

Macrocyclic Orexin Agonists

The present invention relates to novel aryl thiol macrocycles 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 OX₂R), and particularly as agonists of the human orexin-2 receptor (hereinafter also referred to as hOX₂R).

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 (OX₁R) and orexin-2 receptor (OX₂R)) widely expressed throughout the brain. While OX-A binds to both receptors with similar affinity, OX-B binds preferentially to OX₂R. 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, serotonergic neurons of the dorsal raphe, dopaminergic neurons in the ventral tegmental area and cholinergic neurons in the basal forebrain and the pedunculo pontine and laterodorsal tegmental nuclei. Different wake-promoting regions of the brain predominantly express OX₁R or OX₂R, 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 the 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 (Minneapolis, 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 reverse 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).

5 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).

10 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.

15 Narcolepsy is supposed to be the result of an autoimmune disorder which specifically destroys orexin-producing neurons. However, symptoms of narcolepsy (or secondary narcolepsy) can occur during the course of other neurologic disorders and can 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 hypothalamic 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.

25 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 diseases and is suggested to contribute to EDS and sleep disturbances. Such neurodegenerative diseases include 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), amyotrophic lateral sclerosis (Gabery S et al., Loss of metabolism and sleep regulating neuronal populations expressing orexin and oxytocin in the hypothalamus in amyotrophic lateral sclerosis; *Neuropathol Appl Neurobiol*. 2021, 47(7):979-89), 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 especially the case when the patient needs to be awake but his alertness level, secondary to his 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). Particularly for obstructive sleep apnea (OSA) the dysregulation of the orexin system could play a role in its pathogenesis (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 compared to wild-type mice (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 physical or mental exhaustion") with a reduced ability to initiate or perform physical activities that would have previously been easily accomplished, and is accompanied by mental fatigue with poor concentration and memory. Fatigue is not significantly improved by increased rest or sleep and is generally associated with inappropriate episodes of sleep during the day. It is observed in a number of disorders including infections, chronic inflammatory diseases (Arron HE et al.; Myalgic encephalomyelitis/chronic fatigue syndrome: the biology of a neglected disease; *Frontiers*

- immunology. 2024, 15: 1386607), autoimmune diseases (Manjaly Z-M et al.; Pathophysiological and cognitive mechanisms of fatigue in multiple sclerosis; J Neurol Neurosurg Psychiatry. 2019, 90:642-51; Ahn GE et al.; Fatigue in systemic lupus erythematosus; Int J Clin Rheumatol. 2012, 7(2): 217-27), cancer and chemotherapy (Bower JE & Lamkin DM; Inflammation and cancer-related fatigue: Mechanisms, contribution factors, and treatment implications; Brain Beh Immunity. 2013, 30:S48-57), and neurodegenerative and neurological diseases (Kluger BM et al.; Fatigue and fatigability in neurologic illnesses; Neurology. 2013, 80:409-16). Persistent physical and mental fatigue is a prominent symptom of myalgic encephalomyelitis/chronic fatigue syndrome (Arron HE et al.; Myalgic encephalomyelitis/chronic fatigue syndrome: the biology of a neglected disease; Frontiers Immunology. 2024, 15: 1386607). Dysregulation of the orexin system could contribute to fatigue. In rodents, fatigue (or sickness behavior
- 10 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; Gaykema RPA & Goehler LE; Lipopolysaccharide challenge-induced suppression of Fos in hypothalamic orexin neurons: Their potential role in sickness behavior; Brain Beh. Immunity. 2009, 23:926-30). Intracerebroventricular administration of OX-A in lipopolysaccharide-treated rats
- 15 restored normal home-cage exploratory behavior. Similar findings were retrieved in tumor-bearing rats and chemotherapy-treated mice (Weymann KB et al.; A role of orexin in cytotoxic chemotherapy-induced fatigue; Brain Beh. Immun. 2014, 37:84-94) 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
- 20 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).
- These findings suggest that a dysfunction of the orexin system could contribute to fatigue and that an orexin
- 25 receptor agonist could help chronically ill patients with fatigue and 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
- 30 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 serotonergic, noradrenergic, dopaminergic, cholinergic and glutamatergic neurons) with nonspecific thalamic nuclei, the basal forebrain, hypothalamus, and the cerebral cortex. Impairment of the
- 35 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 the orexin system's projections to the wake-promoting areas of the brain and its contribution to the stabilization of wakefulness/arousal, it is well placed to support and regulate consciousness.

- 5 Interestingly, in patients with acute moderate and severe TBI, an 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). Predclinically, in a mouse model of TBI, electromagnetically controlled cortical impact depressed orexin levels in both the hypothalamus and hippocampus, and the diurnal fluctuation amplitudes of orexins were blunted (Willie JT et al.; *Controlled cortical impact traumatic brain injury acutely disrupts wakefulness and extracellular*
 10 *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 righting reflex loss, shortened the coma time, and decreased the delta signal of EEG
 15 (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*
 20 *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*
 25 *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 OX2/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
 30 effects. In rodent models of cerebral ischemia Ox-A reduced the neuronal damage and improved neuronal deficits (Harada S et al.; *Effect of orexin-A on post-ischemic glucose intolerance and neuronal damage; J. Pharmacol. Sci.* 2011, 115:155-63; Yuan LB et al.; *Neuroprotective effect of orexin-A is mediated by an increase of hypoxia-inducible factor-1 activity in rat; Anesthesiology.* 2011, 114: 340-54). In patients with subarachnoid hemorrhage OX-A levels are higher in patients who do not develop delayed ischemic neuronal deficit (Dohi K et al.; *CSF hypocretin-1/orexin-A concentrations in patients with subarachnoid hemorrhage (SAH); Peptides.* 2005, 26:2339-43).

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.

- 10 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).
- 15 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,
- 20 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). Reduced Ox-A was also reported in patients of anorexia nervosa (Steward T et al., Reduced Plasma Orexin-A Concentrations are Associated with Cognitive Deficits in Anorexia Nervosa; *Sci Rep.* 2019, 9(1): 3377-91).
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- 30 Altogether it suggests that an orexin receptor agonist could be an interesting therapeutic option for the treatment of disease associated with 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

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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-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. Serum OX-A levels are lower in children with attention deficit hyperactivity disorder, especially in the inattentive group (Baykal s et al., Decreased serum orexin A levels in drug-naive children with attention deficit and hyperactivity disorder; *Neurol Sci.* 2019, 40(3): 593-602). Additionally, ADD symptoms are more frequent in children and adults with narcolepsy (Miano S et al., The sleep phenotypes of attention deficit hyperactivity disorder: the role of arousal during sleep and implications for treatment; *Med Hypotheses.* 2012; 79(2): 147-53).

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 OX₂R 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 OX₂R 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 and schizophrenia, 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 (Liang S et al., anhedonia in depression and schizophrenia: Brain reward and aversion circuits; Neuropsychiatric Disease and Treatments. 2022, 18:1385-96). 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).

Similarly, studies in animals and humans suggest that abnormal orexin function could contribute to the pathogenesis of post-traumatic stress disorder (PTSD). In rat models of PTSD, decreased activation of orexin neurons during the stressful event predicted the development of PTSD-like symptoms. Activating the orexin system after the stressful event prevented or alleviated PTSD-like symptoms while blocking Hcrt receptors after the stressful event exacerbated PTSD-like symptoms (Cohen S et al., Significance of the orexinergic system in modulating stress-related responses in an animal model of post-traumatic stress disorder; Transl Psychiatry. 2016,

- 6(10): e917; Han D et al., Mechanisms of Memory Impairment Induced by Orexin-A via Orexin 1 and Orexin 2 Receptors in Post-traumatic Stress Disorder Rats; *Neurosci.* 2020, 432:126-36). In humans, decreased plasma and CSF concentration of OX-A has been reported in individuals with combat-related PTSD compared to healthy controls (Strawn JR et al., Low cerebrospinal fluid and plasma orexin-A (hypocretin-1) concentrations in combat-related posttraumatic stress disorder; *Psychoneuroendocrinology.* 2010, 35(7): 1001-7).
- 5 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
- 10 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).
- 15 Overall, it suggests that orexin receptor agonists could have beneficial effect in the therapeutic approach against pain.
- 25 In addition, orexin receptor agonists could be a promising treatment option for daytime function deficits in disorders associated with symptoms of EDS, fatigue, reduced vigilance, attention, motivation or hedonic drive, altered stress regulation or emotions, and pain, with concomitant use of an orexin receptor antagonists at bedtime for the treatment of accompanying sleep disturbances such as in psychiatric disorders (depression, schizophrenia, PTSD, anxiety (Freeman D et al.; Sleep disturbances and psychiatric disorders; *Lancet Psychiatry.* 2020, 7:628-37)), neurodegenerative disorders (Alzheimer's disorder, Dementia with Lewy bodies, Huntington's disease, Parkinson's disease (Fifel K & Videnovic A; Circadian and sleep dysfunctions in neurodegenerative disorder - An update; *Front Neurosci.* 2021, 14:627330; Anghel L et al.; Sleep disorders associated with neurodegenerative diseases; *Diagnostic.* 2023, 13:2898), circadian rhythm sleep wake disorders (Kim MJ et al., Circadian rhythm sleep disorder; *J Clin Outcomes Manag.* 2013, 20(11): 513-28), sleep related breathing disorders (Liu J et al., Pharmacological interventions for the treatment of obstructive sleep apnea syndrome; *Front Med.* 2024,
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11:1359461), and pain (Bigatti SM et al., Sleep disturbances in fibromyalgia syndrome: relationship to pain and depression; *Arthritis Rheum.* 2008, 59(7):961-67):

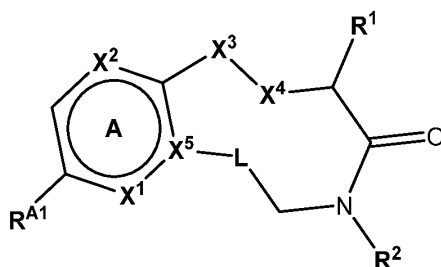
Orexin receptor antagonists are well documented, such as, for example, in WO 2010/131192.

- US 2014/0051700 discloses cyclic guanidinyloxymethyl 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 as 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. WO 2020/167706 discloses 5-alkyl pyrrolidine orexin receptor agonists.
- Macrocyclic orexin receptor agonists are reported in WO 2021/108628, WO 2022/051583, WO 2022/094012, WO 2022/109117, WO 2022/140316, WO 2022/140317, 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 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, WO 2023/017180, WO 2023/167865, WO 2023/167925, WO 2023/199091, WO2023/204308, and WO 2023/232966.
- 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 oxytocin receptors are described in US 5,338,755, US 5,397,801, US 5,481,005, EP 0 469 984, and WO 1993/003013. Synthesis of acyl hydrazides has been described in Singh et al. (*Asian J. Org. Chem.*, 2023, 12(6), 135-140, doi.org/10.1002/ajoc.202300115). Selected pyrrole sulfone derivatives are described as reverse transcriptase inhibitors (Silvestri R. et al., *Il Farmaco*, 2004, 59, 201-210; WO 1996/033171; WO 2008/054605) and indole sulfones as modulators G-protein coupled 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 2010/141805; 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 2010/141805; WO 2013/108857 (US 2014/0329796; EP2805718); WO 2014/098098; WO 2015/052264; WO 2016/128529; WO 2018/015411), 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, WO 98/003503), or as binding VLA-4 (US 6,583,139 B1; WO 98/053814; WO 99/064395). 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 WO 2002/062222/US 2002/049243. Sulfone-comprising pyrrolidin-2-one derivatives are disclosed as inhibitors of Factor XA in WO 2002/100886. Thiazolidine and piperazine carboxamide derivatives are disclosed as modulators of the prostaglandin F receptor in WO 2003/082278 and WO 2004/071390. Piperazine carboxamide derivatives are further disclosed as NS5B enzyme inhibitors in Gentles et al. (Bioorganic Med. Chem. Letters, 2011, 21, 3142-3147). Thiazolidine derivatives are further disclosed as steroid sparring agents in WO 2005/097162. Diazobicyclic sulfone derivatives as inhibitors of FK506 binding proteins are disclosed in WO 2015/110271 and WO 2021/175848. Sulfonamides antagonising N-type calcium channels are disclosed in WO 2005/068448. Synthesis of sulfone-comprising macrocycles is described in Osipyan A. et al. (J. Org. Chem., 2018, 83, 9707-9717) and Reutskaya E. et al. (J. Org. Chem., 2021, 86, 5778-5791).

15

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



Formula (I)

20

wherein

❖ **Ring A** (A in Formula (I)) is a 6-membered aromatic ring, wherein:

25

- **R^{A1}** represents hydrogen, (C₁₋₃)alkyl (notably methyl), (C₁₋₃)alkoxy (notably methoxy), halogen (notably bromo, chloro or fluoro), monocyclic (C₃₋₄)cycloalkyl, or (C₁)fluoroalkyl; [in particular **R^{A1}** represents hydrogen, (C₁₋₃)alkyl (notably methyl), (C₁₋₃)alkoxy (notably methoxy), or halogen (notably chloro or fluoro)];
- **X¹** represents independently N or CR^{A3}, wherein **R^{A3}** represents hydrogen, halogen (notably fluoro), (C₁₋₃)alkyl (notably methyl), or (C₁₋₃)alkoxy (notably methoxy);

➤ X^2 represents independently N or CR^{A2} , wherein R^{A2} represents hydrogen or halogen (notably fluoro); and

➤ X^5 represents C;

5 [in particular **Ring A** represents 6-methyl-pyridin-2,3-diyl, 4-methyl-phen-1,2-diyl, 3-fluoro-4-methyl-phen-1,2-diyl, 5-methyl-pyrazin-2,3-diyl, 3-methoxy-4-methyl-phen-1,2-diyl, 6-fluoro-4-methyl-phen-1,2-diyl, 4-chloro-phen-1,2-diyl, phen-1,2-diyl, 4-fluoro-phen-1,2-diyl, 3,4-difluoro-phen-1,2-diyl, 4-fluoro-3-methyl-phen-1,2-diyl, 3-fluoro-4-methoxy-phen-1,2-diyl, or 3-fluoro-4-methyl-phen-1,2-diyl];

and **L** represents:

10 ➤ linker group **L**¹, wherein the backbone of said linker group **L**¹ is linear and consists of a total of 3 to 6 (notably 4 or 5) backbone atoms; wherein said backbone atoms are independently selected from 3 to 6 (notably 3 to 5) carbon atoms and 0 to 2 (notably 0 or 1) heteroatoms independently selected from O, N or S; wherein said backbone is saturated or partially unsaturated (notably is saturated or mono-unsaturated); wherein said backbone is unsubstituted, or mono-, di- or tri-substituted (notably unsubstituted, or mono- or di-substituted; especially mono- or di-substituted);

15 wherein the substituents are independently selected from the group consisting of:

- (C₁₋₆)alkyl (notably methyl, ethyl, n-propyl, or isopropyl; especially methyl);
- (C₃₋₆)cycloalkan-1,1-diyl (notably cyclopropan-1,1-diyl);
- (C₃₋₆)cycloalkyl (notably cyclopropyl);
- hydroxy;
- 20 ▪ halogen (notably fluoro); and, in addition,
- (C₁₋₃)fluoroalkyl (notably trifluoromethyl);

25 ➤ or linker group **L**², wherein the backbone of said linker group **L**² consists of a total of 4 to 6 backbone atoms; wherein said backbone atoms are independently selected from 3 to 5 carbon atoms and 1 or 2 (notably 1) heteroatom independently selected from O, N or S (notably O or N); wherein said backbone is saturated or partially unsaturated; wherein 2 or 3 adjacent atoms of said backbone atoms are contained in a 3- to 6-membered saturated, partially unsaturated or aromatic cyclic moiety comprising a total of 0 to 3 heteroatoms independently selected from O, N or S; wherein notably said cyclic moiety represents:

- 30 ▪ (C₃₋₆)cycloalkan-diyl (notably (C₃₋₆)cycloalkan-1,2-diyl or (C₃₋₆)cycloalkan-1,3-diyl; in particular cyclopropan-1,2-diyl, cyclobutan-1,2-diyl, cyclopentan-1,2-diyl, cyclohexan-1,2-diyl, cyclobutan-1,3-diyl, cyclopentan-1,3-diyl, or cyclohexan-1,3-diyl);
- phen-diyl (notably phen-1,2-diyl);
- 5- or 6-membered heterocycloalkan-diyl; wherein said heterocycloalkan-diyl is linked to the rest of the molecule via two of its ring atoms that are in ortho or in meta position
- 35 relative to one another (in particular such 5- or 6-membered heterocycloalkan-diyl

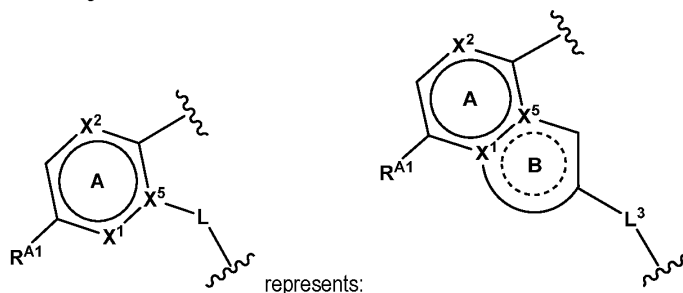
represents pyrrolidin-1,3-diyl, piperidin-1,3-diyl, tetrahydrofuran-2,3-diyl, or tetrahydrofuran-3,4-diyl); or

- 5- or 6-membered heteroaryl-diyl wherein said heteroaryl-diyl is linked to the rest of the molecule via two of its ring atoms that are in meta position relative to one another (in particular such 5- or 6-membered heteroaryl-diyl represents 1*H*-pyrazol-1,3-diyl, pyridin-2,6-diyl, 1,2,4-oxadiazol-3,5-diyl, or 1,3,4-oxadiazol-2,5-diyl);

wherein **L**² is unsubstituted, or mono- or di-substituted (notably unsubstituted or mono-substituted); wherein the substituents are independently selected from the group consisting of: (C₁₋₃)alkyl (notably methyl) and halogen (notably chloro);

[in particular said cyclic moiety represents cyclopropan-1,2-diyl, cyclobutan-1,2-diyl, cyclopentan-1,2-diyl, cyclohexan-1,2-diyl, cyclobutan-1,3-diyl, cyclopentan-1,3-diyl, cyclohexan-1,3-diyl, pyrrolidin-1,3-diyl, piperidin-1,3-diyl, 1*H*-pyrazol-1,3-diyl, tetrahydrofuran-2,3-diyl, tetrahydrofuran-3,4-diyl, pyridin-2,6-diyl, 1,2,4-oxadiazol-3,5-diyl, 1,3,4-oxadiazol-2,5-diyl, phen-1,2-diyl, or 4-chloro-1*H*-pyrazol-1,3-diyl];

❖ or the fragment



Formula (I-B)

wherein

- **Ring A** (A in Formula (I-B)) represents a 6-membered aromatic ring, wherein:

- **X**² represents CH or N (notably CH); and
- **R**^{A1} represents independently hydrogen, (C₁₋₃)alkyl (notably methyl), (C₁₋₃)alkoxy (notably methoxy), halogen (notably chloro or fluoro), monocyclic (C₃₋₄)cycloalkyl, or (C₁)fluoroalkyl; [in particular **R**^{A1} represents methyl];

and **Ring B** (B in Formula (I-B)) represents a 5- to 7-membered (in particular 6-membered) heterocyclic ring; wherein said **Ring B** including ring atoms **X**¹ and **X**⁵ contains a total of 1 or 2 ring heteroatoms; wherein said heteroatoms are independently selected from N, O, or S; [in particular such **Ring A** and **Ring B** together form 2,3-dihydrobenzofuran-2,7-diyl, chroman-2,8-diyl, 1,2,3,4-tetrahydroquinolin-2,8-diyl, or 2,3,4,5-tetrahydrobenzo[b]oxepin-2,9-diyl; in particular such Formula (I-B) represents 4-methyl-2,3-dihydrobenzofuran-2,7-diyl, 5-methyl-chroman-2,8-

diyl, 5-methyl-1,2,3,4-tetrahydroquinolin-2,8-diyl, or 6-methyl-2,3,4,5-tetrahydrobenzo[b]oxepin-2,9-diyl];

➤ **Ring A** (**A** in Formula (I-B)) represents a 6-membered aromatic ring, wherein:

5

- **X²** represents CH or N (notably CH); and
- **R^{A1}** represents independently hydrogen, (C₁₋₃)alkyl (notably methyl), (C₁₋₃)alkoxy (notably methoxy), halogen (notably chloro or fluoro), monocyclic (C₃₋₄)cycloalkyl, or (C₁)fluoroalkyl; [in particular **R^{A1}** represents methyl];

and **Ring B** (**B** in Formula (I-B)) represents a 5-membered heteroaromatic ring; wherein said **Ring B** including ring atoms **X¹** and **X⁵** contains a total of 1 to 3 (preferably 2) ring heteroatoms; wherein said heteroatoms are independently selected from N, O, or S; [in particular such **Ring A** and **Ring B** together form benzo[d]thiazol-2,4-diyl, imidazo[1,2-a]pyridin-2,8-diyl, or 2H-indazol-2,7-diyl; in particular such Formula (I-B) represents 7-methyl-benzo[d]thiazol-2,4-diyl, 5-methyl-imidazo[1,2-a]pyridin-2,8-diyl, or 4-methyl-2H-indazol-2,7-diyl]; or

10

➤ **Ring A** (**A** in Formula (I-B)) represents a 6-membered aromatic ring, wherein:

15

- **X²** represents CH or N (notably CH); and
- **R^{A1}** represents independently hydrogen, (C₁₋₃)alkyl (notably methyl), (C₁₋₃)alkoxy (notably methoxy), halogen (notably chloro or fluoro), monocyclic (C₃₋₄)cycloalkyl, or (C₁)fluoroalkyl; [in particular **R^{A1}** represents methyl];

and **Ring B** (**B** in Formula (I-B)) represents a 6-membered heteroaromatic ring; wherein said **Ring B** including ring atoms **X¹** and **X⁵** contains a total of 1 or 2 ring heteroatoms; wherein said ring heteroatoms are N; [in particular such **Ring A** and **Ring B** together form quinolin-2,8-diyl; in particular such Formula (I-B) represents 5-methyl-quinolin-2,8-diyl];

20

and **L³** represents:

25

- a linear linker group; wherein **L³** consists of a total of 3 or 4 backbone atoms; wherein said backbone atoms are independently selected from 3 or 4 carbon atoms and 0 or 1 heteroatom independently selected from O, N or S (notably O); wherein said backbone is saturated or mono-unsaturated; wherein said backbone is unsubstituted or mono-substituted with (C₁₋₃)alkyl (notably methyl) or halogen (notably fluoro);

30

X³ represents SO₂ or S(=O)(=NR³), wherein **R³** represents hydrogen, (C₁₋₃)alkyl (notably methyl including methyl-d₃), monocyclic (C₃₋₆)cycloalkyl, or phenyl; [in particular **X³** represents SO₂, S(=O)(=NH), S(=O)(=N(CH₃)), or S(=O)(=N(CD₃))];

X⁴ represents:

➤ **NR^{N1}**; wherein:

- **R^{N1}** represents hydrogen or (C₁₋₃)alkyl (notably methyl); and

- R^1 represents (C_{1-5}) alkyl (notably methyl, isopropyl, sec-butyl, or n-butyl) or $-(CH_2)_n-(C_{3-4})$ cycloalkyl wherein n represents the integer 0 or 1 (notably such $-(CH_2)_n-(C_{3-4})$ cycloalkyl represents cyclopropyl or cyclopropyl-methyl);
 - NR^{N1} ; wherein R^1 and R^{N1} together form a ring comprising X^4 , herein **Ring E**, wherein said **Ring E** represents:
 - a 4- to 6-membered (notably 5- or 6-membered) saturated monocyclic heterocycloalkan-diyl comprising X^4 and zero or one ring oxygen atom (notably such heterocycloalkan-diyl represents pyrrolidin-1,2-diyl, piperidin-1,2-diyl, 1,3-oxazinan-2,3-diyl, morpholin-3,4-diyl, or oxazolidin-2,3-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 (notably methyl), halogen (notably fluoro), (C_{1-3}) alkoxy (notably methoxy), hydroxy, phenyl, and cyano (notably the substituents are independently selected from the group consisting of: (C_{1-3}) alkyl (notably methyl), halogen (notably fluoro), and (C_{1-3}) alkoxy (notably methoxy)); [in particular such **Ring E** represents pyrrolidin-1,2-diyl, 3-fluoro-pyrrolidin-1,2-diyl, 4-fluoro-pyrrolidin-1,2-diyl, 4-methyl-pyrrolidin-1,2-diyl, 4-methoxy-pyrrolidin-1,2-diyl, piperidin-1,2-diyl, 1,3-oxazinan-2,3-diyl, morpholin-3,4-diyl, or oxazolidine-2,3-diyl]; or
 - a 6- to 8-membered (notably 6- or 7-membered) saturated spiro, fused, or bridged (notably fused or bridged) bicyclic heterocycloalkan-diyl comprising X^4 ; [in particular such **Ring E** represents 2-azabicyclo[3.1.0]hexan-2,3-diyl, 3-azabicyclo[3.1.0]hexan-2,3-diyl, or 2-azabicyclo[2.2.1]heptan-2,3-diyl];
 - or $CHRC^1$; wherein R^1 and R^{C1} together form a ring comprising X^4 , herein **Ring F**, wherein said **Ring F** represents a monocyclic (C_{5-6}) cycloalkan-diyl (notably cyclopentan-1,2-diyl) or a monocyclic 5- or 6-membered heterocycloalkan-diyl comprising one ring oxygen atom; and
- R^2 represents:
- 3-cyano-3,3-dimethylpropyl;
 - $-(CH_2)_m-(\text{Ring D})$, wherein m is the integer 0 or 1 (notably 0), and **Ring D** represents:
 - a saturated monocyclic (C_{4-7}) cycloalkyl (notably cyclobutyl, cyclopentyl, or cyclohexyl); wherein said (C_{4-7}) cycloalkyl is unsubstituted, mono-, di-, or tri-substituted (especially mono-, or di-substituted); wherein the substituents are independently selected from the group consisting of:
 - (C_{1-3}) alkyl (notably methyl); wherein said (C_{1-3}) alkyl independently is unsubstituted or mono-substituted with cyano (notably cyano-methyl);
 - halogen (notably fluoro);
 - (C_{1-3}) fluoroalkyl;
 - (C_{1-3}) alkoxy (notably methoxy);
 - (C_{3-4}) cycloalkyl (notably cyclopropyl);
 - carbamoyl;

- hydroxy;
- cyano; and
- (C₂₋₃)alkynyl (notably vinyl)

- 5 [in particular such -(CH₂)_m-(**Ring D**) represents 3-cyano-cyclobutyl, 3-(cyanomethyl)-3-methyl-cyclobutyl, 3-cyano-cyclopentyl, 3-hydroxy-cyclopentyl, 3-methoxy-cyclopentyl, 3,3-difluoro-cyclopentyl, 3,3-dimethyl-cyclopentyl, 3-cyano-3-methyl-cyclopentyl, 2-cyano-cyclohexyl, 2-hydroxy-cyclohexyl, 2-methoxy-cyclohexyl, 3-cyano-cyclohexyl, 3-hydroxy-cyclohexyl, 3-methoxy-cyclohexyl, 4-cyano-cyclohexyl, 4-hydroxy-cyclohexyl, 4-(cyanomethyl)-cyclohexyl, 4-methoxy-cyclohexyl, 3-cyano-3-methyl-cyclohexyl, 3,3-difluoro-cyclohexyl, 4-hydroxy-4-methyl-cyclohexyl, 4-cyano-4-methyl-cyclohexyl (as well as its deuterated isotope 4-cyano-4-(methyl-d₃)-cyclohexyl), 4-cyano-4-ethyl-cyclohexyl (as well as its deuterated isotope 4-cyano-4-(ethyl-d₅)-cyclohexyl), 4-cyano-4-cyclopropyl-cyclohexyl, 4,4-dimethyl-cyclohexyl, 4-fluoro-4-methyl-cyclohexyl, 4,4-difluoro-cyclohexyl, 4,4-difluoro-2-hydroxy-cyclohexyl, or 4-vinyl-cyclohexyl];
- 10
- a saturated bicyclic (C₅₋₈)spirocycloalkyl (notably spiro[2.2]pentanyl, spiro[2.3]hexanyl, spiro[2.4]heptanyl, spiro[3.3]heptanyl, or spiro[2.5]octanyl); wherein said (C₅₋₈)spirocycloalkyl is unsubstituted, or mono-, di-, tri- or tetra-substituted; wherein the substituents are independently selected from the group consisting of: halogen (notably fluoro), cyano, and hydroxy;
- 15 [in particular such -(CH₂)_m-(**Ring D**) represents 4-cyano-spiro[2.2]pentan-1-yl, spiro[2.3]hexan-5-yl, 1,1-difluoro-spiro[2.3]hexan-5-yl, 1,1-difluoro-spiro[2.4]heptan-5-yl, spiro[3.3]heptan-2-yl, 6-hydroxy-spiro[3.3]heptan-2-yl, 6,6-difluoro-spiro[3.3]heptan-2-yl, spiro[2.5]octan-6-yl, 1-cyano-spiro[2.5]octan-6-yl, 1,1,2,2-tetrafluoro-spiro[2.5]octan-6-yl, or 1,1-difluoro-spiro[2.5]octan-6-yl];
- 20
- a saturated fused or bridged bicyclic (C₅₋₈)cycloalkyl (notably bicyclo[1.1.1]pentanyl, bicyclo[3.1.0]hexanyl, bicyclo[4.1.0]heptanyl, or octahydropentalen-2-yl); wherein said bicyclic (C₅₋₈)cycloalkyl is unsubstituted, or mono- or di-substituted; wherein the substituents are independently selected from the group consisting of: (C₁₋₃)fluoroalkyl (notably (C₁)fluoroalkyl; especially trifluoromethyl), halogen (notably fluoro), cyano, and carbamoyl [in particular the substituents are independently selected from the group consisting of: (C₁₋₃)fluoroalkyl (notably (C₁)fluoroalkyl; especially trifluoromethyl), and halogen (notably fluoro)];
- 25 [in particular such -(CH₂)_m-(**Ring D**) represents 5-cyano-octahydropentalen-2-yl, 3-trifluoromethyl-bicyclo[1.1.1]pentan-1-yl, bicyclo[4.1.0]heptan-3-yl, 6,6-difluoro-bicyclo[3.1.0]hexan-3-yl, or 7,7-difluoro-bicyclo[4.1.0]heptan-3-yl];
- 30
- a 5- or 6-membered saturated monocyclic heterocycle comprising one ring heteroatomic group selected from O, NR^{N2}, S, or SO₂ (notably O, or NR^{N2}); wherein R^{N2} represents (C₁₋₃)alkyl (notably methyl) or cyanomethyl; (notably such heterocycle represents tetrahydropyranyl or piperidinyl);
- 35 wherein said heterocycle is unsubstituted, or mono-, di-, tri-, or tetra-substituted (and in addition substituted with R^{N2}, if present); wherein the substituents are independently selected from the

group consisting of: (C₁₋₃)alkyl (notably methyl, ethyl, or isopropyl), halogen, (C₁₋₃)fluoroalkyl, and oxo;

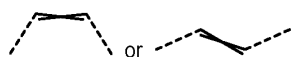
- [in particular such -(CH₂)_m-(**Ring D**) represents tetrahydropyran-3-yl, (tetrahydropyran-3-yl)-methyl, tetrahydropyran-4-yl, 2-methyl-tetrahydropyran-4-yl, 2,2-dimethyl-tetrahydropyran-4-yl, 2,6-dimethyl-tetrahydropyran-4-yl, 6,6-dimethyl-tetrahydropyran-3-yl, 2,2,6,6-tetramethyl-tetrahydropyran-4-yl, 1-methyl-2-oxo-piperidin-4-yl, 1-(cyanomethyl)-pyrrolidin-3-yl, or 1-(cyanomethyl)-3,3-difluoro-pyrrolidin-4-yl];
- a 9-membered saturated spiro bicyclic heterocycle comprising one ring oxygen atom [notably such -(CH₂)_m-(**Ring D**) represents 2-oxa-spiro[3.5]nonan-7-yl];
 - a 7-membered saturated fused or bridged bicyclic heterocycle comprising one ring oxygen atom; [notably such -(CH₂)_m-(**Ring D**) represents 7-oxa-bicyclo[2.2.1]heptan-2-yl].

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, undesigned 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 (12aR*,15aS*)-11-(4,4-difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,13,14,15,15a-decahydrobenzo[b]cyclopenta[e][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one 16,16-dioxide encompasses enantiomerically enriched (12aR,15aS)-11-(4,4-difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,13,14,15,15a-decahydrobenzo[b]cyclopenta[e][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one 16,16-dioxide, (12aS,15aR)-11-(4,4-difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,13,14,15,15a-decahydrobenzo[b]cyclopenta[e][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one 16,16-dioxide, or any mixture of these stereoisomers of said compound.

In drawings of a certain chemical structure (such as in the Table of Examples below), a stereogenic or asymmetric center indicated as "abs" represents said stereogenic or asymmetric center in the respective (R)- or (S)-configuration as drawn. A stereogenic or asymmetric center indicated as "&1" represents said stereogenic or asymmetric center in the respective (RS)-configuration, i.e. comprising the respective (R)- or (S)-configuration or any mixture of epimers at such center.

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). A double bond drawn as a crossed double bond :



is understood as encompassing such double bond in enriched (E)- or in enriched (Z)-configuration, or any stereoisomeric mixture comprising such bond in (E)- and (Z)-configuration.

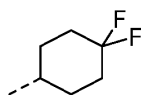
The term "enriched", when used in the context of stereoisomers, is to be understood in the context of the present invention to mean that the respective stereoisomer is present in a ratio of at least 70:30, especially of at least 90:10 (i.e., in a purity of at least 70% by weight, especially of at least 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, *d*) labelled compounds of Formula (I) according to embodiments 1) to 22), 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, *d*) 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, *d*) 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 4,4-difluoro-cyclohexyl 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.

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 22) 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 22), 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 (C₁₋₆)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. An example of **R^{A1}** representing (C₁₋₃)alkyl is methyl. An example of **R^{A2}** representing (C₁₋₃)alkyl is methyl. An example of **R^{A3}** representing (C₁₋₃)alkyl is methyl. Examples of (C₁₋₆)alkyl as substituent of linker group **L¹** are methyl, ethyl, n-propyl, and isopropyl. An example of (C₁₋₃)alkyl as substituent of **L²** or **L³** is methyl. Examples of **R¹** representing (C₁₋₅)alkyl are methyl, isopropyl, sec-butyl, and n-butyl. Examples of **R²** representing (C₁₋₃)alkyl are methyl including methyl-d₃. An example of (C₁₋₃)alkyl as substituent of **Ring E** is methyl. An example of (C₁₋₃)alkyl as substituent of **Ring D** is methyl, ethyl, or isopropyl (notably methyl). An example of **R^{N1}** representing (C₁₋₃)alkyl is methyl. An example of **R^{N2}** representing (C₁₋₃)alkyl is 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 (C₁₋₄)alkoxy group means a group of the formula (C₁₋₄)alkyl-O- in which the term "(C₁₋₄)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 is methoxy. An example of **R^{A1}** representing (C₁₋₃)alkoxy is methoxy. An example of **R^{A3}** representing (C₁₋₃)alkoxy is methoxy. An example of (C₁₋₃)alkoxy as substituent of **Ring E** is methoxy. An example of (C₁₋₃)alkoxy as substituent of **Ring D** 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 (C₁₋₃)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 (C₁₋₃)fluoroalkyl groups are (C₁)fluoroalkyl groups such as difluoromethyl and trifluoromethyl. An example of (C₁₋₃)fluoroalkyl as substituent of **Ring D** is trifluoromethyl.

The term "hydroxy" refers to a group -OH.

- 5 The term "cyano" refers to a group -CN.

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 -(SO₂)-.

The term "carbamoyl" refers to a group -C(=O)(NH₂).

- 10 The term "backbone" refers to the atoms forming the shortest continuous chain of atoms between two points of attachment of a fragment or group to the rest of the molecule. Such a backbone may be unsubstituted or substituted as explicitly defined; it is understood that all positions having a free valency are saturated with hydrogen where appropriate. Such a backbone may be linear, or may comprise a cyclic moiety, i.e., formed when two or more adjacent backbone atoms are linked together to form a cyclic moiety. In the latter case, the atoms of the cyclic moiety contained in the shortest path between the attachment points of the cyclic moiety to the remaining fragment or group are to be considered as backbone atoms.

- 15 Examples of backbones as used for linker group **L¹** are *-O-(CH₂)₂-, *-O-(CH₂)₃-, -(CH₂)₄-, *-S-(CH₂)₃-, *-O-(CH₂)₄-, *(CH₂)-O-(CH₂)₃-, *(CH₂)₃-O-(CH₂)₂-, -(CH₂)₅-, *-NH-(CH₂)₂-CH=CH-, *-NH-(CH₂)₄-, *-CH=CH-(CH₂)₃-, *-O-(CH₂)₂-CH=CH-, *-O-(CH₂)₂-O-(CH₂)₂-, and *-O-(CH₂)₅-; wherein the asterisk indicates the attachment point of linker group **L¹** to **Ring A**; wherein one or more hydrogen atoms along said backbone may be independently replaced with a substituent, as explicitly defined.

- 20 Examples of backbones as used for linker group **L²** are:

- *-O-(CH₂)-(cyclic moiety)-, *-O-(cyclic moiety)-(CH₂)-, *-O-(cyclic moiety)-CH=CH-, *-O-(cyclic moiety)-(CH₂)₂-; wherein notably independently the cyclic moiety of such linker group **L²** represents:
 - (C₃₋₆)cycloalkan-1,2-diyl (in particular cyclopropan-1,2-diyl, cyclobutan-1,2-diyl, cyclopentan-1,2-diyl, or cyclohexan-1,2-diyl);
 - phen-1,2-diyl; or
 - 5- or 6-membered heterocycloalkan-diyl; wherein said heterocycloalkan-diyl is linked to the rest of the molecule via two of its ring atoms that are in ortho position relative to one another (in particular tetrahydrofuran-2,3-diyl or tetrahydrofuran-3,4-diyl); or
- 30 ➤ *(cyclic moiety)-(CH₂)-, *(cyclic moiety)-(CH₂)₂-, *(cyclic moiety)-CH=CH-, *(cyclic moiety)-(CH₂)₃-, *-O-(cyclic moiety)-, *-O-(cyclic moiety)-(CH₂)-, and *-O-(CH₂)-(cyclic moiety)-; wherein notably independently the cyclic moiety of such linker group **L²** represents:
 - (C₃₋₆)cycloalkan-1,3-diyl (in particular cyclobutan-1,3-diyl, cyclopentan-1,3-diyl, or cyclohexan-1,3-diyl);

- 5- or 6-membered heterocycloalkan-diyl; wherein said heterocycloalkan-diyl is linked to the rest of the molecule via two of its ring atoms that are in meta position relative to one another (in particular pyrrolidin-1,3-diyl or piperidin-1,3-diyl);
- 5- or 6-membered heteroaryl-diyl; wherein said heteroaryl-diyl is linked to the rest of the molecule via two of its ring atoms that are in meta position relative to one another (in particular 1*H*-pyrazol-1,3-diyl, pyridin-2,6-diyl, 1,2,4-oxadiazol-3,5-diyl, or 1,3,4-oxadiazol-2,5-diyl);

wherein the asterisk indicates the attachment point of linker group **L**² to **Ring A**; wherein one or more hydrogen atoms along such linker group **L**² may be independently replaced with a substituent, as explicitly defined.

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 (C₃₋₆)cycloalkyl group contains from three to six carbon atoms. Representative examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

The term "(C_{x-y})cycloalkyl", "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 (C₃₋₄)cycloalkyl representing or as part of **R**¹ is cyclopropyl. An example of (C₃₋₆)cycloalkyl as substituent of linker group **L**¹ is cyclopropyl. Examples of (C₄₋₇)cycloalkyl representing **Ring D** are cyclobutyl, cyclopentyl, and cyclohexyl (notably cyclopentyl and cyclohexyl); such **Ring D** is unsubstituted or substituted as explicitly defined. An example of (C₃₋₄)cycloalkyl as substituent of **Ring D** is cyclopropyl.

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).

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. An example of **Ring F** representing a monocyclic (C₅₋₆)cycloalkan-diyl is cyclopentan-1,2-diyl. An example of (C₃₋₆)cycloalkan-1,1-diyl as substituent of linker group **L**¹ is cyclopropan-1,1-diyl. Examples of cyclic moieties of linker group **L**² representing (C₃₋₆)cycloalkan-diyl are (C₃₋₆)cycloalkan-1,2-diyl (notably cyclopropan-1,2-diyl, cyclobutan-1,2-diyl, cyclopentan-1,2-diyl, and cyclohexan-1,2-diyl) and (C₃₋₆)cycloalkan-1,3-diyl (notably cyclobutan-1,3-diyl, cyclopentan-1,3-diyl, and cyclohexan-1,3-diyl); such (C₃₋₆)cycloalkan-diyl is unsubstituted or substituted as explicitly defined.

The term "saturated bicyclic (C_{x-y})spirocycloalkyl" or "saturated spiro 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 spiro-bicyclic hydrocarbon ring containing x to y carbon atoms. Representative examples of saturated

bicyclic (C_{x-y})spirocycloalkyl groups include spiro[2.2]pentanyl, spiro[2.3]hexanyl, spiro[2.4]heptanyl, spiro[3.3]heptanyl, and spiro[2.5]octanyl. Examples of **Ring D** representing a saturated spiro bicyclic (C_{6-8})cycloalkyl are spiro[2.2]pentanyl, spiro[2.3]hexanyl, spiro[2.4]heptanyl, spiro[3.3]heptanyl, and spiro[2.5]octanyl (notably spiro[2.3]hexan-5-yl, spiro[2.4]heptan-5-yl, spiro[3.3]heptan-2-yl, and spiro[2.5]octan-6-yl); such **Ring D** are unsubstituted or substituted as explicitly defined.

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. Representative examples of saturated fused or bridged bicyclic (C_{x-y})cycloalkyl groups include bicyclo[1.1.1]pentanyl, bicyclo[2.1.1]hexanyl, bicyclo[3.1.0]hexanyl, bicyclo[4.1.0]heptanyl, bicyclo[2.2.2]octanyl, and octahydropentalenyl. Examples of **Ring D** representing a saturated fused or bridged bicyclic (C_{5-8})cycloalkyl are bicyclo[1.1.1]pentanyl, bicyclo[3.1.0]hexanyl, and bicyclo[4.1.0]heptanyl, and octahydropentalenyl (notably bicyclo[1.1.1]pentan-1-yl, bicyclo[3.1.0]hexan-3-yl, bicyclo[4.1.0]heptan-3-yl, or octahydropentalen-2-yl); such **Ring D** are unsubstituted or substituted as explicitly defined.

The term "heterocycle" or "saturated monocyclic heterocycle", 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, or 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 heterocycle" or "x- to y-membered saturated monocyclic heterocycle" (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. Representative examples of 4-membered saturated monocyclic heterocycle groups include oxetanyl, azetidiny, and thietanyl; representative examples of 5-membered saturated monocyclic heterocycle groups include tetrahydrofuryl, pyrrolidinyl, tetrahydrothiophenyl, and thiazolidinyl; representative examples of 6-membered saturated monocyclic heterocycle groups include tetrahydropyryl, 1,1-dioxide-tetrahydrothiopyryl, piperidinyl, dioxanyl, morpholinyl, piperazinyl, and hexahydropyrimidinyl; representative examples of 7-membered saturated monocyclic heterocycle groups include oxepanyl. Examples of **Ring D** representing a 5- or 6-membered saturated monocyclic heterocycle are tetrahydropyryl or piperidinyl (notably tetrahydropyran-3-yl, tetrahydropyran-4-yl, or piperidin-4-yl); such **Ring D** are unsubstituted or substituted as explicitly defined.

The term "saturated spiro bicyclic heterocycle", 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 comprising one or two ring heteroatoms or heteroatomic groups independently selected from N, O, S, or 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 saturated spiro bicyclic heterocycle" (x and y each being an integer) refers to such a heterocycle containing x to y ring atoms. An example of **Ring D** representing a 9-membered saturated spiro bicyclic heterocycle is 2-oxa-spiro[3.5]nonan-7-yl (notably 2-oxa-spiro[3.5]nonan-7-yl).

- 5 The term "saturated fused bicyclic heterocycle", 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 comprising one or two ring heteroatoms or heteroatomic groups independently selected from N, O, S, or SO₂; 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 saturated fused bicyclic heterocycle" (x and y each being an integer) refers to such a heterocycle containing x to y ring atoms.

- 15 The term "saturated bridged bicyclic heterocycle", 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 comprising one or two ring heteroatoms or heteroatomic groups independently selected from N, O, S, or SO₂; 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 saturated bridged bicyclic heterocycle" (x and y each being an integer) refers to such a heterocycle containing x to y ring atoms. An example of **Ring D** representing a 7-membered saturated bridged bicyclic heterocycle comprising one ring oxygen atom is 7-oxabicyclo[2.2.1]heptanyl (notably 7-oxabicyclo[2.2.1]heptan-2-yl).

- 20 The term "x- to y-membered heterocycloalkan-diyl" or "x- to y-membered saturated 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 heterocycle as defined before that is bivalently bound; wherein in each instance, the number and nature of ring heteroatoms or heteroatomic groups are explicitly defined. When the cyclic moiety of linker group **L**² represents a 5- or 6-membered heterocycloalkan-diyl, said heterocycloalkan-diyl is linked to the rest of the molecule via two of its ring atoms that are in ortho or in meta position relative to one another; such linkage may be independently via a carbon ring atom or a ring heteroatom of said 5- or 6-membered heterocycloalkan-diyl. Examples of the cyclic moiety of linker group **L**² representing a 5- or 6-membered heterocycloalkan-diyl are pyrrolidin-1,3-diyl, piperidin-1,3-diyl, tetrahydrofuran-2,3-diyl, and tetrahydrofuran-3,4-diyl; such cyclic moieties are unsubstituted or substituted as explicitly defined. When **X**⁴ represents NR^{N1}, and **R**¹ and **R**^{N1} together form a ring comprising **X**⁴, herein **Ring E**, representing a 4- to 6-membered saturated monocyclic heterocycloalkan-diyl comprising **X**⁴ and zero or one ring oxygen atom, the points of attachment of said heterocycloalkan-diyl in Formula (I) are on **X**⁴ and on the carbon atom attached at the asterix to the group *-CO-N(**R**²)-; examples are pyrrolidin-1,2-diyl, piperidin-1,2-diyl, 1,3-oxazinan-2,3-diyl, morpholin-3,4-diyl, and oxazolidin-2,3-diyl; such **Ring E** is

unsubstituted or substituted as explicitly defined. In a particular embodiment, the carbon atom of **Ring E** attached at the asterix to the group $^*\text{--CO--N(R}^2\text{)}$ is not further substituted.

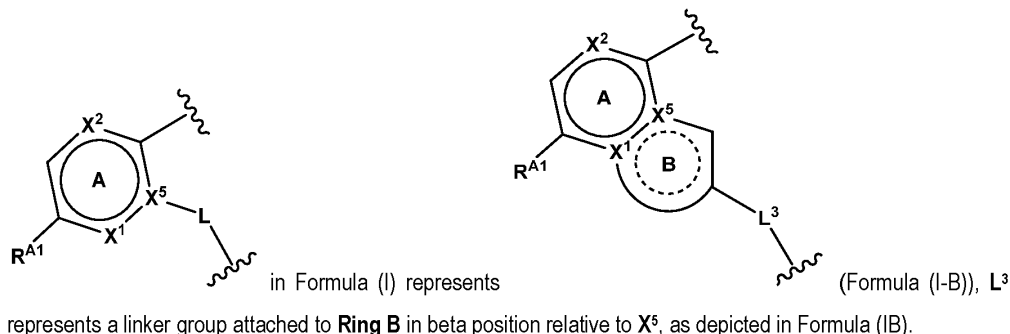
The term "x- to y-membered saturated spiro, fused, or bridged bicyclic heterocycloalkan-diyl" (x and y each being an integer), used alone or in combination and if not explicitly defined in a broader or more narrow way, refers to a bivalently bound saturated spiro, fused or bridged bicyclic hydrocarbon ring containing x to y ring atoms of which one or two (especially one) ring atoms are heteroatoms independently selected from N, O, or S. When X^4 represents $\text{NR}^{\text{N}1}$, and R^1 and $\text{R}^{\text{N}1}$ together form a ring comprising X^4 , herein **Ring E**, representing a 6- to 8-membered (notably 6- or 7-membered) saturated spiro, fused, or bridged bicyclic heterocycloalkan-diyl comprising X^4 , the points of attachment of said heterocycloalkan-diyl in Formula (I) are on X^4 and on the carbon atom attached at the asterix to the group $^*\text{--CO--N(R}^2\text{)}$. An example of **Ring E** representing a 6- to 8-membered bridged bicyclic heterocycloalkan-diyl is 2-azabicyclo[2.2.1]heptan-2,3-diyl. Examples of **Ring E** representing a 6- to 8-membered fused bicyclic heterocycloalkan-diyl are 2-azabicyclo[3.1.0]hexan-2,3-diyl and 3-azabicyclo[3.1.0]hexan-2,3-diyl.

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.

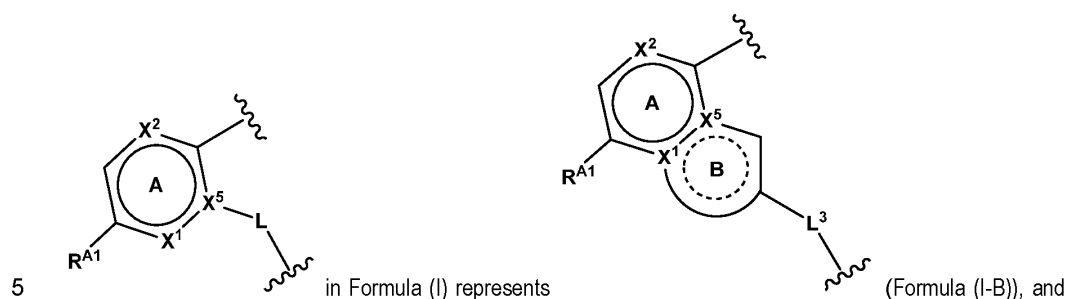
The term "heteroaryl", used alone or in combination, means a 5- to 10-membered monocyclic or bicyclic aromatic ring containing one to a maximum of four heteroatoms (especially one to a maximum three), each independently selected from N, O, or S. Examples of such heteroaryl groups are 5-membered heteroaryl groups such as furanyl, oxazolyl, isoxazolyl, oxadiazolyl, thiophenyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, and tetrazolyl; examples of 6-membered heteroaryl groups are pyridinyl, pyrimidinyl, pyridazinyl, and pyrazinyl; and examples of 8- to 10-membered bicyclic heteroaryl groups are 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.

The term "heteroaryl-diyl", used alone or in combination, means a heteroaryl as defined before that is bivalently bound. When the cyclic moiety of linker group L^2 represents a 5- or 6-membered heteroaryl-diyl, said heteroaryl-diyl is linked to the rest of the molecule via two of its ring atoms that are in meta position relative to one another; such linkage may be independently via a carbon ring atom or a ring heteroatom of said 5- or 6-membered heterocycloalkan-diyl. Examples of a cyclic moiety of linker group L^2 representing a 5- or 6-membered heteroaryl-diyl are 1H-pyrazol-1,3-diyl, pyridin-2,6-diyl, 1,2,4-oxadiazol-3,5-diyl, and 1,3,4-oxadiazol-2,5-diyl; such cyclic moieties are unsubstituted or substituted as explicitly defined.

When the fragment formed by:

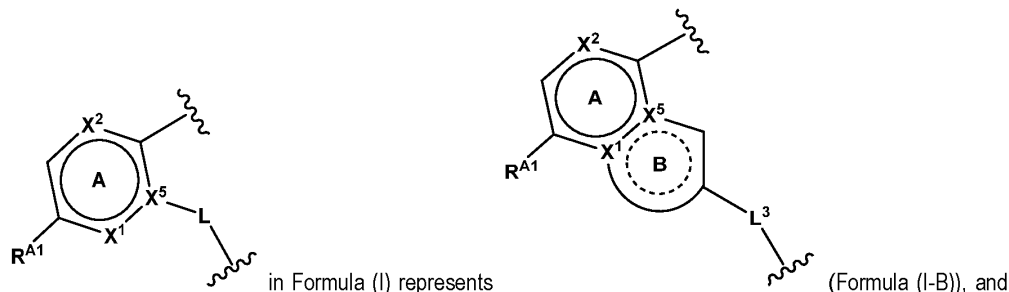


When the fragment formed by:



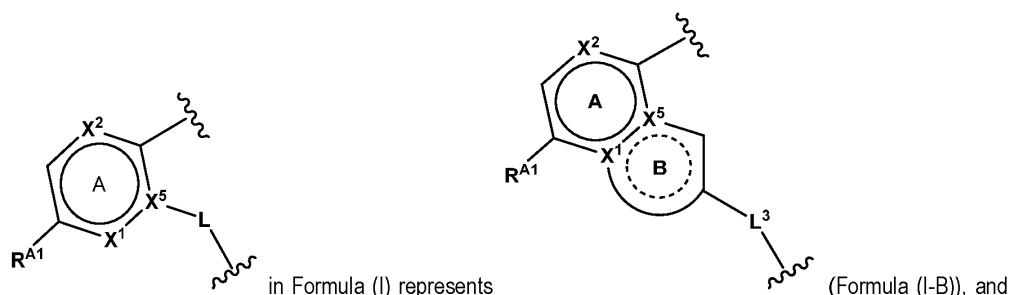
- Ring B** represents a 5-membered heteroaromatic ring, notably X^1 represents C or N, X^2 independently represents C or N, and X^5 independently represents C or N (in particular C); examples of such bicyclic heteroaryl groups formed by **Ring A** and **Ring B** together include 1H-indol-2,7-diyl, 1H-pyrrolo[2,3-c]pyridin-2,7-diyl, 1H-indol-2,4-diyl, 1H-pyrrolo[3,2-c]pyridin-2,4-diyl, benzofuran-2,7-diyl, furo[2,3-c]pyridin-2,7-diyl, benzofuran-2,4-diyl, furo[3,2-c]pyridin-2,4-diyl, benzo[b]thiophen-2,7-diyl, thieno[2,3-c]pyridin-2,7-diyl, benzo[b]thiophen-2,4-diyl, thieno[3,2-c]pyridin-2,4-diyl, benzo[d]oxazol-2,4-diyl, oxazolo[4,5-c]pyridin-2,4-diyl, benzo[d]oxazol-2,7-diyl, oxazolo[5,4-c]pyridin-2,4-diyl, benzo[d]thiazol-2,4-diyl, thiazolo[4,5-c]pyridin-2,4-diyl, benzo[d]thiazol-2,7-diyl, thiazolo[5,4-c]pyridin-2,4-diyl, benzo[d]imidazol-2,7-diyl, 1H-imidazo[4,5-c]pyridin-2,4-diyl, imidazo[1,2-a]pyridin-2,8-diyl, imidazo[1,2-a]pyrazin-2,8-diyl, imidazo[1,2-a]pyridin-2,5-diyl, imidazo[1,2-c]pyrimidin-2,5-diyl, indolizin-2,5-diyl, pyrrolo[1,2-c]pyrimidin-1,6-diyl, 2H-isoindole-2,4-diyl, 2H-pyrrolo[3,4-c]pyridin-2,4-diyl, 2H-indazol-2,4-diyl, 2H-pyrazolo[4,3-c]pyridin-2,4-diyl, 2H-indazol-2,7-diyl, and 2H-pyrazolo[3,4-c]pyridin-2,7-diyl (notably benzo[d]thiazol-2,4-diyl, imidazo[1,2-a]pyridin-2,8-diyl, and 2H-indazol-2,7-diyl); such bicyclic heteroaryl group formed by **Ring A** and **Ring B** are unsubstituted or substituted as explicitly defined.

When the fragment formed by:



- Ring B** represents a 6-membered heteroaromatic ring, notably **X¹** represents C or N, **X²** independently represents C or N, and **X⁵** independently represents C or N; examples of such bicyclic heteroaryl groups formed by **Ring A** and **Ring B** together include naphthalen-1,7-diyl, isoquinolin-1,7-diyl, 5λ⁴-quinolizin-3,6-diyl, 9λ⁴-pyrido[2,1-f]pyrimidin-1,7-diyl, 5λ⁴-quinolizin-1,8-diyl, 5λ⁴-pyrido[1,2-a]pyrazin-1,8-diyl, quinolin-3,5-diyl, 1,6-naphthyridin-3,5-diyl, isoquinolin-3,5-diyl, 2,6-naphthyridin-1,7-diyl, quinolin-2,8-diyl, 1,7-naphthyridin-2,8-diyl, quinoxalin-2,8-diyl, pyrido[3,4-b]pyrazin-3,5-diyl, cinnolin-3,5-diyl, pyrido[4,3-c]pyridazin-3,5-diyl, quinazolin-2,8-diyl, and pyrido[3,4-d]pyrimidin-2,8-diyl (notably quinolin-2,8-diyl); such bicyclic heteroaryl group formed by **Ring A** and **Ring B** are unsubstituted or substituted as explicitly defined.

When the fragment formed by:



- Ring B** represents a 5- to 7-membered heterocyclic ring which is fused with aromatic **Ring A** (wherein **Ring B** contains a total of 1 or 2 ring heteroatoms and said heteroatoms are independently selected from N, O, or S), notably **X¹** represents C, **X²** independently represents C or N, and **X⁵** represents C; examples of fused bicyclic rings formed by **Ring A** and **Ring B** include 2,3-dihydrobenzofuran-2,7-diyl, 2,3-dihydrofuro[2,3-c]pyridin-2,7-diyl, 2,3-dihydrobenzofuran-2,4-diyl, 2,3-dihydrofuro[3,2-c]pyridin-2,4-diyl, indolin-2,7-diyl, 2,3-dihydro-1H-pyrrolo[2,3-c]pyridin-2,7-diyl, indolin-2,4-diyl, 2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-2,4-diyl, 2,3-dihydrobenzo[b]thiophen-2,7-diyl, 2,3-dihydrothieno[2,3-c]pyridin-2,7-diyl, 2,3-dihydrobenzo[b]thiophen-2,4-diyl, 2,3-dihydrothieno[3,2-c]pyridin-2,4-diyl, 2,3-dihydrobenzo[d]thiazol-2,7-diyl, 1,2-dihydrothiazolo[5,4-c]pyridin-2,4-diyl, 2,3-dihydrobenzo[d]thiazol-2,4-diyl, 2,3-dihydrothiazolo[4,5-c]pyridin-2,4-diyl, 1,2,3,4-tetrahydroquinolin-2,8-diyl, 1,2,3,4-tetrahydro-1,7-naphthyridin-2,8-diyl, 1,2,3,4-tetrahydroisoquinolin-3,5-diyl, 1,2,3,4-tetrahydro-2,6-naphthyridin-3,5-diyl, 1,2,3,4-tetrahydroquinolin-3,5-diyl, 1,2,3,4-tetrahydro-1,6-naphthyridin-3,5-diyl, 1,2,3,4-tetrahydroquinoxalin-2,8-diyl,

1,2,3,4-tetrahydropyrido[3,4-b]pyrazin-3,5-diyl, 1,2,3,4-tetrahydroquinazolin-2,8-diyl, 1,2,3,4-tetrahydropyrido[3,4-d]pyrimidin-2,8-diyl, 3,4-dihydro-2H-benzo[b][1,4]oxazin-3,5-diyl, 3,4-dihydro-2H-pyrido[4,3-b][1,4]oxazin-3,5-diyl, chroman-2,8-diyl, 3,4-dihydro-2H-pyrano[2,3-c]pyridin-2,8-diyl, isochroman-3,5-diyl, 3,4-dihydro-1H-pyrano[4,3-c]pyridin-3,5-diyl, chroman-3,5-diyl, 3,4-dihydro-2H-pyrano[3,2-c]pyridin-3,5-diyl, and 2,3,4,5-tetrahydrobenzo[b]oxepin-2,9-diyl (notably 2,3-dihydrobenzofuran-2,7-diyl, 1,2,3,4-tetrahydroquinolin-2,8-diyl, chroman-2,8-diyl, and 2,3,4,5-tetrahydrobenzo[b]oxepin-2,9-diyl); such fused bicyclic ring formed by **Ring A** and **Ring B** is unsubstituted or substituted as explicitly defined.

