



(51) International Patent Classification:

A61K 31/4196 (2006.01) C07D 413/14 (2006.01)
C07D 401/14 (2006.01) A61P 5/06 (2006.01)
C07D 403/06 (2006.01)

(21) International Application Number:

PCT/EP2011/066057

(22) International Filing Date:

16 September 2011 (16.09.2011)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/383,392 16 September 2010 (16.09.2010) US
10177105.3 16 September 2010 (16.09.2010) EP

(71) Applicants (for all designated States except US):

ÆTERNA ZENTARIS GMBH [DE/DE]; Weismüller-
straße 50, 60314 Frankfurt am Main (DE). CENTRE
NATIONAL DE LA RECHERCHE SCIENTIFIQUE
[FR/FR]; 3 rue Michel Ange, F-75794 Paris Cedex 16
(FR). UNIVERSITY OF MONTPELLIER I [FR/FR];
5, boulevard Henri IV, F-34967 Montpellier Cedex 2
(FR). UNIVERSITY OF MONTPELLIER II [FR/FR];
Case Courrier 406, Place Eugène Bataillon, F-34095
Montpellier Cedex 5 (FR).

(72) Inventors: AICHER, Babette; Scheffelstraße 13, 60318

Frankfurt am Main (DE). MÜLLER, Gilbert; Bischof-
sweg 1 A, 60598 Frankfurt am Main (DE). PAULINI,
Klaus; Bahnhofstraße 136c, 63477 Maintal (DE). BLU-
MENSTEIN, Lars; Erich-Kästner-Straße 11, 60388
Frankfurt am Main (DE). SCHMIDT, Peter; Dittersdor-
fer Strasse 42, 61137 Schöneck (DE). GERLACH,
Matthias; Pfarrgasse 1, 63636 Brachtal (DE). TEIFEL,

Michael; Franz-Seliger-Str. 15, 64331 Weiterstadt (DE).
MARTINEZ, Jean; Le Jardin des Muses, 9 rue Jean
Moulin, F-34720 Caux (FR). FEHRENTZ, Jean-Alain;
217 avenue de l'Abrivado, F-34400 St. Nazaire de Pezan
(FR). BLAYO, Anne-Laure; Kergohan, F-56580 Credin
(FR).

(81) Designated States (unless otherwise indicated, for every

kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,
CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO,
DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP,
KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD,
ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI,
NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU,
RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ,
TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA,
ZM, ZW.

(84) Designated States (unless otherwise indicated, for every

kind of regional protection available): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG,
ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ,
TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,
LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK,
SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments (Rule 48.2(h))

(54) Title: NOVEL TRIAZOLE DERIVATIVES WITH IMPROVED RECEPTOR ACTIVITY AND BIOAVAILABILITY PROPERTIES AS GHRELIN ANTAGONISTS OF GROWTH HORMONE SECRETAGOGUE RECEPTORS

(57) Abstract: The present invention provides novel triazole derivatives with improved receptor activity and bioavailability properties as ghrelin analogue ligands of growth hormone secretagogue receptors according to formula (I) that are useful in the treatment or prophylaxis of physiological and/or pathophysiological conditions in mammals, preferably humans, that are mediated by GHS receptors. The present invention further provides GHS receptor antagonists and agonists that can be used for modulation of these receptors and are useful for treating above conditions, in particular alcohol disorder; drug abuse; growth retardation; cachexia; short-, medium- and/or long term regulation of energy balance; short-, medium- and/or long term regulation (stimulation and/or inhibition) of food intake; intake of rewarding food; adipogenesis; adiposity and/or obesity; body weight gain and/or reduction; diabetes, diabetes type I, diabetes type II; tumor cell proliferation; inflammation; inflammatory effects; gastric postoperative ileus; postoperative ileus and/or gastrectomy (ghrelin replacement therapy)".



Novel Triazole Derivatives with Improved Receptor Activity and Bioavailability Properties as Ghrelin Antagonists of Growth Hormone Secretagogue Receptors

Description

5

Technical field:

The invention relates to novel triazole derivatives with improved receptor activity
10 and bioavailability properties that act as ghrelin analogous ligands of growth hormone secretagogue receptors. These compounds are useful in modulating growth hormone plasma levels in mammals as well as in the treatment and/or regulation of various physiological and pathophysiological conditions, such as growth retardation, obesity, food intake, energy balance, and other metabolic disorders, tumor cell proliferation,
15 wound/burn/bone healing, inflammation, and addiction processes like food reward, alcohol-related disorders and drug abuse.

Prior art:

20

Ghrelin, a 28 amino acid peptide with a unique octanoyl modification on Ser-3 (Kojima M et al., Nature 1999, 402: 656-660), was identified as an endogenous ligand for the growth hormone secretagogue receptor type 1a (GHS-R 1a), a G-protein coupled receptor (Howard AD et al., Science 1996, 273: 974-977). Ghrelin is
25 essentially produced in the upper intestinal tract/stomach but lower amounts were also detected in bowel, pancreas, kidney, the immune system, placenta, testes, pituitary, lung and in the hypothalamus (van der Lely AJ et al., Endocrine Rev. 2004, 25: 426-457; Cowley M et al., Neuron 2003, 37: 649-661).

In humans, ghrelin stimulates growth hormone (GH) via a pathway independent
30 from GHRH receptor and in synergy with GHRH on GH secretion (Arvat E et al., J. Clin. Endocrinol. Metab. 2001, 86: 1169-1174). Besides, it also stimulates ACTH, prolactin, cortisol, aldosterone and epinephrine secretion (Arvat E et al., J. Clin. Endocrinol. Metab. 2001, 86: 1169-1174; Nagaya N et al., Am. J. Physiol. Regul. Integr. Comp. Physiol. 2001, 280: R1483-1487; Takaya K et al., J. Clin. Endocrinol.
35 Metab. 2000, 85: 4908-4911).

Ghrelin is thought to participate in metabolism regulation and energy expenditure, so ghrelin expression and secretion into the general circulation from the stomach is expected to be influenced by metabolic hormones. In obese humans, plasma ghrelin levels are reduced, suggesting that the elevated insulin or leptin levels of obese subjects lower ghrelin secretion (Tschop M et al, Diabetes 2001, 50: 707-709).

The release of growth hormone in humans and animals is believed to treat physiological or pathophysiological conditions characterized by a deficiency in growth hormone secretion as well as to treat those conditions which are improved by the anabolic effects of growth hormone.

Initially, clinical applications with GH were limited to treatment of GH-deficient children, but the commercialization of recombinant human growth hormone (rhGH) allowed many studies which showed other potential clinical uses of GH (Strobl JS et al., Pharmacol. Rev. 1994, 46: 1-34; Torosian MH, J. Pediatr. Endocrinol. 1993, 6: 93-97). rhGH has shown promise in the treatment of patients with burns, wounds, bone fractures and more recently in reversing the catabolic effects of glucocorticoids, chemotherapy and AIDS as well as in modifying body composition (Rudman D et al., N. Engl. J. Med. 1990, 323: 1-6; Papadakis MA et al., Ann. Intern. Med. 1996, 124: 708-716; Welle S et al., J. Clin. Endocrinol. Metab. 1996, 81: 3239-3243).

GH, synthesized and stored in the pituitary gland, is released under the control of two known hypothalamic hormones: growth hormone releasing hormone (GHRH) and the inhibitory hormone somatostatin (SRIF). In most cases, GH deficiency is related to a hypothalamic defect and not to a pituitary deficiency in GH. Therefore, as an alternative treatment to rhGH, GH-deficient patients could also be treated with any compound that releases endogenous GH from the pituitary gland. This can either be performed with GHRH which stimulates GH release but also with synthetic growth hormone secretagogues (GHS).

Many synthetic, peptidyl and non-peptidyl GHS, such as GHRPs 1, 2 and 6, Hexarelin, MK-0677, EP-01572, were shown to specifically bind to the then orphan receptor "GHS receptor"—several of them long before ghrelin and ghrelin/GHS receptor were discovered (see "Camanni F et al., Front Neuroendocrinol. 1998, 19: 47-72"; "Casanueva FF et al., Trends Endocrinol. Metab. 1999, 10: 30-38"; "van der Lely AJ et al., Endocrine Rev. 2004, 25: 426-457" for further references). GHS also show potent GH releasing action and have the same biological activities as mentioned above for ghrelin.

GHS were also disclosed in the following patents or patent applications (not exhaustive list): US 6,071,926, US 6,329,342, US 6,194,578, US 2001/0041673, US 6,251,902, US 2001/0020012, US 2002/0013320, US 2002/0002137, WO 95/14666, WO 96/15148, WO 01/96300.

- 5 While the ghrelin/GHS induced GH secretion is mediated by the activation of the ghrelin/GHS receptor type 1a (GHS-R 1a), there is evidence so far that at least some of the other effects of ghrelin and GHS are also mediated by different receptors of the GHS receptor family or even different binding sites on a given GHS receptor.

GHS receptors are concentrated in the hypothalamus-pituitary area but appear also
10 to be distributed in other central and peripheral tissues (Hattori N et al., J. Clin. Endocrinol. Metab. 2001, 86: 4284-4291; Gnanapavan S et al., J. Clin. Endocrinol. Metab. 2002, 87: 2988-2991; Muccioli G et al., J. Endocrinol. 2000, 157: 99-106; Muccioli G et al., Ann. Endocrinol. 2000, 61: 27-31; Muccioli G et al., Eur. J. Pharmacol. 2002, 440: 235-254; Papotti M et al., J. Clin. Endocrinol. Metab. 2000, 85:
15 3803-3807; Cassoni P et al., J. Clin. Endocrinol. Metab. 2001, 86: 1738-1745; Guan XM et al., Brain Res. Mol. Brain Res. 1997, 48: 23-29; Bluett-Pajot MT et al., Endocrine 2001, 14: 1-8; Korbonits M et al., J. Clin. Endocrinol. Metab. 1998, 83: 3624-3630).

Two GHS type 1 receptors have been identified, GHS-R 1a and GHS-R 1b, that in human are presumably expressed by a single gene and alternatively spliced (van der
20 Lely AJ et al., Endocrine Rev. 2004, 25: 426-457; Howard AD et al., Science 1996, 273: 974-977; Smith RG et al., Endocr. Rev. 1997, 18: 621-645; Smith RG et al., Endocrine 2001, 14: 9-14; McKee KK et al., Mol. Endocrinol. 1997, 11: 415-423; Petersenn S, Minerva Endocrinol. 2002; 27: 243-256). Among mammalian species a high degree of sequence identity has been reported for GHS-R 1a (Petersenn S,
25 Minerva Endocrinol. 2002; 27: 243-256: between 91,8% and 95,6%).

Motilin receptor, was discovered as a member of the GHS receptor family, having 52 % identity (Smith RG et al., Endocrine 2001, 14: 9-14; McKee KK et al., Genomics 1997, 46: 426-434). Gastrointestinal motilin receptor 1a and GHS-R 1a show a high similarity (Smith RG et al., Endocrine 2001, 14: 9-14; Feighner SD et al., Science 1999,
30 284: 2184-2188).

Other GHS receptor family members appear to be neurotensin receptor, TRH receptor, GPR38 (FM1), GPR39 (FM2) and FM3 (Smith RG et al., Endocr. Rev. 1997, 18: 621-645; Smith RG et al., Horm. Res. 1999, 51 (Suppl. 3): 1-8; Tan CP et al., Genomics 1998, 52: 223-229; Howard AD et al., Science 1996, 273: 974-977). Further

GHS receptor subtypes appear to exist in a wide variety of central and peripheral tissues (van der Lely AJ et al., *Endocrine Rev.* 2004, 25: 426-457). For instance, a cardiac GHS-R has been reported (Bodart V et al., *Circ. Res.* 1999, 85: 796-802) with a predicted sequence similar to that of CD36, a multifunctional receptor known as glycoprotein IV (Bodart V et al., *Circ. Res.* 2002, 90: 844-849). Cassoni et al. (*J. Clin. Endocrinol. Metab.* 2001, 86: 1738-1745) report the existence of GHS-R subtypes in neoplastic mammary cells that are activated by ligands binding to specific binding sites different from the classical GHS-R type 1. Furthermore, data gathered by these authors support the hypothesis that even different binding site subtypes do exist for GHS-R in peripheral organs, which are possibly due to their endocrine or non-endocrine, but also on their normal or neoplastic nature.

The ubiquity of GHS binding sites explains that independently from their strong growth hormone secretagogue properties, ghrelin as well as synthetic GHS are implicated in several important physiological and pathophysiological conditions.

Accordingly, potential clinical applications include among others

a) Short-, medium- and long-term regulation of energy balance and/or food intake (Tschoep M et al., *Nature* 2000, 407: 908-913; Asakawa A et al., *Gut* 2003, 52: 947-952; US 2001/0020012; Kojima M et al., *Curr. Opin. Pharmacol.* 2002, 2: 665-668; Horvath TL et al., *Curr. Pharm. Des.* 2003, 9: 1383-1395; Wren AM et al., *J. Clin. Endocrinol. Metab.* 2001, 86: 5992-5995)

Expression of GHS-R1a has been shown on neurons of hypothalamus paraventricular nucleus. These neurons send efferents onto key hypothalamic circuits for the control of food intake, like the arcuate nucleus which produces the mediator NPY. It is thought that the stimulation of food intake by ghrelin and/or GHS is mediated by an increase of NPY in the arcuate nucleus (Willesen MG et al., *Neuroendocrin.* 1999, 70: 306-316). Single administration (icv or ip) of anti-ghrelin IgG suppressed acute feeding in lean rats (Bagnasco M et al., *Regul. Pept.* 2003, 111: 161-167). Chronic twice-daily icv administration of anti-ghrelin IgG reduced body weight over a five-day period (Murakami N et al., *J. Endocrinol.* 2002, 174: 283-288).

A recent study using a peptidic GHS-R 1a antagonist, [D-Lys-3]-GHRP-6, showed a reduction of food intake and body weight gain in diet induced obese mice (Asakawa A et al., *Gut*, 2003, 52: 947-952). The fact that peptidyl compounds, initially characterized as growth hormone secretagogues, are able

to stimulate selectively food intake in rats without inducing growth hormone secretion, suggests the existence of a GHS-R subtype different from GHS-R1a in the hypothalamus (Torsello A et al., *Neuroendocrin.* 2000, 72: 327-332; Torsello A et al., *Eur. J. Pharmacol.* 1998, 360: 123-129).

- 5 b) Treatment of adipogenesis, adiposity and/or obesity and reduction of body weight (Tschop M et al., *Nature* 2000, 407: 908-913; Asakawa A et al., *Gut* 2003, 52: 947-952)

10 Chronic administration of ghrelin and/or GHS in freely feeding mice and rats results in increased body weight and decreased fat utilization (Tschop M et al., *Nature* 2000, 407: 908-913). Furthermore, it has been reported that ghrelin and des-octanoyl ghrelin promote adipogenesis in vivo (Thompson NM et al., *Endocrinol.* 2004, 145: 234-242) and inhibit isoproterenol-induced lipolysis in rat adipocytes via a non-type GHS-R 1a (Muccioli G et al., *Eur. J. Pharmacol.* 2004, 498: 27-35). On the other hand, there is also a report describing that the
15 expression of the GHS-R1a in rat adipocytes increases with age and during adipogenesis (Choi K et al., *Endocrinol.* 2003, 144, 754-759).

- c) Treatment of tumor cell proliferation

20 As in the case for other members of the hypothalamus-pituitary axis which regulates the secretion of growth hormone, evidence is emerging to indicate that ghrelin and GHS-receptors may play an important autocrine/paracrine role in some cancers (Jeffery PL et al., *Cytokine Growth Factor Rev.* 2003, 14: 113-122). Specific binding sites for ghrelin, peptidyl- and non-peptidyl GHS are present in tumoral tissues, like prostate cancer cell line PC3 (Jeffery PL et al., *J. Endocrinology* 2002, 172: R7-R11), thyroid tissue (Cassoni P et al., *J. Endocrinol.* 2000, 165: 139-146), lung carcinoma cells CALU-1 (Ghè C et al., *Endocrinol.* 2002, 143: 484-491) and breast carcinomas (Cassoni P et al., *J. Clin. Endocrinol. Metab.* 2001, 86: 1738-1745).

30 In the case of breast, the specific binding sites for GHS were found in tumoral tissue while the normal mammary parenchyma did not reveal such receptors. Synthetic GHS have been reported to inhibit the proliferation of lung carcinoma cells CALU-1 (Ghè C et al., *Endocrinol.* 2002, 143: 484-491) and that of breast carcinoma cell lines (Cassoni P et al., *J. Clin. Endocrinol. Metab.* 2001, 86: 1738-1745).

Both ghrelin and non-acylated ghrelin bind to tumoral tissues. Because non-acylated ghrelin is unable to bind the GHS-R1a, it is likely that the binding site of GHS to tumoral tissues is different from the GHS-R1a. From these data, one can anticipate that the binding site in tumoral tissues recognizes ligands of the GHS-R1a and in addition other not yet characterized chemical structures. Synthetic ligands of GHS-R1a may have therefore the potential to inhibit the proliferation of tumor cells expressing subtypes of GHS receptors.

d) Treatment of inflammation/anti-inflammatory effects

The anti-inflammatory effect of the ghrelin agonist growth hormone-releasing peptide-2 (GHRP-2) in chronic arthritis with clinical manifestations of hypermetabolism and cachexia was demonstrated (Granado M et al., Am. J. Physiol. Endocrinol. Metab. 2005, 288: E486-492). These data suggest that the anti-inflammatory action of GHRP-2 is mediated by activation of ghrelin receptors expressed by immune competent cells.

e) Treatment of cachexia

The anti-cachectic effect of administered recombinant growth hormone in an animal model of cachexia (Roubenoff R et al., Arthritis Rheum. 1997, 40(3): 534-539) could be demonstrated (Ibanez de Caceres I et al., J. Endocrin. 2000, 165(3): 537-544). The findings are also in line with data of patients with rheumatoid arthritis (Roubenoff R et al., J Clin Invest. 1994, 93(6): 2379-2386).

f) Treatment of gastrectomy (ghrelin replacement therapy)

The gastric hormone ghrelin was given to mice subjected to gastrectomy or sham operation (Dornonville de la Cour C et al., Gut 2005, 54(7): 907-913). The results presented show that ghrelin replacement therapy at least partially reverse gastrectomy induced reduction in body weight and body fat.

g) Treatment of (gastric) postoperative ileus

The effect of ghrelin on the motor function of the gastrointestinal tract in rat was evaluated. It could be shown that ghrelin reverses the delayed gastric evacuation and is a strong prokinetic agent useful for the treatment/reversion of postoperative gastric ileus (Trudel L et al., Am J Physiol Gastrointest Liver Physiol 2002, 282(6): G948-G952).

h) Treatment of diabetes (diabetes type I and type II)

5 The effect of ablation of ghrelin in leptin-deficient mice was studied (Sun et al., Cell Metabolism 2006, 3: 379-386). The results show that deletion of ghrelin augments insulin secretion in response to glucose challenge indicating that inhibition of ghrelin or counteracting its activity may be a possible way for the treatment of diabetes including its subtypes I and II (see also WO 03/051389).

- i) Treatment of addiction processes like food reward, alcohol disorders, and drug abuse

10 The mesolimbic dopamine projections, originating from neuronal cell populations in the ventral tegmental area (VTA) and terminating in the ventral striatum and the prefrontal cortex, are linked to anticipatory, appetitive or approach phases of motivated behaviour and are important for anticipatory food reward and food seeking behaviours (Bassareo and Chiara 1999, Neuroscience 89, 637-641; Richardson and Gratton 1998, J Neurosci 18, 9130-9138). Activation of these dopamine projections is also elicited by ingestion of
15 rewarding foods as well as by other rewards, both natural (e.g. sex) and artificial, like alcohol and drug abuse (Berridge and Robinson 1998, Brain Res Brain Res Rev 28, 637-641). There is accumulating evidence that the mesolimbic system is a target for ghrelin. In addition to the hypothalamus, the ghrelin receptor has also been identified in the ventral tegmental area (VTA)
20 and laterodorsal tegmental area (LDTg). More recent findings indicate that the effects of ghrelin on food intake are partly mediated by the mesolimbic dopamine systems involved in reward-seeking behaviour (Jerlhag E. et al. 2006 Addiction Biology 11 :45-54; Jerlhag E, et al. Addict Biol. 2007 12:6-16; Egecioglu E. et al. 2010, Addiction Biology 15, 304-311). In addition, most
25 recent data confirm the suitability of ghrelin antagonists for the treatment of alcohol disorders (WO2009/020419 and Jerlhag et al. 2009. PNAS 106, 11318-11323) and drug abuse (Jerlhag E. et al. 2010, Psychopharmacology 211, 415-422).

