(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 June 2025 (19.06.2025)

WIPO | PCT

(10) International Publication Number
WO 2025/124698 A1

(51) International Patent Classification:
C07D 207/48 (2006.01) *C07D 417/12* (2006.01)
C07D 277/64 (2006.01) *A61P 1/00* (2006.01)
C07D 405/12 (2006.01) *A61P 25/00* (2006.01)
C07D 409/12 (2006.01) *A61K 31/4025* (2006.01)
C07D 413/12 (2006.01)

(21) International Application Number:
PCT/EP2023/085388

(22) International Filing Date:
12 December 2023 (12.12.2023)

(25) Filing Language: English

(26) Publication Language: English

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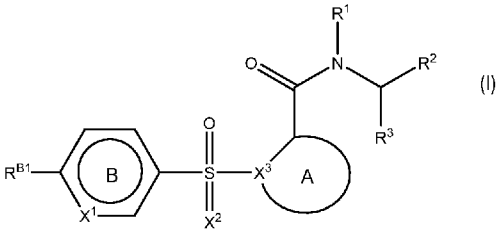
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ,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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, 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, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:
— *with international search report (Art. 21(3))*

(54) Title: ARYL SULFONE AND SULFANONE DERIVATIVES AS OREXIN RECEPTOR MODULATORS



(I)

(57) Abstract: The present invention relates to novel aryl sulfone and sulfanone derivatives of Formula (I), wherein R^1, R^2, R^3, RB^1, X^1, X^2, X^3, Ring A, and Ring B are as described in the description, to pharmaceutically acceptable salts thereof, and to their use as pharmaceuticals. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of Formula (I), and their use as agonists of the orexin-2 receptor (hereinafter also referred to as OX_2R), and particularly as agonists of the human orexin-2 receptor (hereinafter also referred to as hOX_2R).

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Aryl sulfone and sulfanone derivatives as orexin receptor modulators

The present invention relates to novel aryl sulfone and sulfanone derivatives of Formula (I) and their use as pharmaceuticals. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of Formula (I), and their use as agonists of the orexin-2 receptor (hereinafter also referred to as OX_2R), and particularly as agonists of the human orexin-2 receptor (hereinafter also referred to as hOX_2R).

The orexin system (also known as hypocretin system) was discovered in 1998 by two independent research groups and is composed of 2 neuropeptides and 2 receptors (de Lecea L et al.; The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity; Proc Natl Acad Sci U S A. 1998, 95(1):322-7; Sakurai T et al.; Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior; Cell. 1998, 92(5):1 page following 696). Orexin A (OX-A) and orexin B (OX-B) are neuropeptides specifically expressed in a small population of neurons of the lateral, dorsomedial and perifornical hypothalamus. They are proteolytically derived from a single precursor prepro-orexin peptide. Orexin A is a 33 amino acid peptide and orexin B is a 28 amino acid peptide. Orexins bind to two G-protein-coupled receptors (orexin-1 receptor (OX_1R) and orexin-2 receptor (OX_2R)) widely expressed throughout the brain. While OX-A binds to both receptors with similar affinity, OX-B binds preferentially to OX_2R. The wide distribution of orexin fibers and receptors in many parts of the brain suggests that orexins have multiple functions.

The orexin system is recognized as being crucial for the stability of wakefulness and the regulation of vigilance in accordance with various physiological processes (de Lecea L; Hypocretins and the neurobiology of sleep-wake mechanisms; Prog Brain Res. 2012, 198:15-24; Sakurai T; The neural circuit of orexin (hypocretin): maintaining sleep and wakefulness; Nat Rev Neurosci. 2007, 8(3):171-81; Scammell TE et al.; Neural Circuitry of Wakefulness and Sleep; Neuron. 2017, 93(4):747-765). Orexin neurons are primarily active during wakefulness (Lee MG et al.; Discharge of identified orexin/hypocretin neurons across the sleep-waking cycle; J Neurosci. 2005, 25(28):6716-20). They send excitatory projections to wake-promoting neuronal populations such as the histaminergic neurons of the tuberomammillary nucleus, noradrenergic neurons of the locus coeruleus, serotoninergic neurons of the dorsal raphe, dopaminergic neurons in the ventral tegmental area and cholinergic neurons in the basal forebrain and the pedunculopontine and laterodorsal tegmental nuclei. Different wake-promoting regions of the brain predominantly express OX_1R or OX_2R, or both (for review see (Sakurai T; The neural circuit of orexin (hypocretin): maintaining sleep and wakefulness; Nat Rev Neurosci. 2007, 8(3):171-81)). OX-A levels in the brain extracellular and cerebrospinal fluid (CSF) follow a circadian rhythm: they rise during the wake period and drop rapidly during sleep. Increasing orexin levels are necessary to compete with the increasing sleep pressure that builds up during long periods of wakefulness. preventing from falling asleep (Gotter AL et al.; The duration of sleep promoting efficacy by dual orexin receptor antagonists is dependent upon receptor occupancy threshold; BMC Neurosci. 2013, 14:90; Modirrousta M et al.; Orexin and MCH neurons express c-Fos differently after sleep deprivation vs. recovery

and bear different adrenergic receptors; Eur J Neurosci. 2005, 21(10):2807-16; Zeitzer JM et al.; Circadian and homeostatic regulation of hypocretin in a primate model: implications for the consolidation of wakefulness; J Neurosci. 2003, 23(8):3555-60).

Moreover, orexin neurons integrate a variety of signals related to internal or external environment (e.g. emotion, light/dark cycles, sleep pressure, energy balance) and send information to a variety of neuronal systems to adjust the arousal level to the one necessary for an appropriate behavioral response (Inutsuka A et al.; The physiological role of orexin/hypocretin neurons in the regulation of sleep/wakefulness and neuroendocrine functions; Front Endocrinol (Lausanne). 2013, 4:18). For this purpose, they do not only follow a circadian related pattern of activation, but also a behaviour-related burst of firing and are, for example, particularly active in periods of heightened arousal associated with emotion and social interaction (Blouin AM et al.; Human hypocretin and melanin-concentrating hormone levels are linked to emotion and social interaction; Nat Commun. 2013, 4:1547).

Evidence from human and animal studies have demonstrated that narcolepsy type 1, a chronic sleep disorder characterized by excessive daytime sleepiness (EDS), sleep attacks and cataplexy (loss of muscle tone in full consciousness often triggered by positive emotions), is linked to a deficiency in the orexin system (Chemelli RM et al.; Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation; Cell. 1999, 98(4):437-51; Lin L et al.; The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene; Cell. 1999, 98(3):365-76; Peyron C et al.; A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains; Nat Med. 2000, 6(9):991-7; Thannickal TC et al.; Reduced number of hypocretin neurons in human narcolepsy; Neuron. 2000, 27(3):469-74). In human, narcolepsy type 1 has been shown to be caused by the loss of orexin-producing neurons (Peyron C et al.; A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains; Nat Med. 2000, 6(9):991-7) and low OX-A level in the CSF can be used as specific biological measure for the diagnosis (Dauvilliers Y et al.; Narcolepsy and Other Central Hypersomnias; Continuum (Minneap Minn). 2017, 23(4, Sleep Neurology):989-1004). Several genetic animal models (in both mice and dogs) showed that disruption of orexin signaling leads to a narcoleptic phenotype with excessive daytime sleepiness (fragmented wakefulness) and cataplexy (Lin L et al.; The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene; Cell. 1999, 98(3):365-76; Willie JT et al.; Distinct narcolepsy syndromes in Orexin receptor-2 and Orexin null mice: molecular genetic dissection of Non-REM and REM sleep regulatory processes; Neuron. 2003, 38(5):715-30). Central administration of OX-A or ectopic expression of the prepro-orexin transgene in the brain of orexin neuron-ablated mice are able to reversed the narcoleptic phenotype (Mieda M et al.; Orexin peptides prevent cataplexy and improve wakefulness in an orexin neuron-ablated model of narcolepsy in mice; Proc Natl Acad Sci U S A. 2004, 101(13):4649-54). Those data suggest that an orexin receptor agonist would be an appropriate treatment for narcoleptic patients.

In addition, intracerebroventricular (i.c.v.) injections of OX-A in rats or mice increased wakefulness and markedly reduced both non-rapid eye movement (NREM) and REM sleep (Piper DC et al.; The novel brain neuropeptide, orexin-A, modulates the sleep-wake cycle of rats; Eur J Neurosci. 2000, 12(2):726-30; Huang ZL et al.; Arousal effect of orexin A depends on activation of the histaminergic system; Proc Natl Acad Sci U S A. 2001, 98(17):9965-70). Furthermore, optogenetic or chemogenetic studies showed that stimulation of orexin neurons reduced the latency in sleep-to-wake transition from both NREM and REM sleep and induced wakefulness with a very short latency (Adamantidis AR et al.; Neural substrates of awakening probed with optogenetic control of hypocretin neurons; Nature. 2007, 450(7168):420-4; Sasaki K et al.; Pharmacogenetic modulation of orexin neurons alters sleep/wakefulness states in mice; PLoS One. 2011, 6(5):e20360).

Altogether, it suggests that activation of orexin receptors is a promising therapeutic approach for disease associated with difficulties maintaining wakefulness with patients complaining of: feelings of excessive sleepiness; episodes of inadvertently falling asleep, including sleep attacks (episodes of falling asleep without prodromal symptoms of drowsiness); a prolonged main sleep episode that is unrefreshing; recurrent naps in the same day; and sleep inertia (prolonged difficulty waking up, with irritability, automatic behavior, or confusion).

These can be seen in sleep disorders such as the disorders of hypersomnolence. Based on the international classification of sleep disorders, 3rd edition (ICSD-3) (Sateia MJ; International classification of sleep disorders-third edition: highlights and modifications; Chest. 2014, 146(5):1387-1394), central disorders of hypersomnolence include narcolepsy (including narcolepsy type 1 and narcolepsy type 2), idiopathic hypersomnia, Kleine-Levin syndrome, hypersomnia due to a medical disorder, hypersomnia due to a medication or substance, hypersomnia associated with psychiatric disorder and insufficient sleep syndrome.

Narcolepsy is supposed to be the result of an autoimmune disorder which specifically destroy orexin-producing neurons. However, symptoms of narcolepsy (or secondary narcolepsy) can occur during the course of other neurologic disorders and be caused by the underlying condition, e.g. inherited disorders (such as Prader-Willi syndrome, Niemann-Pick C disease, or myotonic dystrophy), tumors or head trauma (particularly when the hypothalamus area is involved) (Kanbayashi T et al.; The pathophysiologic basis of secondary narcolepsy and hypersomnia; Curr Neurol Neurosci Rep. 2011, 11(2):235-41; Nishino S et al.; Symptomatic narcolepsy, cataplexy and hypersomnia, and their implications in the hypothalamic hypocretin/orexin system; Sleep Med Rev. 2005, 9(4):269-310). Reduced orexin levels in CSF were often seen in those symptomatic narcolepsy and EDS cases.

Other immune-mediated disorders can show a disruption of orexin neurotransmission with patients presenting symptoms reminiscent of narcolepsy (Fronczek R et al.; The orexin/hypocretin system in neuropsychiatric disorders: Relation to signs and symptoms; Handb Clin Neurol. 2021, 180:343-358). For some of them, destruction of part of the orexin neurons on top of other cell types have been demonstrated. For example, orexin deficiency in the CSF and narcolepsy-like symptoms have been observed in patients with neuromyelitis optica, multiple sclerosis (Kanbayashi T et al.; The pathophysiologic basis of secondary narcolepsy and hypersomnia; Curr Neurol Neurosci

Rep. 2011, 11(2):235-41; Kanbayashi T et al.; Symptomatic narcolepsy in patients with neuromyelitis optica and multiple sclerosis: new neurochemical and immunological implications; Arch Neurol. 2009, 66(12):1563-6), Guillain-Barré syndrome (Nishino S et al.; CSF hypocretin levels in Guillain-Barre syndrome and other inflammatory neuropathies; Neurology. 2003, 61(6):823-5), or anti-Ma2 encephalitis (Overeem S et al.; Hypocretin-1 CSF levels in anti-Ma2 associated encephalitis; Neurology. 2004, 62(1):138-40).

In neurodegenerative disease, EDS and other sleep disturbances are commonly reported. Loss of orexin neurons has been described in several neurodegenerative disease and is suggested to contribute to EDS and the sleep disturbances, including Alzheimer's (Fronczek R et al.; Hypocretin (orexin) loss in Alzheimer's disease; Neurobiol Aging. 2012, 33(8):1642-50), Parkinson's (Fronczek R et al.; Hypocretin (orexin) loss in Parkinson's disease; Brain. 2007, 130(Pt 6):1577-85; Fronczek R et al.; Hypocretin (orexin) loss and sleep disturbances in Parkinson's Disease; Brain. 2008, 131(Pt 1):e88), Lewy body dementia (Kasanuki K et al.; Neuropathological investigation of hypocretin expression in brains of dementia with Lewy bodies; Neurosci Lett. 2014, 569:68-73), Perry syndrome (Mishima T et al.; Reduced orexin immunoreactivity in Perry syndrome and multiple system atrophy; Parkinsonism Relat Disord. 2017, 42:85-89), multiple system atrophy (Benarroch EE et al.; Involvement of hypocretin neurons in multiple system atrophy; Acta Neuropathol. 2007, 113(1):75-80) and Huntington's diseases (Petersen A et al.; Orexin loss in Huntington's disease; Hum Mol Genet. 2005, 14(1):39-47).

EDS can also be observed in circadian rhythm sleep-wake disorders such as for example delayed sleep-wake phase disorder, shift work or jet lag disorder and result from a misalignment between the body clock and social requirements (Sateia MJ; International classification of sleep disorders-third edition: highlights and modifications; Chest. 2014, 146(5):1387-1394; Gandhi KD et al.; Excessive Daytime Sleepiness: A Clinical Review; Mayo Clin Proc. 2021, 96(5):1288-1301). It is specially the case when the patient needs to be awake but their alertness level secondary to their internal body clock is at its nadir.

Likewise, EDS is accompanying disorders such as obesity, diabetes, depression and objective sleep disturbances such as sleep apnea (Fernandez-Mendoza J et al.; Natural history of excessive daytime sleepiness: role of obesity, weight loss, depression, and sleep propensity; Sleep. 2015, 38(3):351-60). Taking in particular the example of obstructive sleep apnea (OSA), it is suggested that dysregulation of the orexin system could play a role in the pathogenesis of this disorder (Wang W et al.; Orexin: a potential role in the process of obstructive sleep apnea; Peptides. 2013, 42:48-54). Low levels of OX-A in plasma were reported in patients suffering from OSA (Busquets X et al.; Decreased plasma levels of orexin-A in sleep apnea; Respiration. 2004, 71(6):575-9). In addition, in the orexin knockout narcolepsy mouse model, the frequency of spontaneous sleep apneas increased (Nakamura A et al.; Vigilance state-dependent attenuation of hypercapnic chemoreflex and exaggerated sleep apnea in orexin knockout mice; J Appl Physiol (1985). 2007, 102(1):241-8).

Different from EDS, fatigue is a lack of energy ("an overwhelming sense of tiredness, a feeling of exhaustion") with a reduced ability to perform physical activities that would have previously been easily accomplished. It may be

accompanied by mental fatigue with poor concentration and memory, but it is not generally associated with inappropriate episodes of sleep during the day. It is observed in a number of disorders including infections, chronic inflammatory diseases, cancer and neurodegeneration. It is suggested that a dysregulation of the orexin system could contribute to fatigue. In rodents, fatigue (or sickness behavior in animals) induced by lipopolysaccharide was associated with reduced activity of orexin neurons and a reduction of OX-A in the CSF (Grossberg AJ et al.; Inflammation-induced lethargy is mediated by suppression of orexin neuron activity; J Neurosci. 2011, 31(31):11376-86). Intracerebroventricular administration of OX-A in lipopolysaccharide-treated rats restored normal home-cage exploratory behavior. Similar findings were retrieved in tumor-bearing rats indicating that the reduction of orexin signaling could play a role in chronic disease.

In human, Bardsen et al., (Bardsen K et al.; Interleukin-1-related activity and hypocretin-1 in cerebrospinal fluid contribute to fatigue in primary Sjogren's syndrome; J Neuroinflammation. 2019, 16(1):102) showed that OX-A level was decreased in CSF of patients suffering from primary Sjögren's syndrome, a chronic autoimmune disease clinically characterized by inflammation of the exocrine glands where fatigue is an important symptom (Segal B et al.; Prevalence, severity, and predictors of fatigue in subjects with primary Sjogren's syndrome; Arthritis Rheum. 2008, 59(12):1780-7).

It generally suggests that a dysfunction of the orexin system could contribute to fatigue and that an orexin receptor agonist could be helpful in chronically ill patients with fatigue, it could improve their quality of life.

Traumatic brain injury (TBI) can induce disorders of consciousness (DOC) such as syndromes of coma, vegetative state, and minimally conscious state (O'Donnell JC et al.; Challenges and demand for modeling disorders of consciousness following traumatic brain injury; Neurosci Biobehav Rev. 2019, 98:336-346). Consciousness is a complex state including arousal and awareness and the ascending reticular activating system (ARAS) is known to play an essential role in maintaining consciousness (Edlow BL et al.; Neuroanatomic connectivity of the human ascending arousal system critical to consciousness and its disorders; J Neuropathol Exp Neurol. 2012, 71(6):531-46). The ARAS is a complex and diffuse network of neuronal fibers that connects the brainstem reticular formation (such as the nuclei containing serotoninergic, noradrenergic, dopaminergic, cholinergic and glutamatergic neurons) with nonspecific thalamic nuclei, the basal forebrain, hypothalamus, and the cerebral cortex. Impairment of the ARAS can cause loss of consciousness following TBI (Jang SH et al.; The Relation Between Loss of Consciousness, Severity of Traumatic Brain Injury, and Injury of Ascending Reticular Activating System in Patients With Traumatic Brain Injury; Am J Phys Med Rehabil. 2019, 98(12):1067-1071). Monoaminergic drugs acting by increasing for instance dopaminergic levels, norepinephrine levels and acetylcholine levels could have some beneficial impacts on DOC. Given its projections to the wake-promoting system and its contribution to the stabilization of wakefulness/arousal, the orexin system is well placed to support and regulate consciousness. Interestingly, in patients with acute moderate and severe TBI, abnormally low level of OX-A in the CSF was reported (Baumann CR et al.; Hypocretin-1 (orexin A) deficiency in acute traumatic brain injury; Neurology. 2005, 65(1):147-

9). Preclinically, in a mouse model of TBI, it was shown that electromagnetic controlled cortical impact depressed orexin levels in both the hypothalamus and hippocampus, and that the diurnal fluctuation amplitudes of orexins were blunted (Willie JT et al.; Controlled cortical impact traumatic brain injury acutely disrupts wakefulness and extracellular orexin dynamics as determined by intracerebral microdialysis in mice; J Neurotrauma. 2012, 29(10):1908-21). Those data indicate that the orexin system is dysregulated following TBI and an orexin receptor agonist could be a useful therapeutic approach.

In addition, in a model of unconscious rats induced by acute alcohol intoxication, i.c.v. administration of OX-A or OX-B reduced the duration of right reflex loss, shortened the coma time, and decreased the delta signal of EEG (Jia X et al.; Arousal effects of orexin A on acute alcohol intoxication-induced coma in rats; Neuropharmacology. 2012, 62(2):775-83). It suggests that orexin receptor agonists could have an arousal-promoting effect in coma induced by acute alcohol intoxication. Furthermore, intranasal or i.c.v. administration of OX-A facilitated the recovery of arousal in a cardiac arrest- induced coma rat model (Koenig MA et al.; Intraventricular orexin-A improves arousal and early EEG entropy in rats after cardiac arrest; Brain Res. 2009, 1255:153-61; Modi HR et al.; Intranasal post-cardiac arrest treatment with orexin-A facilitates arousal from coma and ameliorates neuroinflammation; PLoS One. 2017, 12(9):e0182707). Orexin agonists could then provide beneficial effects following cardiac failure.

Additionally, in this model of cardiac arrest, OX-A did not only accelerate arousal and behavior recovery, but it also had some anti-inflammatory effects. Other studies raised the potential role of the orexin system in the regulation of inflammation. For instance, Ogawa et al. (Ogawa Y et al.; Peripherally administered orexin improves survival of mice with endotoxin shock; Elife. 2016, 5) showed that, in a model of septic shock in mice, administration of OX-A helped for survival and recovery and that excessive cytokine production was inhibited. In a mouse model of intracerebral hemorrhage, OX-A improved the neurofunctional outcomes and mitigated brain edema (Li T et al.; Orexin A alleviates neuroinflammation via OXR2/CaMKKbeta/AMPK signaling pathway after ICH in mice; J Neuroinflammation. 2020, 17(1):187). It is suggested that OX-A was beneficial because of its anti-inflammatory effects.

Moreover, it is also suggested that orexins facilitate the emergence from anesthetic-induced unconsciousness with anesthesia being either intraperitoneal or gas anesthesia and that inhibiting the orexin signaling delays the emergence (Zhang LN et al.; Orexin-A facilitates emergence from propofol anesthesia in the rat; Anesth Analg. 2012, 115(4):789-96; Kelz MB et al.; An essential role for orexins in emergence from general anesthesia; Proc Natl Acad Sci U S A. 2008, 105(4):1309-14; Zhang LN et al.; Orexin-A facilitates emergence of the rat from isoflurane anesthesia via mediation of the basal forebrain; Neuropeptides. 2016, 58:7-14; Kushikata T et al.; Orexinergic neurons and barbiturate anesthesia; Neuroscience. 2003, 121(4):855-63).

Besides stabilizing wakefulness, the orexins system seems to play a role in the regulation of many other functions such as energy homeostasis, learning and memory, stress/emotion, reward, and pain.

The orexin system is involved in the regulation of feeding behaviors and energy homeostasis. Orexin neurons are sensitive to glucose, leptin and ghrelin with high concentrations of glucose and leptin inhibiting orexinergic neurons, while low concentrations of glucose and ghrelin exciting them (Diano S et al.; Fasting activates the nonhuman primate hypocretin (orexin) system and its postsynaptic targets; Endocrinology. 2003, 144(9):3774-8; Yamanaka A et al.; Hypothalamic orexin neurons regulate arousal according to energy balance in mice; Neuron. 2003, 38(5):701-13). The orexin system is suggested to coordinate the behavioral/wakefulness response to the energy needs (Latifi B et al.; Sleep-Wake Cycling and Energy Conservation: Role of Hypocretin and the Lateral Hypothalamus in Dynamic State-Dependent Resource Optimization; Front Neurol. 2018, 9:790; Chieffi S et al.; Orexin System: The Key for a Healthy Life; Front Physiol. 2017, 8:357). Interestingly, narcoleptic mice show a dysregulation of energy homeostasis. Those mice exhibit obesity despite a significant lower calorie consumption which can be explained, to some extent, by a lower energy expenditure (Zhang S et al.; Sleep/wake fragmentation disrupts metabolism in a mouse model of narcolepsy; J Physiol. 2007, 581(Pt 2):649-63). In addition, the prevalence of obesity is also increased in narcoleptic patients (Mohammadi S et al.; Metabolic profile in patients with narcolepsy: a systematic review and meta-analysis; Sleep Med. 2021, 81:268-284). Studies in rodent models of diet-induced obesity showed that central administration of OX-A protects against obesity (Perez-Leighton CE et al.; Behavioral responses to orexin, orexin receptor gene expression, and spontaneous physical activity contribute to individual sensitivity to obesity; Am J Physiol Endocrinol Metab. 2012, 303(7):E865-74).

Altogether it suggests that an orexin receptor agonist could be an interesting therapeutic option for the treatment of disease associated with a dysregulation of feeding behaviors or energy homeostasis.

The orexin system seems to play a role in learning and memory processes. On one hand, given its recognized role for the stability of wakefulness and the regulation of vigilance in accordance with various physiological processes (de Lecea L; Hypocretins and the neurobiology of sleep-wake mechanisms; Prog Brain Res. 2012, 198:15-24; Sakurai T; The neural circuit of orexin (hypocretin): maintaining sleep and wakefulness; Nat Rev Neurosci. 2007, 8(3):171-81; Scammell TE et al.; Neural Circuitry of Wakefulness and Sleep; Neuron. 2017, 93(4):747-765), it will contribute to the sustained arousal level necessary to learn. On the other hand, the orexin neurons also project to areas involved in learning and memory processing such as the hippocampus (Peyron C et al.; Neurons containing hypocretin (orexin) project to multiple neuronal systems; J Neurosci. 1998, 18(23):9996-10015) which suggest a potential direct effect. Preclinical data have shown that activation of the orexin system can be beneficial for learning and memory. For example, mice data showed that OX-A could contribute to the increase hippocampal plasticity associated with the consolidation of social recognition memory (Yang L et al.; Hypocretin/orexin neurons contribute to hippocampus-dependent social memory and synaptic plasticity in mice; J Neurosci. 2013, 33(12):5275-84). Intranasal administration of OX-A improved the performance altered by sleep loss on a short-term memory task in sleep-deprived rhesus monkeys without altering task performance in alert non-sleep-deprived animals (Deadwyler SA et al.; Systemic and nasal delivery of orexin-A (Hypocretin-1) reduces the effects of sleep deprivation on cognitive performance in nonhuman primates; J Neurosci. 2007, 27(52):14239-47). In addition, i.c.v. injection of

OX-A in wild type mice improved memory processing in 2 different avoidance tasks but also improved memory performance in the senescence-accelerated mouse (SAMP8) strain showing age-related deficits in learning and memory (Jaeger LB et al.; Effects of orexin-A on memory processing; Peptides. 2002, 23(9):1683-8).

Cognitive impairment is a common feature of several neuropsychiatric/neurological disorders and of age/age-related dementias. Age is also affecting the orexin system. Indeed in both human and animals, loss of orexin neurons is reported (for review (Nixon JP et al.; Sleep disorders, obesity, and aging: the role of orexin; Ageing Res Rev. 2015, 20:63-73)). Interestingly, age-related impairments in attentional performance could be improved in rats via intranasal administration of OX-A (Calva CB et al.; Intranasal administration of orexin peptides: Mechanisms and therapeutic potential for age-related cognitive dysfunction; Brain Res. 2020, 1731:145921; Calva CB et al.; Effects of Intranasal Orexin-A (Hypocretin-1) Administration on Neuronal Activation, Neurochemistry, and Attention in Aged Rats; Front Aging Neurosci. 2019, 11:362) suggesting a therapeutic benefit of orexin receptor agonist for age-related cognitive disorders.

Furthermore, local intracerebral infusion of OX-A was able to reduce distractor-induced decreases in attention performance in rats (Zajo KN et al.; Orexin A-induced enhancement of attentional processing in rats: role of basal forebrain neurons; Psychopharmacology (Berl). 2016, 233(4):639-47) suggesting that an orexin-receptor agonist could be useful for the treatment of disorders with attentional deficits.

The orexin system plays a role in behaviours needing motivation (Mahler SV et al.; Motivational activation: a unifying hypothesis of orexin/hypocretin function; Nat Neurosci. 2014, 17(10):1298-303). And motivation (the psychological drive underlying goal-directed behaviour) is important to organize psychological and physiological processes leading to adaptive behaviours. Motivated behaviours support, for example, food seeking, coordinated stress response and the development of coping strategy. Dysregulation of those processes can lead to neuropsychiatric disorders in which orexin receptor agonists could provide beneficial effects.

As an example, stimulation of OX_2R promoted coping responses in a decision-making test during social stress in mice (in this test: promotion of escape behaviour) (Staton CD et al.; Orexin 2 receptor stimulation enhances resilience, while orexin 2 inhibition promotes susceptibility, to social stress, anxiety and depression; Neuropharmacology. 2018, 143:79-94). Stimulation of OX_2R also increased resilience to social stress (i.e. social novelty seeking) (Staton CD et al.; Orexin 2 receptor stimulation enhances resilience, while orexin 2 inhibition promotes susceptibility, to social stress, anxiety and depression; Neuropharmacology. 2018, 143:79-94).

Anhedonia, one of the key symptoms of depression, can be described as the failure to experience pleasure or pursue gratification and encompasses reward-associated disorders such as perturbation in decision-making and motivational drive. Anhedonia symptoms evoke a dysregulation of brain reward processing in which an alteration of the orexin system function could play a role (Coccurello R; Anhedonia in depression symptomatology: Appetite dysregulation and defective brain reward processing; Behav Brain Res. 2019, 372:112041). Several preclinical and clinical studies have shown a link between dysregulation of the orexin system and depression (Khairuddin S et al.;

Dysregulation of the orexinergic system: A potential neuropeptide target in depression; Neurosci Biobehav Rev. 2020, 118:384-396). In Wistar-Kyoto rats, which demonstrate depressive-like behaviours, OX-A immunoreactivity and prepro-orexin mRNA levels were reduced in the hypothalamus compared to Wistar rats (Taheri S et al.; Orexin A immunoreactivity and preproorexin mRNA in the brain of Zucker and WKY rats; Neuroreport. 2001, 12(3):459-64). In animal models of depression induced by chronic, inescapable stressors such as the social defeat model of chronic stress, downregulation of orexin neurotransmission was observed (Lutter M et al.; Orexin signaling mediates the antidepressant-like effect of calorie restriction; J Neurosci. 2008, 28(12):3071-5; Nocjar C et al.; The social defeat animal model of depression shows diminished levels of orexin in mesocortical regions of the dopamine system, and of dynorphin and orexin in the hypothalamus; Neuroscience. 2012, 218:138-53). In patients with major depressive disorder (MDD), lower levels of OX-A in the CSF were reported (Brundin L et al.; Reduced orexin levels in the cerebrospinal fluid of suicidal patients with major depressive disorder; Eur Neuropsychopharmacol. 2007, 17(9):573-9) and depressed patients show blunted diurnal variation in CSF orexin levels (Salomon RM et al.; Diurnal variation of cerebrospinal fluid hypocretin-1 (Orexin-A) levels in control and depressed subjects; Biol Psychiatry. 2003, 54(2):96-104).

In addition, in suicidal attempters, low levels of OX-A in the CSF were correlated with psychiatric symptoms of depression such as lassitude, slowness of movement and higher rating of the overall illness (Brundin L et al.; Orexin and psychiatric symptoms in suicide attempters; J Affect Disord. 2007, 100(1-3):259-63).

Orexin neurons project to many brain regions involved in the regulation of pain, including the spinal dorsal horn, the ventrolateral periaqueductal gray, the rostral ventromedial medulla or the trigeminal caudate nucleus (Peyron C et al.; Neurons containing hypocretin (orexin) project to multiple neuronal systems; J Neurosci. 1998, 18(23):9996-10015). Administration of orexin into the spinal cord or centrally in brain areas associated with the descending pain regulatory circuits reduces nociceptive responses in animal models of inflammatory pain and in chronic neuropathic pain models. Accordingly, intrathecal injections or local injections in pain-regulating brain areas of orexin receptor antagonists modulate pain responses (for review see: (Kang X et al.; Research progress on the mechanism of orexin in pain regulation in different brain regions; Open Life Sci. 2021, 16(1):46-52)). In addition, pain threshold is lower in orexin knockout mice following peripheral local inflammation (Watanabe S et al.; Persistent pain and stress activate pain-inhibitory orexin pathways; Neuroreport. 2005, 16(1):5-8). Interestingly, lower CSF orexin levels were reported in patients suffering from cluster headaches (Barloese M et al.; Reduced CSF hypocretin-1 levels are associated with cluster headache; Cephalalgia. 2015, 35(10):869-76) and the prevalence of migraine is increased in narcoleptic patients (Dahmen N et al.; Increased frequency of migraine in narcoleptic patients: a confirmatory study; Cephalalgia. 2003, 23(1):14-9).

Overall, it suggests that orexin receptor agonists could have beneficial effect in the therapeutic approach against pain.

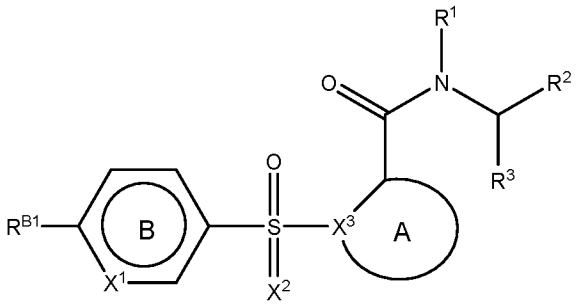
Orexin receptor antagonists are well documented, such as, for example, in WO 2010/131192.

US 2014/0051700 discloses cyclic guanidinyl OX_2R agonists useful for enhanced wakefulness or increased resistance to diet-induced accumulation of body fat, or abbreviated recovery from general anesthesia or jet lag. WO 2014/198880 discloses 2-(2-aminophenoxy)-3-chloronaphthalene-1,4-dione compounds having orexin 2 receptor agonist activities, and their use therapeutic active substances for the treatment of conditions mediated by agonizing the orexin 2 receptor. WO 2017/135306 discloses substituted piperidine compounds having an orexin type 2 receptor agonist activity, and their use as prophylactic or therapeutic agents for narcolepsy. WO 2018/164191 (English-language family member US 2021/0385345) discloses substituted pyrrolidine compounds having an orexin type 2 receptor agonist activity. WO 2019/117148 (English-language family member US 2021/0078955) discloses sulfonamide derivatives showing an orexin receptor agonist activity. WO 2019/027003, WO 2019/027058, WO 2020/004537/US 2021/198240, WO 2020/122092 and WO 2020/122093 disclose heterocyclic compounds having orexin type 2 receptor agonist activity. Macrocyclic orexin receptor agonists are reported in WO 2021/108628, WO 2022/051583, WO 2022/094012, WO 2022/109117, WO 2022/140316, WO 2022/232025, WO 2022/251302, and WO 2022/251304. Orexin receptor agonists are further reported in JP2022012861, JP2022064180, US8258163, WO 2000/047580, WO 2014/006402, WO 2015/088000, WO 2015/152367, WO 2016/133160, WO 2016/199906, WO 2018/164192, WO 2019/112007, WO 2019/191327, WO 2020/004536, WO 2020/158958, WO 2020/167701, WO 2020/167706, WO 2021/026047, WO 2021/048821, WO 2021/048822, WO 2021/107023, WO 2021/065893, WO 2021/106975, WO 2022/014680, WO 2022/040058, WO 2022/040070, WO 2022/051596, WO 2022/119888, WO 2022/132696, WO 2022/140317, WO 2022/187231, WO 2022/207935, WO 2022/233872, WO 2022/250108, WO 2022/269049, WO2023017180, WO2023167865, WO2023167925, WO2023199091, and WO2023204308.

The preparation of N-tosylprolinamides is reported in Walther K. et al. (J. Prakt. Chem, 1987, 329(5), 859-870). Selected N-sulfonyl indoline derivatives having affinity for the vasopressin and ocytocin receptors are described in US 5,338,755, US 5,397,801, US 5,481,005, and EP 0 469 984. Selected pyrrole sulfone derivatives are described as non-nucleoside reverse transcriptase inhibitors (Silvestri R. et al., Il Farmaco, 2004, 59, 201-210; WO 2008/054605) and indole sulfones as modulators G-protein couple receptor GPR119 (WO 2009/105722). Certain thiazolidine sulfonamides are disclosed as prostaglandin F receptor modulators (US 2008/255094). WO 2016/004180 discloses quinoline and quinazoline sulfonamides as O-GlcNAc transferase inhibitors. Certain N-cyclic sulfonamide derivatives are reported as inhibitors/antagonists of STAT3 (Lopez-Tapia F. et al., ACS Med. Chem. Lett., 2018, 9, 250-255; WO 2012/018868; WO 2018/136935; US 10,196,373 B2), of TRPA1 (Chen H. et al., J. Med. Chem., 2018, 61, 3641-3659; WO 2013/108857 (US 2014/0329796; EP2805718); WO 2016/128529), of CCR-9 (WO 2004/073634; US 2004/180892; US 2005/49286; US 2007/293503), of gamma secretase (WO 2005/113542), or of bradykin B2 (US 6,071,917), or as binding VLA-4 (US 6,583,139 B1). Selected azetidine sulfonamides are further reported as STAT3 inhibitors (Brotherton-Pleiss C. et al., J. Med. Chem., 2021, 64, 695-710; WO 2021/016333). WO 2018/015411 discloses certain sulfonylcycloalkyl compounds as TRPA1 modulators. Selected thiol pyrrolidine derivatives are reported as metalloprotease inhibitors in US 2002/049243. The following compounds are known as chemical library compounds:

- *N*-benzyl-*N*-(1,1-dioxidotetrahydrothiophen-3-yl)-1-tosylpyrrolidine-2-carboxamide (CAS 1101176-47-9);
- (R)-*N*-benzyl-*N*-((R)-1,1-dioxidotetrahydrothiophen-3-yl)-1-tosylpyrrolidine-2-carboxamide (Pubchem CID (PID) 25620704);
- (S)-*N*-benzyl-*N*-((R)-1,1-dioxidotetrahydrothiophen-3-yl)-1-tosylpyrrolidine-2-carboxamide (PID 25620707);
- (S)-*N*-benzyl-*N*-((S)-1,1-dioxidotetrahydrothiophen-3-yl)-1-tosylpyrrolidine-2-carboxamide (PID 51731021);
- (R)-*N*-benzyl-*N*-((S)-1,1-dioxidotetrahydrothiophen-3-yl)-1-tosylpyrrolidine-2-carboxamide (PID 124809066);
- *N*-(1,1-dioxidotetrahydrothiophen-3-yl)-*N*-(furan-2-ylmethyl)-1-tosylpyrrolidine-2-carboxamide (CAS 1100238-77-4);
- (2R)-*N*-(1,1-dioxidotetrahydrothiophen-3-yl)-*N*-(furan-2-ylmethyl)-1-tosylpyrrolidine-2-carboxamide (CAS 2180106-48-1);
- (2S)-*N*-(1,1-dioxidotetrahydrothiophen-3-yl)-*N*-(furan-2-ylmethyl)-1-tosylpyrrolidine-2-carboxamide (CAS 956630-44-7);
- (S)-*N*-((R)-1,1-dioxidotetrahydrothiophen-3-yl)-*N*-(furan-2-ylmethyl)-1-tosylpyrrolidine-2-carboxamide (PID 26716027);
- (S)-*N*-((S)-1,1-dioxidotetrahydrothiophen-3-yl)-*N*-(furan-2-ylmethyl)-1-tosylpyrrolidine-2-carboxamide (PID 26716029); and
- *N*-[(2-Methoxyphenyl)methyl]-1-[(4-methylphenyl)sulfonyl]-*N*-[(tetrahydro-2-thienyl)methyl]-2-pyrrolidinecarboxamide (CAS 2716353-53-4).

1) A first aspect of the invention relates to compounds of the Formula (I)



Formula (I)

wherein

Ring B is a 6-membered aromatic ring, wherein:

- **X¹** represents N or C**R^B2**, wherein **R^B2** represents hydrogen, halogen (especially fluoro), (C_{1-3})alkyl (especially methyl), or (C_{1-3})alkoxy (especially methoxy); (in particular **X¹** represents CH, CF, or N); and
- **R^B1** represents independently hydrogen, (C_{1-4})alkyl (especially methyl or ethyl), (C_{1-3})alkoxy (especially methoxy), halogen (especially fluoro, chloro, or iodo), monocyclic (C_{3-4})cycloalkyl (especially cyclopropyl), or (C_1)fluoroalkyl (especially trifluoromethyl); [notably **R^B1** represents independently hydrogen, (C_{1-3})alkyl (especially methyl or ethyl), (C_{1-3})alkoxy (especially methoxy), halogen (especially fluoro, chloro, or iodo), or monocyclic (C_{3-4})cycloalkyl (especially cyclopropyl); in particular **R^B1** represents methyl, ethyl, methoxy, chloro, iodo, or cyclopropyl];

[notably **Ring B** represents p-tolyl, 3-fluoro-4-methylphenyl, 4-methoxyphenyl, 6-methylpyridin-3-yl, 3-fluoro-4-methoxyphenyl, 4-cyclopropylphenyl, 4-chlorophenyl, phenyl, 6-methoxypyridin-3-yl, 4-fluorophenyl, 3-fluorophenyl, 6-fluoropyridin-3-yl, 4-fluoro-3-methylphenyl, 3-methoxyphenyl, 3,4-dimethylphenyl, or 3,4-difluorophenyl, or, in addition, 4-ethylphenyl, 4-iodophenyl, 4-isopropylphenyl, 4-propylphenyl, 4-(*tert*-butyl)phenyl, 4-(*tert*-butyl)-3-fluorophenyl, 4-bromophenyl, 4-(trifluoromethyl)phenyl, 3,4-dichlorophenyl, 4-bromo-3-fluorophenyl, 3-bromo-4-methylphenyl, or 3-chloro-4-methylphenyl; especially **Ring B** represents p-tolyl, 3-fluoro-4-methylphenyl, 4-methoxyphenyl, 6-methylpyridin-3-yl, 3-fluoro-4-methoxyphenyl, 4-cyclopropylphenyl, 4-chlorophenyl, phenyl, 6-methoxypyridin-3-yl, 4-fluorophenyl, 3-fluorophenyl, 6-fluoropyridin-3-yl, 4-fluoro-3-methylphenyl, 3-methoxyphenyl, 3,4-dimethylphenyl, or 3,4-difluorophenyl, or, in addition, 4-ethylphenyl, 4-iodophenyl, 4-isopropylphenyl, 4-propylphenyl, 4-bromophenyl, 3,4-dichlorophenyl, 4-bromo-3-fluorophenyl, 3-bromo-4-methylphenyl, or 3-chloro-4-methylphenyl; in particular **Ring B** represents p-tolyl, 3-fluoro-4-methylphenyl, 4-methoxyphenyl, 6-methylpyridin-3-yl, 3-fluoro-4-methoxyphenyl, 4-cyclopropylphenyl, or 4-chlorophenyl, or, in addition, 4-ethylphenyl, or 4-iodophenyl];

X² represents O or N**R⁴**, wherein **R⁴** represents hydrogen, (C_{1-3})alkyl (especially methyl, ethyl, or isopropyl), monocyclic (C_{3-6})cycloalkyl or phenyl; [in particular **X²** represents O, N-methyl, NH, or N-cyclopropyl];

X³ represents CH or N such that:

- when **X³** represents CH, **Ring A** represents a monocyclic (C_{5-6})cycloalkan-diyl or a monocyclic 5- or 6-membered heterocycloalkan-diyl comprising one ring O atom (especially tetrahydrofuran-diyl or tetrahydro-2*H*-pyran-diyl); [in particular such **Ring A** represents cyclopentane-1,2-diyl]; or
- when **X³** represents N, **Ring A** represents:
  - a 4- to 6-membered saturated monocyclic heterocycloalkan-diyl comprising **X³** and zero or one ring O atom (notably azetidin-diyl, pyrrolidin-diyl, oxazolidin-diyl, or oxazinan-diyl); wherein said heterocycloalkan-diyl is unsubstituted, or mono- or di-substituted (notably unsubstituted or mono-substituted); wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl (especially methyl), halogen (especially fluoro), (C_{1-3})alkoxy (especially methoxy or ethoxy),

hydroxy, and (C_{1-3})alkylidene (especially H_2C=); [notably such **Ring A** represents pyrrolidin-1,2-diyl, 4-methylpyrrolidin-1,2-diyl, 4-fluoropyrrolidin-1,2-diyl, 3-methylenepyrrolidin-1,2-diyl, 5-methylpyrrolidin-1,2-diyl, oxazolidin-2,3-diyl, azetidin-1,2-diyl, 4-methylazetidin-1,2-diyl, 3-fluoropyrrolidin-1,2-diyl, 4-hydroxypyrrolidin-1,2-diyl, 4-methoxypyrrolidin-1,2-diyl, 4-ethoxypyrrolidin-1,2-diyl, 4,4-dimethylpyrrolidin-1,2-diyl, oxazolidin-3,4-diyl, or 1,3-oxazinan-2,3-diyl; in particular such **Ring A** represents pyrrolidin-1,2-diyl, 4-methylpyrrolidin-1,2-diyl, 4-fluoropyrrolidin-1,2-diyl, 3-methylenepyrrolidin-1,2-diyl, 5-methylpyrrolidin-1,2-diyl, or oxazolidin-2,3-diyl];

- a 4- to 6-membered (notably 5-membered) mono-unsaturated monocyclic heterocycloalkan-diyl comprising **X³** and zero or one additional ring N atom (especially dihydro-1*H*-pyrrol-diyl or dihydro-1*H*-pyrazol-diyl); wherein the double bond of said mono-unsaturated heterocycloalkan-diyl does not contain **X³** or the carbon atom attached to the group –CO-N(**R¹**)CH(**R²**)(**R³**); wherein said mono-unsaturated heterocycloalkan-diyl is unsubstituted, or mono- or di-substituted (in particular is unsubstituted); wherein the substituents are independently (C_{1-3})alkyl (especially methyl); [notably such **Ring A** represents 2,3-dihydro-1*H*-pyrrol-1,2-diyl, 4,5-dihydro-1*H*-pyrazol-1,5-diyl, or 3-methyl-4,5-dihydro-1*H*-pyrazol-1,5-diyl; in particular such **Ring A** represents 2,3-dihydro-1*H*-pyrrol-1,2-diyl]; or

- a 6- to 8-membered saturated spiro, fused, or bridged bicyclic heterocycloalkan-diyl comprising **X³;** wherein said bicyclic heterocycloalkan-diyl is unsubstituted, or di-substituted (in particular is unsubstituted); wherein the substituents independently are (C_{1-3})alkyl (especially methyl); (notably such **Ring A** represents azabicyclo[2.2.1]heptan-diyl, azabicyclo[3.1.0]hexan-diyl, or azaspiro[2.4]heptan-diyl, or, in addition, azabicyclo[3.2.0]heptan-diyl or 6,6-dimethyl-3-azabicyclo[3.1.0]hexan-diyl; especially such **Ring A** represents 2-azabicyclo[2.2.1]heptan-1,2-diyl, 2-azabicyclo[3.1.0]hexan-2,3-diyl, 3-azabicyclo[3.1.0]hexan-2,3-diyl, or 5-azaspiro[2.4]heptan-4,5-diyl, or, in addition, 3-azabicyclo[3.2.0]heptan-2,3-diyl or 6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2,3-diyl); [in particular such **Ring A** represents 2-azabicyclo[2.2.1]heptan-1,2-diyl, 2-azabicyclo[3.1.0]hexan-2,3-diyl, or 3-azabicyclo[3.1.0]hexan-2,3-diyl, or, in addition, 3-azabicyclo[3.2.0]heptan-2,3-diyl];

R¹ represents:

- 3-cyano-3,3-dimethylpropyl or 4-cyanobutyl [in particular 3-cyano-3,3-dimethylpropyl];

- a saturated monocyclic (C_{4-6})cycloalkyl (notably cyclopentyl or cyclohexyl); wherein said (C_{4-6})cycloalkyl is unsubstituted, or mono- or di-substituted (notably mono- or di-substituted); wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl (especially methyl or isopropyl), halogen (especially fluoro), (C_{1-3})fluoroalkyl (especially difluoromethyl or trifluoromethyl), (C_{1-3})alkoxy (especially methoxy), carbamoyl, hydroxy, and cyano; [notably such **R¹** represents 3-cyanocyclopentyl, 3-cyano-3-methylcyclopentyl, 3-cyanocyclohexyl, 4-hydroxycyclohexyl, 4-cyanocyclohexyl, 4,4-dimethylcyclohexyl,

4,4-difluorocyclohexyl, 4-cyano-2-hydroxycyclopentyl, 4-fluorocyclohexyl, 3-cyanocyclobutyl, 3-(trifluoromethyl)cyclobutyl, 3-hydroxy-3-(trifluoromethyl)cyclobutyl, 3-fluorocyclopentyl, 3-methoxycyclopentyl, 3-(difluoromethyl)cyclopentyl, 3-carbamoylcyclopentyl, 3-carbamoyl-3-methylcyclopentyl, 3,3-dimethylcyclopentyl, 3,3-difluorocyclopentyl, 4-cyano-2-methoxycyclopentyl, cyclohexyl, 2-hydroxycyclohexyl, 3-hydroxycyclohexyl, 3-methoxycyclohexyl, 4-methylcyclohexyl, 4-isopropylcyclohexyl, 4-methoxycyclohexyl, 3,3-dimethylcyclohexyl, 2,2-difluorocyclohexyl, 3,3-difluorocyclohexyl, or 4-hydroxy-4-methylcyclohexyl, or, in addition, 2-methoxycyclopentyl, or 3-hydroxycyclopentyl; in particular such **R**^{1} represents 3-cyanocyclopentyl, 3-cyano-3-methylcyclopentyl, 3-cyanocyclohexyl, 4-hydroxycyclohexyl, 4-cyanocyclohexyl, 4,4-dimethylcyclohexyl, 4,4-difluorocyclohexyl, 4-cyano-2-hydroxycyclopentyl, or 4-fluorocyclohexyl];

- a mono-unsaturated monocyclic (C_{5-6})cycloalkyl (especially cyclohexenyl); wherein the double bond of said mono-unsaturated (C_{5-6})cycloalkyl does not contain the carbon atom attached to the group -N(CO)CH(**R**^{2})(**R**^{3}); [in particular such **R**^{1} represents cyclohex-3-en-1-yl];

- a saturated bicyclic (C_{6-8})spirocycloalkyl (notably spiro[2.3]hexanyl, spiro[3.3]heptanyl, spiro[2.4]heptanyl, or spiro[2.5]octanyl); wherein said (C_{6-8})spirocycloalkyl is unsubstituted, or mono- or di-substituted (especially di-substituted); wherein the substituents are independently halogen (especially fluoro); [notably such **R**^{1} represents 1,1-difluorospiro[2.3]hexan-5-yl, 1,1-difluorospiro[2.5]octan-6-yl, spiro[3.3]heptan-2-yl, 6,6-difluorospiro[3.3]heptan-2-yl, 1,1-difluorospiro[2.4]heptan-5-yl, or spiro[2.5]octan-6-yl; in particular such **R**^{1} represents 1,1-difluorospiro[2.3]hexan-5-yl or 1,1-difluorospiro[2.5]octan-6-yl];

- a saturated fused or bridged bicyclic (C_{6-8})cycloalkyl (notably bicyclo[2.1.1]hexanyl, bicyclo[4.1.0]heptanyl, or bicyclo[2.2.2]octanyl); wherein said (C_{6-8})cycloalkyl is unsubstituted, or mono- or di-substituted; wherein the substituents are independently selected from the group consisting of: halogen (especially fluoro), cyano and carbamoyl; [notably such **R**^{1} represents bicyclo[4.1.0]heptan-3-yl, 7,7-difluorobicyclo[4.1.0]heptan-3-yl, 4-carbamoylbicyclo[2.1.1]hexan-2-yl, or 4-cyanobicyclo[2.2.2]octan-1-yl; in particular such **R**^{1} represents bicyclo[4.1.0]heptan-3-yl or 7,7-difluorobicyclo[4.1.0]heptan-3-yl]; or

- a 5- or 6-membered saturated monocyclic heterocycloalkyl comprising one ring heteroatomic group selected from O, S, or SO_2 (notably said one ring heteroatomic group is selected from O or SO_2; notably said heterocycloalkyl is tetrahydrothiophen-1,1-dioxide, tetrahydro-2*H*-pyran, tetrahydro-2*H*-thiopyran, tetrahydro-2*H*-thiopyran-1,1-dioxide); wherein said heterocycloalkyl is unsubstituted, or mono- or di-substituted; wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl (especially methyl), halogen (especially fluoro), and (C_{1-3})fluoroalkyl (especially trifluoromethyl); [notably such **R**^{1} represents 1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl, 1,1-dioxidotetrahydrothiophen-3-yl, tetrahydro-2*H*-pyran-4-yl, 3-fluorotetrahydro-2*H*-pyran-4-yl, 2-methyltetrahydro-2*H*-pyran-4-yl, 2-(trifluoromethyl)tetrahydro-2*H*-pyran-4-yl, 2,2-dimethyltetrahydro-2*H*-pyran-4-yl, tetrahydro-2*H*-thiopyran-

4-yl, or tetrahydro-2*H*-pyran-3-yl, or, in addition, 6-methyltetrahydro-2*H*-pyran-3-yl, 6,6-dimethyltetrahydro-2*H*-pyran-3-yl, 3-methyltetrahydro-2*H*-pyran-4-yl, 2,6-dimethyltetrahydro-2*H*-pyran-4-yl, 1,1-dioxidotetrahydro-2*H*-thiopyran-3-yl, or 6-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-3-yl; in particular such **R**^{1} represents 1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl, or, in addition, 1,1-dioxidotetrahydro-2*H*-thiopyran-3-yl, or 6-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-3-yl];

R^{2} represents hydrogen or methyl (especially hydrogen);

R^{3} represents:

- an 8- to 10-membered partially aromatic fused bicyclic ring system comprising a total of zero to three ring heteroatoms independently selected from N, O, or S (notably 2,3-dihydro-1*H*-indenyl, 2,3-dihydrobenzofuranyl, benzo[*d*][1,3]dioxolyl, 6,7-dihydro-5*H*-cyclopentapyridinyl, 2,3-dihydrofuro[3,2]pyridinyl, chromanyl, isochromanyl, or 2,3-dihydrobenzo[*b*][1.4]dioxinyl); wherein said 8- to 10-membered ring system is linked to the rest of the molecule at the aromatic ring moiety; wherein said 8- to 10-membered ring system is unsubstituted, or mono- or di-substituted, wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl (especially methyl), halogen (especially fluoro), and oxo; [notably such **R**^{3} represents 2,3-dihydro-1*H*-inden-5-yl, 2,3-dihydrobenzofuran-6-yl, 5-fluoro-2,3-dihydrobenzofuran-6-yl, benzo[*d*][1,3]dioxol-5-yl, 4-fluoro-2,3-dihydrobenzofuran-6-yl, 7-fluoro-2,3-dihydrobenzofuran-6-yl, 3-methyl-2,3-dihydrobenzofuran-6-yl, 2-methyl-2,3-dihydrobenzofuran-6-yl, 3-oxo-2,3-dihydrobenzofuran-6-yl, benzo[*d*][1,3]dioxol-4-yl, 2,2-difluorobenzo[*d*][1,3]dioxol-5-yl, 6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl, 6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-3-yl, 2,3-dihydrofuro[3,2-*b*]pyridin-6-yl, 2,3-dihydrofuro[3,2-*c*]pyridin-6-yl, chroman-6-yl, chroman-7-yl, isochroman-6-yl, isochroman-7-yl, or 2,3-dihydrobenzo[*b*][1.4]dioxin-6-yl; in particular such **R**^{3} represents 2,3-dihydro-1*H*-inden-5-yl, 2,3-dihydrobenzofuran-6-yl, 5-fluoro-2,3-dihydrobenzofuran-6-yl, benzo[*d*][1,3]dioxol-5-yl, or 4-fluoro-2,3-dihydrobenzofuran-6-yl];

- naphthyl or an 8- to 10-membered heteroaryl comprising a total of one to three ring heteroatoms independently selected from N, O, and S (notably benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiophenyl, furopyridinyl, benzoxadiazolyl, thienopyridinyl, 1*H*-indolyl, quinolinyl, or isoquinolinyl); wherein said 8- to 10-membered heteroaryl is unsubstituted, or mono- or di-substituted (especially unsubstituted or mono-substituted); wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl (especially methyl), halogen (especially fluoro or chloro), and (C_{1-3})alkoxy (especially methoxy) [especially the substituents are independently selected from the group consisting of: (C_{1-3})alkyl (especially methyl) and halogen (especially fluoro or chloro)]; [notably such **R**^{3} represents benzofuran-6-yl, benzo[*d*]oxazol-5-yl, 6-fluorobenzo[*d*]oxazol-5-yl, benzo[*d*]oxazol-6-yl, benzo[*d*]thiazol-5-yl, 2-chlorobenzo[*d*]thiazol-5-yl, benzo[*b*]thiophen-5-yl, benzo[*b*]thiophen-6-yl, furo[3,2-*c*]pyridin-6-yl, 2-methylbenzo[*d*]thiazol-5-yl, benzofuran-2-yl, benzofuran-5-yl, 2-methylbenzofuran-6-yl, benzo[*d*]thiazol-6-

yl, 6-fluoro-2-methylbenzo[*d*]thiazol-5-yl, benzo[*d*]thiazol-2-yl, benzo[*b*]thiophen-2-yl, 2-methylbenzo[*b*]thiophen-5-yl, furo[3,2-*b*]pyridin-6-yl, furo[2,3-*b*]pyridin-6-yl, benzo[*d*]oxazol-2-yl, benzo[*c*][1,2,5]oxadiazol-5-yl, thieno[2,3-*b*]pyridin-2-yl, 1*H*-indol-6-yl, naphthalen-2-yl, quinolin-7-yl, isoquinolin-3-yl, or isoquinolin-7-yl, or, in addition, 2-bromobenzo[*d*]thiazol-5-yl, 4-fluorobenzo[d]thiazol-5-yl, or 2-methoxybenzo[d]thiazol-5-yl; in particular such **R³** represents benzofuran-6-yl, benzo[*d*]oxazol-5-yl, 6-fluorobenzo[*d*]oxazol-5-yl, benzo[*d*]oxazol-6-yl, benzo[*d*]thiazol-5-yl, 2-chlorobenzo[*d*]thiazol-5-yl, benzo[*b*]thiophen-5-yl, benzo[*b*]thiophen-6-yl, furo[3,2-*c*]pyridin-6-yl, or 2-methylbenzo[*d*]thiazol-5-yl, or, in addition, 2-bromobenzo[*d*]thiazol-5-yl]; or

- phenyl or 5- or 6-membered heteroaryl comprising one to three ring heteroatoms independently selected from N, O, and S (notably pyridinyl, thiophenyl, oxazolyl, thiazolyl, isothiazolyl, or isoxazolyl); wherein said phenyl or 5- or 6-membered heteroaryl is independently unsubstituted, or, especially, mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl (especially methyl, ethyl, or isopropyl), halogen (especially fluoro, chloro, or bromo), (C_{1-3})alkoxy (especially methoxy), (C_{1-3})fluoroalkoxy (especially difluoromethoxy), monocyclic (C_{3-6})cycloalkyl (especially cyclopropyl), (C_{1-3})alkylthio (especially methylthio), (C_{1-3})fluoroalkyl (especially trifluoromethyl), cyano, **$NR^{N1}R^{N2}$**, wherein **R^{N1}** and **R^{N2}** independently represent hydrogen or (C_{1-4})alkyl (especially **$NR^{N1}R^{N2}$** represents dimethylamino), and 4- to 6-membered monocyclic heterocycloalkyl (especially azetidinyl or oxetanyl); wherein said heterocycloalkyl is unsubstituted or mono-substituted with halogen (especially fluoro); [notably such **R³** represents p-tolyl, 4-chlorophenyl, 4-bromophenyl, 4-(methylthio)phenyl, 4-chloro-2-fluorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2,4-difluorophenyl, 3-fluoro-4-methylphenyl, phenyl, 2-chlorophenyl, 3-methylphenyl, 3-fluorophenyl, 3-methoxyphenyl, 3-(difluoromethoxy)phenyl, 3-(azetidin-1-yl)phenyl, 3-(3-fluorooxetan-3-yl)phenyl, 4-ethylphenyl, 4-isopropylphenyl, 4-(dimethylamino)phenyl, 4-(difluoromethoxy)phenyl, 4-(trifluoromethyl)phenyl, 2-fluoro-3-methylphenyl, 2,4-dimethylphenyl, 4-fluoro-2-methylphenyl, 2-chloro-4-fluorophenyl, 2-fluoro-4-methoxyphenyl, 2,5-difluorophenyl, 2-fluoro-5-methoxyphenyl, 3-fluoro-5-methoxyphenyl, 3,4-dimethylphenyl, 4-fluoro-3-methylphenyl, 3,4-difluorophenyl, 4-chloro-3-fluorophenyl, 3-chloro-4-methylphenyl, 3-cyano-4-methylphenyl, 3-fluoro-4-methoxyphenyl, 2,3-difluoro-4-methylphenyl, 4-chloro-2,3-difluorophenyl, 4-chloro-2,6-difluorophenyl, 2,4-difluoro-5-methylphenyl, 5-chloropyridin-2-yl, 2-methylthiophen-3-yl, 5-methylthiophen-2-yl, 5-chlorothiophen-2-yl, 3-methylthiophen-2-yl, 5-isopropyloxazol-2-yl, 5-chlorothiazol-2-yl, 5-bromoothiazol-2-yl, 5-isopropylthiazol-2-yl, 2-isopropylthiazol-5-yl, 5-methylisothiazol-4-yl, 5-methylisoxazol-4-yl, 4-ethyl-5-methylisoxazol-3-yl, 5-cyclopropylisoxazol-3-yl, or 5-cyclopropyl-4-ethylisoxazol-3-yl; in particular such **R³** represents p-tolyl, 4-chlorophenyl, 4-bromophenyl, 4-(methylthio)phenyl, 4-chloro-2-fluorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2,4-difluorophenyl, 3-fluoro-4-methylphenyl, or 3-fluoro-4-methoxyphenyl];

with the exception of the following compounds:

- *N*-benzyl-*N*-(1,1-dioxidotetrahydrothiophen-3-yl)-1-tosylpyrrolidine-2-carboxamide;
- (R)-*N*-benzyl-*N*-((R)-1,1-dioxidotetrahydrothiophen-3-yl)-1-tosylpyrrolidine-2-carboxamide;
- (S)-*N*-benzyl-*N*-((R)-1,1-dioxidotetrahydrothiophen-3-yl)-1-tosylpyrrolidine-2-carboxamide;
- (S)-*N*-benzyl-*N*-((S)-1,1-dioxidotetrahydrothiophen-3-yl)-1-tosylpyrrolidine-2-carboxamide;
- (R)-*N*-benzyl-*N*-((S)-1,1-dioxidotetrahydrothiophen-3-yl)-1-tosylpyrrolidine-2-carboxamide;
- *N*-(1,1-dioxidotetrahydrothiophen-3-yl)-*N*-(furan-2-ylmethyl)-1-tosylpyrrolidine-2-carboxamide;
- (2R)-*N*-(1,1-dioxidotetrahydrothiophen-3-yl)-*N*-(furan-2-ylmethyl)-1-tosylpyrrolidine-2-carboxamide;
- (2S)-*N*-(1,1-dioxidotetrahydrothiophen-3-yl)-*N*-(furan-2-ylmethyl)-1-tosylpyrrolidine-2-carboxamide;
- (S)-*N*-((R)-1,1-dioxidotetrahydrothiophen-3-yl)-*N*-(furan-2-ylmethyl)-1-tosylpyrrolidine-2-carboxamide;
- (S)-*N*-((S)-1,1-dioxidotetrahydrothiophen-3-yl)-*N*-(furan-2-ylmethyl)-1-tosylpyrrolidine-2-carboxamide; and
- *N*-[(2-Methoxyphenyl)methyl]-1-[(4-methylphenyl)sulfonyl]-*N*-[(tetrahydro-2-thienyl)methyl]-2-pyrrolidinecarboxamide.

The compounds of Formula (I) may contain one or more stereogenic or asymmetric centers, such as one or more asymmetric carbon atoms, which may be present in (R)- or (S)-configuration. The compounds of Formula (I) may further encompass compounds with one or more double bonds which may be present in Z- or E-configuration and/or compounds with substituents at a ring system which may be present, relative to each other, in cis- or trans-configuration. The compounds of Formula (I) may thus be present as mixtures of stereoisomers or preferably as pure stereoisomers. Mixtures of stereoisomers may be separated in a manner known to a person skilled in the art.

In case a particular compound (or generic structure) is designated as (R)- or (S)-enantiomer, such designation is to be understood as referring to the respective compound (or generic structure) in enriched, especially essentially pure, enantiomeric form. Likewise, in case a specific asymmetric center in a compound is designated as being in (R)- or (S)-configuration or as being in a certain relative configuration, such designation is to be understood as referring to the compound that is in enriched, especially essentially pure, form with regard to the respective configuration of said asymmetric center. In analogy, cis- or trans-designations are to be understood as referring to the respective stereoisomer of the respective relative configuration in enriched, especially essentially pure, form. In case a particular compound (or generic structure) contains one or more stereogenic or asymmetric centers, such as one or more asymmetric carbon atoms, which may be present in (R)- or (S)-configuration, but where one (or more) of said stereogenic or asymmetric centers is not explicitly designated as (R)- or (S)-, it is understood that said stereogenic or asymmetric center may be in (R)- or (S)-configuration. Such compound name or generic structure is understood to encompass the compound / generic structure where such center is in (R)- or (S)-configuration, or any mixture of epimers with regard to such center. Likewise, in case such stereogenic or asymmetric center is designated as being in (RS)-configuration, this means that such stereogenic or asymmetric center in such compound may be present in (R)-configuration, in (S)-configuration, or in any mixture of epimers with regard to such center. In case two or more such stereogenic or asymmetric centers (in undesignated or

designated (RS)-configuration) are present in one molecule, it is understood that the order of absolute configuration does not indicate any defined relative configuration with regard to the two or more centers.

In case any defined relative configuration with regard to the two or more centers is present, such centers are denominated with (R*,R*) or (R*,S*) nomenclature indicating in the first instance that the respective centers are either (R,R) or (S,S), and in the second instance that the respective centers are either (R,S) or (S,R), in each case encompassing any mixture of these stereoisomers including the racemate. It is understood that explicitly designated (R)- or (S)-configuration, undesignated or designated (RS)-configuration, and relative (R*,R*)- or (R*,S*)-configuration can co-exist in one and the same molecule and are to be interpreted accordingly. For example, the compound (1R*,5S*)-(2RS)-N-(benzofuran-6-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide encompasses enantiomerically enriched (1R,2R,5S)-N-(benzofuran-6-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide, (1R,2S,5S)-N-(benzofuran-6-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide, (1S,2R,5R)-N-(benzofuran-6-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide, or (1S,2S,5R)-N-(benzofuran-6-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide, or any mixture of these stereoisomers of said compound. Likewise, the compound (1R*,5S*)-(2S)-N-(benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide encompasses enantiomerically enriched (1S,2S,5R)-N-(benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide, enantiomerically enriched (1R,2S,5S)-N-(benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide, or any mixture thereof.

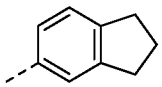
In case a particular compound (or generic structure) is designated as Z- or E-stereoisomer (or in case a specific double bond in a compound is designated as being in Z- or E-configuration), such designation is to be understood as referring to the respective compound (or generic structure) in enriched, especially essentially pure, stereoisomeric form (or to the compound that is in enriched, especially essentially pure, form with regard to the respective configuration of the double bond).

The term "enriched", when used in the context of stereoisomers, is to be understood in the context of the present invention to mean that the respective stereoisomer is present in a ratio of at least 70:30, especially of at least 90:10 (i.e., in a purity of at least 70% by weight, especially of at least 90% by weight), with regard to the respective other stereoisomer / the entirety of the respective other stereoisomers.

The term “essentially pure”, when used in the context of stereoisomers, is to be understood in the context of the present invention to mean that the respective stereoisomer is present in a purity of at least 95% by weight, especially of at least 99% by weight, with regard to the respective other stereoisomer / the entirety of the respective other stereoisomers.

The present invention also includes isotopically labelled, especially 2H (deuterium) labelled compounds of Formula (I) according to embodiments 1) to 24), which compounds are identical to the compounds of Formula (I) except that one or more atoms have each been replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Isotopically labelled, especially 2H (deuterium) labelled compounds of Formula (I) and salts thereof are within the scope of the present invention. Substitution of hydrogen with the heavier isotope 2H (deuterium) may lead to greater metabolic stability, resulting e.g. in increased in-vivo half-life or reduced dosage requirements, or may lead to reduced inhibition of cytochrome P450 enzymes, resulting e.g. in an improved safety profile. In one embodiment of the invention, the compounds of Formula (I) are not isotopically labelled, or they are labelled only with one or more deuterium atoms. In a sub-embodiment, the compounds of formula (I) are not isotopically labelled at all. Isotopically labelled compounds of Formula (I) may be prepared in analogy to the methods described hereinafter, but using the appropriate isotopic variation of suitable reagents or starting materials.

In this patent application, a bond drawn as a dotted line shows the point of attachment of the radical drawn. For example, the radical drawn below



is the 2,3-dihydro-1*H*-inden-5-yl group.

In some instances, the compounds of Formula (I) may contain tautomeric forms. Such tautomeric forms are encompassed in the scope of the present invention. In case tautomeric forms exist of a certain residue, and only one form of such residue is disclosed or defined, the other tautomeric form(s) are understood to be encompassed in such disclosed residue. For example the group 3-oxo-2,3-dihydrobenzofuran-6-yl is to be understood as also encompassing its tautomeric form 3-hydroxy-benzofuran-6-yl.

Where the plural form is used for compounds, salts, pharmaceutical compositions, diseases and the like, this is intended to mean also a single compound, salt, or the like.

Any reference to compounds of Formula (I) according to embodiments 1) to 24) is to be understood as referring also to the salts (and especially the pharmaceutically acceptable salts) of such compounds, as appropriate and expedient.