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 °C and 80 °C, this means that the end points 40 °C and 80 °C 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 °C to Y plus 10 °C, and preferably to an interval extending from Y minus 5 °C to Y plus 5 °C. 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:

Ring A (**A** in Formula (I)) is a 6-membered aromatic ring, wherein:

- **R^{A1}** represents hydrogen, (C₁₋₃)alkyl (notably methyl), (C₁₋₃)alkoxy (notably methoxy), halogen (notably chloro or fluoro), monocyclic (C₃₋₄)cycloalkyl, or (C₁)fluoroalkyl; [in particular **R^{A1}** represents hydrogen, (C₁₋₃)alkyl (notably methyl), or (C₁₋₃)alkoxy (notably methoxy), halogen (notably chloro or fluoro)];
 - **X¹** represents independently N or **CR^{A3}**, wherein **R^{A3}** represents hydrogen, halogen (notably fluoro), (C₁₋₃)alkyl (notably methyl), or (C₁₋₃)alkoxy (notably methoxy);
 - **X²** represents independently N or **CR^{A2}**, wherein **R^{A2}** represents hydrogen or halogen (notably fluoro);
 - and
 - **X⁵** represents C;
- [in particular **Ring A** represents 6-methyl-pyridin-2,3-diyl, 4-methyl-phen-1,2-diyl, 3-fluoro-4-methyl-phen-1,2-diyl, 5-methyl-pyrazin-2,3-diyl, 3-methoxy-4-methyl-phen-1,2-diyl, 6-fluoro-4-methyl-phen-1,2-diyl, 4-chloro-phen-1,2-diyl, phen-1,2-diyl, 4-fluoro-phen-1,2-diyl, 3,4-difluoro-phen-1,2-diyl, 4-fluoro-3-methyl-phen-1,2-diyl, 3-fluoro-4-methoxy-phen-1,2-diyl, or 3-fluoro-4-methyl-phen-1,2-diyl];

and L represents:

- linker group **L¹**, wherein the backbone of said linker group **L¹** is linear and consists of a total of 3 to 6 (notably 4 or 5) backbone atoms; wherein said backbone atoms are independently selected from 3 to 6 (notably 3 to 5) carbon atoms and 0 to 2 (notably 0 or 1) heteroatoms independently selected from O, N or S; wherein said backbone is saturated or partially unsaturated (notably is saturated or mono-unsaturated); wherein said backbone is unsubstituted, or mono-, di- or tri-substituted (notably unsubstituted, or mono- or di-substituted; especially mono- or di-substituted); wherein the substituents are independently selected from the group consisting of:

 - (C₁₋₆)alkyl (notably methyl, ethyl, n-propyl, or isopropyl; especially methyl);
 - (C₃₋₆)cycloalkan-1,1-diyl (notably cyclopropan-1,1-diyl);
 - (C₃₋₆)cycloalkyl (notably cyclopropyl);
 - hydroxy;
 - halogen (notably fluoro); and, in addition,
 - (C₁₋₃)fluoroalkyl (notably trifluoromethyl);
- or linker group **L²**, wherein the backbone of said linker group **L²** consists of a total of 4 to 6 backbone atoms; wherein said backbone atoms are independently selected from 3 to 5 carbon atoms and 1 or 2 (notably 1) heteroatom independently selected from O, N or S (notably O or N); wherein said backbone is saturated or partially unsaturated; wherein 2 or 3 adjacent atoms of said backbone atoms are contained in a 3- to 6-membered saturated, partially unsaturated or aromatic cyclic moiety comprising a total of 0 to 3 heteroatoms independently selected from O, N or S; wherein notably said cyclic moiety represents:

 - (C₃₋₆)cycloalkan-diyl (notably (C₃₋₆)cycloalkan-1,2-diyl or (C₃₋₆)cycloalkan-1,3-diyl; in particular cyclopropan-1,2-diyl, cyclobutan-1,2-diyl, cyclopentan-1,2-diyl, cyclohexan-1,2-diyl, cyclobutan-1,3-diyl, cyclopentan-1,3-diyl, or cyclohexan-1,3-diyl);
 - phen-diyl (notably phen-1,2-diyl);
 - 5- or 6-membered heterocycloalkan-diyl; wherein said heterocycloalkan-diyl is linked to the rest of the molecule via two of its ring atoms that are in ortho or in meta position relative to one another (in particular such 5- or 6-membered heterocycloalkan-diyl represents pyrrolidin-1,3-diyl, piperidin-1,3-diyl, tetrahydrofuran-2,3-diyl, or tetrahydrofuran-3,4-diyl); or
 - 5- or 6-membered heteroaryl-diyl wherein said heteroaryl-diyl is linked to the rest of the molecule via two of its ring atoms that are in meta position relative to one another (in particular such 5- or 6-membered heteroaryl-diyl represents 1*H*-pyrazol-1,3-diyl, pyridin-2,6-diyl, 1,2,4-oxadiazol-3,5-diyl, or 1,3,4-oxadiazol-2,5-diyl);

wherein **L²** is unsubstituted, or mono- or di-substituted (notably unsubstituted or mono-substituted); wherein the substituents are independently selected from the group consisting of: (C₁₋₃)alkyl (notably methyl) and halogen (notably chloro);

5 [in particular said cyclic moiety represents cyclopropan-1,2-diyl, cyclobutan-1,2-diyl, cyclopentan-1,2-diyl, cyclohexan-1,2-diyl, cyclobutan-1,3-diyl, cyclopentan-1,3-diyl, cyclohexan-1,3-diyl, pyrrolidin-1,3-diyl, piperidin-1,3-diyl, 1*H*-pyrazol-1,3-diyl, tetrahydrofuran-2,3-diyl, tetrahydrofuran-3,4-diyl, pyridin-2,6-diyl, 1,2,4-oxadiazol-3,5-diyl, 1,3,4-oxadiazol-2,5-diyl, phen-1,2-diyl, or 4-chloro-1*H*-pyrazol-1,3-diyl].

3) Another embodiment relates to compounds according to embodiment 2), wherein **Ring A** is a 6-membered aromatic ring, wherein:

- **R^{A1}** represents independently hydrogen, (C₁₋₃)alkyl (notably methyl), (C₁₋₃)alkoxy (notably methoxy), or halogen (notably chloro or fluoro);
- 10 ➤ **X¹** represents independently N or **CR^{A3}**, wherein **R^{A3}** represents hydrogen, halogen (notably fluoro), (C₁₋₃)alkyl (notably methyl), or (C₁₋₃)alkoxy (notably methoxy);
- **X²** represents independently N or **CR^{A2}**, wherein **R^{A2}** represents hydrogen or halogen (notably fluoro); and
- **X⁵** represents C.

4) Another embodiment relates to compounds according to embodiment 2), wherein **Ring A** is a 6-membered aromatic ring, wherein:

- **R^{A1}** represents independently hydrogen, (C₁₋₃)alkyl (notably methyl), (C₁₋₃)alkoxy (notably methoxy), or halogen (notably fluoro);
- **X¹** represents independently N or **CR^{A3}**, wherein **R^{A3}** represents hydrogen, halogen (notably fluoro), or (C₁₋₃)alkyl (notably methyl);
- 20 ➤ **X²** represents independently N or **CR^{A2}**, wherein **R^{A2}** represents hydrogen or halogen (notably fluoro); and
- **X⁵** represents C;

[in particular **Ring A** represents 6-methyl-pyridin-2,3-diyl, 4-methyl-phen-1,2-diyl, 3-fluoro-4-methyl-phen-1,2-diyl, 5-methyl-pyrazin-2,3-diyl, 6-fluoro-4-methyl-phen-1,2-diyl, 4-chloro-phen-1,2-diyl, phen-1,2-diyl, 4-fluoro-phen-1,2-diyl, 3,4-difluoro-phen-1,2-diyl, 4-fluoro-3-methyl-phen-1,2-diyl, 3-fluoro-4-methoxy-phen-1,2-diyl, or 3-fluoro-4-methyl-phen-1,2-diyl].

5) Another embodiment relates to compounds according to any one of embodiments 2) to 4), wherein

- ❖ **L** represents linker group **L¹** and the backbone of linker group **L¹** is selected from the group consisting of: *O-(CH₂)₂-, *O-(CH₂)₃-, -(CH₂)₄-, *S-(CH₂)₃-, *O-(CH₂)₄-, *(CH₂)-O-(CH₂)₃-, *(CH₂)₃-O-(CH₂)-, -(CH₂)₅-, *NH-(CH₂)₂-CH=CH-, *NH-(CH₂)₄-, *CH=CH-(CH₂)₃-, *O-(CH₂)₂-CH=CH-, *O-(CH₂)₂-O-(CH₂)-, and *O-(CH₂)₅-, and, in addition, *O-(CH₂)₂-NH-(CH₂)-, (notably from the group consisting of: *O-(CH₂)₃-, *S-(CH₂)₃-, *O-(CH₂)₄-, -(CH₂)₅-, *O-(CH₂)₂-O-(CH₂)-, *NH-(CH₂)₂-CH=CH-, and *NH-(CH₂)₄-, and, in addition, *O-(CH₂)₂-NH-(CH₂)-, wherein the asterisks indicate the attachment point of linker group **L¹** to **Ring A**; wherein said backbone is unsubstituted, or mono- or di-substituted (notably mono- or di-substituted); wherein the substituents are independently selected from the group consisting of:
- 35 • (C₁₋₆)alkyl (notably methyl, ethyl, n-propyl, or isopropyl; especially methyl or ethyl);

- (C₃₋₆)cycloalkan-1,1-diyl (notably cyclopropan-1,1-diyl, i.e. two of said substituents together with the backbone carbon atom to which they are attached form said (C₃₋₆)cycloalkan-1,1-diyl, notably cyclopropan-1,1-diyl group);
 - (C₃₋₆)cycloalkyl (notably cyclopropyl);
 - 5 • hydroxy; and
 - halogen (notably fluoro); and, in addition,
 - (C₁₋₃)fluoroalkyl (notably trifluoromethyl or 2,2,2-trifluoroethyl); or
- ❖ L represents linker group L² and the backbone of linker group L² is selected from the group consisting of:
- *-O-(CH₂)-(cyclic moiety)-, *-O-(cyclic moiety)-(CH₂)-, *-O-(cyclic moiety)-CH=CH-, *-O-(cyclic moiety)-(CH₂)₂-; wherein independently the cyclic moiety of such linker group L² represents:
 - (C₃₋₆)cycloalkan-1,2-diyl (in particular cyclopropan-1,2-diyl, cyclobutan-1,2-diyl, cyclopentan-1,2-diyl, or cyclohexan-1,2-diyl);
 - phen-1,2-diyl; or
 - 5- or 6-membered heterocycloalkan-diyl; wherein said heterocycloalkan-diyl is linked to the
 - 15 rest of the molecule via two of its ring atoms that are in ortho position relative to one another (in particular tetrahydrofuran-2,3-diyl or tetrahydrofuran-3,4-diyl); or
 - *-(cyclic moiety)-(CH₂)-, *-(cyclic moiety)-(CH₂)₂-, *-(cyclic moiety)-CH=CH-, *-(cyclic moiety)-(CH₂)₃-, *-O-(cyclic moiety)-, *-O-(cyclic moiety)-(CH₂)-, and *-O-(CH₂)-(cyclic moiety)-; wherein independently the cyclic moiety of such linker group L² represents:
 - (C₃₋₆)cycloalkan-1,3-diyl (in particular cyclobutan-1,3-diyl, cyclopentan-1,3-diyl, or cyclohexan-1,3-diyl);
 - 5- or 6-membered heterocycloalkan-diyl; wherein said heterocycloalkan-diyl is linked to the
 - 20 rest of the molecule via two of its ring atoms that are in meta position relative to one another (in particular pyrrolidin-1,3-diyl or piperidin-1,3-diyl);
 - 5- or 6-membered heteroaryl-diyl; wherein said heteroaryl-diyl is linked to the rest of the
 - 25 molecule via two of its ring atoms that are in meta position (also referred to as 1,3-diyl position) relative to one another (in particular 1*H*-pyrazol-1,3-diyl, pyridin-2,6-diyl, 1,2,4-oxadiazol-3,5-diyl, or 1,3,4-oxadiazol-2,5-diyl);

wherein the asterisks indicate the attachment point of linker group L² to **Ring A**; wherein said L² is unsubstituted, or mono- or di-substituted (notably unsubstituted or mono-substituted); wherein the substituents are independently selected from the group consisting of: (C₁₋₃)alkyl (notably methyl) and halogen (notably chloro).

6) Another embodiment relates to compounds according to any one of embodiments 2) to 4), wherein in case L represents linker group L¹; said linker group L¹ independently is:

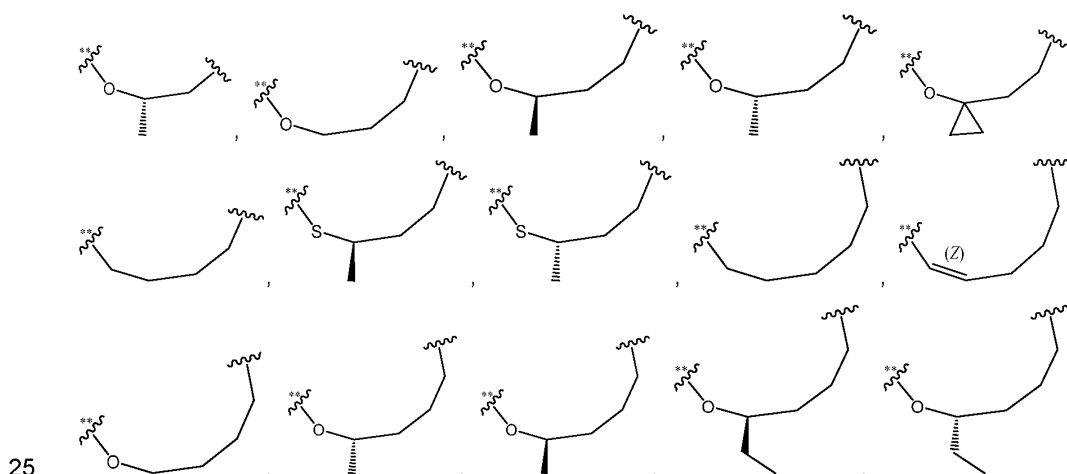
**O-CH(CH₃)-CH₂-; **O-CH₂-CH₂-CH₂-; **O-CH(CH₃)-CH₂-CH₂-; **O-cyclopropan-1,1-diyl-CH₂-CH₂-; -CH₂-CH₂-CH₂-CH₂-; **S-CH(CH₃)-CH₂-CH₂-; -CH₂-CH₂-CH₂-CH₂-CH₂-; **CH=CH-CH₂-CH₂-CH₂-; **O-CH₂-CH₂-CH₂-CH₂-; **O-CH(CH₃)-CH₂-CH₂-CH₂-; **O-CH(ethyl)-CH₂-CH₂-CH₂-; **O-CH(*n*-propyl)-

- CH₂-CH₂-CH₂-; **O-CH(isopropyl)-CH₂-CH₂-CH₂-; **O-CH(cyclopropyl)-CH₂-CH₂-CH₂-; **O-CH₂-CH(CH₃)-CH₂-CH₂-; **O-CH₂-CH₂-CH(CH₃)-CH₂-; **O-CH₂-CH₂-CH(ethyl)-CH₂-; **O-CH₂-CF₂-CH₂-CH₂-; **O-CH₂-CH₂-C(CH₃)₂-CH₂-; **O-CH₂-CH₂-cyclopropan-1,1-diyl-CH₂-; **O-CH₂-CH₂-C(hydroxy)(cyclopropyl)-CH₂-; **O-CH₂-CH₂-CH₂-CH(CH₃)-; **O-CH(CH₃)-CH₂-CH=CH-; **CH₂-O-CH₂-CH₂-CH₂-; **CH₂-CH₂-CH₂-O-CH₂-; **O-CH(CH₃)-CH₂-O-CH₂-; **NH-CH₂-CH₂-CH₂-CH₂-; **N(CH₃)-CH₂-CH₂-CH₂-CH₂-; **N(CH₃)-CH₂-CH₂-CH=CH-; **NH-CH(CH₃)-CH₂-CH=CH-; **NH-CH(CH₃)-CH₂-CH₂-CH₂-; or **O-CH₂-CH₂-CH₂-CH₂-CH₂-;
- or, in addition to the above-listed, **O-CH(ethyl)-CH₂-O-CH₂-; **O-CH(CH₃)-CH₂-CH(CH₃)-CH₂-; **O-CH₂-CH₂-N(cyclopropyl)-CH₂-; **O-CH(CH₃)-CH₂-N(cyclopropyl)-CH₂-; **O-CH(CF₃)-CH₂-CH₂-CH₂-; **O-CH₂-CH₂-CH(CF₃)-CH₂-; **O-CH₂-CH₂-N(2,2,2-trifluoroethyl)-CH₂-; or **O-CH₂-CH₂-CH=CH-;
- wherein in subembodiment L represents linker group L¹;

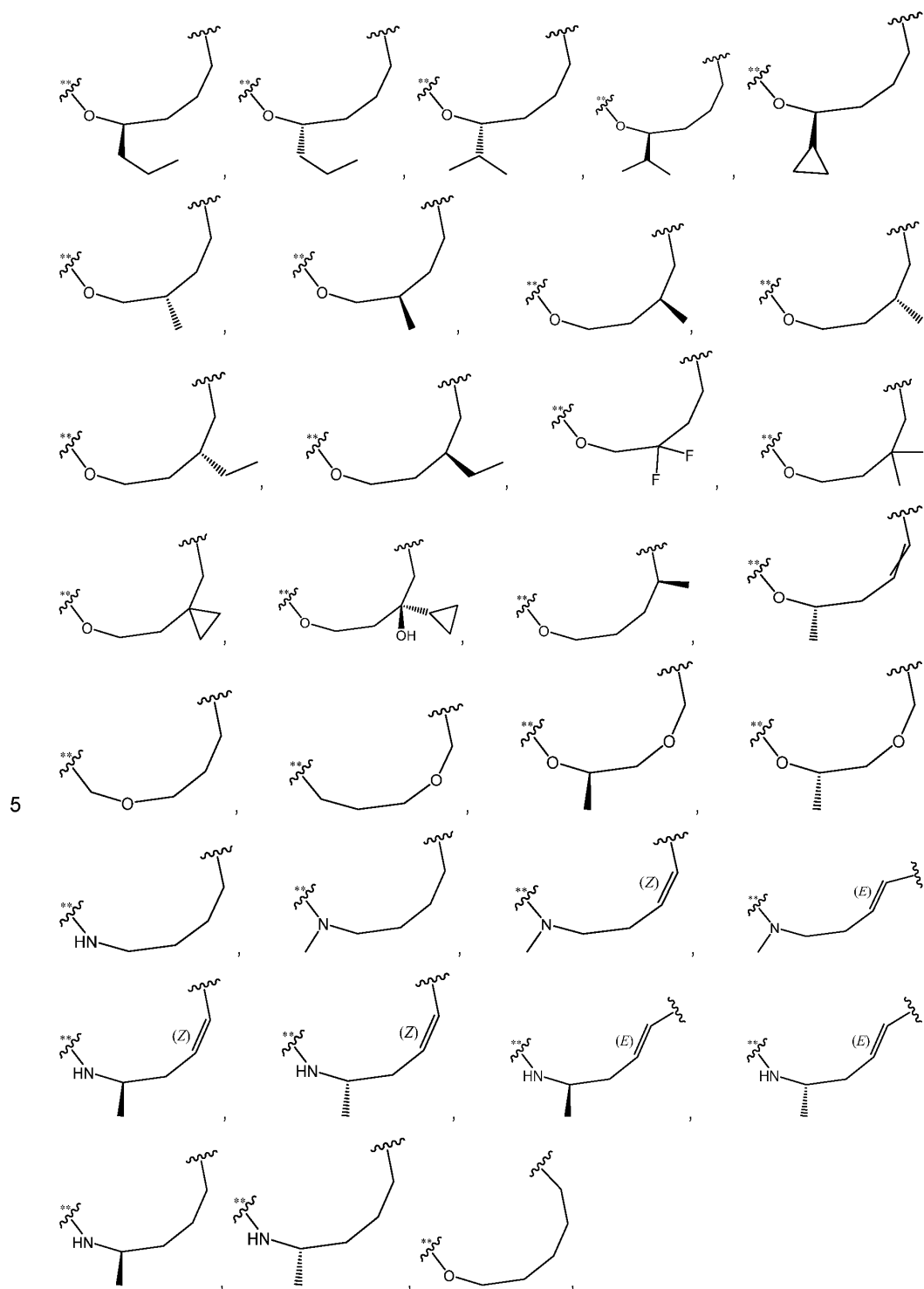
wherein especially linker group L¹ is independently selected from:

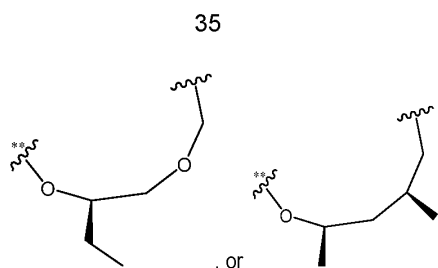
- **O-CH₂-CH₂-CH₂-; **O-CH(CH₃)-CH₂-CH₂-; **S-CH(CH₃)-CH₂-CH₂-; -CH₂-CH₂-CH₂-CH₂-CH₂-; **O-CH₂-CH₂-CH₂-CH₂-; **O-CH(CH₃)-CH₂-CH₂-CH₂-; **O-CH(ethyl)-CH₂-CH₂-CH₂-; **O-CH(n-propyl)-CH₂-CH₂-CH₂-; **O-CH(isopropyl)-CH₂-CH₂-CH₂-; **O-CH₂-CH(CH₃)-CH₂-CH₂-; **O-CH₂-CH₂-CH(CH₃)-CH₂-; **O-CH₂-CH₂-CH(ethyl)-CH₂-; **O-CH₂-CF₂-CH₂-CH₂-; **N(CH₃)-CH₂-CH₂-CH₂-CH₂-; **N(CH₃)-CH₂-CH₂-CH=CH-; **NH-CH(CH₃)-CH₂-CH=CH-; or **NH-CH(CH₃)-CH₂-CH₂-CH₂-;
- or, in addition to the above-listed, **O-CH(CH₃)-CH₂-O-CH₂-; **O-CH(ethyl)-CH₂-O-CH₂-; **O-CH(CH₃)-CH₂-CH(CH₃)-CH₂-; **O-CH(CF₃)-CH₂-CH₂-CH₂-; or **O-CH₂-CH₂-CH(CF₃)-CH₂-;
- wherein the double asterisks indicate the attachment point of linker group L¹ to Ring A.

7) Another embodiment relates to compounds according to any one of embodiments 2) to 4), wherein L represents linker group L¹; wherein linker group L¹ is selected from:



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or, in addition to the above-listed:

, or ;

wherein the double asterisks indicate the attachment point of linker group **L¹** to **Ring A**.

8) Another embodiment relates to compounds according to any one of embodiments 2) to 4), wherein **L** represents linker group **L²**; wherein linker group **L²** is selected from:

- 5 ➤ *-O-(CH₂)-(cyclic moiety)-, *-O-(cyclic moiety)-(CH₂)-, *-O-(cyclic moiety)-CH=CH-, or *-O-(cyclic moiety)-(CH₂)₂-; wherein notably independently the cyclic moiety of such linker group **L²** represents:
- (C₃₋₆)cycloalkan-1,2-diyl (in particular cyclopropan-1,2-diyl, cyclobutan-1,2-diyl, cyclopentan-1,2-diyl, or cyclohexan-1,2-diyl);
 - phen-1,2-diyl; or
 - 10 ○ 5- or 6-membered heterocycloalkan-diyl; wherein said heterocycloalkan-diyl is linked to the rest of the molecule via two of its ring atoms that are in ortho position relative to one another (in particular tetrahydrofuran-2,3-diyl or tetrahydrofuran-3,4-diyl); or
- *(cyclic moiety)-(CH₂)-, *(cyclic moiety)-(CH₂)₂-, *(cyclic moiety)-CH=CH-, *(cyclic moiety)-(CH₂)₃-, *-O-(cyclic moiety)-, *-O-(cyclic moiety)-(CH₂)-, or *-O-(CH₂)-(cyclic moiety)-; wherein notably independently
- 15 the cyclic moiety of such linker group **L²** represents:
- (C₃₋₆)cycloalkan-1,3-diyl (in particular cyclobutan-1,3-diyl, cyclopentan-1,3-diyl, or cyclohexan-1,3-diyl);
 - 5- or 6-membered heterocycloalkan-diyl; wherein said heterocycloalkan-diyl is linked to the rest of the molecule via two of its ring atoms that are in meta position relative to one another (in particular pyrrolidin-1,3-diyl or piperidin-1,3-diyl); or
 - 20 ○ 5- or 6-membered heteroaryl-diyl; wherein said heteroaryl-diyl is linked to the rest of the molecule via two of its ring atoms that are in meta position relative to one another (in particular 1*H*-pyrazol-1,3-diyl, pyridin-2,6-diyl, 1,2,4-oxadiazol-3,5-diyl, or 1,3,4-oxadiazol-2,5-diyl);

wherein said linker group **L²** is unsubstituted or mono-substituted with halogen (notably chloro);

25 wherein the asterisks indicate the attachment point of linker group **L²** to **Ring A**.

9) Another embodiment relates to compounds according to any one of embodiments 1) to 8), wherein in case **L** represents linker group **L²**; said linker group **L²** independently is:

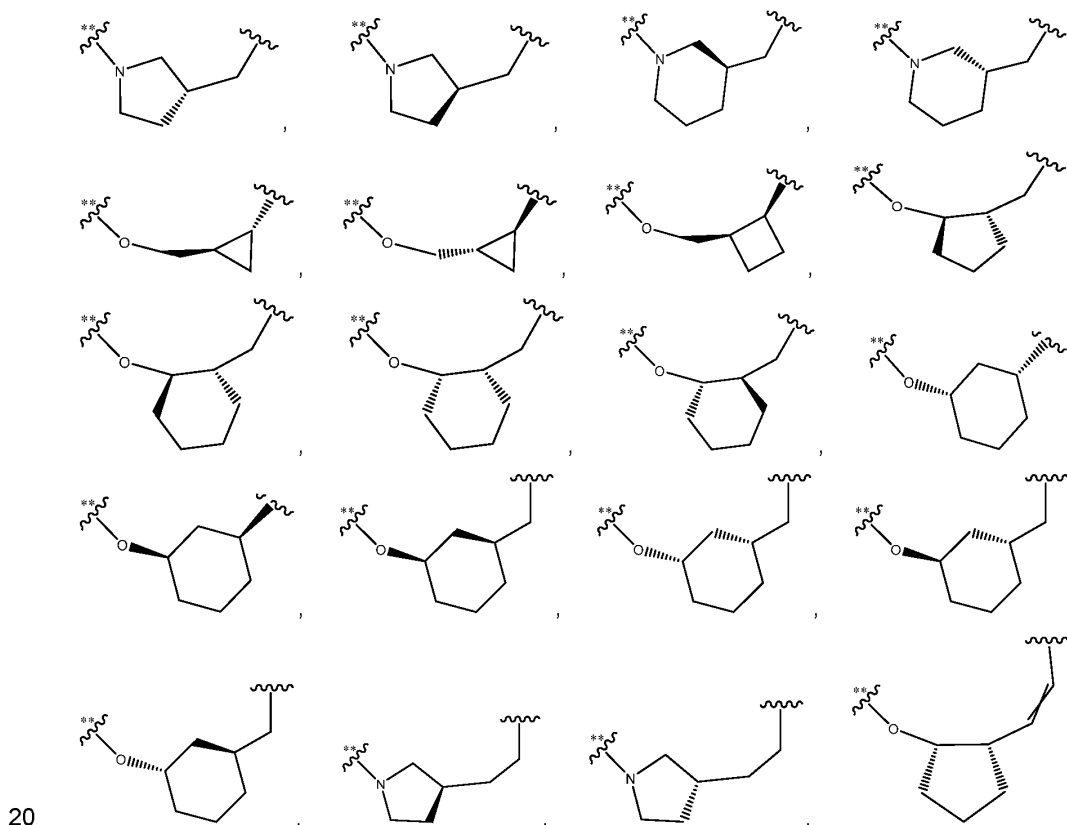
- 30 **-(pyrrolidin-1*,3-diyl)-CH₂-; **-(piperidin-1*,3-diyl)-CH₂-; **-O-CH₂-(cyclopropan-1,2-diyl)-; **-O-CH₂-(cyclobutan-1,2-diyl)-; **-O-(cyclopentan-1,2-diyl)-CH₂-; **-O-(cyclohexan-1,2-diyl)-CH₂-; **-O-(cyclohexan-1,3-diyl)-; **-O-(cyclohexan-1,3-diyl)-CH₂-; **-(pyrrolidin-1*,3-diyl)-CH₂-CH₂-; **-O-(cyclopentan-1,2-diyl)-CH=CH-; **-O-(cyclopentan-1,3-diyl)-CH₂-; **-O-(cyclopentan-1,2-diyl)-CH₂-CH₂-;

- 5 **O-CH2-(cyclobutan-1,3-diyl)-; **O-(tetrahydrofuran-3,4-diyl)-CH2-CH2-; **-(4-chloro-pyrazol-1,3*-diyl)-CH2-CH2-; **O-(tetrahydrofuran-2,3*-diyl)-CH2-CH2-; **O-(cyclobutan-1,2-diyl)-CH2-CH2-; **O-CH2-CH2-(cyclopropan-1,2-diyl)-; **O-([1,3,4]oxadiazol-2,5-diyl)-CH2-; **O-(phen-1,2-diyl)-CH2-CH2-; **-(pyridin-2,6-diyl)-CH2-CH2-; **-[1,2,4]oxadiazol-3*,5-diyl)-CH2-CH2-CH2-; **O-(cyclobutan-1,3-diyl)-CH2-CH2-; **O-(tetrahydrofuran-2,4*-diyl)-CH2-; **O-(tetrahydropyran-2,4*-diyl)-CH2-; **O-(piperidin-1,3*-diyl)-CH2-; **O-CH2-(cyclopentan-1,3-diyl)-; **O-(tetrahydropyran-3,5-diyl)-CH2-; or **O-(cyclohexan-1,2-diyl)-CH2-CH2-;
- or, in addition to the above-listed, **O-CH2-(cyclopropan-1,2-diyl)-CH2-; **O-CH(CH3)-CH2-(cyclopropan-1,2-diyl)-; **-(pyrazol-1,3*-diyl)-CH2-CH2-; or **O-(cyclopentan-1,2-diyl)-O-CH2-;

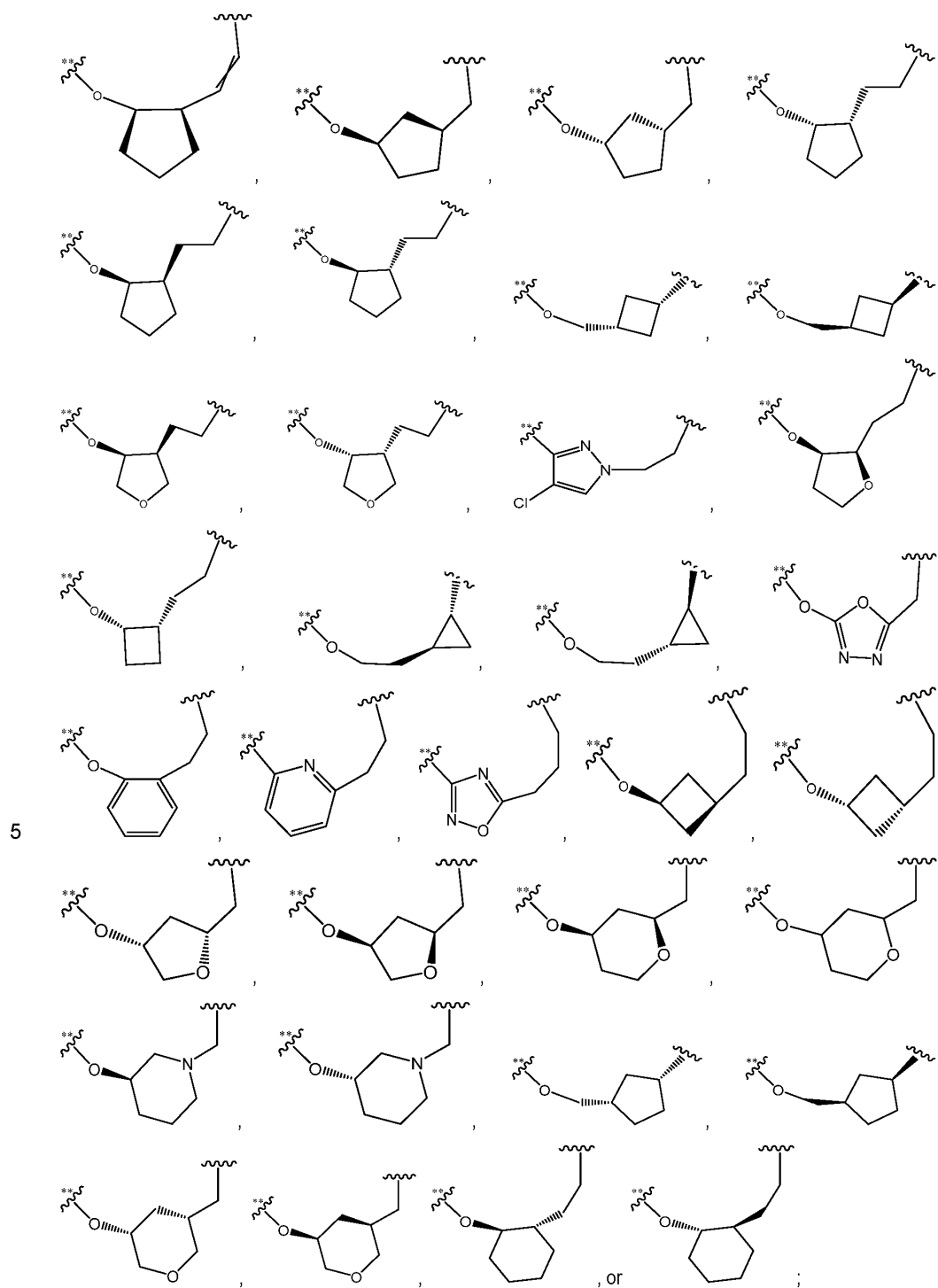
10 wherein in a subembodiment **L** represents linker group **L²**;

wherein the double asterisks indicate the attachment point of linker group **L²** to **Ring A**; and, where applicable, the single asterisks indicate the attachment point of the linker oxygen atom which is attached to **Ring A**, or of **Ring A**, as the case may be.

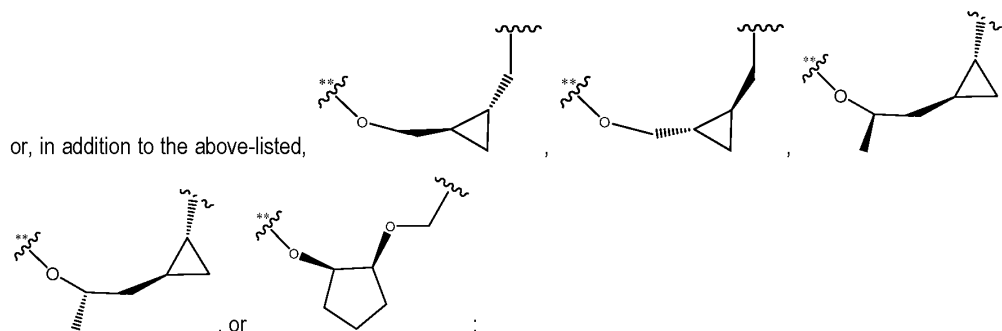
- 10) Another embodiment relates to compounds according to any one of embodiments 2) to 4), wherein **L** represents
- 15 linker group **L²**; wherein linker group **L²** is selected from:



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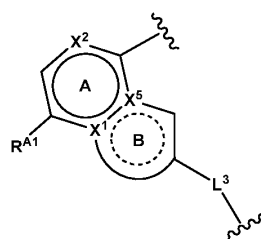


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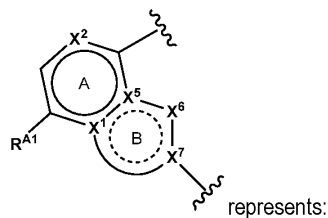
wherein the double asterisk indicates the attachment point of linker group L^2 to **Ring A**.

11) Another embodiment relates to compounds according to embodiment 1), wherein **Ring A** and **L** together represent:

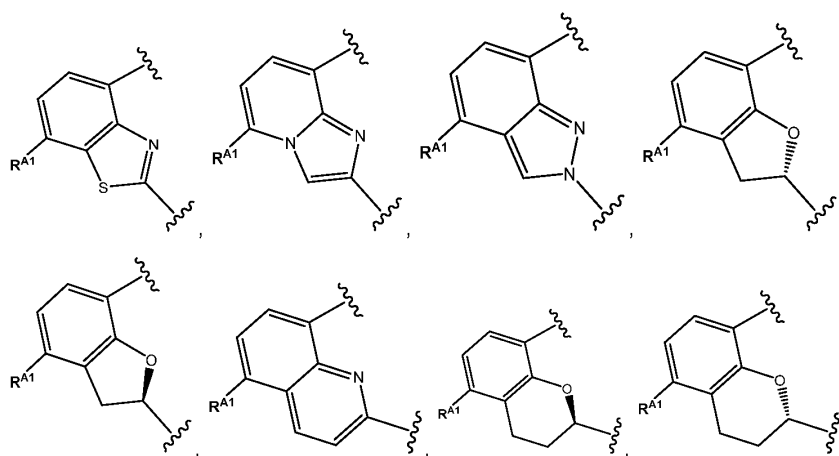


Formula (I-B).

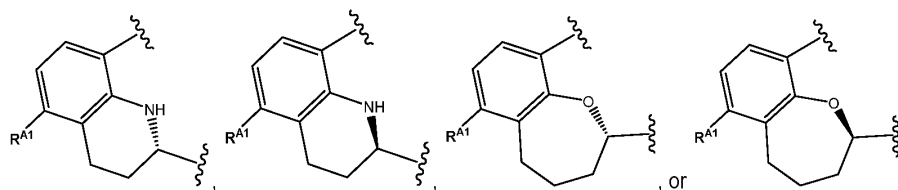
12) Another embodiment relates to compounds according to embodiment 11), wherein the fragment:



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wherein in the above groups R^{A1} independently is as defined in embodiment 1).

13) Another embodiment relates to compounds according to any one of embodiments 1) to 12), wherein X^3 represents SO_2 or $S(O)(NR^3)$, wherein R^3 represents hydrogen or (C_{1-3}) alkyl (notably methyl including methyl- d_3).

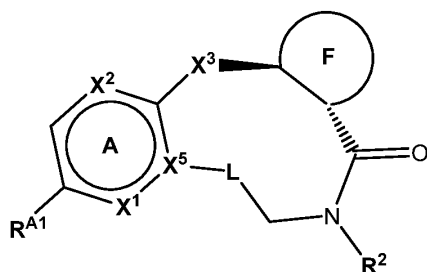
- 5 14) Another embodiment relates to compounds according to any one of embodiments 1) to 13), wherein X^4 represents CHR^{C1} , and R^1 and R^{C1} together form a ring comprising X^4 , herein **Ring F**, wherein **Ring F** represents a monocyclic (C_{5-6}) cycloalkan-diyl (notably cyclopentan-1,2-diyl).

In a sub-embodiment of embodiment 14), X^3 notably represents SO_2 , $S(=O)(=NH)$, or $S(=O)(=N(CH_3))$; especially SO_2 or $S(=O)(=N(CH_3))$.

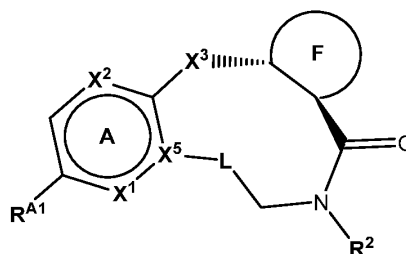
- 10 15) Another embodiment relates to compounds according to embodiment 14), wherein the substituents $-X^3-(\text{Ring A})$ and $-C(=O)NR^2$ of **Ring F** are in relative trans configuration.

When X^4 represents CH, the compounds of Formula (I) contain at least two stereogenic centers which are situated at the two carbon atoms of **Ring F** that link **Ring F** to $-X^3-(\text{Ring A})$ and to $-C(=O)NR^2$. Thus, according to this embodiment, a compound of Formula (I) represents either a compound of Formula (II-F), or a compound of Formula

- 15 (III-F), or any mixture thereof:



Formula (II-F)



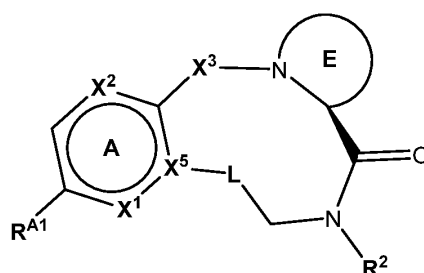
Formula (III-F);

in a particular embodiment, the compounds of Formula (I) are also compounds of Formula (III-F).

- 16) Another embodiment relates to compounds according to any one of embodiments 1) to 13), wherein X^4 represents NR^{N1} , and R^1 and R^{N1} together form a ring comprising X^4 , herein **Ring E**, wherein said **Ring E** is, mutatis mutandis, as defined in embodiment 1), especially **Ring E** is pyrrolidin-1,2-diyl.

17) Another embodiment relates to compounds according to embodiment 16), wherein the compounds of Formula (I) represents a compound of Formula (II-E):

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Formula (II-E).

In a sub-embodiment of embodiment of embodiment 17), the compounds of Formula (I) represents a compound of Formula (II-E) and:

- 5
 - **Ring A** represents a 6-membered aromatic ring as defined in embodiment 4);
 - **L** represents linker group **L**¹; notably **L** represents linker group **L**¹ as defined in any one of embodiments 5) to 7);
 - **X**³ is as defined in embodiment 13); and
 - **R**² is as defined in embodiment 21).
- 10 18) Another embodiment relates to compounds according to embodiment 16) or 17), wherein **Ring E** represents:
 - a 5- or 6-membered saturated monocyclic heterocycloalkan-diyl comprising **X**⁴ and zero or one ring oxygen atom (notably pyrrolidin-1,2-diyl, piperidin-1,2-diyl, 1,3-oxazinan-2,3-diyl, morpholin-3,4-diyl, or oxazolidin-2,3-diyl); wherein said heterocycloalkan-diyl is unsubstituted or mono-substituted; wherein the substituents are independently selected from the group consisting of: (C₁₋₃)alkyl (notably methyl), halogen (notably fluoro), and (C₁₋₃)alkoxy (notably methoxy); [in particular such **Ring E** represents pyrrolidin-1,2-diyl, 3-fluoro-pyrrolidin-1,2-diyl, 4-fluoro-pyrrolidin-1,2-diyl, 4-methyl-pyrrolidin-1,2-diyl, 4-methoxy-pyrrolidin-1,2-diyl, piperidin-1,2-diyl, 1,3-oxazinane-2,3-diyl, morpholin-3,4-diyl, or oxazolidine-2,3-diyl]; or
 - a 6- or 7-membered saturated fused or bridged bicyclic heterocycloalkan-diyl comprising **X**⁴; [in particular such **Ring E** represents 2-azabicyclo[3.1.0]hexan-2,3-diyl, 3-azabicyclo[3.1.0]hexan-2,3-diyl, or 2-azabicyclo[2.2.1]heptan-2,3-diyl].
- 15
- 20 19) Another embodiment relates to compounds according to embodiment 16) or 17), wherein said **Ring E** represents:
 - a 5- or 6-membered saturated monocyclic heterocycloalkan-diyl comprising **X**⁴ and zero or one ring oxygen atom (notably pyrrolidin-1,2-diyl, piperidin-1,2-diyl, 1,3-oxazinan-2,3-diyl, morpholin-3,4-diyl, or oxazolidin-2,3-diyl); wherein said heterocycloalkan-diyl unsubstituted or mono-substituted; wherein the substituents are independently selected from the group consisting of: (C₁₋₃)alkyl (notably methyl), halogen (notably fluoro), and (C₁₋₃)alkoxy (notably methoxy); [in particular such **Ring E** represents pyrrolidin-1,2-diyl, 4-fluoro-pyrrolidin-1,2-diyl, 4-methyl-pyrrolidin-1,2-diyl, 4-methoxy-pyrrolidin-1,2-diyl, piperidin-1,2-diyl, 1,3-oxazinane-2,3-diyl, morpholin-3,4-diyl, or oxazolidine-2,3-diyl]; or
- 25

- a 6-membered saturated fused bicyclic heterocycloalkan-diyl comprising **X⁴**; [in particular such **Ring E** represents 2-azabicyclo[3.1.0]hexan-2,3-diyl or 3-azabicyclo[3.1.0]hexan-2,3-diyl].

20) Another embodiment relates to compounds according to any one of embodiments 1) to 19), wherein **R²** represents:

- 5
- 3-cyano-3,3-dimethylpropyl;
 - $-(CH_2)_m-(\text{Ring D})$, wherein **m** is the integer 0 or 1 (notably 0), and **Ring D** represents:
 - a saturated monocyclic (C_{4-7})cycloalkyl (notably cyclobutyl, cyclopentyl, or cyclohexyl); wherein said (C_{4-7})cycloalkyl is mono-, di-, or tri-substituted; wherein the substituents are independently selected from the group consisting of:

10

 - (C_{1-3})alkyl (notably methyl); wherein said (C_{1-3})alkyl is unsubstituted or mono-substituted with cyano (notably cyano-methyl);
 - halogen (notably fluoro);
 - (C_{1-3})alkoxy (notably methoxy);
 - (C_{3-4})cycloalkyl (notably cyclopropyl);

15

 - hydroxy; and
 - cyano;

[in particular such $-(CH_2)_m-(\text{Ring D})$ represents 3-cyano-cyclobutyl, 3-(cyanomethyl)-3-methyl-cyclobutyl, (3,3-difluorocyclobutyl)-methyl, 2-hydroxy-cyclopentyl, 2-methoxy-cyclopentyl, 3-cyano-cyclopentyl, 3-hydroxy-cyclopentyl, 3-methoxy-cyclopentyl, 3,3-difluoro-cyclopentyl, 2-cyano-cyclohexyl, 2-hydroxy-cyclohexyl, 2-methoxy-cyclohexyl, 3-cyano-cyclohexyl, 3-hydroxy-cyclohexyl, 3-methoxy-cyclohexyl, 4-cyano-cyclohexyl, 4-hydroxy-cyclohexyl, 4-(cyanomethyl)-cyclohexyl, 4-methoxy-cyclohexyl, 2-hydroxy-2-methyl-cyclohexyl, 3-cyano-3-methyl-cyclohexyl, 3,3-difluoro-cyclohexyl, 4-hydroxy-4-methyl-cyclohexyl, 4-cyclopropyl-4-hydroxy-cyclohexyl, 4-cyano-4-methyl-cyclohexyl, 4-cyano-4-cyclopropyl-cyclohexyl, 4,4-dimethyl-cyclohexyl, 4-fluoro-4-methyl-cyclohexyl, 4,4-difluoro-cyclohexyl, 4,4-difluoro-2-hydroxy-cyclohexyl, or 4,4-difluoro-2-methoxy-cyclohexyl];

20

 - a saturated bicyclic (C_{5-8})spirocycloalkyl (notably spiro[2.2]pentanyl, spiro[2.3]hexanyl, spiro[2.4]heptanyl, spiro[3.3]heptanyl, or spiro[2.5]octanyl); wherein said (C_{5-8})spirocycloalkyl is unsubstituted, or mono-, di-, tri- or tetra-substituted; wherein the substituents are independently selected from the group consisting of: halogen (notably fluoro), cyano, and hydroxy; [in particular such $-(CH_2)_m-(\text{Ring D})$ represents 4-cyano-spiro[2.2]pentan-1-yl, spiro[2.3]hexan-5-yl, 1,1-difluoro-spiro[2.3]hexan-5-yl, 1,1-difluoro-spiro[2.4]heptan-5-yl, spiro[3.3]heptan-2-yl, 6-hydroxy-spiro[3.3]heptan-2-yl, 6,6-difluoro-spiro[3.3]heptan-2-yl, spiro[2.5]octan-6-yl, 1-cyano-spiro[2.5]octan-6-yl, 1,1,2,2-tetrafluoro-spiro[2.5]octan-6-yl, or 1,1-difluoro-spiro[2.5]octan-6-yl];

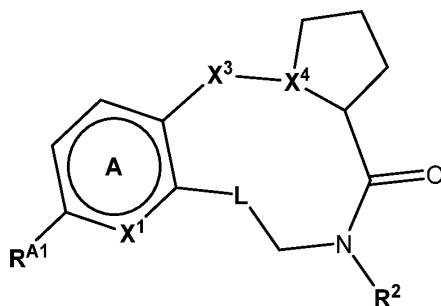
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 - a saturated fused or bridged bicyclic (C_{5-8})cycloalkyl (notably bicyclo[1.1.1]pentanyl, bicyclo[3.1.0]hexanyl, bicyclo[4.1.0]heptanyl, or octahydropentalen-2-yl); wherein said bicyclic
- 30
- 35

- (C₅₋₈)cycloalkyl is unsubstituted, or mono- or di-substituted; wherein the substituents are independently selected from the group consisting of: (C₁₋₃)fluoroalkyl (notably (C₁)fluoroalkyl; especially trifluoromethyl), halogen (notably fluoro), and cyano; [in particular such -(CH₂)_m-(**Ring D**) represents 5-cyano-octahydropentalen-2-yl, 3-trifluoromethyl-bicyclo[1.1.1]pentan-1-yl, 6,6-difluoro-bicyclo[3.1.0]hexan-3-yl, bicyclo[4.1.0]heptan-3-yl, or 7,7-difluoro-bicyclo[4.1.0]heptan-3-yl];
- 5
- a 5- or 6-membered saturated monocyclic heterocycle comprising one ring heteroatomic group selected from O, NR^{N2}, or SO₂; wherein R^{N2} represents (C₁₋₃)alkyl (notably methyl); (notably such heterocycle represents tetrahydropyranyl or piperidiny); wherein said heterocycle is
- 10
- unsubstituted, or mono-, di-, tri-, or tetra-substituted; wherein the substituents are independently selected from the group consisting of: (C₁₋₃)alkyl (notably methyl, ethyl, or isopropyl) and oxo; [in particular such -(CH₂)_m-(**Ring D**) represents tetrahydropyran-3-yl, (tetrahydropyran-3-yl)-methyl, tetrahydropyran-4-yl, 2-isopropyl-tetrahydropyran-4-yl, 2-methyl-tetrahydropyran-4-yl, 2,2-
- 15
- dimethyl-tetrahydropyran-4-yl, 2,2-diethyl-tetrahydropyran-4-yl, 2,6-dimethyl-tetrahydropyran-4-yl, 6,6-dimethyl-tetrahydropyran-3-yl, 2,2,6,6-tetramethyl-tetrahydropyran-4-yl, or 1-methyl-2-oxo-piperidin-4-yl];
- a 9-membered saturated spiro bicyclic heterocycle comprising one ring oxygen atom [notably such -(CH₂)_m-(**Ring D**) represents 2-oxa-spiro[3.5]nonan-7-yl]; or
 - a 7-membered saturated fused or bridged bicyclic heterocycle comprising one ring oxygen atom;
- 20
- [notably such -(CH₂)_m-(**Ring D**) represents 7-oxa-bicyclo[2.2.1]heptan-2-yl]; .
- 21) Another embodiment relates to compounds according to any one of embodiments 1) to 19), wherein R² represents:
- 3-cyano-3,3-dimethylpropyl;
 - **Ring D**, wherein **Ring D** represents:
- 25
- a saturated monocyclic (C₄₋₇)cycloalkyl (notably cyclopentyl or cyclohexyl); wherein said (C₄₋₇)cycloalkyl is mono-, di-, or tri-substituted; wherein the substituents are independently selected from the group consisting of:
- 30
- (C₁₋₃)alkyl (notably methyl); wherein said (C₁₋₃)alkyl is unsubstituted or mono-substituted with cyano (notably cyano-methyl);
 - halogen (notably fluoro);
 - (C₁₋₃)alkoxy (notably methoxy);
 - (C₃₋₄)cycloalkyl (notably cyclopropyl);
 - hydroxy; and
 - cyano;
- 35
- [in particular such **Ring D** represents 3-(cyanomethyl)-3-methyl-cyclobutyl, 3-cyano-cyclopentyl, 3,3-difluoro-cyclopentyl, 2-cyano-cyclohexyl, 2-hydroxy-cyclohexyl, 2-methoxy-cyclohexyl, 3-

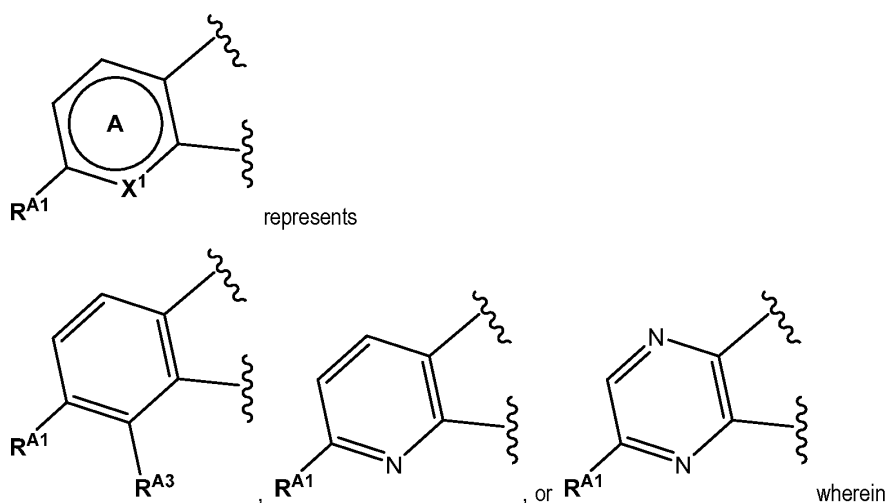
- cyano-cyclohexyl, 3-hydroxy-cyclohexyl, 3-methoxy-cyclohexyl, 4-cyano-cyclohexyl, 4-hydroxy-cyclohexyl, 4-(cyanomethyl)-cyclohexyl, 3-cyano-3-methyl-cyclohexyl, 3,3-difluoro-cyclohexyl, 4-cyano-4-methyl-cyclohexyl, 4-cyano-4-cyclopropyl-cyclohexyl, 4,4-dimethyl-cyclohexyl, 4-fluoro-4-methyl-cyclohexyl, 4,4-difluoro-cyclohexyl, or 4,4-difluoro-2-hydroxy-cyclohexyl];
- 5 o a saturated bicyclic (C_{5-8})spirocycloalkyl (notably spiro[2.3]hexanyl, spiro[2.4]heptanyl, spiro[3.3]heptanyl, or spiro[2.5]octanyl); wherein said (C_{5-8})spirocycloalkyl is unsubstituted, or mono-, di-, tri- or tetra-substituted; wherein the substituents are independently selected from the group consisting of: halogen (notably fluoro) and cyano; [in particular such **Ring D** represents
- 10 1,1-difluoro-spiro[2.3]hexan-5-yl, 1,1-difluoro-spiro[2.4]heptan-5-yl, spiro[3.3]heptan-2-yl, spiro[2.5]octan-6-yl, 1-cyano-spiro[2.5]octan-6-yl, 1,1,2,2-tetrafluoro-spiro[2.5]octan-6-yl, or 1,1-difluoro-spiro[2.5]octan-6-yl];
- 15 o a saturated fused or bridged bicyclic (C_{5-8})cycloalkyl (notably bicyclo[3.1.0]hexanyl, bicyclo[4.1.0]heptanyl, or octahydropentalen-2-yl); wherein said bicyclic (C_{5-8})cycloalkyl is unsubstituted, or mono- or di-substituted; wherein the substituents are independently selected from the group consisting of: halogen (notably fluoro) and cyano; [in particular such **Ring D** represents
- 20 5-cyano-octahydropentalen-2-yl, 6,6-difluoro-bicyclo[3.1.0]hexan-3-yl, bicyclo[4.1.0]heptan-3-yl, or 7,7-difluoro-bicyclo[4.1.0]heptan-3-yl];
- 25 o a 5- or 6-membered saturated monocyclic heterocycle comprising one ring heteroatomic group selected from O or SO_2 (notably such heterocycle represents tetrahydropyranyl or piperidinyl); wherein said heterocycle is unsubstituted, or mono-, di-, tri-, or tetra-substituted; wherein the substituents are independently (C_{1-3})alkyl (notably methyl or ethyl); [in particular such **Ring D** represents tetrahydropyran-4-yl, 2-methyl-tetrahydropyran-4-yl, 2,2-dimethyl-tetrahydropyran-4-yl, 2,2-diethyl-tetrahydropyran-4-yl, 2,6-dimethyl-tetrahydropyran-4-yl, 6,6-dimethyl-tetrahydropyran-3-yl, or 2,2,6,6-tetramethyl-tetrahydropyran-4-yl].

25 22) Another aspect of the invention relates to compounds of Formula (IV)



Formula (IV)

wherein the fragment



- R^{A1} independently represents hydrogen, (C_{1-3}) alkyl (notably methyl), (C_{1-3}) alkoxy (notably methoxy), or halogen (notably chloro or fluoro); and

- 5 ➤ R^{A3} , if present, independently represents hydrogen, halogen (notably fluoro), or (C_{1-3}) alkyl (notably methyl);

[in particular said fragment represents 6-methyl-pyridin-2,3-diyl, 4-methyl-phen-1,2-diyl, 3-fluoro-4-methyl-phen-1,2-diyl, or 5-methyl-pyrazin-2,3-diyl];

L represents:

- 10 • linker group L^1 wherein such linker group L^1 independently is:
- $**O-CH(CH_3)-CH_2-$; $**O-CH_2-CH_2-CH_2-$; $**O-CH(CH_3)-CH_2-CH_2-$; $**O-cyclopropan-1,1-diyl-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-CH_2-$; $**S-CH(CH_3)-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-CH_2-CH_2-$; $**CH=CH-CH_2-CH_2-CH_2-$; $**O-CH_2-CH_2-CH_2-CH_2-$; $**O-CH(CH_3)-CH_2-CH_2-CH_2-$; $**O-CH(ethyl)-CH_2-CH_2-CH_2-$; $**O-CH(n-propyl)-CH_2-CH_2-CH_2-$; $**O-CH(isopropyl)-CH_2-CH_2-CH_2-$; $**O-CH(cyclopropyl)-CH_2-CH_2-CH_2-$; $**O-CH_2-CH(CH_3)-CH_2-CH_2-$; $**O-CH_2-CH_2-CH(CH_3)-CH_2-$; $**O-CH_2-CH_2-CH(ethyl)-CH_2-$; $**O-CH_2-CF_2-CH_2-CH_2-$; $**O-CH_2-CH_2-C(CH_3)_2-CH_2-$; $**O-CH_2-CH_2-cyclopropan-1,1-diyl-CH_2-$; $**O-CH_2-CH_2-C(hydroxy)(cyclopropyl)-CH_2-$; $**O-CH_2-CH_2-CH_2-CH(CH_3)-$; $**O-CH(CH_3)-CH_2-CH=CH-$; $**CH_2-O-CH_2-CH_2-CH_2-$; $**CH_2-CH_2-CH_2-O-CH_2-$; $**O-CH(CH_3)-CH_2-O-CH_2-$; $**NH-CH_2-CH_2-CH_2-CH_2-$; $**N(CH_3)-CH_2-CH_2-CH_2-CH_2-$; $**N(CH_3)-CH_2-CH_2-CH=CH-$; $**NH-CH(CH_3)-CH_2-CH_2-CH_2-$; or $**O-CH_2-CH_2-CH_2-CH_2-CH_2-$; $**O-CH(ethyl)-CH_2-O-CH_2-$; $**O-CH_2-CF_2-CH_2-CH_2-$; $**O-CH(CH_3)-CH_2-CH(CH_3)-CH_2-$; $**O-CH_2-CH_2-N(cyclopropyl)-CH_2-$; $**O-CH(CH_3)-CH_2-N(cyclopropyl)-CH_2-$; $**O-CH(CF_3)-CH_2-CH_2-CH_2-$; $**O-CH_2-CH_2-CH(CF_3)-CH_2-$; or $**O-CH_2-CH_2-N(2,2,2-trifluoroethyl)-CH_2-$;
- 15 [especially such linker group L^1 is $**O-CH_2-CH_2-CH_2-$; $**O-CH(CH_3)-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-CH_2-CH_2-$; $**O-CH_2-CH_2-CH_2-CH_2-$; $**O-CH(CH_3)-CH_2-CH_2-CH_2-$; $**O-CH(ethyl)-CH_2-CH_2-CH_2-$; $**O-CH(n-propyl)-CH_2-CH_2-CH_2-$; $**O-CH_2-CH(CH_3)-CH_2-CH_2-$; $**O-CH_2-CH_2-CH(CH_3)-CH_2-$; $**O-CH_2-CH_2-CH(ethyl)-CH_2-$; $**O-CH_2-CF_2-CH_2-CH_2-$; $**N(CH_3)-CH_2-CH_2-CH_2-CH_2-$; $**N(CH_3)-CH_2-CH_2-CH=CH-$; $**NH-CH(CH_3)-CH_2-$
- 25

CH=CH-; **NH-CH(CH₃)-CH₂-CH₂-CH₂-; **O-CH(CH₃)-CH₂-O-CH₂-; **O-CH(ethyl)-CH₂-O-CH₂-; **O-CH(CH₃)-CH₂-CH(CH₃)-CH₂-; **O-CH(CF₃)-CH₂-CH₂-CH₂-; or **O-CH₂-CH₂-CH(CF₃)-CH₂-;

wherein the double asterisks indicate the attachment point of said linker group **L**¹ to **Ring A**;

or

- 5 • linker group **L**²; wherein such linker group **L**² independently is:
- **-(pyrrolidin-1*,3-diyl)-CH₂-; **-(piperidin-1*,3-diyl)-CH₂-; **O-CH₂-(cyclopropan-1,2-diyl)-; **O-CH₂-(cyclobutan-1,2-diyl)-; **O-(cyclopentan-1,2-diyl)-CH₂-; **O-(cyclohexan-1,2-diyl)-CH₂-; **O-(cyclohexan-1,3-diyl)-; **O-(cyclohexan-1,3-diyl)-CH₂-; **-(pyrrolidin-1*,3-diyl)-CH₂-CH₂-; **O-(cyclopentan-1,2-diyl)-CH=CH-; **O-(cyclopentan-1,3-diyl)-CH₂-; **O-(cyclopentan-1,2-diyl)-CH₂-CH₂-; **O-CH₂-(cyclobutan-1,3-diyl)-;
- 10 **O-(tetrahydrofuran-3,4-diyl)-CH₂-CH₂-; **-(4-chloro-pyrazol-1,3*-diyl)-CH₂-CH₂-; **O-(tetrahydrofuran-2,3*-diyl)-CH₂-CH₂-; **O-(cyclobutan-1,2-diyl)-CH₂-CH₂-; **O-CH₂-CH₂-(cyclopropan-1,2-diyl)-; **O-([1,3,4]oxadiazol-2,5-diyl)-CH₂-; **O-(phen-1,2-diyl)-CH₂-CH₂-; **-(pyridin-2,6-diyl)-CH₂-CH₂-; **-(1,2,4]oxadiazol-3*,5-diyl)-CH₂-CH₂-CH₂-; **O-(cyclobutan-1,3-diyl)-CH₂-CH₂-; **O-(tetrahydrofuran-2,4*-diyl)-CH₂-; **O-(tetrahydropyran-2,4*-diyl)-CH₂-; **O-(piperidin-1,3*-diyl)-CH₂-; **O-CH₂-(cyclopentan-1,3-diyl)-;
- 15 **O-(tetrahydropyran-3,5-diyl)-CH₂-; **O-(cyclohexan-1,2-diyl)-CH₂-CH₂-; **O-CH₂-(cyclopropan-1,2-diyl)-CH₂-; **O-CH(CH₃)-CH₂-(cyclopropan-1,2-diyl)-; **-(pyrazol-1,3*-diyl)-CH₂-CH₂-; or **O-(cyclopentan-1,2-diyl)-O-CH₂-; [especially **O-(cyclopentan-1,2-diyl)-CH₂-; **O-(cyclohexan-1,2-diyl)-CH₂-; **O-(cyclohexan-1,3-diyl)-; **O-(cyclohexan-1,3-diyl)-CH₂-; **O-(cyclopentan-1,3-diyl)-CH₂-; **O-(cyclopentan-1,2-diyl)-CH₂-CH₂-; **O-CH₂-CH₂-(cyclopropan-1,2-diyl)-; **O-CH(CH₃)-CH₂-(cyclopropan-1,2-diyl)-; **O-(tetrahydrofuran-2,4*-diyl)-CH₂-; **-(pyrrolidin-1*,3-diyl)-CH₂-CH₂-; or **O-(cyclopentan-1,2-diyl)-O-CH₂-];
- 20

wherein the double asterisks indicate the attachment point of linker group **L**² to **Ring A**; and, where applicable, the single asterisks indicate the attachment point of the linker oxygen atom which is attached to **Ring A**, or of **Ring A**, as the case may be;

X³ represents SO₂ or S(O)(NR³), wherein **R**³ represents hydrogen or methyl (including methyl-*d*3), [in particular **X**³ represents SO₂, S(=O)(=NH), S(=O)(=N(CH₃)), or S(=O)(=N(CD₃))];

25

X⁴ represents N or CH; and

R² represents:

- cyclopentyl or cyclohexyl; wherein said cyclopentyl or cyclohexyl independently is mono-, or di-substituted; wherein the substituents are independently selected from the group consisting of (C₁₋₃)alkyl (notably methyl),
- 30 halogen (notably fluoro), and cyano;
- [in particular 3-cyano-cyclopentyl, 3,3-difluoro-cyclopentyl, 3,3-dimethyl-cyclopentyl, 3-cyano-3-methyl-cyclopentyl, 3-cyano-cyclohexyl, 4-cyano-cyclohexyl, 3-cyano-3-methyl-cyclohexyl, 3,3-difluoro-cyclohexyl, 4-cyano-4-methyl-cyclohexyl (as well as its deuterated isotope 4-cyano-4-(methyl-*d*3)-cyclohexyl), 4-cyano-4-ethyl-cyclohexyl (as well as its deuterated isotope 4-cyano-4-(ethyl-*d*5)-cyclohexyl), 4,4-dimethyl-cyclohexyl,
- 35 4-fluoro-4-methyl-cyclohexyl, 4,4-difluoro-cyclohexyl]; or

- a saturated bicyclic (C₆₋₈)spirocycloalkyl (notably spiro[2.3]hexanyl, or spiro[2.5]octanyl); wherein said (C₆₋₈)spirocycloalkyl is unsubstituted, or di-substituted with fluoro; [in particular 1,1-difluoro-spiro[2.3]hexan-5-yl, 1,1-difluoro-spiro[2.4]heptan-5-yl, 6,6-difluoro-spiro[3.3]heptan-2-yl, or 1,1-difluoro-spiro[2.5]octan-6-yl].