30 Further fields of application comprise acceleration of recovery of patients having undergone major surgery (e.g. US 6,194,578); accelerating the recovery of burn patients (e.g. US 6,194,578); attenuating protein catabolic response after a major operation (e.g. US 6,194,578); reducing cachexia and protein loss due to acute or chronic illness (e.g. US 6,194,578); treating central nervous system disorders of patients undergoing a medical procedure in combination with antidepressants (e.g.

US 2002/0002137 A1); acceleration of bone fracture repair and cartilage growth (e.g. US 6,194,578); treatment or prevention of osteoporosis; stimulation of the immune system; accelerating wound healing (e.g. US 6,194,578); treatment of growth retardation associated with the Prader-Willi syndrome, Turner's syndrome and obesity;
5 treatment of intrauterine growth retardation, skeletal dysplasia, hypercortisolism and Cushing's syndrome; treatment of osteochondrodysplasias, Noonan's syndrome, schizophrenia, depressions and Alzheimer's disease; treatment of pulmonary dysfunction and ventilator dependency; treatment of hyperinsulinemia including nesidioblastosis; adjuvant treatment for ovulation induction; prevention of the age-
10 related decline of thymic function; improvement in muscle strength and mobility (e.g. US 6,194,578); maintenance of skin thickness (e.g. US 6,194,578); improvement of sleep quality (e.g. US 6,071,926); prevention of congestive heart failure alone (e.g. US 6,329,342; US 6,194,578) and in combination with corticotropin releasing factor antagonists (e.g. US 2001/0041673); metabolic homeostasis or renal homeostasis (e.g.
15 in the frail elderly)(e.g. US 6,194,578); improving glycemic control (e.g. US 6,251,902); treatment of systemic lupus erythematosus and inflammatory bowel disease (e.g. US 2002/0013320); treating or preventing frailty associated with aging or obesity (e.g. US 6,194,578); as well as stimulation of osteoblasts.

Animals were not forgotten in potential applications such as stimulation of food
20 intake (Wren AM et al., Diabetes 2001, 50: 2540-2547), stimulation of the immune system in companion animals and treatment of disorder of aging, growth promotion in livestock and stimulation of wool growth in sheep.

Compounds containing triazole moieties have been widely recognized in the medicinal chemistry due to their various biological activities. The following patent
25 families are all directed to heterocyclic compounds that are said to show certain biological action for use in different medicinal indications. Triazole moieties are implicitly or explicitly contained.

Triazole derivatives as Ghrelin Analogue Ligands of Growth Hormone Secretagogue Receptors having good receptor affinity are disclosed in WO07/020013.
30 WO 2004/111015 discloses modulators of the glucocorticoid receptor. WO 2004/052280 describes anti-angiogenic compounds as inhibitors of tyrosine kinase activity of VEGF receptors and their use in cancer. WO 2004/096795 also discloses tyrosine kinase inhibitors, preferably C-FMS inhibitors. WO 03/011831 and WO 03/011210 both describe heteroarylheteroalkylamine derivatives as inhibitors of

nitric oxide synthase. WO 02/00651 is directed to Factor XA inhibitors for use in thromboembolic disorders. WO 01/94318 and WO 01/94317 both describe chemical libraries of substituted azole derivatives and methods of their synthesis for use in drug discovery high-throughput screening. However, they fail to provide any biological activity or any medicinal use nor do they name specific compounds. WO 00/76971 and WO 00/76970 both claim serine protease inhibitors useful as antithrombotic agents. WO 01/36395 discloses triazole derivatives as farnesyl transferase inhibitors. WO 96/33176 and US 5,703,092 are directed to hydroxamic acid compounds as metalloprotease and TNF inhibitors. WO 93/09095 describes 2-heterocyclicethylamine derivatives and their use in neurological and neurodegenerative disorders. WO 2004/103270 claims compounds for the treatment of thrombosis, in particular Factor Xla inhibitors. WO 98/38177, US 6,506,782, US 6,849,650 and US 2003/0130188 all describe heterocyclic compounds as inhibitors of beta-amyloid peptide release or its synthesis for use in Alzheimer's disease.

Heterocyclic compounds that may be useful as GHS have also been described in the literature.

WO 00/54729, for instance, discloses heterocyclic aromatic compounds as GH secretagogues which are said to stimulate endogenous production and/or release of GH and can also contain triazole moieties. In addition, a method for increasing levels of endogenous GH or increasing the endogenous production or release of GH administering such GHS is described. Furthermore, a method is provided for preventing or treating osteoporosis (improving bone density and/or strength), or treating obesity, or increasing muscle mass and/or muscle strength and function in elderly humans, or reversal or prevention of frailty in elderly humans administering such GHS.

However, although claiming *in vivo* GH release, WO 00/54729 fails to actually prove such effect. Neither *in vitro* nor *in vivo* data are contained that demonstrate any stimulation of or increase in endogenous production and/or release of GH.

Besides, WO 00/54729 fails to describe and show action of those claimed compounds on any biological target, i.e. claimed compounds are not shown/described to be ligands of one or more specific receptors, for instance of a receptor family, that bind to them and modulate their activity.

Furthermore, WO 00/54729 fails to describe and demonstrate inhibitory and/or antagonistic activity of claimed compounds. As a matter of fact, such compounds are

not shown to decrease levels of endogenous GH and/or inhibit or decrease endogenous production and/or release of GH. Nor is an inhibitory action on any receptor mentioned nor made obvious.

US 6,525,203, US 6,518,292 US 6,660,760 are members of the same patent family
5 as WO 00/54729 that, however, do not comprise triazole moieties as claimed subject matter any more. With regard to biological activity, the above stated facts as for WO 00/54729 apply.

WO 2004/021984 describes heterocyclic aromatic compounds GH secretagogues which are said to be useful in stimulating endogenous production or release of GH.
10 However, claimed compounds consists of bi- to tetracyclic aromatic rings and do not contain triazoles.

Analogous to WO 00/54729 *in vivo* GH release is claimed, but neither *in vitro* nor *in vivo* data are contained that demonstrate any stimulation of or increase in endogenous production and/or release of GH. With regard to biological activity, the same stated
15 facts as for WO 00/54729 apply.

WO 97/23508 claims compounds of peptide mimetic nature as GHS and are said to act directly on pituitary cells *in vitro* to release GH therefrom and show improved properties, such as improved resistance to proteolytic degradation and improved bioavailability. In addition, claimed compounds could also be administered *in vivo* to
20 increase GH release. The compounds are peptide derivatives and do not explicitly contain triazole moieties.

However, once again and in analogy to above WO 00/54729 and WO 2004/021984, WO 97/23508 fails to exhibit any *in vitro* or *in vivo* data that demonstrate the claimed effects such as direct action on pituitary cells, GH release
25 therefrom and improved properties. Furthermore, with regard to biological targets and inhibitory/antagonistic activity, the above stated facts as for WO 00/54729 apply.

US 6,127,391, US 5,977,178 and US 6,555,570 are members of the same patent family as WO 97/23508. The facts as stated for WO 97/23508 do apply.

The compounds described in this invention were designed to exhibit improved
30 activity against ghrelin receptors of at least factor three compared to a representative compound, i.e. compound 50 disclosed in WO07/020013.

Furthermore, the compounds described in this invention are expected to possess improved oral bioavailability. Chemical synthesis was directed to modify residues R2, R5, and R7 in order to provide compounds with improved ADME properties.

In comparison to the compounds disclosed in WO07/020013, the compounds
5 described herein exhibit improved properties in at least one of the following parameters, which are widely accepted to be essential for reasonable oral bioavailability (Caldwell GW. 2000, Curr Opin Drug Discov Devel. 3(1), 30-41; Thomas VH. et al. 2006, Expert Opin Drug Metab Toxicol 2(4), 591-608):

CaCo-2 permeability: $P_{APP} (a \rightarrow b) > 1 \times 10^{-6} \text{ cm/s}$

10 No evidence of efflux as indicated by $b \rightarrow a/a \rightarrow b$ ratio < 2

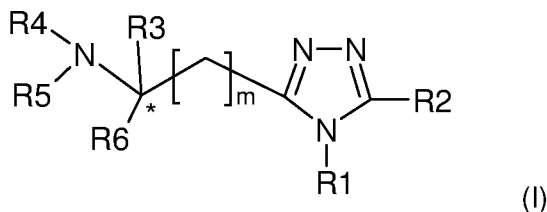
Metabolic stability: In in vitro microsomal stability studies, a rat CL of $< 50 \text{ ml/min/kg}$ (alternatively, $>30\%$ remaining at 60 min)

Hence, the present invention has the object to provide novel compounds with improved receptor antagonistic activity and ADME properties which can be employed
15 for the treatment of physiological and/or pathophysiological conditions in mammals, in particular humans, that are mediated by GHS receptors. It is another object of the present invention to provide agonists of GHS receptors for those treatments. It is also another object of the underlying invention to provide inverse agonists for the above treatment where the treatment is achieved by modulation of GHS receptors. A further
20 object of the present invention is to provide partial agonists/antagonists of GHS receptors for those treatments.

Description of the invention

The object of the invention has been surprisingly solved in one aspect by providing compounds according to formula (I)

5



wherein:

(A)

10 **R1** and **R2** are independently of one another selected from the group consisting of "hydrogen atom, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl" which are optionally substituted in the alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and/or
 15 heterocyclylalkyl group by up to 3 substituents independently selected from the group consisting of "halogen, -F, -Cl, -Br, -I, -N₃, -CN, -NR₇R₈, -NR₁₁R₁₂, -OH, -NO₂, alkyl, aryl, heteroaryl, arylalkyl, -O-alkyl, -O-aryl, -O-arylalkyl, -C(O)O-alkyl, -C(O)O-cycloalkyl, -C(O)O-cycloalkylalkyl, -C(O)O-aryl, -C(O)O-arylalkyl, -C(O)O-heteroaryl, -C(O)O-heteroarylalkyl, -C(O)O-heterocyclyl, -C(O)O-heterocyclylalkyl, -C(O)NR₉R₁₀, -C(S)NR₉R₁₀;";

20 one of radicals **R3** and **R4** is a hydrogen atom, whereas the other radical is selected from the group consisting of "hydrogen atom, alkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, -alkyl-O-aryl, -alkyl-O-arylalkyl, -alkyl-O-heteroaryl, -alkyl-O-heteroarylalkyl, -alkyl-O-heterocyclyl, alkyl-O-heterocyclylalkyl, -alkyl-CO-aryl, -alkyl-CO-arylalkyl, -alkyl-CO-heteroaryl, -alkyl-CO-heteroarylalkyl, -alkyl-CO-heterocyclyl, -alkyl-CO-heterocyclylalkyl, -alkyl-C(O)O-aryl, -alkyl-C(O)O-arylalkyl, -alkyl-C(O)O-heteroaryl, -alkyl-C(O)O-heteroarylalkyl, -alkyl-C(O)O-heterocyclyl, -alkyl-C(O)O-heterocyclylalkyl, -alkyl-CO-NH₂, -alkyl-CO-OH, -alkyl-NH₂, -alkyl-NH-
 25 C(NH)-NH₂, alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl, alkyl-S-alkyl, alkyl-S-H"

30

which are optionally substituted in the aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and/or heterocyclylalkyl group by up to 3 substituents independently selected from the group consisting of "halogen, -F, -Cl, -Br, -I, -N₃, -CN, -NR₇R₈, -OH, -NO₂, alkyl, aryl, arylalkyl, -O-alkyl, -O-CF₃, -O-aryl, -O-arylalkyl";

5 **R5** is selected from the group consisting of "-C(S)alkyl, -C(S)-cycloalkyl, -C(S)-cycloalkylalkyl, -C(S)-aryl, -C(S)-arylalkyl, -C(S)-heteroaryl, -C(S)-heteroarylalkyl, -C(S)-heterocyclyl, -C(S)-heterocyclylalkyl, -C(O)O-alkyl, -C(O)O-cycloalkyl, -C(O)O-cycloalkylalkyl, -C(O)O-aryl, -C(O)O-arylalkyl, -C(O)O-heteroaryl, -C(O)O-heteroarylalkyl, -C(O)O-heterocyclyl, -C(O)O-heterocyclylalkyl, -C(O)NR₉R₁₀, -C(S)NR₉R₁₀"; which are optionally substituted
10 in the alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and/or heterocyclylalkyl group by up to 3 substituents independently selected from the group consisting of "halogen, -F, -Cl, -Br, -I, -N₃, -CN, -CF₃, -NR₇R₈, -OH, -NO₂, -NH₂, alkyl, aryl, arylalkyl, -OH, -O-alkyl, -O-aryl, -O-arylalkyl";
15

R6 is selected from the group consisting of "hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl";

R7 and R8 are independently of one another selected from the group consisting of "hydrogen atom, alkyl, cycloalkyl, and cycloalkylalkyl";

20 **R9 and R10** are independently of one another selected from the group consisting of "hydrogen atom, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, arylalkyl, and heteraryloalkyl";

R11 is a "hydrogen atom",

R12 is independently of one another selected from the group consisting of "-C(O)H, -C(O)-alkyl; -C(O)-cycloalkyl, -C(O)-cycloalkylalkyl, -C(O)-aryl, -C(O)-arylalkyl, -C(O)-heteroaryl, -C(O)-heteroarylalkyl, -C(O)-heterocyclyl, -C(O)-heterocyclylalkyl",
25

Or

30 **(B)**

R1 is independently of one another selected from the group consisting of "hydrogen atom, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl,

arylalkyl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl" which are optionally substituted in the alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and/or heterocyclylalkyl group by up to 3 substituents independently selected from the group consisting of "halogen, -F, -Cl, -Br, -I, -N₃, -CN, -NR₇R₈, -OH, -NO₂, alkyl, aryl, arylalkyl, -O-alkyl, -O-aryl, -O-arylalkyl";

R2 is an "alkyl group", which is substituted by up to 2 substituents independently selected from the group consisting of "Aryl, Heteroaryl, -C(O)O-alkyl, -C(O)O-cycloalkyl, -C(O)O-cycloalkylalkyl, -C(O)O-aryl, -C(O)O-arylalkyl, -C(O)O-heteroaryl, -C(O)O-heteroarylalkyl, -C(O)O-heterocyclyl, -C(O)O-heterocyclylalkyl, -C(O)NR₉R₁₀, -NR₁₁R₁₂", and in the case of aryl, heteroaryl the alkylgroup has to be in addition substituted with -NR₁₁R₁₂;

one of radicals **R3** and **R4** is a hydrogen atom, whereas the other radical is selected from the group consisting of "hydrogen atom, alkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, -alkyl-O-aryl, -alkyl-O-arylalkyl, -alkyl-O-heteroaryl, -alkyl-O-heteroarylalkyl, -alkyl-O-heterocyclyl, alkyl-O-heterocyclylalkyl, -alkyl-CO-aryl, -alkyl-CO-arylalkyl, -alkyl-CO-heteroaryl, -alkyl-CO-heteroarylalkyl, -alkyl-CO-heterocyclyl, -alkyl-CO-heterocyclylalkyl, -alkyl-C(O)O-aryl, -alkyl-C(O)O-arylalkyl, -alkyl-C(O)O-heteroaryl, -alkyl-C(O)O-heteroarylalkyl, -alkyl-C(O)O-heterocyclyl, -alkyl-C(O)O-heterocyclylalkyl, -alkyl-CO-NH₂, -alkyl-CO-OH, -alkyl-NH₂, -alkyl-NH-C(NH)-NH₂, alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl, alkyl-S-alkyl, alkyl-S-H" which are optionally substituted in the aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and/or heterocyclylalkyl group by up to 3 substituents independently selected from the group consisting of "halogen, -F, -Cl, -Br, -I, -N₃, -CN, -NR₇R₈, -OH, -NO₂, alkyl, aryl, arylalkyl, -O-alkyl, -O-aryl, -O-arylalkyl";

R5 is selected from the group consisting of "hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, -CO-alkyl, -CO-cycloalkyl, -CO-cycloalkylalkyl, -CO-aryl, -CO-arylalkyl, -CO-heteroaryl, -CO-heteroarylalkyl, -CO-heterocyclyl, -CO-heterocyclylalkyl, -CO-C*(R₉R₁₀)-NH₂, -CO-CH₂-C*(R₉R₁₀)-NH₂, -CO-C*(R₉R₁₀)-CH₂-NH₂, alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl" which are optionally substituted by up to 3 substituents independently selected from the

group consisting of "halogen, -F, -Cl, -Br, -I, -N₃, -CN, -NR₇R₈, -OH, -NO₂, alkyl, aryl, arylalkyl, -O-alkyl, -O-aryl, -O-arylalkyl";

5 **R6** is selected from the group consisting of "hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl";

R7 and **R8** are independently of one another selected from the group consisting of "hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl";

10 **R9** and **R10** are independently of one another selected from the group consisting of "hydrogen atom, alkyl, natural amino acid side chain, unnatural amino acid side chain";

R11 is a "hydrogen atom";

15 **R12** is independently of one another selected from the group consisting of "-C(O)H, -C(O)-alkyl; -C(O)-cycloalkyl, -C(O)-cycloalkylalkyl, -C(O)-aryl, -C(O)-arylalkyl, -C(O)-heteroaryl, -C(O)-heteroarylalkyl, -C(O)-heterocyclyl, -C(O)-heterocyclylalkyl";

in terms of **(A)** and **(B)**

m is 0, 1 or 2; and

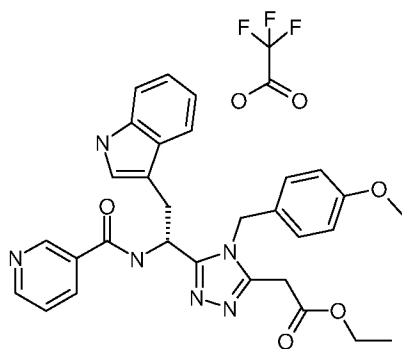
* means a carbon atom of R or S configuration when chiral;

20 that can be used for the manufacture of a medicament for the treatment or prophylaxis of physiological and/or pathophysiological conditions in mammals that are mediated by GHS receptors.

