	CH ₂	CO ₂ -t-Bu
110	4-Cl-Bz	CH ₂ CH ₂	CH ₂	CH ₂ -Ph
111	4-Cl-Bz	CH ₂ CH ₂ CH ₂	-	H
112	4-Cl-Bz	CH ₂ CH ₂ CH ₂	-	CH ₃
113	4-Cl-Bz	CH ₂ CH ₂ CH ₂	-	CH ₂ CH ₃
114	4-Cl-Bz	CH ₂ CH ₂ CH ₂	-	CH ₂ CH ₂ CH ₃
115	4-Cl-Bz	CH ₂ CH ₂ CH ₂	-	isopropyl
116	4-Cl-Bz	CH ₂ CH ₂ CH ₂	-	cyclopropyl
117	4-Cl-Bz	CH ₂ CH ₂ CH ₂	-	CH ₂ -cyclopropyl
118	4-Cl-Bz	CH ₂ CH ₂ CH ₂	-	acetyl
119	4-Cl-Bz	CH ₂ CH ₂ CH ₂	-	CO ₂ -t-Bu
120	4-Cl-Bz	CH ₂ CH ₂ CH ₂	-	CH ₂ -Ph
121	4-F-Bz	CH ₂	CH ₂	H
122	4-F-Bz	CH ₂	CH ₂	CH ₃
123	4-F-Bz	CH ₂	CH ₂	CH ₂ CH ₃
124	4-F-Bz	CH ₂	CH ₂	CH ₂ CH ₂ CH ₃
125	4-F-Bz	CH ₂	CH ₂	isopropyl
126	4-F-Bz	CH ₂	CH ₂	cyclopropyl
127	4-F-Bz	CH ₂	CH ₂	CH ₂ -cyclopropyl
128	4-F-Bz	CH ₂	CH ₂	acetyl
129	4-F-Bz	CH ₂	CH ₂	CO ₂ -t-Bu
130	4-F-Bz	CH ₂	CH ₂	CH ₂ -Ph
131	4-F-Bz	CH ₂	CH ₂ CH ₂	H
132	4-F-Bz	CH ₂	CH ₂ CH ₂	CH ₃
133	4-F-Bz	CH ₂	CH ₂ CH ₂	CH ₂ CH ₃

#	R ¹	A ¹	A ²	R ⁵
134	4-F-Bz	CH ₂	CH ₂ CH ₂	CH ₂ CH ₂ CH ₃
135	4-F-Bz	CH ₂	CH ₂ CH ₂	isopropyl
136	4-F-Bz	CH ₂	CH ₂ CH ₂	cyclopropyl
137	4-F-Bz	CH ₂	CH ₂ CH ₂	CH ₂ -cyclopropyl
138	4-F-Bz	CH ₂	CH ₂ CH ₂	acetyl
139	4-F-Bz	CH ₂	CH ₂ CH ₂	CO ₂ -t-Bu
140	4-F-Bz	CH ₂	CH ₂ CH ₂	CH ₂ -Ph
141	4-F-Bz	-	CH ₂ CH ₂ CH ₂	H
142	4-F-Bz	-	CH ₂ CH ₂ CH ₂	CH ₃
143	4-F-Bz	-	CH ₂ CH ₂ CH ₂	CH ₂ CH ₃
144	4-F-Bz	-	CH ₂ CH ₂ CH ₂	CH ₂ CH ₂ CH ₃
145	4-F-Bz	-	CH ₂ CH ₂ CH ₂	isopropyl
146	4-F-Bz	-	CH ₂ CH ₂ CH ₂	cyclopropyl
147	4-F-Bz	-	CH ₂ CH ₂ CH ₂	CH ₂ -cyclopropyl
148	4-F-Bz	-	CH ₂ CH ₂ CH ₂	acetyl
149	4-F-Bz	-	CH ₂ CH ₂ CH ₂	CO ₂ -t-Bu
150	4-F-Bz	-	CH ₂ CH ₂ CH ₂	CH ₂ -Ph
151	4-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	H
152	4-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	CH ₃
153	4-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ CH ₃
154	4-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ CH ₂ CH ₃
155	4-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	isopropyl
156	4-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	cyclopropyl
157	4-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ -cyclopropyl
158	4-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	acetyl
159	4-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	CO ₂ -t-Bu
160	4-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ -Ph
161	4-F-Bz	CH ₂ CH ₂	CH ₂	H
162	4-F-Bz	CH ₂ CH ₂	CH ₂	CH ₃
163	4-F-Bz	CH ₂ CH ₂	CH ₂	CH ₂ CH ₃
164	4-F-Bz	CH ₂ CH ₂	CH ₂	CH ₂ CH ₂ CH ₃

#	R ¹	A ¹	A ²	R ⁵
165	4-F-Bz	CH ₂ CH ₂	CH ₂	isopropyl
166	4-F-Bz	CH ₂ CH ₂	CH ₂	cyclopropyl
167	4-F-Bz	CH ₂ CH ₂	CH ₂	CH ₂ -cyclopropyl
168	4-F-Bz	CH ₂ CH ₂	CH ₂	acetyl
169	4-F-Bz	CH ₂ CH ₂	CH ₂	CO ₂ -t-Bu
170	4-F-Bz	CH ₂ CH ₂	CH ₂	CH ₂ -Ph
171	4-F-Bz	CH ₂ CH ₂ CH ₂	-	H
172	4-F-Bz	CH ₂ CH ₂ CH ₂	-	CH ₃
173	4-F-Bz	CH ₂ CH ₂ CH ₂	-	CH ₂ CH ₃
174	4-F-Bz	CH ₂ CH ₂ CH ₂	-	CH ₂ CH ₂ CH ₃
175	4-F-Bz	CH ₂ CH ₂ CH ₂	-	isopropyl
176	4-F-Bz	CH ₂ CH ₂ CH ₂	-	cyclopropyl
177	4-F-Bz	CH ₂ CH ₂ CH ₂	-	CH ₂ -cyclopropyl
178	4-F-Bz	CH ₂ CH ₂ CH ₂	-	acetyl
179	4-F-Bz	CH ₂ CH ₂ CH ₂	-	CO ₂ -t-Bu
180	4-F-Bz	CH ₂ CH ₂ CH ₂	-	CH ₂ -Ph
181	2-F-Bz	CH ₂	CH ₂	H
182	2-F-Bz	CH ₂	CH ₂	CH ₃
183	2-F-Bz	CH ₂	CH ₂	CH ₂ CH ₃
184	2-F-Bz	CH ₂	CH ₂	CH ₂ CH ₂ CH ₃
185	2-F-Bz	CH ₂	CH ₂	isopropyl
186	2-F-Bz	CH ₂	CH ₂	cyclopropyl
187	2-F-Bz	CH ₂	CH ₂	CH ₂ -cyclopropyl
188	2-F-Bz	CH ₂	CH ₂	acetyl
189	2-F-Bz	CH ₂	CH ₂	CO ₂ -t-Bu
190	2-F-Bz	CH ₂	CH ₂	CH ₂ -Ph
191	2-F-Bz	CH ₂	CH ₂ CH ₂	H
192	2-F-Bz	CH ₂	CH ₂ CH ₂	CH ₃
193	2-F-Bz	CH ₂	CH ₂ CH ₂	CH ₂ CH ₃
194	2-F-Bz	CH ₂	CH ₂ CH ₂	CH ₂ CH ₂ CH ₃
195	2-F-Bz	CH ₂	CH ₂ CH ₂	isopropyl

#	R ¹	A ¹	A ²	R ⁵
196	2-F-Bz	CH ₂	CH ₂ CH ₂	cyclopropyl
197	2-F-Bz	CH ₂	CH ₂ CH ₂	CH ₂ -cyclopropyl
198	2-F-Bz	CH ₂	CH ₂ CH ₂	acetyl
199	2-F-Bz	CH ₂	CH ₂ CH ₂	CO ₂ -t-Bu
200	2-F-Bz	CH ₂	CH ₂ CH ₂	CH ₂ -Ph
201	2-F-Bz	-	CH ₂ CH ₂ CH ₂	H
202	2-F-Bz	-	CH ₂ CH ₂ CH ₂	CH ₃
203	2-F-Bz	-	CH ₂ CH ₂ CH ₂	CH ₂ CH ₃
204	2-F-Bz	-	CH ₂ CH ₂ CH ₂	CH ₂ CH ₂ CH ₃
205	2-F-Bz	-	CH ₂ CH ₂ CH ₂	isopropyl
206	2-F-Bz	-	CH ₂ CH ₂ CH ₂	cyclopropyl
207	2-F-Bz	-	CH ₂ CH ₂ CH ₂	CH ₂ -cyclopropyl
208	2-F-Bz	-	CH ₂ CH ₂ CH ₂	acetyl
209	2-F-Bz	-	CH ₂ CH ₂ CH ₂	CO ₂ -t-Bu
210	2-F-Bz	-	CH ₂ CH ₂ CH ₂	CH ₂ -Ph
211	2-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	H
212	2-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	CH ₃
213	2-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ CH ₃
214	2-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ CH ₂ CH ₃
215	2-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	isopropyl
216	2-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	cyclopropyl
217	2-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ -cyclopropyl
218	2-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	acetyl
219	2-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	CO ₂ -t-Bu
220	2-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ -Ph
221	2-F-Bz	CH ₂ CH ₂	CH ₂	H
222	2-F-Bz	CH ₂ CH ₂	CH ₂	CH ₃
223	2-F-Bz	CH ₂ CH ₂	CH ₂	CH ₂ CH ₃
224	2-F-Bz	CH ₂ CH ₂	CH ₂	CH ₂ CH ₂ CH ₃
225	2-F-Bz	CH ₂ CH ₂	CH ₂	isopropyl
226	2-F-Bz	CH ₂ CH ₂	CH ₂	cyclopropyl

#	R ¹	A ¹	A ²	R ⁵
227	2-F-Bz	CH ₂ CH ₂	CH ₂	CH ₂ -cyclopropyl
228	2-F-Bz	CH ₂ CH ₂	CH ₂	acetyl
229	2-F-Bz	CH ₂ CH ₂	CH ₂	CO ₂ -t-Bu
230	2-F-Bz	CH ₂ CH ₂	CH ₂	CH ₂ -Ph
231	2-F-Bz	CH ₂ CH ₂ CH ₂	-	H
232	2-F-Bz	CH ₂ CH ₂ CH ₂	-	CH ₃
233	2-F-Bz	CH ₂ CH ₂ CH ₂	-	CH ₂ CH ₃
234	2-F-Bz	CH ₂ CH ₂ CH ₂	-	CH ₂ CH ₂ CH ₃
235	2-F-Bz	CH ₂ CH ₂ CH ₂	-	isopropyl
236	2-F-Bz	CH ₂ CH ₂ CH ₂	-	cyclopropyl
237	2-F-Bz	CH ₂ CH ₂ CH ₂	-	CH ₂ -cyclopropyl
238	2-F-Bz	CH ₂ CH ₂ CH ₂	-	acetyl
239	2-F-Bz	CH ₂ CH ₂ CH ₂	-	CO ₂ -t-Bu
240	2-F-Bz	CH ₂ CH ₂ CH ₂	-	CH ₂ -Ph
241	3-F-Bz	CH ₂	CH ₂	H
242	3-F-Bz	CH ₂	CH ₂	CH ₃
243	3-F-Bz	CH ₂	CH ₂	CH ₂ CH ₃
244	3-F-Bz	CH ₂	CH ₂	CH ₂ CH ₂ CH ₃
245	3-F-Bz	CH ₂	CH ₂	isopropyl
246	3-F-Bz	CH ₂	CH ₂	cyclopropyl
247	3-F-Bz	CH ₂	CH ₂	CH ₂ -cyclopropyl
248	3-F-Bz	CH ₂	CH ₂	acetyl
249	3-F-Bz	CH ₂	CH ₂	CO ₂ -t-Bu
250	3-F-Bz	CH ₂	CH ₂	CH ₂ -Ph
251	3-F-Bz	CH ₂	CH ₂ CH ₂	H
252	3-F-Bz	CH ₂	CH ₂ CH ₂	CH ₃
253	3-F-Bz	CH ₂	CH ₂ CH ₂	CH ₂ CH ₃
254	3-F-Bz	CH ₂	CH ₂ CH ₂	CH ₂ CH ₂ CH ₃
255	3-F-Bz	CH ₂	CH ₂ CH ₂	isopropyl
256	3-F-Bz	CH ₂	CH ₂ CH ₂	cyclopropyl
257	3-F-Bz	CH ₂	CH ₂ CH ₂	CH ₂ -cyclopropyl

#	R ¹	A ¹	A ²	R ⁵
258	3-F-Bz	CH ₂	CH ₂ CH ₂	acetyl
259	3-F-Bz	CH ₂	CH ₂ CH ₂	CO ₂ -t-Bu
260	3-F-Bz	CH ₂	CH ₂ CH ₂	CH ₂ -Ph
261	3-F-Bz	-	CH ₂ CH ₂ CH ₂	H
262	3-F-Bz	-	CH ₂ CH ₂ CH ₂	CH ₃
263	3-F-Bz	-	CH ₂ CH ₂ CH ₂	CH ₂ CH ₃
264	3-F-Bz	-	CH ₂ CH ₂ CH ₂	CH ₂ CH ₂ CH ₃
265	3-F-Bz	-	CH ₂ CH ₂ CH ₂	isopropyl
266	3-F-Bz	-	CH ₂ CH ₂ CH ₂	cyclopropyl
267	3-F-Bz	-	CH ₂ CH ₂ CH ₂	CH ₂ -cyclopropyl
268	3-F-Bz	-	CH ₂ CH ₂ CH ₂	acetyl
269	3-F-Bz	-	CH ₂ CH ₂ CH ₂	CO ₂ -t-Bu
270	3-F-Bz	-	CH ₂ CH ₂ CH ₂	CH ₂ -Ph
271	3-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	H
272	3-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	CH ₃
273	3-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ CH ₃
274	3-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ CH ₂ CH ₃
275	3-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	isopropyl
276	3-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	cyclopropyl
277	3-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ -cyclopropyl
278	3-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	acetyl
279	3-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	CO ₂ -t-Bu
280	3-F-Bz	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ -Ph
281	3-F-Bz	CH ₂ CH ₂	CH ₂	H
282	3-F-Bz	CH ₂ CH ₂	CH ₂	CH ₃
283	3-F-Bz	CH ₂ CH ₂	CH ₂	CH ₂ CH ₃
284	3-F-Bz	CH ₂ CH ₂	CH ₂	CH ₂ CH ₂ CH ₃
285	3-F-Bz	CH ₂ CH ₂	CH ₂	isopropyl
286	3-F-Bz	CH ₂ CH ₂	CH ₂	cyclopropyl
287	3-F-Bz	CH ₂ CH ₂	CH ₂	CH ₂ -cyclopropyl
288	3-F-Bz	CH ₂ CH ₂	CH ₂	acetyl

#	R ¹	A ¹	A ²	R ⁵
289	3-F-Bz	CH ₂ CH ₂	CH ₂	CO ₂ -t-Bu
290	3-F-Bz	CH ₂ CH ₂	CH ₂	CH ₂ -Ph
291	3-F-Bz	CH ₂ CH ₂ CH ₂	-	H
292	3-F-Bz	CH ₂ CH ₂ CH ₂	-	CH ₃
293	3-F-Bz	CH ₂ CH ₂ CH ₂	-	CH ₂ CH ₃
294	3-F-Bz	CH ₂ CH ₂ CH ₂	-	CH ₂ CH ₂ CH ₃
295	3-F-Bz	CH ₂ CH ₂ CH ₂	-	isopropyl
296	3-F-Bz	CH ₂ CH ₂ CH ₂	-	cyclopropyl
297	3-F-Bz	CH ₂ CH ₂ CH ₂	-	CH ₂ -cyclopropyl
298	3-F-Bz	CH ₂ CH ₂ CH ₂	-	acetyl
299	3-F-Bz	CH ₂ CH ₂ CH ₂	-	CO ₂ -t-Bu
300	3-F-Bz	CH ₂ CH ₂ CH ₂	-	CH ₂ -Ph
301	CH ₂ -c-Hex	CH ₂	CH ₂	H
302	CH ₂ -c-Hex	CH ₂	CH ₂	CH ₃
303	CH ₂ -c-Hex	CH ₂	CH ₂	CH ₂ CH ₃
304	CH ₂ -c-Hex	CH ₂	CH ₂	CH ₂ CH ₂ CH ₃
305	CH ₂ -c-Hex	CH ₂	CH ₂	isopropyl
306	CH ₂ -c-Hex	CH ₂	CH ₂	cyclopropyl
307	CH ₂ -c-Hex	CH ₂	CH ₂	CH ₂ -cyclopropyl
308	CH ₂ -c-Hex	CH ₂	CH ₂	acetyl
309	CH ₂ -c-Hex	CH ₂	CH ₂	CO ₂ -t-Bu
310	CH ₂ -c-Hex	CH ₂	CH ₂	CH ₂ -Ph
311	CH ₂ -c-Hex	CH ₂	CH ₂ CH ₂	H
312	CH ₂ -c-Hex	CH ₂	CH ₂ CH ₂	CH ₃
313	CH ₂ -c-Hex	CH ₂	CH ₂ CH ₂	CH ₂ CH ₃
314	CH ₂ -c-Hex	CH ₂	CH ₂ CH ₂	CH ₂ CH ₂ CH ₃
315	CH ₂ -c-Hex	CH ₂	CH ₂ CH ₂	isopropyl
316	CH ₂ -c-Hex	CH ₂	CH ₂ CH ₂	cyclopropyl
317	CH ₂ -c-Hex	CH ₂	CH ₂ CH ₂	CH ₂ -cyclopropyl
318	CH ₂ -c-Hex	CH ₂	CH ₂ CH ₂	acetyl
319	CH ₂ -c-Hex	CH ₂	CH ₂ CH ₂	CO ₂ -t-Bu

#	R ¹	A ¹	A ²	R ⁵
320	CH ₂ -c-Hex	CH ₂	CH ₂ CH ₂	CH ₂ -Ph
321	CH ₂ -c-Hex	-	CH ₂ CH ₂ CH ₂	H
322	CH ₂ -c-Hex	-	CH ₂ CH ₂ CH ₂	CH ₃
323	CH ₂ -c-Hex	-	CH ₂ CH ₂ CH ₂	CH ₂ CH ₃
324	CH ₂ -c-Hex	-	CH ₂ CH ₂ CH ₂	CH ₂ CH ₂ CH ₃
325	CH ₂ -c-Hex	-	CH ₂ CH ₂ CH ₂	isopropyl
326	CH ₂ -c-Hex	-	CH ₂ CH ₂ CH ₂	cyclopropyl
327	CH ₂ -c-Hex	-	CH ₂ CH ₂ CH ₂	CH ₂ -cyclopropyl
328	CH ₂ -c-Hex	-	CH ₂ CH ₂ CH ₂	acetyl
329	CH ₂ -c-Hex	-	CH ₂ CH ₂ CH ₂	CO ₂ -t-Bu
330	CH ₂ -c-Hex	-	CH ₂ CH ₂ CH ₂	CH ₂ -Ph
331	CH ₂ -c-Hex	CH ₂ CH ₂	CH ₂ CH ₂	H
332	CH ₂ -c-Hex	CH ₂ CH ₂	CH ₂ CH ₂	CH ₃
333	CH ₂ -c-Hex	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ CH ₃
334	CH ₂ -c-Hex	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ CH ₂ CH ₃
335	CH ₂ -c-Hex	CH ₂ CH ₂	CH ₂ CH ₂	isopropyl
336	CH ₂ -c-Hex	CH ₂ CH ₂	CH ₂ CH ₂	cyclopropyl
337	CH ₂ -c-Hex	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ -cyclopropyl
338	CH ₂ -c-Hex	CH ₂ CH ₂	CH ₂ CH ₂	acetyl
339	CH ₂ -c-Hex	CH ₂ CH ₂	CH ₂ CH ₂	CO ₂ -t-Bu
340	CH ₂ -c-Hex	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ -Ph
341	CH ₂ -c-Hex	CH ₂ CH ₂	CH ₂	H
342	CH ₂ -c-Hex	CH ₂ CH ₂	CH ₂	CH ₃
343	CH ₂ -c-Hex	CH ₂ CH ₂	CH ₂	CH ₂ CH ₃
344	CH ₂ -c-Hex	CH ₂ CH ₂	CH ₂	CH ₂ CH ₂ CH ₃
345	CH ₂ -c-Hex	CH ₂ CH ₂	CH ₂	isopropyl
346	CH ₂ -c-Hex	CH ₂ CH ₂	CH ₂	cyclopropyl
347	CH ₂ -c-Hex	CH ₂ CH ₂	CH ₂	CH ₂ -cyclopropyl
348	CH ₂ -c-Hex	CH ₂ CH ₂	CH ₂	acetyl
349	CH ₂ -c-Hex	CH ₂ CH ₂	CH ₂	CO ₂ -t-Bu
350	CH ₂ -c-Hex	CH ₂ CH ₂	CH ₂	CH ₂ -Ph

#	R ¹	A ¹	A ²	R ⁵
351	CH ₂ -c-Hex	CH ₂ CH ₂ CH ₂	-	H
352	CH ₂ -c-Hex	CH ₂ CH ₂ CH ₂	-	CH ₃
353	CH ₂ -c-Hex	CH ₂ CH ₂ CH ₂	-	CH ₂ CH ₃
354	CH ₂ -c-Hex	CH ₂ CH ₂ CH ₂	-	CH ₂ CH ₂ CH ₃
355	CH ₂ -c-Hex	CH ₂ CH ₂ CH ₂	-	isopropyl
356	CH ₂ -c-Hex	CH ₂ CH ₂ CH ₂	-	cyclopropyl
357	CH ₂ -c-Hex	CH ₂ CH ₂ CH ₂	-	CH ₂ -cyclopropyl
358	CH ₂ -c-Hex	CH ₂ CH ₂ CH ₂	-	acetyl
359	CH ₂ -c-Hex	CH ₂ CH ₂ CH ₂	-	CO ₂ -t-Bu
360	CH ₂ -c-Hex	CH ₂ CH ₂ CH ₂	-	CH ₂ -Ph
361	(CH ₂) ₃ CH ₃	CH ₂	CH ₂	H
362	(CH ₂) ₃ CH ₃	CH ₂	CH ₂	CH ₃
363	(CH ₂) ₃ CH ₃	CH ₂	CH ₂	CH ₂ CH ₃
364	(CH ₂) ₃ CH ₃	CH ₂	CH ₂	CH ₂ CH ₂ CH ₃
365	(CH ₂) ₃ CH ₃	CH ₂	CH ₂	isopropyl
366	(CH ₂) ₃ CH ₃	CH ₂	CH ₂	cyclopropyl
367	(CH ₂) ₃ CH ₃	CH ₂	CH ₂	CH ₂ -cyclopropyl
368	(CH ₂) ₃ CH ₃	CH ₂	CH ₂	acetyl
369	(CH ₂) ₃ CH ₃	CH ₂	CH ₂	CO ₂ -t-Bu
370	(CH ₂) ₃ CH ₃	CH ₂	CH ₂	CH ₂ -Ph
371	(CH ₂) ₃ CH ₃	CH ₂	CH ₂ CH ₂	H
372	(CH ₂) ₃ CH ₃	CH ₂	CH ₂ CH ₂	CH ₃
373	(CH ₂) ₃ CH ₃	CH ₂	CH ₂ CH ₂	CH ₂ CH ₃
374	(CH ₂) ₃ CH ₃	CH ₂	CH ₂ CH ₂	CH ₂ CH ₂ CH ₃
375	(CH ₂) ₃ CH ₃	CH ₂	CH ₂ CH ₂	isopropyl
376	(CH ₂) ₃ CH ₃	CH ₂	CH ₂ CH ₂	cyclopropyl
377	(CH ₂) ₃ CH ₃	CH ₂	CH ₂ CH ₂	CH ₂ -cyclopropyl
378	(CH ₂) ₃ CH ₃	CH ₂	CH ₂ CH ₂	acetyl
379	(CH ₂) ₃ CH ₃	CH ₂	CH ₂ CH ₂	CO ₂ -t-Bu
380	(CH ₂) ₃ CH ₃	CH ₂	CH ₂ CH ₂	CH ₂ -Ph
381	(CH ₂) ₃ CH ₃	-	CH ₂ CH ₂ CH ₂	H