23) Another embodiment relates to compounds according to embodiment 1) which are selected from the following example compounds (wherein the chemical name of the compound is as in the experimental part, and the structure is as in the Table of Examples herein below):

- 1.1; 1.2; 1.3; 1.4; 1.6; 1.5; 1.7; 1.8; 1.9; 1.10; 1.11; 1.12; 1.13; 1.14; 1.15; 1.18; 1.19; 1.20; 1.21; 1.22; 1.23; 1.24; 1.25; 1.26; 1.27; 1.28; 1.29; 1.30; 1.31; 1.32; 1.33; 1.34; 1.35; 1.36; 1.37; 1.38; 1.39; 1.40; 1.41; 1.42; 1.43; 1.44; 1.45; 1.46; 1.48; 1.49; 1.50; 1.51; 1.52; 1.53; 1.54; 1.55; 1.56; 1.57; 1.58; 1.59; 1.60; 1.61; 1.62; 1.63; 1.64; 1.65; 1.66; 1.67; 1.68; 1.69; 1.70; 1.71; 1.72; 1.73; 1.74; 1.75; 1.76; 1.77; 1.78; 3.1; 1.79; 1.80; 1.296; 1.81; 1.82; 1.83; 1.84; 1.85; 1.86; 1.87; 1.88; 1.89; 1.90; 1.91; 1.92; 1.93; 1.94; 1.95; 1.96; 1.97; 1.98; 1.99; 1.100; 1.297; 1.101; 1.102; 1.103; 1.104; 1.105; 1.107; 1.298; 1.108; 1.109; 1.110; 1.112; 1.113; 1.118; 1.119; 1.120; 1.121; 1.122; 1.123; 3.2; 1.124; 1.125; 1.126; 1.127; 1.128; 1.129; 1.130; 1.131; 1.132; 2.1; 1.133; 2.2; 2.3; 1.134; 2.4; 1.299; 1.135; 3.3; 1.136; 3.6; 3.7; 3.5; 3.4; 1.137; 1.138; 1.139; 1.140; 1.141; 1.142; 1.143; 1.144; 1.145; 1.146; 4.1; 1.149; 1.150; 1.300; 1.162; 1.166; 1.167; 1.168; 1.301; 1.302; 1.303; 1.173; 1.177; 1.178; 1.179; 1.183; 1.184; 1.185; 1.188; 2.5; 2.6; 1.189; 2.7; 2.8; 1.190; 1.191; 1.192; 1.193; 1.194; 1.196; 2.9; 2.10; 2.11; 2.12; 2.13; 2.14; 2.138; 2.16; 1.197; 1.202; 1.203; 1.204; 1.207; 1.208; 1.209; 1.210; 1.211; 1.213; 1.214; 1.215; 1.218; 1.219; 1.220; 1.221; 1.223; 1.224; 1.225; 1.226; 1.227; 1.228; 1.229; 1.230; 1.231; 1.232; 1.233; 1.234; 1.235; 1.236; 1.237; 1.238; 1.239; 1.240; 1.241; 1.242; 1.243; 1.247; 1.248; 1.249; 1.250; 1.252; 1.253; 1.254; 1.256; 1.257; 1.259; 1.320; 1.260; 1.261; 1.262; 1.263; 1.264; 1.266; 1.267; 1.268; 1.269; 1.270; 1.271; 1.272; 1.273; 1.275; 1.276; 1.277; 1.278; 2.26; 2.28; 2.30; 2.32; 2.34; 2.36; 1.279; 1.280; 1.324; 2.38; 2.39; 2.41; 2.42; 1.281; 1.282; 1.283; 1.284; 1.285; 1.286; 1.289; 1.291; 1.292; 1.293; 1.294; 1.325; 1.326; 1.327; 1.328; 1.329; 1.330; 1.331; 1.332; 1.333; 1.334; 2.43; 2.44; 2.45; 2.46; 2.47; 2.48; 2.49; 2.50; 2.51; 2.52; 1.335; 1.336; 1.337; 1.338; 1.339; 1.342; 1.344; 1.345; 1.346; 2.53; 2.54; 2.55; 2.56; 2.57; 2.58; 2.59; 2.60; 2.61; 2.62; 2.63; 2.64; 1.347; 2.65; 2.66; 2.67; 2.69; 2.70; 1.348; 1.349; 1.350; 1.351; 1.352; 1.353; 1.354; 1.355; 1.356; 1.357; 1.358; 1.359; 1.360; 4.2; 4.3; 4.4; 4.6; 1.363; 1.364; 1.365; 1.366; 1.367; 1.368; 1.369; 1.370; 1.371; 1.372; 1.373; 4.7; 4.8; 4.9; 4.10; 2.71; 2.72; 1.374; 1.375; 1.376; 1.377; 1.378; 1.379; 1.380; 1.381; 1.384; 1.385; 1.386; 1.387; 1.388; 1.389; 1.390; 1.391; 1.392; 1.393; 1.394; 1.395; 1.396; 1.397; 1.398; 1.399; 1.400; 1.401; 1.402; 1.403; 1.404; 1.405; 1.406; 1.407; 1.408; 1.409; 1.410; 1.411; 1.412; 1.413; 1.414; 1.415; 1.416; 1.417; 1.418; 1.425; 1.428; 1.429; 1.430; 1.431; 1.432; 1.433; 1.434; 1.435; 1.437; 1.438; 1.439; 1.440; 1.441; 1.442; 1.443; 1.444; 1.445; 1.446; 1.447; 1.448; 1.449; 1.450; 1.451; 1.452; 1.453; 1.454; 1.455; 1.456; 1.457; 1.458; 1.459; 1.460; 1.461; 1.462; 1.463; 1.464; 1.465; 1.466; 1.469; 2.73; 2.75; 2.76; 2.78; 2.77; 2.79; 1.472; 1.473; 1.475; 1.476; 1.477; 2.80; 2.81; 2.82; 1.478; 1.480; 1.482; 1.483; 1.484; 1.485; 1.487; 1.488; 1.489; 1.493; 1.494; 1.495; 1.496; 1.497; 1.501; 1.504; 2.83; 2.84; 2.85; 2.86; 2.87; 2.88; 1.505; 2.89; 2.139; 2.90; 2.92; 2.140; 2.93; 1.507; 1.508; 1.509; 1.512; 1.514; 1.517; 1.518; 1.522; 1.527; 1.529; 2.94; 2.95; 1.532; 1.533; 1.534; 1.535; 1.536; 1.537; 1.538; 1.539; 1.540; 1.541; 1.542; 1.543; 1.544; 1.545; 1.547; 1.548; 2.96; 2.97; 1.551; 2.98; 2.99; 2.100; 2.101; 2.102; 1.554; 2.103; 2.104; 1.556; 1.558; 2.105;

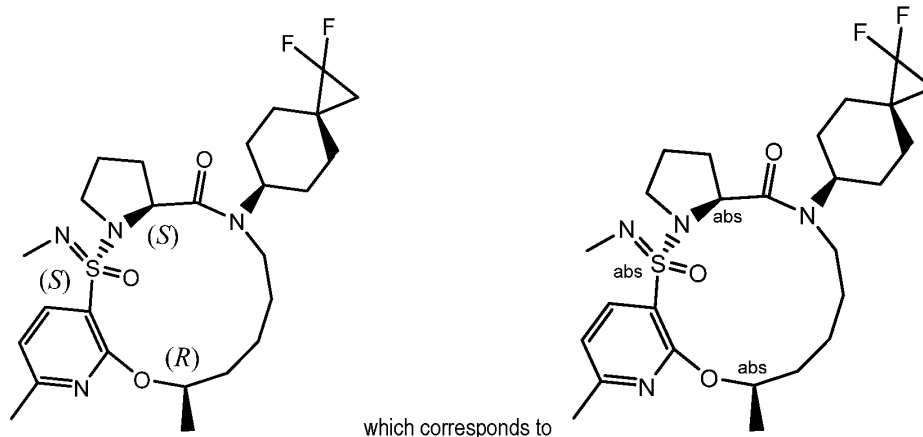
- 2.106; 1.559; 1.560; 2.107; 2.141; 2.108; 1.579; 2.109; 1.581; 1.582; 1.590; 1.591; 1.592; 1.593; 1.594; 1.595; 1.596; 2.110; 1.599; 1.600; 1.601; 2.111; 1.605; 1.608; 1.609; 1.610; 2.112; 2.114; 2.113; 2.115; 2.116; 2.117; 2.118; 1.615; 2.120; 2.121; 2.122; 2.123; 1.617; 1.618; 1.619; 1.620; 1.629; 2.125; 2.126; 2.127; 1.631; 1.633; 1.634; 1.635; 1.638; 1.639; 1.641; 1.642; 1.643; 1.644; 1.645; 1.646; 1.647; 2.128; 2.129; 2.130; 2.131; 2.132;
- 5 2.133; 2.134; 2.135; 2.136; 2.137; 1.650; 2.142; 2.143; 2.144; 2.145; 1.653; 2.146; 2.147; 1.654; 1.655; 2.148; 1.657; 1.658; 1.659; 1.660; 1.661; 1.662; 2.149; 2.150; 2.151; 2.152; 2.153; 1.663; 2.154; 2.155; 1.664; 1.665; 1.666; 1.667; 1.668; 1.669; 1.671; 1.672; 1.673; 2.160; 2.161; 1.674; 1.675; 1.676; 1.677; 2.162; 2.163; 2.164; 1.679; 1.680; 1.681; 1.682; 1.683; 1.684; 1.685; 1.689; 1.690; 1.691; 1.692; 1.693; 2.167; 1.700; 1.701; 1.703; 2.168; 1.707; 2.169; 2.170; 2.171; 2.173; 2.175; 1.710; 1.711; and 1.712.
- 10 24) Another embodiment relates to a compound according to embodiment 1) which is :
 (6R,12aS,15aR)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,13,14,15,15a-decahydrocyclopenta[e]pyrido[2,3-b][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one 16,16-dioxide;
 (6R,12aS,17S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-17-imino-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide;
- 15 (6R,12aS,17S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-17-(methylimino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide;
 (6R,11aS)-10-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide;
- 20 (6R,12aS)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide;
 (6R,12aS)-11-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide;
 (1R,4s)-4-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-
- 25 b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile; or
 (1R,4s)-4-((6R,12aS)-4-Fluoro-3,6-dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile.
- 25) In addition to the compounds listed in embodiment 23), a further embodiment relates to a compound according to embodiment 1) which is:
- 30 (6R,12aS,17S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-17-(methylimino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide;
 (6R,12aS,17S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-17-((methyl-d3)imino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-
- 35 12-one 17-oxide;

- (1²S,5¹S,5³S,2R)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-2-imino-3⁶-methyl-2λ⁶-4-oxa-2λ⁶-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide;
- (1²S,5¹R,5³R,2S)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-2-imino-3⁶-methyl-2λ⁶-4-oxa-2λ⁶-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide
- 5 (1R,4s)-1-Methyl-4-((1²S,5¹R,5³R,2S)-3⁶-methyl-2-(methylimino)-2-oxido-9-oxo-2λ⁶-4-oxa-2λ⁶-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile;
- (1R,4s)-4-((6R,12aS,17S)-3,6-Dimethyl-17-(methylimino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ⁴-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile;
- 10 (1R,4s)-4-((6R,12aS,17S)-3,6-Dimethyl-17-(methylimino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile;
- (1R,4s)-4-((8R,12aS,17S)-3,8-Dimethyl-17-(methylimino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile;
- 15 (1R,4s)-1-Methyl-4-((1²S,5¹R,5³R,2S)-3⁴-methyl-2-(methylimino)-2-oxido-9-oxo-2λ⁶-4-oxa-2λ⁶-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile;
- (1R,4s)-1-Methyl-4-((6R,8R,12aS,17S)-3,6,8-trimethyl-17-(methylimino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile;
- 20 (6R,12aS,17S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-17-((methyl-d3)imino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ⁴-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide;
- (1R,4s)-4-((6R,12aS,17S)-3,6-Dimethyl-17-((methyl-d3)imino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ⁴-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile;
- 25 (1R,4s)-4-((6R,12aS,17S)-3,6-Dimethyl-17-((methyl-d3)imino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile;
- (1R,4s)-4-((8R,12aS,17S)-3,8-Dimethyl-17-((methyl-d3)imino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile;
- 30 (1R,4s)-1-Methyl-4-((6R,8R,12aS,17S)-3,6,8-trimethyl-17-(methylimino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ⁴-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile;
- 35

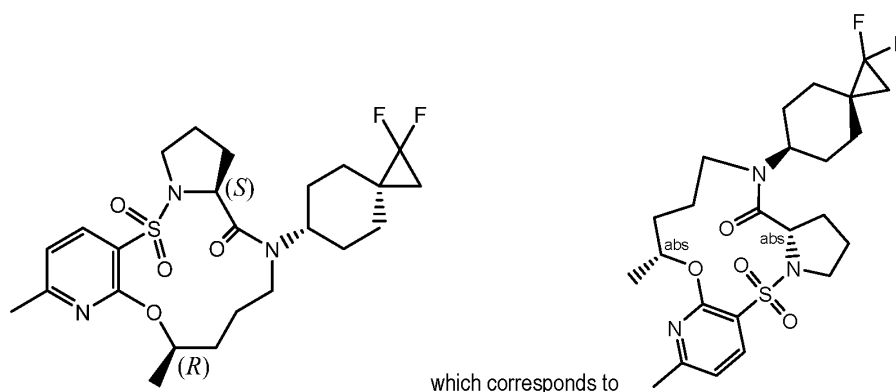
(1R,4s)-4-((6R,12aS)-6-Ethyl-3-methyl-17,17-dioxido-12-oxo-6,7,9,10,12a,13,14,15-octahydropyrido[2,3-e]pyrrolo[1,2-h][1,4]dioxo[7]thia[8,11]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile.

For avoidance of doubt, the chemical names of said example compounds as listed in embodiments 22) to 25) are disclosed in the experimental part; and the corresponding structures of said example compounds are as shown in the experimental part, notably in the **Table of Examples** below, wherein, in case of doubt the depicted structure shall prevail.

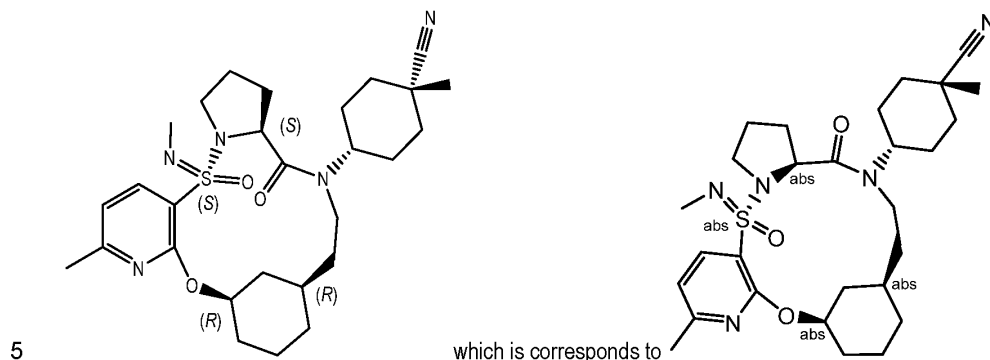
Thus, for example, the compound of example 2.14: (6R,12aS,17S)-11-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-17-(methylimino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide has the structure depicted in the **Table of Examples**, wherein said compound is in enriched absolute configuration as drawn:



Likewise, the compound of example 1.40: (6R,11aS)-10-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide has the structure depicted in the **Table of Examples**, wherein said compound is in enriched absolute configuration as drawn:



Likewise, the compound of example 2.60: (1R,4s)-1-Methyl-4-((1²S,5¹R,5³R,2S)-3⁶-methyl-2-(methylimino)-2-oxido-9-oxo-2λ⁶-4-oxa-2λ⁶-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile, has the structure depicted in the **Table of Examples**, wherein said compound is in enriched absolute configuration as drawn:



The compounds of formula (I) according to embodiments 1) to 25) 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 notably parenteral administration (including especially intravenous administration, as well as intramuscular or subcutaneous administration, or topical application or inhalation).

10

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.

15

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 25).

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.

20

The compounds of Formula (I) according to any one of embodiments 1) to 25) are useful for the prevention / prophylaxis or treatment of diseases or disorders relating to the OX2R receptor, and notably in disease and disorders in which agonism of OX2R plays a role. Disease and disorders in which agonism of OX2R plays a role

25

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 25) 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;
- 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:
 - (chronic) fatigue accompanied by poor concentration and memory;
 - (chronic) fatigue associated with infections (viral or bacterial), (chronic) inflammatory diseases, cancer or chemotherapy, or neurological diseases or neurodegeneration;
 - (chronic) fatigue associated with autoimmune diseases including Sjögren's syndrome and multiple sclerosis; or
 - fatigue associated with myalgic encephalomyelitis/chronic fatigue 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 physical and/or mental exhaustion").

Further disease and disorders in which agonism of OX2R plays a role include:

- eating disorders;
- obesity, particularly obesity in narcoleptic subjects;
- attention deficit disorders, including attention deficit hyperactivity disorder (ADHD);
- neuropsychiatric disorders, notably mood disorders, in particular mood disorders associated with reduced hedonic drive, particularly depression (such as major depressive disorder (MDD)), schizophrenia, addiction, or PTSD;
- 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 OX2R plays a role in:

- disorders of consciousness, notably coma, vegetative state and minimally conscious state induced by traumatic brain injury; and
 - recovery of arousal following unconsciousness associated with cardiac arrest or acute alcohol intoxication,
- 5 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 25) 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

10 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.

15 The compounds of Formula (I) according to any one of embodiments 1) to 25) 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

20 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 25);
- and one or more additional therapeutic agents.

25 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 25);
 - and instructions how to use said pharmaceutical composition for improving wakefulness in a subject
- 30 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) and Formula (III).

Compounds of the present invention may be further characterized with regard to their general pharmacokinetic and

35 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 **R¹**, **R²**, **R^{A1}**, **X¹**, **X²**, **X³**, **X⁴**, **L**, **X⁵**, **Ring A**, **Ring B**, **Ring E**, **Ring F**, 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 **R¹**, **R²**, **R^{A1}**, **X¹**, **X²**, **X³**, **X⁴**, **X⁵**, **L**, **Ring A**, **Ring B**, **Ring E**, **Ring F** 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*.

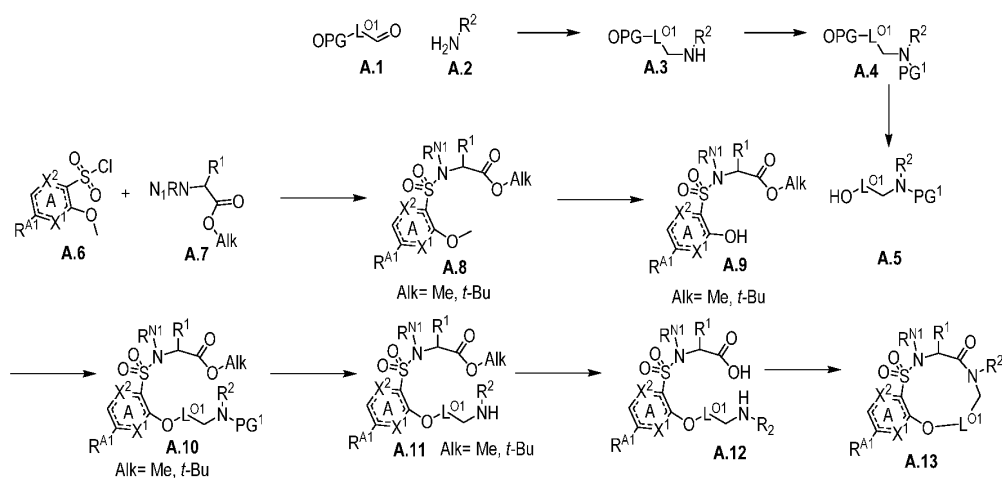
General preparation routes:

The general route described here below allows to prepare compounds of Formula I. The synthesis of some specific examples might not be included and differ from the general route described here. In this case, the synthesis of these specific compounds is described in the experimental procedure here below.

Preparation of Sulfonamide Compounds (Examples 1.x)

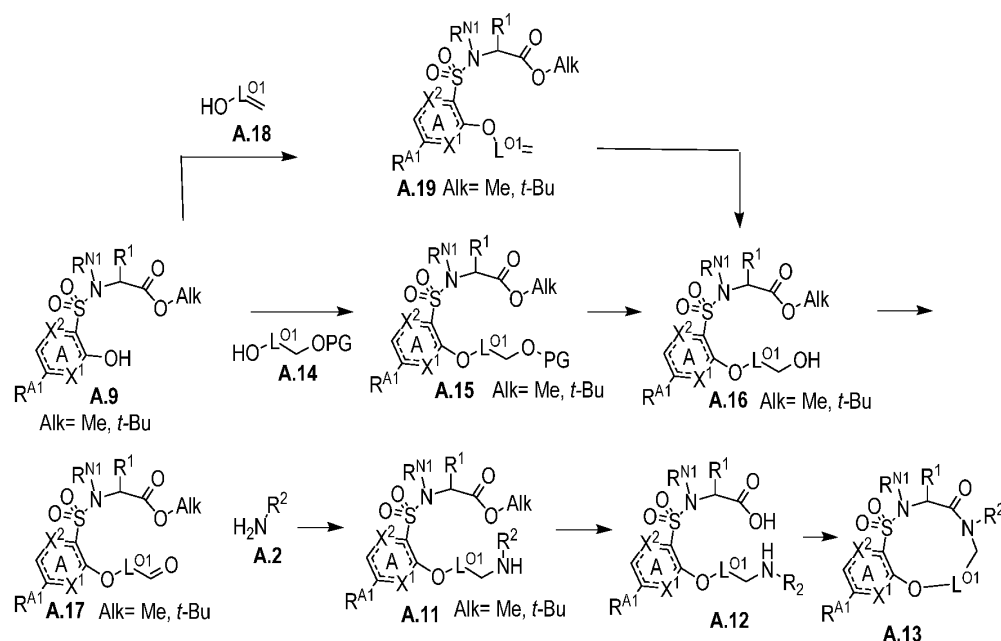
Compound **A.13**, belonging to Formula (I) wherein **X³**=SO₂, **X⁴**=NR^{N1}, **X⁵**=C, and wherein **L** is linked to **Ring A** by an O atom (i.e., **L** represents O-L^{O1}), can be prepared as described in Scheme A.1. Aldehyde **A.1** can be reacted with a primary amine (or the corresponding salt, like HCl or TFA salts) in presence of a primary amine **A.2** using a solvent such as MeOH or THF, or DCM and in presence of a reducing agent such as NaBH₄, NaBH₃CN or NaBH(OAc)₃ to give secondary amine **A.3**. Aldehyde **A.1**, wherein **PG** is an appropriate hydroxy protecting group such as TBDPS-, TBDMS-, or Bn, can be prepared from commercially available scaffolds following procedures

known in the literature and familiar to the person skilled in the art or as reported in the experimental procedure here below. Secondary amine **A.3** can be protected with an appropriate protecting group (**PG**¹) such as Boc, Cbz, Bn or other using standard protection methods known in the literature and familiar to the person skilled in the art to give intermediate **A.4**. The protected primary alcohol (**PG**) of **A.4** can be deprotected using standard procedures known in the literature and familiar to the person skilled in the art to yield **A.5**. Amine **A.7** is condensed with a sulfonyl chloride **A.6** in a solvent such as DCM, DMF, MeCN and in presence of a base such as TEA or DIPEA to give **A.8**. Intermediate **A.6** can be commercially available, prepared following procedures known in the literature, or prepared as described in the experimental part here below. Intermediate **A.8** can be demethylated using BBr₃ in a solvent such as DCM to yield **A.9**. Intermediate **A.9** can be reacted with primary alcohol **A.5** in a Mitsunobu reaction using a reagent such as DEAD or DIAD and PPh₃ in a solvent such as THF to yield **A.10**. The amine protecting group (**PG**¹) can be removed with standard procedures known in the literature and familiar to the person skilled in the art to yield **A.11**. The ester functional group of **A.11** can be deprotected under acidic or basic conditions to yield **A.12**. When Alk=Me, the hydrolysis can occur in presence of a base such as LiOH in a solvent such as THF/H₂O, while when Alk= *t*-Bu the hydrolysis can occur under acidic conditions using TFA in a solvent such as DCM or HCl in 1,4-dioxane. Finally, intermediate **A.12** can be cyclized via an intermolecular amide coupling 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 to yield macrocycle **A.13**.

Scheme A.1. Synthesis of sulfonamide macrocycles **A.13**

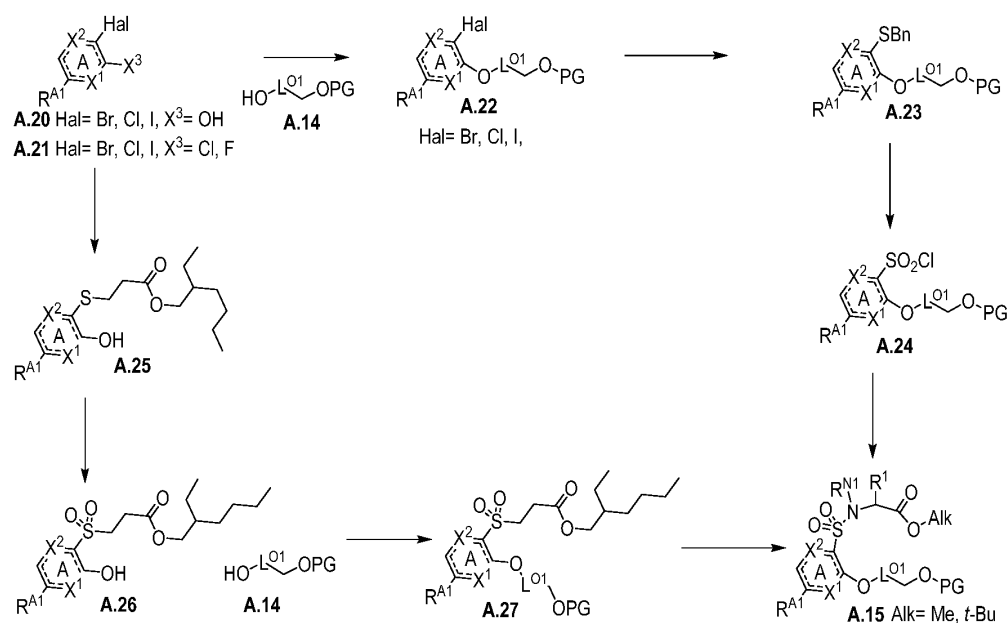
Alternatively, macrocycles **A.13** can be prepared as described in Scheme A.2. Hydroxy scaffold **A.14**, wherein **PG** is an appropriate protecting group such as Bn, TBDMS, TBDPS, or similar, can be reacted with **A.9** in a Mitsunobu reaction using a coupling reagent such as DEAD or DIAD and PPh₃ in a solvent such as THF to yield **A.15**. Mono-protected diols **A.14** can be prepared following known procedure described in the literature or in analogy to it, or as reported in the experimental part here below. Protecting group cleavage using standard deprotection methods known in the literature and familiar to the person skilled in the art leads to derivative **A.16**. Oxidation of the primary

- alcohol of derivative **A.16** using oxalyl chloride and TEA in DMSO, or sulfur trioxide pyridine complex and TEA in DMSO can yield aldehyde **A.17**. Aldehyde **A.17** can be reacted with a primary amine (or the corresponding salt, like HCl or TFA salts) (**A.2**) using a solvent such as MeOH or THF, or DCM and in presence of a reducing agent such as NaBH₄, NaBH₃CN or NaBH(AcOAc)₃ to give secondary amine **A.11**. Hydrolysis of the ester functional
- 5 group of **A.11** into the corresponding carboxylic acid (**A.12**) can be performed in a similar way as described for above. Intermediate **A.12** can be cyclized via an intermolecular amide coupling 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 to yield macrocycle **A.13**. Intermediate **A.16** can alternatively be prepared by reacting intermediate **A.9** with terminal alkene alcohol **A.18** via a Mitsunobu reaction using a reagent such as
- 10 DEAD or DIAD and PPh₃ in a solvent such as THF to give **A.19**. Terminal alkene **A.19** can undergo a hydroboration/oxidation using BH₃.THF complex in a solvent such as THF, followed by oxidation using an oxidizing agent as H₂O₂ and an aqueous soln. of NaOH in a solvent such as THF to yield **A.16**. Intermediate **A.16** can be oxidized into the corresponding aldehyde (**A.17**) for example using a reagent such as SO₃.pyridine in a solvent such as DMSO and a base as TEA, oxalyl chloride and TEA in DMSO, or again Dess-Martin periodinane in a
- 15 solvent such as DCM. Aldehyde **A.17** can be reacted with primary amine **A.2** in presence of a reducing agent such as NaBH₄, NaBH₃CN or NaBH(OAc)₃ in a solvent such as MeOH or THF, or DCM to give secondary amine **A.11**. Intermediate **A.11** can be converted to **A.13** as described here above in Scheme A.1.

Scheme A.2. Alternative synthesis of sulfonamide macrocycles **A.13**

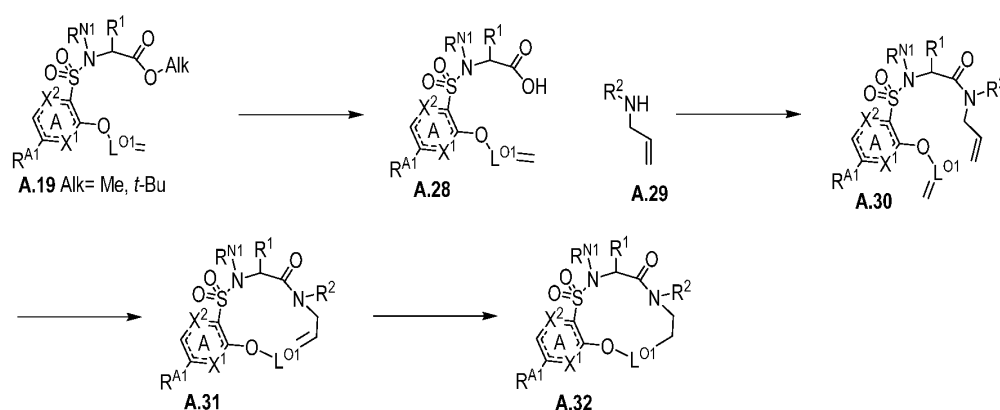
- 20 An alternative route for the preparation of key intermediate **A.15** is described in Scheme A.3. Reaction of scaffold **A.20** via a Mitsunobu reaction using a reagent such as DEAD or DIAD and PPh₃ in a solvent such as THF yields

- A.22.** Alternatively, **A.22** can also be prepared from **A.21** via a S_NAr reaction with **A.14** using a base such as NaH in a solvent such as THF. Intermediate **A.22** can be reacted in presence of a catalyst such as $Pd_2(dba)_3$ and a ligand such as XantPhos or a precatalyst such as Xanthphos-Pd-G3 or Xanthphos-Pd-G2, mercaptan, a base such as DIPEA in a solvent like 1,4-dioxane and under heating. As an alternative, intermediate **A.23** can be prepared by
- 5 lithium-halogen exchange treating **A.22** with a reagent such as *n*-BuLi and reacting the resulting organolithium reagent with benzyl disulfide in a solvent such as THF, or by a S_NAr reaction in presence of mercaptan and a base such as NaH in a solvent such as DMF at rt. Intermediate **A.23** can be converted into its analogue sulfonyl chloride **A.24** by treatment with 1,3-dichloro-5,5-dimethylhydantoin in a solvent mixture as 1,4-dioxane. Reaction between **A.24** and amine **A.7** in a solvent such as DCM, DMF, or MeCN and in presence of a base such as TEA or DIPEA
- 10 yields intermediate **A.15**. Finally, intermediate **A.15** can also be prepared treating **A.20** with 2-ethylhexyl 3-mercaptopropionate in presence of a catalyst as $Pd_2(dba)_3$ and a ligand as Xantphos and a base such as DIPEA in a solvent as toluene and at a temperature of 90°C to give **A.25**. In turn, intermediate **A.25** can be oxidized using an oxidant such as *m*-CPBA in a solvent such as DCM at rt into sulfone **A.26**. Reaction between **A.26** and primary alcohol **A.14** in presence of a reagent such as DEAD or DIAD and PPh_3 in a solvent such as THF yields **A.27**.
- 15 Intermediate **A.27** can be treated with NaOMe soln. in MeOH in a solvent such as THF, followed by NCS to give the corresponding sulfonyl chloride which can be reacted with **A.7** and a base such as TEA in THF to yield intermediate **A.15**. Intermediate **A.15** can be converted to macrocycles **A.13** following the same procedure here above in Scheme A.2.



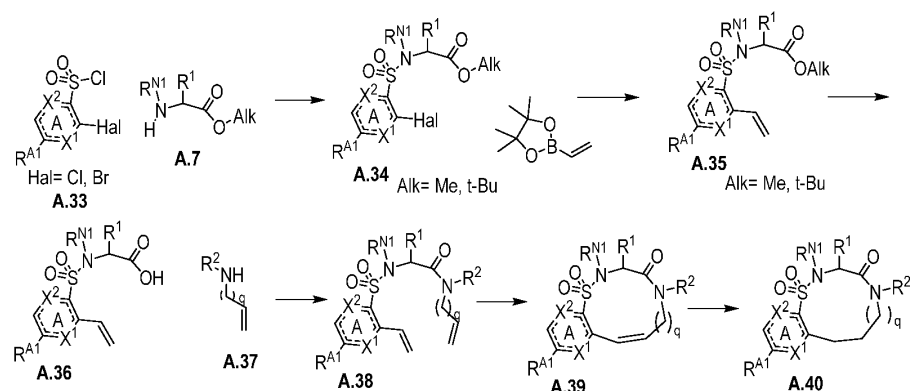
20 Scheme A.3. Alternative synthesis of sulfonamide intermediate **A.15**

- In another aspect, macrocycles **A.32**, belonging to Formula (I) wherein $X^3 = SO_2$, $X^4 = NR^{N1}$, $X^5 = C$, and wherein **L** is linked to **Ring A** by an O atom (i.e., **L** represents O- L^{O1}) can also be prepared as described in Scheme **A.4** starting from intermediate **A.19** by ester hydrolysis. When $Alk = Me$, the hydrolysis can occur in presence of a base such as LiOH in a solvent such as THF/ H_2O , while when $Alk = t-Bu$ the hydrolysis can occur under acidic conditions using
- 5 TFA in a solvent such as DCM or HCl in 1,4-dioxane to give **A.28**. Reaction between carboxylic **A.28** and secondary amine **A.29** in presence of a coupling reagent such as TBTU, HBTU, HATU, EDC (or similar) and a base such as DIPEA, TEA or N-methylmorpholine in a solvent such as THF, DMF, DCM or MeCN yields **A.30**. Amines **A.29** are either known in the literature or can be prepared using known methodologies in the literature and familiar to the person skilled in the art. Intermediate **A.30** can be treated with a catalyst such as 2nd generation Grubbs Catalyst
- 10 or similar in a solvent such as DCM at reflux to give macrocycle **A.31**. Finally, the endocyclic double bond can be reduced by treating **A.31** with a catalyst such as Pd/C and H_2 in a solvent such as MeOH or EtOH to give macrocycles **A.32**.

Scheme A.4. Synthesis of sulfonamide macrocycles **A.32**

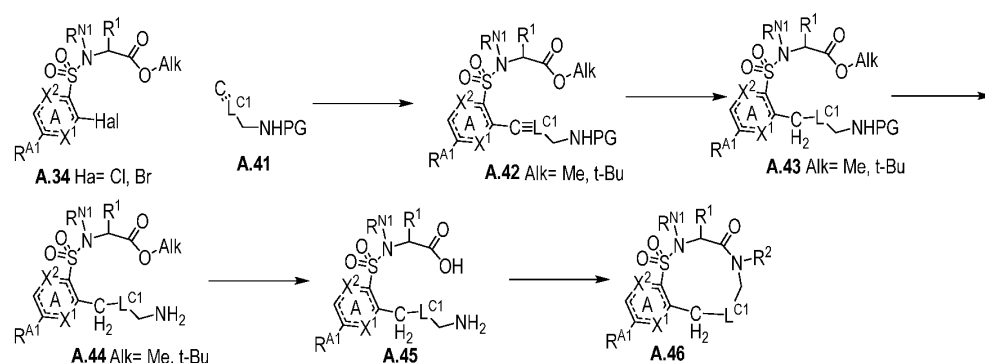
- Compound **A.40**, belonging to Formula (I) wherein $X^3 = SO_2$, $X^4 = NR^{N1}$, $X^5 = C$, and wherein **L** is linked to **Ring A** by a C atom and **L** represents an unsubstituted carbon chain (such that $q = 1$ to 5), can be prepared as described in Scheme A.5. Intermediate **A.34** can be prepared by treating sulfonyl chloride **A.33** with amine **A.7** in a solvent such as DCM, DMF, MeCN and in presence of a base such as TEA or DIPEA. Intermediate **A.34** can be reacted with 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane and a catalyst such as (dppf)PdCl₂-CH₂Cl₂, a base such as K₂CO₃,
- 20 in a solvent such as dioxane/ H_2O to yield **A.35**. Hydrolysis of the ester can occur in presence of a base such as LiOH in a solvent such as THF/ H_2O when $Alk = Me$, or under acidic conditions using TFA in a solvent such as DCM or HCl in 1,4-dioxane when $Alk = t-Bu$ to give **A.36**. Intermediate **A.36** can be condensed with amine **A.37** using a coupling reagent such as BTU, HBTU, HATU, EDC (or similar) and a base such as DIPEA, TEA or N-methylmorpholine in a solvent such as THF, DMF, DCM or MeCN to yield **A.38**. Amine **A.37** can be prepared using
- 25 known methodologies in the literature and familiar to the person skilled in the art. Reaction of **A.38** with a catalyst such as such as 2nd generation Grubbs catalyst or similar in a solvent such as DCM can give macrocycle **A.39**. The

endocyclic double bond of **A.39** can be reduced in presence of a catalyst such as Pd/C under a H₂ atm in a solvent such as MeOH or EtOH to give macrocycles **A.40**.



Scheme A.5. Synthesis of sulfonamide macrocycles **A.40**.

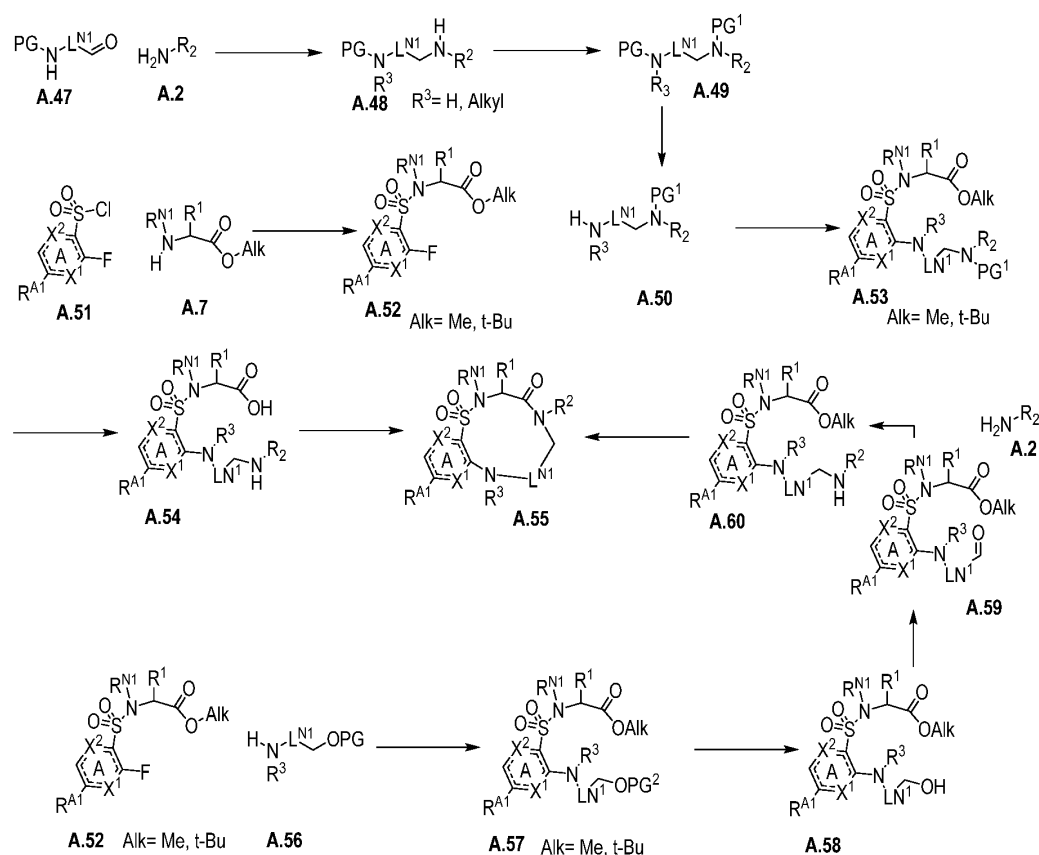
- 5 Macrocycles **A.46**, belonging to Formula I wherein $X^3 = SO_2$, $X^4 = NR^{N1}$, $X^5 = C$, and wherein **L** is linked to **Ring A** by a C atom (i.e., **L** represents C-L^{C1}), can be prepared as described in Scheme A.6. Intermediate **A.34** can be treated with a terminal alkyne (**A.41**) in presence of a catalyst as for example Pd(PPh₃)₄, a co-catalyst such as CuI and a base such as Et₃N or DIPEA in a solvent such as DMF to yield **A.42**. Terminal alkynes **A.41** are either commercially available, known in the literature, or can be prepared from simple scaffolds using methodologies known in the literature and familiar to the person skilled in the art. Intermediate **A.42** can be reduced in presence of a catalyst such as Pd/C under a H₂ atm in a pressurized autoclave or using a flow reactor to yield **A.43**. Deprotection of **A.43** using methodologies known in the literature and familiar to the person skilled in the art can yield **A.44**. Hydrolysis of **A.44** to **A.45** can be performed as described here above for the preparation of **A.36**. Finally, intermediate **A.45** can be converted into macrocycle **A.46** in presence of coupling reagent such as BTU, HBTU, HATU, EDC (or similar) and a base such as DIPEA, TEA or N-methylmorpholine in a solvent such as THF, DMF, DCM or MeCN.
- 15



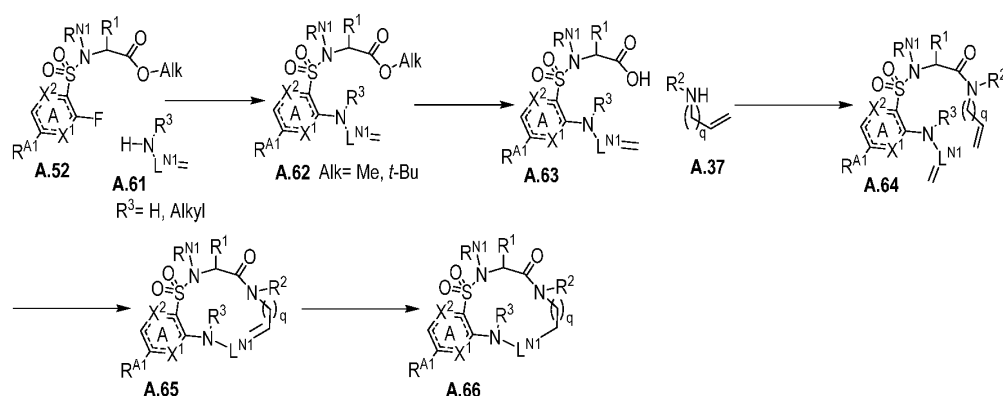
Scheme A.6. Synthesis of macrocycle compounds **A.46**.

Compound **A.55**, belonging to Formula (I) wherein $X^3=SO_2$, $X^4=NR^{N1}$, $X^5=C$, and wherein **L** is linked to **Ring A** by a N atom (i.e., **L** represents N-**L^{N1}**), can be prepared as described in Scheme A.7. Intermediate **A.52** can be prepared by treating sulfonyl chloride **A.51** with amine **A.7** in a solvent such as DCM, DMF, MeCN and in presence of a base such as TEA or DIPEA. Intermediate **A.52** can be reacted with amine **A.50** in presence of a base such as DIPEA or TEA in a solvent such as DMSO to yield **A.53**. Amines **A.50** can be prepared reacting amine **A.47** (commercially available, known in the literature, or prepared from known methodologies familiar to the person skilled in the art) and primary amine **A.2** (or the corresponding salt, like HCl or TFA salts) using a solvent such as MeOH or THF, or DCM and in presence of a reducing agent such as $NaBH_4$, $NaBH_3CN$ or $NaBH(AcOAc)_3$ to give secondary amine **A.48**, followed by orthogonal **PG** deprotection using methodologies known to the person skilled in the art to give **A.50**. Intermediate **A.53** can be deprotected (**PG¹**) using methodologies known in the literature and the ester can be hydrolysed using a base such as LiOH in a solvent such as THF/ H_2O when $Alk=Me$, or under acidic conditions using TFA in a solvent such as DCM or HCl in 1,4-dioxane when $Alk=t-Bu$, to give intermediate **A.54**. Intramolecular cyclization of **A.54** can be conducted using a coupling reagent such as BTU, HBTU, HATU, EDC (or similar) and a base such as DIPEA, TEA or N-methylmorpholine in a solvent such as THF, DMF, DCM or MeCN to yield **A.55**. Alternatively, **A.52** can be reacted with amine **A.56** in presence of a base such as DIPEA or TEA in a solvent such as DMSO to yield **A.57**. Amine **A.56** can be commercially available or prepared following procedures known in the literature. Intermediate **A.57** can be deprotected using known methodologies familiar to the person skilled in the art. Treatment of **A.58** using oxalyl chloride and TEA in DMSO, or sulfur trioxide pyridine complex and TEA in DMSO can yield aldehyde **A.59**. Aldehyde **A.59** can be reacted with a primary amine (or the corresponding salt, like HCl or TFA salts) (**A.2**) using a solvent such as MeOH or THF, or DCM and in presence of a reducing agent such as $NaBH_4$, $NaBH_3CN$ or $Na(AcOAc)_3$ to give **A.60**. Hydrolysis of the ester functional group into the corresponding carboxylic acid can be performed in a similar way as described here above in Scheme A.1. The resulting carboxylic acid can be coupled intramolecularly by amide coupling 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 to give **A.55**.

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Scheme A.7. Synthesis of macrocycle compounds **A.55**.

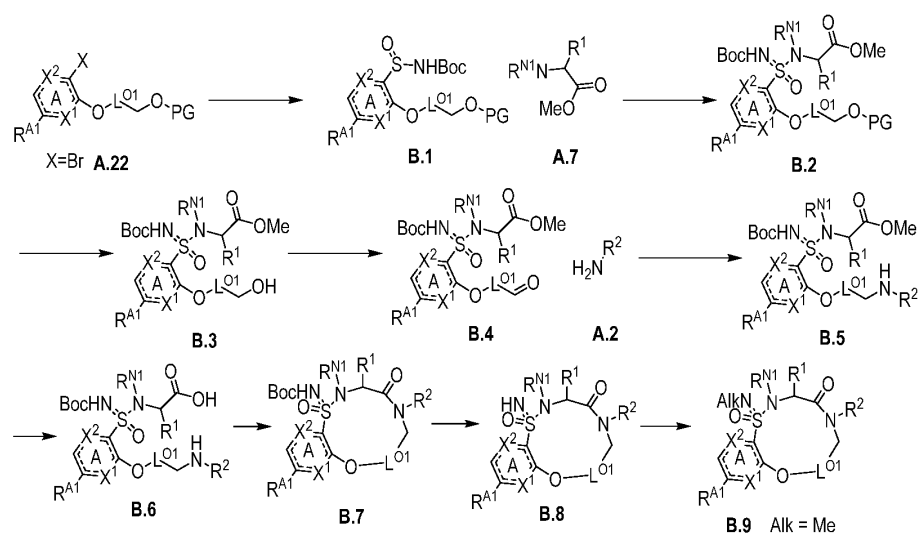
- Compound **A.66**, belonging to Formula (I) wherein $X^3 = SO_2$, $X^4 = NR^{N1}$, $X^5 = C$, and wherein **L** is linked to **Ring A** by a N atom (i.e., **L** represents N-L^{N1}) and q=1 to 4, can be prepared as described in Scheme A.8. Intermediate **A.52**
- 5 can be reacted with amine **A.61** in presence of a base such as DIPEA or TEA in a solvent such as DMSO to yield **A.62**. Hydrolysis of the ester as described here above yields **A.63**. Reaction between carboxylic **A.63** and secondary amine **A.37** (or the corresponding salt, like HCl or TFA salts) in presence of a coupling reagent such as TBTU, HBTU, HATU, EDC (or similar) and a base such as DIPEA, TEA or N-methylmorpholine in a solvent such as THF, DMF, DCM or MeCN can yield **A.64**. Intermediate **A.64** can be treated with a catalyst such as 2nd
- 10 generation Grubbs catalyst or similar in a solvent such as DCM at reflux to give macrocycle **A.65**. Double bond reduction can be performed treating **A.65** with a catalyst such as Pd/C and H₂ in a solvent such as MeOH or EtOH to give macrocycles **A.66**.

Scheme A.8. Synthesis of sulfonamide macrocycles **A.66**

Preparation of SIA Compounds (Examples 2.x)

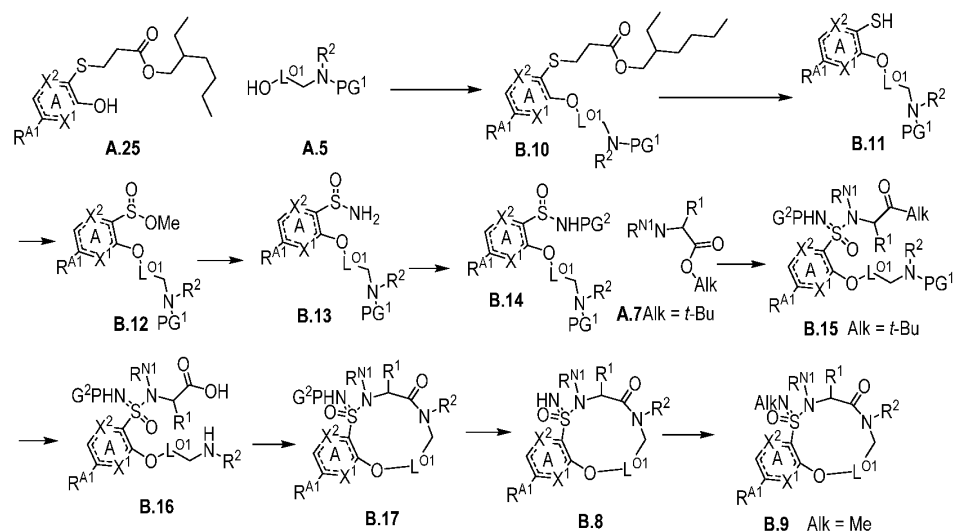
Compounds **B.8** and **B.9**, belonging to Formula (I) wherein $X^3 = S(O)(NR^3)$, $R^3 = H/Alkyl$, $X^4 = NR^{N1}$, $X^5 = C$, and wherein

- L** is linked to **Ring A** by an O atom (i.e., **L** represents O-**L**¹), can be prepared as described in Scheme B.1. Intermediate **B.1** can be prepared by lithium-halogen exchange treating **A.22** with a reagent such as *n*-BuLi and reacting the resulting organolithium reagent with *tert*-butyl (oxo- λ^4 -sulfaneylidene)carbamate in a solvent such as THF. Sulfonamide **B.1** can be treated with *tert*-butyl hypochlorite to give the corresponding sulfonylimidoyl chloride, which can be reacted with amine **A.7** and a base such as DIPEA in DCM to yield SIA **B.2**. Hydroxy protecting group cleavage using standard deprotection methods known in the literature and familiar to the person skilled in the art leads to derivative **B.3**. Oxidation of the primary alcohol using oxalyl chloride, TEA and DMSO in DCM can yield aldehyde **B.4**. Aldehyde **B.4** can be reacted with a primary amine (or the corresponding salt, like HCl salts) (**A.2**) in presence of a base, such as DIPEA using a solvent such as MeOH and in presence of a reducing agent such as NaBH₄ to give secondary amine **B.5**. Hydrolysis of the ester functional group of **B.5** into the corresponding carboxylic acid can be performed in a similar way as described for the hydrolysis of **A.11** into **A.12** to give **B.6**. Intermediate **B.6** can be cyclized *via* an intermolecular amide coupling in a solvent such as DMF in presence of a coupling reagent such as HATU and a base such as DIPEA to yield macrocycle **B.7**. Sulfonimidamide Boc protecting group cleavage using standard deprotection methods known in the literature and familiar to the person skilled in the art leads to derivative **B.8**. Alkylation of intermediate **B.8** can be performed in the presence of alkyl iodide and NaH as a base in DMF to afford **B.9**. Generated diastereomers can be separated either by prep HPLC, flash chromatography or chiral SFC chromatography.

Scheme B.1. Synthesis of macrocycle compounds **B.8** and **B.9**.

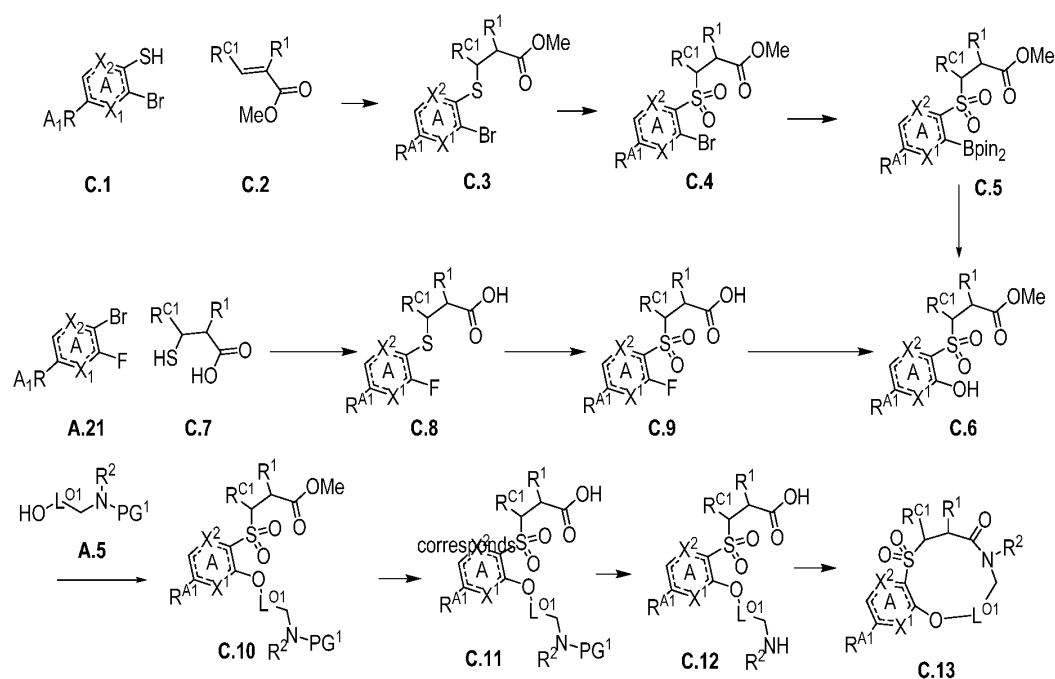
- Alternatively, derivatives **B.8** and **B.9** can be prepared as described in Scheme B.2. Thioether **A.25** can react with alcohol **A.5** via a Mitsunobu reaction using a reagent such as DEAD and PPh_3 in a solvent such as THF to yield **B.10**. Reacting intermediate **B.10** with a base such as NaOMe in MeOH provides the corresponding thiol **B.11**. Thiol **B.11** can be oxidized into its corresponding sulfinate ester **B.12** by reaction with NBS and MeOH in a solvent such as DCM. Sulfinate ester **B.12** can be converted into sulfonamide with general structure **B.13** by reaction with LiHMDS in a solvent like THF and hydrolysis with sat. aq. NH_4Cl . The resulting sulfonamide can be protected with an appropriate protecting group (PG^2) such as Fmoc to yield **B.14** using standard protection methods known in the literature and familiar to the person skilled in the art. Compound **B.14** can be condensed with amine **A.7** in presence of a chlorinating agent such as *tert*-butyl hypochlorite in a solvent such as DCM to give intermediate **B.15**. Hydroxy and amine protecting group cleavage using standard deprotection methods known in the literature and familiar to the person skilled in the art leads to derivative **B.16**. Intermediate **B.16** can be cyclized via an intermolecular amide coupling in a solvent such as DMF in presence of a coupling reagent such as HATU and a base such as DIPEA to yield macrocycle **B.17**. Deprotection of PG^2 using standard deprotection methods known in the literature and familiar to the person skilled in the art leads to derivative **B.8**. Alkylation of intermediate **B.8** can be performed in the presence of alkyl iodide and NaH as a base in DMF to afford **B.9**. Generated diastereomers can be separated either by prep HPLC, flash chromatography or chiral SFC chromatography.