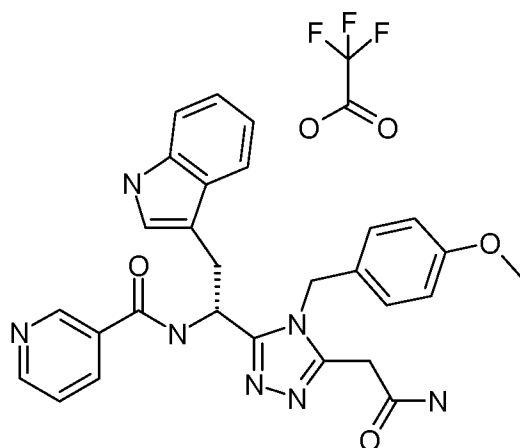
In a further aspect, the object of the invention has surprisingly been achieved by providing novel triazole compounds selected from the group consisting of:

25

compound 1 [5-{(R)-2-(1H-Indol-3-yl)-1-[(pyridine-3-carbonyl)-amino]-ethyl}-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-acetic acid ethyl ester;

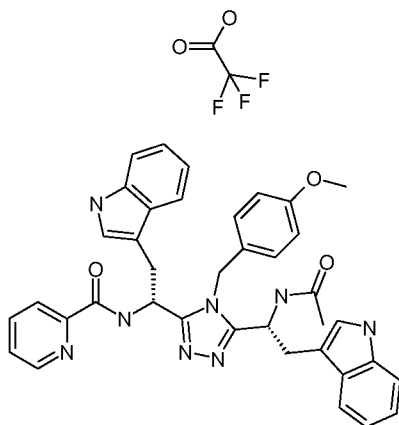


compound 2 N-[(R)-1-[5-Carbamoylmethyl-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-nicotinamide;

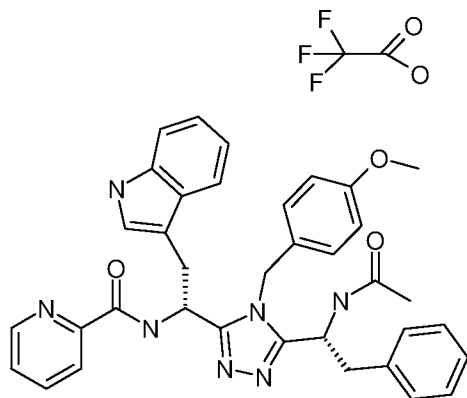


5

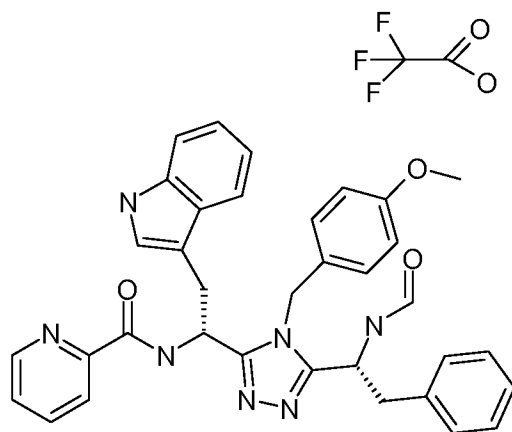
compound 3 Pyridine-2-carboxylic acid [(R)-1-[5-[(R)-1-acetylamino-2-(1H-indol-3-yl)-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-amide;



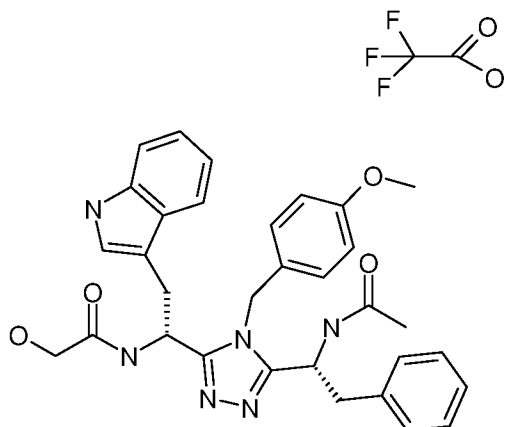
compound 4 Pyridine-2-carboxylic acid [(R)-1-[5-((R)-1-acetylamino-2-phenylethyl)-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-amide;



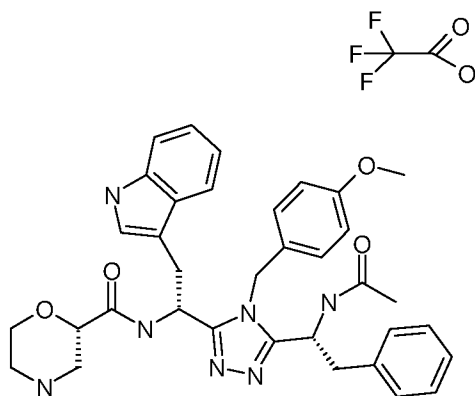
5 **compound 5** Pyridine-2-carboxylic acid [(R)-1-[5-((R)-1-formylamino-2-phenylethyl)-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-amide;



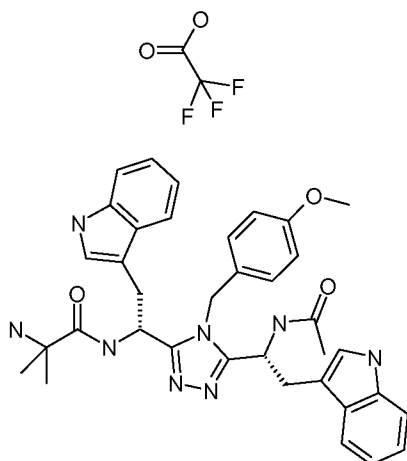
compound 6 N-[(R)-1-[5-((R)-1-Acetylamino-2-phenyl-ethyl)-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-2-hydroxy-acetamide;



5 **compound 7** (S)-Morpholine-2-carboxylic acid [(R)-1-[5-((R)-1-acetylamino-2-phenyl-ethyl)-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-amide;

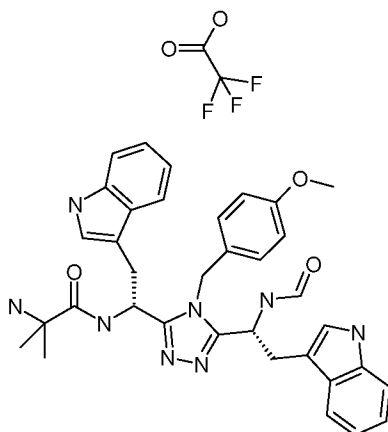


10 **compound 8** N-[(R)-1-[5-[(R)-1-Acetylamino-2-(1H-indol-3-yl)-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-2-amino-2-methyl-propionamide;



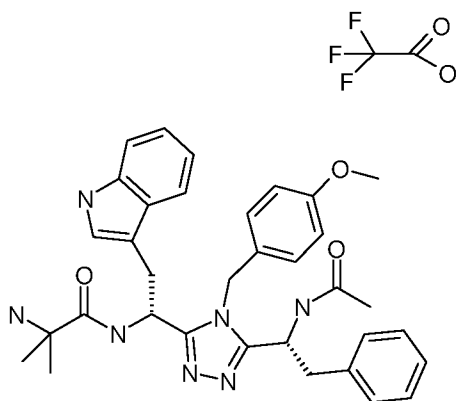
compound 9 2-Amino-N-[(R)-1-[5-[(R)-1-formylamino-2-(1H-indol-3-yl)-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-2-methyl-propionamide;

5

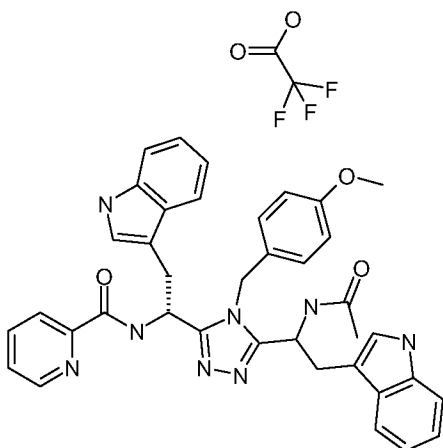


compound 10 N-[(R)-1-[5-((R)-1-Acetylamino-2-phenyl-ethyl)-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-2-amino-2-methyl-propionamide;

10

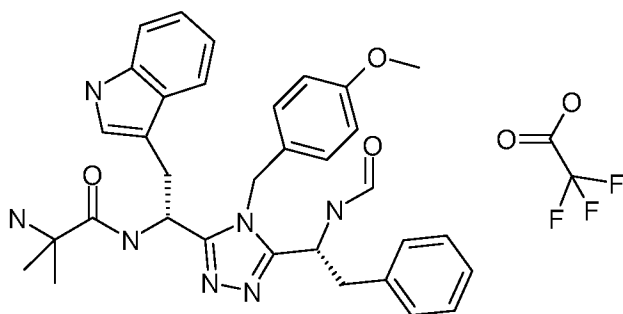


compound 11 Pyridine-2-carboxylic acid [(R)-1-[5-[1-acetylamino-2-(1H-indol-3-yl)-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-amide;



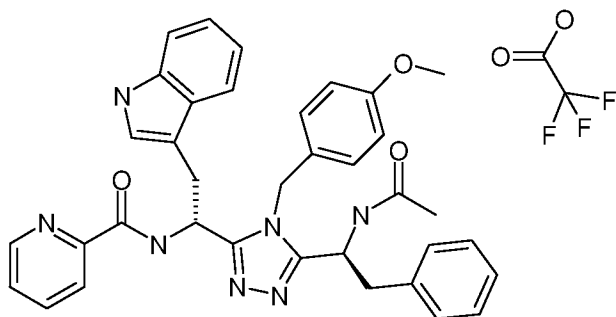
5

compound 12 2-Amino-N-[(R)-1-[5-((R)-1-formylamino-2-phenyl-ethyl)-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-2-methyl-propionamide;

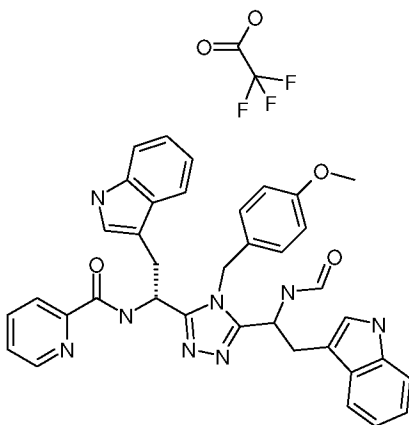


10

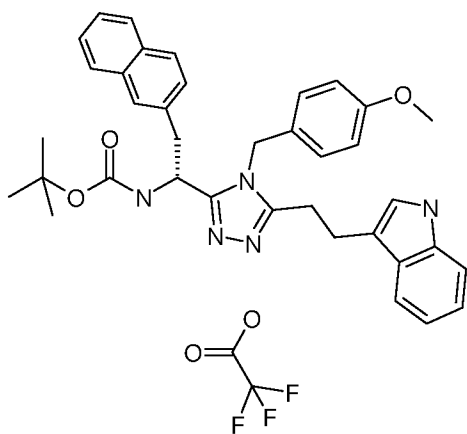
compound 13 Pyridine-2-carboxylic acid [(R)-1-[5-((S)-1-acetylamino-2-phenyl-ethyl)-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-amide;



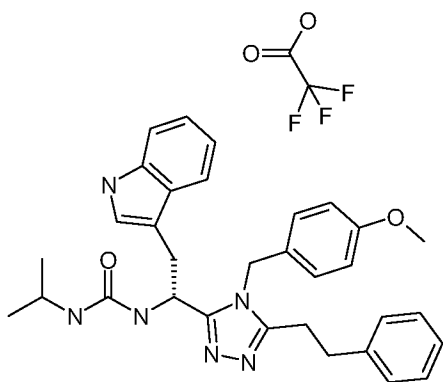
5 **compound 14** Pyridine-2-carboxylic acid [(R)-1-[5-[1-formylamino-2-(1H-indol-3-yl)-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-amide;



10 **compound 15** {(R)-1-[5-[2-(1H-Indol-3-yl)-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-naphthalen-2-yl-ethyl}-carbamic acid tert-butyl ester;

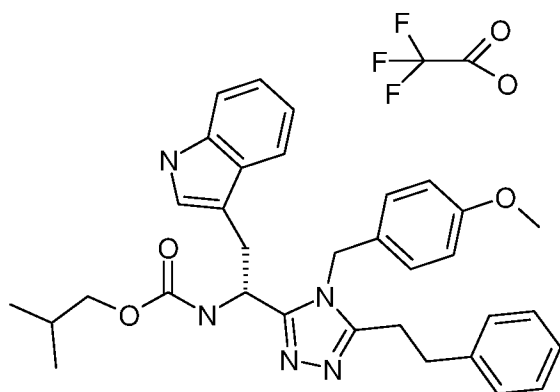


compound 16 1-[(R)-2-(1H-Indol-3-yl)-1-[4-(4-methoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl]-3-isopropyl-urea;

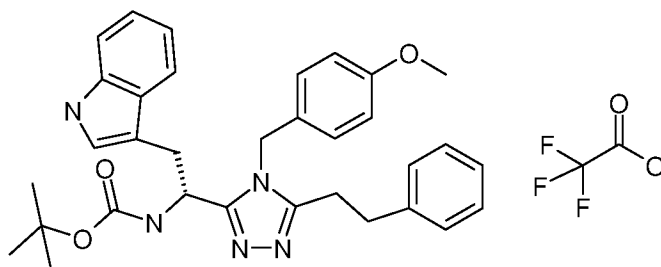


5

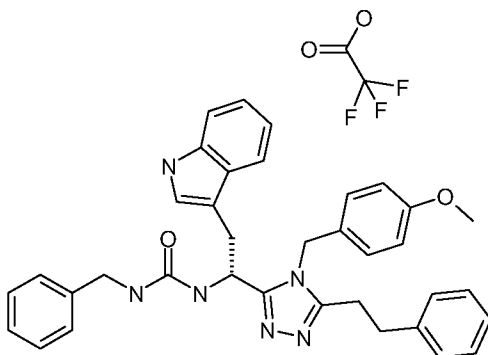
compound 17 {(R)-2-(1H-Indol-3-yl)-1-[4-(4-methoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl}-carbamic acid isobutyl ester;



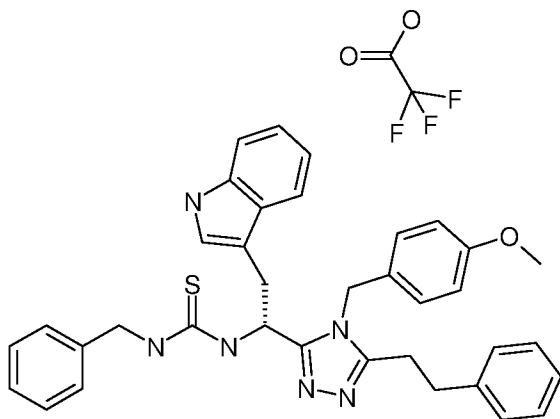
compound 18 {(R)-2-(1H-indol-3-yl)-1-[4-(4-methoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl}-carbamic acid tert-butyl ester;



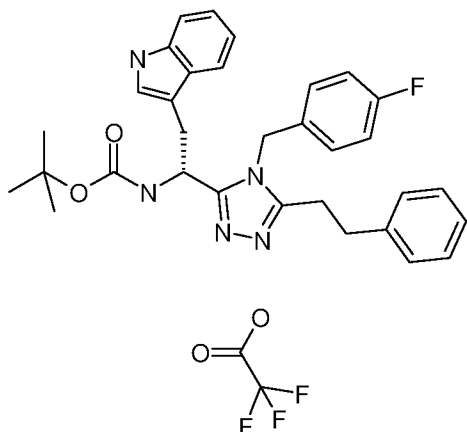
5 **compound 19** 1-Benzyl-3-[(R)-2-(1H-indol-3-yl)-1-[4-(4-methoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl]-urea;



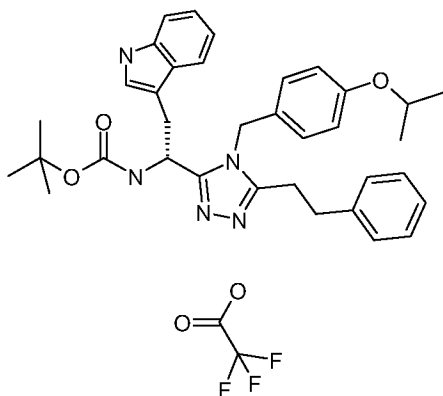
10 **compound 20** 1-Benzyl-3-[(R)-2-(1H-indol-3-yl)-1-[4-(4-methoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl]-thiourea;



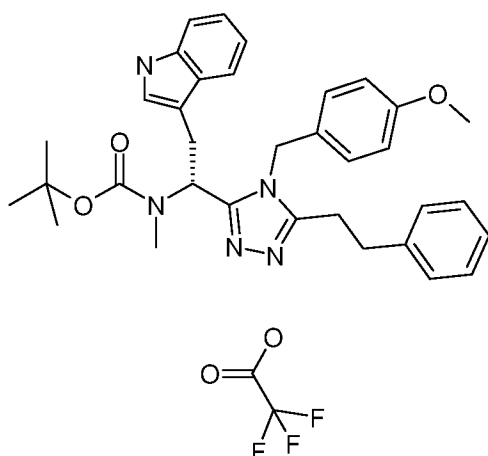
compound 21 [(R)-1-[4-(4-Fluoro-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-carbamic acid tert-butyl ester;



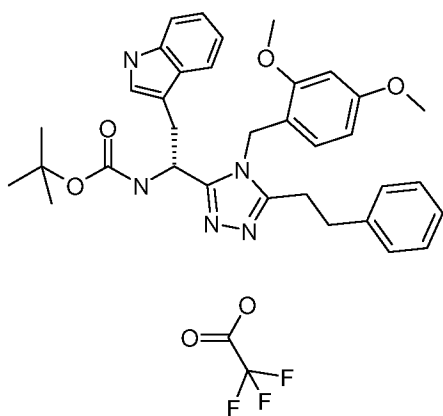
5 **compound 22** {(R)-2-(1H-Indol-3-yl)-1-[4-(4-isopropoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl}-carbamic acid tert-butyl ester;



10 **compound 23** {(R)-2-(1H-Indol-3-yl)-1-[4-(4-methoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl}-methyl-carbamic acid tert-butyl ester;

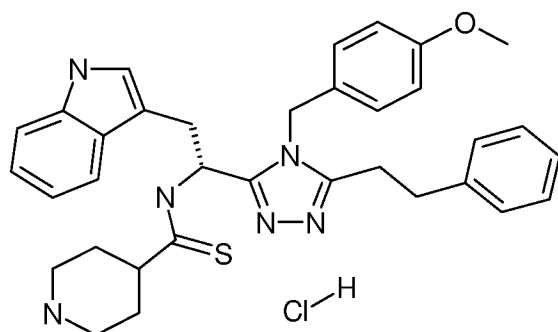


compound 24 [(R)-1-[4-(2,4-Dimethoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-carbamic acid tert-butyl ester;

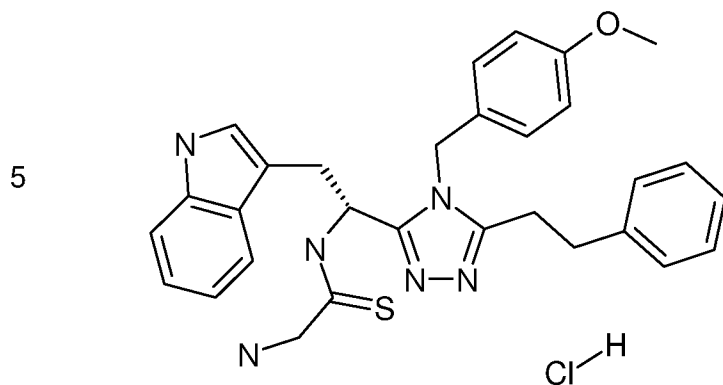


5

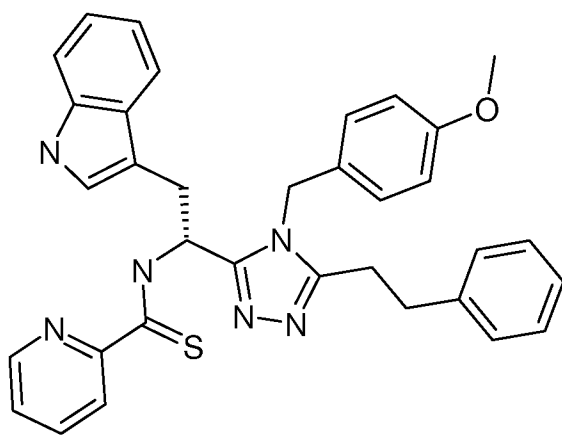
compound 25 Piperidine-4-carbothioic acid {(R)-2-(1H-indol-3-yl)-1-[4-(4-methoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl}-amide;



compound 26 2-Amino-N-[(R)-2-(1H-indol-3-yl)-1-[4-(4-methoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl]-thioacetamide;



10 **compound 27** Pyridine-2-carbothioic acid [(R)-2-(1H-indol-3-yl)-1-[4-(4-methoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl]-amide;



and the physiologically tolerated salts thereof.

The chemical names of the substances were generated using the AutoNom 2000
15 for ISIS/Draw Add-In.

For the avoidance of doubt, if chemical name and chemical structure of the above illustrated compounds do not correspond by mistake, the chemical structure is regarded to unambiguously define the compound.

In a preferred embodiment these compounds can be used for the manufacture of a medicament for the treatment or prophylaxis of physiological and/or pathophysiological conditions in mammals that are mediated by GHS receptors.