#	R ¹	A ¹	A ²	R ⁵
382	(CH ₂) ₃ CH ₃	-	CH ₂ CH ₂ CH ₂	CH ₃
383	(CH ₂) ₃ CH ₃	-	CH ₂ CH ₂ CH ₂	CH ₂ CH ₃
384	(CH ₂) ₃ CH ₃	-	CH ₂ CH ₂ CH ₂	CH ₂ CH ₂ CH ₃
385	(CH ₂) ₃ CH ₃	-	CH ₂ CH ₂ CH ₂	isopropyl
386	(CH ₂) ₃ CH ₃	-	CH ₂ CH ₂ CH ₂	cyclopropyl
387	(CH ₂) ₃ CH ₃	-	CH ₂ CH ₂ CH ₂	CH ₂ -cyclopropyl
388	(CH ₂) ₃ CH ₃	-	CH ₂ CH ₂ CH ₂	acetyl
389	(CH ₂) ₃ CH ₃	-	CH ₂ CH ₂ CH ₂	CO ₂ -t-Bu
390	(CH ₂) ₃ CH ₃	-	CH ₂ CH ₂ CH ₂	CH ₂ -Ph
391	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	CH ₂ CH ₂	H
392	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	CH ₂ CH ₂	CH ₃
393	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ CH ₃
394	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ CH ₂ CH ₃
395	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	CH ₂ CH ₂	isopropyl
396	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	CH ₂ CH ₂	cyclopropyl
397	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ -cyclopropyl
398	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	CH ₂ CH ₂	acetyl
399	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	CH ₂ CH ₂	CO ₂ -t-Bu
400	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	CH ₂ CH ₂	CH ₂ -Ph
401	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	CH ₂	H
402	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	CH ₂	CH ₃
403	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	CH ₂	CH ₂ CH ₃
404	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	CH ₂	CH ₂ CH ₂ CH ₃
405	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	CH ₂	isopropyl
406	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	CH ₂	cyclopropyl
407	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	CH ₂	CH ₂ -cyclopropyl
408	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	CH ₂	acetyl
409	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	CH ₂	CO ₂ -t-Bu
410	(CH ₂) ₃ CH ₃	CH ₂ CH ₂	CH ₂	CH ₂ -Ph
411	(CH ₂) ₃ CH ₃	CH ₂ CH ₂ CH ₂	-	H
412	(CH ₂) ₃ CH ₃	CH ₂ CH ₂ CH ₂	-	CH ₃

#	R ¹	A ¹	A ²	R ⁵
413	(CH ₂) ₃ CH ₃	CH ₂ CH ₂ CH ₂	-	CH ₂ CH ₃
414	(CH ₂) ₃ CH ₃	CH ₂ CH ₂ CH ₂	-	CH ₂ CH ₂ CH ₃
415	(CH ₂) ₃ CH ₃	CH ₂ CH ₂ CH ₂	-	isopropyl
416	(CH ₂) ₃ CH ₃	CH ₂ CH ₂ CH ₂	-	cyclopropyl
417	(CH ₂) ₃ CH ₃	CH ₂ CH ₂ CH ₂	-	CH ₂ -cyclopropyl
418	(CH ₂) ₃ CH ₃	CH ₂ CH ₂ CH ₂	-	acetyl
419	(CH ₂) ₃ CH ₃	CH ₂ CH ₂ CH ₂	-	CO ₂ -t-Bu
420	(CH ₂) ₃ CH ₃	CH ₂ CH ₂ CH ₂	-	CH ₂ -Ph

-: single bond

Ph: Phenyl

t-Bu: tert. Butyl

4-F-Bz: 4-Fluorobenzyl

5 4-Cl-Bz: 4-Chlorobenzyl

3-F-Bz: 3-Fluorobenzyl

2-F-Bz: 2-Fluorobenzyl

c-Hex: Cyclohexyl

10 The invention in particular relates to the compounds of formula I which are selected from the group consisting of:

N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(morpholinomethyl)-1H-pyrazol-1-yl)nicotinamide;

15 N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((2,6-dimethylmorpholino)methyl)-1H-pyrazol-1-yl)nicotinamide;

N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((cis-2,6-dimethylmorpholino)methyl)-1H-pyrazol-1-yl)nicotinamide;

N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((trans-2,6-dimethylmorpholino)methyl)-1H-pyrazol-1-yl)nicotinamide;

20 N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((4,4-difluoropiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide;

N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(5-benzyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-2-yl)nicotinamide;

N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((4-phenylpiperidin-1-yl)methyl)-1H-

- pyrazol-1-yl)nicotinamide;
2-(3-((2H-benzo[b][1,4]oxazin-4(3H)-yl)methyl)-1H-pyrazol-1-yl)-N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)nicotinamide;
N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(piperidin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide;
5 2-(3-((2H-benzo[b][1,4]oxazin-4(3H,4aH,5H,6H,7H,8H,8aH)-yl)methyl)-1H-pyrazol-1-yl)-N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)nicotinamide;
2-(3-((2H-benzo[b][1,4]oxazin-4(3H,4aHS,5H,6H,7H,8H,8aHS)-yl)methyl)-1H-pyrazol-1-yl)-N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)nicotinamide;
10 2-(3-((2H-benzo[b][1,4]oxazin-4(3H,4aHS,5H,6H,7H,8H,8aHR)-yl)methyl)-1H-pyrazol-1-yl)-N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)nicotinamide;
N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((2-phenylmorpholino)methyl)-1H-pyrazol-1-yl)nicotinamide;
N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(pyrrolidin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide;
15 N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(azetidin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide;
N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((4-(trifluoromethyl)piperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide;
20 N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-{3-[(5,5-difluorohexahydrocyclopenta[c]pyrrol-2(1H)-yl)methyl]-1H-pyrazol-1-yl}nicotinamide;
N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((dihydro-1H-furo[3,4-c]pyrrol-5(3H,6H,6aH)-yl)methyl)-1H-pyrazol-1-yl)nicotinamide;
N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(indolin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide;
25 N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((methyl(phenyl)amino)methyl)-1H-pyrazol-1-yl)nicotinamide;
N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-[3-(2-oxa-7-azaspiro[3.5]non-7-ylmethyl)-1H-pyrazol-1-yl]nicotinamide;
30 N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-{3-[(diethylamino)methyl]-1H-pyrazol-1-yl}nicotinamide;
N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(isoindolin-2-ylmethyl)-1H-pyrazol-1-yl)nicotinamide;

- N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-(3-{[cyclohexyl(methyl)amino]methyl}-1H-pyrazol-1-yl)nicotinamide;
- N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-(3-{[benzyl(methyl)amino]methyl}-1H-pyrazol-1-yl)nicotinamide;
- 5 N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-[3-(3,4-dihydro-2(1H)-isoquinolinylmethyl)-1H-pyrazol-1-yl]nicotinamide;
- N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((4-tert-butylpiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide;
- N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((4-methylpiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide;
- 10 N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((methyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)methyl)-1H-pyrazol-1-yl)nicotinamide;
- N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((cyclopropyl(methyl)amino)methyl)-1H-pyrazol-1-yl)nicotinamide;
- 15 N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-(3-{[(6R)-6-(4-fluorophenyl)-3-azabicyclo[3.2.0]hept-3-yl]methyl}-1H-pyrazol-1-yl)nicotinamide;
- N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((phenylamino)methyl)-1H-pyrazol-1-yl)nicotinamide;
- N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-{3-[(3-phenyl-1-pyrrolidinyl)methyl]-1H-pyrazol-1-yl}nicotinamide;
- 20 N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-(3-{[5-(trifluoromethyl)-1,3-dihydro-2H-isoindol-2-yl]methyl}-1H-pyrazol-1-yl)nicotinamide;
- N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-{3-[(5-fluoro-1,3-dihydro-2H-isoindol-2-yl)methyl]-1H-pyrazol-1-yl}nicotinamide;
- 25 N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-{3-[(4-phenyl-1-piperazinyl)methyl]-1H-pyrazol-1-yl}nicotinamide;
- N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-{3-[(4-fluoro-1,3-dihydro-2H-isoindol-2-yl)methyl]-1H-pyrazol-1-yl}nicotinamide;
- N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-{3-[(1,1-dioxido-4-thiomorpholinyl)methyl]-1H-pyrazol-1-yl}nicotinamide;
- 30 N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-{3-[1-(1,3-dihydro-2H-isoindol-2-yl)ethyl]-1H-pyrazol-1-yl}nicotinamide;
- N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-{3-[(1-oxo-1,3-dihydro-2H-isoindol-2-

- yl)methyl]-1H-pyrazol-1-yl} nicotinamide;
N-(1-amino-1,2-dioxo-3-heptanyl)-2-[3-(1-piperidinylmethyl)-1Hpyrazol-1-yl]nicotinamide;
N-(1-amino-1,2-dioxo-3-heptanyl)-2-{3-[(4,4-difluoro-1-piperidinyl)methyl]-1H-
5 pyrazol-1-yl} nicotinamide;
N-(1-amino-1,2-dioxo-3-heptanyl)-2-[3-(1,3-dihydro-2H-isoindol-2-ylmethyl)-1H-pyrazol-1-yl]nicotinamide;
N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-(5-benzyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-2-yl)nicotinamide;
10 N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-[5-(cyclopropylmethyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-2-yl]nicotinamide;
N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-(4,5,6,7-tetrahydro-2Hpyrazolo[4,3-c]pyridin-2-yl)nicotinamide;
tert-butyl 2-(3-(4-amino-3,4-dioxo-1-phenylbutan-2-ylcarbamoyl)pyridin-2-yl)-4,6-
15 dihydropyrrolo[3,4-c]pyrazole-5(2H)-carboxylate;
N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-(5,6-dihydropyrrolo[3,4-c]pyrazol-2(4H)-yl)nicotinamide;
tert-butyl 2-(3-(4-amino-3,4-dioxo-1-phenylbutan-2-ylcarbamoyl)pyridin-2-yl)-2,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridine-6-carboxylate;
20 N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-(4,5,6,7-tetrahydro-pyrazolo[3,4-c]pyridin-2-yl)nicotinamide;
tert-butyl 2-(3-(4-amino-3,4-dioxo-1-phenylbutan-2-ylcarbamoyl)pyridin-2-yl)-2,5,6,7-tetrahydro-4H-pyrazolo[4,3-b]pyridine-4-carboxylate;
N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-(4,5,6,7-tetrahydro-pyrazolo[4,3-
25 b]pyridin-2-yl)nicotinamide;
N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-(4-benzyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-b]pyridin-2-yl)nicotinamide;
N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-[3-(1-methyl-4-piperidinyl)-1H-pyrazol-1-yl]nicotinamide;
30 N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-(6-ethyl-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridin-2-yl)nicotinamide;

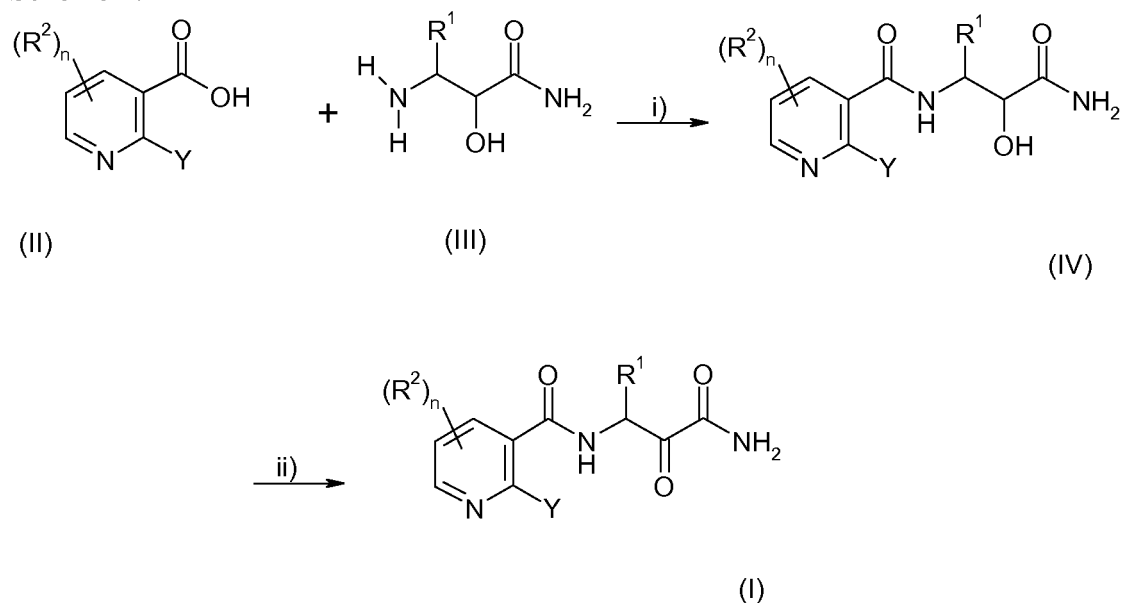
the tautomers thereof, the hydrates thereof, the prodrugs thereof and the

pharmaceutically suitable salts thereof.

The compounds of the invention of the general formula I and the starting materials used to prepare them can be prepared in analogy to known processes of organic chemistry as are described in standard works of organic chemistry, e.g. Houben-Weyl, "Methoden der Organischen Chemie", Thieme-Verlag, Stuttgart, Jerry March "Advanced Organic Chemistry", 5th edition, Wiley & Sons and the literature cited therein, and R. Larock, "Comprehensive Organic Transformations", 2nd edition, Weinheim, 1999 and the literature cited therein. The carboxamide compounds of the invention of the general formula I are advantageously prepared by the methods described below and/or in the experimental section.

The compounds of the formula I can be prepared in analogy to the schemes and methods described in WO 99/54305, pp. 6-10 and in WO 2008/080969, pp. 65-70. An important access to compounds of the formula I is depicted in scheme 1.

Scheme 1:



In scheme 1, R^1 , R^2 , Y and n exhibit the aforementioned meanings.

20

In a first step i), a carboxylic acid II is converted by reaction with an amino hydroxy amide III into a corresponding hydroxy diamide IV. In this connection, conventional peptide coupling methods are ordinarily used, as are described for example in R.

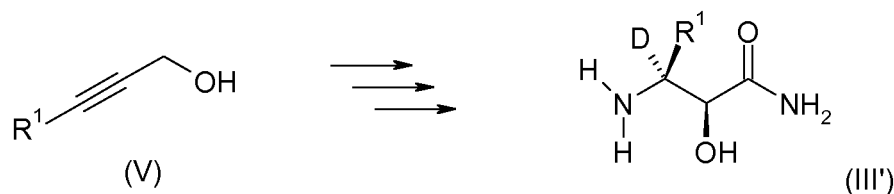
C. Larock, Comprehensive Organic Transformations, VCH Publisher, 1989, pages 972-976, or in Houben-Weyl, Methoden der organischen Chemie, 4th edition, E5, Chap. V. It may be advantageous firstly to activate the carboxylic acid II. For this purpose, for example, the carboxylic acid II is reacted with a coupling agent, e.g. a carbodiimide such as dicyclohexylcarbodiimide (DCC), CDI (carbonyldiimidazole), carbonyldipyrzole, DCI (diisopropylcarbodiimide) or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), preferably in the presence of hydroxybenzotriazole (HOBt), nitrophenol, pentafluorophenol, 2,4,5-trichlorophenol or N-hydroxysuccinimide, to obtain an activated ester IIa. It may further be advantageous to prepare the activated ester IIa in the presence of a base, for example a tertiary amine. Further suitable coupling agents for step I are those mentioned for step iii) in Scheme 3 below, such as benzotriazole derivatives, pyridinotriazole derivatives and phosphonium activators. The activated ester IIa is subsequently reacted with the amino hydroxy amide of the formula III or its hydrohalide salt to give the hydroxy diamide IV. The reaction normally takes place in anhydrous inert solvents such as chlorinated hydrocarbons, e.g. dichloromethane or dichloroethane, ethers, e.g. tetrahydrofuran or 1,4-dioxane, or carboxamides, e.g. N,N-dimethylformamide, N,N-dimethylacetamide or N-methylpyrrolidone. Step i) is ordinarily carried out at temperatures in the range from -20°C to +25°C.

Subsequently, in a second step ii), the hydroxy diamide compound IV is oxidized to the carboxamide compound I' of the invention. Various conventional oxidation reactions are suitable for this (see R. C. Larock, Comprehensive Organic Transformations, VCH Publisher, 1989, page 604 et seq.) such as, for example, Swern oxidation and Swern analogous oxidations (T.T. Tidwell, Synthesis **1990**, pp. 857-870) or Pfitzner-Moffatt oxidation. Suitable oxidizing agents are dimethyl sulfoxide (DMSO) in combination with dicyclohexylcarbodiimide or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, dimethyl sulfoxide in combination with the pyridine-SO₃ complex or dimethyl sulfoxide in combination with oxalyl chloride, sodium hypochloride/TEMPO (S. L. Harbenson et al., J. Med. Chem. **1994**, 37, 2918-2929) or hypervalent iodine compounds (periodinane), such as 2-iodoxybenzoic acid (IBX) (J. Org. Chem. **1995**, 60, 7272) or the Dess-Martin periodinane (J. Org. Chem. **1983**, 48, 4155). Depending on the oxidizing agent used, the oxidation of the hydroxy amide compound IV takes place at

temperatures of from -50 to +35°C.

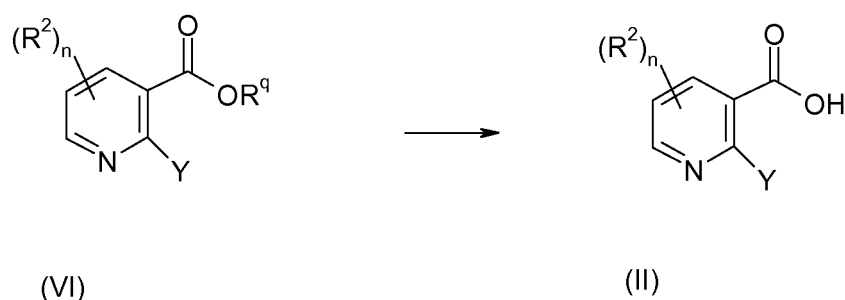
The amino hydroxy amides III can be obtained by purchase or can be prepared by processes disclosed in the literature, e.g. the compounds III are accessible via the
5 synthesis described in S. L. Harbenson et al., J. Med. Chem. **1994**, 37, 2918-2929 or J. P. Burkhardt et al., Tetrahedron Lett. **1988**, 29, 3433-3436.

The 3-(S)-diastereomers III' of the propanamide derivatives III which are deuterated in the 3-position, can be synthesized starting from alkinol X in analogy to a 9-step process
10 described by F. Maltais et al., J. Med. Chem. **2009**, 52 (24), 7993-8001 (DOI 10.1021/jm901023f), as shown below. According to this process chiral resolution of the intermediately obtained racemic mixture is achieved via amidation with deoxycholic acid. By employing compounds III' in the respective synthetic routes of scheme 1, compounds I which are S-configured at the carbon atom carrying the radical R¹ are
15 accessible.



The carboxylic acid II can be prepared by hydrolyzing the corresponding carboxylic
20 ester VI with acids or bases under generally customary conditions (see scheme 2). The hydrolysis preferably takes place with bases such as alkali metal or alkaline earth metal hydroxides, for example lithium hydroxide, sodium hydroxide or potassium hydroxide in aqueous medium, such as a mixture of water and organic solvents, e.g. alcohols such as methanol or ethanol, ethers such as tetrahydrofuran or dioxane, at room temperature
25 or elevated temperature such as 25-100°C.

Scheme 2:

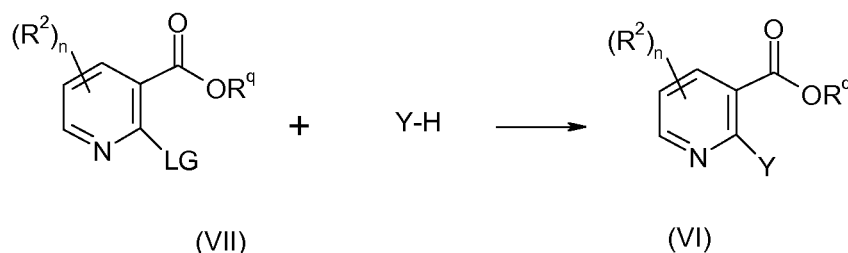


In formulae II and VI, R^2 , Y and n have the aforementioned meanings. In formula VI, R^g is alkyl, preferably C_1 - C_6 -alkyl.

5

The carboxylic ester of the formula VI can advantageously be obtained by reacting the carboxylic ester of the general formula VII with a Y-H, see scheme 3.

Scheme 3:



10

In scheme 3, LG represents a nucleophilically displaceable leaving group. Examples of suitable nucleophilically displaceable leaving groups are halogen, e.g. chlorine or bromine, or sulfonates like mesylate or tosylate. R^g is alkyl, preferably C_1 - C_6 -alkyl. R^2 , Y and n have the aforementioned meanings.

15

As shown in scheme 3, an ester VII is reacted with an appropriate pyrazole compound of the formula Y-H, where Y is as defined above and where Y is in particular a radical Y2, where the hydrogen atom of Y-H is located on the pyrazole nitrogen. The reaction is ordinarily carried out under conventional conditions in the presence of a base in an inert solvent at elevated temperature. It may be advantageous, where appropriate, to carry out the reaction in the presence of catalytically active amounts of a transition metal, in particular of a metal of group 10 or 11 in the periodic table.

The reaction is preferably carried out at elevated temperature without diluent or in an inert solvent such as an ether, e.g. tetrahydrofuran or dioxane, carboxamides such as

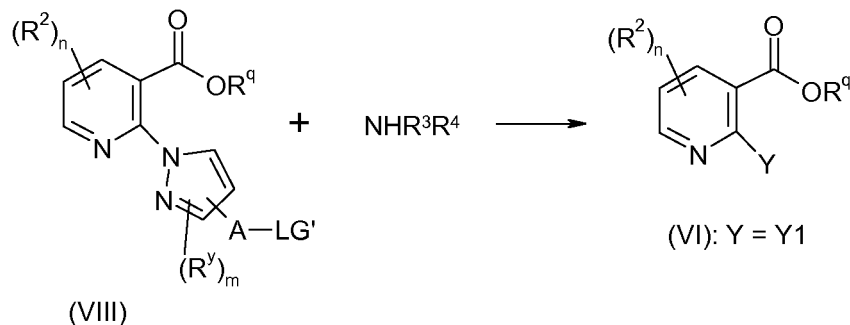
25

N,N-dimethylformamide, N,N-dimethylacetamide or N-methylpyrrolidone, or an aromatic hydrocarbon such as benzene, toluene or o-, m- or p-xylene. The reaction takes place in the presence of inorganic or organic bases and of a crown ether. Suitable inorganic bases are alkali metal or alkaline earth metal amides such as sodium amide, alkali metal or alkaline earth metal carbonates such as potassium carbonate or cesium carbonate or alkali metal hydrides such as sodium hydride. Suitable organic bases are tertiary amines, such as, for example, trimethylamine or triethylamine. A suitable crown ether is 18-crown-6. A Cu(I) salt such as, for example, CuI, CuCN, Cu₂O is added, where appropriate, as catalyst (see, for example, US 4,826,835 and WO 88/00468).

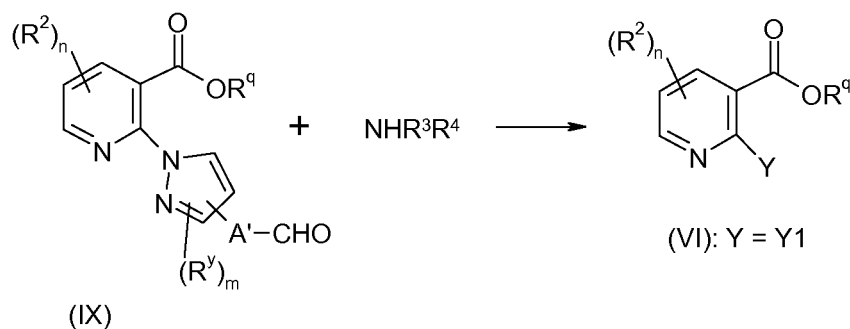
The nicotinic acid ester derivatives VII and the pyrazole compounds can be purchased or can be prepared by conventional methods.

The nicotinic acid ester derivatives VI, where Y is a radical Y-1, may also be prepared from nicotinic acid ester derivatives of the formula VIII or IX (see schemes 4a and 4b):

Scheme 5a:



20 Scheme 5b:



In Schemes 5a and 5b, A, R², R³, R⁴, R^q, R^y, m and n are as defined above. A' is

(CH₂)_{p-1} with p being 1, 2, 3 or 4, where one or two hydrogen atoms may be replaced by a radical R⁶, where A is attached to the 3- or 4-position of the pyrazole radical and where R⁶ is as defined above and in particular hydrogen. LG' represents a nucleophilically displaceable leaving group. Examples of suitable nucleophilically displaceable leaving groups are halogen, e.g. chlorine or bromine, or sulfonates like mesylate or tosylate.

10

The reaction depicted in scheme 5a can be performed by conventional nucleophilic substitution reactions as described e.g. in R. Larock, "Comprehensive Organic Transformations", 2nd edition, Weinheim, 1999, pp. 397-400.

The reaction depicted in scheme 5b can be performed by conventional reductive amination reactions as described e.g. in R. Larock, "Comprehensive Organic Transformations", 2nd edition, Weinheim, 1999, pp.421-425.

15 The reaction mixtures are worked up in a conventional way, e.g. by mixing with water, separating the phases and, where appropriate, purifying the crude products by chromatography. The intermediates and final products in some cases result in the form of colorless or pale brownish, viscous oils which are freed of volatiles or purified under reduced pressure and at moderately elevated temperature. If the intermediates and final products are obtained as solids, the purification can also take place by recrystallization or digestion.

25

If individual compounds I are not obtainable by the routes described above, they can be prepared by derivatization of other compounds I.