The term "pharmaceutically acceptable salts" refers to salts that retain the desired biological activity of the subject compound and exhibit minimal undesired toxicological effects. Such salts include inorganic or organic acid and/or base addition salts depending on the presence of basic and/or acidic groups in the subject compound. For reference see for example “Handbook of Pharmaceutical Salts. Properties, Selection and Use.”, P. Heinrich Stahl, Camille G. Wermuth (Eds.), Wiley-VCH, 2008; and “Pharmaceutical Salts and Co-crystals”, Johan Wouters and Luc Quéré (Eds.), RSC Publishing, 2012.

Definitions provided herein are intended to apply uniformly to the compounds of Formula (I), as defined in any one of embodiments 1) to 24), and, *mutatis mutandis*, throughout the description and the claims unless an otherwise expressly set out definition provides a broader or narrower definition. It is well understood that a definition or preferred definition of a term defines and may replace the respective term independently of (and in combination with) any definition or preferred definition of any or all other terms as defined herein.

Whenever a substituent is denoted as optional, it is understood that such substituent may be absent, in which case all positions having a free valency (to which such optional substituent could have been attached to; such as for example in an aromatic ring the ring carbon atoms and / or the ring nitrogen atoms having a free valency) are substituted with hydrogen where appropriate.

The term “halogen” means fluorine, chlorine, bromine, or iodine; especially fluorine, chlorine, or bromine; preferably fluorine or chlorine.

The term “alkyl”, used alone or in combination and if not explicitly defined in a broader or more narrow way, refers to a saturated straight or branched chain hydrocarbon group containing one to six carbon atoms. The term “(C_{x-y})alkyl” (x and y each being an integer), refers to an alkyl group as defined before, containing x to y carbon atoms. For example a (C_{1-6})alkyl group contains from one to six carbon atoms. Examples of alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, 3-methyl-butyl, 2,2-dimethyl-propyl, and 3,3-dimethyl-butyl. For avoidance of any doubt, in case a group is referred to as e.g. propyl or butyl, it is meant to be n-propyl, respectively n-butyl. Preferred are methyl and ethyl. Most preferred is methyl. Examples of $\mathbf{R^{B1}}$ representing (C_{1-4})alkyl are especially (C_{1-3})alkyl groups such as methyl or ethyl, especially methyl. When $\mathbf{X^1}$ represents C$\mathbf{R^{B2}}$, an example of $\mathbf{R^{B2}}$ representing (C_{1-3})alkyl is methyl. An example of (C_{1-3})alkyl as substituent of **Ring A** is methyl. Examples of (C_{1-3})alkyl as substituent of a group $\mathbf{R^1}$ are methyl and isopropyl (especially methyl). Examples of (C_{1-3})alkyl as substituent of a group $\mathbf{R^3}$ are methyl, ethyl, and isopropyl (especially methyl). When $\mathbf{X^2}$ is N$\mathbf{R^4}$, examples of $\mathbf{R^4}$ representing (C_{1-3})alkyl are methyl, ethyl, and isopropyl (especially methyl).

The term “alkoxy”, used alone or in combination and if not explicitly defined in a broader or more narrow way, refers to an alkyl-O- group wherein the alkyl group is as defined before. The term “(C_{x-y})alkoxy” (x and y each being an integer) refers to an alkoxy group as defined before containing x to y carbon atoms. For example a (C_{1-4})alkoxy group means a group of the formula (C_{1-4})alkyl-O- in which the term “(C_{1-4})alkyl” has the previously given significance. Examples of alkoxy groups are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec.-butoxy, and tert.-butoxy. Preferred are methoxy. An example of $\mathbf{R^{B1}}$ representing (C_{1-3})alkoxy is methoxy. When $\mathbf{X^1}$ represents C$\mathbf{R^{B2}}$, an example of $\mathbf{R^{B2}}$ representing (C_{1-3})alkoxy is methoxy. An example of (C_{1-3})alkoxy as substituent of a **Ring A** is methoxy or ethoxy. An example of (C_{1-3})alkoxy as substituent of a group $\mathbf{R^1}$ is methoxy. An example of (C_{1-3})alkoxy as substituent of a group $\mathbf{R^3}$ is methoxy.

The term "fluoroalkyl", used alone or in combination and if not explicitly defined in a broader or more narrow way, refers to an alkyl group as defined before containing one to three carbon atoms in which one or more (and possibly

all) hydrogen atoms have been replaced with fluorine. The term "(C_{x-y})fluoroalkyl" (x and y each being an integer) refers to a fluoroalkyl group as defined before containing x to y carbon atoms. For example a (C_{1-3})fluoroalkyl group contains from one to three carbon atoms in which one to seven hydrogen atoms have been replaced with fluorine. Representative examples of fluoroalkyl groups include trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, and 2,2,2-trifluoroethyl; especially trifluoromethyl. Preferred are (C_{1-3})fluoroalkyl groups such as trifluoromethyl. An example of $\mathbf{R^{B1}}$ representing (C_1)fluoroalkyl is trifluoromethyl. Examples of (C_{1-3})fluoroalkyl as substituent of a group $\mathbf{R^1}$ are difluoromethyl and trifluoromethyl. An example of (C_{1-3})fluoroalkyl as substituent of a group $\mathbf{R^3}$ is trifluoromethyl.

The term "fluoroalkoxy", used alone or in combination and if not explicitly defined in a broader or more narrow way, refers to an alkoxy group as defined before containing one to three carbon atoms in which one or more (and possibly all) hydrogen atoms have been replaced with fluorine. The term "(C_{x-y})fluoroalkoxy" (x and y each being an integer) refers to a fluoroalkoxy group as defined before containing x to y carbon atoms. For example, a (C_{1-3})fluoroalkoxy group contains from one to three carbon atoms in which one to seven hydrogen atoms have been replaced with fluorine. Representative examples of fluoroalkoxy groups include trifluoromethoxy, difluoromethoxy, 2-fluoroethoxy, 2,2-difluoroethoxy, and 2,2,2-trifluoroethoxy. Preferred are (C_1)fluoroalkoxy groups such as trifluoromethoxy and difluoromethoxy, as well as 2,2,2-trifluoroethoxy. An example of (C_{1-3})fluoroalkoxy as substituent of a group $\mathbf{R^3}$ isdifluoromethoxy.

The term "cyano" refers to a group -CN. A particular example of $\mathbf{R^1}$ representing a saturated monocyclic (C_{4-6})cycloalkyl with a cyano substituent is 3-cyanocyclopentyl; in particular, such cyano substituent of $\mathbf{R^1}$ representing 3-cyanocyclopentyl is in relative cis configuration with respect to the bond, from the ring carbon at position 1 of 3-cyanocyclopentyl, linking $\mathbf{R^1}$ to the rest of Formula (I) [notably such $\mathbf{R^1}$ representing 3-cyanocyclopentyl is (1R,3S)-3-cyanocyclopentyl].

The term "oxo" refers to a group =O which is preferably attached to a chain or ring carbon or sulfur atom as for example in a carbonyl group -(CO)-, or a sulfonyl group -(SO_2)-.

The term "(C_{x-y})alkylidene" (x and y each being an integer), used alone or in combination and if not explicitly defined in a broader or more narrow way, refers to an alkyl group as defined before, containing x to y carbon atoms, wherein said alkyl group is linked to the rest of the molecule via a double bond. An example of (C_{1-3})alkylidene is the methylidene (also referred to as methylene) group H_2C=.

The term "cycloalkyl", used alone or in combination and if not explicitly defined in a broader or more narrow way, refers to a saturated monocyclic hydrocarbon ring containing three to eight carbon atoms. The term "(C_{x-y})cycloalkyl" (x and y each being an integer), refers to a cycloalkyl containing x to y carbon atoms. For example, a (C_{3-6})cycloalkyl group contains from three to six carbon atoms.

The term "monocyclic (C_{x-y})cycloalkyl" or "saturated monocyclic (C_{x-y})cycloalkyl", refers to a saturated monocyclic cycloalkyl group as defined before, containing x to y carbon atoms. Examples of monocyclic cycloalkyl groups are

cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. An example of R^{B1} representing a monocyclic (C_{3-4})cycloalkyl is cyclopropyl. Preferred examples of R^1 representing a saturated monocyclic (C_{4-6})cycloalkyl are cyclopentyl and cyclohexyl; wherein said groups are unsubstituted or substituted as explicitly defined. When X^2 is NR^4, a preferred example of R^4 representing a monocyclic (C_{3-6})cycloalkyl is cyclopropyl. An example of (C_{3-6})cycloalkyl as substituent of a group R^3 is cyclopropyl.

The term "(C_{x-y})cycloalkan-diyl" or "monocyclic (C_{x-y})cycloalkan-diyl" (x and y each being an integer), used alone or in combination and if not explicitly defined in a broader or more narrow way, refers to bivalently bound cycloalkyl group, as defined before, containing x to y carbon atoms. When X^3 represents CH and **Ring A** represents a monocyclic (C_{5-6})cycloalkan-diyl, the points of attachment of said (C_{5-6})cycloalkan-diyl in Formula (I) are on X^3 and on a carbon atom neighboring X^3; examples are cyclopentane-1,2-diyl and cyclohexane-1,2-diyl (especially cyclopentane-1,2-diyl).

The term "saturated bicyclic (C_{x-y})spirocycloalkyl" (x and y each being an integer), used alone or in combination and if not explicitly defined in a broader or more narrow way, refers to a saturated spiro-bicyclic hydrocarbon ring containing x to y carbon atoms. Examples of R^1 representing a saturated bicyclic (C_{6-8})spirocycloalkyl are spiro[2.3]hexanyl, spiro[3.3]heptanyl, spiro[2.4]heptanyl, and spiro[2.5]octanyl (especially spiro[2.3]hexanyl and spiro[2.5]octanyl); such saturated bicyclic (C_{6-8})spirocycloalkyl are unsubstituted or substituted as explicitly defined. Particular examples of such R^1 representing a saturated bicyclic (C_{6-8})spirocycloalkyl are 1,1-difluorospiro[2.3]hexan-5-yl, 1,1-difluorospiro[2.5]octan-6-yl, spiro[3.3]heptan-2-yl, 6,6-difluorospiro[3.3]heptan-2-yl, and 1,1-difluorospiro[2.4]heptan-5-yl, and spiro[2.5]octan-6-yl (especially 1,1-difluorospiro[2.3]hexan-5-yl and 1,1-difluorospiro[2.5]octan-6-yl).

The term "saturated fused or bridged bicyclic (C_{x-y})cycloalkyl" (x and y each being an integer), used alone or in combination and if not explicitly defined in a broader or more narrow way, refers to a saturated fused or bridged bicyclic hydrocarbon ring containing x to y carbon atoms. Examples of R^1 representing a saturated bridged bicyclic (C_{6-8})cycloalkyl are bicyclo[2.1.1]hexanyl, bicyclo[4.1.0]heptanyl, and bicyclo[2.2.2]octanyl (especially bicyclo[4.1.0]heptanyl); such R^1 are unsubstituted or substituted as explicitly defined. Particular examples of such R^1 representing a saturated fused bicyclic (C_{6-8})cycloalkyl are bicyclo[4.1.0]heptan-3-yl, 7,7-difluorobicyclo[4.1.0]heptan-3-yl, 4-carbamoylbicyclo[2.1.1]hexan-2-yl, and 4-cyanobicyclo[2.2.2]octan-1-yl (especially bicyclo[4.1.0]heptan-3-yl and 7,7-difluorobicyclo[4.1.0]heptan-3-yl). In one example when R^1 represents a bicyclo[4.1.0]heptanyl, the fused cyclopropyl ring of such bicyclo[4.1.0]heptanyl is such that its two bonds to the bridgehead ring carbon atoms of the fused cyclohexane ring of such bicyclo[4.1.0]heptanyl are in relative cis configuration; notably, such bicyclo[4.1.0]heptanyl may be a (1S,6S)-bicyclo[4.1.0]heptanyl. A particular example of R^1 representing bicyclo[4.1.0]heptan-3-yl is (1S,3S,6S)-bicyclo[4.1.0]heptan-3-yl; such R^1 is unsubstituted or substituted as explicitly defined.

The term "mono-unsaturated monocyclic (C_{x-y})cycloalkyl" (x and y each being an integer), used alone or in combination and if not explicitly defined in a broader or more narrow way, refers to a mono-unsaturated monocyclic hydrocarbon ring containing x to y carbon atoms (i.e., said ring comprises a single unsaturated (double) bond and otherwise contains saturated bonds). In one embodiment when **R¹** is a mono-unsaturated monocyclic (C_{5-6})cycloalkyl, the unsaturated (double) bond of such (C_{5-6})cycloalkyl does not contain the carbon atom attached to the group -N(CO)CH(**R²**)(**R³**); such an **R¹** is unsubstituted or substituted as explicitly defined. An example of such an **R¹** is cyclohexenyl, notably cyclohex-3-en-1-yl.

The term "heterocycle", "heterocycloalkyl", or "saturated monocyclic heterocycloalkyl", used alone or in combination and if not explicitly defined in a broader or more narrow way, refers to a saturated monocyclic hydrocarbon ring comprising one or two ring heteroatoms or heteroatomic groups independently selected from N, O, S, and SO_2; wherein it is understood that in each instance, the number and nature of ring heteroatoms or heteroatomic groups are as explicitly defined or may be defined more narrowly (i.e., such ring contains / comprises the defined ring heteroatom(s) or heteroatomic groups, and no further ring heteroatoms or heteroatomic groups). The term "x- to y-membered heterocycloalkyl" or "x- to y-membered saturated monocyclic heterocycloalkyl" (x and y each being an integer) refers to such a heterocycle containing x to y ring atoms. Such heterocycles are unsubstituted or substituted as explicitly defined. When **R¹** is a 5- or 6-membered saturated monocyclic heterocycloalkyl, such **R¹** may be unsubstituted or substituted as explicitly defined; examples of such **R¹** are tetrahydrothiophen-1,1-dioxide, tetrahydro-2*H*-pyran, and tetrahydro-2*H*-thiopyran-1,1-dioxide (particular examples of such **R¹** are 1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl, 1,1-dioxidotetrahydrothiophen-3-yl, tetrahydro-2*H*-pyran-4-yl, 3-fluorotetrahydro-2*H*-pyran-4-yl, 2-methyltetrahydro-2*H*-pyran-4-yl, 2-(trifluoromethyl)tetrahydro-2*H*-pyran-4-yl, 2,2-dimethyltetrahydro-2*H*-pyran-4-yl, tetrahydro-2*H*-thiopyran-4-yl, and tetrahydro-2*H*-pyran-3-yl; and, in addition to the before listed: 6-methyltetrahydro-2*H*-pyran-3-yl, 6,6-dimethyltetrahydro-2*H*-pyran-3-yl, 3-methyltetrahydro-2*H*-pyran-4-yl, 2,6-dimethyltetrahydro-2*H*-pyran-4-yl, 1,1-dioxidotetrahydro-2*H*-thiopyran-3-yl, and 6-methyl-1,1-dioxidotetrahydro-2H-thiopyran-3-yl; especially 1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl, 1,1-dioxidotetrahydro-2*H*-thiopyran-3-yl, and 6-methyl-1,1-dioxidotetrahydro-2H-thiopyran-3-yl). Examples of a 4- to 6-membered monocyclic heterocycloalkyl as a substituent of a group **R³** representing phenyl are notably 4-membered monocyclic heterocycloalkyl groups (especially azetidinyl or oxetanyl); wherein such heterocycloalkyl is unsubstituted or mono-substituted with halogen (especially fluoro); particular examples are azetidin-1-yl and 3-fluorooxetan-3-yl.

The term "x- to y-membered heterocycloalkan-diyl" or "monocyclic x- to y-membered heterocycloalkan-diyl" (x and y each being an integer), used alone or in combination and if not explicitly defined in a broader or more narrow way, refers to a bivalently bound heterocycloalkyl as defined before; wherein in each instance, the number and nature of ring heteroatoms or heteroatomic groups are explicitly defined. When **X³** represents CH and **Ring A** represents a monocyclic 5- or 6-membered heterocycloalkan-diyl comprising one ring O atom, the points of attachment of said heterocycloalkan-diyl in Formula (I) are on **X³** and the carbon atom attached to the group–CO-N(**R¹**)CH(**R²**)(**R³**); examples are tetrahydrofuran-2,3-diyl and tetrahydro-2*H*-pyran-3,4-diyl. When **X³** represents N and **Ring A**

represents a 4- to 6-membered saturated monocyclic heterocycloalkan-diyl comprising **X³** and zero or one ring O atom, the points of attachment of said heterocycloalkan-diyl in Formula (I) are on **X³** and on the carbon atom attached to the group –CO-N(**R¹**)CH(**R²**)(**R³**); examples are azetidin-diyl, pyrrolidin-diyl, oxazolidin-diyl (notably oxazolidin-2,3-diyl or oxazolidin-3,4-diyl), and oxazinan-diyl (notably 1,3-oxazinan-2,3-diyl); such **Ring A** may be unsubstituted, or substituted as explicitly defined. In a particular embodiment, the carbon atom of **Ring A** attached to the group –CO-N(**R¹**)CH(**R²**)(**R³**) is not further substituted.

The term "x- to y-membered mono-unsaturated monocyclic heterocycloalkan-diyl" (x and y each being an integer), used alone or in combination and if not explicitly defined in a broader or more narrow way, refers to a bivalently bound monocyclic hydrocarbon ring containing x to y ring atoms of which one or two (especially one) ring atoms are heteroatoms independently selected from N, O, and S, and wherein said ring comprises a single unsaturated (double) bond and otherwise contains saturated bonds. When **X³** represents N and **Ring A** represents a 4- to 6-membered (notably 5-membered) mono-unsaturated monocyclic heterocycloalkan-diyl comprising **X³** and zero or one additional ring N atom, and no further ring heteroatoms (notably a 5-membered mono-unsaturated monocyclic heterocycloalkan-diyl; especially dihydro-1*H*-pyrrol-diyl or dihydro-1*H*-pyrazol-diyl), the points of attachment of said mono-unsaturated heterocycloalkan-diyl in Formula (I) are on **X³** and on the carbon atom attached to the group –CO-N(**R¹**)CH(**R²**)(**R³**), e.g., are in 1,2 arrangement, and the unsaturated (double) bond of said mono-unsaturated heterocycloalkan-diyl does not contain **X³** or the carbon atom attached to the group –CO-N(**R¹**)CH(**R²**)(**R³**). Such **Ring A** may be unsubstituted or substituted as explicitly defined; particular examples are 2,3-dihydro-1*H*-pyrrol-1,2-diyl, 4,5-dihydro-1*H*-pyrazol-1,5-diyl, and 3-methyl-4,5-dihydro-1*H*-pyrazol-1,5-diyl (especially 2,3-dihydro-1*H*-pyrrol-1,2-diyl). In a particular embodiment, the carbon atom of **Ring A** attached to the group –CO-N(**R¹**)CH(**R²**)(**R³**) is not further substituted.

The term "x- to y-membered saturated spiro, fused, or bridged bicyclic heterocycloalkyl" refers to a saturated spiro, fused, or bridged bicyclic hydrocarbon ring containing x to y ring atoms of which one or two (especially one) ring atoms are heteroatoms independently selected from N, O, and S. The term "x- to y-membered saturated spiro, fused, or bridged bicyclic heterocycloalkan-diyl" refers to a saturated spiro, fused, or bridged bicyclic hydrocarbon ring containing x to y ring atoms of which one or two (especially one) ring atoms are heteroatoms independently selected from N, O, and S, wherein the saturated spiro, fused, or bridged bicyclic hydrocarbon ring is bivalently bound. Such saturated spiro, fused, or bridged bicyclic heterocycloalkyl or heterocycloalkan-diyl are unsubstituted or substituted as explicitly defined. When **Ring A** is a 6- to 8-membered saturated spiro, fused, or bridged bicyclic heterocycloalkan-diyl comprising **X³** representing N, the points of attachment of said heterocycloalkan-diyl in Formula (I) are on **X³** and on the carbon atom attached to the group –CO-N(**R¹**)CH(**R²**)(**R³**), e.g., are in 1,2 arrangement. Accordingly, the term "x- to y-membered saturated spiro bicyclic heterocycloalkyl" (x and y each being an integer), used alone or in combination and if not explicitly defined in a broader or more narrow way, refers to a saturated spiro-bicyclic hydrocarbon ring containing x to y ring atoms of which one or two (especially one) ring atoms are heteroatoms independently selected from N, O, and S (especially N). Likewise the term "x- to y-

membered saturated spiro bicyclic heterocycloalkan-diyl" refers to an x- to y-membered saturated spiro bicyclic heterocycloalkyl as defined before which is bivalently bound. An example of such **Ring A** representing a 6- to 8-membered saturated spiro bicyclic heterocycloalkan-diyl is azaspiro[2.4]heptane-diyl (especially 5-azaspiro[2.4]heptane-4,5-diyl). Accordingly, the term "x- to y-membered saturated fused bicyclic heterocycloalkyl" (x and y each being an integer), used alone or in combination and if not explicitly defined in a broader or more narrow way, refers to a saturated fused-bicyclic hydrocarbon ring containing x to y ring atoms of which one or two (especially one) ring atoms are heteroatoms independently selected from N, O, and S (especially N). Likewise the term "x- to y-membered saturated fused bicyclic heterocycloalkan-diyl" refers to an x- to y-membered saturated fuse bicyclic heterocycloalkyl as defined before which is bivalently bound. When **Ring A** is a 6- to 8-membered saturated fused bicyclic heterocycloalkan-diyl comprising $\mathbf{X^3}$ representing N, the carbon atom of **Ring A** attached to the group –CO-N($\mathbf{R^1}$)CH($\mathbf{R^2}$)($\mathbf{R^3}$) is not shared between the two cycles of such bicycle. An example of such **Ring A** representing a 6- to 8-membered saturated fused bicyclic heterocycloalkan-diyl is azabicyclo[3.1.0]hexan-diyl (especially 2-azabicyclo[3.1.0]hexan-2,3-diyl or 3-azabicyclo[3.1.0]hexan-2,3-diyl); an additional example of such **Ring A** representing a 6- to 8-membered saturated fused bicyclic heterocycloalkan-diyl is azabicyclo[3.2.0]heptan-diyl (especially 3-azabicyclo[3.2.0]heptan-2,3-diyl). Accordingly the term "x- to y-membered saturated bridged bicyclic heterocycloalkyl" (x and y each being an integer), used alone or in combination and if not explicitly defined in a broader or more narrow way, refers to a saturated bridged bicyclic hydrocarbon ring containing x to y ring atoms of which one or two (especially one) ring atoms are heteroatoms independently selected from N, O, and S (especially N). Likewise the term "x- to y-membered saturated bridged bicyclic heterocycloalkan-diyl" refers to an x- to y-membered saturated bridged bicyclic heterocycloalkyl as defined before which is bivalently bound. When **Ring A** is a 6- to 8-membered bridged saturated bicyclic heterocycloalkan-diyl comprising $\mathbf{X^3}$ representing N, the carbon atom of **Ring A** attached to the group–CO-N($\mathbf{R^1}$)CH($\mathbf{R^2}$)($\mathbf{R^3}$) is not a bridgehead atom. An example of such **Ring A** representing a 6- to 8-membered bridged saturated bicyclic heterocycloalkan-diyl is azabicyclo[2.2.1]heptan-diyl (especially 2-azabicyclo[2.2.1]heptan-1,2-diyl). In a particular case of a 6- to 8-membered saturated spiro, fused, or bridged bicyclic heterocycloalkan-diyl comprising $\mathbf{X^3}$ representing N, such group contains 6 to 8 ring atoms, including $\mathbf{X^3}$ representing nitrogen, and no further heteroatoms.

The term "aryl", used alone or in combination, means phenyl or naphthyl, especially phenyl. The above-mentioned aryl groups are unsubstituted or substituted as explicitly defined.

When $\mathbf{R^3}$ represents phenyl, such phenyl may be unsubstituted or substituted as explicitly defined. Whenever $\mathbf{R^3}$ represents phenyl, notably such phenyl groups are mono-, di- or tri-substituted, wherein especially one of said substituents is attached in para or meta (in particular in para) position with regard to the point of attachment of the rest of the molecule. In one embodiment wherein $\mathbf{R^3}$ represents phenyl, such phenyl groups are mono-substituted in para position with regard to the point of attachment of the rest of the molecule, or are independently di-substituted in para and one meta position, or in para and one ortho position, with regard to the point of attachment of the rest of the molecule. Especially such substituent in para position is (C_{1-3})alkyl (notably methyl, ethyl, or isopropyl),

halogen (notably fluoro, chloro, or bromo), (C_{1-3})alkoxy (notably methoxy), (C_{1-3})fluoroalkoxy (notably difluoromethoxy), (C_{1-3})alkylthio (notably methylthio), (C_{1-3})fluoroalkyl (notably trifluoromethyl), or $\mathbf{NR^{N1}R^{N2}}$, wherein $\mathbf{R^{N1}}$ and $\mathbf{R^{N2}}$ independently represent hydrogen or (C_{1-4})alkyl (especially $\mathbf{NR^{N1}R^{N2}}$ represents dimethylamino). The remaining substituent(s), if present, especially are independently selected from (C_{1-3})alkyl (especially methyl), halogen (notably fluoro or chloro), and cyano. Particular examples of $\mathbf{R^3}$ representing phenyl are p-tolyl, 4-chlorophenyl, 4-bromophenyl, 4-(methylthio)phenyl, 4-chloro-2-fluorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2,4-difluorophenyl, 3-fluoro-4-methylphenyl, phenyl, 2-chlorophenyl, 3-methylphenyl, 3-fluorophenyl, 3-methoxyphenyl, 3-(difluoromethoxy)phenyl, 3-(azetidin-1-yl)phenyl, 3-(3-fluorooxetan-3-yl)phenyl, 4-ethylphenyl, 4-isopropylphenyl, 4-(dimethylamino)phenyl, 4-(difluoromethoxy)phenyl, 4-(trifluoromethyl)phenyl, 2-fluoro-3-methylphenyl, 2,4-dimethylphenyl, 4-fluoro-2-methylphenyl, 2-chloro-4-fluorophenyl, 2-fluoro-4-methoxyphenyl, 2,5-difluorophenyl, 2-fluoro-5-methoxyphenyl, 3-fluoro-5-methoxyphenyl, 3,4-dimethylphenyl, 4-fluoro-3-methylphenyl, 3,4-difluorophenyl, 4-chloro-3-fluorophenyl, 3-chloro-4-methylphenyl, 3-cyano-4-methylphenyl, 3-fluoro-4-methoxyphenyl, 2,3-difluoro-4-methylphenyl, 4-chloro-2,3-difluorophenyl, 4-chloro-2,6-difluorophenyl, and 2,4-difluoro-5-methylphenyl. Examples of such $\mathbf{R^3}$ representing a para-substituted phenyl are p-tolyl, 4-chlorophenyl, 4-bromophenyl, 4-(methylthio)phenyl, 4-chloro-2-fluorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2,4-difluorophenyl, 3-fluoro-4-methylphenyl, 4-ethylphenyl, 4-isopropylphenyl, 4-(dimethylamino)phenyl, 4-(difluoromethoxy)phenyl, 4-(trifluoromethyl)phenyl, 2,4-dimethylphenyl, 4-fluoro-2-methylphenyl, 2-chloro-4-fluorophenyl, 2-fluoro-4-methoxyphenyl, 3,4-dimethylphenyl, 4-fluoro-3-methylphenyl, 3,4-difluorophenyl, 4-chloro-3-fluorophenyl, 3-chloro-4-methylphenyl, 3-cyano-4-methylphenyl, 4-fluoro-4-methoxyphenyl, 2,3-difluoro-4-methylphenyl, 4-chloro-2,3-difluorophenyl, 4-chloro-2,6-difluorophenyl, and 2,4-difluoro-5-methylphenyl (especially p-tolyl, 4-chlorophenyl, 4-bromophenyl, 4-(methylthio)phenyl, 4-chloro-2-fluorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2,4-difluorophenyl, and 3-fluoro-4-methylphenyl, and, in addition to the before listed: 3-fluoro-4-methoxyphenyl).

The term "heteroaryl", used alone or in combination, means a 5- to 10-membered monocyclic or bicyclic aromatic ring containing one to a maximum of four heteroatoms (especially one to a maximum three), each independently selected from N, O, and S. Examples of such heteroaryl groups are 5-membered heteroaryl groups such as furanyl, oxazolyl, isoxazolyl, oxadiazolyl, thiophenyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, and tetrazolyl; 6-membered heteroaryl groups such as pyridinyl, pyrimidinyl, pyridazinyl, and pyrazinyl; and 8- to 10-membered bicyclic heteroaryl groups such as indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzothiophenyl, furopyridinyl, indazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzotriazolyl, benzoxadiazolyl, benzothiadiazolyl, thienopyridinyl, quinolinyl, isoquinolinyl, naphthyridinyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, pyrrolopyridinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, pyrrolopyrazinyl, imidazopyridinyl, imidazopyridazinyl, and imidazothiazolyl. The above-mentioned heteroaryl groups are unsubstituted or substituted as explicitly defined.

When **R³** represents a 5- or 6-membered heteroaryl, such heteroaryl as used for **R³** comprises one to three ring heteroatoms independently selected from N, O, and S, wherein such heteroaryl is especially linked to the rest of the molecule via a ring carbon atom. Such **R³** is notably pyridinyl, thiophenyl, oxazolyl, thiazolyl, isothiazolyl, or isoxazolyl; such 5- or 6-membered heteroaryl is unsubstituted or, especially, substituted as explicitly defined. Examples of such **R³** are 5-chloropyridin-2-yl, 2-methylthiophen-3-yl, 5-methylthiophen-2-yl, 5-chlorothiophen-2-yl, 3-methylthiophen-2-yl, 5-isopropyloxazol-2-yl, 5-chlorothiazol-2-yl, 5-bromoothiazol-2-yl, 5-isopropylthiazol-2-yl, 2-isopropylthiazol-5-yl, 5-methylisothiazol-4-yl, 5-methylisoxazol-4-yl, 4-ethyl-5-methylisoxazol-3-yl, 5-cyclopropylisoxazol-3-yl, and 5-cyclopropyl-4-ethylisoxazol-3-yl (especially 5-chloropyridin-2-yl, 2-methylthiophen-3-yl, 5-methylthiophen-2-yl, 5-chlorothiophen-2-yl, 3-methylthiophen-2-yl, 5-isopropyloxazol-2-yl, 5-chlorothiazol-2-yl, 5-bromoothiazol-2-yl, 5-isopropylthiazol-2-yl, 2-isopropylthiazol-5-yl, 5-methylisothiazol-4-yl, 5-methylisoxazol-4-yl, and 4-ethyl-5-methylisoxazol-3-yl).

The term "8- to 10-membered heteroaryl" refers to a bicyclic heteroaryl group as defined before, wherein said 8- to 10-membered heteroaryl especially comprises in total one to a maximum of three (in particular one or two) heteroatoms independently selected from N, O, and S. Notably, the such term refers to a 9- or 10-membered heteroaryl groups, such as especially indazolyl, benzoimidazolyl, indolyl, benzotriazolyl, benzooxazolyl, quinoxalinyl, isoquinolinyl, quinolinyl, pyrrolopyridinyl, and imidazopyridinyl. The above groups are unsubstituted or substituted as explicitly defined. Examples of **R³** representing an 8- to 10-membered heteroaryl are benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiophenyl, furopyridinyl, benzoxadiazolyl, thienopyridinyl, 1*H*-indolyl, quinolinyl, and isoquinolinyl (especially benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiophenyl, and furopyridinyl); wherein such 8- to 10-membered heteroaryl is unsubstituted or substituted as defined. Particular examples of such **R³** are benzofuran-6-yl, benzo[*d*]oxazol-5-yl, 6-fluorobenzo[*d*]oxazol-5-yl, benzo[*d*]oxazol-6-yl, benzo[*d*]thiazol-5-yl, 2-chlorobenzo[*d*]thiazol-5-yl, benzo[*b*]thiophen-5-yl, benzo[*b*]thiophen-6-yl, furo[3,2-*c*]pyridin-6-yl, 2-methylbenzo[*d*]thiazol-5-yl, benzofuran-2-yl, benzofuran-5-yl, 2-methylbenzofuran-6-yl, benzo[*d*]thiazol-6-yl, 6-fluoro-2-methylbenzo[*d*]thiazol-5-yl, benzo[*d*]thiazol-2-yl, benzo[*b*]thiophen-2-yl, 2-methylbenzo[*b*]thiophen-5-yl, furo[3,2-*b*]pyridin-6-yl, furo[2,3-*b*]pyridin-6-yl, benzo[*d*]oxazol-2-yl, benzo[*c*][1,2,5]oxadiazol-5-yl, thieno[2,3-*b*]pyridin-2-yl, 1*H*-indol-6-yl, quinolin-7-yl, isoquinolin-3-yl, and isoquinolin-7-yl; and, in addition to the before listed: 2-bromobenzo[*d*]thiazol-5-yl, 4-fluorobenzo[*d*]thiazol-5-yl, and 2-methoxybenzo[*d*]thiazol-5-yl (especially benzofuran-6-yl, benzo[*d*]oxazol-5-yl, 6-fluorobenzo[*d*]oxazol-5-yl, benzo[*d*]oxazol-6-yl, benzo[*d*]thiazol-5-yl, 2-chlorobenzo[*d*]thiazol-5-yl, benzo[*b*]thiophen-5-yl, benzo[*b*]thiophen-6-yl, furo[3,2-*c*]pyridin-6-yl, and 2-methylbenzo[*d*]thiazol-5-yl; and, in addition to the before listed: 2-bromobenzo[*d*]thiazol-5-yl).

The term "8- to 10-membered partially aromatic fused bicyclic ring system" refers to a 5- or 6-membered aromatic ring (especially a 6-membered aromatic ring) which is fused to a (C_{5-6})cycloalkyl or to a 5- or 6-membered heterocycle, as defined before, wherein said fused ring system comprises in total zero to a maximum of three heteroatoms independently selected from N, O, and S. When **R³** represents an 8- to 10-membered partially aromatic fused bicyclic ring system, such ring system is linked to the rest of the molecule at the aromatic ring moiety,

especially at an aromatic ring carbon; such 8- to 10-membered partially aromatic fused bicyclic ring system is unsubstituted or substituted as explicitly defined; wherein it is understood that any oxo substituent is attached to the non-aromatic ring of such ring system. Examples of **R³** representing an 8- to 10-membered partially aromatic fused bicyclic ring system are phenyl or pyridine which are fused to a (C_{5-6})cycloalkyl or 5- or 6-membered heterocycloalkyl ring, as defined before (wherein it is understood that the total of heteroatoms comprised in the thus-formed bicyclic ring system is zero to three); notably, examples of **R³** representing an 8- to 10-membered partially aromatic fused bicyclic ring system are 2,3-dihydro-1*H*-indenyl, 2,3-dihydrobenzofuranyl, benzo[*d*][1,3]dioxolyl, 6,7-dihydro-5*H*-cyclopentapyridinyl, 2,3-dihydrofuro[3,2]pyridinyl, chromanyl, isochromanyl, and 2,3-dihydrobenzo[*b*][1.4]dioxinyl); wherein such ring system is linked to the rest of the molecule at the aromatic ring moiety; wherein such ring system is unsubstituted or substituted as explicitly defined. Examples of such **R³** representing an 8- to 10-membered partially aromatic fused bicyclic ring system are 2,3-dihydro-1*H*-inden-5-yl, 2,3-dihydrobenzofuran-6-yl, 5-fluoro-2,3-dihydrobenzofuran-6-yl, benzo[*d*][1,3]dioxol-5-yl, 4-fluoro-2,3-dihydrobenzofuran-6-yl, 7-fluoro-2,3-dihydrobenzofuran-6-yl, 3-methyl-2,3-dihydrobenzofuran-6-yl, 2-methyl-2,3-dihydrobenzofuran-6-yl, 3-oxo-2,3-dihydrobenzofuran-6-yl, benzo[*d*][1,3]dioxol-4-yl, 2,2-difluorobenzo[*d*][1,3]dioxol-5-yl, 6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl, 6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-3-yl2,3-dihydrofuro[3,2-*b*]pyridin-6-yl, 2,3-dihydrofuro[3,2-*c*]pyridin-6-yl, chroman-6-yl, chroman-7-yl, isochroman-6-yl, isochroman-7-yl, and 2,3-dihydrobenzo[*b*][1.4]dioxin-6-yl; particular examples of such **R³** are 2,3-dihydro-1*H*-inden-5-yl, 2,3-dihydrobenzofuran-6-yl, 5-fluoro-2,3-dihydrobenzofuran-6-yl, benzo[*d*][1,3]dioxol-5-yl, and 4-fluoro-2,3-dihydrobenzofuran-6-yl. For avoidance of doubt, certain groups having tautomeric forms which are considered predominantly non-aromatic, such as for example 3-oxo-2,3-dihydrobenzofuran-6-yl, are defined herein as 8- to 10-membered partially aromatic fused bicyclic heterocyclyl groups, even though the corresponding tautomeric form (3-hydroxy-benzofuran-6-yl) could in some instances be considered as a 8- to 10-membered heteroaryl; such tautomeric form being encompassed in the scope.

Whenever the word “between” is used to describe a numerical range, it is to be understood that the end points of the indicated range are explicitly included in the range. For example: if a temperature range is described to be between 40 ºC and 80 ºC, this means that the end points 40 ºC and 80 ºC are included in the range; or if a variable is defined as being an integer between 1 and 4, this means that the variable is the integer 1, 2, 3, or 4.

Unless used regarding temperatures, the term “about” placed before a numerical value “X” refers in the current application to an interval extending from X minus (10% of X) to X plus (10% of X), and preferably to an interval extending from X minus (5% of X) to X plus (5% of X). Likewise, the term “about” placed before a numerical range “X to Y” refers in the current application to an interval extending from X minus (10% of X) to Y plus (10% of Y), and preferably to an interval extending from X minus (5% of X) to Y plus (5% of Y). In the particular case of temperatures, the term “about” placed before a temperature “Y” refers in the current application to an interval extending from the temperature Y minus 10 ºC to Y plus 10 ºC, and preferably to an interval extending from Y minus 5 ºC to Y plus 5 ºC. Besides, the term “room temperature” as used herein refers to a temperature of about 25°C.

Further embodiments of the invention are presented hereinafter:

2) Another embodiment relates to compounds according to embodiment 1), wherein **X¹** represents CH, CF, or N (in particular **X¹** represents CH or CF).

3) Another embodiment relates to compounds according to embodiment 1) or 2), wherein **R^{B1}** represents independently (C_{1-3})alkyl, (C_{1-3})alkoxy, halogen, or monocyclic (C_{3-4})cycloalkyl; [especially **R^{B1}** represents independently methyl, ethyl, methoxy, chloro, iodo, or cyclopropyl; in particular **R^{B1}** represents independently methyl or methoxy].

4) Another embodiment relates to compounds according to embodiment 1), wherein

Ring B represents p-tolyl, 3-fluoro-4-methylphenyl, 4-methoxyphenyl, 6-methylpyridin-3-yl, 3-fluoro-4-methoxyphenyl, 4-cyclopropylphenyl, 4-chlorophenyl, phenyl, 6-methoxypyridin-3-yl, 4-fluorophenyl, 3-fluorophenyl, 6-fluoropyridin-3-yl, 4-fluoro-3-methylphenyl, 3-methoxyphenyl, 3,4-dimethylphenyl, or 3,4-difluorophenyl, or, in addition, 4-ethylphenyl, 4-isopropylphenyl, 4-propylphenyl, 4-(*tert*-butyl)phenyl, 4-(*tert*-butyl)-3-fluorophenyl, 4-(trifluoromethyl)phenyl, 4-bromophenyl, 4-iodophenyl, 3,4-dichlorophenyl, 4-bromo-3-fluorophenyl, 3-bromo-4-methylphenyl, or 3-chloro-4-methylphenyl [notably p-tolyl, 4-ethylphenyl, 4-isopropylphenyl, 4-propylphenyl, 3-fluoro-4-methylphenyl, 4-methoxyphenyl, 6-methylpyridin-3-yl, 3-fluoro-4-methoxyphenyl, 4-cyclopropylphenyl, 4-chlorophenyl, 4-bromophenyl, 4-iodophenyl, phenyl, 6-methoxypyridin-3-yl, 4-fluorophenyl, 3-fluorophenyl, 6-fluoropyridin-3-yl, 4-fluoro-3-methylphenyl, 3-methoxyphenyl, 3,4-dimethylphenyl, 3,4-difluorophenyl, 3,4-dichlorophenyl, 4-bromo-3-fluorophenyl, 3-bromo-4-methylphenyl, or 3-chloro-4-methylphenyl; especially **Ring B** represents p-tolyl, 3-fluoro-4-methylphenyl, 4-methoxyphenyl, 6-methylpyridin-3-yl, 3-fluoro-4-methoxyphenyl, 4-cyclopropylphenyl, or 4-chlorophenyl, or, in addition, 4-ethylphenyl, or 4-iodophenyl; in particular **Ring B** represents p-tolyl, 3-fluoro-4-methylphenyl, or 4-methoxyphenyl].

5) Another embodiment relates to compounds according to any one of embodiments 1) to 4), wherein **X²** represents O or N**R⁴**, wherein **R⁴** represents hydrogen, methyl, or cyclopropyl [in particular **X²** represents O or N**R⁴**, wherein **R⁴** represents hydrogen or methyl].

6) Another embodiment relates to compounds according to any one of embodiments 1) to 4), wherein **X²** represents O.

7) Another embodiment relates to compounds according to any one of embodiments 1) to 6), wherein **X³** represents CH or N such that:

- when **X³** represents CH, **Ring A** represents a monocyclic (C_{5-6})cycloalkan-diyl or a monocyclic 5- or 6-membered heterocycloalkan-diyl comprising one ring O atom (especially tetrahydrofuran-diyl or tetrahydro-2*H*-pyran-diyl); [in particular such **Ring A** represents cyclopentane-1,2-diyl]; or
- when **X³** represents N, **Ring A** represents:

- a 4- or 5-membered saturated monocyclic heterocycloalkan-diyl comprising **X³** and zero ring O atoms (notably azetidin-diyl or pyrrolidin-diyl); wherein said heterocycloalkan-diyl is unsubstituted, or mono- or di-substituted (notably unsubstituted or mono-substituted); wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl (especially methyl), halogen (especially fluoro), (C_{1-3})alkoxy (especially methoxy or ethoxy), hydroxy, and (C_{1-3})alkylidene (especially H_2C=); [especially such **Ring A** represents pyrrolidin-1,2-diyl, 4-methylpyrrolidin-1,2-diyl, 4-fluoropyrrolidin-1,2-diyl, 3-methylenepyrrolidin-1,2-diyl, 5-methylpyrrolidin-1,2-diyl, azetidin-1,2-diyl, 4-methylazetidin-1,2-diyl, 3-fluoropyrrolidin-1,2-diyl, 4-hydroxypyrrolidin-1,2-diyl, 4-methoxypyrrolidin-1,2-diyl, 4-ethoxypyrrolidin-1,2-diyl, or 4,4-dimethylpyrrolidin-1,2-diyl; in particular **Ring A** represents pyrrolidin-1,2-diyl, 4-methylpyrrolidin-1,2-diyl, 4-fluoropyrrolidin-1,2-diyl, 3-methylenepyrrolidin-1,2-diyl, or 5-methylpyrrolidin-1,2-diyl];

- an unsubstituted 5- or 6-membered saturated monocyclic heterocycloalkan-diyl comprising **X³** and one ring O atom (notably oxazolidin-diyl or oxazinan-diyl, especially oxazolidin-diyl); [especially such **Ring A** represents oxazolidin-2,3-diyl, oxazolidin-3,4-diyl, or 1,3-oxazinan-2,3-diyl; in particular such **Ring A** represents oxazolidin-2,3-diyl];

- a 5-membered mono-unsaturated monocyclic heterocycloalkan-diyl comprising **X³** and zero additional ring N atoms (notably dihydro-1*H*-pyrrol-diyl); wherein the double bond of said mono-unsaturated heterocycloalkan-diyl does not contain **X³** or the carbon atom attached to the group –CO-N(**R¹**)CH(**R²**)(**R³**); [in particular such **Ring A** represents 2,3-dihydro-1*H*-pyrrol-1,2-diyl];

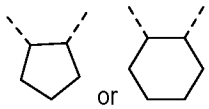
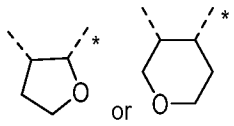
- a 5-membered mono-unsaturated monocyclic heterocycloalkan-diyl comprising **X³** and one additional ring N atom (especially dihydro-1*H*-pyrazol-diyl); wherein the double bond of said mono-unsaturated heterocycloalkan-diyl does not contain **X³** or the carbon atom attached to the group –CO-N(**R¹**)CH(**R²**)(**R³**); wherein said heterocycloalkan-diyl is unsubstituted or mono-substituted with (C_{1-3})alkyl (especially methyl); [in particular such **Ring A** represents 4,5-dihydro-1*H*-pyrazol-1,5-diyl or 3-methyl-4,5-dihydro-1*H*-pyrazol-1,5-diyl]; or

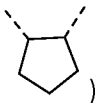
- a 6- to 7-membered saturated spiro, fused, or bridged bicyclic heterocycloalkan-diyl comprising **X³;** wherein said bicyclic heterocycloalkan-diyl is unsubstituted, or di-substituted (in particular is unsubstituted); wherein the substituents independently are (C_{1-3})alkyl (especially methyl); (notably such **Ring A** represents azabicyclo[2.2.1]heptan-diyl, azabicyclo[3.1.0]hexan-diyl, or azaspiro[2.4]heptan-diyl, or, in addition, azabicyclo[3.2.0]heptan-diyl; especially such **Ring A** represents 2-azabicyclo[2.2.1]heptan-1,2-diyl, 2-azabicyclo[3.1.0]hexan-2,3-diyl, 3-azabicyclo[3.1.0]hexan-2,3-diyl, or 5-azaspiro[2.4]heptan-4,5-diyl, or, in addition, 3-azabicyclo[3.2.0]heptan-2,3-diyl, or 6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2,3-diyl); [in particular

such **Ring A** represents 2-azabicyclo[2.2.1]heptan-1,2-diyl, 2-azabicyclo[3.1.0]hexan-2,3-diyl, or 3-azabicyclo[3.1.0]hexan-2,3-diyl, or, in addition, 3-azabicyclo[3.2.0]heptan-2,3-diyl].

8) Another embodiment relates to compounds according to any one of embodiments 1) to 7), wherein $\mathbf{X^3}$ represents CH.

9) Another embodiment relates to compounds according to embodiment 8), wherein **Ring A** is:

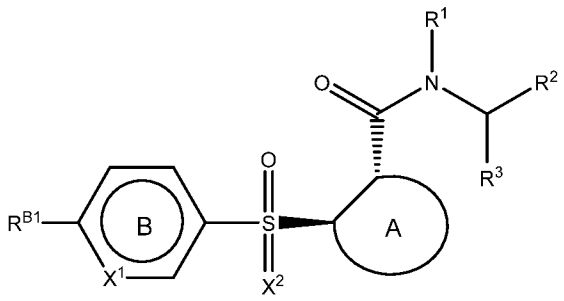
-  ; or
-  ;

(in particular **Ring A** is );

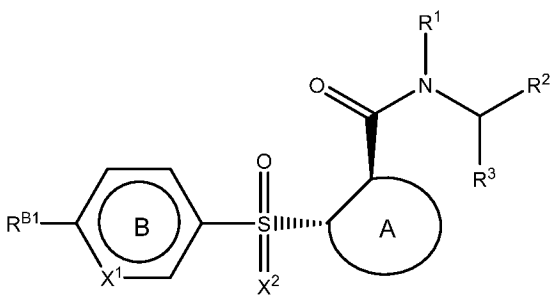
wherein the asterisks indicate the point of attachment of the substituent -C(=O)N$\mathbf{R^1}$-CH_2($\mathbf{R^2}$)($\mathbf{R^3}$).

10) Another embodiment relates to compounds according to embodiment 8) or 9), wherein the substituents -S(=O)(=$\mathbf{X^2}$)-(**Ring B**) and -C(=O)N$\mathbf{R^1}$-CH_2($\mathbf{R^2}$)($\mathbf{R^3}$) of **Ring A** are in relative trans configuration.

When $\mathbf{X^3}$ represents CH, the compounds of Formula (I) contain at least two stereogenic centers which are situated at the two carbon atoms of **Ring A** that link **Ring A** to -S(=O)(=$\mathbf{X^2}$)-(**Ring B**) and to -C(=O)N$\mathbf{R^1}$-CH_2($\mathbf{R^2}$)($\mathbf{R^3}$). Thus, according to this embodiment, a compound of Formula (I) represents either a compound of Formula (II), or a compound of Formula (III), or any mixture thereof (especially enantiomerically-enriched compound of Formula (II)):



Formula (II)



Formula (III).

In such a case, in the present application, the relative configuration of stereoisomers is thus denoted as follows: for example the compound (1R*,2S*)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide having the relative configuration (1R*,2S*) refers to the compounds (1R,2S)-2-

(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide, or (1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide, or any mixture of these stereoisomers including the racemate (denominated rac-(1R*,2S*)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide).

11) Another embodiment relates to compounds according to any one of embodiments 1) to 7), wherein **X^3** represents N.

12) Another embodiment relates to compounds according to embodiment 11), wherein **Ring A** represents:

- pyrrolidin-diyl; wherein said pyrrolidin-diyl is unsubstituted, or mono-substituted with (C_{1-3})alkyl (especially methyl), halogen (especially fluoro), (C_{1-3})alkoxy (especially methoxy or ethoxy), hydroxy, or (C_{1-3})alkylidene (especially H_2C=); or di-substituted with (C_{1-3})alkyl (especially methyl) or halogen (especially fluoro); [especially such **Ring A** represents pyrrolidin-1,2-diyl, 4-methylpyrrolidin-1,2-diyl, 4-fluoropyrrolidin-1,2-diyl, 3-methylenepyrrolidin-1,2-diyl, 5-methylpyrrolidin-1,2-diyl, 4,4-dimethylpyrrolidin-1,2-diyl, 3-fluoropyrrolidin-1,2-diyl, 4-hydroxypyrrolidin-1,2-diyl, 4-methoxypyrrolidin-1,2-diyl, or 4-ethoxypyrrolidin-1,2-diyl; in particular such **Ring A** represents pyrrolidin-1,2-diyl, 4-methylpyrrolidin-1,2-diyl, 4-fluoropyrrolidin-1,2-diyl, 3-methylenepyrrolidin-1,2-diyl, or 5-methylpyrrolidin-1,2-diyl];
- oxazolidin-diyl; [in particular such **Ring A** represents oxazolidin-2,3-diyl];
- dihydro-1*H*-pyrrol-diyl; wherein the double bond of said dihydro-1*H*-pyrrol-diyl does not contain **X^3** or the carbon atom attached to the group –CO-N(**R^1**)CH(**R^2**)(**R^3**); [in particular such **Ring A** represents 2,3-dihydro-1*H*-pyrrol-1,2-diyl]; or
- a 6- to 7-membered saturated spiro, fused, or bridged bicyclic heterocycloalkan-diyl comprising **X^3;** wherein said bicyclic heterocycloalkan-diyl is unsubstituted, or di-substituted (in particular is unsubstituted); wherein the substituents independently are (C_{1-3})alkyl (especially methyl); (notably such **Ring A** represents azabicyclo[2.2.1]heptan-diyl, azabicyclo[3.1.0]hexan-diyl, or azaspiro[2.4]heptan-diyl, or, in addition, azabicyclo[3.2.0]heptan-diyl; especially such **Ring A** represents 2-azabicyclo[2.2.1]heptan-1,2-diyl, 2-azabicyclo[3.1.0]hexan-2,3-diyl, 3-azabicyclo[3.1.0]hexan-2,3-diyl, or 5-azaspiro[2.4]heptan-4,5-diyl, or, in addition, 3-azabicyclo[3.2.0]heptan-2,3-diyl, or 6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2,3-diyl); [in particular such **Ring A** represents 2-azabicyclo[2.2.1]heptan-1,2-diyl, 2-azabicyclo[3.1.0]hexan-2,3-diyl, or 3-azabicyclo[3.1.0]hexan-2,3-diyl, or, in addition, 3-azabicyclo[3.2.0]heptan-2,3-diyl].

13) Another embodiment relates to compounds according to embodiment 11), wherein **Ring A** represents pyrrolidin-1,2-diyl, 4-methylpyrrolidin-1,2-diyl, 4-fluoropyrrolidin-1,2-diyl, 3-methylenepyrrolidin-1,2-diyl, 2,3-

dihydro-1*H*-pyrrol-1,2-diyl, 2-azabicyclo[2.2.1]heptan-1,2-diyl, 2-azabicyclo[3.1.0]hexan-2,3-diyl, or 3-azabicyclo[3.1.0]hexan-2,3-diyl, or, in addition, 3-azabicyclo[3.2.0]heptan-2,3-diyl.

14) Another embodiment relates to compounds according to any one of embodiments 1) to 13), wherein

R^{1} represents:

- 3-cyano-3,3-dimethylpropyl or 4-cyanobutyl (notably 3-cyano-3,3-dimethylpropyl);
- a saturated monocyclic (C_{4-6})cycloalkyl; wherein said (C_{4-6})cycloalkyl is mono- or di-substituted; wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl (especially methyl or isopropyl), halogen (especially fluoro), (C_{1-3})fluoroalkyl (especially difluoromethyl or trifluoromethyl), (C_{1-3})alkoxy (especially methoxy), carbamoyl, hydroxy, and cyano;
- a mono-unsaturated monocyclic (C_{5-6})cycloalkyl (especially cyclohexenyl); wherein the double bond of said mono-unsaturated (C_{5-6})cycloalkyl does not contain the carbon atom attached to the group -N(CO)CH(**R**^{2})(**R**^{3}); [in particular such **R**^{1} represents cyclohex-3-en-1-yl];
- a saturated bicyclic (C_{6-8})spirocycloalkyl (notably spiro[2.3]hexanyl, spiro[3.3]heptanyl, spiro[2.4]heptanyl, or spiro[2.5]octanyl); wherein said (C_{6-8})spirocycloalkyl is unsubstituted or di-substituted with fluoro; [in particular such **R**^{1} represents 1,1-difluorospiro[2.3]hexan-5-yl, 1,1-difluorospiro[2.5]octan-6-yl, spiro[3.3]heptan-2-yl, 6,6-difluorospiro[3.3]heptan-2-yl, 1,1-difluorospiro[2.4]heptan-5-yl, or spiro[2.5]octan-6-yl];
- a saturated fused or bridged bicyclic (C_{6-8})cycloalkyl (notably bicyclo[2.1.1]hexanyl, bicyclo[4.1.0]heptanyl, or bicyclo[2.2.2]octanyl); wherein said (C_{6-8})cycloalkyl is unsubstituted or di-substituted with fluoro; [in particular such **R**^{1} represents bicyclo[4.1.0]heptan-3-yl, 7,7-difluorobicyclo[4.1.0]heptan-3-yl]; or
- a 6-membered saturated monocyclic heterocycloalkyl comprising one ring heteroatomic group selected from O, S, and SO_2 (notably said heterocycloalkyl is tetrahydro-2*H*-pyran, tetrahydro-2*H*-thiopyran, or tetrahydro-2*H*-thiopyran-1,1-dioxide); wherein said heterocycloalkyl is unsubstituted, or mono- or di-substituted; wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl (especially methyl), halogen (especially fluoro), and (C_{1-3})fluoroalkyl (especially trifluoromethyl); [in particular such **R**^{1} represents 1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl, tetrahydro-2*H*-pyran-4-yl, 3-fluorotetrahydro-2*H*-pyran-4-yl, 2-methyltetrahydro-2*H*-pyran-4-yl, 2-(trifluoromethyl)tetrahydro-2*H*-pyran-4-yl, 2,2-dimethyltetrahydro-2*H*-pyran-4-yl, or tetrahydro-2*H*-pyran-3-yl, or, in addition, 3-methyltetrahydro-2*H*-pyran-4-yl, 6-methyltetrahydro-2*H*-pyran-3-yl, 6,6-dimethyltetrahydro-2*H*-pyran-3-yl, 2,6-dimethyltetrahydro-2*H*-pyran-4-yl, or 1,1-dioxidotetrahydro-2*H*-thiopyran-3-yl].

15) Another embodiment relates to compounds according to any one of embodiments 1) to 13), wherein

R^{1} represents:

- 3-cyano-3,3-dimethylpropyl or 4-cyanobutyl (notably 3-cyano-3,3-dimethylpropyl);
- cyclobutyl; wherein said cyclobutyl is mono- or di-substituted; wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl (especially methyl), halogen (especially fluoro), (C_{1-3})fluoroalkyl (especially trifluoromethyl), hydroxy, and cyano; [in particular such **R¹** represents 3-cyanocyclobutyl, 3-(trifluoromethyl)cyclobutyl, or 3-hydroxy-3-(trifluoromethyl)cyclobutyl];
- cyclopentyl; wherein said (C_{4-6})cycloalkyl is mono- or di-substituted; wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl (especially methyl), halogen (especially fluoro), (C_{1-3})fluoroalkyl (especially difluoromethyl), (C_{1-3})alkoxy (especially methoxy), carbamoyl, hydroxy, and cyano; [especially such **R¹** represents 3-cyanocyclopentyl, 3-cyano-3-methylcyclopentyl, 4-cyano-2-hydroxycyclopentyl, 3-fluorocyclopentyl, 3-methoxycyclopentyl, 3-(difluoromethyl)cyclopentyl, 3-carbamoylcyclopentyl, 3-carbamoyl-3-methylcyclopentyl, 3,3-dimethylcyclopentyl, 3,3-difluorocyclopentyl, or 4-cyano-2-methoxycyclopentyl, or, in addition, 2-methoxycyclopentyl, or 3-hydroxycyclopentyl; in particular such **R¹** represents 3-cyanocyclopentyl, 3-cyano-3-methylcyclopentyl, or 4-cyano-2-hydroxycyclopentyl];
- cyclohexyl; wherein said (C_{4-6})cycloalkyl is mono- or di-substituted; wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl (especially methyl or isopropyl), halogen (especially fluoro), (C_{1-3})alkoxy (especially methoxy), carbamoyl, hydroxy, and cyano; [especially such **R¹** represents 3-cyanocyclohexyl, 4-hydroxycyclohexyl, 4-cyanocyclohexyl, 4,4-dimethylcyclohexyl, 4,4-difluorocyclohexyl, 4-fluorocyclohexyl, 2-hydroxycyclohexyl, 3-hydroxycyclohexyl, 3-methoxycyclohexyl, 4-methylcyclohexyl, 4-isopropylcyclohexyl, 4-methoxycyclohexyl, 3,3-dimethylcyclohexyl, 2,2-difluorocyclohexyl, 3,3-difluorocyclohexyl, or 4-hydroxy-4-methylcyclohexyl; in particular such **R¹** represents 3-cyanocyclohexyl, 4-hydroxycyclohexyl, 4-cyanocyclohexyl, 4,4-dimethylcyclohexyl, 4,4-difluorocyclohexyl, or 4-fluorocyclohexyl];
- cyclohexenyl; wherein the double bond of said cyclohexenyl does not contain the carbon atom attached to the group -N(CO)CH(**R²**)(**R³**); [in particular such **R¹** represents cyclohex-3-en-1-yl];
- a saturated bicyclic (C_{6-8})spirocycloalkyl (notably spiro[2.3]hexanyl, spiro[3.3]heptanyl, spiro[2.4]heptanyl, or spiro[2.5]octanyl); wherein said (C_{6-8})spirocycloalkyl is unsubstituted or di-substituted with fluoro; [in particular such **R¹** represents 1,1-difluorospiro[2.3]hexan-5-yl, 1,1-difluorospiro[2.5]octan-6-yl, spiro[3.3]heptan-2-yl, 6,6-difluorospiro[3.3]heptan-2-yl, 1,1-difluorospiro[2.4]heptan-5-yl, or spiro[2.5]octan-6-yl];
- a saturated fused or bridged bicyclic (C_{6-8})cycloalkyl (notably bicyclo[2.1.1]hexanyl, bicyclo[4.1.0]heptanyl, or bicyclo[2.2.2]octanyl); wherein said (C_{6-8})cycloalkyl is unsubstituted or di-substituted with fluoro; [in particular such **R¹** represents bicyclo[4.1.0]heptan-3-yl, 7,7-difluorobicyclo[4.1.0]heptan-3-yl]; or

- a 5- or 6-membered (preferably 6-membered) saturated monocyclic heterocycloalkyl comprising one ring heteroatomic group selected from O, S, and SO_2 (notably said heterocycloalkyl is tetrahydrothiophen-1,1-dioxide, tetrahydro-2*H*-pyran, tetrahydro-2*H*-thiopyran, or tetrahydro-2*H*-thiopyran-1,1-dioxide); wherein said heterocycloalkyl is unsubstituted, or mono- or di-substituted; wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl (especially methyl), halogen (especially fluoro), and (C_{1-3})fluoroalkyl (especially trifluoromethyl); [in particular such **R¹** represents 1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl, 1,1-dioxidotetrahydrothiophen-3-yl, tetrahydro-2*H*-pyran-4-yl, 3-fluorotetrahydro-2*H*-pyran-4-yl, 2-methyltetrahydro-2*H*-pyran-4-yl, 2-(trifluoromethyl)tetrahydro-2*H*-pyran-4-yl, 2,2-dimethyltetrahydro-2*H*-pyran-4-yl, or tetrahydro-2*H*-pyran-3-yl, or, in addition, 3-methyltetrahydro-2*H*-pyran-4-yl, 6-methyltetrahydro-2*H*-pyran-3-yl, 6,6-dimethyltetrahydro-2*H*-pyran-3-yl, 2,6-dimethyltetrahydro-2*H*-pyran-4-yl, or 1,1-dioxidotetrahydro-2*H*-thiophen-3-yl].

16) Another embodiment relates to compounds according to any one of embodiments 1) to 13), wherein

R¹ represents:

- 3-cyano-3-methylbutyl;
- a saturated monocyclic (C_{5-6})cycloalkyl; wherein said (C_{5-6})cycloalkyl is mono- or di-substituted; wherein the substituents are independently selected from the group consisting of: methyl, fluoro, hydroxy, and cyano; [especially such **R¹** represents 3-cyanocyclopentyl, 3-cyanocyclohexyl, 4-hydroxycyclohexyl, 4-cyanocyclohexyl, 4,4-dimethylcyclohexyl, 4,4-difluorocyclohexyl, 4-cyano-2-hydroxycyclopentyl, or 4-fluorocyclohexyl];
- cyclohex-3-en-1-yl;
- a saturated bicyclic (C_{6-8})spirocycloalkyl (notably spiro[2.3]hexanyl or spiro[2.5]octanyl); wherein said (C_{6-8})spirocycloalkyl is di-substituted with fluoro; [notably such **R¹** represents 1,1-difluorospiro[2.3]hexan-5-yl, 1,1-difluorospiro[2.5]octan-6-yl];
- a saturated fused or bridged bicyclic (C_{6-8})cycloalkyl (notably bicyclo[4.1.0]heptanyl); wherein said (C_{6-8})cycloalkyl is unsubstituted or di-substituted with fluoro; [notably such **R¹** represents bicyclo[4.1.0]heptan-3-yl, 7,7-difluorobicyclo[4.1.0]heptan-3-yl]; or
- tetrahydro-2*H*-thiopyran-1,1-dioxide.

17) Another embodiment relates to compounds according to any one of embodiments 1) to 13), wherein

R¹ represents:

- a saturated monocyclic (C_{5-6})cycloalkyl; wherein said (C_{5-6})cycloalkyl is mono-substituted with cyano or hydroxy; or di-substituted with methyl or di-substituted with fluoro; [in particular such **R¹** represents 3-

cyanocyclopentyl, 3-cyanocyclohexyl, 4-hydroxycyclohexyl, 4-cyanocyclohexyl, 4,4-dimethylcyclohexyl, or 4,4-difluorocyclohexyl];

- a saturated bicyclic (C_{6-8})spirocycloalkyl (notably spiro[2.3]hexanyl or spiro[2.5]octanyl); wherein said (C_{6-8})spirocycloalkyl is di-substituted with fluoro; [in particular such **R¹** represents 1,1-difluorospiro[2.3]hexan-5-yl, 1,1-difluorospiro[2.5]octan-6-yl]; or
- bicyclo[4.1.0]heptan-3-yl;
- or, in addition, 1,1-dioxidotetrahydro-2*H*-thiopyran-3-yl.

18) Another embodiment relates to compounds according to any one of embodiments 1) to 17), wherein

R³ represents:

- a 9- or 10-membered partially aromatic fused bicyclic ring system comprising a total of zero to three ring heteroatoms independently selected from N, O, and S (notably 2,3-dihydro-1*H*-indenyl, 2,3-dihydrobenzofuranyl, benzo[*d*][1,3]dioxolyl, 6,7-dihydro-5*H*-cyclopentapyridinyl, 2,3-dihydrofuro[3,2]pyridinyl, chromanyl, isochromanyl, or 2,3-dihydrobenzo[*b*][1.4]dioxinyl); wherein said 9- or 10-membered ring system is linked to the rest of the molecule at the aromatic ring moiety; wherein said 9- or 10-membered ring system is unsubstituted, or mono-, or di-substituted, wherein the substituents are independently selected from the group consisting of: halogen (especially fluoro) and oxo; [in particular such **R³** represents 2,3-dihydro-1*H*-inden-5-yl, 2,3-dihydrobenzofuran-6-yl, 5-fluoro-2,3-dihydrobenzofuran-6-yl, benzo[*d*][1,3]dioxol-5-yl, 4-fluoro-2,3-dihydrobenzofuran-6-yl, 7-fluoro-2,3-dihydrobenzofuran-6-yl, 3-methyl-2,3-dihydrobenzofuran-6-yl, 2-methyl-2,3-dihydrobenzofuran-6-yl, 3-oxo-2,3-dihydrobenzofuran-6-yl, benzo[*d*][1,3]dioxol-4-yl, 2,2-difluorobenzo[*d*][1,3]dioxol-5-yl, 6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl, 6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-3-yl2,3-dihydrofuro[3,2-*b*]pyridin-6-yl, 2,3-dihydrofuro[3,2-*c*]pyridin-6-yl, chroman-6-yl, chroman-7-yl, isochroman-6-yl, isochroman-7-yl, or 2,3-dihydrobenzo[*b*][1.4]dioxin-6-yl];
- naphthyl or a 8- to 10-membered heteroaryl comprising a total of one to three ring heteroatoms independently selected from N, O, and S (notably such **R³** represents a 9- or 10-membered heteroaryl; especially benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiophenyl, furopyridinyl, benzoxadiazolyl, thienopyridinyl, 1*H*-indolyl, quinolinyl, or isoquinolinyl); wherein said naphthyl or 8- to 10-membered heteroaryl is independently unsubstituted, or mono- or di-substituted, wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl (especially methyl) and halogen (especially fluoro or chloro): [in particular such **R³** represents benzofuran-6-yl, benzo[*d*]oxazol-5-yl, 6-fluorobenzo[*d*]oxazol-5-yl, benzo[*d*]oxazol-6-yl, benzo[*d*]thiazol-5-yl, 2-chlorobenzo[*d*]thiazol-5-yl, benzo[*b*]thiophen-5-yl, benzo[*b*]thiophen-6-yl, furo[3,2-*c*]pyridin-6-yl, 2-methylbenzo[*d*]thiazol-5-yl, benzo[*b*]thiophen-2-yl, 2-methylbenzo[*b*]thiophen-5-yl, benzofuran-2-yl, benzofuran-5-yl, 2-methylbenzofuran-6-yl, benzo[*d*]thiazol-2-yl, benzo[*d*]oxazol-2-yl, thieno[2,3-*b*]pyridin-2-yl, 1*H*-indol-6-yl,

furo[3,2-*b*]pyridin-6-yl, furo[2,3-*b*]pyridin-6-yl, 6-fluoro-2-methylbenzo[*d*]thiazol-5-yl, benzo[*d*]thiazol-6-yl, benzo[*c*][1,2,5]oxadiazol-5-yl, naphthalen-2-yl, quinolin-7-yl, isoquinolin-3-yl, or isoquinolin-7-yl, or, in addition, 2-bromobenzo[*d*]thiazol-5-yl, 4-fluorobenzo[*d*]thiazol-5-yl, or 2-methoxybenzo[*d*]thiazol-5-yl];

- phenyl; wherein said phenyl is mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl (especially methyl, ethyl, or isopropyl), halogen (especially fluoro, chloro, or bromo), (C_{1-3})alkoxy (especially methoxy), (C_{1-3})fluoroalkoxy (especially difluoromethoxy), a monocyclic 4- to 6-membered heterocycloalkyl (especially azetidinyl or oxetanyl); wherein heterocycloalkyl is unsubstituted or mono-substituted with halogen (especially fluoro), monocyclic (C_{3-6})cycloalkyl (especially cyclopropyl), (C_{1-3})alkylthio (especially methylthio), (C_{1-3})fluoroalkyl (especially trifluoromethyl), cyano, and $\mathbf{NR^{N1}R^{N2}}$, wherein $\mathbf{R^{N1}}$ and $\mathbf{R^{N2}}$ independently represent hydrogen or (C_{1-4})alkyl (especially $\mathbf{NR^{N1}R^{N2}}$ represents dimethylamino); [in particular such $\mathbf{R^3}$ represents p-tolyl, 4-chlorophenyl, 4-bromophenyl, 4-(methylthio)phenyl, 4-chloro-2-fluorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2,4-difluorophenyl, 3-fluoro-4-methylphenyl, 2-chlorophenyl, 3-methylphenyl, 3-fluorophenyl, 3-methoxyphenyl, 3-(difluoromethoxy)phenyl, 3-(azetidin-1-yl)phenyl, 3-(3-fluorooxetan-3-yl)phenyl, 4-ethylphenyl, 4-isopropylphenyl, 4-(dimethylamino)phenyl, 4-(difluoromethoxy)phenyl, 4-(trifluoromethyl)phenyl, 2-fluoro-3-methylphenyl, 2,4-dimethylphenyl, 4-fluoro-2-methylphenyl, 2-chloro-4-fluorophenyl, 2-fluoro-4-methoxyphenyl, 2,5-difluorophenyl, 2-fluoro-5-methoxyphenyl, 3-fluoro-5-methoxyphenyl, 3,4-dimethylphenyl, 4-fluoro-3-methylphenyl, 3,4-difluorophenyl, 4-chloro-3-fluorophenyl, 3-chloro-4-methylphenyl, 3-cyano-4-methylphenyl, 4-fluoro-4-methoxyphenyl, 2,3-difluoro-4-methylphenyl, 4-chloro-2,3-difluorophenyl, 4-chloro-2,6-difluorophenyl, or 2,4-difluoro-5-methylphenyl]; or
- a 5- or 6-membered heteroaryl comprising one to three ring heteroatoms independently selected from N, O, and S (notably pyridinyl, thiophenyl, oxazolyl, thiazolyl, or isoxazolyl); wherein said 5- or 6-membered heteroaryl is independently mono- or di-substituted, wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl (especially methyl, ethyl, or isopropyl), halogen (especially fluoro, chloro, or bromo), (C_{1-3})alkoxy (especially methoxy), (C_{1-3})fluoroalkoxy (especially difluoromethoxy), monocyclic (C_{3-6})cycloalkyl (especially cyclopropyl), (C_{1-3})alkylthio (especially methylthio), (C_{1-3})fluoroalkyl (especially trifluoromethyl), cyano, $\mathbf{NR^{N1}R^{N2}}$, wherein $\mathbf{R^{N1}}$ and $\mathbf{R^{N2}}$ independently represent hydrogen or (C_{1-4})alkyl (especially $\mathbf{NR^{N1}R^{N2}}$ represents dimethylamino), and 4- to 6-membered monocyclic heterocycloalkyl (especially azetidinyl or oxetanyl); wherein said heterocycloalkyl is unsubstituted or mono-substituted with halogen (especially fluoro); [in particular such $\mathbf{R^3}$ represents 5-chloropyridin-2-yl, 2-methylthiophen-3-yl, 5-methylthiophen-2-yl, 5-chlorothiophen-2-yl, 3-methylthiophen-2-yl, 5-isopropyloxazol-2-yl, 5-chlorothiazol-2-yl, or 5-bromoothiazol-2-yl].