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Scheme B.2. Alternative synthesis of macrocycle compounds **B.8** and **B.9**.*Preparation of Sulfone Compounds (Examples 3.x)*

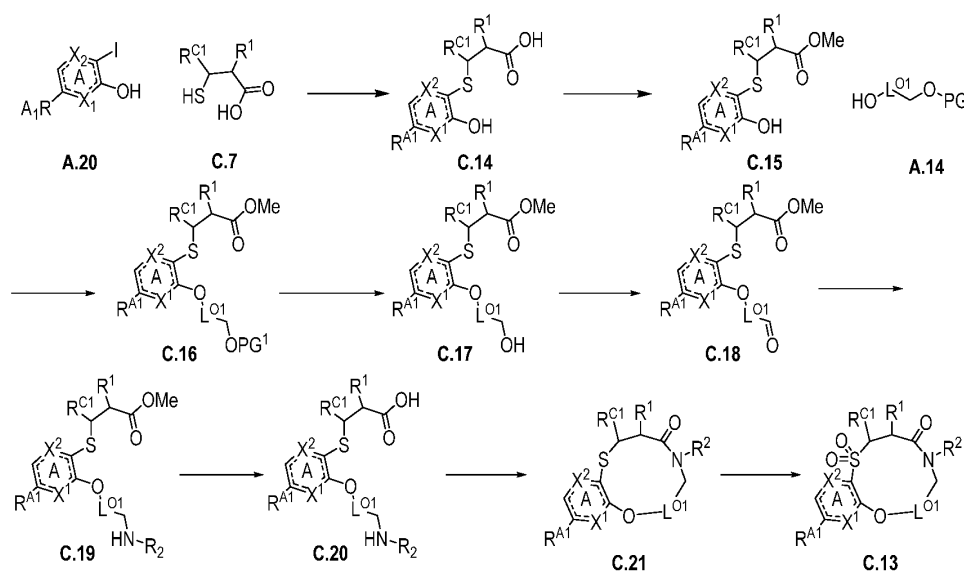
- Compounds **C.13**, belonging to Formula (I) wherein $X^3 = SO_2$, $X^4 = CHR^{c1}$, $X^5 = C$, and wherein **L** is linked to **Ring A** by an O atom (i.e., **L** represents O- L^{o1}), can be prepared as described in Scheme C.1. Michael addition between
- 5 arylthiol **C.1** and commercially available α,β -unsaturated ester **C.2** in a solvent such as piperidine yields thioether **C.3**. Intermediate **C.3** can be oxidized in presence of an oxidant such as m-CPBA and a base such as $NaHCO_3$, in a solvent such as DCM to provide sulfone **C.4**. Intermediate **C.5** can be prepared by treating **C.4** with 4,4,5,5-tetramethyl-1,3,2-dioxaborolane in presence of a catalyst such as $PdCl_2(MeCN)_2$, a ligand such as SPhos and a
- 10 base such as TEA in a solvent such as dioxane. Intermediate **C.5** can be oxidized in presence of an oxidant such as H_2O_2 and a base such as NaOH in a solvent such as THF to provide intermediate **C.6**. Alternatively, **C.6** can be synthesized reacting scaffold **A.21** with thiol **C.7** in presence of a catalyst such as XantPhos Pd G2 and a base such as DIPEA in dioxane to give the corresponding thioether **C.8**. In turn, intermediate **C.8** can be oxidized using an oxidant such as m-CPBA and a base such as $NaHCO_3$ in a solvent such as DCM to provide sulfone **C.9**.
- 15 Intermediate **C.9** can be treated with aqueous acid such as HCl (6M) in a solvent such as MeOH at reflux to give derivative **C.6**. Scaffold **C.6** can be reacted with alcohol **A.5** via a Mitsunobu reaction using a reagent such as DEAD and PPh_3 in a solvent such as THF to yield derivative **C.10**. Hydrolysis of the ester functional group of **C.10** into the corresponding carboxylic acid can be performed in a similar way as described for the hydrolysis of **A.11** into **A.12** to give **C.11**. Amine protecting group cleavage using standard deprotection methods known in the
- 20 literature and familiar to the person skilled in the art leads to derivative **C.12**. Intermediate **C.12** can be cyclized via an intermolecular amide coupling in a solvent such as DMF in presence of a coupling reagent such as HATU and a base such as DIPEA to yield macrocycle **C.13**. Generated diastereomers can be separated either by prep HPLC, flash chromatography or chiral SFC chromatography.

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Scheme C.1. Synthesis of macrocycle compounds **C.13**.

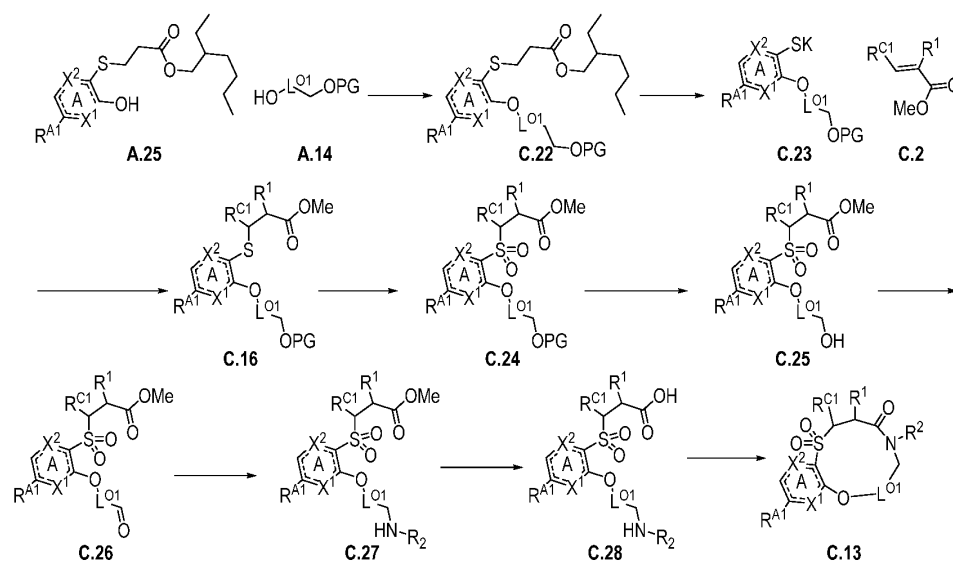
- An alternative synthesis of macrocycles **C.13** is depicted in Scheme C.2. Building block **A.20** can be reacted with thiol **C.7** in presence of a catalyst such as XantPhos Pd G2 and a base such as DIPEA in dioxane to give the corresponding thioether **C.14**. Thioether **C.14** can be treated with an acid such as sulfuric acid in MeOH at reflux to give derivative **C.15**. Ester **C.15** can be reacted with alcohol **A.14** via a Mitsunobu reaction using a reagent such as DEAD and PPh₃ in a solvent such as THF to yield derivative **C.16**. Hydroxy protecting group cleavage (**PG**¹) using standard deprotection methods known in the literature and familiar to the person skilled in the art leads to derivative **C.17**. Oxidation of the primary alcohol using oxalyl chloride, TEA and DMSO in DCM can yield aldehyde **C.18**. Aldehyde **C.18** can be reacted with a primary amine (or the corresponding salt, like HCl salts) in a solvent such as MeOH and in presence of a reducing agent such as NaBH(OAc)₃ to give secondary amine **C.19**. Hydrolysis of the ester functional group of **C.19** into the corresponding carboxylic acid can be performed in a similar way as described here above for the hydrolysis of **A.11** into **A.2** to give **C.20**. Intermediate **C.20** can be cyclized via an intermolecular amide coupling in a solvent such as MeCN in presence of a coupling reagent such as HATU and a base such as DIPEA to yield macrocycle **C.21**. Intermediate **C.21** can be oxidized with an oxidant such as m-CPBA in a solvent such as DCM to give sulfone macrocycle **C.13**.

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Scheme C.2. Alternative synthesis of macrocycle compounds **C.13**.

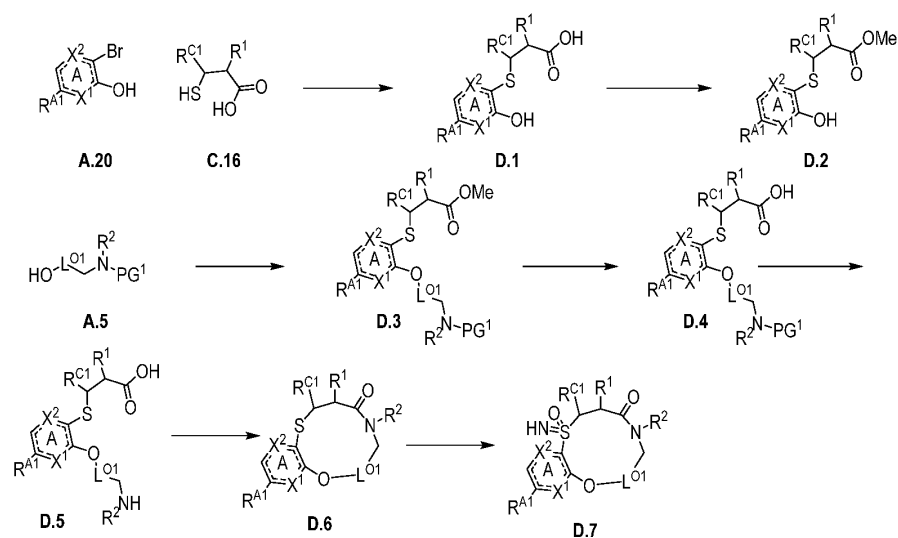
- On the other hand, intermediate **A.25** can be reacted with alcohol **A.14** via a Mitsunobu reaction using a reagent such as DEAD and PPh_3 in a solvent such as THF to yield derivative **C.22** as described in Scheme C.3. Intermediate
- 5 **C.22** can be treated with a base such as potassium tert-butoxide in a solvent such as THF to give molecule **C.23**. In turn, Michael addition between intermediate **C.23** and commercially available α,β -unsaturated ester **C.2** in a solvent such as piperidine yields thioether **C.16**. Intermediate **C.16** can be oxidized in presence of an oxidant such as m-CPBA and in a solvent such as DCM to provide sulfone **C.24**. Hydroxy protecting group cleavage using standard deprotection methods known in the literature and familiar to the person skilled in the art leads to derivative
 - 10 **C.25**. Oxidation of the primary alcohol using an oxidant such as NaOCl in presence of TEMPO, KBr and a base such as NaHCO_3 and in a solvent such as DCM can yield aldehyde **C.26**. Aldehyde **C.26** can be reacted with a primary amine (or the corresponding salt, like HCl salts) in a solvent such as MeOH and in presence of an acid such as AcOH and a reducing agent such as $\text{NaBH}(\text{CN})_3$ to give secondary amine **C.27**. Hydrolysis of the ester functional group of **C.27** into the corresponding carboxylic acid can be performed in a similar way as described for
 - 15 the hydrolysis of **A.11** into **A.12** to give **C.28**. Intermediate **C.28** can be cyclized via an intermolecular amide coupling in a solvent such as MeCN in presence of a coupling reagent such as HATU and a base such as DIPEA to yield macrocycle **C.13**.

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Scheme C.3. Alternative synthesis of macrocycle compounds **C.13**.*Preparation of Sulfoximine Compounds (Examples 4.x)*

- Compounds **D.7**, belonging to Formula (I) wherein $X^3 = S(O)(NR^3)$, $R^3 = H, \text{ Alkyl}$, $X^4 = CHR^{C1}$, and wherein **L** is linked to **Ring A** by an O atom (i.e., **L** represents O- L^{O1}), can be prepared as described in Scheme D.1. Scaffold **A.20** can react with thiol **C.16** in presence of a catalyst such as XantPhos Pd G2 and a base such as DIPEA in dioxane to give the corresponding thioether **D.1**. Esterification of the carboxylic acid functional group of **D.1** into the corresponding ester can be performed in MeOH in presence of an acid such as sulfuric acid to give ester **D.2**. Intermediate **D.2** can react with alcohol **A.5** via a Mitsunobu reaction using a reagent such as DEAD and PPh_3 in a solvent such as THF to yield **D.3**. Hydrolysis of the ester functional group of **D.3** into the corresponding carboxylic acid can be performed in a similar way as described for the hydrolysis of **A.11** into **A.12** to give **D.4**. Amine protecting group cleavage using standard deprotection methods known in the literature and familiar to the person skilled in the art leads to derivative **D.5**. Intermediate **D.5** can be cyclized via an intermolecular amide coupling in a solvent such as DMF in presence of a coupling reagent such as HATU and a base such as DIPEA to yield macrocycle **D.6**. Oxidation of thioether **D.6** can be performed using an oxidant such as (diacetoxyiodo)benzene in presence of ammonium carbamate in a solvent such as MeOH to give sulfoximine **D.7**. Generated diastereomers can be separated either by prep HPLC, flash chromatography or chiral SFC chromatography.

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Scheme D.1. Synthesis of macrocycle compounds D.7

Experimental Part

5 Abbreviations (as used herein and in the description above):

Ac	Acetyl (such as in OAc = acetate, AcOH = acetic acid)
AcOH	Acetic acid
Alk	Alkyl (as explicitly defined)
anh.	Anhydrous
10 aq.	aqueous
atm	Atm
tBME	<i>tert</i> -Butylmethylether
Boc	<i>tert</i> -Butoxycarbonyl
Boc ₂ O	di- <i>tert</i> -Butyl dicarbonate
15 tBuOCl	<i>tert</i> -Butyl hypochlorite
BSA	Bovine serum albumine
Bu	Butyl such as in tBu = <i>tert</i> -butyl = tertiary butyl
ca.	circa
CAS	Chemical Abstracts Services
20 conc.	Concentrated
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCDMH	1,3-Dichloro-5,5-dimethylhydantoin
DCM	Dichloromethane

	DEA	Diethylamine
	DEAD	Diethyl azodicarboxylate
	DIAD	Bis(isopropyl) azodicarboxylate
	DIPEA	Diisopropylethylamine
5	DMAP	4-Dimethylaminopyridine
	DME	Dimethoxyethane
	DMEM	Dulbecco's modified eagle medium
	DMF	<i>N,N</i> -Dimethylformamide
	DMSO	Dimethyl sulfoxide
10	dppf	1,1'-Bis(diphenylphosphino)ferrocene
	EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
	ELSD	Evaporative Light-Scattering Detection
	eq	Equivalent(s)
	ES	Electron spray
15	Et	Ethyl
	Et ₂ O	Diethyl ether
	EtOAc	Ethyl acetate
	EtOH	Ethanol
	Ex.	Example
20	FBS	Fetal bovine serum
	FC	Flash Chromatography on silica gel
	FCS	Foatal calf serum
	h	Hour(s)
	Hal	Halogen (as explicitly defined)
25	HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
	HBSS	Hank's balanced salt soln.
	HBTU	2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
	HEK293	Human embryonic kidney 293 cells
30	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
35	IP1	Intracellular inositol-1-phosphate
	iPr	isopropyl

	iPrOAc	Isopropyl acetate
	KHMDS	Potassium hexamethyldisilazide
	LC-MS	Liquid chromatography – Mass Spectroscopy
	LiHMDS	Lithium hexamethyldisilazide
5	Lit.	Literature
	M	Exact mass (as used for LC-MS)
	M	Molarity [mol L ⁻¹]
	m-CPBA	3-Chloroperbenzoic acid
	Me	Methyl
10	MeCN	Acetonitrile
	MeOH	Methanol
	Mel	Methyl iodide
	MHz	Megahertz
	FC	Medium performance liquid chromatography
15	2-MeTHF	2-Methyltetrahydrofuran
	min	Minute(s)
	MS	Mass spectroscopy
	Ms	Mesyl such as OMs
	N	Normality
20	NBS	N-Bromosuccinimide
	NMP	N-Methyl-2-pyrrolidone
	Org.	Organic
	PdCl ₂ (MeCN) ₂	Bis(acetonitrile)palladium(II) chloride
	Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium(0)
25	Pd(OAc) ₂	Palladium diacetate
	Pd(PPh ₃) ₄	Tetrakis(triphenylphosphine)palladium(0)
	PG	Protecting group
	Ph	Phenyl
	PL-HCO ₃	Polymer supported hydrogen carbonate
30	Pr	propyl
	Prep.	Preparative
	PrOH	Propanol
	PTFE	Polytetrafluoroethylene
	PyCloP	Chlorotripyrrolidinophosphonium hexafluorophosphate
35	PyrSO ₃	Sulfur trioxide pyridine complex
	rac	Racemic or racemate

	Rf	Retention factor
	rt	Room temperature
	sat.	Saturated
	SIA	Sulfonimidamide compound(s)
5	SFC	Supercritical fluid chromatography
	soln.	Solution
	TBAF	Tetra-n-butylammonium fluoride
	TBTU	2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate
	<i>t</i> Bu	<i>tert</i> -Butyl
10	<i>t</i> BuOH	<i>tert</i> -Buthanol
	TEA	Triethylamine
	TEMPO	2,2,6,6-Tetramethylpiperidinyloxy
	Tf	Triflate such as OTf
	TFA	Trifluoroacetic acid
15	THF	Tetrahydrofuran
	TLC	Thin layer chromatography
	TMP	2,2,6,6-Tetramethylpiperidine
	TMSI	Trimethylsilyl iodide
	<i>t</i> _R	Retention time
20	Ts	Tosyl such as OTs
	UPLC	Ultra performance liquid chromatography
	Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
	Xanthphos Pd G3	Chloro[(4,5-bis(diphenylphosphino)-9,9-dimethylxanthene)-2-(2'-amino-1,1'-biphenyl)]palladium(II) (CAS: 1445085-97-1)

25

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 atm of N₂. Compounds were purified by flash column chromatography on silica gel or by prep. HPLC. Compounds described

30 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 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 H₂O/ 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

- 10 LC-MS 2

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 H₂O/ 0.04% NH₃ [c(NH₃) = 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

LC-MS 3

- 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: H₂O + 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 4

- LC-MS- conditions: Analytical UPLC on a Waters BEH C18 (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 H₂O/ 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

Preparative LC-MS methods used:

- Prep. HPLC/MS purifications 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 H₂O/formic acid 0.02% (A) and MeCN (B) (acidic conditions) or H₂O/ammonia 0.02% (A) and MeCN (B) (basic conditions).

Preparative chiral SFC methods used:

- Prep. chiral SFC purifications were performed on a Sepiatec Prep SFC 360 system. Following parameters were used:
- 10 *Prep. chiral SFC 1:* A ChiralCel OZ-H column (30 x 250mm, 5µm) 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.
- Prep. chiral SFC 2:* 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:
- 15 backpressure 100 bar, temperature postheater 25 °C, temperature preheater 40 °C, and temperature column department 40 °C.
- Prep. chiral SFC 3:* A ChiralPak IJ column (30 x 250 mm, 5 µm) was used. The modifier was MeOH (10%), run for 6.5 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.
- 20 *Prep. chiral SFC 4:* A Regis (R,R)-Whelk-O1 column (30 x 250 mm, 5 µm) was used. The modifier was MeCN/2-PrOH 50:50 (30%), run for 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.
- Prep. chiral SFC 5:* A Chiralpak ID column (30 x 250 mm, 5 µm) was used. The modifier was 2-PrOH (45%), run for 5 min and at a flow rate of 160 mL/min. The following system settings were used: backpressure 100 bar, temperature postheater 35 °C, temperature preheater 40 °C, and temperature column department 40 °C.
- 25 *Prep. chiral SFC 6:* A ChiralPak OX-H column (30 x 250 mm, 5 µm) was used. The modifier was MeCN/EtOH 50:50 (20 to 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.
- 30 °C.

Prep. chiral SFC 7: A ChiralPak IH column (30 x 250 mm, 5 μ m) was used. The modifier was MeCN/EtOH 50:50 (45%), run for 3 min and at a flow rate of 160 mL/min. The following system settings were used: backpressure 100 bar, temperature postheater 35 °C, temperature preheater 40 °C, and temperature column department 40 °C.

- 5 *Prep. chiral SFC 8:* A ChiralPak IB column (30 x 250 mm, 5 μ m) was used. The modifier was MeOH (10%), run for 3.25 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.

Prep. chiral SFC 9: A Chiralcel OX-H (30 x 250mm 5 μ m) was used. The modifier was MeCN/EtOH 50:50 (40%), run for 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.

- 10 *Prep. chiral SFC 10:* A Chiralcel OX-H (30 x 250mm 5 μ m) was used. The modifier was MeCN/EtOH 50:50 (35%), run for 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.

- 15 *Prep. chiral SFC 11:* A ChiralPak IC, (30 x 250mm 5 μ m) was used. The modifier was MeCN/EtOH/DEA 50:50:0,1 (45%), 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.

Prep. chiral SFC 12: A Chiralcel OX-H (30 x 250mm 5 μ m) was used. The modifier was MeCN/EtOH 50:50 (30%), run for 8 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.

- 20 *Prep. chiral SFC 13:* A Chiralcel OX-H (30 x 250mm 5 μ m) was used. The modifier was MeCN/EtOH 50:50 (30%), run for 7.5 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.

Prep. chiral SFC 14: A ChiralCel OZ-H column (30 x 250mm, 5 μ m) was used. The modifier was EtOH, run for 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.

- 25 *Prep. chiral SFC 15:* A Regis (R,R)-Whelk-O1 column (30 x 250 mm, 5 μ m) was used. The modifier was MeCN/2-ProOH 50:50 (35%), 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.

- 30 *Prep. chiral SFC 16:* A ChiralPak AY-H column (30 x 250 mm, 5 μ m) was used. The modifier was MeCN/EtOH 50:50 (40%), 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.

Prep. chiral SFC 17: A ChiralPak IG column (30 x 250 mm, 5 µm) was used. The modifier was MeOH (20%), run for 6.5 min and at a flow rate of 160 mL/min. The following system settings were used: backpressure 100 bar, temperature preheater 40 °C, temperature postheater 35 °C, and temperature column department 40 °C.

- 5 *Prep. chiral SFC 18:* A ChiralPak IH 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 postheater 25 °C, temperature preheater 40 °C, and temperature column department 40 °C.

Prep. chiral SFC 19: A ChiralPak IG column (30 x 250 mm, 5 µm) was used. The modifier was MeOH (35%), run for 4 min and at a flow rate of 160 mL/min. The following system settings were used: backpressure 100 bar, temperature preheater 40 °C, temperature postheater 35 °C, and temperature column department 40 °C.

- 10 *Prep. chiral SFC 20:* A ChiralPak IF column (30 x 250 mm, 5 µm) was used. The modifier was AcCN/EtOH/DEA 50:50:0.1 (40%), run for 4 min and at a flow rate of 160 mL/min. The following system settings were used: backpressure 100 bar, temperature preheater 40 °C, temperature postheater 35 °C, and temperature column department 40 °C.

- 15 *Prep. chiral SFC 21:* A ChiralPak IF column (30 x 250 mm, 5 µm) was used. The modifier was AcCN/EtOH 50:50 (40%), run for 5 min and at a flow rate of 160 mL/min. The following system settings were used: backpressure 100 bar, temperature preheater 40 °C, temperature postheater 35 °C, and temperature column department 40 °C.

HMNR

Bruker 500 MHz, Spectrometer Avance HD, 5mm DCH Cyoprobe

Bruker 400 MHz, Spectrometer Avance II, 5 mm BBO probehead

20 FC

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

Phase-separator

Phase separator cartridges used were Isolute® purchased from Biotage

Solid Phase Extraction

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

Flow reactor for hydrogenation:

H-Cube Pro from ThalesNano equipped with ThalesNano CatCart catalyst cartridge system, 30 mm L

Preparation of Examples:

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

- 30 **Example 1.1 (S)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:**

((5-Chloro-2-methoxy-4-methylphenyl)sulfonyl)-L-proline: L-Proline (23.40 g, 0.20 mol, 1 eq) was dissolved in H₂O (140 mL), then aq. 50% NaOH sln. (23.7 mL, 0.45 mol, 2.2 eq) was added. 5-Chloro-2-methoxy-4-

methylbenzenesulfonyl chloride (50.90 g, 0.19 mol, 0.95 eq) was suspended in THF (90 mL) and added over 15 min to the mixture. The solvent was partially removed under reduced pressure. Aq. 25% HCl soln. was added to the colorless soln. to reach pH 1. DCM was added and the org. layer was washed with H₂O. The org. layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure to give the title compound. LC-MS (1): t_R= 0.87 min; [M+H]⁺: 334.2.

Methyl ((5-chloro-2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate: BBr₃ (40.00 g, 0.16 mol, 2.5 eq) was dissolved in DCM (150 mL) and the soln. was cooled to 0°C. A soln. of ((5-chloro-2-methoxy-4-methylphenyl)sulfonyl)-L-proline (106.00 g, 0.064 mol, 1 eq) in DCM (110 mL) was slowly added and the soln. stirred for 1h at 0°C. The soln. was cooled down to 0°C and MeOH (38.6 mL, 0.96 mol, 15 eq) was slowly added and stirred for 5h. H₂O was added followed by aq. sat. Na₂CO₃ soln.. The layers were separated. The org. layer was washed with aq. 1M Na₂CO₃ soln. and with aq. 1M HCl soln., dried over MgSO₄, filtered, and the solvent removed under reduced pressure to give the title compound. LC-MS (1): t_R= 0.87 min; [M+H]⁺: 334.2.

Methyl ((2-(benzyloxy)-5-chloro-4-methylphenyl)sulfonyl)-L-prolinate: Methyl ((5-chloro-2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate (22.50 g, 0.067 mol, 1 eq) was dissolved in DMF (94 mL) and K₂CO₃ (14.00 g, 0.10 mol, 1.5 eq) was added followed by benzyl bromide (7.9 mL, 0.065 mol, 1 eq). The mixture was heated to 45°C and stirred for 1h. The mixture was cooled down to rt and H₂O was added. The mixture was diluted with *i*PrOAc. The org. layer was separated and washed with aq. sat. NaHCO₃ soln. and H₂O. The org. layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure to give the title compound. LC-MS (1): t_R= 1.07 min; [M+H]⁺: 424.3.

((2-(Benzyloxy)-5-chloro-4-methylphenyl)sulfonyl)-L-proline: Methyl ((2-(benzyloxy)-5-chloro-4-methylphenyl)sulfonyl)-L-prolinate (30.40 g, 0.072 mol, 1 eq) was dissolved in MeOH (130 mL) and aq. 32% NaOH soln. (13.3 mL, 0.14 mol, 2 eq) in H₂O (440 mL) was then added. The mixture was stirred at rt for 1h and aq. 32% NaOH soln. (7 mL) was added again and the mixture was stirred for 40 min. The mixture was extracted with DCM. The org. layer was washed with aq. 1M HCl soln. The org. layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure to give the title compound. LC-MS (1): t_R= 0.97 min; [M+H]⁺: 410.3.

***tert*-Butyl ((2-(benzyloxy)-5-chloro-4-methylphenyl)sulfonyl)-L-prolinate:** *t*BuOH (40.70 g, 0.55 mol, 7.5 eq) was dissolved in 2-MeTHF (209 mL). Then ((2-(benzyloxy)-5-chloro-4-methylphenyl)sulfonyl)-L-proline (30.00 g, 0.073 mol, 1 eq) was added followed by DMAP (1.79 g, 0.015 mol, 0.2 eq). A soln. of Boc₂O (22.40 g, 0.10 mol, 1.4 eq) in 2-MeTHF (104 mL) was added dropwise and the soln. was stirred for 30 min at rt. Imidazole (2.49 g, 0.037 mol, 0.5 eq) was added and the mixture was stirred for 30 min. Aq. 1M HCl soln. was slowly added and the layers were separated. The org. layer was washed with H₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. To the residue, *t*BME (250 mL) was added forming a precipitate. Hept. was added and the suspension was vigorously stirred for 30 min, filtered, and washed with Hept. The solid was dried under reduced pressure to give the title compound. LC-MS (1): t_R= 1.16 min; [M+H]⁺: 466.2.

***tert*-Butyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate:** *tert*-Butyl ((2-(benzyloxy)-5-chloro-4-methylphenyl)sulfonyl)-L-prolinate (25.00 g, 0.054 mol, 1 eq) and sodium acetate anhydrous (8.74 g, 0.11 mol, 2 eq) were suspended in MeOH (110 mL). Pd(OH)₂/C (20 wt. %, wet, 4.00 g, 0.006 mol, 0.1 eq) was added and the mixture was heated at 50°C under a H₂ atm. overnight. The mixture was then filtered and washed with MeOH. The filtrate was evaporated under reduced pressure and the residue was dissolved in tBME and washed with aq. sat. NaHCO₃ soln., aq. 1M HCl soln., and H₂O to give the title compound. LC-MS (1): t_R = 0.95 min; [M+H]⁺: 342.3.

N-(5-((*tert*-Butyldimethylsilyl)oxy)pentyl)-4,4-difluorocyclohexan-1-amine: 4,4-Difluorocyclohexan-1-amine (600 mg, 4.31 mmol, 1 eq) was dissolved in THF (40 mL). 5-[(*tert*-Butyldimethylsilyl)oxy]pentanal (1.03 g, 4.52 mmol, 1.05 eq) in THF (10 mL) was added at rt followed by AcOH (0.25 mL, 4.31 mmol, 1 eq). The mixture was stirred for 30 min, then NaBH(OAc)₃ (1.44 g, 6.46 mmol, 1.5 eq) was added and the mixture was stirred at rt overnight. The reaction was poured into aq. sat. NaHCO₃ soln. and extracted with EtOAc. The org. layer was washed once with H₂O, dried over MgSO₄, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. ¹H NMR (500 MHz, CDCl₃) δ: 0.06 (s, 6 H), 0.91 (s, 9 H), 1.36-1.42 (m, 2 H), 1.51-1.67 (m, 6 H), 1.71-1.84 (m, 2 H), 1.99-2.03 (m, 3 H), 2.16 (m, 2 H), 2.73 (m, 2 H), 2.79 (t, *J* = 9.9 Hz, 1 H), 3.62 (t, *J* = 6.4 Hz, 2 H).

***tert*-Butyl (5-((*tert*-butyldimethylsilyl)oxy)pentyl)(4,4-difluorocyclohexyl)carbamate:** N-(5-((*tert*-Butyldimethylsilyl)oxy)pentyl)-4,4-difluorocyclohexan-1-amine (660 mg, 1.97 mmol, 1 eq) and TEA (0.68 mL, 4.92 mmol, 2.5 eq) were dissolved in DCM (40 mL). The mixture was cooled to 0°C and Boc₂O (520 mg, 2.36 mmol, 1.2 eq) was added. The resulting mixture was stirred at rt overnight. The reaction mixture was partitioned between DCM and brine. The org. layer was washed with brine. The org. layer was separated through a phase separator cartridge and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 1.30 min; [M+H]⁺: 436.3.

***tert*-Butyl (4,4-difluorocyclohexyl)(5-hydroxypentyl)carbamate:** *tert*-Butyl (5-((*tert*-butyldimethylsilyl)oxy)pentyl)(4,4-difluorocyclohexyl)carbamate (351 mg, 0.81 mmol, 1 eq) was dissolved in THF (10 mL). TBAF·3H₂O (254 mg, 0.81 mmol, 1 eq) was added dropwise at 0°C. The reaction was then allowed to stir at rt overnight. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc and washed with H₂O and brine. The org. layer was dried over MgSO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 0.95 min; [M+H]⁺: 322.1.

***tert*-Butyl ((2-((5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** A soln. of *tert*-butyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate (175 mg, 0.51 mmol, 1 eq) in THF (8 mL) was cooled to 0°C. *tert*-butyl (4,4-difluorocyclohexyl)(5-hydroxypentyl)carbamate (214 mg, 0.67 mmol, 1.3 eq) and PPh₃ (177 mg, 0.67 mmol, 1.3 eq) were added followed by DEAD (~40% in toluene, 0.60 mL, 1.23 mmol, 2.4 eq). After the addition, the mixture was allowed to warm up to rt and stirred for 72h. The solvent was removed under reduced pressure and the residue was taken up in Et₂O and

filtered. The solvent was removed under reduced pressure and the residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.23 min; $[M+H]^+$: 645.3.

((2-((5-((4,4-Difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)sulfonyl)-L-proline: *tert*-Butyl ((2-((5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate (240 mg, 0.37 mmol, 1 eq) was dissolved in DCM (10 mL). TFA (2.0 mL, 26.10 mmol, 70 eq) was added at rt and the resulting mixture was stirred for 1h. The solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.23 min; $[M+H]^+$: 489.2.

(S)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide: ((2-((5-((4,4-Difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)sulfonyl)-L-proline (417 mg, 0.85 mmol, 1 eq) was dissolved in DMF (12 mL). DIPEA (1.2 mL, 6.82 mmol, 8 eq) and HATU (389 mg, 1.02 mmol, 1.2 eq) were added at rt and the mixture was stirred at rt for 5 min. The solvent was removed under reduced pressure and the residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.01 min; $[M+H]^+$: 471.2.

Example 1.2 (6S,10aS)-9-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10a,11,12,13-octahydro-10H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacycloundecin-10-one 15,15-dioxide:

(R)-N-(3-((*tert*-Butyldimethylsilyl)oxy)butyl)-4,4-difluorocyclohexan-1-amine: 4,4-Difluorocyclohexan-1-amine (220 mg, 1.58 mmol, 1 eq) was dissolved in THF (40 mL) and (R)-3-((*tert*-butyldimethylsilyl)oxy)butanal (WO2016208602 A1) (335 mg, 1.66 mmol, 1.05 eq) in THF (10 mL) was added at rt followed by AcOH (0.09 mL, 1.58 mmol, 1 eq). The mixture was stirred for 30 min, then $\text{NaBH}(\text{OAc})_3$ (528 mg, 2.37 mmol, 1.5 eq) was added and the mixture was stirred at rt overnight. The reaction mixture was poured into aq. sat. NaHCO_3 soln. and extracted with EtOAc. The org. layer was washed with H_2O , dried over MgSO_4 , filtered, and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. ^1H NMR (500 MHz, CDCl_3) δ : 0.07 (d, J = 4.4 Hz, 6 H), 0.90 (s, 9 H), 1.17 (d, J = 6.1 Hz, 3 H), 1.60-1.87 (m, 5 H), 2.00-2.03 (m, 4 H), 2.13-2.19 (m, 2 H), 2.77-2.88 (m, 3 H), 3.91-3.95 (m, 1 H).

***tert*-Butyl (R)-3-((*tert*-butyldimethylsilyl)oxy)butyl(4,4-difluorocyclohexyl)carbamate:** (R)-N-(3-((*tert*-Butyldimethylsilyl)oxy)butyl)-4,4-difluorocyclohexan-1-amine (308 mg, 0.96 mmol, 1 eq) and TEA (0.33 mL, 2.39 mmol, 2.5 eq) were dissolved in DCM (40 mL). The mixture was cooled to 0°C and Boc_2O (253 mg, 1.15 mmol, 1.2 eq) was added and the mixture was stirred at rt overnight. The reaction mixture was partitioned between DCM and brine. The org. layer was washed with brine. The org. layer was separated through a phase separator cartridge and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 1.27 min; $[M+H]^+$: 422.3.

***tert*-Butyl (R)-(4,4-difluorocyclohexyl)(3-hydroxybutyl)carbamate:** *tert*-Butyl (R)-3-((*tert*-butyldimethylsilyl)oxy)butyl(4,4-difluorocyclohexyl)carbamate (288 mg, 0.68 mmol, 1 eq) was dissolved in THF (14 mL). $\text{TFA} \cdot 3\text{H}_2\text{O}$ (216 mg, 0.68 mmol, 1 eq) was added dropwise at 0°C. The reaction was then allowed to stir at rt for 1h. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc, washed with

H₂O and brine. The org. layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure to give the title compound. The crude product was used without further purification in the next step. LC-MS (1): t_R= 0.96 min; [M+H]⁺: 308.3.

tert-Butyl ((2-(((S)-4-((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)butan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using *tert*-butyl (R)-{(4,4-difluorocyclohexyl)(3-hydroxybutyl)carbamate and *tert*-butyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R= 1.22 min; [M+H]⁺: 631.3.

((2-(((S)-4-((4,4-Difluorocyclohexyl)amino)butan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-proline: Was synthesized using *tert*-butyl ((2-(((S)-4-((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)butan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R= 0.72 min; [M+H]⁺: 475.2.

(6S,10aS)-9-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10a,11,12,13-octahydro-10H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacycloundecin-10-one 15,15-dioxide: Was synthesized using ((2-(((S)-4-((4,4-difluorocyclohexyl)amino)butan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-proline in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R= 0.98 min; [M+H]⁺: 457.3.

Example 1.3 (6R,11aS)-10-(4,4-Difluorocyclohexyl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide:

(S)-N-(4-((tert-Butyldimethylsilyl)oxy)pentyl)-4,4-difluorocyclohexan-1-amine: 4,4-Difluorocyclohexan-1-amine (415 mg, 2.98 mmol, 1 eq) was dissolved in THF (7 mL). Then (S)-4-((tert-butyldimethylsilyl)oxy)pentanal (J. Org. Chem. (2004), 69(3), 891-898) (335 mg, 1.66 mmol, 1.05 eq) in THF (10 mL) was added at rt, followed by AcOH (0.17 mL, 2.98 mmol, 1 eq). The mixture was stirred for 30 min, then NaBH(OAc)₃ (821 mg, 3.87 mmol, 1.3 eq) was added and the mixture was stirred at rt overnight. The reaction mixture was poured into aq. sat. NaHCO₃ soln. and extracted with EtOAc. The org. layer was washed with H₂O, dried over MgSO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. ¹H NMR (500 MHz, CDCl₃) δ: 0.07 (d, J = 2.6 Hz, 6 H), 0.91 (s, 9 H), 1.15 (d, J = 6.1 Hz, 3 H), 1.40-1.84 (m, 9 H), 1.89-1.93 (m, 2 H), 2.07-2.20 (m, 2 H), 2.61-2.64 (m, 3 H), 3.80-3.84 (m, 1 H).

tert-Butyl (S)-4-((tert-butyldimethylsilyl)oxy)pentyl(4,4-difluorocyclohexyl)carbamate: (S)-N-(4-((tert-Butyldimethylsilyl)oxy)pentyl)-4,4-difluorocyclohexan-1-amine (579 mg, 1.73 mmol, 1 eq) and TEA (0.60 mL, 4.31 mmol, 2.5 eq) were dissolved in DCM (40 mL). The mixture was cooled to 0°C and Boc₂O (456 mg, 2.07 mmol, 1.2 eq) was added. The resulting mixture was stirred at rt overnight. The reaction mixture was partitioned between DCM and brine. The org. layer was washed with brine. The org. layer was separated through a phase separator cartridge and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R= 1.31 min; [M+H]⁺: 436.4.

***tert*-Butyl (S)-(4,4-difluorocyclohexyl)(4-hydroxypentyl)carbamate:** *tert*-Butyl (S)-(4-((*tert*-butyldimethylsilyloxy)pentyl)(4,4-difluorocyclohexyl)carbamate (350 mg, 0.80 mmol, 1 eq) was dissolved in THF (25 mL). TFA.3H₂O (259 mg, 0.82 mmol, 1.02 eq) was added dropwise at 0°C. The reaction was then allowed to stir at rt for 1h. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc, washed with H₂O and brine. The org. layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. LC-MS (1): t_R= 0.94 min; [M+H]⁺: 322.2.

***tert*-Butyl ((2-(((R)-5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl (S)-(4,4-difluorocyclohexyl)(4-hydroxypentyl)carbamate and *tert*-butyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R= 1.24 min; [M+H]⁺: 645.4.

((2-(((R)-5-((4,4-Difluorocyclohexyl)amino)pentan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-proline: Was synthesized using *tert*-butyl ((2-(((R)-5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R= 0.73 min; [M+H]⁺: 489.0.

(6R,11aS)-10-(4,4-Difluorocyclohexyl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide: Was synthesized using ((2-(((R)-5-((4,4-difluorocyclohexyl)amino)pentan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-proline in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R= 1.02 min; [M+H]⁺: 471.3.

Example 1.4 (6S,11aS)-10-(4,4-Difluorocyclohexyl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide: Was synthesized using (R)-4-((*tert*-butyldimethylsilyloxy)pentanal (Chemistry Asian J. (2013), 8(7), 1391-1394) in analogy to Example 1.3 to give the title compound. LC-MS (1): t_R= 1.03 min; [M+H]⁺: 471.3.

Example 1.5 (6S,12aS)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,10,11,12a,13,14,15-octahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:

***tert*-Butyl ((4-methyl-2-(((S)-pent-4-en-2-yl)oxy)phenyl)sulfonyl)-L-prolinate:** *tert*-Butyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate (160 mg, 0.47 mmol, 1 eq) was dissolved in THF (9 mL). The soln. was cooled to 0°C. Then (2R)-pent-4-en-2-ol (55 mg, 0.61 mmol, 1.3 eq) and PPh₃ (162 mg, 0.61 mmol, 1.3 eq) were added followed by DEAD (~40% in toluene, 0.55 mL, 1.13 mmol, 2.4 eq). After the addition, the mixture was allowed to warm up to rt and stirred overnight. After this time Et₂O was added and the mixture was filtered. The solvent was removed under reduced pressure and the residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R= 1.13 min; [M+H]⁺: 410.3.

((4-Methyl-2-(((S)-pent-4-en-2-yl)oxy)phenyl)sulfonyl)-L-proline: *tert*-Butyl ((4-methyl-2-(((S)-pent-4-en-2-yl)oxy)phenyl)sulfonyl)-L-prolinate (80 mg, 0.20 mmol, 1 eq) was dissolved in DCM (6 mL). TFA (1.1 mL, 13.70 mmol, 70 eq) was added at rt and the resulting mixture was stirred at rt for 2h. The solvent was removed under

reduced pressure and the residue was used without further purification in the next step. LC-MS (1): t_R = 0.90 min; $[M+H]^+$: 354.2.

N-Allyl-4,4-difluorocyclohexan-1-amine: 4,4-Difluorocyclohexanone (600 mg, 4.29 mmol, 1 eq) was dissolved in THF (25 mL). Allylamine (0.34 mL, 4.51 mmol, 1.05 eq) in THF (5 mL) was added at rt followed by AcOH (0.25 mL, 4.29 mmol, 1 eq). The mixture was stirred for 30 min, then $NaBH(OAc)_3$ (1.44 g, 6.44 mmol, 1.5 eq) was added and the mixture was stirred at rt overnight. Aq. 10% Na_2CO_3 soln. was added and the mixture was extracted with EtOAc. The aq. layer was basified with aq. 1M NaOH soln., and extracted with EtOAc. The org. layer was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (EtOAc to 10% MeOH) to give the title compound. LC-MS (1): t_R = 0.47 min; $[M+H]^+$: 176.4.

(S)-N-Allyl-N-(4,4-difluorocyclohexyl)-1-((4-methyl-2-((S)-pent-4-en-2-yl)oxy)phenyl)sulfonylpyrrolidine-2-carboxamide: ((4-Methyl-2-((S)-pent-4-en-2-yl)oxy)phenyl)sulfonyl-L-proline (80 mg, 0.23 mmol, 1 eq) was dissolved in DMF (1 mL). DIPEA (0.12 mL, 0.68 mmol, 3 eq), PyCloP (117 mg, 0.27 mmol, 1.2 eq) and N-allyl-4,4-difluorocyclohexan-1-amine (55.5 mg, 0.32 mmol, 1.4 eq) were added. The mixture was stirred at rt overnight. The soln. was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.13 min; $[M+H]^+$: 410.3.

(6S,12aS)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,10,11,12a,13,14,15-octahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide: (S)-N-allyl-N-(4,4-difluorocyclohexyl)-1-((4-methyl-2-((S)-pent-4-en-2-yl)oxy)phenyl)sulfonylpyrrolidine-2-carboxamide (30 mg, 0.059 mmol, 1 eq) was dissolved in DCM (1 mL) under N_2 atm. Grubbs Catalyst, 2nd generation (1.3 mg, 47 μ mol, 0.025 eq) was added and the soln. was stirred at 45°C for 1h. The solvent was removed under reduced pressure and the residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.02 min; $[M+H]^+$: 483.3.

Example 1.6 (6S,12aS)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide: (6S,12aS)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,10,11,12a,13,14,15-octahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide (20 mg, 0.041 mmol, 1 eq) was dissolved in EtOH (2 mL). The reaction flask was purged with N_2 and 10% Pd/C (1 mg) was added. The reaction mixture was stirred under a H_2 atm at rt for 1h. The mixture was filtered over a Celite pad and washed with EtOH. The solvent was removed under reduced pressure and the residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.04 min; $[M+H]^+$: 485.3.

Example 1.7 (S)-11-(4,4-Dimethylcyclohexyl)-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:

tert-Butyl ((2-((5-hydroxypentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: At 0°C and under a N_2 atm, DEAD (~40% in toluene, 1.4 mL, 2.93 mmol, 2 eq) was added to a stirred soln. of 1,5-pentanediol (0.80 mL, 7.32 mmol, 5 eq) and PPh_3 (468 mg, 1.76 mmol, 1.2 eq) in THF (17 mL). The mixture was stirred for 10 min. A soln. of tert-butyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate (500 mg, 1.46 mmol, 1 eq) in THF (6 mL) was added dropwise

and the reaction was stirred at rt for 1h. The reaction mixture was diluted with Et₂O and washed with aq. 1M HCl soln., aq. sat. NaHCO₃ soln., and H₂O. The org. layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (DCM to 5% MeOH) to give the title compound. LC-MS (1): t_R= 0.98 min; [M+H]⁺: 428.1.

- 5 ***tert*-Butyl ((4-methyl-2-((5-oxopentyl)oxy)phenyl)sulfonyl)-L-prolinate**: At -78°C under N₂ atm, DMSO (0.13 mL, 1.85 mmol, 2.7 eq) was added dropwise to a stirred soln. of oxalyl chloride (0.09 mL, 1.03 mmol, 1.5 eq) in DCM (10 mL). The mixture was stirred at -78°C for 10 min, then a soln. of *tert*-butyl ((2-((5-hydroxypentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate (293 mg, 0.69 mmol, 1 eq) in DCM (4 mL) was added dropwise. After stirring for another 10 min, Et₃N (0.50 mL, 3.43 mmol, 5 eq) was added dropwise. The reaction was stirred at -78°C for another 10 min and then allowed to slowly warm up to -20°C. Aq. 1M HCl soln. was added and the mixture was extracted with Et₂O. The org. layer was washed with aq. sat. NaHCO₃ soln. and H₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The crude product was used without further purification in the next step. LC-MS (1): t_R= 1.03 min; [M+H]⁺: 426.1.

- 15 ***tert*-Butyl ((2-((4,4-dimethylcyclohexyl)amino)pentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate**: At rt, NaBH(OAc)₃ (32 mg, 0.14 mmol, 1.5 eq) was added to a soln. of *tert*-butyl ((4-methyl-2-((5-oxopentyl)oxy)phenyl)sulfonyl)-L-prolinate (40 mg, 0.09 mmol, 1 eq) and 4,4-dimethylcyclohexan-1-amine (20 µL, 0.11 mmol, 1.2 eq) in THF (1 mL) and the reaction mixture was stirred at rt overnight. The reaction was poured onto aq. sat. NaHCO₃ soln. and extracted with DCM. The layers were separated by phase separator and the org. layer was evaporated under reduced pressure. The residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R= 0.95 min; [M+H]⁺: 537.5.

- 25 **((2-((5-((4,4-Dimethylcyclohexyl)amino)pentyl)oxy)-4-methylphenyl)sulfonyl)-L-proline**: At rt, *tert*-butyl ((2-((5-((4,4-dimethylcyclohexyl)amino)pentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate (40 mg, 0.075 mmol, 1 eq) was dissolved in DCM (2 mL), then TFA (0.11 mL, 1.49 mmol, 20 eq) was added and the mixture was stirred at rt for 6h. The solvent was removed under reduced pressure and the crude product was used without further purification in the next step. LC-MS (1): t_R= 0.82 min; [M+H]⁺: 481.1.

- 30 **(S)-11-(4,4-Dimethylcyclohexyl)-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide**: At rt, HATU (32 mg, 0.082 mmol, 1.1 eq) and DIPEA (32 µL, 0.19 mmol, 2.5 eq) were added to a stirred soln. of ((2-((5-((4,4-dimethylcyclohexyl)amino)pentyl)oxy)-4-methylphenyl)sulfonyl)-L-proline (42 mg, 0.075 mmol, 1 eq) in DMF (2 mL) and the soln. was stirred at rt for 30 min. The soln. was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R= 1.13 min; [M+H]⁺: 463.1.

Example 1.8 (S)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydropyrido[2,3-l]pyrrolo[1,2-b][1]thia[2,5,11]triazacyclotridecin-12(5H)-one 17,17-dioxide:

- 35 **Methyl ((2-chloro-6-methylpyridin-3-yl)sulfonyl)-L-prolinate**: L-Proline methyl ester hydrochloride (5.10 g, 30.50 mmol, 1 eq) was dissolved in DCM (120 mL). DIPEA (15.7 mL, 91.50 mmol, 3 eq) and DMAP (372 mg, 3.05

mmol, 0.1 eq) were added at rt. The reaction was cooled to 0°C and 2-chloro-6-methylpyridine-3-sulfonyl chloride (7.47 g, 31.40 mmol, 1.03 eq) was added. The mixture was stirred at rt overnight. The mixture was quenched with aq. sat. NaHCO₃ soln. and extracted with DCM. The org. layer was washed once with H₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R= 0.81 min; [M+H]⁺: 319.1.

((2-Chloro-6-methylpyridin-3-yl)sulfonyl)-L-proline: Methyl ((2-chloro-6-methylpyridin-3-yl)sulfonyl)-L-prolinate (5.00 g, 15.70 mmol, 1 eq) was dissolved in THF (120 mL) and aq. 1 M LiOH soln. (47.1 mL, 47.10 mmol, 3 eq) was added. The soln. was stirred during 1h at rt. The mixture was quenched with aq. 2M HCl soln. until pH 1 and extracted with EtOAc. The combined org. layers were dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The crude product was used without further purification in the next step. LC-MS (1): t_R= 0.67 min; [M+H]⁺: 305.1.

((2-(Allylamino)-6-methylpyridin-3-yl)sulfonyl)-L-proline: ((2-Chloro-6-methylpyridin-3-yl)sulfonyl)-L-proline (620 mg, 2.03 mmol, 1 eq) and allylamine (0.46 mL, 6.10 mmol, 3 eq) were dissolved in TMP (2 mL) and the reaction mixture was stirred at 90°C for 8 days. The reaction mixture was cooled down to rt. The soln. was purified by acidic prep. HPLC to give the title compound. LC-MS (1): t_R= 0.75 min; [M+H]⁺: 326.3.

N-(But-3-en-1-yl)-4,4-difluorocyclohexan-1-amine: 4,4-Difluorocyclohexanone (600 mg, 4.29 mmol, 1 eq) was dissolved in THF (25 mL). 3-Buten-1-amine (327 mg, 4.51 mmol, 1.05 eq) in THF (5 mL) was added followed by AcOH (0.25 mL, 4.29 mmol, 1 eq). The mixture was stirred for 30 min, then NaBH(OAc)₃ (1.44 g, 6.44 mmol, 1.5 eq) was added and the mixture was stirred at rt overnight. The reaction was poured into aq. sat. NaHCO₃ soln. and extracted with EtOAc. The org. layer was washed with H₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (EtOAc to 10% MeOH) to give the title compound. LC-MS (1): t_R= 0.48 min; [M+H]⁺: 190.4.

(S)-1-((2-(Allylamino)-6-methylpyridin-3-yl)sulfonyl)-N-(but-3-en-1-yl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide: ((2-(Allylamino)-6-methylpyridin-3-yl)sulfonyl)-L-proline (100 mg, 0.31 mmol, 1 eq) was dissolved in DMF (1 mL). DIPEA (0.16 mL, 0.92 mmol, 3 eq), PyCloP (159 mg, 0.37 mmol, 1.2 eq) and N-(but-3-en-1-yl)-4,4-difluorocyclohexan-1-amine (64 mg, 0.34 mmol, 1.1 eq) were added. The mixture was stirred at rt overnight. The soln. was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R= 1.05 min; [M+H]⁺: 497.2.

(S)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,9,10,11,12a,13,14,15-octahydropyrido[2,3-l]pyrrolo[1,2-b][1]thia[2,5,11]triazacyclotridecin-12(5H)-one 17,17-dioxide: (S)-1-((2-(Allylamino)-6-methylpyridin-3-yl)sulfonyl)-N-(but-3-en-1-yl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide (96 mg, 0.19 mmol, 1 eq) was dissolved in THF (5 mL) and Hoveyda-Grubbs Catalyst (18 mg, 0.029 mmol, 0.15 eq) was added. The soln. was degassed with a N₂ flow and stirred at 65°C for 1h. Hoveyda-Grubbs Catalyst (18 mg, 0.029 mmol, 0.15 eq) was added again and the reaction mixture was stirred at 65°C overnight. The mixture was cooled to rt and the solvent

was removed under reduced pressure. The residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 0.89 min; $[M+H]^+$: 469.3.

(S)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydropyrido[2,3-l]pyrrolo[1,2-b][1]thia[2,5,11]triazacyclotridecin-12(5H)-one 17,17-dioxide: (S)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,9,10,11,12a,13,14,15-octahydropyrido[2,3-l]pyrrolo[1,2-b][1]thia[2,5,11]triazacyclotridecin-12(5H)-one 17,17-dioxide (36 mg, 0.077 mmol, 1 eq) was dissolved in EtOH (1 mL). The reaction flask was purged with N_2 and 10% Pd/C (1 mg) was added. The reaction was stirred under H_2 atm for 1h. The mixture was filtered and washed with EtOH. The solvent was removed under reduced pressure and the residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 0.90 min; $[M+H]^+$: 471.0.

Example 1.9 (S)-5-(4,4-Difluorocyclohexyl)-13-methyl-1,2,3,3a,6,7,8,9-octahydrobenzo[l]pyrrolo[1,2-b][1]thia[2,5]diazacyclotridecin-4(5H)-one 16,16-dioxide:

***tert*-Butyl ((2-bromo-4-methylphenyl)sulfonyl)-L-prolinate:** TEA (2.9 mL, 21.10 mmol, 2 eq) was added dropwise to a soln. of 2-bromo-4-methylbenzene-1-sulfonyl chloride (3.00 g, 10.60 mmol, 1 eq) and L-proline *t*-butyl ester (2.0 mL, 11.60 mmol, 1.1 eq) in DCM (75 mL) at 0°C. The reaction was stirred at rt overnight. The reaction mixture was diluted with aq. sat. $NaHCO_3$ soln. and the layers were separated. The org. layer was washed with H_2O , dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure to give the title compound. LC-MS (1): t_R = 1.06 min; $[M+H]^+$: 405.9.

***tert*-Butyl ((4-methyl-2-vinylphenyl)sulfonyl)-L-prolinate:** A soln. of *tert*-butyl ((2-bromo-4-methylphenyl)sulfonyl)-L-prolinate (215 mg, 0.53 mmol, 1 eq), 2-ethenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (129 mg, 0.80 mmol, 1.5 eq), (dppf) $PdCl_2 \cdot CH_2Cl_2$ (43 mg, 0.053 mmol, 0.1 eq) and K_2CO_3 (220 mg, 1.60 mmol, 3 eq) in dioxane/ H_2O (4:1, 5 mL) was degassed for 15 min and stirred at 90°C over the weekend. The reaction mixture was diluted with aq. 1M HCl soln. and EtOAc. The layers were separated and the org. layer was washed with aq. sat. $NaHCO_3$ soln., H_2O , and brine. The org. layer was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give the title compound. LC-MS (1): t_R = 1.06 min; $[M+H]^+$: 352.3.

((4-Methyl-2-vinylphenyl)sulfonyl)-L-proline: TFA (0.40 mL, 5.69 mmol, 10 eq) was added to a soln. of *tert*-butyl ((4-methyl-2-vinylphenyl)sulfonyl)-L-prolinate (200 mg, 0.57 mmol, 1 eq) in DCM (3 mL) and the mixture was stirred at rt for 1.5h. The solvent was removed under reduced pressure. The crude product was used without further purification in the next step. LC-MS (1): t_R = 0.82 min; $[M+H]^+$: 296.2.

4,4-Difluoro-N-(hex-5-en-1-yl)cyclohexan-1-amine: A soln. of 4,4-difluorocyclohexanone (300 mg, 2.15 mmol, 1 eq), 1-amino-5-hexene (247 mg, 2.36 mmol, 1.1 eq) and AcOH (0.12 mL, 2.15 mmol, 1 eq) in THF (10 mL) was stirred at rt for 30 min. Then, $NaBH(OAc)_3$ (719 mg, 3.22 mmol, 1.5 eq) was added and the mixture was stirred at rt overnight. The reaction was poured into aq. sat. $NaHCO_3$ soln. and extracted with EtOAc. The org. layer was washed with H_2O , dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude product was used without further purification in the next step. LC-MS (1): t_R = 0.62 min; $[M+H]^+$: 218.3.

(S)-N-(4,4-Difluorocyclohexyl)-N-(hex-5-en-1-yl)-1-((4-methyl-2-vinylphenyl)sulfonyl)pyrrolidine-2-carboxamide: DIPEA (0.40 mL, 2.29 mmol, 4 eq) was added to a soln. of ((4-methyl-2-vinylphenyl)sulfonyl)-L-proline (169 mg, 0.57 mmol, 1 eq) and HATU (269 mg, 0.69 mmol, 1.2 eq) in DMF (2 mL). The yellow soln. was stirred for 10 min at rt and a soln. of 4,4-difluoro-N-(hex-5-en-1-yl)cyclohexan-1-amine (137 mg, 0.63 mmol, 1.1 eq) in DMF (0.5 mL) was added. The mixture was stirred at rt overnight. The reaction mixture was purified by acidic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.14 min; $[M+H]^+$: 495.3.

(S)-5-(4,4-Difluorocyclohexyl)-13-methyl-1,2,3,3a,6,7,8,9-octahydrobenzo[*l*]pyrrolo[1,2-b][1]thia[2,5]diazacyclotridecin-4(5H)-one 16,16-dioxide: A soln. of (S)-N-(4,4-difluorocyclohexyl)-N-(hex-5-en-1-yl)-1-((4-methyl-2-vinylphenyl)sulfonyl)pyrrolidine-2-carboxamide (19 mg, 0.038 mmol, 1 eq) in toluene (1 mL) was evacuated and purged with N_2 atm. Grubbs Catalyst, 2nd generation (2 mg, 19 μ mol, 0.05 eq) was added and the mixture was stirred at 110°C for 1h. The solvent was removed under reduced pressure and the residue was purified by acidic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.10 min; $[M+H]^+$: 467.0.

Example 1.10 to Example 1.11 were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((2-((5-hydroxypentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.7. LC-MS data of Example 1.10 to Example 1.11 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R (min)	$[M+H]^+$
1.10	(S)-11-(1,1-Difluorospiro[2.3]hexan-5-yl)-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[<i>b</i>]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.03	469.0
1.11	(S)-11-(1,1-Difluorospiro[2.5]octan-6-yl)-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[<i>b</i>]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.08	497.2

Example 1.12 (S)-5-(4,4-Difluorocyclohexyl)-13-methyl-1,2,3,3a,6,7,8,9,10,11-decahydrobenzo[*l*]pyrrolo[1,2-b][1]thia[2,5]diazacyclotridecin-4(5H)-one 16,16-dioxide: A mixture of (S)-5-(4,4-difluorocyclohexyl)-13-methyl-1,2,3,3a,6,7,8,9-octahydrobenzo[*l*]pyrrolo[1,2-b][1]thia[2,5]diazacyclotridecin-4(5H)-one 16,16-dioxide (77 mg, 0.17 mmol, 1 eq) was dissolved in EtOH (5 mL). The reaction flask was purged with N_2 and 10% Pd/C (10 mg, 94 μ mol, 0.06 eq) was added and the reaction mixture was stirred under a H_2 atm at rt for 1h. The mixture was filtered over a Celite pad and washed with EtOH. The solvent was removed under reduced pressure and the residue was purified by acidic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.12 min; $[M+H]^+$: 469.3.

Example 1.13 (6R,12aS)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[*b*]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide: Was synthesized using *tert*-butyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate and (2S)-pent-4-en-2-ol in analogy to Example 1.6 to give the title compound. LC-MS (1): t_R = 1.05 min; $[M+H]^+$: 485.0.

Example 1.14 (6R,11aS)-10-(1,1-Difluorospiro[2.3]hexan-5-yl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide:

(RS)-5-((tert-Butyldimethylsilyl)oxy)pentan-2-ol: At rt, a soln. of *tert*-butyl(chloro)dimethylsilane (1.59 g, 10.00 mmol, 1 eq) in DCM (10 mL) was added dropwise to a stirred soln. of 1,4-pentanediol (1.0 mL, 10.00 mmol, 1 eq) and imidazole (1.38 g, 20.00 mmol, 2 eq) in DCM (40 mL) within 1h. The reaction was stirred for 30 min. The mixture was diluted with DCM and washed with aq. 1M HCl soln. and H₂O. The org. layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The crude product was used without further purification in the next step. ¹H NMR (500 MHz, CDCl₃) δ: 3.83-3.84 (m, 1 H), 3.65-3.72 (m, 2 H), 2.63 (s, 1 H), 1.59-1.70 (m, 3 H), 1.45-1.58 (m, 1 H), 0.91-0.94 (m, 10 H), 0.09 (m, 6 H).