30

The compounds of the invention exhibit extremely low K_i values in relation to the inhibition of calpain and thus permit efficient inhibition of calpain, especially calpain I, at low serum levels. The compounds of the invention ordinarily exhibit K_i values in relation to the inhibition of calpain in vitro of < 1500 nM, preferably < 800 nM, in particular < 400 nM and specifically ≤ 250 nM. The compounds of the invention are therefore particularly suitable for the treatment of disorders associated with an elevated calpain activity.

In addition, the compounds of the invention are selective calpain inhibitors, i.e. the inhibition of other cysteine proteases such as cathepsin B, cathepsin K, cathepsin L or cathepsin S takes place only at concentrations which are distinctly higher than the concentrations necessary for inhibition of calpain. Accordingly, the compounds of the invention ought to show distinctly fewer side effects than the prior art compounds which are comparatively unselective in relation to inhibition of calpain and likewise inhibit other cysteine proteases.

Compounds preferred according to the invention accordingly have a selectivity in relation to inhibition of cathepsin B, expressed in the form of the ratio of the K_i for inhibition of cathepsin B to the K_i for inhibition of calpain of ≥ 5 , in particular ≥ 9 and specifically ≥ 30 .

Compounds preferred according to the invention accordingly have a selectivity in relation to inhibition of cathepsin K, expressed in the form of the ratio of the K_i for inhibition of cathepsin K to the K_i for inhibition of calpain of ≥ 5 , in particular ≥ 9 and specifically ≥ 30 .

Compounds preferred according to the invention accordingly have a selectivity in relation to inhibition of cathepsin L, expressed in the form of the ratio of the K_i for inhibition of cathepsin L to the K_i for inhibition of calpain of ≥ 5 , in particular ≥ 10 and specifically ≥ 50 .

Compounds preferred according to the invention accordingly have a selectivity in relation to inhibition of cathepsin S, expressed in the form of the ratio of the K_i for inhibition of cathepsin S to the K_i for inhibition of calpain of ≥ 5 , in particular ≥ 10 and specifically ≥ 50 .

In addition, the compounds of the present invention feature an improved stability in the cytosole of human cells, which markedly contributes to their good overall metabolic stability. The cytosolic stability can be measured for example by incubating a solution of a compound of the invention with liver cytosole from particular species (for example rat, dog, monkey or human) and determining the half-life of the compound under these

conditions. It is possible to conclude from larger half-lives that the metabolic stability of the compound is improved. The stability in the presence of human liver cytosole is of particular interest because it makes it possible to predict the metabolic degradation of the compound in the human liver. Compounds with enhanced cytosolic stability
5 therefore are likely to be degraded at reduced rates in the liver. Slower metabolic degradation in the liver in turn can lead to higher and/or longer-lasting concentrations (effective levels) of the compound in the body, so that the elimination half-life of the compounds of the invention is increased. Increased and/or longer-lasting effective levels may lead to a better efficacy of the compound in the treatment or prophylaxis of various
10 calpain-dependent diseases. An improved metabolic stability may additionally lead to an increased bioavailability after oral administration, because the compound is subjected, after being absorbed in the intestine, to less metabolic degradation in the liver (termed the first pass effect). An increased oral bioavailability may, because the concentration (effective level) of the compound is increased, lead to a better efficacy of
15 the compound after oral administration.

Accordingly, due to their improved cytosolic stability the compounds of the invention remain in the cytosol for extended periods, i.e. have a decreased cytosolic clearance, and therefore ought to show enhanced human pharmacokinetics.
20

Compounds preferred according to the invention accordingly have a cytosolic clearance in human liver cytosol of $\leq 30 \mu\text{l}/\text{min}/\text{mg}$, in particular of $\leq 15 \mu\text{l}/\text{min}/\text{mg}$.

The improved cytosolic stability of the compounds according to the present invention is
25 probably primarily due to their reduced susceptibility to aldo-keto reductases (AKRs) which mediate the metabolic degradation of compounds having a carbonyl group in the liver cytosole of humans and monkeys. Thus, the AKR-catalyzed reduction of the ketoamides of formula I should be less pronounced than that of less stable ketoamides. Hence, the ratio of the concentration of the parent compound, i.e. the ketamide of
30 formula I, to the concentration of the metabolite, i.e. the hydroxyamide stemming from the ketoamide, is a measure for the stability of the compounds of the invention.

Compounds preferred according to the invention accordingly have, after an incubation

in human hepatocytes for 4 hours, a concentration ratio of the hydroxyamide metabolite to their corresponding parent compound of formula I of ≤ 5 , in particular ≤ 2 and specifically ≤ 0.5 .

- 5 Owing to their inhibitory effect on calpain, their selectivity for calpain in comparison with other cysteine proteases and their cytosolic stability the compounds of the present invention, including their tautomers, their hydrates and their pharmaceutically suitable salts are particularly suitable for the treatment of a disorder or of a condition which is associated with an elevated calpain activity as are described for example in the prior art
10 cited at the outset.

- Disorders associated with an elevated calpain activity are in particular neurodegenerative disorders, especially those neurodegenerative disorders occurring as a result of a chronic brain supply deficit, of an ischemia (stroke) or of a trauma such as
15 brain trauma, and the neurodegenerative disorders Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and Huntington's disease, also multiple sclerosis and the damage to the nervous system associated therewith, especially damage to the optic nerve (optic neuritis) and the nerves which control the movement of the eye. Accordingly, preferred embodiments of the invention relate to the treatment of
20 neurodegenerative disorders, especially of the aforementioned neurodegenerative disorders in humans, and to the use of the compounds of the invention of the formula I, their tautomers and their pharmaceutically suitable salts for the manufacture of a medicament for the treatment of these disorders.

- 25 Disorders associated with an elevated calpain activity also include epilepsy. Accordingly, preferred embodiments of the invention relate to the treatment of epilepsy in humans, and to the use of the compounds of the invention for the manufacture of a medicament for the treatment of epilepsy.

- 30 The disorders or conditions associated with an elevated calpain activity also include pain and painful conditions. Accordingly, preferred embodiments of the invention relate to the treatment of pain and painful conditions in mammals, especially in humans, and to the use of the compounds of the invention for the manufacture of a medicament for

the treatment of pain and painful conditions.

The disorders or conditions associated with an elevated calpain activity also include damage to the heart following cardiac ischemias, damage to the kidneys following renal
5 ischemias, skeletal muscle damage, muscular dystrophies, damage arising through proliferation of smooth muscle cells, coronary vasospasms, cerebral vasospasms, macular degeneration, cataracts of the eyes, or restenosis of blood vessels following angioplasty. Accordingly, preferred embodiments of the invention relate to the treatment of diseases or conditions associated with damage to the heart following
10 cardiac ischemias, damage to the kidneys following renal ischemias, skeletal muscle damage, muscular dystrophies, damage arising through proliferation of smooth muscle cells, coronary vasospasms, cerebral vasospasms, macular degeneration, cataracts of the eyes, or restenosis of blood vessels following angioplasty in mammals, especially in humans, and to the use of the compounds of the invention for the manufacture of a
15 medicament for the treatment of these disorders.

It has further emerged that inhibition of calpain brings about cytotoxic effects on tumor cells. Accordingly, the compounds of the invention are suitable for the chemotherapy of tumors and metastasis thereof. Preferred embodiments of the invention therefore relate
20 to the use of the compounds of the invention in the therapy of tumors and metastases, and to their use for the manufacture of a medicament for the therapy of tumors and metastases.

It has further been found that various impairments associated with an HIV disorder, especially nerve damage (HIV-induced neurotoxicity), are mediated by calpain and therefore inhibition of calpain allows such impairments to be treated or alleviated.
25 Accordingly, the compounds of the invention are suitable for the treatment of HIV patients. Preferred embodiments of the invention therefore relate to the use of the compounds of the invention for the treatment of HIV-infected patients, especially the
30 treatment of those impairments caused by an HIV-induced neurotoxicity, and to their use for the manufacture of a medicament for the treatment of HIV patients.

It has further been found that the release of interleukin-I, TNF or beta-amyloid peptides

(A β or A β -peptides) can be reduced or completely inhibited by calpain inhibitors.

Accordingly, impairments or disorders associated with an elevated interleukin-I, TNF or A β level can be treated by using the compounds of the invention of the formula I, their tautomers and their pharmaceutically suitable salts. Preferred embodiments of the invention therefore relate to the use of the compounds of the invention for the treatment of impairments or disorders associated with an elevated interleukin-I, TNF or A β level such as rheumatism, rheumatoid arthritis and to their use for the manufacture of a medicament for the treatment of such impairments or disorders.

It has further emerged that inhibition of calpain is suitable for the treatment of protozoan infection (protist infection) like malaria or toxoplasmosis (Li et al., *Mol Biochem Parasitol.* 2007; 155(1): 26–32; Jung et al. *Archives of Pharmacal Research* (2009), 32(6), 899-906). Hence, the compounds of the present invention are particularly suitable for treating protozoan infections like malaria or toxoplasmosis and to their use for the manufacture of a medicament for the treatment of such impairments or disorders.

Besides their improved cytosolic stability the compounds of the present invention are also distinguished by a good stability against degradation in liver microsomes. The microsomal stability of a compound can be measured for example by incubating a solution of this compound with liver microsomes from particular species (for example rat, dog or human) and determining the half-life of the compound under these conditions (RS Obach, *Curr Opin Drug Discov Devel.* **2001**, 4, 36-44). Their good microsomal stability contributes to the enhanced overall metabolic stability of the compounds of the invention.

The compounds of the present invention are further distinguished by exhibiting an improved pharmacological activity, compared with the carboxamide compounds disclosed in the prior art, in patients or relevant animal models allowing prognostic statements for use in treatment.

The present invention also relates to pharmaceutical compositions (i.e. medicaments) which comprise at least one compound of the present invention and, where appropriate,

one or more suitable drug carriers.

These drug carriers are chosen according to the pharmaceutical form and the desired mode of administration.

5

The compounds of the present invention can be used to manufacture pharmaceutical compositions for oral, sublingual, subcutaneous, intramuscular, intravenous, topical, intratracheal, intranasal, transdermal or rectal administration, and be administered to animals or humans in unit dose forms, mixed with conventional pharmaceutical carriers, for the prophylaxis or treatment of the above impairments or diseases.

10

Suitable unit dose forms include forms for oral administration, such as tablets, gelatin capsules, powders, granules and solutions or suspensions for oral intake, forms for sublingual, buccal, intratracheal or intranasal administration, aerosols, implants, forms of subcutaneous, intramuscular or intravenous administration and forms of rectal administration.

15

The compounds of the invention can be used in creams, ointments or lotions for topical administration.

20

In order to achieve the desired prophylactic or therapeutic effect, the dose of the active basic ingredient may vary between 0.01 and 50 mg per kg of body weight and per day.

25

Each unit dose may comprise from 0.05 to 5000 mg, preferably 1 to 1000 mg, of the active ingredient in combination with a pharmaceutical carrier. This unit dose can be administered 1 to 5 times a day, so that a daily dose of from 0.5 to 25000 mg, preferably 1 to 5000 mg, is administered.

30

If a solid composition is prepared in the form of tablets, the main ingredient is mixed with a pharmaceutical carrier such as gelatin, starch, lactose, magnesium stearate, talc, silicon dioxide or the like.

The tablets may be coated with sucrose, a cellulose derivative or another suitable

substance or be treated otherwise in order to display a prolonged or delayed activity and in order to release a predetermined amount of the active basic ingredient continuously.

5 A preparation in the form of gelatin capsules is obtained by mixing the active ingredient with an extender and taking up the resulting mixture in soft or hard gelatin capsules.

10 A preparation in the form of a syrup or elixir or for administration in the form of drops may comprise active ingredients together with a sweetener, which is preferably calorie-free, methylparaben or propylparaben as antiseptics, a flavoring and a suitable coloring.

The water-dispersible powders or granules may comprise the active ingredients mixed with dispersants, wetting agents or suspending agents such as polyvinylpyrrolidones, and sweeteners or taste improvers.

15 Rectal administration is achieved by the use of suppositories which are prepared with binders which melt at the rectal temperature, for example cocobutter or polyethylene glycols. Parenteral administration is effected by using aqueous suspensions, isotonic salt solutions or sterile and injectable solutions which comprise pharmacologically suitable dispersants and/or wetting agents, for example propylene glycol or polyethylene glycol.

20 The active basic ingredient may also be formulated as microcapsules or liposomes/centrosomes, if suitable with one or more carriers or additives.

25 In addition to the compounds of the general formula I, their tautomers, their hydrates or their pharmaceutically suitable salts, the compositions of the invention may comprise further active basic ingredients which may be beneficial for the treatment of the impairments or diseases indicated above.

30 The present invention thus further relates to pharmaceutical compositions in which a plurality of active basic ingredients are present together, where at least one thereof is a compound of the invention.

The following examples illustrate the invention without restricting it. Depending on the

management of the reaction and working up, the compounds of the invention are present as mixtures of compounds of the formula I and of the corresponding hydrates of the formula I-H. Conversion into the pure carbonyl compounds generally takes place by treating the substances with HCl in an inert solvent.

5

Abbreviations: EDC for N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride; DMSO for dimethyl sulfoxide; MTB for methyl tert.butyl ether; TFA for trifluoroacetic acid.

10 I. Preparation examples

The intermediates used were either commercially available or prepared according to the procedures described in WO 2008/080969, WO 2011/076811 and WO 2011/076812.

15 Example A: Ethyl 2-(3-formyl-1H-pyrazol-1-yl)nicotinate

To ethyl 2-chloronicotinate (8 g, 43.1 mmol) and 1H-pyrazole-3-carbaldehyde (4.6 g, 47.9 mmol) in N,N-dimethylformamide (80 mL) K₂CO₃ (12 g, 87 mmol), 18-CROWN-6 (0.5 g, 1.892 mmol) and KI (0.4 g, 2.410 mmol) were added, the mixture heated to 120°C for 1hr and then stirred overnight at room temperature.

20 The mixture then was concentrated, 250 mL of dichloromethane added, washed subsequently with water and brine, dried (MgSO₄), filtered and concentrated to give 11.2 g of a yellow oil. Purification by chromatography over silica gel (eluent CH₂Cl₂ +0-6% methanol) and evaporation of the combined product fractions gave 8.3 g of the title compound as amorphous solid.

25 ESI-MS [M+H]⁺: 246.1. ¹H-NMR (400 MHz, DMSO), δ [ppm]: 9.96 (s), 8.77 (m, 1H), 8.67 (m, 1H), 8.26 (m, 1H), 7.67 (m, 1H), 7.06 (d, 1H), 4.25 (q, 2H), 1.12 (t, 3H).

Example B: Ethyl 2-(3-(hydroxymethyl)-1H-pyrazol-1-yl)nicotinate

To ethyl 2-(3-formyl-1H-pyrazol-1-yl)nicotinate (6 g, 9.79 mmol) in ethanol (100 mL) at 10°C NaBH₄ (0.741 g, 19.57 mmol) was added and stirred at 25°C for 1hr. For work
30 up the mixture was poured into 200 mL of ice water, extracted twice with ethyl acetate, the combined organic layers subsequently washed with water and brine, dried (MgSO₄), filtered and concentrated to give 7.2 g of a yellow oil. Purification by chromatography

over silica gel (eluent CH_2Cl_2 + 0-10% methanol) gave 2.36 g of the corresponding title compound as clear oil; ESI-MS $[\text{M}+\text{H}]^+$: 248.1.

Example C: Ethyl 2-(3-(chloromethyl)-1H-pyrazol-1-yl)nicotinate

- 5 To a solution of ethyl 2-(3-(hydroxymethyl)-1H-pyrazol-1-yl)nicotinate (3.76 g, 13.69 mmol) in dichloromethane (100 mL) thionyl chloride (1.1 mL, 15.07 mmol) was added dropwise under stirring. After the reaction was completed, the mixture was concentrated and purified by chromatography over silica gel (eluent CH_2Cl_2 +0-5% methanol) to give 3.7 g of the title compound as clear oil; ESI-MS $[\text{M}+\text{H}]^+$: 266.1. ^1H -NMR (400 MHz, DMSO), δ [ppm]: 8.64 (dd, 1H), 8.49 (d, 1H), 8.13 (dd, 1H), 7.53 (dd, 1H), 6.65 (d, 10 2H), 4.23 (q, 2H), 1.17 (t, 3H).

1.2. Preparation of compounds of the general formula I

- 15 EXAMPLE 1: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(morpholinomethyl)-1H-pyrazol-1-yl)nicotinamide

1.1 Ethyl 2-(3-(morpholinomethyl)-1H-pyrazol-1-yl)nicotinate

- To a solution of ethyl 2-(3-formyl-1H-pyrazol-1-yl)nicotinate (400 mg, 1.631 mmol) and morpholine (220 μL , 2.53 mmol) in acetonitrile (25 mL) NaCNBH_4 (130mg, 2.069 20 mmol) was added, and the pH adjusted to 5-6 by adding glacial acetic acid (110 μL , 1.922 mmol). The mixture was stirred at room temperature for 1 h, another portion of NaCNBH_4 (30 mg, 0.477 mmol) added and stirred for 2 hrs. For work up the mixture was concentrated, dissolved in 100 mL of dichloromethane, washed subsequently with 25 water and brine, dried (MgSO_4), filtered off and concentrated to give 710 mg of the crude title product. Purification by chromatography over silica gel (CH_2Cl_2 /3%-5% methanol) and concentration yielded 518 mg of the title compound as clear oil; ESI-MS $[\text{M}+\text{H}]^+$: 317.20.

- 30 1.2 2-(3-(Morpholinomethyl)-1H-pyrazol-1-yl)nicotinic acid

To ethyl 2-(3-(morpholinomethyl)-1H-pyrazol-1-yl)nicotinate (370 mg, 1.170 mmol) in methanol (20 mL) and water (2 mL) NaOH (2m solution; 1.7mL) was added and the mixture heated to reflux for 90 min. The reaction mixture was concentrated, taken up in

water, 1.7 mL of 2n HCl added and concentrated again. The obtained solid was treated with 20 mL of acetone, the remainder filtered off and dried to give 295 mg of the acid as off-white amorphous solid; ESI-MS $[M+H]^+$: 289.2.

5 1.3 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-(morpholinomethyl)-1H-pyrazol-1-yl)nicotinamide

N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC) (280 mg, 1.461 mmol), 1-hydroxybenzotriazole hydrate (220 mg, 1.437 mmol) and triethylamine (Et_3N) (220 μ L) were successively added to a suspension of 2-(3-(morpholinomethyl)-1H-pyrazol-1-yl)nicotinic acid (350 mg, 1.214 mmol) and 3-amino-2-hydroxy-4-phenylbutanamide (260 mg, 1.339 mmol) in CH_2Cl_2 (40 mL) at 5°C, and the mixture was stirred at 5°C for about 5 minutes. A pH of 8 was adjusted by adding 50 μ L of Et_3N , the mixture stirred for 1 hour at 5°C and then overnight at room temperature. Dichloromethane (50 mL) was added, washed subsequently with water and brine, dried (MgSO₄) and concentrated in vacuo to give 430 mg of a yellow oil, which was purified by chromatography over silica gel (eluent CH_2Cl_2 / methanol) to give 260 mg of an amorphous white solid; ESI-MS $[M+H]^+$: 465.2

20 1.4 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(morpholinomethyl)-1H-pyrazol-1-yl)nicotinamide

To a solution of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-(morpholinomethyl)-1H-pyrazol-1-yl)nicotinamide (70 mg, 0.151 mmol) in DMSO (3 mL) EDC (240 mg, 1.252 mmol) and - after stirring for 5min- 2,2-dichloroacetic acid (50 μ L, 0.609 mmol) were added, and the mixture stirred for 15min at room temperature. 60 mL of a 1:1 mixture of brine and sat. NaHCO₃-solution (60 mL) was added, the stirring continued for 10 min, extracted with ethylacetate (3x 50 mL), the combined organic layers dried (MgSO₄), filtered off and concentrated in vacuo to give 170 mg of the crude product as yellow oil. Treatment with 15 mL of methyl-tert.butylether (MTB) and further purification of the precipitate formed by chromatography over silica gel (CH_2Cl_2 / methanol) afforded 15 mg of the title compound as amorphous white solid; ESI-MS $[M+H]^+$: 463.2. ¹H-NMR (400 MHz, DMSO), δ [ppm]: 8.95 (d, 1H), 8.51 (m, 1H), 8.30 (d, 1H), 8.05 (s, 1H), 7.82 (m, 1H), 7.70 (m, 1H), 7.44 (m, 1H), 7.30 (m, 5H), 6.38 (d, 1H), 5.38 (m, 1H), 3.53 (m, 4H),

3.15 and 2.88 (each dd, 1H), 2.29 (m, 4H).

EXAMPLE 2: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((2,6-dimethylmorpholino)methyl)-1H-pyrazol-1-yl)nicotinamide (mixture of cis and trans diastereomer)

2.1 Ethyl 2-(3-((2,6-dimethylmorpholino)methyl)-1H-pyrazol-1-yl)nicotinate (mixture of cis and trans diastereomer)

Ethyl 2-(3-(chloromethyl)-1H-pyrazol-1-yl)nicotinate (650 mg, 2.446 mmol), 2,6-dimethylmorpholine (0.482 mL, 3.91 mmol) and K₂CO₃ (1082 mg, 7.83 mmol) in acetonitrile (25 mL) were stirred over night at room temperature. The mixture was concentrated, the remaining solid partitioned between 60 mL of water and dichloromethane, the organic layer separated, dried (MgSO₄), filtered and concentrated again to yield 870 mg of the title compound as clear oil; ESI-MS [M+H]⁺: 345.2.

2.2 Sodium 2-(3-((2,6-dimethylmorpholino)methyl)-1H-pyrazol-1-yl)nicotinic acid
To ethyl 2-(3-((2,6-dimethylmorpholino)methyl)-1H-pyrazol-1-yl)nicotinate (870 mg, 2.021 mmol) in ethanol (30 mL) 2 molar NaOH (1.4 mL, 2.80 mmol) was added, and the mixture heated to reflux. After completion of the reaction the mixture was concentrated in vacuo, co-evaporated twice with acetone, and the obtained solid dried. Treatment with n-pentane and drying afforded 820 mg of the title compound as sodium salt, which was used in the next steps without further purification.

2.3 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((2,6-dimethylmorpholino)methyl)-1H-pyrazol-1-yl)nicotinamide

Coupling of sodium 2-(3-((2,6-dimethylmorpholino)methyl)-1H-pyrazol-1-yl)nicotinate (400 mg, 0.946 mmol) und 3-amino-2-hydroxy-4-phenylbutanamide (220 mg, 1.135 mmol) according to the procedure described for example 1.3 and work-up gave 448 mg of the crude product, which further purified by treatment with a mixture of 30 mL of n-pentane/MTB (10 mL). Filtration and drying gave 388 mg of amorphous white solid; ESI-MS [M+H]⁺: 493.2.

2.4 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((2,6-dimethylmorpholino)-methyl)-1H-pyrazol-1-yl)nicotinamide

The mixture of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((2,6-dimethylmorpholino)methyl)-1H-pyrazol-1-yl)nicotinamide (200 mg, 0.406 mmol) and 2-iodobenzoic acid (303 mg, 0.487 mmol) in DMSO (6 mL) was stirred over night at room temperature, then cooled to 15°C, and quenched by addition of 15% aqueous NaHCO₃-solution (15 mL), water (10 mL) and CH₂Cl₂ (20 mL). The organic layer was separated, washed with water and tried to give 160 mg of a mixture of title compound and starting material, which was treated again with 200 mg of 2-iodobenzoic acid and quenched following the procedure described. 110 mg of the crude product were purified by chromatography over silica gel (eluent CH₂Cl₂ +0-12% methanol) to afford the title compound as two individual diastereomers.

EXAMPLE 2a (tlc CH₂Cl₂/ methanol 9:1 R_f : 0.28): 15 mg, ESI-MS [M+H]⁺: 491.2.
¹H-NMR (400 MHz, DMSO), δ [ppm]: 8.89 (m, 1H), 8.51 (m, 1H), 8.31 (m, 1H), 8.00 (m, 1H), 7.77 (m, 1H), 7.71 (m, 1H), 7.29 (m, 5H), 6.37 (m, 1H), 5.38 (m, 1H), 3.85 (m, 2H), 3.16 (overlapping with water), 2.89 (m, 1H), 2.34 (m 2H), 2.02 (m, 2H), 1.10 (m, 6H).

EXAMPLE 2b (tlc CH₂Cl₂/ methanol 9:1 R_f : 0.32): 31 mg, ESI-MS [M+H]⁺: 491.2.
¹H-NMR (400 MHz, DMSO), δ [ppm]: 8.90 (m, 1H), 8.51 (m, 1H), 8.32 (m, 1H), 8.04 (m, 1H), 7.82 (m, 1H), 7.77 (m, 1H), 7.46 (m, 1H), 7.29 (m, 4H), 7.23 (m, 1H), 6.38 (m, 1H), 5.38 (m, 1H), 3.48 (m, 2H), 3.31 (overlapping with water), 3.18 and 2.90 (each m, 1H), 2.62(, 2H), 1.58 (m, 2H), 1.01 (m, 6H).