19) Another embodiment relates to compounds according to any one of embodiments 1) to 17), wherein

$\mathbf{R^3}$ represents:

- a 9- or 10-membered partially aromatic fused bicyclic ring system comprising a total of zero to three ring heteroatoms independently selected from N, O, and S (notably 2,3-dihydro-1*H*-inden-5-yl, 2,3-dihydrobenzofuran-6-yl, benzo[*d*][1,3]dioxol-5-yl, benzo[*d*][1,3]dioxol-4-yl, 6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl, 6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-3-yl, 2,3-dihydrofuro[3,2-*b*]pyridin-6-yl, 2,3-dihydrofuro[3,2-*c*]pyridin-6-yl, chroman-6-yl, chroman-7-yl, isochroman-6-yl, isochroman-7-yl, or 2,3-dihydrobenzo[*b*][1.4]dioxin-6-yl); wherein said 9- or 10-membered ring system is linked to the rest of the molecule at the aromatic ring moiety; wherein said 9- or 10-membered ring system is unsubstituted, or mono-, or di-substituted, wherein the substituents are independently selected from the group consisting of: halogen (especially fluoro) and oxo; [in particular such **R³** represents 2,3-dihydro-1*H*-inden-5-yl, 2,3-dihydrobenzofuran-6-yl, 5-fluoro-2,3-dihydrobenzofuran-6-yl, benzo[*d*][1,3]dioxol-5-yl, 4-fluoro-2,3-dihydrobenzofuran-6-yl, 7-fluoro-2,3-dihydrobenzofuran-6-yl, 3-methyl-2,3-dihydrobenzofuran-6-yl, 2-methyl-2,3-dihydrobenzofuran-6-yl, 3-oxo-2,3-dihydrobenzofuran-6-yl, benzo[*d*][1,3]dioxol-4-yl, 2,2-difluorobenzo[*d*][1,3]dioxol-5-yl, 6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl, 6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-3-yl, 2,3-dihydrofuro[3,2-*b*]pyridin-6-yl, 2,3-dihydrofuro[3,2-*c*]pyridin-6-yl, chroman-6-yl, chroman-7-yl, isochroman-6-yl, isochroman-7-yl, or 2,3-dihydrobenzo[*b*][1.4]dioxin-6-yl];

- a 9- or 10-membered heteroaryl comprising a total of one to three ring heteroatoms independently selected from N, O, and S (notably benzofuran-2-yl, benzofuran-5-yl, benzofuran-6-yl, benzo[*d*]oxazol-5-yl, benzo[*d*]oxazol-6-yl, benzo[*d*]oxazol-2-yl, benzo[*d*]thiazol-5-yl, benzo[*d*]thiazol-6-yl, benzo[d]thiazol-2-yl, benzo[*b*]thiophen-2-yl, benzo[*b*]thiophen-5-yl, benzo[*b*]thiophen-6-yl, furo[3,2-*c*]pyridin-6-yl, furo[3,2-*b*]pyridin-6-yl, benzo[*c*][1,2,5]oxadiazol-5-yl, thieno[2,3-*b*]pyridin-2-yl, 1*H*-indol-6-yl, quinolin-7-yl, isoquinolin-3-yl, or isoquinolin-7-yl); wherein said 9- or 10-membered heteroaryl is unsubstituted, or mono- or di-substituted, wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl (especially methyl) and halogen (especially fluoro or chloro): [in particular such **R³** represents benzofuran-6-yl, benzo[*d*]oxazol-5-yl, 6-fluorobenzo[*d*]oxazol-5-yl, benzo[*d*]oxazol-6-yl, benzo[*d*]thiazol-5-yl, 2-chlorobenzo[*d*]thiazol-5-yl, benzo[*b*]thiophen-5-yl, benzo[*b*]thiophen-6-yl, furo[3,2-*c*]pyridin-6-yl, 2-methylbenzo[*d*]thiazol-5-yl, benzo[*b*]thiophen-2-yl, 2-methylbenzo[*b*]thiophen-5-yl, benzofuran-2-yl, benzofuran-5-yl, 2-methylbenzofuran-6-yl, benzo[*d*]thiazol-2-yl, benzo[*d*]oxazol-2-yl, thieno[2,3-*b*]pyridin-2-yl, 1*H*-indol-6-yl, furo[3,2-*b*]pyridin-6-yl, furo[2,3-*b*]pyridin-6-yl, 6-fluoro-2-methylbenzo[*d*]thiazol-5-yl, benzo[*d*]thiazol-6-yl, benzo[*c*][1,2,5]oxadiazol-5-yl, quinolin-7-yl, isoquinolin-3-yl, or isoquinolin-7-yl], or, in addition, 2-bromobenzo[*d*]thiazol-5-yl, 4-fluorobenzo[*d*]thiazol-5-yl, or 2-methoxybenzo[*d*]thiazol-5-yl;

- phenyl; wherein said phenyl is mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl (especially methyl, ethyl, or isopropyl), halogen (especially fluoro, chloro, or bromo), (C_{1-3})alkoxy (especially methoxy), (C_{1-3})fluoroalkoxy (especially difluoromethoxy), (C_{1-3})alkylthio (especially methylthio), (C_{1-3})fluoroalkyl (especially trifluoromethyl), cyano, and **$NR^{N1}R^{N2}$**, wherein **R^{N1}** and **R^{N2}** independently represent hydrogen or (C_{1-4})alkyl (especially **$NR^{N1}R^{N2}$** represents

dimethylamino); [in particular such **R³** represents p-tolyl, 4-chlorophenyl, 4-bromophenyl, 4-(methylthio)phenyl, 4-chloro-2-fluorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2,4-difluorophenyl, 3-fluoro-4-methylphenyl, 2-chlorophenyl, 3-methylphenyl, 3-fluorophenyl, 3-methoxyphenyl, 3-(difluoromethoxy)phenyl, 4-ethylphenyl, 4-isopropylphenyl, 4-(dimethylamino)phenyl, 4-(difluoromethoxy)phenyl, 4-(trifluoromethyl)phenyl, 2-fluoro-3-methylphenyl, 2,4-dimethylphenyl, 4-fluoro-2-methylphenyl, 2-chloro-4-fluorophenyl, 2-fluoro-4-methoxyphenyl, 2,5-difluorophenyl, 2-fluoro-5-methoxyphenyl, 3-fluoro-5-methoxyphenyl, 3,4-dimethylphenyl, 4-fluoro-3-methylphenyl, 3,4-difluorophenyl, 4-chloro-3-fluorophenyl, 3-chloro-4-methylphenyl, 3-cyano-4-methylphenyl, 4-fluoro-4-methoxyphenyl, 2,3-difluoro-4-methylphenyl, 4-chloro-2,3-difluorophenyl, 4-chloro-2,6-difluorophenyl, or 2,4-difluoro-5-methylphenyl]; or

- a 5-membered heteroaryl comprising one to three ring heteroatoms independently selected from N, O, and S (notably thiophen-3-yl, thiophen-2-yl, oxazol-2-yl, thiazol-2-yl, thiazol-5-yl, isothiazol-4-yl, isoxazol-3-yl, or isoxazol-4-yl); wherein said 5-membered heteroaryl is independently mono- or di-substituted, wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl (especially methyl, ethyl, or isopropyl) and halogen (especially chloro, or bromo); [in particular such **R³** represents 2-methylthiophen-3-yl, 5-methylthiophen-2-yl, 5-chlorothiophen-2-yl, 3-methylthiophen-2-yl, 5-isopropyloxazol-2-yl, 5-chlorothiazol-2-yl, 5-bromoothiazol-2-yl, 5-isopropylthiazol-2-yl, 2-isopropylthiazol-5-yl, 5-methylisothiazol-4-yl, 4-ethyl-5-methylisoxazol-3-yl, or 5-methylisoxazol-4-yl]; or
- pyridinyl (especially pyridin-2-yl); wherein said pyridinyl is mono-substituted with halogen (especially chloro); [in particular such **R³** represents 5-chloropyridin-2-yl].

20) Another embodiment relates to compounds according to any one of embodiments 1) to 17), wherein

R³ represents:

- a 9- or 10-membered partially aromatic fused bicyclic ring system comprising a total of zero to three ring heteroatoms independently selected from N, O, and S (notably 2,3-dihydro-1*H*-inden-5-yl, 2,3-dihydrobenzofuran-6-yl, or benzo[*d*][1,3]dioxol-5-yl); wherein said 9- or 10-membered ring system is linked to the rest of the molecule at the aromatic ring moiety; wherein said 9- or 10-membered ring system is unsubstituted, or mono-substituted with halogen (especially fluoro); [in particular such **R³** represents 2,3-dihydro-1*H*-inden-5-yl, 2,3-dihydrobenzofuran-6-yl, 5-fluoro-2,3-dihydrobenzofuran-6-yl, benzo[*d*][1,3]dioxol-5-yl, or 4-fluoro-2,3-dihydrobenzofuran-6-yl;
- a 9- or 10-membered heteroaryl comprising a total of one to three ring heteroatoms independently selected from N, O, and S (notably benzofuran-6-yl, benzo[*d*]oxazol-5-yl, benzo[*d*]oxazol-6-yl, benzo[*d*]thiazol-5-yl, benzo[*b*]thiophen-5-yl, benzo[*b*]thiophen-6-yl, or furo[3,2-*c*]pyridin-6-yl); wherein said 9- or 10-membered heteroaryl is unsubstituted, or mono- or di-substituted, wherein the substituents are independently selected

from the group consisting of: (C_{1-3})alkyl (especially methyl) and halogen (especially chloro): [in particular such **R³** represents benzofuran-6-yl, benzo[*d*]oxazol-5-yl, 6-fluorobenzo[*d*]oxazol-5-yl, benzo[*d*]oxazol-6-yl, benzo[*d*]thiazol-5-yl, 2-chlorobenzo[*d*]thiazol-5-yl, benzo[*b*]thiophen-5-yl, benzo[*b*]thiophen-6-yl, furo[3,2-*c*]pyridin-6-yl, or 2-methylbenzo[*d*]thiazol-5-yl, or, in addition, 2-bromobenzo[*d*]thiazol-5-yl]; or

- phenyl; wherein said phenyl is mono- or di-substituted, wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl (especially methyl), halogen (especially fluoro, chloro, or bromo), (C_{1-3})alkoxy (especially methoxy), and (C_{1-3})alkylthio (especially methylthio); [in particular such **R³** represents p-tolyl, 4-chlorophenyl, 4-bromophenyl, 4-(methylthio)phenyl, 4-chloro-2-fluorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2,4-difluorophenyl, or 3-fluoro-4-methylphenyl, or, in addition, 3-fluoro-4-methoxyphenyl].

21) Another embodiment relates to compounds according to any one of embodiments 1) to 17), wherein

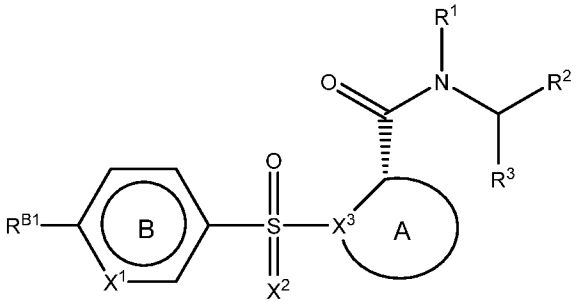
R³ represents:

- a 9- or 10-membered partially aromatic fused bicyclic ring system selected from 2,3-dihydro-1*H*-inden-5-yl, 2,3-dihydrobenzofuran-6-yl, and benzo[*d*][1,3]dioxol-5-yl; wherein said 9- or 10-membered ring system is linked to the rest of the molecule at the aromatic ring moiety; wherein said 9- or 10-membered ring system is unsubstituted, or mono-substituted with halogen (especially fluoro); [in particular such **R³** represents 2,3-dihydro-1*H*-inden-5-yl, 2,3-dihydrobenzofuran-6-yl, 5-fluoro-2,3-dihydrobenzofuran-6-yl, or benzo[*d*][1,3]dioxol-5-yl];

- a 9- or 10-membered heteroaryl selected from benzofuran-6-yl, benzo[*d*]oxazol-5-yl, benzo[*d*]oxazol-6-yl, and benzo[*d*]thiazol-5-yl; wherein said 9- or 10-membered heteroaryl is unsubstituted, or mono-substituted with halogen (fluoro or chloro): [in particular such **R³** represents benzofuran-6-yl, benzo[*d*]oxazol-5-yl, 6-fluorobenzo[*d*]oxazol-5-yl, benzo[*d*]oxazol-6-yl, benzo[*d*]thiazol-5-yl, or 2-chlorobenzo[*d*]thiazol-5-yl]; or

- phenyl; wherein said phenyl is mono- or di-substituted, wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl (especially methyl), halogen (especially fluoro, chloro, or bromo), (C_{1-3})alkoxy (especially methoxy), and (C_{1-3})alkylthio (especially methylthio); (wherein especially the substituents are independently selected from the group consisting of: (C_{1-3})alkyl (especially methyl), halogen (especially fluoro, chloro, or bromo), and (C_{1-3})alkylthio (especially methylthio)); [in particular such **R³** represents p-tolyl, 4-chlorophenyl, 4-bromophenyl, 4-(methylthio)phenyl, or 4-chloro-2-fluorophenyl, or, in addition, 3-fluoro-4-methoxyphenyl].

22) Another aspect of the invention relates to compounds of the Formula (I) according to any one of embodiments 1) to 21) which are also compounds of the Formula (IV) (i.e., the absolute configuration of the ring carbon atom to which the group -C(=O)N**R¹**-CH_2(**R²**)(**R³**) is attached, is as depicted in Formula (IV) below):



Formula (IV).

23) Another embodiment relates to compounds according to embodiment 1) which are selected from the following compounds:

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzo[b]thiophen-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzo[b]thiophen-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-6-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-6-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(1,1-dioxo-hexahydro-1λ^6-thiopyran-4-yl)-amide;

(1R*,5S*)-(2RS)-N-(benzo[d]oxazol-6-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1S,2S,5R)-N-(benzo[d]oxazol-6-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-(benzo[d]oxazol-6-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(2S,4S)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;

(2S,4S)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(2S,4S)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;
(2S,4S)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzo[b]thiophen-5-ylmethyl-(4-fluoro-cyclohexyl)-amide;
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzo[b]thiophen-5-ylmethyl-(4-hydroxy-cyclohexyl)-amide;
(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-6-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;
(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(2S)-N-(benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-(4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(1R,3S,4S)-2-(Toluene-4-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid benzothiazol-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;
(2S)-N-(benzofuran-6-ylmethyl)-N-(cyclohex-3-en-1-yl)-1-tosylpyrrolidine-2-carboxamide;
(1R,3S,4S)-2-(Toluene-4-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid benzooxazol-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;
(1R,3S,4S)-2-(Toluene-4-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid benzooxazol-6-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;
(1R,3S,4S)-2-(Toluene-4-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid benzofuran-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(1R,3S,4S)-2-(Toluene-4-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(1R,3S,4S)-2-(Toluene-4-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid benzooxazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(1R*,5S*)-(2RS)-N-(benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(1S,2S,5R)-N-(benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(1R,2S,5S)-N-(benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(2S,4S)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(2S,4S)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-6-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;

(1R,3S,4S)-2-(Toluene-4-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid benzooxazol-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(2S)-N-(benzo[b]thiophen-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-tosylpyrrolidine-2-carboxamide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (2,3-dihydro-benzofuran-6-ylmethyl)-(4,4-dimethyl-cyclohexyl)-amide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (2,3-dihydro-benzofuran-6-ylmethyl)-(1,1-dioxo-hexahydro-1λ^6-thiopyran-4-yl)-amide;

(1R*,5S*)-(2RS)-N-(benzofuran-6-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1S,2S,5R)-N-(benzofuran-6-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-(benzofuran-6-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,3S,4S)-2-(Toluene-4-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid benzofuran-6-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(4-hydroxy-cyclohexyl)-amide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-6-ylmethyl-(4-hydroxy-cyclohexyl)-amide;

(2S)-N-(benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-tosylpyrrolidine-2-carboxamide;

(2S)-N-(benzo[d]oxazol-6-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-tosylpyrrolidine-2-carboxamide;

(2S)-N-(benzo[d]oxazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-tosylpyrrolidine-2-carboxamide;

(2S)-N-(bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-1-tosylpyrrolidine-2-carboxamide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (2,3-dihydro-benzofuran-6-ylmethyl)-(4-hydroxy-cyclohexyl)-amide;

(1R*,5S*)-(2RS)-N-(benzo[d]oxazol-5-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1S,2S,5R)-N-(benzo[d]oxazol-5-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-(benzo[d]oxazol-5-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R*,5S*)-(2RS)-N-(benzo[d]oxazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1S,2S,5R)-(benzo[d]oxazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(1R,2S,5S)-(benzo[d]oxazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(1R*,5S*)-(2RS)-N-(benzo[d]thiazol-5-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(1S,2S,5R)-N-(benzo[d]thiazol-5-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(1R,2S,5S)-N-(benzo[d]thiazol-5-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;
(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;
(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (2,3-dihydro-benzofuran-6-ylmethyl)-(4,4-dimethyl-cyclohexyl)-amide;
(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;
(2S)-N-(benzofuran-6-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-tosylpyrrolidine-2-carboxamide;
(2S,4S)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;
(S)-N-(4,4-Difluorocyclohexyl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-1-tosylpyrrolidine-2-carboxamide;
(2S,4S)-N-(benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-4-fluoro-1-tosylpyrrolidine-2-carboxamide;
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(5-fluoro-2,3-dihydro-benzofuran-6-ylmethyl)-amide;
(1R,3S,5R)-2-(Toluene-4-sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;
(2S,4S)-N-(benzo[d]oxazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-4-fluoro-1-tosylpyrrolidine-2-carboxamide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-fluoro-2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(2S)-N-(benzo[d]oxazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-((4-methoxyphenyl)sulfonyl)pyrrolidine-2-carboxamide;

(2S)-N-(benzo[d]oxazol-6-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-((4-methoxyphenyl)sulfonyl)pyrrolidine-2-carboxamide;

(2S)-N-(benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-((4-methoxyphenyl)sulfonyl)pyrrolidine-2-carboxamide;

(2S)-N-(bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-1-((4-methoxyphenyl)sulfonyl)pyrrolidine-2-carboxamide;

(S)-4-Methylene-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(S)-N-(benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((R)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(S)-N-(benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((S)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(2S,4S)-4-Fluoro-1-(4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1R,3R,6R)-bicyclo[4.1.0]hept-3-yl-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(S)-N-(benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(S)-N-(4,4-difluorocyclohexyl)-N-(furo[3,2-c]pyridin-6-ylmethyl)-1-tosylpyrrolidine-2-carboxamide;

(1R,3S,5R)-2-(4-Methoxy-benzenesulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(1R*,5S*)-(2RS)-3-(4-Methoxy-benzenesulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(1S,2S,5R)-3-(4-Methoxy-benzenesulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(1R,2S,5S)-3-(4-Methoxy-benzenesulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(1R,3S,5R)-2-(4-Methoxy-benzenesulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(1R,3S,5R)-N-(benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-2-tosyl-2-azabicyclo[3.1.0]hexane-3-carboxamide;

(1R,3S,5R)-N-(benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-2-((4-methoxyphenyl)sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxamide;

(1R,3S,5R)-N-(bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-2-tosyl-2-azabicyclo[3.1.0]hexane-3-carboxamide;

(1R,3S,5R)-N-(bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-2-((4-methoxyphenyl)sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxamide;

(1R,3S,5R)-2-(4-Methoxy-benzenesulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid benzooxazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(1S,2S,5R)-N-(benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,3S,5R)-2-(Toluene-4-sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(1R,2S,5S)-3-(Toluene-4-sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(1S,2S,5R)-3-(Toluene-4-sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(1R,2S,5S)-N-(bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1S,2S,5R)-N-(bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(S)-N-(benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((S)-4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide ;

(S)-N-(benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((R)-4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(1R*,5S*)-(2RS)-3-(4-Methoxy-benzenesulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(1S,2S,5R)-3-(4-Methoxy-benzenesulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(1R,2S,5S)-3-(4-Methoxy-benzenesulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(1R*,5S*)-(2RS)-N-(benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-3-((4-methoxyphenyl)sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1S,2S,5R)-N-(benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-3-((4-methoxyphenyl)sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-(benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-3-((4-methoxyphenyl)sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R*,5S*)-(2RS)-N-(bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-3-((4-methoxyphenyl)sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1S,2S,5R)-N-(bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-3-((4-methoxyphenyl)sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-(bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-3-((4-methoxyphenyl)sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(2S)-N-(benzofuran-6-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-(N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(1R,3S,5R)-2-(Toluene-4-sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-fluoro-2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(1R,3S,5R)-2-(Toluene-4-sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (4,4-difluoro-cyclohexyl)-(5-fluoro-2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(S)-1-(3-Fluoro-4-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(S)-1-(3-Fluoro-4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(S)-1-(4-Chloro-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(S)-1-(4-Cyclopropyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(2S,5R)-5-Methyl-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(2S)-N-(4,4-difluorocyclohexyl)-N-(1-(2,3-dihydrobenzofuran-6-yl)ethyl)-1-tosylpyrrolidine-2-carboxamide;

(S)-1-(Toluene-4-sulfonyl)-2,3-dihydro-1H-pyrrole-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(1R,3S,4S)-N-(bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-2-((6-methylpyridin-3-yl)sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxamide;

(1R,3S,4S)-2-(6-Methyl-pyridine-3-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzo[1,3]dioxol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(2S)-N-(benzo[d][1,3]dioxol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-tosylpyrrolidine-2-carboxamide;

(2S)-N-(benzofuran-6-ylmethyl)-1-(N-cyclopropyl-4-methylphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide;

(2S)-N-(benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-(3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(2S)-N-(4,4-difluorocyclohexyl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-1-(3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(2S)-N-(benzo[d][1,3]dioxol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(2S)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-(methylthio)benzyl)pyrrolidine-2-carboxamide;
(2S)-N-(benzofuran-6-ylmethyl)-1-(N-cyclopropyl-3-fluoro-4-methylphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide;
(2S)-1-(N-cyclopropyl-3-fluoro-4-methylphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)pyrrolidine-2-carboxamide;
(2S)-N-(benzo[d]thiazol-5-ylmethyl)-1-(N-cyclopropyl-3-fluoro-4-methylphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide;
(1R*,2S*)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(2S)-N-(benzofuran-6-ylmethyl)-1-(N-cyclopropyl-4-methoxyphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide;
(2S)-N-(4-chlorobenzyl)-1-(N-cyclopropyl-4-methylphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(1R*,2S*)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzo[1,3]dioxol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(1R*,2S*)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzooxazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(2S)-N-(4-chlorobenzyl)-N-(4,4-dimethylcyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(2S)-N-(4-chlorobenzyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-((4-ethynyl-2-hydroxycyclopentyl)pyrrolidine-2-carboxamide;
(2S)-N-(4-chlorobenzyl)-N-(1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide;
(2S)-N-(1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide;

(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzooxazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(2S)-N-((3S,5R)-1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide;

(2S)-N-(4-chlorobenzyl)-N-((3S,5R)-1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(2S)-N-(4-chlorobenzyl)-N-(1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(2S)-N-(4-chlorobenzyl)-N-((3S,6R)-1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(1S,2R)-N-(bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-2-tosylcyclopentane-1-carboxamide;

(1S,2R)-N-(benzo[d][1,3]dioxol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-2-tosylcyclopentane-1-carboxamide;

(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzo[1,3]dioxol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide;

(2S)-N-(4-chloro-2-fluorobenzyl)-N-(1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(2S)-N-(1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide;

(2S)-N-(4-chloro-2-fluorobenzyl)-N-(1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(2S)-N-(4-Chlorobenzyl)-N-((1R*,3S*)-3-cyanocyclopentyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(2S)-N-(4-Chloro-2-fluorobenzyl)-N-((3S,5r)-1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(2S)-N-(4-Chloro-2-fluorobenzyl)-N-((3S,6r)-1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(2S)-N-((3S,6r)-1,1-Difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide;

(1S,2R)-N-(4-chlorobenzyl)-N-((1S*,3R*)-3-cyanocyclopentyl)-2-tosylcyclopentane-1-carboxamide;

(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide;

(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (1,1-difluoro-spiro[2.5]oct-6-yl)-(4-methoxy-benzyl)-amide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(4-cyano-cyclohexyl)-amide;
(2S)-N-(4-Chlorobenzyl)-N-((1R*,3R*)-3-cyanocyclopentyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(2S,4S)-N-(4-chlorobenzyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-4-methylpyrrolidine-2-carboxamide;
(2S,4S)-N-(4-chlorobenzyl)-N-(1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-4-methylpyrrolidine-2-carboxamide;
(2S,4S)-N-(4-chlorobenzyl)-N-(4,4-difluorocyclohexyl)-1-(N,4-dimethylphenylsulfonimidoyl)-4-methylpyrrolidine-2-carboxamide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzooxazol-5-ylmethyl-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (1,1-difluoro-spiro[2.5]oct-6-yl)-(4-methyl-benzyl)-amide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (1,1-difluoro-spiro[2.5]oct-6-yl)-(4-methylsulfanyl-benzyl)-amide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-2-fluoro-benzyl)-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzo[1,3]dioxol-5-ylmethyl-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(2-fluoro-4-methyl-benzyl)-amide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-2-fluoro-benzyl)-(4-cyano-cyclohexyl)-amide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(2,4-difluoro-benzyl)-amide;
(1S,2R)-N-(4-Cyanocyclohexyl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-2-tosylcyclopentane-1-carboxamide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(4-methylsulfanyl-benzyl)-amide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(4-methyl-benzyl)-amide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-bromo-benzyl)-(4-cyano-cyclohexyl)-amide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(4-fluoro-benzyl)-amide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(3-cyano-3,3-dimethyl-propyl)-amide;

(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (7,7-difluoro-bicyclo[4.1.0]hept-3-yl)-(4-methyl-benzyl)-amide;

(2S,4S)-N-(4-chlorobenzyl)-N-(1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-4-fluoropyrrolidine-2-carboxamide;

(2S,4S)-N-(4-chloro-2-fluorobenzyl)-N-(1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-4-methylpyrrolidine-2-carboxamide;

(S)-N-((1R*,3S*)-3-cyanocyclopentyl)-N-(4-methylbenzyl)-1-tosylpyrrolidine-2-carboxamide;

(S)-N-(4-chlorobenzyl)-N-((1R*,3S*)-3-cyanocyclopentyl)-1-tosylpyrrolidine-2-carboxamide;

(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid ((1S*,3R*)-3-cyano-cyclopentyl)-(4-methyl-benzyl)-amide;

(2S,4S)-N-(4-Chlorobenzyl)-N-((3R,5s)-1,1-difluorospiro[2.3]hexan-5-yl)-1-(R)-(N,4-dimethylphenylsulfonimidoyl)-4-methylpyrrolidine-2-carboxamide;

(2RS)-N-((1R*,3S*)-3-Cyanocyclopentyl)-N-(4-methylbenzyl)-3-tosyloxazolidine-2-carboxamide;

(2RS)-N-((1R*,3S*)-3-Cyanocyclopentyl)-N-(4-chlorobenzyl)-3-tosyloxazolidine-2-carboxamide;

(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (3-cyano-3,3-dimethyl-propyl)-(4-methyl-benzyl)-amide;

(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (3-cyano-3,3-dimethyl-propyl)-indan-5-ylmethyl-amide;

(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-2-fluoro-benzyl)-(3-cyano-3,3-dimethyl-propyl)-amide;

(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-bromo-benzyl)-(3-cyano-3,3-dimethyl-propyl)-amide;

(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid ((1R*,3R*)-3-cyano-cyclohexyl)-(4-methyl-benzyl)-amide;

(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-((1R,3S)-3-cyano-cyclopentyl)-amide;

(1S,2R)-N-((1R*,3S*)-3-Cyanocyclopentyl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-2-tosylcyclopentane-1-carboxamide;

(1S,2R)-N-(7,7-Difluorobicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-2-tosylcyclopentane-1-carboxamide;

(1S,2R)-N-((1R*,3R*)-3-Cyanocyclohexyl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-2-tosylcyclopentane-1-carboxamide;

(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid ((1R*,3S*)-3-cyano-cyclopentyl)-(3-fluoro-4-methyl-benzyl)-amide;

(2S,4S)-N-(4-chloro-2-fluorobenzyl)-N-(1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-4-fluoropyrrolidine-2-carboxamide;

(2S,4S)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-4-methyl-N-(4-methylbenzyl)pyrrolidine-2-carboxamide;

(1S,2R)-N-((1r,4S)-4-cyanocyclohexyl)-N-(4-(methyl-d3)benzyl)-2-tosylcyclopentane-1-carboxamide;

(1S,2R)-N-(4-Chloro-2-fluorobenzyl)-N-((1R*,3S*)-3-cyanocyclopentyl)-2-tosylcyclopentane-1-carboxamide;

(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzooxazol-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4,4-difluoro-cyclohexyl)-(6-fluoro-benzooxazol-5-ylmethyl)-amide;

(1S,2R)-N-(4-chlorobenzyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-2-((R)-4-methylphenylsulfonimidoyl)cyclopentane-1-carboxamide;

(1S,2R)-N-(4-chlorobenzyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-2-((S)-4-methylphenylsulfonimidoyl)cyclopentane-1-carboxamide;

(2S)-N-(4-chlorobenzyl)-N-((1R)-3-cyano-3-methylcyclopentyl)-1-tosylpyrrolidine-2-carboxamide;

(1S,2R)-N-(4-chlorobenzyl)-N-((1R,3S)-3-cyanocyclopentyl)-2-((R)-4-methylphenylsulfonimidoyl)cyclopentane-1-carboxamide;

(1S,2R)-N-(4-chlorobenzyl)-N-((1R,3S)-3-cyanocyclopentyl)-2-((S)-4-methylphenylsulfonimidoyl)cyclopentane-1-carboxamide;

(1S,2R)-N-(4-chlorobenzyl)-N-((1R)-3-cyano-3-methylcyclopentyl)-2-tosylcyclopentane-1-carboxamide;

(S)-N-((3R,5s)-1,1-difluorospiro[2.3]hexan-5-yl)-N-(4-methylbenzyl)-1-((S)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(S)-N-((3S,5r)-1,1-difluorospiro[2.3]hexan-5-yl)-N-(4-methylbenzyl)-1-((S)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(S)-N-((1S*,3R*)-3-Cyanocyclopentyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide;

(S)-N-((1S*,3S*)-3-Cyanocyclopentyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide;

(S)-N-(4-chlorobenzyl)-N-((1R,3S)-3-cyanocyclopentyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(S)-N-((1R,3S)-3-cyanocyclopentyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide;

(S)-1-(3-Fluoro-4-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(S)-N-(benzo[d]thiazol-5-ylmethyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-1-tosylpyrrolidine-2-carboxamide;

(S)-N-(benzo[d]thiazol-5-ylmethyl)-N-((3R,5s)-1,1-difluorospiro[2.3]hexan-5-yl)-1-tosylpyrrolidine-2-carboxamide;
(S)-N-(benzo[d]thiazol-5-ylmethyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-1-((3-fluoro-4-methylphenyl)sulfonyl)pyrrolidine-2-carboxamide;
(S)-N-(benzo[d]thiazol-5-ylmethyl)-N-((3R,5s)-1,1-difluorospiro[2.3]hexan-5-yl)-1-((3-fluoro-4-methylphenyl)sulfonyl)pyrrolidine-2-carboxamide;
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2-methyl-benzothiazol-5-ylmethyl)-amide;
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (2-chloro-benzothiazol-5-ylmethyl)-(4,4-difluoro-cyclohexyl)-amide;
(S)-1-(3-Fluoro-4-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (2-chloro-benzothiazol-5-ylmethyl)-(4,4-difluoro-cyclohexyl)-amide;
(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (2-chloro-benzothiazol-5-ylmethyl)-(4,4-difluoro-cyclohexyl)-amide;
(S)-N-(benzo[d]thiazol-5-ylmethyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-1-((4-methoxyphenyl)sulfonyl)pyrrolidine-2-carboxamide;
(S)-N-(benzo[d]thiazol-5-ylmethyl)-N-((3R,5s)-1,1-difluorospiro[2.3]hexan-5-yl)-1-((4-methoxyphenyl)sulfonyl)pyrrolidine-2-carboxamide; and

(1R,2S,5S)-N-(benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide.

24) Further compounds according to embodiment 1) are selected from the following compounds:
(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((R)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3R,5s)-1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(S)-1-(3-Fluoro-4-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(1S,3S,6S)-bicyclo[4.1.0]hept-3-yl-amide;
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(1S,3S,6S)-bicyclo[4.1.0]hept-3-yl-amide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(1S,3R,6S)-bicyclo[4.1.0]hept-3-yl-amide;

(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(1S,3S,6S)-bicyclo[4.1.0]hept-3-yl-amide;

(S)-1-(4-Iodo-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide;

(S)-1-(3-Fluoro-4-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide;

(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3R,5s)-1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-4-methoxy-N-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(S)-1-(4-Ethyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide;

(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((1S,3S,6S)-bicyclo[4.1.0]heptan-3-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((1S,3S,6S)-bicyclo[4.1.0]heptan-3-yl)-1-((R)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((1S,3S,6S)-bicyclo[4.1.0]heptan-3-yl)-1-((R)-3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((1S,3S,6S)-bicyclo[4.1.0]heptan-3-yl)-1-((R)-4-methoxy-N-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(1R*,2S*,5S*)-3-(Toluene-4-sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid benzothiazol-5-ylmethyl-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide;

(1R*,2S*,5S*)-3-(Toluene-4-sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid benzothiazol-5-ylmethyl-(1,1-difluoro-spiro[2.3]hex-5-yl)-amide;

(1R*,2S*,5S*)-3-(Toluene-4-sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2-methyl-benzothiazol-5-ylmethyl)-amide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (2-bromo-benzothiazol-5-ylmethyl)-(4,4-difluoro-cyclohexyl)-amide;

(S)-1-(3-Fluoro-4-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (2-bromo-benzothiazol-5-ylmethyl)-(4,4-difluoro-cyclohexyl)-amide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(3-methoxy-cyclohexyl)-amide;

(S)-1-(3-Fluoro-4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(S)-N-((2-Chlorobenzo[d]thiazol-5-yl)methyl)-N-(4,4-difluorocyclohexyl)-1-((R)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(S)-N-((2-Bromobenzo[d]thiazol-5-yl)methyl)-N-(4,4-difluorocyclohexyl)-1-((R)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(S)-N-((2-Chlorobenzo[d]thiazol-5-yl)methyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(S)-N-((2-Chlorobenzo[d]thiazol-5-yl)methyl)-N-(4,4-difluorocyclohexyl)-1-((R)-3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(S)-N-((2-Chlorobenzo[d]thiazol-5-yl)methyl)-N-(4,4-difluorocyclohexyl)-1-((R)-4-methoxy-N-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(6-methyl-1,1-dioxo-hexahydro-1λ^6-thiopyran-3-yl)-amide;
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(1,1-dioxo-hexahydro-1λ^6-thiopyran-3-yl)-amide;
(1S*,2S*,5R*)-3-(Toluene-4-sulfonyl)-3-azabicyclo[3.2.0]heptane-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(1R*,2S*,5S*)-3-(Toluene-4-sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(1R*,2S*,5S*)-N-Benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide; and
(1R,2S,5S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-3-((R)-N,4-dimethylphenylsulfonimidoyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide.

The compounds of Formula (I) according to embodiments 1) to 24) and their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical compositions for enteral (such especially oral e.g. in form of a tablet or a capsule) or parenteral administration (including topical application or inhalation).

The production of the pharmaceutical compositions can be effected in a manner which will be familiar to any person skilled in the art (see for example Remington, The Science and Practice of Pharmacy, 21st Edition (2005), Part 5, “Pharmaceutical Manufacturing” [published by Lippincott Williams & Wilkins]) by bringing the described compounds of Formula (I) or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

The present invention also relates to a method for the prevention / prophylaxis or treatment of a disease or disorder mentioned herein comprising administering to a subject a pharmaceutically active amount of a compound of Formula (I) according to embodiments 1) to 24).

For avoidance of any doubt, if compounds are described as useful for the prevention / prophylaxis or treatment of certain diseases, such compounds are likewise suitable for use in the preparation of a medicament for the prevention / prophylaxis or treatment of said diseases. Likewise, such compounds are also suitable in a method for the prevention / prophylaxis or treatment of such diseases, comprising administering to a subject (mammal, especially human) in need thereof, an effective amount of such compound.

The compounds of Formula (I) according to any one of embodiments 1) to 24) are useful for the prevention / prophylaxis or treatment of diseases or disorders relating to the OX_2R receptor, and notably in disease and disorders in which agonism of OX_2R plays a role. Disease and disorders in which agonism of OX_2R plays a role are particularly disease and disorders associated with difficulties maintaining wakefulness. Subjects presenting disease and disorders associated with difficulties maintaining wakefulness complain of: feelings of excessive sleepiness; episodes of inadvertently falling asleep, including sleep attacks (episodes of falling asleep without prodromal symptoms of drowsiness); a prolonged main sleep episode that is unrefreshing; recurrent naps in the same day; or sleep inertia (prolonged difficulty waking up, with irritability, automatic behavior or confusion).

Thus, the compounds of Formula (I) according to embodiments 1) to 24) are useful for improving wakefulness in a subject (especially in a subject having hypersomnia or narcolepsy, or presenting excessive daytime sleepiness (EDS)).

The term “improving wakefulness in a subject” refers to improving symptoms of, or to the prevention / prophylaxis or treatment of:

- hypersomnia, particularly prevention / prophylaxis or treatment of:
  - narcolepsy; including especially narcolepsy type 1 and narcolepsy type 2;
  - secondary narcolepsy associated with inherited disorders (such as Prader-Willi syndrome, Niemann-Pick C disease, or myotonic dystrophy);
  - secondary narcolepsy associated with tumors, especially symptoms of narcolepsy associated with tumors that involve the hypothalamus area;
  - secondary narcolepsy associated with head trauma, especially symptoms of narcolepsy associated with head trauma affecting the hypothalamic area;
  - idiopathic hypersomnia; or
  - Kleine-Levin syndrome;
- excessive daytime sleepiness (EDS), particularly:
  - improving symptoms of EDS in subjects having a circadian rhythm sleep-wake disorder, particularly improving symptoms of EDS in subjects having: delayed sleep-wake phase disorder, shift work disorder, or jet lag disorder;

- improving symptoms of EDS due to or associated with a medical disorder, wherein said medical disorder is especially an objective sleep disturbance, obesity, diabetes, a neurodegenerative disorder, an auto-immune disorder, a psychiatric disorder, or insufficient sleep syndrome; in particular:
  - Improving symptoms of EDS associated with objective sleep disturbances (notably sleep apnea);
  - improving symptoms of EDS associated with obesity and/or diabetes;
  - improving symptoms of EDS associated with a neurodegenerative disorder, notably associated with: Alzheimer's, Parkinson's, Lewy body dementia, Perry syndrome, multiple system atrophy, or Huntington's disease;
  - improving symptoms reminiscent of narcolepsy in subjects having an auto-immune disorder (especially neuromyelitis optica, multiple sclerosis, Guillain-Barré syndrome, or anti-Ma2 encephalitis);
  - improving symptoms of EDS / treatment of hypersomnia associated with a psychiatric disorder, such as depression; or
  - improving symptoms of EDS / treatment of hypersomnia associated with insufficient sleep syndrome; or
- improving symptoms of EDS / treatment of hypersomnia due to a medication or substance; or

- fatigue (especially including chronic fatigue), particularly:
  - fatigue accompanied by mental fatigue with poor concentration and memory;
  - fatigue associated with infections (viral or bacterial), chronic inflammatory diseases, cancer, or neurodegeneration; or
  - fatigue associated with autoimmune disease primary Sjögren's syndrome.

The term “narcolepsy type 1” describes a chronic sleep disorder characterized by excessive daytime sleepiness (EDS), sleep attacks, hallucinations, sleep paralysis, sleep disruption and cataplexy (loss of muscle tone in full consciousness often triggered by positive emotions).

The term “narcolepsy type 2” describes a chronic sleep disorder characterized by excessive daytime sleepiness (EDS), sleep attacks, hallucinations, sleep paralysis, sleep disruption and without cataplexy (loss of muscle tone in full consciousness often triggered by positive emotions).

Fatigue is characterized by a lack of energy ("an overwhelming sense of tiredness, a feeling of exhaustion").

Further disease and disorders in which agonism of OX_2R plays a role include:

- eating disorders;
- obesity, particularly obesity in narcoleptic subjects;
- attention deficit disorders;

- neuropsychiatric disorders, notably mood disorders, particularly depression (such as major depressive disorder (MDD));
- pain, particularly inflammatory pain, or chronic neuropathic pain;
- inflammation, particularly inflammation following cardiac arrest, intracerebral hemorrhage, or septic shock; and
- cognitive impairments, particularly age-related deficits in learning and memory or cognitive impairments due to sleep loss.

Additionally, agonism of OX_2R plays a role in:

- disorders of consciousness, notably coma, vegetative state and minimally conscious state induced by traumatic brain injury;
- recovery of arousal following unconsciousness associated with cardiac arrest or acute alcohol intoxication, or following anesthetic-induced unconsciousness.

It is to be understood that in the context of using compounds of Formula (I) according to embodiments 1) to 24) for improving wakefulness in a subject (especially in a subject having hypersomnia or narcolepsy, or presenting excessive daytime sleepiness (EDS)), other symptoms or disease characteristics of that subject may be concurrently improved. For example, in the context of using compounds of Formula (I) according to embodiments 1) to 24) for improving symptoms of EDS due to or associated with diabetes, other symptoms or disease characteristics of that subject may be concurrently improved, e.g., in addition to improving wakefulness in a diabetic subject, diabetic parameters may be improved.

In the context of the present invention, the term “subject” refers to a mammal, especially a human; in the context of a certain diagnosis or disease, the term “subject” and “patient” are to be understood as being interchangeable.

The compounds of Formula (I) according to any one of embodiments 1) to 24) are in particular useful as therapeutic agents for the prevention / prophylaxis or treatment of a disease and disorders associated with difficulties maintaining wakefulness. They can be used as single therapeutic agents or in combination with one or more additional therapeutic agents. Such therapeutic agents include modafinil, pitolisant, sodium oxybate, solriamfetol, armodafinil, dextroamphetamine, methylphenidate, clarithromycin, venlafaxine, clomipramine and lithium (see for example Maski K. et al. J Clin Sleep Med. 2021, 17(9), 1881-1893; Bassetti C. et al. Eur J Neurol. 2021, 00, 1-16).

The invention, thus, also relates to pharmaceutical compositions comprising a pharmaceutically acceptable carrier material, and:

- a compound of Formula (I) according to any one of embodiments 1) to 24);
- and one or more additional therapeutic agents.

The invention, thus, further relates to a kit comprising

- a pharmaceutical composition, said composition comprising a pharmaceutically acceptable carrier material, and:
- a compound of Formula (I) according to any one of embodiments 1) to 24);
- and instructions how to use said pharmaceutical composition for improving wakefulness in a subject presenting excessive daytime sleepiness (EDS).

Besides, any preferences and (sub-)embodiments indicated for the compounds of Formula (I) (whether for the compounds themselves, salts thereof, compositions containing the compounds or salts thereof, or uses of the compounds or salts thereof, etc.) apply *mutatis mutandis* to compounds of Formula (II), Formula (III) and Formula (IV).

Compounds of the present invention may be further characterized with regard to their general pharmacokinetic and pharmacological properties using conventional assays well known in the art; for example relating to their bioavailability in different species (such as rat or dog) including metabolic stability potentially affecting (human) bioavailability and/or dosage requirements, or relating to their ability to cross the blood-brain barrier, using for example a human P-glycoprotein 1 (MDR 1) substrate assay, or an in vivo assay to determine drug concentrations in the brain, e.g. in rats after oral dosing; or relating to their functional behavior in different disease related animal models (for example: the general stimulant effect of the compound using Electroencephalography (EEG) and Electromyography (EMG) signal measurements [Yukitake H et al.; TAK-925, an orexin 2 receptor-selective agonist, shows robust wake-promoting effects in mice; Pharmacol Biochem Behav. 2019, 187:172794], the effect of the compound on narcolepsy-cataplexy symptoms [Irukayama-Tomobe Y et al.; Nonpeptide orexin type-2 receptor agonist ameliorates narcolepsy-cataplexy symptoms in mouse models; Proc Natl Acad Sci U S A. 2017, 114(22):5731-5736]); or for their properties with regard to drug safety and/or toxicological properties using conventional assays well known in the art, for example relating to cytochrome P450 enzyme inhibition and time dependent inhibition, pregnane X receptor (PXR) activation, glutathione binding, or phototoxic behavior.

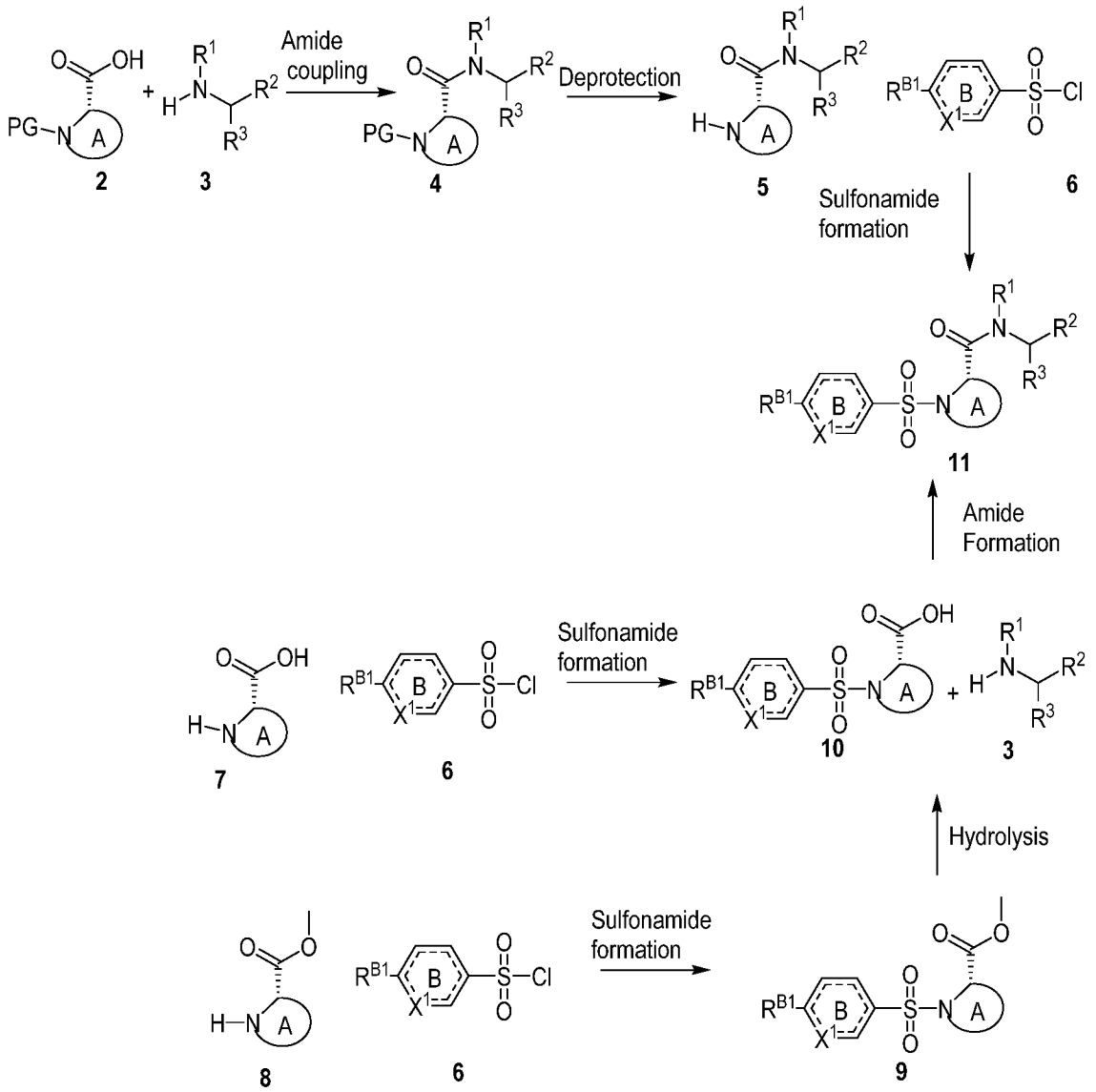
Preparation of compounds of Formula (I)

A further aspect of the invention is a process for the preparation of compounds of Formula (I). Compounds according to Formula (I) of the present invention can be prepared from commercially available or well known starting materials according to the methods described in the experimental part, by analogous methods, or according to the general sequence of reactions outlined below, wherein $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^{B1}}$, $\mathbf{X^1}$, $\mathbf{X^2}$, $\mathbf{X^3}$, **Ring A**, and **Ring B** are as defined for Formula (I). Other abbreviations used herein are explicitly defined, or are as defined in the experimental section. In some instances the generic groups $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^{B1}}$, $\mathbf{X^1}$, $\mathbf{X^2}$ and $\mathbf{X^3}$ might be incompatible with the assembly illustrated in the schemes below and so will require the use of protecting groups (PG). The use of protecting groups is well known in the art (see for example “Protective Groups in Organic Synthesis", T.W. Greene, P.G.M. Wuts, Wiley-Interscience, 1999). For the purposes of this discussion, it will be assumed that such protecting

groups as necessary are in place. The compounds obtained may also be converted into salts, especially pharmaceutically acceptable salts thereof in a manner known *per se*.

General preparation routes:

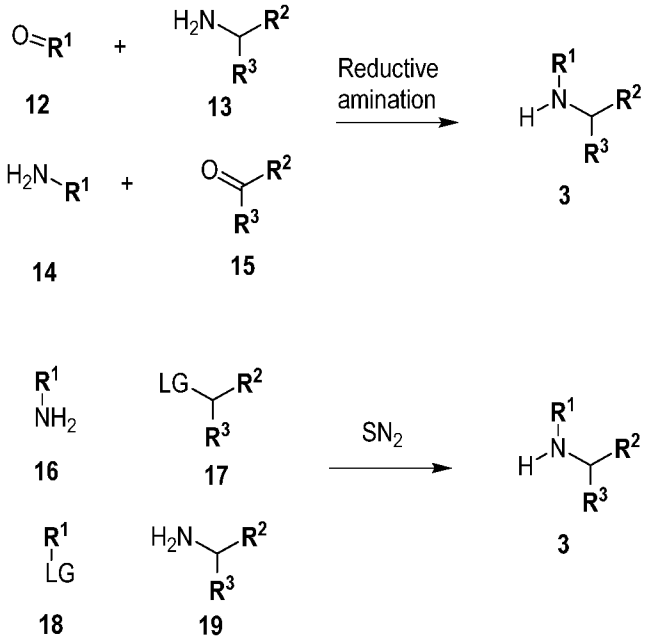
Compound **11**, belonging to Formula (I) wherein X^2=O and X^3= N can be prepared by an amide coupling reaction between an appropriate carboxylic acid with structure **2** and an appropriate amine with structure **3** (or the corresponding salt, like HCl or TFA salts) in a solvent such as THF, DMF, DCM or MeCN in presence of a coupling reagent such as TBTU, HBTU, HATU, EDC or similar and a base such as DIPEA, TEA or N-methylmorpholine (Scheme **1**). Compound **4** can be deprotected using standard deprotection methods known in the literature and familiar to the person skilled in the art to give **5** (or the corresponding salt, like HCl or TFA salts). Amine **5** is condensed with a sulfonyl chloride **6** in solvent such as DCM, DMF, MeCN and in presence of a base such as TEA or DIPEA to give **11**. Alternatively, an amino acid with structure **7** can be reacted with a sulfonyl chloride **6** in a solvent mixture such as DMF/Water and an inorganic base such as $NaHCO_3$ to give **10**. Acid **10** can be converted into compound with structure **11** either by amide coupling with an amine **3** (or the corresponding salt, like HCl or TFA salts) in a solvent such as THF, DMF, DCM or MeCN in presence of a coupling reagent such as TBTU, HBTU, HATU, EDC (or similar) and a base such as DIPEA, TEA or N-methylmorpholine or by conversion of **10** into its corresponding acid chloride by reaction with a reagent such as oxalyl chloride and DMF or thionyl chloride in a solvent such as toluene followed by condensation with **3** (or the corresponding salt, like HCl or TFA salts) in a solvent such as DCM and in presence of an organic base as TEA or DIPEA. Compounds having structure **10** can alternatively be prepared by sulfonamide formation from ester **8** with sulfonyl chloride **6** in a solvent such as DCM, DMF, MeCN and in presence of a base as TEA or DIPEA, followed by ester hydrolysis using a base such as LiOH or NaOH in a mixture of solvents such as THF/Water. Compounds with structure **2**, **6**, **7** and **8** are either commercially available or prepared as described in the literature.

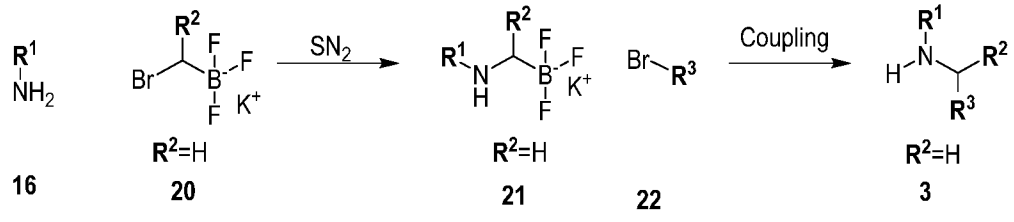


Scheme 1. Synthesis of sulfonamide compound **11**

Amines of structure **3** can be synthesized by reductive amination reaction between an aldehyde or a ketone (**12** or **15**) and a primary amine such as **13** or **14** (or the corresponding salt, like HCl or TFA salts) as described in the Scheme 2 using a solvent such as MeOH or THF and in presence of a reducing agent such as $NaBH_4$, $NaBH_3CN$ or $Na(AcO)_3BH$. Starting materials **12**, **13**, **14** and **15** are either commercially available or prepared from commercially available reagents using conventional reactions well known in the art. Alternatively, amine with structure **3** can be prepared by SN_2 reaction between primary amines **16** or **19** (or the corresponding salt, like HCl or TFA salts) and **17** or **18** (where LG is either a halide, OMs, OTs, OTf or any appropriate leaving group) in a solvent such as MeCN and in presence of a base as K_2CO_3. In an other aspect, amine **3**, wherein R^2= H, can be prepared by Suzuki-Miyaura cross-coupling between an organotrifluoroborate (**21**) and an alkyl bromide (**22**) as

described by Molander *et al.* (Chemistry, 2012, 18(31), 9564-70) in presence of a catalyst such as $P(tBu)_3Pd$ G2 and a base such as Cs_2CO_3 in a solvent mixture such as THF/Water. Organotrifluoroborate **21** can be prepared as described in the literature by reaction between **16** (or the corresponding salt, like HCl or TFA salts) and potassium bromotrifluoroborate **20** in a solvent mixture such as THF/t-BuOH.



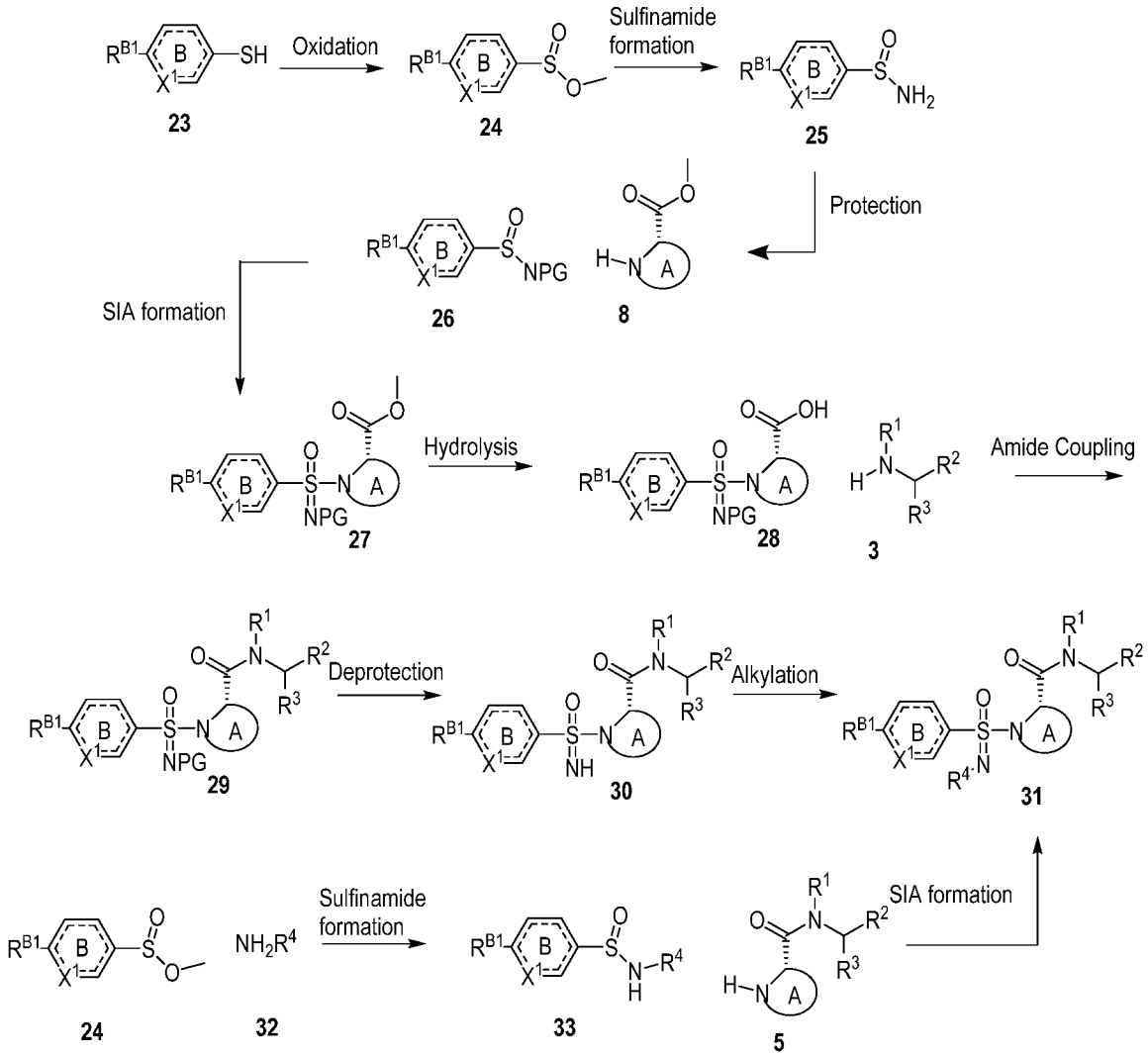


Scheme 2. Synthesis of amines with general structure **3**

Sulfonimidamide (SIA) compounds with structure **31**, belonging to Formula (I) wherein X^2= NR^4 and X^3= N can be prepared as described in Scheme 3. A commercially available arylthiol **23** can be oxidized into its corresponding sulfinate ester **24** by reaction with NBS and MeOH in a solvent such as DCM. Sulfinate ester **24** can be converted into sulfinamide with general structure **25** by reaction with LiHMDS in a solvent like THF and hydrolysis with sat. aq. NH_4Cl. The resulting sulfinamide can be protected with an appropriate protecting group (PG) to yield **26** using standard protection methods known in the literature and familiar to the person skilled in the art. Compound **26** can be condensed with **8** in presence of a chlorinating agent such as *tert*-butyl hypochlorite or *N*-chlorosuccinimide in a solvent such as DCM or 1,2-dichloroethane to give SIA intermediate **27**. The ester functional group can be

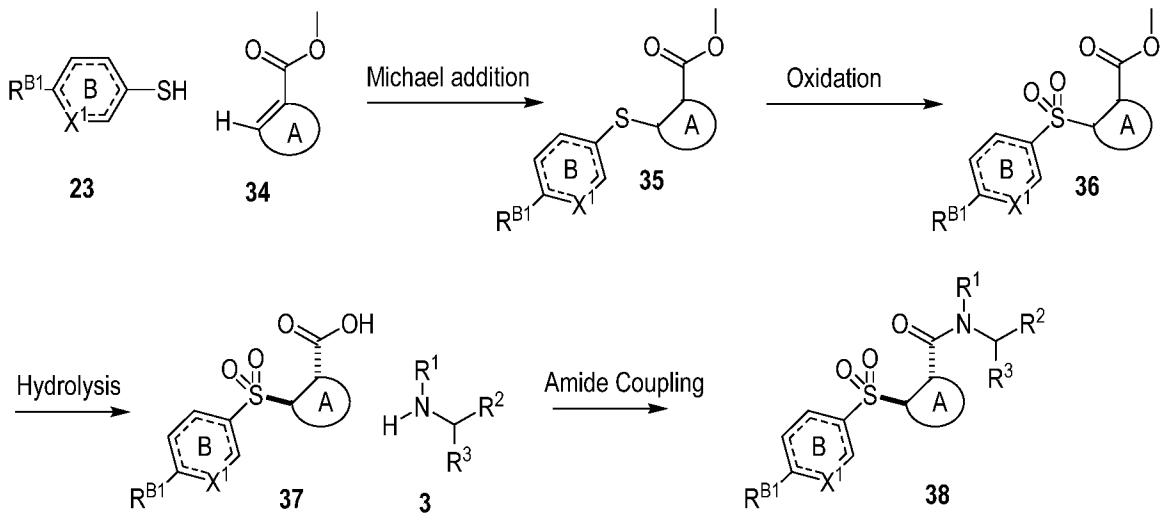
hydrolysed into the corresponding carboxylic acid (**28**) in presence of aq. LiOH soln. and a solvent such as THF. Subsequent amide coupling between **28** and a secondary amine (**3**) (or the corresponding salt, like HCl or TFA salts) in a solvent such as THF, DMF, DCM or MeCN in presence of a coupling reagent such as TBTU, HBTU, HATU, EDC (or similar) and a base such as DIPEA, TEA or N-methylmorpholine yields **29**. Protecting group cleavage using standard protection methods known in the literature and familiar to the person skilled in the art leads to derivative **30**. Alkylation of **30** can be performed with a base such as NaH or KOtBu and an alkyl halide as alkylating agent to obtain **31**. If not commercially available, arylthiol **23** can be prepared with methodologies described in the literature or as described here below in the experimental part.

Alternatively, the -N**R**^{4} group can be introduced in an early stage by condensation between primary amine **32** (or the corresponding salt, like HCl or TFA salts) and **24** using a base as n-BuLi in THF to yield sulfinamide **33**. SIA formation between **33** and **5** using similar conditions as described herein before yields final compounds **31**. Diastereomers can be separated either by prep HPLC, flash chromatography (FC) or chiral SFC chromatography at the final step (**31**) or at the level of **27**, **29** or **30**.



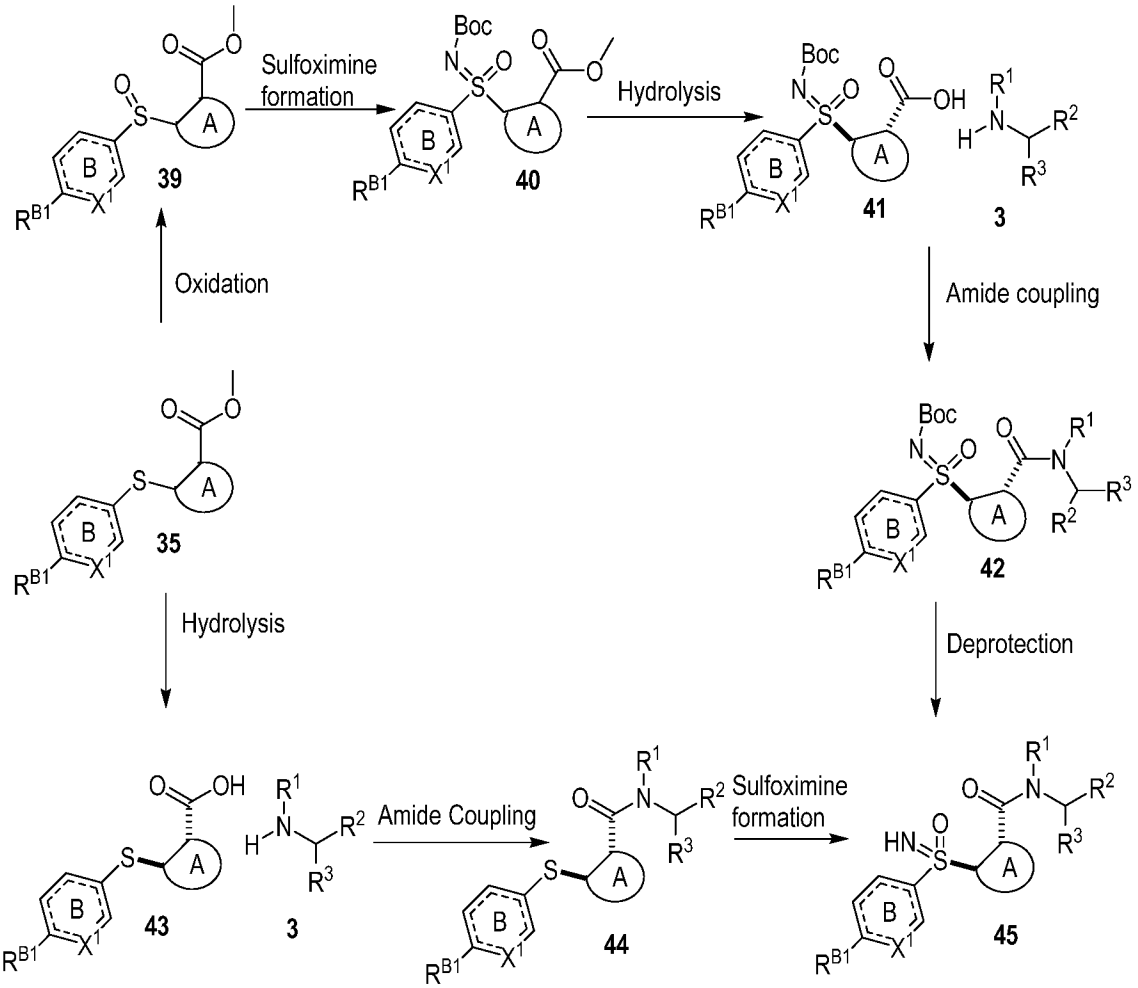
Scheme 3. Synthesis of SIA compound **31**

Sulfone compounds with structure **38**, belonging to Formula (I) wherein X^2= O and X^3= C can be prepared as described in Scheme 4. Michael addition between arylthiol **23** and commercially available α,β-unsaturated ester **34** in a solvent such as piperidine yields racemic thioether **35**. Intermediate **35** can be oxidized in presence of an oxidant such as MCPBA and in a solvent such as DCM to lead to sulfone **36**. Derivative **36** can be hydrolysed using standard methods as described herein before into its corresponding carboxylic acid **37**. Subsequent amide coupling between **37** and a secondary amine (**3**) (or the corresponding salt, like HCl or TFA salts) in a solvent such as THF, DMF, DCM or MeCN in presence of a coupling reagent such as TBTU, HBTU, HATU, EDC, pyClop (or similar) and a base such as DIPEA, TEA or N-methylmorpholine yields **38**.