10 tert-Butyl ((2-(((RS)-5-((tert-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using *tert*-butyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate and (RS)-5-((tert-Butyldimethylsilyl)oxy)pentan-2-ol in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 1.30 min; [M+H]⁺: 542.0.

15 tert-Butyl ((2-(((RS)-5-hydroxypentan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: *tert*-Butyl ((2-(((RS)-5-((tert-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate (2.34 g, 4.32 mmol, 1 eq) was dissolved in THF (45 mL). Then 1M TBAF soln. in THF (5.2 mL, 5.18 mmol, 1.2 eq) was added at once and the soln. was stirred at rt for 2h. The reaction was diluted with Et₂O and washed with H₂O. The org. layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (DCM to 5% MeOH) to give the title compound. LC-MS (1): t_R = 0.97 min; [M+H]⁺: 428.1.

20 tert-Butyl ((4-methyl-2-(((RS)-5-oxopentan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate: Was synthesized using *tert*-butyl ((2-(((RS)-5-hydroxypentan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.7 to give the title compound. LC-MS (1): t_R = 1.04 min; [M+H]⁺: 426.3.

25 tert-Butyl ((2-(((RS)-5-((1,1-difluorospiro[2.3]hexan-5-yl)amino)pentan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using *tert*-butyl ((4-methyl-2-(((RS)-5-oxopentan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate and 1,1-difluorospiro[2.3]hexan-5-amine hydrochloride in analogy to Example 1.7 to give the title compound. LC-MS (1): t_R = 0.90 and 0.91 min; [M+H]⁺: 543.0.

30 ((2-(((RS)-5-((1,1-Difluorospiro[2.3]hexan-5-yl)amino)pentan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-proline: Was synthesized using *tert*-butyl ((2-(((RS)-5-((1,1-difluorospiro[2.3]hexan-5-yl)amino)pentan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.7 to give the title compound. LC-MS (1): t_R = 0.75 and 0.76 min; [M+H]⁺: 487.0.

(6R,11aS)-10-(1,1-Difluorospiro[2.3]hexan-5-yl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide: Was synthesized using ((2-(((RS)-5-((1,1-difluorospiro[2.3]hexan-5-yl)amino)pentan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-proline in analogy to Example 1.7 to give the title compound. LC-MS (1): t_R = 1.03 min; [M+H]⁺: 469.3.

Example 1.15 to **Example 1.21** were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((4-methyl-2-(((RS)-5-oxopentan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.14. LC-MS data of Example 1.15 to Example 1.21 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R (min)	[M+H] ⁺
1.15	(6RS,11aS)-10-(1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide	1.07	497.0
1.18	(6RS,11aS)-10-(4,4-Dimethylcyclohexyl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide	1.13	463.3
1.19	(1R*,3S*)-3-((6SR,11aS)-3,6-Dimethyl-16,16-dioxido-11-oxo-6,7,8,9,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-yl)cyclopentane-1-carbonitrile	0.94	446.0
1.20	(6RS,11aS)-10-(6,6-Difluorobicyclo[3.1.0]hexan-3-yl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide	1.02 and 1.04	469.0
1.21	(1R,3s)-3-((6RS,11aS)-3,6-Dimethyl-16,16-dioxido-11-oxo-6,7,8,9,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-yl)cyclobutane-1-carbonitrile	0.91 and 0.92	432.0

5 Example 1.22 (S)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:

5-((3-Bromo-6-methylpyridin-2-yl)oxy)pentan-1-ol: DEAD (~ 40% in toluene, 9.40 mL, 20.40 mmol, 2 eq) was added dropwise to a stirred soln. of 3-bromo-6-methylpyridin-2-ol (2.00 g, 10.20 mmol, 1 eq), 1,5-pentanediol (5.60 mL, 51.10 mmol, 5 eq) and PPh₃ (3.25 g, 12.30 mmol, 1.2 eq) in THF (50 mL) at 0°C under N₂ atm. The reaction was warmed to rt and stirred for 3h. The reaction was diluted with Et₂O and washed with brine. The org. layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The crude was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R= 0.90 min; [M+H]⁺: 276.1.

3-Bromo-2-((5-((*tert*-butyldimethylsilyl)oxy)pentyl)oxy)-6-methylpyridine: A soln. of *tert*-butyl(chloro)dimethylsilane (1.06 g, 6.69 mmol, 1.1 eq) in DCM (10 mL) was added dropwise to a stirred soln. of 5-((3-bromo-6-methylpyridin-2-yl)oxy)pentan-1-ol (1.67 g, 6.08 mmol, 1 eq) and imidazol (832 mg, 12.20 mmol, 2 eq) in DCM (30 mL) at 0°C under N₂ atmosphere. The reaction was warmed to rt and stirred for 2h. The mixture was diluted with DCM and washed with brine. The org. layer was dried over MgSO₄, filtered, and the solvent removed

under reduced pressure. The crude product was used without further purification in the next step. LC-MS (1): t_R = 1.31 min; $[M+H]^+$: 388.0.

3-(Benzylthio)-2-((5-((*tert*-butyldimethylsilyl)oxy)pentyl)oxy)-6-methylpyridine: A soln. of 3-bromo-2-((5-((*tert*-butyldimethylsilyl)oxy)pentyl)oxy)-6-methylpyridine (815 mg, 2.10 mmol, 1 eq) in THF (15 mL) was cooled to -78°C. *n*-BuLi 1.6M in hexanes (1.6 mL, 2.52 mmol, 1.2 eq) was added dropwise while maintaining a temperature below -75°C. After 10 min, a soln. of benzyl disulfide (55 mg, 2.20 mmol, 1.05 eq) in THF (5 mL) was added dropwise at -78°C. The reaction mixture was stirred at -75°C for 1h, quenched with H₂O and extracted with DCM. The org. layer was washed with H₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 1.34 min; $[M+H]^+$: 432.1.

2-((5-((*tert*-Butyldimethylsilyl)oxy)pentyl)oxy)-6-methylpyridine-3-sulfonyl chloride: At 0°C, AcOH (0.5 mL, 8.86 mmol, 2 eq) and H₂O (0.16 mL, 8.86 mmol, 2 eq) were added to a stirred soln. of 3-(benzylthio)-2-((5-((*tert*-butyldimethylsilyl)oxy)pentyl)oxy)-6-methylpyridine (1.81 g, 4.43 mmol, 1 eq) in THF (25 mL). A soln. of 1,3-dichloro-5,5-dimethylhydantoin (2.62 g, 13.30 mmol, 3 eq) in THF (2 mL) was added dropwise. The reaction mixture was further stirred at 0°C for 15 min and then warmed to rt. After 10 min at rt, the reaction was diluted with DCM and washed with aq. sat. NaHCO₃ soln. The org. layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The crude product was used without further purification in the next step. LC-MS (1): t_R = 1.29 min; $[M+H]^+$: 408.2.

***tert*-Butyl ((2-((5-((*tert*-butyldimethylsilyl)oxy)pentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate:** At 0°C, a sol. of 2-((5-((*tert*-butyldimethylsilyl)oxy)pentyl)oxy)-6-methylpyridine-3-sulfonyl chloride (613 mg, 1.50 mmol, 1eq) in DCM (5 mL) was added dropwise to a stirred soln. of L-proline *t*-butyl ester (0.26 mL, 1.50 mmol, 1 eq) and DIPEA (1.3 mL, 7.51 mmol, 5.0 eq) in DCM (5 mL). The reaction mixture was slowly warmed to rt and stirred for 15 min. The reaction was diluted with DCM and extracted with aq. sat. NaHCO₃ soln. The org. layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 1.30 min; $[M+H]^+$: 543.3.

***tert*-Butyl ((2-((5-hydroxypentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate:** At rt and under N₂ atm, TBAF 1M soln. in THF (1.3 mL, 4.49 mmol, 8.5 eq) was added to a stirred soln. of *tert*-butyl ((2-((5-((*tert*-butyldimethylsilyl)oxy)pentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate (288 mg, 0.53 mmol, 1 eq) in THF (8 mL) and the reaction mixture was stirred at rt for 1h. The reaction was diluted with DCM and washed with aq. sat. NaHCO₃ soln. The org. layer was dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 0.97 min; $[M+H]^+$: 429.1.

***tert*-Butyl ((6-methyl-2-((5-oxopentyl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate:** To a soln. of oxalyl chloride (47 μ L, 0.54 mmol, 1.5 eq) in DCM (1.5 mL) at -78°C was added a soln. of DMSO (68 μ L, 0.96 mmol, 2.7 eq) in DCM (1.5 mL) dropwise while maintaining a temperature below -70°C. After stirring for another 10 min, a soln. of *tert*-

butyl ((2-((5-hydroxypentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate (153 mg, 0.36 mmol, 1 eq) in DCM (3 mL) was added dropwise by keeping the temperature below -75°C. After stirring for another 10 min., TEA (0.25 mL, 1.79 mmol, 5 eq) was added and the soln. was stirred at -78°C for 30 min. The soln. was warmed to rt and stirred for 1 h. The reaction was diluted with DCM and washed with aq. sat. NaHCO₃ soln. The org. layer was dried over
 5 MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 1.02 min; [M+H]⁺: 427.1.

tert-Butyl ((2-((5-((4,4-difluorocyclohexyl)amino)pentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate: To a soln. of *tert*-butyl ((6-methyl-2-((5-oxopentyl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate (671 mg, 1.57 mmol, 1 eq) in MeOH (16 mL) were added successively 4,4-difluorocyclohexan-1-amine (263 mg, 1.89 mmol, 1.2 eq) and
 10 NaBH(OAc)₃ (500 mg, 2.36 mmol, 1.5 eq). The resulting mixture was allowed to stir at rt overnight. The mixture was poured onto aq. sat. NaHCO₃ soln. and extracted with DCM. The combined org. layers were washed with brine, dried over MgSO₄, filtered, and the solvent was removed under reduced pressure. The crude product was used without further purification in the next step. LC-MS (1): t_R = 0.87 min; [M+H]⁺: 546.4.

((2-((5-((4,4-Difluorocyclohexyl)amino)pentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-proline: To a soln. of *tert*-butyl ((2-((5-((4,4-difluorocyclohexyl)amino)pentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate (810 mg, 1.48 mmol, 1 eq) in DCM (10 mL) was added TFA (1.0 mL, 13.10 mmol, 8.8 eq) dropwise at 0°C. The mixture was allowed to stir at 0°C for 10 min and then was allowed to warm up to rt. The solvent was removed under reduced pressure. The residue was dissolved in toluene and removed under reduced pressure. The crude product was used without further purification in the next step. LC-MS (1): t_R = 0.71 min; [M+H]⁺: 490.3.

20 **(S)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:** ((2-((5-((4,4-difluorocyclohexyl)amino)pentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-proline (43 mg, 0.09 mmol, 1 eq) was dissolved in DMF (4 mL). DIPEA (0.12 mL, 0.70 mmol, 8 eq) and HATU (40 mg, 0.11 mmol, 1.2 eq) were added at rt and the mixture was stirred for 15 min. The soln. was purified by basic prep. HPLC to give the title compound.
 25 LC-MS (1): t_R = 1.02 min; [M+H]⁺: 472.0.

Example 1.23 to Example 1.25 were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((4-methyl-2-(((RS)-5-oxopentan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.14. LC-MS data of Example 1.23 to Example 1.25 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R (min)	[M+H] ⁺
1.23	(6RS,11aS)-10-(6,6-Difluorospiro[3.3]heptan-2-yl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide	1.04	483.0
1.24	(6RS,11aS)-10-((RS)-3,3-Difluorocyclopentyl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide	1.00	457.0
1.25	(6RS,11aS)-3,6-Dimethyl-10-(spiro[3.3]heptan-2-yl)-7,8,9,10,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide	1.08 and 1.10	447.1

Example 1.26 (1³R,4²S)-6-(4,4-Difluorocyclohexyl)-2⁶-methyl-3-thia-6-aza-2(2,3)-pyridina-1(1,3)-piperidina-4(1,2)-pyrrolidinacyclooctaphan-5-one 3,3-dioxide:

tert-Butyl (R)-3-(2-((4,4-difluorocyclohexyl)amino)ethyl)piperidine-1-carboxylate: Was synthesized using 4,4-difluorocyclohexan-1-amine and *tert*-butyl (3R)-3-(2-oxoethyl)piperidine-1-carboxylate in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R= 0.74 min; [M+H]⁺: 347.4.

tert-Butyl (R)-3-(2-(((benzyloxy)carbonyl)(4,4-difluorocyclohexyl)amino)ethyl)piperidine-1-carboxylate: Benzyl chloroformate (0.32 mL, 2.22 mmol, 1.1 eq) was added to a soln. of *tert*-butyl (R)-3-(2-((4,4-difluorocyclohexyl)amino)ethyl)piperidine-1-carboxylate (700 mg, 2.02 mmol, 1 eq) and DIPEA (0.42 mL, 2.42 mmol, 1.2 eq) in DCM (13 mL) at 0°C. The mixture was stirred at 0°C for 1 h. The mixture was diluted with aq. sat. NaHCO₃ soln. and DCM. The layers were separated, the org. layer was washed with H₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R= 1.18 min; [M+H]⁺: 481.2.

Benzyl (R)-(4,4-difluorocyclohexyl)(2-(piperidin-3-yl)ethyl)carbamate hydrochloride: 4M HCl soln. in dioxane (5.0 mL, 20.10 mmol, 10 eq) was added to a soln. of *tert*-butyl (R)-3-(2-(((benzyloxy)carbonyl)(4,4-difluorocyclohexyl)amino)ethyl)piperidine-1-carboxylate (968 mg, 2.01 mmol, 1 eq) in DCM (10 mL), and the reaction mixture was stirred at rt for 1h. The solvent was removed under reduced pressure. The crude product was used without further purification in the next step. LC-MS (1): t_R= 0.77 min; [M+H]⁺: 381.2.

((2-((R)-3-(2-(((Benzyloxy)carbonyl)(4,4-difluorocyclohexyl)amino)ethyl)piperidin-1-yl)-6-methylpyridin-3-yl)sulfonyl)-L-proline: A mixture of ((2-chloro-6-methylpyridin-3-yl)sulfonyl)-L-proline (275 mg, 0.90 mmol, 1 eq), (R)-(4,4-difluorocyclohexyl)(2-(piperidin-3-yl)ethyl)carbamate hydrochloride (752 mg, 1.80 mmol, 2 eq), and TMP (1.5 mL, 9.02 mmol, 10 eq) in DMF (5 mL) was stirred at 90°C for 3 days. The mixture was allowed to cool to rt, and was diluted with aq. 1M HCl soln. and EtOAc. The layers were separated, the org. layer was washed with H₂O and brine, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by acidic prep. HPLC to give the title compound. LC-MS (1): t_R= 1.12 min; [M+H]⁺: 649.4.

Methyl ((2-((R)-3-(2-((4,4-difluorocyclohexyl)amino)ethyl)piperidin-1-yl)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate: ((2-((R)-3-(2-((Benzyloxy)carbonyl)(4,4-difluorocyclohexyl)amino)ethyl)piperidin-1-yl)-6-methylpyridin-3-yl)sulfonyl)-L-proline (480 mg, 0.74 mmol, 1 eq) was dissolved in MeOH (8 mL). Aq. conc. HCl (0.35 mL, 3.70 mmol, 5 eq) and Pd/C (10%, wet, 50 mg) were added. The mixture was evacuated and purged with N₂, then with H₂, and was stirred under a H₂ atm for 8 days. The mixture was filtered through Celite, and the solvent removed under reduced pressure. The residue was dissolved in EtOH (7.5 mL), AcOH (0.21 mL) and Pd/C (10%, wet, 100 mg) were added. The mixture was purged as previously, and stirred under a H₂ atm overnight. AcOH (0.21 mL, 3.70 mmol, 5 eq) was added again and the mixture was stirred overnight under a H₂ atm. The mixture was filtered through a Whatmann® filter, washed with EtOH and the solvent removed under reduced pressure. The residue was purified by FC (DCM (0.5% NH₃) to 25% MeOH) to give the title compound. LC-MS (1): t_R= 0.82 min; [M+H]⁺: 529.3.

((2-((R)-3-(2-((4,4-Difluorocyclohexyl)amino)ethyl)piperidin-1-yl)-6-methylpyridin-3-yl)sulfonyl)-L-proline: Was synthesized using methyl ((2-((R)-3-(2-((4,4-difluorocyclohexyl)amino)ethyl)piperidin-1-yl)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.8 to give the title compound. LC-MS (1): t_R= 0.75 min; [M+H]⁺: 515.3.

(1³R,4²S)-6-(4,4-Difluorocyclohexyl)-2⁶-methyl-3-thia-6-aza-2(2,3)-pyridina-1(1,3)-piperidina-4(1,2)-pyrrolidinacyclooctaphan-5-one 3,3-dioxide: Was synthesized using ((2-((R)-3-(2-((4,4-difluorocyclohexyl)amino)ethyl)piperidin-1-yl)-6-methylpyridin-3-yl)sulfonyl)-L-proline in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R= 1.04 min; [M+H]⁺: 497.2.

Example 1.27 to Example 1.29 were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((2-((5-hydroxypentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.7. LC-MS data of Example 1.27 to Example 1.29 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R (min)	[M+H] ⁺
1.27	(1R*,3S*)-3-((S)-3-Methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclopentane-1-carbonitrile	0.93	446.3
1.28	(S)-3-Methyl-11-(spiro[3.3]heptan-2-yl)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.09	447.1
1.29	(1R,3s)-3-((S)-3-Methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclobutane-1-carbonitrile	0.92	432.0

Example 1.30 **(6S,12aS)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,10,11,12a,13,14,15-octahydrobenzo[e]pyrrolo[1,2-h][1,4]dioxo[7]thia[8,11]diazacyclotridecin-12(9H)-one 17,17-dioxide** and

Example 1.31 (6R,12aS)-11-(4,4-difluorocyclohexyl)-3,6-dimethyl-6,7,10,11,12a,13,14,15-octahydrobenzo[e]pyrrolo[1,2-h][1,4]dioxo[7]thia[8,11]diazacyclotridecin-12(9H)-one 17,17-dioxide:

2-(2-((4,4-Difluorocyclohexyl)amino)ethoxy)ethan-1-ol: Was synthesized using 4,4-difluorocyclohexanone and 2-(2-aminoethoxy)ethan-1-ol in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 0.38 min; $[M+H]^+$: 224.4.

***tert*-Butyl (4,4-difluorocyclohexyl)(2-(2-hydroxyethoxy)ethyl)carbamate:** Was synthesized using 2-(2-((4,4-difluorocyclohexyl)amino)ethoxy)ethan-1-ol in analogy to Example 1.2 to give the title compound. LC-MS (1): t_R = 0.89 min; $[M+H]^+$: 324.4.

***tert*-Butyl (4,4-difluorocyclohexyl)(2-(2-oxoethoxy)ethyl)carbamate:** Was synthesized using *tert*-butyl (4,4-difluorocyclohexyl)(2-(2-hydroxyethoxy)ethyl)carbamate in analogy to Example 1.7 to give the title compound. LC-MS (1): t_R = 0.95 min; $[M+H]^+$: 322.1.

***tert*-Butyl (RS)-(4,4-difluorocyclohexyl)(2-(2-hydroxypropoxy)ethyl)carbamate:** *tert*-Butyl (4,4-difluorocyclohexyl)(2-(2-oxoethoxy)ethyl)carbamate (110 mg, 0.34 mmol, 1 eq) was dissolved in THF (4 mL), and the soln. was cooled to -78°C. 3M MeMgBr soln. in Et₂O (0.10 mL, 0.41 mmol, 1.2 eq) was added dropwise at -78°C. After addition, the mixture was stirred overnight while being allowed to warm up to rt. 3M MeMgBr soln. in Et₂O (0.07 mL, 0.21 mmol, 0.6 eq) was added at rt. After 7h, 3M MeMgBr soln. in Et₂O (0.21 mmol, 0.6 eq) was added again. After 3 days, 3M MeMgBr soln. in Et₂O (0.07 mL, 0.21 mmol 0.6 eq) were added. The reaction was quenched with aq. sat. NH₄Cl soln. DCM was added and the layers were separated. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 0.92 min; $[M+H]^+$: 338.1.

***tert*-Butyl ((2-(((RS)-1-(2-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)ethoxy)propan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl (RS)-(4,4-difluorocyclohexyl)(2-(2-hydroxypropoxy)ethyl)carbamate and *tert*-butyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 1.23 min; $[M+H]^+$: 661.3.

((2-(((RS)-1-(2-((4,4-Difluorocyclohexyl)amino)ethoxy)propan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-proline: Was synthesized using *tert*-butyl ((2-(((RS)-1-(2-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)ethoxy)propan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 0.74 and 0.76 min; $[M+H]^+$: 505.0.

(6S,12aS)-11-(4,4-difluorocyclohexyl)-3,6-dimethyl-6,7,10,11,12a,13,14,15-octahydrobenzo[e]pyrrolo[1,2-h][1,4]dioxo[7]thia[8,11]diazacyclotridecin-12(9H)-one 17,17-dioxide and (6R,12aS)-11-(4,4-difluorocyclohexyl)-3,6-dimethyl-6,7,10,11,12a,13,14,15-octahydrobenzo[e]pyrrolo[1,2-h][1,4]dioxo[7]thia[8,11]diazacyclotridecin-12(9H)-one 17,17-dioxide: Were synthesized using ((2-(((RS)-1-(2-((4,4-difluorocyclohexyl)amino)ethoxy)propan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-proline in analogy to Example 1.1. The stereoisomers were separated by basic prep. HPLC to give (6S,12aS)-11-(4,4-difluorocyclohexyl)-3,6-

dimethyl-6,7,10,11,12a,13,14,15-octahydrobenzo[e]pyrrolo[1,2-h][1,4]dioxo[7]thia[8,11]diazacyclotridecin-12(9H)-one 17,17-dioxide and (6R,12aS)-11-(4,4-difluorocyclohexyl)-3,6-dimethyl-6,7,10,11,12a,13,14,15-octahydrobenzo[e]pyrrolo[1,2-h][1,4]dioxo[7]thia[8,11]diazacyclotridecin-12(9H)-one 17,17-dioxide. The absolute configuration at the methyl-center was attributed arbitrarily. First eluting diastereomer: LC-MS (1): t_R = 1.00 min; [M+H]⁺: 487.3. Second eluting diastereomer: LC-MS (1): t_R = 1.00 min; [M+H]⁺: 487.3.

Example 1.32 (6R,11aS)-10-(4,4-Difluorocyclohexyl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide:

(RS)-3-Bromo-2-((5-((tert-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-6-methylpyridine: Was synthesized using (RS)-5-((tert-butyldimethylsilyl)oxy)pentan-2-ol and 3-bromo-6-methylpyridin-2-ol in analogy to Example 1.22 to give the title compound. LC-MS (1): t_R = 1.31 min; [M+H]⁺: 387.8.

(RS)-3-(Benzylthio)-2-((5-((tert-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-6-methylpyridine: Was synthesized using (RS)-3-bromo-2-((5-((tert-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-6-methylpyridine in analogy to Example 1.22 to give the title compound. LC-MS (1): t_R = 1.35 min; [M+H]⁺: 432.1.

(RS)-2-((5-((tert-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-6-methylpyridine-3-sulfonyl chloride: Was synthesized using (RS)-3-(benzylthio)-2-((5-((tert-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-6-methylpyridine in analogy to Example 1.22 to give the title compound. LC-MS (1): t_R = 1.30 min; [M+H]⁺: 408.0.

tert-Butyl ((2-(((RS)-5-((tert-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate: Was synthesized using (RS)-2-((5-((tert-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-6-methylpyridine-3-sulfonyl chloride and L-proline tert-butyl ester in analogy to Example 1.22 to give the title compound. LC-MS (1): t_R = 1.32 min; [M+H]⁺: 543.1.

tert-Butyl ((2-(((R)-5-hydroxypentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate and tert-butyl ((2-(((S)-5-hydroxypentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate: At rt and under N₂ atm, 1M TBAF soln. in THF (3.8 mL, 3.83 mmol, 4 eq) was added to a stirred soln. of tert-butyl ((2-(((RS)-5-((tert-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate (520 mg, 0.96 mmol, 1 eq) in THF (10 mL) and the reaction mixture was stirred at rt for 1h. The reaction was diluted with EtOAc and washed with aq. sat. NaHCO₃ soln. The org. layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 50% EtOAc) to give tert-butyl ((2-(((S)-5-hydroxypentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate (first eluting diastereomer) and tert-butyl ((2-(((R)-5-hydroxypentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate (second eluting diastereomer). First eluting diastereomer: LC-MS (1): t_R = 0.99 min; [M+H]⁺: 429.1. Second eluting diastereomer: LC-MS (1): t_R = 0.98 min; [M+H]⁺: 429.1.

tert-Butyl ((6-methyl-2-(((R)-5-oxopentan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate: Was synthesized using tert-butyl ((2-(((R)-5-hydroxypentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.22 to give the title compound. LC-MS (1): t_R = 1.04 min; [M+H]⁺: 427.1.

- tert-Butyl ((2-(((R)-5-((4,4-difluorocyclohexyl)amino)pentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((6-methyl-2-(((R)-5-oxopentan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate and 4,4-difluorocyclohexan-1-amine in analogy to Example 1.22 to give the title compound. LC-MS (1): t_R = 0.89 min; $[M+H]^+$: 546.4.
- 5 **((2-(((R)-5-((4,4-Difluorocyclohexyl)amino)pentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-proline:** Was synthesized using *tert*-butyl ((2-(((R)-5-((4,4-difluorocyclohexyl)amino)pentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.22 to give the title compound. LC-MS (1): t_R = 0.73 min; $[M+H]^+$: 490.0.
- 10 **(6R,11aS)-10-(4,4-Difluorocyclohexyl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide:** Was synthesized using ((2-(((R)-5-((4,4-difluorocyclohexyl)amino)pentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-proline in analogy to Example 1.22 to give the title compound. LC-MS (1): t_R = 1.03 min; $[M+H]^+$: 472.0.
- Example 1.33. (6S,11aS)-10-(4,4-Difluorocyclohexyl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide:**
- 15 **tert-Butyl ((6-methyl-2-(((S)-5-oxopentan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((2-(((S)-5-hydroxypentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.22 to give the title compound. LC-MS (1): t_R = 1.05 min; $[M+H]^+$: 427.3.
- tert-Butyl ((2-(((S)-5-((4,4-difluorocyclohexyl)amino)pentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((6-methyl-2-(((S)-5-oxopentan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate and 4,4-difluorocyclohexan-1-amine in analogy to Example 1.22 to give the title compound. LC-MS (1): t_R = 0.90 min; $[M+H]^+$: 546.4.
- 20 **((2-(((S)-5-((4,4-Difluorocyclohexyl)amino)pentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-proline:** Was synthesized using *tert*-butyl ((2-(((S)-5-((4,4-difluorocyclohexyl)amino)pentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.22 to give the title compound. LC-MS (1): t_R = 0.73 min; $[M+H]^+$: 490.0.
- 25 **(6S,11aS)-10-(4,4-Difluorocyclohexyl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide:** Was synthesized using ((2-(((S)-5-((4,4-difluorocyclohexyl)amino)pentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-proline in analogy to Example 1.22 to give the title compound. LC-MS (1): t_R = 1.05 min; $[M+H]^+$: 472.0.
- 30 **Example 1.34 (6R,11aS)-3,6-Dimethyl-10-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)-7,8,9,10,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide:**
- tert-Butyl ((4-methyl-2-(((RS)-5-((3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)amino)pentan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((4-methyl-2-(((RS)-5-oxopentan-2-

yl)oxy)phenyl)sulfonyl)-L-prolinate and 3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-amine hydrochloride in analogy to Example 1.14 to give the title compound. LC-MS (1): t_R= 0.93 and 0.94 min; [M+H]⁺: 561.4.

((4-Methyl-2-(((RS)-5-((3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)amino)pentan-2-yl)oxy)phenyl)sulfonyl)-L-proline: Was synthesized using *tert*-butyl ((4-methyl-2-(((RS)-5-((3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)amino)pentan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.14 to give the title compound. LC-MS (1): t_R= 0.77 and 0.79 min; [M+H]⁺: 505.0.

(6R,11aS)-3,6-Dimethyl-10-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)-7,8,9,10,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide and (6S,11aS)-3,6-Dimethyl-10-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)-7,8,9,10,11a,12,13,14-

octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide: Were synthesized using (6RS,11aS)-3,6-dimethyl-10-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)-7,8,9,10,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide in analogy to Example 1.14. The crude was purified basic prep. HPLC to give (6R,11aS)-3,6-dimethyl-10-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)-7,8,9,10,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide (first eluting diastereomer) and (6S,11aS)-3,6-Dimethyl-10-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)-7,8,9,10,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide (second eluting diastereomer). First eluting diastereomer: LC-MS (1): t_R= 1.08 min; [M+H]⁺: 487.3. Second eluting diastereomer: LC-MS (1): t_R= 1.09 min; [M+H]⁺: 487.3.

Example 1.35 to Example 1.38 were synthesized using the appropriate amine or amine salt derivative, *tert*-butyl ((6-methyl-2-(((R)-5-oxopentan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate or *tert*-Butyl ((6-methyl-2-(((S)-5-oxopentan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.32. LC-MS data of Example 1.35 to Example 1.38 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R (min)	[M+H] ⁺
1.35	(6R,11aS)-10-(3,3-Difluorocyclopentyl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide	1.01	458.1
1.36	(6R,11aS)-10-(4,4-Dimethylcyclohexyl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide	1.14	464.1
1.37	(6R,11aS)-3,6-Dimethyl-10-(spiro[3.3]heptan-2-yl)-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide	1.10	448.1

1.38	(6S,11aS)-10-(4,4-Dimethylcyclohexyl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide	1.16	462.4
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Example 1.39 (S)-3-Chloro-11-(4,4-difluorocyclohexyl)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:

tert-Butyl ((2-bromo-4-chlorophenyl)sulfonyl)-L-prolinate: *tert*-Butyl L-prolinate (0.10 mL, 0.58 mmol, 1 eq), DMAP (7 mg, 0.06 mmol, 0.1 eq) and DIPEA (3.0 mL, 57.40 mmol, 98 eq) were dissolved in MeCN (3 mL). Then 2-bromo-4-chlorobenzenesulfonyl chloride (175 mg, 0.60 mmol, 1 eq) in MeCN (2 mL) was added. The reaction mixture was stirred at rt for 35 min. The solvent was removed under reduced pressure. The residue was purified by FC (Hept to 20% EtOAc) to give the title compound. LC-MS (1): t_R = 1.09 min; $[M+H]^+$: 425.9.

tert-Butyl ((4-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)-L-prolinate: *tert*-Butyl ((2-bromo-4-chlorophenyl)sulfonyl)-L-prolinate (208 mg, 0.49 mmol, 1 eq), $PdCl_2(MeCN)_2$ (5 mg, 0.04 mmol, 0.04 eq) and SPhos (8 mg, 0.020 mmol, 0.04 eq) were added to a microwave vial. The vial was sealed, evacuated and backfilled with argon. Then dioxane (2 mL), TEA (0.15 mL, 1.07 mmol, 3 eq) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.08 mL, 0.53 mmol, 1.5 eq) were added. The reaction mixture was stirred at 100°C for 2.5h. The reaction mixture was filtered through a pad of celite and rinsed with EtOAc. The solvent was removed under reduced pressure. The residue was purified by FC (Hept to 20% EtOAc) to give the title compound. LC-MS (1): t_R = 1.16 min; $[M+H]^+$: 472.0.

tert-Butyl ((4-chloro-2-hydroxyphenyl)sulfonyl)-L-prolinate: *tert*-Butyl ((4-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)-L-prolinate (157 mg, 0.33 mmol, 1 eq) was dissolved in THF (1 mL). The soln. was cooled to 0°C. Aq. 1M NaOH soln. (0.75 mL, 0.75 mmol, 2.25 eq) and aq. 30% (w/w) soln. (0.07 mL, 0.67 mmol, 2 eq) were added dropwise consecutively. The reaction mixture was stirred at 0°C for 30 min, then warmed to rt and further stirred for 2h. Then, H₂O and DCM were added to the reaction mixture. The aq. layer was extracted with DCM. The combined org. layers were dried over Na₂SO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by acidic prep. HPLC to give the title compound. LC-MS (1): t_R = 0.98 min; $[M+H]^+$: 362.0.

tert-Butyl ((2-((5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-4-chlorophenyl)sulfonyl)-L-prolinate: *tert*-Butyl ((4-chloro-2-hydroxyphenyl)sulfonyl)-L-prolinate (56 mg, 0.16 mmol, 1 eq) was dissolved in THF (2.5 mL). The soln. was cooled to 0°C. Then *tert*-butyl (4,4-difluorocyclohexyl)(5-hydroxypentyl)carbamate (65 mg, 0.20 mmol, 1.3 eq) and PPh₃ (50 mg, 0.19 mmol, 1.2 eq) were added followed by DEAD (~40% in toluene, 0.11 mL, 0.23 mmol, 1.5 eq). After the addition, the mixture was allowed to warm up to rt and stirred for 2h. The reaction mixture was diluted with DCM and washed with aq. 1M HCl soln. and aq. sat. NaHCO₃ soln. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.26 min; $[M+H]^+$: 665.0.

((4-Chloro-2-((5-((4,4-difluorocyclohexyl)amino)pentyl)oxy)phenyl)sulfonyl)-L-proline: *tert*-Butyl ((2-((5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-4-chlorophenyl)sulfonyl)-L-prolinate (33 mg, 0.05 mmol, 1 eq) was dissolved in DCM (1 mL). Then TFA (0.15 mL, 1.97 mmol, 40 eq) was added. The reaction mixture was stirred at rt for 1h. The solvent was removed under reduced pressure to give the title compound. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.76 min; $[M+H]^+$: 508.9.

(S)-3-Chloro-11-(4,4-difluorocyclohexyl)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide: ((4-Chloro-2-((5-((4,4-difluorocyclohexyl)amino)pentyl)oxy)phenyl)sulfonyl)-L-proline (46 mg, 0.09 mmol, 1 eq) was dissolved in DMF (1 mL). Then DIPEA (0.12 mL, 0.72 mmol, 8 eq) and HATU (41 mg, 0.11 mmol, 1.2 eq) were added. The reaction mixture was stirred at rt for 20 min. The residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.05 min; $[M+H]^+$: 490.9.

Example 1.40 (6R,11aS)-10-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide:

Benzyl ((3s,6s)-1,1-difluorospiro[2.5]octan-6-yl)carbamate and benzyl ((3r,6r)-1,1-difluorospiro[2.5]octan-6-yl)carbamate: At 0°C and under a N₂ atm, 1,1-difluorospiro[2.5]octan-6-amine hydrochloride (5.0 g, 24.00 mmol, 1 eq) was dissolved in MeCN (120 mL). DIPEA (9.0 mL, 52.80 mmol, 2.22 eq) was added. Benzyl chloroformate (4.3 mL, 28.80 mmol, 1.2 eq) was added dropwise and the reaction was stirred at 0°C for 30 min. The soln. was partially evaporated under reduced pressure and the residue was diluted with Et₂O and washed with aq. 1M HCl soln., aq. sat. NaHCO₃ soln. The org. layer was separated, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The crude was purified by recrystallization from Hept/toluene. The diastereomeric mixture was purified by chiral SFC (SFC 8 method) to give benzyl ((3s,6s)-1,1-difluorospiro[2.5]octan-6-yl)carbamate (first eluting diastereomer) and benzyl ((3r,6r)-1,1-difluorospiro[2.5]octan-6-yl)carbamate (second eluting diastereomer). First eluting diastereomer: LC-MS (1): t_R = 1.01 min; $[M+H]^+$: 296.2. Second eluting diastereomer: LC-MS (1): t_R = 1.00 min; $[M+H]^+$: 296.2.

(3s,6s)-1,1-Difluorospiro[2.5]octan-6-amine hydrochloride: Benzyl ((3s,6s)-1,1-difluorospiro[2.5]octan-6-yl)carbamate (1.15 g, 3.89 mmol, 1 eq) was dissolved in MeOH (40 mL) and the flask was flushed with argon. Pd/C (10%, ~50% H₂O, 207 mg, 0.097 mmol, 0.025 eq) was added and the reaction was stirred at rt under a H₂ atm for 30 min. The reaction mixture was filtered through a 0.45 µm PTFE filter and washed with MeOH. Aq. 1.25M HCl soln. in MeOH (62.0 mL, 77.90 mmol, 20 eq) was added and the solvent removed under reduced pressure to give the title compound. LC-MS (1): t_R = 0.43 min; $[M+H]^+$: not seen. ¹H NMR (500 MHz, DMSO) δ : 7.80-8.27 (m), 3.01-3.20 (m, 1 H), 1.94-2.05 (m, 2 H), 1.66-1.81 (m, 2 H), 1.52-1.59 (m, 2 H), 1.30-1.40 (m, 2 H), 1.26 (t, J = 8.6 Hz, 2 H).

(6R,11aS)-10-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide: Was synthesized using *tert*-butyl ((6-methyl-2-(((R)-5-oxopentan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate and (3s,6s)-

1,1-difluorospiro[2.5]octan-6-amine hydrochloride in analogy to Example 1.32 to give the title compound. LC-MS (1): t_R = 1.09 min; $[M+H]^+$: 498.2.

Example 1.41 (6R,11aS)-10-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide:

- 5 **Benzyl ((3s,5s)-1,1-difluorospiro[2.3]hexan-5-yl)carbamate and benzyl ((3r,6r)-1,1-difluorospiro[2.5]octan-6-yl)carbamate:** 1,1-Difluorospiro[2.3]hexan-5-amine hydrochloride (3.00 g, 16.80 mmol, 1 eq) was dissolved in MeCN (50 mL). Then, DIPEA (6.3 mL, 36.90 mmol, 2.2 eq) was added and the reaction mixture was cooled to 0°C. Benzyl chloroformate (3.0 mL, 20.20 mmol, 1.2 eq) was added dropwise and the reaction was stirred at 0°C for 2h. The soln. was partially evaporated under reduced pressure and the residue was diluted with Et₂O and washed with
- 10 aq. 1M HCl soln., aq. sat. NaHCO₃ soln. and H₂O. The org. layer was separated, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The crude was purified by recrystallization from Hept / toluene. The diastereomeric mixture was purified by chiral SFC (SFC 9 method) to give benzyl ((3s,5s)-1,1-difluorospiro[2.3]hexan-5-yl)carbamate (first eluting diastereomer) and benzyl ((3r,5r)-1,1-difluorospiro[2.3]hexan-5-yl)carbamate (second eluting diastereomer). First eluting diastereomer: LC-MS (1): t_R = 0.96 min; $[M+H]^+$: 309..
- 15 Second eluting diastereomer: LC-MS (1): t_R = 0.95 min; $[M+H]^+$: 309.1.

- (3s,5s)-1,1-Difluorospiro[2.3]hexan-5-amine hydrochloride:** Benzyl ((3s,5s)-1,1-difluorospiro[2.3]hexan-5-yl)carbamate (1.34 g, 5.01 mmol, 1.0 eq) was dissolved in MeOH (50 mL) and the flask was flushed with argon. Pd/C (10%, ~50% H₂O, 267 mg, 0.13 mmol, 0.025 eq) was added and the reaction was stirred at rt under a H₂ atm for 30 min. The reaction mixture was filtered through a 0.45 µm PTFE filter and washed with MeOH. 1.25 M HCl
- 20 soln. in MeOH (75.0 mL, 100.00 mmol, 20 eq) was added and the solvent removed under reduced pressure to give the title compound. ¹H NMR (500 MHz, MeOD) δ : 4.05 (quint, J = 7.5 Hz, 1 H), 2.52-2.54 (m, 4 H), 1.44 (t, J = 8.6 Hz, 2 H).

- (6R,11aS)-10-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide:** Was
- 25 synthesized using *tert*-butyl ((6-methyl-2-(((R)-5-oxopentan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate and (3s,5s)-1,1-difluorospiro[2.3]hexan-5-amine hydrochloride in analogy to Example 1.22 to give the title compound. LC-MS (1): t_R = 1.03 min; $[M+H]^+$: 487.0.

- Example 1.42 to Example 1.43** were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((6-methyl-2-(((S)-5-oxopentan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.32. LC-MS
- 30 data of Example 1.42 to Example 1.43 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R (min)	[M+H] ⁺
1.42	(6S,11aS)-10-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide	1.10	498.0
1.43	(6S,11aS)-10-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide	1.05	470.0

Example 1.44 (6R,11aS)-10-((3S,6r)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide:

(3r,6r)-1,1-Difluorospiro[2.5]octan-6-amine hydrochloride: Benzyl ((3r,6r)-1,1-difluorospiro[2.5]octan-6-yl)carbamate (Example 1.40) (50 mg, 0.17 mmol, 1 eq) was dissolved in MeOH (3 mL) and the flask was flushed with argon. Pd/C (10%, ~50% H₂O, 9.0 mg, 0.004 mmol, 0.025 eq) was added and the reaction was stirred at rt under a H₂ atm for 30 min. The reaction mixture was filtered through a 0.45 µm PTFE filter and washed with MeOH. 1.25M HCl soln. in MeOH (2.7 mL, 3.39 mmol, 20 eq) was added and the solvent removed under reduced pressure to give the title compound. LC-MS (1): t_R= 0.45 min; [M+H]⁺: not seen. ¹H NMR (500 MHz, DMSO) δ: 7.94-8.25 (m, 3 H), 3.00-3.18 (m, 1 H), 1.88-2.04 (m, 2 H), 1.67-1.72 (m, 2 H), 1.33-1.57 (m, 4 H), 1.24 (t, J = 8.6 Hz, 2 H).

(6R,11aS)-10-((3S,6r)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide: Was synthesized using (3r,6r)-1,1-difluorospiro[2.5]octan-6-amine hydrochloride and *tert*-butyl ((6-methyl-2-(((R)-5-oxopentan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-proline in analogy to Example 1.32 to give the title compound. LC-MS (1): t_R= 1.09 min; [M+H]⁺: 498.0.

Example 1.45 (6R,11aS)-10-((3S,5r)-1,1-Difluorospiro[2.3]hexan-5-yl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide:

(3r,5r)-1,1-Difluorospiro[2.3]hexan-5-amine hydrochloride: Benzyl ((3r,5r)-1,1-difluorospiro[2.3]hexan-5-yl)carbamate (Example 1.41) (1.75 g, 5.01 mmol, 1 eq) was dissolved in MeOH (50 mL) and the flask was flushed with argon. Pd/C (10%, ~50% H₂O, 348 mg, 0.13 mmol, 0.025 eq) was added and the reaction was stirred at rt under a H₂ atm for 30 min. The reaction mixture was filtered through a 0.45 µm PTFE filter and washed with MeOH. 1.25M HCl soln. in MeOH (105.0 mL, 131.00 mmol, 20 eq) was added and the solvent removed under reduced pressure to give the title compound. LC-MS (1): t_R= 0.31 min; [M+H]⁺: 134.2.

(6R,11aS)-10-((3S,5r)-1,1-Difluorospiro[2.3]hexan-5-yl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide: Was synthesized using (3r,5r)-1,1-difluorospiro[2.3]hexan-5-amine hydrochloride and *tert*-butyl ((6-methyl-2-(((R)-5-

oxopentan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate to Example 1.32 to give the title compound. LC-MS (1): t_R = 1.04 min; $[M+H]^+$: 470.0.

Example 1.46 (6S,11aS)-10-((3S,5r)-1,1-difluorospiro[2.3]hexan-5-yl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide: Was synthesized using (3r,5r)-1,1-difluorospiro[2.3]hexan-5-amine hydrochloride and *tert*-butyl ((6-methyl-2-((S)-5-oxopentan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.32 to give the title compound. LC-MS (1): t_R = 1.06 min; $[M+H]^+$: 470.0.

Example 1.48 to Example 1.50 were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((6-methyl-2-((5-oxopentyl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.22. LC-MS data of Example 1.48 to Example 1.50 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R (min)	$[M+H]^+$
1.48	(S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.08	498.0
1.49	(S)-11-((3S,6r)-1,1-Difluorospiro[2.5]octan-6-yl)-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.07	497.7
1.50	(S)-11-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.02	470.0

Example 1.51 (6R,12aS)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:

(S)-6-((*tert*-Butyldimethylsilyl)oxy)hexan-2-ol: 0.5M 3-((*tert*-Butyldimethylsiloxy)propyl)magnesium bromide soln. in THF (4.1 mL, 2.05 mmol, 1.2 eq) was added dropwise to a stirred suspension of CuI (33 mg, 0.17 mmol, 0.1 eq) in THF (1 mL) at 0°C under argon. After stirring for 5 min at 0°C, a soln. of (S)-(-)-propylene oxide (0.12 mL, 1.70 mmol, 1 eq) in THF (1 mL) was added dropwise. The mixture was allowed to warm up to rt and stirred for 1.5h. The mixture was poured onto aq. sat. NH_4Cl soln. and extracted with Et_2O . The org. layer was washed with H_2O , dried over Na_2SO_4 , filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 1.06 min; $[M+H]^+$: 233.2.

(R)-3-Bromo-2-((6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridine: DEAD (~40% in toluene, 0.50 mL, 1.02 mmol, 2 eq) was added dropwise to a stirred soln. of 3-bromo-6-methylpyridin-2-ol (100 mg, 0.51 mmol, 1 eq), (S)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-ol (198 mg, 0.51 mmol, 1 eq) and PPh_3 (163 mg, 0.61 mmol, 1.2 eq) in THF (5 mL) at 0°C under argon. The mixture was stirred for 30 min at 0°C. The reaction was diluted with

Et₂O and washed with aq. 1M HCl soln., aq. sat. NaHCO₃ soln. and H₂O. The org. layer was dried over Na₂SO₄ and evaporated. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R= 1.33 min; [M+H]⁺: 402.0.

5 **(R)-3-(Benzylthio)-2-((6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridine:** A soln. of (R)-3-bromo-2-((6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridine (165 mg, 0.31 mmol, 1 eq) in THF (2 mL) was cooled to -78°C. 1.6M n-BuLi soln. in hexanes (0.23 mL, 0.37 mmol, 1.2 eq) was added while maintaining the temperature below -70°C. After 20 min, a soln. of benzyl disulfide (157 mg, 0.62 mmol, 2 eq) in THF (1 mL) was added dropwise at -70°C. The reaction was allowed to warm up to rt. The mixture was quenched with H₂O and extracted with Et₂O. The org. layer was washed with H₂O, dried over Na₂SO₄ and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R= 1.36 min; [M+H]⁺: 446.4.

15 **(R)-2-((6-((*tert*-Butyldimethylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridine-3-sulfonyl chloride:** At 0°C, AcOH (0.36 mL, 0.63 mmol, 2 eq) and H₂O (0.11 mL, 0.63 mmol, 2 eq) were added to a stirred soln. of (R)-3-(benzylthio)-2-((6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridine (135 mg, 0.31 mmol, 1 eq) in THF (2 mL). Then a soln. of DCDMH (189 mg, 0.94 mmol, 3 eq) in THF (1 mL) was added dropwise. The reaction was diluted with DCM and washed with aq. sat. NaHCO₃ soln. and H₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R= 1.33 min; [M+H]⁺: 422.2.

20 ***tert*-Butyl ((2-(((R)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate:** A soln. of (R)-2-((6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridine-3-sulfonyl chloride (213 mg, 0.30 mmol, 1 eq) in DCM (1 mL) was added dropwise to a soln. of *tert*-butyl L-prolinate (59 mg, 0.33 mmol, 1.1 eq) and DIPEA (0.26 mL, 1.51 mmol, 5 eq) in DCM (2 mL). The soln. was stirred at rt for 10 min. The soln. was then diluted with Et₂O and washed with aq. 1M HCl soln., aq. sat. NaHCO₃ soln. and H₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R= 1.34 min; [M+H]⁺: 557.2.

30 ***tert*-Butyl ((2-(((R)-6-hydroxyhexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate:** *tert*-Butyl ((2-(((R)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate (405 mg, 0.73 mmol, 1 eq) was dissolved in THF (8 mL). 1M TBAF soln. in THF (2.9 mL, 2.91 mmol, 4 eq) was added dropwise at rt. The reaction was then allowed to stir at rt for 1h. The solvent was removed under reduced pressure and the residue was dissolved in Et₂O and washed with H₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R= 1.01 min; [M+H]⁺: 443.1.

35 ***tert*-Butyl ((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate:** A soln. of oxalyl chloride (0.10 mL, 1.17 mmol, 1.5 eq) in DCM (12 mL) was cooled to -78°C. DMSO (0.15 mL, 2.10 mmol, 2.7 eq) was added dropwise while maintaining the temperature below -70°C. After stirring for another 10 min, a soln. of *tert*-butyl ((2-

((*(R)*-6-hydroxyhexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate (344 mg, 0.78 mmol, 1 eq) in DCM (4 mL) was added dropwise, still keeping the temperature below -70°C. After 10 min stirring, TEA (1.0 mL, 7.42 mmol, 5 eq) was added and the soln. was stirred at -78°C for 30 min. Then the reaction mixture was allowed to warm up to rt. After 1h, the mixture was diluted with Et₂O and washed with aq. 1M HCl soln., aq. sat. NaHCO₃ soln., and H₂O.

- 5 The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R= 1.06 min; [M+H]⁺: 441.1.

***tert*-Butyl ((2-(((*(R)*-6-((4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate:** A soln. of *tert*-butyl ((6-methyl-2-(((*(R)*-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate (15 mg, 0.034 mmol, 1 eq) and DIPEA (7 μL, 0.041 mmol, 1.2 eq) in MeOH (0.5 mL) was added to 4,4-difluorocyclohexylamine hydrochloride (6 mg, 0.034 mmol, 1 eq). NaBH(OAc)₃ (11 mg, 0.051 mmol, 1.5 eq) was added and the mixture was shaken at rt overnight. The mixture was quenched with aq. sat. NaHCO₃ soln. and diluted with DCM. The layers were separated through a phase separator. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure, to give the title compound. The crude product was used in the next step without further purification. LC-MS (1): t_R= 0.90 min; [M+H]⁺: 560.4.

- 15 **((2-(((*(R)*-6-((4,4-Difluorocyclohexyl)amino)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-proline:** TFA (0.10 mL, 1.36 mmol, 40 eq) was added to a soln. of *tert*-butyl ((2-(((*(R)*-6-((4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate (19 mg, 0.034 mmol, 1 eq) in DCM (0.5 mL). The mixture was shaken at rt for 2h. The solvent was removed under reduced pressure to give the title compound. The crude product was used in the next step without further purification. LC-MS (1): t_R= 0.74 min; [M+H]⁺: 504.3.

- 20 **(6*R*,12*aS*)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12*a*,13,14,15-decahydro-12*H*-pyrido[2,3-*b*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:** DIPEA (29 μL, 0.17 mmol, 5 eq) and HATU (17 mg, 0.044 mmol, 1.3 eq) were added to a soln. of ((2-(((*(R)*-6-((4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-proline (17 mg, 0.034 mmol, 1 eq) in DMF (1 mL). The mixture was stirred at rt for 1h. Additional DIPEA (20 μL, 0.12 mmol, 3.5 eq) and HATU (9 mg, 0.024 mmol, 0.7 eq) were added until the reaction showed no further conversion. The title compound was isolated from the reaction mixture by basic prep. HPLC. LC-MS (1): t_R=1.06 min; [M+H]⁺: 486.0.

Example 1.52 to Example 1.54 were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((6-methyl-2-(((*(R)*-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.51. LC-MS data of Example 1.52 to Example 1.54 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R (min)	[M+H] ⁺
1.52	(6R,12aS)-11-(4,4-Dimethylcyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.16	478.1
1.53	(6R,12aS)-3,6-Dimethyl-11-(spiro[3.3]heptan-2-yl)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.12	462.1
1.54	(6R,12aS)-3,6-Dimethyl-11-(tetrahydro-2H-pyran-4-yl)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	0.93	451.8

Example 1.55 (6R,11aS)-10-(4,4-Difluorocyclohexyl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydrobenzo[k]pyrrolo[1,2-b][1,10]dithia[2,5]diazacyclododecin-11(6H)-one 16,16-dioxide and **Example 1.56** (6S,11aS)-10-(4,4-Difluorocyclohexyl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-

5 octahydrobenzo[k]pyrrolo[1,2-b][1,10]dithia[2,5]diazacyclododecin-11(6H)-one 16,16-dioxide:

tert-Butyl ((2-(((RS)-5-hydroxypentan-2-yl)thio)-4-methylphenyl)sulfonyl)-L-prolinate: A suspension of K₂CO₃ (144 mg, 1.04 mmol, 0.5 eq) in xylene (4 mL) was cooled to 0°C and 4-mercaptopentan-1-ol (250 mg, 2.08 mmol, 1 eq) was added dropwise. This mixture was stirred at rt for 1.5h. Another flask was charged with *tert*-butyl ((2-bromo-4-methylphenyl)sulfonyl)-L-prolinate (770 mg, 1.90 mmol, 0.9 eq), Pd₂(dba)₃ (294 mg, 0.31 mmol, 0.15 eq), xantphos (217 mg, 0.37 mmol, 0.18 eq) and xylene (20 mL). This flask was evacuated and purged with N₂, and stirred at rt for 20 min. This mixture was then added to the potassium thiolate soln. above, and the resulting mixture was heated to reflux for 3 days. The mixture was allowed to cool to rt, and was diluted with H₂O and EtOAc. The org. layer was washed with H₂O and brine, dried with MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R= 1.01 min; [M+H]⁺: 444.3.

tert-Butyl ((4-methyl-2-(((RS)-5-oxopentan-2-yl)thio)phenyl)sulfonyl)-L-prolinate: Was synthesized using *tert*-butyl ((2-(((RS)-5-hydroxypentan-2-yl)thio)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.7 to give the title compound. LC-MS (1): t_R= 1.06 min; [M+H]⁺: 442.3.

tert-Butyl ((2-(((RS)-5-((4,4-difluorocyclohexyl)amino)pentan-2-yl)thio)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using *tert*-butyl ((4-methyl-2-(((RS)-5-oxopentan-2-yl)thio)phenyl)sulfonyl)-L-prolinate and 4,4-difluorocyclohexan-1-amine in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R= 0.90; [M+H]⁺: 561.3.

((2-(((RS)-5-((4,4-Difluorocyclohexyl)amino)pentan-2-yl)thio)-4-methylphenyl)sulfonyl)-L-proline: 4M HCl soln. in dioxane (1.1 mL, 4.46 mmol, 10 eq) was added to a soln. of *tert*-butyl ((2-(((RS)-5-((4,4-difluorocyclohexyl)amino)pentan-2-yl)thio)-4-methylphenyl)sulfonyl)-L-prolinate (250 mg, 0.45 mmol, 1 eq) in DCM

(5 mL) at 0°C. The mixture was stirred overnight while warming up to rt. The solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.74; $[M+H]^+$: 505.3.

- (6R,11aS)-10-(4,4-difluorocyclohexyl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydrobenzo[k]pyrrolo[1,2-b][1,10]dithia[2,5]diazacyclododecin-11(6H)-one 16,16-dioxide and (6S,11aS)-10-(4,4-difluorocyclohexyl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydrobenzo[k]pyrrolo[1,2-b][1,10]dithia[2,5]diazacyclododecin-11(6H)-one 16,16-dioxide:** Were synthesized using ((2-(((RS)-5-((4,4-difluorocyclohexyl)amino)pentan-2-yl)thio)-4-methylphenyl)sulfonyl)-L-proline in analogy to Example 1.1 to give the title compounds. The stereoisomers were separated by acidic prep HPLC to give (6R,11aS)-10-(4,4-difluorocyclohexyl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydrobenzo[k]pyrrolo[1,2-b][1,10]dithia[2,5]diazacyclododecin-11(6H)-one 16,16-dioxide (first eluting diastereomer) and (6S,11aS)-10-(4,4-difluorocyclohexyl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydrobenzo[k]pyrrolo[1,2-b][1,10]dithia[2,5]diazacyclododecin-11(6H)-one 16,16-dioxide (second eluting diastereomer). First eluting diastereomer: LC-MS (1): t_R = 1.04 min; $[M+H]^+$: 487.3. Second eluting diastereomer: LC-MS (1): t_R = 1.07 min; $[M+H]^+$: 487.3. The absolute stereochemistry at the methyl center was attributed arbitrarily.
- Example 1.57 to Example 1.58** were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.51, followed by prep. chiral SFC (SFC 5 method) to separate the stereoisomers. LC-MS data of Example 1.57 to Example 1.58 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R (min)	$[M+H]^+$
1.57	(6R,12aS)-11-(((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.12	512.2
1.58	(6R,12aS)-11-(((3S,6r)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.11	512.0

- Example 1.59 (1³R,4²S)-6-(4,4-Difluorocyclohexyl)-2⁵-methyl-3-thia-6-aza-1(1,3),4(1,2)-dipyrrolidina-2(1,2)-benzenacyclooctaphan-5-one 3,3-dioxide and Example 1.60 (1³S,4²S)-6-(4,4-Difluorocyclohexyl)-2⁵-methyl-3-thia-6-aza-1(1,3),4(1,2)-dipyrrolidina-2(1,2)-benzenacyclooctaphan-5-one 3,3-dioxide:**

- Methyl ((2-fluoro-4-methylphenyl)sulfonyl)-L-prolinate:** A soln. of methyl L-prolinate hydrochloride (2.09 g, 12.00 mmol, 1 eq), DIPEA (6.2 mL, 35.90 mmol, 3 eq), and DMAP (146 mg, 1.20 mmol, 0.1 eq) in DCM (50 mL) was cooled to 0°C. 2-Fluoro-4-methylbenzenesulphonyl chloride (2.50 g, 12.00 mmol, 1 eq) was added, and the clear light yellow soln. was stirred overnight while warming up to rt. Aq. sat. NaHCO₃ soln. was added. The layers were separated, the org. layer was washed with H₂O, dried over MgSO₄, filtered, and the solvent removed under

reduced pressure. The residue was purified by FC (Hept to 75% EtOAc) to give the title compound. LC-MS (1): t_R = 0.88; $[M+H]^+$: 302.2.

5 **((2-Fluoro-4-methylphenyl)sulfonyl)-L-proline:** Aq. 2M LiOH soln. (17.0 mL, 33.40 mmol, 3 eq) was added to a soln. of methyl ((2-fluoro-4-methylphenyl)sulfonyl)-L-prolinate (3.35 g, 11.10 mmol, 1 eq) in THF (45 mL). The mixture was stirred for 1h, and the solvent was partially removed under reduced pressure. The residue was cooled to 0°C and acidified to pH 1 with aq. conc. HCl soln. (ca. 5 mL). The mixture was extracted with EtOAc. The org. layer was washed with H₂O and brine, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.75; $[M+H]^+$: 288.2.

10 ***tert*-Butyl-(RS)-3-(2-((4,4-difluorocyclohexyl)amino)ethyl)pyrrolidine-1-carboxylate:** Was synthesized using *tert*-butyl-(RS)-3-(2-oxoethyl)pyrrolidine-1-carboxylate and 4,4-difluorocyclohexan-1-amine in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 0.70; $[M+H]^+$: 333.3.

***tert*-Butyl-(RS)-3-(2-(((benzyloxy)carbonyl)(4,4-difluorocyclohexyl)amino)ethyl)pyrrolidine-1-carboxylate:**
15 Benzyl chloroformate (0.17 mL, 1.19 mmol, 1.1 eq) was added dropwise to a soln. of *tert*-butyl-(RS)-3-(2-((4,4-difluorocyclohexyl)amino)ethyl)pyrrolidine-1-carboxylate (360 mg, 1.08 mmol, 1 eq) and DIPEA (0.22 mL, 1.30 mmol, 1.2 eq) in DCM (8 mL) at 0°C. The mixture was stirred for 1h at 0°C, and was diluted with aq. sat. NaHCO₃ soln. and DCM. The org. layer was separated through a phase separator and washed with H₂O. The org. layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R = 1.15; $[M+H]^+$: 467.4.

20 **Benzyl-(RS)-(4,4-difluorocyclohexyl)(2-(pyrrolidin-3-yl)ethyl)carbamate hydrochloride:** TFA (0.81 mL, 10.50 mmol, 10 eq) was added to a soln. of *tert*-butyl-(RS)-3-(2-(((benzyloxy)carbonyl)(4,4-difluorocyclohexyl)amino)ethyl)pyrrolidine-1-carboxylate (491 mg, 1.05 mmol, 1 eq) in DCM (10 mL) at 0 °C, and the mixture was stirred at 0°C for 1.5h. The mixture was quenched with aq. 10% Na₂CO₃ soln. and extracted with DCM. The org. layer was washed with H₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.75; $[M+H]^+$: 367.4.