EXAMPLE 3: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((4,4-difluoropiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide trifluoroacetate

3.1 Ethyl 2-(3-((4,4-difluoropiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinate
The mixture of ethyl 2-(3-(chloromethyl)-1H-pyrazol-1-yl)nicotinate (500 mg, 1.882 mmol), 4,4-difluoropiperidine (328 mg, 2.7 mmol), and K₂CO₃ were stirred at room temperature in acetonitrile (25 mL) until completion of the reaction. The mixture was concentrated, partitioned between water and dichlormethane (60 mL), the organic layer separated, washed twice with water, dried (MgSO₄), filtered and dried to give a brown

oil, which then was purified by chromatography over silica gel (CH_2Cl_2 + methanol) to yield 620 mg of the title compound as clear oil. ESI-MS $[\text{M}+\text{H}]^+$: 351.15.

^1H -NMR (400 MHz, DMSO), δ [ppm]: 8.65 (m, 1H), 8.48 (m, 1H), 8.15 (m, 1H), 7.45 (m, 1H), 6.51 (m, 1H), 4.25 (q, 2H), 3.65 (d, 1H), 3.25 (d, overlapped with water), 2.5 (overlapped with DMSO), 1.95 (m, 4H).

3.2 2-(3-((4,4-Difluoropiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinic acid, sodium salt

Treatment of ethyl 2-(3-((4,4-difluoropiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinate (620 mg, 1.770 mmol) in ethanol (30 mL) with 1.2 mL of a 2M NaOH, concentration of the reaction mixture and drying of the obtained solid gave 610 mg of the acid as sodium salt as an amorphous solid; ESI-MS $[\text{M}+\text{H}]^+$: 323.1.

3.3 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((4,4-difluoropiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide

Coupling of sodium 2-(3-((4,4-difluoropiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinate (310 mg, 0.900 mmol) and 3-amino-2-hydroxy-4-phenylbutanamide (227 mg, 1.171 mmol) in N,N-dimethylformamide (20 mL) according to example 1.3 and work-up gave 449 mg of the title compound; ESI-MS $[\text{M}+\text{H}]^+$: 499.2.

3.4 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((4,4-difluoropiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide trifluoroacetate

To a solution of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((4,4-difluoropiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide (200 mg, 0.401 mmol) in DMSO (5 mL) and dichloromethane (25 mL) EDC (615 mg, 3.21 mmol) and - after stirring for 5 min - 2,2-dichloroacetic acid (120 μL , 1.455 mmol) were added, and the mixture stirred for 5 min at room temperature. 20 mL of a cooled sat. NaHCO_3 -solution were added, the organic layer separated and washed with brine (3x), dried (MgSO_4), filtered off, and 2.1 eq. of 1M HCl in diethylether added to the filtrate. After stirring the precipitate formed was filtered, washed with MTB and dried to give an amorphous solid, which was further purified by prep. HPLC (column: xTerra prepMS C18 19x150mm 5 μm ; eluent: water + 0.1% TFA/ methanol + 0.1% TFA; flow: 15 mL/min). Lyophilisation of the combined product fractions afforded 71 mg of a white amorphous

solid; ESI-MS $[M+H]^+$: 497.2. ^1H -NMR (400 MHz, DMSO), δ [ppm]: 9.03 (m, 1H), 8.58 (m, 1H), 8.40 (m, 1H), 8.08 (m, 1H), 7.82 (m, 2H), 7.55 (m, 1H), 7.28 (m, 5H), 6.62 (m, 1H), 5.35 (m, 1H), 4.32 and 4.10 (each m 1H), 3.65 (broad, overlapping with water), 3.14 and 2.84 (each dd, 1H), 2.26 (broad, 4H).

5

EXAMPLE 4: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(5-benzyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-2-yl)nicotinamide

4.1 Ethyl 2-(5-benzyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-2-yl)nicotinate

10 The mixture of 5-benzyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine (1.0 g, 4.69 mmol), ethyl 2-chloronicotinate (1.55 g, 8.35 mmol), K_2CO_3 (1.7 g, 12.30 mmol), 18-CROWN-6 (0.2 g, 0.757 mmol) and KI (0.13 g, 0.783 mmol) in N,N-dimethylformamide (15 mL) was heated to 140°C under stirring. After completion of the reaction the mixture was concentrated, the remainder dissolved in 250 mL of
15 dichloromethane, washed subsequently with water (3x 30mL) and brine, dried ($MgSO_4$), filtered and concentrated to give 2.21 g of a brown oil, which was purified by chromatography over silica gel (eluent CH_2Cl_2 / methanol). 200 mg of the title compound was obtained as a white amorphous solid; ESI-MS $[M+H]^+$: 363.2.

20 4.2 2-(5-Benzyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-2-yl)nicotinic acid, sodium salt

Treatment of ethyl 2-(5-benzyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-2-yl)nicotinate (110 mg, 0.304 mmol) in ethanol (10 mL) with 0.5 mL of 1M NaOH and work-up afforded 106 mg of the title compound as sodium salt; ESI-MS $[M+H]^+$:
25 335.2.

4.3 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(5-benzyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-2-yl)nicotinamide

Coupling of sodium 2-(5-benzyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-2-yl)nicotinate (106 mg, 0.297 mmol) and 3-amino-2-hydroxy-4-phenylbutanamide (80
30 mg, 0.412 mmol) in N,N-dimethylformamide (10 mL) according to example 1.3 and work-up gave 197 mg of the title compound a amorphous solid; ESI-MS $[M+H]^+$: 511.2.

4.4 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(5-benzyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-2-yl)nicotinamide

To a solution of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(5-benzyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-2-yl)nicotinamide (45 mg, 0.088 mmol) in DMSO (1200 μ L) at room temperature, EDC (160 mg, 0.835 mmol) was added, and after 5 min of stirring 2,2-dichloroacetic acid (40 μ L, 0.487 mmol). The mixture was stirred for 45 min at room temperature, and then 10 mL of brine and 10 mL of saturated aqueous NaHCO₃-solution were added, the precipitate formed filtered off and dried in vacuo. The yellow solid obtained was crystallized from 2-propanol, the resulting precipitate washed and treated with MTB and n-pentane to afford 27 mg of an off-white amorphous solid; ESI-MS [M+H]⁺: 509.2. ¹H-NMR (400 MHz, DMSO), δ [ppm]: 8.86 (m, 1H), 8.47 (m, 1H), 8.07 (m, 1H), 7.98 (m, 1H), 7.76 (m, 1H), 7.65 (m, 1H), 7.35-7.18 (m, 11H), 5.33 (m, 1H), 4.05 (m, 1H), 3.68 (s, 2H), 3.45-3.16 (m, overlapping with water), 2.91 (dd, 1H), 2.72 (m, 4H).

Applying the routes and procedures described above the following examples were prepared:

20 EXAMPLE 5: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((4-phenylpiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide

5.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((4-phenylpiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide

25 500 mg of a clear oil was obtained; ESI-MS [M+H]⁺: 509.2.

5.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((4-phenylpiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide

To a solution of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((4-phenylpiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide (100 mg, 0.186 mmol) in dichloromethane (3 mL) at room temperature DMSO (300 μ L), N,N'-dichyclohexylcarbodiimide (380 mg, 1.842 mmol) and 2,2-dichloroacetic acid (40 μ L, 0.487 mmol) were added, and the mixture stirred for 1.5 h at room temperature. After completion of

the reaction the mixture was filtered, the filtrate diluted with 30 mL of water, extracted with ethylacetate, the aqueous layer then adjusted to pH 8 by adding NaHCO₃, then extracted again with ethyl acetate (3x 30 mL), the combined organic layers washed with brine, dried (MgSO₄), filtered and concentrated to give 80 mg of a yellow amorphous solid. Purification by chromatography over silica gel (CH₂Cl₂/ methanol) and concentration afforded 25 mg of the title compound as white amorphous solid; ESI-MS [M+H]⁺: 537.2.

EXAMPLE 6: 2-(3-((2H-Benzo[b][1,4]oxazin-4(3H)-yl)methyl)-1H-pyrazol-1-yl)-N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)nicotinamide

6.1 2-(3-((2H-Benzo[b][1,4]oxazin-4(3H)-yl)methyl)-1H-pyrazol-1-yl)-N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)nicotinamide
358 mg of a yellow amorphous solid; mixture of diastereomers; ESI-MS [M+H]⁺: 513.2

6.2 2-(3-((2H-Benzo[b][1,4]oxazin-4(3H)-yl)methyl)-1H-pyrazol-1-yl)-N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)nicotinamide
Oxidation of 2-(3-((2H-benzo[b][1,4]oxazin-4(3H)-yl)methyl)-1H-pyrazol-1-yl)-N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)nicotinamide (210 mg, 0.410 mmol) in DMSO (6 mL) with 2-iodobenzoic acid as described for example 2.4 gave 220 mg of a yellow solid, which was purified by chromatography over silica gel (eluent CH₂Cl₂ +0-15% methanol). After concentration the obtained solid was recrystallized from 2-propanol to give 78 mg of the title compound as an amorphous solid; ESI-MS [M+H]⁺: 511.2. ¹H-NMR (400 MHz, DMSO), δ [ppm]: 8.97 (m, 1H), 8.55 (m, 1H), 8.29 (m, 1H), 8.09 (m, 1H), 7.84 (m, 1H), 7.70 (m, 1H), 7.44 (m, 1H), 7.31 (m, 4H), 7.22 (m, 1H), 6.82 (m, 1H), 6.70 (m, 1H), 6.61 (m, 1H), 6.50 (m, 1H), 6.34 (m, 1H), 5.44 (m, 1H), 4.26 (d, 1H), 4.20 (d, 1H), 4.12 (m, 2H), 3.25 (m, 3H), 2.88 (dd, 1H).

EXAMPLE 7: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(piperidin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide hydrochloride

7.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-(piperidin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide

1960 mg of a yellow amorphous solid was obtained; mixture of diastereomers; ESI-MS

5 [M+H]⁺: 463.2.

7.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(piperidin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide hydrochloride

Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-(piperidin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide (200 mg, 0.432 mmol) according to the
10 procedure described in example 3.4 and treatment of the obtained crude product with diisopropylether afforded the title compound as white amorphous solid; 78 mg; ESI-MS [M+H]⁺: 461.2.

15 EXAMPLE 8: 2-(3-((2H-Benzo[b][1,4]oxazin-4(3H,4aH,5H,6H,7H,8H,8aH)-yl)methyl)-1H-pyrazol-1-yl)-N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)nicotinamide trifluoroacetate (mixtures of diastereomer)

8.1 2-(3-((2H-Benzo[b][1,4]oxazin-4(3H,4aH,5H,6H,7H,8H,8aH)-yl)methyl)-1H-pyrazol-1-yl)-N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)nicotinamide
20 The reaction was carried out in analogy to example 1.3. After completion of the reaction the mixture was concentrated, subsequently 30 mL of water, 10 mL of sat. NaHCO₃-solution and 30 mL of dichloromethane added. The remaining solid was filtered off and dried to give 120 mg of a white amorphous solid (*diastereomere 1*: tlc CH₂Cl₂/methanol 9:1 R_f: 0.37); ESI-MS [M+H]⁺: 519.3. The organic layer was separated,
25 washed, dried and concentrated, and the remaining solid purified by chromatography over silica gel (eluent CH₂Cl₂ +0-15% methanol) to give 320 mg of a white amorphous solid (*diastereomere 2 and 3*: tlc CH₂Cl₂/methanol 9:1 R_f: 0.29 and 0.27); ESI-MS [M+H]⁺: 519.3.

30

8.2.a 2-(3-((2H-Benzo[b][1,4]oxazin-4(3H,4aH,5H,6H,7H,8H,8aH)-yl)methyl)-1H-pyrazol-1-yl)-N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)nicotinamide trifluoroacetate, diastereomere 1,

Oxidation of 2-(3-((2H-benzo[b][1,4]oxazin-4(3H,4aH,5H,6H,7H,8H,8aH)-yl)methyl)-1H-pyrazol-1-yl)-N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)nicotinamide (diastereomers 2 and 3: 200 mg, 0.386 mmol) as described in example 3.4, purification of the crude product by prep. HPLC and lyophilisation afforded the title compound as
5 white amorphous solid; ESI-MS $[M+H]^+$: 517.2.

8.2.b 2-(3-((2H-Benzo[b][1,4]oxazin-4(3H,4aH,5H,6H,7H,8H,8aH)-yl)methyl)-1H-pyrazol-1-yl)-N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)nicotinamide trifluoroacetate, diastereomere 2

10 Oxidation of 2-(3-((2H-benzo[b][1,4]oxazin-4(3H,4aH,5H,6H,7H,8H,8aH)-yl)methyl)-1H-pyrazol-1-yl)-N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)nicotinamide (diastereomer 1: 115 mg, 0.222 mmol) as described in example 3.4, purification of the crude product by prep. HPLC and lyophilisation afforded 53 mg of the title compound as white amorphous solid; ESI-MS $[M+H]^+$: 517.2. $^1\text{H-NMR}$ (400 MHz, DMSO), δ
15 [ppm]: 10.10 (broad), 9.00 (m, 1H), 8.58 (m, 1H), 8.43 (m, 1H), 8.10 (m, 1H), 7.86 (m, 1H), 7.77 (m, 1H), 7.56 (m, 1H), 7.28 (m, 5H), 6.67 (m, 1H), 5.37 (m, 1H), 4.23 (m, 1H), 3.86 (m, 1H), 3.69 (m, 1H), 3.3-3.02 (m, overlapping with water), 2.86 (m, 2H), 2.51-2.34 (m, overlapping with DMSO), 1.91-1.64 (m, 3H) 1.26 (m, 4H).

20 EXAMPLE 9: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((2-phenylmorpholino)methyl)-1H-pyrazol-1-yl)nicotinamide trifluoroacetate

9.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((2-phenylmorpholino)methyl)-1H-pyrazol-1-yl)nicotinamide
25 892 mg, mixture of diastereomers; ESI-MS $[M+H]^+$: 541.2.

9.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((2-phenylmorpholino)methyl)-1H-pyrazol-1-yl)nicotinamide trifluoroacetate
Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((2-phenylmorpholino)methyl)-1H-pyrazol-1-yl)nicotinamide (200 mg, 0.370 mmol) as
30 described in example 3.4, purification of the crude product by prep. HPLC and lyophilisation afforded the title compound as white amorphous solid; 51 mg, ESI-MS $[M+H]^+$: 539.2.

¹H-NMR (400 MHz, DMSO), δ [ppm]: 9.09 (m, 1H), 8.58 (m, 1H), 8.49 (m, 1H), 8.14 (m, 1H), 7.90 (m, 1H), 7.77 (m, 1H), 7.54 (m, 1H), 7.50-7.20 (m, 10H), 6.65 (m, 1H), 5.36 (m, 1H), 4.77 (m, 1H), 4.31-2.78 (m).

5 EXAMPLE 10: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(pyrrolidin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide trifluoroacetate

10.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-(pyrrolidin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide

10 343 mg, mixture of diastereomers; ESI-MS [M+H]⁺: 449.2.

10.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(pyrrolidin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide trifluoroacetate

Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-(pyrrolidin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide (190 mg, 0.424 mmol) as described in example 15 3.4, purification of the crude product by prep. HPLC and lyophilisation afforded the title compound as white amorphous solid; 22 mg, ESI-MS [M+H]⁺: 447.2.

¹H-NMR (400 MHz, DMSO), δ [ppm]: 10.67 (broad), 9.09 (m, 1H), 8.58 (m, 1H), 8.42 (m, 1H), 8.17 (m, 1H), 7.92 (m, 1H), 7.77 (m, 1H), 7.54 (m, 1H), 7.32 (m, 5H), 6.64 (m, 20 1H), 5.41 (m, 1H), 4.41 (broad), 4.27 and 4.10 (each d, 1H), 3.18 (dd, 1H), 3.04 (m, 2H), 2.84 (dd, 1H), 1.85 (m, 4H).

EXAMPLE 11: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(azetidin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide trifluoroacetate

25

11.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-(azetidin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide

274 mg, mixture of diastereomers; ESI-MS [M+H]⁺: 435.2.

30 11.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(azetidin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide trifluoroacetate

Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-(azetidin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide (255 mg, 0.587 mmol) as described in example

3.4, purification of the crude product by prep. HPLC and lyophilisation afforded the title compound as white amorphous solid; 14 mg, ESI-MS $[M+H]^+$: 433.2. $^1\text{H-NMR}$ (400 MHz, DMSO), δ [ppm]: 10.74 (broad), 9.09 (m, 1H), 8.57 (m, 1H), 8.42 (m, 1H), 8.20 (m, 1H), 7.94 (m, 1H), 7.75 (m, 1H), 7.53 (m, 1H), 7.31 (m, 5H), 6.58 (m, 1H), 5.45 (m, 1H), 4.24 (broad), 4.11 and 4.00 (each d, 1H), 3.85 (m, 4H), 3.17 (dd, 1H), 2.83 (dd, 1H), 2.37 (m, 1H), 2.30 (m, 1H).

EXAMPLE 12: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((4-(trifluoromethyl)piperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide trifluoroacetate

10

12.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((4-(trifluoromethyl)piperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide
70 mg, mixture of diastereomers; ESI-MS $[M+H]^+$: 531.2.

12.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((4-(trifluoromethyl)piperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide trifluoroacetate

Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((4-(trifluoromethyl)piperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide (200 mg, 0.377 mmol) as described in example 3.4, purification of the crude product by prep. HPLC and lyophilisation afforded the title compound as white amorphous solid; 25 mg, ESI-MS $[M+H]^+$: 529.2. $^1\text{H-NMR}$ (400 MHz, DMSO), δ [ppm]: 10.36 (broad), 9.10 (m, 1H), 8.58 (m, 1H), 8.43 (m, 1H), 8.15 (m, 1H), 7.92 (m, 1H), 7.81 (m, 1H), 7.55 (m, 1H), 7.31 (m, 5H), 6.65 (m, 1H), 5.36 (m, 1H), 4.23 and 4.03 (each d, 1H), 3.50 (m, 1H), 3.40 (m, 1H), 3.14 (dd, 1H), 2.91 (m, 2H), 2.74 (m, 1H), 2.59 (m, 1H), 2.03 and 1.73 (each m, 2H).

25

EXAMPLE 13: N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-{3-[(5,5-difluorohexahydrocyclopenta[c]pyrrol-2(1H)-yl)methyl]-1H-pyrazol-1-yl}nicotinamide trifluoroacetate

30

13.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((5,5-difluorohexahydrocyclopenta[c]pyrrol-2(1H)-yl)methyl)-1H-pyrazol-1-yl)nicotinamide

5 200 mg, mixture of diastereomers; ESI-MS $[M+H]^+$: 525.2.

13.2 N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-{3-[(5,5-difluorohexahydrocyclopenta[c]pyrrol-2(1H)-yl)methyl]-1H-pyrazol-1-yl}nicotinamide trifluoroacetate

10 Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((5,5-difluorohexahydrocyclopenta[c]pyrrol-2(1H)-yl)methyl)-1H-pyrazol-1-yl)nicotinamide (124 mg, 0.236 mmol) as described in example 3.4, purification of the crude product by prep. HPLC and lyophilisation afforded the title compound as white amorphous solid; 61 mg, ESI-MS $[M+H]^+$: 523.2. $^1\text{H-NMR}$ (400 MHz, DMSO), δ [ppm]: 10.15 (broad), 8.97 (m, 15 1H), 8.59 (m, 1H), 8.43 (m, 1H), 8.08 (m, 1H), 7.84 (m, 2H), 7.53 (m, 1H), 7.28 (m, 5H), 6.61 (m, 1H), 5.37 (m, 1H), 4.10 (m, 1H), 3.75 (m, 1H), 3.18 (m, overlapping with water), 3.10-2.75 (m, 3H), 2.35 (m, 4H), 2.13 (m, 3H).

EXAMPLE 14: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((dihydro-1H-furo[3,4-c]pyrrol-5(3H,6H,6aH)-yl)methyl)-1H-pyrazol-1-yl)nicotinamide trifluoroacetate

14.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((dihydro-1H-furo[3,4-c]pyrrol-5(3H,6H,6aH)-yl)methyl)-1H-pyrazol-1-yl)nicotinamide

25 655 mg, mixture of diastereomers; ESI-MS $[M+H]^+$: 491.2.

14.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((dihydro-1H-furo[3,4-c]pyrrol-5(3H,6H,6aH)-yl)methyl)-1H-pyrazol-1-yl)nicotinamide trifluoroacetate

Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((dihydro-1H-furo[3,4-c]pyrrol-5(3H,6H,6aH)-yl)methyl)-1H-pyrazol-1-yl)nicotinamide (205 mg, 30 0.418 mmol) as described in example 3.4, purification of the crude product by prep. HPLC and lyophilisation afforded the title compound as white amorphous solid (mixture of diastereomeres); 113mg, ESI-MS $[M+H]^+$: 489.0.

EXAMPLE 15: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(indolin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide

5 15.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-(indolin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide

482 mg, mixture of diastereomers; ESI-MS $[M+H]^+$: 497.25.

10 15.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(indolin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide

Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-(indolin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide (200 mg, 0.403 mmol) as described in example 3.4, purification of the crude product by prep. HPLC and lyophilisation afforded the title compound as white amorphous solid; 38 mg, ESI-MS $[M+H]^+$: 495.20. $^1\text{H-NMR}$ (400 MHz, DMSO), δ [ppm]: 8.93 (m, 1H), 8.51 (m, 1H), 8.29 (m, 1H), 8.03 (m, 1H), 7.79 (m, 1H), 7.72 (m, 1H), 7.43 (m, 1H), 7.28 (m, 5H), 7.21 (m, 1H), 6.97 (m, 2H), 6.59 (m, 2H), 6.35 (m, 1H), 5.41 (m, 1H), 4.09 (m, 2H), 3.19 (m, overlapping with water) 2.92-2.85 (m, 3H).

20 EXAMPLE 16:

16.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((methyl(phenyl)amino)methyl)-1H-pyrazol-1-yl)nicotinamide

677 mg, mixture of diastereomers; ESI-MS $[M+H]^+$: 485.2.

25 16.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((methyl(phenyl)amino)methyl)-1H-pyrazol-1-yl)nicotinamide

Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((methyl(phenyl)amino)methyl)-1H-pyrazol-1-yl)nicotinamide (200 mg, 0.413 mmol) as described in example 1.4. The reaction was quenched by addition of 50 mL of a sat. NaHCO₃-solution at 4°C, the precipitate formed was isolated and crystallized from 2-propanol to give 61 mg of a white amorphous solid; ESI-MS $[M+H]^+$: 483.2. $^1\text{H-NMR}$ (400 MHz, DMSO), δ [ppm]: 8.95 (m, 1H), 8.51 (m, 1H), 8.26 (m, 1H), 8.01 (m, 1H), 7.87 (m, 1H), 7.71 (m, 1H), 7.42 (m, 1H), 7.31 (m, 4H), 7.25 (m, 1H), 7.13 (m, 2H),

6.75 (m, 2H), 6.60 (m, 1H), 6.22 (m, 1H), 5.45 (m, 1H), 4.29 (s, 2H), 3.18 (dd, 1H), 2.89 (m, 4H).

EXAMPLE 17: 2-(3-(2-Oxa-7-azaspiro[3.5]nonan-7-ylmethyl)-1H-pyrazol-1-yl)-N-(4-
5 amino-3,4-dioxo-1-phenylbutan-2-yl)nicotinamide trifluoroacetate

17.1 2-(3-(2-Oxa-7-azaspiro[3.5]nonan-7-ylmethyl)-1H-pyrazol-1-yl)-N-(4-amino-3-
hydroxy-4-oxo-1-phenylbutan-2-yl)nicotinamide

36 mg, mixture of diastereomers; ESI-MS $[M+H]^+$: 505.3.

10

17.2 2-(3-(2-Oxa-7-azaspiro[3.5]nonan-7-ylmethyl)-1H-pyrazol-1-yl)-N-(4-amino-3,4-
dioxo-1-phenylbutan-2-yl)nicotinamide trifluoroacetate

Oxidation of 2-(3-(2-oxa-7-azaspiro[3.5]nonan-7-ylmethyl)-1H-pyrazol-1-yl)-N-(4-
amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)nicotinamide (180 mg, 0.357 mmol) as
15 described in example 3.4, purification of the crude product by prep. HPLC and
lyophilisation afforded the title compound as white amorphous solid; 44 mg, ESI-MS
 $[M+H]^+$: 502.3.

EXAMPLE 18:

20 18.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((diethylamino)methyl)-
1H-pyrazol-1-yl)nicotinamide

478 mg, mixture of diastereomers; ESI-MS $[M+H]^+$: 451.2.

25 18.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((diethylamino)methyl)-1H-
pyrazol-1-yl)nicotinamide trifluoroacetate

Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-
((diethylamino)methyl)-1H-pyrazol-1-yl)nicotinamide (250 mg, 0.555 mmol) as
described in example 3.4, purification of the crude product by prep. HPLC and
lyophilisation afforded the title compound as white amorphous solid; 48 mg, ESI-MS
30 $[M+H]^+$: 449.2.