5 In a further preferred embodiment all triazole compounds as illustrated herein, i.e. generically (by above formula (I) and different R radicals) and explicitly, in the following referred to as the compounds of the (present) invention, can be used for the manufacture of a medicament for the treatment or prophylaxis of physiological and/or pathophysiological conditions in mammals that are mediated by GHS receptors and
10 where the treatment is achieved by modulation of GHS receptors.

The terms indicated for explanation of the above compounds of formula (I) always, unless indicated otherwise in the description or in the claims, have the following meanings:

15 The term "substituted" means that the corresponding radical or group has one or more substituents. Where a radical has a plurality of substituents, and a selection of various substituents is specified, the substituents are selected independently of one another and need not be identical. The term "unsubstituted" means that the corresponding group has no substituent. The term "optionally substituted" means that
20 the corresponding group is either unsubstituted or substituted by one or more substituents. The term "substituted by up to 3 substituents" means that the corresponding radical or group is substituted either by one or by two or three substituents.

The term "alkyl" includes for the purposes of this invention acyclic saturated
25 hydrocarbons having C1-C12 carbon atoms, which may be straight-chain or branched. The term "alkyl" preferably stands for alkyl chains of 1 to 8, particularly preferably 1 to 6, carbon atoms. Examples of suitable alkyl radicals are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, tert-pentyl, 2- or 3-methyl-pentyl, n-hexyl, isohexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl, n-dodecyl.

30 The term "cycloalkyl" stands for a saturated or partially unsaturated non-aromatic cyclic hydrocarbon group/radical, containing 1 to 3 rings, including monocyclic alkyl, bicyclic alkyl and tricyclic alkyl, and containing a total of 3 to 20 carbon atoms forming the rings, preferably 3 to 10, most preferably (C3-C8)-cycloalkyl. Examples of suitable cycloalkyl radicals are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl,
35 cyclooctyl, cyclodecyl, cyclohexenyl, cyclopentenyl, cyclooctadienyl.

The term "cycloalkylalkyl" refers to a radical in which the cycloalkyl group is linked via an alkyl group, where the alkyl and cycloalkyl groups have the meanings defined herein, preferably a (C3-C8)-cycloalkyl-(C1-C4)-alkyl radical. Examples thereof are cyclopropylmethyl, cyclohexylmethyl, cyclopentylethyl, cyclohexenylethyl.

5 The term "alkenyl" includes for the purposes of this invention acyclic unsaturated or partially unsaturated hydrocarbons having C2-C12 carbon atoms, which may be straight-chain or branched and contain one or more double bonds. The term "alkenyl" preferably stands for alkenyl chains of 2 to 8, particularly preferably 2 to 6, carbon atoms. Examples are vinyl, propenyl, butenyl, pentenyl, hexenyl, and octadienyl and
10 the like.

 The term "alkynyl" refers to acyclic unsaturated or partially unsaturated hydrocarbons having C2-C12 carbon atoms, which may be straight-chain or branched and contain one or more triple bonds. The term "alkynyl" preferably stands for alkynyl chains of 2 to 8, particularly preferably 2 to 6, carbon atoms. Examples are propynyl,
15 butynyl, pentynyl, hexynyl.

 The term "aryl" refers to aromatic hydrocarbon systems having 3 to 14, preferably 5 to 14, carbon atoms, which may also be fused to further saturated, (partially) unsaturated or aromatic cyclic systems. Examples of "aryl" are inter alia phenyl, biphenyl, naphthyl and anthracenyl, but also indanyl, indenyl, or 1,2,3,4-
20 tetrahydronaphthyl.

 The term "heteroaryl" refers to a 5-, 6- or 7-membered cyclic aromatic radical which comprises at least 1, where appropriate also 2, 3, 4 or 5 heteroatoms, preferably nitrogen, oxygen and/or sulfur, where the heteroatoms are identical or different. The number of nitrogen atoms is preferably between 0 and 3, and that of the oxygen and
25 sulfur atoms is between 0 and 1. The term "heteroaryl" also includes systems in which the aromatic cycle is part of a bi- or polycyclic system, such as were the aromatic cycle is fused to an aryl, cycloalkyl, heteroaryl or heterocyclyl group as defined herein via any desired and possible ring member of the heteroaryl radical. Examples of "heteroaryl" include pyrrolyl, thienyl, furyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl,
30 pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, quinolinyl, and isoquinolinyl.

 The terms "arylalkyl" and "heteroarylalkyl" refer to radicals in which the aryl or heteroaryl radical is linked via an alkyl group, where the alkyl, aryl and heteroaryl groups have the meanings defined herein. Preferred "arylalkyl" groups are phenyl-(C₁-C₄)-alkyl radicals, preferably benzyl or phenylethyl radicals. Preferred "heteroarylalkyl"

groups are indolyl-(C₁-C₄)-alkyl radicals, preferably 1*H*-indole-3-yl-methyl or 2(1*H*-indole-3-yl)-ethyl.

The term "heterocyclyl" refers to a mono- or polycyclic system of 3 to 14, preferably 5 or 6 to 14 ring atoms which may be exclusively carbon atoms. However, the cyclic system may also comprise 1, 2, 3, 4, or 5 heteroatoms, in particular nitrogen, oxygen and/or sulfur. The cyclic system may be saturated, mono- or polyunsaturated but may not be aromatic. In the case of a cyclic system consisting of at least two rings the rings may be fused or spiro- or otherwise connected. The "heterocyclyl" radical may be attached at any carbon or heteroatom which results in the creation of a stable structure. Examples include pyrrolidinyl, thiapyrrolidinyl, piperidinyl, piperazinyl, oxapiperazinyl, oxapiperidinyl and oxadiazolyl.

The term "heterocyclylalkyl" refers to radicals in which the heterocyclyl group is linked via an alkyl group, where the alkyl and heterocyclyl groups have the meanings defined herein.

The terms "alkylsulfonyl", "arylsulfonyl" and "arylalkylsulfonyl" refer to radicals in which the alkyl, aryl or arylalkyl group is linked via a -SO₂- group, where the alkyl, aryl and arylalkyl groups have the meanings defined herein. Examples are methylsulfonyl and phenylsulfonyl.

The term "halogen", "halogen atom" or "halogen substituent" (Hal-) refers to one, where appropriate, a plurality of fluorine (F, fluoro), bromine (Br, bromo), chlorine (Cl, chloro), or iodine (I, iodo) atoms. The designations "dihalogen", "trihalogen" and "perhalogen" refer respectively to two, three and four substituents, where each substituent can be selected independently from the group consisting of fluorine, chlorine, bromine and iodine. "Halogen" preferably means a fluorine, chlorine or bromine atom.

The term "natural alpha-amino acid side chain" for the purpose of the present invention refers to all side chains of the known 20 proteinogenic alpha-amino acids as well as to side chains of naturally occurring (i.e. in any biological systems) alpha-amino acids, such as for instance selenocystein, pyrrolysine, citrulline, ornithine, homocysteine, *N*-methyларiginine, *N*-acetyllysine, gamma-carboxyglutamate, 5-hydroxylysine, 3-methylhistidine and/or *N,N,N*-trimethyllysine. In this connection "side chain" refers to the residue that is attached to the alpha-carbon atom, e.g. methyl in case of an Ala side chain or benzyl in case of a Phe side chain.

The term "unnatural alpha amino acid side chain" for the purpose of the present invention refers to all side chains of known alpha-amino acids that are not proteinogenic nor are known to occur naturally (i.e. in any biological systems). Examples are norleucine, cyclohexylglycine, 2-naphthylalanine, substituted alpha-amino acids (e.g. halogen substituted Tyr or Phe) as well as protected alpha-amino acid side chains, where a protection group such as Fmoc, Boc, Z, CBZ, Alloc, trityl, acetyl and/or benzyl is directly attached/reacted to a functionalization (e.g. amino, hydroxy and/or carboxy residue). In this connection "side chain" is referred to as for "natural alpha amino acid side chains".

- 10 Above embodiments of radicals R1 to R12 that possess functionalization (e.g. amino, hydroxy and/or carboxy residues), such as alkyl-CO-NH₂, -alkyl-CO-OH, -alkyl-NH₂, -alkyl-NH-C(NH)-NH₂, -CO-C*(R9R10)-NH₂, -CO-CH₂-C*(R9R10)-NH₂, -CO-C*(R9R10)-CH₂-NH₂ and/or 2-amino-2-carbonyl-propane (2-amino-isobutyric acid/Aib residue), may be protected with protection groups as mentioned above. Such
- 15 protection group carrying embodiments are regarded as belonging to/ within the scope and spirit of the invention.

- All stereoisomers of the compounds of the invention are contemplated, either in a mixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the carbon atoms including any one of the R
- 20 radicals. Consequently, compounds of the invention can exist in the form of their racemates, in the form of the pure enantiomers and/or diastereomers or in the form of mixtures of these enantiomers and/or diastereomers. The mixtures may have any desired mixing ratio of the stereoisomers. All these different stereochemical forms and mixtures are within the scope of the present invention.

- 25 Thus, for example, the compounds of the invention which have one or more centers of chirality and which occur as racemates or as diastereomer mixtures can be fractionated by methods known per se into their optical pure isomers, i.e. enantiomers or diastereomers. The separation of the compounds of the invention can take place by column separation on chiral or nonchiral phases or by recrystallization from an
- 30 optionally optically active solvent or with use of an optically active acid or base or by derivatization with an optically active reagent such as, for example, an optically active alcohol, and subsequent elimination of the radical.

 Where possible, the compounds of the invention may be in the form of the tautomers.

It is likewise possible for the compounds of the invention to be in the form of any desired prodrugs such as, for example, esters, carbonates or phosphates, in which cases the actually biologically active form is released only through metabolism. Any compound that can be converted in vivo to provide the bioactive agent (i.e. a
5 compound of the invention) is a prodrug within the scope and spirit of the invention.

Various forms of prodrugs are well known in the art and are described for instance in:

- (i) The Practice of Medicinal Chemistry (Wermuth CG et al., Chapter 31, Academic Press 1996);
- 10 (ii) Design of Prodrugs (editor: Bundgaard H, Elsevier 1985); and
- (iii) A Textbook of Drug Design and Development (Krogsgaard-Larson P and Bundgaard H, eds., Chapter 5: 113 – 191, Harwood Academic Publishers 1991).

Said references are incorporated herein by reference.

15 It is further known that chemical substances are converted in the body into metabolites which may where appropriate likewise elicit the desired biological effect - in some circumstances even in more pronounced form.

Any biologically active compound that was converted in vivo by metabolism from any compound of the invention is a metabolite within the scope and spirit of the
20 invention.

The compounds of the invention can, if they have a sufficiently basic group such as, for example, a primary, secondary or tertiary amine, be converted with inorganic and organic acids into salts. The pharmaceutically acceptable salts of the compounds of the invention are preferably formed with hydrochloric acid, hydrobromic acid, iodic acid,
25 sulfuric acid, phosphoric acid, methanesulfonic acid, p-toluenesulfonic acid, carbonic acid, formic acid, acetic acid, sulfoacetic acid, trifluoroacetic acid, oxalic acid, malonic acid, maleic acid, succinic acid, tartaric acid, racemic acid, malic acid, embonic acid, mandelic acid, fumaric acid, lactic acid, citric acid, taurocholic acid, glutaric acid, stearic acid, glutamic acid or aspartic acid. The salts which are formed are, inter alia,
30 hydrochlorides, chlorided, hydrobromides, bromides, iodides, sulfates, phosphates, methanesulfonates, tosylates, carbonates, bicarbonates, formates, acetates, sulfoacetates, triflates, oxalates, malonates, maleates, succinates, tartrates, malates, embonates, mandelates, fumarates, lactates, citrates, glutarate, stearate, aspartates

and glutamates. The stoichiometry of the salts formed from the compounds of the invention may moreover be an integral or non-integral multiple of one.

The compounds of the invention can, if they contain a sufficiently acidic group such as, for example, the carboxy, sulfonic acid, phosphoric acid or a phenolic group, be converted with inorganic and organic bases into their physiologically tolerated salts. Examples of suitable inorganic bases are ammonium, sodium hydroxide, potassium hydroxide, calcium hydroxide, and of organic bases are ethanolamine, diethanolamine, triethanolamine, ethylenediamine, t-butylamine, t-octylamine, dehydroabietylamine, cyclohexylamine, dibenzylethylene-diamine and lysine. The stoichiometry of the salts formed from the compounds of the invention can moreover be an integral or non-integral multiple of one.

It is likewise possible for the compounds of the invention to be in the form of their solvates and, in particular, hydrates which can be obtained for example by crystallization from a solvent or from aqueous solution. It is moreover possible for one, two, three or any number of solvate or water molecules to combine with the compounds of the invention to give solvates and hydrates.

It is known that chemical substances form solids which exist in different order states which are referred to as polymorphic forms or modifications. The various modifications of a polymorphic substance may differ greatly in their physical properties. The compounds of the invention can exist in various polymorphic forms, and certain modifications may moreover be metastable. All these polymorphic forms of the compounds of the invention are to be regarded as belonging to the invention.

The triazole derivatives (compounds of the invention) as illustrated herein are ghrelin analogue ligands of GHS receptors. Thus, the aforementioned compounds of the invention are suitable for the treatment or prophylaxis of physiological and/or pathophysiological conditions mediated by GHS receptors and/or physiological and/or pathophysiological conditions which can be influenced by modulation of these receptors, and thus prevented, treated and/or alleviated.

For the purpose of the present invention, the term "treatment" is also intended to include prophylactic treatment or alleviation.

The term "ghrelin analogue ligand" or "ligand" is intended to refer for the purposes of the present invention to every compound which binds in any way to a receptor (the receptors in the present invention being GHS or ghrelin receptors) and induces either

activation, inhibition and/or another conceivable effect at this receptor. The term "ghrelin analogue ligand" or "ligand" thus includes agonists, antagonists, partial agonists/antagonists, inverse agonists and other ligands which cause an effect at the receptor which is similar to the effect of agonists, antagonists, partial
5 agonists/antagonists or inverse agonist.

For the purpose of the present invention, the term "GHS or ghrelin receptor antagonist" or "antagonist of GHS or ghrelin receptors" refers to compounds of the invention that bind to GHS or ghrelin receptors but do not elicit a proper activation of the receptors as assessed by recording an increase of intracellular calcium and increase of
10 cAMP response element-driven reporter gene expression, which is characteristic for activation of these G-protein coupled receptors (GPCRs).

The ability to properly inactivate the GHS-R1A receptors is assessed for any compound of the invention by comparing the degree of inhibition (decrease of intracellular calcium and decrease of cAMP response element-driven reporter gene expression) of
15 GHS-R 1a by the compound to be tested (at varying concentrations in the range of 10^{-10} M to 10^{-4} M) in the presence of saturating concentrations of ghrelin (0%) compared to the basal level (100%). Such assessment can be readily performed by the skilled artisan due to his expert knowledge. The output is a percentage value for each compound to be tested.

20 Any compound of the invention that does not show a degree of activation (increase of intracellular calcium and increase of cAMP response element-driven reporter gene expression) of GHS-R 1a of at least 20 % as assessed in accordance with above specification is regarded as not eliciting a proper activation and therefore not as GHS or ghrelin receptor agonist. Preferably such compounds do show an antagonizing effect
25 (counteraction/decrease) on ghrelin and/or other GHS stimulated intracellular calcium increase, prevent such stimulation or even act as inverse agonists. An inverse agonists is an ligand which binds to the same receptor binding site as an agonist or antagonist but causes an inhibition of the basal/constitutive activity of the receptor. Such compounds may furthermore exhibit an inhibitory activity on GH secretion and/or on other
30 physiological or pathophysiological conditions or effects, such as food intake or lipogenesis. Their effects may be dissociated. Thus, they may have no impact at all on GH secretion while inhibiting other physiological effects. They may even stimulate other physiological effects.

For the purpose of the present invention, the term "GHS receptor agonist" or "agonist of GHS receptors" refers to compounds of the invention that bind to GHS receptors and elicit a proper activation of the receptor as assessed by recording an increase of intracellular calcium or increase of cAMP response element-driven reporter gene expression, which is characteristic for activation of G-protein coupled receptors.

Any compound of the invention that shows a degree of activation (increase of intracellular calcium and increase of cAMP response element-driven reporter gene expression) of GHS-R 1a of at least 20 % as assessed in accordance with above specification is regarded as eliciting a proper activation and therefore as GHS receptor agonist. Such compounds may mimic the effects of ghrelin and/or GHS on GH secretion and for instance food intake or lipogenesis. Like for antagonists, the effects of agonist compounds may be dissociated from the GH secretory effect. Such compounds may even antagonize (counteract/decrease) ghrelin and/or other GHS stimulated intracellular calcium increase.

The term "GHS receptor" or "GHS-R" or "ghrelin receptor" is intended to comprise for the purposes of the present invention receptors that bind at least one known peptidyl and/or non-peptidyl GHS and/or ghrelin. The term "GHS receptor" or "GHS-R" or "ghrelin receptor" is also intended to comprise different GHS binding sites in the various tissues and/or organs as illustrated herein, that bind at least one known peptidyl and/or non-peptidyl GHS and/or ghrelin and which are probably not yet characterized GHS-R subtypes.

Binding of a given known peptidyl and/or non-peptidyl GHS and/or ghrelin can be easily verified by the skilled artisan on the basis of his expert knowledge, e.g. by appropriate binding assays which represent only routine experimentation.

Such GHS receptors may be stimulated/activated by ghrelin (ghrelin responsive) or may not be stimulated/activated by ghrelin (ghrelin non-responsive) – with regard to both acylated and non-acylated ghrelin, respectively. Stimulation/activation of such receptors may cause but does not compulsorily have to elicit GH production and/or GH secretion and/or increase GH plasma levels.

Preferably such GHS receptors are selected from the group consisting of "GHS type 1 receptor, GHS-R 1a, GHS-R 1b, motilin receptor, motilin receptor 1a, neurotensin receptor, TRH receptor, GPR38 (FM1), GPR39 (FM2), FM3, GHS binding site, GHS-R subtype, cardiac GHS-R, mammary GHS-R".

More preferably, such GHS receptors are selected from the group consisting of "GHS type 1 receptor, GHS-R 1a, GHS-R 1b" and most preferably are GHS-R 1a.

As discussed herein, GHS receptors (including GHS binding sites and GHS-R subtypes) are known to be concentrated in the hypothalamus-pituitary area but also
5 appear to be distributed in other central and peripheral tissues. Furthermore, they are also expressed in various tumoral tissues, even in tumoral tissues from organs that do not express these receptors under physiological conditions.

For the purposes of the present invention, all these GHS receptor (including GHS binding sites and GHS-R subtypes) expressing organs and/or tissues are intended to
10 be comprised by the scope of the present invention. Expression of GHS receptors (including GHS binding sites and GHS-R subtypes) in a given organ and/or tissue can be easily verified by the skilled artisan on the basis of his expert knowledge, e.g. by appropriate molecular biologic assays, such as immunofluorescence or immunoprecipitation assays, which represent only routine experimentation.

15 Preferably, such GHS receptors are located in tissues and/or organs selected from the group consisting of "endocrine tissue, exocrine tissue, peripheral tissue, adipose/fat tissue, brain, hypothalamus, thalamus, hippocampus, striatum, cortex, pituitary, central nervous system, spinal cord, gland, adrenal gland, thyroid gland, salivary gland, mammary gland, neuron, bowel, intestine, stomach, heart, liver, pancreas, kidney, bile,
20 gall, bladder, prostate, spleen, muscle, skeletal muscle, aorta, artery, vein, immune cell, leukocyte, lymphocyte, T cell, B cell, granulocyte, monocyte, macrophage, dendritic cell, mast cell, NK cell, neutrophil, eosinophil, basophil, lymph node, bone, bone marrow, tonsil, thymus, placenta, testes, ovary, uterus, lung, adipocyte, tumor/cancer cell, carcinoma cell, prostate cancer cell, thyroid cancer cell, lung cancer
25 cell, breast cancer cell".

As illustrated supra, the compounds of the invention are ghrelin analogue ligands of GHS receptors. They can be administered to various mammalian species, including human, for the treatment or prophylaxis of physiological and/or pathophysiological condition in such mammals.