((2-((RS)-3-(2-(((Benzyloxy)carbonyl)(4,4-difluorocyclohexyl)amino)ethyl)pyrrolidin-1-yl)-4-methylphenyl)sulfonyl)-L-proline:
30 A microwave vial was charged with ((2-fluoro-4-methylphenyl)sulfonyl)-L-proline (125 mg, 0.44 mmol, 1 eq), benzyl-(RS)-(4,4-difluorocyclohexyl)(2-(pyrrolidin-3-yl)ethyl)carbamate hydrochloride (319 mg, 0.87 mmol, 2 eq), DIPEA (0.22 mL, 1.31 mmol, 3 eq) and DMSO (2 mL). The mixture was stirred at 110°C for 3 days. The mixture was allowed to cool to rt, and was diluted with H₂O and EtOAc. The layers were separated and the org. layer was washed with H₂O and brine. The org. layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.03; $[M+H]^+$: 634.4.

((2-((RS)-3-(2-((4,4-Difluorocyclohexyl)amino)ethyl)pyrrolidin-1-yl)-4-methylphenyl)sulfonyl)-L-proline: A suspension of ((2-((RS)-3-(2-(((benzyloxy)carbonyl)(4,4-difluorocyclohexyl)amino)ethyl)pyrrolidin-1-yl)-4-methylphenyl)sulfonyl)-L-proline (170 mg, 0.27 mmol, 1 eq), Pd/C (10%, wet, 50 mg) and aq. conc. HCl soln. (0.13 mL, 1.34 mmol, 5 eq) in EtOH (1 mL) was evacuated and purged with N₂, then H₂, and stirred under H₂ atm for 2h.

5 The reaction mixture was diluted with EtOH, filtered through a 0.45 µm PTFE filter and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.70; [M+H]⁺: 500.0.

(1³R,4²S)-6-(4,4-Difluorocyclohexyl)-2⁵-methyl-3-thia-6-aza-1(1,3),4(1,2)-dipyrrolidina-2(1,2)-benzenacyclooctaphan-5-one 3,3-dioxide and (1³S,4²S)-6-(4,4-Difluorocyclohexyl)-2⁵-methyl-3-thia-6-aza-1(1,3),4(1,2)-dipyrrolidina-2(1,2)-benzenacyclooctaphan-5-one 3,3-dioxide: Were synthesized using ((2-((RS)-3-(2-((4,4-difluorocyclohexyl)amino)ethyl)pyrrolidin-1-yl)-4-methylphenyl)sulfonyl)-L-proline in analogy to Example 1.1. The mixture of diastereomers was separated by chiral SFC (SFC 2 method) to give (1³R,4²S)-6-(4,4-Difluorocyclohexyl)-2⁵-methyl-3-thia-6-aza-1(1,3),4(1,2)-dipyrrolidina-2(1,2)-benzenacyclooctaphan-5-one 3,3-dioxide and (1³S,4²S)-6-(4,4-difluorocyclohexyl)-2⁵-methyl-3-thia-6-aza-1(1,3),4(1,2)-dipyrrolidina-2(1,2)-benzenacyclooctaphan-5-one 3,3-dioxide. The stereochemistry at the pyrrolidine was attributed arbitrarily. First eluting diastereomer: LC-MS (1): t_R = 1.03 min; [M+H]⁺: 482.3. Second eluting diastereomer: LC-MS (1): t_R = 1.06 min; [M+H]⁺: 482.2.

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Example 1.61 (6S,12aS)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1,4]oxa[4,5]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide: Was synthesized using (R)-(+)-propylene oxide in analogy to Example 1.51 to give the title compound. LC-MS (1): t_R = 1.07 min; [M+H]⁺: 486.0.

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Example 1.62 (1³R,4²S)-6-(4,4-Difluorocyclohexyl)-2⁵-methyl-3-thia-6-aza-1(1,3)-piperidina-4(1,2)-pyrrolidina-2(1,2)-benzenacyclooctaphan-5-one 3,3-dioxide and Example 1.63 (1³S,4²S)-6-(4,4-Difluorocyclohexyl)-2⁵-methyl-3-thia-6-aza-1(1,3)-piperidina-4(1,2)-pyrrolidina-2(1,2)-benzenacyclooctaphan-5-one 3,3-dioxide:

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Benzyl (RS)-3-(2-((4,4-difluorocyclohexyl)amino)ethyl)piperidine-1-carboxylate: Was synthesized using *rac*-benzyl (RS)-3-(2-oxoethyl)piperidine-1-carboxylate and 4,4-difluorocyclohexan-1-amine in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 0.75; [M+H]⁺: 381.4.

Benzyl (RS)-3-(2-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)ethyl)piperidine-1-carboxylate: Was synthesized using benzyl (RS)-3-(2-((4,4-difluorocyclohexyl)amino)ethyl)piperidine-1-carboxylate in analogy to Example 1.2 to give the title compound. LC-MS (1): t_R = 1.19; [M+H]⁺: 481.3.

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***tert*-Butyl (RS)-(4,4-difluorocyclohexyl)(2-(piperidin-3-yl)ethyl)carbamate:** Pd/C (10%, wet, 160 mg) was added to a soln. of benzyl (RS)-3-(2-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)ethyl)piperidine-1-carboxylate (715 mg, 1.49 mmol, 1 eq) in EtOH (15 mL). The reaction mixture was evacuated and purged with N₂, then with H₂, and was stirred under a H₂ atm for 1h. The reaction mixture was purged with N₂, and filtered over a

35

0.45 µm PTFE filter. The filtrate was evaporated under reduced pressure. The residue was dissolved in DCM, filtered over Celite, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R =0.74; $[M+H]^+$: 347.3.

((2-((RS)-3-(2-((tert-Butoxycarbonyl)(4,4-difluorocyclohexyl)amino)ethyl)piperidin-1-yl)-4-

- 5 **methylphenyl)sulfonyl)-L-proline:** A vial was charged with ((2-fluoro-4-methylphenyl)sulfonyl)-L-proline (220 mg, 0.77 mmol, 1 eq), *tert*-butyl (RS)-(4,4-difluorocyclohexyl)(2-(piperidin-3-yl)ethyl)carbamate (531 mg, 1.53 mmol, 2 eq), DIPEA (0.40 mL, 2.30 mmol, 3 eq) and DMSO (3 mL). The flask was sealed and the mixture was stirred at 110°C for 10 days. The mixture was allowed to cool to rt, and was diluted with H₂O and EtOAc. The layers were separated, the org. layer was washed with H₂O and brine, dried over MgSO₄, filtered, and the solvent removed
10 under reduced pressure. The residue was purified by acidic prep. HPLC to give the title compound. LC-MS (1): t_R =1.11; $[M+H]^+$: 614.4.

((2-((RS)-3-(2-((4,4-Difluorocyclohexyl)amino)ethyl)piperidin-1-yl)-4-methylphenyl)sulfonyl)-L-proline: 4M HCl soln. in dioxane (0.55 mL, 2.18 mmol, 5 eq) was added to a soln. of ((2-((RS)-3-(2-((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)ethyl)piperidin-1-yl)-4-methylphenyl)sulfonyl)-L-proline (268 mg, 0.44 mmol, 1 eq) in DCM
15 (2 mL). The mixture was stirred at rt for 2h. The solvents were removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R =0.77; $[M+H]^+$: 514.2.

(1³R,4²S)-6-(4,4-Difluorocyclohexyl)-2⁵-methyl-3-thia-6-aza-1(1,3)-piperidina-4(1,2)-pyrrolidina-2(1,2)-benzenacyclooctaphan-5-one 3,3-dioxide and (1³S,4²S)-6-(4,4-difluorocyclohexyl)-2⁵-methyl-3-thia-6-aza-1(1,3)-piperidina-4(1,2)-pyrrolidina-2(1,2)-benzenacyclooctaphan-5-one 3,3-dioxide: Was synthesized using
20 ((2-((RS)-3-(2-((4,4-difluorocyclohexyl)amino)ethyl)piperidin-1-yl)-4-methylphenyl)sulfonyl)-L-proline in analogy to Example 1.1. The mixture of diastereomers was purified by acidic prep. HPLC to give (1³R,4²S)-6-(4,4-Difluorocyclohexyl)-2⁵-methyl-3-thia-6-aza-1(1,3)-piperidina-4(1,2)-pyrrolidina-2(1,2)-benzenacyclooctaphan-5-one 3,3-dioxide and (1³S,4²S)-6-(4,4-difluorocyclohexyl)-2⁵-methyl-3-thia-6-aza-1(1,3)-piperidina-4(1,2)-pyrrolidina-2(1,2)-benzenacyclooctaphan-5-one 3,3-dioxide. The stereochemistry at the piperidine center was
25 attributed arbitrarily. First eluting diastereomer: LC-MS (1): t_R = 0.84min; $[M+H]^+$: 496.2. Second eluting diastereomer: LC-MS (1): t_R = 1.08 min; $[M+H]^+$: 496.3.

Example 1.64 (6S,12aS)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,13,14,15,16-decahydrobenzo[b]pyrido[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12(12aH)-one 18,18-dioxide:

- (R)-6-((tert-Butyldimethylsilyl)oxy)hexan-2-ol:** Was synthesized using (3-((tert-butylidimethylsilyl)oxy)propyl)magnesium bromide and (R)-(+)-propylene oxide in analogy to Example 1.61 to give
30 the title compound. LC-MS (1): t_R = 1.02 min; $[M+H]^+$: 233.2.

- (S)-((5-(2-Bromo-5-methylphenoxy)hexyl)oxy)(tert-butyl)dimethylsilane:** 2-Bromo-5-methylphenol (747 mg, 3.92 mmol, 1.3 eq) was dissolved in THF (47 mL). The soln. was cooled to 0°C. (R)-6-((tert-butylidimethylsilyl)oxy)hexan-2-ol (700 mg, 3.01 mmol, 1 eq) and PPh₃ (962 mg, 3.61 mmol, 1.2 eq) were added
35 followed by DEAD (~40% in toluene, 2.2 mL, 4.52 mmol, 1.5 eq). After the addition, the mixture was allowed to

warm up to rt and stirred for 2h. The reaction mixture was diluted with DCM and washed with aq. 1M HCl soln. The org. layer was treated with aq. 1M NaOH soln. and the aq. layer was extracted with DCM. The org. layers were combined, dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 5% EtOAc) to give the title compound. LC-MS (1): t_R= 1.32 min; [M+H]⁺: 403.0.

- 5 **(S)-5-(2-Bromo-5-methylphenoxy)hexan-1-ol:** (S)-((5-(2-Bromo-5-methylphenoxy)hexyl)oxy)(*tert*-butyl)dimethylsilane (678 mg, 1.69 mmol, 1 eq) was dissolved in THF (17 mL). 1M TBAF soln. in THF (2.0 mL, 2.03 mmol, 1.2 eq) was added and stirred at rt for 1h. The reaction mixture was diluted with DCM. The org. layer was washed with H₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 45% EtOAc) to give the title compound. LC-MS (1): t_R= 0.97 min; [M+H]⁺: 328.0.

- 10 **(S)-5-(2-Bromo-5-methylphenoxy)hexanal:** Oxalyl chloride (0.16 mL, 1.83 mmol, 1.5 eq) was dissolved in DCM (20 mL) and the soln. was cooled to -78°C under argon atm. DMSO (0.23 mL, 3.29 mmol, 2.7 eq) was added dropwise while maintaining a temperature below -70°C. After stirring for another 10 min, a soln. of (S)-5-(2-bromo-5-methylphenoxy)hexan-1-ol (350 mg, 1.22 mmol, 1 eq) in DCM (5 mL) was added dropwise. After stirring for another 10 min, TEA (0.85 mL, 6.09 mmol, 5 eq) was added and the reaction mixture was stirred at -78°C for 30 min. Then the soln. was allowed to warm up to rt. The reaction mixture was diluted with Et₂O and washed with aq. 1M HCl soln., aq. sat. NaHCO₃ soln. and H₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 45% EtOAc) to give the title compound. LC-MS (1): t_R= 1.02 min; [M+H]⁺: not seen.

- 20 **(S)-N-(5-(2-Bromo-5-methylphenoxy)hexyl)-4,4-difluorocyclohexan-1-amine:** (S)-5-(2-Bromo-5-methylphenoxy)hexanal (625 mg, 2.19 mmol, 1 eq) was dissolved in MeOH (15 mL). Then 4,4-difluorocyclohexylamine hydrochloride (427 mg, 2.41 mmol, 1.1 eq) and DIPEA (0.75 mL, 4.38 mmol, 2 eq) were added and the soln. was stirred at rt overnight. NaBH₄ (91 mg, 2.41 mmol, 1.1 eq) was then added to the reaction mixture and stirring was continued for 10 min. The reaction mixture was diluted with EtOAc and washed with aq. sat. NaHCO₃ soln. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure to give the title compound. The crude product was used in the next step without further purification. LC-MS (1): t_R= 0.86 min; [M+H]⁺: 404.0.

- 30 ***tert*-Butyl (S)-(5-(2-bromo-5-methylphenoxy)hexyl)(4,4-difluorocyclohexyl)carbamate:** (S)-N-(5-(2-Bromo-5-methylphenoxy)hexyl)-4,4-difluorocyclohexan-1-amine (712 mg, 1.76 mmol, 1 eq) was dissolved in DCM (5 mL). TEA (0.52 mL, 3.70 mmol, 2.1 eq) and Boc₂O (0.45 mL, 1.94 mmol, 1.1 eq) were added. The reaction mixture was stirred at rt for 20 min. The reaction mixture was diluted with DCM and washed with aq. 1M HCl soln. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 45% EtOAc) to give the title compound. LC-MS (1): t_R= 1.26 min; [M+H]⁺: 503.9.

- 35 ***tert*-Butyl (S)-(5-(2-(benzylthio)-5-methylphenoxy)hexyl)(4,4-difluorocyclohexyl)carbamate:** *tert*-Butyl (S)-(5-(2-bromo-5-methylphenoxy)hexyl)(4,4-difluorocyclohexyl)carbamate (455 mg, 0.90 mmol, 1 eq), Pd₂(dba)₃ (83 mg,

0.09 mmol, 0.1 eq) and XantPhos (108 mg, 0.18 mmol, 0.2 eq) were added in a vial. The vial was sealed, evacuated and purged with argon. Dioxane (7 mL), DIPEA (0.32 mL, 1.80 mmol, 2 eq) and benzyl mercaptan (0.13 mL, 1.08 mmol, 1.2 eq) were added. The reaction mixture was stirred at 100°C overnight. H₂O was added and the reaction mixture was extracted with DCM. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 15% EtOAc) to give the title compound. LC-MS (1): t_R= 1.29 min; [M+H]⁺: 548.1.

***tert*-Butyl (S)-5-(2-(chlorosulfonyl)-5-methylphenoxy)hexyl(4,4-difluorocyclohexyl)carbamate:** *tert*-Butyl (S)-5-(2-(benzylthio)-5-methylphenoxy)hexyl(4,4-difluorocyclohexyl)carbamate (277 mg, 0.38 mmol, 1 eq) was dissolved in THF (12 mL). Then AcOH (44 µL, 0.77 mmol, 2 eq) and H₂O (14 µL, 0.77 mmol, 2 eq) were added. The soln. was cooled to 0°C. DCDMH (232 mg, 1.15 mmol, 3 eq) was added in one portion. The reaction mixture was warmed to rt and stirred for 20 min. Aq. sat. NaHCO₃ soln. was added and the reaction mixture was extracted with DCM. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R= 1.24 min; [M+H]⁺: 524.0.

***tert*-Butyl (S)-1-((2-(((S)-6-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-4-methylphenyl)sulfonyl)piperidine-2-carboxylate:** *tert*-Butyl (S)-piperidine-2-carboxylate (13 mg, 0.042 mmol, 1.1 eq), DMAP (0.5 mg, 0.004 mmol, 0.1 eq), and DIPEA (20 µL, 0.11 mmol, 3 eq) was dissolved in MeCN (0.5 mL). Then *tert*-butyl (S)-5-(2-(chlorosulfonyl)-5-methylphenoxy)hexyl(4,4-difluorocyclohexyl)carbamate (40 mg, 0.04 mmol, 1 eq) in MeCN (0.5 mL) was added. The reaction mixture was stirred at rt overnight. The crude product was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R= 1.30 min; [M+H]⁺: 673.8.

((2-(((S)-6-((4,4-Difluorocyclohexyl)amino)hexan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-proline: Was synthesized using *tert*-butyl (S)-1-((2-(((S)-6-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-4-methylphenyl)sulfonyl)piperidine-2-carboxylate in analogy to Example 1.39 to give the title compound. LC-MS (1): t_R= 0.80 min; [M+H]⁺: 517.0.

(6S,12aS)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,13,14,15,16-decahydrobenzo[b]pyrido[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12(12aH)-one 18,18-dioxide: Was synthesized using ((2-(((S)-6-((4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-proline in analogy to Example 1.39 to give the title compound. LC-MS (1): t_R= 1.12 min; [M+H]⁺: 499.0.

Example 1.65 (6R,12aS)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,13,14,15,16-decahydrobenzo[b]pyrido[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12(12aH)-one 18,18-dioxide: Was synthesized using (S)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-ol, 2-bromo-5-methylphenol, 4,4-difluorocyclohexylamine hydrochloride, and *tert*-Butyl (S)-piperidine-2-carboxylate in analogy to Example 1.64 to give the title compound. LC-MS (1): t_R= 1.12 min; [M+H]⁺: 499.0.

Example 1.66 (3R,10R)-5-(4,4-Difluorocyclohexyl)-2,3,10,13-tetramethyl-2,3,5,6,7,8,9,10-octahydro-4H-benzo[b][1]oxa[4]thia[5,8]diazacyclotridecin-4-one 1,1-dioxide: Was synthesized using *tert*-butyl methyl-D-

alaninate hydrochloride in analogy to Example 1.65 to give the title compound. LC-MS (1): t_R = 1.08 min; $[M+H]^+$: 473.0.

Example 1.67 to Example 1.72 were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.51. The diastereoisomers were separated by prep. chiral SFC (SFC 5 method). LC-MS data of Example 1.67 to Example 1.72 are listed in the table below. The LC-MS conditions used were LC-MS (1). The stereocenters of the amide substituent were arbitrarily defined.

Ex. N°	Name	t_R (min)	$[M+H]^+$
1.67	(6R,12aS)-11-((S)-3,3-Difluorocyclopentyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.04	472.2
1.68	(6R,12aS)-11-((R)-3,3-Difluorocyclopentyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.04	472.2
1.69	(6R,12aS)-11-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.06	484.1
1.70	(6R,12aS)-11-((3S,5r)-1,1-Difluorospiro[2.3]hexan-5-yl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.06	484.2
1.71	(6R,12aS)-11-((3S,5R)-1,1-Difluorospiro[2.4]heptan-5-yl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.09	498.1
1.72	(6R,12aS)-11-((3S,5S)-1,1-Difluorospiro[2.4]heptan-5-yl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.09	498.1

Example 1.73 to Example 1.74 were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((6-methyl-2-(((S)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.61. LC-MS data of Example 1.73 to Example 1.74 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R (min)	[M+H] ⁺
1.73	(6S,12aS)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.12	512.0
1.74	(6S,12aS)-11-((3S,6r)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.12	512.0

Example 1.75 (1²S,5¹S,5³R)-9-(4,4-Difluorocyclohexyl)-3⁴-methyl-4-oxa-2-thia-9-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclobutanacyclodecaphan-10-one 2,2-dioxide:

Ethyl (E)-3-((1r,3r)-3-((*tert*-butyldiphenylsilyl)oxy)cyclobutyl)acrylate: A suspension of NaH (ca 60% in mineral oil, 67 mg, 1.68 mmol, 1.06 eq) in DME (6 mL) was cooled to 0°C. Triethylphosphonoacetate (0.34 mL, 1.68 mmol, 1.06 eq) was added at 0°C, and the mixture was stirred for 10 min at 0°C, then for 30 min at rt. A soln. of (1r,3r)-3-((*tert*-butyldiphenylsilyl)oxy)cyclobutane-1-carbaldehyde (WO2021124172) (535 mg, 1.58 mmol, 1 eq) in DME (1 mL) was added dropwise at rt. The mixture was stirred at rt for 1h, and was diluted with Et₂O and H₂O. The aq. layer was extracted with Et₂O. The combined org. layers were dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R=1.28; [M+H]⁺: 450.2.

Ethyl 3-((1r,3s)-3-((*tert*-butyldiphenylsilyl)oxy)cyclobutyl)propanoate: Ethyl (E)-3-((1r,3r)-3-((*tert*-butyldiphenylsilyl)oxy)cyclobutyl)acrylate (389 mg, 0.95 mmol, 1 eq) was dissolved in EtOAc (4 mL) and MeOH (10 mL). Pd/C 10 % (95 mg) was added under N₂. The flask was purged with N₂, then with H₂. The mixture was stirred at rt under a H₂ atm for 1h. The mixture was filtered through a Whatman® paper, and the solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R=1.30; [M+H]⁺: 411.2.

3-((1r,3s)-3-((*tert*-Butyldiphenylsilyl)oxy)cyclobutyl)propanal: A soln. of ethyl 3-((1r,3s)-3-((*tert*-butyldiphenylsilyl)oxy)cyclobutyl)propanoate (391 mg, 0.95 mmol, 1 eq) in DCM (30 mL). was cooled to -78 °C. 1M Diisobutylaluminum hydride soln. in DCM (1.0 mL, 1.00 mmol, 1.05 eq) was added dropwise at -78 °C. The mixture was stirred at -78 °C for 4.5 h and quenched by the addition of MeOH (3.00 mL). The reaction mixture was added onto an aq. sat. Rochelle salt soln. , and was extracted with Et₂O. The combined org. layers were washed with H₂O and brine, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. ¹H-NMR (CDCl₃, 400 MHz): 7.65 (m, 4H), 7.40 (m, 6H), 4.40 (quint., J = 6.7 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 2.25-2.10 (m, 5H), 1.90 (m, 2H), 1.63 (q, J = 7.8 Hz, 2H), 1.24 (t, J = 7.1 Hz, 3H), 1.04 (s, 9H).

N-(3-((1*r*,3*s*)-3-((*tert*-butyldiphenylsilyl)oxy)cyclobutyl)propyl)-4,4-difluorocyclohexan-1-amine: Was synthesized using 3-((1*r*,3*s*)-3-((*tert*-butyldiphenylsilyl)oxy)cyclobutyl)propanal and 4,4-difluorocyclohexan-1-amine in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R =1.02; $[M+H]^+$: 486.4.

***tert*-Butyl 3-((1*r*,3*s*)-3-((*tert*-butyldiphenylsilyl)oxy)cyclobutyl)propyl(4,4-difluorocyclohexyl)carbamate:**
 5 Was synthesized using N-(3-((1*r*,3*s*)-3-((*tert*-butyldiphenylsilyl)oxy)cyclobutyl)propyl)-4,4-difluorocyclohexan-1-amine in analogy to Example 1.2 to give the title compound. LC-MS (1): t_R =1.41; $[M+H]^+$: 452.3.

***tert*-Butyl (4,4-difluorocyclohexyl)(3-((1*r*,3*s*)-3-hydroxycyclobutyl)propyl)carbamate:** *tert*-Butyl 3-((1*r*,3*s*)-3-((*tert*-butyldiphenylsilyl)oxy)cyclobutyl)propyl(4,4-difluorocyclohexyl)carbamate (235 mg, 0.40 mmol, 1 eq) was dissolved in THF (15 mL). TBAF·3H₂O (152 mg, 0.48 mmol, 1.2 eq) was added portionwise at 0°C. The reaction
 10 was stirred overnight while warming up to rt. The solvents were removed under reduced pressure, and the residue was dissolved in EtOAc. The mixture was washed with H₂O and brine. The org. layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R =1.00; $[M+H]^+$: 338.3.

***tert*-Butyl ((2-((1*r*,3*R*)-3-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)propyl)cyclobutoxy)-4-methylphenyl)sulfonyl)-L-prolinate:** A soln. of *tert*-butyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate (100 mg, 0.29 mmol, 1 eq) in THF (8 mL) was cooled to 0°C. *tert*-Butyl (4,4-difluorocyclohexyl)(3-((1*r*,3*s*)-3-hydroxycyclobutyl)propyl)carbamate (132 mg, 0.38 mmol, 1.3 eq) and PPh₃ (101 mg, 0.38 mmol, 1.3 eq) were added, followed by DEAD (~40% in toluene, 0.34 mL, 0.70 mmol, 2.4 eq). After the addition, the mixture was allowed to warm up to rt, and then heated to reflux. After 17h, the mixture was allowed to cool to rt, and the solvents
 15 were removed under reduced pressure. Et₂O was added and the mixture was filtered. The solvent was removed under reduced pressure. The residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R =1.28; $[M+H]^+$: 671.5.

((2-((1*r*,3*R*)-3-((4,4-Difluorocyclohexyl)amino)propyl)cyclobutoxy)-4-methylphenyl)sulfonyl)-L-proline:
tert-Butyl ((2-((1*r*,3*R*)-3-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)propyl)cyclobutoxy)-4-methylphenyl)sulfonyl)-L-prolinate (68 mg, 0.10 mmol, 1 eq) was dissolved in DCM (7 mL). TFA (0.55 mL, 7.1 mmol, 70 eq) was added at rt, and the resulting mixture was stirred at rt for 75 min. The solvents were removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R =0.75; $[M+H]^+$: 515.3.

(1*2*S,5*1*S,5*3*R)-9-(4,4-Difluorocyclohexyl)-3*4*-methyl-4-oxa-2-thia-9-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclobutanacyclodecaphan-10-one 2,2-dioxide: Was synthesized using ((2-((1*r*,3*R*)-3-((4,4-difluorocyclohexyl)amino)propyl)cyclobutoxy)-4-methylphenyl)sulfonyl)-L-proline in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R =1.08; $[M+H]^+$: 497.2.

Example 1.76 (S)-12-(4,4-Difluorocyclohexyl)-3-methyl-7,8,9,10,11,12,13*a*,14,15,16-decahydrobenzo[*b*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotetradecin-13(6*H*)-one 18,18-dioxide:

***tert*-Butyl ((2-((6-hydroxyhexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using 1,6-hexanediol in analogy to Example 1.7 to give the title compound. LC-MS (1): t_R = 1.01 min; $[M+H]^+$: 442.3.

***tert*-Butyl ((4-methyl-2-((6-oxohexyl)oxy)phenyl)sulfonyl)-L-prolinate:** Oxalyl chloride (30 μ L, 0.34 mmol, 1.5 eq) was dissolved in DCM (6 mL) and the soln. was cooled to -78°C under argon atm. DMSO (43 μ L, 0.61 mmol, 2.7 eq) was added dropwise while maintaining a temperature below -70°C. After stirring for another 10 min, a soln. of *tert*-butyl ((2-((6-hydroxyhexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate (100 mg, 0.23 mmol, 1 eq) in DCM (3 mL) was added dropwise. After stirring for another 10 min, TEA (0.16 mL, 1.13 mmol, 5 eq) was added and the reaction mixture was stirred at -78°C for 30 min. The soln. was allowed to warm up to rt. The reaction mixture was diluted with DCM and washed with aq. sat. NaHCO₃. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 1.06 min; $[M+H]^+$: 440.0.

***tert*-Butyl ((2-((5-((4,4-difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** *tert*-Butyl ((4-methyl-2-((6-oxohexyl)oxy)phenyl)sulfonyl)-L-prolinate (20 mg, 0.046 mmol, 1 eq) was dissolved in MeOH (1 mL). 4,4-Difluorocyclohexylamine hydrochloride (12 mg, 0.068 mmol, 1.5 eq) and DIPEA (13 μ L, 0.077 mmol, 1.7 eq) were added and the soln. was stirred at rt for 1h. NaBH(OAc)₃ (19 mg, 0.091 mmol, 2 eq) was then added to the reaction mixture and stirring was continued for 10 min. The reaction mixture was diluted with DCM and washed with aq. sat. NaHCO₃. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.91 min; $[M+H]^+$: 559.3.

((2-((5-((4,4-Difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)sulfonyl)-L-proline: *tert*-Butyl ((2-((5-((4,4-difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate (25 mg, 0.046 mmol, 1 eq) was dissolved in DCM (1.5 mL). Then TFA (0.25 mL, 3.18 mmol, 70 eq) was added. The reaction mixture was stirred at rt for 1h. The solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.77 min; $[M+H]^+$: 503.2.

(S)-12-(4,4-Difluorocyclohexyl)-3-methyl-7,8,9,10,11,12,13a,14,15,16-decahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotetradecin-13(6H)-one 18,18-dioxide: ((2-((5-((4,4-Difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)sulfonyl)-L-proline (23 mg, 0.05 mmol, 1 eq) was dissolved in DMF (1 mL). Then DIPEA (61 μ L, 0.36 mmol, 8 eq) and HATU (20 mg, 0.05 mmol, 1.2 eq) were added. The reaction mixture was stirred at rt for 6h. The residue was purified by acidic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.09 min; $[M+H]^+$: 485.0.

Example 1.77 (S)-10-(4,4-Difluorocyclohexyl)-3-methyl-7,8,9,10,11a,12,13,14-octahydro-11H-spiro[benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecine-6,1'-cyclopropan]-11-one 16,16-dioxide:

Methyl 4-bromo-2-(2-bromo-5-methylphenoxy)butanoate: 2-Bromo-5-methylphenol (3.00 g, 15.70 mmol, 1 eq) was dissolved in DMF (33 mL) and K₂CO₃ (2.39 g, 17.30 mmol, 1.1 eq) was added. The mixture was stirred for 30 min at rt, and methyl 2,4-dibromobutyrate (2.5 mL, 17.30 mmol, 1.1 eq) was added. The resulting suspension was

stirred at rt for 3 days. The mixture was diluted with EtOAc and was washed with H₂O. The org. layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R=1.05; [M+H]⁺: not seen.

Methyl 1-(2-bromo-5-methylphenoxy)cyclopropane-1-carboxylate: A soln. of methyl 4-bromo-2-(2-bromo-5-methylphenoxy)butanoate (3.31 g, 9.04 mmol, 1 eq) in THF (40 mL) was cooled to 0°C. KOtBu (1.18 g, 9.95 mmol, 1.1 eq) was added in several portions within 5 min, while temperature was kept below 5°C. The resulting mixture was stirred at 0°C for 15 min and was partitioned between H₂O and EtOAc. The layers were separated and the aq. layer was extracted with EtOAc. The combined org. layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R=0.98; [M+H]⁺: 287.1.

(1-(2-Bromo-5-methylphenoxy)cyclopropyl)methanol: A soln. of methyl 1-(2-bromo-5-methylphenoxy)cyclopropane-1-carboxylate (800 mg, 2.81 mmol, 1 eq) in DCM (80 mL) was cooled to -78 °C. 1M Diisobutylaluminum hydride soln. in DCM (5.9 mL, 5.90 mmol, 2.1 eq) was added dropwise at -78 °C. The mixture was stirred at -78 °C for 1h, and was allowed to slowly warm up to rt. After 2h and at -50 °C, MeOH (10 mL) was added. The reaction mixture was poured onto aq. sat. Rochelle salt soln. and was extracted with Et₂O. The combined org. layers were washed with H₂O and brine, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R=0.86; [M+H]⁺: not seen.

1-(2-Bromo-5-methylphenoxy)cyclopropane-1-carbaldehyde: Was synthesized using (1-(2-bromo-5-methylphenoxy)cyclopropyl)methanol in analogy to Example 1.7 to give the title compound. LC-MS (1): t_R=0.94; [M+H]⁺: not seen.

Ethyl (E)-3-(1-(2-bromo-5-methylphenoxy)cyclopropyl)acrylate: Ethyl (triphenylphosphoranylidene)acetate (341 mg, 0.93 mmol, 1.05 eq) was added to a soln. of 1-(2-bromo-5-methylphenoxy)cyclopropane-1-carbaldehyde (226 mg, 0.89 mmol, 1 eq) in toluene (6 mL). The mixture was stirred at reflux for 1h, and was allowed to cool to rt. The mixture was diluted with aq. sat. NaHCO₃ soln. and EtOAc. The layers were separated, and the org. layer was washed with H₂O and brine, dried with MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R=1.06; [M+H]⁺: 325.1.

Ethyl 3-(1-(2-bromo-5-methylphenoxy)cyclopropyl)propanoate: A vial was charged with ethyl (E)-3-(1-(2-bromo-5-methylphenoxy)cyclopropyl)acrylate (200 mg, 0.62 mmol, 1 eq), p-toluenesulfonyl hydrazide (827 mg, 4.31 mmol, 7 eq) and toluene (12 mL). The suspension was stirred at 100°C for 2 days. The mixture was allowed to cool to rt, and diluted with EtOAc and H₂O. The layers were separated, the org. layer was washed with brine, dried with MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R=1.08; [M+H]⁺: 327.1.

3-(1-(2-Bromo-5-methylphenoxy)cyclopropyl)propanal: A soln. of ethyl 3-(1-(2-bromo-5-methylphenoxy)cyclopropyl)propanoate (171 mg, 0.52 mmol, 1 eq) in DCM (8 mL) was cooled to -78 °C. 1M

Diisobutylaluminum hydride soln. in DCM (0.6 mL, 0.57 mmol, 1.1 eq) was added dropwise at -78°C, and the mixture was stirred at -78 °C for 1h. MeOH (1 mL) was added. The resulting mixture was poured onto aq. sat. Rochelle salt soln. , and was extracted with Et₂O. The combined org. layers were washed with H₂O and brine , dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R=1.00; [M+H]⁺: not seen.

***N*-(3-(1-(2-Bromo-5-methylphenoxy)cyclopropyl)propyl)-4,4-difluorocyclohexan-1-amine:** Was synthesized using 3-(1-(2-bromo-5-methylphenoxy)cyclopropyl)propanal and 4,4-difluorocyclohexan-1-amine in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R=0.85; [M+H]⁺: 402.1.

***tert*-Butyl (3-(1-(2-bromo-5-methylphenoxy)cyclopropyl)propyl)(4,4-difluorocyclohexyl)carbamate:** Was synthesized using *N*-(3-(1-(2-bromo-5-methylphenoxy)cyclopropyl)propyl)-4,4-difluorocyclohexan-1-amine in analogy to Example 1.2 to give the title compound. LC-MS (1): t_R=1.25; [M+H]⁺: 504.2.

***tert*-Butyl (3-(1-(2-(benzylthio)-5-methylphenoxy)cyclopropyl)propyl)(4,4-difluorocyclohexyl)carbamate:** Was synthesized using *tert*-butyl (3-(1-(2-bromo-5-methylphenoxy)cyclopropyl)propyl)(4,4-difluorocyclohexyl)carbamate in analogy to Example 3.2 to give the title compound. LC-MS (1): t_R=1.29; [M+H]⁺: 546.2.

***tert*-Butyl (3-(1-(2-(chlorosulfonyl)-5-methylphenoxy)cyclopropyl)propyl)(4,4-difluorocyclohexyl)carbamate:** A soln. of *tert*-butyl (3-(1-(2-(benzylthio)-5-methylphenoxy)cyclopropyl)propyl)(4,4-difluorocyclohexyl)carbamate (62 mg, 0.11 mmol, 1 eq) in THF (1 mL) was cooled to -10°C. AcOH (13 µL, 0.23 mmol, 2 eq) and H₂O (4 µL, 0.23 mmol, 2 eq) were added. At -10°C, a soln. of DCDMH (69 mg, 0.34 mmol, 3 eq) in THF (1 mL) was added dropwise. After 5 min at -10°C, the mixture was diluted with Et₂O and washed with aq. sat. NaHCO₃ soln. and H₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R=1.22; [M+H]⁺: 522.2.

***tert*-Butyl ((2-(1-(3-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)propyl)cyclopropoxy)-4-methylphenyl)sulfonyl)-L-prolinate:** *tert*-Butyl (3-(1-(2-(chlorosulfonyl)-5-methylphenoxy)cyclopropyl)propyl)(4,4-difluorocyclohexyl)carbamate (59 mg, 0.11 mmol, 1 eq) was dissolved in DCM. *tert*-Butyl L-prolinate (22 µL, 0.12 mmol, 1.1 eq), DIPEA (0.06 mL, 0.34 mmol, 3 eq), and DMAP (1.4 mg, 0.011 mmol, 0.1 eq) were added. The resulting mixture was stirred overnight at rt. The mixture was washed with aq. 1M HCl soln., aq. sat. NaHCO₃, and brine. The org. layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. Purification of the crude by basic prep. HPLC gave the title compound. LC-MS (1): t_R=1.25; [M+H]⁺: 657.2.

((2-(1-(3-((4,4-Difluorocyclohexyl)amino)propyl)cyclopropoxy)-4-methylphenyl)sulfonyl)-L-proline: Was synthesized using *tert*-butyl ((2-(1-(3-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)propyl)cyclopropoxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R=0.75; [M+H]⁺: 501.2.

(S)-10-(4,4-Difluorocyclohexyl)-3-methyl-7,8,9,10,11a,12,13,14-octahydro-11H-spiro[benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecine-6,1'-cyclopropan]-11-one 16,16-dioxide: Was synthesized using ((2-(1-(3-((4,4-difluorocyclohexyl)amino)propyl)cyclopropoxy)-4-methylphenyl)sulfonyl)-L-proline in analogy to Example 1.1 to give the title compound. LC-MS (1): $t_R=1.02$; $[M+H]^+$: 483.2.

5 **Example 1.78 (S)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydropyrido[2,3-l]pyrrolo[1,2-b][1]thia[2,5]diazacyclotridecin-12(5H)-one 17,17-dioxide:**

tert-Butyl ((2-chloro-6-methylpyridin-3-yl)sulfonyl)-L-prolinate: L-Proline *tert*-butyl ester (1.0 mL, 5.84 mmol, 1 eq) was dissolved in DCM (50 mL). DIPEA (3.0 mL, 17.50 mmol, 3 eq) and DMAP (71.3 mg, 0.58 mmol, 0.1 eq) were added at rt. The mixture was cooled to 0°C and 2-chloro-6-methylpyridine-3-sulfonyl chloride (1.43 g, 6.01 mmol, 1.03 eq) was added. The mixture was stirred overnight at rt. Aq. sat. NaHCO₃ soln., was added, and the resulting mixture was extracted with DCM. The org. layer was washed with H₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): $t_R=0.97$; $[M+H]^+$: 361.2.

tert-Butyl ((2-(6-((*tert*-butoxycarbonyl)amino)hex-1-yn-1-yl)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate: *tert*-Butyl ((2-chloro-6-methylpyridin-3-yl)sulfonyl)-L-prolinate (500 mg, 1.39 mmol, 1 eq), *tert*-butyl hex-5-yn-1-ylcarbamate (310 mg, 1.52 mmol, 1.1 eq), CuI (26 mg, 0.14 mmol, 0.1 eq) and Et₃N (0.6 mL, 4.30 mmol, 3.1 eq) was dissolved in DMF (8 mL). The mixture was degassed with N₂ for 5 min. Pd(PPh₃)₄ (80 mg, 0.07 mmol, 0.05 eq) was added, and the resulting mixture was heated to 85°C for 2 days. The mixture was allowed to cool to rt, filtered through Celite, and the solvents were removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): $t_R=1.06$; $[M+H]^+$: 522.3.

tert-Butyl ((2-(6-((*tert*-butoxycarbonyl)amino)hexyl)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate: *tert*-Butyl ((2-(6-((*tert*-butoxycarbonyl)amino)hex-1-yn-1-yl)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate (390 mg, 0.75 mmol, 1 eq) was reduced in an H-Cube® Pro with a Pd/C cartridge (10%, 7 cm) under a flow of EtOH and with H₂ (10 bar). The mixture was filtered through Celite, and the solvent was removed under reduced pressure. The residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): $t_R=1.05$; $[M+H]^+$: 526.3.

tert-Butyl ((2-(6-(4,4-difluorocyclohexyl)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate: *tert*-Butyl ((2-(6-((*tert*-butoxycarbonyl)amino)hexyl)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate (50 mg, 0.095 mmol, 1 eq) was dissolved in DCM (4 mL). TFA (73 µL, 0.95 mmol, 10 eq) was added, and the resulting mixture was stirred at rt for 30 min. The solvents were removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): $t_R=0.73$; $[M+H]^+$: 426.1.

tert-Butyl ((2-(6-((4,4-difluorocyclohexyl)amino)hexyl)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate: Was synthesized using *tert*-butyl ((2-(6-aminohexyl)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.1 to give the title compound. LC-MS (1): $t_R=0.84$; $[M+H]^+$: 544.2.

((2-(6-((4,4-Difluorocyclohexyl)amino)hexyl)-6-methylpyridin-3-yl)sulfonyl)-L-proline: *tert*-Butyl ((2-(6-((4,4-difluorocyclohexyl)amino)hexyl)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate (43 mg, 0.079 mmol, 1 eq) was dissolved in DCM (4 mL). TFA (61 μ L, 0.79 mmol, 10 eq) was added, and the resulting mixture was stirred at rt for 17h. TFA (61 μ L, 0.79 mmol, 10 eq) was added again, and the mixture was stirred overnight. The solvent s were removed under reduced pressure to give the crude title compound. The crude product was used in the next step without further purification. LC-MS (1): t_R =0.66; $[M+H]^+$: 488.2.

(S)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydropyrido[2,3-l]pyrrolo[1,2-b][1]thia[2,5]diazacyclotridecin-12(5H)-one 17,17-dioxide: Was synthesized using ((2-(6-((4,4-difluorocyclohexyl)amino)hexyl)-6-methylpyridin-3-yl)sulfonyl)-L-proline in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R =0.92; $[M+H]^+$: 470.0.

Example 1.79 (6RS,12aS)-6-Cyclopropyl-11-(4,4-difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:

Methyl 5-((4,4-difluorocyclohexyl)amino)pentanoate: Was synthesized using methyl 5-oxopentanoate (Carter et al., *J. Org. Chem.* **2013**, *78*, 2213–2247) and 4,4-difluorocyclohexan-1-amine in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R =0.52; $[M+H]^+$: 250.6.

Methyl 5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentanoate: Was synthesized using methyl 5-((4,4-difluorocyclohexyl)amino)pentanoate in analogy to Example 1.2 to give the title compound. LC-MS (1): t_R =1.05; $[M+H]^+$: 350.3.

***tert*-Butyl (4,4-difluorocyclohexyl)(5-hydroxypentyl)carbamate:** A soln. of methyl 5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentanoate (4.29 g, 12.30 mmol, 1 eq) in THF (200 mL) was cooled to -78 °C. LiAlH₄ (13.5 mL, 13.50 mmol, 1.1 eq) was added dropwise at -78°C, and the mixture was stirred at -78°C for 30 min, before being allowed to slowly warm up. After 3h at -45°C, MeOH (5 mL) was added. The resulting mixture was poured onto an aq. sat. Rochelle salt soln. (35 mL), and was extracted with Et₂O. The combined org. layers were washed with H₂O and brine, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R =0.95; $[M+H]^+$: 321.9.

***tert*-Butyl (4,4-difluorocyclohexyl)(5-oxopentyl)carbamate:** Was synthesized using *tert*-butyl (4,4-difluorocyclohexyl)(5-hydroxypentyl)carbamate in analogy to Example 1.7 to give the title compound. LC-MS (1): t_R =1.00; $[M+H]^+$: 320.1.

***tert*-Butyl (5-cyclopropyl-5-hydroxypentyl)(4,4-difluorocyclohexyl)carbamate:** To a soln. of *tert*-butyl (4,4-difluorocyclohexyl)(5-oxopentyl)carbamate (95.8 mg, 0.30 mmol, 1 eq) in THF (4 mL) was added dropwise 0.5M cyclopropylmagnesium bromide soln. in THF (0.6 mL, 0.30 mmol, 1 eq) at -78 °C. The mixture was stirred at -78°C for 2h. The mixture was stirred overnight while warming up to rt. Aq. sat. NH₄Cl soln. was carefully added. The mixture was extracted with EtOAc. The combined org. layers were dried over MgSO₄, filtered, and the solvent

removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R =1.04; $[M+H]^+$: 362.3.

tert-Butyl ((2-(((RS)-5-((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)-1-cyclopropylpentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using *tert*-butyl (5-cyclopropyl-5-hydroxypentyl)(4,4-difluorocyclohexyl)carbamate in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R =1.30; $[M+H]^+$: 685.4.

((2-(((RS)-5-((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)-1-cyclopropylpentyl)oxy)-4-methylphenyl)sulfonyl)-L-proline: Was synthesized using *tert*-butyl ((2-(((RS)-5-((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)-1-cyclopropylpentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.9 to give the title compound. LC-MS (1): t_R =0.80 and 0.84; $[M+H]^+$: 529.2.

(6RS,12aS)-6-Cyclopropyl-11-(4,4-difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide: Was synthesized using ((2-(((RS)-5-((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)-1-cyclopropylpentyl)oxy)-4-methylphenyl)sulfonyl)-L-proline in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R =1.12; $[M+H]^+$: 511.2.

Example 1.80 (12aS*,12bS*,13aR*)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,12b,13,13a,14-decahydrocyclopropa[3,4]pyrrolo[1,2-e]pyrido[2,3-b][1]oxa[4]thia[5,8]diazacyclotridecin-12(12aH)-one 16,16-dioxide:

5-((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl methanesulfonate: *tert*-Butyl (4,4-difluorocyclohexyl)(5-hydroxypentyl)carbamate (3.50 g, 10.90 mmol, 1 eq) was dissolved in DCM (35 mL). TEA (1.8 mL, 13.10 mmol, 1.2 eq) and DMAP (134 mg, 1.09 mmol, 0.1 eq) were added. The soln. was cooled to 0°C. Methanesulfonyl chloride (1.0 mL, 13.10 mmol, 1.2 eq) was added dropwise. The reaction mixture was stirred at 0°C for 1h. The reaction mixture was diluted with DCM and washed with H₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 1.02 min; $[M+H]^+$: 400.0.

3-(Benzylthio)-6-methylpyridin-2-ol: 3-Bromo-6-methylpyridin-2-ol (500 mg, 2.66 mmol, 1 eq) was dissolved in dioxane (5 mL), then XantPhos Pd G2 (118 mg, 0.13 mmol, 0.05 eq), DIPEA (0.90 mL, 5.19 mmol, 1.95 eq) and benzyl mercaptan (0.35 mL, 2.93 mmol, 1.1 eq) were added under argon atm. The reaction mixture was stirred at 100°C for 2h. The solvent was removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 0.77 min; $[M+H]^+$: 232.1.

tert-Butyl (5-((3-(benzylthio)-6-methylpyridin-2-yl)oxy)pentyl)(4,4-difluorocyclohexyl)carbamate: 3-(Benzylthio)-6-methylpyridin-2-ol (500 mg, 2.16 mmol, 1 eq) was dissolved in DMF (6 mL). 5-((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl methanesulfonate (881 mg, 2.20 mmol, 1.02 eq) and Cs₂CO₃ (1.42 g, 4.32 mmol, 2 eq) were added. The reaction mixture was stirred at 100°C for 1h. The reaction mixture was diluted with DCM and washed with H₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed

under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 1.30 min; $[M+H]^+$: 535.2.

***tert*-Butyl (5-((3-(chlorosulfonyl)-6-methylpyridin-2-yl)oxy)pentyl)(4,4-difluorocyclohexyl)carbamate:** *tert*-Butyl (5-((3-(benzylthio)-6-methylpyridin-2-yl)oxy)pentyl)(4,4-difluorocyclohexyl)carbamate (599 mg, 1.12 mmol, 1 eq) was dissolved in dioxane (14 mL). Then H₂O (40 μ L, 2.24 mmol, 2 eq) and DCDMH (450 mg, 2.24 mmol, 2 eq) were added. The reaction mixture was stirred at rt for 10 min, diluted with DCM and washed with aq. sat. NaHCO₃ soln. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure to give the title compound. The crude product was used in the next step without further purification. LC-MS (1): t_R = 1.23 min; $[M+MeCN+H]^+$: 511.0.

***tert*-Butyl (1*S**,2*S**,5*R**)-3-((2-((5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylate:** *tert*-Butyl (5-((3-(chlorosulfonyl)-6-methylpyridin-2-yl)oxy)pentyl)(4,4-difluorocyclohexyl)carbamate (45 mg, 0.21 mmol, 1.1 eq), DIPEA (0.10 mL, 0.60 mmol, 3 eq) and DMAP (2.3 mg, 0.02 mmol, 0.1 eq) were dissolved in MeCN (1 mL). Then *tert*-butyl (1*S**,2*S**,5*R**)-3-azabicyclo[3.1.0]hexane-2-carboxylate (95 mg, 0.19 mmol, 1 eq) was added. The reaction mixture was stirred at rt overnight. The solvent was removed under reduced pressure. The residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.26 min; $[M+H]^+$: 657.7.

(1*S,2*S**,5*R**)-3-((2-((5-((4,4-Difluorocyclohexyl)amino)pentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid:** *tert*-Butyl (1*S**,2*S**,5*R**)-3-((2-((5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylate (71 mg, 0.11 mmol, 1 eq) was dissolved in DCM (1 mL). Then TFA (0.58 mL, 7.60 mmol, 70 eq) was added. The reaction mixture was stirred at rt for 1h. The solvent was removed under reduced pressure to give the title compound. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.75 min; $[M+H]^+$: 501.9.

(12*aS,12*bS**,13*aR**)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,12*b*,13,13*a*,14-decahydrocyclopropa[3,4]pyrrolo[1,2-*e*]pyrido[2,3-*b*][1]oxa[4]thia[5,8]diazacyclotridecin-12(12*aH*)-one 16,16-dioxide:** DIPEA (0.10 mL, 0.60 mmol, 6 eq) and HATU (57 mg, 0.15 mmol, 1.5 eq) were dissolved in DMF (25 mL). (1*S**,2*S**,5*R**)-3-((2-((5-((4,4-Difluorocyclohexyl)amino)pentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (50 mg, 0.10 mmol, 1 eq) in DMF (1 mL) was added. The reaction mixture was stirred at rt for 2h. The residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.04 min; $[M+H]^+$: 483.9.

Example 1.81 (S)-5-(4,4-Difluorocyclohexyl)-2,3,13-trimethyl-2,3,5,6,7,8,9,10-octahydro-4H-pyrido[2,3-*b*][1]oxa[4]thia[5,8]diazacyclotridecin-4-one 1,1-dioxide:

(S)-5-(4,4-Difluorocyclohexyl)-3,13-dimethyl-2,3,5,6,7,8,9,10-octahydro-4H-pyrido[2,3-*b*][1]oxa[4]thia[5,8]diazacyclotridecin-4-one 1,1-dioxide: Was synthesized using *tert*-butyl L-alaninate hydrochloride in analogy to Example 1.80 to give the title compound. LC-MS (1): t_R = 0.99 min; $[M+H]^+$: 446.0.

(S)-5-(4,4-Difluorocyclohexyl)-2,3,13-trimethyl-2,3,5,6,7,8,9,10-octahydro-4H-pyrido[2,3-b][1]oxa[4]thia[5,8]diazacyclotridecin-4-one 1,1-dioxide: (S)-5-(4,4-Difluorocyclohexyl)-3,13-dimethyl-2,3,5,6,7,8,9,10-octahydro-4H-pyrido[2,3-b][1]oxa[4]thia[5,8]diazacyclotridecin-4-one 1,1-dioxide (20 mg, 0.045 mmol, 1 eq) was dissolved in DMF (2 mL). NaH (60% in mineral oil, 8.2 mg, 0.22 mmol, 5 eq) was added and the reaction mixture was stirred for 10 min before adding MeI (0.03 mL, 0.45 mmol, 10 eq). The reaction mixture was stirred at rt for 30 min. The residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.04 min; $[M+H]^+$: 460.0.

Example 1.82 (6R,12aS)-11-(4,4-Difluorocyclohexyl)-6-ethyl-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide and Example 1.83 (6S,12aS)-11-(4,4-Difluorocyclohexyl)-6-ethyl-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide: Were synthesized using ethylmagnesium bromide in analogy to Example 1.79. The stereoisomers were separated by prep. SFC (SFC 14 method) to give (6R,12aS)-11-(4,4-Difluorocyclohexyl)-6-ethyl-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide and (6S,12aS)-11-(4,4-difluorocyclohexyl)-6-ethyl-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide. First eluting diastereomer: LC-MS (1): t_R = 1.10 min; $[M+H]^+$: 499.2. Second eluting diastereomer: LC-MS (1): t_R = 1.10 min; $[M+H]^+$: 499.2. The stereochemistry at the ethyl center was attributed arbitrarily.

Example 1.84 (8R,12aS)-11-(4,4-Difluorocyclohexyl)-3,8-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:

Methyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate: Methyl ((5-chloro-2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate (5.25 g, 15.70 mmol, 1 eq) was dissolved in MeOH (40 mL). To the resulting soln., NaOAc (2.58 g, 31.50 mmol, 2 eq) and Pd(OH)₂ (1.10 g, 1.57 mmol, 1 eq) were added. The mixture was stirred at 50°C for 2h and then at rt overnight. The mixture was filtered on a Celite pad and the solvent was removed under reduced pressure. The residue was dissolved in tBME and extracted with aq. sat. NaHCO₃ soln. The organic layer was washed with H₂O and evaporated under reduced pressure. The residue was dissolved in toluene and the solvent was removed under reduced pressure. The residue was recrystallised from isopropanol to give the title compound. LC-MS (1): t_R = 0.80 min; $[M+H]^+$: 300.1.

Methyl ((2-(((S)-5-hydroxy-3-methylpentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate and Methyl ((2-(((R)-5-hydroxy-3-methylpentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: Were synthesized using methyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate and 3-methyl-1,5-pentanediol in analogy to Example 1.1 to give the title compound. Separation of the diastereoisomers by prep. chiral SFC (SFC 19 method) gave methyl ((2-(((R)-5-hydroxy-3-methylpentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate (first eluting diastereomer) and methyl ((2-(((S)-5-hydroxy-3-methylpentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate (second eluting diastereomer). First eluting

diastereomer: LC-MS (1): t_R = 0.89 min; $[M+H]^+$: 400.3. Second eluting diastereomer: LC-MS (1): t_R = 0.89 min; $[M+H]^+$: 400.3.

5 **Methyl ((4-methyl-2-(((S)-3-methyl-5-oxopentyl)oxy)phenyl)sulfonyl)-L-prolinate:** Was synthesized using methyl ((2-(((R)-5-hydroxy-3-methylpentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.7 to give the title compound. LC-MS (1): t_R = 0.94; $[M+H]^+$: 398.3.

Methyl ((2-(((R)-5-((4,4-difluorocyclohexyl)amino)-3-methylpentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using methyl ((4-methyl-2-(((S)-3-methyl-5-oxopentyl)oxy)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 0.82; $[M+H]^+$: 517.3.

10 **((2-(((R)-5-((4,4-Difluorocyclohexyl)amino)-3-methylpentyl)oxy)-4-methylphenyl)sulfonyl)-L-proline:** Was synthesized using methyl ((2-(((R)-5-((4,4-difluorocyclohexyl)amino)-3-methylpentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.8 to give the title compound. LC-MS (1): t_R = 0.75; $[M+H]^+$: 503.3.

15 **(8R,12aS)-11-(4,4-Difluorocyclohexyl)-3,8-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:** Was synthesized using methyl ((2-(((R)-5-((4,4-difluorocyclohexyl)amino)-3-methylpentyl)oxy)-4-methylphenyl)sulfonyl)-L-proline in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 1.04; $[M+H]^+$: 484.9.

Example 1.85 (8S,12aS)-11-(4,4-Difluorocyclohexyl)-3,8-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:

20 **Methyl ((4-methyl-2-(((R)-3-methyl-5-oxopentyl)oxy)phenyl)sulfonyl)-L-prolinate:** Was synthesized using methyl ((2-(((S)-5-hydroxy-3-methylpentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.7 to give the title compound. LC-MS (1): t_R = 0.96; $[M+H]^+$: 398.3.

Methyl ((2-(((S)-5-((4,4-difluorocyclohexyl)amino)-3-methylpentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using methyl ((4-methyl-2-(((R)-3-methyl-5-oxopentyl)oxy)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 0.83; $[M+H]^+$: 517.3.

25 **((2-(((S)-5-((4,4-Difluorocyclohexyl)amino)-3-methylpentyl)oxy)-4-methylphenyl)sulfonyl)-L-proline:** Was synthesized using methyl ((2-(((S)-5-((4,4-difluorocyclohexyl)amino)-3-methylpentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.8 to give the title compound. LC-MS (1): t_R = 0.76; $[M+H]^+$: 503.3.

30 **(8S,12aS)-11-(4,4-Difluorocyclohexyl)-3,8-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:** Was synthesized using methyl ((2-(((S)-5-((4,4-difluorocyclohexyl)amino)-3-methylpentyl)oxy)-4-methylphenyl)sulfonyl)-L-proline in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 1.04; $[M+H]^+$: 485.3.

- Example 1.86** (12aS,13aR,14aR)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,13,13a,14,14a-decahydrocyclopropa[4,5]pyrrolo[1,2-e]pyrido[2,3-b][1]oxa[4]thia[5,8]diazacyclotridecin-12(12aH)-one 16,16-dioxide:
- Methyl** (1R,3S,5R)-2-((2-((5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylate: Was synthesized using *tert*-butyl (5-((3-(chlorosulfonyl)-6-methylpyridin-2-yl)oxy)pentyl)(4,4-difluorocyclohexyl)carbamate and methyl (1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3-carboxylate in analogy to Example 1.80 to give the title compound. LC-MS (1): *t_R*= 1.17 min; [M+H]⁺: 615.9.
- (1R,3S,5R)-2-((2-((5-((4,4-Difluorocyclohexyl)amino)pentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid:** Methyl (1R,3S,5R)-2-((2-((5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylate (74 mg, 0.12 mmol, 1 eq) was dissolved in THF (1 mL). Then aq. 1M LiOH soln. (0.24 mL, 0.24 mmol, 2 eq) was added. The reaction mixture was stirred at rt overnight. The solvent was removed under reduced pressure. The residue was dissolved in DCM (1.5 mL) and TFA (0.65 mL, 8.42 mmol, 70 eq) was added. The reaction mixture was stirred at rt for 1h. The solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): *t_R*= 0.73 min; [M+H]⁺: 501.9.
- (12aS,13aR,14aR)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,13,13a,14,14a-decahydrocyclopropa[4,5]pyrrolo[1,2-e]pyrido[2,3-b][1]oxa[4]thia[5,8]diazacyclotridecin-12(12aH)-one 16,16-dioxide:** Was synthesized using (1R,3S,5R)-2-((2-((5-((4,4-difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)sulfonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid in analogy to Example 1.80 to give the title compound. LC-MS (1): *t_R*= 1.02 min; [M+H]⁺: 483.9.
- Example 1.87 to Example 1.89** were synthesized using the appropriate amino acid and *tert*-butyl (5-((3-(chlorosulfonyl)-6-methylpyridin-2-yl)oxy)pentyl)(4,4-difluorocyclohexyl)carbamate in analogy to Example 1.80. LC-MS data of Example 1.87 to Example 1.89 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	<i>t_R</i> (min)	[M+H] ⁺
1.87	(12aS,14S)-11-(4,4-Difluorocyclohexyl)-14-fluoro-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	0.99	489.9
1.88	(12aS,14S)-11-(4,4-Difluorocyclohexyl)-14-methoxy-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.00	501.9

1.89	(12aS,14S)-11-(4,4-Difluorocyclohexyl)-3,14-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.05	485.9
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Example 1.90 (7R,12aS)-11-(4,4-Difluorocyclohexyl)-3,7-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide and Example 1.91 (7S,12aS)-11-(4,4-Difluorocyclohexyl)-3,7-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-

5 benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:

Methyl 2-methylhex-5-enoate: A soln. of $i\text{Pr}_2\text{NH}$ (1.2 mL, 8.35 mmol, 1.2 eq) in THF (10 mL) was cooled to 0°C. 1.6M $n\text{-BuLi}$ soln. in hexanes (5.2 mL, 8.35 mmol, 1.2 eq) was added dropwise at 0°C. The mixture was stirred for 30 min at 0°C and was cooled to -78°C. A soln. of 5-hexenoic acid methyl ester (1.0 mL, 6.96 mmol, 1 eq) in THF (10 mL) was added dropwise at -78°C. The mixture was stirred for 30 min at this temperature, and MeI (2.2 mL, 34.80 mmol, 5 eq) was added. After the addition, the mixture was stirred for 15 min at -78°C, then overnight while warming up slowly to rt. Aq. sat. NH_4Cl soln. and Et_2O were added. The org. layer was separated, dried over MgSO_4 , filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% Et_2O) to give the title compound.

Methyl 2-methyl-5-oxopentanoate: Methyl 2-methylhex-5-enoate (720 mg, 5.06 mmol, 1 eq) was dissolved in dioxane (42 mL) and H_2O (14 mL). 2,6-Lutidine (1.2 mL, 10.10 mmol, 2 eq), OsO_4 (2.5% in $t\text{BuOH}$, 64 μL , 0.20 mmol, 0.04 eq), and NaIO_4 (4.33 g, 20.30 mmol, 4 eq) were successively added. The resulting mixture was stirred overnight. H_2O and DCM were added. The layers were separated, and the aq. layer was extracted with DCM. The combined org. layers were washed with brine, dried over MgSO_4 , filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification.

Methyl 5-((4,4-difluorocyclohexyl)amino)-2-methylpentanoate: Was synthesized using methyl 2-methyl-5-oxopentanoate and 4,4-difluorocyclohexylamine hydrochloride in analogy to Example 1.1 to give the title compound. LC-MS (1): $t_R=0.58$; $[\text{M}+\text{H}]^+$: 264.3.