EXAMPLE 19: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(isoindolin-2-ylmethyl)-1H-pyrazol-1-yl)nicotinamide

19.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-(isoindolin-2-ylmethyl)-1H-pyrazol-1-yl)nicotinamide

240 mg, mixture of diastereomers; ESI-MS $[M+H]^+$: 497.2.

19.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(isoindolin-2-ylmethyl)-1H-pyrazol-1-yl)nicotinamide

10 Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-(isoindolin-2-ylmethyl)-1H-pyrazol-1-yl)nicotinamide (1.05 g, 2.115 mmol) as described in example 1.4, treatment of the crude product with ethyl acetate gave the title compound as white amorphous solid; 421 mg, ESI-MS $[M+H]^+$: 495.2. $^1\text{H-NMR}$ (400 MHz, DMSO), δ [ppm]: 8.97 (m, 1H), 8.55 (m, 1H), 8.32 (m, 1H), 8.03 (m, 1H), 7.79 (m, 1H), 7.72 (m, 1H), 7.42 (m, 1H), 7.29-7.15 (m, 9H), 6.47 (m, 1H), 5.42 (m, 1H), 3.80 (s, 4H), 3.68 (m, 2H), 3.15 and 2.87 (each dd, 1H).

EXAMPLE 20: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((cyclohexyl(methyl)amino)methyl)-1H-pyrazol-1-yl)nicotinamide trifluoroacetate

20

20.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((cyclohexyl(methyl)amino)methyl)-1H-pyrazol-1-yl)nicotinamide

816 mg, mixture of diastereomers; ESI-MS $[M+H]^+$: 491.2.

25 20.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((cyclohexyl(methyl)amino)methyl)-1H-pyrazol-1-yl)nicotinamide trifluoroacetate

Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((cyclohexyl(methyl)amino)methyl)-1H-pyrazol-1-yl)nicotinamide (200 mg, 0.408 mmol) as described in example 3.4, purification of the crude product by prep. HPLC and lyophilisation afforded the title compound as white amorphous solid; 78 mg, ESI-MS $[M+H]^+$: 489.2.

EXAMPLE 21: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-
((benzyl(methyl)amino)methyl)-1H-pyrazol-1-yl)nicotinamide trifluoroacetate

21.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-
5 ((benzyl(methyl)amino)methyl)-1H-pyrazol-1-yl)nicotinamide
874 mg, mixture of diastereomers; ESI-MS $[M+H]^+$: 499.2.

21.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((benzyl(methyl)amino)methyl)-
1H-pyrazol-1-yl)nicotinamide trifluoroacetate

10 Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-
((benzyl(methyl)amino)methyl)-1H-pyrazol-1-yl)nicotinamide (200 mg, 0.401 mmol)
as described in example 3.4, purification of the crude product by prep. HPLC and
lyophilisation afforded the title compound as white amorphous solid; 105 mg, ESI-MS
 $[M+H]^+$: 497.2. $^1\text{H-NMR}$ (400 MHz, DMSO), δ [ppm]: 9.97 (broad), 8.99 (m, 1H), 8.61
15 (m, 1H), 8.45 (m, 1H), 8.07 (m, 1H), 7.80 (m, 2H), 7.50 (m, 7H), 7.19 (m, 5H), 6.65 (m,
1H), 5.34 (m, 1H), 4.38-3.90 (m, 4H), 3.10 and 2.76 (each dd, 1H), 2.55 (s, overlapping
with DMSO).

EXAMPLE 22: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((3,4-
20 dihydroisoquinolin-2(1H)-yl)methyl)-1H-pyrazol-1-yl)nicotinamide

22.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((3,4-
dihydroisoquinolin-2(1H)-yl)methyl)-1H-pyrazol-1-yl)nicotinamide
690 mg, mixture of diastereomers; ESI-MS $[M+H]^+$: 511.2.

25

22.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((3,4-dihydroisoquinolin-2(1H)-
yl)methyl)-1H-pyrazol-1-yl)nicotinamide

Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((3,4-
dihydroisoquinolin-2(1H)-yl)methyl)-1H-pyrazol-1-yl)nicotinamide (200 mg, 0.392
30 mmol) as described in example 1.4, recrystallization of the crude product from
 $\text{CH}_2\text{Cl}_2/\text{MTB}$ gave the title compound as white amorphous solid; 52 mg, ESI-MS
 $[M+H]^+$: 509.2. $^1\text{H-NMR}$ (400 MHz, DMSO), δ [ppm]: 8.98 (m, 1H), 8.59 (m, 1H),
8.42 (m, 1H), 8.07 (m, 1H), 7.83 (m, 1H), 7.74 (m, 1H), 7.44 (m, 1H), 7.29-7.15 (m,

5H), 7.10-7.00 (m, 4H), 6.43 (m, 1H), 5.43 (m, 1H), 3.48 (m, 4H), 3.17 and 2.91 (each dd, 1H), 2.91 (m, 2H), 2.61 (m, 2H).

EXAMPLE 23: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((4-tert-

5 butylpiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide

23.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((4-tert-butylpiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide

670 mg, mixture of diastereomers; ESI-MS $[M+H]^+$: 519.2.

10

23.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((4-tert-butylpiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide

Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((4-tert-butylpiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide (200 mg, 0.386 mmol) as

15 described in example 1.4, recrystallization of the crude product from CH_2Cl_2 /MTB gave the title compound as white amorphous solid; 34 mg, ESI-MS $[M+H]^+$: 517.2.

^1H -NMR (400 MHz, DMSO), δ [ppm]: 8.94 (m, 1H), 8.52 (m, 1H), 8.30 (m, 1H), 8.05 (m, 1H), 7.82 (m, 1H), 7.74 (m, 1H), 7.43 (m, 5H), 6.37 (m, 1H), 5.36 (m, 1H), 3.27 (m, overlapping with water), 2.88 (m, 3H), 1.75 (m, 2H), 1.54 (m, 2h), 1.15 (m, 2H), 0.82

20 (m, 11H).

EXAMPLE 24: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((4-methylpiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide trifluoroacetate

25 24.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((4-methylpiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide

265 mg, mixture of diastereomers; ESI-MS $[M+H]^+$: 477.2.

24.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((4-methylpiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide trifluoroacetate

30

Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((4-methylpiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide (260 mg, 0.546 mmol) as described in example 3.4, purification of the crude product by prep. HPLC and

lyophilisation afforded the title compound as white amorphous solid; 52 mg, ESI-MS $[M+H]^+$: 475.2.

EXAMPLE 25:

5 25.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((methyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)methyl)-1H-pyrazol-1-yl)nicotinamide
529 mg, mixture of diastereomers; ESI-MS $[M+H]^+$: 573.2.

10 25.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((methyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)methyl)-1H-pyrazol-1-yl)nicotinamide
trifluoroacetate

Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((methyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)methyl)-1H-pyrazol-1-yl)nicotinamide (200 mg, 0.349 mmol) as described in example 3.4, purification of the crude product by prep.
15 HPLC and lyophilisation afforded the title compound as white amorphous solid; 108 mg, ESI-MS $[M+H]^+$: 471.2.

EXAMPLE 26:

20 26.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((cyclopropyl(methyl)amino)methyl)-1H-pyrazol-1-yl)nicotinamide
595 mg, mixture of diastereomers; ESI-MS $[M+H]^+$: 449.2.

25 26.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((cyclopropyl(methyl)amino)methyl)-1H-pyrazol-1-yl)nicotinamide
trifluoroacetate

Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((cyclopropyl(methyl)amino)methyl)-1H-pyrazol-1-yl)nicotinamide (200 mg, 0.446 mmol) as described in example 3.4, purification of the crude product by prep. HPLC and lyophilisation afforded the title compound as white amorphous solid; 78 mg, ESI-
30 MS $[M+H]^+$: 447.2.

EXAMPLE 27: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(((6R)-6-(4-fluorophenyl)-3-azabicyclo[3.2.0]heptan-3-yl)methyl)-1H-pyrazol-1-yl)nicotinamide

trifluoroacetate

27.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-(((6R)-6-(4-fluorophenyl)-3-azabicyclo[3.2.0]heptan-3-yl)methyl)-1H-pyrazol-1-yl)nicotinamide

516 mg, mixture of diastereomers; ESI-MS $[M+H]^+$: 569.2.

27.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(((6R)-6-(4-fluorophenyl)-3-azabicyclo[3.2.0]heptan-3-yl)methyl)-1H-pyrazol-1-yl)nicotinamide

10 trifluoroacetate

Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-(((6R)-6-(4-fluorophenyl)-3-azabicyclo[3.2.0]heptan-3-yl)methyl)-1H-pyrazol-1-yl)nicotinamide (155 mg, 0.273 mmol) as described in example 3.4, purification of the crude product by prep. HPLC and lyophilisation afforded the title compound as white amorphous solid; 46 mg, ESI-MS $[M+H]^+$: 567.2.

EXAMPLE 28: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((phenylamino)methyl)-1H-pyrazol-1-yl)nicotinamide

20 28.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((phenylamino)methyl)-1H-pyrazol-1-yl)nicotinamide

120 mg, mixture of diastereomers; ESI-MS $[M+H]^+$: 471.2.

25 28.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((phenylamino)methyl)-1H-pyrazol-1-yl)nicotinamide

Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((phenylamino)methyl)-1H-pyrazol-1-yl)nicotinamide (120 mg, 0.255 mmol) as described in example 3.4, purification of the crude product by prep. HPLC and lyophilisation afforded the title compound as white amorphous solid; 3.8 mg, ESI-MS $[M+H]^+$: 469.2. $^1\text{H-NMR}$ (400 MHz, DMSO), δ [ppm]: 8.96 (m, 1H), 8.52 (m, 1H), 8.29 (m, 1H), 8.05 (m, 1H), 7.85 (m, 1H), 7.71 (m, 1H), 7.45 (m, 1H), 7.21 (m, 6H), 7.06 (m, 2H), 6.56 (m, 1H), 6.36 (m, 1H), 5.42 (m, 1H), 4.08 (m, 2H), 3.19 and 2.90 (each dd, 1H).

EXAMPLE 29: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((3-phenylpyrrolidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide

5 29.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((3-phenylpyrrolidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide

668 mg, mixture of diastereomers; ESI-MS $[M+H]^+$: 525.3.

10 29.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((3-phenylpyrrolidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide

Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((phenylamino)methyl)-1H-pyrazol-1-yl)nicotinamide (120 mg, 0.255 mmol) as described in example 1.4, subsequent crystallization of the crude product from 2-propanole and then from ethylacetat afforded the title compound as white amorphous
15 solid; 80 mg, ESI-MS $[M+H]^+$: 523.3. $^1\text{H-NMR}$ (400 MHz, DMSO), δ [ppm]: 8.93 (m, 1H), 8.50(m, 1H), 8.32 (m, 1H), 8.06 (m, 1H), 7.82 (m, 1H), 7.71 (m, 1H), 7.42-7.25 (m, 10H), 6.42 (m, 1H), 5.38 (m, 1H), 3.49 (m, 2H), 3.25 (m, 1H), 3.17 (dd, 1H), 2.88 (m, 2H), 2.63 (m, 2H), 2.39 (m, 1H), 2.21 (m, 1H), 1.72 (m, 1H).

20 EXAMPLE 30: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-1H-pyrazol-1-yl)nicotinamide trifluoroacetate

30.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-1H-pyrazol-1-yl)nicotinamide

25 795 mg, mixture of diastereomers; ESI-MS $[M+H]^+$: 565.3.

30.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-1H-pyrazol-1-yl)nicotinamide trifluoroacetate

Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-1H-pyrazol-1-yl)nicotinamide (250 mg, 0.443 mmol) as described in example 3.4, purification of the crude product by prep. HPLC and lyophilisation afforded the title compound as white amorphous solid; 162 mg, ESI-MS $[M+H]^+$: 563.2. $^1\text{H-NMR}$ (400 MHz, DMSO), δ [ppm]: 9.03 (m, 1H), 8.58 (m, 1H),

8.43 (m, 1H), 8.10 (m, 1H), 7.87 (m, 1H), 7.82 (m, 2H), 7.76 (m, 1H), 7.65 (m, 1H), 7.56 (m, 1H), 7.19 (m, 5H), 6.66 (m, 1H), 5.42 (m, 1H), 4.66- 4.22 (m, 6h), 3.14 and 2.80 (each dd, 1H).

5 EXAMPLE 31: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((5-fluoroisoindolin-2-yl)methyl)-1H-pyrazol-1-yl)nicotinamide trifluoroacetate

31.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((5-fluoroisoindolin-2-yl)methyl)-1H-pyrazol-1-yl)nicotinamide

10 319 mg, mixture of diastereomers; ESI-MS $[M+H]^+$: 515.2.

31.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((5-fluoroisoindolin-2-yl)methyl)-1H-pyrazol-1-yl)nicotinamide trifluoroacetate

Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((5-fluoroisoindolin-2-yl)methyl)-1H-pyrazol-1-yl)nicotinamide (319 mg, 0.620 mmol) as
15 described in example 3.4, purification of the crude product by prep. HPLC and lyophilisation afforded the title compound as white amorphous solid; 70 mg, ESI-MS $[M+H]^+$: 513.2. $^1\text{H-NMR}$ (400 MHz, DMSO), δ [ppm]: 11.11 (broad), 9.05 (m, 1H), 8.59 (m, 1H), 8.43 (m, 1H), 8.10 (m, 1H), 7.88 (m, 1H), 7.82 (m, 1H), 7.55 (m, 1H),
20 7.45 (m, 1H), 7.31 (m, 1H), 7.20 (m, 6H), 6.66 (m, 1H), 5.41 (m, 1H), 4.75 (m, 2H), 4.46 (m, 2H), 4.25 (m, 2H), 3.14 and 2.81 (each dd, 1H).

EXAMPLE 32: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((4-phenylpiperazin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide trifluoroacetate

25

32.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((3-phenylpyrrolidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide

860 mg, mixture of diastereomers; ESI-MS $[M+H]^+$: 540.3.

30 32.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((4-phenylpiperazin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide trifluoroacetate

Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((4-phenylpiperazin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide (250 mg, 0.463 mmol) as

described in example 3.4, purification of the crude product by prep. HPLC and lyophilisation afforded the title compound as white amorphous solid; 156 mg, ESI-MS $[M+H]^+$: 538.2. $^1\text{H-NMR}$ (400 MHz, DMSO), δ [ppm]: 9.98 (broad), 9.07 (m, 1H), 8.61 (m, 1H), 8.47 (m, 1H), 8.11 (m, 1H), 7.89 (m, 1H), 7.84 (m, 1H), 7.57 (m, 1H), 7.27 (m, 7H), 7.02 (m, 2H), 6.88 (m, 1H), 6.65 (m, 1H), 5.40 (m, 1H), 4.35 (m, 1H), 4.06 (m, 1H), 3.80 (m, 2H), 3.50 (overlapping with water), 3.15 (dd, 1H), 2.96 (m, 2H), 2.86 (dd, 1H).

EXAMPLE 33: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((4-fluoroisoindolin-2-yl)methyl)-1H-pyrazol-1-yl)nicotinamide trifluoroacetate

33.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((4-fluoroisoindolin-2-yl)methyl)-1H-pyrazol-1-yl)nicotinamide
505 mg, mixture of diastereomers; ESI-MS $[M+H]^+$: 515.2.

15

33.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((4-fluoroisoindolin-2-yl)methyl)-1H-pyrazol-1-yl)nicotinamide trifluoroacetate
Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((4-fluoroisoindolin-2-yl)methyl)-1H-pyrazol-1-yl)nicotinamide (230 mg, 0.447 mmol)) as described in example 3.4, purification of the crude product by prep. HPLC and lyophilisation afforded the title compound as white amorphous solid; 118 mg, ESI-MS $[M+H]^+$: 513.2. $^1\text{H-NMR}$ (400 MHz, DMSO), δ [ppm]: 11.15 (broad), 8.99 (m, 1H), 8.59 (m, 1H), 8.43 (m, 1H), 8.07 (m, 1H), 7.78 (m, 2H), 7.54 (m, 1H), 7.45 (m, 1H), 7.20 (m, 8H), 6.66 (m, 1H), 5.39 (m, 1H), 4.85-4.17 (m, 6H), 3.14 and 2.80 (each dd, 1H).

25

EXAMPLE 34: N-(4-Amino-3,4-dioxo-1-phenyl-2-butanyl)-2-{3-[(1,1-dioxido-4-thiomorpholinyl)methyl]-1H-pyrazol-1-yl}nicotinamide trifluoroacetate

34.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenyl-2-butanyl)-2-{3-[(1,1-dioxido-4-thiomorpholinyl)methyl]-1H-pyrazol-1-yl}nicotinamide
550 mg, mixture of diastereomers; ESI-MS $[M+H]^+$: 513.2.

30

34.2 N-(4-Amino-3,4-dioxo-1-phenyl-2-butanyl)-2-{3-[(1,1-dioxido-4-thiomorpholinyl)methyl]-1H-pyrazol-1-yl}nicotinamide trifluoroacetate

Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenyl-2-butanyl)-2-{3-[(1,1-dioxido-4-thiomorpholinyl)methyl]-1H-pyrazol-1-yl}nicotinamide (150 mg, 0.293 mmol) as

- 5 described in example 3.4, purification of the crude product by prep. HPLC and lyophilisation afforded the title compound as white amorphous solid; 70 mg, ESI-MS $[M+H]^+$: 511.2. $^1\text{H-NMR}$ (400 MHz, DMSO), δ [ppm]: 8.94 (m, 1H), 8.58 (m, 1H), 8.33 (m, 1H), 8.04 (m, 1H), 7.81 (m, 1H), 7.75 (m, 1H), 7.48 (m, 1H), 7.30 (m, 4H), 7.24 (m, 1H), 6.48 (m, 1H), 5.36 (m, 1H), 3.56 (overlapping with water), 3.17 (m, 5H),
10 3.03 (broad), 2.86 (dd, 1H).

EXAMPLE 35: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(1-(isoindolin-2-yl)ethyl)-1H-pyrazol-1-yl)nicotinamide trifluoroacetate

- 15 35.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-(1-(isoindolin-2-yl)ethyl)-1H-pyrazol-1-yl)nicotinamide
460 mg, mixture of diastereomers; ESI-MS $[M+H]^+$: 511.2.

- 35.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(1-(isoindolin-2-yl)ethyl)-1H-pyrazol-1-yl)nicotinamide trifluoroacetate
20 Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-(1-(isoindolin-2-yl)ethyl)-1H-pyrazol-1-yl)nicotinamide (200 mg, 0.392 mmol) as described in example 3.4, purification of the crude product by prep. HPLC and lyophilisation afforded the title compound as white amorphous solid; mixture of diastereomeres, 77 mg, ESI-MS
25 $[M+H]^+$: 509.2.

EXAMPLE 36: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((1-oxoisoindolin-2-yl)methyl)-1H-pyrazol-1-yl)nicotinamide

- 30 36.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((1-oxoisoindolin-2-yl)methyl)-1H-pyrazol-1-yl)nicotinamide
100 mg, mixture of diastereomers; ESI-MS $[M+H]^+$: 511.2.

36.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((1-oxoisoindolin-2-yl)methyl)-1H-pyrazol-1-yl)nicotinamide

Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-((1-oxoisoindolin-2-yl)methyl)-1H-pyrazol-1-yl)nicotinamide (100 mg, 0.196 mmol) as described in
5 example 1.4, purification by chromatography over Chromabond-RP C18 (eluent water + 0-60% acetonitril + 0.5% glacial acetic acid) and recrystallization of the crude product from 2-propanol afforded the title compound as white amorphous solid; 12 mg, ESI-MS $[M+H]^+$: 509.2.

10 EXAMPLE 37: N-(1-Amino-1,2-dioxoheptan-3-yl)-2-(3-(piperidin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide

37.1 N-(1-Amino-2-hydroxy-1-oxoheptan-3-yl)-2-(3-(piperidin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide

15 Coupling with 3-amino-2-hydroxyheptanamide hydrochloride according to the procedure described for example 1.3 afforded 284 mg of the title compound; ESI-MS $[M+H]^+$: 465.2.

20 37.2 N-(1-Amino-1,2-dioxoheptan-3-yl)-2-(3-(piperidin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide

Oxidation of N-(1-amino-2-hydroxy-1-oxoheptan-3-yl)-2-(3-(piperidin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide (180 mg, 0.378 mmol) as described in example 1.4 and treatment of the crude product with a mixture of ethyl acetate and MTB 1:1, filtering off the remaining solid and drying gave the title compound as white amorphous solid; 63
25 mg, ESI-MS $[M+H]^+$: 427.2. $^1\text{H-NMR}$ (400 MHz, DMSO), δ [ppm]: 8.67 (d, 1H), 8.51 (m, 1H), 8.33 (m, 1H), 7.99 (m, 1H), 7.82 (m, 1H), 7.75 (m, 1H), 7.44 (m, 1H), 6.40 (m, 1H), 5.07 (m, 1H), 3.40 (s, 2H), 2.33 (m, 4H), 1.76 (m, 1H), 1.48 (m, 5H), 1.36 (m, 6H), 0.87 (m, 3H).

30 EXAMPLE 38: N-(1-Amino-1,2-dioxoheptan-3-yl)-2-(3-((4,4-difluoropiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide

38.1 N-(1-Amino-2-hydroxy-1-oxoheptan-3-yl)-2-(3-((4,4-difluoropiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide

Coupling with 3-amino-2-hydroxyheptanamide hydrochloride according to the
5 procedure described for example 1.3 afforded 340 mg of the title compound; ESI-MS $[M+H]^+$: 429.2.

38.2 N-(1-Amino-1,2-dioxoheptan-3-yl)-2-(3-((4,4-difluoropiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide

10 Oxidation of N-(1-amino-2-hydroxy-1-oxoheptan-3-yl)-2-(3-((4,4-difluoropiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide (140 mg, 0.301 mmol) as described in example 1.4 and treatment of the crude product with MTB, filtering off the remaining solid and drying gave the title compound as white amorphous solid; 74 mg, ESI-MS $[M+H]^+$: 463.2. $^1\text{H-NMR}$ (400 MHz, DMSO), δ [ppm]: 8.70 (d, 1H), 8.53 (dd, 1H),
15 8.31 (m, 1H), 7.99 (m, 1H), 7.82 (m, 1H), 7.75 (m, 1H), 7.45 (m, 1H), 6.43 (m, 1H), 5.07 (m, 1H), 3.53 (s, 2H), 1.94 (m, 4H), 1.74 (m, 1H), 1.50 (m, 1H), 1.31 (m, 4H), 0.87 (m, 3H).

EXAMPLE 39: N-(1-Amino-1,2-dioxoheptan-3-yl)-2-(3-(isoindolin-2-ylmethyl)-1H-pyrazol-1-yl)nicotinamide
20

39.1 N-(1-Amino-2-hydroxy-1-oxoheptan-3-yl)-2-(3-(isoindolin-2-ylmethyl)-1H-pyrazol-1-yl)nicotinamide

Coupling with 3-amino-2-hydroxyheptanamide hydrochloride according to the
25 procedure described for example 1.3 afforded 463 mg of the title compound; ESI-MS $[M+H]^+$: 463.3.

39.2 N-(1-Amino-1,2-dioxoheptan-3-yl)-2-(3-(isoindolin-2-ylmethyl)-1H-pyrazol-1-yl)nicotinamide

30 Oxidation of the compound of example 39.1 (180 mg, 0.389 mmol) as described in example 1.4 and treatment of the crude product with ethylacetate/MTB, filtering off the remaining solid and drying gave the title compound as white amorphous solid; 77 mg, ESI-MS $[M+H]^+$: 461.2. $^1\text{H-NMR}$ (400 MHz, DMSO), δ [ppm]: 8.73 (d, 1H), 8.54 (dd,

1H), 8.40 (m, 1H), 8.00 (m, 1H), 7.85 (m, 1H), 7.75 (m, 1H), 7.47 (m, 1H), 7.22 (m, 2H), 7.19 (m, 2H), 6.48 (m, 1H), 5.11 (m, 1H), 3.89 (s, 4H), 3.84 (s, 2H), 1.77 (m, 1H), 1.51 (m, 1H), 1.29 (m, 4H), 0.81 (m, 3H).

5 EXAMPLE 40: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(5-benzyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-2-yl)nicotinamide

40.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(5-benzyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-2-yl)nicotinamide

10 Coupling according to the procedure described for example 1.3 and purification of the crude product by chromatography over silica gel (eluent: dichloromethane/ methanol) afforded 45 mg of the title compound; ESI-MS $[M+H]^+$: 511.2.

40.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(5-benzyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-2-yl)nicotinamide

15 Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(5-benzyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-2-yl)nicotinamide (45 mg, 0.088 mmol) as described in example 1.4 and treatment of the crude product with MTB, filtering off the remaining solid and drying gave the title compound as white amorphous solid; 27 mg, 20 ESI-MS $[M+H]^+$: 509.2.

EXAMPLE 41: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(5-(cyclopropylmethyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-2-yl)nicotinamide

25 41.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(5-(cyclopropylmethyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-2-yl)nicotinamide

Coupling according to the procedure described for example 1.3 and purification of the crude product by chromatography over silica gel (eluent: dichloromethane/ methanol) afforded 200 mg of the title compound; ESI-MS $[M+H]^+$: 475.2.