30 For the purpose of the present invention, all mammalian species are regarded as being comprised. Preferably, such mammals are selected from the group consisting of "human, domestic animals, cattle, livestock, pets, cow, sheep, pig, goat, horse, pony, donkey, hinny, mule, hare, rabbit, cat, dog, guinea pig, hamster, rat, mouse". More preferably, such mammals are human.

The compounds of the invention being non-peptidic ghrelin analogue ligands of GHS receptors are surprisingly characterized by a more than threefold improved binding affinity to such receptors for most of them, compared to a representative example, i.e. compound 50 disclosed in WO07/020013. The compounds of the invention for instance
5 may preferably exhibit an IC_{50} value of less than 100 nM for binding to human GHS-R 1a. Most preferably, such compounds may exhibit an IC_{50} value of less than 10 nM for binding to human GHS-R 1a.

Due to their surprisingly strong receptor binding, the compounds of the invention can be advantageously administered at lower doses compared to other less potent binders as
10 disclosed in WO07/020013 while still achieving equivalent or even superior desired biological effects. In addition, such a dose reduction may advantageously lead to less or even no medicinal adverse effects. Further, the high binding specificity of the compounds of the invention may translate into a decrease of undesired side effects on its own regardless of the dose applied.

15 Furthermore, the compounds of the invention, being of non-peptidic nature, are resistant to degradation by enzymes of the gastro-intestinal tract. Hence, they offer the advantage to be given by oral route. They surprisingly display an improved metabolic stability and/or an improved bioavailability. Hence, again an advantageous dose reduction may be achievable which may cause less or even no side effects.

20 The compounds of the invention can be agonists, antagonists or partial agonists/antagonists or inverse agonists of GHS or ghrelin receptors as illustrated and defined herein.

The compounds of the invention can either be antagonists or agonists of GHS receptors as illustrated and defined herein.

25 GHS receptor antagonists of the present invention can for instance be employed for the inhibition of GHS receptors stimulated by ghrelin and/or other GHS thus decreasing and/or blocking GH production and/or secretion and/or GH plasma levels. In addition, such GHS receptor antagonists may also be employed for the inhibition or prevention of physiological or pathophysiological effects of ghrelin which are not related to GH
30 production and/or GH secretion.

Therefore, GHS receptor antagonists of the present invention are suitable for the treatment and/or prophylaxis of various physiological and pathophysiological conditions as disclosed herein, in particular for the short-, medium- and/or long term regulation of

energy balance, the short-, medium- and/or long term regulation (stimulation and/or inhibition) of food intake, the treatment of adipogenesis, adiposity and/or obesity, body weight gain and/or reduction and the treatment of tumor cell proliferation.

In contrast, GHS receptor agonists of the present invention can for instance be
5 employed for the activation of GHS receptors and stimulation/increase of GH production and/or GH secretion and would thus have similar effects or uses as growth hormone itself, ghrelin and/or known GHS.

Thus, GHS receptor agonists of the present invention are suitable for the treatment and/or prophylaxis of various physiological and pathophysiological conditions as disclosed
10 herein, in particular for growth retardation, cachexia, inflammation, inflammatory effects, gastric postoperative ileus, postoperative ileus and/or gastrectomy (ghrelin replacement therapy).

For the purpose of the present invention, all physiological and/or pathophysiological conditions are intended to be comprised that are known to be mediated by GHS
15 receptors.

Preferably, these physiological and/or pathophysiological conditions are selected from the group consisting of "acute fatigue syndrome and muscle loss following election surgery, adipogenesis, adiposity, age-related decline of thymic function, age-related functional decline ("ARFD") in the elderly, aging disorder in companion animals,
20 alcohol-related disorders, Alzheimer's disease, anorexia (e.g. associated with cachexia or aging); anxiety, blood pressure (lowering), body weight gain/reduction, bone fracture repair (acceleration), bone remodeling stimulation, cachexia and protein loss reduction due to chronic illness such as cancer or AIDS, cardiac dysfunctions (e.g. associated with valvular disease, myocardial infarction, cardiac hypertrophy or congestive heart
25 failure), cardiomyopathy, cartilage growth stimulation, catabolic disorders in connection with pulmonary dysfunction and ventilator dependency, catabolic side effects of glucocorticoids, catabolic state of aging, central nervous system disorders (in combination with antidepressants), chronic dialysis, chronic fatigue syndrome (CFS), cognitive function improvement (e.g. in dementia, Alzheimer's disease), complicated
30 fractures (e.g. distraction osteogenesis), complications associated with transplantation, congestive heart failure (alone/in combination with corticotropin releasing factor antagonists), Crohn's disease and ulcerative colitis, Cushing's syndrome, dementia, depressions, drug abuse, short-, medium- and/or long-term regulation of energy balance, short-, medium- and/or long-term regulation of food

intake (stimulation and/or inhibition), intake of rewarding food, frailty (e.g. in elderly humans), gastrectomy (ghrelin replacement therapy), gastric postoperative ileus, glycemic control improvement, growth hormone release stimulation in the elderly, growth hormone replacement in stressed patients, growth promotion in livestock, growth retardation associated with the Prader-Willi syndrome and Turner's syndrome, growth retardation in connection with Crohn's disease, growth retardation, hair/nail growth maintenance, hip fractures, hunger, hypercortisolism, hyperinsulinemia including nesidioblastosis, hypothermia, immune deficiency in individuals with a depressed T4/T8 cell ratio, immune response improvement to vaccination, immune system stimulation in companion animals, immune system stimulation, immunosuppression in immunosuppressed patients, inflammation or inflammatory effects, inflammatory bowel disease, insulin resistance in the heart, insulin resistance in type 2 diabetic patients, insulin resistance including NIDDM, diabetes, diabetes type I, diabetes type II, intrauterine growth retardation, irritable bowel syndrome, lipodystrophy (e.g. HIV-induced), metabolic homeostasis maintenance, milk production increase in livestock, muscle mass/strength increase, muscle mobility improvement, muscle strength improvement, muscle strength/function maintenance in elderly humans, muscular atrophy, musculoskeletal impairment (e.g. in elderly), Noonan's syndrome, obesity and growth retardation associated with obesity, osteoblast stimulation, osteochondrodysplasias, osteoporosis, ovulation induction (adjuvant treatment), physiological short stature including growth hormone deficient children, postoperative ileus, protein catabolic response attenuation after major surgery/trauma, protein kinase B activity enhancement, psychosocial deprivation, pulmonary dysfunction and ventilator dependency, pulmonary function improvement, pulsatile growth hormone release induction, recovery of burn patients and reducing hospitalization of burn patients (acceleration), renal failure or insufficiency resulting from growth retardation, renal homeostasis maintenance in the frail elderly, sarcopenia, schizophrenia, sensory function maintenance (e.g. hearing, sight, olfaction and taste), short bowel syndrome, short stature associated with chronic illness, skeletal dysplasia, skin thickness maintenance, sleep disorders, sleep quality improvement, thrombocytopenia, thymic development stimulation, tooth repair or growth, tumor cell proliferation, ventricular dysfunction or reperfusion events, wasting in connection with AIDS, wasting in connection with chronic liver disease, wasting in connection with chronic obstructive pulmonary disease (COPD), wasting in connection with multiple sclerosis or other

neurodegenerative disorders, wasting secondary to fractures, wool growth stimulation in sheep, wound healing (acceleration), wound healing delay”.

More preferably these physiological and/or pathophysiological conditions are selected from the group consisting of “alcohol-related disorders; drug abuse; growth
5 retardation, cachexia, short-, medium- and/or long term regulation of energy balance; short-, medium- and/or long term regulation (stimulation and/or inhibition) of food intake; intake of rewarding food; adipogenesis, adiposity and/or obesity; body weight gain and/or reduction; diabetes, diabetes type I, diabetes type II, tumor cell proliferation; inflammation, inflammatory effects, gastric postoperative ileus, postoperative
10 ileus and/or gastrectomy (ghrelin replacement therapy)”.

More recent findings indicate that the effects of ghrelin on food intake are partly mediated by the mesolimbic dopamine systems involved in reward-seeking behaviour (Jerlhag E. et al. 2006 Addiction Biology 11 :45-54; Jerlhag E, et al. Addict Biol. 2007 12:6-16; Egecioglu E. et al. 2010, Addiction Biology 15, 304-311). In addition, most
15 recent data confirm the suitability of ghrelin antagonists for the treatment of alcohol-related disorders (WO2009/020419 and Jerlhag et al. 2009. PNAS 106, 11318-11323) and drug abuse (Jerlhag E. et al. 2010, Psychopharmacology 211, 415-422).

In a further aspect of the present invention, the compounds of the invention may be used in combination with at least one additional pharmacologically active substance.

20 Such additional pharmacologically active substance may be other compounds of the present invention and/or other “suitable therapeutic agents” useful in the treatment and/or prophylaxis of the aforementioned physiological and/or pathophysiological conditions. The additional pharmacologically active substance may be an antagonist of GHS receptors and/or an agonist of GHS receptors depending on the purpose of the
25 combined use. Selection and combination of the additional pharmacologically active substance(s) can be easily performed by the skilled artisan on the basis of his expert knowledge and depending on the purpose of the combined use and physiological and/or pathophysiological conditions targeted.

In a preferred embodiment, the compounds of the invention are used for the
30 treatment and/or prophylaxis of the aforementioned physiological and/or pathophysiological conditions in the form of a medicament, where such medicament comprises at least one additional pharmacologically active substance.

In another preferred embodiment, the compounds of the invention are used for the treatment and/or prophylaxis of the aforementioned physiological and/or pathophysiological conditions in the form of a medicament, where the medicament is applied before and/or during and/or after treatment with at least one additional
5 pharmacologically active substance.

The above mentioned "suitable therapeutic agents" include: "GHS, anti-diabetic agents; anti-osteoporosous agents; anti-obesity agents; anti-inflammatory agents; anti-anxiety agents; anti-depressants; anti-hypertensive agents; anti-platelet agents; antithrombotic and thrombolytic agents; cardiac glycosides; cholesterol/lipid lowering
10 agents; mineralocorticoid receptor antagonists; phosphodiesterase inhibitors; protein tyrosine kinase inhibitors; thyroid mimetics (including thyroid receptor antagonists); anabolic agents; HIV or AIDS therapies; therapies useful in the treatment of Alzheimer's disease and other cognitive disorders; therapies useful in the treatment of sleeping disorders; anti-proliferative agents; anti-tumor agents; anti-ulcer and
15 gastroesophageal reflux disease agents; progestin receptor agonists ("PRA");estrogen; testosterone; a selective estrogen receptor modulator; a selective androgen receptor modulator; parathyroid hormone; and/or bisphosphonate", and preferably, a "suitable therapeutic agents" is selected of the group consisting of this agents.

20 Examples of suitable GHS for use in combination with the compounds of the present invention include GHRP-6, GHRP-1 as described in U.S. Patent No. 4,411,890; and publications WO 89/07110 and WO 89/07111 and B-HT920 or growth hormone releasing factor and its analogs or growth hormone and its analogs or somatomedins including IGF-1 and IGF-2 as well as GHS described in WO 01/96300.

25 Examples of suitable anti-diabetic agents for use in combination with the compounds of the present invention include biguanides (e.g. metformin), glucosidase inhibitors (e.g. acarbose), insulins (including insulin secretagogues or insulin sensitizers), meglitinides (e.g. repaglinide), sulfonylureas (e.g., glimepiride, glyburide and glipizide), biguanide/glyburide combinations (e.g., glucovance), thiozolidinediones
30 (e.g. troglitazone, rosiglitazone and pioglitazone), PPAR-alpha agonists, PPAR-gamma agonists, PPAR alpha/gamma dual agonists, SGLT2 inhibitors, inhibitors of fatty acid binding protein (aP2) such as those disclosed in US patent 6,548,529, glucagon-like peptide-1 (GLP-1), and dipeptidyl peptidase IV (DP4) inhibitors.

Examples of suitable anti-osteoporosous agents for use in combination with the compounds of the present invention include alendronate, risedronate, raloxifene, calcitonin, non-steroidal progestin receptor agonists, RANK ligand agonists, calcium sensing receptor antagonists, TRAP inhibitors, selective estrogen receptor modulators (SERM), estrogen and AP-1 inhibitors.

Examples of suitable anti-obesity agents for use in combination with the compounds of the present invention include endocannabinoid receptor antagonists, e.g. CB1 receptor antagonists such as rimonabant (1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl-, monohydrochloride; CAS Registry Number: 158681-13-1; SR-141716A; US patent 5,624,941), aP2 inhibitors such as those disclosed in US patent 6,548,529, PPAR gamma antagonists, PPAR delta agonists, and orlistat.

Examples of suitable antiinflammatory agents for use in combination with the compounds of the present invention include prednisone, dexamethasone, Enbrel, cyclooxygenase inhibitors (i.e., COX-1 and/or COX-2 inhibitors such as NSAIDs, aspirin, indomethacin, ibuprofen, piroxicam, Naproxen, Celebrex, Vioxx), CTLA4-Ig agonists/antagonists, CD40 ligand antagonists, integrin antagonists, alpha4 beta7 integrin antagonists, cell adhesion inhibitors, interferon gamma antagonists, ICAM-1, tumor necrosis factor (TNF) antagonists (e.g., infliximab, OR1384), prostaglandin synthesis inhibitors, budesonide, clofazimine, CNI-1493, CD4 antagonists (e.g., priliximab), p38 mitogen-activated protein kinase inhibitors, protein tyrosine kinase (PTK) inhibitors, IKK inhibitors, and therapies for the treatment of irritable bowel syndrome (e.g., zelmec and Maxi-K openers such as those disclosed in US Patent No. 6,184,231).

Examples of suitable anti-anxiety agents for use in combination with the compounds of the present invention include diazepam, lorazepam, buspirone, oxazepam, and hydroxyzine pamoate.

Examples of suitable anti-depressants for use in combination with the compounds of the present invention include citalopram, fluoxetine, nefazodone, sertraline, and paroxetine.

Examples of suitable anti-hypertensive agents for use in combination with the compounds of the present invention include beta adrenergic blockers, calcium channel blockers (L-type and T-type; e.g. diltiazem, verapamil, nifedipine, amlodipine and mybefradii), diuretics (e.g., chlorothiazide, hydrochlorothiazide, flumethiazide,

hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid, tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride, spironolactone), renin inhibitors, ACE inhibitors (e.g., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, 5 delapril, pentopril, quinapril, ramipril, lisinopril), AT-1 receptor antagonists (e.g., losartan, irbesartan, valsartan), ET receptor antagonists (e.g., sitaxsentan, atrsentan and compounds disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265, Dual ET/All antagonist (e.g., compounds disclosed in WO 00/01389), neutral endopeptidase (NEP) inhibitors, vasopepsidase inhibitors (dual NEP-ACE inhibitors) (e.g., omapatrilat and 10 gemopatrilat), and nitrates.

Examples of suitable anti-platelet agents for use in combination with the compounds of the present invention include GPIIb/IIIa blockers (e.g., abciximab, eptifibatide, tirofiban), P2Y₁₂ antagonists (e.g., clopidogrel, ticlopidine, CS-747), thromboxane receptor antagonists (e.g., ifetroban), aspirin, and PDE-III inhibitors (e.g., 15 dipyridamole) with or without aspirin.

Examples of suitable cardiac glycosides for use in combination with the compounds of the present invention include digitalis and ouabain.

Examples of suitable cholesterol/lipid lowering agents for use in combination with the compounds of the present invention include HMG-CoA reductase inhibitors [e.g., 20 pravastatin, lovastatin, atorvastatin, simvastatin, NK-104 (a.k.a. itavastatin, or nisvastatin or nisbastatin) and ZD-4522 (a.k.a. rosuvastatin, or atavastatin or visastatin)], squalene synthetase inhibitors, fibrates, bile acid sequestrants, ACAT inhibitors, MTP inhibitors, lipooxygenase inhibitors, cholesterol absorption inhibitors, and cholesterol ester transfer protein inhibitors (e.g., CP-529414).

25 Examples of suitable mineralocorticoid receptor antagonists for use in combination with the compounds of the present invention include spironolactone and eplerinone.

Examples of suitable phosphodiesterase inhibitors for use in combination with the compounds of the present invention include PDE III inhibitors such as cilostazol, and PDE V inhibitors such as sildenafil.

30 Examples of suitable thyroid mimetics for use in combination with the compounds of the present invention include thyrotropin, polythyroid, KB-130015, and dronedarone.

Examples of suitable anabolic agents for use in combination with the compounds of the present invention include testosterone and SARMs.

Examples of suitable HIV or AIDS therapies for use in combination with the compounds of the present invention include indinavir sulfate, saquinavir, saquinavir mesylate, amprenavir, ritonavir, lopinavir, ritonavir/lopinavir combinations, lamivudine, zidovudine, lamivudine/zidovudine combinations, zalcitabine, didanosine, stavudine,
5 and megestrol acetate.

Examples of suitable therapies for treatment of Alzheimer's disease and cognitive disorders for use in combination with the compounds of the present invention include donepezil, tacrine, revastigmine, 5HT₆, gamma secretase inhibitors, beta secretase inhibitors, SK channel blockers, Maxi-K blockers, and KCNQs blockers.

10 Examples of suitable therapies for treatment of sleeping disorders for use in combination with the compounds of the present invention include melatonin analogs, melatonin receptor antagonists, ML1B agonists, and GABA/NMDA receptor antagonists.

Examples of suitable anti-proliferative agents for use in combination with the
15 compounds of the present invention include cyclosporin A, taxol, FK 506, and adriamycin.

Examples of suitable anti-tumor agents for use in combination with the compounds of the present invention include taxol, adriamycin, epothilones, cisplatin and carboplatin.

20 Examples of suitable a selective estrogen receptor modulator for use in combination with the compounds of the present invention include tamoxifen and raloxifene.

Examples of suitable a selective androgen receptor modulator for use in combination with the compounds of the present invention include such disclosed in
25 Edwards, J. P. et al., Bio. Med. Chem. Let., 9, 1003-1008 (1999) and Hamann, L. G. et al., J. Med. Chem., 12, 210-212 (1999).

Examples of suitable a bisphosphonate for use in combination with the compounds of the present invention include MK-217 (alendronate).

The above other therapeutic agents, when employed in combination with the
30 compounds of the present invention, may be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

In a preferred embodiment, the compounds of the invention are used for the treatment and/or prophylaxis of the aforementioned physiological and/or pathophysiological conditions in the form of a medicament, where such medicament comprises as additional pharmacologically active substance an endocannabinoid
5 receptor antagonist, preferably a CB1 receptor antagonist, most preferably rimonabant (1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl-, monohydrochloride; CAS Registry Number: 158681-13-1; SR-141716A; US patent 5,624,941) and as compound of the invention a GHS-R antagonist.

In another preferred embodiment, the compounds of the invention are used for the
10 treatment and/or prophylaxis of the aforementioned physiological and/or pathophysiological conditions in the form of a medicament, where the medicament is applied before and/or during and/or after treatment with at least one additional pharmacologically active substance, where such additional pharmacologically active substance is an endocannabinoid receptor antagonist, preferably a CB1 receptor
15 antagonist, most preferably rimonabant (1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl-, monohydrochloride; CAS Registry Number: 158681-13-1; SR-141716A; US patent 5,624,941) and the compound of the invention is a GHS-R antagonist.

The compounds of the present invention can be administered in a known manner.
20 The route of administration may thereby be any route which effectively transports the active compound to the appropriate or desired site of action, for example orally or non-orally, in particular topically, transdermally, pulmonary, rectally, intravaginally, nasally or parenteral or by implantation. Oral administration is preferred.

The compounds of the invention are converted into a form which can be
25 administered and are mixed where appropriate with pharmaceutically acceptable carriers or diluents. Suitable excipients and carriers are described for example in Ullman's Encyclopedia of Technical Chemistry, Vol. 4, (1953), 1-39; Journal of Pharmaceutical Sciences, Vol. 52 (1963), 918 et seq.; H. v. Czetsch-Lindenwald, "Hilfsstoffe für Pharmazie und angrenzende Gebiete"; Pharm. Ind. 2, 1961, 72 et seq.;
30 Dr. H.P. Fiedler, „Lexikon der Hilfsstoffe für Pharmazie, Kosmetik and angrenzende Gebiete“, Cantor KG, Aulendorf in Württemberg, 1971.