Scheme 4. Synthesis of sulfone compound **38**

Sulfoximine compounds with structure **45**, belonging to Formula (I) wherein X^2=NH and X^3= C can be prepared as described in Scheme 5. Compound **35** can be hydrolysed into **43** using a base such as LiOH in a solvent mixture as H_2O/THF. Amide coupling between acid **43** and amine **3** (or the corresponding salt, like HCl or TFA salts) in a solvent such as THF, DMF, DCM or MeCN in presence of a coupling reagent such as TBTU, HBTU, HATU, EDC (or similar) and a base such as DIPEA, TEA or N-methylmorpholine gives **44**. Thioether **44** is treated with an oxidant such as iodobenzene diacetate and ammonium carbamate in a solvent like MeOH to yield sulfoximine **45**. Alternatively, **35** can be oxidized in the first step using hydrogen peroxide in a solvent as hexafluoro-2-propanol to yield **39**. Sulfoxide **39** can be treated with iodobenzene diacetate and magnesium peroxide in presence of *tert*-butyl carbamate and rhodium (II) acetate in a solvent such as DCM to give Boc-protected sulfoximine **40**. Ester **40** can be hydrolysed as described herein before to yield carboxylic acid **41**. Amide coupling between **41** and amine **3** (or the corresponding salt, like HCl or TFA salts) in a similar way as described in this paragraph can yield to Boc-protected intermediate **42**. Deprotection of the Boc protecting group can be performed in a presence of an acid such as HCl or TFA and in a solvent such as 1,4-dioxane to lead to desired product **45**. Generated diastereomers (**40**, **41**, **42** or **45**) can be separated either by prep HPLC, Flash chromatography or chiral SFC chromatography.



Scheme 5. Synthesis of sulfoximine compound **45**

Experimental Part

Abbrevations (as used herein and in the description above):

Ac	Acetyl (such as in OAc = acetate, AcOH = acetic acid)
AcOH	Acetic acid
AIBN	2,2'-Azobis(2-methylpropionitrile)
anh.	Anhydrous
aq.	aqueous
atm	Atmosphere
tBME	tert-Butylmethylether
Boc	*tert*-Butoxycarbonyl
Boc_2O	di-*tert*-Butyl dicarbonate
tBuOCl	tert-Buthyl hypochlorite

BSA	Bovine serum albumine
Bu	Butyl such as in tBu = *tert*-butyl = tertiary butyl
conc.	Concentrated
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DEA	Diethylamine
DIPEA	Diisopropylethylamine
DME	Dimethoxyethane
DMEM	Dulbecco's modified eagle medium
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ELSD	Evaporative Light-Scattering Detection
eq	Equivalent(s)
ES	Electron spray
Et	Ethyl
EtI	Ethyl Iodide
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
Ex.	Example
FBS	Fetal bovine serum
FC	Flash Chromatography on silica gel
FCS	Foatal calf serum
h	Hour(s)
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
HBSS	Hank's balanced salt solution
HBTU	2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HEK293	Human embryonic kidney 293 cells
HEPES	4-(2-Hydroxyethyl)-piperazine-1-ethanesulfonic acid
Hept	Heptane
^{1}H-NMR	Nuclear magnetic resonance of the proton
HPLC	High performance liquid chromatography

HTRF	Homogeneous Time Resolved Fluorescence
IP1	Intracellular inositol-1-phosphate
LC-MS	Liquid chromatography – Mass Spectroscopy
LiHMDS	Lithium hexamethyldisilazide
Lit.	Literature
LG	Leaving group
M	Exact mass (as used for LC-MS)
M	Molarity [mol L^{-1}]
MCPBA	3-Chloroperbenzoic acid
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
MeI	Methyl iodide
MHz	Megahertz
µl	Microliter
µm	Micrometer
min	Minute(s)
MS	Mass spectroscopy
Ms	Mesyl such as OMs
N	Normality
NaH	Sodium hydride
NMP	N-Methyl-2-pyrrolidone
$Pd(OAc)_2$	Palladium diacetate
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
PG	Protecting group
PL-HCO_3	Polymer supported hydrogen carbonate
Ph	Phenyl
Prep	Preparative
PTFE	Polytetrafluoroethylene
PyCloP	Chlorotripyrrolidinophosphonium hexafluorophosphate
$PyrSO_3$	Sulfur trioxide pyridine complex
Rf	Retention factor
rac	racemic or racemate
rt	Room temperature
sat. aq.	saturated aqueous

SIA	Sulfonimidamide compound(s)
SFC	Supercritical fluid chromatography
soln.	Solution
TBME	*tert*-Butyl methyl ether
TBTU	2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate
*t*Bu	*tert*-Butyl
TEA	Triethylamine
Tf	Triflate such as OTf
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
t_R	Retention time
Ts	Tosyl such as OTs
UPLC	Ultra performance liquid chromatography

I. Chemistry

All temperatures are stated in °C. Commercially available starting materials were used as received without further purification. Unless otherwise specified, all reactions were carried out in oven-dried glassware under an atmosphere of nitrogen. Compounds were purified by flash column chromatography on silica gel or by preparative HPLC. Compounds described in the invention are characterised by LC-MS data (retention time t_R is given in min; molecular weight obtained from the mass spectrum is given in g/mol) using the conditions listed below. In cases where compounds of the present invention appear as a mixture of conformational isomers, particularly visible in their LC-MS spectra, the retention time of the most abundant conformer is given. Racemates can be separated into their enantiomers by preparative HPLC or SFC

LC-MS conditions

LC-MS (1)

LC-MS-conditions: Analytical. Pump: Waters Acquity Binary, Solvent Manager, MS: Waters SQ Detector or Xevo TQD, DAD: Acquity UPLC PDA Detector. Column: Acquity UPLC CSH C18 1.7 µm, 2.1 x 50 mm from Waters, thermostated in the Acquity UPLC Column Manager at 60°C. Eluents: A1: H_2O + 0.05 % formic acid; B1: MeCN + 0.045 % formic acid. Method: Gradient: 2 % B to 98 % B over 2.0 min. Flow: 1.0 mL/min. Detection at 214 nm and MS, retention time t_R is given in min.

LC-MS (2)

LC-MS- conditions: Analytical UPLC on a Agilent Zorbax RRHD SB-Aq (2.1x50mm, 1.8 μm); detection at 210 nM and MS; UPLC/MS analyses are performed on Acquity UPLC setup; the column temperature is 40°C; Gradient of water/ 0.04% TFA (A) and MeCN (B). The eluent flow rate was 0.8 mL/min and the characteristics of the eluting mixture proportion in function of the time t from start of the elution are summarized in the table below (a linear gradient being used between two consecutive time points):

t (min)	0	1.2	1.9	2.1
Solvent A (%)	95	5	5	95
Solvent B (%)	5	95	95	5

LC-MS (3)

LC-MS- conditions: Analytical UPLC on a Waters BEH C18 (2.1x50 mm, 2.5 μm); detection at 210 nM and MS; UPLC/MS analyses are performed on Acquity UPLC setup; the column temperature is 40°C; gradient of water/ 0.04% NH_3 [c(NH_3) = 13 mmol/l] (A) and MeCN (B). The eluent flow rate was 0.8 mL/min and the characteristics of the eluting mixture proportion in function of the time t from start of the elution are summarized in the table below (a linear gradient being used between two consecutive time points):

t (min)	0	1.2	1.9	2.1
Solvent A (%)	95	5	5	95
Solvent B (%)	5	95	95	5

Preparative LC-MS methods used:

Preparative HPLC/MS purifications (prep. HPLC) are performed on a Gilson HPLC system, equipped with a Gilson 215 autosampler, Gilson 333/334 pumps, Finnigan AQA MS detector system, and a Dionex UV detector, using a Waters Xbridge C18 or a Waters Atlantis column, with a linear gradient of water/formic acid 0.02% (A) and MeCN (B) (acidic prep. HPLC conditions) or water/ammonia 0.02% (A) and MeCN (B) (basic prep. HPLC conditions).

Preparative chiral SFC methods used:

Preparative chiral SFC purifications were performed on a Sepiatec Prep SFC 360 system. Following parameters were used:

Preparative chiral SFC 1: A ChiralPak AD-H column (30 x 250mm, 5um) was used. The modifier was MeCN/MeOH 1:1, run for 4 min and at a flow rate of 160 mL/min. The following system settings were used: backpressure 100 bar, temperature pumphead 5 °C, temperature fraction module 20 °C, and temperature column department 40 °C

Preparative chiral SFC 2: A ChiralCel OZ-H column (30 x 250mm, 5um) was used. The modifier was EtOH/MeCN 1:1, run for 4 min and at a flow rate of 160 mL/min. The following system settings were used: backpressure 100 bar, temperature pumphead 4 °C, temperature fraction module 20 °C, and temperature column department 40 °C.

Preparative chiral SFC 3: A ChiralPak IC column (30 x 250 mm, 5 μm) was used. The modifier was EtOH (25%), run for 4.5 min and at a flow rate of 160 mL/min. The following system settings were used: backpressure 100 bar, temperature pumphead 5 °C, temperature fraction module 20 °C, and temperature column department 40 °C.

Preparative chiral SFC 4: A ChiralPak AD-H column (30 x 250 mm, 5 μm) was used. The modifier was EtOH (25%), run for 4:45 min and at a flow rate of 160 mL/min. The following system settings were used: backpressure 100 bar, temperature pumphead 5 °C, temperature fraction module 20 °C, and temperature column department 40 °C.

Preparative chiral SFC 5: A ChiralPak IB column (30 x 250 mm, 5 μm) was used. The modifier was MeCN/EtOH/DEA 50:50:0.1 (20%), run for 6.94 min and at a flow rate of 160 mL/min. The following system settings were used: backpressure 100 bar, temperature pumphead 5 °C, temperature fraction module 20 °C, and temperature column department 40 °C.

Preparative chiral SFC 6: A ChiralPak IE column (30 x 250 mm, 5 μm) was used. The modifier was MeCN/EtOH/DEA 50:50:0.1 (45%), run for 5.62 min and at a flow rate of 160 mL/min. The following system settings were used: backpressure 100 bar, temperature pumphead 5 °C, temperature fraction module 20 °C, and temperature column department 40 °C.

Preparative chiral SFC 7: A ChiralPak AZ-H column (30 x 250 mm, 5 μm) was used. The modifier was MeOH (10%), run for 6 min and at a flow rate of 160 mL/min. The following system settings were used: backpressure 100 bar, temperature pumphead 5 °C, temperature fraction module 20 °C, and temperature column department 40 °C.

Preparative chiral SFC 8: A ChiralPak ID column (30 x 250 mm, 5 μm) was used. The modifier was AcCN/EtOH 1:1 (45%), run for 6 min and at a flow rate of 160 mL/min. The following system settings were used: backpressure 100 bar, temperature pumphead 5 °C, temperature fraction module 20 °C, and temperature column department 40 °C.

Preparative chiral SFC 9: A ChiralPak ID column (30 x 250 mm, 5 μm) was used. The modifier was AcCN/EtOH 1:1 (35%), run for 6 min and at a flow rate of 160 mL/min. The following system settings were used: backpressure 100 bar, temperature pumphead 5 °C, temperature fraction module 20 °C, and temperature column department 40 °C.

Preparative chiral SFC 10: A ChiralPak ID column (30 x 250 mm, 5 μm) was used. The modifier was AcCN/EtOH 1:1 (50%), run for 6 min and at a flow rate of 160 mL/min. The following system settings were used: backpressure 100 bar, temperature pumphead 5 °C, temperature fraction module 20 °C, and temperature column department 40 °C.

FC

FC (Flash Chromatography) was performed using a combiflash from Teledyne ISCO.

Phase-separator

Phase separator cartriges used were Isolute® purchased from Biotage

Solid Phase Extraction

Ion exchange was performed using cationic exchange sorbent (Isolute® SXC) purchased from Biotage.

Preparation of Examples:

Methods for the preparation of sulfonamides compounds (Examples 1.x)

Example 1.1: (S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (1,1-dioxo-hexahydro-1λ⁶-thiopyran-4-yl)-(4-fluoro-benzyl)-amide:

4-((4-Fluorobenzyl)amino)tetrahydro-2H-thiopyran 1,1-dioxide: A soln. of 4-aminotetrahydro-2H-thiopyran 1,1-dioxide hydrochloride (2500 mg, 13.2 mmol, 1 eq) and TEA (3.67 mL, 26.4 mmol, 2 eq) in DMF/THF 1:1 (80 mL) was stirred at rt under nitrogen atmosphere. 4-Fluorobenzaldehyde (1.45 mL, 13.2 mmol, 1 eq) and AcOH (1.51 mL, 26.4 mmol, 2 eq) were added and stirred at rt for 1h. Sodium triacetoxyborohydride (6639 mg, 39.6 mmol, 3 eq) was then added portionwise. The reaction mixture was stirred overnight at rt. Water and aq. 2M HCl. were added and the mixture was washed with EtOAc. The aq. layer was basified with aq. 1M NaOH and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (DCM to DCM/MeOH 99:1) to give the title compound (1059 mg, 47%) as a white solid. LC-MS (2): t_R = 0.43 min; $[M+H]^+$: 257.97.

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (1,1-dioxo-hexahydro-1λ⁶-thiopyran-4-yl)-(4-fluoro-benzyl)-amide: A soln. of tosyl-L-proline (700 mg, 2.57 mmol), 4-((4-fluorobenzyl)amino)tetrahydro-2H-thiopyran 1,1-dioxide, HATU (1468 mg, 3.86 mmol) and DIPEA (1.87 mL, 10.9 mmol) in DMF (25 mL) was stirred at rt overnight. HATU (294 mg, 0.772 mmol) was added again and the soln. stirred for 2 supplementary hours. Aq. 2M HCl soln. was added and the mixture extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by acidic prep. HPLC to give the title compound (855 mg, 65%) as a white solid. LC-MS (1): t_R= 1.025 min; $[M+H]^+$: 509.3.

Example 1.2: (S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-5-ylmethyl-(1,1-dioxo-hexahydro-1λ⁶-thiopyran-4-yl)-amide

4-((Benzofuran-5-ylmethyl)amino)tetrahydro-2H-thiopyran 1,1-dioxide: A soln. of 4-aminotetrahydro-2H-thiopyran 1,1-dioxide (1500 mg, 9.55 mmol) and TEA (1.33 mL, 9.55 mmol) in DMF/THF 1:1 (45 mL) was stirred at rt under nitrogen. 1-Benzofuran-5-carbaldehyde (1424 mg, 9.55 mmol) and AcOH (1.09 mL, 19.1 mmol) were

added. After 1h sodium triacetoxyborohydride (4173 mg, 19.1 mmol) was added portionwise. The reaction mixture was stirred overnight at rt. Aq. 2M HCl soln. was added and the mixture extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (DCM to DCM/MeOH 99:1) to give the title compound (1587 mg, 59%) as a yellow solid. LC-MS (2): t_R = 0.49 min; $[M+H]^+$: 280.19.

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-5-ylmethyl-(1,1-dioxo-hexahydro-1λ⁶-thiopyran-4-yl)-amide: The product was synthesized as described in Example 1.1 using 4-((benzofuran-5-ylmethyl)amino)tetrahydro-2H-thiopyran 1,1-dioxide and N-tosyl-L-proline to give the title compound as a white solid. LC-MS (1): t_R = 1.036 min; $[M+H]^+$: 531.3.

Example 1.3: (S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzyl-(4,4-dimethyl-cyclohexyl)-amide:

N-benzyl-4,4-dimethylcyclohexan-1-amine hydrochloride: At rt, to a soln. of 4,4-dimethylcyclohexan-1-amine (23 mg, 0.18 mmol) and DIPEA (31.4 µL, 0.18 mmol) in MeOH (0.550 mL) was added a soln. of benzaldehyde (15.5 µL, 0.15 mmol) in MeOH (0.1 mL) and the solution was stirred at rt for 4h. $NaBH_4$ (7.50 mg, 0.197 mmol) was added and the mixture was stirred at rt overnight. Aq. 2M HCl was added and the mixture was washed with EtOAc. The aq. layer was basified with sat. aq. $NaHCO_3$ and extracted with EtOAc. A 1.25 M soln. of HCl in MeOH (0.500 mL) was added and the solvent was removed under reduced pressure to give the title compound as a white solid. LC-MS (2): t_R= 0.57 min; $[M+H]^+$: 226.18.

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzyl-(4,4-dimethyl-cyclohexyl)-amide: Was synthesized as described in Example 1.1 using N-benzyl-4,4-dimethylcyclohexan-1-amine hydrochloride salt and N-tosyl-L-proline to give the title compound as a white solid. LC-MS (1): t_R= 1.437 min; $[M+H]^+$: 469.2.

Example 1.4 to **Example 1.23** were synthesized using the appropriate amine or amine salt derivative, the appropriate aldehyde or ketone as described in Example 1.3. LC-MS data of Example 1.4 to Example 1.23 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
1.4	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzyl-(4,4-difluoro-cyclohexyl)-amide	1.248	477.3
1.5	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-dimethyl-cyclohexyl)-(4-fluoro-benzyl)-amide	1.436	487.2
1.6	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide	1.444	509.3
1.7	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-fluoro-benzyl)-amide	1.255	495.3

1.8	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.262	517.3
1.9	(2S)-N-Benzyl-N-(3,3-difluorocyclohexyl)-1-tosylpyrrolidine-2-carboxamide	1.257	477.2
1.10	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-bromo-benzyl)-(4,4-difluoro-cyclohexyl)-amide	1.340	555.1
1.11	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (2,4-difluoro-benzyl)-(4,4-difluoro-cyclohexyl)-amide	1.290	513.2
1.12	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (5-chloro-thiophen-2-ylmethyl)-(4,4-difluoro-cyclohexyl)-amide	1.333	517.2
1.13	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(3-methoxy-benzyl)-amide	1.246	507.2
1.14	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(3-methyl-benzyl)-amide	1.313	491.2
1.15	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-methoxy-benzyl)-amide	1.231	507.3
1.16	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-methyl-benzyl)-amide	1.311	491.3
1.17	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-trifluoromethyl-benzyl)-amide	1.333	545.2
1.18	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide	1.318	511.2
1.19	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-5-ylmethyl)-amide	1.230	519.3
1.20	(S)-N-(4,4-Difluorocyclohexyl)-N-(furo[3,2-b]pyridin-6-ylmethyl)-1-tosylpyrrolidine-2-carboxamide	1.066	518.3
1.21	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzo[b]thiophen-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.316	533.3
1.22	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (3,4-difluoro-benzyl)-(4,4-difluoro-cyclohexyl)-amide	1.276	513.2
1.23	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (2,2-difluoro-benzo[1,3]dioxol-5-ylmethyl)-(4,4-difluoro-cyclohexyl)-amide	1.337	557.2

Example 1.24: (S)-N-((RS)-1-(4-chlorophenyl)ethyl)-N-(4,4-difluorocyclohexyl)-1-tosylpyrrolidine-2-carboxamide

Tosyl-L-prolinoyl chloride: To a suspension of tosyl-L-proline (3.00 g, 11.1 mmol, 1 eq) in toluene (78 mL) was added oxalyl chloride (2.68 mL, 30.4 mmol, 2.733 eq) and DMF (0.028 mL). The reaction was stirred for 1h at room temperature. The reaction mixture was evaporated under reduced pressure to give the title compound (2.90 g, 91%) as an off-white solid.

N-(1-(4-Chlorophenyl)ethyl)-4,4-difluorocyclohexan-1-amine: A mixture of rac-4-chloro-alpha-methylbenzylamine (125 mg, 0.798 mmol), 4,4-difluorocyclohexan-1-one (160 mg, 1.2 mmol), AcOH (0.167 mL, 1.2 mmol) and sodium triacetoxyborohydride 97% (534 mg, 2.39 mmol) in THF (4.00 mL) was stirred at rt overnight. The reaction mixture was partitioned between aq. 1M HCl and EtOAc. The layers were separated and the aq. layer was basified with solid $NaHCO_3$ and extracted with EtOAc (2x). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give the title compound as a yellow oil. LC-MS (2): t_R = 0.70 min; $[M+H]^+$: 274.08.

(S)-N-((RS)-1-(4-Chlorophenyl)ethyl)-N-(4,4-difluorocyclohexyl)-1-tosylpyrrolidine-2-carboxamide: A solution of tosyl-L-prolinoyl chloride (35.7 mg, 0.124 mmol, 1 eq), N-(1-(4-chlorophenyl)ethyl)-4,4-difluorocyclohexan-1-amine (33.9 mg, 0.124 mmol, 1 eq) and DIPEA (0.0499 mL, 0.291 mmol, 2.35 eq) in DCM (1.2 mL) was stirred at rt over 3 days. The reaction mixture was washed with brine. The organic layer was separated through a phase-separator cartridge and concentrated under reduced pressure. The crude residue was purified by prep. HPLC to give the title compound as a white solid. LC-MS (1): t_R= 1.365 min; $[M+H]^+$: 525.3.

Example 1.25 to **Example 1.32** were synthesized using the appropriate amine or amine salt derivative and the appropriate aldehyde or ketone as described in Example 1.3. LC-MS data of Example 1.25 to Example 1.32 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
1.25	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-dimethyl-cyclohexyl)-(4-methyl-benzyl)-amide	1.489	483.4
1.26	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-dimethyl-cyclohexyl)-amide	1.499	503.2
1.27	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzo[b]thiophen-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide	1.497	525.3
1.28	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-bromo-benzyl)-(4,4-dimethyl-cyclohexyl)-amide	1.514	547.3
1.29	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (5-chloro-thiophen-2-ylmethyl)-(4,4-dimethyl-cyclohexyl)-amide	1.511	509.1
1.30	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-dimethyl-cyclohexyl)-(4-methoxy-benzyl)-amide	1.416	499.2

1.31	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (2,4-difluoro-benzyl)-(4,4-dimethyl-cyclohexyl)-amide	1.472	505.4
1.32	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-dimethyl-cyclohexyl)-naphthalen-2-ylmethyl-amide	1.518	519.4

Example 1.33 (2S,4S)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzyl-(4,4-dimethyl-cyclohexyl)-amide:

tert-Butyl (2S,4S)-2-(benzyl(4,4-dimethylcyclohexyl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate: tert-Butyl (2S,4S)-2-(benzyl(4,4-dimethylcyclohexyl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate (48 mg, 0.2 mmol, 1 eq) was dissolved in DMF (1.00 mL). HATU (80 mg, 0.21mmol, 1.05 eq) and DIPEA (0.11 mL, 0.6 mmol, 3 eq) were added followed after 15 min by N-benzyl-4,4-dimethylcyclohexan-1-amine (45 mg, 0.2 mmol, 1 eq). The reaction was stirred at rt overnight. The mixture was purified by prep. HPLC to give the title compound (78 mg, 90%). LC-MS (2): t_R = 1.11 min; $[M+H]^+$: 434.13.

(2S,4S)-N-Benzyl-N-(4,4-dimethylcyclohexyl)-4-fluoropyrrolidine-2-carboxamide hydrochloride: tert-Butyl (2S,4S)-2-(benzyl(4,4-dimethylcyclohexyl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate (77.9 mg, 0.18 mmol, 1.00 eq) was dissolved in DCM (6.00 mL). 4M HCl in 1,4-dioxane (3.00 mL) was added and the mixture was stirred at rt overnight. The solvent was removed under reduced pressure to give the title compound (66.3 mg, 100%) as a yellow solid. LC-MS (2): t_R= 0.79 min; $[M+H]^+$: 333.36.

(2S,4S)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzyl-(4,4-dimethyl-cyclohexyl)-amide: To a soln. of (2S,4S)-N-benzyl-N-(4,4-dimethylcyclohexyl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (66.3 mg, 0.18 mmol, 1.00 eq) in DCM (2 mL) at 0°C was added TEA (0.052 mL, 0.38 mmol, 2.1 eq) followed by p-toluenesulfonyl chloride (38.5 mg, 0.20 mmol, 1.1 eq), and the mixture was stirred at rt overnight. The mixture was purified by prep. HPLC to give the title compound (68 mg, 78%) as a white solid. LC-MS (1): t_R= 1.388 min; $[M+H]^+$: 487.3.

Example 1.34 to **Example 1.42** were synthesized using the appropriate amine or amine salt derivative and the appropriate aldehyde or ketone as described in Example 1.3. LC-MS data of Example 1.34 to Example 1.42 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
1.34	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(5-methyl-thiophen-2-ylmethyl)-amide	1.298	497.2
1.35	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,4-dimethyl-benzyl)-amide	1.358	505.3

1.36	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (5-chloro-pyridin-2-ylmethyl)-(4,4-difluoro-cyclohexyl)-amide	1.238	512.2
1.37	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-2,6-difluoro-benzyl)-(4,4-difluoro-cyclohexyl)-amide	1.349	547.2
1.38	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (5-chloro-thiazol-2-ylmethyl)-(4,4-difluoro-cyclohexyl)-amide	1.254	518.3
1.39	(S)-N-(4,4-Difluorocyclohexyl)-N-(thieno[2,3-b]pyridin-2-ylmethyl)-1-tosylpyrrolidine-2-carboxamide	1.181	534.2
1.40	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-bromo-benzyl)-(tetrahydro-pyran-4-yl)-amide	1.191	521.3
1.41	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzo[b]thiophen-5-ylmethyl-(tetrahydro-pyran-4-yl)-amide	1.171	499.3
1.42	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-isopropyl-cyclohexyl)-(4-methyl-benzyl)-amide	1.542	497.4

Example 1.43 (1R*,5S*)-(2RS)-3-(Toluene-4-sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid benzyl-(4,4-dimethyl-cyclohexyl)-amide:

(1R*,5S*)-(2RS)-3-Tosyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid: A soln. of cis-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (90 mg, 0.708 mmol, 1 eq) in sat. aq. $NaHCO_3$ (4.00 mL) and DMF (4.00 mL) was cooled to 0°C and p-toluenesulfonyl chloride (207 mg, 1.06 mmol, 1.5 eq) was added at 0°C. The mixture was then warmed to rt and stirred for 17h. DMF was removed under reduced pressure. The residue was acidified with aq. 1M HCl and extracted with DCM. The combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the title compound (192 mg, 96%) as a white solid. LC-MS (2): t_R= 0.76 min; $[M+H]^+$: 282.16.

(1R*,5S*)-(2RS)-3-(Toluene-4-sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid benzyl-(4,4-dimethyl-cyclohexyl)-amide: Was synthesized as described in Example 1.1 using N-benzyl-4,4-dimethylcyclohexan-1-amine hydrochloride and (1R*,5S*)-(2RS)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid to give the title compound as a white solid. LC-MS (1): t_R= 1.456 min; $[M+H]^+$: 481.4.

Example 1.44 to **Example 1.46** were synthesized using the appropriate amine or amine salt derivative, the appropriate aldehyde or ketone, the appropriate carboxylic acid as described in Example 1.33. LC-MS data of Example 1.44 to Example 1.46 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
1.44	(1R,3S,4S)-2-(Toluene-4-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid benzyl-(4,4-dimethyl-cyclohexyl)-amide	1.504	495.4
1.45	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide	1.368	526.3
1.46	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(3-fluoro-4-methyl-benzyl)-amide	1.310	509.4

Example 1.47 (S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide:

5-(Bromomethyl)benzo[d]oxazole: To a soln. of 5-methylbenzoxazole (1000 mg, 7.47 mmol, 1 eq) and N-bromosuccinimide (1729 mg, 9.71 mmol, 1.3 eq) in bromobenzene (20 mL) was added AIBN (25 mg, 0.149 mmol, 0.02 eq) and the soln. was stirred at 90°C for 16h. The reaction mixture was concentrated. The residue was purified by FC (Hept to Hept/EtOAc 9:1) to give the title compound (0.785 g, 50%) as a yellow solid. R_f (Hept/ EtOAc)= 0.55. LC-MS (2): t_R = 0.78 min; $[M+H]^+$: 212.04.

N-(Benzo[d]oxazol-5-ylmethyl)-4,4-difluorocyclohexan-1-amine: 4,4-Difluoro-cyclohexylamine hydrochloride (2455 mg, 13.9 mmol, 1 eq) and potassium carbonate (4843 mg, 34.7 mmol, 2.5 eq) were suspended in MeCN (100 mL) and the resulting beige suspension was stirred at rt. 5-(Bromomethyl)benzo[d]oxazole (2942 mg, 13.9 mmol, 1 eq) in MeCN (40 mL) was then added and the reaction mixture was stirred at rt for 20h. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by FC (Hept to Hept/ (EtOAc + 2% Et_3N) 6:4) to give the title compound (3.037 g, 79%) as a pale yellow oil that solidified upon standing. LC-MS (3): t_R= 0.78 min; $[M+H]^+$: 267.20.

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide: N-(Benzo[d]oxazol-5-ylmethyl)-4,4-difluorocyclohexan-1-amine (205 mg, 0.77 mmol, 1 eq) was dissolved in DMF (7 mL) and DIPEA (0.329 mL, 1.92 mmol, 2.5 eq) followed by tosyl-L-prolinoyl chloride (233 mg, 0.77 mmol, 1 eq). The resulting pale yellow solution was stirred at rt for 3.5 h. The reaction mixture was diluted with EtOAc, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by FC (Hept to Hept/EtOAc 7:3) to give the title compound (357 mg, 90%) as a white solid. R_f (Hept/ EtOAc 2:8)= 0.50. LC-MS (1): t_R = 1.133 min; $[M+H]^+$: 518.2.

Example 1.48 (S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide:

N-(Benzo[d]oxazol-5-ylmethyl)-4,4-dimethylcyclohexan-1-amine: Was synthesized using 4,4-dimethylcyclohexan-1-amine and 5-(bromomethyl)benzo[d]oxazole as described in Example 1.47 to give the title compound as an orange oil. LC-MS (2): t_R = 0.66 min; $[M+H]^+$: 259.32.

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide: Was synthesized using N-(benzo[d]oxazol-5-ylmethyl)-4,4-dimethylcyclohexan-1-amine and N-tosyl-L-proline as described in Example 1.1 to give the title compound as a white solid. LC-MS (1): t_R = 1.314 min; $[M+H]^+$: 510.2.

Example 1.49 to **Example 1.51** were synthesized using the appropriate amine or amine salt derivative, the appropriate aldehyde or ketone, N-toluenesulfonyl-L-proline as described in Example 1.33. LC-MS data of Example 1.49 to Example 1.51 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
1.49	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzo[b]thiophen-6-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide	1.490	525.2
1.50	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzo[b]thiophen-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.309	533.3
1.51	(2S)-N-(benzo[b]thiophen-5-ylmethyl)-N-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-tosylpyrrolidine-2-carboxamide	1.258	527.2

Example 1.52 (S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-6-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide:

Benzofuran-6-ylmethanol: Ethyl chloroformate (0.179 mL, 1.82 mmol, 1 eq) was added dropwise to the iced-cooled soln. of benzofuran-6-carboxylic acid (301 mg, 1.82 mmol, 1 eq) and TEA (0.297 mL, 2.09 mmol, 1.15 eq) in THF (7.3 mL). The resulting soln. was stirred at 0 °C for 1h. A soln. of sodium borohydride (206 mg, 5.45 mmol, 3 eq) in water (2.90 mL) was added dropwise at 0 °C to the reaction mixture and stirring was continued at the same temperature for 1h. The reaction mixture was diluted with EtOAc and washed with aq. 1M HCl, sat aq. $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to Hept/EtOAc 7:3) to give the title compound as a light yellow oil. LC-MS (2): t_R = 0.64 min; mass not seen.

Benzofuran-6-carbaldehyde: A suspension of benzofuran-6-ylmethanol (140 mg, 0.841 mmol, 1 eq) and manganese(IV) oxide (activated, 185 mg, 2.1 mmol, 2.5 eq) in DCM (8.4 mL) was stirred at rt overnight. Manganese(IV) oxide (185 mg, 2.1 mmol, 2.5 eq) was added again to the mixture and stirring was continued at rt for 3h. The reaction mixture was filtered over a polyproplylene fritted cartridge and the solid was washed with DCM. The filtrate was concentrated under reduced pressure to give the title compound as a yellow oil. LC-MS (2): t_R =

0.77 min; mass not seen. ^{1}H NMR (500 MHz, DMSO) δ: 10.07 (s, 1 H), 8.28 (d, J = 2.2 Hz, 1 H), 8.16 (m, 1 H), 7.87 (m, 1 H), 7.83 (m, 1 H), 7.13 (dd, J_1 = 1.0 Hz, J_2 = 2.2 Hz, 1 H).

N-(Benzofuran-6-ylmethyl)-4,4-dimethylcyclohexan-1-amine: Was synthesized using benzofuran-6-carbaldehyde and 4,4-dimethylcyclohexan-1-amine as described in Example 1.1 to give the title compound. LC-MS (2): t_R = 0.77 min; $[M+H]^+$: 258.11.

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-6-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide: Was synthesized using N-(benzofuran-6-ylmethyl)-4,4-dimethylcyclohexan-1-amine and N-toluenesulfonyl-L-proline as described in Example 1.1 to give the title compound. LC-MS (1): t_R = 1.441 min; $[M+H]^+$: 509.4.

Example 1.53 (S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide:

N-(Benzofuran-6-ylmethyl)-4,4-difluorocyclohexan-1-amine: Was synthesized using benzofuran-6-carbaldehyde and 4,4-difluorocyclohexan-1-amine as described in Example 1.1 to give the title compound. LC-MS (2): t_R = 0.65 min; $[M+H]^+$: 266.21.

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide: Was synthesized using N-(benzofuran-6-ylmethyl)-4,4-difluorocyclohexan-1-amine and N-toluenesulfonyl-L-proline as described in Example 1.1 to give the title compound. LC-MS (1): t_R = 1.265 min; $[M+H]^+$: 517.2.

Example 1.54 (S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide:

N-(Benzo[d]thiazol-5-ylmethyl)-4,4-difluorocyclohexan-1-amine: Was synthesized using 4,4-difluorocyclohexan-1-amine and benzothiazole-5-carbaldehyde as described in Example 1.1 to give the title compound. LC-MS (2): t_R = 0.56 min; $[M+H]^+$: 283.23.

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide: Was synthesized using N-(benzo[d]thiazol-5-ylmethyl)-4,4-difluorocyclohexan-1-amine and N-toluenesulfonyl-L-proline as described in Example 1.1 to give the title compound. LC-MS (1): t_R = 1. 167 min; $[M+H]^+$: 534.2.

Example 1.55 to **Example 1.60** were synthesized using the appropriate amine or amine salt derivative, the appropriate aldehyde or ketone, N-toluenesulfonyl-L-proline as described in Example 1.1. LC-MS data of Example 1.55 to Example 1.60 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
1.55	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(tetrahydro-pyran-4-yl)-amide	0.994	500.3

1.56	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-2-fluoro-benzyl)-(4,4-difluoro-cyclohexyl)-amide	1.353	529.2
1.57	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-dimethylamino-benzyl)-amide	1.151	520.2
1.58	(2S)-N-(benzo[b]thiophen-5-ylmethyl)-N-((2S*,4S*)-2-methyltetrahydro-2H-pyran-4-yl)-1-tosylpyrrolidine-2-carboxamide	1.204	513.3
1.59	(2S)-N-(benzo[b]thiophen-5-ylmethyl)-N-((2R*,4S*)-2-methyltetrahydro-2H-pyran-4-yl)-1-tosylpyrrolidine-2-carboxamide	1.220	513.3
1.60	(2S)-N-(Benzo[b]thiophen-5-ylmethyl)-N-(trans-3-fluorotetrahydro-2H-pyran-4-yl)-1-tosylpyrrolidine-2-carboxamide	1.196	517.2

Example 1.61 (S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(tetrahydro-pyran-4-yl)-amide: Was synthesized using 4-aminotetrahydropyran, 5-(bromomethyl)benzo[d]oxazole and N-toluenesulfonyl-L-proline as described in Example 1.47. LC-MS (1): t_R= 0.965 min; $[M+H]^+$: 484.2.

Example 1.62 (S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-6-ylmethyl-(tetrahydro-pyran-4-yl)-amide: Was synthesized as described in Example 1.47 using 4-aminotetrahydropyran, 6-(bromomethyl)benzo[d]oxazole (US2006173183A1) and N-toluenesulfonyl-L-proline. LC-MS (1): t_R = 0.946 min; $[M+H]^+$: 484.3.

Examples 1.63 to **Example 1.65** were synthesized as described in Example 1.47 using the appropriate amine or amine salt derivative, 6-(bromomethyl)benzo[d]oxazole and N-toluenesulfonyl-L-proline. LC-MS data of Example 1.63 to Example 1.65 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
1.63	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-6-ylmethyl-(1,1-dioxo-hexahydro-1λ^6-thiopyran-4-yl)-amide	0.882	532.3
1.64	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.122	518.2
1.65	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-6-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide	1.302	510.4

Example 1.66 (2S,4S)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide: Was synthesized using the appropriate amine or amine salt to give the title compound as described in Example 1.33. LC-MS (1): t_R = 1.291 min; $[M+H]^+$: 529.2.

Example 1.67 to **Example 1.68** were synthesized as described in Example 1.1 using the appropriate amine or amine salt derivative and N-toluenesulfonyl-L-proline. LC-MS data of Example 1.67 to Example 1.68 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
1.67	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-6-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide	1.334	526.4
1.68	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.150	534.2

Example 1.69 (2S)-N-(Benzofuran-6-ylmethyl)-N-(tetrahydro-2H-pyran-3-yl)-1-tosylpyrrolidine-2-carboxamide: Was synthesized using oxan-3-amine hydrochloride, benzofuran-6-carbaldehyde and N-toluenesulfonyl-L-proline as described in Example 1.53 to give the title compound as a white solid. LC-MS (1): t_R= 1.154 min; $[M+H]^+$: 483.2.

Example 1.70 (S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(1,1-dioxo-hexahydro-1λ⁶-thiopyran-4-yl)-amide: was synthesized as described in Example 1.47 using 5-(bromomethyl)benzo[d]oxazole, 4-aminotetrahydro-2h-thiopyran 1,1-dioxide and N-toluenesulfonyl-L-proline to give the title compound as a white solid. LC-MS (2): t_R= 0.84 min; $[M+H]^+$: 532.17.

Example 1.71 (S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (5-bromo-thiazol-2-ylmethyl)-(4,4-difluoro-cyclohexyl)-amide: Was synthesized as described in Example 1.24 using 4,4-difluorocyclohexylamine, 5-bromo-1,3-thiazole-2-carbaldehyde and tosyl-L-prolinoyl chloride to give the title compound as a white solid. LC-MS (1): t_R= 1.257 min; $[M+H]^+$: 562.2.

Example 1.72 (1R*,5S*)-(2RS)-N-(Benzo[d]oxazol-6-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide:

N-(Benzo[d]oxazol-6-ylmethyl)-4,4-dimethylcyclohexan-1-amine: Was synthesized as described in Example 1.47 using 6-(bromomethyl)benzo[d]oxazole (US2006173183A1) and 4,4-dimethylcyclohexan-1-amine to give the title compound as a pale brown solid. LC-MS (2): t_R= 0.67 min; $[M+H]^+$: 259.33.

(1R*,5S*)-(2RS)-N-(benzo[d]oxazol-6-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide: Was synthesized as described in Example 1.1 using N-(benzo[d]oxazol-6-ylmethyl)-4,4-dimethylcyclohexan-1-amine and (1R*,5S*)-(2RS)-3-Tosyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid to give the title compound as a white solid. LC-MS (1): t_R= 1.337 min; $[M+H]^+$: 522.3.

Example 1.73 (2S,4S)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-6-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide: Was synthesized as described in Example 1.33 using N-

(benzo[d]oxazol-6-ylmethyl)-4,4-dimethylcyclohexan-1-amine and N-boc-cis-4-fluoro-L-proline to give the title compound as a white solid. LC-MS (1): t_R= 1.264 min; $[M+H]^+$: 528.2.

Example 1.74 to **Example 1.95** were synthesized according to the procedures described herein before using the appropriate amine or amine salt derivative, the appropriate aldehyde or ketone and the appropriate substituted proline or proline ester. LC-MS data of Example 1.74 to Example 1.95 are listed in the table below.

Ex. N	Name	t_R	$[M+H]^+$	LC-MS conditions
1.74	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-2-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.314	517.2	1
1.75	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-2-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide	1.487	509.4	1
1.76	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzo[b]thiophen-2-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.361	533.1	1
1.77	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzo[b]thiophen-2-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide	1.521	525.2	1
1.78	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-2-ylmethyl-(1,1-dioxo-hexahydro-1λ^6-thiopyran-4-yl)-amide	1.083	531.2	1
1.79	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-2-ylmethyl-(1,1-dioxo-hexahydro-1λ^6-thiopyran-4-yl)-amide	0.995	532.2	1
1.80	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-2-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.266	534.2	1
1.81	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-2-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide	1.437	526.3	1
1.82	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzo[b]thiophen-2-ylmethyl-(1,1-dioxo-hexahydro-1λ^6-thiopyran-4-yl)-amide	1.123	547.1	1
1.83	(2S)-N-(Benzo[b]thiophen-5-ylmethyl)-N-(cyclohex-3-en-1-yl)-1-tosylpyrrolidine-2-carboxamide	1.362	495.2	1
1.84	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(1H-indol-6-ylmethyl)-amide	1.217	516.4	1
1.85	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-dimethyl-cyclohexyl)-(1H-indol-6-ylmethyl)-amide	1.383	508.4	1

1.86	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (1,1-dioxo-hexahydro-1λ⁶-thiopyran-4-yl)-(1H-indol-6-ylmethyl)-amide	1.009	530.3	1
1.87	(2S,4S)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide	1.310	544.2	1
1.88	(2S,4S)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.01	552.17	2
1.89	(2S,4S)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide	1.270	528.4	1
1.90	(2S,4S)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	0.99	536.22	2
1.91	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzo[b]thiophen-5-ylmethyl-(4-fluoro-cyclohexyl)-amide	1.296	515.3	1
1.92	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-6-ylmethyl-(tetrahydro-pyran-4-yl)-amide	1.114	483.2	1
1.93	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzo[b]thiophen-5-ylmethyl-(4-fluoro-cyclohexyl)-amide	1.297	515.2	1
1.94	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzo[b]thiophen-5-ylmethyl-spiro[2.5]oct-6-yl-amide	1.455	523.3	1
1.95	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzo[b]thiophen-5-ylmethyl-(4-hydroxy-cyclohexyl)-amide	1.110	513.2	1

Example 1.96 (S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-dimethyl-cyclohexyl)-(4-methyl-benzyl)-amide:

Methyl ((4-methoxyphenyl)sulfonyl)-L-prolinate: To a soln. of L-proline methyl ester hydrochloride (607 mg, 3.56 mmol, 2.5 eq) and DIPEA (0.731 mL, 4.27 mmol, 3 eq) in MeCN (27.5 mL, 526 mmol, 369.9 eq) was added 4-methoxybenzenesulfonyl chloride (300 mg, 1.42 mmol, 1 eq) at rt and the reaction mixture was stirred for 3 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to Hept/EtOAc 1:1) to give the title compound (350 mg, 82%) as a yellow solid. LC-MS (2): t_R= 0.82 min; $[M+H]^+$: 300.24.

Lithium ((4-methoxyphenyl)sulfonyl)-L-prolinate: To a solution of methyl ((4-methoxyphenyl)sulfonyl)-L-prolinate (350 mg, 1.15 mmol, 1 eq) in THF (7.5 mL, 91.3 mmol, 79.23 eq) was added aq. 1M LiOH soln. (1.44 mL, 1.44 mmol, 1.25 eq) and the resulting mixture was stirred at rt over 3 days. The reaction mixture was concentrated

under reduced pressure and dried under reduced pressure to give the title compound (350 mg, 98%) as a white solid. LC-MS (2): t_R= 0.69 min; $[M+H]^+$: 286.21.

4,4-Dimethyl-N-(4-methylbenzyl)cyclohexan-1-amine: Was synthesized using *p*-tolualdehyde and 4,4-dimethylcyclohexan-1-amine as described in Example 1.3 to give the title compound as a colorless oil. LC-MS (2): t_R= 0.75 min; $[M+H]^+$: 232.35.

(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-dimethyl-cyclohexyl)-(4-methyl-benzyl)-amide: A soln. of lithium ((4-methoxyphenyl)sulfonyl)-L-prolinate (20 mg, 0.0659 mmol, 1 eq), HATU (28.8 mg, 0.0758 mmol, 1.15 eq) and DIPEA (0.0339 mL, 0.198 mmol, 3 eq) in DMF (0.2mL) was stirred for 1h at rt. 4,4-dimethyl-N-(4-methylbenzyl)cyclohexan-1-amine (0.0725 mmol, 1.1 eq) in DMF (0.2 mL) was added and the reaction mixture was stirred for 1h. The reaction mixture was purified by acidic prep. HPLC to give the title compound (20.5 mg, 62%) as an orange solid. LC-MS (1): t_R= 1.444 min; $[M+H]^+$: 499.2.

Examples 1.97 to **Example 1.100** were synthesized using the appropriate amine or amine salt derivative, the appropriate aldehyde or ketone and lithium ((4-methoxyphenyl)sulfonyl)-L-prolinate following the procedure described in Example 1.96. LC-MS data of Example 1.97 to Example 1.100 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
1.97	(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-6-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide	1.397	525.3
1.98	(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzyl-(4,4-difluoro-cyclohexyl)-amide	1.200	493.3
1.99	(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-methyl-benzyl)-amide	1.258	507.3
1.100	(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.214	533.3

Example 1.101 to **Example 1.145** were synthesized according to the procedures described herein before using the appropriate amine or amine salt derivative, the appropriate aldehyde or ketone, tosyl-L-prolinoyl chloride or the appropriate substituted proline or proline ester. LC-MS data of Example 1.101 to Example 1.145 are listed in the table below.

Ex. N°	Name	t_R	$[M+H]^+$	LC-MS conditions

1.101	(2S,4S)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.01	536.22	2
1.102	(1R,3S,4S)-2-(Toluene-4-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid benzothiazol-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide	1.422	552.3	1
1.103	(2S)-N-(Benzo[d]oxazol-6-ylmethyl)-N-(cyclohex-3-en-1-yl)-1-tosylpyrrolidine-2-carboxamide	1.149	480.3	1
1.104	(2S)-N-(Benzofuran-6-ylmethyl)-N-(cyclohex-3-en-1-yl)-1-tosylpyrrolidine-2-carboxamide	1.307	479.2	1
1.105	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (5-cyclopropyl-isoxazol-3-ylmethyl)-(4,4-difluoro-cyclohexyl)-amide	1.208	508.3	1
1.106	(1R,3S,4S)-2-(Toluene-4-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid benzooxazol-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide	1.382	536.4	1
1.107	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2-methyl-benzo[b]thiophen-5-ylmethyl)-amide	1.386	547.2	1
1.108	(1R,3S,4S)-2-(Toluene-4-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid benzooxazol-6-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide	1.379	536.4	1
1.109	(1R,3S,4S)-2-(Toluene-4-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid benzofuran-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.328	543.2	1
1.110	(1R,3S,4S)-2-(Toluene-4-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.235	560.2	1
1.111	(1R,3S,4S)-2-(Toluene-4-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid benzooxazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.201	544.2	1
1.112	(1R*,5S*)-(2RS)-N-(benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide	1.09	530.09	2
1.113	(2S,4S)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.228	535.2	1
1.114	(2S,4S)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-6-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide	1.398	527.2	1
1.115	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-dimethyl-cyclohexyl)-(2-methyl-benzofuran-6-ylmethyl)-amide	1.501	523.3	1

1.116	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (1,1-dioxo-hexahydro-1λ⁶-thiopyran-4-yl)-(2-methyl-benzofuran-6-ylmethyl)-amide	1.102	545.2	1
1.117	(1R,3S,4S)-2-(Toluene-4-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid benzooxazol-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.07	544.22	2
1.118	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2-methyl-benzofuran-6-ylmethyl)-amide	1.325	531.2	1
1.119	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(5-isopropyl-oxazol-2-ylmethyl)-amide	1.224	510.3	1
1.120	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(3-difluoromethoxy-benzyl)-amide	1.264	543.3	1
1.121	(2S)-N-(benzo[b]thiophen-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-tosylpyrrolidine-2-carboxamide	1.411	509.2	1
1.122	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.237	519.2	1
1.123	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (2,3-dihydro-benzofuran-6-ylmethyl)-(4,4-dimethyl-cyclohexyl)-amide	1.415	511.4	1
1.124	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (2,3-dihydro-benzofuran-6-ylmethyl)-(tetrahydro-pyran-4-yl)-amide	1.078	485.2	1
1.125	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (2,3-dihydro-benzofuran-6-ylmethyl)-(1,1-dioxo-hexahydro-1λ⁶-thiopyran-4-yl)-amide	1.005	533.2	1
1.126	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzo[b]thiophen-5-ylmethyl-(4-methoxy-cyclohexyl)-amide	1.301	527.2	1
1.127	(S)-N-(benzo[b]thiophen-5-ylmethyl)-N-((1R*,3S*)-3-hydroxycyclohexyl)-1-tosylpyrrolidine-2-carboxamide	1.116	513.3	1
1.128	(S)-N-(benzo[b]thiophen-5-ylmethyl)-N-((1S*,3S*)-3-hydroxycyclohexyl)-1-tosylpyrrolidine-2-carboxamide	1.181	513.2	1
1.129	(S)-N-(benzo[b]thiophen-5-ylmethyl)-N-((1R*,3S*)-3-fluorocyclopentyl)-1-tosylpyrrolidine-2-carboxamide	1.268	501.1	1
1.130	(1R*,5S*)-(2RS)-N-(benzofuran-6-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide	1.466	521.3	1

1.131	(1R,3S,4S)-2-(Toluene-4-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid benzofuran-6-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide	1.509	535.2	1
1.132	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-6-ylmethyl-(4-hydroxy-cyclohexyl)-amide	0.901	498.3	1
1.133	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(4-hydroxy-cyclohexyl)-amide	0.84	498.07	2
1.134	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-6-ylmethyl-(4-hydroxy-cyclohexyl)-amide	1.050	497.2	1
1.135	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4-hydroxy-cyclohexyl)-amide	1.102	491.3	1
1.136	(S)-1-Benzenesulfonyl-pyrrolidine-2-carboxylic acid benzofuran-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.210	503.3	1
1.137	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(5-methyl-isoxazol-4-ylmethyl)-amide	1.108	482.3	1
1.138	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (3-azetidin-1-yl-benzyl)-(4,4-difluoro-cyclohexyl)-amide	1.285	532.4	1
1.139	(2S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-tosylpyrrolidine-2-carboxamide	1.252	510.2	1
1.140	(2S)-N-(Benzo[d]thiazol-6-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-tosylpyrrolidine-2-carboxamide	1.234	510.3	1
1.141	(2S)-N-(Benzo[d]oxazol-6-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-tosylpyrrolidine-2-carboxamide	1.209	494.2	1
1.142	(2S)-N-(Benzo[d]oxazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-tosylpyrrolidine-2-carboxamide	1.216	494.2	1
1.143	(2S)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-1-tosylpyrrolidine-2-carboxamide	1.320	495.3	1
1.144	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (2,3-dihydro-benzofuran-6-ylmethyl)-(4-hydroxy-cyclohexyl)-amide	1.015	499.2	1
1.145	(S)-N-(4,4-Difluorocyclohexyl)-N-(isochroman-6-ylmethyl)-1-tosylpyrrolidine-2-carboxamide	1.210	533.3	1

Example 1.146 (S)-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-[3-(3-fluoro-oxetan-3-yl)-benzyl]-amide:

3-(3-(Diethoxymethyl)phenyl)oxetan-3-ol: To a soln. of 3-bromobenzaldehyde diethyl acetal (0.787 mL, 3.78 mmol, 1 eq) in THF (12 mL) cooled to -78°C was added under nitrogen n-butyllithium (1.6 M in hexanes, 2.84 mL, 4.54 mmol, 1.2 eq). The mixture was stirred at -78°C for 40 min. 3-Oxetanone (545 mg, 7.56 mmol, 2 eq) in THF (3 mL) was added dropwise and the reaction mixture was stirred at -78°C for 30 min. The mixture was allowed to warm up to rt and stirred for 30 min. The reaction mixture was quenched with sat. aq. NH_4Cl and extracted with EtOAc. The organic layer was washed twice with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by FC (Hept to Hept/EtOAc 7:3) to give the title compound (0.373 g, 39%) as a colorless glue. ^1H NMR (500 MHz, DMSO) *δ*: 7.64 (t, *J* = 1.6 Hz, 1 H), 7.58 (m, 1 H), 7.41 (t, *J* = 7.6 Hz, 1 H), 7.33 (m, 1 H), 6.38 (s, 1 H), 5.51 (s, 1 H), 4.78 (d, *J* = 6.8 Hz, 2 H), 4.66 (d, *J* = 6.8 Hz, 2 H), 3.53 (m, 4 H), 1.15 (t, *J* = 7.0 Hz, 6 H). LC-MS (2): t_R = 0.77 min; $[M+H]^+$: not seen.

3-(3-Fluorooxetan-3-yl)benzaldehyde: Diethylaminosulfur trifluoride (0.121 mL, 0.892 mmol, 1.5 eq) was added at - 78°C to a stirred solution of 3-(3-(diethoxymethyl)phenyl)oxetan-3-ol in DCM (8.5 mL) and was stirred for 15 min. The reaction mixture was allowed to warm to 0 °C. Aq. 1M NaOH was added carefully and extracted with DCM. The organic layer was separated and washed twice with brine. The organic layer was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to Hept/EtOAc 7:3) to give the title compound (39.5 mg, 37%) as a white solid. R_f (Hept/EtOAc 9:1)= 0.18. ^1H NMR (500 MHz, d_6-DMSO) *δ*: 10.09 (s, 1 H), 8.10 (d, *J* = 1.5 Hz, 1 H), 7.97-7.99 (m, 1 H), 7.92 (m, 1 H), 7.74 (t, *J* = 7.7 Hz, 1 H), 4.93-5.05 (m, 4 H). LC-MS (2): t_R = 0.71 min; $[M+H]^+$: not seen.

4,4-Difluoro-N-(3-(3-fluorooxetan-3-yl)benzyl)cyclohexan-1-amine: A mixture of 4,4-difluorocyclohexan-1-amine (13.9 mg, 0.1 mmol, 1 eq), 3-(3-fluorooxetan-3-yl)benzaldehyde (18 mg, 0.1 mmol, 1 eq) and sodium triacetoxyborohydride (44.6 mg, 0.2 mmol, 2 eq) in THF (1 mL) was stirred at rt for 4h. The reaction mixture was partitioned between DCM and aq. sat. $NaHCO_3$. The organic layer was separated through a phase separator cartridge and concentrated under reduced pressure to give the title compound (34 mg, 100 %) as a yellow oil. LC-MS (2): t_R= 0.61 min; $[M+H]^+$: 300.27.

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-[3-(3-fluoro-oxetan-3-yl)-benzyl]-amide: Was synthesized using 4,4-difluoro-N-(3-(3-fluorooxetan-3-yl)benzyl)cyclohexan-1-amine and tosyl-L-prolinoyl chloride as described in Example 1.24 to give the title compound. LC-MS (1): t_R= 1.212 min; $[M+H]^+$: 551.2.

Examples 1.147 (1R*,5S*)-(2RS)-N-(Benzo[d]oxazol-5-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide: Was synthesized using cis-3-azabicyclo[3.1.0]hexane-2-carboxylic acid, p-toluenesulfonyl chloride and N-(benzo[d]oxazol-5-ylmethyl)-4,4-dimethylcyclohexan-1-amine as described in Example 1.1 to give the title compound. LC-MS (1): t_R= 1.341 min; $[M+H]^+$: 522.2.

Example 1.148 (S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (5-cyclopropyl-4-ethyl-isoxazol-3-ylmethyl)-(4,4-difluoro-cyclohexyl)-amide:

tert-Butyl ((5-cyclopropylisoxazol-3-yl)methyl)carbamate: A soln. of 1-(5-cyclopropyl-3-isoxazolyl)methanamine (800 mg, 5.79 mmol, 1 eq), di-tert-butyl dicarbonate (1.61 mL, 6.95 mmol, 1.2 eq) and TEA (0.806 mL, 5.79 mmol, 1 eq) was stirred in DCM (14.5 mL) for 5 min at 0°C. The soln. was then warmed up to rt and stirred overnight. The soln. was diluted with EtOAc and washed with water, aq. sat. $NaHCO_3$, and brine. The organic layer was dried with $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept/EtOAc 6:4) to give the title compound (896 mg, 65%) as a off white solid. LC-MS (2): t_R= 0.85 min; $[M+H]^+$: 239.17.

tert-Butyl ((5-cyclopropyl-4-iodoisoxazol-3-yl)methyl)carbamate: In a 25 ml double neck flask tert-butyl ((5-cyclopropylisoxazol-3-yl)methyl)carbamate (202 mg, 0.848 mmol, 1 eq) was added to a suspension of silver trifluoroacetate (225 mg, 1.02 mmol, 1.2 eq) in DCM (4 mL), and stirred for 30 min at rt. I_2 (264 mg, 1.02 mmol, 1.2 eq) was added to the suspension and stirred at rt. After 30 min the suspension was heated under reflux for 5 h and stirred overnight at rt. The suspension was diluted with DCM and filtered. The clear solution was washed with aq. 5% $NaHSO_3$, aq. sat. $NaHCO_3$, H_2O, and brine. The organic layer was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified with FC (Hexanes/EtOAc 8:2) to give the title compound as a white solid. LC-MS (2): t_R= 0.95 min; $[M+H]^+$: 365.01.

tert-Butyl ((5-cyclopropyl-4-vinylisoxazol-3-yl)methyl)carbamate: tert-Butyl ((5-cyclopropyl-4-iodoisoxazol-3-yl)methyl)carbamate (102 mg, 0.28 mmol, 1 eq), K_2CO_3 (77.4 mg, 0.56 mmol, 2 eq), $Pd(PPh_3)_4$ (32.4 mg, 0.028 mmol, 0.1 eq) and 2,4,6-trivinylcyclotriboroxane pyridine complex (67.4 mg, 0.28 mmol, 1 eq) were dissolved in DME (2.60 mL) and water (0.90 mL) and the reaction mixture was degassed for 3 min then stirred at 100°C for 1h. The reaction mixture was cooled down to rt, diluted with DCM, and washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by FC (Hept to Hept/EtOAc 8:2) to give the title compound (67 mg, 91%) as a brown solid. R_f (Hept/ EtOAc 7:3)= 0.43; LC-MS (3): t_R= 1.01 min; $[M+H]^+$: 265.28.

tert-Butyl ((5-cyclopropyl-4-ethylisoxazol-3-yl)methyl)carbamate: tert-Butyl ((5-cyclopropyl-4-vinylisoxazol-3-yl)methyl)carbamate (66 mg, 0.25 mmol, 1 eq) was dissolved in EtOH (6 mL) and Pd/C (10% Pd, ~50% H_2O, 26.6 mg, 0.025 mmol, 0.1 eq) was added. The reaction mixture was degassed under vacuum and filled in with H_2 with the help of a balloon. The reaction mixture was then stirred at rt for 16h. The reaction mixture was filtered through a Celite® pad and the solvent was removed under reduced pressure to give the title compound (64.7 mg; 97%) as a pale solid which was used as such in the next step without further purification. LC-MS (3): t_R= 1.01 min; $[M+H]^+$: 267.23.

(5-Cyclopropyl-4-ethylisoxazol-3-yl)methanamine hydrochloride: HCl (4M in dioxane, 1.36 mL, 5.45 mmol, 22 eq) was added dropwise to a solution of tert-butyl ((5-cyclopropyl-4-ethylisoxazol-3-yl)methyl)carbamate (66 mg, 0.248 mmol, 1 eq) in DCM (2.5 mL) and the reaction mixture was stirred at rt for 2h. The reaction mixture was concentrated under reduced pressure to give the title compound (62.7 mg, 100%) as a yellow oil which was used

as such in next step without further purification. LC-MS (3): t_R= 0.67 min; $[M+H]^+$: 167.14. ^{1}H NMR (500 MHz, d_6-DMSO) *δ*: 8.56 (s, 2 H), 4.11 (bs, 2 H), 2.46 (q, *J* = 7.6 Hz, 2 H), 1.09 (t, *J* = 7.5 Hz), 2.11-2.21 (m, 1 H), 1.09 (t, *J* = 7.5 Hz), 1.05-1.08 (m), 0.91-0.94 (m, 2 H).

N-((5-Cyclopropyl-4-ethylisoxazol-3-yl)methyl)-4,4-difluorocyclohexan-1-amine: Was synthesized using (5-cyclopropyl-4-ethylisoxazol-3-yl)methanamine hydrochloride and 4,4-difluorocyclohexanone as described in Example 1.146 to give the title compound. LC-MS (3): t_R= 1.04 min; $[M+H]^+$: 285.25.

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (5-cyclopropyl-4-ethyl-isoxazol-3-ylmethyl)-(4,4-difluoro-cyclohexyl)-amide: Was synthesized using N-((5-cyclopropyl-4-ethylisoxazol-3-yl)methyl)-4,4-difluorocyclohexan-1-amine and tosyl-L-prolinoyl chloride as described in Example 1.24 to give the title compound. LC-MS (1): t_R= 1.305 min; $[M+H]^+$: 536.04.

Examples 1.149 to **Example 1.152** were synthesized according to the procedures described herein before using the appropriate amine or amine salt derivative, the appropriate aldehyde or ketone and the appropriate amino acid or aminoester and the appropriate sulfonyl chloride. LC-MS data of Example 1.149 to Example 1.152 are listed in the table below.

Ex. N°	Name	t_R	$[M+H]^+$	LC-MS conditions
1.149	(1R*,5S*)-(2RS)-N-(Benzo[d]oxazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide	1.02	530.11	2
1.150	(1R*,5S*)-(2RS)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide	1.372	538.4	1
1.151	(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide	1.298	542.3	1
1.152	(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.124	550.2	1

Example 1.153 (S)-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-ethyl-5-methyl-isoxazol-3-ylmethyl)-amide:

tert-Butyl ((5-methylisoxazol-3-yl)methyl)carbamate: A soln. of 1-(5-methylisoxazol-3-yl)methanamine (270 mg, 2.41 mmol, 1 eq), di-tert-butyl dicarbonate (0.67 mL, 2.89 mmol, 1.2 eq), and TEA (0.335 mL, 2.41 mmol, 1 eq) was stirred in DCM (5.5 mL) for 5 min at 0°C. The solution was then warmed up to rt and stirred overnight. The soln. was diluted with EtOAc and washed with water, aq. sat. $NaHCO_3$, and brine. The organic layer was dried with

$MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept/EtOAc 7:3) to give the title compound (455 mg, 89%) as an off white solid. LC-MS (3): t_R= 0.78 min; $[M+H]^+$: 213.28.

tert-Butyl ((4-iodo-5-methylisoxazol-3-yl)methyl)carbamate: In a 25 ml double neck flask tert-butyl ((5-methylisoxazol-3-yl)methyl)carbamate (454 mg, 2.14 mmol, 1 eq) was added to a suspension of silver trifluoroacetate (579 mg, 2.57 mmol, 1.2 eq) in DCM (10 mL), and stirred for 30 min at rt. I_2 (653 mg, 2.57 mmol, 1.2 eq) was added to the suspension and stirred at rt overnight. After 30 min the suspension was heated under reflux for 5 h and stirred overnight at rt. The suspension was diluted with DCM and filtered. The clear soln. was washed with $NaHSO_3$, $NaHCO_3$, H_2O, and brine. The organic layer was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified with FC (Hexanes/EtOAc 9:1) to give the title compound (0.508 g, 70%) as a white solid. LC-MS (3): t_R= 0.93 min; $[M+H]^+$: 339.12.

tert-Butyl ((5-methyl-4-vinylisoxazol-3-yl)methyl)carbamate: tert-Butyl ((4-iodo-5-methylisoxazol-3-yl)methyl)carbamate (150 mg, 0.444 mmol, 1 eq), K_2CO_3 (123 mg, 0.887 mmol, 2 eq), $Pd(PPh_3)_4$ (51.3 mg, 0.0444 mmol, 0.1 eq) and 2,4,6-trivinylcyclotriboroxane pyridine complex (107 mg, 0.444 mmol, 1 eq) were dissolved in DME (4.1 mL) and water (1.4 mL) and the reaction mixture was degassed for 3 min then stirred at 100°C for 30 min. The reaction mixture was cooled to rt, diluted with DCM, and washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by FC (Hept to Hept/EtOAc 9/1) to give the title compound (94 mg; 89%) as a pale brown solid. LC-MS (3): t_R= 0.90 min; $[M+H]^+$: 239.22.

tert-Butyl ((4-ethyl-5-methylisoxazol-3-yl)methyl)carbamate: tert-Butyl ((5-methyl-4-vinylisoxazol-3-yl)methyl)carbamate (46.5 mg, 0.195 mmol, 1 eq) was dissolved in EtOH (4.5 mL) and Pd/C (10% Pd, ~50% H_2O, 20.8 mg, 0.0195 mmol, 0.1 eq) was added. The reaction mixture was degassed with vacuum and then filled with H_2 with a balloon. The reaction mixture was then stirred at rt for 16h. The reaction mixture was filtered through Celite® pad and the solvent was removed under reduced pressure to give the title compound (43 mg; 92%) as a pale solid which was used as such in the next step without further purification. LC-MS (3): t_R = 0.91 min; $[M+H]^+$: 241.25.

(4-Ethyl-5-methylisoxazol-3-yl)methanamine hydrochloride: HCl (4M in dioxane, 0.955 mL, 3.82 mmol, 22 eq) was added dropwise to a soln. of (4-ethyl-5-methylisoxazol-3-yl)methanamine (46.9 mg, 0.195 mmol, 1 eq) in DCM (2.0 mL) and the reaction mixture was stirred at rt for 3h. The reaction mixture was concentrated under reduced pressure to give the title compound (62.7 mg, 100%) as a yellow oil which was used as such in next step without further purification. LC-MS (3): t_R= 0.54 min; $[M+H]^+$: 141.16.

N-((4-Ethyl-5-methylisoxazol-3-yl)methyl)-4,4-difluorocyclohexan-1-amine: Was synthesized using (4-ethyl-5-methylisoxazol-3-yl)methanamine hydrochloride and 4,4-difluorocyclohexanone as described in Example 1.146 to give the title compound. LC-MS (3): t_R= 0.95 min; $[M+H]^+$: 259.32.

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-ethyl-5-methyl-isoxazol-3-ylmethyl)-amide: Was synthesized using N-((4-ethyl-5-methylisoxazol-3-yl)methyl)-4,4-difluorocyclohexan-1-amine and tosyl-L-prolinoyl chloride as described in Example 1.24 to give the title compound. LC-MS (1): t_R= 1.241 min; $[M+H]^+$: 510.2.

Example 1.154 to **Example 1.164** were synthesized according to the procedures described herein before using the appropriate amine or amine salt derivative, the appropriate aldehyde and the appropriate amino acid or aminoester and the appropriate sulfonyl chloride. LC-MS data of Example 1.154 to Example 1.164 are listed in the table below.