Methyl 5-((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)-2-methylpentanoate: Was synthesized using methyl methyl 5-((4,4-difluorocyclohexyl)amino)-2-methylpentanoate in analogy to Example 1.2 to give the title compound. LC-MS (1): $t_R=1.10$; $[\text{M}+\text{H}]^+$: 364.3.

tert-Butyl (4,4-difluorocyclohexyl)(5-hydroxy-4-methylpentyl)carbamate: A soln. of methyl 5-((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)-2-methylpentanoate (300 mg, 0.83 mmol, 1 eq) in THF (10 mL) was cooled to -78°C. 1M LiAlH_4 soln. in THF (0.91 mL, 0.91 mmol, 1.1 eq) was added dropwise at -78°C, and the mixture was stirred at this temperature for 30 min. The mixture was stirred overnight while warming up slowly to rt. MeOH (1 mL) was added. The resulting mixture was poured onto aq. sat. Rochelle salt soln., and was extracted with Et_2O . The combined org. layers were washed with H_2O and brine, dried over MgSO_4 , filtered, and the solvent

removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R=1.00; [M+H]⁺: 336.3.

tert-Butyl ((2-(((RS)-5-((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)-2-methylpentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using *tert*-butyl (4,4-difluorocyclohexyl)(5-hydroxy-4-methylpentyl)carbamate and *tert*-butyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R=1.27; [M+H]⁺: 658.9.

((2-(((RS)-5-((4,4-Difluorocyclohexyl)amino)-2-methylpentyl)oxy)-4-methylphenyl)sulfonyl)-L-proline: Was synthesized using *tert*-butyl ((2-(((RS)-5-((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)-2-methylpentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R=0.76 and 0.77; [M+H]⁺: 503.1.

(7R,12aS)-11-(4,4-Difluorocyclohexyl)-3,7-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide and (7S,12aS)-11-(4,4-difluorocyclohexyl)-3,7-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide: Were synthesized using ((2-(((RS)-5-((4,4-difluorocyclohexyl)amino)-2-methylpentyl)oxy)-4-methylphenyl)sulfonyl)-L-proline in analogy to Example 1.1. The stereoisomers were separated by basic prep. HPLC to give (7R,12aS)-11-(4,4-Difluorocyclohexyl)-3,7-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide (first eluting diastereomer) and (7S,12aS)-11-(4,4-difluorocyclohexyl)-3,7-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide (second eluting diastereomer). First eluting diastereomer: LC-MS (1): t_R= 1.08 min; [M+H]⁺: 485.1. Second eluting diastereomer: LC-MS (1): t_R= 1.09 min; [M+H]⁺: 485.1.

Example 1.92 to Example 1.93 were synthesized using the appropriate amino acid in analogy to Example 1.80. LC-MS data of Example 1.92 to Example 1.93 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R (min)	[M+H] ⁺
1.92	(12aS,13S,16R)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,13,14,15,16-decahydro-13,16-methanodipyrido[2,3-b:1',2'-e][1]oxa[4]thia[5,8]diazacyclotridecin-12(12aH)-one 18,18-dioxide	1.07	498.5
1.93	(S)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,13,14,15,16-decahydrodipyrido[2,3-b:1',2'-e][1]oxa[4]thia[5,8]diazacyclotridecin-12(12aH)-one 18,18-dioxide	1.09	485.9

Example 1.94 (S)-3-((S)-sec-Butyl)-5-(4,4-difluorocyclohexyl)-13-methyl-2,3,5,6,7,8,9,10-octahydro-4H-pyrido[2,3-b][1]oxa[4]thia[5,8]diazacyclotridecin-4-one 1,1-dioxide: Was synthesized using *tert*-butyl (2S,3S)-2-amino-3-methylpentanoate hydrochloride in analogy to Example 1.80 to give the title compound. LC-MS (1): t_R = 1.09 min; $[M+H]^+$: 487.9.

- 5 **Example 1.95** (6S,12aS)-11-(4,4-Difluorocyclohexyl)-6-isopropyl-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide or (6R,12aS)-11-(4,4-Difluorocyclohexyl)-6-isopropyl-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide : Was synthesized using 2M iPrMgCl soln. in THF in analogy to Example 1.82 to give the title compound. The diastereomeric mixture
10 stereoisomer was isolated by prep. chiral SFC (SFC 18 method) to give (6S,12aS)-11-(4,4-difluorocyclohexyl)-6-isopropyl-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one (6S,12aS)-11-(4,4-difluorocyclohexyl)-6-isopropyl-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one. The stereochemistry at the isopropyl stereocenter was attributed arbitrarily. First eluting diastereomer: LC-MS (1): t_R = 1.12 min; $[M+H]^+$: 513.2. Second eluting diastereomer: LC-MS (1): t_R = 1.12 min; $[M+H]^+$: 513.2.

- Example 1.96** (6R,12aS)-11-(4,4-Difluorocyclohexyl)-3-methyl-6-propyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide and
Example 1.97 (6S,12aS)-11-(4,4-Difluorocyclohexyl)-3-methyl-6-propyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide: Were
20 synthesized using 2M PrMgCl soln. in Et₂O in analogy to Example 1.82 to give the title compound. The stereoisomers were separated by basic prep. HPLC to give (6R,12aS)-11-(4,4-Difluorocyclohexyl)-3-methyl-6-propyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide (first eluting diastereomer) and (6S,12aS)-11-(4,4-difluorocyclohexyl)-3-methyl-6-propyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one
25 17,17-dioxide (second eluting diastereomer). The stereochemistry at the propyl stereocenter was attributed arbitrarily. First eluting diastereomer: LC-MS (1): t_R = 1.13 min; $[M+H]^+$: 513.2. Second eluting diastereomer: LC-MS (1): t_R = 1.13 min; $[M+H]^+$: 513.2.

- Example 1.98** (9aS,14aS*,17aS*)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,12,14a,15,16,17,17a-decahydrobenzo[b]cyclopenta[1]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10(11H)-one 5,5-dioxide:
30 ***tert*-Butyl ((2-(((1S*,2S*)-2-ethynylcyclopentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate**: *tert*-Butyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate (500 mg, 1.46 mmol, 1 eq), (1R*,2S*)-2-ethynylcyclopentan-1-ol (187 mg, 1.61 mmol, 1.1 eq) and PPh₃ polymer-bound, (100-200 mesh, ca. 1.6 mmol/g, 1.19 g, 1.90 mmol, 1.3 eq) were suspended in THF (14 mL) and stirred at 0°C. DIAD (0.39 mL, 1.90 mmol, 1.3 eq) was added dropwise and the reaction mixture was stirred at rt for 2h. The reaction mixture was diluted with EtOAc, filtered, and the solvent was

removed under reduced pressure. The residue was purified by FC (Hept to 20% EtOAc) to give the title compound. LC-MS (1): t_R = 1.11 min; $[M+H]^+$: 433.8.

tert-Butyl ((4-methyl-2-(((1S*,2S*)-2-vinylcyclopentyl)oxy)phenyl)sulfonyl)-L-prolinate: *tert*-Butyl ((2-(((1S*,2S*)-2-ethynylcyclopentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate (167 mg, 0.39 mmol, 1 eq) was dissolved in EtOH (4 mL) and Lindlar Catalyst (4 mg, 0.039 mmol, 0.1 eq) was added. The reaction mixture was stirred at rt for 18h under a H₂ atm. Lindlar Catalyst (41 mg, 0.39 mmol, 1 eq) was added again under and the reaction mixture was stirred at rt for 40h. The mixture was filtered through a pad of Celite, rinsed with DCM and the solvent was removed under reduced pressure. The residue was purified by acidic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.18 min; $[M+H]^+$: 436.2.

((4-Methyl-2-(((1S*,2S*)-2-vinylcyclopentyl)oxy)phenyl)sulfonyl)-L-proline: *tert*-Butyl ((4-methyl-2-(((1S*,2S*)-2-vinylcyclopentyl)oxy)phenyl)sulfonyl)-L-prolinate (107 mg, 0.246 mmol, 1 eq) was dissolved in 4M HCl soln. in dioxane (2.5 mL, 9.83 mmol, 40 eq) and the resulting soln. was stirred at rt for 16h. The solvent was removed under reduced pressure. The crude product was used without further purification. LC-MS (1): t_R = 0.96 min; $[M+H]^+$: 480.2.

(S)-N-Allyl-N-(4,4-difluorocyclohexyl)-1-((4-methyl-2-(((1S*,S*)-2-vinylcyclopentyl)oxy)phenyl)sulfonyl)pyrrolidine-2-carboxamide: ((4-Methyl-2-(((1S*,2S*)-2-vinylcyclopentyl)oxy)phenyl)sulfonyl)-L-proline (114 mg, 0.24 mmol, 1 eq) was dissolved in DMF (2 mL) then DIPEA (0.13 mL, 0.73 mmol, 3 eq) followed by HATU (124 mg, 0.32 mmol, 1.3 eq) were added. N-Allyl-4,4-difluorocyclohexan-1-amine (43 mg, 0.24 mmol, 1 eq) was immediately added and the soln. was stirred at rt for 2.5h. The reaction mixture was filtered and purified by acidic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.16 min; $[M+H]^+$: 537.2.

(9aS,14aS*,17aR*)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,12,14a,15,16,17,17a-decahydrobenzo[b]cyclopenta[l]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10(11H)-one 5,5-dioxide: (S)-N-Allyl-N-(4,4-difluorocyclohexyl)-1-((4-methyl-2-(((1S*,2S*)-2-vinylcyclopentyl)oxy)phenyl)sulfonyl)pyrrolidine-2-carboxamide (90 mg, 0.17 mmol, 1 eq) and Grubbs Catalyst, 2nd Generation (14 mg, 0.017 mmol, 0.1 eq) were dissolved in DCM (33 mL) and the reaction mixture was stirred at 40°C for 5h. The solvent was removed under reduced pressure and the residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.08 min; $[M+H]^+$: 509.2.

Example 1.99 (9aS,14aS,17aS)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,12,13,14,14a,15,16,17,17a-dodecahydrobenzo[b]cyclopenta[l]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10(11H)-one 5,5-dioxide and Example 1.100 (9aS,14aR,17aR)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,12,13,14,14a,15,16,17,17a-dodecahydrobenzo[b]cyclopenta[l]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10(11H)-one 5,5-dioxide: (9aS,14aSR,17aSR)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,12,14a,15,16,17,17a-decahydrobenzo[b]cyclopenta[l]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10(11H)-one 5,5-dioxide (35 mg, 0.07 mmol, 1 eq) was dissolved in MeOH (1 mL) and 10% Pd/C (7 mg, 0.007 mmol, 0.1 eq) was added. The reaction was stirred at rt for 1h under H₂ atm. The

mixture was filtered through a Celite pad, rinsed with DCM and the solvent was removed under reduced pressure. The residue was purified by acidic prep. HPLC to give (9aS,14aS,17aS)-11-(4,4-difluorocyclohexyl)-2-methyl-7,8,9,9a,12,13,14,14a,15,16,17,17a-dodecahydrobenzo[b]cyclopenta[l]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10(11H)-one 5,5-dioxide and (9aS,14aR,17aR)-11-(4,4-difluorocyclohexyl)-2-methyl-7,8,9,9a,12,13,14,14a,15,16,17,17a-dodecahydrobenzo[b]cyclopenta[l]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10(11H)-one 5,5-dioxide. The absolute stereochemistry at the cyclopentane ring was arbitrarily assigned. First eluting diastereomer: LC-MS (1): t_R = 1.10 min; $[M+H]^+$: 511.2. Second eluting diastereomer: LC-MS (1): t_R = 1.14 min; $[M+H]^+$: 511.2.

Example 1.101 (S)-3-Cyclopropyl-5-(4,4-difluorocyclohexyl)-13-methyl-2,3,5,6,7,8,9,10-octahydro-4H-pyrido[2,3-b][1]oxa[4]thia[5,8]diazacyclotridecin-4-one 1,1-dioxide: Was synthesized using (S)-methyl 2-amino-2-cyclopropylacetate hydrochloride and *tert*-butyl (5-((3-(chlorosulfonyl)-6-methylpyridin-2-yl)oxy)pentyl)(4,4-difluorocyclohexyl)carbamate in analogy to Example 1.86 to give the title compound. LC-MS (1): t_R = 1.04 min; $[M+H]^+$: 472.0.

Example 1.102 to Example 1.105 were synthesized using (S)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-ol, 2-bromo-5-methylphenol, and the appropriate amino acid in analogy to Example 1.64. LC-MS data of Example 1.102 to Example 1.105 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R (min)	$[M+H]^+$
1.102	(6R,12aS,13aR,14aR)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,13,13a,14,14a-decahydrobenzo[b]cyclopropa[4,5]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12(12aH)-one 16,16-dioxide	1.04	496.9
1.103	(6R,12aS,14S)-11-(4,4-Difluorocyclohexyl)-14-fluoro-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.06	503.0
1.104	(6R,12aS,14S)-11-(4,4-Difluorocyclohexyl)-14-methoxy-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.05	514.9
1.105	(6R,12aS,14S)-11-(4,4-Difluorocyclohexyl)-3,6,14-trimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.07	499.0

Example 1.107 (S)-3-Cyclopropyl-5-(4,4-difluorocyclohexyl)-2,13-dimethyl-2,3,5,6,7,8,9,10-octahydro-4H-pyrido[2,3-b][1]oxa[4]thia[5,8]diazacyclotridecin-4-one 1,1-dioxide: Was synthesized using (S)-3-cyclopropyl-5-(4,4-difluorocyclohexyl)-13-methyl-2,3,5,6,7,8,9,10-octahydro-4H-pyrido[2,3-b][1]oxa[4]thia[5,8]diazacyclotridecin-4-one 1,1-dioxide in analogy to Example 1.81 to give the title compound. LC-MS (1): t_R = 1.09 min; $[M+H]^+$: 486.0.

Example 1.108: (6R,12aS)-11-(6,6-Difluorobicyclo[3.1.0]hexan-3-yl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:

(RS)-6-((tert-Butyldimethylsilyl)oxy)hexan-2-ol: A soln. of *tert*-butyldimethylsilyl chloride (5.05 g, 33.50 mmol, 1 eq) in DCM (30 mL) was added dropwise during 1h to a stirred soln. of 1,5-hexanediol (4.0 g, 33.50 mmol, 1 eq) and imidazole (4.56 g, 67.00 mmol, 2 eq) in DCM (90 mL) at rt. After the addition, the reaction was stirred at rt for 1h. The mixture was washed with aq. 1M HCl soln. and H₂O. The org. layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The crude product was used without further purification. LC-MS (1): t_R= 0.53 min; [M+H]⁺: 233.3.

tert-Butyl ((2-(((RS)-6-((tert-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:
10 Was synthesized using (RS)-6-((tert-butyldimethylsilyl)oxy)hexan-2-ol and *tert*-butyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.14 to give the title compound. LC-MS (1): t_R= 1.34 min; [M+H]⁺: 556.3.

tert-Butyl ((2-(((R)-6-hydroxyhexan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate and tert-butyl ((2-(((S)-6-hydroxyhexan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using *tert*-butyl ((2-(((RS)-6-
15 ((tert-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.14. The diastereomeric mixture was purified by chiral SFC (SFC 11 Method) to give *tert*-butyl ((2-(((S)-6-hydroxyhexan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate (first eluting diastereomer) and *tert*-butyl ((2-(((R)-6-hydroxyhexan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate (second eluting diastereomer). First eluting diastereomer: LC-MS (1): t_R= 1.01 min; [M+H]⁺: 442.0. Second eluting diastereomer: LC-MS (1): t_R= 1.00 min; [M+H]⁺: 442.0.

tert-Butyl ((4-methyl-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate: Was synthesized using *tert*-
20 butyl ((2-(((R)-6-hydroxyhexan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.14 to give the title compound. LC-MS (1): t_R= 1.06 min; [M+H]⁺: 440.2.

tert-Butyl ((2-(((2R)-6-((6,6-difluorobicyclo[3.1.0]hexan-3-yl)amino)hexan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using *tert*-butyl ((4-methyl-2-(((R)-6-oxohexan-2-
25 yl)oxy)phenyl)sulfonyl)-L-prolinate and 6,6-difluorobicyclo[3.1.0]hexan-3-amine hydrochloride in analogy to Example 1.14 to give the title compound. LC-MS (1): t_R= 0.91 min; [M+H]⁺: 557.3.

((2-(((2R)-6-((6,6-Difluorobicyclo[3.1.0]hexan-3-yl)amino)hexan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-proline: Was synthesized using *tert*-butyl ((2-(((2R)-6-((6,6-difluorobicyclo[3.1.0]hexan-3-yl)amino)hexan-2-
30 yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to example 1.14 to give the title compound. LC-MS (1): t_R= 0.75 and 0.76 min; [M+H]⁺: 501.2.

(6R,12aS)-11-(6,6-Difluorobicyclo[3.1.0]hexan-3-yl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide: Was synthesized using ((2-
(((2R)-6-((6,6-difluorobicyclo[3.1.0]hexan-3-yl)amino)hexan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-proline in analogy to Example 1.14 to give the title compound. LC-MS (1): t_R= 1.06 min; [M+H]⁺: 483.2.

Example 1.109 to **Example 1.113** were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((4-methyl-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.14. LC-MS data of Example 1.109 to Example 1.113 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R (min)	[M+H] ⁺
1.109	(1R*,3S*)-3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.01	474.2
1.110	(6R,12aS)-11-((3RS)-Bicyclo[4.1.0]heptan-3-yl)-3,6-Dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.09	461.3
1.112	(6R,12aS)-3,6-Dimethyl-11-(spiro[2.5]octan-6-yl)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.13	475.3
1.113	(6R,12aS)-3,6-Dimethyl-11-(2-oxaspiro[3.5]nonan-7-yl)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	0.98	491.3

- 5 **Example 1.118** to **Example 1.123** were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.51. LC-MS data of Example 1.118 to Example 1.123 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R (min)	[M+H] ⁺
1.118	(6R,12aS)-11-(6,6-Difluorobicyclo[3.1.0]hexan-3-yl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.07	484.2
1.119	(1R*,3R*)-3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.00	475.3
1.120	(1R*,3R*)-3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.01	474.2
1.121	(6R,12aS)-11-((3RS)-Bicyclo[4.1.0]heptan-3-yl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.10	462.3

1.122	(6R,12aS)-3,6-Dimethyl-11-(spiro[2.5]octan-6-yl)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.24	476.2
1.123	(6R,12aS)-3,6-Dimethyl-11-(2-oxaspiro[3.5]nonan-7-yl)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	0.99	492.3

Example 1.124 (¹S,5'S,5³S)-8-(4,4-Difluorocyclohexyl)-3⁴-methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide and **Example 1.125** (¹S,5'R,5³R)-8-(4,4-Difluorocyclohexyl)-3⁴-methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide:

Methyl 2-((1R*,3R*)-3-hydroxycyclohexyl)acetate: At -75°C, 1M L-Selectride soln. in THF (41.2 mL, 41.20 mmol, 1.1 eq) was added dropwise to a stirred soln. of methyl 2-(3-oxocyclohexyl)acetate (6.38 g, 37.50 mmol, 1 eq) in THF (60 mL) while maintaining a temperature below -70°C during 40 min. The reaction was stirred for another 45 min at -78°C. Aq. sat. Rochelle's salt soln. was added and the reaction was allowed to warm up to 0°C and stirred vigorously for 10 min. The reaction was then extracted with EtOAc. The combined org. layers were dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 80% EtOAc) to give the title compound. ¹H NMR (500 MHz, CDCl₃) δ: 4.09 (t, J = 2.9 Hz, 1 H), 3.68 (s, 3 H), 2.25-2.30 (m, 1 H), 2.24-2.22 (m, 2 H), 1.67-1.80 (m, 4 H), 1.48-1.56 (m, 3 H), 1.34 (m, 1 H), 1.03-1.10 (m, 1 H).

(1R*,3S*)-3-(2-Hydroxyethyl)cyclohexan-1-ol: At rt, 1M LiAlH₄ soln. in THF (11.9 mL, 11.90 mmol, 1.1 eq) was added dropwise to a stirred soln. of methyl 2-((1R*,3R*)-3-hydroxycyclohexyl)acetate (1.87 g, 10.90 mmol, 1 eq) in THF (27 mL). The reaction was cooled with a H₂O bath and was stirred for another 15 min. The reaction was quenched by portionwise addition of Glauber's salt and stirred for 15 min. Aq. 2M HCl soln. was added and the mixture was stirred for another 10 min. H₂O was added and the reaction was extracted with DCM. The combined org. layers were dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification.

(1R*,3S*)-3-(2-((tert-Butyldiphenylsilyl)oxy)ethyl)cyclohexan-1-ol: At rt, 1M *tert*-butyl(chloro)diphenylsilane soln. in DCM (10.0 mL, 10.00 mmol, 1.05 eq) was added quickly to a stirred soln. of (1R*,3S*)-3-(2-hydroxyethyl)cyclohexan-1-ol (1.38 g, 9.57 mmol, 1 eq) and imidazole (1.30 g, 19.10 mmol, 2 eq) in DCM (48 mL). The resulting suspension was stirred at rt for 30 min.. Aq. 1M HCl soln. was added and the mixture was extracted with DCM. The aq. layer was washed with DCM. The combined org. layers were dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 30% EtOAc) to give the title compound. LC-MS (1): t_R = 1.24 min; [M+H]⁺: not seen. ¹H NMR (400 MHz, CDCl₃) δ: 7.68-7.70 (m, 4 H), 7.39-7.45 (m, 6 H), 4.01 (d, J = 2.5 Hz, 1 H), 3.72 (t, J = 6.8 Hz, 2 H), 1.87 (m, 1 H), 1.60-1.69 (m, 4 H), 1.41-1.53 (m, 6 H), 1.27-1.31 (m, 4 H), 1.07 (m, 9 H).

(RS)-2-Ethylhexyl 3-((2-hydroxy-4-methylphenyl)thio)propanoate: To a stirred soln. of 2-bromo-5-methylphenol (2.00 g, 10.50 mmol, 1 eq) in toluene (10 mL) was added $\text{Pd}_2(\text{dba})_3$ (495 mg, 0.52 mmol, 0.05 eq), Xantphos (638 mg, 1.05 mmol, 0.1 eq) and DIPEA (3.6 mL, 21.00 mmol, 2 eq) in sequence. After degassing the soln. with a N_2 stream, 2-ethylhexyl 3-mercaptopropionate (3.0 mL, 12.90 mmol, 1.2 eq) was added and the resulting mixture was stirred at 90°C overnight. After cooling to rt, the soln. was diluted with EtOAc and aq. 1M HCl soln. The solids were filtered off over a pad of Celite. The layers were separated and the org. layer was washed with brine, dried over MgSO_4 , filtered, and the solvent removed under reduced pressure. The crude residue was purified by FC (Hept to 2% EtOAc) to give the title compound. LC-MS (1): t_R = 1.16 min; $[\text{M}+\text{H}]^+$: 325.2.

(RS)-2-Ethylhexyl 3-((2-hydroxy-4-methylphenyl)sulfonyl)propanoate: Under N_2 atm and at 0°C, m-CPBA (2.29 g, 10.20 mmol, 2 eq) was added portionwise to a stirred soln. of (RS)-2-ethylhexyl 3-((2-hydroxy-4-methylphenyl)thio)propanoate (1.66 g, 5.10 mmol, 1 eq) in DCM (20 mL). The resulting suspension was vigorously stirred at rt for 1h15 min. The white solid was filtered off and washed with DCM. The filtrate was washed with aq. sat. NaHCO_3 soln. and separated through a phase-separator cartridge. The solvent was removed under reduced pressure. The crude product was used without further purification. LC-MS (1): t_R = 1.03 min; $[\text{M}+\text{H}]^+$: 357.0.

(RS)-2-Ethylhexyl 3-((2-(((1R*,3R*)-3-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)propanoate: (RS)-2-Ethylhexyl 3-((2-hydroxy-4-methylphenyl)sulfonyl)propanoate (826 mg, 2.32 mmol, 1 eq), (1R*,3S*)-3-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)cyclohexan-1-ol (975 mg, 2.55 mmol, 1.1 eq) and PPh_3 (830 mg, 3.01 mmol, 1.3 eq) were suspended in THF (23 mL) and stirred at 0°C under N_2 . DIAD (0.60 mL, 3.01 mmol, 1.3 eq) was added dropwise and the reaction mixture was stirred at rt for 1h30 min. The solvent was removed under reduced pressure and the residue was purified by FC (Hept to 10% EtOAc) to give the title compound. LC-MS (1): t_R = 1.42 min; $[\text{M}+\text{H}]^+$: 721.0.

tert-Butyl ((2-(((1R*,3R*)-3-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: A 0.5M NaOMe soln. in MeOH (0.52 mL, 0.26 mmol, 1 eq) was added at rt to the stirred soln. of (RS)-2-ethylhexyl 3-((2-(((1R*,3R*)-3-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)propanoate (187 mg, 0.26 mmol, 1 eq) in MeOH (3 mL) and THF (5 mL). The resulting soln. was stirred at rt for 30 min. The solvent was removed under reduced pressure. The residue was suspended in THF (5 mL) and NCS (39 mg, 0.29 mmol, 1.1 eq) was added at rt. The mixture was stirred at rt for 30 min. The mixture was cooled down to 0°C and a soln. of L-proline *t*-butyl ester (70 μL , 0.41 mmol, 1.6 eq) and TEA (0.18 mL, 1.29 mmol, 5 eq) in THF (3 mL) was added dropwise. Stirring was continued at rt for 5 min. The reaction mixture was partitioned between EtOAc and aq. 1M HCl soln.. The org. layer was washed with aq. sat. NaHCO_3 soln. and brine, then dried over MgSO_4 , filtered, and the solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 1.39 min; $[\text{M}+\text{H}]^+$: 706.0.

tert-Butyl ((2-(((1R*,3R*)-3-(2-hydroxyethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: 1M TBAF soln. in THF (0.38 mL, 0.38 mmol, 1.55 eq) was added dropwise at rt, to the stirred soln. of tert-butyl ((2-(((1R*,3R*)-3-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate (181 mg, 0.25 mmol, 1

eq) in THF (3 mL). The soln. was stirred at rt for 1h. The reaction mixture was partitioned between EtOAc and aq. sat. NaHCO₃ soln. The org. layer was washed with brine, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R = 1.03 min; [M+H]⁺: 467.8.

- 5 **tert-Butyl ((4-methyl-2-(((1R*,3S*)-3-(2-oxoethyl)cyclohexyl)oxy)phenyl)sulfonyl)-L-prolinate:** *tert*-Butyl ((2-(((1R*,3R*)-3-(2-hydroxyethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate (610 mg, 1.30 mmol, 1 eq) was dissolved in DCM (13 mL). DIPEA (0.90 mL, 5.24 mmol, 4 eq) was added and the mixture was cooled to 0°C. Sulfur trioxide pyridine complex (449 mg, 2.74 mmol, 2.1 eq) in DMSO (2 mL) was added dropwise and the reaction mixture was stirred at rt for 1h. The reaction mixture was partitioned between aq. 1M HCl soln. and DCM. The layers were separated and the org. layer was washed with brine, dried with MgSO₄, filtered, and the solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 1.09 min; [M+H]⁺: 466.1.

- tert-Butyl ((2-(((1R*,3R*)-3-(2-((4,4-difluorocyclohexyl)amino)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((4-methyl-2-(((1R*,3S*)-3-(2-oxoethyl)cyclohexyl)oxy)phenyl)sulfonyl)-L-prolinate and 4,4-difluorocyclohexan-1-amine hydrochloride in analogy to Example 1.7 to give the title compound. LC-MS (1): t_R = 0.92 and 0.93 min; [M+H]⁺: 585.4.

- ((2-(((1R*,3R*)-3-(2-((4,4-Difluorocyclohexyl)amino)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-proline:** Was synthesized using *tert*-butyl ((2-(((1R*,3R*)-3-(2-((4,4-difluorocyclohexyl)amino)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.7 to give the title compound. LC-MS (1): t_R = 0.77 and 0.79 min; [M+H]⁺: 529.4.

- (12S,51S,53S)-8-(4,4-Difluorocyclohexyl)-34-methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide and (12S,51R,53R)-8-(4,4-difluorocyclohexyl)-34-methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide:** Were synthesized using ((2-(((1R*,3R*)-3-(2-((4,4-difluorocyclohexyl)amino)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-proline in analogy to Example 1.7. The soln. was purified by acidic prep. HPLC to give (1²S,5¹S,5³S)-8-(4,4-difluorocyclohexyl)-34-methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide and (1²S,5¹S,5³S)-8-(4,4-difluorocyclohexyl)-34-methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide. The absolute stereochemistry at the cyclohexyl ring was attributed arbitrarily. First eluting diastereomer: LC-MS (1): t_R = 1.10 min; [M+H]⁺: 511.2. Second eluting diastereomer: LC-MS (1): t_R = 1.13 min; [M+H]⁺: 511.2.

Example 1.126 (6R,12aS)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrazino[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide and Example 1.127 (6S,12aS)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrazino[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:

(RS)-3-((6-((*tert*-Butyldimethylsilyl)oxy)hexan-2-yl)oxy)-2-chloro-5-methylpyrazine: (RS)-6-((*tert*-Butyldimethylsilyl)oxy)hexan-2-ol (406 mg, 1.75 mmol, 1 eq) was dissolved in THF (8 mL) and the mixture was cooled to 0°C. NaH (ca 60 % dispersion in mineral oil, 80 mg, 1.92 mmol, 1.1 eq) was added and the mixture was stirred for 15 min at 0°C. A soln. of 2,3-dichloro-5-methylpyrazine (300 mg, 1.75 mmol, 1 eq) in THF (0.5 mL) was added. The mixture was stirred at 0°C for 3h, then overnight while slowly warming to rt. H₂O was added, and the mixture was diluted with EtOAc. The layers were separated, the org. layer was washed with H₂O and brine, dried with MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by acidic prep. HPLC to give the title compound. LC-MS (1): t_R= 1.31 min; [M+H]⁺: 359.3.

(RS)-2-(Benzylthio)-3-((6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-5-methylpyrazine: A suspension of NaH (ca 60 % dispersion in mineral oil, 87.1 mg, 2.27 mmol, 1.6 eq) in DMF (10 mL) was cooled to 0°C. Benzyl mercaptan (0.25 mL, 2.13 mmol, 1.5 eq) was added dropwise, and the mixture was stirred for 5 min at 0°C. A soln. of (RS)-3-((6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-2-chloro-5-methylpyrazine (510 mg, 1.42 mmol, 1 eq) in DMF (5 mL) was added dropwise over 5 min, and the mixture was stirred at 0°C for 2h. H₂O was added, and the mixture was diluted with EtOAc. The layers were separated, the org. layer was washed with H₂O and brine, dried with MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by acidic prep. HPLC to give the title compound. LC-MS (1): t_R= 1.38 min; [M+H]⁺: 447.2.

(RS)-3-((6-((*tert*-Butyldimethylsilyl)oxy)hexan-2-yl)oxy)-5-methylpyrazine-2-sulfonyl chloride: To a soln. of (RS)-2-(benzylthio)-3-((6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-5-methylpyrazine (487 mg, 1.09 mmol, 1 eq) in dioxane (6 mL) was added H₂O (40 µL, 2.18 mmol, 2 eq). DCDMH (430 mg, 2.18 mmol, 2 eq) was added, and the mixture was stirred for 20 min. Aq. sat. NaHCO₃ soln. was added, and the mixture was extracted with EtOAc. The org. layer was washed with H₂O, dried with MgSO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R= 1.29 min; [M+H]⁺: 423.2.

***tert*-Butyl ((3-(((RS)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-5-methylpyrazin-2-yl)sulfonyl)-L-prolinate:** A soln. of (RS)-3-((6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-5-methylpyrazine-2-sulfonyl chloride (461 mg, 1.09 mmol, 1 eq) in DCM (3 mL) was cooled to 0°C. DIPEA (0.75 mL, 4.36 mmol, 4 eq) was added, followed by a soln. of L-proline *tert*-butyl ester (0.38 mL, 2.18 mmol, 2 eq) in DCM (2.5 mL). The resulting mixture was stirred at 0°C for 30 min. Aq. sat. NaHCO₃ soln. was added, and the mixture was diluted with DCM. The layers were separated, the org. layer was washed with H₂O, dried with MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R= 1.32 min; [M+H]⁺: 558.3.

***tert*-Butyl ((3-(((RS)-6-hydroxyhexan-2-yl)oxy)-5-methylpyrazin-2-yl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((3-(((RS)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-5-methylpyrazin-2-yl)sulfonyl)-L-prolinate in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R= 0.96 min; [M+H]⁺: 444.0.

***tert*-Butyl ((3-(((RS)-6-((4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-5-methylpyrazin-2-yl)sulfonyl)-L-prolinate:** (Cyanomethyl)trimethylphosphonium iodide (Phanstiel IV, *J. Med. Chem.* 2004, 47, 6055) (197 mg, 0.81

mmol, 2.4 eq) was added to a soln. of *tert*-butyl ((3-(((*RS*)-6-((4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-5-methylpyrazin-2-yl)sulfonyl)-L-proline (150 mg, 0.34 mmol, 1 eq), 4,4-difluorocyclohexan-1-amine (113 mg, 0.81 mmol, 2.4 eq) and DIPEA (0.15 mL, 0.88 mmol, 2.6 eq) in MeCN (3 mL). The mixture was stirred under reflux overnight. The mixture was allowed to cool to rt and aq. sat. NaHCO₃ soln. was added. The mixture was diluted with DCM. The layers were separated, the org. layer was washed with H₂O, dried with MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (MeOH to 90% EtOAc (0.5% aq. conc. NH₃))) and by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 0.87 min; [M+H]⁺: 561.2.

((3-(((*RS*)-6-((4,4-Difluorocyclohexyl)amino)hexan-2-yl)oxy)-5-methylpyrazin-2-yl)sulfonyl)-L-proline: Was synthesized using *tert*-butyl ((3-(((*RS*)-6-((4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-5-methylpyrazin-2-yl)sulfonyl)-L-proline in analogy to Example 1.9 to give the title compound. LC-MS (1): t_R = 0.70 and 0.72 min; [M+H]⁺: 505.2.

(6*R*,12*aS*)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12*a*,13,14,15-decahydro-12*H*-pyrazino[2,3-*b*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide and (6*S*,12*aS*)-11-(4,4-difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12*a*,13,14,15-decahydro-12*H*-pyrazino[2,3-*b*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide: Were synthesized using ((3-(((*RS*)-6-((4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-5-methylpyrazin-2-yl)sulfonyl)-L-proline in analogy to Example 1.1. The stereoisomers were separated by prep. chiral SFC (SFC 15 method) to give (6*R*,12*aS*)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12*a*,13,14,15-decahydro-12*H*-pyrazino[2,3-*b*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide and (6*S*,12*aS*)-11-(4,4-difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12*a*,13,14,15-decahydro-12*H*-pyrazino[2,3-*b*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide. The absolute stereochemistry of the Me was arbitrarily attributed. First eluting diastereomer: LC-MS (1): t_R = 0.99 min; [M+H]⁺: 486.9. Second eluting diastereomer: LC-MS (1): t_R = 0.99 min; [M+H]⁺: 486.9.

Example 1.128 (6*R*,12*aS*,12*bS*,13*aR*)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12*b*,13,13*a*,14-decahydrobenzo[*b*]cyclopropa[3,4]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-12(12*aH*)-one 16,16-dioxide: Was synthesized using (*S*)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-ol and *rel*-(1*R*,2*R*,5*S*)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid in analogy to Example 1.64 to give (6*R*,12*aS**,12*bS**,13*aR**)-11-(4,4-difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12*b*,13,13*a*,14-decahydrobenzo[*b*]cyclopropa[3,4]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-12(12*aH*)-one 16,16-dioxide. The stereoisomers were separated by prep. chiral SFC separation (SFC 3 method) to give (6*R*,12*aS*,12*bS*,13*aR*)-11-(4,4-difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12*b*,13,13*a*,14-decahydrobenzo[*b*]cyclopropa[3,4]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-12(12*aH*)-one 16,16-dioxide (first eluting diastereomer) and (6*R*,12*aR*,12*bR*,13*aS*)-11-(4,4-difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12*b*,13,13*a*,14-decahydrobenzo[*b*]cyclopropa[3,4]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-12(12*aH*)-one 16,16-dioxide (second eluting diastereomer). First eluting

diastereomer: LC-MS (1): t_R = 1.07 min; $[M+H]^+$: 496.9. Second eluting diastereomer: LC-MS (1): t_R = 1.08 min; $[M+H]^+$: 496.9.

Example 1.129 (11aR,13aS,16aS)-15-(4,4-Difluorocyclohexyl)-8-methyl-1,2,3,11a,12,13,13a,14,15,16a-decahydrobenzo[b]cyclobuta[j]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-16(11H)-one 5,5-dioxide
 5 or (11aS,13aR,16aS)-15-(4,4-Difluorocyclohexyl)-8-methyl-1,2,3,11a,12,13,13a,14,15,16a-decahydrobenzo[b]cyclobuta[j]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-16(11H)-one 5,5-dioxide :

((1R*,2S*)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)cyclobutyl)methanol: A soln. of *tert*-butyldimethylsilyl chloride (370 mg, 2.45 mmol, 1 eq) in DCM (3 mL) was added over 5 min at 0°C to a stirred soln. of cis-bishydroxymethylcyclobutane (300 mg, 2.45 mmol, 1 eq) and imidazole (334 mg, 4.91 mmol, 2 eq) in DCM (9 mL).
 10 The reaction was stirred at 0°C for 1h. The mixture was washed with aq. 1M HCl soln. and H₂O. The org. layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 1.06 min; $[M+H]^+$: 231.3.

Methyl ((2-(((1R*,2S*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclobutyl)methoxy)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using ((1R*,2S*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclobutyl)methanol and methyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate in
 15 analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 1.28 min; $[M+H]^+$: 512.2.

Methyl ((2-(((1R*,2S*)-2-(hydroxymethyl)cyclobutyl)methoxy)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using methyl ((2-(((1R*,2S*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclobutyl)methoxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 0.88 and
 20 0.90 min; $[M+H]^+$: 398.2.

Methyl ((2-(((1R*,2S*)-2-formylcyclobutyl)methoxy)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using methyl ((2-(((1R*,2S*)-2-(hydroxymethyl)cyclobutyl)methoxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.7 to give the title compound. LC-MS (1): t_R = 0.92 min; $[M+H]^+$: 396.0.

Methyl ((2-(((1R*,2S*)-2-(((4,4-difluorocyclohexyl)amino)methyl)cyclobutyl)methoxy)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using methyl ((2-(((1R*,2S*)-2-formylcyclobutyl)methoxy)-4-methylphenyl)sulfonyl)-L-prolinate and 4,4-difluorocyclohexan-1-amine in analogy to Example 1.1 to give the title
 25 compound. LC-MS (1): t_R = 0.83 min; $[M+H]^+$: 514.9.

proline: Was synthesized using methyl ((2-(((1R*,2S*)-2-(((4,4-difluorocyclohexyl)amino)methyl)cyclobutyl)methoxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example
 30 1.8 to give the title compound. LC-MS (1): t_R = 0.75 and 0.76 min; $[M+H]^+$: 501.2.

(11aR,13aS,16aS)-15-(4,4-Difluorocyclohexyl)-8-methyl-1,2,3,11a,12,13,13a,14,15,16a-decahydrobenzo[b]cyclobuta[j]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-16(11H)-one 5,5-dioxide

and (11aS,13aR,16aS)-15-(4,4-Difluorocyclohexyl)-8-methyl-1,2,3,11a,12,13,13a,14,15,16a-decahydrobenzo[b]cyclobuta[j]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-16(11H)-one 5,5-dioxide :
 ((1R*,2S*)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)cyclobutyl)methanol: Was synthesized using ((2-(((1R*,2S*)-2-(((4,4-difluorocyclohexyl)amino)methyl)cyclobutyl)methoxy)-4-methylphenyl)sulfonyl)-L-proline in analogy to Example 1.1. The mixture of diastereomers was separated by prep. chiral SFC (SFC 16 method) to give (11aR,13aS,16aS)-15-(4,4-difluorocyclohexyl)-8-methyl-1,2,3,11a,12,13,13a,14,15,16a-decahydrobenzo[b]cyclobuta[j]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-16(11H)-one 5,5-dioxide and (11aS,13aR,16aS)-15-(4,4-difluorocyclohexyl)-8-methyl-1,2,3,11a,12,13,13a,14,15,16a-decahydrobenzo[b]cyclobuta[j]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-16(11H)-one 5,5-dioxide. The absolute stereochemistry at the cyclobutyl ring was attributed arbitrarily. First eluting diastereomer: LC-MS (1): t_R = 1.05 min; $[M+H]^+$: 483.1. Second eluting diastereomer: LC-MS (1): t_R = 1.07 min; $[M+H]^+$: 483.1.

Example 1.130 (S)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,10,11,12a,13,14,15-octahydrospiro[benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecine-8,1'-cyclopropan]-12(9H)-one 17,17-dioxide:

***tert*-Butyl ((2-(2-(1-(2-hydroxyethyl)cyclopropyl)ethoxy)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using 2,2'-(cyclopropane-1,1-diyl)bis(ethan-1-ol) and *tert*-butyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 1.02 min; $[M+H]^+$: 454.2.

***tert*-Butyl ((4-methyl-2-(2-(1-(2-oxoethyl)cyclopropyl)ethoxy)phenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((2-(2-(1-(2-hydroxyethyl)cyclopropyl)ethoxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.7 to give the title compound. LC-MS (1): t_R = 1.07 min; $[M+H]^+$: 452.0.

***tert*-Butyl ((2-(2-(1-(2-((4,4-difluorocyclohexyl)amino)ethyl)cyclopropyl)ethoxy)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((4-methyl-2-(2-(1-(2-oxoethyl)cyclopropyl)ethoxy)phenyl)sulfonyl)-L-prolinate and 4,4-difluorocyclohexylamine hydrochloride in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 0.93 min; $[M+H]^+$: 571.0.

((2-(2-(1-(2-((4,4-Difluorocyclohexyl)amino)ethyl)cyclopropyl)ethoxy)-4-methylphenyl)sulfonyl)-L-proline: Was synthesized using *tert*-butyl ((2-(2-(1-(2-((4,4-difluorocyclohexyl)amino)ethyl)cyclopropyl)ethoxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.8 to give the title compound. LC-MS (1): t_R = 0.78 min; $[M+H]^+$: 514.9.

(S)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,10,11,12a,13,14,15-octahydrospiro[benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecine-8,1'-cyclopropan]-12(9H)-one 17,17-dioxide: Was synthesized using ((2-(2-(1-(2-((4,4-difluorocyclohexyl)amino)ethyl)cyclopropyl)ethoxy)-4-methylphenyl)sulfonyl)-L-proline in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 1.06 min; $[M+H]^+$: 497.2.

Example 1.131 (S)-11-(4,4-Difluorocyclohexyl)-3,8,8-trimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide: Was synthesized using *tert*-

butyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate, 5-((tert-butyldimethylsilyl)oxy)-3,3-dimethylpentan-1-ol, and 4,4-difluorocyclohexylamine hydrochloride in analogy to Example 1.130 to give the title compound. LC-MS (1): t_R = 1.08 min; $[M+H]^+$: 499.1.

Example 1.132 (12aR,13S)-11-(4,4-Difluorocyclohexyl)-13-fluoro-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:

(2R,3S)-1-((2-((5-((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)sulfonyl)-3-fluoropyrrolidine-2-carboxylic acid: Was synthesized using *tert*-butyl (5-(2-(chlorosulfonyl)-5-methylphenoxy)pentyl)(4,4-difluorocyclohexyl)carbamate and (2R,3S)-3-fluoropyrrolidine-2-carboxylic acid in analogy to Example 1.80 to give the title compound. LC-MS (1): t_R = 1.09 min; $[M+H]^+$: 607.9.

(2R,3S)-1-((2-((5-((4,4-Difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)sulfonyl)-3-fluoropyrrolidine-2-carboxylic acid: (2R,3S)-1-((2-((5-((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)sulfonyl)-3-fluoropyrrolidine-2-carboxylic acid (10 mg, 0.02 mmol, 1 eq) was dissolved in 4M HCl soln. in dioxane (40 μ L, 0.17 mmol, 10 eq). The reaction mixture was stirred at rt for 1.5h. The solvent was removed under reduced pressure to give the title compound. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.73 min; $[M+H]^+$: 507.9.

(12aR,13S)-11-(4,4-Difluorocyclohexyl)-13-fluoro-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide: Was synthesized using (2R,3S)-1-((2-((5-((4,4-difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)sulfonyl)-3-fluoropyrrolidine-2-carboxylic acid in analogy to Example 1.80 to give the title compound. LC-MS (1): t_R = 1.04 min; $[M+H]^+$: 489.9.

Example 1.133 (S)-5-(4,4-Difluorocyclohexyl)-13-methyl-1,2,3,3a,6,7,8,9-octahydro-11H-benzo[c]pyrrolo[1,2-f][1]oxa[5]thia[6,9]diazacyclotridecin-4(5H)-one 16,16-dioxide:

2-(Benzylthio)-5-methylbenzoic acid: A pre-dried vial was charged with 2-bromo-5-methylbenzoic acid (500 mg, 2.28 mmol, 1 eq), benzyl mercaptan (0.40 mL, 3.42 mmol, 1.5 eq), $Pd_2(dba)_3$ (108 mg, 0.11 mmol, 0.05 eq), xantphos (132 mg, 0.23 mmol, 0.1 eq), DIPEA (0.78 mL, 4.56 mmol, 2 eq), and dioxane (9 mL). The vial was sealed, evacuated, purged with argon, and stirred at 100°C for 4h. The mixture was allowed to cool to rt and was diluted with aq. 1M HCl soln. and EtOAc. The layers were separated and the org. layer was washed with H₂O and brine. The org. layer was dried with MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 40% EtOAc) to give the title compound. LC-MS (1): t_R = 0.94 min; $[M+H]^+$: 259.0.

(2-(Benzylthio)-5-methylphenyl)methanol: 1M LiAlH₄ soln. in THF (3.40 mL, 3.42 mmol, 1.5 eq) was added dropwise over 10 min to a soln. of 2-(benzylthio)-5-methylbenzoic acid (589 mg, 2.28 mmol, 1 eq) in THF (23 mL) at 0°C. The mixture was stirred overnight while being allowed to warm up to rt. The mixture was poured onto a mixture of aq. 5% H₂SO₄ soln. and ice, and was diluted with EtOAc. The layers were separated, the org. layer was washed with H₂O and brine, dried with MgSO₄, filtered, and the solvent removed under reduced pressure. The

residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R = 0.95 min; $[M+H]^+$: not seen.

Benzyl(2-(bromomethyl)-4-methylphenyl)sulfane: CBr_4 (316 mg, 0.94 mmol, 1.2 eq) and PPh_3 (251 mg, 0.94 mmol, 1.2 eq) were added to a soln. of (2-(benzylthio)-5-methylphenyl)methanol (209 mg, 0.79 mmol, 1 eq) in DCM (8 mL) at 0°C, and the mixture was stirred overnight under N_2 atm, while warming up to rt. The solvent was removed under reduced pressure, and the crude was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 1.13 min; $[M+H]^+$: not seen.

4-((4,4-Difluorocyclohexyl)amino)butan-1-ol: To a soln. of 4,4-difluorocyclohexanone (200 mg, 1.46 mmol, 1 eq) and 4-amino-1-butanol (131 mg, 1.46 mmol, 1 eq) in THF (6 mL) were added AcOH (84 μ L, 1.46 mmol, 1 eq) and $NaBH(OAc)_3$ (489 mg, 2.19 mmol, 1.5 eq). The mixture was stirred at rt overnight. Aq. sat. $NaHCO_3$ soln. was added, and the mixture was diluted with DCM. The layers were separated and the aq. layer was extracted with DCM/MeOH (ca. 7/3). The combined org. layers were dried with $MgSO_4$, filtered, and the solvent removed under reduced pressure to give the crude title compound. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.42 min; $[M+H]^+$: 209.3.

tert-Butyl (4,4-difluorocyclohexyl)(4-hydroxybutyl)carbamate: To a soln. of 4-((4,4-difluorocyclohexyl)amino)butan-1-ol (290 mg, 1.40 mmol, 1 eq) in DCM (6 mL) at 0°C were added Et_3N (0.29 mL, 2.10 mmol, 1.5 eq) and Boc_2O (0.39 mL, 1.68 mmol, 1.2 eq). The mixture was stirred overnight while being allowed to warm up to rt. The mixture was quenched with aq. sat. NH_4Cl soln. and diluted with DCM. The layers were separated, the org. layer was washed with H_2O , dried with $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 75% EtOAc) to give the title compound. LC-MS (1): t_R = 0.91 min; $[M+H]^+$: 308.2.

tert-Butyl (4-((2-(benzylthio)-5-methylbenzyl)oxy)butyl)(4,4-difluorocyclohexyl)carbamate: A pre-dried flask was charged with tert-butyl (4,4-difluorocyclohexyl)(4-hydroxybutyl)carbamate (174 mg, 0.57 mmol, 1.1 eq) and DMF (4 mL), and the mixture was cooled to 0°C. NaH (ca 60 % dispersion in mineral oil, 24 mg, 0.62 mmol, 1.2 eq) was added, and the mixture was stirred at 0°C for 15 min. A soln of benzyl(2-(bromomethyl)-4-methylphenyl)sulfane (158 mg, 0.51 mmol, 1 eq) in DMF (1 mL) was added dropwise, and the mixture was stirred at rt overnight. Aq. sat. $NaHCO_3$ soln. was added, and the mixture was diluted with EtOAc. The layers were separated, the org. layer was washed with H_2O and brine, dried with $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 20% EtOAc) to give the title compound. LC-MS (1): t_R = 1.29 min; $[M+H]^+$: 534.3.

tert-Butyl (4-((2-(chlorosulfonyl)-5-methylbenzyl)oxy)butyl)(4,4-difluorocyclohexyl)carbamate: To a soln. of tert-butyl (4-((2-(benzylthio)-5-methylbenzyl)oxy)butyl)(4,4-difluorocyclohexyl)carbamate (122 mg, 0.23 mmol, 1 eq) in dioxane (3 mL) was added H_2O (83 μ L, 0.46 mmol, 2 eq). DCDMH (90 mg, 0.46 mmol, 2 eq) was added, and the mixture was stirred at rt for 15 min. Aq. sat. $NaHCO_3$ soln. was added, and the mixture was diluted with DCM. The org. layer was separated through a phase separator, washed with H_2O , and the solvent removed under

reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 1.24 min; $[M+H]^+$: 510.2.

- tert-Butyl ((2-((4-((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)butoxy)methyl)-4-methylphenyl)sulfonyl)-L-prolinate:** To a soln. of *tert*-butyl (4-((2-(chlorosulfonyl)-5-methylbenzyl)oxy)butyl)(4,4-difluorocyclohexyl)carbamate (117 mg, 0.23 mmol, 1 eq) in DCM (3 mL) at rt were added DIPEA (0.16 mL, 0.92 mmol, 4 eq) and L-proline *t*-butyl ester (79 μ L, 0.46 mmol, 2 eq). The mixture was stirred at rt for 1h. The mixture was quenched with aq. 1M HCl soln., and diluted with DCM. The layers were separated through a phase separator, the org. layer was washed with H₂O, dried over MgSO₄, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 40% EtOAc) to give the title compound. LC-MS (1): t_R = 1.25 min; $[M+H]^+$: 645.0.
- 5 **(2-((4-((4,4-Difluorocyclohexyl)amino)butoxy)methyl)-4-methylphenyl)sulfonyl)-L-proline:** TFA (0.34 mL, 4.50 mmol, 20 eq) was added to a soln. of *tert*-butyl ((2-((4-((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)butoxy)methyl)-4-methylphenyl)sulfonyl)-L-prolinate (145 mg, 0.23 mmol, 1 eq) in DCM (3 mL), and the mixture was stirred at rt overnight. The solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.72 min; $[M+H]^+$: 489.0.
- 10 **(S)-5-(4,4-Difluorocyclohexyl)-13-methyl-1,2,3,3a,6,7,8,9-octahydro-11H-benzo[c]pyrrolo[1,2-f][1]oxa[5]thia[6,9]diazacyclotridecin-4(5H)-one 16,16-dioxide:** Was synthesized using ((2-((4-((4,4-difluorocyclohexyl)amino)butoxy)methyl)-4-methylphenyl)sulfonyl)-L-proline in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 1.04 min; $[M+H]^+$: 471.2.
- 15

- Example 1.134 (6R,12aS)-11-((1R,4S)-4-Hydroxy-4-methylcyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:** Was synthesized using *trans*-4-amino-1-methylcyclohexanol hydrochloride and *tert*-butyl ((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.51 to give the title compound. LC-MS (1): t_R = 0.91 min; $[M+H]^+$: 480.2.
- 20

- Example 1.135 (S)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,11,12,13,14-octahydro-10H-dibenzo[b,l]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide:**
- 25

- tert-Butyl (3-(2-(benzyloxy)phenyl)prop-2-yn-1-yl)carbamate:** 1-(Benzyloxy)-2-iodobenzene (500 mg, 1.58 mmol, 1 eq), N-Boc-propargylamine (263 mg, 1.66 mmol, 1.05 eq), and TEA (2.0 mL, 13.90 mmol, 8.8 eq) were suspended in DMF (22 mL). Pd(PPh₃)₂Cl₂ (56 mg, 0.08 mmol, 0.05 eq) and CuI (61 mg, 0.32 mmol, 0.2 eq) were added and the reaction mixture was degassed for 5 min under a N₂ stream and stirred at 80°C for 2h. The reaction mixture was partitioned between EtOAc and H₂O. The org. layer was washed with brine, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 15% EtOAc) to give the title compound. LC-MS (1): t_R = 1.08 min; $[M+H]^+$: 282.2.
- 30

3-(2-(Benzyloxy)phenyl)prop-2-yn-1-amine hydrochloride: 4M HCl soln. in dioxane (3.3 mL, 13.30 mmol, 15 eq) was added dropwise to a soln. of *tert*-butyl (3-(2-(benzyloxy)phenyl)prop-2-yn-1-yl)carbamate (300 mg, 0.89

mmol, 1 eq) in DCM (9 mL) at 0°C and the reaction mixture was stirred at rt for 1h15 min. The solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.69 min; $[M+H]^+$: 238.3.

- 5 **N-(3-(2-(Benzyloxy)phenyl)prop-2-yn-1-yl)-4,4-difluorocyclohexan-1-amine:** 3-(2-(Benzyloxy)phenyl)prop-2-yn-1-amine hydrochloride (243 mg, 0.89 mmol, 1 eq) was dissolved in THF (3 mL). 4,4-difluorocyclohexanone (136 mg, 0.98 mmol, 1.1 eq) in THF (3 mL) was added at rt followed by AcOH (0.10 mL, 1.78 mmol, 2 eq). The mixture was stirred for 2h, then $\text{NaBH}(\text{OAc})_3$ (475 mg, 2.13 mmol, 2.4 eq) was added and the mixture was stirred at rt for 5h. $\text{NaBH}(\text{OAc})_3$ (475 mg, 2.13 mmol, 2.4 eq) was added again and the mixture was stirred at rt overnight. The reaction mixture was poured onto aq. sat. NaHCO_3 soln. and extracted with EtOAc. The org. layer was washed with
- 10 H_2O , dried over MgSO_4 , filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 20% EtOAc) to give the title compound. LC-MS (1): t_R = 0.82 min; $[M+H]^+$: 356.3.

- tert*-Butyl (3-(2-(benzyloxy)phenyl)prop-2-yn-1-yl)(4,4-difluorocyclohexyl)carbamate:** To a soln. of N-(3-(2-(benzyloxy)phenyl)prop-2-yn-1-yl)-4,4-difluorocyclohexan-1-amine (128 mg, 0.36 mmol, 1 eq) and TEA (0.12 mL, 0.90 mmol, 2.5 eq) in DCM (4 mL) was added at rt a soln. of Boc_2O (0.12 mL, 0.54 mmol, 1.5 eq) in DCM (4 mL).
- 15 The resulting mixture was stirred at rt for 5h. The reaction mixture was partitioned between DCM and brine. The org. layer was washed with brine, separated through a phase-separator and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 5% EtOAc) to give the title compound. LC-MS (1): t_R = 1.19 min; $[M+H]^+$: 456.0.

- tert*-Butyl (4,4-difluorocyclohexyl)(3-(2-hydroxyphenyl)propyl)carbamate:** *tert*-Butyl (3-(2-(benzyloxy)phenyl)prop-2-yn-1-yl)(4,4-difluorocyclohexyl)carbamate (154 mg, 0.34 mmol, 1 eq) was dissolved in MeOH (4 mL) and Pd/C (10% Pd, ca. 50% H_2O , 36 mg, 0.03 mmol, 0.1 eq) was added. The reaction mixture was stirred at rt under a H_2 atm for 2h. The reaction mixture was filtered through a PTFE 0.45 μm filter, rinsed with MeOH and the solvent was removed under reduced pressure. The crude material was used in the next step without further purification. LC-MS (1): t_R = 1.06 min; $[M+H]^+$: 370.2.

- 25 **((2-Bromo-4-methylphenyl)sulfonyl)-L-proline:** L-proline (1.91 g, 16.50 mmol, 1 eq) was dissolved in aq. 2M NaOH soln. (33.0 mL, 65.90 mmol, 4 eq). The soln. was cooled to 0°C and 2-bromo-4-methyl-benzenesulfonyl chloride (4.67 g, 16.50 mmol, 1 eq) in THF (25 mL) was added dropwise at 0°C. The reaction mixture was stirred at rt for 3h. The solvent was removed under reduced pressure and the residue was acidified with aq. 1M HCl soln. to pH: 1-2 and extracted with EtOAc. The org. layer was dried over MgSO_4 , filtered, and the solvent removed under
- 30 reduced pressure to give the title compound. LC-MS (1): t_R = 0.79 min; $[M+H]^+$: 348.1.

- ((2-(2-(3-((*tert*-Butoxycarbonyl)(4,4-difluorocyclohexyl)amino)propyl)phenoxy)-4-methylphenyl)sulfonyl)-L-proline:** ((2-Bromo-4-methylphenyl)sulfonyl)-L-proline (82 mg, 0.24 mmol, 1 eq), *tert*-butyl (4,4-difluorocyclohexyl)(3-(2-hydroxyphenyl)propyl)carbamate (87 mg, 0.24 mmol, 1 eq), CuI (14 mg, 0.07 mmol, 0.3 eq) and Cs_2CO_3 (78 mg, 0.24 mmol, 1 eq) were dissolved in toluene (3 mL) and the mixture was stirred at 115°C
- 35 for 1h. ((2-Bromo-4-methylphenyl)sulfonyl)-L-proline (82 mg, 0.24 mmol, 1 eq), CuI (14 mg, 0.07 mmol, 0.3 eq)

and Cs₂CO₃ (78 mg, 0.24 mmol, 1 eq) were added again and the reaction mixture was stirred at 115°C for 2h. The reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was purified by acidic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.13 min; [M+H]⁺: 637.3.

((2-(2-(3-((4,4-Difluorocyclohexyl)amino)propyl)phenoxy)-4-methylphenyl)sulfonyl)-L-proline

- 5 **hydrochloride:** 4M HCl soln. in dioxane (0.52 mL, 2.06 mmol, 30 eq) was added to a soln. of ((2-(2-(3-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)propyl)phenoxy)-4-methylphenyl)sulfonyl)-L-proline (44 mg, 0.069 mmol, 1 eq) in DCM (1 mL) and the reaction mixture was stirred at rt for 1h. The solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.80 min; [M+H]⁺: 536.9.

- 10 **(S)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,11,12,13,14-octahydro-10H-dibenzo[b,l]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide:** HATU (105 mg, 0.28 mmol, 4 eq) and DIPEA (94 µL, 0.55 mmol, 8 eq) were dissolved in DMF (18 mL) and the reaction mixture was stirred at 50°C. ((2-(2-(3-((4,4-Difluorocyclohexyl)amino)propyl)phenoxy)-4-methylphenyl)sulfonyl)-L-proline hydrochloride (39 mg, 0.069 mmol, 1 eq) was dissolved in DMF (6 mL) and the soln. was added *via* syringe pump over 2h to the reaction mixture. After
15 the addition, the reaction mixture was stirred at rt for 16h. The solvent was removed under reduced pressure and purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.07 min; [M+H]⁺: 518.9.

Example 1.136 (S)-11-(4,4-Difluorocyclohexyl)-4-fluoro-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:

- Benzyl (3-fluoro-2-methoxy-4-methylphenyl)sulfane:** 1-Bromo-3-fluoro-2-methoxy-4-methylbenzene (500 mg, 2.21 mmol, 1 eq) was dissolved in dioxane (5 mL). Then XantPhos Pd G2 (98 mg, 0.11 mmol, 0.05 eq), DIPEA (0.74 mL, 4.32 mmol, 1.95 eq) and benzyl mercaptan (0.29 mL, 2.44 mmol, 1.1 eq) were added under argon atm. The reaction mixture was stirred at 100°C for 2h. The solvent was removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 1.09 min; [M+H]⁺: not seen.

- 3-Fluoro-2-methoxy-4-methylbenzenesulfonyl chloride:** Benzyl (3-fluoro-2-methoxy-4-methylphenyl)sulfane (420 mg, 1.60 mmol, 1 eq) was dissolved in dioxane (6 mL). Then H₂O (58 µL, 3.20 mmol, 2 eq) and DCDMH (644 mg, 3.20 mmol, 2 eq) were added. The reaction mixture was stirred at rt for 30 min. The reaction mixture was diluted with EtOAc and washed with aq. sat. NaHCO₃ soln. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure to give the title compound. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.98 min; [M+H]⁺: not seen.