Oral administration can take place for example in solid form as tablet, capsule, gel capsule, coated tablet, granulation or powder, but also in the form of a drinkable solution. The compounds of the invention can for oral administration be combined with

known and ordinarily used, physiologically tolerated excipients and carriers such as, for example, gum arabic, talc, starch, sugars such as, for example, mannitol, methylcellulose, lactose, gelatin, surface-active agents, magnesium stearate, cyclodextrins, aqueous or nonaqueous carriers, diluents, dispersants, emulsifiers, lubricants, preservatives and flavorings (e.g. essential oils). The compounds of the invention can also be dispersed in a microparticulate, e.g. nanoparticulate, composition.

Non-oral administration can take place for example by intravenous, subcutaneous, intramuscular injection of sterile aqueous or oily solutions, suspensions or emulsions, by means of implants or by ointments, creams or suppositories. Administration as sustained release form is also possible where appropriate. Implants may comprise inert materials, e.g. biodegradable polymers or synthetic silicones such as, for example, silicone rubber. Intravaginal administration is possible for example by means of vaginal rings. Intrauterine administration is possible for example by means of diaphragms or other suitable intrauterine devices. Transdermal administration is additionally provided, in particular by means of a formulation suitable for this purpose and/or suitable means such as, for example, patches.

The dosage may vary within a wide range depending on type and/or severity of the physiological and/or pathophysiological condition, the mode of administration, the age, gender, bodyweight and sensitivity of the subject to be treated. It is within the ability of a skilled worker to determine a "pharmacologically effective amount" of a compound of the invention and/or additional pharmacologically active substance. Administration can take place in a single dose or a plurality of separate dosages.

A suitable unit dose is, for example, from 0.001 mg to 100 mg of the active ingredient, i.e. at least one compound of the invention and, where appropriate, at least one additional pharmacologically active substance, per kg of a patient's bodyweight.

In another aspect, the present invention relates to a pharmaceutical composition comprising a pharmacologically active amount of at least one triazole compound selected from the group consisting of: compound 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26 and/or 27,

In a further aspect, such a pharmaceutical composition may additionally comprise at least one pharmaceutically acceptable carrier and/or excipient and/or may comprise at least one further pharmacologically active substance.

In a preferred embodiment, such further pharmacologically active substance is an endocannabinoid receptor antagonist, preferably a CB1 receptor antagonist, most preferably rimonabant [1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl-, monohydrochloride].

- 5 Concerning the pharmaceutical compositions of the invention, at least one of the triazole compounds as listed above is present in a pharmacologically effective amount, preferably in a unit dose, e.g. the aforementioned unit dose, specifically and preferably in an administration form which makes oral administration possible. Furthermore, reference may be made to that already said in connection with the possible uses and
- 10 administrations of the compounds of the invention.

GHS-R 1a receptor assays

Mouse LTK- cells (ATCC CCL-1.3) were stably transfected with a plasmid containing the CMV minimal promoter (CMVmin) linked to three cAMP response elements (CRE) followed by a luciferase reporter gene. Based on this parental cell
5 line, single cell clones stably overexpressing the human, rat or mouse GHS-R1A have been established and characterized with respect to suitability for the different assay formats.

For receptor competitive binding studies, iodinated ghrelin was used as a tracer at conditions of about 80% saturation binding. Different concentrations of the test
10 compounds were analyzed for displacement of the tracer. For this purpose, the suspension of intact cells plus tracer mix and different test compound concentrations was layered on top of silicon/paraffin oil, incubated for 60 min at 37°C and subjected to centrifugation. After freezing in liquid nitrogen the cell pellets were separated from the supernatant by cutting the tubes in the intermediate silicon/paraffin oil section and
15 analyzed by γ -radiation analysis. The amount of unspecific binding was determined by including unlabeled ghrelin at 1 μ M final concentration.

For the CRE/Luc reporter gene assay, the mouse LTK- cells stably expressing the human GHS-1RA and a luciferase reporter gene under the control of CRE elements and the CMV minimal promoter were incubated for 6h with 1 μ M rolipram in the
20 presence of different concentrations of AEZS-130. Subsequently, cells were lysed and ATP bioluminescence was measured in the luminescence mode on FlexStation3 (Molecular Devices).

For determination of calcium release the respective cell line was loaded with Fluo-4 NW Calcium Assay Kit (Molecular Probes / Invitrogen # F10741) for 80min @ 37°C.
25 After 15 minutes of preincubation with different concentrations of the test compounds ghrelin was added and the signal was monitored for 60 seconds by a FlexStation3 microplate reader (Molecular Devices).

All data were calculated in % inhibition according to cells treated with saturating concentrations of ghrelin (NeoMPS #sc1357) as negative (0% inhibition), and non-
30 treated cells as positive control (100%). IC₅₀ values were determined by using the GraphPad Prism analysis program (GraphPad Software).

In the following **table 1** results obtained for selected compounds of the invention are presented in comparison to compound 50 disclosed in WO07/020013. Values given

are either single measurements or mean values of up to nine independent experiments performed in duplicate (binding) or quadruplicate (functional assays) measurements.

**Table 1: Shown in table 1A and 1B on the next two pages are mean IC₅₀ values
5 for ghrelin antagonistic activity of selected compounds against ghrelin receptors
of men, rats and mice.**

Ghrelin receptor IC₅₀ values shown in bold letters are at least three fold improved compared to the respective IC₅₀ value obtained for compound 50 disclosed in WO07/020013.

		Inhibition of the Ghrelin Receptor					
		Human Ghrelin Receptor Antagonist		Rat Ghrelin Receptor Antagonist		Mouse Ghrelin Receptor Antagonist	
		Competitive Binding	CRE/Luc Reporter Gene Assay	Calcium Release	Calcium Release	Calcium Release	Calcium Release
Compound	MW	IC50 [μ M]	IC50 [μ M]	IC50 [μ M]	IC50 [μ M]	IC50 [μ M]	IC50 [μ M]
Cpd 50 WO07/ 020013	545	0.0163	0.1334	0.0629	3.831	2.496	
Cpd 3	767	0.0006	0.0022	0.0025	0.0299	0.0292	
Cpd 4	728	0.0013	0.0043	0.0020	0.2390	0.0687	
Cpd 6	681	0.0030	0.0078	0.0021			
Cpd 5	714	0.0034	0.0083	0.0031	0.2901	0.0893	
Cpd 7	736	0.0034	0.0095	0.0038			

Table 1A

		Inhibition of the Ghrelin Receptor					
		Human Ghrelin Receptor Antagonist		Rat Ghrelin Receptor Antagonist		Mouse Ghrelin Receptor Antagonist	
		Competitive Binding	CRE/Luc Reporter Gene Assay	Calcium Release	Calcium Release	Calcium Release	Calcium Release
Compound	MW	IC50 [μ M]	IC50 [μ M]	IC50 [μ M]	IC50 [μ M]	IC50 [μ M]	IC50 [μ M]
Cpd 50 WO07/ 020013	545	0.0163	0.1334	0.0629	3.831	2.496	
Cpd 1	653		0.0128	0.0030			
Cpd 17	666	0.0086	0.0211	0.0314	0.9248	0.6065	
Cpd 8	747	0.0014	0.0224	0.0191	1.053	0.3632	
Cpd 15	716	0.0165	0.0249	0.0399			
Cpd 9	733	0.0032	0.0586	0.0326			

Table 1B

In vitro safety assessment

For detection of MDR-1 (P-glycoprotein, Pgp) ATPase activity commercially available membrane preparations of MDR-1 overexpressing SF9 insect cells (SB-MDR1-Sf9-ATPase Membrane; 2,5mg/500 μ L; Solvo / tebu-bio # 168SB-MDR1-Sf9-ATPase) were used. Since transport by MDR-1 is ATP-dependent, ATP consumption indicates transport activity of MDR-1. ATP consumption is detected as a decrease in luminescence from a second reaction with a recombinant firefly luciferase by using the Pgp-GloTM Assay Kit (Promega # V3591).

The PredictorTM hERG Fluorescence Polarization Assay (Invitrogen, Karlsruhe, GER) determines whether test compounds block the hERG channel [Piper, D.R. *et al.*, Assay Drug Dev Technol. 2008, 6(2):213-23]. The assay uses a membrane fraction containing hERG channel protein (PredictorTM hERG Membrane) and a high-affinity red fluorescent hERG channel ligand, or "tracer" (PredictorTM hERG Tracer Red), in a homogenous, fluorescence polarization (FP)-based format. Compounds that bind to the hERG channel protein (competitors) are identified by their ability to displace the tracer, resulting in a lower fluorescence polarization. The assay was performed according to guidelines of the manufacturer

Direct and metabolism-dependent inhibition of CYP enzymes are assessed with specific marker substrates by a HPLC-based UV detection method in human liver microsomes. Incubations are carried out as doublets with final concentrations ranging from 0.01 to 200 μ M (30min, 37°C). Metabolism-dependent inhibition was assessed by incubation for 30 minutes in the presence of NADPH prior to the addition of marker substrate to allow the generation of metabolites. Percent inhibition is plotted against concentration to calculate or extrapolate IC₅₀ values from the sigmoid curve.

25

Table 2: Shown in table 2A and 2B on the next two pages are the EC₅₀ results of in vitro safety parameter, i.e. inhibition of the human transporter MDR-1 (Pgp), the hERG cardiac channel, and the CYP3A4 enzyme.

Results depicted in bold letters are at least two fold improved with respect to the respective result obtained for compound 50 disclosed in WO07/020013.

30

In vitro Safety Assessment						
	Inhibition of MDR1 ATPase	hERG Predictor	CYP3A4 Inhibition Testosterone	CYP3A4 Inhibition Testosterone Preincubation	CYP3A4 Inhibition Midazolam	CYP3A4 Inhibition Midazolam Preincubation
Compound	EC50 [μ M]	EC50 [μ M]	EC50 [μ M]	EC50 [μ M]	EC50 [μ M]	EC50 [μ M]
Cpd 50 WO07/ 020013	6.95	8.17	6.3		7.3	3
Cpd 3	38.6	no inhibition			3.2	0.98
Cpd 4	no full dose response	no full dose response			3.9	2.3
Cpd 6	no inhibition	no inhibition	34.3	1.4		
Cpd 5	no inhibition	no full dose response			3.8	1.2
Cpd 7	1.08	no inhibition	27.0	1.1		

Table 2A

In vitro Safety Assessment						
	Inhibition of MDR1 ATPase	hERG Predictor	CYP3A4 Inhibition Testosterone	CYP3A4 Inhibition Testosterone Preincubation	CYP3A4 Inhibition Midazolam	CYP3A4 Inhibition Midazolam Preincubation
Compound	EC50 [μ M]	EC50 [μ M]	EC50 [μ M]	EC50 [μ M]	EC50 [μ M]	EC50 [μ M]
Cpd 50 WO07/ 020013	6.95	8.17	6.3		7.3	3
Cpd 1						
Cpd 17	no full dose response	3.68	10.4	2.0		
Cpd 8	195.6	no inhibition	31.2	0.9		
Cpd 15	16.3					
Cpd 9	0.836	no full dose response	>10-30	1.5		

Table 2B

In vitro microsomal stability and permeability (CaCo-2 cells)

Metabolic stability in liver microsomes of different species (in the presence of NADPH, 1 mg/ml microsomal protein) was evaluated at 37°C over time in triplicates at a test concentration of 10µM. Loss of parent compound is measured by an HPLC-based UV detection method. For prediction of rat hepatic clearance half-lives ($t_{1/2}$) were fitted from first-order rate constant k (min^{-1}) obtained from the slope of time versus \ln % remaining. Half-lives were used to calculate *in vitro* CL_{int} and predict rat hepatic clearance by using following scaling factors for the rat: 44.8 mg microsomal protein / g liver, 40 g liver weight per kg of b.w., 55.2 ml/min/kg liver blood flow.

For the CaCo-2 permeability assay 80.000 CaCo-2 cells (ATCC HTB-37) were seeded in DMEM supplemented with 10% FCS, 1% Penicillin/Streptomycin and 1% non-essential amino acids per 24well transwell plate (Corning 3397) and were grown for 21 days by changing the media every second day. On day 21 the medium was replaced by HBSS buffer (Invitrogen #14065) supplemented with 0.25% and 1% BSA for the donor and acceptor compartment, respectively. The compounds were added to the respective donor compartment in a concentration of 3 or 5 µM and were incubated for 2 hours at 37°C. The respective compound concentrations were determined by LC-MS analytics using an API 2000. Data analysis was performed as described by Sun and Pang 2008, Drug Metabolism and Disposition 36, 102-123.

20

Table 3: Shown in table 3A and 3B on the next two pages are the in vitro stability assessment results after incubation of the compounds with human liver microsomes in % remaining after 1 hour as well as the intestinal permeability prediction by measuring flux of the compounds through a CaCo-2 cell layer.

Results depicted in bold letters are at least two fold improved with respect to the respective result obtained for compound 50 disclosed in WO07/020013.

	In vitro Stability				In vitro Permeability		
	Stability in Liver Microsomes				CaCo-2 Assay		
	Human	Rat	Dog	Mouse	Papp [cm.s-1]. 10-6 ab	Papp [cm.s-1]. 10-6 ba	ba/ab
Compound	% Remaining after 1h Incubation @37 °C / 1mg/ml Liver Microsomes						
Cpd 50 WO07/ 020013	28.6	39.2	36	0	0.1	15.58	155.8
Cpd 3		38.5			0.37 ± 0.02	17.19± 0.42	51.86
Cpd 4	9.1	46.7		0.0 (@30min)	1.41 +/-0.07	25.39+/-1.09	18.04
Cpd 6		27.1					
Cpd 5	0	41.9		0.0 (@30min)	1.26+/-0.16	16.78+/-0.2	13.34
Cpd 7		82.7					

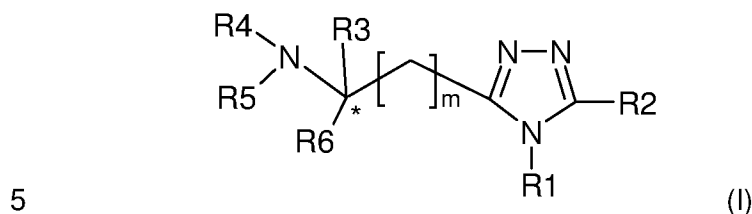
Table 3A

	In vitro Stability				In vitro Permeability		
	Stability in Liver Microsomes				CaCo-2 Assay		
	Human	Rat	Dog	Mouse	Papp [cm.s-1]. 10-6 ab	Papp [cm.s-1]. 10-6 ba	ba/ab
Compound	% Remaining after 1h Incubation @37°C / 1mg/ml Liver Microsomes						
Cpd 50 WO07/ 020013	28.6	39.2	36	0	0.1	15.58	155.8
Cpd 1							
Cpd 17	0	24.8		0.0 (@30min)	22.41+/-5.7	10.04+/-2.45	0.45
Cpd 8		64.3			0.08 ± 0.08	0.74± 0.03	9.25
Cpd 15		37.8					
Cpd 9		54.8					

Table 3B

Claims:

1. Use of a compound according to formula (I)



wherein:

(A)

- 10 **R1** and **R2** are independently of one another selected from the group consisting of
 “hydrogen atom, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl,
 arylalkyl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, alkylsulfonyl, arylsulfonyl,
 arylalkylsulfonyl” which are optionally substituted in the alkyl, cycloalkyl,
 cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and/or
 15 heterocyclylalkyl group by up to 3 substituents independently selected from the
 group consisting of “halogen, -F, -Cl, -Br, -I, -N₃, -CN, -NR₇R₈, -NR₁₁R₁₂, -
 OH, -NO₂, alkyl, aryl, heteroaryl, arylalkyl, -O-alkyl, -O-aryl, -O-arylalkyl, -
 C(O)O-alkyl, -C(O)O-cycloalkyl, -C(O)O-cycloalkylalkyl, -C(O)O-aryl, -
 C(O)O-arylalkyl, -C(O)O-heteroaryl, -C(O)O-heteroarylalkyl, -C(O)O-
 20 heterocyclyl, -C(O)O-heterocyclylalkyl, -C(O)NR₉R₁₀, -C(S)NR₉R₁₀;”;
 one of radicals **R3** and **R4** is a hydrogen atom, whereas the other radical is
 selected from the group consisting of “hydrogen atom, alkyl, aryl, heteroaryl,
 arylalkyl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, -alkyl-O-aryl, -alkyl-O-
 arylalkyl, -alkyl-O-heteroaryl, -alkyl-O-heteroarylalkyl, -alkyl-O-heterocyclyl,
 25 alkyl-O-heterocyclylalkyl, -alkyl-CO-aryl, -alkyl-CO-arylalkyl, -alkyl-CO-
 heteroaryl, -alkyl-CO-heteroarylalkyl, -alkyl-CO-heterocyclyl, -alkyl-CO-
 heterocyclylalkyl, -alkyl-C(O)O-aryl, -alkyl-C(O)O-arylalkyl, -alkyl-C(O)O-
 heteroaryl, -alkyl-C(O)O-heteroarylalkyl, -alkyl-C(O)O-heterocyclyl, -alkyl-
 C(O)O-heterocyclylalkyl, -alkyl-CO-NH₂, -alkyl-CO-OH, -alkyl-NH₂, -alkyl-NH-
 30 C(NH)-NH₂, alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl, alkyl-S-alkyl, alkyl-S-H”

- 58 -

which are optionally substituted in the aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and/or heterocyclylalkyl group by up to 3 substituents independently selected from the group consisting of "halogen, -F, -Cl, -Br, -I, -N₃, -CN, -NR₇R₈, -OH, -NO₂, alkyl, aryl, arylalkyl, -O-alkyl, -O-CF₃, -O-aryl, -O-arylalkyl";

5 **R5** is selected from the group consisting of "-C(S)alkyl, -C(S)-cycloalkyl, -C(S)-cycloalkylalkyl, -C(S)-aryl, -C(S)-arylalkyl, -C(S)-heteroaryl, -C(S)-heteroarylalkyl, -C(S)-heterocyclyl, -C(S)-heterocyclylalkyl, -C(O)O-alkyl, -C(O)O-cycloalkyl, -C(O)O-cycloalkylalkyl, -C(O)O-aryl, -C(O)O-arylalkyl, -C(O)O-heteroaryl, -C(O)O-heteroarylalkyl, -C(O)O-heterocyclyl, -C(O)O-heterocyclylalkyl, -C(O)NR₉R₁₀, -C(S)NR₉R₁₀"; which are optionally substituted
10 in the alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and/or heterocyclylalkyl group by up to 3 substituents independently selected from the group consisting of "halogen, -F, -Cl, -Br, -I, -N₃, -CN, -CF₃, -NR₇R₈, -OH, -NO₂, -NH₂, alkyl, aryl, arylalkyl, -O-alkyl, -O-aryl, -O-arylalkyl";

15 **R6** is selected from the group consisting of "hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl";

R7 and R8 are independently of one another selected from the group consisting of "hydrogen atom, alkyl, cycloalkyl, and cycloalkylalkyl";

R9 and R10 are independently of one another selected from the group consisting
20 of "hydrogen atom, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl";

R11 is a "hydrogen atom",

R12 is independently of one another selected from the group consisting of "-C(O)H, -C(O)-alkyl; -C(O)-cycloalkyl, -C(O)-cycloalkylalkyl, -C(O)-aryl, -C(O)-arylalkyl, -C(O)-heteroaryl, -C(O)-heteroarylalkyl, -C(O)-heterocyclyl, -C(O)-heterocyclylalkyl",
25

Or

(B)

30 **R1** is independently of one another selected from the group consisting of "hydrogen atom, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, alkylsulfonyl, arylsulfonyl,

arylalkylsulfonyl" which are optionally substituted in the alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and/or heterocyclylalkyl group by up to 3 substituents independently selected from the group consisting of "halogen, -F, -Cl, -Br, -I, -N₃, -CN, -NR₇R₈, -OH, -NO₂, alkyl, aryl, arylalkyl, -O-alkyl, -O-aryl, -O-arylalkyl";