30

41.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(5-(cyclopropylmethyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-2-yl)nicotinamide

Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(5-

(cyclopropylmethyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-2-yl)nicotinamide (100 mg, 0.211 mmol) as described in example 1.4 and recrystallization of the crude product from 2-propanole gave the title compound as white amorphous solid; 30 mg, ESI-MS $[M+H]^+$: 473.2.

5

EXAMPLE 42: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-2-yl)nicotinamide hydrochloride

42.1 tert-Butyl 2-(3-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-ylcarbamoyl)pyridin-
10 2-yl)-6,7-dihydro-2H-pyrazolo[4,3-c]pyridine-5(4H)-carboxylate

Coupling according to the procedure described for example 1.3 and purification of the crude product by chromatography over silica gel (eluent: dichloromethane/ methanol) afforded 180 mg of the title compound; ESI-MS $[M+H]^+$: 521.2.

15 42.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-2-yl)nicotinamide hydrochloride

Oxidation of tert-butyl 2-(3-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-ylcarbamoyl)pyridin-2-yl)-6,7-dihydro-2H-pyrazolo[4,3-c]pyridine-5(4H)-carboxylate (170 mg, 0.327 mmol) as described in example 1.4 gave 105 mg of an amorphous solid;
20 ESI-MS $[M+H]^+$: 519.2.

70 mg of the obtained Boc-protected compound in 10 mL of dichloromethane were treated with 200 μ L of 4M HCl in dioxane over night, the mixture concentrated and the obtained solid treated again with dichloromethane gave 39 mg of a white-yellow amorphous solid; ESI-MS $[M+H]^+$: 419.2.

25

EXAMPLE 43: tert-Butyl 2-(3-(4-amino-3,4-dioxo-1-phenylbutan-2-ylcarbamoyl)pyridin-2-yl)-4,6-dihydropyrrolo[3,4-c]pyrazole-5(2H)-carboxylate

43.1 tert-Butyl 2-(3-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-ylcarbamoyl)pyridin-
30 2-yl)-4,6-dihydropyrrolo[3,4-c]pyrazole-5(2H)-carboxylate

Coupling according to the procedure described for example 1.3 and treatment of the obtained crude product with water afforded 90 mg of the title compound; ESI-MS $[M+H]^+$: 507.2.

43.2 tert-Butyl 2-(3-(4-amino-3,4-dioxo-1-phenylbutan-2-ylcarbamoyl)pyridin-2-yl)-4,6-dihydropyrrolo[3,4-c]pyrazole-5(2H)-carboxylate

Oxidation of tert-butyl 2-(3-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-ylcarbamoyl)pyridin-2-yl)-4,6-dihydropyrrolo[3,4-c]pyrazole-5(2H)-carboxylate (88 mg, 0.174 mmol) as described in example 1.4 and purification by chromatography over Chromabond RP-C18 (eluent: water/acetonitrile) gave 55 mg of an amorphous solid; ESI-MS $[M+H]^+$: 505.2. ^1H -NMR (400 MHz, DMSO), δ [ppm]: 8.83 (m, 1H), 8.52 (m, 1H), 8.15 (m, 1H), 8.06 (m, 1H), 7.84 (m, 1H), 7.72 (m, 1H), 7.44 (m, 1H), 7.23 (m, 4H), 7.17 (m, 1H), 5.26 (m, 1H), 4.35 (m, 2H), 4.18 (m, 1H), 4.0 (m, 1H), 3.09 (m, 1H), 2.73 (m, 1H), 1.49 (s, 9H).

EXAMPLE 44: N-(4-Amino-3,4-dioxo-1-phenyl-2-butanyl)-2-(5,6-dihydropyrrolo[3,4-c]pyrazol-2(4H)-yl)nicotinamide hydrochloride

15

To a solution of tert-butyl 2-(3-(4-amino-3,4-dioxo-1-phenylbutan-2-ylcarbamoyl)pyridin-2-yl)-4,6-dihydropyrrolo[3,4-c]pyrazole-5(2H)-carboxylate (50 mg, 0.099 mmol) in dichloromethane (10 mL) 400 μ L of 4M HCl in dioxan were added and stirred over night at room temperature. The mixture then was concentrated, the remainder treated with MTB and the remaining solid then further purified by chromatography over Chromabond RP-C18 (eluent: water/acetonitrile) to give 30 mg of the title compound; ESI-MS $[M+H]^+$: 405.1. ^1H -NMR (400 MHz, DMSO), δ [ppm]: 10.41 (broad), 8.93 (m, 1H), 8.54 (m, 1H), 8.21 (m, 1H), 8.06 (m, 1H), 7.85 (m, 1H), 7.71 (m, 1H), 7.49 (m, 1H), 7.26 (m, 5H), 5.33 (m, 1H), 4.35-4.16 (m, 5H), 3.12 (m, 1H), 2.84 (m, 1H).

25

EXAMPLE 45: tert-Butyl 2-(3-(4-amino-3,4-dioxo-1-phenylbutan-2-ylcarbamoyl)pyridin-2-yl)-2,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridine-6-carboxylate

45.1 tert-Butyl 2-(3-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-ylcarbamoyl)pyridin-2-yl)-4,5-dihydro-2H-pyrazolo[3,4-c]pyridine-6(7H)-carboxylate

30

Coupling according to the procedure described for example 1.3 and treatment of the obtained crude product with water afforded 90 mg of the title compound; ESI-MS $[M+H]^+$: 521.2.

45.2 tert-Butyl 2-(3-(4-amino-3,4-dioxo-1-phenylbutan-2-ylcarbamoyl)pyridin-2-yl)-
2,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridine-6-carboxylate

Oxidation of tert-butyl 2-(3-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-
5 ylcarmoyl)pyridin-2-yl)-4,5-dihydro-2H-pyrazolo[3,4-c]pyridine-6(7H)-carboxylate
(170 mg, 0.327 mmol) as described in example 1.4 and purification by chromatography
over Chromabond RP-C18 (eluent: water/acetonitrile) gave 84 mg of an amorphous
solid; ESI-MS $[M+H]^+$: 519.2.

10 EXAMPLE 46: N-(4-Amino-3,4-dioxo-1-phenyl-2-butanyl)-2-(4,5,6,7-tetrahydro-
pyrazolo[3,4-c]pyridin-2-yl)nicotinamide hydrochloride

To a solution of tert-butyl 2-(3-(4-amino-3,4-dioxo-1-phenylbutan-2-
ylcarbamoyl)pyridin-2-yl)-2,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridine-6-carboxylate
15 in dioxane (5ml) 400 μ L of 4M HCl in dioxane were added and stirred over night at
room temperature. The mixture then was concentrated, and the remainder purified by
chromatography over Chromabond RP-C18 (eluent: water/acetonitrile) to give 24mg of
the title compound; ESI-MS $[M+H]^+$: 419.2.

20 EXAMPLE 47: tert-Butyl 2-(3-(4-amino-3,4-dioxo-1-phenylbutan-2-
ylcarbamoyl)pyridin-2-yl)-2,5,6,7-tetrahydro-4H-pyrazolo[4,3-b]pyridine-4-carboxylate

47.1 tert-Butyl 2-(3-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-ylcarbamoyl)pyridin-
2-yl)-6,7-dihydro-2H-pyrazolo[4,3-b]pyridine-4(5H)-carboxylate
25 Coupling according to the procedure described for example 1.3 and treatment of the
obtained crude product with water afforded 600 mg of the title compound; ESI-MS
 $[M+H]^+$: 521.2.

47.2 tert-Butyl 2-(3-(4-amino-3,4-dioxo-1-phenylbutan-2-ylcarbamoyl)pyridin-2-yl)-
30 2,5,6,7-tetrahydro-4H-pyrazolo[4,3-b]pyridine-4-carboxylate

Oxidation of the compound from example 47.1 as described in example 1.4 and
purification by chromatography over Chromabond RP-C18 (eluent: water/acetonitrile)

gave 84 mg of an amorphous solid; ESI-MS $[M+H]^+$: 519.2. $^1\text{H-NMR}$ (400 MHz, DMSO), δ [ppm]: 8.80 (m, 1H), 8.46 (m, 2H), 7.99 (m, 1H), 7.75 (m, 1H), 7.63 (m, 1H), 7.39 (m, 1H), 7.23 (m, 4H), 5.36 (m, 1H), 3.62 (m, 2H), 3.12 (dd, 1H), 2.87 (dd, 1H), 2.66 (m, 1H), 2.50 (overlapping with DMSO), 1.87 (m, 2H), 1.50 (s, 9H).

5

EXAMPLE 48: N-(4-Amino-3,4-dioxo-1-phenyl-2-butanyl)-2-(4,5,6,7-tetrahydro-pyrazolo[4,3-b]pyridin-2-yl)nicotinamide hydrochloride

To a solution of the compound from example 47.1 (400 mg, 0.771 mmol) in
10 dichloromethane (25ml) 1mL of 4M HCl in dioxane was added and stirred over night at room temperature. The mixture then was filtered, the obtained precipitate washed with dichloromethane and dried to give 346 mg of the title compound; ESI-MS $[M+H]^+$: 419.2. $^1\text{H-NMR}$ (400 MHz, DMSO), δ [ppm]: 8.95 (m, 1H), 8.53 (m, 1H), 8.46 (m, 1H), 8.06 (m, 1H), 7.78 (m, 1H), 7.72 (m, 1H), 7.46 (m, 1H), 7.22 (m, 5H), 5.35 (m,
15 1H), 3.31 (m, 2H), 3.14 (dd, 1H), 2.89 (dd, 1H), 2.61 (m, 1H), 2.50 (overlapping with DMSO), 1.98 (m, 2H).

EXAMPLE 49: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(4-benzyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-b]pyridin-2-yl)nicotinamide

20

49.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(4-benzyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-b]pyridin-2-yl)nicotinamide

Coupling according to the procedure described for example 1.3 and treatment of the obtained crude product with water afforded 1340 mg of the title compound; ESI-MS
25 $[M+H]^+$: 511.2.

49.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(4-benzyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-b]pyridin-2-yl)nicotinamide

Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(4-benzyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-b]pyridin-2-yl)nicotinamide (150 mg, 0.294 mmol) as
30 described in example 2.4 and purification by chromatography over silica gel (eluent: dichloromethane/methanol) afforded the title compound as an amorphous solid; 11 mg, ESI-MS $[M+H]^+$: 509.2. $^1\text{H-NMR}$ (400 MHz, DMSO), δ [ppm]: 8.62 (m, 1H), 8.35 (m,

2H), 7.76 (m, 1H), 7.50 (m, 1H), 7.35-7.12 (m, 12H), 5.85 (s, 1H), 4.36 (m, 1H), 4.20 (s, 2H), 3.20 (m, 2H), 2.93 (m, 2H), 2.71 (m, 3H), 1.94 (m, 2H).

EXAMPLE 50: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(1-methylpiperidin-4-yl)-1H-pyrazol-1-yl)nicotinamide

50.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-(1-methylpiperidin-4-yl)-1H-pyrazol-1-yl)nicotinamide

Coupling of 2-(3-(1-methylpiperidin-4-yl)-1H-pyrazol-1-yl)nicotinic acid (360 mg, 1.257 mmol) and 3-amino-2-hydroxy-4-phenylbutanamide (293 mg, 1.509 mmol) in dichloromethane (50mL) according to the procedure described for example 1.3 and recrystallization from ethylacetate afforded 273 mg of the title compound; ESI-MS $[M+H]^+$: 463.3.

50.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(1-methylpiperidin-4-yl)-1H-pyrazol-1-yl)nicotinamide

Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(3-(1-methylpiperidin-4-yl)-1H-pyrazol-1-yl)nicotinamide (150 mg, 0.324 mmol) as described in example 1.4 and purification by chromatography over silica gel afforded the title compound as an amorphous solid; 18 mg, ESI-MS $[M+H]^+$: 461.2.

EXAMPLE 51: N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(6-ethyl-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridin-2-yl)nicotinamide trifluoroacetate

51.1 N-(4-Amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(6-ethyl-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridin-2-yl)nicotinamide

To a solution of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridin-2-yl)nicotinamide hydrochloride (210 mg, 0.460 mmol) in methanol (15ml) first acetaldehyde (150 μ L, 2.66 mmol) and after 30 minutes NaCN(BH₄)₄ (40 mg, 0.637 mmol) and glacial acetic acid (20 μ L, 0.349 mmol) were added and stirred over night. The mixture was concentrated, 20 mL of water, 10 mL NaHCO₃-solution and 20 mL of dichloromethane added, the organic layer separated, washed 2x with water, dried with MgSO₄, filtered and concentrated to give 85 mg of an

amorphous solid; ESI-MS $[M+H]^+$: 449.2.

51.2 N-(4-Amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(6-ethyl-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridin-2-yl)nicotinamide trifluoroacetate

- 5 Oxidation of N-(4-amino-3-hydroxy-4-oxo-1-phenylbutan-2-yl)-2-(6-ethyl-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridin-2-yl)nicotinamide (85 mg, 0.190 mmol) and purification as described in example 3.4 afforded the title compound as an amorphous solid; 18 mg, ESI-MS $[M+H]^+$: 447.2.

10 II Enzyme inhibition in vitro:

Testing for blockade of the corresponding enzymic activities was carried out by means of kinetic fluorescence assays (excitation 390 nm, emission 460 nm).

- 15 Apparent K_i values were calculated from the experimentally determined IC_{50} values by the Cheng-Prusoff relation assuming a reversible competitive enzyme inhibition. The K_m values of the substrates used under the assay conditions indicated above were: 90 μM (Z-Phe-Arg-AMC, cathepsin B), 10 μM (Z-Gly-Pro-Arg-AMC, cathepsin K), 2 μM (Z-Phe-Arg-AMC, cathepsin L), and 30 μM (Z-Val-Val-Arg-AMC, cathepsin S).
- 20 The indicated K_i values are averages of the inhibition constants calculated on the basis of 2 to 4 independent dose-effect plots.

The following assays were used:

- 25 1. Calpain I:
20 nM calpain-I –isolated from human erythrocytes (Calbiochem #208713), 100 μM Suc-Leu-Tyr-AMC (Bachem #I-1355) as substrate in buffer with 62 mM imidazole, 0.3 mM $CaCl_2$, 0.10% CHAPS, 0.05% BSA, 1 mM DTT at pH 7.3 and room temperature.
- 30 2. Cathepsin B:
0.25 nM cathepsin B – isolated from human liver (Calbiochem #219362), 100 μM Z-Phe-Arg-AMC (Bachem #I-1160) as substrate 50 mM MES, 2 mM EDTA, 0.05% Brij 35, 2.5 mM L-cysteine, pH 6.0, room temperature.

3. Cathepsin K:

3 nM cathepsin K –activated from recombinant human procathepsin K from E. coli (Calbiochem #342001), 10 μ M Z-Gly-Pro-Arg-AMC (Biomol #P-142) as substrate in 50 mM MES, 2 mM EDTA, 0.05% Brij 35, 2.5 mM L-cysteine, pH 6.0, room

5 temperature.

4. Cathepsin L:

1 nM cathepsin L – isolated from human liver (Calbiochem #219402), 2 μ M Z-Phe-Arg-AMC (Bachem #I-1160) as substrate in 50 mM MES, 2 mM EDTA, 0.05% Brij 35, 2.5 mM L-cysteine, pH 6.0, room temperature.

10 5. Cathepsin S:

0.5 nM recombinant human cathepsin S from E. coli (Calbiochem #219343), 20 μ M Z-Val-Val-Arg-AMC (Bachem #I-1540) as substrate in 50 mM MES, 2 mM EDTA, 0.05% Brij 35, 2.5 mM L-cysteine, pH 6.0, room temperature.

15 The results of the in vitro determination are indicated in Table 1. The following abbreviations are used in Table 1:

In the "Calpain activity" column, +++ stands for a calpain K_i ($K_i(\text{calpain})$) of < 250 nM, ++ means $250 \text{ nM} \leq K_i(\text{calpain})$ of ≤ 400 nM, + means $400 \text{ nM} < K_i(\text{Calpain})$

20 ≤ 800 nM and o means $800 \text{ nM} < K_i(\text{Calpain}) \leq 1000$ nM.

The "Sel. cat. B" column indicates the $K_i(\text{cathepsin B})/K_i(\text{calpain})$ ratio. In this connection, +++ means a $K_i(\text{cathepsin B})/K_i(\text{calpain})$ ratio of > 30 , ++ means $9 < K_i(\text{cathepsin B})/K_i(\text{calpain}) \leq 30$, and + means $5 \leq K_i(\text{cathepsin B})/K_i(\text{calpain}) \leq 9$ and

25 o means $K_i(\text{cathepsin B})/K_i(\text{calpain}) < 5$.

The "Sel. cat. K" column indicates the $K_i(\text{cathepsin K})/K_i(\text{calpain})$ ratio. In this connection, +++ means a $K_i(\text{cathepsin K})/K_i(\text{calpain})$ ratio of > 30 , ++ means $9 < K_i(\text{cathepsin K})/K_i(\text{calpain}) \leq 30$, and + means $5 \leq K_i(\text{cathepsin K})/K_i(\text{calpain}) \leq 9$ and

30 o means $K_i(\text{cathepsin K})/K_i(\text{calpain}) < 5$.

The "Sel. cat. L" column indicates the $K_i(\text{cathepsin L})/K_i(\text{calpain})$ ratio. In this connection, +++ means a $K_i(\text{cathepsin L})/K_i(\text{calpain})$ ratio of > 50 , ++ means $10 <$

Ki(cathepsin L)/Ki(calpain) ≤ 50 , and + means $5 \leq \text{Ki(cathepsin L)/Ki(calpain)} \leq 10$ and o means $\text{Ki(cathepsin L)/Ki(calpain)} < 5$.

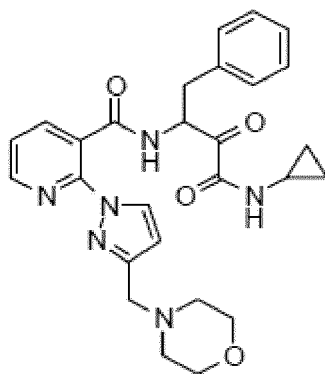
- 5 The "Sel. cat. S" column indicates the Ki(cathepsin S)/Ki(calpain) ratio. In this connection, +++ means a Ki(cathepsin S)/Ki(calpain) ratio of > 50 , ++ means $10 < \text{Ki(cathepsin S)/Ki(calpain)} \leq 50$, and + means $5 \leq \text{Ki(cathepsin S)/Ki(calpain)} \leq 10$ and o means $\text{Ki(cathepsin S)/Ki(calpain)} < 5$.

Table 1:

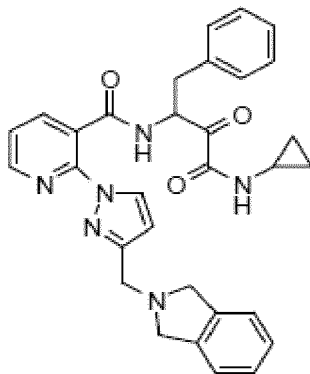
Example	Calpain activity	Sel cat. B	Sel cat. K	Sel cat. L	Sel cat. S	human cytCL	cyno cytCL
1	+++	o	o	+	+++	++	++
2a	+++	o	o	o	+++	++	++
2b	+++	o	o	o	++	++	++
3	+++	+	o	++	+++	++	++
4	+++	o	o	+	+++	+	++
5	+++	o	o	++	+++	++	++
6	+++	+	++	+++	+++	+	+
7	+++	o	o	o	++	++	++
8a	+++	o	o	o	+++	++	++
8b	+++	o	o	o	+++	++	++
9	+++	+	o	+	+++	+	+
10	++	o	o	o	+++	++	++
11	++	o	o	o	+++	++	++
12	+++	o	o	o	+++	+	++
13	+++	o	o	o	+++	++	++
14	+++	o	o	o	+++	++	++
15	+++	+	++	+++	++	+	+
16	+++	+	++	+++	+++	+	+
17	+++	o	o	o	++	++	++
18	++	o	o	o	++	++	++
19	+++	o	o	+	+++	+	++

Example	Calpain activity	Sel cat. B	Sel cat. K	Sel cat. L	Sel cat. S	human cytCL	cyno cytCL
20	+++	o	o	o	++	++	++
21	+++	o	o	o	+++	+	++
22	+++	o	o	+	+++	+	++
23	+++	o	o	+	+++	+	++
24	+++	o	o	o	+++	++	++
25	+++	o	o	o	+++	+	+
26	+++	o	o	o	+++	+	++
27	+++	o	o	+	+++	+	+
28	+++	+	+	+++	++	+	+
29	+++	o	o	o	+++	+	+
30	+++	o	o	++	+++	+	+
31	+++	o	o	+	+++	+	++
32	+++	o	o	++	+++	+	++
33	+++	o	o	+	+++	+	+
34	+++	o	o	+++	++	++	++
35	+++	+	o	o	+++	+	++
36	+++	++	++	+++	+++	+	+
37	+++	o	o	o	o	++	++
38	+++	o	o	o	o	+	++
39	+++	o	o	+	++	+	+
40	+++	o	o	+	+++	+	++
41	+++	o	o	o	++	++	++
42	+++	o	o	o	+	++	++
43	+++	o	++	+++	++	+	+
44	+++	o	o	o	++	++	++
45	+++	o	o	++	++	+	+
46	+++	o	o	o	+	++	++
C1*	#	o	o	o	o	++	++
C2**	o	o	o	o	+	+	++

C1*
Calpain activity
Ki > 1000 nM



C2**



As can be seen from Table 1 the compounds of formula I according to the invention feature improved Calpain activity over related compounds C1 and C2 carrying a cyclopropyl group at the amino nitrogen atom.

5

III Spectrin molt-4 assay to determine cellular calpain inhibition:

The following solutions and buffers were employed:

- HBS (for 40 ml): 800 μ l 1M HEPES; 2.16 ml 100 mM KCl; 4.8 ml 1M NaCl;
10 3.59 ml 5% glucose; 60 μ l 1M MgSO₄; 400 μ l 100 mM Na pyruvate, 28.19 ml water; pH 7.2-7.5.
- lysis buffer (for 20 ml): 400 μ l 1M Tris pH 8.2; 2.74 ml 1M NaCl; 520 μ l 0.5M EDTA; 2 ml 10% triton X-100; 0.8 ml (= 1:25) CompletePlus (1 tablet/2 ml H₂O); 200 μ l 100 mM Pefabloc; 13.34 ml water, pH 8.2.
- 15 - TBST (10x) (for 1l): 100 mM Tris (12.1 g); 1.5M NaCl (87 g); 1% Tween 20 (10 g), adjusted to pH 8.

The assay design and procedure were as disclosed by Chatterjee; BMC **1998**, 6,

pp. 509-522; the EC_{50} values are calculated from the percentage degradation of spectrin as a function of the dose.

Cell culture conditions: the molt-4 cells are maintained in RPMI 1640 + GlutamaxTM I medium (Gibco) with 10% FCS and 50 μ g/ml gentamicin at 37°C, 5% CO₂ and split 1:15 twice a week.

Preparation of the molt-4 cells: the cells are washed, counted and taken up in a concentration of 2×10^7 cells/ml in HBS buffer.

10

Dilution of the inhibitor substances: all the inhibitors are dissolved in a concentration of 10^{-2} M in DMSO. The stock solution is then diluted 1:15 in DMSO ($= 6.67 \times 10^{-4}$ M).

Thereafter the stock solution diluted 1:15 is diluted 1:4 in DMSO in two steps ($= 1.67 \times 10^{-4}$ M and 4.17×10^{-5} M). Thereafter, these three solutions are further diluted 1:50 in HBS buffer to give solutions having a concentration of 1.33×10^{-5} M, 3.36×10^{-6} M and 8.34×10^{-7} M.

15

Test mixture: for each mixture, 10^6 cells (see above) are introduced into a 1.5 ml Eppendorf tube. To these are added in each case 150 μ l of the diluted substances (final conc. 10^{-5} M; 2.5×10^{-6} M and 6.25×10^{-7} M) and thoroughly mixed. A negative control and a positive control are used as controls. In this case, initially only 150 μ l of HBS buffer is pipetted onto the cells. All the mixtures are incubated at 37°C, 5% CO₂ in an incubator for 10 min. Thereafter, except for the negative control, in each case CaCl₂ (final conc. 5 mM) and ionomycin (final conc. 5 μ M) are added, thoroughly mixed and incubated at 37°C, 5% CO₂ in an incubator for 30 min. Then centrifuge at 700 g for 5 min. The supernatants are discarded and the pellets are taken up in 20 μ l of lysis buffer. The mixtures are subsequently placed on ice for 30-60 min and then centrifuged at 15000g for 15 min. The supernatants are removed and put into new Eppendorf tubes. The protein determination is then carried out thereon, e.g. with a MicroBCA assay (Pierce).