Ex. N°	Name	t_R	$[M+H]^+$	LC-MS conditions
1.154	(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide	1.08	526.16	2
1.155	(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-6-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide	1.253	526.4	1
1.156	(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	0.98	534.19	2
1.157	(S)-3-(Toluene-4-sulfonyl)-oxazolidine-4-carboxylic acid benzofuran-6-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide	1.411	511.2	1
1.158	(2S,4S)-4-Hydroxy-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzyl-(4,4-dimethyl-cyclohexyl)-amide	1.12	485.20	2
1.159	(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.080	534.2	1
1.160	(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (2,3-dihydro-benzofuran-6-ylmethyl)-(4,4-dimethyl-cyclohexyl)-amide	1.372	527.3	1
1.161	(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.193	535.2	1
1.162	(2S)-N-(4,4-Difluorocyclohexyl)-N-((2-methyl-2,3-dihydrobenzofuran-6-yl)methyl)-1-tosylpyrrolidine-2-carboxamide	1.285	533.3	1
1.163	(S)-N-(4,4-Difluorocyclohexyl)-N-(isochroman-7-ylmethyl)-1-tosylpyrrolidine-2-carboxamide	1.221	533.3	1
1.164	(2S)-N-(Benzofuran-6-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-tosylpyrrolidine-2-carboxamide	1.350	493.3	1

Example 1.165 (1S,2S,5R)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide: Was prepared as described herein before using (1S,2S,5R)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid hydrochloride and N-(benzo[d]thiazol-5-ylmethyl)-4,4-difluorocyclohexan-1-amine to give the title compound as a white solid. LC-MS (2): t_R= 1.05 min, $[M+H]^+$: 546.08.

Example 1.166 to **Example 1.188** were synthesized according to the procedures described herein before using the appropriate amine or amine salt derivative, the appropriate aldehyde and the appropriate amino acid or aminoester and the appropriate sulfonyl chloride. LC-MS data of Example 1.166 to Example 1.188 are listed in the table below.

Ex. N°	Name	t_R	$[M+H]^+$	LC-MS conditions
1.166	(2S)-N-(4,4-Difluorocyclohexyl)-N-((3-methyl-2,3-dihydrobenzofuran-6-yl)methyl)-1-tosylpyrrolidine-2-carboxamide	1.286	533.4	1
1.167	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid chroman-7-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.290	533.2	1
1.168	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(3-oxo-2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.126	533.2	1
1.169	(S)-3-(Toluene-4-sulfonyl)-oxazolidine-4-carboxylic acid benzofuran-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.238	519.3	1
1.170	(S)-3-(Toluene-4-sulfonyl)-oxazolidine-4-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.151	536.1	1
1.171	(S)-3-(Toluene-4-sulfonyl)-oxazolidine-4-carboxylic acid benzooxazol-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide	1.285	512.2	1
1.172	(S)-3-(Toluene-4-sulfonyl)-oxazolidine-4-carboxylic acid benzooxazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.117	520.2	1
1.173	(2S,4S)-4-Ethoxy-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzyl-(4,4-dimethyl-cyclohexyl)-amide	1.461	513.4	1
1.174	(2S,4S)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.201	537.2	1
1.175	(2S)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-(3-methoxybenzyl)-1-tosylpyrrolidine-2-carboxamide	1.327	483.3	1
1.176	(S)-N-(4,4-Difluorocyclohexyl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-1-tosylpyrrolidine-2-carboxamide	1.389	517.2	1

1.177	(2S,4S)-4-Fluoro-1-(4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.066	552.1	1
1.178	(2S,4S)-4-Fluoro-1-(4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.092	568.3	1
1.179	(2S,4S)-4-Fluoro-1-(4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.164	553.2	1
1.180	(2S,4S)-4-Fluoro-1-(4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide	1.229	544.3	1
1.181	(2S,4S)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-4-fluoro-1-tosylpyrrolidine-2-carboxamide	1.276	513.3	1
1.182	(2S,4S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-4-fluoro-1-tosylpyrrolidine-2-carboxamide	1.205	528.3	1
1.183	(2S)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-((5-methylisoxazol-4-yl)methyl)-1-tosylpyrrolidine-2-carboxamide	1.180	458.3	1
1.184	(2S,4S)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-4-fluoro-1-((4-methoxyphenyl)sulfonyl)pyrrolidine-2-carboxamide	1.235	529.4	1
1.185	(S)-1-(Toluene-4-sulfonyl)-azetidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.180	505.2	1
1.186	(S)-1-(Toluene-4-sulfonyl)-azetidine-2-carboxylic acid benzooxazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.069	504.3	1
1.187	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(3-fluoro-5-methoxy-benzyl)-amide	1.271	525.2	1
1.188	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2-fluoro-5-methoxy-benzyl)-amide	1.276	525.2	1

Example 1.189 (S)-1-Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(5-fluoro-2,3-dihydro-benzofuran-6-ylmethyl)-amide:

Potassium (((4,4-difluorocyclohexyl)amino)methyl)trifluoroborate: An oven-dried microwave vial equipped with a stirrer bar was charged with potassium (bromomethyl)trifluoroborate (3347 mg, 15 mmol, 1 eq), sealed and

put under a N_2 atmosphere. Then THF (5 mL), t-BuOH (3.75 mL) and 4,4-difluorocyclohexan-1-amine (2508 mg, 18 mmol, 1.2 eq) in THF (2.5 mL) were added. The resulting mixture was placed in an oil bath at rt and then gradually heated to 60 °C and stirred at this temperature overnight. The suspension was cooled down to rt and concentrated, the solid was suspended in hot (~ 50-60 °C) MeCN (120 mL). The white precipitate was filtered off on a 0.45 micron Whatmann filter. The filtrate was concentrated and the same operation was repeated. The filtrate was concentrated and dissolved in a minimal amount of hot MeCN (30 mL). Then, Et_2O was added dropwise. The precipitate was filtered off and washed with Et_2O/Heptane. The white powder was dried under high vacuum to give the title compound (2.03 g, 62%) as a white solid. LC-MS (3): t_R= 0.46 min; $[M-H]^+$: 215.98; ^1H NMR (500 MHz, d_6-DMSO) δ: 7.67 (s, 2 H), 2.87-3.09 (m, 1 H), 2.05-2.11 (m, 4 H), 1.79-1.98 (m, 2 H), 1.75 (m, 2 H), 1.48-1.56 (m, 2 H).

4,4-Difluoro-N-((5-fluorobenzofuran-6-yl)methyl)cyclohexan-1-amine: An oven-dried microwave vial equipped with a stirrer bar was charged with 6-bromo-5-fluorobenzofuran (WO20140274695) (148 mg, 0.69 mmol, 1 eq), potassium (((4,4-difluorocyclohexyl)amino)methyl)trifluoroborate (193 mg, 0.889 mmol, 1.289 eq), $P(tBu)_3Pd$ G2 (35.4 mg, 0.069 mmol, 0.1 eq) and Cs_2CO_3 (674 mg, 2.07 mmol, 3 eq), sealed, and placed under N_2 atmosphere. Then, THF (7 mL) and water (7 mL) were added and the resulting mixture was degassed for 5 min under a nitrogen stream and then stirred at 90 °C (pre-heated heating block) overnight. The residue was purified by cation exchange resin. The basic fractions were further purified by prep. HPLC to give the title compound (25.2 mg, 13%) as a yellow oil. LC-MS (2): t_R= 0.65 min; $[M+H]^+$: 284.25.

4,4-Difluoro-N-((5-fluoro-2,3-dihydrobenzofuran-6-yl)methyl)cyclohexan-1-amine: To a solution of 4,4-difluoro-N-((5-fluorobenzofuran-6-yl)methyl)cyclohexan-1-amine (24 mg, 0.0846 mmol, 1 eq) in EtOH (1 mL) was added Pd/C (10% Pd, 50% H_2O, 9 mg, 0.0085 mmol, 0.1 eq) and the mixture was stirred at rt under a H_2 atmosphere overnight. The mixture was filtered over Celite®, and wahed with EtOH. The filtrate was concentrated under reduced pressure to give the title compound (23.7 mg, 97 %) as a light yellow oil. LC-MS (2): t_R= 0.62 min; $[M+H]^+$: 286.24.

(S)-N-(4,4-Difluorocyclohexyl)-N-((5-fluoro-2,3-dihydrobenzofuran-6-yl)methyl)-1-tosylpyrrolidine-2-carboxamide: Was synthesized using 4,4-difluoro-N-((5-fluoro-2,3-dihydrobenzofuran-6-yl)methyl)cyclohexan-1-amine and tosyl-L-prolinoyl chloride as described in Example 1.24 to give the title compound as a white solid. LC-MS (1): t_R = 1.260 min; $[M+H]^+$: 537.2.

Example 1.190 to **Example 1.196** were synthesized according to the procedures described herein before using the appropriate amine or amine salt derivative, the appropriate aldehyde or ketone, the appropriate amino acid or aminoester and the appropriate sulfonyl chloride. LC-MS data of Example 1.190 to Example 1.196 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
1.190	(1S,3S,5S)-2-(Toluene-4-sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.290	531.2

1.191	(1S,3S,5S)-2-(Toluene-4-sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid benzooxazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.186	530.2
1.192	(1R,3S,5R)-2-(Toluene-4-sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.230	531.2
1.193	(2S,4S)-N-(benzo[d]oxazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-4-fluoro-1-tosylpyrrolidine-2-carboxamide	1.175	512.2
1.194	(2S)-N-(bicyclo[4.1.0]heptan-3-yl)-1-((4-methoxyphenyl)sulfonyl)-N-((5-methylisoxazol-4-yl)methyl)pyrrolidine-2-carboxamide	1.136	474.2
1.195	(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-dimethyl-cyclohexyl)-(5-methyl-isoxazol-4-ylmethyl)-amide	1.237	490.2
1.196	(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(5-methyl-isoxazol-4-ylmethyl)-amide	1.071	498.2

Example 1.197 (S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-fluoro-2,3-dihydro-benzofuran-6-ylmethyl)-amide:

2-(2,5-Dibromo-3-fluorophenoxy)ethan-1-ol: 2,5-Dibromo-1,3-difluorobenzene (2500 mg, 9.01 mmol, 1 eq) was dissolved in NMP (1.9 mL) and ethylene glycol (2.53 mL, 45.1 mmol, 5 eq) was added. Potassium tert-butoxide (1217 mg, 10.8 mmol, 1.203 eq) was added portionwise at 0 °C and the resulting mixture was stirred at 90 °C overnight. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed twice with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by FC (Hept to Hept/EtOAc 7:3) to give the title compound (1.402 g, 50%) as a white solid. LC-MS (2): t_R = 0.86 min; $[M+H]^+$: not seen; ^1H NMR (500 MHz,d_6-DMSO) δ: 7.31 (dd, J_1 = 2.0 Hz, J_2 = 8.1 Hz, 1 H), 7.23 (t, J = 1.8 Hz, 1 H), 4.92 (t, J = 5.3 Hz, 1 H), 4.15 (m, 2 H), 3.74 (m, 2 H).

2,5-Dibromo-1-(2-bromoethoxy)-3-fluorobenzene: PBr_3 (0.214 mL, 2.24 mmol, 0.5013 eq) was added dropwise to a solution of 2-(2,5-dibromo-3-fluorophenoxy)ethan-1-ol (1400 mg, 4.46 mmol, 1 eq) in toluene (9.2 mL) at 0°C. The resulting yellow solution was stirred at 90 °C for 4h. The reaction mixture was cooled to 0 °C and aq. 1M NaOH was added dropwise. The white suspension was filtered on a Celite® pad and the cake was washed with EtOAc. The filtrates were washed 3x with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by FC (Hept to Hept/EtOAc 95:5) to give the title compound (1.126 g, 67%) as as a white solid. LC-MS (2): t_R = 1.06 min; $[M+H]^+$: not seen; ^1H NMR (400 MHz, d_6-DMSO) δ: 7.36 (d, J = 8.1 Hz, 1 H), 7.24-7.28 (m, 1 H), 4.44-4.53 (m, 2 H), 3.80-3.87 (m, 2 H).

4-Fluoro-2,3-dihydrobenzofuran-6-carbaldehyde: To a stirred solution of 2,5-dibromo-1-(2-bromoethoxy)-3-fluorobenzene (900 mg, 2.39 mmol, 1 eq) in dry THF (8.4 mL) at -78 °C, n-butyllithium 1.6 M in hexanes (1.65 mL, 2.64 mmol, 1.106 eq) was added dropwise under nitrogen for 45 min. After this time n-Butyllithium 1.6 M in hexanes

(1.65 mL, 2.64 mmol, 1.106 eq) was added again and the resulting mixture was stirred for additional 45min at -78 °C. DMF (0.368 mL, 4.78 mmol, 2 eq) was then added dropwise at -78 °C and the mixture was stirred at this temperature for 30min. The reaction mixture was allowed to reach rt and was then quenched with sat. aq. NH_4Cl and extracted with EtOAc. The organic layer was washed twice with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with FC (Hept to Hept/EtOAc 9:1) to give the title compound (270 mg, 68%) as a white solid. LC-MS (2): t_R = 0.79 min; $[M+H]^+$: not seen;^{1}H NMR (500 MHz, d_6-DMSO) δ: 9.89 (d, J = 1.5 Hz, 1 H), 7.27 (dd, J_1 = 1.0 Hz, J_2 = 8.5 Hz, 1 H), 7.14 (d, J = 0.9 Hz, 1 H), 4.70 (t, J = 8.8 Hz, 2 H), 3.33 (t, J = 9.0 Hz, 2 H).

4,4-Difluoro-N-((4-fluoro-2,3-dihydrobenzofuran-6-yl)methyl)cyclohexan-1-amine: Was synthesized using 4-fluoro-2,3-dihydrobenzofuran-6-carbaldehyde and 4,4-difluorocyclohexan-1-amine as described in Example 1.146 to give the title compound as a light yellow oil. LC-MS (2): t_R = 0.64 min; [M+H]+: 286.32.

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-fluoro-2,3-dihydro-benzofuran-6-ylmethyl)-amide: Was synthesized using 4,4-difluoro-N-((4-fluoro-2,3-dihydrobenzofuran-6-yl)methyl)cyclohexan-1-amine and tosyl-L-prolinoyl chloride as described in Example 1.24 to give the title compound as a white solid. LC-MS (1): t_R = 1.256 min; $[M+H]^+$: 537.4.

Example 1.198 to **Example 1.208** were synthesized according to the procedures described herein before using the appropriate amine or amine salt derivative, the appropriate aldehyde or ketone, the appropriate amino acid or aminoester and the appropriate sulfonyl chloride. LC-MS data of Example 1.198 to Example 1.208 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
1.198	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(6,7-dihydro-5H-[1]pyrindin-2-ylmethyl)-amide	1.054	518.3
1.199	(2S)-N-(Benzo[d]oxazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-((4-methoxyphenyl)sulfonyl)pyrrolidine-2-carboxamide	1.167	510.2
1.200	(2S)-N-(Benzo[d]oxazol-6-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-((4-methoxyphenyl)sulfonyl)pyrrolidine-2-carboxamide	1.152	510.3
1.201	(2S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-((4-methoxyphenyl)sulfonyl)pyrrolidine-2-carboxamide	1.204	526.2
1.202	(2S)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-1-((4-methoxyphenyl)sulfonyl)pyrrolidine-2-carboxamide	1.279	511.2
1.203	(2S)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrofuro[3,2-b]pyridin-6-yl)methyl)-1-tosylpyrrolidine-2-carboxamide	1.070	496.3

1.204	5-(Toluene-4-sulfonyl)-5-aza-spiro[2.4]heptane-4-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.297	545.4
1.205	N-(4,4-difluorocyclohexyl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-4-methyl-1-tosylazetidine-2-carboxamide	1.256	519.3
1.206	(S)-4-Methylene-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.283	531.3
1.207	N-(4,4-Difluorocyclohexyl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-4-methyl-1-tosylazetidine-2-carboxamide	1.212	535.2
1.208	rac-4,4-Dimethyl-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.322	547.4

Example 1.209 (2S,4S)-4-Fluoro-1-(4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1S,3R,6S)-bicyclo[4.1.0]hept-3-yl-(2,3-dihydro-benzofuran-6-ylmethyl)-amide, Example 1.210 (2S,4S)-4-fluoro-1-(4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1R,3R,6R)-bicyclo[4.1.0]hept-3-yl-(2,3-dihydro-benzofuran-6-ylmethyl)-amide and Example 1.211 (2S,4S)-4-fluoro-1-(4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1S,3R,6S)-bicyclo[4.1.0]hept-3-yl-(2,3-dihydro-benzofuran-6-ylmethyl)-amide: Were obtained by preparative chiral separation (SFC 1 method) of (2S,4S)-N-(bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-4-fluoro-1-((4-methoxyphenyl)sulfonyl)pyrrolidine-2-carboxamide (Example 1.184) to give Example 1.209 (first eluting), 1.210 (second eluting) and Example 1.211 (third eluting). Stereochemistry was arbitrarily assigned. Example 1.209: LC-MS (1): t_R = 1.246 min; $[M+H]^+$: 529.2; Example 1.210: LC-MS (1): t_R = 1.240 min; $[M+H]^+$: 529.2 and Example 1.211: LC-MS (1): t_R = 1.234 min; $[M+H]^+$: 529.2.

Example 1.212 to **Example 1.234** were synthesized according to the procedures described herein before using the appropriate amine or amine salt derivative, the appropriate aldehyde or ketone, the appropriate amino acid or aminoester and the appropriate sulfonyl chloride. LC-MS data of Example 1.212 to Example 1.234 are listed in the table below.

Ex. N°	Name	t_R	$[M+H]^+$	LC-MS conditions
1.212	(S)-N-(4,4-difluorocyclohexyl)-N-(furo[3,2-c]pyridin-6-ylmethyl)-1-tosylpyrrolidine-2-carboxamide	0.999	518.3	1
1.213	(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-fluoro-2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.215	553.3	1

1.214	(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(5-fluoro-2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.05	553.19	2
1.215	(1R,3S,5R)-2-(4-Methoxy-benzenesulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.186	547.2	1
1.216	(1R*,5S*)-(2RS)-3-(4-Methoxy-benzenesulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.151	562.2	1
1.217	(2S,4R)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.219	537.2	1
1.218	(1R,3S,5R)-2-(4-Methoxy-benzenesulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.119	562.2	1
1.219	(1R,3S,5R)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-2-tosyl-2-azabicyclo[3.1.0]hexane-3-carboxamide	1.244	522.1	1
1.220	(1R,3S,5R)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-2-((4-methoxyphenyl)sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxamide	1.198	538.2	1
1.221	(1R,3S,5R)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-2-tosyl-2-azabicyclo[3.1.0]hexane-3-carboxamide	1.314	507.2	1
1.222	(1R,3S,5R)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-2-((4-methoxyphenyl)sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxamide	1.265	523.2	1
1.223	(1R,3S,5R)-2-(4-Methoxy-benzenesulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid benzooxazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	0.96	546.07	3
1.224	(1R,3S,5R)-2-(Toluene-4-sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.155	546.3	1
1.225	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid indan-5-ylmethyl-(tetrahydro-pyran-4-yl)-amide	1.237	483.3	1
1.226	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(5-methyl-isothiazol-4-ylmethyl)-amide	1.146	498.3	1

1.227	(S)-N-(4,4-Difluorocyclohexyl)-N-(quinolin-7-ylmethyl)-1-tosylpyrrolidine-2-carboxamide	0.969	528.3	1
1.228	(S)-N-(4,4-Difluorocyclohexyl)-N-(isoquinolin-7-ylmethyl)-1-tosylpyrrolidine-2-carboxamide	0.856	528.3	1
1.229	(S)-N-(4,4-Difluorocyclohexyl)-N-(isoquinolin-3-ylmethyl)-1-tosylpyrrolidine-2-carboxamide	1.171	528.3	1
1.230	(S)-N-(4,4-Difluorocyclohexyl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-1-((4-methoxyphenyl)sulfonyl)pyrrolidine-2-carboxamide	1.340	533.2	1
1.231	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(6,7-dihydro-5H-[2]pyrindin-3-ylmethyl)-amide	0.896	518.2	1
1.232	(S)-N-(4,4-Difluorocyclohexyl)-N-(furo[2,3-b]pyridin-6-ylmethyl)-1-tosylpyrrolidine-2-carboxamide	1.179	518.3	1
1.233	(1R,2S,5S)-3-(Toluene-4-sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.262	531.2	1
1.234	(1R,2S,5S)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide	1.346	507.3	1

Example 1.235 (S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(7-fluoro-2,3-dihydro-benzofuran-6-ylmethyl)-amide:

4,4-Difluoro-N-((7-fluorobenzofuran-6-yl)methyl)cyclohexan-1-amine: Was synthesized using potassium (((4,4-difluorocyclohexyl)amino)methyl)trifluoroborate and 6-bromo-7-fluoro-2,3-dihydrobenzofuran as described in Example 1.189 to give the title compound as a yellow oil. LC-MS (2): t_R = 0.66 min; $[M+H]^+$: 284.20.

4,4-Difluoro-N-((7-fluoro-2,3-dihydrobenzofuran-6-yl)methyl)cyclohexan-1-amine: Was synthesized using 4,4-difluoro-N-((7-fluorobenzofuran-6-yl)methyl)cyclohexan-1-amine as described in Example 1.189 to give the title compound as a yellow oil. LC-MS (2): t_R = 0.62 min; $[M+H]^+$: 286.35.

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(7-fluoro-2,3-dihydro-benzofuran-6-ylmethyl)-amide: Was synthesized using 4,4-difluoro-N-((7-fluoro-2,3-dihydrobenzofuran-6-yl)methyl)cyclohexan-1-amine and tosyl-L-prolinoyl chloride as described in Example 1.189 to give the title compound as a white solid. LC-MS (1): t_R = 1.249 min; $[M+H]^+$: 537.3.

Example 1.236 to **Example 1.266** were synthesized according to the procedures described herein before using the appropriate amine or amine salt derivative, the appropriate aldehyde or ketone, the appropriate amino acid or

aminoester and the appropriate sulfonyl chloride. LC-MS data of Example 1.236 to Example 1.266 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
1.236	(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(7-fluoro-2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.211	553.2
1.237	(2S,4S)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(5-methyl-isoxazol-4-ylmethyl)-amide	1.091	500.1
1.238	(2S,4S)-N-(Bicyclo[4.1.0]heptan-3-yl)-4-fluoro-N-((5-methylisoxazol-4-yl)methyl)-1-tosylpyrrolidine-2-carboxamide	1.141	476.4
1.239	(1R*,5S*)-(2RS)-3-(Toluene-4-sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(5-methyl-isoxazol-4-ylmethyl)-amide	1.137	494.3
1.240	(1R*,5S*)-(2RS)-N-(bicyclo[4.1.0]heptan-3-yl)-N-((5-methylisoxazol-4-yl)methyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide	1.216	470.2
1.241	(1R*,5S*)-(2RS)-3-(4-Methoxy-benzenesulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(5-methyl-isoxazol-4-ylmethyl)-amide	1.094	510.3
1.242	(1R*,5S*)-(2RS)-3-N-(bicyclo[4.1.0]heptan-3-yl)-3-((4-methoxyphenyl)sulfonyl)-N-((5-methylisoxazol-4-yl)methyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide	1.170	486.2
1.243	(1R*,5S*)-(2RS)-3-(4-Methoxy-benzenesulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.219	547.2
1.244	(1S*,5R*)-(2RS)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-3-((4-methoxyphenyl)sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide	1.228	538.3
1.245	(1R*,5S*)-(2RS)-N-(bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-3-((4-methoxyphenyl)sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide	1.304	523.2
1.246	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-furo[3,2-c]pyridin-6-ylmethyl)-amide	0.749	520.3
1.247	(1R,3S,5R)-2-(Toluene-4-sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (4,4-difluoro-cyclohexyl)-(5-methyl-isoxazol-4-ylmethyl)-amide	1.111	494.2
1.248	(1R,3S,5R)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-((5-methylisoxazol-4-yl)methyl)-2-tosyl-2-azabicyclo[3.1.0]hexane-3-carboxamide	1.173	470.3
1.249	(1R,3S,5R)-N-(Bicyclo[4.1.0]heptan-3-yl)-2-((4-methoxyphenyl)sulfonyl)-N-((5-methylisoxazol-4-yl)methyl)-2-azabicyclo[3.1.0]hexane-3-carboxamide	1.126	486.3

1.250	(1R,3S,5R)-2-(Toluene-4-sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-fluoro-2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.253	549.3
1.251	(1R,3S,5R)-2-(4-Methoxy-benzenesulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-fluoro-2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.211	565.2
1.252	(1R,3S,5R)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-((4-fluoro-2,3-dihydrobenzofuran-6-yl)methyl)-2-tosyl-2-azabicyclo[3.1.0]hexane-3-carboxamide	1.333	525.4
1.253	(1R,3S,5R)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-((4-fluoro-2,3-dihydrobenzofuran-6-yl)methyl)-2-((4-methoxyphenyl)sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxamide	1.286	541.3
1.254	(1R,3S,5R)-2-(Toluene-4-sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (4,4-difluoro-cyclohexyl)-(5-fluoro-2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.252	549.2
1.255	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2-isopropyl-thiazol-5-ylmethyl)-amide	1.221	526.2
1.256	(S)-1-(3-Fluoro-4-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.270	537.2
1.257	(S)-1-(3-Fluoro-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.213	523.3
1.258	(S)-1-(4-Fluoro-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.216	523.2
1.259	(S)-1-(4-Fluoro-3-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.262	537.3
1.260	(S)-1-(6-Methyl-pyridine-3-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.106	520.3
1.261	(S)-1-(6-Methoxy-pyridine-3-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.192	536.2
1.262	(S)-1-(3-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.204	535.3
1.263	(S)-1-(3-Fluoro-4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.210	553.2
1.264	(S)-1-(4-Chloro-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.281	539.2
1.265	(S)-1-(4-Cyclopropyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.290	545.2

1.266	(2S,5R)-5-Methyl-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.311	533.3

Example 1.267 (S)-2-(Toluene-4-sulfonyl)-3,4-dihydro-2H-pyrazole-3-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide: Was synthesized using (S)-1-(tert-butoxycarbonyl)-4,5-dihydro-1H-pyrazole-5-carboxylic acid (WO2012122450), N-((2,3-dihydrobenzofuran-6-yl)methyl)-4,4-difluorocyclohexan-1-amine, and 4-methylbenzenesulfonyl chloride as described in Example 1.33 to give the title compound as a white solid. LC-MS (2): t_R = 1.01 min; $[M+H]^+$: 518.33.

Example 1.268 (S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(5-isopropyl-thiazol-2-ylmethyl)-amide:

4,4-Difluoro-N-((5-isopropylthiazol-2-yl)methyl)cyclohexan-1-amine: Was synthesized using 4,4-difluorocyclohexan-1-amine and 5-(propan-2-yl)-1,3-thiazole-2-carbaldehyde as described in Example 1.1 to give the title compound as a yellow oil. LC-MS (2): t_R = 1.02 min; $[M+H]^+$: 275.08.

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(5-isopropyl-thiazol-2-ylmethyl)-amide: Was synthesized using 4,4-difluoro-N-((5-isopropylthiazol-2-yl)methyl)cyclohexan-1-amine and tosyl-L-prolinoyl chloride as described in Example 1.189 to give the title compound as a off-white solid. LC-MS (1): t_R = 1.281 min; $[M+H]^+$: 526.3.

Example 1.269 (2S)-N-(4,4-Difluorocyclohexyl)-N-(1-(2,3-dihydrobenzofuran-6-yl)ethyl)-1-tosylpyrrolidine-2-carboxamide:

(2S)-N-(1-(Benzofuran-6-yl)ethyl)-N-(4,4-difluorocyclohexyl)-1-tosylpyrrolidine-2-carboxamide: Was synthesized using 1-(benzofuran-6-yl)ethan-1-one, 4,4-difluorocyclohexan-1-amine, and tosyl-L-prolinoyl chloride as described in Example 1.189 to give the title compound as a off-white solid. LC-MS (2): t_R = 0.67 min; $[M+H]^+$: 280.25.

(2S)-N-(4,4-Difluorocyclohexyl)-N-(1-(2,3-dihydrobenzofuran-6-yl)ethyl)-1-tosylpyrrolidine-2-carboxamide: To a soln. of (2S)-N-(1-(benzofuran-6-yl)ethyl)-N-(4,4-difluorocyclohexyl)-1-tosylpyrrolidine-2-carboxamide (26 mg, 0.049 mmol, 1 eq) in EtOH (0.5 mL) was added Pd/C (10%, 5.2 mg, 0.0049 mmol, 0.1 eq) and the reaction mixture was stirred under a H_2 atmosphere overnight. The reaction mixture was filtered over Celite®, and the cake was washed with EtOH. The filtrate was concentrated under reduced pressure to give the title compound (21.6 mg, 83%) as a light yellow glue. LC-MS(1): t_R = 1.290 min; $[M+H]^+$: 533.4.

Example 1.270 (S)-1-(Toluene-4-sulfonyl)-2,3-dihydro-1H-pyrrole-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide:

Methyl (S)-2-((4-Methylphenyl)sulfonamido)pent-4-ynoate: p-Toluenesulfonyl chloride (320 mg, 1.66 mmol, 1.1 eq) was added at rt to a stirred solution of L-propargylglycine methyl ester hydrochloride (250 mg, 1.51 mmol, 1 eq) and DIPEA (0.647 mL, 3.78 mmol, 2.5 eq) in DCM (10 mL). The resulting mixture was stirred at rt overnight. The reaction mixture was diluted with DCM and washed once with brine. The organic layer was separated through a phase separator cartridge and concentrated under reduced pressure. The residue was purified by FC (Hept to Hept/EtOAc 7:3) to give the title compound (305 mg, 72 %) as a white solid. LC-MS (2): t_R = 0.83 min; $[M+H]^+$: 282.21.

(S)-1-Tosyl-2,3-dihydro-1H-pyrrole-2-carboxylic acid: A microwave vial equipped with a stirrer bar was charged with methyl (S)-2-((4-methylphenyl)sulfonamido)pent-4-ynoate (96 mg, 0.341 mmol, 1 eq), Pd (II) acetate (7.66 mg, 0.0341 mmol, 0.1 eq), triphenylphosphine (18.1 mg, 0.0682 mmol, 0.2 eq) and K_2CO_3 (236 mg, 1.71 mmol, 5 eq), and then sealed. THF (3.4 mL) was added under nitrogen and the resulting mixture was degassed for 5 min under a nitrogen stream and then stirred at 45 °C for 24h. Lithium hydroxide monohydrate (21.5 mg, 0.512 mmol, 1.5 eq) was added and the mixture was stirred at rt for 4h and then diluted with EtOAc and water. The layers were separated. The aq. layer was slowly acidified to pH=1-2 using aq. 1M HCl and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the title compound (88 mg, 97%) as a beige solid, which was used as such in the next step without further purification. LC-MS (2): t_R = 0.74 min; $[M+H]^+$: 268.23.

(S)-1-(Toluene-4-sulfonyl)-2,3-dihydro-1H-pyrrole-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide: Was synthesized using (S)-1-tosyl-2,3-dihydro-1H-pyrrole-2-carboxylic acid and N-((2,3-dihydrobenzofuran-6-yl)methyl)-4,4-difluorocyclohexan-1-amine as described in Example 1.33 to give the title compound as a beige solid. LC-MS(1): t_R = 1.228 min; $[M+H]^+$: 517.2.

Example 1.271 to **Example 1.301** were synthesized according to the procedures described herein before using the appropriate amine or amine salt derivative, the appropriate aldehyde or ketone, the appropriate amino acid or aminoester and the appropriate sulfonyl chloride. LC-MS data of Example 1.271 to Example 1.301 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
1.271	(1R,3S,5R)-N-(4,4-Difluorocyclohexyl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-2-((6-methoxypyridin-3-yl)sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxamide	1.329	546.3
1.272	(1R,3S,5R)-2-(6-Methoxy-pyridine-3-sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.179	548.2
1.273	(1R,3S,5R)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-2-((6-methoxypyridin-3-yl)sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxamide	1.252	524.3

1.274	(S)-N-(4,4-Difluorocyclohexyl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-1-((6-methoxypyridin-3-yl)sulfonyl)pyrrolidine-2-carboxamide	1.347	534.3
1.275	(2S)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-1-((6-methoxypyridin-3-yl)sulfonyl)pyrrolidine-2-carboxamide	1.279	512.3
1.276	(2S)-N-(Bicyclo[4.1.0]heptan-3-yl)-1-((6-methoxypyridin-3-yl)sulfonyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.353	484.3
1.277	(2S)-N-(bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-1-((6-methoxypyridin-3-yl)sulfonyl)pyrrolidine-2-carboxamide	1.443	510.2
1.278	(1R,3S,5R)-N-(bicyclo[4.1.0]heptan-3-yl)-2-((6-methoxypyridin-3-yl)sulfonyl)-N-(4-methylbenzyl)-2-azabicyclo[3.1.0]hexane-3-carboxamide	1.338	496.2
1.279	(S)-N-(4,4-Difluorocyclohexyl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-1-((6-methylpyridin-3-yl)sulfonyl)pyrrolidine-2-carboxamide	1.271	518.3
1.280	(2S)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-1-((6-methylpyridin-3-yl)sulfonyl)pyrrolidine-2-carboxamide	1.361	494.4
1.281	(2S)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-1-((6-methylpyridin-3-yl)sulfonyl)pyrrolidine-2-carboxamide	1.188	496.3
1.282	(S)-1-(6-Methyl-pyridine-3-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-methyl-benzyl)-amide	1.186	492.2
1.283	(2S)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-(4-methylbenzyl)-1-((6-methylpyridin-3-yl)sulfonyl)pyrrolidine-2-carboxamide	1.276	468.3
1.284	(2S)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-((5-isopropylthiazol-2-yl)methyl)-1-tosylpyrrolidine-2-carboxamide	1.356	502.3
1.285	(S)-2-(Toluene-4-sulfonyl)-3,4-dihydro-2H-pyrazole-3-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-methyl-benzyl)-amide	1.242	490.2
1.286	(1R,3S,4S)-N-(bicyclo[4.1.0]heptan-3-yl)-2-((6-methoxypyridin-3-yl)sulfonyl)-N-(4-methylbenzyl)-2-azabicyclo[2.2.1]heptane-3-carboxamide	1.436	510.3
1.287	(1R,3S,4S)-2-(6-Methoxy-pyridine-3-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-methyl-benzyl)-amide	1.340	534.2
1.288	(1R,3S,4S)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-2-((6-methoxypyridin-3-yl)sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxamide	1.516	536.4
1.289	(1R,3S,4S)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-2-((6-methoxypyridin-3-yl)sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxamide	1.357	538.3
1.290	(S)-1-Benzenesulfonyl-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.181	505.3

1.291	(1R,3S,5R)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-2-((6-methylpyridin-3-yl)sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxamide	1.181	508.2
1.292	(1R,3S,5R)-2-(6-Methyl-pyridine-3-sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.097	532.3
1.293	(1R,3S,4S)-2-(6-Methyl-pyridine-3-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-methyl-benzyl)-amide	1.273	518.2
1.294	(1R,3S,4S)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-2-((6-methylpyridin-3-yl)sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxamide	1.275	522.2
1.295	(1R,3S,4S)-2-(6-Methyl-pyridine-3-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.182	546.2
1.296	(1R,3S,4S)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-(4-methylbenzyl)-2-((6-methylpyridin-3-yl)sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxamide	1.351	494.4
1.297	(1R,3S,5R)-N-(bicyclo[4.1.0]heptan-3-yl)-N-(4-methylbenzyl)-2-((6-methylpyridin-3-yl)sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxamide	1.258	480.2
1.298	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzo[1,3]dioxol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.211	521.3
1.299	(2S)-N-(Benzo[d][1,3]dioxol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-tosylpyrrolidine-2-carboxamide	1.301	497.2
1.300	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzo[1,3]dioxol-4-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.235	521.3
1.301	(S)-1-(6-Fluoro-pyridine-3-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide	1.166	524.3

Example 1.302 rac-5-Methyl-2-(toluene-4-sulfonyl)-3,4-dihydro-2H-pyrazole-3-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-methyl-benzyl)-amide:

1-(tert-Butyl) 5-ethyl 3-methyl-4,5-dihydro-1H-pyrazole-1,5-dicarboxylate: Copper(II) chloride (26.9 mg, 0.2 mmol, 0.2 eq) was added to a solution of tert-butyl (E)-2-(1-chloropropan-2-ylidene)hydrazine-1-carboxylate (207 mg, 1 mmol, 1 eq), ethyl diazoacetate (0.363 mL, 3 mmol, 3 eq), and Na_2CO_3 (530 mg, 5 mmol, 5 eq) in DCM (8 mL), and the reaction mixture was stirred at rt for 5h. The mixture was then filtered through a Celite® pad and washed with DCM. After removal of the solvent, the residue was purified by FC (Hept to Hept/EtOAc 1:1) to give the title compound (200 mg, 78%) as a yellow oil. Rf (Hept/EtOAc 1:1)= 0.25; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.70 (dd, J_1 = 5.8 Hz, J_2 = 12.2 Hz, 1 H), 4.19-4.29 (m, 2 H), 3.18 (dd, J_1 = 17.9 Hz, J_2 = 12.6 Hz, 1 H), 2.85 (dd, J_1 =

18.0 Hz, J_2 = 6.0 Hz, 1 H), 2.05 (s, 3H), 1.47-1.56 (m, 9 H), 1.30 (t, J = 7.1 Hz, 3 H); LC-MS (2): t_R = 0.76 min; $[M+H]^+$: not seen.

5-(Ethoxycarbonyl)-3-methyl-4,5-dihydro-1H-pyrazol-1-ium trifluoroacetate: TFA (0.3 mL) was added to a soln. of 1-(tert-butyl) 5-ethyl 3-methyl-4,5-dihydro-1H-pyrazole-1,5-dicarboxylate (80 mg, 0.312 mmol, 1 eq) in DCM (3 mL). The resulting brownish soln. was stirred at rt for 1h. The reaction mixture was concentrated under reduced pressure to give the title compound as a yellow oil which was used as such in the next step without further purification. LC-MS (2): t_R = 0.39 min; $[M+H]^+$: 157.28.

Ethyl 3-methyl-1-tosyl-4,5-dihydro-1H-pyrazole-5-carboxylate: 5-(Ethoxycarbonyl)-3-methyl-4,5-dihydro-1H-pyrazol-1-ium trifluoroacetate (84.3 mg, 0.312 mmol, 1 eq) was dissolved in MeCN (2.6 mL) and K_2CO_3 (151 mg, 1.09 mmol, 3.5 eq) was added followed by p-toluenesulfonyl chloride (60.7 mg, 0.312 mmol, 1 eq). The mixture was heated under reflux for 1h. Water was added and the mixture was extracted with DCM and separated through a separation cartridge. The solvent was removed under reduced pressure and the residue was purified by FC (Hept to Hep/EtOAc 6:4) to give the title compound (22.6 mg, 23%) as a white solid. LC-MS (2): t_R= 0.84 min; $[M+H]^+$: 311.11.

3-Methyl-1-tosyl-4,5-dihydro-1H-pyrazole-5-carboxylic acid: At rt, ethyl 3-methyl-1-tosyl-4,5-dihydro-1H-pyrazole-5-carboxylate (23 mg, 0.0741 mmol, 1 eq) was dissolved in THF (0.37 mL), then lithium hydroxide monohydrate (4.71 mg, 0.111 mmol, 1.5 eq) was added and the mixture was stirred at rt during 4h. The mixture was acidified with aq. 1M HCl and extracted with DCM. The layers were separated with a phase separator. The solvent was removed under reduced pressure to give the title compound as a white solid which was used as such in the next step without further purification. LC-MS (2): t_R= 0.66 min; $[M+H]^+$: 283.13.

rac-5-Methyl-2-(toluene-4-sulfonyl)-3,4-dihydro-2H-pyrazole-3-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-methyl-benzyl)-amide: Was synthesized using 3-methyl-1-tosyl-4,5-dihydro-1H-pyrazole-5-carboxylic acid and 4,4-difluoro-N-(4-methylbenzyl)cyclohexan-1-amine as described in Example 1.1 to give the title compound as a white solid. LC-MS(1): t_R= 1.254 min; $[M+H]^+$: 504.3.

Example 1.303 to **Example 1.319** were synthesized according to the procedures described herein before using the appropriate amine or amine salt derivative, the appropriate aldehyde or ketone, the appropriate amino acid or aminoester and the appropriate sulfonyl chloride. LC-MS data of Example 1.303 to Example 1.319 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
1.303	rac-2-(Toluene-4-sulfonyl)-3,4-dihydro-2H-pyrazole-3-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-methylsulfanyl-benzyl)-amide	1.233	522.1
1.304	rac-(R)-N-(4,4-Difluorocyclohexyl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-1-tosyl-4,5-dihydro-1H-pyrazole-5-carboxamide	1.314	516.4

1.305	rac-2-(Toluene-4-sulfonyl)-3,4-dihydro-2H-pyrazole-3-carboxylic acid benzo[1,3]dioxol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.146	520.1
1.306	(S)-N-((1R*,3S*)-3-cyanocyclopentyl)-N-(4-methylbenzyl)-1-tosylpyrrolidine-2-carboxamide	1.185	466.2
1.307	(S)-N-(4-chlorobenzyl)-N-((1R*,3S*)-3-cyanocyclopentyl)-1-tosylpyrrolidine-2-carboxamide	1.202	486.2
1.308	rac-3-(Toluene-4-sulfonyl)-oxazolidine-2-carboxylic acid benzo[1,3]dioxol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.222	523.3
1.309	3-(Toluene-4-sulfonyl)-[1,3]oxazinane-2-carboxylic acid benzo[1,3]dioxol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.285	537.4
1.310	(2RS)-N-((1R*,3S*)-3-Cyanocyclopentyl)-N-(4-methylbenzyl)-3-tosyloxazolidine-2-carboxamide	1.181	468.3
1.311	(2RS)-N-((1R*,3S*)-3-Cyanocyclopentyl)-N-(4-chlorobenzyl)-3-tosyloxazolidine-2-carboxamide	1.201	488.2
1.312	5-Methyl-2-(toluene-4-sulfonyl)-3,4-dihydro-2H-pyrazole-3-carboxylic acid (4-chloro-benzyl)-(1,1-difluoro-spiro[2.3]hex-5-yl)-amide	1.279	522.3
1.313	rac-3-(Toluene-4-sulfonyl)-oxazolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide	1.330	513.2
1.314	3-(Toluene-4-sulfonyl)-oxazolidine-2-carboxylic acid (4-chloro-benzyl)-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide	1.385	539.3
1.315	3-(Toluene-4-sulfonyl)-oxazolidine-2-carboxylic acid (1,1-difluoro-spiro[2.5]oct-6-yl)-(4-methyl-benzyl)-amide	1.373	519.3
1.316	3-(Toluene-4-sulfonyl)-oxazolidine-2-carboxylic acid (1,1-difluoro-spiro[2.3]hex-5-yl)-(4-methyl-benzyl)-amide	1.321	491.2
1.317	3-(Toluene-4-sulfonyl)-oxazolidine-2-carboxylic acid (4-chloro-benzyl)-(1,1-difluoro-spiro[2.3]hex-5-yl)-amide	1.333	511.1
1.318	rac-3-(Toluene-4-sulfonyl)-oxazolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-methyl-benzyl)-amide	1.316	493.2
1.319	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-carbamoyl-bicyclo[2.1.1]hex-1-yl)-(4-chloro-benzyl)-amide	1.037	516.3

Example 1.320 (2S)-N-(3-Carbamoylcyclopentyl)-N-(4-chlorobenzyl)-1-tosylpyrrolidine-2-carboxamide:

Methyl 3-((4-chlorobenzyl)amino)cyclopentane-1-carboxylate: Was synthesized as described in Example 1.1 using 4-chlorobenzylamine and methyl 3-oxocyclopentane-1-carboxylate to give the title compound as a pale yellow oil. LC-MS (2): t_R = 0.61 min; $[M+H]^+$: 268.30.

3-((4-Chlorobenzyl)amino)cyclopentane-1-carboxamide: Methyl 3-((4-chlorobenzyl)amino)cyclopentane-1-carboxylate (120 mg, 0.448 mmol) was dissolved in NH_3 (7M in methanol, 2.1 mL, 15 mmol) and the reaction mixture was stirred at 85°C for 4 days. Fresh NH_3 (7M in methanol, 4.2 mL, 30 mmol, 67 eq) was added and the reaction mixture was stirred at 85°C for 21h. The reaction mixture was concentrated under reduced pressure and the residue was purified by FC (DCM to DCM/(MeOH+3% Et_3N) 9:1) to give the title compound (61.3 mg, 54%) as a beige sticky solid. LC-MS (2): t_R= 0.49 and 0.52 min; $[M+H]^+$: 253.35.

(2S)-N-(3-carbamoylcyclopentyl)-N-(4-chlorobenzyl)-1-tosylpyrrolidine-2-carboxamide: Was synthesized as described in Example 1.24 using tosyl-L-prolinoyl chloride and 3-((4-chlorobenzyl)amino)cyclopentane-1-carboxamide to give the title compound as a white solid. LC-MS (1): t_R= 1.026 min; $[M+H]^+$: 504.4.

Example 1.321 (S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4-cyano-bicyclo[2.2.2]oct-1-yl)-amide: Was synthesized as described in Example 1.320 using tosyl-L-prolinoyl chloride, 4-aminobicyclo[2.2.2]octane-1-carbonitrile hydrochloride and 4-chlorobenzaldehyde to give the title compound as a white solid. LC-MS (1): t_R= 1.316 min; $[M+H]^+$: 526.4.

Example 1.322 (2S)-N-((1R)-3-Carbamoyl-3-methylcyclopentyl)-N-(4-chlorobenzyl)-1-tosylpyrrolidine-2-carboxamide:

Methyl (1S,3R)-3-(dibenzylamino)cyclopentane-1-carboxylate: Sodium carbonate (2.05 g, 18.9 mmol) was dissolved in H_2O (5.7 mL) and DCM (11.4 mL) was added. Methyl (1R,3R)-3-aminocyclopentane-1-carboxylate hydrochloride (850 mg, 4.73 mmol) was added portionwise followed by benzyl bromide (1.18 mL, 9.7 mmol). The reaction mixture was stirred at 40°C for 22h. The reaction mixture was partitionned between EtOAc and water. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by FC (Hept to Hept/ EtOAc 9:1) to give the title compound (1.335 g, 87%) as a colourless oil. R_f (Hept/EtOAc 9:1)= 0.26. LC-MS (2): t_R= 0.72 min; $[M+H]^+$: 324.29.

Methyl (3R)-3-(dibenzylamino)-1-methylcyclopentane-1-carboxylate: Lithium diisopropylamide solution (1.0 M in THF/hexanes, 2.32 mL, 2.32 mmol) was stirred at -78°C. A soln. of methyl (1S,3R)-3-(dibenzylamino)cyclopentane-1-carboxylate (250 mg, 0.773 mmol) in THF (7.7 mL) was added dropwise at -78°C and the reaction mixture was stirred at -78°C for 30 min. Iodomethane (0.292 mL, 4.64 mmol) in THF (1.5 mL) was added dropwise. The cooling bath was removed and the reaction mixture was stirred for 30 min. The reaction mixture was poured into sat. aq. NH_4Cl (50 ml) and extracted with EtOAc (75 ml). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The

residue was purified by FC (Hept to Hept/ EtOAc 95:5) to give the title compound (214 mg; 82%) as a colourless oil. R_f (Hept/EtOAc 9:1)= 0.38. LC-MS (2): t_R= 0.76 min; $[M+H]^+$: 338.18.

(3R)-3-(Dibenzylamino)-1-methylcyclopentane-1-carboxylic acid: Methyl (3R)-3-(dibenzylamino)-1-methylcyclopentane-1-carboxylate (231 mg, 0.725 mmol) was dissolved in H_2O (8 mL) and THF (2 mL) and lithium hydroxide monohydrate (134 mg, 3.17 mmol) was added at rt. The reaction mixture was stirred at rt for 14h then at 70°C for 5.5h. The reaction mixture was poured into cold aq. 1M HCl and was extracted once with DCM and with DCM/MeOH 10% (3×50ml). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give the title compound (293 mg, 100%) as a white solid. The compound was used as such in the next step without further purification. LC-MS (2): tR= 0.69; $[M+H]^+$: 324.28.

(3R)-3-(Dibenzylamino)-1-methylcyclopentane-1-carboxamide: At rt, (3R)-3-(dibenzylamino)-1-methylcyclopentane-1-carboxylic acid (205 mg, 0.634 mmol) was dissolved in DMF (6 mL), then DIPEA (0.554 mL, 3.17 mmol) and HATU (497 mg, 1.27 mmol) were added. After stirring for 5 minutes, NH_4Cl (170 mg, 3.17 mmol) was added. The resulting solution was stirred at rt for 1h. The reaction mixture was filtered through a PTFE 0.45µm filter and purified by basic prep. HPLC to give the title compound (199 mg, 97%) as a pale orange sticky oil. LC-MS (2): t_R= 0.62 and 0.64 min; $[M+H]^+$: 323.33

(3R)-3-Amino-1-methylcyclopentane-1-carboxamide: (3R)-3-(Dibenzylamino)-1-methylcyclopentane-1-carboxamide (116 mg, 0.36 mmol) was dissolved in MeOH (3.6 mL) and Pd/C (10% Pd,~50% H_2O 76.6 mg, 0.0719 mmol) was added. The reaction mixture was stirred at rt under a pressure of H_2 (5 bars) for 18h.The reaction mixture was filtered through Celite® and the filtrate was concentrated to give the title compound (48 mg, 94%) as a colorless oil. The compound was used as such in the next step without further purification.

(3R)-3-((4-Chlorobenzyl)amino)-1-methylcyclopentane-1-carboxamide: Was synthesized as described in Example 1.1 using (3R)-3-amino-1-methylcyclopentane-1-carboxamide and 4-chlorobenzaldehyde (62 mg, 0.432 mmol) to give the title compound as a off-white solid. LC-MS (2): t_R= 0.52 and 0.56 min; $[M+H]^+$: 267.37.

(2S)-N-((1R)-3-Carbamoyl-3-methylcyclopentyl)-N-(4-chlorobenzyl)-1-tosylpyrrolidine-2-carboxamide: Was synthesized as described in Example 1.24 using (3R)-3-((4-chlorobenzyl)amino)-1-methylcyclopentane-1-carboxamide and tosyl-L-prolinoyl chloride to give the title compound as a white solid. LC-MS (1): t_R= 1.088 min; $[M+H]^+$: 518.4.

Example 1.323 (2S)-N-(4-chlorobenzyl)-N-((1R)-3-cyano-3-methylcyclopentyl)-1-tosylpyrrolidine-2-carboxamide: (2S)-N-((1R)-3-Carbamoyl-3-methylcyclopentyl)-N-(4-chlorobenzyl)-1-tosylpyrrolidine-2-carboxamide (30 mg, 0.0579 mmol) was dissolved in DCM (1 mL). Triethylamine (0.024 mL, 0.174 mmol) was added and the reaction mixture was stirred at 0°C. Trifluoroacetic anhydride (0.0179 mL, 0.127 mmol) was added and the resulting solution was stirred at 0°C for 1h. Water was added and the reaction mixture was stirred for 10 min and filtered over phase separator. The organic phase was concentrated under reduced pressure and the

residue was purified by basic prep. HPLC to give the title compound (24 mg, 85%) as a white solid. LC-MS (1): t_R= 1.259 min; $[M+H]^+$: 500.4.

Example 1.324 (S)-1-(3-Fluoro-4-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide: Was synthesized following the procedures described herein before using the appropriate amine or amine salt derivative, the appropriate aldehyde and the appropriate amino acid or aminoester and the appropriate sulfonyl chloride to give the title compound as a white solid. LC-MS (1): t_R= 1.203 min; $[M+H]^+$: 552.4.

Example 1.325 and Example 1.326: (S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-1-tosylpyrrolidine-2-carboxamide and (S)-N-(benzo[d]thiazol-5-ylmethyl)-N-((3S,6r)-1,1-difluorospiro[2.5]octan-6-yl)-1-tosylpyrrolidine-2-carboxamide: Were synthesized following the procedures described herein before using the appropriate amine or amine salt derivative, the appropriate aldehyde and (S)-methyl pyrrolidine-2-carboxylate hydrochloride to give (S)-N-(benzo[d]thiazol-5-ylmethyl)-N-(1,1-difluorospiro[2.5]octan-6-yl)-1-tosylpyrrolidine-2-carboxamide as a 1:1 mixture of diastereomers. The diastereomeric mixture was separated by chiral SFC (SFC 5 method) to give (S)-N-(benzo[d]thiazol-5-ylmethyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-1-tosylpyrrolidine-2-carboxamide (first eluting diastereomer) and (S)-N-(benzo[d]thiazol-5-ylmethyl)-N-((3S,6r)-1,1-difluorospiro[2.5]octan-6-yl)-1-tosylpyrrolidine-2-carboxamide (second eluting diastereomer) both as a white solids. Stereochemistry was arbitrarily assigned. (S)-N-(benzo[d]thiazol-5-ylmethyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-1-tosylpyrrolidine-2-carboxamide: LC-MS (1): t_R= 1.241min, $[M+H]^+$: 560.5. (S)-N-(benzo[d]thiazol-5-ylmethyl)-N-((3S,6r)-1,1-difluorospiro[2.5]octan-6-yl)-1-tosylpyrrolidine-2-carboxamide: LC-MS (1): t_R= 1.243 min, $[M+H]^+$: 560.4.

Example 1.327 and Example 1.328: (S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3R,5s)-1,1-difluorospiro[2.3]hexan-5-yl)-1-tosylpyrrolidine-2-carboxamide and (S)-N-(benzo[d]thiazol-5-ylmethyl)-N-((3S,5r)-1,1-difluorospiro[2.3]hexan-5-yl)-1-tosylpyrrolidine-2-carboxamide: Were synthesized following the procedures described herein before using the appropriate amine or amine salt derivative, the appropriate aldehyde and tosyl-L-proline to give (S)-N-(benzo[d]thiazol-5-ylmethyl)-N-(1,1-difluorospiro[2.3]hexan-5-yl)-1-tosylpyrrolidine-2-carboxamide as a 1:1 mixture of diastereomers. The diastereomeric mixture was separated by chiral SFC (SFC 6 method) to give (S)-N-(benzo[d]thiazol-5-ylmethyl)-N-((3R,5s)-1,1-difluorospiro[2.3]hexan-5-yl)-1-tosylpyrrolidine-2-carboxamide (first eluting diastereomer) and (S)-N-(benzo[d]thiazol-5-ylmethyl)-N-((3S,5r)-1,1-difluorospiro[2.3]hexan-5-yl)-1-tosylpyrrolidine-2-carboxamide (second eluting diastereomer) both as a white solids. Stereochemistry was arbitrarily assigned. (S)-N-(benzo[d]thiazol-5-ylmethyl)-N-((3R,5s)-1,1-difluorospiro[2.3]hexan-5-yl)-1-tosylpyrrolidine-2-carboxamide: LC-MS (1): t_R= 1.176 min, $[M+H]^+$: 532.4. (S)-N-(benzo[d]thiazol-5-ylmethyl)-N-((3S,5r)-1,1-difluorospiro[2.3]hexan-5-yl)-1-tosylpyrrolidine-2-carboxamide: LC-MS (1): t_R= 1.186 min, $[M+H]^+$: 532.4.

Example 1.329 to **Example 1.332** were synthesized as described in Example 1.326 using the appropriate amine or amine salt derivative, the appropriate aldehyde, the appropriate amino acid or aminoester and the appropriate sulfonyl chloride. LC-MS data of Example 1.329 to Example 1.332 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
1.329	(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-1-((3-fluoro-4-methylphenyl)sulfonyl)pyrrolidine-2-carboxamide	1.274	578.4
1.330	(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3S,6r)-1,1-difluorospiro[2.5]octan-6-yl)-1-((3-fluoro-4-methylphenyl)sulfonyl)pyrrolidine-2-carboxamide	1.273	578.4
1.331	(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3R,5s)-1,1-difluorospiro[2.3]hexan-5-yl)-1-((3-fluoro-4-methylphenyl)sulfonyl)pyrrolidine-2-carboxamide	1.211	550.4
1.332	(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3S,5r)-1,1-difluorospiro[2.3]hexan-5-yl)-1-((3-fluoro-4-methylphenyl)sulfonyl)pyrrolidine-2-carboxamide	1.221	550.4

Example 1.333 to **Example 1.334** were synthesized according to the procedures described herein before using the appropriate amine or amine salt derivative, the appropriate aldehyde or ketone, the appropriate amino acid or aminoester and the appropriate sulfonyl chloride. LC-MS data of Example 1.333 to Example 1.334 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
1.333	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2-methyl-benzothiazol-5-ylmethyl)-amide	1.221	548.5
1.334	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(6-fluoro-2-methyl-benzothiazol-5-ylmethyl)-amide	1.266	566.4

Example 1.335 (S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (2-chloro-benzothiazol-5-ylmethyl)-(4,4-difluoro-cyclohexyl)-amide:

(2-Chlorobenzo[d]thiazol-5-yl)methanol: At 0°C under argon, $LiAlH_4$ (17.9 mg, 0.472 mmol) was added portionwise to a stirred solution of ethyl 2-chlorobenzo[d]thiazole-5-carboxylate (100 mg, 0.393 mmol) in THF (3.9 ml) (exothermic). The reaction was stirred for 10 minutes. Na_2SO_4 salt (1000 mg) was added (gas evolution) and the mixture was stirred vigorously for 3.5h. The suspension was filtered over Celite® and evaporated under reduced pressure to give the title compound (80 mg, 100%) as a yellow solid. LC-MS (2): t_R= 0.70 min, $[M+H]^+$: 200.19.

2-Chlorobenzo[d]thiazole-5-carbaldehyde: A round bottom double neck flask charged with (2-chlorobenzo[d]thiazol-5-yl)methanol (80 mg, 0.401 mmol) was purged and refilled with argon three times. MnO_2

activated (106 mg, 1.2 mmol) was added and the material diluted with DCM (4 mL, 62.6 mmol). The reaction mixture was stirred at rt overnight. MnO_2 activated (106 mg, 1.2 mmol, 3 eq) was added again and the reaction mixture was stirred again for 24h. The reaction mixture was filtered through Celite® and washed with DCM. The filtrate was concentrated under reduced pressure to give the title compound (52 mg, 66%) as a white solid. LC-MS (2): t_R= 0.81 min, $[M+H]^+$: not seen.

N-((2-Chlorobenzo[d]thiazol-5-yl)methyl)-4,4-difluorocyclohexan-1-amine: Was synthesized as described in Example 1.3 using 2-chlorobenzo[d]thiazole-5-carbaldehyde and 4,4-difluorocyclohexan-1-amine hydrochloride to give the title compound as a colorless oil. LC-MS (2): t_R= 0.66 min, [M+H]+: 317.20.

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (2-chloro-benzothiazol-5-ylmethyl)-(4,4-difluoro-cyclohexyl)-amide: Was synthesized as described in Example 1.1 using N-((2-chlorobenzo[d]thiazol-5-yl)methyl)-4,4-difluorocyclohexan-1-amine and tosyl-L-pyroline to give the title compound as a white solid. LC-MS (1): t_R= 1.329 min, $[M+H]^+$: 568.4.

Example 1.336 to **Example 1.345** were synthesized according to the procedures described herein before using the appropriate amine, the appropriate amino acid or aminoester and the appropriate sulfonyl chloride. LC-MS data of Example 1.336 to Example 1.345 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$	LC-MS conditions
1.336	(S)-1-(3-Fluoro-4-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2-methyl-benzothiazol-5-ylmethyl)-amide	1.254	566.4	1
1.337	(S)-1-(3-Fluoro-4-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(6-fluoro-2-methyl-benzothiazol-5-ylmethyl)-amide	1.294	584.4	1
1.338	(S)-1-(3-Fluoro-4-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (2-chloro-benzothiazol-5-ylmethyl)-(4,4-difluoro-cyclohexyl)-amide	1.358	586.4	1
1.339	(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2-methyl-benzothiazol-5-ylmethyl)-amide	1.176	564.5	1
1.340	(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(6-fluoro-2-methyl-benzothiazol-5-ylmethyl)-amide	1.223	582.4	1
1.341	(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (2-chloro-benzothiazol-5-ylmethyl)-(4,4-difluoro-cyclohexyl)-amide	1.286	584.4	1

1.342	(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-1-((4-methoxyphenyl)sulfonyl)pyrrolidine-2-carboxamide	1.198	576.4	1
1.343	(S)-N-(benzo[d]thiazol-5-ylmethyl)-N-((3R,5s)-1,1-difluorospiro[2.3]hexan-5-yl)-1-((4-methoxyphenyl)sulfonyl)pyrrolidine-2-carboxamide	1.132	548.4	1
1.344	(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3S,5r)-1,1-difluorospiro[2.3]hexan-5-yl)-1-((4-methoxyphenyl)sulfonyl)pyrrolidine-2-carboxamide	1.141	548.4	1
1.345	(1R,2S,5S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide	1.04	545.93	2

Example 1.346 and Example 1.347 (S)-1-(3-Fluoro-4-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(1R,3R,6R)-bicyclo[4.1.0]hept-3-yl-amide and (S)-1-(3-Fluoro-4-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(1S,3S,6S)-bicyclo[4.1.0]hept-3-yl-amide: Were obtained by chiral SFC separation (SFC 8 method) of (2S)-N-(benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-((3-fluoro-4-methylphenyl)sulfonyl)pyrrolidine-2-carboxamide, synthesized according to the procedures described herein before using benzozhiazole-5-carbaldehyde, L-proline, and 3-fluoro-4-methylbenzene sulfonyl chloride. (S)-1-(3-Fluoro-4-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(1R,3R,6R)-bicyclo[4.1.0]hept-3-yl-amide: LC-MS (1): t_R= 1.292 min, $[M+H]^+$: 527.17. (S)-1-(3-Fluoro-4-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(1S,3S,6S)-bicyclo[4.1.0]hept-3-yl-amide: LC-MS (1): t_R= 1.288 min, $[M+H]^+$: 527.17 .

Example 1.348 to **Example 1.350** were obtained by chiral SFC separation (SFC 9 method) separation of (2S)-N-(benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-tosylpyrrolidine-2-carboxamide, synthesized according to the procedures described herein before using benzozhiazole-5-carbaldehyde, bicyclo[4.1.0]heptan-3-amine and N-p-tosyl-L-proline. LC-MS data of Example 1.348 to Example 1.350 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
1.348	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(1R,3R,6R)-bicyclo[4.1.0]hept-3-yl-amide	1.260	509.18
1.349	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(1R,3R,6R)-bicyclo[4.1.0]hept-3-yl-amide	1.253	509.18

1.350	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(1R,3R,6R)-bicyclo[4.1.0]hept-3-yl-amide	1.252	509.18

Example 1.351 and Example 1.352 (S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(1R,3R,6R)-bicyclo[4.1.0]hept-3-yl-amide and (S)-1-(4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(1S,3S,6S)-bicyclo[4.1.0]hept-3-yl-amide: Were obtained by chiral SFC separation (SFC 10 method) of (2S)-N-(benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-((4-methoxyphenyl)sulfonyl)pyrrolidine-2-carboxamide, synthesized according to the procedure described in Example 1.96 using benzozhiazole-5-carbaldehyde, bicyclo[4.1.0]heptan-3-amine and lithium ((4-methoxyphenyl)sulfonyl)-L-prolinate. (S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(1R,3R,6R)-bicyclo[4.1.0]hept-3-yl-amide: LC-MS (1): t_R= 1.209min, $[M+H]^+$: 525.18. (S)-1-(4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(1S,3S,6S)-bicyclo[4.1.0]hept-3-yl-amide: LC-MS (1): t_R= 1.205 min, $[M+H]^+$: 525.18.

Example 1.353 (S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide:

N-(4-Chlorobenzyl)-4,4-difluorocyclohexan-1-amine: DIPEA (9.42 mL, 0.055 mol, 1.1 eq) was added to a solution of 4,4-difluorocyclohexan-1-amine hydrochloride (8.58 g, 0.05 mol, 1 eq) and 4-chlorobenzaldehyde (7.25 g, 0.05 mol, 1 eq) in MeOH (338 mL). The clear solution was stirred at rt overnight. $NaBH_4$ (2.08 g, 0.055 mol, 1.1 eq) was added in portions and the mixture was stirred at rt for 45 min. The reaction mixture was quenched with aq. sat. $NaHCO_3$. Most of the solvent was evaporated under reduced pressure and the residue was diluted with EtOAc. The layers were separated and the org. layer was washed with water and brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by FC (Hept to Hept/EtOAc 1:1) to give the title compound.

tert-Butyl (S)-2-((4-chlorobenzyl)(4,4-difluorocyclohexyl)carbamoyl)pyrrolidine-1-carboxylate: To a solution of (tert-butoxycarbonyl)-L-proline (7 g, 0.0325 mol, 1 eq) and HATU (14.8 g, 0.039 mol, 1.2 eq) in DMF (110 mL) was added DIPEA (11.1 mL, 0.065 mol, 2 eq). The resulting solution was stirred at rt. After 10 min, a solution of N-(4-chlorobenzyl)-4,4-difluorocyclohexan-1-amine (9.52 g, 0.0356 mol, 1.093 eq) in DMF (20 mL) was added. The brown solution was stirred overnight. The reaction mixture was diluted with EtOAc and extracted with aq. 1M HCl soln., aq. sat. $NaHCO_3$, water and brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by FC (Hept to Hept/EA 6:4) to give the title compound.

(S)-N-(4-Chlorobenzyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide: 4M HCL in dioxane (61.8 mL, 0.247 mol, 10 eq) was added dropwise to a solution tert-butyl (S)-2-((4-chlorobenzyl)(4,4-difluorocyclohexyl)carbamoyl)pyrrolidine-1-carboxylate (11.8 g, 0.0247 mol, 1 eq) in DCM (100 mL) at 0 °C. The

reaction mixture was stirred allowed to reach rt overnight. The reaction mixture was cooled to 0 °C and quenched with aq. sat. $NaHCO_3$. The layers were separated and the org. layer was washed with aq. sat. $NaHCO_3$, water, and brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give the title compound.

(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide: 4-Methoxybenzenesulfonyl chloride (23 mg, 0.11 mmol, 1.1 eq), (S)-N-(4-chlorobenzyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide (37.6 mg, 0.1 mmol, 1 eq), and TEA (0.0696 mL, 0.5 mmol, 5 eq) were dissolved in ACN (1 mL). The reaction mixture was stirred rt overnight. The reaction mixture was purified by basic prep. HPLC to give the title compound.

Example 1.354 to **Example 1.371** were synthesized according to the procedures described herein before using N-(4-chlorobenzyl)-4,4-difluorocyclohexan-1-amine and the appropriate sulfonyl chloride. LC-MS data of Example 1.354 to Example 1.371 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
1.354	(S)-1-(4-Fluoro-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide	1.301	514.13
1.355	(S)-1-(4-Chloro-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide	1.364	530.10
1.356	(S)-1-(4-Isopropyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide	1.422	538.19
1.357	(S)-1-(3,4-Dimethyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide	1.364	524.17
1.358	(S)-1-(3-Bromo-4-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide	1.427	588.07
1.359	(S)-1-(4-Bromo-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide	1.381	574.05
1.360	(S)-1-(4-tert-Butyl-3-fluoro-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide	1.498	570.19
1.361	(S)-1-(4-Iodo-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide	1.398	622.04
1.362	(S)-1-(4-Propyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide	1.432	538.19
1.363	(S)-1-(3-Chloro-4-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide	1.411	544.12
1.364	(S)-1-(3,4-Dichloro-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide	1.441	564.06

1.365	(S)-1-(3-Fluoro-4-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide	1.354	528.15
1.366	(S)-1-(4-tert-Butyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide	1.460	552.20
1.367	(S)-1-(4-Bromo-3-fluoro-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide	1.397	592.04
1.368	(S)-1-(6-Methyl-pyridine-3-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide	1.205	511.15
1.369	(S)-1-(4-Trifluoromethyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide	1.388	564.13
1.370	(S)-1-(6-Methoxy-pyridine-3-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide	1.281	527.15
1.371	(S)-1-(4-Ethyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide	1.377	524.17

Example 1.372 to **Example 1.378** were synthesized according to the procedure described in Example 1.33 using the appropriate aldehyde, the appropriate amine or amine salt, the appropriate amino acid and the appropriate sulfonyl chloride. LC-MS data of Example 1.372 to Example 1.378 are listed in the table below.