R₂ is an "alkyl group", which is substituted by up to 2 substituents independently selected from the group consisting of "Aryl, Heteroaryl, -C(O)O-alkyl, -C(O)O-cycloalkyl, -C(O)O-cycloalkylalkyl, -C(O)O-aryl, -C(O)O-arylalkyl, -C(O)O-heteroaryl, -C(O)O-heteroarylalkyl, -C(O)O-heterocyclyl, -C(O)O-heterocyclylalkyl, -C(O)NR₉R₁₀, -NR₁₁R₁₂", and in the case of aryl, heteroaryl the alkylgroup has to be in addition substituted with -NR₁₁R₁₂;

one of radicals **R₃** and **R₄** is a hydrogen atom, whereas the other radical is selected from the group consisting of "hydrogen atom, alkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, -alkyl-O-aryl, -alkyl-O-arylalkyl, -alkyl-O-heteroaryl, -alkyl-O-heteroarylalkyl, -alkyl-O-heterocyclyl, -alkyl-O-heterocyclylalkyl, -alkyl-CO-aryl, -alkyl-CO-arylalkyl, -alkyl-CO-heteroaryl, -alkyl-CO-heteroarylalkyl, -alkyl-CO-heterocyclyl, -alkyl-CO-heterocyclylalkyl, -alkyl-C(O)O-aryl, -alkyl-C(O)O-arylalkyl, -alkyl-C(O)O-heteroaryl, -alkyl-C(O)O-heteroarylalkyl, -alkyl-C(O)O-heterocyclyl, -alkyl-C(O)O-heterocyclylalkyl, -alkyl-CO-NH₂, -alkyl-CO-OH, -alkyl-NH₂, -alkyl-NH-C(NH)-NH₂, alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl, alkyl-S-alkyl, alkyl-S-H" which are optionally substituted in the aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and/or heterocyclylalkyl group by up to 3 substituents independently selected from the group consisting of "halogen, -F, -Cl, -Br, -I, -N₃, -CN, -NR₇R₈, -OH, -NO₂, alkyl, aryl, arylalkyl, -O-alkyl, -O-aryl, -O-arylalkyl";

R₅ is selected from the group consisting of "hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, -CO-alkyl, -CO-cycloalkyl, -CO-cycloalkylalkyl, -CO-aryl, -CO-arylalkyl, -CO-heteroaryl, -CO-heteroarylalkyl, -CO-heterocyclyl, -CO-heterocyclylalkyl, -CO-C*(R₉R₁₀)-NH₂, -CO-CH₂-C*(R₉R₁₀)-NH₂, -CO-C*(R₉R₁₀)-CH₂-NH₂, alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl" which are optionally substituted by up to 3 substituents independently selected from the group consisting of "halogen, -F, -Cl, -Br, -I, -N₃, -CN, -NR₇R₈, -OH, -NO₂, alkyl, aryl, arylalkyl, -O-alkyl, -O-aryl, -O-arylalkyl";

- 60 -

R6 is selected from the group consisting of "hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl";

R7 and **R8** are independently of one another selected from the group consisting of "hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl";

5 **R9** and **R10** are independently of one another selected from the group consisting of "hydrogen atom, alkyl, natural amino acid side chain, unnatural amino acid side chain";

R11 is a "hydrogen atom";

10 **R12** is independently of one another selected from the group consisting of "-C(O)H, -C(O)-alkyl; -C(O)-cycloalkyl, -C(O)-cycloalkylalkyl, -C(O)-aryl, -C(O)-arylalkyl, -C(O)-heteroaryl, -C(O)-heteroarylalkyl, -C(O)-heterocyclyl, -C(O)-heterocyclylalkyl";

in terms of **(A)** and **(B)**

15 m is 0, 1 or 2; and

* means a carbon atom of R or S configuration when chiral;

for the manufacture of a medicament for the treatment or prophylaxis of physiological and/or pathophysiological conditions in mammals that are mediated by GHS receptors.

20

2. The use of a compound according to formula (I) as claimed in claim 1, where according to **(A)**

25 **R1** and **R2** are independently of one another selected from the group consisting of "hydrogen atom, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl" which are optionally substituted in the alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and/or heterocyclylalkyl group by up to 3 substituents independently selected from the group consisting of "halogen, -F, -Cl, -Br, -I, -N₃, -CN, -NR₇R₈, -NR₁₁R₁₂, -

30 OH, -NO₂, alkyl, aryl, heteroaryl, arylalkyl, -O-alkyl, -O-aryl, -O-arylalkyl, -C(O)O-alkyl, -C(O)O-cycloalkyl, -C(O)O-cycloalkylalkyl, -C(O)O-aryl, -

- 61 -

C(O)O-arylalkyl, -C(O)O-heteroaryl, -C(O)O-heteroarylalkyl, -C(O)O-heterocyclyl, -C(O)O-heterocyclylalkyl, -C(O)NR₉R₁₀, -C(S)NR₉R₁₀;”;

one of radicals **R3** and **R4** is a hydrogen atom, whereas the other radical is selected from the group consisting of “hydrogen atom, alkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, -alkyl-O-aryl, -alkyl-O-arylalkyl, -alkyl-O-heteroaryl, -alkyl-O-heteroarylalkyl, -alkyl-O-heterocyclyl, alkyl-O-heterocyclylalkyl, -alkyl-CO-aryl, -alkyl-CO-arylalkyl, -alkyl-CO-heteroaryl, -alkyl-CO-heteroarylalkyl, -alkyl-CO-heterocyclyl, -alkyl-CO-heterocyclylalkyl, -alkyl-C(O)O-aryl, -alkyl-C(O)O-arylalkyl, -alkyl-C(O)O-heteroaryl, -alkyl-C(O)O-heteroarylalkyl, -alkyl-C(O)O-heterocyclyl, -alkyl-C(O)O-heterocyclylalkyl, -alkyl-CO-NH₂, -alkyl-CO-OH, -alkyl-NH₂, -alkyl-NH-C(NH)-NH₂, alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl, alkyl-S-alkyl, alkyl-S-H” which are optionally substituted in the aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and/or heterocyclylalkyl group by up to 3 substituents independently selected from the group consisting of “halogen, -F, -Cl, -Br, -I, -N₃, -CN, -NR₇R₈, -OH, -NO₂, alkyl, aryl, arylalkyl, -O-alkyl, -O-CF₃, -O-aryl, -O-arylalkyl”;

R5 is selected from the group consisting of “-C(S)alkyl, -C(S)-cycloalkyl, -C(S)-cycloalkylalkyl, -C(S)-aryl, -C(S)-arylalkyl, -C(S)-heteroaryl, -C(S)-heteroarylalkyl, -C(S)-heterocyclyl, -C(S)-heterocyclylalkyl, -C(O)O-alkyl, -C(O)O-cycloalkyl, -C(O)O-cycloalkylalkyl, -C(O)O-aryl, -C(O)O-arylalkyl, -C(O)O-heteroaryl, -C(O)O-heteroarylalkyl, -C(O)O-heterocyclyl, -C(O)O-heterocyclylalkyl, -C(O)NR₉R₁₀, -C(S)NR₉R₁₀”; which are optionally substituted in the alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and/or heterocyclylalkyl group by up to 3 substituents independently selected from the group consisting of “halogen, -F, -Cl, -Br, -I, -N₃, -CN, -CF₃, -NR₇R₈, -OH, -NO₂, -NH₂, alkyl, aryl, arylalkyl, -OH, -O-alkyl, -O-aryl, -O-arylalkyl”;

R6 is selected from the group consisting of “hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl”;

R7 and R8 are independently of one another selected from the group consisting of “hydrogen atom, alkyl, cycloalkyl, and cycloalkylalkyl”;

R9 and R10 are independently of one another selected from the group consisting of “hydrogen atom, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl”;

R11 is a "hydrogen atom";

R12 is independently of one another selected from the group consisting of "-C(O)H, -C(O)-alkyl; -C(O)-cycloalkyl, -C(O)-cycloalkylalkyl, -C(O)-aryl, -C(O)-arylalkyl, -C(O)-heteroaryl, -C(O)-heteroarylalkyl, -C(O)-heterocyclyl, -C(O)-heterocyclylalkyl";

m is 0, 1 or 2; and

* means a carbon atom of R or S configuration when chiral.

3. The use of a compound according to formula (I) as claimed in claims 1, where according to **(B)**

R1 is independently of one another selected from the group consisting of "hydrogen atom, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl" which are optionally substituted in the alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and/or heterocyclylalkyl group by up to 3 substituents independently selected from the group consisting of "halogen, -F, -Cl, -Br, -I, -N₃, -CN, -NR⁷R⁸, -OH, -NO₂, alkyl, aryl, arylalkyl, -O-alkyl, -O-aryl, -O-arylalkyl";

R2 is an "alkyl group", which is substituted by up to 2 substituents independently selected from the group consisting of "Aryl, Heteroaryl, -C(O)O-alkyl, -C(O)O-cycloalkyl, -C(O)O-cycloalkylalkyl, -C(O)O-aryl, -C(O)O-arylalkyl, -C(O)O-heteroaryl, -C(O)O-heteroarylalkyl, -C(O)O-heterocyclyl, -C(O)O-heterocyclylalkyl, -C(O)NR⁹R¹⁰, -NR¹¹R¹²", and in the case of aryl, heteroaryl the alkyl group has to be in addition substituted with -NR¹¹R¹²;

one of radicals **R3** and **R4** is a hydrogen atom, whereas the other radical is selected from the group consisting of "hydrogen atom, alkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, -alkyl-O-aryl, -alkyl-O-arylalkyl, -alkyl-O-heteroaryl, -alkyl-O-heteroarylalkyl, -alkyl-O-heterocyclyl, -alkyl-O-heterocyclylalkyl, -alkyl-CO-aryl, -alkyl-CO-arylalkyl, -alkyl-CO-heteroaryl, -alkyl-CO-heteroarylalkyl, -alkyl-CO-heterocyclyl, -alkyl-CO-heterocyclylalkyl, -alkyl-C(O)O-aryl, -alkyl-C(O)O-arylalkyl, -alkyl-C(O)O-heteroaryl, -alkyl-C(O)O-heteroarylalkyl, -alkyl-C(O)O-heterocyclyl, -alkyl-

C(O)O-heterocyclalkyl, -alkyl-CO-NH₂, -alkyl-CO-OH, -alkyl-NH₂, -alkyl-NH-C(NH)-NH₂, alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl, alkyl-S-alkyl, alkyl-S-H” which are optionally substituted in the aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclalkyl and/or heterocyclalkyl group by up to 3 substituents independently selected from the group consisting of “halogen, -F, -Cl, -Br, -I, -N₃, -CN, -NR₇R₈, -OH, -NO₂, alkyl, aryl, arylalkyl, -O-alkyl, -O-aryl, -O-arylalkyl”;

R5 is selected from the group consisting of “hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclalkyl, heterocyclalkyl, -CO-alkyl, -CO-cycloalkyl, -CO-cycloalkylalkyl, -CO-aryl, -CO-arylalkyl, -CO-heteroaryl, -CO-heteroarylalkyl, -CO-heterocyclalkyl, -CO-heterocyclalkyl, -CO-C*(R₉R₁₀)-NH₂, -CO-CH₂-C*(R₉R₁₀)-NH₂, -CO-C*(R₉R₁₀)-CH₂-NH₂, alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl” which are optionally substituted by up to 3 substituents independently selected from the group consisting of “halogen, -F, -Cl, -Br, -I, -N₃, -CN, -NR₇R₈, -OH, -NO₂, alkyl, aryl, arylalkyl, -O-alkyl, -O-aryl, -O-arylalkyl”;

R6 is selected from the group consisting of “hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl”;

R7 and **R8** are independently of one another selected from the group consisting of “hydrogen atom, alkyl, cycloalkyl, cycloalkylalkyl”;

R9 and **R10** are independently of one another selected from the group consisting of “hydrogen atom, alkyl, natural amino acid side chain, unnatural amino acid side chain”;

R11 is a “hydrogen atom”;

R12 is independently of one another selected from the group consisting of “-C(O)H, -C(O)-alkyl; -C(O)-cycloalkyl, -C(O)-cycloalkylalkyl, -C(O)-aryl, -C(O)-arylalkyl, -C(O)-heteroaryl, -C(O)-heteroarylalkyl, -C(O)-heterocyclalkyl, -C(O)-heterocyclalkyl”;

m is 0, 1 or 2; and

* means a carbon atom of R or S configuration when chiral.

4. The use of a compound according to formula (I) as claimed in claim 1, where R₂ is an “alkyl group”, which is substituted by up to 2 substituents independently selected from the group consisting of “Aryl, Heteroaryl, -C(O)O-alkyl, -C(O)O-

- 64 -

cycloalkyl, $-\text{C}(\text{O})\text{O}-\text{cycloalkylalkyl}$, $-\text{C}(\text{O})\text{O}-\text{aryl}$, $-\text{C}(\text{O})\text{O}-\text{arylalkyl}$, $-\text{C}(\text{O})\text{O}-\text{heteroaryl}$, $-\text{C}(\text{O})\text{O}-\text{heteroarylalkyl}$, $-\text{C}(\text{O})\text{O}-\text{heterocyclyl}$, $-\text{C}(\text{O})\text{O}-\text{heterocyclylalkyl}$, $-\text{C}(\text{O})\text{NR}_9\text{R}_{10}$, $-\text{NR}_{11}\text{R}_{12}$ “, and in the case of aryl, heteroaryl the alkylgroup has to be in addition substituted with $-\text{NR}_{11}\text{R}_{12}$;

- 5 **R9** and **R10** are independently of one another selected from the group consisting of “hydrogen atom, alkyl, natural amino acid side chain, unnatural amino acid side chain”;

R11 is a “hydrogen atom”,

- 10 **R12** is independently of one another selected from the group consisting of “ $-\text{C}(\text{O})\text{H}$, $-\text{C}(\text{O})-\text{alkyl}$; $-\text{C}(\text{O})-\text{cycloalkyl}$, $-\text{C}(\text{O})-\text{cycloalkylalkyl}$, $-\text{C}(\text{O})-\text{aryl}$, $-\text{C}(\text{O})-\text{arylalkyl}$, $-\text{C}(\text{O})-\text{heteroaryl}$, $-\text{C}(\text{O})-\text{heteroarylalkyl}$, $-\text{C}(\text{O})-\text{heterocyclyl}$, $-\text{C}(\text{O})-\text{heterocyclylalkyl}$ ”.

5. The use of a compound according to formula (I) as claimed in claim 1, where:

- 15 **R5** is selected from the group consisting of “ $-\text{C}(\text{S})\text{alkyl}$, $-\text{C}(\text{S})-\text{cycloalkyl}$, $-\text{C}(\text{S})-\text{cycloalkylalkyl}$, $-\text{C}(\text{S})-\text{aryl}$, $-\text{C}(\text{S})-\text{arylalkyl}$, $-\text{C}(\text{S})-\text{heteroaryl}$, $-\text{C}(\text{S})-\text{heteroarylalkyl}$, $-\text{C}(\text{S})-\text{heterocyclyl}$, $-\text{C}(\text{S})-\text{heterocyclylalkyl}$, $-\text{C}(\text{O})\text{O}-\text{alkyl}$, $-\text{C}(\text{O})\text{O}-\text{cycloalkyl}$, $-\text{C}(\text{O})\text{O}-\text{cycloalkylalkyl}$, $-\text{C}(\text{O})\text{O}-\text{aryl}$, $-\text{C}(\text{O})\text{O}-\text{arylalkyl}$, $-\text{C}(\text{O})\text{O}-\text{heteroaryl}$, $-\text{C}(\text{O})\text{O}-\text{heteroarylalkyl}$, $-\text{C}(\text{O})\text{O}-\text{heterocyclyl}$, $-\text{C}(\text{O})\text{O}-\text{heterocyclylalkyl}$, $-\text{C}(\text{O})\text{NR}_9\text{R}_{10}$, $-\text{C}(\text{S})\text{NR}_9\text{R}_{10}$ ” ; which are optionally substituted in the alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and/or heterocyclylalkyl group by up to 3 substituents independently selected from the group consisting of “halogen, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{N}_3$, $-\text{CN}$, $-\text{CF}_3$, $-\text{NR}_7\text{R}_8$, $-\text{OH}$, $-\text{NO}_2$, $-\text{NH}_2$, alkyl, aryl, arylalkyl, $-\text{OH}$, $-\text{O}-\text{alkyl}$, $-\text{O}-\text{aryl}$, $-\text{O}-\text{arylalkyl}$ ”;
- 20
- 25

R7 and **R8** are independently of one another selected from the group consisting of “hydrogen atom, alkyl, cycloalkyl, and cycloalkylalkyl”;

- 30 **R9** and **R10** are independently of one another selected from the group consisting of “hydrogen atom, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, arylalkyl, and heteraryloalkyl”.

6. The use as claimed in any of claims 1 to 4 where the compound is selected from the group consisting of:

5 **compound 1** [5-{(R)-2-(1H-Indol-3-yl)-1-[(pyridine-3-carbonyl)-amino]-ethyl}-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-acetic acid ethyl ester;

compound 2 N-[(R)-1-[5-Carbamoylmethyl-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-nicotinamide;

10 **compound 3** Pyridine-2-carboxylic acid [(R)-1-[5-[(R)-1-acetylamino-2-(1H-indol-3-yl)-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-amide;

compound 4 Pyridine-2-carboxylic acid [(R)-1-[5-[(R)-1-acetylamino-2-phenyl-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-amide;

15 **compound 5** Pyridine-2-carboxylic acid [(R)-1-[5-[(R)-1-formylamino-2-phenyl-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-amide;

compound 6 N-[(R)-1-[5-[(R)-1-Acetylamino-2-phenyl-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-2-hydroxy-acetamide;

20 **compound 7** (S)-Morpholine-2-carboxylic acid [(R)-1-[5-[(R)-1-acetylamino-2-phenyl-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-amide;

compound 8 N-[(R)-1-[5-[(R)-1-Acetylamino-2-(1H-indol-3-yl)-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-2-amino-2-methyl-propionamide;

25 **compound 9** 2-Amino-N-[(R)-1-[5-[(R)-1-formylamino-2-(1H-indol-3-yl)-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-2-methyl-propionamide;

- compound 10** N-[(R)-1-[5-((R)-1-Acetylamino-2-phenyl-ethyl)-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-2-amino-2-methyl-propionamide;
- 5 **compound 11** Pyridine-2-carboxylic acid [(R)-1-[5-[1-acetylamino-2-(1H-indol-3-yl)-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-amide;
- compound 12** 2-Amino-N-[(R)-1-[5-((R)-1-formylamino-2-phenyl-ethyl)-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-2-methyl-propionamide;
- 10 **compound 13** Pyridine-2-carboxylic acid [(R)-1-[5-((S)-1-acetylamino-2-phenyl-ethyl)-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-amide;
- compound 14** Pyridine-2-carboxylic acid [(R)-1-[5-[1-formylamino-2-(1H-indol-3-yl)-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-amide;
- compound 15** {(R)-1-[5-[2-(1H-Indol-3-yl)-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-naphthalen-2-yl-ethyl}-carbamic acid tert-butyl ester;
- 15 **compound 16** 1-[(R)-2-(1H-Indol-3-yl)-1-[4-(4-methoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl]-3-isopropyl-urea;
- compound 17** {(R)-2-(1H-Indol-3-yl)-1-[4-(4-methoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl}-carbamic acid isobutyl ester;
- 20 **compound 18** {(R)-2-(1H-Indol-3-yl)-1-[4-(4-methoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl}-carbamic acid tert-butyl ester;
- compound 19** 1-Benzyl-3-[(R)-2-(1H-indol-3-yl)-1-[4-(4-methoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl]-urea;
- compound 20** 1-Benzyl-3-[(R)-2-(1H-indol-3-yl)-1-[4-(4-methoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl]-thiourea;

- 67 -

compound 21 [(R)-1-[4-(4-Fluoro-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-carbamic acid tert-butyl ester;

compound 22 {(R)-2-(1H-Indol-3-yl)-1-[4-(4-isopropoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl}-carbamic acid tert-butyl ester;

5 **compound 23** {(R)-2-(1H-Indol-3-yl)-1-[4-(4-methoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl}-methyl-carbamic acid tert-butyl ester;

compound 24 [(R)-1-[4-(2,4-Dimethoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-carbamic acid tert-butyl ester;

10 **compound 25** Piperidine-4-carbothioic acid {(R)-2-(1H-indol-3-yl)-1-[4-(4-methoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl}-amide;

compound 26 2-Amino-N-[(R)-2-(1H-indol-3-yl)-1-[4-(4-methoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl]-thioacetamide;

compound 27 Pyridine-2-carbothioic acid {(R)-2-(1H-indol-3-yl)-1-[4-(4-methoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl}-amide;

15 and the physiologically tolerated salts thereof.