25

30

SDS-PAGE electrophoresis: 10 μ g of total protein from each mixture are put into a new Eppendorf tube and, after pipetting in the same volume of 2 $\times$ Tris-glycine SDS sample

buffer (Invitrogen) and 1/10 volume of 1M DTT, thoroughly mixed and heated at 95°C for 15 min. The solutions are briefly centrifuged and loaded onto a 6% SDS gel (Invitrogen). The gel is run at 100V with 1× Tris-glycine laemmli buffer (Biomol) until the lower band of the marker has reached the base of the gel.

5

Western blotting: the gel is removed from the apparatus and blotted onto nitrocellulose in 1× Tris-glycine transfer buffer (Invitrogen) + 20% methanol with 1.5 A/cm² in a FastBlot chamber (Biometra) for 30 min. The nitrocellulose filter is removed, briefly washed in TBST buffer and blocked in TBST/5% milk powder for 1 h at RT (room temperature). The blocked nitrocellulose is then incubated with an anti-spectrin Ab (Chemicon) (1:10000 in TBST/5% milk powder) at RT for 3 h or at 4°C overnight. The nitrocellulose is washed 3× in TBST buffer. It is then incubated with anti-mouse IgG (POD) antibody (Sigma) (1:10000 in TBST/5% milk powder) at room temperature for 1 h.

15

The nitrocellulose is then washed 5× in TBST buffer. In the next step, 5 ml of prepared solution of the SuperSignal[®] West Pico chemiluminescence substrate (Pierce) are put on the filter and incubated for 5 min. The nitrocellulose is then taken out of the solution, gently dabbed dry and inserted into a development folder film (Tropix). A digital image analysis system (VersaDoc, Biorad) is used to record and quantify the ECL (QuantityOne), and the percentage degradation of spectrin is calculated from the data. Graph-pad prism is used to fit the percentage spectrum degradation as a function of the dose to a sigmoidal dose-effect plot (top fixed at 100% and bottom at 0%), and the EC 50% is calculated.

25

IV Assay for determining cytosolic clearance of compounds of formula I:

For comparison purposes data measured with human liver cytosol were contrasted with those obtained with cynomolgus monkey liver cytosol.

30

0.5 µM of a compound to be tested was incubated with 1mg/ml of human liver cytosol as well as monkey liver cytosol at 37°C in 0.5 M of phosphate buffer at pH 7.5 while shaking (commercial sources: female cynomolgus liver cytosol from Tebu bio, human

liver cytosol from BDgentest).

In each case aliquots of 65 µl were taken after 0, 5, 10 and 15 min and transferred into wells of a wellplate which were immediately filled with 130 µl of ethanol to stop the reaction. The samples were kept frozen until analysis on a LC/MS/MS system (Applied

5 Biosystems SCIEX 4000).

Read out parameters were the loss of parent compounds, from which the half life periods ($T_{1/2}$) were calculated from. Based on these data the parameters cytosolic clearance (cytCL), scaled clearance (CLs) and predicted clearance (CLp) were calculated using the following equations:

- 10 1) $\text{cytCL} = (\ln 2/T_{1/2}) \times [\text{cytosolic protein}] \times 1000$
 2) $\text{CLs} = \text{cytCL} \times [\text{cytosolic yield}] / 1,000,000 \times 60$
 3) $\text{CLp} = (\text{CLs} + \text{hepatic plasma flow}) / \text{hepatic plasma flow} / \text{CLs}$

To assess the stability of the compounds tested the clearance ranges were adjusted to the
 15 hepatic plasma flow of the different species according to the following scheme:

stable = from 0 to about 1/3 of the hepatic plasma flow;

moderately stable = from about 1/3 to about 2/3 of the hepatic plasma flow;

instable = more than 2/3 of the hepatic plasma flow.

20 Based on this adjustment the following qualifiers were assigned to evaluate the cytosolic stabilities of the compounds tested:

<i>cytCL</i>	symbol	human	cynomolgus monkey (cyno)
stable	++	0-14 µl/min/mg	0-18 µl/min/mg
moderately stable	+	14-70 µl/min/mg	18-90 µl/min/mg
instable	-	> 70 µl/min/mg	> 90 µl/min/mg

The cytCL data obtained this way for the compounds of the Examples 1 to 46 are
 25 depicted in Table 1 above.

V In-vitro assay for determining degradation of compounds I into the corresponding hydroxyamide metabolites in hepatocytes:

5 Each compound to be tested (10 μ l) was incubated in monkey and also in human hepatocytes to determine the concentration ratio of hydroxyamide metabolite to the compound of formula I as parent compound. Incubations were carried out at 37°C for 0 and 4 hours in a 24-well plate, each well holding 0.5 ml hepatocyte medium with about 500,000 cells/ml. At the end of each time point, 1 ml of acetonitrile/ethanol (1/1, v/v)
10 was added to each well to quench the reaction. The solutions were vortexed and mixed thoroughly. An aliquot was subjected to LC-UV-MS/MS analysis at UV wavelength of 254 nm. Identities of compounds I tested and their corresponding hydroxyamide metabolites were confirmed by MS/MS analysis and by comparison with synthetic standards. UV areas for each test compound and its hydroxylamide metabolite were
15 integrated. The concentration ratios of hydroxyamide metabolites to parent compounds (M/P ratios) were determined as ratios of the UV areas of metabolites to those of the compounds I, assuming that extinction coefficients ϵ_P and ϵ_M are approximately identical. The M/P ratios obtained this way for incubations were terminated after 4 hours.

20

VI In-vivo determination of the ratio of hydroxyamide metabolite to the parent compound I in plasma of cynomolgus monkeys

The tested compounds were prepared as a solution for either intravenous or oral
25 administration to groups of female cynomolgus monkeys. For intravenous dosing, the compounds were prepared in a 10% DMSO / PEG-400 vehicle at a concentration of 2 mg/ml. For oral dosing, the compounds were prepared in a lipid based vehicle at a concentration of 3 mg/ml. Groups of three monkeys received either a 1 mg/kg (0.5 ml/kg) intravenous dose or a 3 mg/kg (1 ml/kg) oral dose. The intravenous dose was
30 administered as a slow bolus in a saphenous vein; the oral dose was administered by gastric intubation and was followed by ~5 ml water. Serial blood samples were obtained from each animal at selected time points up to 24 hours after drug administration. Plasma was separated from the blood by centrifugation and stored frozen (<-15C) until

analysis. Parent compounds I and the selected metabolites were separated from plasma using protein precipitation with mixture of methanol, acetonitrile and water. The supernatant was evaporated to dryness with a stream of dry nitrogen. The samples were reconstituted with an aliquot of mobile phase, followed by quantification by HPLC-MS/MS. Standard curves for both parent and the selected metabolites were prepared from authentic standards in blank monkey plasma; standards were analyzed simultaneously with the samples. The plasma concentration of each sample was calculated by least squares linear regression analysis of the peak area ratio (parent or metabolite/internal standard) of the spiked plasma standards versus concentration.

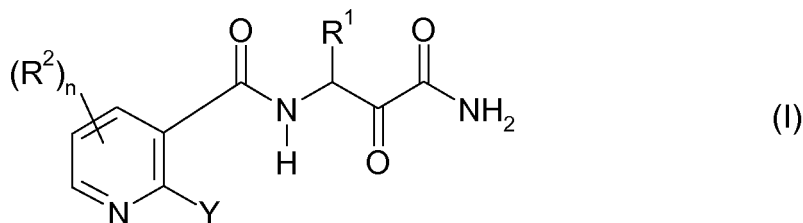
10

Peak plasma concentrations ($C_{\max}$) and the time to peak plasma concentration ($T_{\max}$) were read directly from the plasma concentration data for each monkey. The plasma concentration data for both parent and metabolite were submitted to multi-exponential curve fitting using WinNonlin. The area under the plasma concentration-time curve from 0 to t hours (time of the last measurable plasma concentration) after dosing (AUC_{0-t}) was calculated using the linear trapezoidal rule for the plasma concentration-time profiles. The residual area extrapolated to infinity, determined as the final measured plasma concentration (C_t) divided by the terminal elimination rate constant (β), was added to AUC_{0-t} to produce the total area under the curve ($AUC_{0-\infty}$). The apparent total plasma clearance (CL_p) was calculated by dividing the administered dose by the $AUC_{0-\infty}$. The initial volume of distribution (V_c) was calculated as the dose divided by the extrapolated concentration at time = 0 (C_0). The volume of distribution at steady state, V_{ss} , was estimated as a product of the plasma clearance (CL_p) and the mean residence time (MRT); the terminal-phase volume of distribution (V_β), was derived from the plasma clearance value (CL_p) divided by the plasma elimination rate constant (β). The bioavailability was calculated as the dose-normalized $AUC_{0-\infty}$ from the oral dose divided by the corresponding value derived from the intravenous dose. Metabolite to parent ratios were calculated as the $C_{\max}$ (metabolite)/ $C_{\max}$ (parent) or $AUC(\text{metabolite})/AUC(\text{parent})$ for the peak concentrations and area under the curve, respectively.

30

Claims:

1. A carboxamide compound of the formula I



in which

R^1 is C_1 - C_{10} -alkyl, C_2 - C_{10} -alkenyl, C_2 - C_{10} -alkynyl, where the last 3 radicals mentioned may be partly or completely halogenated and/or have 1, 2 or 3 substituents R^{1a} , C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl- C_1 - C_4 -alkyl, where a CH_2 group in the cycloalkyl moiety of the last two radicals mentioned may be replaced by O, NH, or S, or two adjacent C atoms may form a double bond, where the cycloalkyl moiety may further have 1, 2, 3 or 4 radicals R^{1b} , aryl, hetaryl, aryl- C_1 - C_6 -alkyl, aryl- C_2 - C_6 -alkenyl, hetaryl- C_1 - C_4 -alkyl or hetaryl- C_2 - C_6 -alkenyl, where aryl and hetaryl in the last 6 radicals mentioned may be unsubstituted or may carry 1, 2, 3 or 4 identical or different radicals R^{1c} ; where

R^{1a} is selected independently of one another from the group consisting of OH, SH, COOH, CN, OCH_2COOH , C_1 - C_6 -alkoxy, C_1 - C_6 -haloalkoxy, C_3 - C_7 -cycloalkyloxy, C_1 - C_6 -alkylthio, C_1 - C_6 -haloalkylthio, $COOR^{a1}$, $CONR^{a2}R^{a3}$, $SO_2NR^{a2}R^{a3}$, $-NR^{a2}-SO_2-R^{a4}$, $NR^{a2}-CO-R^{a5}$, SO_2-R^{a4} and $NR^{a6}R^{a7}$;

R^{1b} is selected independently of one another from the group consisting of OH, SH, COOH, CN, OCH_2COOH , halogen, phenyl which optionally has 1, 2 or 3 substituents R^{1d} ,

C₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-alkylthio, where the alkyl moieties in the last 3 substituents mentioned may be partly or completely halogenated and/or have 1, 2 or 3 substituents R^{1a},

COOR^{b1}, CONR^{b2}R^{b3}, SO₂NR^{b2}R^{b3}, NR^{b2}-SO₂-R^{b4}, NR^{b2}-CO-R^{b5},
 5 SO₂-R^{b4} and NR^{b6}R^{b7},

in addition two R^{1b} radicals may together form a C₁-C₄-alkylene group, or 2 R^{1b} radicals bonded to adjacent C atoms of cycloalkyl may form together with the carbon atoms to which they are bonded also a benzene ring,

10 R^{1c} is selected independently of one another from the group consisting of OH, SH, halogen, NO₂, NH₂, CN, COOH, OCH₂COOH, C₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-alkoxy-C₁-C₄-alkyl, C₁-C₆-alkylthio, where the alkyl moieties in the last 4 substituents mentioned may be partly or
 15 completely halogenated and/or have 1, 2 or 3 substituents R^{1a}, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₄-alkyl, C₃-C₇-cycloalkyloxy, where the cycloalkyl moiety of the last three radicals mentioned may have 1, 2, 3 or 4 R^{1b} radicals,

aryl, hetaryl, O-aryl, O-CH₂-aryl, where the last three radicals mentioned are unsubstituted in the aryl moiety or may carry 1, 2, 3 or
 20 4 R^{1d} radicals,

COOR^{c1}, CONR^{c2}R^{c3}, SO₂NR^{c2}R^{c3}, NR^{c2}-SO₂-R^{c4}, NR^{c2}-CO-R^{c5},
 SO₂-R^{c4},

-(CH₂)_p-NR^{c6}R^{c7} with p = 0, 1, 2, 3, 4, 5 or 6 and

25 O-(CH₂)_q-NR^{c6}R^{c7} with q = 2, 3, 4, 5 or 6; where

or two radicals R^{1b} or two radicals R^{1c} bonded to adjacent C atoms form together with the C atoms to which they are bonded a 4, 5, 6 or
 30 7-membered, optionally substituted carbocycle or an optionally substituted heterocycle which has 1, 2 or 3 different or identical heteroatoms from the group of O, N and S as ring members;

R^{1d} is selected from the group consisting of halogen, OH, SH, NO₂,

COOH, C(O)NH₂, CHO, CN, NH₂, OCH₂COOH, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkoxy, C₁-C₆-haloalkoxy, C₁-C₆-alkylthio, C₁-C₆-haloalkylthio, CO-C₁-C₆-alkyl, CO-O-C₁-C₆-alkyl, NH-C₁-C₆-alkyl, NHCHO, NH-C(O)C₁-C₆-alkyl, and SO₂-C₁-C₆-alkyl;

5

R² is selected from the group consisting of halogen, NH₂, CN, CF₃, CHF₂, CH₂F, O-CF₃, O-CHF₂, O-CH₂F, COOH, OCH₂COOH, C₁-C₂-alkyl, C₁-C₂-alkoxy, C₁-C₂-alkoxy-C₁-C₂-alkyl, C₁-C₂-alkylthio and CH₂NRR', where

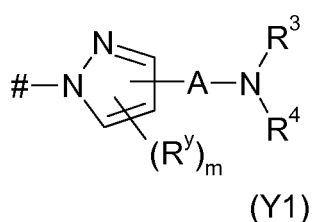
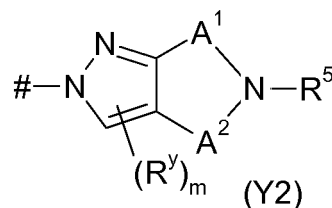
10

R and R' are selected independently of one another from the group consisting of hydrogen and C₁-C₄-alkyl;

n is 0, 1 or 2;

15

Y is a radical of the formulae Y1 or Y2



where # indicates the point of attachment of Y to the pyridine ring;

20

A is (CH₂)_p with p being 1, 2, 3 or 4, where one or two hydrogen atoms may be replaced by a radical R⁶, where A is attached to the 3- or 4-position of the pyrazole radical;

25

A¹ is (CH₂)_q with q being 0, 1, 2 or 3, where one or two hydrogen atoms may be replaced by halogen or C₁-C₄-alkyl;

A² is (CH₂)_r with r being 0, 1, 2 or 3, where one or two hydrogen atoms may be replaced by halogen or C₁-C₄-alkyl;

provided that $r + q$ is 2, 3, 4, 5 or 6;

m is 0 or 1;

5

R^y is selected from the group consisting of halogen, NH_2 , CN , CF_3 , CHF_2 , CH_2F , $O-CF_3$, $O-CHF_2$, $O-CH_2F$, $COOH$, OCH_2COOH , C_1-C_2 -alkyl, C_1-C_2 -alkoxy, C_1-C_2 -alkoxy- C_1-C_2 -alkyl and C_1-C_2 -alkylthio;

10

R^3 is selected from the group consisting of hydrogen, C_1-C_6 -alkyl, C_1-C_6 -haloalkyl, C_1-C_6 -alkyl which has 1, 2 or 3 substituents R^{3a} , C_3-C_7 -cycloalkyl, C_3-C_7 -cycloalkyl- C_1-C_4 -alkyl, where the cycloalkyl moiety of the last 2 radicals mentioned may have 1, 2, 3 or 4 radicals R^{3b} , C_2-C_6 -alkenyl or C_2-C_6 -alkynyl, where alkenyl and alkynyl, in the last 2 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{3a} , phenyl or phenyl- C_1-C_4 -alkyl, where phenyl in the last 2 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{3c} , and a radical $C(=O)R^{3d}$;

15

20

R^{3a} is selected from the group consisting of OH , SH , CN , C_1-C_6 -alkoxy, C_1-C_6 -haloalkoxy, C_3-C_7 -cycloalkyloxy, C_1-C_6 -alkylthio, C_1-C_6 -haloalkylthio, $COOR^{a1}$, $CONR^{a2}R^{a3}$, $SO_2NR^{a2}R^{a3}$, $-NR^{a2}-SO_2-R^{a4}$, $NR^{a2}-CO-R^{a5}$, SO_2-R^{a4} and $NR^{a6}R^{a7}$,

25

R^{3b} is selected from the group consisting of OH , SH , CN , halogen, C_1-C_6 -alkyl, C_1-C_6 -alkoxy, C_1-C_6 -alkylthio, where the alkyl moieties in the last 3 substituents mentioned may be partly or completely halogenated and/or have 1, 2 or 3 substituents R^{3a} , phenyl which optionally has 1, 2 or 3 substituents R^{3c} , $COOR^{b1}$, $CONR^{b2}R^{b3}$, $SO_2NR^{b2}R^{b3}$, $NR^{b2}-SO_2-R^{b4}$, $NR^{b2}-CO-R^{b5}$, SO_2-R^{b4} and $NR^{b6}R^{b7}$, or

30

two R^{3b} radicals may together also form a C_1-C_4 -alkylene group, or 2 R^{3b} radicals bonded to adjacent C atoms of cycloalkyl may form together with the carbon atoms to which they are bonded also a

benzene ring,

5 R^{3c} is selected from the group consisting of halogen, OH, SH, NO₂, C(O)NH₂, CHO, CN, NH₂, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkoxy, C₁-C₆-haloalkoxy, C₁-C₆-alkylthio, C₁-C₆-haloalkylthio, CO-C₁-C₆-alkyl, CO-O-C₁-C₆-alkyl, NH-C₁-C₆-alkyl, NH-C(O)C₁-C₆-alkyl, and SO₂-C₁-C₆-alkyl;

10 R^{3d} is selected from the group consisting of C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkyl which has 1, 2 or 3 substituents R^{3a} , C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₄-alkyl, where the cycloalkyl moiety of the last 2 radicals mentioned is unsubstituted or may have 1, 2, 3 or 4 radicals R^{3b} , phenyl which optionally has 1, 2 or 3 substituents R^{3c} ,

15 R^4 is selected from the group consisting of hydrogen, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkyl which has 1, 2 or 3 substituents R^{4a} , C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₄-alkyl, where the cycloalkyl moiety of the last 2 radicals mentioned may have 1, 2, 3 or 4 radicals R^{4b} , C₂-C₆-alkenyl or C₂-C₆-alkynyl, where alkenyl and alkynyl, in the last 2 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{4a} , 20 phenyl and phenyl-C₁-C₄-alkyl, where phenyl in the last 2 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{4c} , where R^{4a} is as defined for R^{3a} , R^{4b} is as defined for R^{3b} , and R^{4c} is as defined for R^{3c} ,

25 or the moiety NR³R⁴ in formula Y1 is a saturated, N-bound 4-, 5-, 6-, or 7-membered heteromonocyclic or 7-, 8-, 9-, or 10-membered heterobicyclic radical, where said heteromonocyclic and the heterobicyclic radical, in addition to the nitrogen atom, may have 1 or 2 further heteroatoms or heteroatom moieties as ring members, which are selected from O, S, S(O), 30 S(O)₂ and NR^{4d}, where said heteromonocyclic radical may carry a fused benzene ring and where said heteromonocyclic and the heterobicyclic radical are unsubstituted or may be substituted by 1, 2, 3 or 4 radicals R^{4e} ;

- 5 R^{4d} is selected from the group consisting of hydrogen, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkyl which has 1, 2 or 3 substituents R^{4a} , C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₄-alkyl, where the cycloalkyl moiety of the last 2 radicals mentioned is unsubstituted or may have 1, 2, 3 or 4 radicals R^{4b} , phenyl and phenyl-C₁-C₄-alkyl where the phenyl ring of the last 2 radicals mentioned is unsubstituted or may have 1, 2 or 3 substituents R^{4c} ,
- 10 R^{4e} is selected from the group consisting of halogen, OH, SH, NO₂, C(O)NH₂, CHO, CN, NH₂, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkoxy, C₁-C₆-haloalkoxy, C₁-C₆-alkylthio, C₁-C₆-haloalkylthio, COOR^{b1}, CONR^{b2}R^{b3}, SO₂NR^{b2}R^{b3}, NR^{b2}-SO₂-R^{b4}, NR^{b2}-CO-R^{b5}, SO₂-R^{b4}, and phenyl which optionally has 1, 2 or 3 substituents R^{4c} ;
- 15 R^5 has one of the meanings given for R^3 or is a radical COOR^{b1};
- R^6 if present, is selected from halogen or C₁-C₄-alkyl, or
- 20 R^6 together with R^4 forms a bivalent radical (CH₂)_s with s being 1, 2 or 3, where one or two hydrogen atoms may be replaced by halogen or C₁-C₄-alkyl;
- and where
- 25 R^{a1} , R^{b1} and R^{c1} are independently of one another selected from the group consisting of C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkyl which has 1, 2 or 3 substituents R^{1a} , or C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₄-alkyl, C₃-C₇-heterocycloalkyl-C₁-C₄-alkyl, C₁-C₆-alkoxy-C₁-C₄-alkyl, aryl, aryl-C₁-C₄-alkyl, hetaryl and hetaryl-C₁-C₄-alkyl, where
- 30 aryl and hetaryl in the last 4 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{1d} ,
- R^{a2} , R^{b2} and R^{c2} are independently of one another selected from the group

consisting of H, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkyl which has 1, 2 or 3 substituents R^{1a}, or C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₄-alkyl, C₃-C₇-heterocycloalkyl-C₁-C₄-alkyl, C₁-C₆-alkoxy-C₁-C₄-alkyl, aryl, aryl-C₁-C₄-alkyl, hetaryl and hetaryl-C₁-C₄-alkyl, where aryl and hetaryl in the last 4 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{1d},

R^{a3}, R^{b3} and R^{c3} are independently of one another selected from the group consisting of H, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkyl which has 1, 2 or 3 substituents R^{1a}, or C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₄-alkyl, C₃-C₇-heterocycloalkyl-C₁-C₄-alkyl, C₁-C₆-alkoxy-C₁-C₄-alkyl, aryl, aryl-C₁-C₄-alkyl, hetaryl and hetaryl-C₁-C₄-alkyl, where aryl and hetaryl in the last 4 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{1d}, or the two radicals R^{a2} and R^{a3}, or R^{b2} and R^{b3} or R^{c2} and R^{c3} form together with the N atom a 3 to 7-membered, optionally substituted nitrogen heterocycle which may optionally have 1, 2 or 3 further different or identical heteroatoms from the group of O, N, S as ring members,

R^{a4}, R^{b4} and R^{c4} are independently of one another selected from the group consisting of C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkyl which has 1, 2 or 3 substituents R^{1a}, or C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₄-alkyl, C₃-C₇-heterocycloalkyl-C₁-C₄-alkyl, C₁-C₆-alkoxy-C₁-C₄-alkyl, aryl, aryl-C₁-C₄-alkyl, hetaryl and hetaryl-C₁-C₄-alkyl, where aryl and hetaryl in the last 4 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{1d}, and

R^{a5}, R^{b5} and R^{c5} have independently of one another the meanings mentioned for R^{a1}, R^{b1} and R^{c1};

R^{a6}, R^{b6} and R^{c6} are independently of one another selected from the group consisting of H, C₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-haloalkyl, C₁-C₆-alkyl which has 1, 2 or 3 substituents R^{1a}, or C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-

- 5 C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₄-alkyl, C₃-C₇-heterocycloalkyl-C₁-C₄-alkyl, C₁-C₆-alkoxy-C₁-C₄-alkyl, CO-C₁-C₆-alkyl, CO-O-C₁-C₆-alkyl, SO₂-C₁-C₆-alkyl, aryl, hetaryl, O-aryl, OCH₂-aryl, aryl-C₁-C₄-alkyl, hetaryl-C₁-C₄-alkyl, CO-aryl, CO-hetaryl, CO-(aryl-C₁-C₄-alkyl), CO-(hetaryl-C₁-C₄-alkyl), CO-O-aryl, CO-O-hetaryl, CO-O-(aryl-C₁-C₄-alkyl), CO-O-(hetaryl-C₁-C₄-alkyl), SO₂-aryl, SO₂-hetaryl, SO₂-(aryl-C₁-C₄-alkyl) and SO₂-(hetaryl-C₁-C₄-alkyl), where aryl and hetaryl in the last 18 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{1d}, and
- 10 R^{a7}, R^{b7} and R^{c7} are independently of one another selected from the group consisting of H, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkyl which has 1, 2 or 3 substituents R^{1a}, or C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₄-alkyl, C₃-C₇-heterocycloalkyl-C₁-C₄-alkyl, C₁-C₆-alkoxy-C₁-C₄-alkyl, aryl, aryl-C₁-C₄-alkyl, hetaryl and hetaryl-C₁-C₄-alkyl,
- 15 where aryl and hetaryl in the last 4 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{1d}, or the two radicals R^{a6} and R^{a7}, or R^{b6} and R^{b7} or R^{c6} and R^{c7} form together with the N atom a 3 to 7-membered, optionally substituted nitrogen heterocycle which may optionally have 1, 2 or 3 further different or
- 20 identical heteroatoms from the group of O, N and S as ring members,

the tautomers thereof, the hydrates thereof, the prodrugs thereof and the pharmaceutically suitable salts thereof.