Ex. N°	Name	t_R	$[M+H]^+$	LC-MS conditions
1.372	(1R*,2S*,5S*)-3-(Toluene-4-sulfonyl)-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid benzothiazol-5-ylmethyl-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide	1.267	571.18	1
1.373	(1R*,2S*,5S*)-3-(Toluene-4-sulfonyl)-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid benzothiazol-5-ylmethyl-(1,1-difluoro-spiro[2.3]hex-5-yl)-amide	1.210	543.15	1
1.374	rac-(1R*,2S*,5S*)-3-(Toluene-4-sulfonyl)-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2-methyl-benzothiazol-5-ylmethyl)-amide	1.246	559.18	1
1.375	rac-(1R*,2S*,5S*)-3-(Toluene-4-sulfonyl)-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(6-fluoro-2-methyl-benzothiazol-5-ylmethyl)-amide	1.06	577.96	2

1.376	(1S,2S,5R)-3-(3-Fluoro-4-methyl-benzenesulfonyl)-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2-methyl-benzothiazol-5-ylmethyl)-amide	1.292	577.17	1
1.377	(1S,2S,5R)-3-(3-Fluoro-4-methyl-benzenesulfonyl)-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(6-fluoro-2-methyl-benzothiazol-5-ylmethyl)-amide	1.328	595.16	1
1.378	(1S,2S,5R)-3-(4-Methoxy-benzenesulfonyl)-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2-methyl-benzothiazol-5-ylmethyl)-amide	1.214	575.17	1

Example 1.379 (S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (2-bromo-benzothiazol-5-ylmethyl)-(4,4-difluoro-cyclohexyl)-amide:

(2-Bromobenzo[d]thiazol-5-yl)methanol: At -78°C and under argon athmosphere, 1 M DIBAL soln. in DCM (13 mL, 13 mmol, 4 eq) was added dropwise to a stirred solution of ethyl 2-bromobenzo[d]thiazole-5-carboxylate (950 mg, 3.32 mmol, 1 eq) in THF (30 mL). The reaction was stirred for 30 min at -78°C, then allowed to warm up at 0°C and stirred at 0°C for 3h. The reaction mixture was diluted with water and the mixture was extracted with DCM twice. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was used as such in the next step without further purification. LC-MS (2): t_R= 0.70 min; $[M+H]^+$: 244.05.

2-Bromobenzo[d]thiazole-5-carbaldehyde: In a round-bottom, double neck flask and under argon atmosphere, to a solution of (2-bromobenzo[d]thiazol-5-yl)methanol (750 mg, 3.08 mmol, 1 eq) in DCM (30.8 mL, 482 mmol, 156.3 eq) was added activated Manganese(IV) oxide (813 mg, 9.25 mmol, 3 eq) and the mixture was stirred at rt overnight. Activated Manganese(IV) oxide (813 mg, 9.25 mmol, 3 eq) was added again and the reaction mixture was stirred overnight. The reaction mixture was filtered through Celite® and washed with DCM. The filtrate was concentrated under reduced pressure to give the title compond. LC-MS (2): t_R= 0.77 min; $[M+H]^+$: 241.91.

N-((2-Bromobenzo[d]thiazol-5-yl)methyl)-4,4-difluorocyclohexan-1-amine: Was synthesized using 2-bromobenzo[d]thiazole-5-carbaldehyde and 4,4-dimethylcyclohexan-1-amine and following the procedure described in Example 1.1 to give the title compound. LC-MS (2): t_R = 0.67 min; $[M+H]^+$: 361.05.

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (2-bromo-benzothiazol-5-ylmethyl)-(4,4-difluoro-cyclohexyl)-amide: Was synthesized using N-((2-bromobenzo[d]thiazol-5-yl)methyl)-4,4-difluorocyclohexan-1-amine and tosyl-L-proline and following the procedure described in Example 1.1 to give the title compound. LC-MS (1): t_R = 1.336 min; $[M+H]^+$: 611.07.

Example 1.380 to **Example 1.381:** were synthesized according to the procedure described in Example 1.96 using N-((2-bromobenzo[d]thiazol-5-yl)methyl)-4,4-difluorocyclohexan-1-amine, L-proline methyl ester hydrochloride and the appropriate sulfonyl chloride. LC-MS data of Example 1.380 to Example 1.381 are listed in the table below.

Ex. N°	Name	t_R	$[M+H]^+$
1.380	(S)-1-(3-Fluoro-4-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (2-bromo-benzothiazol-5-ylmethyl)-(4,4-difluoro-cyclohexyl)-amide	1.364	629.06
1.381	(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (2-bromo-benzothiazol-5-ylmethyl)-(4,4-difluoro-cyclohexyl)-amide	1.293	627.07

Example 1.382 (S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2-methoxy-benzothiazol-5-ylmethyl)-amide:

(2-Chlorobenzo[d]thiazol-5-yl)methanol: At -78°C under argon, DIBAL (1.0 M in methylene chloride, 5.5 mL, 5.48 mmol, 4 eq) was added portionwise to a stirred solution of ethyl 2-chlorobenzo[d]thiazole-5-carboxylate (350 mg, 1.38 mmol, 1 eq) in THF (12.5 mL). The reaction was stirred for 30 min at -78°C, then allowed to warm up to rt and stirred overnight. The reaction mixture was diluted with water. The mixture was extracted with DCM twice. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give the title compound which was used as such in the next step without further purification. LC-MS (2): t_R= 0.70 min; $[M+H]^+$: 200.20.

2-Chlorobenzo[d]thiazole-5-carbaldehyde: In a round-bottom, double-neck flask under N_2 atmosphere, (2-chlorobenzo[d]thiazol-5-yl)methanol (277 mg, 1.39 mmol, 1 eq) was dissolved in DCM (14 mL) and manganese(IV) oxide (365 mg, 4.16 mmol, 3 eq) was added. The mixture was stirred at rt for 3h, filtered through Celite® and washed with DCM. The filtrate was concentrated under reduced pressure to giver the title compound which was used as such in the next step without further purification. LC-MS (2): t_R= 0.82 min; $[M+H]^+$: not seen.

N-((2-Chlorobenzo[d]thiazol-5-yl)methyl)-4,4-difluorocyclohexan-1-amine: Was synthesized using 2-chlorobenzo[d]thiazole-5-carbaldehyde and 4,4-dimethylcyclohexan-1-amine and following the procedure described in Example 1.1 to give the title compound. LC-MS (2): t_R = 0.66 min; $[M+H]^+$: 317.21.

4,4-Difluoro-N-((2-methoxybenzo[d]thiazol-5-yl)methyl)cyclohexan-1-amine: In a sealed microwave tube, N-((2-chlorobenzo[d]thiazol-5-yl)methyl)-4,4-difluorocyclohexan-1-amine (100 mg, 0.316 mmol, 1 eq) was treated with 0.5 M NaOMe in methanol (1.97 mL, 0.789 mmol, 2.5 eq) and heated to 50 °C with conventional heating (50°C) for 1 hour. The reaction mixture was diluted with water and extracted twice with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (DCM to DCM/MeOH 9.5:0.5) to give the title compound. LC-MS (2): t_R= 0.65 min; $[M+H]^+$: 313.26 .

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2-methoxy-benzothiazol-5-ylmethyl)-amide: Was synthesized using 4,4-difluoro-N-((2-methoxybenzo[d]thiazol-5-yl)methyl)cyclohexan-1-amine and tosyl-L-proline and following the procedure described in Example 1.1 to give the title compound. LC-MS (1): t_R = 1.285 min; $[M+H]^+$: 563.17.

Example 1.383 to **Example 1.394:** were synthesized according to the procedures described herein before using the appropriate amine or amine salt derivative, the appropriate aldehyde or ketone, the appropriate amino acid or aminoester and the appropriate sulfonyl chloride. LC-MS data of Example 1.383 to Example 1.394 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
1.383	(S)-1-(3-Fluoro-4-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2-methoxy-benzothiazol-5-ylmethyl)-amide	1.316	581.16
1.384	(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2-methoxy-benzothiazol-5-ylmethyl)-amide	1.241	579.17
1.385	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(3-methoxy-cyclohexyl)-amide	1.356	504.18
1.386	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-((1S,3R)-3-hydroxy-cyclopentyl)-amide	1.103	476.15
1.387	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-((1R,2R)-2-methoxy-cyclopentyl)-amide	1.311	490.17
1.388	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(3-methoxy-cyclohexyl)-amide	1.281	504.18
1.389	(S)-1-(3-Fluoro-4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.144	567.15
1.390	(2S)-N-(4-chlorobenzyl)-N-(2-methyltetrahydro-2H-pyran-4-yl)-1-tosylpyrrolidine-2-carboxamide	1.213	490.17
1.391	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-((2R,4S,6S)-2,6-dimethyl-tetrahydro-pyran-4-yl)-amide	1.276	504.18
1.392	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(2-methyl-tetrahydro-pyran-4-yl)-amide	1.230	490.17
1.393	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-((S)-2,2-dimethyl-tetrahydro-pyran-4-yl)-amide	1.262	504.18
1.394	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-((2R,4R,6S)-2,6-dimethyl-tetrahydro-pyran-4-yl)-amide	1.281	504.18

Example 1.395 (S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-fluoro-benzothiazol-5-ylmethyl)-amide:

N-((2-Fluoro-3-(hydroxymethyl)phenyl)carbamothioyl)benzamide: At rt, benzoyl isothiocyanate (0.194 mL, 1.41 mmol, 1.05 eq) was added to a solution of (3-amino-2-fluorophenyl)methanol (200 mg, 1.35 mmol, 1 eq) in MeCN (4 ml). The reaction was stirred at rt for 1h. The suspension was filtered and washed with MeCN. The solid was dried under reduced pressure to give the title compound. LC-MS (2): t_R= 0.84 min; $[M+H]^+$: 305.2.

1-(3-Bromo-2-fluorophenyl)thiourea: N-((2-fluoro-3-(hydroxymethyl)phenyl)carbamothioyl)benzamide (3100 mg, 10.2 mmol, 1 eq) was treated with aq. 2M NaOH (25.4 mL, 50.8 mmol, 5 eq) and heated to 100°C for 1h. The mixture was concentrated under reduced pressure and the residue dissolved in EtOAc and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and evaporated to give the title compound. LC-MS (2): t_R= 0.65 min; $[M+H]^+$: 249.03.

5-Bromo-4-fluorobenzo[d]thiazol-2-amine: Bromine (0.922 mL, 17.8 mmol, 2 eq) was added to a stirred solution of 1-(3-bromo-2-fluorophenyl)thiourea (2220 mg, 8.91 mmol, 1 eq) in 1,2-dichloroethane (56.5 mL, 710 mmol, 79.62 eq) at rt. The mixture was stirred at 85° overnight. The solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc and washed with aq. sat. $NaHCO_3$. The organic layer was washed once with water, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (DCM to DCM/MeOH 9.5:0.5) to give the title compound. LC-MS (2): t_R= 0.75 min; $[M+H]^+$: 247.01.

5-Bromo-4-fluorobenzo[d]thiazole: To a solution of 5-bromo-4-fluorobenzo[d]thiazol-2-amine (1190 mg, 4.82 mmol, 1 eq) in THF (7.9 ml) at rt, was added isopentyl nitrite (1.42 mL, 10.1 mmol, 2.1 eq) and the solution was refluxed for 2h. After cooling to rt, the solvent was evaporated under reduced pressure. The residue was purified by FC (Hept to Hept/EtOAc 7.5:2.5) to give the title compound. LC-MS (2): t_R= 0.84 min; $[M+H]^+$: 274.94.

4-Fluorobenzo[d]thiazole-5-carbonitrile: At rt and under N_2 atmosphere, zinc cyanide (300 mg, 2.5 mmol, 0.7 eq), Zn (58.5 mg, 0.894 mmol, 0.25 eq), tris(dibenzylideneacetone)dipalladium(0) (164 mg, 0.179 mmol, 0.05003 eq) and 1,1'-bis(diphenylphosphino)ferrocene (158 mg, 0.277 mmol, 0.0775 eq) were added to a solution of 5-bromo-4-fluorobenzo[d]thiazole (830 mg, 3.58 mmol, 1 eq) in NMP (7.7 ml). The mixture was stirred at 110°C for 24h. After cooling to rt, the reaction was diluted with EtOAc and washed with water. The organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by FC (Hept to Hept/EtOAc 1:1) to give the tittle compound. LC-MS (2): t_R= 0.73 min; $[M+H]^+$: not seen.

4-Fluorobenzo[d]thiazole-5-carbaldehyde: To a mixture of 4-fluorobenzo[d]thiazole-5-carbonitrile (220 mg, 1.23 mmol, 1 eq) in pyridine (2.7 mL), water (1.3 mL), AcOH (1.3 mL), under N_2 atmosphere and at rt, was added sodium hypophosphite (530 mg, 6.17 mmol, 5 eq) and Raney nickel (85% in H_2O, 1245 mg, 12.3 mmol, 10 eq). The reaction was stirred at 50°C for 2h, diluted with EtOAc and filtered over a 0.45 µm PTFE syringe filter. The filtrate was

extracted with aq. 1M HCl soln., sat. $NaHCO_3$ and water. The organic layer was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give the title compound. LC-MS (2): t_R= 0.67 min; $[M+H]^+$: not seen.

4,4-Difluoro-N-((4-fluorobenzo[d]thiazol-5-yl)methyl)cyclohexan-1-amine: Was synthesized as described in Example 1.3 using 4-fluorobenzo[d]thiazole-5-carbaldehyde and 4,4-difluorocyclohexan-1-amine hydrochloride to give the title compound. LC-MS (2): t_R= 0.56 min, $[M+H]^+$: 301.07.

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-fluoro-benzothiazol-5-ylmethyl)-amide: Was sintesized using 4,4-difluoro-N-((4-fluorobenzo[d]thiazol-5-yl)methyl)cyclohexan-1-amine and tosyl-L-proline and following the procedure described in Example 1.1 to give the title compound. LC-MS (1): t_R = 1.189 min; $[M+H]^+$: 551.15.

Example 1.396 to **Example 1.412** were synthesized according to the procedures described herein before using the appropriate amine or amine salt derivative, the appropriate aldehyde or ketone, the appropriate amino acid or aminoester and the appropriate sulfonyl chloride. LC-MS data of Example 1.396 to Example 1.412 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
1.396	(S)-1-(3-Fluoro-4-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-fluoro-benzothiazol-5-ylmethyl)-amide	1.221	569.14
1.397	(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-fluoro-benzothiazol-5-ylmethyl)-amide	1.142	567.15
1.398	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(6-methyl-1,1-dioxo-hexahydro-1λ^6-thiopyran-3-yl)-amide	1.166	538.14
1.399	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(1,1-dioxo-hexahydro-1λ^6-thiopyran-3-yl)-amide	1.121	524.12
1.400	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-((3RS,4SR)-3-fluoro-tetrahydro-pyran-4-yl)-amide	1.191	494.14
1.401	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(3-methyl-tetrahydro-pyran-4-yl)-amide	1.202	490.17
1.402	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(6-methyl-tetrahydro-pyran-3-yl)-amide	1.288	490.17
1.403	rac-(1S*,2S*,5R*)-3-(Toluene-4-sulfonyl)-3-aza-bicyclo[3.2.0]heptane-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.262	559.18
1.404	(1R,2S,5S)-6,6-Dimethyl-3-(toluene-4-sulfonyl)-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.292	573.19

1.405	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-((R)-2,2-dimethyl-tetrahydro-pyran-4-yl)-amide	1.265	504.18
1.406	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-((S)-2,2-dimethyl-tetrahydro-pyran-4-yl)-amide	1.259	504.18
1.407	rac-(1R*,2S*,5S*)-3-(Toluene-4-sulfonyl)-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.196	545.16
1.408	(1R*,2S*,5S*)-N-Benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide	1.283	521.18
1.409	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-((2R,4S)-2-methyl-tetrahydro-pyran-4-yl)-amide	1.211	490.17
1.410	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-((2R,4R)-2-methyl-tetrahydro-pyran-4-yl)-amide	1.229	490.17
1.411	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-((2S,4R)-2-methyl-tetrahydro-pyran-4-yl)-amide	1.229	490.17
1.412	(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-((2S,4S)-2-methyl-tetrahydro-pyran-4-yl)-amide	1.216	490.17

Methods for the preparation of sulfoniminamides (SIA) compounds (Examples 2.x)

Example 2.1 (2S)-N-Benzyl-N-(4,4-dimethylcyclohexyl)-1-(4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide:

tert-Butyl (p-tolylsulfinyl)carbamate: A soln. of 4-methyl-benzenesulfinamide (200 mg, 1.22 mmol, 1 eq) in THF (5.5 mL, 1.22 mmol, 1 eq) was cooled to 0°C under nitrogen atmosphere. Lithium bis(trimethylsilyl)amide solution (1.0 M in THF, 3.06 mL, 3.06 mmol, 2.5 eq) was added and the resulting orange soln. was stirred at 0°C for 30 minutes. Di-tert-butyl dicarbonate (0.426 mL, 1.84 mmol, 1.5 eq) was added dropwise and the reaction mixture stirred at 0°C for 2 hours. The reaction mixture was quenched with aq. sat. $NaHCO_3$ and extracted three times with EtOAc. The combined organic layers were dired with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by FC (Hept to Hept/EtOAc 7:3) to give the title compound (mixture of 2 diasteromers, 108 mg, 34%) as a white solid. LC-MS (2): t_R = 0.84 min; $[M-CH_3]^+$: 241.19.

tert-Butyl (chloro(oxo)(p-tolyl)-λ^6-sulfaneylidene)carbamate: A soln. of tert-butyl (p-tolylsulfinyl)carbamate (388 mg, 1.45 mmol, 1 eq) and N-chlorosuccinimide (593 mg, 4.35 mmol, 3 eq) in MeCN (13.9 mL, 265 mmol, 182.8 eq) was stirred at rt overnight. The reaction mixture was quenched with water and extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a yellow solid (824 mg) that was used as a crude. LC-MS (2): t_R = 1.06 min; $[M+H]^+$: 289.89.

Methyl (*N*-(tert-butoxycarbonyl)-4-methylphenylsulfonimidoyl)-*L*-prolinate: A soln. of *tert*-butyl (chloro(oxo)(p-tolyl)-λ^6-sulfaneylidene)carbamate (824 mg, 1.42 mmol, 1 eq) and *L*-proline methyl ester hydrochloride (607 mg, 3.55 mmol, 2.5 eq) in a mixture MeCN (27.5 mL, 526 mmol, 369.9 eq) and DIPEA (0.73 mL, 4.27 mmol, 3 eq) was stirred at rt for 3 h. The reaction mixture was quenched with cold water and extracted three times with EtOAc. The combined organic layer was dired over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by FC (Hept to Hept/EtOAc 7:3) to give the title compound (546 mg, quant.) as a yellow oil. LC-MS (2): t_R = 0.95 min and 0.96 min; $[M+H]^+$: 383.16.

Lithium (*N*-(tert-butoxycarbonyl)-4-methylphenylsulfonimidoyl)-*L*-prolinate: Aq. 1M LiOH (0.324 mL, 0.324 mmol, 1.25 eq) was added to a solution of methyl (*N*-(tert-butoxycarbonyl)-4-methylphenylsulfonimidoyl)-*L*-prolinate (100 mg, 0.259 mmol, 1 eq) in THF (1.69 mL, 20.5 mmol, 79 eq) and the mixture was stirred at rt overnight. The reaction mixture was concentrated to give the title compound (104 mg, quant.) as white solid. LC-MS (2): t_R = 0.85 min; $[M+H]^+$: 369.20.

***t*ert-Butyl (((S)-2-(benzyl(4,4-dimethylcyclohexyl)carbamoyl)pyrrolidin-1-yl)(oxo)(p-tolyl)-λ^6-sulfaneylidene)carbamate:** A soln. of lithium (*N*-(tert-butoxycarbonyl)-4-methylphenylsulfonimidoyl)-*L*-prolinate (20 mg, 0.0543 mmol, 1 eq) and HATU (21.7 mg, 0.057 mmol, 1.05 eq) in a mixture of DMF (0.2 mL) and DIPEA (0.0279 mL, 0.163 mmol, 3 eq) was stirred at rt for 1 h. A soln. of *N*-benzyl-4,4-dimethylcyclohexan-1-amine hydrochloride (13 mg, 0.0597 mmol, 1.1 eq) in DMF (0.2 mL) was then added and the resulting mixture stirred for an additional hour. The reaction mixture was acidified with formic acid and directly purified by basic prep. HPLC to give the title compound (18 mg, 58%) as a white solid. LC-MS (2): t_R = 1.21 min and 1.22 min; $[M+H]^+$: 569.31.

(2*S*)-*N*-Benzyl-*N*-(4,4-dimethylcyclohexyl)-1-(4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide: A soln. of *t*ert-butyl (((S)-2-(benzyl(4,4-dimethylcyclohexyl)carbamoyl)pyrrolidin-1-yl)(oxo)(p-tolyl)-λ^6-sulfaneylidene)carbamate (15 mg, 0.0264 mmol, 1 eq) in a mixture of MeCN (0.2 mL, 3.83 mmol, 137.8 eq) and TFA (0.2 mL, 2.61 mmol, 93.9 eq) was stirred at 35°C for 2 h. The reaction mixture was diluted with DMF/NH_3 (25% in water) and purified by basic prep. HPLC to give the title compound (6.6 mg, 57%) as an orange solid. LC-MS (1): t_R = 1.341 min; $[M+H]^+$: 468.3.

The same step can be achieved as follow: to a solution of Boc-protected compound (1 eq) in MeCN (0.13 M) at rt was added iodotrimethylsilane (2 eq). The resulting solution was stirred for 5 minutes before a few drops of NH_4OH were added. The solution was evaporated under reduced pressure and the residue purified by FC or prep. HPLC.

Example 2.2 to **Example 2.5** were synthesized as described in Example 2.1 using the appropriate amine or amine salt derivative and lithium (*N*-(tert-butoxycarbonyl)-4-methylphenylsulfonimidoyl)-*L*-prolinate. LC-MS data of Example 2.2 to Example 2.5 are listed in the table below.

Ex. N°	Name	t_R	$[M+H]^+$	LC-MS conditions
2.2	(2S)-N-(Benzofuran-6-ylmethyl)-N-(4,4-dimethylcyclohexyl)-1-(4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.385	482.0	1
2.3	(2S)-N-(Benzofuran-6-ylmethyl)-N-(4,4-dimethylcyclohexyl)-1-(4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.361	508.0	1
2.4	(2S)-N-(Benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-(4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	0.97	516.27	2
2.5	(2*S*)-*N*-(4,4-Difluorocyclohexyl)-*N*-(4-methylbenzyl)-1-(4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	0.99	490.30	2

Example 2.6 (2*S*)-*N*-(Benzofuran-6-ylmethyl)-*N*-(4,4-dimethylcyclohexyl)-1-(4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide:

(Tritylimino)-λ^4-sulfanone: To a solution triphenylmethylamine (3000 mg, 11.5 mmol, 1 eq) in Et_2O (90 mL) at rt were sussessively added dropwise Et_3N (3.46 mL, 24 mmol, 2.1 eq) and thionyl chloride (0.844 mL, 11.5 mmol, 1 eq). The obtained light yellow suspension was stirred at rt for 2 h. The suspension was filtered over Celite®, washed with Et_2O and the solvents evaporated under reduced pressure. The obtained light yellow solid (3.51 g, 100%) was used in the next step without further purification.

Methyl (4-methoxy-*N*-tritylphenylsulfonimidoyl)-*L*-prolinate: 4-Methoxyphenylmagnesium bromide 0.5 M in THF (23.0 mL, 11.5 mmol, 1 eq) was added dropwise to a stirred soln. of (tritylimino)-λ^4-sulfanone (3513 mg, 11.5 mmol, 1 eq) in THF (71 ml) at 0°C under argon. The resulting yellow solution was stirred at 0°C for 5 minutes. tBuOCl (1457 mg, 12.1 mmol, 1.05 eq) was added dropwise (exothermic) at 0°C and the mixture was stirred for another 15 minutes before *L*-proline methyl ester hydrochloride (2062 mg, 12.1 mmol, 1.05 eq) and Et_3N (3.53 mL, 25.3 mmol, 2.2 eq) in THF (15 ml) were added. The resulting orange suspension was stirred overnight at rt. The pale yellow suspension was poured onto aq. sat. $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to Hept/EtOAc 1:1) to give the title compound (2.36 g, 38%) as a light yellow foam. LC-MS (2): t_R = 1.12 min; $[M+H]^+$: 541.2.

(4-Methoxy-*N*-tritylphenylsulfonimidoyl)-*L*-proline: LiOH (1 M in H_2O, 21.1 mL, 21.1 mmol, 5 eq) was added to a solution of methyl (4-methoxy-*N*-tritylphenylsulfonimidoyl)-*L*-prolinate (2286 mg, 4.23 mmol, 1 eq) in THF (21 mL) at rt and the resulting mixture was stirred overnight. The reaction mixture was diluted with water and the pH adjusted to 5 with aq. 1 M HCl. The product was extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure ti give the title compound (1.917 g, 86%) as an orange foam. LC-MS (2): t_R = 1.11 min; $[M+H]^+$: 527.2.

(2*S*)-*N*-(Benzofuran-6-ylmethyl)-*N*-(4,4-dimethylcyclohexyl)-1-(4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide: DIPEA (0.0223 mL, 0.13 mmol, 1.3 eq) was added to a soln. of (4-methoxy-*N*-tritylphenylsulfonimidoyl)-*L*-proline (52.7 mg, 0.1 mmol, 1 eq), *N*-(benzofuran-6-ylmethyl)-4,4-dimethylcyclohexan-1-amine (0.1 mmol, 1 eq) and HATU (45.6 mg, 0.12 mmol, 1.2 eq) in DMF (0.5 mL). The resulting mixture was stirred at 60°C for 1.5 h. The reaction mixture was acidified with HCl (4M in dioxane, 0.075 mL, 0.3 mmol, 3 eq), further stirred at rt for 30 minutes and purified by acidic prep. HPLC to give the title compound (13 mg, 25%) as a colorless oil. LC-MS (1): t_R = 1.286 min; $[M+H]^+$: 524.2.

Example 2.7 to **Example 2.14** were synthesized as described in Example 2.6 using the appropriate amine or amine salt derivative and (4-methoxy-*N*-tritylphenylsulfonimidoyl)-*L*-proline. LC-MS data of Example 2.7 to Example 2.14 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
2.7	(2S)-N-Benzyl-N-(4,4-dimethylcyclohexyl)-1-(4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.271	484.3
2.8	(2S)-N-(Benzo[d]oxazol-5-ylmethyl)-N-(4,4-dimethylcyclohexyl)-1-(4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.153	525.2
2.9	(2S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-dimethylcyclohexyl)-1-(4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.198	541.3
2.10	(2S)-N-(4,4-Difluorocyclohexyl)-1-(4-methoxyphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.141	506.6
2.11	(2S)-N-(Benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-(4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.101	532.4
2.12	(2S)-N-(Benzo[d]oxazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-(4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide	0.974	533.3
2.13	(2S)-N-(Benzo[d]oxazol-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-(4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide	0.960	533.2
2.14	(2S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-(4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.017	549.3

Example 2.15 to **Example 2.22** were synthesized as described in Example 2.1 using the appropriate amine or amine salt derivative and lithium (*N*-(tert-butoxycarbonyl)-4-methylphenylsulfonimidoyl)-*L*-prolinate followed by Boc deprotection using HCl (4M/ in dioxane). LC-MS data of Example 2.15 to Example 2.22 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
2.15	(2S)-N-(Benzo[d]oxazol-5-ylmethyl)-N-(4,4-dimethylcyclohexyl)-1-(4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.204	509.3
2.16	(2S)-N-(Benzo[d]oxazol-6-ylmethyl)-N-(4,4-dimethylcyclohexyl)-1-(4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.187	509.4
2.17	(2S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-dimethylcyclohexyl)-1-(4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.240	525.3
2.18	(2S)-N-((2,3-Dihydrobenzofuran-6-yl)methyl)-N-(4,4-dimethylcyclohexyl)-1-(4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.313	510.3
2.19	(2S)-N-(Benzo[d]oxazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-(4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.011	517.3
2.20	(2S)-N-(Benzo[d]oxazol-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-(4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	0.998	517.4
2.21	(2S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-(4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.051	533.3
2.22	(2S)-N-(4,4-Difluorocyclohexyl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-1-(4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.117	518.3

Example 2.23 to **Example 2.24** were synthesized as described in Example 2.6 using the appropriate amine or amine salt derivative and (4-methoxy-*N*-tritylphenylsulfonimidoyl)-*L*-proline. LC-MS data of Example 2.23 to Example 2.24 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
2.23	(2S)-N-(4,4-Difluorocyclohexyl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-1-(4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.083	534.3
2.24	(2S)-N-((2,3-Dihydrobenzofuran-6-yl)methyl)-N-(4,4-dimethylcyclohexyl)-1-(4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.261	526.3

Examples 2.25 to Example 2.26 were synthesized as described for Example 2.1 using the appropriate amine or amine salt derivative and lithium (*N*-(tert-butoxycarbonyl)-4-methylphenylsulfonimidoyl)-*L*-prolinate followed by Boc deprotection using HCl (4M in dioxane). LC-MS data of Example 2.25 to Example 2.26 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
2.25	(S)-N-(Benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((R)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.150	516.3
2.26	(S)-N-(Benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((S)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.166	516.3

Example 2.27 (2*S*)-*N*-(4,4-Difluorocyclohexyl)-1-(*N*-ethyl-4-methylphenylsulfonimidoyl)-*N*-(4-methylbenzyl)pyrrolidine-2-carboxamide: NaH (60% in mineral oil, 4.49 mg, 0.112 mmol, 2 eq) was added to a stirred soln. of (2*S*)-*N*-(4,4-difluorocyclohexyl)-*N*-(4-methylbenzyl)-1-(4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide (27.5 mg, 0.0562 mmol, 1 eq) in DMF (1 mL) at rt and the resulting mixture was stirred for 15 minutes. Iodoethane (6.8 µL, 0.0842 mmol, 1.5 eq) was added dropwise and the mixture was stirred for another 30 minutes. The reaction is quenched with a few drops of water, filtered and purified by basic prep. HPLC to give the title compound (20.2 g, 69%) as a white solid. LC-MS (2): t_R= 0.96 min; $[M+H]^+$: 518.3.

Example 2.28 (2*S*)-*N*-(4,4-Difluorocyclohexyl)-1-(*N*,4-dimethylphenylsulfonimidoyl)-*N*-(4-methylbenzyl)pyrrolidine-2-carboxamide: NaH (60% in mineral oil, 4.49 mg, 0.112 mmol, 2 eq) was added to a stirred solution of (2*S*)-*N*-(4,4-difluorocyclohexyl)-*N*-(4-methylbenzyl)-1-(4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide (27.5 mg, 0.0562 mmol, 1 eq) in DMF (1 mL) at rt and the resulting mixture was stirred for 15 minutes. MeI (0.00531 mL, 0.0842 mmol, 1.5 eq) was added dropwise and the mixture was stirred for another 30 minutes. The reaction is quenched with a few drops of water, filtered and purified by basic prep. HPLC to give the title compound (20 g, 71%) as a white solid. LC-MS (2): t_R= 0.95 min; $[M+H]^+$: 504.3.

Example 2.29 to **Example 2.46** were synthesized as described in Example 2.27 using the appropriate (4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide and the appropriate alkylating agent. LC-MS data of Example 2.29 to Example 2.46 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
2.29	(2S)-N-(Benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-(N-ethyl-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.212	544.3
2.30	(S)-N-(Benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.192	530.2
2.31	(2S)-N-(Benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-(4-methoxy-N-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.088	546.4
2.32	(2S)-N-(Benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-(N-ethyl-4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.112	560.4

2.33	(2S)-N-(4,4-Difluorocyclohexyl)-1-(4-methoxy-N-methylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.102	520.4
2.34	(2S)-N-(4,4-Dimethylcyclohexyl)-1-(N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.403	496.3
2.35	(2S)-N-(4,4-Dimethylcyclohexyl)-1-(N-ethyl-4-methylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.443	510.4
2.36	(2S)-N-(Benzofuran-6-ylmethyl)-N-(4,4-dimethylcyclohexyl)-1-(N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.352	522.4
2.37	(2S)-N-(Benzofuran-6-ylmethyl)-N-(4,4-dimethylcyclohexyl)-1-(N-ethyl-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.391	536.4
2.38	(2S)-N-(Benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-(N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.168	530.4
2.39	(2S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-dimethylcyclohexyl)-1-(N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.251	539.3
2.40	(2S)-N-((2,3-Dihydrobenzofuran-6-yl)methyl)-N-(4,4-dimethylcyclohexyl)-1-(N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.322	524.3
2.41	(2S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-dimethylcyclohexyl)-1-(N-ethyl-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.286	553.4
2.42	(2S)-N-((2,3-Dihydrobenzofuran-6-yl)methyl)-N-(4,4-dimethylcyclohexyl)-1-(N-ethyl-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.362	538.4
2.43	(2S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-(N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.044	547.3
2.44	(2S)-N-(4,4-Difluorocyclohexyl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-1-(N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.133	532.4
2.45	(2S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-(N-ethyl-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.114	561.3
2.46	(2S)-N-(4,4-Difluorocyclohexyl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-1-(N-ethyl-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.184	546.4

Example 2.47 (*S*)-*N*-(Benzofuran-6-ylmethyl)-*N*-(4,4-difluorocyclohexyl)-1-((*S*)-4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide and Example 2.48 (*S*)-*N*-(benzofuran-6-ylmethyl)-*N*-(4,4-difluorocyclohexyl)-1-((*R*)-4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide:

Methyl 4-methoxybenzenesulfinate: At 0°C under argon, *N*-bromosuccinimide (3700 mg, 20.8 mmol, 2 eq) was added in one portion to a solution of 4-methoxythiophenol (1.30 mL, 10.4 mmol, 1 eq) in CH_2Cl_2 (52 mL) and MeOH

(52 mL). The ice bath was removed and the reaction was stirred at rt for 1 h. The reaction mixture was poured onto aq. sat. $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by FC (CH_2Cl_2 to CH_2Cl_2/MeOH 95:5) to give the title compound (1.93 g, 100%) as a light pink liquid. LC-MS (2): t_R = 0.73 min; $[M+H]^+$: 182.2.

4-Methoxybenzenesulfinamide: Lithium bis(trimethylsilyl)amide (1.0 M in THF, 15.5 mL, 15.5 mmol, 1.498 eq) was added dropwise to a stirred soln. of methyl 4-methoxybenzenesulfinate (1928 mg, 10.4 mmol, 1 eq) in THF (15.5 mL) at -78°C under argon. The mixture was stirred at -78°C for 10 min, then the cooling bath was removed and the reaction was allowed to warm up to rt while stirring for another 1.5 h. Aq. sat. NH_4Cl (40 mL) was added to quench the reaction and the mixture was stirred at rt for 30 minutes. The reaction mixture was poured onto water and extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was obtained as a orange solid (1.48 g) that was pure enough to be used in the next step without further purification. LC-MS (2): t_R = 0.52 min; $[M+H]^+$: 172.07.

***tert*-Butyl ((4-methoxyphenyl)sulfinyl)carbamate:** At 0°C under argon, lithium bis(trimethylsilyl)amide (1 M in THF, 6.43 mL, 6.13 mmol, 2.1 eq) was added dropwise to a stirred soln. of 4-methoxybenzenesulfinamide (500 mg, 2.92 mmol, 1 eq) in THF (11 mL). The mixture was stirred at 0°C for 1 h, then a solution of di-tert-butyl dicarbonate (1.02 mL, 4.38 mmol, 1.5 eq) in THF (2 mL) was added dropwise. The ice bath was removed and the solution was stirred at rt overnight. The reaction mixture was quenched with aq. sat. $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure. The residue was purified by FC (Hept to Hept/EtOAc 6:4) to give the title compound (0.603 g, 76%) as a white solid. LC-MS (2):t_R = 0.81 min; $[M+H]^+$: 272.27.

Methyl (*N*-(tert-butoxycarbonyl)-4-methoxyphenylsulfonimidoyl)-*L*-prolinate*:* At 0°C under argon, *tert*-butyl ((4-methoxyphenyl)sulfinyl)carbamate (950 mg, 3.5 mmol, 1 eq) was dissolved in CH_2Cl_2 (25 mL), then *t*BuOCl (570 mg, 5.25 mmol, 1.5 eq) was added dropwise and the resulting light yellow solution was stirred at 0°C for 30 minutes. *L*-Proline methyl ester hydrochloride (598 mg, 3.5 mmol, 1 eq) and Et_3N (1.95 mL, 14 mmol, 4 eq) in CH_2Cl_2 (10 mL) were added and the resulting solution was stirred for another 30 minutes. The reaction was poured onto aq. 0.1 M HCl and extracted with Et_2O. The organic layer was washed with aq. sat. $NaHCO_3$ and water, dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure to give 1.5 g of a yellow oil as crude product. The crude was purified by prep. HPLC to give the title compound (1.01 g, 72%) as a colorless oil. LC-MS (2): t_R= 0.93 and 0.94 min (mixture of 2 epimers); $[M+H]^+$: 399.23.

(*N*-(*tert*-Butoxycarbonyl)-4-methoxyphenylsulfonimidoyl)-*L*-proline: To a soln. of methyl (*N*-(tert-butoxycarbonyl)-4-methoxyphenylsulfonimidoyl)-*L*-prolinate (764 mg, 1.92 mmol, 1 eq) in THF (19 mL) at rt was added aq. 1 M LiOH (3.8 mL, 3.83 mmol, 2 eq) and the turbid, colorless mixture was stirred at rt overnight. The mixture was diluted with Et_2O and extracted with aq. 0.1 M HCl. The organic layer was washed with water, dried

over Na_2SO_4, evaporated, filtered, and the solvent removed under reduced pressure to give the title compound (715 mg, 97%) as a white foam. LC-MS (2): t_R= 0.83 min (mixture of 2 epimers); $[M+H]^+$: 385.15.

***tert*-Butyl (((*S*)-2-((benzofuran-6-ylmethyl)(4,4-difluorocyclohexyl)carbamoyl)pyrrolidin-1-yl)(4-methoxyphenyl)(oxo)-λ⁶-sulfaneylidene)carbamate:** To a soln. of (*N*-(*tert*-butoxycarbonyl)-4-methoxyphenylsulfonimidoyl)-*L*-proline (577 mg, 1.5 mmol, 1 eq) in DMF (13 mL) at rt, were added DIPEA (0.514 mL, 3 mmol, 2 eq) and HATU (685 mg, 1.8 mmol, 1.2 eq). The obtained yellow solution was stirred at rt for 10 min before a soln. of *N*-(benzofuran-6-ylmethyl)-4,4-difluorocyclohexan-1-amine (437 mg, 1.58 mmol, 1.05 eq) in DMF (2 mL) was added. The mixture was stirred at rt for 2.5 hours. The yellow soln. was diluted with Et_2O and washed with aq. 0.1 M HCl, aq. sat. $NaHCO_3$ and with H_2O. The organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure to give 180 mg of a light yellow foam as a crude product. The residue was purified by FC (Hept to Hept/EtOAc 3:2) to give the title compound (734 mg, 77%) as a white solid. LC-MS (2):t_R= 1.12 min; $[M+H]^+$: 632.38.

(*S*)-*N*-(Benzofuran-6-ylmethyl)-*N*-(4,4-difluorocyclohexyl)-1-((*S*)-4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide and (*S*)-*N*-(benzofuran-6-ylmethyl)-*N*-(4,4-difluorocyclohexyl)-1-((*R*)-4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide: Iodotrimethylsilane (0.256 mL, 1.74 mmol, 1.5 eq) was added to a stirred soln. of *tert*-butyl (((*S*)-2-((benzofuran-6-ylmethyl)(4,4-difluorocyclohexyl)carbamoyl)pyrrolidin-1-yl)(4-methoxyphenyl)(oxo)-λ⁶-sulfaneylidene)carbamate (734 mg, 1.16 mmol, 1 eq) in MeCN (23 mL). After stirring for 10 min, the yellow solution was poured onto aq. sat. $NaHCO_3$ and extracted with Et_2O. The organic layer was washed once with water, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by FC (CH_2Cl_2 to CH_2Cl_2/MeOH 95:5) to give the title compounds both as white foams. First eluting diastereomer (Example 2.47, 252 mg, 41%). LC-MS (1): t_R = 1.184 min; $[M+H]^+$: 532.3. Second eluting diastereomer (Example 2.48, 282 mg, 46%). LC-MS (1): t_R= 1.121 min; $[M+H]^+$: 532.2.

Example 2.49 (*S*)-*N*-(Benzofuran-6-ylmethyl)-*N*-(4,4-difluorocyclohexyl)-1-((*R*)-4-methoxy-*N*-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide: NaH (60% in mineral oil, 37 mg, 0.925 mmol, 1.5 eq) was added to a stirred solution of (*S*)-*N*-(benzofuran-6-ylmethyl)-*N*-(4,4-difluorocyclohexyl)-1-((*R*)-4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide (318 mg, 0.617 mmol, 1 eq) in DMF (6.2 mL) at rt. The resulting yellow, slightly turbid soln. was stirred at rt for 40 min before MeI (0.0465 mL, 0.739 mmol, 1.236 eq) was added. Stirring was continued for an additional 10 minutes. About 1 mL of water was added (gas evolution) and after stirring for 5 min, the slightly solution was filtered over a 0.45 µm PTFE syringe filter. The filtrate was purified by basic prep. HPLC to give the title compound (248 mg, 76%) as a white solid. LC-MS (1): t_R= 1.099 min; $[M+H]^+$: 546.4.

Example 2.50 to Example 2.76 were synthesized as described in Example 2.27 using the appropriate (4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide and the appropriate alkylating agent. LC-MS data of Example 2.50 to Example 2.76 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
2.50	(2S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-(N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.144	523.2
2.51	(2S)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-1-(N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.199	508.4
2.52	(2S)-N-(Bicyclo[4.1.0]heptan-3-yl)-1-(N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.286	480.4
2.53	(2S)-N-(Benzofuran-6-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-(N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.247	506.2
2.54	(2S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-(4-methoxy-N-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	0.993	563.3
2.55	(2S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-dimethylcyclohexyl)-1-(4-methoxy-N-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.153	555.4
2.56	(2S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-(4-methoxy-N-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.051	539.3
2.57	(2S)-N-(4,4-Difluorocyclohexyl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-1-(4-methoxy-N-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.054	548.4
2.58	(2S)-N-((2,3-Dihydrobenzofuran-6-yl)methyl)-N-(4,4-dimethylcyclohexyl)-1-(4-methoxy-N-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.231	540.4
2.59	(2S)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-1-(4-methoxy-N-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.107	524.4
2.60	(2S)-N-(4,4-Dimethylcyclohexyl)-1-(4-methoxy-N-methylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.303	512.4
2.61	(2S)-N-(Bicyclo[4.1.0]heptan-3-yl)-1-(4-methoxy-N-methylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.187	496.4
2.62	(2S)-N-(Benzofuran-6-ylmethyl)-N-(4,4-dimethylcyclohexyl)-1-(4-methoxy-N-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.261	538.4
2.63	(2S)-N-(Benzofuran-6-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-(4-methoxy-N-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.160	522.3
2.64	(2S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-(N-ethyl-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.182	537.4

2.65	(2S)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-1-(N-ethyl-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.256	522.4
2.66	(2S)-N-(Bicyclo[4.1.0]heptan-3-yl)-1-(N-ethyl-4-methylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.350	494.3
2.67	(2S)-N-(Benzofuran-6-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-(N-ethyl-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.296	520.4
2.68	(2S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-(N-ethyl-4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.027	577.3
2.69	(2S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-dimethylcyclohexyl)-1-(N-ethyl-4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.186	569.4
2.70	(2S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-(N-ethyl-4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.091	553.3
2.71	(2S)-N-(4,4-Difluorocyclohexyl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-1-(N-ethyl-4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.086	562.4
2.72	(2S)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-1-(N-ethyl-4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.160	538.4
2.73	(2S)-N-(Benzofuran-6-ylmethyl)-N-(4,4-dimethylcyclohexyl)-1-(N-ethyl-4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.296	552.3
2.74	(2S)-N-(Benzofuran-6-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-(N-ethyl-4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.176	536.4
2.75	(2S)-N-(4,4-Dimethylcyclohexyl)-1-(N,4-dimethylphenylsulfonimidoyl)-N-(furo[3,2-c]pyridin-6-ylmethyl)pyrrolidine-2-carboxamide	1.036	523.3
2.76	(2S)-N-(Bicyclo[4.1.0]heptan-3-yl)-1-(N,4-dimethylphenylsulfonimidoyl)-N-(furo[3,2-c]pyridin-6-ylmethyl)pyrrolidine-2-carboxamide	0.920	507.2

Example 2.77 (1*R*,3*S*,5*R*)-*N*-(4,4-Difluorocyclohexyl)-*N*-((2,3-dihydrobenzofuran-6-yl)methyl)-2-(4-methylphenylsulfonimidoyl)-2-azabicyclo[3.1.0]hexane-3-carboxamide:

***tert*-Butyl (1*R*,3*S*,5*R*)-3-((4,4-difluorocyclohexyl)((2,3-dihydrobenzofuran-6-yl)methyl)carbamoyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate:** To a mixture of (1*R*,3*S*,5*R*)-2-[(tert-butoxy)carbonyl]-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (193 mg, 0.823 mmol, 1 eq) and HATU (387 mg, 0.988 mmol, 1.2 eq) in DMF (13 mL) at rt was added DIPEA (0.288 mL, 1.65 mmol, 2 eq). The obtained reaction mixture was stirred at rt for 10 min before *N*-((2,3-dihydrobenzofuran-6-yl)methyl)-4,4-difluorocyclohexan-1-amine (250 mg, 0.823 mmol, 1 eq) was added and the mixture was stirred at rt for an additional 1 h. The mixture was purified by prep. HPLC to give the title compound (293 mg, 74%) as a yellow oil. LC-MS (2): t_R= 1.04 min; $[M+H]^+$: 477.3.

(1*R*,3*S*,5*R*)-*N*-(4,4-Difluorocyclohexyl)-*N*-((2,3-dihydrobenzofuran-6-yl)methyl)-2-azabicyclo[3.1.0]hexane-3-carboxamide: *tert*-Butyl (1*R*,3*S*,5*R*)-3-((4,4-difluorocyclohexyl)((2,3-dihydrobenzofuran-6-yl)methyl)carbamoyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (290 mg, 0.593 mmol, 1 eq), was dissolved in HCl (4.0 M in dioxane, 0.775 mL, 2.96 mmol, 5 eq) and the resulting colorless solution was stirred at rt overnight. The solvent was evaporated under reduced pressure, the residue was diluted with DMF/H_2O and a few drops of DIPEA and filtered. The soln. was directly purified by prep. HPLC to give the title compound (201 mg, quant.) as a white solid. LC-MS (2): t_R= 0.74 min; $[M+H]^+$: 377.24.

***tert*-Butyl (((1*R*,3*S*,5*R*)-3-((4,4-difluorocyclohexyl)((2,3-dihydrobenzofuran-6-yl)methyl)carbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl)(oxo)(p-tolyl)-λ^6-sulfaneylidene)carbamate:** To a soln. of *tert*-butyl (p-tolylsulfinyl)carbamate (14.1 mg, 0.0552 mmol, 1 eq) in DCM (1.03 mL) at 0°C, was added tBuOCl (6 mg, 0.0552 mmol, 1 eq). The reaction mixture was stirred for 10 minutes before a solution of (1*R*,3*S*,5*R*)-*N*-(4,4-difluorocyclohexyl)-*N*-((2,3-dihydrobenzofuran-6-yl)methyl)-2-azabicyclo[3.1.0]hexane-3-carboxamide (21 mg, 0.0552 mmol, 1 eq) and Et_3N (0.0307 mL, 0.221 mmol, 4 eq) in DCM (0.2 mL) was added. After stirring at 0°C for an additional 15 minutes, the pH of the reaction mixture was adjusted to 2 with aq. 0.1 M HCl and the resulting mixture was extracted with Et_2O. The organic layer was washed with sat. aq. $NaHCO_3$ and water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep. HPLC to give the title compound as a white solid (26 mg, 75%). LC-MS (2): t_R= 1.12 min; $[M+H]^+$: 630.32

(1*R*,3*S*,5*R*)-*N*-(4,4-Difluorocyclohexyl)-*N*-((2,3-dihydrobenzofuran-6-yl)methyl)-2-(4-methylphenylsulfonimidoyl)-2-azabicyclo[3.1.0]hexane-3-carboxamide: Iodotrimethylsilane (0.0121 mL, 0.0826 mmol, 2 eq) was added to a stirred soln. of *tert*-butyl (((1*R*,3*S*,5*R*)-3-((4,4-difluorocyclohexyl)((2,3-dihydrobenzofuran-6-yl)methyl)carbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl)(oxo)(p-tolyl)-λ^6-sulfaneylidene)carbamate (26 mg, 0.0413 mmol, 1 eq) in MeCN (0.7 mL). After stirring for 10 minutes, the yellow soln. was poured onto aq. sat. $NaHCO_3$ and extracted with EtOAc. The organic layer was washed once with water, dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure. The residue was purified by FC (Hept to Hept/EtOAc 3:2) to give the title compound (16 mg, 73%) as a yellowish solid. LC-MS (1): t_R= 1.151 min; $[M+H]^+$: 530.4.

Example 2.78 (1*R*,3*S*,5*R*)-*N*-(4,4-Difluorocyclohexyl)-*N*-((2,3-dihydrobenzofuran-6-yl)methyl)-2-(4-methoxyphenylsulfonimidoyl)-2-azabicyclo[3.1.0]hexane-3-carboxamide: Was synthesized as described in Example 2.77 using *tert*-butyl ((4-methoxyphenyl)sulfinyl)carbamate to give the title. LC-MS (2): t_R= 0.93 and 0.97 min; $[M+H]^+$: 546.02.

Example 2.79 to **Example 2.83** were synthesized as described in Example 2.77 using the appropriate Boc protected proline and the appropriate Boc protected sulfinamide. LC-MS data of Example 2.79 to Example 2.83 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
2.79	(2S,4S)-N-(4,4-Difluorocyclohexyl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-4-fluoro-1-(4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.105	536.4
2.80	(1*R*,3*S*,5*R*)-*N*-(4,4-Difluorocyclohexyl)-*N*-((2,3-dihydrobenzofuran-6-yl)methyl)-2-(*N*,4-dimethylphenylsulfonimidoyl)-2-azabicyclo[3.1.0]hexane-3-carboxamide	1.187	544.4
2.81	(1R,3S,5R)-N-(4,4-Difluorocyclohexyl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-2-(4-methoxy-N-methylphenylsulfonimidoyl)-2-azabicyclo[3.1.0]hexane-3-carboxamide	1.120	560.4
2.82	(2S,4S)-N-(4,4-Difluorocyclohexyl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-1-(N,4-dimethylphenylsulfonimidoyl)-4-fluoropyrrolidine-2-carboxamide	1.150	550.3
2.83	(2S,4S)-N-(4,4-Difluorocyclohexyl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-4-fluoro-1-(4-methoxy-N-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.080	566.4

Example 2.84 (2*S*)-*N*-(Benzofuran-6-ylmethyl)-1-(*N*-cyclopentyl-4-methylphenylsulfonimidoyl)-*N*-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide:

Methyl 4-methylbenzenesulfinate: At 0°C under argon, N-bromosuccinimide (1489 mg, 8.28 mmol, 2.1 eq) was added portionwise to a stirred solution of 4-methylbenzenethiol (500 mg, 3.95 mmol, 1 eq) in DCM (10 mL) and MeOH (10 mL) while maintaining a temperature below 10°C. The ice bath was removed and the soln. was stirred at rt for 1h. The reaction mixture was quenched at rt with aq. sat. $NaHCO_3$. The mixture was diluted with DCM and the layerrs were separated. The org. layer was washed with H_2O, dried over Na_2SO_4, filtered ,and the solvent was evaporated under reduced pressure to give the title compound (770 mg, quant.) as a light yellow oil. The crude was used in the next step without further purification. LC-MS (2): t_R= 0.77 min; $[M+H]^+$: 171.01.

***N*-Cyclopentyl-4-methylbenzenesulfinamide:** At 0°C, nBuLi (1.6 M in hexanes, 0.375 mL, 0.6 mmol, 2 eq) was added dropwise to a stirred soln. of cyclopentanamine (38.3 mg, 0.45 mmol, 1.5 eq) in THF (1 mL). After stirring for 20 min, a soln. of methyl 4-methylbenzenesulfinate (51.1 mg, 0.3 mmol, 1 eq) in THF (1 mL) was added. The reaction was stirred at 0°C for 30 min, quenched with H_2O and diluted with DCM. The layers were separated and the organic layer was evaporated under reduced pressure to give the title compound (48.4 mg, 72%) as a yellow oil which was used in the next step without further purification. LC-MS (2): t_R= 0.86 min; $[M+H]^+$: 224.19

(2*S*)-*N*-(Benzofuran-6-ylmethyl)-1-(*N*-cyclopentyl-4-methylphenylsulfonimidoyl)-*N*-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide: To a soln. of *N*-cyclopentyl-4-methylbenzenesulfinamide (30.1 mg, 0.132 mmol, 1.5 eq) in DCM (0.75 mL) at rt, was added tBuOCl (19.2 mg, 0.177 mmol, 2 eq). The reaction mixture was stirred for 30 min before a soln. of (*S*)-*N*-(benzofuran-6-ylmethyl)-*N*-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide (32.2 mg, 0.0883 mmol, 1 eq) and DIPEA (0.00453 mL, 0.265 mmol, 3 eq) in DCM (0.75 mL) was added. After stirring at rt for an additional 2 h, the solvents were evaporated under reduced pressure and the residue

was diluted with DMF and purified by basic prep. HPLC to yield the title compound as a white solid (6.2 mg, 12%). LC-MS (2): t_R= 1.00 min; $[M+H]^+$: 584.22.

Example 2.85 to **Example 2.91** were synthesized as described in Example 2.84 using the appropriate amine and the appropriate pyrrolidine-2-carboxamide. LC-MS data of Example 2.85 to Example 2.91 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
2.85	(2S)-N-(Benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-(N-isopropyl-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.194	558.4
2.86	(2S)-N-(Benzofuran-6-ylmethyl)-1-(N-cyclopropyl-4-methylphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide	1.296	556.4
2.87	(2S)-N-(Benzofuran-6-ylmethyl)-1-(N-cyclohexyl-4-methylphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide	1.340	598.4
2.88	(2S)-N-(Benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-(4-methyl-N-phenylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.422	592.4
2.89	(2S)-1-(N-Cyclopropyl-4-methylphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)pyrrolidine-2-carboxamide	1.258	558.4
2.90	(2S)-1-(N-Cyclopentyl-4-methylphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)pyrrolidine-2-carboxamide	1.281	586.4
2.91	(2S)-N-(4,4-Difluorocyclohexyl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-1-(4-methyl-N-phenylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.401	594.4

Example 2.92 to **Example 2.96** were synthesized as described in Example 2.84 using the appropriate arylthiol derivative, the appropriate alkylamine and the appropriate pyrrolidine-2-carboxamide. LC-MS data of Example 2.92 to Example 2.96 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
2.92	(2S)-N-(Benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-(4-fluoro-N-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.191	534.3
2.93	(2S)-N-(Benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-(3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.254	548.4
2.94	(2S)-N-(4,4-Difluorocyclohexyl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-1-(3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.226	550.4
2.95	(2S)-N-(Benzofuran-6-ylmethyl)-1-(3,4-difluoro-N-methylphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide	1.260	552.3

2.96	(2S)-N-(Benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-(N,3,4-trimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.179	544.3

Example 2.97 to **Example 2.124** were synthesized according to the procedure described in Example 2.49 using 4-methylbenzenesulfinamide and the appropriate amine. LC-MS data of Example 2.97 to Example 2.124 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$	LC-MS conditions
2.97	(2S)-N-(4,4-Difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-fluoro-3-methylbenzyl)pyrrolidine-2-carboxamide	1.231	522.3	1
2.98	(2S)-N-(2-Chlorobenzyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.249	524.3	1
2.99	(2S)-N-(4,4-Difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(3-fluorobenzyl)pyrrolidine-2-carboxamide	1.174	508.2	1
2.100	(2S)-N-(2,3-Difluoro-4-methylbenzyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.266	540.4	1
2.101	(2S)-N-(2,4-Difluorobenzyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.214	526.3	1
2.102	(2S)-N-(4,4-Difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(3-methoxybenzyl)pyrrolidine-2-carboxamide	1.153	520.3	1
2.103	(2S)-N-(2,5-Difluorobenzyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.191	526.3	1
2.104	(2S)-N-(4,4-Difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(2-fluoro-4-methoxybenzyl)pyrrolidine-2-carboxamide	1.182	538.4	1
2.105	(2S)-N-(4,4-Difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(naphthalen-2-ylmethyl)pyrrolidine-2-carboxamide	1.260	540.4	2
2.106	(2S)-N-(4,4-Difluorocyclohexyl)-N-(3,4-dimethylbenzyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.266	518.4	1

2.107	(2S)-N-(4,4-Difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-isopropylbenzyl)pyrrolidine-2-carboxamide	1.336	532.3	1
2.108	(2S)-N-(4-Chlorobenzyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.243	524.3	1
2.109	(2S)-N-(Benzo[d][1,3]dioxol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.114	534.4	1
2.110	(2S)-N-(4,4-Difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-ethylbenzyl)pyrrolidine-2-carboxamide	1.279	518.4	1
2.111	(2S)-N-(3-Chloro-4-methylbenzyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.289	538.4	1
2.112	(2S)-N-(4,4-Difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(3-fluoro-4-methylbenzyl)pyrrolidine-2-carboxamide	1.228	522.4	1
2.113	(2S)-N-(4,4-Difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(3-ethynyl-4-methylbenzyl)pyrrolidine-2-carboxamide	1.143	529.3	1
2.114	(2S)-N-(4,4-Difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(2-fluoro-3-methylbenzyl)pyrrolidine-2-carboxamide	1.244	522.3	1
2.115	(2S)-N-(4,4-Difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-(methylthio)benzyl)pyrrolidine-2-carboxamide	1.217	536.3	1
2.116	(2S)-N-(2,4-Difluoro-5-methylbenzyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.274	540.3	1
2.117	(2S)-N-(4,4-Difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-fluoro-2-methylbenzyl)pyrrolidine-2-carboxamide	1.216	522.4	1
2.118	(2S)-N-(4,4-Difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(2-fluoro-4-methylbenzyl)pyrrolidine-2-carboxamide	1.242	522.4	1
2.119	(2S)-N-(4-Chlorobenzyl)-N-(4,4-difluorocyclohexyl)-1-((R)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	0.99	510.20	2

2.120	(2S)-N-(4,4-Difluorocyclohexyl)-N-(4-(dimethylamino)benzyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.030	533.3	1
2.121	(2S)-N-(4,4-Difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-fluorobenzyl)pyrrolidine-2-carboxamide	1.164	508.3	1
2.122	(2S)-N-(4-Chloro-3-fluorobenzyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.252	542.3	1
2.123	(2S)-N-(4,4-Difluorocyclohexyl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.309	530.3	1
2.124	(2S)-N-(4,4-Difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-((5-methylisoxazol-3-yl)methyl)pyrrolidine-2-carboxamide	1.009	495.2	1

Example 2.125 to **Example 2.126** were synthesized as described in Example 2.84 the appropriate arylthiol, the appropriate alkylamine and the appropriate pyrrolidine-2-carboxamide. LC-MS data of Example 2.125 to Example 2.126 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
2.125	(2S)-N-(4-Chloro-2-fluorobenzyl)-N-(4,4-difluorocyclohexyl)-1-(3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.349	560.3
2.126	(2S)-N-(4-Chloro-2-fluorobenzyl)-N-(4,4-difluorocyclohexyl)-1-(4-methoxy-N-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.206	558.2

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Example 2.127 to **Example 2.129** were synthesized as described in Example 2.49 using 4-methylbenzenesulfinamide and the appropriate amine or amine salt. LC-MS data of Example 2.127 to Example 2.129 are listed in the table below.

Ex. N°	Name	t_R	$[M+H]^+$	LC-MS conditions
2.127	(2S)-N-(4-Chloro-2-fluorobenzyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	0.98	542.111	2
2.128	(2S)-N-(4-Chloro-2,3-difluorobenzyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.305	560.2	1

2.129	(2S)-N-(4-Chloro-2,6-difluorobenzyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.256	560.3	1

Example 2.130 to **Example 2.156** were synthesized as described in Example 2.84 using the appropriate arylthiol, the appropriate alkylamine the appropriate pyrrolidine-2-carboxamide. LC-MS data of Example 2.130 to Example 2.156 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
2.130	(2S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-(3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.149	565.3
2.131	(2S)-N-(4,4-Difluorocyclohexyl)-1-(3-fluoro-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.302	522.3
2.132	(2S)-N-(4-Chlorobenzyl)-N-(4,4-difluorocyclohexyl)-1-(3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.316	542.3
2.133	(2S)-N-(4,4-Difluorocyclohexyl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-1-(3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.392	548.4
2.134	(2S)-N-(Benzofuran-6-ylmethyl)-1-(N-cyclopropyl-3-fluoro-4-methylphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide	1.354	574.4
2.135	(2S)-1-(N-Cyclopropyl-3-fluoro-4-methylphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)pyrrolidine-2-carboxamide	1.328	576.4
2.136	(2S)-N-(Benzo[d]thiazol-5-ylmethyl)-1-(N-cyclopropyl-3-fluoro-4-methylphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide	1.261	591.3
2.137	(2S)-1-(N-Cyclopropyl-3-fluoro-4-methylphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.404	548.4
2.138	(2S)-N-(4-Chlorobenzyl)-1-(N-cyclopropyl-3-fluoro-4-methylphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide	1.417	568.2
2.139	(2S)-1-(N-Cyclopropyl-3-fluoro-4-methylphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)pyrrolidine-2-carboxamide	1.486	574.3
2.140	(2S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-(4-methyl-N-phenylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.345	609.3
2.141	(2S)-N-(4,4-Difluorocyclohexyl)-1-(4-methyl-N-phenylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.471	566.3

2.142	(2S)-N-(4-Chlorobenzyl)-N-(4,4-difluorocyclohexyl)-1-(4-methyl-N-phenylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.481	586.2
2.143	(2S)-N-(4,4-Difluorocyclohexyl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-1-(4-methyl-N-phenylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.541	592.4
2.144	(2S)-N-(4-Chlorobenzyl)-N-(4,4-difluorocyclohexyl)-1-(4-methoxy-N-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.122	540.3
2.145	(2S)-N-(4,4-Difluorocyclohexyl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-1-(4-methoxy-N-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.214	546.4
2.146	(2S)-N-(Benzofuran-6-ylmethyl)-1-(N-cyclopropyl-4-methoxyphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide	1.217	572.4
2.147	(2S)-1-(N-Cyclopropyl-4-methoxyphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)pyrrolidine-2-carboxamide	1.185	574.4
2.148	(2S)-N-(Benzo[d]thiazol-5-ylmethyl)-1-(N-cyclopropyl-4-methoxyphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide	1.113	589.4
2.149	(2S)-1-(N-Cyclopropyl-4-methoxyphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.270	546.4
2.150	(2S)-N-(4-Chlorobenzyl)-1-(N-cyclopropyl-4-methoxyphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide	1.286	566.3
2.151	(2S)-1-(N-Cyclopropyl-4-methoxyphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)pyrrolidine-2-carboxamide	1.362	572.4
2.152	(2S)-N-(Benzo[d]thiazol-5-ylmethyl)-1-(N-cyclopropyl-4-methylphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide	1.192	573.4
2.153	(2S)-1-(N-Cyclopropyl-4-methylphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.349	530.4
2.154	(2S)-N-(4-Chlorobenzyl)-1-(N-cyclopropyl-4-methylphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide	1.360	560.3
2.155	(2S)-1-(N-Cyclopropyl-4-methylphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)pyrrolidine-2-carboxamide	1.435	556.4
2.156	(2S)-N-(Benzofuran-6-ylmethyl)-1-(N-cyclobutyl-4-methylphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide	1.319	570.3

Example 2.157 to **Example 2.181** were synthesized as described in Example 2.49 using 4-methylbenzenesulfinamide and the appropriate amine or amine salt. LC-MS data of Example 2.157 to Example 2.181 are listed in the table below.

Ex. N°	Name	t_R	$[M+H]^+$	LC-MS conditions
2.157	(2S)-N-(4-Chlorobenzyl)-N-cyclohexyl-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.310	488.3	1
2.158	(2S)-N-(4-Chlorobenzyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylcyclohexyl)pyrrolidine-2-carboxamide	1.367	502.3	1
2.159	(2S)-N-(4-Chlorobenzyl)-N-(4,4-dimethylcyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.423	516.4	1
2.160	(2S)-N-(4-Chlorobenzyl)-N-(6,6-difluorospiro[3.3]heptan-2-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.257	536.2	1
2.161	(2S)-N-(4-Chlorobenzyl)-N-(3,3-difluorocyclopentyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.214	510.3	1
2.162	(2S)-N-(4-Chlorobenzyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-((4-ethynyl-2-hydroxycyclopentyl)pyrrolidine-2-carboxamide	0.983	515.3	1
2.163	(2S)-N-(4-Chlorobenzyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)pyrrolidine-2-carboxamide	1.005	538.2	1
2.164	(2S)-N-(4-Chlorobenzyl)-N-(1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.245	522.2	1
2.165	(2S)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-(4-chlorobenzyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.329	500.2	1
2.166	(2S)-N-(4-Chlorobenzyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(3-ethynylcyclobutyl)pyrrolidine-2-carboxamide	1.068	485.3	1
2.167	(2S)-N-(4-Chlorobenzyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-hydroxycyclohexyl)pyrrolidine-2-carboxamide	0.985	504.3	1
2.168	(2S)-N-(4-Chlorobenzyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(spiro[3.3]heptan-2-yl)pyrrolidine-2-carboxamide	1.366	500.3	1
2.169	(2S)-N-(4-Chlorobenzyl)-1-((R)-N-cyclopropyl-4-methylphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide	1.371	550.3	1
2.170	(2S)-N-(1,1-Difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.215	502.3	1

2.171	(2S)-N-((3R,5S)-1,1-Difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.225	502.3	1
2.172	(2S)-N-((3S,5R)-1,1-Difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.215	502.3	1
2.173	(2S)-N-(4-Chlorobenzyl)-N-((3R,5S)-1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.246	522.3	1
2.174	(2S)-N-(4-Chlorobenzyl)-N-((3S,5R)-1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.236	522.3	1
2.175	(2S)-N-(4-Chlorobenzyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(3-hydroxy-3-(trifluoromethyl)cyclobutyl)pyrrolidine-2-carboxamide	1.119	544.3	1
2.176	(2S)-N-(4-Chlorobenzyl)-N-(1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.18	550.13	2
2.177	(2S)-N-(4-Chlorobenzyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(2-(trifluoromethyl)tetrahydro-2H-pyran-4-yl)pyrrolidine-2-carboxamide	1.236	558.3	1
2.178	(2S)-N-(4-Chlorobenzyl)-N-((3R,6S)-1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.311	550.3	1
2.179	(2S)-N-(4-Chlorobenzyl)-N-((3S,6R)-1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.306	550.3	1
2.180	(2S)-N-(4-chlorobenzyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-((1R,3R)-3-methoxycyclopentyl)pyrrolidine-2-carboxamide	1.133	504.3	1
2.181	(2S)-N-(4-Chlorobenzyl)-N-(4-cyano-2-methoxycyclopentyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.121	529.3	1

Example 2.182 to **Example 2.187** were synthesized as described in Example 2.84 using the appropriate arylthiol derivative, the appropriate alkylamine and the appropriate pyrrolidine-2-carboxamide. LC-MS data of Example 2.182 to Example 2.187 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
2.182	(2S)-N-(1,1-Difluorospiro[2.3]hexan-5-yl)-1-(3-fluoro-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.320	520.2
2.183	(2S)-N-(4-Chlorobenzyl)-N-(1,1-difluorospiro[2.3]hexan-5-yl)-1-(3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.328	540.3

2.184	(2S)-N-(4-Chloro-2-fluorobenzyl)-N-(1,1-difluorospiro[2.3]hexan-5-yl)-1-(3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.366	558.2
2.185	(2S)-N-(1,1-Difluorospiro[2.5]octan-6-yl)-1-(3-fluoro-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.376	548.4
2.186	(2S)-N-(4-Chlorobenzyl)-N-(1,1-difluorospiro[2.5]octan-6-yl)-1-(3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.387	568.3
2.187	(2S)-N-(4-Chloro-2-fluorobenzyl)-N-(1,1-difluorospiro[2.5]octan-6-yl)-1-(3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.420	586.2

Example 2.188 to Example 2.197 were synthesized as described in Example 2.49 using 4-methylbenzenesulfinamide and the appropriate amine. LC-MS data of Example 2.188 to Example 2.197 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
2.188	(2S)-N-(4-Chloro-2-fluorobenzyl)-N-(1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.286	540.3
2.189	(2S)-N-(1,1-Difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.284	530.4
2.190	(2S)-N-(4-Chloro-2-fluorobenzyl)-N-(1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.01	568.20
2.191	(2S)-N-(4-Chlorobenzyl)-N-((1R*,3S*)-3-cyanocyclopentyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.106	499.3
2.192	(2S)-N-(4-Chloro-2-fluorobenzyl)-N-((3R,5s)-1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.288	540.3
2.193	(2S)-N-(4-Chloro-2-fluorobenzyl)-N-((3S,5r)-1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.273	540.3
2.194	(2S)-N-(4-Chloro-2-fluorobenzyl)-N-((3S,6r)-1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.350	568.3
2.195	(2S)-N-((3S,6r)-1,1-Difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.291	530.4
2.196	(2S)-N-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.291	530.3
2.197	(2S)-N-(4-Chlorobenzyl)-N-((1R*,3R*)-3-cyanocyclopentyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.111	499.4

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Example 2.198 (2S,4S)-N-(4-Chlorobenzyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-4-methylpyrrolidine-2-carboxamide:

1-(*tert*-Butyl) 2-methyl (2*S*,4*S*)-4-methylpyrrolidine-1,2-dicarboxylate: To a soln. of (4*S*)-1-Boc-4-methyl-*L*-proline (150 mg, 0.635 mmol, 1 eq) in DCM (0.6 mL) and MeOH (0.6 mL) was added dropwise trimethylsilyldiazomethane (ca. 10% in hexane, ca. 0.6mol/L, 1.1 mL, 0.698 mmol, 1.1 eq). The obtained yellow soln. was diluted with DCM and aq. sat. $NaHCO_3$. The layers were seperated and the aq. layer was extracted once with DCM. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound (191 mg, quant.) as a white solid. LC-MS (2): t_R= 0.88 min; $[M+H]^+$: 244.23.