7. The use as claimed in any of claims 1 to 6 where the treatment is achieved by modulation of GHS receptors.

20 8. The use as claimed in any of claims 1 to 7 where the compound is a GHS receptor antagonist.

9. The use as claimed in claim 8, where the GHS receptor antagonist is selected from the group consisting of: **compound 1-24, 26 and/or compound 27**.

25

10. The use as claimed in any of claims 1 to 6 where the compound is a GHS receptor agonist.

11. The use as claimed in claim 10, where the GHS receptor agonist is selected from the group consisting of: **compound 25**.
12. The use as claimed in any of claims 1 to 7 where the compound is a GHS
5 receptor inverse agonist.
13. The use as claimed in any of claims 1 to 7 where the compound is a GHS receptor partial agonist/antagonist.
- 10 14. The use as claimed in any of claims 1 to 13 where the mammal is selected from the group consisting of "human, domestic animals, cattle, livestock, pets, cow, sheep, pig, goat, horse, pony, donkey, hinny, mule, hare, rabbit, cat, dog, guinea pig, hamster, rat, mouse" and preferably is human.
- 15 15. The use as claimed in any of claims 1 to 14 where the GHS receptors are selected from the group consisting of "GHS type 1 receptor, GHS-R 1a, GHS-R 1b, motilin receptor, motilin receptor 1a, neurotensin receptor, TRH receptor, GPR38 (FM1), GPR39 (FM2), FM3, GHS-R subtype, GHS binding site, cardiac GHS-R, mammary GHS-R", preferably is selected from the group consisting of
20 "GHS type 1 receptor, GHS-R 1a, GHS-R 1b" and most preferably are GHS-R 1a.
16. The use as claimed in any of claims 1 to 15 where physiological and/or pathophysiological conditions are selected from the group consisting of "acute
25 fatigue syndrome and muscle loss following election surgery, adipogenesis, adiposity, age-related decline of thymic function, age-related functional decline ("ARFD") in the elderly, aging disorder in companion animals, alcohol-related disorders, Alzheimer's disease, anorexia (e.g. associated with cachexia or aging); anxiety, blood pressure (lowering), body weight gain/reduction, bone
30 fracture repair (acceleration), bone remodeling stimulation, cachexia and protein loss reduction due to chronic illness such as cancer or AIDS, cardiac dysfunctions (e.g. associated with valvular disease, myocardial infarction, cardiac hypertrophy or congestive heart failure), cardiomyopathy, cartilage growth stimulation, catabolic disorders in connection with pulmonary
35 dysfunction and ventilator dependency, catabolic side effects of glucocorticoids,

catabolic state of aging, central nervous system disorders (in combination with antidepressants), chronic dialysis, chronic fatigue syndrome (CFS), cognitive function improvement (e.g. in dementia, Alzheimer's disease), complicated fractures (e.g. distraction osteogenesis), complications associated with transplantation, congestive heart failure (alone/in combination with corticotropin releasing factor antagonists), Crohn's disease and ulcerative colitis, Cushing's syndrome, dementia, depressions, drug abuse, short-, medium- and/or long-term regulation of energy balance, short-, medium- and/or long-term regulation of food intake (stimulation and/or inhibition), intake of rewarding food, frailty (e.g. in elderly humans), gastrectomy (ghrelin replacement therapy), gastric postoperative ileus, glycemic control improvement, growth hormone release stimulation in the elderly, growth hormone replacement in stressed patients, growth promotion in livestock, growth retardation associated with the Prader-Willi syndrome and Turner's syndrome, growth retardation in connection with Crohn's disease, growth retardation, hair/nail growth maintenance, hip fractures, hunger, hypercortisolism, hyperinsulinemia including nesidioblastosis, hypothermia, immune deficiency in individuals with a depressed T4/T8 cell ratio, immune response improvement to vaccination, immune system stimulation in companion animals, immune system stimulation, immunosuppression in immunosuppressed patients, inflammation or inflammatory effects, inflammatory bowel disease, insulin resistance in the heart, insulin resistance in type 2 diabetic patients, insulin resistance including NIDDM, diabetes, diabetes type I, diabetes type II, intrauterine growth retardation, irritable bowel syndrome, lipodystrophy (e.g. HIV-induced), metabolic homeostasis maintenance, milk production increase in livestock, muscle mass/strength increase, muscle mobility improvement, muscle strength improvement, muscle strength/function maintenance in elderly humans, muscular atrophy, musculoskeletal impairment (e.g. in elderly), Noonan's syndrome, obesity and growth retardation associated with obesity, osteoblast stimulation, osteochondrodysplasias, osteoporosis, ovulation induction (adjuvant treatment), physiological short stature including growth hormone deficient children, postoperative ileus, protein catabolic response attenuation after major surgery/trauma, protein kinase B activity enhancement, psychosocial deprivation, pulmonary dysfunction and ventilator dependency, pulmonary function improvement, pulsatile growth hormone release induction, recovery of burn patients and reducing hospitalization of burn

- patients (acceleration), renal failure or insufficiency resulting from growth retardation, renal homeostasis maintenance in the frail elderly, sarcopenia, schizophrenia, sensory function maintenance (e.g. hearing, sight, olfaction and taste), short bowel syndrome, short stature associated with chronic illness, skeletal dysplasia, skin thickness maintenance, sleep disorders, sleep quality improvement, thrombocytopenia, thymic development stimulation, tooth repair or growth, tumor cell proliferation, ventricular dysfunction or reperfusion events, wasting in connection with AIDS, wasting in connection with chronic liver disease, wasting in connection with chronic obstructive pulmonary disease (COPD), wasting in connection with multiple sclerosis or other neurodegenerative disorders, wasting secondary to fractures, wool growth stimulation in sheep, wound healing (acceleration) and/or wound healing delay".
17. The use as claimed in claim 16 where physiological and/or pathophysiological conditions are selected from the group consisting of "alcohol-related disorders; drug abuse; growth retardation, cachexia, short-, medium- and/or long term regulation of energy balance; short-, medium- and/or long term regulation (stimulation and/or inhibition) of food intake; intake of rewarding food; adipogenesis, adiposity and/or obesity; body weight gain and/or reduction; diabetes, diabetes type I, diabetes type II, tumor cell proliferation; inflammation, inflammatory effects, gastric postoperative ileus, postoperative ileus and/or gastrectomy (ghrelin replacement therapy)"
18. The use as claimed in any of claims 1 to 17 where such medicament comprises at least one additional pharmacologically active substance.
19. The use as claimed in claim 18, where such medicament comprises a GHS receptor antagonist and an endocannabinoid receptor antagonist, preferably a CB1 receptor antagonist, most preferably rimonabant [1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl-, monohydrochloride] as additional pharmacologically active substance.

20. The use as claimed in any of claims 1 to 19 where the medicament is applied before and/or during and/or after treatment with at least one additional pharmacologically active substance.
- 5 21. The use as claimed in claim 20, where the medicament comprises a GHS receptor antagonist and the additional pharmacologically active substance is an endocannabinoid receptor antagonist, preferably a CB1 receptor antagonist, most preferably rimonabant [1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl-, monohydrochloride].
- 10 22. A triazole compound selected from the group consisting of:
- compound 1** [5-{(R)-2-(1H-Indol-3-yl)-1-[(pyridine-3-carbonyl)-amino]-ethyl}-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-acetic acid ethyl ester;
- compound 2** N-[(R)-1-[5-Carbamoylmethyl-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-nicotinamide;
- 15 **compound 3** Pyridine-2-carboxylic acid [(R)-1-[5-[(R)-1-acetylamino-2-(1H-indol-3-yl)-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-amide;
- compound 4** Pyridine-2-carboxylic acid [(R)-1-[5-[(R)-1-acetylamino-2-phenyl-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-amide;
- 20 **compound 5** Pyridine-2-carboxylic acid [(R)-1-[5-[(R)-1-formylamino-2-phenyl-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-amide;
- compound 6** N-[(R)-1-[5-[(R)-1-Acetylamino-2-phenyl-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-2-hydroxy-acetamide;
- 25 **compound 7** (S)-Morpholine-2-carboxylic acid [(R)-1-[5-[(R)-1-acetylamino-2-phenyl-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-amide;

- compound 8** N-[(R)-1-[5-[(R)-1-Acetylamino-2-(1H-indol-3-yl)-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-2-amino-2-methyl-propionamide;
- 5 **compound 9** 2-Amino-N-[(R)-1-[5-[(R)-1-formylamino-2-(1H-indol-3-yl)-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-2-methyl-propionamide;
- compound 10** N-[(R)-1-[5-[(R)-1-Acetylamino-2-phenyl-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-2-amino-2-methyl-propionamide;
- 10 **compound 11** Pyridine-2-carboxylic acid [(R)-1-[5-[1-acetylamino-2-(1H-indol-3-yl)-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-amide;
- compound 12** 2-Amino-N-[(R)-1-[5-[(R)-1-formylamino-2-phenyl-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-2-methyl-propionamide;
- 15 **compound 13** Pyridine-2-carboxylic acid [(R)-1-[5-[(S)-1-acetylamino-2-phenyl-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-amide;
- compound 14** Pyridine-2-carboxylic acid [(R)-1-[5-[1-formylamino-2-(1H-indol-3-yl)-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-amide;
- 20 **compound 15** {(R)-1-[5-[2-(1H-Indol-3-yl)-ethyl]-4-(4-methoxy-benzyl)-4H-[1,2,4]triazol-3-yl]-2-naphthalen-2-yl-ethyl}-carbamic acid tert-butyl ester;
- compound 16** 1-[(R)-2-(1H-Indol-3-yl)-1-[4-(4-methoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl]-3-isopropyl-urea;
- compound 17** {(R)-2-(1H-Indol-3-yl)-1-[4-(4-methoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl}-carbamic acid isobutyl ester;
- 25 **compound 18** {(R)-2-(1H-Indol-3-yl)-1-[4-(4-methoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl}-carbamic acid tert-butyl ester;

- 73 -

compound 19 1-Benzyl-3-((R)-2-(1H-indol-3-yl)-1-[4-(4-methoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl)-urea;

compound 20 1-Benzyl-3-((R)-2-(1H-indol-3-yl)-1-[4-(4-methoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl)-thiourea;

5 **compound 21** [(R)-1-[4-(4-Fluoro-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-carbamic acid tert-butyl ester;

compound 22 {(R)-2-(1H-Indol-3-yl)-1-[4-(4-isopropoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl}-carbamic acid tert-butyl ester;

10 **compound 23** {(R)-2-(1H-Indol-3-yl)-1-[4-(4-methoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl}-methyl-carbamic acid tert-butyl ester;

compound 24 [(R)-1-[4-(2,4-Dimethoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-2-(1H-indol-3-yl)-ethyl]-carbamic acid tert-butyl ester;

compound 25 Piperidine-4-carbothioic acid {(R)-2-(1H-indol-3-yl)-1-[4-(4-methoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl}-amide;

15 **compound 26** 2-Amino-N-((R)-2-(1H-indol-3-yl)-1-[4-(4-methoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl)-thioacetamide;

compound 27 Pyridine-2-carbothioic acid {(R)-2-(1H-indol-3-yl)-1-[4-(4-methoxy-benzyl)-5-phenethyl-4H-[1,2,4]triazol-3-yl]-ethyl}-amide;

and the physiologically tolerated salts thereof.

20

23. A pharmaceutical composition comprising a pharmacologically active amount of at least one compound as claimed in claim 22.

25 24. The pharmaceutical composition as claimed in claim 23, where the active ingredient is present in a unit dose of from 0.001 mg to 100 mg per kg of a patient's bodyweight.

- 74 -

25. The pharmaceutical composition as claimed in any of claims 23 to 24, where the composition additionally comprises at least one pharmaceutically acceptable carrier and/or excipient.
- 5
26. The pharmaceutical composition as claimed in any of claims 23 to 25, where the composition comprises at least one further pharmacologically active substance.
- 10
27. The pharmaceutical composition as claimed in claim 26, where the further pharmacologically active substance is an endocannabinoid receptor antagonist, preferably a CB1 receptor antagonist, most preferably rimonabant [1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl-, monohydrochloride].
- 15

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2011/066057

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/4196 C07D401/14 C07D403/06 C07D413/14 A61P5/06
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 1 958 631 A1 (AETERNA ZENTARIS GMBH [DE]; AETERNA ZENTARIS INC [CA]) 20 August 2008 (2008-08-20) claims	1-27
Y	WO 2007/020013 A2 (ZENTARIS GMBH [DE]; LE CT MATIONAL DE LA RECH SCIE [FR]; UNIV MONTPELL) 22 February 2007 (2007-02-22) claims	1-27
Y	WO 00/54729 A2 (SQUIBB BRISTOL MYERS CO [US]) 21 September 2000 (2000-09-21) claims	1-27
	----- -/-	

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

9 February 2012

Date of mailing of the international search report

16/02/2012

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Steendijk, Martin

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2011/066057

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/115503 A1 (AETERNA ZENTARIS GMBH [DE]; CENTRE NAT RECH SCIENT [FR]; UNIV MONTPELL) 24 September 2009 (2009-09-24)	21
Y	claims pages 42-43	1-27
Y	----- WO 2010/051447 A1 (ELIXIR PHARMACEUTICALS INC [US]; SAUNDERS JEFFREY O [US]) 6 May 2010 (2010-05-06) claims	1-27
X	----- DEMANGE L ET AL: "Synthesis and pharmacological in vitro and in vivo evaluations of novel triazole derivatives as ligands of the ghrelin receptor. 1", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 50, no. 8, 1 January 2007 (2007-01-01), pages 1939-1957, XP002504163, ISSN: 0022-2623, DOI: DOI:10.1021/JM070024H	21
Y	table 1 see scheme 1, intermediates for compounds 16c, 19b, 23c	1-27
X	----- MOULIN ALINE ET AL: "Toward potent ghrelin receptor ligands based on trisubstituted 1,2,4-triazole structure. 2. Synthesis and pharmacological in vitro and in vivo evaluations", JOURNAL OF MEDICINAL CHEMISTRY, vol. 50, no. 23, November 2007 (2007-11), pages 5790-5806, XP002620541, ISSN: 0022-2623	21
Y	table 1 5798-5799	1-27
X	----- LIPINSKI C A ET AL: "BIOISOSTERIC PROTOTYPE DESIGN OF BIARYL IMIDAZOLYL AND TRIAZOLYL COMPETITIVE HISTAMINE H-2-RECEPTOR ANTAGONISTS", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 29, no. 11, 1 January 1986 (1986-01-01), pages 2154-2163, XP002260193, ISSN: 0022-2623, DOI: DOI:10.1021/JM00161A005 table II	1,2,5,7, 8,10, 12-18,20
X	----- EP 0 074 229 A1 (PFIZER [US]) 16 March 1983 (1983-03-16) pages 47,50-51 ----- -/--	1,2,5,7, 8,10, 12-18,20

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2011/066057

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 790 641 A1 (ASTELLAS PHARMA INC [JP]) 30 May 2007 (2007-05-30) page 38 -----	1,2,5,7, 8,10, 12-18,20
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; GRECHISHKIN, L. L. ET AL: "Effect of derivatives of 3-(.beta.-aminoethyl)-1,2,4-triazole on the histamine H1- and H2-receptors", XP002637212, retrieved from STN Database accession no. 1977:511279 abstract & PHARMACOLOGY , 15(6), 512-18 CODEN: PHMGBN; ISSN: 0031-7012, 1977, -----	1,3,4,7, 8,10, 12-18,20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2011/066057

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 11(completely); 1, 2, 4-10, 12-27(partially)

compounds of formula (I) and use thereof, wherein R5 represents a group -C(S)A (A representing any group falling with the definition in the claims)

2. claims: 1, 2, 4-10, 12-27(all partially)

compounds of formula (I) and use thereof, wherein R5 represents a group -C(0)Q (Q representing any heteroatom linked group falling within the definition in the claims)

3. claims: 3(completely); 1, 2, 4, 6-10, 12-27(partially)

compounds of formula (I) and use thereof, wherein R5 does not represents a group -C(S)R or -COR

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2011/066057

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
EP 1958631	A1	20-08-2008	EP	1958631	A1	20-08-2008
			US	2009042905	A1	12-02-2009
			WO	2008098977	A1	21-08-2008

WO 2007020013	A2	22-02-2007	AR	059026	A1	12-03-2008
			AU	2006281594	A1	22-02-2007
			CA	2620280	A1	22-02-2007
			JP	2009504697	A	05-02-2009
			KR	20080059145	A	26-06-2008
			US	2007037857	A1	15-02-2007
			US	2010331343	A1	30-12-2010
			WO	2007020013	A2	22-02-2007

WO 0054729	A2	21-09-2000	AR	029157	A1	18-06-2003
			AU	3512500	A	04-10-2000
			BG	105843	A	31-05-2002
			BR	0008937	A	24-09-2002
			CA	2367461	A1	21-09-2000
			CN	1344160	A	10-04-2002
			CO	5280063	A1	30-05-2003
			CZ	20013254	A3	12-06-2002
			EE	200100479	A	16-12-2002
			EP	1175213	A2	30-01-2002
			GE	P20033080	B	10-06-2003
			HU	0201787	A2	28-09-2002
			JP	2002539141	A	19-11-2002
			LT	2001087	A	25-04-2002
			LV	12752	A	20-11-2001
			NO	20014407	A	08-11-2001
			PE	15902000	A1	01-04-2001
			PL	364046	A1	13-12-2004
			SK	12272001	A3	08-10-2002
			TR	200102780	T2	21-08-2002
			UY	26056	A1	31-10-2000
			WO	0054729	A2	21-09-2000

WO 2009115503	A1	24-09-2009	AR	070918	A1	12-05-2010
			CA	2718744	A1	24-09-2009
			EP	2103602	A1	23-09-2009
			EP	2265593	A1	29-12-2010
			JP	2011514376	A	06-05-2011
			KR	20110074954	A	05-07-2011
			TW	201000467	A	01-01-2010
			US	2009239877	A1	24-09-2009
			WO	2009115503	A1	24-09-2009

WO 2010051447	A1	06-05-2010	CN	102271679	A	07-12-2011
			EP	2349266	A1	03-08-2011
			WO	2010051447	A1	06-05-2010

EP 0074229	A1	16-03-1983	AR	230994	A1	31-08-1984
			AU	534063	B2	05-01-1984
			AU	8784182	A	31-03-1983
			CA	1177485	A1	06-11-1984
			DE	3270423	D1	15-05-1986
			DK	386882	A	07-04-1983
			EP	0074229	A1	16-03-1983
			ES	8308324	A1	16-11-1983

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2011/066057

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
		FI 822999 A	01-03-1983	
		GR 77241 A1	11-09-1984	
		HU 188328 B	28-04-1986	
		IE 53586 B1	21-12-1988	
		IL 66673 A	29-04-1986	
		JP 58046083 A	17-03-1983	
		PH 17423 A	08-08-1984	
		PL 238095 A1	26-03-1984	
		PT 75481 A	01-09-1982	
		YU 196382 A	20-03-1985	

EP 1790641	A1	30-05-2007	CA 2580409 A1	23-03-2006
			CN 101014578 A	08-08-2007
			EP 1790641 A1	30-05-2007
			KR 20070058613 A	08-06-2007
			US 2007259854 A1	08-11-2007
			WO 2006030805 A1	23-03-2006