- 25 2. The carboxamide compound of claim 1, wherein R¹ is selected from the group consisting of C₁-C₁₀-alkyl which may be partly or completely halogenated and/or have 1, 2 or 3 substituents R^{1a}, C₃-C₇-cycloalkyl-methyl, where the cycloalkyl moiety may have 1, 2, 3 or 4 radicals R^{1b},
- 30 benzyl and hetaryl-methyl, where phenyl and hetaryl in the last 2 radicals mentioned may be unsubstituted or carry 1, 2, 3 or 4 identical or different radicals R^{1c}.

3. The carboxamide compound of claim 2, wherein R^1 is benzyl, which may be unsubstituted or carry 1 or 2 identical or different radicals selected from halogen, C_1 - C_2 -alkyl and C_1 - C_2 -alkoxy.
- 5
4. The carboxamide compound of any of the preceding claims, wherein n is 0 or 1 and, when $n = 1$, R^2 is selected from F, Cl, CN, CF_3 , C_1 - C_2 -alkyl and C_1 - C_2 -alkoxy.
- 10
5. The carboxamide compound of any of the preceding claims, wherein m is 0.
6. The carboxamide compound of any of the preceding claims, wherein Y is a radical of the formula $Y1$.
- 15
7. The carboxamide compound of claim 6, wherein the moiety $A-NR^3R^4$ in formula $Y1$ is located in the 3-position of the pyrazole ring.
8. The carboxamide compound of claim 6 or 7, wherein the moiety A is a bivalent radical of the formula $CH-R^p(CH_2)_z$, where the carbon atom which carries R^p is bound to the pyrazole ring, and where
- 20
- R^p is hydrogen or methyl or together with together with R^4 forms a bivalent radical of the formula $(CH_2)_s$ with s being 1, 2 or 3, and
- z is 0, 1 or 2.
- 25
9. The carboxamide compound of any of claims 6 to 8, wherein
- R^3 is C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl- C_1 - C_4 -alkyl, where the cycloalkyl moiety of the last 2 radicals mentioned may have 1, 2, 3 or 4 radicals R^{3b} ,
- 30
- phenyl or phenyl- C_1 - C_4 -alkyl, where phenyl in the last 2 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{3c} ,
- R^{3b} is selected from the group consisting of halogen, C_1 - C_6 -alkyl, which

may be partly or completely halogenated,

phenyl which optionally has 1, 2 or 3 substituents R^{3c} ;

R^{3c} is selected from halogen, OH, SH, NO_2 , $C(O)NH_2$, CHO, CN, NH_2 ,
C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkoxy, C₁-C₆-haloalkoxy, C₁-C₆-alkylthio, C₁-C₆-haloalkylthio, CO-C₁-C₆-alkyl, CO-O-C₁-C₆-alkyl,
NH-C₁-C₆-alkyl, NH-C(O)-C₁-C₆-alkyl, and SO₂-C₁-C₆-alkyl;

R^4 is hydrogen, C₁-C₆-alkyl or C₁-C₆-haloalkyl.

10. The carboxamide compound of any of claims 6 to 9, wherein the moiety NR^3R^4 in formula Y1 is a saturated, N-bound 4-, 5-, 6-, or 7-membered heteromonocyclic or 7-, 8-, 9-, or 10-membered heterobicyclic radical, where said heteromonocyclic and the heterobicyclic radical, in addition to the nitrogen atom, may have 1 further heteroatom or heteroatom moiety as ring member, which are selected from O, S, S(O)₂ and NR^{4d} , where said heteromonocyclic radical may carry a fused benzene ring and where said heteromonocyclic and the heterobicyclic radical are unsubstituted or may be substituted by 1, 2, 3 or 4 radicals R^{4e} ;

R^{4d} is selected from the group consisting of hydrogen, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkyl which has 1, 2 or 3 substituents R^{4a} , C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₄-alkyl, where the cycloalkyl moiety of the last 2 radicals mentioned is unsubstituted or may have 1, 2, 3 or 4 radicals R^{4b} , phenyl and benzyl where the phenyl ring of the last 2 radicals mentioned is unsubstituted or may have 1, 2 or 3 substituents R^{4c} ;

R^{4e} is selected from the group consisting of halogen, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkoxy, C₁-C₆-haloalkoxy, C₁-C₆-alkylthio, C₁-C₆-haloalkylthio and phenyl.

11. The carboxamide compound of any of claims 6 to 10, wherein the moiety NR^3R^4 in formula Y1 represents a radical which is selected from the group consisting of 4-morpholinyl, 4-thiomorpholinyl, 1,1-dioxothiomorpholin-4-yl, 2,6-

dimethylmorpholin-4-yl, 2-phenylmorpholin-4-yl, 1-azetidiny, 1-pyrrolidinyl, 3-phenylpyrrolidin-1-yl, 1-azepanyl, 1-piperidinyl, 4-methylpiperidin-1-yl, 4-ethylpiperidin-1-yl, 4-propylpiperazin-1-yl, 4-cyclopropylmethylpiperazin-1-yl, 4-cyclopropylpiperazin-1-yl, 4-phenylpiperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-(trifluoromethyl)piperidin-1-yl, 4-(tert.-butyl)piperidin-1-yl, 4-methylpiperazin-1-yl, 4-phenylpiperazin-1-yl, dimethylamino, diethylamino, diisopropylamino, N-phenylamino, N-methyl-N-phenylamino, N-cyclopropyl-N-methylamino, N-cyclohexyl-N-methylamino, N-benzyl-N-methylamino, N-cyclohexylmethyl-N-methylamino, N-methyl-N-isopropylamino, N-cyclopropyl-N-phenyl, N-cyclopropyl-N-benzyl, N-(4-trifluoromethylcyclohexyl)methyl-N-methylamino, 3,4-dihydro-2H-1,4-benzoxazin-4-yl, cis-octahydrobenzo-[1,4]oxazin-4-yl, trans-octahydrobenzo[1,4]oxazin-4-yl, 5,5-difluoroocta-hydrocyclopenta[c]pyrrol-2-yl, hexahydrofuro[3,4-c]pyrrol-5-yl, 2,3-dihydroindol-1-yl, 2-oxa-7-azaspiro[3.5]nonane-7-yl, 2,3-dihydro-1H-isoindole-2-yl, 5-trifluoromethyl-2,3-dihydro-1H-isoindole-2-yl, 4-trifluoro-2,3-dihydro-1H-isoindole-2-yl, 2,3-dihydroisoindole-1-one-2-yl, 1,2,3,4-tetrahydroisoquinoline-2-yl, 3-azabicyclo[3.2.0]heptane-3-yl and 6-(4-fluorophenyl)-3-azabicyclo[3.2.0]heptane-3-yl.

12. The carboxamide compound of claim 8, wherein

R^3 is C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl- C_1 - C_4 -alkyl, where the cycloalkyl moiety of the last 2 radicals mentioned may have 1, 2, 3 or 4 radicals R^{3b} ,
phenyl or phenyl- C_1 - C_4 -alkyl, where phenyl in the last 2 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{3c} ,

R^{3b} is selected from the group consisting of C_1 - C_6 -alkyl, which may be partly or completely halogenated,
phenyl which optionally has 1, 2 or 3 substituents R^{3c} ,

R^{3c} is selected from halogen, OH, SH, NO_2 , $C(O)NH_2$, CHO, CN, NH_2 , C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_1 - C_6 -alkoxy, C_1 - C_6 -haloalkoxy, C_1 - C_6 -alkylthio, C_1 - C_6 -haloalkylthio, CO- C_1 - C_6 -alkyl, CO-O- C_1 - C_6 -alkyl,

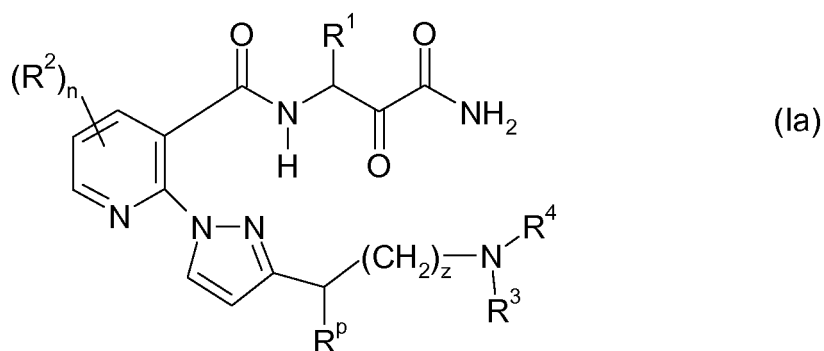
NH-C₁-C₆-alkyl, NH-C(O)C₁-C₆-alkyl, and SO₂-C₁-C₆-alkyl;

wherein R^p together with R⁴ forms a bivalent radical of the formula (CH₂)_s with s being 1, 2 or 3.

5

13. The carboxamide compound of claim 12, wherein the moiety A-NR³R⁴ in formula Y1 represents a radical which is selected from the group consisting of azetidin-3-yl, pyrrolidin-3-yl, 1-methylpyrrolidin-3-yl, piperidin-3-yl, 1-methylpiperidin-3-yl, piperidin-4-yl, 1-methylpiperidin-4-yl, 1-ethylpiperidin-4-yl, 1-propylpiperidin-4-yl, 1-cyclopropylpiperidin-4-yl and 1-benzylpiperidin-4-yl,.
- 10

14. The carboxamide compound of any of claims 6 to 13, having the following formula Ia



15

where R¹, R², R³, R⁴ and n are as defined in any of the preceding claims,

R^p is hydrogen, methyl or ethyl, or

R^p together with R⁴ forms a bivalent radical of the formula (CH₂)_s with s being 1, 2 or 3, and

20 z is 0, 1 or 2

the tautomers thereof, the hydrates thereof, the prodrugs thereof and the pharmaceutically suitable salts thereof.

15. The carboxamide compound of any of claims 1 to 5, wherein Y is a radical of the formula Y2.
- 25

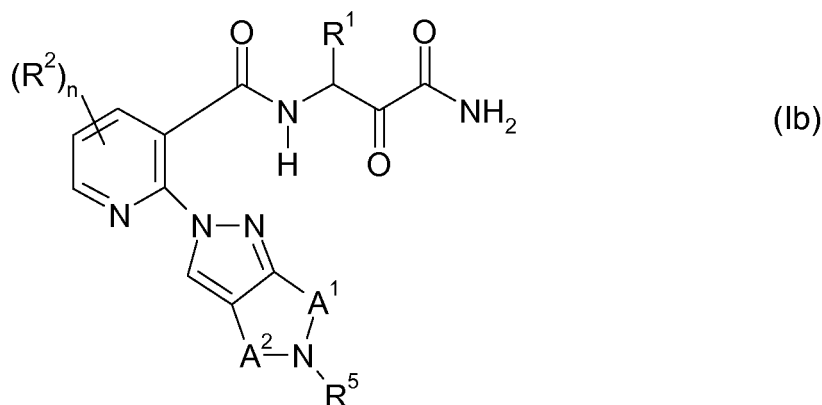
16. The carboxamide compound of claim 15, wherein the moiety A¹ is a single bond,

CH₂ or CH₂CH₂ and the moiety A² is CH₂, CH₂CH₂ or CH₂CH₂CH₂.

17. The carboxamide compound of any of claims 15 or 16, wherein .
- 5 R⁵ is hydrogen, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₄-alkyl, where the cycloalkyl moiety of the last 2 radicals mentioned may have 1, 2, 3 or 4 radicals R^{3b}, phenyl, phenyl-C₁-C₄-alkyl, where phenyl in the last 2 radicals mentioned are unsubstituted or have 1, 2 or 3 substituents R^{3c}, or
- 10 a radical a radical COOR^{b1}, where
- R^{3b} is selected from the group consisting of C₁-C₆-alkyl, which may be partly or completely halogenated, phenyl which optionally has 1, 2 or 3 substituents R^{3c},
- R^{3c} is selected from halogen, OH, SH, NO₂, C(O)NH₂, CHO, CN, NH₂,
- 15 C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkoxy, C₁-C₆-haloalkoxy, C₁-C₆-alkylthio, C₁-C₆-haloalkylthio, CO-C₁-C₆-alkyl, CO-O-C₁-C₆-alkyl, NH-C₁-C₆-alkyl, NH-C(O)C₁-C₆-alkyl, and SO₂-C₁-C₆-alkyl;
- R^{b1} is selected from the group consisting of C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₄-alkyl, phenyl and phenyl-C₁-C₄-alkyl, where
- 20 phenyl in the last 2 radicals mentioned is unsubstituted or has 1, 2 or 3 substituents R^{1d}, which are selected from the group consisting of halogen, C₁-C₆-alkyl, C₁-C₆-alkoxy and C₁-C₆-haloalkyl.
18. The carboxamide compound of any of claims 15 to 17, wherein the radical of the
- 25 formula Y2 is selected from the group consisting of 4,5,6,7-tetrahydropyrazolo[3,4-c]pyridin-2-yl, 6-(C₁-C₄-alkyl)-4,5,6,7-tetrahydropyrazolo[3,4-c]pyridin-2-yl, 6-(tert.-butoxycarbonyl)-4,5,6,7-tetrahydropyrazolo[3,4-c]pyridin-2-yl, 6-benzyl-4,5,6,7-tetrahydropyrazolo[3,4-c]pyridin-2-yl, 6-cyclopropylmethyl-4,5,6,7-tetrahydropyrazolo[3,4-c]pyridin-2-yl, 4,5,6,7-tetrahydropyrazolo[4,3-c]pyridin-2-yl, 5-(C₁-C₄-alkyl)-4,5,6,7-tetrahydropyrazolo[4,3-c]pyridin-2-yl, 5-(tert.-butoxycarbonyl)-4,5,6,7-tetrahydropyrazolo[4,3-c]pyridin-2-yl, 5-benzyl-4,5,6,7-tetrahydropyrazolo[4,3-c]pyridin-2-yl, 5-cyclopropylmethyl-4,5,6,7-tetrahydropyrazolo[4,3-c]pyridin-2-
- 30

yl, 2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-2-yl, 5-(C₁-C₄-alkyl)-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-2-yl, 5-benzyl-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-2-yl, 5-(tert.-butoxycarbonyl)-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-2-yl, 4,5,6,7-tetrahydropyrazolo[4,3-c]pyridin-2-yl, 5-(C₁-C₄-alkyl)-4,5,6,7-tetrahydropyrazolo[4,3-b]pyridin-2-yl, 5-(tert.-butoxycarbonyl)-4,5,6,7-tetrahydropyrazolo[4,3-b]pyridin-2-yl, 5-benzyl-4,5,6,7-tetrahydropyrazolo[4,3-b]pyridin-2-yl and 5-cyclopropylmethyl-4,5,6,7-tetrahydropyrazolo[4,3-b]pyridin-2-yl.

19. The carboxamide compound of any of claims 1 to 5 and 15 to 18, having the following formula Ib



where R¹, R², R⁵ and n are as defined above and where

A¹ is (CH₂)_q with q being 0, 1 or 2;

A² is (CH₂)_r with r being 1, 2 or 3;

where q + r is 1, 2 or 3,

the tautomers thereof, the hydrates thereof, the prodrugs thereof and the pharmaceutically suitable salts thereof.

20. The carboxamide compound of claim 1 which is selected from the group consisting of

N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(morpholinomethyl)-1H-pyrazol-1-yl)nicotinamide;

- N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((2,6-dimethylmorpholino)methyl)-1H-pyrazol-1-yl)nicotinamide;
N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((cis-2,6-dimethylmorpholino)methyl)-1H-pyrazol-1-yl)nicotinamide;
5 N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((trans-2,6-dimethylmorpholino)-methyl)-1H-pyrazol-1-yl)nicotinamide;
N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((4,4-difluoropiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide;
N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(5-benzyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-2-yl)nicotinamide;
10 N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((4-phenylpiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide;
2-(3-((2H-benzo[b][1,4]oxazin-4(3H)-yl)methyl)-1H-pyrazol-1-yl)-N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)nicotinamide;
15 N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(piperidin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide;
2-(3-((2H-benzo[b][1,4]oxazin-4(3H,4aH,5H,6H,7H,8H,8aH)-yl)methyl)-1H-pyrazol-1-yl)-N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)nicotinamide;
2-(3-((2H-benzo[b][1,4]oxazin-4(3H,4aHS,5H,6H,7H,8H,8aHS)-yl)methyl)-1H-pyrazol-1-yl)-N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)nicotinamide;
20 2-(3-((2H-benzo[b][1,4]oxazin-4(3H,4aHS,5H,6H,7H,8H,8aHR)-yl)methyl)-1H-pyrazol-1-yl)-N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)nicotinamide;
N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((2-phenylmorpholino)methyl)-1H-pyrazol-1-yl)nicotinamide;
25 N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(pyrrolidin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide;
N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(azetidin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide;
N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((4-(trifluoromethyl)piperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide;
30 N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-{3-[(5,5-difluorohexahydrocyclopenta[c]pyrrol-2(1H)-yl)methyl]-1H-pyrazol-1-yl}nicotinamide;
N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((dihydro-1H-furo[3,4-c]pyrrol-

- 5(3H,6H,6aH)-yl)methyl)-1H-pyrazol-1-yl)nicotinamide;
N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(indolin-1-ylmethyl)-1H-pyrazol-1-yl)nicotinamide;
N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((methyl(phenyl)amino)methyl)-1H-pyrazol-1-yl)nicotinamide;
5 N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-[3-(2-oxa-7-azaspiro[3.5]non-7-ylmethyl)-1H-pyrazol-1-yl]nicotinamide;
N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-{3-[(diethylamino)methyl]-1H-pyrazol-1-yl}nicotinamide;
10 N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-(isoindolin-2-ylmethyl)-1H-pyrazol-1-yl)nicotinamide;
N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-(3-{[cyclohexyl(methyl)amino]methyl}-1H-pyrazol-1-yl)nicotinamide;
N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-(3-{[benzyl(methyl)amino]methyl}-1H-pyrazol-1-yl)nicotinamide;
15 N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-[3-(3,4-dihydro-2(1H)-isoquinolinylmethyl)-1H-pyrazol-1-yl]nicotinamide;
N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((4-tert-butylpiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide;
20 N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((4-methylpiperidin-1-yl)methyl)-1H-pyrazol-1-yl)nicotinamide;
N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((methyl((4-(trifluoromethyl)cyclohexyl)methyl)amino)methyl)-1H-pyrazol-1-yl)nicotinamide;
25 N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((cyclopropyl(methyl)amino)methyl)-1H-pyrazol-1-yl)nicotinamide;
N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-(3-{[(6R)-6-(4-fluorophenyl)-3-azabicyclo[3.2.0]hept-3-yl]methyl}-1H-pyrazol-1-yl)nicotinamide;
N-(4-amino-3,4-dioxo-1-phenylbutan-2-yl)-2-(3-((phenylamino)methyl)-1H-pyrazol-1-yl)nicotinamide;
30 N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-{3-[(3-phenyl-1-pyrrolidiny)methyl]-1H-pyrazol-1-yl}nicotinamide;
N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-(3-{[5-(trifluoromethyl)-1,3-

- 5 dihydro-2H-isoindol-2-yl)methyl}-1H-pyrazol-1-yl)nicotinamide;
N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-{3-[(5-fluoro-1,3-dihydro-2H-isoindol-2-yl)methyl]-1H-pyrazol-1-yl}nicotinamide;
N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-{3-[(4-phenyl-1-piperazinyl)methyl]-1H-pyrazol-1-yl}nicotinamide;
N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-{3-[(4-fluoro-1,3-dihydro-2H-isoindol-2-yl)methyl]-1H-pyrazol-1-yl}nicotinamide;
N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-{3-[(1,1-dioxido-4-thiomorpholinyl)methyl]-1H-pyrazol-1-yl}nicotinamide;
10 N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-{3-[1-(1,3-dihydro-2H-isoindol-2-yl)ethyl]-1H-pyrazol-1-yl}nicotinamide;
N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-{3-[(1-oxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1H-pyrazol-1-yl}nicotinamide;
N-(1-amino-1,2-dioxo-3-heptanyl)-2-[3-(1-piperidinylmethyl)-1H-pyrazol-1-yl]nicotinamide;
15 N-(1-amino-1,2-dioxo-3-heptanyl)-2-{3-[(4,4-difluoro-1-piperidinyl)methyl]-1H-pyrazol-1-yl}nicotinamide;
N-(1-amino-1,2-dioxo-3-heptanyl)-2-[3-(1,3-dihydro-2H-isoindol-2-ylmethyl)-1H-pyrazol-1-yl]nicotinamide;
20 N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-(5-benzyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-2-yl)nicotinamide;
N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-[5-(cyclopropylmethyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-2-yl]nicotinamide;
N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-(4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-2-yl)nicotinamide;
25 tert-butyl 2-(3-(4-amino-3,4-dioxo-1-phenylbutan-2-ylcarbamoyl)pyridin-2-yl)-4,6-dihydropyrrolo[3,4-c]pyrazole-5(2H)-carboxylate;
N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-(5,6-dihydropyrrolo[3,4-c]pyrazol-2(4H)-yl)nicotinamide;
30 tert-butyl 2-(3-(4-amino-3,4-dioxo-1-phenylbutan-2-ylcarbamoyl)pyridin-2-yl)-2,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridine-6-carboxylate;
N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-(4,5,6,7-tetrahydro-pyrazolo[3,4-c]pyridin-2-yl)nicotinamide;

- tert-butyl 2-(3-(4-amino-3,4-dioxo-1-phenylbutan-2-ylcarbamoyl)pyridin-2-yl)-2,5,6,7-tetrahydro-4H-pyrazolo[4,3-b]pyridine-4-carboxylate;
N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-(4,5,6,7-tetrahydro-pyrazolo[4,3-b]pyridin-2-yl)nicotinamide;
- 5 N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-(4-benzyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-b]pyridin-2-yl)nicotinamide;
N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-[3-(1-methyl-4-piperidiny)-1H-pyrazol-1-yl]nicotinamide;
- 10 N-(4-amino-3,4-dioxo-1-phenyl-2-butanyl)-2-(6-ethyl-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridin-2-yl)nicotinamide;
- the tautomers thereof, the hydrates thereof, the prodrugs thereof and the pharmaceutically suitable salts thereof.
- 15 21. The carboxamide compound of any of the preceding claims, which has the S configuration at the carbon atom carrying the group R¹.
22. The carboxamide compound of any of the preceding claims for use in therapy.
- 20 23. A pharmaceutical composition comprising at least one carboxamide compound as of any of claims 1 to 21 and a carrier.
24. The carboxamide compound of any of claims 1 to 21 for the treatment of a disorder, an impairment or a condition which is associated with an elevated
- 25 calpain activity.
25. The carboxamide compound of any of claims 1 to 21 for the treatment of neurodegenerative disorders or impairments.
- 30 26. The carboxamide compound of any of claims 1 to 21, where a neurodegenerative disorder occurring as a result of a chronic brain supply deficit, an ischemia or a trauma is involved.

27. The carboxamide compound of any of claims 1 to 21 for the treatment of Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis or Huntington's disease.
- 5 28. The carboxamide compound of any of claims 1 to 21 for the treatment of multiple sclerosis and concomitant damage to the nervous system.
29. The carboxamide compound of any of claims 1 to 21 for the treatment of epilepsy.
- 10 30. The carboxamide compound of any of claims 1 to 21 for the treatment of pain.
31. The carboxamide compound of any of claims 1 to 21 for the treatment of damage to the heart following cardiac ischemias, skeletal muscle damage, muscular dystrophies, damage resulting from proliferation of smooth muscle cells, coronary vasospasms, cerebral vasospasms, macular degeneration, cataracts of the eyes, or
15 restenosis of the blood vessels following angioplasty.
32. The carboxamide compound of any of claims 1 to 21 for the treatment of damages to the kidney or chronic kidney diseases.
- 20 33. The carboxamide compound of any of claims 1 to 21 for the chemotherapy of tumors and metastasis thereof.
34. The carboxamide compound of any of claims 1 to 21 for the treatment of HIV
25 patients.
35. The carboxamide compound of any of claims 1 to 21 for the treatment of a disorder or an impairment associated with an elevated interleukin-I, TNF or A β level.
- 30 36. The carboxamide compound of any of claims 1 to 21 for the treatment of a disorder or an impairment associated with a protozoan infection such as malaria or toxoplasmosis.

37. A method for the therapeutic and/or prophylactic treatment of a mammal requiring a treatment, by administering an effective amount of at least one compound as claimed in any of claims 1 to 21 for the treatment of a disease, of a condition or of an impairment as set forth in any of claims 24 to 36.
38. The use of a carboxamide compound as claimed in any of claims 1 to 21 for preparing a medicament for the treatment of a disease, of a condition or of an impairment as set forth in any of claims 24 to 36.