Methyl (2*S*,4*S*)-4-methylpyrrolidine-2-carboxylate: 1-(*tert*-Butyl) 2-methyl (2*S*,4*S*)-4-methylpyrrolidine-1,2-dicarboxylate (191 mg, 0.785 mmol, 1 eq) was treated with HCl (4.0 M in dioxane, 0.8 mL, 3.14 mmol, 4 eq) and the resulting soln. was stirred at rt for 1 h. Upon completion the soln. was concentrated under reduced pressure to give the desired product (157 mg, quant.) as a white solid. LC-MS (2): t_R= 0.34 min; $[M+H]^+$: 144.20.

Methyl (2S,4S)-1-((R)-N-(tert-butoxycarbonyl)-4-methylphenylsulfonimidoyl)-4-methylpyrrolidine-2-carboxylate: A soln. of methyl (2*S*,4*S*)-4-methylpyrrolidine-2-carboxylate (112 mg, 0.783 mmol, 1 eq) and Et_3N (0.327 mL, 2.35 mmol, 3 eq) in DCM (0.2 mL) was added to a soln. of tert-butyl (chloro(oxo)(p-tolyl)-λ^6-sulfaneylidene)carbamate (200 mg, 0.783 mmol, 1 eq) in DCM (6.8 mL) and the obtained reaction mixture was stirred for 15 min at rt. The mixture was diluted with water and MeCN and filtered. The obtained solution was purified by basic prep HPLC to give 2 diastereomers:

Methyl (2*S*,4*S*)-1-((*R*)-*N*-(*tert*-butoxycarbonyl)-4-methylphenylsulfonimidoyl)-4-methylpyrrolidine-2-carboxylate: yellow oil (118 mg, 38%). LC-MS (2): t_R= 0.99 min; $[M+H]^+$: 397.17 and

Methyl (2*S*,4*S*)-1-((*S*)-*N*-(*tert*-butoxycarbonyl)-4-methylphenylsulfonimidoyl)-4-methylpyrrolidine-2-carboxylate: yellow oil (112 mg, 36%). LC-MS (2): t_R= 1.01 min; $[M+H]^+$: 397.16.

(2S,4S)-1-((R)-N-(tert-Butoxycarbonyl)-4-methylphenylsulfonimidoyl)-4-methylpyrrolidine-2-carboxylic acid: To a soln. of methyl (2*S*,4*S*)-1-((*R*)-*N*-(*tert*-butoxycarbonyl)-4-methylphenylsulfonimidoyl)-4-methylpyrrolidine-2-carboxylate (118 mg, 0.298 mmol, 1 eq) in THF (1.98 mL, 24.4 mmol, 82.02 eq) was added aq. 1 M LiOH (0.625 mL, 0.625 mmol, 2.1 eq) and the resulting soln. was stirred at rt. After 3 h, the reaction mixture was concentrated under reduced pressure, diluted with water, EtOAc and 1 mL of aq. 1 M HCl. The aq. phase was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to give the title compound (112 mg, 99%) as a white solid. LC-MS (2): t_R= 0.90 min; $[M+H]^+$: 383.17.

***tert*-Butyl (((2S,4S)-2-((4-chlorobenzyl)(4,4-difluorocyclohexyl)carbamoyl)-4-methylpyrrolidin-1(R)-yl)(oxo)(p-tolyl)-λ^6-sulfaneylidene)carbamate:** To a soln. of (2S,4S)-1-((*R*)-*N*-(*tert*-butoxycarbonyl)-4-methylphenylsulfonimidoyl)-4-methylpyrrolidine-2-carboxylic acid (35 mg, 0.0915 mmol, 1 eq) in DMF (0.177) at

0°C was added HATU (38.3 mg, 0.101 mmol, 1.1 eq). After 5 min., was added a soln. of *N*-(4-chlorobenzyl)-4,4-difluorocyclohexan-1-amine (26.1 mg, 0.101 mmol, 1.1 eq) and DIPEA (0.0627 mL, 0.366 mmol, 4 eq) in DCM (1 mL) and the resulting reaction mixture was further stirred for 20 min. Upon completion, DMF was added and the solvents were removed under reduced pressure. The residue was purified by basic prep. HPLC to yield the title compound (16.7 mg, 29%) as a white solid. LC-MS (2): t_R= 1.18 min; $[M+H]^+$: 624.25.

(2*S*,4*S*)-*N*-(4-Chlorobenzyl)-*N*-(4,4-difluorocyclohexyl)-4-methyl-1-((*R*)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide: Iodotrimethylsilane (0.0118 mL, 0.0803 mmol, 3 eq) was added to a stirred solution of *tert*-butyl (((2S,4S)-2-((4-chlorobenzyl)(4,4-difluorocyclohexyl)carbamoyl)-4-methylpyrrolidin-1(R)-yl)(oxo)(p-tolyl)-λ^6-sulfaneylidene)carbamate (16.7 mg, 0.0268 mmol, 1 eq) in MeCN (0.18 mL). The resulting reaction mixture was stirred for 10 minutes at rt, diluted with aq. 25% NH_3 soln. and a few drops of DMF, and purified by prep. HPLC to yield the title compound (11 mg, 78%) as a white solid. LC-MS (2): t_R= 1.02 min; $[M+H]^+$: 524.19.

(2*S*,4*S*)-N-(4-Chlorobenzyl)-*N*-(4,4-difluorocyclohexyl)-1-((*R*)-*N*,4-dimethylphenylsulfonimidoyl)-4-methylpyrrolidine-2-carboxamide: Trimethyloxonium tetrafluoroborate (7.8 mg, 0.05 mmol, 1 eq) was added to a soln. of (2*S*,4*S*)-*N*-(4-chlorobenzyl)-*N*-(4,4-difluorocyclohexyl)-4-methyl-1-((*R*)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide (26 mg, 0.05 mmol, 1 eq) in DCM (0.5 mL) and the reaction mixture was stirred at rt. After 30 min, the resulting mixture was washed with aq. sat. $NaHCO_3$. The organic layer was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in DMF/H_2O and purified by basic prep. HPLC to give the title compound (6.8 mg, 25%) as a white solid. LC-MS (2) t_R= 0.97 min; $[M+H]^+$: 538.18.

Example 2.199 to **Example 2.244** were synthesized as described in Example 2.198 using the appropriate substituted pyrrolidine and the appropriate amine. LC-MS data of Example 2.199 to Example 2.244 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
2.199	(2S,4S)-N-(4-Chlorobenzyl)-N-(1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-4-methylpyrrolidine-2-carboxamide	1.305	536.3
2.200	(2S,4S)-N-(4-Chlorobenzyl)-N-(1,1-difluorospiro[2.5]octan-6-yl)-1-((S)-N,4-dimethylphenylsulfonimidoyl)-4-methylpyrrolidine-2-carboxamide	1.358	564.3
2.201	(2S,4S)-N-(4-Chlorobenzyl)-N-(4,4-difluorocyclohexyl)-1-((S)-N,4-dimethylphenylsulfonimidoyl)-4-methylpyrrolidine-2-carboxamide	1.263	538.3
2.202	(2S,4S)-N-(4-Chlorobenzyl)-N-(1,1-difluorospiro[2.3]hexan-5-yl)-1-((S)-N,4-dimethylphenylsulfonimidoyl)-4-methylpyrrolidine-2-carboxamide	1.281	536.3

2.203	(2S,4S)-N-(4-Chlorobenzyl)-N-(1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-4-methylpyrrolidine-2-carboxamide	1.333	564.3
2.204	(2S,4S)-N-(4-Chlorobenzyl)-N-(4,4-difluorocyclohexyl)-1-(N,4-dimethylphenylsulfonimidoyl)-4-methylpyrrolidine-2-carboxamide	1.292	538.4
2.205	(2R,3S)-N-(4-Chlorobenzyl)-N-(4,4-difluorocyclohexyl)-1-(N,4-dimethylphenylsulfonimidoyl)-3-fluoropyrrolidine-2-carboxamide	1.295	542.3
2.206	(2S,4S)-N-(4-Chlorobenzyl)-N-(1,1-difluorospiro[2.5]octan-6-yl)-1-((S)-N,4-dimethylphenylsulfonimidoyl)-4-fluoropyrrolidine-2-carboxamide	1.301	568.3
2.207	(2S,4S)-N-(4-Chlorobenzyl)-N-(1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-4-fluoropyrrolidine-2-carboxamide	1.301	568.3
2.208	(2R,3S)-N-(4-Chlorobenzyl)-N-(1,1-difluorospiro[2.5]octan-6-yl)-1-((S)-N,4-dimethylphenylsulfonimidoyl)-3-fluoropyrrolidine-2-carboxamide	1.361	568.3
2.209	(2R,3S)-N-(4-Chlorobenzyl)-N-(1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-3-fluoropyrrolidine-2-carboxamide	1.363	568.3
2.210	(2S,4S)-N-(4-Chlorobenzyl)-N-(4,4-difluorocyclohexyl)-1-((S)-N,4-dimethylphenylsulfonimidoyl)-4-fluoropyrrolidine-2-carboxamide	1.236	542.3
2.211	(2S,4S)-N-(4-Chlorobenzyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-4-fluoropyrrolidine-2-carboxamide	1.235	542.3
2.212	(2R,3S)-N-(4-Chlorobenzyl)-N-(1,1-difluorospiro[2.3]hexan-5-yl)-1-((S)-N,4-dimethylphenylsulfonimidoyl)-3-fluoropyrrolidine-2-carboxamide	1.306	540.3
2.213	(2R,3S)-N-(4-Chlorobenzyl)-N-(1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-3-fluoropyrrolidine-2-carboxamide	1.302	540.3
2.214	(2S,4S)-N-(4-Chlorobenzyl)-N-(1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-4-fluoropyrrolidine-2-carboxamide	1.243	540.3
2.215	(2S,4S)-N-(1,1-Difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-4-methyl-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.286	516.3
2.216	(2S,4S)-N-(4-Chloro-2-fluorobenzyl)-N-(1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-4-methylpyrrolidine-2-carboxamide	1.345	554.3
2.217	(2S,4S)-N-(1,1-Difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-4-methyl-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.341	544.4
2.218	(2S,4S)-N-(4-Chlorobenzyl)-N-((3R,5s)-1,1-difluorospiro[2.3]hexan-5-yl)-1-(R)-(N,4-dimethylphenylsulfonimidoyl)-4-methylpyrrolidine-2-carboxamide	1.296	536.3

2.219	(2S,4S)-N-(4-Chlorobenzyl)-N-((3S,5r)-1,1-difluorospiro[2.3]hexan-5-yl)-1-(R)-(N,4-dimethylphenylsulfonimidoyl)-4-methylpyrrolidine-2-carboxamide	1.305	536.3
2.220	(1S,2S,5R)-N-(4-Chlorobenzyl)-N-(1,1-difluorospiro[2.3]hexan-5-yl)-3-((R)-N,4-dimethylphenylsulfonimidoyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide	1.315	534.3
2.221	(1S,2S,5R)-N-(4-Chlorobenzyl)-N-(4,4-difluorocyclohexyl)-3-((R)-N,4-dimethylphenylsulfonimidoyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide	1.304	536.3
2.222	(2R,3S)-N-(4,4-Difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-3-fluoro-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.283	522.2
2.223	(2S,4S)-N-(4,4-Difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-4-fluoro-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.212	522.4
2.224	(2S,4S)-N-(4-Chloro-2-fluorobenzyl)-N-(4,4-difluorocyclohexyl)-1-((S)-N,4-dimethylphenylsulfonimidoyl)-4-fluoropyrrolidine-2-carboxamide	1.276	560.3
2.225	(2S,4S)-N-(4-Chloro-2-fluorobenzyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-4-fluoropyrrolidine-2-carboxamide	1.272	560.3
2.226	(2S,4S)-N-(1,1-Difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-4-fluoro-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.225	520.3
2.227	(2S,4S)-N-(4-Chloro-2-fluorobenzyl)-N-(1,1-difluorospiro[2.3]hexan-5-yl)-1-((S)-N,4-dimethylphenylsulfonimidoyl)-4-fluoropyrrolidine-2-carboxamide	1.285	558.3
2.228	(2S,4S)-N-(4-Chloro-2-fluorobenzyl)-N-(1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-4-fluoropyrrolidine-2-carboxamide	1.281	558.3
2.229	(2S,4S)-N-(4,4-Difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-4-methyl-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.273	518.4
2.230	(2S,4S)-N-(4,4-Difluorocyclohexyl)-1-(N,4-dimethylphenylsulfonimidoyl)-4-methoxy-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.217	534.5
2.231	(S)-N-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-N-(4-methylbenzyl)-1-((R)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.226	488.4
2.232	(S)-N-((3S,5r)-1,1-Difluorospiro[2.3]hexan-5-yl)-N-(4-methylbenzyl)-1-((R)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.212	488.4
2.233	(S)-N-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-N-(4-methylbenzyl)-1-((S)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.218	488.4
2.234	(S)-N-((3S,5r)-1,1-Difluorospiro[2.3]hexan-5-yl)-N-(4-methylbenzyl)-1-((S)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.201	488.4

2.235	(S)-N-(4-Chlorobenzyl)-N-((1s,3R)-3-cyanocyclobutyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.074	485.4
2.236	(S)-N-(4-Chlorobenzyl)-N-(4-cyanobutyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.076	487.4
2.237	(S)-N-((1S*,3R*)-3-Cyanocyclopentyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.074	479.5
2.238	(S)-N-((1S*,3S*)-3-Cyanocyclopentyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.086	479.5
2.239	(2S,4S)-N-(4-Chlorobenzyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-4-methoxypyrrolidine-2-carboxamide	1.240	554.5
2.240	(S)-N-(4-Chlorobenzyl)-N-((1R,3S)-3-cyanocyclopentyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.102	499.4
2.241	(S)-N-(4-Chlorobenzyl)-N-((1S,3S)-3-cyanocyclopentyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.110	499.4
2.242	(S)-N-(4-Chlorobenzyl)-N-((1R,3R)-3-cyanocyclopentyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.112	499.4
2.243	(S)-N-((1R,3S)-3-Cyanocyclopentyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.076	479.4
2.244	(S)-N-((1S,3S)-3-Cyanocyclopentyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide	1.087	479.5

Example 2.245 (S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((R)-3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide:

Methyl ((R)-N-(tert-butoxycarbonyl)-3-fluoro-4-methylphenylsulfonimidoyl)-L-prolinate: Was synthesized using 3-fluoro-4-methylthiophenol and L-proline methyl ester hydrochloride as described in Example 2.47. The crude was purified by FC (Hept to Hept/EtOAc 6:4) to give methyl ((S)-N-(tert-butoxycarbonyl)-3-fluoro-4-methylphenylsulfonimidoyl)-L-prolinate (first eluting diastereomer) and methyl ((R)-N-(tert-butoxycarbonyl)-3-fluoro-4-methylphenylsulfonimidoyl)-L-prolinate (second eluting diastereomer). Methyl ((S)-N-(tert-butoxycarbonyl)-3-fluoro-4-methylphenylsulfonimidoyl)-L-prolinate: LC-MS (2): t_R= 0.98 min; $[M+H]^+$: 401.07. Methyl ((R)-N-(tert-butoxycarbonyl)-3-fluoro-4-methylphenylsulfonimidoyl)-L-prolinate: LC-MS (2): t_R= 0.97 min; $[M+H]^+$: 401.10.

((R)-N-(tert-Butoxycarbonyl)-3-fluoro-4-methylphenylsulfonimidoyl)-L-proline: Was synthesized using methyl ((R)-N-(tert-butoxycarbonyl)-3-fluoro-4-methylphenylsulfonimidoyl)-L-prolinate as described in Example 2.47. LC-MS (2): t_R= 0.87 min; $[M+H]^+$: 387.21.

tert-Butyl ((R)-((S)-2-((benzo[d]thiazol-5-ylmethyl)(4,4-difluorocyclohexyl)carbamoyl)pyrrolidin-1-yl)(3-fluoro-4-methylphenyl)(oxo)-λ⁶-sulfaneylidene)carbamate: Was synthesized using ((R)-N-(tert-butoxycarbonyl)-3-fluoro-4-methylphenylsulfonimidoyl)-L-proline and N-(benzo[d]thiazol-5-ylmethyl)-4,4-difluorocyclohexan-1-amine as described in Example 2.47. LC-MS (2): t_R= 1.11 min; $[M+H]^+$: 651.26.

(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((R)-3-fluoro-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide: Was synthesized using tert-butyl ((R)-((S)-2-((benzo[d]thiazol-5-ylmethyl)(4,4-difluorocyclohexyl)carbamoyl)pyrrolidin-1-yl)(3-fluoro-4-methylphenyl)(oxo)- λ⁶-sulfaneylidene)carbamate as described in Example 2.47. LC-MS (2): t_R= 0.97 min; $[M+H]^+$: 551.17.

(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((R)-3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide: Was synthesized as described in Example 2.47 using (S)-N-(benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((R)-3-fluoro-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide. LC-MS (1): t_R= 1.156 min; $[M+H]^+$: 564.18.

Example 2.246 (S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((R)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide:

Methyl ((R)-N-(tert-butoxycarbonyl)-4-methylphenylsulfonimidoyl)-L-prolinate: Was synthesized using 4-methylbenzenethiol and L-proline methyl ester hydrochloride as described in Example 2.47. The crude was purified by FC (Hept to Hept/EtOAc 6:4) to give methyl ((S)-N-(tert-butoxycarbonyl)-4-methylphenylsulfonimidoyl)-L-prolinate (first eluting diastereomer) and methyl ((R)-N-(tert-butoxycarbonyl)-4-methylphenylsulfonimidoyl)-L-prolinate (second eluting diastereomer). Methyl ((R)-N-(tert-butoxycarbonyl)-4-methylphenylsulfonimidoyl)-L-prolinate: LC-MS (2): t_R= 0.96 min; $[M+H]^+$: 383.19.

(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((R)-4-methylphenylsulfonimidoyl) pyrrolidine-2-carboxamide: Was synthesized using methyl ((R)-N-(tert-butoxycarbonyl)-4-methylphenylsulfonimidoyl)-L-prolinate and N-(benzo[d]thiazol-5-ylmethyl)-4,4-difluorocyclohexan-1-amine as described in Example 2.47 to give the title compound. LC-MS (1): t_R= 1.053 min; $[M+H]^+$: 532.18.

Example 2.247 (S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((R)-4-methoxy-N-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide:

Methyl ((R)-N-(tert-butoxycarbonyl)-4-methoxyphenylsulfonimidoyl)-L-prolinate: Was synthesized using 4-methoxythiophenol and L-proline methyl ester hydrochloride as described in Example 2.47. The crude was purified by FC (Hept to Hept/EtOAc 1:1) to give methyl ((S)-N-(tert-butoxycarbonyl)-4-methoxyphenylsulfonimidoyl)-L-prolinate (first eluting diastereomer) and methyl ((R)-N-(tert-butoxycarbonyl)-4-methoxyphenylsulfonimidoyl)-L-prolinate (second eluting diastereomer). Methyl ((S)-N-(tert-butoxycarbonyl)-4-methylphenylsulfonimidoyl)-L-prolinate: LC-MS (2): t_R= 0.93 min; $[M+H]^+$: 399.18. Methyl ((R)-N-(tert-butoxycarbonyl)-4-methylphenylsulfonimidoyl)-L-prolinate: LC-MS (2): t_R= 0.92 min; $[M+H]^+$: 399.17.

(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((R)-4-methoxy-N-methylphenyl sulfonimidoyl)pyrrolidine-2-carboxamide: Was synthesized using methyl ((R)-N-(tert-butoxycarbonyl)-4-methoxyphenylsulfonimidoyl)-L-prolinate and N-(benzo[d]thiazol-5-ylmethyl)-4,4-difluorocyclohexan-1-amine as described in Example 2.47 to give the title compound. LC-MS (1): t_R= 0.991 min; $[M+H]^+$: 562.19.

Example 2.248 (S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide: Was synthesized using (S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((R)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide as described in Example 2.47 to give the title compound. LC-MS (1): t_R= 1.066 min; $[M+H]^+$: 546.19.

Example 2.249 to **Example 2.277** were synthesized as described herein before using the appropriate thiophenol, L-proline methyl ester hydrochloride, the appropriate aminde or aminde salt, and the appropriate aldehyde. LC-MS data of Example 2.249 to Example 2.277 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
2.249	(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.131	558.19
2.250	(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3R,5s)-1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.063	530.16
2.251	(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.139	572.21
2.252	(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3R,5s)-1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.071	544.18
2.253	(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.231	590.20
2.254	(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3R,5s)-1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.164	562.17
2.255	(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-4-methoxy-N-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.059	588.20
2.256	(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3R,5s)-1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-4-methoxy-N-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	0.995	560.17
2.257	(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((1S,3R,6S)-bicyclo[4.1.0]heptan-3-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.148	522.21
2.258	(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((1R,3S,6R)-bicyclo[4.1.0]heptan-3-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.149	522.21

2.259	(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((1R,3R,6R)-bicyclo[4.1.0]heptan-3-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.13	522.21
2.260	(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((1S,3S,6S)-bicyclo[4.1.0]heptan-3-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.141	522.21
2.261	(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((1S,3S,6S)-bicyclo[4.1.0]heptan-3-yl)-1-((R)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.136	508.20
2.262	(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((1S,3S,6S)-bicyclo[4.1.0]heptan-3-yl)-1-((R)-3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.242	540.20
2.263	(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((1S,3S,6S)-bicyclo[4.1.0]heptan-3-yl)-1-((R)-4-methoxy-N-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.053	538.21
2.264	(S)-N-(4,4-Difluorocyclohexyl)-N-((2-methylbenzo[d]thiazol-5-yl)methyl)-1-((R)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.106	546.19
2.265	(S)-N-(4,4-Difluorocyclohexyl)-N-((6-fluoro-2-methylbenzo[d]thiazol-5-yl)methyl)-1-((R)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.157	564.18
2.266	(S)-N-(4,4-Difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-((2-methylbenzo[d]thiazol-5-yl)methyl)pyrrolidine-2-carboxamide	1.121	560.21
2.267	(S)-N-(4,4-Difluorocyclohexyl)-1-((R)-3-fluoro-N,4-dimethylphenylsulfonimidoyl)-N-((2-methylbenzo[d]thiazol-5-yl)methyl)pyrrolidine-2-carboxamide	1.211	578.20
2.268	(S)-N-((2-Chlorobenzo[d]thiazol-5-yl)methyl)-N-(4,4-difluorocyclohexyl)-1-((R)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.216	566.14
2.269	(S)-N-((2-Bromobenzo[d]thiazol-5-yl)methyl)-N-(4,4-difluorocyclohexyl)-1-((R)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.224	610.09
2.270	(S)-N-((2-Chlorobenzo[d]thiazol-5-yl)methyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.241	580.15
2.271	(S)-N-((2-Bromobenzo[d]thiazol-5-yl)methyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.251	624.10
2.272	(S)-N-(4,4-Difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-((4-fluorobenzo[d]thiazol-5-yl)methyl)pyrrolidine-2-carboxamide	1.091	564.18
2.273	(S)-N-((2-Chlorobenzo[d]thiazol-5-yl)methyl)-N-(4,4-difluorocyclohexyl)-1-((R)-3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.323	598.15
2.274	(S)-N-((2-Bromobenzo[d]thiazol-5-yl)methyl)-N-(4,4-difluorocyclohexyl)-1-((R)-3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.331	642.09

2.275	(S)-N-(4,4-Difluorocyclohexyl)-1-((R)-3-fluoro-N,4-dimethylphenylsulfonimidoyl)-N-((4-fluorobenzo[d]thiazol-5-yl)methyl)pyrrolidine-2-carboxamide	1.178	582.17
2.276	(S)-N-((2-Chlorobenzo[d]thiazol-5-yl)methyl)-N-(4,4-difluorocyclohexyl)-1-((R)-4-methoxy-N-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.163	596.15
2.277	(S)-N-((2-Bromobenzo[d]thiazol-5-yl)methyl)-N-(4,4-difluorocyclohexyl)-1-((R)-4-methoxy-N-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide	1.172	640.10

Example 2.278 to **Example 2.279** were synthesized using 4-methylbenzenethiol, the appropriate substituted L-proline methyl ester hydrochloride, and N-(benzo[d]thiazol-5-ylmethyl)-4,4-difluorocyclohexan-1-amine as described in Example 2.247. LC-MS data of Example 2.278 to Example 2.279 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
2.278	(1R,2S,5S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-3-((R)-N,4-dimethylphenylsulfonimidoyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide	1.114	558.19
2.279	(1S,2S,5R)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-3-((R)-N,4-dimethylphenylsulfonimidoyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide	1.146	558.19

Methods for the preparation of sulfone compounds (Examples 3.x)

Example 3.1 rac-(1R*,2S*)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide:

Methyl 2-(p-tolylthio)cyclopentane-1-carboxylate: A mixture of 4-methylbenzenethiol (4.5 g, 35.5 mmol, 1 eq) and methyl 1-cyclopentenecarboxylic acid (8.96 mL, 71 mmol, 2 eq) in piperidine (90 mL) was heated to 70°C and stirred at the same temperature for 1.5h. The mixture was partitioned between aq. 1M HCl and EtOAc. The layers were separated and the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by FC (Hept to Hept/EtOAc, 9:1) to give the title compound (cis/trans 2:8, 6.516 g, 73%) as a pink oil. LC-MS (2): t_R= 1.04 and 1.06 min; $[M+H]^+$: 251.28.

Methyl 2-tosylcyclopentane-1-carboxylate: To an ice-cooled suspension of methyl 2-(p-tolylthio)cyclopentane-1-carboxylate (177 mg, 0.707 mmol, 1 eq) and $NaHCO_3$ (179 mg, 2.12 mmol, 3 eq) in DCM (7 mL), 3-chloroperbenzoic acid (<77%, 475 mg, 2.12 mmol, <3 eq) was added portionwise. The reaction mixture was stirred at 0 °C for 2 hours then diluted with aq. 1M NaOH. and DCM. The layers were separated. The aq. layer was extracted with DCM and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the title compound (cis/trans 5:95, 183 mg, 92%) as a colorless oil that solidified upon

standing. The crude product was used as such in the next step without further purification. LC-MS (2): t_R= 0.85 min and 0.88 min; $[M+H]^+$: 283.18.

rac-(1R*,2S*)-2-Tosylcyclopentane-1-carboxylic acid: To a mixture of methyl 2-tosylcyclopentane-1-carboxylate (182 mg, 0.645 mmol, 1 eq) in THF (3 mL) and H_2O (3 mL), lithium hydroxide monohydrate (270 mg, 6.45 mmol, 10 eq) was added. The mixture was stirred at 50 °C for 2 h. The mixture was then allowed to cool to rt and was acidified to pH 3 with aq. 1M HCl. The mixture was partitioned between water and DCM. The layers were separated. The aq. layer was extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure The residue was purified by acidic prep. HPLC to give the title compound (single diastereomer, 121 mg, 70%) as a white solid. LC-MS (2): t_R= 0.75 min; $[M+H]^+$: 269.16.

rac-(1R*,2S*)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-2-tosylcyclopentane-1-carboxamide: A soln. of rac-(1R*,2S*)-2-tosylcyclopentane-1-carboxylic acid (40 mg, 0.146 mmol, 1 eq) in DCM (3.8 mL) was treated with oxalyl chloride (0.0142 mL, 0.161 mmol, 1.1 eq) and DMF (3 drops). The resulting mixture was stirred at rt for 15 min. A solution of N-(benzo[d]thiazol-5-ylmethyl)-4,4-difluorocyclohexan-1-amine (41.2 mg, 0.146 mmol, 1 eq) and DIPEA (0.0525 mL, 0.307 mmol, 2.1 eq) in DCM (0.8 mL) was then added and the mixture was stirred at rt overnight. The solvent was removed under reduced pressure and the residue, redissolved in DMF (1.65 mL), was purified by basic prep. HPLC to give the title compound (56.8 mg, 73%) of a white foam. LC-MS (1): t_R= 1.209 min, $[M+H]^+$: 533.2.

Example 3.2 (1S,2R)-2-(toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide: Was obtained by preparative chiral separation (SFC 2 method) of rac-(1R*,2S*)-N-(benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-2-tosylcyclopentane-1-carboxamide (103 mg, 0.194 mmol, 1 eq) to give the title compound as a white solid. LC-MS (1): t_R= 1.201 min, $[M+H]^+$: 533.3.

Example 3.3 to **Example 3.7** were synthesized according to the procedures described herein before using the appropriate amine or amine salt derivative, the appropriate aldehyde or ketone, and rac-(1R,2S)-2-tosylcyclopentane-1-carboxylic acid. LC-MS data of Example 3.3 to to Example 3.7 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
3.3	rac-(1R*,2S*)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzo[1,3]dioxol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.251	520.2
3.4	rac-(1R*,2S*)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzooxazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.165	517.4
3.5	rac-(1R*,2S*)-N-(4,4-difluorocyclohexyl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-2-tosylcyclopentane-1-carboxamide	1.418	516.4

3.6	rac-(1R*,2S*)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide	1.359	510.2
3.7	rac-(1R*,2S*)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4,4-difluoro-cyclohexyl)-(4-methyl-benzyl)-amide	1.342	490.2

Example 3.8: rac-(1R*,2S*)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-2-tosylcyclohexane-1-carboxamide:

Methyl 2-(p-tolylthio)cyclohexane-1-carboxylate: A mixture of 4-methylbenzenethiol (700 mg, 5.52 mmol, 1 eq) and methyl 1-cyclohexene-1-carboxylate (1.51 mL, 11 mmol, 2 eq) in piperidine (5.5 mL) was stirred at 70 °C for 4h. The mixture was partitioned between aq. 1M HCl and EtOAc. The layers were separated and the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by FC (Hept to Hept/EtOAc 7:3) to give the title compound (cis/trans 3:7, 810 mg, 55%) as a colorless oil. Rf (Hept/EtOAc 1:9)= 0.295. LC-MS (2): t_R= 1.10 min, $[M+H]^+$: 265.22.

Methyl 2-tosylcyclohexane-1-carboxylate: To an ice-cooled suspension of methyl 2-(p-tolylthio)cyclohexane-1-carboxylate (200 mg, 0.756 mmol, 1 eq) and $NaHCO_3$ (191 mg, 2.27 mmol, 3 eq) in DCM (6 mL) was added 3-chloroperbenzoic acid (<77%, 315 mg, 1.41 mmol, <3 eq) portionwise. The reaction mixture was stirred at 0 °C for 3h then diluted with aq. 1M NaOH. and DCM. The layers were separated. The aq. layer was extracted with DCM and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the title compound (cis/trans 3:7, 0.230 g, quant.). The product was used as such in the next step without further purification. LC-MS (2): t_R= 0.92 min; $[M+H]^+$: 297.20.

rac-(1R*,2S*)-2-Tosylcyclohexane-1-carboxylic acid: To a soln. of methyl 2-tosylcyclohexane-1-carboxylate (230 mg, 0.753 mmol, 1 eq) in THF (3.5 mL) and water (3.5 mL) was added $LiOH \cdot H_2O$ (316 mg, 7.53 mmol, 10 eq) and the mixture was stirred at 50°C for 2h. The soln. was cooled down to rt and MeOH (0.8 mL) was added. The mixture was stirred at rt overnight. The mixture was acidified to pH~ 3 with aq. 1M HCl. and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by acidic prep. HPLC to give the title compound (single diastereomer, 77 mg, 36%) as a white foam. LC-MS (2): t_R= 0.79 min; $[M+H]^+$: 283.22.

rac-(1S*,2R*)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-2-tosylcyclohexane-1-carboxamide: Was prepared using rac-(1S*,2R*)-2-tosylcyclohexane-1-carboxylic acid and N-(benzo[d]thiazol-5-ylmethyl)-4,4-difluorocyclohexan-1-amine as described in Example 3.1 to give the title compound as a white solid. LC-MS (2): t_R= 1.267 min; $[M+H]^+$: 547.2.

Example 3.9 (1S,2R)-2-(toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide:

(1S,2R)-2-tosylcyclopentane-1-carboxylic acid: Was obtained by preparative chiral separation (SFC 3 method) of rac-(1S,2R)-2-tosylcyclopentane-1-carboxylic acid (10.990 g, 38.9 mmol, 1 eq) to give (1S,2R)-2-tosylcyclopentane-1-carboxylic acid (first eluting enantiomer) (5.07 g, 48%) and (1R,2S)-2-tosylcyclopentane-1-carboxylic acid (second eluting enantiomer) (5.06 g, 48%) both as colorless oils. (1S,2R)-2-tosylcyclopentane-1-carboxylic acid: LC-MS (2): t_R= 0.75 min; $[M+H]^+$: 269.17. (1R, 2S)-2-tosylcyclopentane-1-carboxylic acid: LC-MS (2): t_R= 0.75 min; $[M+H]^+$: 269.17.

(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide: To a soln. of (1S,2R)-2-tosylcyclopentane-1-carboxylic acid (30 mg, 0.112 mmol, 1 eq) and DIPEA (0.0402 mL, 0.235 mmol, 2.1 eq) in DMF (0.7 mL) was added HATU (52.6 mg, 0.134 mmol, 1.2 eq). The resulting yellow mixture was stirred at rt for 3 min and a soln. of N-(4-chlorobenzyl)-4,4-difluorocyclohexan-1-amine (29 mg, 0.112 mmol, 1 eq) in DMF (0.4 mL) was added. The resulting mixture was stirred at rt overnight. The mixture was purified by basic prep. HPLC to give the title compound (30 mg, 53%) as a white solid. LC-MS(1): t_R= 1.357 min; $[M+H]^+$: 510.2.

Example 3.10 to Example 3.21 were synthesized according to the procedures described herein before using the appropriate amine or amine salt derivative, the appropriate aldehyde or ketone and (1S,2R)-2-tosylcyclopentane-1-carboxylic acid. LC-MS data of Example 3.10 to Example 3.21 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
3.10	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzooxazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.166	517.3
3.11	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4,4-difluoro-cyclohexyl)-(5-methyl-isoxazol-4-ylmethyl)-amide	1.146	481.2
3.12	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4,4-difluoro-cyclohexyl)-(4-methyl-benzyl)-amide	1.343	490.2
3.13	(1S,2R)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-2-tosylcyclopentane-1-carboxamide	1.362	494.4
3.14	(1S,2R)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-((5-methylisoxazol-4-yl)methyl)-2-tosylcyclopentane-1-carboxamide	1.214	457.3
3.15	(1S,2R)-N-(Benzo[d][1,3]dioxol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-2-tosylcyclopentane-1-carboxamide	1.338	496.3

3.16	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzo[1,3]dioxol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.246	520.3
3.17	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzo[1,3]dioxol-5-ylmethyl-cyclohexyl-amide	1.337	484.2
3.18	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide	1.420	536.2
3.19	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(4,4-dimethyl-cyclohexyl)-amide	1.536	502.2
3.20	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(1,1-difluoro-spiro[2.4]hept-5-yl)-amide	1.391	522.2
3.21	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(1,1-difluoro-spiro[2.3]hex-5-yl)-amide	1.356	508.2

Example 3.22 rac-(1R*,2S*)-2-(4-Methoxy-benzenesulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide:

Methyl 2-((4-methoxyphenyl)thio)cyclopentane-1-carboxylate: A mixture of 4-methoxythiophenol (0.317 mL, 2.5 mmol, 1 eq) and methyl 1-cyclopentenecarboxylic acid (0.631 mL, 5 mmol, 2 eq) in piperidine (5 mL) was stirred at 70 °C for 1.5 h. The mixture was allowed to cool to rt and partitioned between aq. 1M HCl. and EtOAc. The layers were separated. The aq. layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by FC (Hept to Hept/EtOAc 85:15) to give the title compound (cis/trans 3:7, 0.552 mg, 83%) as a yellow oil. The product was used as such in the next step without further purification. R_f = 0.22 (Hept/EtOAc 9:1); LC-MS (2): t_R= 1.00 min and 1.02 min; $[M+H]^+$: 267.20.

Methyl 2-((4-methoxyphenyl)sulfonyl)cyclopentane-1-carboxylate: To an ice-cooled suspension of methyl 2-((4-methoxyphenyl)thio)cyclopentane-1-carboxylate (552 mg, 2.07 mmol, 1 eq) and $NaHCO_3$ (524 mg, 6.22 mmol, 3 eq) in DCM (20 mL), 3-chloroperbenzoic acid (<77%, 475 mg, 2.12 mmol, <3 eq) was added portionwise. The reaction mixture was stirred at 0 °C for 8 h and then at rt for 12 h. The reaction mixture was diluted with aq. 1M NaOH. and DCM. The layers were separated. The aq. layer was extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the title compound (cis/trans 3:7, 573 mg, 93%) as a colorless oil that solidified upon standing. The product was used as such in the next step without further purification. LC-MS (2): t_R= 0.82 min and 0.85 min; $[M+H]^+$: 299.20.

rac-(1R*,2S*)-2-((4-Methoxyphenyl)sulfonyl)cyclopentane-1-carboxylic acid: To a mixture of methyl 2-((4-methoxyphenyl)sulfonyl)cyclopentane-1-carboxylate (573 mg, 1.92 mmol, 1 eq) in THF (9 mL) and water (9 mL), lithium hydroxide monohydrate (806 mg, 19.2 mmol, 10 eq) was added. The mixture was stirred at 50 °C for 2 hours. The mixture was allowed to cool to rt and acidified to pH ~3 with aq. 1M HCl. The mixture was partitioned

between water and DCM (50 mL). The layers were separated. The aq. layer was extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by acidic prep. HPLC to give the title compound (single diastereomer, 0.295 g, 54%) as a white solid. LC-MS (2): t_R= 0.82 min; $[M+H]^+$: 285.19.

rac-(1R*,2S*)-2-(4-Methoxy-benzenesulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide: Was synthesized using rac-(1S*,2R*)-2-((4-methoxyphenyl)sulfonyl)cyclopentane-1-carboxylic acid and N-(4-chlorobenzyl)-4,4-difluorocyclohexan-1-amine as described in Example 3.9 to give the title compound as a white solid. LC-MS(1): t_R= 1.310 min; $[M+H]^+$: 526.3.

Example 3.23 (1R*,2S*)-2-(4-chloro-benzenesulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide: Was synthesized using methyl cyclopent-1-ene-1-carboxylate, 4-chlorobenzenethiol and N-(4-chlorobenzyl)-1,1-difluorospiro[2.5]octan-6-amine as described in Example 3.22 to give the title compound as a white solid. LC-MS(1): t_R= 1.446 min; $[M+H]^+$: 556.1.

Example 3.24 (1R*,2S*)-2-(3-fluoro-4-methyl-benzenesulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide: Was synthesized using methyl cyclopent-1-ene-1-carboxylate, 3-fluoro-4-methylthiophenol and N-(4-chlorobenzyl)-1,1-difluorospiro[2.5]octan-6-amine as described in Example 3.22 to give the title compound as a white solid. LC-MS(1): t_R= 1.443 min; $[M+H]^+$: 554.2.

Example 3.25 to Example 3.117 were synthesized according to the procedures described herein before using the appropriate amine or amine salt derivative, the appropriate aldehyde or ketone, the appropriate α,β-unsaturated ester, and the appropriate benzenethiol. LC-MS data of Example 3.25 to Example 3.117 are listed in the table below.

Ex. N°	Name	t_R	$[M+H]^+$	LC-MS conditions
3.25	(1S,2R)-N-(4-chlorobenzyl)-N-((1S*,3R*)-3-cyanocyclopentyl)-2-tosylcyclopentane-1-carboxamide	1.229	485.3	1
3.26	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide	1.418	536.3	1
3.27	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (1,1-difluoro-spiro[2.5]oct-6-yl)-(4-methoxy-benzyl)-amide	1.332	532.4	1
3.28	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(4-cyano-cyclohexyl)-amide	1.246	499.3	1
3.29	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (1,1-difluoro-spiro[2.5]oct-6-yl)-(5-methyl-isoxazol-4-ylmethyl)-amide	1.221	507.2	1

3.30	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-spiro[2.5]oct-6-yl-amide	1.492	500.3	1
3.31	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-((1R*,3R*)-3-cyano-cyclopentyl)-amide	1.243	485.2	1
3.32	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzooxazol-5-ylmethyl-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide	1.238	543.3	1
3.33	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (1,1-difluoro-spiro[2.5]oct-6-yl)-(4-methyl-benzyl)-amide	1.404	516.4	1
3.34	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (1,1-difluoro-spiro[2.5]oct-6-yl)-(4-methylsulfanyl-benzyl)-amide	1.394	548.3	1
3.35	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-2-fluoro-benzyl)-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide	1.446	554.3	1
3.36	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid chroman-6-ylmethyl-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide	1.381	558.4	1
3.37	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzo[1,3]dioxol-5-ylmethyl-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide	1.315	546.3	1
3.38	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzooxazol-2-ylmethyl-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide	1.303	543.3	1
3.39	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(2-fluoro-4-methoxy-benzyl)-amide	1.183	513.2	1
3.40	(1S,2R)-N-(4-Cyanocyclohexyl)-N-(quinolin-7-ylmethyl)-2-tosylcyclopentane-1-carboxamide	0.890	516.4	1
3.41	(1S,2R)-N-(4-Cyanocyclohexyl)-N-(isoquinolin-7-ylmethyl)-2-tosylcyclopentane-1-carboxamide	0.770	516.4	1
3.42	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(2-methyl-thiophen-3-ylmethyl)-amide	1.206	485.2	1
3.43	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(5-methyl-thiophen-2-ylmethyl)-amide	1.203	485.3	1
3.44	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(4-fluoro-3-methyl-benzyl)-amide	1.249	497.2	1
3.45	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-3-fluoro-benzyl)-(4-cyano-cyclohexyl)-amide	1.271	517.3	1
3.46	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(2-fluoro-4-methyl-benzyl)-amide	1.258	497.4	1

3.47	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-2,3-difluoro-benzyl)-(4-cyano-cyclohexyl)-amide	1.289	535.3	1
3.48	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-2-fluoro-benzyl)-(4-cyano-cyclohexyl)-amide	1.276	517.2	1
3.49	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-2,6-difluoro-benzyl)-(4-cyano-cyclohexyl)-amide	1.260	535.3	1
3.50	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (3-chloro-4-methyl-benzyl)-(4-cyano-cyclohexyl)-amide	1.301	513.3	1
3.51	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(2,4-difluoro-benzyl)-amide	1.202	501.3	1
3.52	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(5-methyl-isoxazol-4-ylmethyl)-amide	1.032	470.4	1
3.53	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (5-chloro-pyridin-2-ylmethyl)-(4-cyano-cyclohexyl)-amide	1.140	500.3	1
3.54	(1S,2R)-N-(4-Cyanocyclohexyl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-2-tosylcyclopentane-1-carboxamide	1.310	505.3	1
3.55	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(4-methylsulfanyl-benzyl)-amide	1.223	511.3	1
3.56	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(4-ethyl-benzyl)-amide	1.284	493.3	1
3.57	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(4-methoxy-benzyl)-amide	1.150	495.3	1
3.58	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(3-methoxy-benzyl)-amide	1.170	495.2	1
3.59	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(4-methyl-benzyl)-amide	1.224	479.3	1
3.60	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(3-methyl-thiophen-2-ylmethyl)-amide	1.195	485.3	1
3.61	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(2,4-dimethyl-benzyl)-amide	1.281	493.3	1
3.62	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(5-cyclopropyl-isoxazol-3-ylmethyl)-amide	1.126	496.3	1
3.63	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-bromo-benzyl)-(4-cyano-cyclohexyl)-amide	1.270	543.1	1

3.64	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(3-fluoro-4-methoxy-benzyl)-amide	1.156	513.3	1
3.65	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(2,3-dihydro-benzo[1,4]dioxin-6-ylmethyl)-amide	1.124	523.4	1
3.66	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(4-fluoro-benzyl)-amide	1.178	483.3	1
3.67	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (2-chloro-4-fluoro-benzyl)-(4-cyano-cyclohexyl)-amide	1.256	517.3	1
3.68	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(4-difluoromethoxy-benzyl)-amide	1.192	531.3	1
3.69	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(3-difluoromethoxy-benzyl)-amide	1.210	531.2	1
3.70	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(4-dimethylamino-benzyl)-amide	0.988	508.3	1
3.71	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(3-cyano-3,3-dimethyl-propyl)-amide	1.272	487.3	1
3.72	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(3,3-dimethyl-cyclohexyl)-amide	1.529	502.2	1
3.73	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(7,7-difluoro-bicyclo[4.1.0]hept-3-yl)-amide	1.396	522.3	1
3.74	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (7,7-difluoro-bicyclo[4.1.0]hept-3-yl)-(4-methoxy-benzyl)-amide	1.306	518.3	1
3.75	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (7,7-difluoro-bicyclo[4.1.0]hept-3-yl)-(4-methyl-benzyl)-amide	1.381	502.4	1
3.76	(1S,2R)-N-(4-Chlorobenzyl)-N-(1,1-dioxidotetrahydrothiophen-3-yl)-2-tosylcyclopentane-1-carboxamide	1.142	510.1	1
3.77	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(1,1-dioxo-hexahydro-1λ^6-thiopyran-4-yl)-amide	1.124	524.3	1
3.78	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(3,3-dimethyl-cyclopentyl)-amide	1.489	488.2	1
3.79	(1S,2R)-N-(4-chlorobenzyl)-N-((1S*,2S*)-2-hydroxycyclohexyl)-2-tosylcyclopentane-1-carboxamide	1.287	490.3	1
3.80	(1S,2R)-N-(4-Chlorobenzyl)-N-((1R*,3S*)-3-hydroxycyclohexyl)-2-tosylcyclopentane-1-carboxamide	1.152	490.3	1

3.81	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(4-hydroxy-4-methyl-cyclohexyl)-amide	1.156	504.3	1
3.82	(1S,2R)-N-(Bicyclo[4.1.0]heptan-3-yl)-N-(4-chlorobenzyl)-2-tosylcyclopentane-1-carboxamide	1.451	486.2	1
3.83	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(3-cyano-cyclobutyl)-amide	1.201	471.2	1
3.84	(1S,2R)-N-(4-chlorobenzyl)-N-((1S*,3R*)-3-hydroxycyclohexyl)-2-tosylcyclopentane-1-carboxamide	1.211	490.3	1
3.85	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(3-trifluoromethyl-cyclobutyl)-amide	1.371	514.2	1
3.86	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid ((1S*,3R*)-3-cyano-cyclopentyl)-(4-methyl-benzyl)-amide	1.210	465.3	1
3.87	(1R*,2S*)-2-(Toluene-4-sulfonyl)-cyclohexanecarboxylic acid (4-chloro-benzyl)-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide	1.479	550.3	1
3.88	(1R*,2S*)-2-(4-Methoxy-benzenesulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide	1.375	552.2	1
3.89	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(tetrahydro-thiopyran-4-yl)-amide	1.346	492.1	1
3.90	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(4-fluoro-cyclohexyl)-amide	1.340	492.2	1
3.91	(3R*,4R*)-3-(Toluene-4-sulfonyl)-tetrahydro-pyran-4-carboxylic acid (4-chloro-benzyl)-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide	1.14	552.17	2
3.92	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (3-cyano-3,3-dimethyl-propyl)-(4-methyl-benzyl)-amide	1.254	467.4	1
3.93	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (3-cyano-3,3-dimethyl-propyl)-indan-5-ylmethyl-amide	1.336	493.3	1
3.94	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-2-fluoro-benzyl)-(3-cyano-3,3-dimethyl-propyl)-amide	1.291	505.3	1
3.95	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-bromo-benzyl)-(3-cyano-3,3-dimethyl-propyl)-amide	1.287	531.3	1
3.96	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid ((1R*,3R*)-3-cyano-cyclohexyl)-(4-methyl-benzyl)-amide	1.255	479.2	1

3.97	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid ((1S*,3R*)-3-methoxy-cyclohexyl)-(4-methyl-benzyl)-amide	1.296	484.4	1
3.98	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-((1R,3S)-3-cyano-cyclopentyl)-amide	1.234	485.2	1
3.99	(1S,2R)-N-((1R*,3S*)-3-Cyanocyclopentyl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-2-tosylcyclopentane-1-carboxamide	1.294	491.4	1
3.100	(1S,2R)-N-(4,4-Difluorocyclohexyl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-2-tosylcyclopentane-1-carboxamide	1.418	516.3	1
3.101	(1S,2R)-N-(1,1-Difluorospiro[2.3]hexan-5-yl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-2-tosylcyclopentane-1-carboxamide	1.428	514.4	1
3.102	(1S,2R)-N-(1,1-Difluorospiro[2.5]octan-6-yl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-2-tosylcyclopentane-1-carboxamide	1.476	542.4	1
3.103	(1S,2R)-N-((3RS)-Bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-2-tosylcyclopentane-1-carboxamide	1.518	492.4	1
3.104	(1S,2R)-N-(7,7-Difluorobicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-2-tosylcyclopentane-1-carboxamide	1.463	528.2	1
3.105	(1S,2R)-N-((1R*,3R*)-3-Cyanocyclohexyl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-2-tosylcyclopentane-1-carboxamide	1.333	505.4	1
3.106	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid ((1R*,3S*)-3-cyano-cyclopentyl)-(3,4-dimethyl-benzyl)-amide	1.262	479.4	1
3.107	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid ((1R*,3S*)-3-cyano-cyclopentyl)-(3-fluoro-4-methyl-benzyl)-amide	1.225	483.4	1
3.108	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid ((1R*,3S*)-3-cyano-cyclopentyl)-(2,2-difluoro-benzo[1,3]dioxol-5-ylmethyl)-amide	1.258	531.3	1
3.109	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid ((1R*,3S*)-3-cyano-cyclopentyl)-(2,4-dimethyl-benzyl)-amide	1.261	479.3	1
3.110	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid ((1R*,3S*)-3-cyano-cyclopentyl)-(3,4-difluoro-benzyl)-amide	1.189	487.3	1
3.111	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid ((1R*,3S*)-3-cyano-cyclopentyl)-(2,5-difluoro-benzyl)-amide	1.183	487.2	1
3.112	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(2-trifluoromethyl-tetrahydro-pyran-4-yl)-amide	1.343	544.3	1

3.113	(1S,2R)-N-((1r,4S)-4-Cyanocyclohexyl)-N-(4-(methyl-d3)benzyl)-2-tosylcyclopentane-1-carboxamide	1.222	482.4	1
3.114	(1S,2R)-N-((1s,4R)-4-Cyanocyclohexyl)-N-(4-(methyl-d3)benzyl)-2-tosylcyclopentane-1-carboxamide	1.243	482.2	1
3.115	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(3-hydroxy-3-trifluoromethyl-cyclobutyl)-amide	1.242	530.1	1
3.116	(1S,2R)-N-(4-Chloro-2-fluorobenzyl)-N-((1R*,3S*)-3-cyanocyclopentyl)-2-tosylcyclopentane-1-carboxamide	1.261	503.4	1
3.117	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4,4-difluoro-cyclohexyl)-(1H-indol-6-ylmethyl)-amide	1.250	515.5	1

Example 3.119 (1S,2R)-N-(4-chlorobenzyl)-N-((1R*,3S*)-3-(difluoromethyl)cyclopentyl)-2-tosylcyclopentane-1-carboxamide:

rac-((1R*,3S*)-3-((4-Chlorobenzyl)amino)cyclopentyl)methanol: A soln. of 4-chlorobenzaldehyde (250 mg, 1.74 mmol) and rac-[(1R*,3S*)-3-aminocyclopentyl]methanol (211 mg, 1.74 mmol) in MeOH (9 mL) was stirred at rt overnight. $NaBH_4$ (98.9 mg, 2.61 mmol, 1.5 eq) was added and the mixture stirred at rt for 5h. The mixture was quenched with aq. sat. $NaHCO_3$ and extracted with DCM. The organic layer was filtered through a phase separator and the filtrate concentrated under reduced pressure to give the title compound (408 mg, 98%) which was used as such in the next step without further purification. LC-MS (2): t_R= 0.54 min; $[M+H]^+$: 240.31.

rac-tert-Butyl (4-chlorobenzyl)((1R*,3S*)-3-(hydroxymethyl)cyclopentyl)carbamate: To a soln. of rac-((1R*,3S*)-3-((4-chlorobenzyl)amino)cyclopentyl)methanol (148 mg, 0.617 mmol) in DCM (5.3 mL) was added DIPEA (0.211 mL, 1.23 mmol), followed by di-tert-butyl dicarbonate (0.143 mL, 0.617 mmol) and the resulting mixture was stirred at rt overnight. The mixture was quenched with water and extracted with DCM. The organic layer was filtered through a phase separator and the filtrate concentrated under reduced pressure to give the title compound (210 mg, quant.) as a pale yellow oil. The compound was used as such in the next step without further purification. LC-MS (2): t_R= 1.01 min; $[M+H]^+$: 340.26.

rac-tert-Butyl (4-chlorobenzyl)((1R*,3S*)-3-formylcyclopentyl)carbamate: A soln. of rac-tert-butyl (4-chlorobenzyl)((1R*,3S*)-3-(hydroxymethyl)cyclopentyl)carbamate (96 mg, 0.234 mmol) and DIPEA (0.153 mL, 0.891 mmol) in DCM (0.8 mL) was cooled to -10°C before a solution of $Pyr{\cdot}SO_3$ (91.2 mg, 0.258 mmol) in DMSO (0.25 mL, 3.52 mmol, 15 eq) was added dropwise. After 30 min the cooling bath was removed and the milky mixture stirred at rt for 2h. The reaction mixture was quenched with water and extracted with DCM. The organic layer was filtered through a phase separator and the filtrate concentrated under reduced pressure. The residue was purified by FC (Hept to Hept/EtOAc 7:3) to give the title compound (64 mg, 81%) as a colorless oil. LC-MS (2): t_R= 1.08 min; $[M+H]^+$: 338.12.

rac-tert-Butyl (4-chlorobenzyl)((1R*,3S*)-3-(difluoromethyl)cyclopentyl)carbamate: To a soln. of rac-tert-butyl (4-chlorobenzyl)((1R*,3S*)-3-formylcyclopentyl)carbamate (64 mg, 0.189 mmol) in DCM (0.4 mL) 0°C, was added dropwise Deoxo-Fluor, (2.7M in toluene, 0.379 mL, 0.14 mmol). The mixture was stirred while warming up from 0°C to rt over 2h30. Water was added and the mixture was extracted with DCM. The organic layer was filtered through a phase separator and the filtrate concentrated under reduced pressure. The residue was purified by FC (Hept to Hept/EtOAc 7:3) to give the title compound (11 mg, 16%).

rac-(1R*,3S*)-N-(4-Chlorobenzyl)-3-(difluoromethyl)cyclopentan-1-amine: A soln. of rac-tert-butyl (4-chlorobenzyl)((1R*,3S*)-3-(difluoromethyl)cyclopentyl)carbamate (11 mg, 0.0306 mmol) in DCM (0.2 mL) was treated with HCl (4M in dioxane, 0.031 mL, 0.124 mmol) at 0°C and the mixture was stirred at rt overnight. HCl (4M in dioxane, 0.076 mL) was added again and the mixture was stirred at rt for 7h. The mixture was transfered in a sealed vial, TFA (23.6 µL, 0.306 mmol) was added and the mixture heated at 40°C for 3 days. The mixture was concentrated under reduced pressure to give the title compound (9 mg, quant.). The compound was used as such without further purification in the next step. LC-MS (2): t_R= 0.65 min; $[M+H]^+$: 260.34.

(1S,2R)-N-(4-Chlorobenzyl)-N-((1R*,3S*)-3-(difluoromethyl)cyclopentyl)-2-tosylcyclopentane-1-carboxamide: A soln. of (1S,2R)-2-tosylcyclopentane-1-carboxylic acid (8 mg, 0.0298 mmol) in DCM (0.25 mL) was treated with oxalyl chloride (0.0053 mL, 0.0626 mmol) and DMF (2 drops). The soln. was stirred at rt for 15 min before a soln. of rac-(1R*,3S*)-N-(4-chlorobenzyl)-3-(difluoromethyl)cyclopentan-1-amine (20.4 mg, 0.0224 mmol) and DIPEA (0.0306 mL, 0.179 mmol) in DCM (0.15 mL) were added. The mixture was stirred at rt for 4 days. The crude was diluted with MeCN and purified by acidic prep. HPLC to give the title compound (0.6 mg, 4%) as white solid. LC-MS (1): t_R= 1.346 min; $[M+H]^+$: 510.4.

Example 3.120 to **Example 3.126** were synthesized according to the procedures described herein before using the appropriate amine or amine salt derivative, the appropriate aldehyde or ketone and (1S,2R)-2-tosylcyclopentane-1-carboxylic acid. LC-MS data of Example 3.120 to Example 3.126 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
3.120	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzo[1,2,5]oxadiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.263	518.4
3.121	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzooxazol-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide	1.162	517.4
3.122	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4,4-difluoro-cyclohexyl)-(6-fluoro-benzooxazol-5-ylmethyl)-amide	1.221	535.4
3.123	(1S,2R)-N-(3-Carbamoylcyclopentyl)-N-(4-chlorobenzyl)-2-tosylcyclopentane-1-carboxamide	1.052	503.4

3.124	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(6,6-dimethyl-tetrahydro-pyran-3-yl)-amide	1.351	504.4
3.125	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(3,3-difluoro-cyclohexyl)-amide	1.361	510.4
3.126	(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(2,2-difluoro-cyclohexyl)-amide	1.421	510.4

Example 3.127 (2R*,3S*)-3-(Toluene-4-sulfonyl)-tetrahydro-furan-2-carboxylic acid (4-chloro-benzyl)-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide:

rac-(2R*,3S*)-3-(p-Tolylthio)tetrahydrofuran-2-carboxylic acid: To a soln. of n-BuLi, (2.5M in hexanes, 4.9 mL, 12.3 mmol) in THF (8 mL) at 0°C was added portionwise 4-methylbenzenethiol (2437 mg, 19.2 mmol). The mixture was stirred at 0°C for 5 min before a solution of methyl 4,5-dihydrofuran-2-carboxylate (224 mg, 1.75 mmol) in THF (8 mL) was added dropwise. The flask was warmed to rt and heated to 70°C for 3h. The mixture was cooled to 0°C before being partitioned between aq. 2M HCl and DCM. The layers were separated and the aq. layer was extracted twice with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by acidic prep. HPLC to give rac-(2R*,3R*)-3-(p-tolylthio)tetrahydrofuran-2-carboxylic acid (58 mg, 14%) and rac-(2R*,3S*)-3-(p-tolylthio)tetrahydrofuran-2-carboxylic acid (65 mg, 16%). rac-(2R*,3R*)-3-(p-Tolylthio)tetrahydrofuran-2-carboxylic acid: LC-MS (2): t_R= 0.76 min; $[M+H]^+$: not seen. rac-(2R*,3S*)-3-(p-Tolylthio)tetrahydrofuran-2-carboxylic acid: LC-MS (2): t_R= 0.81 min; $[M+H]^+$: not seen.

(2R*,3S*)-N-(4-Chlorobenzyl)-N-(1,1-difluorospiro[2.5]octan-6-yl)-3-(p-tolylthio)tetrahydrofuran-2-carboxamide: To a soln. of rac-(2R*,3S)*-3-(p-tolylthio)tetrahydrofuran-2-carboxylic acid (32 mg, 0.134 mmol) and N-(4-chlorobenzyl)-1,1-difluorospiro[2.5]octan-6-amine (38.4 mg, 0.134 mmol, 1 eq) in DMF (1 mL) was added DIPEA (0.0805 mL, 0.47 mmol, 3.5 eq), followed by PyClop (79.3 mg, 0.188 mmol, 1.4 eq). The mixture was stirred at rt for 3 days. The reaction mixture was purified by acidic prep. HPLC to give the title compound (49 mg, 72%) as a colorless oil. LC-MS (2): t_R= 1.22 min; $[M+H]^+$: 506.24.

(2R*,3S*)-3-(Toluene-4-sulfonyl)-tetrahydro-furan-2-carboxylic acid (4-chloro-benzyl)-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide: To an ice-cooled soln. of (2R*,3S*)-N-(4-chlorobenzyl)-N-(1,1-difluorospiro[2.5]octan-6-yl)-3-(p-tolylthio)tetrahydrofuran-2-carboxamide (49 mg, 0.0968 mmol, 1 eq) and $NaHCO_3$ (24.4 mg, 0.29 mmol, 3 eq) in DCM (1 mL) was added MCPBA (<77%, 50.0 mg, 0.29 mmol, <3 eq) portionwise. The reaction mixture was stirred at 0°C for 2h. At 0°C the reaction mixture was diluted with DCM and aq. 1M NaOH was added. The layers were separated, the organic layer was filtered through a phase separator and the filtrate concentrated under reduced pressure. The residue was purified by acidic prep. HPLC to give the title compound (30 mg, 58%) as a white foam. LC-MS (1): t_R= 1.388 min; $[M+H]^+$: 538.4.

Example 3.128 to Example 3.129 were synthesized according to the procedures described herein before using the appropriate amine or amine salt derivative and the appropriate carboxylic acid. LC-MS data of Example 3.128 to Example 3.129 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
3.128	(1R*,2S*)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide	1.421	536.4
3.129	(1S,2R)-N-(4-Chlorobenzyl)-N-((1R)-3-cyano-3-methylcyclopentyl)-2-tosylcyclopentane-1-carboxamide	1.288	499.4

Methods for the preparation of sulfoximine compounds (Examples 4.x)

Example 4.1 rac-(1S*,2R*)-N-(Benzo[d][1,3]dioxol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-2-(4-methylphenylsulfonimidoyl)cyclopentane-1-carboxamide:

rac-(1S*,2R*)-2-(p-Tolylthio)cyclopentane-1-carboxylic acid: To a soln. of methyl 2-(p-tolylthio)cyclopentane-1-carboxylate (501 mg, 2 mmol, 1 eq) in THF (8 mL) and MeOH (2 mL), aq. 1M NaOH (2.5 mL) was added. The mixture was stirred at rt for 5 hours. The organic solvents were removed under reduced pressure. The residue was diluted with water and extracted with EtOAc. The aq. layer was acidified with aq. 1M HCl. The mixture was extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by acidic prep. HPLC to give the title compound (0.192, 41%) as a colorless oil. LC-MS (2): t_R= 0.93 min; $[M+H]^+$: 237.18.

rac-(1S*,2R*)-N-(Benzo[d][1,3]dioxol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-2-(p-tolylthio)cyclopentane-1-carboxamide: To a soln. of rac-(1S*,2R*)-2-(p-tolylthio)cyclopentane-1-carboxylic acid (192 mg, 0.812 mmol, 1 eq) in DCM (8 mL), oxalyl chloride (0.107 mL, 1.22 mmol, 1.5 eq) and DMF (3 drops) were added. The mixture was stirred at rt for 30 min. A soln. of N-(benzo[d][1,3]dioxol-5-ylmethyl)-4,4-difluorocyclohexan-1-amine (219 mg, 0.812 mmol, 1 eq) and DIPEA (0.306 mL, 1.79 mmol, 2.2 eq) in DCM (2 mL) was added dropwise. The mixture was stirred at rt for 20 h. The reaction mixture was diluted with DCM and washed with sat. aq. $NaHCO_3$. The layers were separated. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by acidic prep. HPLC to give the title compound (68 mg, 17%) as a yellow oil. LC-MS (2): t_R= 1.18 min; $[M+H]^+$: 488.27.

rac-(1S*,2R*)-N-(Benzo[d][1,3]dioxol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-2-(4-methylphenylsulfonimidoyl)cyclopentane-1-carboxamide: To a soln. of rac-(1S*,2R*)-N-(benzo[d][1,3]dioxol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-2-(p-tolylthio)cyclopentane-1-carboxamide (68 mg, 0.139 mmol, 1 eq) and ammonium carbamate (22.9 mg, 0.279 mmol, 2 eq) in MeOH (1 mL), iodobenzene diacetate (118 mg, 0.349 mmol, 2.5 eq) was added. The mixture was stirred at rt for 2 h. The reaction mixture was concentrated under reduced

pressure. The residue was dissolved in DMF and aq. ammonia and purified by basic prep. HPLC to give the title compound (11 mg, 15%) as white solid. LC-MS(1): t_R= 1.130 min; $[M+H]^+$: 519.4.

Example 4.2 and Example 4.3 (1S,2R)-N-(4-Chlorobenzyl)-N-(4,4-difluorocyclohexyl)-2-((R)-4-methylphenylsulfonimidoyl)cyclopentane-1-carboxamide and (1S,2R)-N-(4-chlorobenzyl)-N-(4,4-difluorocyclohexyl)-2-((S)-4-methylphenylsulfonimidoyl)cyclopentane-1-carboxamide:

(1R,2S)-N-(4-Chlorobenzyl)-N-(4,4-difluorocyclohexyl)-2-(p-tolylthio)cyclopentane-1-carboxamide and (1S,2R)-N-(4-chlorobenzyl)-N-(4,4-difluorocyclohexyl)-2-(p-tolylthio)cyclopentane-1-carboxamide: To a soln. of rac-(1S*,2R*)-2-(p-tolylthio)cyclopentane-1-carboxylic acid (880 mg, 1.86 mmol, 1 eq), N-(4-chlorobenzyl)-4,4-difluorocyclohexan-1-amine (484 mg, 1.86 mmol, 1 eq), and DIPEA (0.956 mL, 5.59 mmol, 3 eq) in DMF (9 mL) was added PyCloP (942 mg, 2.23 mmol, 1.2 eq). The mixture was stirred at rt overnight. The reaction mixture was diluted with DCM and washed with sat. $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by FC (Hept to Hept/EtOAc 1:1) followed by acidic prep. HPLC to give the title compound (447 mg, 50%) as a colorless oil. The racemic mixture was separated by chiral SFC (SFC 4 method) to give (1S,2R)-N-(4-chlorobenzyl)-N-(4,4-difluorocyclohexyl)-2-(p-tolylthio)cyclopentane-1-carboxamide (first eluting enantiomer, 166 mg) and (1R,2S)-N-(4-chlorobenzyl)-N-(4,4-difluorocyclohexyl)-2-(p-tolylthio)cyclopentane-1-carboxamide (second eluting enantiomer, 162 mg) both as a white solids. (1S,2R)-N-(4-chlorobenzyl)-N-(4,4-difluorocyclohexyl)-2-(p-tolylthio)cyclopentane-1-carboxamide: LC-MS (2): t_R= 1.20 min, $[M+H]^+$: 478.21. (1R,2S)-N-(4-chlorobenzyl)-N-(4,4-difluorocyclohexyl)-2-(p-tolylthio)cyclopentane-1-carboxamide: LC-MS (2): t_R= 1.20 min, $[M+H]^+$: 478.22.

(1S,2R)-N-(4-Chlorobenzyl)-N-(4,4-difluorocyclohexyl)-2-((R)-4-methylphenylsulfonimidoyl)cyclopentane-1-carboxamide and (1S,2R)-N-(4-chlorobenzyl)-N-(4,4-difluorocyclohexyl)-2-((S)-4-methylphenylsulfonimidoyl)cyclopentane-1-carboxamide:

To a soln. of (1S,2R)-N-(4-chlorobenzyl)-N-(4,4-difluorocyclohexyl)-2-(p-tolylthio)cyclopentane-1-carboxamide (80 mg, 0.167 mmol, 1 eq) and ammonium carbamate (27.5 mg, 0.335 mmol, 2 eq) in MeOH (1.2 mL) was added iodobenzene diacetate (142 mg, 0.418 mmol, 2.5 eq). The mixture was stirred at rt for 3h. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in MeCN and purified by acidic prep. HPLC to give Example 4.2 (first eluting diastereomer, 23 mg, 27%) and Example 4.3 (second eluting diastereomer, 11 mg, 13%) both as white solids. Stereochemistry at sulfur was arbitrarily assigned. Example 4.2: LC-MS(1): t_R= 1.221 min; $[M+H]^+$: 509.2. Example 4.3: LC-MS (1): t_R= 1.243 min; $[M+H]^+$: 509.3.

Example 4.4 to **Example 4.5** were synthesized according to the procedures described herein before using the appropriate amine or amine salt derivative and (1S,2R)-2-tosylcyclopentane-1-carboxylic acid. LC-MS data of Example 4.4 to Example 4.5 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
4.4	(1S,2R)-N-(4-Chlorobenzyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-2-((R)-4-methylphenylsulfonimidoyl)cyclopentane-1-carboxamide	1.287	535.5
4.5	(1S,2R)-N-(4-Chlorobenzyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-2-((S)-4-methylphenylsulfonimidoyl)cyclopentane-1-carboxamide	1.318	535.4

Example 4.6 (1S,2R)-N-(4-Chlorobenzyl)-N-((1R,3S)-3-cyanocyclopentyl)-2-((R)-4-methylphenylsulfonimidoyl)cyclopentane-1-carboxamide and Example 4.7 (1S,2R)-N-(4-Chlorobenzyl)-N-((1R,3S)-3-cyanocyclopentyl)-2-((S)-4-methylphenylsulfonimidoyl)cyclopentane-1-carboxamide:

tert-Butyl ((1R,3S)-3-cyanocyclopentyl)carbamate: Isobutyl chloroformate (2.50 mL, 0.019 mol, 1.5 eq) was added dropwise to a solution of (+)-(1S,3R)-N-Boc-3-aminocyclopentane carboxylic acid (3 g, 0.0127 mol, 1 eq) and Et_3N (2.65 mL, 0.019 mol, 1.5 eq) in THF (30 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. Ammonium hydroxide solution (30-33% NH_3 in H_2O (30.5 mL, 0.235 mol, 18.52 eq)) was added dropwise and the reaction mixture was stirred at rt for 5.5h. Water was added and the mixture was extracted with EtOAc. The org. layer was washed with aq. 1M NaOH soln., water, and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was dissolved in THF (70 mL) and cooled to 0 °C. Et_3N (8.5 mL, 0.061 mol, 4.8 eq) was added, followed by trifluoroacetic anhydride (2.85 mL, 0.0203 mol, 1.6 eq) and the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with ice cold water and extracted with DCM. The org. layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by FC (Hept to Hept/EtOAc 2.5:7.5) to give the title compound. LC-MS (3): t_R= 0.78 min; $[M+H]^+$: 211.40.

(1R,3S)-3-Cyanocyclopentan-1-aminium 2,2,2-trifluoroacetate: A solution of tert-butyl ((1R,3S)-3-cyanocyclopentyl)carbamate (2.18 g, 0.0104 mol, 1 eq) in DCM (30 mL) was cooled to 0 °C. Trifluoroacetic acid (8.00 mL, 0.104 mol, 10 eq) was added slowly and the reaction mixture was stirred at rt. for 2.5h. The reaction mixture was concentrated to give the title compound which was used as such in the next step without further purification. LC-MS (3): t_R= 0.35 min; $[M+H]^+$: not seen.

(1S,3R)-3-((4-Chlorobenzyl)amino)cyclopentane-1-carbonitrile: A solution of (1R,3S)-3-cyanocyclopentan-1-aminium 2,2,2-trifluoroacetate (4120 mg, 10.1 mmol, 1 eq), 4-chlorobenzaldehyde (1450 mg, 10.1 mmol, 1 eq) and AcOH (0.580 mL, 10.1 mmol, 1 eq) in THF (40 mL) was stirred for 15 min. Sodium triacetoxyborohydride (3383 mg, 15.2 mmol, 1.5 eq) was added in 3 portions and the reaction mixture was stirred at rt for 3h. The reaction mixture was quenched with aq. sat. $NaHCO_3$. The pH was adjusted to pH 9 with solid Na_2CO_3. The product was extracted with DCM and the org. layer was washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the title compound. LC-MS (3): t_R= 0.91 min; $[M+H]^+$: 235.31.

(1S,2R)-2-(p-Tolylthio)cyclopentane-1-carboxylic acid: Was obtained by prep. chiral HPLC separation (SFC 7 method) of rac-(1R*,2S*)-2-tosylcyclopentane-1-carboxylic acid to give (1R,2S)-2-(p-tolylthio)cyclopentane-1-

carboxylic acid (first eluting enantiomer) and (1S,2R)-2-(p-tolylthio)cyclopentane-1-carboxylic acid (second eluting enantiomer). (1R,2S)-2-(p-Tolylthio)cyclopentane-1-carboxylic acid: LC-MS (2): t_R= 0.92 min, $[M+H]^+$: not seen. (1S,2R)-2-(p-Tolylthio)cyclopentane-1-carboxylic acid: LC-MS (2): t_R= 0.92 min, $[M+H]^+$: not seen.

(1S,2R)-N-(4-Chlorobenzyl)-N-((1R,3S)-3-cyanocyclopentyl)-2-(p-tolylthio)cyclopentane-1-carboxamide: To a solution of (1S,2R)-2-(p-tolylthio)cyclopentane-1-carboxylic acid (1558 mg, 6.59 mmol, 1 eq), (1S,3R)-3-((4-chlorobenzyl)amino)cyclopentane-1-carbonitrile (1630 mg, 6.94 mmol, 1.053 eq) and DIPEA (3.95 mL, 23.1 mmol, 3.5 eq) in DMF (33 mL) was added chlorotripyrrolidinophosphonium hexafluorophosphate (3972 mg, 9.23 mmol, 1.4 eq). The yellow solution was stirred at rt for 4 h. The reaction mixture was quenched with aq. sat. $NaHCO_3$ and diluted with water and DCM. The layers were separated and the org. layer was washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified by FC (Hept to Hept/EOAc 1:1) to give the title compound. LC-MS (2): t_R= 1.16 min, $[M+H]^+$: 453.03.

(1S,2R)-N-(4-Chlorobenzyl)-N-((1R,3S)-3-cyanocyclopentyl)-2-((R)-4-methylphenylsulfonimidoyl)cyclopentane-1-carboxamide and (1S,2R)-N-(4-chlorobenzyl)-N-((1R,3S)-3-cyanocyclopentyl)-2-((S)-4-methylphenylsulfonimidoyl)cyclopentane-1-carboxamide: Iodobenzene diacetate (3314 mg, 9.88 mmol, 2.5 eq) was added to a solution of (1S,2R)-N-(4-chlorobenzyl)-N-((1R,3S)-3-cyanocyclopentyl)-2-(p-tolylthio)cyclopentane-1-carboxamide (1790 mg, 3.95 mmol, 1 eq) and ammonium carbamate (649 mg, 7.9 mmol, 2 eq) in MeOH (30 mL). The reaction mixture was stirred at rt for 1h. The solvent was removed under reduced pressure. The residue was purified by acidic prep-HPLC to give (1S,2R)-N-(4-chlorobenzyl)-N-((1R,3S)-3-cyanocyclopentyl)-2-((R)-4-methylphenylsulfonimidoyl)cyclopentane-1-carboxamide and (1S,2R)-N-(4-chlorobenzyl)-N-((1R,3S)-3-cyanocyclopentyl)-2-((S)-4-methylphenylsulfonimidoyl) cyclopentane-1-carboxamide. First eluting diastereomer of (1S,2R)-N-(4-chlorobenzyl)-N-((1R,3S)-3-cyanocyclopentyl)-2-((RS)-4-methylphenylsulfonimidoyl)cyclopentane-1-carboxamide: LC-MS (1): t_R= 1.078 min, $[M+H]^+$: 484.4. Second eluting diastereomer of (1S,2R)-N-(4-chlorobenzyl)-N-((1R,3S)-3-cyanocyclopentyl)-2-((RS)-4-methylphenylsulfonimidoyl)cyclopentane-1-carboxamide: LC-MS (1): t_R= 1.112 min, $[M+H]^+$: 484.4.

II-Biological assays

IP1 accumulation assay

Agonistic activity on the human orexin-2 receptor (hOX_2R) have been measured for each example compound using an intracellular inositol-1-phosphate (IP1) accumulation assay (IP-One Gq assay kit, Cisbio) according to manufacturer's instructions with following modifications:

Human embryonic kidney 293 (HEK293) cells expressing the human Orexin-2 receptor (hOX_2R), are grown in culture medium DMEM (Thermo Fisher Scientific) containing 500 mg/ml geneticin, 100 U/ml penicillin, 100 mg/ml streptomycin and 10% heat inactivated fetal bovine serum (FBS) (Thermo Fisher Scientific). Cells are allowed to grow to 80% confluence at 37°C in 5% CO_2. On the day of the assay, cells are washed with PBS (Thermo Fisher

Scientific) and harvested using cell dissociation buffer (Thermo Fisher Scientific). After counting, cells are pelleted by centrifugation at 120 g for 5 min and resuspended in Hank's buffered saline solution supplemented with 20 mM HEPES, 0.375 g/L sodium-bicarbonate, 0.05 M lithium chloride and adjusted to pH 7.4 (hereafter called Stimulation buffer). The cells are seeded at 25'000 cells/well into 384-well white HiBase small volume plates (Greiner Bio-One). Agonist example compounds are dissolved in DMSO as 10 mM stock solutions, serially diluted in DMSO and further diluted to 4-times their final concentration in Stimulation buffer supplemented with 0.2% bovine serum albumin (BSA). Human Orexin-A peptide (OxA) is prepared as 1 mM stock solution in H_2O, diluted to 4-times its final concentration in Stimulation buffer supplemented with 0.2% BSA.

Dilution series of agonist example compounds and OxA are added to the seeded cells and IP1 accumulation is allowed for 5.5 h at 37°C in 5% CO_2. The assay is terminated by addition of lysis buffer containing IP1-detection reagents according to the kit's instructions. After 1 h lysis at room temperature, Homogeneous Time Resolved Fluorescence (HTRF) is acquired at wavelengths of 665 nm and 620 nm following excitation at 337 nm using a PHERAstar FSX plate reader (BMG Labtech).

Analysis

Measured HTRF ratios 665 nm/620 nm are exported using the PHERAstar® acquisition software (BMG Labtech). Analysis is performed in IC50 Studio software (Idorsia Pharmaceuticals ltd.) so that HTRF data is normalized to the responses obtained with 0.5% DMSO and 200 nM OxA, representing 0% and 100% responses, respectively. Potency (EC_{50}) and efficacy (Emax) values are calculated for each example compound using non-linear regression analysis with a 4-parameter curve fitting. Note: alternatively, potency and efficacy calculations can be achieved using a commercially available software such as Prism 7.0 (GraphPad).

EC_{50} value corresponds to the compound concentration that activates 50% of the maximum response obtained with 200 nM OxA and Emax corresponds to the maximum response compared to the maximum response obtained with 200 nM OxA.

The calculated EC_{50} and efficacy Emax values may fluctuate depending on the daily cellular assay performance. Fluctuations of this kind are known to those skilled in the art. EC_{50} and Emax values from several measurements are given as median values.

Agonistic activities of example compounds on hOX_2R are displayed in Tables 1-3.

Table 1

Ex. Number	**EC_{50} [nM]**	**Emax %**	**Ex. Number**	**EC_{50} [nM]**	**Emax %**	**Ex. Number**	**EC_{50} [nM]**	**Emax %**	**Ex. Number**	**EC_{50} [nM]**	**Emax %**
1.1	372	100	**1.101**	145	98	**1.201**	17	93	**1.301**	159	100

1.2	196	97	**1.102**	31	96	**1.202**	26	95	**1.302**	253	101
1.3	378	93	**1.103**	85	97	**1.203**	309	91	**1.303**	241	101
1.4	292	97	**1.104**	38	98	**1.204**	105	89	**1.304**	454	114
1.5	129	88	**1.105**	136	75	**1.205**	269	89	**1.305**	350	93
1.6	165	99	**1.106**	19	99	**1.206**	11	104	**1.306**	2	99
1.7	143	98	**1.107**	415	103	**1.207**	311	90	**1.307**	2	103
1.8	122	99	**1.108**	38	93	**1.208**	123	96	**1.308**	240	103
1.9	431	95	**1.109**	1	100	**1.209**	432	85	**1.309**	472	102
1.10	98	98	**1.110**	3	99	**1.210**	37	101	**1.310**	29	102
1.11	194	102	**1.111**	6	100	**1.211**	156	99	**1.311**	24	105
1.12	135	99	**1.112**	11	96	**1.212**	36	98	**1.312**	437	105
1.13	151	96	**1.113**	13	98	**1.213**	105	94	**1.313**	479	91
1.14	295	98	**1.114**	15	97	**1.214**	54	88	**1.314**	136	98
1.15	189	100	**1.115**	182	96	**1.215**	21	98	**1.315**	167	98
1.16	63	98	**1.116**	82	97	**1.216**	15	108	**1.316**	233	99
1.17	335	97	**1.117**	5	92	**1.217**	83	98	**1.317**	253	99
1.18	60	100	**1.118**	76	97	**1.218**	14	100	**1.318**	326	99
1.19	207	97	**1.119**	383	69	**1.219**	7	95	**1.319**	498	104
1.20	242	98	**1.120**	359	77	**1.220**	12	89	**1.320**	57	107
1.21	46	101	**1.121**	28	92	**1.221**	13	98	**1.321**	273	104
1.22	302	99	**1.122**	11	101	**1.222**	23	94	**1.322**	73	103
1.23	199	97	**1.123**	33	97	**1.223**	16	90	**1.323**	1	112
1.24	204	96	**1.124**	253	101	**1.224**	8	106	**1.324**	5	97
1.25	164	92	**1.125**	32	102	**1.225**	73	102	**1.325**	1	101
1.26	112	97	**1.126**	295	83	**1.226**	79	101	**1.326**	329	94
1.27	161	98	**1.127**	58	101	**1.227**	159	98	**1.327**	3	105

1.28	106	95	**1.128**	55	101	**1.228**	122	101	**1.328**	366	84
1.29	231	92	**1.129**	213	96	**1.229**	316	100	**1.329**	1	103
1.30	220	106	**1.130**	20	109	**1.230**	57	94	**1.330**	409	95
1.31	161	101	**1.131**	24	98	**1.231**	187	95	**1.331**	4	101
1.32	278	100	**1.132**	129	100	**1.232**	253	96	**1.332**	480	90
1.33	209	99	**1.133**	34	104	**1.233**	5	96	**1.333**	43	98
1.34	73	98	**1.134**	14	101	**1.234**	6	100	**1.334**	131	99
1.35	453	101	**1.135**	81	93	**1.235**	125	108	**1.335**	3	101
1.36	288	100	**1.136**	78	96	**1.236**	223	94	**1.336**	69	100
1.37	205	99	**1.137**	71	104	**1.237**	358	101	**1.337**	123	98
1.38	270	72	**1.138**	413	92	**1.238**	399	100	**1.338**	4	104
1.39	470	89	**1.139**	11	96	**1.239**	69	92	**1.339**	229	96
1.40	441	98	**1.140**	57	72	**1.240**	56	99	**1.340**	478	85
1.41	179	98	**1.141**	10	94	**1.241**	228	96	**1.341**	31	97
1.42	136	99	**1.142**	4	95	**1.242**	160	91	**1.342**	4	103
1.43	127	97	**1.143**	13	97	**1.243**	31	92	**1.343**	19	105
1.44	180	86	**1.144**	40	100	**1.244**	26	98	**1.344**	492	75
1.45	45	91	**1.145**	213	97	**1.245**	30	103	**1.345**	5	101
1.46	60	96	**1.146**	397	65	**1.246**	352	92	**1.346**	104	94
1.47	5	96	**1.147**	6	99	**1.247**	170	96	**1.347**	7	96
1.48	32	94	**1.148**	302	83	**1.248**	133	86	**1.348**	89	94
1.49	95	100	**1.149**	5	99	**1.249**	335	85	**1.349**	3	99
1.50	23	104	**1.150**	16	98	**1.250**	43	90	**1.350**	8	89
1.51	98	90	**1.151**	45	92	**1.251**	104	87	**1.351**	157	95
1.52	17	84	**1.152**	21	98	**1.252**	73	90	**1.352**	4	100
1.53	5	95	**1.153**	365	96	**1.253**	103	90	**1.353**	72	104

1.54	5	101	**1.154**	23	91	**1.254**	6	101	**1.354**	309	103
1.55	295	96	**1.155**	56	92	**1.255**	500	83	**1.355**	118	84
1.56	80	92	**1.156**	12	96	**1.256**	6	103	**1.356**	89	99
1.57	75	106	**1.157**	348	89	**1.257**	93	100	**1.357**	154	93
1.58	126	96	**1.158**	67	99	**1.258**	85	111	**1.358**	401	92
1.59	79	97	**1.159**	36	105	**1.259**	305	102	**1.359**	74	104
1.60	123	97	**1.160**	45	93	**1.260**	125	95	**1.360**	413	60
1.61	419	107	**1.161**	23	101	**1.261**	129	100	**1.361**	28	114
1.62	445	107	**1.162**	195	85	**1.262**	473	96	**1.362**	94	91
1.63	133	104	**1.163**	55	105	**1.263**	28	95	**1.363**	157	92
1.64	16	101	**1.164**	3	98	**1.264**	50	101	**1.364**	421	74
1.65	20	102	**1.166**	131	85	**1.265**	48	89	**1.365**	49	100
1.66	98	103	**1.167**	109	95	**1.266**	38	98	**1.366**	96	102
1.67	153	95	**1.168**	236	95	**1.267**	353	90	**1.367**	128	99
1.68	220	95	**1.169**	141	100	**1.268**	108	96	**1.368**	420	102
1.69	235	97	**1.170**	412	102	**1.269**	24	100	**1.369**	101	94
1.70	31	98	**1.171**	334	94	**1.270**	17	104	**1.370**	374	85
1.71	65	88	**1.172**	355	93	**1.271**	116	92	**1.371**	23	97
1.72	34	99	**1.173**	385	82	**1.272**	90	103	**1.372**	4	102
1.73	72	99	**1.174**	25	100	**1.273**	112	108	**1.373**	11	106
1.74	189	94	**1.175**	134	99	**1.274**	209	91	**1.374**	50	98
1.75	278	86	**1.176**	24	96	**1.275**	180	95	**1.375**	101	97
1.76	85	99	**1.177**	50	99	**1.276**	293	80	**1.376**	158	92
1.77	247	107	**1.178**	115	100	**1.277**	160	75	**1.377**	429	92
1.78	231	85	**1.179**	54	98	**1.278**	136	90	**1.378**	497	90
1.79	393	58	**1.180**	196	95	**1.279**	125	87	**1.379**	23	102

1.80	291	80	**1.181**	53	100	**1.280**	136	94	**1.380**	29	103
1.81	472	87	**1.182**	40	102	**1.281**	118	91	**1.381**	79	97
1.82	88	96	**1.183**	67	100	**1.282**	376	89	**1.382**	188	103
1.83	133	103	**1.184**	62	89	**1.283**	314	96	**1.383**	295	94
1.84	72	103	**1.185**	219	97	**1.284**	241	72	**1.384**	470	87
1.85	82	102	**1.186**	235	100	**1.285**	369	96	**1.385**	133	89
1.86	98	101	**1.187**	409	59	**1.286**	83	84	**1.386**	350	89
1.87	28	96	**1.188**	247	74	**1.287**	74	116	**1.387**	317	89
1.88	32	100	**1.189**	26	109	**1.288**	79	89	**1.388**	40	95
1.89	7	103	**1.190**	112	97	**1.289**	71	91	**1.389**	14	95
1.90	19	94	**1.191**	55	103	**1.290**	271	100	**1.390**	51	108
1.91	30	102	**1.192**	10	97	**1.291**	56	92	**1.391**	242	98
1.92	86	100	**1.193**	26	101	**1.292**	74	99	**1.392**	79	97
1.93	108	97	**1.194**	265	90	**1.293**	101	96	**1.393**	229	109
1.94	161	99	**1.195**	297	88	**1.294**	22	99	**1.394**	132	105
1.95	41	97	**1.196**	445	94	**1.295**	39	102	**1.395**	147	99
1.96	170	90	**1.165**	4	91	**1.296**	73	99	**1.396**	74	97
1.97	26	95	**1.197**	42	103	**1.297**	195	99	**1.397**	216	90
1.98	494	88	**1.198**	412	97	**1.298**	3	100	**1.398**	36	100
1.99	84	97	**1.199**	11	111	**1.299**	8	100	**1.399**	9	101
1.100	8	99	**1.200**	22	93	**1.300**	272	93	**1.400**	265	92
									1.401	246	97
									1.402	354	103
									1.403	20	97
									1.404	153	103
									1.405	97	111

									1.406	140	113
									1.407	6	101
									1.408	10	97
									1.409	197	107
									1.410	72	107
									1.411	94	90
									1.412	242	92

Table 2:

Ex. Number	**EC_{50} [nM]**	**Emax %**	**Ex. Number**	**EC_{50} [nM]**	**Emax %**	**Ex. Number**	**EC_{50} [nM]**	**Emax %**
2.1	220	110	**2.101**	220	98	**2.201**	234	99
2.2	58	97	**2.102**	129	89	**2.202**	271	110
2.3	52	97	**2.103**	308	77	**2.203**	64	90
2.4	42	100	**2.104**	484	110	**2.204**	27	100
2.5	58	99	**2.105**	455	84	**2.205**	160	95
2.6	69	100	**2.106**	300	93	**2.206**	72	100
2.7	330	99	**2.107**	357	68	**2.207**	40	94
2.8	230	94	**2.108**	56	99	**2.208**	201	99
2.9	220	93	**2.109**	24	100	**2.209**	75	95
2.10	160	91	**2.110**	253	91	**2.210**	372	84
2.11	68	95	**2.111**	376	93	**2.211**	81	94
2.12	250	94	**2.112**	196	91	**2.212**	444	84
2.13	461	86	**2.113**	180	67	**2.213**	118	100
2.14	470	100	**2.114**	310	69	**2.214**	61	88
2.15	83	96	**2.115**	31	110	**2.215**	365	110

2.16	203	91	**2.116**	180	84	**2.216**	25	120
2.17	110	92	**2.117**	275	71	**2.217**	65	110
2.18	150	99	**2.118**	143	93	**2.218**	13	93
2.19	130	95	**2.119**	57	110	**2.219**	451	89
2.20	270	93	**2.120**	260	92	**2.220**	280	90
2.21	111	98	**2.121**	137	110	**2.221**	218	82
2.22	155	99	**2.122**	118	120	**2.222**	137	120
2.23	319	98	**2.123**	113	95	**2.223**	66	120
2.24	275	87	**2.124**	267	110	**2.224**	470	120
2.25	23	100	**2.125**	377	110	**2.225**	69	96
2.26	28	98	**2.126**	252	110	**2.226**	53	120
2.27	216	100	**2.127**	65	120	**2.227**	377	110
2.28	131	97	**2.128**	276	95	**2.228**	44	120
2.29	65	97	**2.129**	105	110	**2.229**	26	96
2.30	20	99	**2.130**	83	93	**2.230**	342	93
2.31	85	98	**2.131**	134	95	**2.231**	212	94
2.32	173	86	**2.132**	161	99	**2.232**	363	86
2.33	240	92	**2.133**	187	98	**2.233**	10	100
2.34	76	85	**2.134**	30	140	**2.234**	49	91
2.35	190	100	**2.135**	48	94	**2.235**	350	100
2.36	60	94	**2.136**	47	110	**2.236**	440	97
2.37	144	92	**2.137**	110	100	**2.237**	16	110
2.38	151	100	**2.138**	171	92	**2.238**	49	120
2.39	187	96	**2.139**	257	98	**2.239**	150	100
2.40	189	92	**2.140**	307	92	**2.240**	3	110
2.41	175	98	**2.141**	352	65	**2.241**	284	100

2.42	366	90	**2.142**	337	70	**2.242**	401	100
2.43	142	100	**2.143**	214	51	**2.243**	6	110
2.44	117	99	**2.144**	352	100	**2.244**	419	100
2.45	281	100	**2.145**	499	84	**2.245**	52	100
2.46	220	100	**2.146**	49	99	**2.246**	43	100
2.47	39	96	**2.147**	171	100	**2.247**	115	100
2.48	35	99	**2.148**	131	130	**2.248**	50	91
2.49	75	99	**2.149**	237	100	**2.249**	10	99
2.50	63	95	**2.150**	247	98	**2.250**	62	97
2.51	87	93	**2.151**	429	91	**2.251**	8	110
2.52	136	94	**2.152**	75	100	**2.252**	40	110
2.53	30	94	**2.153**	87	110	**2.253**	6	88
2.54	215	97	**2.154**	50	96	**2.254**	18	89
2.55	292	99	**2.155**	219	93	**2.255**	27	96
2.56	146	98	**2.156**	210	97	**2.256**	75	87
2.57	243	99	**2.157**	260	99	**2.257**	76	99
2.58	460	88	**2.158**	111	110	**2.258**	344	84
2.59	207	94	**2.159**	26	110	**2.259**	79	96
2.60	224	90	**2.160**	450	94	**2.260**	23	110
2.61	270	91	**2.161**	253	98	**2.261**	24	110
2.62	136	89	**2.162**	41	110	**2.262**	17	100
2.63	58	95	**2.163**	97	110	**2.263**	44	100
2.64	157	99	**2.164**	29	98	**2.264**	153	93
2.65	152	94	**2.165**	71	110	**2.265**	263	100
2.66	182	91	**2.166**	402	110	**2.266**	378	100
2.67	74	94	**2.167**	198	93	**2.267**	403	97

2.68	400	95	**2.168**	253	110	**2.268**	15	100
2.69	490	93	**2.169**	101	110	**2.269**	28	100
2.70	340	86	**2.170**	38	110	**2.270**	18	90
2.71	500	97	**2.171**	460	100	**2.271**	66	92
2.72	400	89	**2.172**	31	100	**2.272**	372	97
2.73	340	80	**2.173**	473	93	**2.273**	11	91
2.74	150	93	**2.174**	9	95	**2.274**	51	94
2.75	430	95	**2.175**	252	110	**2.275**	282	92
2.76	300	100	**2.176**	2	110	**2.276**	39	100
2.77	56	100	**2.177**	126	110	**2.277**	230	96
2.78	127	99	**2.178**	168	110	**2.278**	34	95
2.79	207	100	**2.179**	2	110	**2.279**	117	100
2.80	133	110	**2.180**	452	110			
2.81	384	110	**2.181**	352	93			
2.82	164	110	**2.182**	69	100			
2.83	370	110	**2.183**	193	99			
2.84	302	98	**2.184**	116	100			
2.85	460	100	**2.185**	60	100			
2.86	42	120	**2.186**	56	100			
2.87	348	66	**2.187**	58	100			
2.88	164	97	**2.188**	29	99			
2.89	99	94	**2.189**	11	100			
2.90	495	88	**2.190**	10	98			
2.91	259	91	**2.191**	8	110			
2.92	252	110	**2.192**	346	85			
2.93	24	100	**2.193**	11	99			

2.94	45	99	**2.194**	3	99			
2.95	348	88	**2.195**	301	93			
2.96	226	100	**2.196**	2.9	100			
2.97	151	94	**2.197**	18	110			
2.98	281	70	**2.198**	23	91			
2.99	334	99	**2.199**	28	93			
2.100	307	91	**2.200**	130	110			

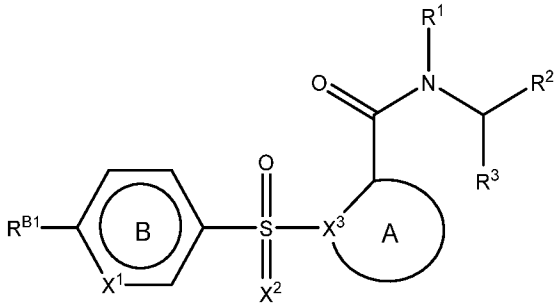
Table 3:

Ex. Number	**EC50 [nM]**	**Emax %**	**Ex. Number**	**EC50 [nM]**	**Emax %**	**Ex. Number**	**EC50 [nM]**	**Emax %**
3.1	44	100	**3.51**	46	110	**3.101**	173	92
3.2	18	100	**3.52**	163	100	**3.102**	90	96
3.3	37	98	**3.53**	163	100	**3.103**	115	99
3.4	25	110	**3.54**	12	100	**3.104**	40	96
3.5	140	94	**3.55**	16	95	**3.105**	45	97
3.6	177	91	**3.56**	62	94	**3.106**	50	110
3.7	180	98	**3.57**	83	100	**3.107**	29	120
3.8	58	97	**3.58**	220	100	**3.108**	79	93
3.9	47	95	**3.59**	26	100	**3.109**	99	110
3.10	11	97	**3.60**	75	100	**3.110**	224	110
3.11	468	100	**3.61**	210	91	**3.111**	220	110
3.12	66	120	**3.62**	460	99	**3.112**	245	91
3.13	34	110	**3.63**	15	98	**3.113**	11	110
3.14	464	110	**3.64**	262	96	**3.114**	86	93
3.15	24	120	**3.65**	292	110	**3.115**	346	88
3.16	25	110	**3.66**	33	97	**3.116**	25	110
3.17	58	98	**3.67**	192	110	**3.117**	117	100
3.18	11	120	**3.68**	146	96			
3.19	186	110	**3.69**	380	100	**3.119**	189	88
3.20	343	100	**3.70**	52	99	**3.120**	303	95

3.21	84	88	**3.71**	23	110	**3.121**	25	88
3.22	217	86	**3.72**	246	62	**3.122**	6	100
3.23	295	93	**3.73**	54	100	**3.123**	225	98
3.24	214	94	**3.74**	145	110	**3.124**	314	100
3.25	15	100	**3.75**	47	91	**3.125**	99	98
3.26	9	110	**3.76**	139	100	**3.126**	316	99
3.27	28	100	**3.77**	210	100	**3.127**	432	85
3.28	13	97	**3.78**	318	76	**3.128**	88	97
3.29	289	100	**3.79**	383	59	**3.129**	10	86
3.30	302	60	**3.80**	499	88			
3.31	174	97	**3.81**	447	90	**4.1**	107	100
3.32	16	100	**3.82**	118	84	**4.2**	155	90
3.33	28	83	**3.83**	395	91	**4.3**	130	93
3.34	8	89	**3.84**	349	88	**4.4**	8	97
3.35	21	89	**3.85**	401	56	**4.5**	12	110
3.36	189	83	**3.86**	23	100	**4.6**	14	97
3.37	26	99	**3.87**	92	94	**4.7**	18	99
3.38	351	100	**3.88**	124	78			
3.39	71	95	**3.89**	368	87			
3.40	370	100	**3.90**	218	98			
3.41	192	94	**3.91**	159	100			
3.42	212	100	**3.92**	22	98			
3.43	71	100	**3.93**	23	98			
3.44	101	92	**3.94**	20	100			
3.45	67	90	**3.95**	22	100			
3.46	30	100	**3.96**	13	95			
3.47	80	94	**3.97**	302	93			
3.48	30	110	**3.98**	15	110			
3.49	56	110	**3.99**	14	100			
3.50	72	89	**3.100**	57	92			

Claims

1. A compound of Formula (I)



Formula (I)

wherein

Ring B is a 6-membered aromatic ring, wherein:

- **X^1** represents N or C**R^{B2}**, wherein **R^{B2}** represents hydrogen, halogen, (C_{1-3})alkyl, or (C_{1-3})alkoxy; and
- **R^{B1}** represents independently hydrogen, (C_{1-4})alkyl, (C_{1-3})alkoxy, halogen, monocyclic (C_{3-4})cycloalkyl, or (C_1)fluoroalkyl;

X^2 represents O or N**R^4**, wherein **R^4** represents hydrogen, (C_{1-3})alkyl, monocyclic (C_{3-6})cycloalkyl or phenyl;

X^3 represents CH or N such that:

- when **X^3** represents CH, **Ring A** represents a monocyclic (C_{5-6})cycloalkan-diyl or a monocyclic 5- or 6-membered heterocycloalkan-diyl comprising one ring O atom; or
- when **X^3** represents N, **Ring A** represents:
  - a 4- to 6-membered saturated monocyclic heterocycloalkan-diyl comprising **X^3** and zero or one ring O atom; wherein said heterocycloalkan-diyl is unsubstituted, or mono- or di-substituted; wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl, halogen, (C_{1-3})alkoxy, hydroxy, and (C_{1-3})alkylidene;
  - a 4- to 6-membered mono-unsaturated monocyclic heterocycloalkan-diyl comprising **X^3** and zero or one additional ring N atom; wherein the double bond of said mono-unsaturated heterocycloalkan-diyl does not contain **X^3** or the carbon atom attached to the group –CO-N(**R^1**)CH(**R^2**)(**R^3**); wherein said mono-unsaturated heterocycloalkan-diyl is unsubstituted, or mono- or di-substituted; wherein the substituents are independently (C_{1-3})alkyl; or
  - a 6- to 8-membered saturated spiro, fused, or bridged bicyclic heterocycloalkan-diyl comprising **X^3**;

R^1 represents:

- 3-cyano-3,3-dimethylpropyl or 4-cyanobutyl;
- a saturated monocyclic (C_{4-6})cycloalkyl; wherein said (C_{4-6})cycloalkyl is unsubstituted, or mono- or di-substituted; wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl, halogen, (C_{1-3})fluoroalkyl, (C_{1-3})alkoxy, carbamoyl, hydroxy, and cyano;
- a mono-unsaturated monocyclic (C_{5-6})cycloalkyl; wherein the double bond of said mono-unsaturated (C_{5-6})cycloalkyl does not contain the carbon atom attached to the group -N(CO)CH(R^2)(R^3);
- a saturated bicyclic (C_{6-8})spirocycloalkyl; wherein said (C_{6-8})spirocycloalkyl is unsubstituted, or mono- or di-substituted; wherein the substituents are independently halogen;
- a saturated fused or bridged bicyclic (C_{6-8})cycloalkyl; wherein said (C_{6-8})cycloalkyl is unsubstituted, or mono- or di-substituted; wherein the substituents are independently selected from the group consisting of: halogen, cyano and carbamoyl; or
- a 5- or 6-membered saturated monocyclic heterocycloalkyl comprising one ring heteroatomic group selected from O, S, or SO_2; wherein said heterocycloalkyl is unsubstituted, or mono- or di-substituted; wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl, halogen, and (C_{1-3})fluoroalkyl;

R^2 represents hydrogen or methyl;

R^3 represents:

- an 8- to 10-membered partially aromatic fused bicyclic ring system comprising a total of zero to three ring heteroatoms independently selected from N, O, or S; wherein said 8- to 10-membered ring system is linked to the rest of the molecule at the aromatic ring moiety; wherein said 8- to 10-membered ring system is unsubstituted, or mono- or di-substituted, wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl, halogen and oxo;
- naphthyl or an 8- to 10-membered heteroaryl comprising a total of one to three ring heteroatoms independently selected from N, O, and S; wherein said 8- to 10-membered heteroaryl is unsubstituted, or mono- or di-substituted, wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl and halogen; or
- phenyl or 5- or 6-membered heteroaryl comprising one to three ring heteroatoms independently selected from N, O, and S; wherein said phenyl or 5- or 6-membered heteroaryl is independently unsubstituted, or mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting

of: (C_{1-3})alkyl, halogen, (C_{1-3})alkoxy, (C_{1-3})fluoroalkoxy, monocyclic (C_{3-6})cycloalkyl, (C_{1-3})alkylthio, (C_{1-3})fluoroalkyl, cyano, $\mathbf{NR^{N1}R^{N2}}$, wherein $\mathbf{R^{N1}}$ and $\mathbf{R^{N2}}$ independently represent hydrogen or (C_{1-4})alkyl;

or a pharmaceutically acceptable salt thereof;

with the exception of the following compounds:

- *N*-benzyl-*N*-(1,1-dioxidotetrahydrothiophen-3-yl)-1-tosylpyrrolidine-2-carboxamide;
- (R)-*N*-benzyl-*N*-((R)-1,1-dioxidotetrahydrothiophen-3-yl)-1-tosylpyrrolidine-2-carboxamide;
- (S)-*N*-benzyl-*N*-((R)-1,1-dioxidotetrahydrothiophen-3-yl)-1-tosylpyrrolidine-2-carboxamide;
- (S)-*N*-benzyl-*N*-((S)-1,1-dioxidotetrahydrothiophen-3-yl)-1-tosylpyrrolidine-2-carboxamide;
- (R)-*N*-benzyl-*N*-((S)-1,1-dioxidotetrahydrothiophen-3-yl)-1-tosylpyrrolidine-2-carboxamide;
- *N*-(1,1-dioxidotetrahydrothiophen-3-yl)-*N*-(furan-2-ylmethyl)-1-tosylpyrrolidine-2-carboxamide;
- (2R)-*N*-(1,1-dioxidotetrahydrothiophen-3-yl)-*N*-(furan-2-ylmethyl)-1-tosylpyrrolidine-2-carboxamide;
- (2S)-*N*-(1,1-dioxidotetrahydrothiophen-3-yl)-*N*-(furan-2-ylmethyl)-1-tosylpyrrolidine-2-carboxamide;
- (S)-*N*-((R)-1,1-dioxidotetrahydrothiophen-3-yl)-*N*-(furan-2-ylmethyl)-1-tosylpyrrolidine-2-carboxamide;
- (S)-*N*-((S)-1,1-dioxidotetrahydrothiophen-3-yl)-*N*-(furan-2-ylmethyl)-1-tosylpyrrolidine-2-carboxamide; and
- *N*-[(2-Methoxyphenyl)methyl]-1-[(4-methylphenyl)sulfonyl]-*N*-[(tetrahydro-2-thienyl)methyl]-2-pyrrolidinecarboxamide.

2. A compound of Formula (I) according to claim 1, wherein $\mathbf{R^{B1}}$ represents independently (C_{1-4})alkyl, (C_{1-3})alkoxy, halogen, monocyclic (C_{3-4})cycloalkyl, or (C_1)fluoroalkyl;

or a pharmaceutically acceptable salt thereof.

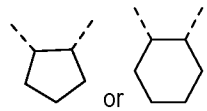
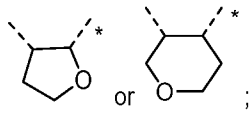
3. A compound of Formula (I) according to claim 1 or 2, wherein $\mathbf{X^3}$ represents CH or N such that:

- when $\mathbf{X^3}$ represents CH, **Ring A** represents a monocyclic (C_{5-6})cycloalkan-diyl or a monocyclic 5- or 6-membered heterocycloalkan-diyl comprising one ring O atom; or
- when $\mathbf{X^3}$ represents N, **Ring A** represents:
  - a 4- or 5-membered saturated monocyclic heterocycloalkan-diyl comprising $\mathbf{X^3}$ and zero ring O atoms; wherein said heterocycloalkan-diyl is unsubstituted, or mono- or di-substituted; wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl, halogen, (C_{1-3})alkoxy, hydroxy, and (C_{1-3})alkylidene;
  - an unsubstituted 5- or 6-membered saturated monocyclic heterocycloalkan-diyl comprising $\mathbf{X^3}$ and one ring O atom;

- a 5-membered mono-unsaturated monocyclic heterocycloalkan-diyl comprising **X³** and zero additional ring N atoms; wherein the double bond of said mono-unsaturated heterocycloalkan-diyl does not contain **X³** or the carbon atom attached to the group –CO-N(**R¹**)CH(**R²**)(**R³**);
- a 5-membered mono-unsaturated monocyclic heterocycloalkan-diyl comprising **X³** and one additional ring N atom; wherein the double bond of said mono-unsaturated heterocycloalkan-diyl does not contain **X³** or the carbon atom attached to the group –CO-N(**R¹**)CH(**R²**)(**R³**); wherein said heterocycloalkan-diyl is unsubstituted or mono-substituted with (C_{1-3})alkyl; or
- a 6- to 7-membered saturated spiro, fused, or bridged bicyclic heterocycloalkan-diyl comprising **X³**;

or a pharmaceutically acceptable salt thereof.

4. A compound of Formula (I) according to any one of claims 1 to 3, wherein **X³** represents CH and **Ring A** is:

-  ; or
-  ;

wherein the asterisks indicate the point of attachment of the substituent -C(=O)N**R¹**-CH_2(**R²**)(**R³**);

or a pharmaceutically acceptable salt thereof.

5. A compound of Formula (I) according to any one of claims 1 to 3, wherein **X³** represents N and **Ring A** represents:

- pyrrolidin-diyl; wherein said pyrrolidin-diyl is unsubstituted, or mono-substituted with (C_{1-3})alkyl, halogen, (C_{1-3})alkoxy, hydroxy, or (C_{1-3})alkylidene; or di-substituted with (C_{1-3})alkyl or halogen;
- oxazolidin-diyl;
- dihydro-1*H*-pyrrol-diyl; wherein the double bond of said dihydro-1*H*-pyrrol-diyl does not contain **X³** or the carbon atom attached to the group –CO-N(**R¹**)CH(**R²**)(**R³**); or
- a 6- to 7-membered saturated spiro, fused, or bridged bicyclic heterocycloalkan-diyl comprising **X³**;

or a pharmaceutically acceptable salt thereof.

6. A compound of Formula (I) according to any one of claims 1 to 5, wherein **R¹** represents:

- 3-cyano-3-methylbutyl;

- a saturated monocyclic (C_{5-6})cycloalkyl; wherein said (C_{5-6})cycloalkyl is mono- or di-substituted; wherein the substituents are independently selected from the group consisting of: methyl, fluoro, hydroxy, and cyano;
- cyclohex-3-en-1-yl;
- a saturated bicyclic (C_{6-8})spirocycloalkyl;
- a saturated fused or bridged bicyclic (C_{6-8})cycloalkyl; wherein said (C_{6-8})cycloalkyl is unsubstituted or di-substituted with fluoro; or
- tetrahydro-2*H*-thiopyran-1,1-dioxide
- or 1,1-dioxidotetrahydro-2*H*-thiopyran-3-yl;

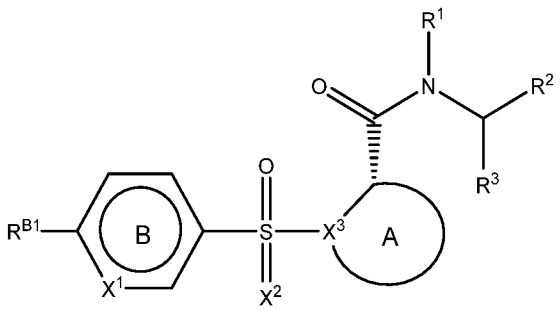
or a pharmaceutically acceptable salt thereof.

7. A compound of Formula (I) according to any one of claims 1 to 6, wherein **R^3** represents:

- a 9- or 10-membered partially aromatic fused bicyclic ring system comprising a total of zero to three ring heteroatoms independently selected from N, O, and S; wherein said 9- or 10-membered ring system is linked to the rest of the molecule at the aromatic ring moiety; wherein said 9- or 10-membered ring system is unsubstituted, or mono-substituted with halogen;
- a 9- or 10-membered heteroaryl comprising a total of one to three ring heteroatoms independently selected from N, O, and S ; wherein said 9- or 10-membered heteroaryl is unsubstituted, or mono- or di-substituted, wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl and halogen: or
- phenyl; wherein said phenyl is mono- or di-substituted, wherein the substituents are independently selected from the group consisting of: (C_{1-3})alkyl, halogen, (C_{1-3})alkoxy, and (C_{1-3})alkylthio;

or a pharmaceutically acceptable salt thereof.

8. A compound of Formula (I) according to any one of claims 1 to 7, which are also compounds of the Formula (IV):



Formula (IV);

or a pharmaceutically acceptable salt thereof.

9. A compound of Formula (I) according to claim 1, selected from the group consisting of:
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzo[b]thiophen-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzo[b]thiophen-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-6-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-6-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(1,1-dioxo-hexahydro-λ^6-thiopyran-4-yl)-amide;
(1R*,5S*)-(2RS)-N-(benzo[d]oxazol-6-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(1S,2S,5R)-N-(benzo[d]oxazol-6-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(1R,2S,5S)-N-(benzo[d]oxazol-6-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(2S,4S)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;
(2S,4S)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(2S,4S)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;
(2S,4S)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzo[b]thiophen-5-ylmethyl-(4-fluoro-cyclohexyl)-amide;
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzo[b]thiophen-5-ylmethyl-(4-hydroxy-cyclohexyl)-amide;
(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-6-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;

(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(2S)-N-(benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-(4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(1R,3S,4S)-2-(Toluene-4-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid benzothiazol-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;

(2S)-N-(benzofuran-6-ylmethyl)-N-(cyclohex-3-en-1-yl)-1-tosylpyrrolidine-2-carboxamide;

(1R,3S,4S)-2-(Toluene-4-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid benzooxazol-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;

(1R,3S,4S)-2-(Toluene-4-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid benzooxazol-6-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;

(1R,3S,4S)-2-(Toluene-4-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid benzofuran-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(1R,3S,4S)-2-(Toluene-4-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(1R,3S,4S)-2-(Toluene-4-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid benzooxazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(1R*,5S*)-(2RS)-N-(benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1S,2S,5R)-N-(benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-(benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(2S,4S)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(2S,4S)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-6-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;

(1R,3S,4S)-2-(Toluene-4-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid benzooxazol-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(2S)-N-(benzo[b]thiophen-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-tosylpyrrolidine-2-carboxamide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (2,3-dihydro-benzofuran-6-ylmethyl)-(4,4-dimethyl-cyclohexyl)-amide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (2,3-dihydro-benzofuran-6-ylmethyl)-(1,1-dioxo-hexahydro-1λ⁶-thiopyran-4-yl)-amide;
(1R*,5S*)-(2RS)-N-(benzofuran-6-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(1S,2S,5R)-N-(benzofuran-6-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(1R,2S,5S)-N-(benzofuran-6-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(1R,3S,4S)-2-(Toluene-4-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid benzofuran-6-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(4-hydroxy-cyclohexyl)-amide;
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzofuran-6-ylmethyl-(4-hydroxy-cyclohexyl)-amide;
(2S)-N-(benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-tosylpyrrolidine-2-carboxamide;
(2S)-N-(benzo[d]oxazol-6-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-tosylpyrrolidine-2-carboxamide;
(2S)-N-(benzo[d]oxazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-tosylpyrrolidine-2-carboxamide;
(2S)-N-(bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-1-tosylpyrrolidine-2-carboxamide;
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (2,3-dihydro-benzofuran-6-ylmethyl)-(4-hydroxy-cyclohexyl)-amide;
(1R*,5S*)-(2RS)-N-(benzo[d]oxazol-5-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(1S,2S,5R)-N-(benzo[d]oxazol-5-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(1R,2S,5S)-N-(benzo[d]oxazol-5-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(1R*,5S*)-(2RS)-N-(benzo[d]oxazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(1S,2S,5R)-(benzo[d]oxazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(1R,2S,5S)-(benzo[d]oxazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(1R*,5S*)-(2RS)-N-(benzo[d]thiazol-5-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(1S,2S,5R)-N-(benzo[d]thiazol-5-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-(benzo[d]thiazol-5-ylmethyl)-N-(4,4-dimethylcyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;

(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(4,4-dimethyl-cyclohexyl)-amide;

(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzooxazol-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (2,3-dihydro-benzofuran-6-ylmethyl)-(4,4-dimethyl-cyclohexyl)-amide;

(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(2S)-N-(benzofuran-6-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-tosylpyrrolidine-2-carboxamide;

(2S,4S)-4-Fluoro-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(S)-N-(4,4-Difluorocyclohexyl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-1-tosylpyrrolidine-2-carboxamide;

(2S,4S)-N-(benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-4-fluoro-1-tosylpyrrolidine-2-carboxamide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(5-fluoro-2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(1R,3S,5R)-2-(Toluene-4-sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(2S,4S)-N-(benzo[d]oxazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-4-fluoro-1-tosylpyrrolidine-2-carboxamide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-fluoro-2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(2S)-N-(benzo[d]oxazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-((4-methoxyphenyl)sulfonyl)pyrrolidine-2-carboxamide;

(2S)-N-(benzo[d]oxazol-6-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-((4-methoxyphenyl)sulfonyl)pyrrolidine-2-carboxamide;

(2S)-N-(benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-((4-methoxyphenyl)sulfonyl)pyrrolidine-2-carboxamide;

(2S)-N-(bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-1-((4-methoxyphenyl)sulfonyl)pyrrolidine-2-carboxamide;

(S)-4-Methylene-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(S)-N-(benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((R)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(S)-N-(benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((S)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(2S,4S)-4-Fluoro-1-(4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (1R,3R,6R)-bicyclo[4.1.0]hept-3-yl-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(S)-N-(benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(S)-N-(4,4-difluorocyclohexyl)-N-(furo[3,2-c]pyridin-6-ylmethyl)-1-tosylpyrrolidine-2-carboxamide;

(1R,3S,5R)-2-(4-Methoxy-benzenesulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(1R*,5S*)-(2RS)-3-(4-Methoxy-benzenesulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(1S,2S,5R)-3-(4-Methoxy-benzenesulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(1R,2S,5S)-3-(4-Methoxy-benzenesulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(1R,3S,5R)-2-(4-Methoxy-benzenesulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(1R,3S,5R)-N-(benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-2-tosyl-2-azabicyclo[3.1.0]hexane-3-carboxamide;

(1R,3S,5R)-N-(benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-2-((4-methoxyphenyl)sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxamide;

(1R,3S,5R)-N-(bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-2-tosyl-2-azabicyclo[3.1.0]hexane-3-carboxamide;

(1R,3S,5R)-N-(bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-2-((4-methoxyphenyl)sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxamide;

(1R,3S,5R)-2-(4-Methoxy-benzenesulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid benzooxazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(1S,2S,5R)-N-(benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,3S,5R)-2-(Toluene-4-sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(1R,2S,5S)-3-(Toluene-4-sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;
(1S,2S,5R)-3-(Toluene-4-sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;
(1R,2S,5S)-N-(bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(1S,2S,5R)-N-(bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(S)-N-(benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((S)-4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide ;
(S)-N-(benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((R)-4-methoxyphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(1R*,5S*)-(2RS)-3-(4-Methoxy-benzenesulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;
(1S,2S,5R)-3-(4-Methoxy-benzenesulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;
(1R,2S,5S)-3-(4-Methoxy-benzenesulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;
(1R*,5S*)-(2RS)-N-(benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-3-((4-methoxyphenyl)sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(1S,2S,5R)-N-(benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-3-((4-methoxyphenyl)sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(1R,2S,5S)-N-(benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-3-((4-methoxyphenyl)sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(1R*,5S*)-(2RS)-N-(bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-3-((4-methoxyphenyl)sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(1S,2S,5R)-N-(bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-3-((4-methoxyphenyl)sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(1R,2S,5S)-N-(bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-3-((4-methoxyphenyl)sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(2S)-N-(benzofuran-6-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-(N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(1R,3S,5R)-2-(Toluene-4-sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (4,4-difluoro-cyclohexyl)-(4-fluoro-2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(1R,3S,5R)-2-(Toluene-4-sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (4,4-difluoro-cyclohexyl)-(5-fluoro-2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(S)-1-(3-Fluoro-4-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(S)-1-(3-Fluoro-4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(S)-1-(4-Chloro-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(S)-1-(4-Cyclopropyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(2S,5R)-5-Methyl-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(2S)-N-(4,4-difluorocyclohexyl)-N-(1-(2,3-dihydrobenzofuran-6-yl)ethyl)-1-tosylpyrrolidine-2-carboxamide;

(S)-1-(Toluene-4-sulfonyl)-2,3-dihydro-1H-pyrrole-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(1R,3S,4S)-N-(bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-2-((6-methylpyridin-3-yl)sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxamide;

(1R,3S,4S)-2-(6-Methyl-pyridine-3-sulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid (4,4-difluoro-cyclohexyl)-(2,3-dihydro-benzofuran-6-ylmethyl)-amide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzo[1,3]dioxol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(2S)-N-(benzo[d][1,3]dioxol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-1-tosylpyrrolidine-2-carboxamide;

(2S)-N-(benzofuran-6-ylmethyl)-1-(N-cyclopropyl-4-methylphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide;

(2S)-N-(benzofuran-6-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-(3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(2S)-N-(4,4-difluorocyclohexyl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-1-(3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(2S)-N-(benzo[d][1,3]dioxol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(2S)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-(methylthio)benzyl)pyrrolidine-2-carboxamide;

(2S)-N-(benzofuran-6-ylmethyl)-1-(N-cyclopropyl-3-fluoro-4-methylphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide;
(2S)-1-(N-cyclopropyl-3-fluoro-4-methylphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)pyrrolidine-2-carboxamide;
(2S)-N-(benzo[d]thiazol-5-ylmethyl)-1-(N-cyclopropyl-3-fluoro-4-methylphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide;
(1R*,2S*)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(2S)-N-(benzofuran-6-ylmethyl)-1-(N-cyclopropyl-4-methoxyphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide;
(2S)-N-(4-chlorobenzyl)-1-(N-cyclopropyl-4-methylphenylsulfonimidoyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(1R*,2S*)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzo[1,3]dioxol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(1R*,2S*)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzooxazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(2S)-N-(4-chlorobenzyl)-N-(4,4-dimethylcyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(2S)-N-(4-chlorobenzyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-((4-ethynyl-2-hydroxycyclopentyl)pyrrolidine-2-carboxamide;
(2S)-N-(4-chlorobenzyl)-N-(1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide;
(2S)-N-(1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzooxazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(2S)-N-((3S,5R)-1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide;
(2S)-N-(4-chlorobenzyl)-N-((3S,5R)-1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(2S)-N-(4-chlorobenzyl)-N-(1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(2S)-N-(4-chlorobenzyl)-N-((3S,6R)-1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(1S,2R)-N-(bicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydrobenzofuran-6-yl)methyl)-2-tosylcyclopentane-1-carboxamide;
(1S,2R)-N-(benzo[d][1,3]dioxol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-2-tosylcyclopentane-1-carboxamide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzo[1,3]dioxol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide;
(2S)-N-(4-chloro-2-fluorobenzyl)-N-(1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(2S)-N-(1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide;
(2S)-N-(4-chloro-2-fluorobenzyl)-N-(1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(2S)-N-(4-Chlorobenzyl)-N-((1R*,3S*)-3-cyanocyclopentyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(2S)-N-(4-Chloro-2-fluorobenzyl)-N-((3S,5r)-1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(2S)-N-(4-Chloro-2-fluorobenzyl)-N-((3S,6r)-1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(2S)-N-((3S,6r)-1,1-Difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide;
(1S,2R)-N-(4-chlorobenzyl)-N-((1S*,3R*)-3-cyanocyclopentyl)-2-tosylcyclopentane-1-carboxamide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (1,1-difluoro-spiro[2.5]oct-6-yl)-(4-methoxy-benzyl)-amide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(4-cyano-cyclohexyl)-amide;
(2S)-N-(4-Chlorobenzyl)-N-((1R*,3R*)-3-cyanocyclopentyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(2S,4S)-N-(4-chlorobenzyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-4-methylpyrrolidine-2-carboxamide;
(2S,4S)-N-(4-chlorobenzyl)-N-(1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-4-methylpyrrolidine-2-carboxamide;

(2S,4S)-N-(4-chlorobenzyl)-N-(4,4-difluorocyclohexyl)-1-(N,4-dimethylphenylsulfonimidoyl)-4-methylpyrrolidine-2-carboxamide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzooxazol-5-ylmethyl-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (1,1-difluoro-spiro[2.5]oct-6-yl)-(4-methyl-benzyl)-amide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (1,1-difluoro-spiro[2.5]oct-6-yl)-(4-methylsulfanyl-benzyl)-amide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-2-fluoro-benzyl)-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzo[1,3]dioxol-5-ylmethyl-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(2-fluoro-4-methyl-benzyl)-amide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-2-fluoro-benzyl)-(4-cyano-cyclohexyl)-amide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(2,4-difluoro-benzyl)-amide;
(1S,2R)-N-(4-Cyanocyclohexyl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-2-tosylcyclopentane-1-carboxamide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(4-methylsulfanyl-benzyl)-amide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(4-methyl-benzyl)-amide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-bromo-benzyl)-(4-cyano-cyclohexyl)-amide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-cyano-cyclohexyl)-(4-fluoro-benzyl)-amide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-(3-cyano-3,3-dimethyl-propyl)-amide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (7,7-difluoro-bicyclo[4.1.0]hept-3-yl)-(4-methyl-benzyl)-amide;
(2S,4S)-N-(4-chlorobenzyl)-N-(1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-4-fluoropyrrolidine-2-carboxamide;
(2S,4S)-N-(4-chloro-2-fluorobenzyl)-N-(1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-4-methylpyrrolidine-2-carboxamide;
(S)-N-((1R*,3S*)-3-cyanocyclopentyl)-N-(4-methylbenzyl)-1-tosylpyrrolidine-2-carboxamide;
(S)-N-(4-chlorobenzyl)-N-((1R*,3S*)-3-cyanocyclopentyl)-1-tosylpyrrolidine-2-carboxamide;
(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid ((1S*,3R*)-3-cyano-cyclopentyl)-(4-methyl-benzyl)-amide;

(2S,4S)-N-(4-Chlorobenzyl)-N-((3R,5s)-1,1-difluorospiro[2.3]hexan-5-yl)-1-(R)-(N,4-dimethylphenylsulfonimidoyl)-4-methylpyrrolidine-2-carboxamide;

(2RS)-N-((1R*,3S*)-3-Cyanocyclopentyl)-N-(4-methylbenzyl)-3-tosyloxazolidine-2-carboxamide;

(2RS)-N-((1R*,3S*)-3-Cyanocyclopentyl)-N-(4-chlorobenzyl)-3-tosyloxazolidine-2-carboxamide;

(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (3-cyano-3,3-dimethyl-propyl)-(4-methyl-benzyl)-amide;

(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (3-cyano-3,3-dimethyl-propyl)-indan-5-ylmethyl-amide;

(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-2-fluoro-benzyl)-(3-cyano-3,3-dimethyl-propyl)-amide;

(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-bromo-benzyl)-(3-cyano-3,3-dimethyl-propyl)-amide;

(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid ((1R*,3R*)-3-cyano-cyclohexyl)-(4-methyl-benzyl)-amide;

(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4-chloro-benzyl)-((1R,3S)-3-cyano-cyclopentyl)-amide;

(1S,2R)-N-((1R*,3S*)-3-Cyanocyclopentyl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-2-tosylcyclopentane-1-carboxamide;

(1S,2R)-N-(7,7-Difluorobicyclo[4.1.0]heptan-3-yl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-2-tosylcyclopentane-1-carboxamide;

(1S,2R)-N-((1R*,3R*)-3-Cyanocyclohexyl)-N-((2,3-dihydro-1H-inden-5-yl)methyl)-2-tosylcyclopentane-1-carboxamide;

(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid ((1R*,3S*)-3-cyano-cyclopentyl)-(3-fluoro-4-methyl-benzyl)-amide;

(2S,4S)-N-(4-chloro-2-fluorobenzyl)-N-(1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-4-fluoropyrrolidine-2-carboxamide;

(2S,4S)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-4-methyl-N-(4-methylbenzyl) pyrrolidine-2-carboxamide;

(1S,2R)-N-((1r,4S)-4-cyanocyclohexyl)-N-(4-(methyl-d3)benzyl)-2-tosylcyclopentane-1-carboxamide;

(1S,2R)-N-(4-Chloro-2-fluorobenzyl)-N-((1R*,3S*)-3-cyanocyclopentyl)-2-tosylcyclopentane-1-carboxamide;

(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid benzooxazol-6-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(1S,2R)-2-(Toluene-4-sulfonyl)-cyclopentanecarboxylic acid (4,4-difluoro-cyclohexyl)-(6-fluoro-benzooxazol-5-ylmethyl)-amide;

(1S,2R)-N-(4-chlorobenzyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-2-((R)-4-methylphenylsulfonimidoyl) cyclopentane-1-carboxamide;
(1S,2R)-N-(4-chlorobenzyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-2-((S)-4-methylphenylsulfonimidoyl) cyclopentane-1-carboxamide;
(2S)-N-(4-chlorobenzyl)-N-((1R)-3-cyano-3-methylcyclopentyl)-1-tosylpyrrolidine-2-carboxamide;
(1S,2R)-N-(4-chlorobenzyl)-N-((1R,3S)-3-cyanocyclopentyl)-2-((R)-4-methylphenylsulfonimidoyl)cyclopentane-1-carboxamide;
(1S,2R)-N-(4-chlorobenzyl)-N-((1R,3S)-3-cyanocyclopentyl)-2-((S)-4-methylphenylsulfonimidoyl)cyclopentane-1-carboxamide;
(1S,2R)-N-(4-chlorobenzyl)-N-((1R)-3-cyano-3-methylcyclopentyl)-2-tosylcyclopentane-1-carboxamide;
(S)-N-((3R,5s)-1,1-difluorospiro[2.3]hexan-5-yl)-N-(4-methylbenzyl)-1-((S)-4-methylphenylsulfonimidoyl) pyrrolidine-2-carboxamide;
(S)-N-((3S,5r)-1,1-difluorospiro[2.3]hexan-5-yl)-N-(4-methylbenzyl)-1-((S)-4-methylphenylsulfonimidoyl) pyrrolidine-2-carboxamide;
(S)-N-((1S*,3R*)-3-Cyanocyclopentyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide;
(S)-N-((1S*,3S*)-3-Cyanocyclopentyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide;
(S)-N-(4-chlorobenzyl)-N-((1R,3S)-3-cyanocyclopentyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(S)-N-((1R,3S)-3-cyanocyclopentyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)-N-(4-methylbenzyl)pyrrolidine-2-carboxamide;
(S)-1-(3-Fluoro-4-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(S)-N-(benzo[d]thiazol-5-ylmethyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-1-tosylpyrrolidine-2-carboxamide;
(S)-N-(benzo[d]thiazol-5-ylmethyl)-N-((3R,5s)-1,1-difluorospiro[2.3]hexan-5-yl)-1-tosylpyrrolidine-2-carboxamide;
(S)-N-(benzo[d]thiazol-5-ylmethyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-1-((3-fluoro-4-methylphenyl)sulfonyl)pyrrolidine-2-carboxamide;
(S)-N-(benzo[d]thiazol-5-ylmethyl)-N-((3R,5s)-1,1-difluorospiro[2.3]hexan-5-yl)-1-((3-fluoro-4-methylphenyl)sulfonyl)pyrrolidine-2-carboxamide;
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2-methyl-benzothiazol-5-ylmethyl)-amide;
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (2-chloro-benzothiazol-5-ylmethyl)-(4,4-difluoro-cyclohexyl)-amide;

(S)-1-(3-Fluoro-4-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (2-chloro-benzothiazol-5-ylmethyl)-(4,4-difluoro-cyclohexyl)-amide;

(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (2-chloro-benzothiazol-5-ylmethyl)-(4,4-difluoro-cyclohexyl)-amide;

(S)-N-(benzo[d]thiazol-5-ylmethyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-1-((4-methoxyphenyl)sulfonyl)pyrrolidine-2-carboxamide;

(S)-N-(benzo[d]thiazol-5-ylmethyl)-N-((3R,5s)-1,1-difluorospiro[2.3]hexan-5-yl)-1-((4-methoxyphenyl)sulfonyl)pyrrolidine-2-carboxamide;

(1R,2S,5S)-N-(benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((R)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3R,5s)-1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(S)-1-(3-Fluoro-4-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(1S,3S,6S)-bicyclo[4.1.0]hept-3-yl-amide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(1S,3S,6S)-bicyclo[4.1.0]hept-3-yl-amide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(1S,3R,6S)-bicyclo[4.1.0]hept-3-yl-amide;

(S)-1-(4-Methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(1S,3S,6S)-bicyclo[4.1.0]hept-3-yl-amide;

(S)-1-(4-Iodo-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide;

(S)-1-(3-Fluoro-4-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide;

(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3R,5s)-1,1-difluorospiro[2.3]hexan-5-yl)-1-((R)-3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-1-((R)-4-methoxy-N-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(S)-1-(4-Ethyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(4,4-difluoro-cyclohexyl)-amide;
(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((1S,3S,6S)-bicyclo[4.1.0]heptan-3-yl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((1S,3S,6S)-bicyclo[4.1.0]heptan-3-yl)-1-((R)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((1S,3S,6S)-bicyclo[4.1.0]heptan-3-yl)-1-((R)-3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-((1S,3S,6S)-bicyclo[4.1.0]heptan-3-yl)-1-((R)-4-methoxy-N-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(1R*,2S*,5S*)-3-(Toluene-4-sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid benzothiazol-5-ylmethyl-(1,1-difluoro-spiro[2.5]oct-6-yl)-amide;
(1R*,2S*,5S*)-3-(Toluene-4-sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid benzothiazol-5-ylmethyl-(1,1-difluoro-spiro[2.3]hex-5-yl)-amide;
(1R*,2S*,5S*)-3-(Toluene-4-sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (4,4-difluoro-cyclohexyl)-(2-methyl-benzothiazol-5-ylmethyl)-amide;
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (2-bromo-benzothiazol-5-ylmethyl)-(4,4-difluoro-cyclohexyl)-amide;
(S)-1-(3-Fluoro-4-methyl-benzenesulfonyl)-pyrrolidine-2-carboxylic acid (2-bromo-benzothiazol-5-ylmethyl)-(4,4-difluoro-cyclohexyl)-amide;
(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(3-methoxy-cyclohexyl)-amide;
(S)-1-(3-Fluoro-4-methoxy-benzenesulfonyl)-pyrrolidine-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;
(S)-N-((2-Chlorobenzo[d]thiazol-5-yl)methyl)-N-(4,4-difluorocyclohexyl)-1-((R)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(S)-N-((2-Bromobenzo[d]thiazol-5-yl)methyl)-N-(4,4-difluorocyclohexyl)-1-((R)-4-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(S)-N-((2-Chlorobenzo[d]thiazol-5-yl)methyl)-N-(4,4-difluorocyclohexyl)-1-((R)-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(S)-N-((2-Chlorobenzo[d]thiazol-5-yl)methyl)-N-(4,4-difluorocyclohexyl)-1-((R)-3-fluoro-N,4-dimethylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;
(S)-N-((2-Chlorobenzo[d]thiazol-5-yl)methyl)-N-(4,4-difluorocyclohexyl)-1-((R)-4-methoxy-N-methylphenylsulfonimidoyl)pyrrolidine-2-carboxamide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(6-methyl-1,1-dioxo-hexahydro-1λ⁶-thiopyran-3-yl)-amide;

(S)-1-(Toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid (4-chloro-benzyl)-(1,1-dioxo-hexahydro-1λ⁶-thiopyran-3-yl)-amide;

(1S*,2S*,5R*)-3-(Toluene-4-sulfonyl)-3-azabicyclo[3.2.0]heptane-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(1R*,2S*,5S*)-3-(Toluene-4-sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid benzothiazol-5-ylmethyl-(4,4-difluoro-cyclohexyl)-amide;

(1R*,2S*,5S*)-N-Benzo[d]thiazol-5-ylmethyl)-N-(bicyclo[4.1.0]heptan-3-yl)-3-tosyl-3-azabicyclo[3.1.0]hexane-2-carboxamide; and

(1R,2S,5S)-N-(Benzo[d]thiazol-5-ylmethyl)-N-(4,4-difluorocyclohexyl)-3-((R)-N,4-dimethylphenylsulfonimidoyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide;

or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising, as active principle, one or more compounds according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.

11. A compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, for use as a medicament.

12. A compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, for use in improving wakefulness.

13. A compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof:

- for use in the treatment of hypersomnia including narcolepsy, narcolepsy associated with inherited disorders; narcolepsy associated with tumors, narcolepsy associated with head trauma, idiopathic hypersomnia, or Kleine-Levin syndrome;
- for use in improving symptoms of excessive daytime sleepiness (EDS) including:
  - improving symptoms of EDS in subjects having a circadian rhythm sleep-wake disorder;
  - improving symptoms of EDS due to or associated with a medical disorder, wherein said medical disorder is especially an objective sleep disturbance, obesity, diabetes, a neurodegenerative disorder, an auto-immune disorder, a psychiatric disorder, or insufficient sleep syndrome;
  - improving symptoms of EDS due to a medication or substance;
- for use in the treatment of fatigue; or
- for use in the treatment of eating disorders, obesity, neuropsychiatric disorders, pain, inflammation, or cognitive impairments associated with diminished wakefulness.

14. Use of a compound of Formula (I) as defined in any one of claims 1 to 9, or of a pharmaceutically acceptable salt thereof, in the preparation of a medicament for improving wakefulness.

15. A method for improving wakefulness comprising administering to a subject in need thereof an effective amount of a compound of Formula (I) as defined in any one of claims 1 to 9, or of a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2023/085388

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D207/48 C07D277/64 C07D405/12 C07D409/12 C07D413/12
C07D417/12 A61P1/00 A61P25/00 A61K31/4025

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)

A61P 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 practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 4 067 344 A1 (SUMITOMO PHARMA CO LTD [JP]) 5 October 2022 (2022-10-05) paragraph [0493] - paragraph [0497]; claim 1; examples 1-161	1-15
A	EP 3 816 153 A1 (TAKEDA PHARMACEUTICALS CO [JP]) 5 May 2021 (2021-05-05) paragraph [0312] - paragraph [0318]; claim 1; examples 1-46; table 2	1-15
A	WO 2022/207935 A1 (OREXIA THERAPEUTICS LTD [GB]) 6 October 2022 (2022-10-06) paragraph [0002]; claim 1; examples 1-21; table 1	1-15

☐ 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

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"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	Date of mailing of the international search report
6 June 2024	17/06/2024

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

Information on patent family members

International application No
PCT/EP2023/085388

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