- 30 ***tert*-Butyl ((3-fluoro-2-methoxy-4-methylphenyl)sulfonyl)-L-prolinate:** *tert*-Butyl L-prolinate (0.10 mL, 0.58 mmol, 1 eq), DMAP (7 mg, 0.06 mmol, 0.1 eq) and DIPEA (3.00 mL, 57.40 mmol, 98 eq) were dissolved in MeCN (3 mL). 3-Fluoro-2-methoxy-4-methylbenzenesulfonyl chloride (300 mg, 1.75 mmol, 1 eq) in MeCN (2 mL) was added. The reaction mixture was stirred at rt for 3h. The reaction mixture was diluted with DCM and washed with aq. sat. NaHCO₃ soln. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced

pressure. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R = 1.05 min; $[M+H]^+$: 374.2.

((3-Fluoro-2-hydroxy-4-methylphenyl)sulfonyl)-L-proline: *tert*-Butyl ((3-fluoro-2-methoxy-4-methylphenyl)sulfonyl)-L-prolinate (450 mg, 1.21 mmol, 1 eq) was dissolved in DCM (5 mL). Then 1M BBr₃ soln. in DCM (1.80 mL, 1.81 mmol, 1.5 eq) was added. The reaction mixture was stirred at rt for 30 min. The reaction mixture was quenched with aq. sat. NaHCO₃ soln. and extracted with DCM. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.71 min; $[M+H]^+$: 304.1.

Methyl ((3-fluoro-2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate: ((3-Fluoro-2-hydroxy-4-methylphenyl)sulfonyl)-L-proline (345 mg, 1.14 mmol, 1 eq) was dissolved in MeOH (3 mL). Then H₂SO₄ (1 mol%) was added. The reaction mixture was stirred at reflux for 4h. The reaction mixture was cooled to rt and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R = 0.81 min; $[M+H]^+$: 318.1.

Methyl ((2-((5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-3-fluoro-4-methylphenyl)sulfonyl)-L-prolinate: Methyl ((3-fluoro-2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate (345 mg, 1.09 mmol, 1 eq) was dissolved in THF (5 mL). The soln. was cooled to 0°C. Then *tert*-butyl (4,4-difluorocyclohexyl)(5-hydroxypentyl)carbamate (419 mg, 1.30 mmol, 1.2 eq) and PPh₃ (347 mg, 1.30 mmol, 1.2 eq) were added, followed by DEAD (~40% in toluene, 1.1 mL, 2.18 mmol, 2 eq). After the addition, the mixture was allowed to warm up to rt and stirred overnight. The solvent was removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 1.21 min; $[M+H]^+$: 621.2.

((2-((5-((4,4-Difluorocyclohexyl)amino)pentyl)oxy)-3-fluoro-4-methylphenyl)sulfonyl)-L-proline: Methyl ((2-((5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-3-fluoro-4-methylphenyl)sulfonyl)-L-prolinate (250 mg, 0.40 mmol, 1 eq) was dissolved in THF (2 mL). Aq. 1M LiOH soln. (8.1 mL, 8.10 mmol, 20 eq) was added. The reaction mixture was stirred at rt for 3h. The solvent was removed under reduced pressure. The residue was dissolved in dioxane (2 mL) and 4M HCl soln. in dioxane (0.25 mL, 0.81 mmol, 2 eq) was added. The reaction mixture was stirred at rt for 2h. The solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 1.15 min; $[M+H]^+$: 606.9.

(S)-11-(4,4-Difluorocyclohexyl)-4-fluoro-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide: ((2-((5-((4,4-Difluorocyclohexyl)amino)pentyl)oxy)-3-fluoro-4-methylphenyl)sulfonyl)-L-proline (200 mg, 0.40 mmol, 1 eq) was dissolved in DCM (5 mL). This soln. was added dropwise to a soln. of DIPEA (0.54 mL, 3.16 mmol, 8 eq) and HATU (180 mg, 0.48 mmol, 1.2 eq) in DCM (25 mL). The reaction mixture was stirred at rt for 72h. The solvent was removed under reduced pressure. The residue was purified by acidic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.10 min; $[M+H]^+$: 488.9.

Example 1.137 to Example 1.141 were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.51. LC-MS data of Example 1.137 to Example 1.141 are listed in the table below.

Ex. N°	Name	t _R (min)	[M+H] ⁺	LC-MS
1.137	(6R,12aS)-3,6-Dimethyl-11-((RS)-1-methyl-2-oxopiperidin-4-yl)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	0.84	479.2	2
1.138	(6R,12aS)-11-((1s,4R)-4-Hydroxycyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	0.89	466.4	2
1.139	(6R,12aS)-11-((1R*,2S*)-2-Hydroxycyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.03	466.0	2
1.140	(6R,12aS)-11-((1R*,2R*)-2-Hydroxycyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	0.94 and 0.95	466.2	1
1.141	(1R,4s)-4-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.00	475.3	1

5 Example 1.142 (1R,3R)-3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile:

***tert*-Butyl ((1*R*,3*R*)-3-carbamoylcyclohexyl)carbamate:** (1*R*,3*R*)-3-(*tert*-Butoxycarbonylamino)cyclohexanecarboxylic acid (5.00 g, 20.60 mmol, 1 eq) was suspended in THF (33 mL) and the suspension was cooled to -10°C. TEA (5.70 mL, 41.10 mmol, 2 eq) and ethyl chloroformate (2.30 mL, 23.60 mmol, 1.15 eq) were added slowly. The cooling bath was removed upon addition and the reaction was stirred at rt for 3h. The reaction mixture was cooled again to -10°C and aq. 25% NH₄OH soln. (19.20 mL, 123.00 mmol, 6 eq) was added slowly. The reaction mixture was stirred at rt overnight. The solvent was removed under reduced

pressure and the mixture was diluted with cold H₂O. The precipitate was collected by filtration and washed with H₂O. The solvent was removed until the product precipitated and the suspension was placed in an ice bath for 1h. The mixture was filtered and the solid was washed with cold H₂O. The combined solids were dried under reduced pressure at 50°C to give the title compound. LC-MS (1): t_R= 0.65 min; [M+H]⁺: 243.1.

- 5 ***tert*-Butyl ((1R,3R)-3-cyanocyclohexyl)carbamate:** *tert*-Butyl ((1R,3R)-3-carbamoylcyclohexyl)carbamate (3.76 g, 15.50 mmol, 1 eq) was suspended in DCM (40 mL). The suspension was cooled to -10°C. Then TEA (4.30 mL, 31.00 mmol, 2 eq) and trifluoroacetic anhydride (2.30 mL, 16.50 mmol, 1 eq) were added. The reaction mixture was stirred at -10°C for 3h and then diluted with H₂O and DCM. The org. layer was washed with H₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R= 0.83 min; [M+H]⁺: 225.2.

- 10 **(1R,3R)-3-Aminocyclohexane-1-carbonitrile 2,2,2-trifluoroacetate:** To a soln. of *tert*-butyl ((1R,3R)-3-cyanocyclohexyl)carbamate (2.67 g, 11.90 mmol, 1 eq) in DCM (38 mL) was added TFA (11.0 mL, 143.00 mmol, 12 eq) and the mixture was stirred at rt for 1.5h. The solvent was removed under reduced pressure and then azeotroped with toluene and dried under reduced pressure again. The residue was diluted in Me-THF and the resulting suspension was sonicated and filtered. The white solid was dried under reduced pressure to give the title compound.

- 15 **(1R,3R)-3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile:** Was synthesized using (1R,3R)-3-aminocyclohexane-1-carbonitrile 2,2,2-trifluoroacetate and *tert*-butyl ((4-methyl-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.7 to give the title compound. LC-MS (1): t_R= 0.99 min; [M+H]⁺: 474.1.

Example 1.143 (1S,3S)-3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile:

- tert*-Butyl ((1S,3S)-3-carbamoylcyclohexyl)carbamate:** (1S,3S)-3-(*tert*-Butoxycarbonylamino)cyclohexanecarboxylic acid (5.00 g, 20.60 mmol, 1 eq) was suspended in THF (33 mL) and the suspension was cooled to -10°C. TEA (5.7 mL, 41.10 mmol, 2 eq) and ethyl chloroformate (2.3 mL, 23.60 mmol, 1.15 eq) were added slowly. The reaction mixture was warmed to rt and further stirred at rt for 3h. The reaction mixture was cooled again to -10°C and aq. 25% NH₄OH soln. (19.2 mL, 123.00 mmol, 6 eq) was added slowly. The reaction mixture was stirred at rt overnight. The solvent was removed under reduced pressure and the mixture was diluted with cold H₂O. The precipitate was collected by filtration and washed with H₂O. The solvent was removed until the product precipitated and the suspension was placed in an ice bath for 1h. The mixture was filtered and the solid was washed with cold H₂O. The combined solids were dried under reduced pressure at 50°C to give the title compound. LC-MS (1): t_R= 0.65 min; [M+H]⁺: 243.2.

- 35 ***tert*-Butyl ((1S,3S)-3-cyanocyclohexyl)carbamate:** *tert*-Butyl ((1S,3S)-3-carbamoylcyclohexyl)carbamate (4.22 g, 17.40 mmol, 1 eq) was suspended in DCM (30 mL). The suspension was cooled to -10°C. TEA (4.8 mL, 34.80

mmol, 2 eq) and trifluoroacetic anhydride (2.6 mL, 18.50 mmol, 1 eq) were slowly added. The reaction mixture was stirred at -10°C for 3h and then diluted with H₂O and DCM. The org. layer was washed with H₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R= 0.83 min; [M+H]⁺: 225.2.

- 5 **(1S,3S)-3-Aminocyclohexane-1-carbonitrile 2,2,2-trifluoroacetate:** To a soln. of *tert*-butyl ((1S,3S)-3-cyanocyclohexyl)carbamate (3.43 g, 15.30 mmol, 1 eq) in DCM (50 mL) was added TFA (14.2 mL, 143.00 mmol, 12 eq) and the mixture was stirred at rt for 1.5h. The solvent was removed under reduced pressure and then azeotroped with toluene and dried under reduced pressure. The residue was diluted in Me-THF and the resulting suspension was sonicated and filtered. The white solid was dried under reduced pressure to give the title compound.
- 10 compound.

(1S,3S)-3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-

benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile: Was synthesized using (1S,3S)-3-aminocyclohexane-1-carbonitrile 2,2,2-trifluoroacetate and *tert*-butyl ((4-methyl-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.7 to give the title compound. LC-MS (1): t_R= 0.99 min; [M+H]⁺: 474.0.

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Example 1.144 to Example 1.145 were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.51. LC-MS data of Example 1.44 to Example 1.145 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R (min)	[M+H] ⁺
1.144	(1R,3R)-3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.00	475.4
1.145	(1S,3S)-3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.01	475.4

- 20 **Example 1.146 (S)-11-(4,4-Difluorocyclohexyl)-1-fluoro-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:**

2-(Benzylthio)-3-fluoro-5-methylphenol: 3-Fluoro-2-iodo-5-methylphenol (100 mg, 0.40 mmol, 1 eq) was dissolved in dioxane (1.5 mL). Then XantPhos Pd G2 (40 mg, 0.05 mmol, 0.05 eq), DIPEA (0.13 mL, 0.77 mmol, 1.95 eq) and benzyl mercaptan (61 µL, 0.52 mmol, 1.3 eq) were added under argon atm. The reaction mixture was stirred at 100°C overnight. The solvent was removed under reduced pressure. The residue was purified by FC (Hept to 20% EtOAc) to give the title compound. LC-MS (1): t_R= 0.98 min; [M+H]⁺: not seen.

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***tert*-Butyl (5-(2-(benzylthio)-3-fluoro-5-methylphenoxy)pentyl)(4,4-difluorocyclohexyl)carbamate:** 2-(Benzylthio)-3-fluoro-5-methylphenol (95 mg, 0.38 mmol, 1 eq) was dissolved in THF (6 mL). The soln. was cooled to 0°C. Then *tert*-butyl (4,4-difluorocyclohexyl)(5-hydroxypentyl)carbamate (160 mg, 0.50 mmol, 1.3 eq) and PPh₃ (122 mg, 0.46 mmol, 1.2 eq) were added followed by DEAD (~40% in toluene, 0.28 mL, 0.57 mmol, 1.5 eq). After the addition, the mixture was allowed to warm up to rt and stirred overnight. Aq. 1M HCl soln. was added and the aq. layer was extracted with DCM. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 20% EtOAc) to give the title compound. LC-MS (1): t_R= 1.31 min; [M+H]⁺: 552.0.

***tert*-Butyl (5-(2-(chlorosulfonyl)-3-fluoro-5-methylphenoxy)pentyl)(4,4-difluorocyclohexyl)carbamate:** *tert*-Butyl (5-(2-(benzylthio)-3-fluoro-5-methylphenoxy)pentyl)(4,4-difluorocyclohexyl)carbamate (100 mg, 0.18 mmol, 1 eq) was dissolved in dioxane (2.5 mL). Then H₂O (7 µL, 0.36 mmol, 2 eq) and DCDMH (73 mg, 0.36 mmol, 2 eq) were added. The reaction mixture was stirred at rt for 10 min. The reaction mixture was diluted with DCM and washed with aq. sat. NaHCO₃ soln. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure to give the title compound. The crude product was used in the next step without further purification. LC-MS (1): t_R= 1.24 min; [M+H]⁺: 527.9.

***tert*-Butyl ((2-((5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-6-fluoro-4-methylphenyl)sulfonyl)-L-prolinate:** *tert*-Butyl L-prolinate (34 µL, 0.20 mmol, 1.1 eq), DMAP (14 µL, 0.054 mmol, 0.3 eq) and DIPEA (92 µL, 0.54 mmol, 3 eq) were dissolved in MeCN (1 mL). Then *tert*-butyl (5-(2-(chlorosulfonyl)-3-fluoro-5-methylphenoxy)pentyl)(4,4-difluorocyclohexyl)carbamate (95 mg, 0.18 mmol, 1 eq) in MeCN (1 mL) was added. The reaction mixture was stirred at rt overnight. The solvent was removed under reduced pressure. The residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R= 1.25 min; [M+H]⁺: 663.0.

((2-((5-((4,4-Difluorocyclohexyl)amino)pentyl)oxy)-6-fluoro-4-methylphenyl)sulfonyl)-L-proline: *tert*-Butyl ((2-((5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-6-fluoro-4-methylphenyl)sulfonyl)-L-prolinate (97 mg, 0.14 mmol, 1 eq) was dissolved in DCM (1 mL). Then TFA (0.80 mL, 10.00 mmol, 70 eq) was added. The reaction mixture was stirred at rt overnight. The solvent was removed under reduced pressure to give the title compound. The crude product was used in the next step without further purification. LC-MS (1): t_R= 0.74 min; [M+H]⁺: 506.9.

(S)-11-(4,4-Difluorocyclohexyl)-1-fluoro-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide: ((2-((5-((4,4-Difluorocyclohexyl)amino)pentyl)oxy)-6-fluoro-4-methylphenyl)sulfonyl)-L-proline (71 mg, 0.14 mmol, 1 eq) was dissolved in DCM (4 mL). This soln. was added dropwise to a soln. of DIPEA (0.12 mL, 0.70 mmol, 5 eq) and HATU (160 mg, 0.42 mmol, 3 eq) in DCM (15 mL). The reaction mixture was stirred at rt overnight. The solvent was removed under reduced pressure. The residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R= 1.02 min; [M+H]⁺: 488.9.

Example 1.149 (1²S,6¹R,6³R)-8-(4,4-Difluorocyclohexyl)-3⁴-methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-6(1,3)-cyclobutanacyclononaphan-9-one 2,2-dioxide:

5 **((1s,3s)-3-(((tert-Butyldimethylsilyl)oxy)methyl)cyclobutyl)methanol**: A soln. of *tert*-butyldimethylsilyl chloride (389 mg, 2.58 mmol, 1 eq) in DCM (5 mL) was added over 5 min into a soln. of *cis*-3-(hydroxymethyl)cyclobutylmethanol (300 mg, 2.58 mmol, 1 eq) and imidazole (352 mg, 5.17 mmol, 2 eq) in DCM (10 mL) at 0°C. The mixture was stirred at 0°C for 1.5h, and aq. 1M HCl soln. and DCM were added. The layers were separated, the org. layer was washed with H₂O, dried with MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R= 1.00 min; [M+H]⁺: 231.2.

10 **Methyl ((2-(((1s,3R)-3-(((tert-butyldimethylsilyl)oxy)methyl)cyclobutyl)methoxy)-4-methylphenyl)sulfonyl)-L-prolinate**: Was synthesized using ((1s,3s)-3-(((tert-butyldimethylsilyl)oxy)methyl)cyclobutyl)methanol and methyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R= 1.25 min; [M+H]⁺: 512.2.

15 **Methyl ((2-(((1s,3R)-3-(hydroxymethyl)cyclobutyl)methoxy)-4-methylphenyl)sulfonyl)-L-prolinate**: Was synthesized using methyl ((2-(((1s,3R)-3-(((tert-butyldimethylsilyl)oxy)methyl)cyclobutyl)methoxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R= 0.88 min; [M+H]⁺: 398.0.

20 **Methyl ((2-(((1s,3R)-3-formylcyclobutyl)methoxy)-4-methylphenyl)sulfonyl)-L-prolinate**: Methyl ((2-(((1s,3R)-3-(hydroxymethyl)cyclobutyl)methoxy)-4-methylphenyl)sulfonyl)-L-prolinate (190 mg, 0.48 mmol, 1 eq) was dissolved in DCM (15 mL). DIPEA (0.33 mL, 1.92 mmol, 4 eq) was added and the mixture was cooled to -10°C. Sulfur trioxide pyridine complex (165 mg, 1.00 mmol, 2.1 eq) in DMSO (1 mL) was added dropwise over a period of 10 min. After addition, the mixture was stirred at -10°C for 30 min, and was allowed to warm up to rt. After 1.5h, the mixture was partitioned between H₂O and DCM. The layers were separated, and the aq. layer was extracted with DCM. The combined org. layers were washed with brine, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R= 0.92 min; [M+H]⁺: 396.0.

30 **Methyl ((2-(((1s,3R)-3-(((4,4-difluorocyclohexyl)amino)methyl)cyclobutyl)methoxy)-4-methylphenyl)sulfonyl)-L-prolinate**: Was synthesized using methyl ((2-(((1s,3R)-3-formylcyclobutyl)methoxy)-4-methylphenyl)sulfonyl)-L-prolinate and 4,4-difluorocyclohexan-1-amine in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R= 0.81 min; [M+H]⁺: 514.9.

((2-(((1s,3R)-3-(((4,4-Difluorocyclohexyl)amino)methyl)cyclobutyl)methoxy)-4-methylphenyl)sulfonyl)-L-proline: Was synthesized using methyl ((2-(((1s,3R)-3-(((4,4-difluorocyclohexyl)amino)methyl)cyclobutyl)methoxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.8 to give the title compound. LC-MS (1): t_R= 0.74 min; [M+H]⁺: 501.2.

(1²S,6¹R,6³R)-8-(4,4-Difluorocyclohexyl)-3⁴-methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-6(1,3)-cyclobutanacyclononaphan-9-one 2,2-dioxide: Was synthesized using methyl ((2-(((1s,3R)-3-(((4,4-difluorocyclohexyl)amino)methyl)cyclobutyl)methoxy)-4-methylphenyl)sulfonyl)-L-proline in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R= 1.06 min; [M+H]⁺: 483.1.

- 5 **Example 1.150 (1aR,12aS,15aR)-14-(4,4-Difluorocyclohexyl)-5-methyl-1,1a,2,10,11,12,12a,14,15,15a-decahydro-13H-benzo[b]cyclopropa[j]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-13-one 8,8-dioxide or (1aS,12aS,15aS)-14-(4,4-Difluorocyclohexyl)-5-methyl-1,1a,2,10,11,12,12a,14,15,15a-decahydro-13H-benzo[b]cyclopropa[j]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-13-one 8,8-dioxide** : Was prepared using trans-[2-(hydroxymethyl)cyclopropyl]methanol in analogy to Example 1.149. The stereoisomers were
 10 separated by acidic prep. HPLC to give (1aR,12aS,15aR)-14-(4,4-difluorocyclohexyl)-5-methyl-1,1a,2,10,11,12,12a,14,15,15a-decahydro-13H-benzo[b]cyclopropa[j]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-13-one 8,8-dioxide and (1aS,12aS,15aS)-14-(4,4-difluorocyclohexyl)-5-methyl-1,1a,2,10,11,12,12a,14,15,15a-decahydro-13H-benzo[b]cyclopropa[j]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-13-one 8,8-dioxide The stereochemistry at the cyclopropyl ring was
 15 attributed arbitrarily. First eluting diastereomer: LC-MS (1): t_R= 0.99 min; [M+H]⁺: 469.2. Second eluting diastereomer: LC-MS (1): t_R= 1.00 min; [M+H]⁺: 469.2.

- Example 1.162 (1R,4s)-4-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile:** Was synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((4-methyl-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.14. LC-MS data of Example 1.162 to Example 1.164
 20 are listed in the table below. LC-MS (1): t_R= 0.99 min; [M+H]⁺: 474.4.**Example 1.166 (1²S,5¹R,5³S)-8-(4,4-difluorocyclohexyl)-34-methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide and Example 1.167 (1²S,5¹S,5³R)-8-(4,4-Difluorocyclohexyl)-34-methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide:**
 25

- tert*-Butyl (2-((1R*,3R*)-3-hydroxycyclohexyl)ethyl)carbamate:** *tert*-Butyl N-[2-(3-oxocyclohexyl)ethyl]carbamate (1.00 g, 3.94 mmol, 1 eq) was dissolved in MeOH (40 mL) and the soln. was stirred at 0°C. NaBH₄ (194 mg, 5.12 mmol, 1.3 eq) was added and the reaction mixture was stirred at 0°C for 30 min. The reaction mixture was partitioned between EtOAc and aq. sat. NH₄Cl soln. . The org. layer was washed with brine,
 30 dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 40% EtOAc) to give the title compound. LC-MS (1): t_R= 0.79 min; [M+H]⁺: 244.3.

- (1R*,3R*)-3-(2-((*tert*-Butoxycarbonyl)amino)ethyl)cyclohexyl methanesulfonate:** *tert*-Butyl (2-((1R*,3R*)-3-hydroxycyclohexyl)ethyl)carbamate (356 mg, 1.46 mmol, 1 eq) was dissolved in DCM (14 mL) and was stirred at 0°C. TEA (0.61 mL, 4.39 mmol, 3 eq) and methanesulfonyl chloride (0.34 mL, 4.38 mmol, 3 eq) were added and
 35 the reaction mixture was stirred at 0°C for 10 min. The reaction mixture was partitioned between aq. sat. NaHCO₃

soln. and DCM. The org. layer was separated through a phase separator cartridge and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 25% EtOAc) to give the title compound. LC-MS (1): t_R = 0.92 min; $[M+H]^+$: 322.1.

Methyl ((2-(((1R*,3S*)-3-(2-((*tert*-butoxycarbonyl)amino)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: Methyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate (471 mg, 1.57 mmol, 1.1 eq) was dissolved in MeCN (14 mL). Cs_2CO_3 (942 mg, 2.86 mmol, 2 eq) and (1R*,3R*)-3-(2-((*tert*-butoxycarbonyl)amino)ethyl)cyclohexyl methanesulfonate (460 mg, 1.43 mmol, 1 eq) were added. The reaction mixture was stirred at 90°C for 6 days. The reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was purified by FC (Hep to 35% EtOAc) to give the title compound. LC-MS (1): t_R = 1.12 min; $[M+H]^+$: 525.3.

Methyl ((2-(((1R*,3S*)-3-(2-aminoethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate hydrochloride: 4M HCl soln. in dioxane (2.1 mL, 8.35 mmol, 30 eq) was added to a soln. of methyl ((2-(((1R*,3S*)-3-(2-((*tert*-butoxycarbonyl)amino)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate (146 mg, 0.28 mmol, 1 eq) in DCM (3 mL) and the reaction mixture was stirred at rt for 1h. The solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.73 and 0.74 min; $[M+H]^+$: 425.2.

Methyl ((2-(((1R*,3S*)-3-(2-((4,4-difluorocyclohexyl)amino)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate hydrochloride: Methyl ((2-(((1R*,3S*)-3-(2-aminoethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate hydrochloride (123 mg, 0.22 mmol, 1 eq) and 4,4-difluorocyclohexanone (117 mg, 0.87 mmol, 4 eq) were dissolved in THF (2 mL) and MeOH (2 mL). AcOH (50 μ L, 0.87 mmol, 4 eq) was added and the reaction mixture was stirred at 70°C for 1h. $NaBH(OAc)_3$ (243 mg, 1.09 mmol, 5 eq) was added and the reaction mixture was stirred at 70°C for 20h. 4,4-Difluorocyclohexanone (117 mg, 0.87 mmol, 4 eq) and AcOH (50 μ L, 0.87 mmol, 4 eq) were added again and the reaction mixture was stirred at 70°C for 1h. $NaBH(OAc)_3$ (243 mg, 1.09 mmol, 5 eq) was added again and the reaction mixture was stirred at 70°C for 2h. The reaction mixture was poured onto aq. sat. $NaHCO_3$ soln. and extracted with EtOAc. The org. layer was washed with brine, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 0.86 min; $[M+H]^+$: 543.3.

Lithium ((2-(((1R*,3S*)-3-(2-((4,4-difluorocyclohexyl)amino)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: Methyl ((2-(((1R*,3S*)-3-(2-((4,4-difluorocyclohexyl)amino)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate hydrochloride (47 mg, 0.09 mmol, 1 eq) was suspended in H_2O (0.5 mL) and THF (1 mL). LiOH (18 mg, 0.42 mmol, 4.8 eq) was added. The reaction mixture was stirred at rt for 21h. The solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.79 and 0.80 min; $[M+H]^+$: 529.2.

(1²S,5¹R,5³S)-8-(4,4-Difluorocyclohexyl)-34-methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide and (1²S,5¹S,5³R)-8-(4,4-Difluorocyclohexyl)-34-

methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide: Were synthesized using lithium ((2-(((1R*,3S*)-3-(2-((4,4-difluorocyclohexyl)amino)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.7. The residue was purified by basic prep. HPLC to give (1²S,5¹R,5³S)-8-(4,4-difluorocyclohexyl)-34-methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide and (1²S,5¹S,5³R)-8-(4,4-difluorocyclohexyl)-34-methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide. The stereochemistry at the cyclohexyl ring was arbitrarily assigned. First eluting diastereomer: LC-MS (1): t_R = 1.11 min; [M+H]⁺: 511.3. Second eluting diastereomer: LC-MS (1): t_R = 1.17; [M+H]⁺: 511.3.

Example 1.168 (8R,12aS)-11-(4,4-Difluorocyclohexyl)-8-ethyl-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:

tert-Butyl ((2-(((R)-3-ethyl-5-hydroxypentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using tert-butyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate and 3-ethylpentane-1,5-diol in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 1.05 min; [M+H]⁺: 456.3.

tert-Butyl ((2-(((R)-3-ethyl-5-oxopentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using tert-butyl ((2-(((R)-3-ethyl-5-hydroxypentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.7 to give the title compound. LC-MS (1): t_R = 1.11 min; [M+H]⁺: 454.2.

tert-Butyl ((2-(((R)-5-((4,4-difluorocyclohexyl)amino)-3-ethylpentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using tert-butyl ((2-(((R)-3-ethyl-5-oxopentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate and 4,4-difluorocyclohexyl-1-amine in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 0.94 min; [M+H]⁺: 573.4.

((2-(((R)-5-((4,4-Difluorocyclohexyl)amino)-3-ethylpentyl)oxy)-4-methylphenyl)sulfonyl)-L-proline: Was synthesized using tert-butyl ((2-(((R)-5-((4,4-difluorocyclohexyl)amino)-3-ethylpentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.9 to give the title compound. LC-MS (1): t_R = 0.79 min; [M+H]⁺: 517.0.

(8R,12aS)-11-(4,4-Difluorocyclohexyl)-8-ethyl-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide: Was synthesized using ((2-(((R)-5-((4,4-difluorocyclohexyl)amino)-3-ethylpentyl)oxy)-4-methylphenyl)sulfonyl)-L-proline in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 1.09 min; [M+H]⁺: 499.2.

Example 1.173 (6R,12aS)-11-((1R,2S)-2-Methoxycyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide: was synthesized using the appropriate amine or amine salt derivative and tert-butyl ((4-methyl-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.1. LC-MS (1): t_R = 1.11 min; [M+H]⁺: 479.2.

Example 1.177 to Example 1.185 were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.51. LC-MS data of Example 1.177 to Example 1.185 are listed in the table below.

Ex. N°	Name	t _R (min)	[M+H] ⁺
1.177	(6R,12aS)-3,6-Dimethyl-11-((S)-tetrahydro-2H-pyran-3-yl)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.07	508.4
1.178	(6R,12aS)-11-(4-Fluoro-4-methylcyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.07	482.2
1.179	(1S,4r)-4-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.00	475.3
1.181	(6R,12aS)-11-((RS)-2,2-Dimethyltetrahydro-2H-pyran-4-yl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	0.99	480.4
1.183	(6R,12aS)-11-((1R*,2SR,4S*)-7-Oxabicyclo[2.2.1]heptan-2-yl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	0.96 and 0.97	464.3
1.184	(6R,12aS)-11-((2R,4SR,6S)-2,6-Dimethyltetrahydro-2H-pyran-4-yl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.00	480.4
1.185	(6R,12aS)-11-((1R*,2S*)-2-Methoxycyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxid	1.10 and 1.11	480.4

5 Example 1.188 (S)-5-(4,4-Difluorocyclohexyl)-13-methyl-1,2,3,3a,6,7,10,11-octahydro-9H-benzo[i]pyrrolo[2,1-f][1]oxa[8]thia[4,7]diazacyclotridecin-4(5H)-one 16,16-dioxide:

***tert*-Butyl ((2-(3-(2-hydroxyethoxy)prop-1-yn-1-yl)-4-methylphenyl)sulfonyl)-L-prolinate:** *tert*-Butyl ((2-bromo-4-methylphenyl)sulfonyl)-L-prolinate (200 mg, 0.50 mmol, 1 eq), 2-(prop-2-yn-1-yloxy)ethan-1-ol (83 mg, 0.74 mmol, 1.5 eq), CuI (19 mg, 0.10 mmol, 0.2 eq) and Et₃N (0.22 mL, 1.53 mmol, 3.1 eq) in DMF (5 mL) were degassed with N₂ for 5 min. Pd(PPh₃)₄ (57 mg, 0.05 mmol, 0.1 eq) was added, and the resulting mixture was heated to 85°C. After 2 days stirring, the mixture was cooled to rt, filtered through Celite, and the solvent removed under reduced

pressure. The residue was purified by acidic prep. HPLC to give the title compound. LC-MS (1): t_R = 0.94 min; $[M+H]^+$: 368.0.

- tert-Butyl ((2-(3-(2-hydroxyethoxy)propyl)-4-methylphenyl)sulfonyl)-L-prolinate:** *tert*-Butyl ((2-(3-(2-hydroxyethoxy)propyl)-4-methylphenyl)sulfonyl)-L-prolinate (150 mg, 0.35 mmol, 1 eq) was dissolved in EtOH (5 mL). Pd/C (10%, wet, 15 mg, 0.14 mmol, 0.4 eq) was added, and the flask was purged with N₂, then with H₂. The mixture was stirred at rt under a H₂ atm for 17 h. Pd/C (10%, wet, 15 mg, 0.14 mmol, 0.4 eq) was added again, the flask was purged with N₂, and then H₂. The same procedure was repeated for 6 days. The black mixture was filtered with a Whatman filter, and rinsed with EtOH. The solvent was removed under reduced pressure. The residue was purified by acidic prep. HPLC to give the title compound. LC-MS (1): t_R = 0.95 min; $[M+H]^+$: 372.0.
- 5 **tert-Butyl ((4-methyl-2-(3-(2-oxoethoxy)propyl)phenyl)sulfonyl)-L-prolinate:** A soln. of *tert*-butyl ((2-(3-(2-hydroxyethoxy)propyl)-4-methylphenyl)sulfonyl)-L-prolinate (60 mg, 0.14 mmol, 1 eq) in DCM (3 mL) was cooled to 0°C. Dess-Martin periodinane (69 mg, 0.15 mmol, 1.1 eq) was added at 0°C. The mixture was stirred at 0°C for 45 min. The mixture was warmed to rt and stirred overnight. DCM was added and the mixture was washed with aq. sat. NaHCO₃ soln. The org. layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure.
- 10 to give the title compound. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.90 min; $[M+H]^+$: not seen.
- 15

- tert-Butyl ((2-(3-(2-((4,4-difluorocyclohexyl)amino)ethoxy)propyl)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((4-methyl-2-(3-(2-oxoethoxy)propyl)phenyl)sulfonyl)-L-prolinate and 4,4-difluorocyclohexyl-1-amine in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 0.91 min; $[M+H]^+$: 544.9.
- 20

((2-(3-(2-((4,4-Difluorocyclohexyl)amino)ethoxy)propyl)-4-methylphenyl)sulfonyl)-L-proline: Was synthesized using *tert*-butyl ((2-(3-(2-((4,4-difluorocyclohexyl)amino)ethoxy)propyl)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.9 to give the title compound. LC-MS (1): t_R = 0.72 min; $[M+H]^+$: 489.9.

- (S)-5-(4,4-Difluorocyclohexyl)-13-methyl-1,2,3,3a,6,7,10,11-octahydro-9H-benzo[*i*]pyrrolo[2,1-f][1]oxa[8]thia[4,7]diazacyclotridecin-4(5H)-one 16,16-dioxide:** Was synthesized using ((2-(3-(2-((4,4-difluorocyclohexyl)amino)ethoxy)propyl)-4-methylphenyl)sulfonyl)-L-proline in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 1.02 min; $[M+H]^+$: 471.2.
- 25

Example 1.189 (S)-5-(4,4-Difluorocyclohexyl)-13-methyl-1,2,3,3a,6,7,8,9,10,11-decahydrobenzo[*i*]pyrrolo[1,2-b][1]thia[2,5,11]triazacyclotridecin-4(5H)-one 16,16-dioxide:

- tert-Butyl ((2-fluoro-4-methylphenyl)sulfonyl)-L-prolinate:** *tert*-Butyl L-prolinate (2.10 mL, 12.00 mmol, 1 eq), DMAP (146 mg, 1.20 mmol, 0.1 eq) and DIPEA (6.2 mL, 35.90 mmol, 3 eq) were dissolved in DCM (50 mL). The soln. was cooled to 0°C. Then 2-fluoro-4-methylbenzenesulfonyl chloride (2.50 g, 12.00 mmol, 1 eq) was added portionwise. The reaction mixture was warmed to rt and stirred overnight. Aq. sat. NaHCO₃ soln. was added and the aq. layer was extracted with DCM. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed
- 30

under reduced pressure. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R = 1.03 min; $[M+H]^+$: 344.2.

tert-Butyl ((2-(but-3-en-1-ylamino)-4-methylphenyl)sulfonyl)-L-prolinate: *tert-Butyl* ((2-fluoro-4-methylphenyl)sulfonyl)-L-prolinate (50 mg, 0.15 mmol, 1 eq) was dissolved in DMSO (1 mL). Then 3-buten-1-amine (27 μ L, 0.29 mmol, 2 eq) and DIPEA (0.25 mL, 1.46 mmol, 10 eq) were added. The reaction mixture was stirred at 120°C overnight. H₂O was added and the org. layer was extracted with Et₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 30% EtOAc) to give the title compound. LC-MS (1): t_R = 1.13 min; $[M+H]^+$: 395.2.

((2-(But-3-en-1-ylamino)-4-methylphenyl)sulfonyl)-L-proline: *tert-Butyl* ((2-(but-3-en-1-ylamino)-4-methylphenyl)sulfonyl)-L-prolinate (37 mg, 0.09 mmol, 1 eq) was dissolved in DCM (1 mL). Then TFA (0.36 mL, 4.69 mmol, 50 eq) was added. The reaction mixture was stirred at rt for 6h. The solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.92 min; $[M+H]^+$: 339.2.

(S)-N-Allyl-1-((2-(but-3-en-1-ylamino)-4-methylphenyl)sulfonyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide: ((2-(But-3-en-1-ylamino)-4-methylphenyl)sulfonyl)-L-proline (39 mg, 0.09 mmol, 1 eq) was dissolved in DMF (1 mL). Then HATU (49 mg, 0.13 mmol, 1.5 eq), DIPEA (60 μ L, 0.35 mmol, 4 eq) and N-allyl-4,4-difluorocyclohexan-1-amine (23 mg, 0.13 mmol, 1.5 eq) were added. The reaction mixture was stirred at rt overnight. Et₂O was added and the org. layer and washed with aq. 0.1M HCl soln., aq. sat. NaHCO₃ soln. and H₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure to give the title compound. The crude product was used in the next step without further purification. LC-MS (1): t_R = 1.14 min; $[M+H]^+$: 496.3.

(S)-5-(4,4-Difluorocyclohexyl)-13-methyl-1,2,3,3a,6,9,10,11-octahydrobenzo[*l*]pyrrolo[1,2-b][1]thia[2,5,11]triazacyclotridecin-4(5H)-one 16,16-dioxide: (S)-N-Allyl-1-((2-(but-3-en-1-ylamino)-4-methylphenyl)sulfonyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide (28 mg, 0.06 mmol, 1 eq) was dissolved in DCM (6 mL) under argon atm. Hoveyda- Grubbs catalyst, 2nd generation (2 mg, 0.003 mmol, 0.05 eq) was added. The reaction mixture was stirred at 45°C for 1h. The solvent was removed under reduced pressure. The residue was purified by FC (Hept to 80% EtOAc) to give the title compound. LC-MS (1): t_R = 1.04 min; $[M+H]^+$: 468.1.

(S)-5-(4,4-Difluorocyclohexyl)-13-methyl-1,2,3,3a,6,7,8,9,10,11-decahydrobenzo[*l*]pyrrolo[1,2-b][1]thia[2,5,11]triazacyclotridecin-4(5H)-one 16,16-dioxide: (S)-5-(4,4-Difluorocyclohexyl)-13-methyl-1,2,3,3a,6,9,10,11-octahydrobenzo[*l*]pyrrolo[1,2-b][1]thia[2,5,11]triazacyclotridecin-4(5H)-one 16,16-dioxide (19 mg, 0.042 mmol, 1 eq) was dissolved in MeOH (2 mL). The reaction flask was purged with N₂ and 10% Pd/C (2 mg) was added. The reaction was stirred under H₂ atm overnight. The reaction mixture was filtered. The solvent was removed under reduced pressure and the residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.08 min; $[M+H]^+$: 470.0.

Example 1.190 (8R,12aS)-8-Cyclopropyl-11-(4,4-difluorocyclohexyl)-8-hydroxy-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide or (8S,12aS)-8-Cyclopropyl-11-(4,4-difluorocyclohexyl)-8-hydroxy-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide :

Methyl ((2-(2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1,3-dioxolan-2-yl)ethoxy)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using methyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate and 2-(2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1,3-dioxolan-2-yl)ethan-1-ol (WO2008108834) in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 1.20 min; $[M+H]^+$: 558.3.

10 Methyl ((2-(2-(2-hydroxyethyl)-1,3-dioxolan-2-yl)ethoxy)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using methyl ((2-(2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1,3-dioxolan-2-yl)ethoxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 0.82 min; $[M+H]^+$: 444.0.

15 Methyl ((2-(2-(2-((4,4-difluorocyclohexyl)amino)ethyl)-1,3-dioxolan-2-yl)ethoxy)-4-methylphenyl)sulfonyl)-L-prolinate: (Cyanomethyl)(trimethyl)phosphonium iodide (570 mg, 2.23 mmol, 2.4 eq) was added to a solution of methyl ((2-(2-(2-hydroxyethyl)-1,3-dioxolan-2-yl)ethoxy)-4-methylphenyl)sulfonyl)-L-prolinate (412 mg, 0.93 mmol, 1 eq), 4,4-difluorocyclohexan-1-amine (314 mg, 2.23 mmol, 2.4 eq) and DIPEA (0.41 mL, 2.42 mmol, 2.6 eq) in MeCN (10 mL) and the mixture was stirred under reflux for 6.5 h. The reaction mixture was cooled to rt and diluted with aq. sat. NaHCO_3 and DCM. The org. layer was washed with H_2O , dried over **20** MgSO_4 , filtered, and the solvent removed under reduced pressure. The residue was purified by FC (DCM to 10% MeOH/0.5% NH_3) to give the title compound. LC-MS (1): t_R = 0.80 min; $[M+H]^+$: 560.8.

(2-(2-(2-((4,4-Difluorocyclohexyl)amino)ethyl)-1,3-dioxolan-2-yl)ethoxy)-4-methylphenyl)sulfonyl)-L-proline: Was synthesized using methyl ((2-(2-(2-((4,4-difluorocyclohexyl)amino)ethyl)-1,3-dioxolan-2-yl)ethoxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.8 to give the title compound. LC-MS (1): **25** t_R = 0.73 min; $[M+H]^+$: 547.0.

(S)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,10,11,12a,13,14,15-octahydrospiro[benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-8,2'-[1,3]dioxolan]-12(9H)-one 17,17-dioxide: Was synthesized using ((2-(2-(2-((4,4-difluorocyclohexyl)amino)ethyl)-1,3-dioxolan-2-yl)ethoxy)-4-methylphenyl)sulfonyl)-L-proline in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 0.98 min; $[M+H]^+$: 528.9.

30 (S)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,10,11,12a,13,14,15-octahydro-8H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-8,12(9H)-dione 17,17-dioxide: A soln. of (S)-11-(4,4-difluorocyclohexyl)-3-methyl-6,7,10,11,12a,13,14,15-octahydrospiro[benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-8,2'-[1,3]dioxolan]-12(9H)-one 17,17-dioxide (280 mg, 0.53 mmol, 1 eq) in THF (6 mL) was cooled to 0°C. Aq. conc. HCl soln. (0.52 mL, 5.30 mmol, 10 eq) was added and the mixture was **35** stirred at 0°C for 10 min and then at rt for 19h. Aq. sat. NaHCO_3 soln. and EtOAc were added. The layers were

separated, the org. layer was washed with H₂O and brine, dried with MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R= 0.93 min; [M+H]⁺: 485.0.

- (8R,12aS)-8-Cyclopropyl-11-(4,4-difluorocyclohexyl)-8-hydroxy-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide**
or (8S,12aS)-8-Cyclopropyl-11-(4,4-difluorocyclohexyl)-8-hydroxy-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide: (S)-11-(4,4-difluorocyclohexyl)-3-methyl-6,7,10,11,12a,13,14,15-octahydro-8H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-8,12(9H)-dione 17,17-dioxide (40 mg, 0.083 mmol, 1 eq) was dissolved in THF (1 mL) and the soln. was cooled to 0°C. 0.5M Cyclopropylmagnesium bromide soln. in THF 0.18 mL, 0.091 mmol, 1.1 eq) was added, and the mixture was stirred at 0°C for 1.25h and then at rt for 3.5h. 0.5M cyclopropylmagnesium bromide soln. in THF (0.18 mL, 0.091 mmol, 1.1 eq) was added again, and the mixture was stirred at rt for 3 days. The mixture was quenched with aq. sat. NH₄Cl soln., and diluted with DCM. The layers were separated by phase separator, washed with H₂O and the solvent removed under reduced pressure. The residue was purified by basic prep. HPLC to give the title compound. The stereochemistry at the quaternary cyclopropyl ring was attributed arbitrarily. LC-MS (2): t_R= 0.94 min; [M+H]⁺: 527.3.

- Example 1.191 (6R,12aS)-11-((1R*,3S*)-3-Hydroxycyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:** Was synthesized using *cis*-3-aminocyclohexanol hydrochloride and *tert*-butyl ((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.51 to give the title compound. LC-MS (2): t_R= 1.13 min; [M+H]⁺: 466.0.

Example 1.192 (6R,12aS)-11-(4,4-Difluorocyclohexyl)-4-fluoro-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:

- Methyl ((2-(((R)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-3-fluoro-4-methylphenyl)sulfonyl)-L-prolinate:** Methyl ((3-fluoro-2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate (300 mg, 0.95 mmol, 1 eq) was dissolved in THF (5 mL). The soln. was cooled to 0°C. Then (S)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-ol (264 mg, 1.13 mmol, 1.2 eq) and PPh₃ (302 mg, 1.13 mmol, 1.2 eq) were added followed by DEAD (~40% in toluene, 1.9 mL, 1.89 mmol, 2 eq). After the addition, the mixture was allowed to warm up to rt and stirred overnight. The solvent was removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R= 1.35 min; [M+H]⁺: not seen.

Methyl ((3-fluoro-2-(((R)-6-hydroxyhexan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: Methyl ((2-(((R)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-3-fluoro-4-methylphenyl)sulfonyl)-L-prolinate (350 mg, 0.66 mmol, 1 eq) was dissolved in THF (8 mL). Then 1M TBAF soln. in THF (7.9 mL, 7.9 mmol, 12 eq) was added. The reaction mixture was stirred at rt for 30 min. The reaction mixture was diluted with DCM and washed with aq. sat. NaHCO₃

soln. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R= 0.93 min; [M+H]⁺: 418.1.

Methyl ((3-fluoro-4-methyl-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate: Oxalyl chloride (49 µL, 0.55 mmol, 1.5 eq) was dissolved in DCM (2 mL) and the soln. was cooled to -78°C under argon atm. Then DMSO (70 µL, 0.99 mmol, 2.7 eq) was added dropwise while maintaining a temperature below -70°C. After stirring for another 10 min, a soln. of methyl ((3-fluoro-2-(((R)-6-hydroxyhexan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate (153 mg, 0.37 mmol, 1 eq) in DCM (3 mL) was added dropwise. After stirring for another 10 min, TEA (0.26 mL, 1.83 mmol, 5 eq) was added and the reaction mixture was stirred at -78°C for 30 min. Then the soln. was allowed to warm up to rt. The reaction mixture was diluted with DCM and washed with aq. sat. NaHCO₃ soln. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure.. The crude product was used in the next step without further purification. LC-MS (1): t_R= 0.99 min; [M+H]⁺: 416.2.

Methyl ((2-(((R)-6-((4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-3-fluoro-4-methylphenyl)sulfonyl)-L-prolinate: Methyl ((3-fluoro-4-methyl-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate (50 mg, 0.12 mmol, 1 eq) was dissolved in MeOH (1 mL). Then 4,4-difluorocyclohexylamine hydrochloride (32 mg, 0.18 mmol, 1.5 eq) and DIPEA (40 µL, 0.21 mmol, 1.7 eq) were added. The reaction mixture was stirred at rt for 1h. NaBH(OAc)₃ (51 mg, 0.24 mmol, 2 eq) was added. The soln. was further stirred at rt for 1h. The reaction mixture was diluted with DCM and extracted with aq. sat. NaHCO₃ soln. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (DCM to 20% MeOH) to give the title compound. LC-MS (1): t_R= 0.84 min; [M+H]⁺: 535.0.

((2-(((R)-6-((4,4-Difluorocyclohexyl)amino)hexan-2-yl)oxy)-3-fluoro-4-methylphenyl)sulfonyl)-L-proline: Methyl ((2-(((R)-6-((4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-3-fluoro-4-methylphenyl)sulfonyl)-L-prolinate (55 mg, 0.10 mmol, 1 eq) was dissolved in THF (1 mL). Then aq. 1M LiOH soln. (0.21 mL, 0.21 mmol, 2 eq) was added. The reaction mixture was stirred at rt for 3h. The solvent was removed under reduced pressure. The residue was dissolved in aq. 1M HCl soln. The aq. layer was extracted with DCM. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R= 0.93 min; [M+H]⁺: 418.1.

(6R,12aS)-11-(4,4-Difluorocyclohexyl)-4-fluoro-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide: Was synthesized using ((2-(((R)-6-((4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-3-fluoro-4-methylphenyl)sulfonyl)-L-proline in analogy to Example 1.136 to give the title compound. LC-MS (1): t_R= 1.11 min; [M+H]⁺: 503.3.

Example 1.193 (1S*,3S*)-3-((6R,12aS)-4-Fluoro-3,6-dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile formate: Was synthesized using trans-3-aminocyclohexanecarbonitrile hydrochloride and methyl ((3-fluoro-4-methyl-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.192 to give the title compound. LC-MS (1): t_R= 1.06 min; [M+H]⁺: 492.3.

Example 1.194 (9aS,13aS,16aS)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,11,12,13,13a,14,15,16,16a-dodecahydro-10H-benzo[b]cyclopenta[k]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10-one 5,5-dioxide or (9aS,13aR,16aR)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,11,12,13,13a,14,15,16,16a-dodecahydro-10H-benzo[b]cyclopenta[k]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10-one 5,5-dioxide:

(1R*,2S*)-2-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)cyclopentan-1-ol and (1R*,2R*)-2-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)cyclopentan-1-ol: 2-(2-Hydroxyethyl)cyclopentan-1-ol (1.00 g, 7.68 mmol, 1 eq) was dissolved in DCM (25 mL). Imidazole (800 mg, 11.50 mmol, 1.5 eq) and DMAP (94 mg, 0.77 mmol, 0.1 eq) were added at rt, then the resulting soln. was cooled to 0°C. 1M *tert*-Butylchlorodiphenylsilane soln. in DCM (8.5 mL, 8.50 mmol, 1.1 eq) in DCM (10 mL) was added dropwise. The reaction mixture was partitioned between DCM and aq. 1M HCl soln. The org. layer was washed with brine and separated through a phase separator. The solvent was removed under reduced pressure. The residue was purified by FC (Hept to 5% EtOAc) to give (1R*,2R*)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopentan-1-ol (first eluting isomer) and (1R*,2S*)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopentan-1-ol (second eluting diastereomer). First eluting diastereomer: LC-MS (1): t_R = 1.21 min; [M+H]⁺: 369.1. Second eluting diastereomer: LC-MS (1): t_R = 1.20 min; [M+H]⁺: 369.1.

(RS)-2-Ethylhexyl 3-((2-(((1R*,2R*)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopentyl)oxy)-4-methylphenyl)sulfonyl)propanoate: DIAD (0.11 mL, 0.55 mmol, 1.3 eq) was added dropwise at 0°C, to a stirred mixture of *rac*-(R)-2-ethylhexyl 3-((2-hydroxy-4-methylphenyl)sulfonyl)propanoate (150 mg, 0.42 mmol, 1 eq), (1R*,2S*)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopentan-1-ol (180 mg, 0.49 mmol, 1.15 eq) and PPh₃ polymer bound (100-200 mesh, ca. 1.6 mmol/g, 360 mg, 0.55 mmol, 1.3 eq) in THF (4 mL) and the mixture was stirred for 1.5h. The resin was filtered off and washed with DCM and MeOH. The solvent was removed under reduced pressure and the residue was purified by FC (Hept to 10% EtOAc) to give the title compound. LC-MS (1): t_R = 1.43 min; [M+H]⁺: 707.8.

***tert*-Butyl ((2-(((1R*,2R*)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using (RS)-2-ethylhexyl 3-((2-(((1R*,2R*)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopentyl)oxy)-4-methylphenyl)sulfonyl)propanoate and L-proline *t*-butyl ester in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R = 1.39 min; [M+H]⁺: 692.0.

***tert*-Butyl ((2-(((1R*,2R*)-2-(2-hydroxyethyl)cyclopentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((2-(((1R*,2S*)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R = 1.02 and 1.03 min; [M+H]⁺: 454.3.

***tert*-Butyl ((4-methyl-2-(((1R*,2R*)-2-(2-oxoethyl)cyclopentyl)oxy)phenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((2-(((1R*,2R*)-2-(2-hydroxyethyl)cyclopentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R = 1.09; [M+H]⁺: 452.1.

tert-Butyl ((2-(((1R*,2R*)-2-(2-((4,4-difluorocyclohexyl)amino)ethyl)cyclopentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using *tert*-butyl ((4-methyl-2-(((1R*,2R*)-2-(2-oxoethyl)cyclopentyl)oxy)phenyl)sulfonyl)-L-prolinate and 4,4-difluoro-cyclohexylamine hydrochloride in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R = 0.93 min; $[M+H]^+$: 571.1.

- 5 **((2-(((1R*,2R*)-2-(2-((4,4-Difluorocyclohexyl)amino)ethyl)cyclopentyl)oxy)-4-methylphenyl)sulfonyl)-L-proline hydrochloride:** A soln. of *tert*-butyl ((2-(((1R*,2R*)-2-(2-((4,4-difluorocyclohexyl)amino)ethyl)cyclopentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate (11 mg, 0.02 mmol, 1 eq) in 4M HCl soln. in dioxane (0.2 mL) was stirred at rt for 3.5h. The solvent was removed under reduced pressure. The crude product was used without further purification. LC-MS (1): t_R = 0.77 and 0.78 min; $[M+H]^+$: 515.2.
- 10 **(9aS,13aR,16aR)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,11,12,13,13a,14,15,16,16a-dodecahydro-10H-benzo[b]cyclopenta[k]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10-one 5,5-dioxide and (9aS,13aS,16aS)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,11,12,13,13a,14,15,16,16a-dodecahydro-10H-benzo[b]cyclopenta[k]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10-one 5,5-dioxide:** Were synthesized using ((2-(((1R*,2R*)-2-(2-((4,4-difluorocyclohexyl)amino)ethyl)cyclopentyl)oxy)-4-methylphenyl)sulfonyl)-L-proline hydrochloride in analogy to Example 1.124. The residue was purified by basic prep. HPLC to give (9aS,13aR,16aR)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,11,12,13,13a,14,15,16,16a-dodecahydro-10H-benzo[b]cyclopenta[k]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10-one 5,5-dioxide and (9aS,13aS,16aS)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,11,12,13,13a,14,15,16,16a-dodecahydro-10H-benzo[b]cyclopenta[k]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10-one 5,5-dioxide. The stereochemistry at the cyclopentyl ring was attributed arbitrarily. First eluting diastereomer: LC-MS (1): t_R = 1.04 min; $[M+H]^+$: 497.0. Second eluting diastereomer: LC-MS (1): t_R = 1.07 min; $[M+H]^+$: 497.0.

Example 1.196 (1'S,5'S*,5'R*)-7-(4,4-Difluorocyclohexyl)-34-methyl-4-oxa-2-thia-7-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclooctaphan-8-one 2,2-dioxide:

- Ethyl (1R*,3R*)-3-hydroxycyclohexane-1-carboxylate:** 1M L-Selectride soln. in THF (4.0 mL, 4.00 mmol, 1.15 eq) was added dropwise, at -78 °C to a stirred soln. of ethyl 3-oxocyclohexanecarboxylate (600 mg, 3.42 mmol, 1 eq) in THF (16 mL) and the mixture was stirred for 45 min at -78°C. The mixture was quenched at 0°C with aq. sat. Rochelle's salt soln. and then diluted with EtOAc. The mixture was vigorously stirred at rt and the layers were separated. The aq. layer was extracted with EtOAc. The combined org. layers were dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 20% EtOAc) to give the title compound (*trans/cis* 9:1). ¹H NMR (500 MHz, DMSO-*d*₆) δ : 4.47 (d, J = 3.5 Hz, 1 H), 4.04 (q, J = 7.1 Hz, 2 H), 3.80-3.84 (m, 1 H), 2.64-2.69 (m, 1 H), 1.55-1.72 (m, 4 H), 1.33-1.49 (m, 4 H), 1.17 (t, J = 7.1 Hz, 3 H).

- (1R*,3R*)-3-(Hydroxymethyl)cyclohexan-1-ol:** 1M LiAlH₄ soln. in THF (3.2 mL, 3.20 mmol, 1.1 eq) was added dropwise, at 0°C, to a stirred soln. of ethyl (1R*,3R*)-3-hydroxycyclohexane-1-carboxylate (491 mg, 2.85 mmol, 1 eq) in THF (10 mL). The resulting soln. was stirred at 0°C for 45 min. The reaction mixture was quenched by addition of H₂O (0.2 mL) followed by aq. 15% NaOH soln. and H₂O. The reaction mixture was stirred at rt until a

fine white powder was formed. The solid was filtered over a pad of Celite, and the filtrate was the solvent was removed under reduced pressure. The residue was purified by FC (DCM to 5% MeOH) to give the title compound (*trans/cis* 9:1). ¹H NMR (500 MHz, DMSO-*d*₆) δ: 4.30 (t, *J* = 5.4 Hz, 1 H), 4.22 (d, *J* = 3.4 Hz, 1 H), 3.83-3.86 (m, 1 H), 3.17-3.23 (m, 2 H), 1.73-1.80 (m, 1 H), 1.49-1.61 (m, 4 H), 1.31-1.39 (m, 2 H), 1.13 (m, 1 H), 0.90-0.99 (m, 1 H).

5

(1R*,3R*)-3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)cyclohexan-1-ol: (1R*,3R*)-3-(hydroxymethyl)cyclohexan-1-ol (280 mg, 2.15 mmol, 1 eq) was dissolved in DCM (7 mL). Imidazole (224 mg, 3.23 mmol, 1.5 eq) and DMAP (26 mg, 0.22 mmol, 0.1 eq) were added at rt, and the resulting soln. was cooled to 0°C. 1M *tert*-Butylchlorodiphenylsilane soln. in DCM (2.40 mL, 2.40 mmol, 1.1 eq) in DCM (4 mL) was added dropwise. The reaction mixture was then partitioned between DCM and aq. 1M HCl soln. The org. layer was washed with brine and filtered through a phase separator. The solvent was removed under reduced pressure. The residue was purified by FC (Hept to 10% EtOAc) to give the title compound. LC-MS (1): *t*_R = 1.19 min; [M+H]⁺: 369.3.

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(RS)-2-Ethylhexyl 3-(((1S*,3R*)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)propanoate: Was synthesized using *rac*-(R)-2-ethylhexyl 3-((2-hydroxy-4-methylphenyl)sulfonyl)propanoate and (1R*,3R*)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclohexan-1-ol in analogy to Example 1.124 to give the title compound. LC-MS (1): *t*_R = 1.41 min; [M+H]⁺: 707.3.

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***tert*-Butyl ((2-(((1S*,3R*)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using (RS)-2-ethylhexyl 3-((2-(((1S*,3R*)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)propanoate and *tert*-butyl L-prolinate in analogy to Example 1.124 to give the title compound. LC-MS (1): *t*_R = 1.38 min; [M+H]⁺: 692.4.

20

***tert*-Butyl ((2-(((1S*,3R*)-3-(hydroxymethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((2-(((1S*,3R*)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.124 to give the title compound. LC-MS (1): *t*_R = 1.01 min; [M+H]⁺: 454.1.

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***tert*-Butyl ((2-(((1S*,3R*)-3-formylcyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((2-(((1S*,3R*)-3-(hydroxymethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.124 to give the title compound. LC-MS (1): *t*_R = 1.07 min; [M+H]⁺: 451.8.

***tert*-Butyl ((2-(((1S*,3R*)-3-((4,4-difluorocyclohexyl)amino)methyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((2-(((1S*,3R*)-3-formylcyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate and 4,4-difluorocyclohexan-1-amine hydrochloride in analogy to Example 1.124 to give the title compound. LC-MS (1): *t*_R = 0.90 and 0.91 min; [M+H]⁺: 471.1.

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((2-(((1S*,3R*)-3-((4,4-Difluorocyclohexyl)amino)methyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-proline hydrochloride: Was synthesized using *tert*-butyl ((2-(((1S*,3R*)-3-((4,4-

difluorocyclohexyl)amino)methyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.194 to give the title compound. LC-MS (1): t_R= 0.90 and 0.91 min; [M+H]⁺: 471.1.

5 **(1²S,5¹S*,5³R*)-7-(4,4-Difluorocyclohexyl)-3⁴-methyl-4-oxa-2-thia-7-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclooctaphan-8-one 2,2-dioxide:** Was synthesized using ((2-(((1S*,3R*)-3-(((4,4-difluorocyclohexyl)amino)methyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-proline hydrochloride in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R= 1.07 and 1.08 min; [M+H]⁺: 497.0.

Example 1.197 to Example 1.206 were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((4-methyl-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.1. LC-MS data of Example 1.197 to Example 1.206 are listed in the table below.

Ex. N°	Name	t _R (min)	[M+H] ⁺
1.197	(1R*,3R*)-3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclopentane-1-carbonitrile	0.99	460.4
1.201	(6R,12aS)-11-((RS)-2,2-Diethyltetrahydro-2H-pyran-4-yl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.07	507.4
1.202	(1S,4r)-4-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	1.03	488.4
1.203	(1R,4s)-4-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	1.03	488.4
1.204	(6R,12aS)-11-(4-Fluoro-4-methylcyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.06	481.2
1.206	(6R,12aS)-11-((1R*,2S*)-4,4-Difluoro-2-hydroxycyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.00	501.5

Example 1.207 to Example 1.221 were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.51. LC-MS

data of Example 1.207 to Example 1.221 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R (min)	[M+H] ⁺
1.207	(6R,12aS)-3,6-Dimethyl-11-(((RS)-tetrahydro-2H-pyran-3-yl)methyl)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	0.96	466.2
1.208	(6R,12aS)-11-((1S,4R)-4-Methoxycyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.02	480.4
1.209	(6R,12aS)-11-((RS)-3,3-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.06	486.4
1.210	(6R,12aS)-11-(6-Hydroxyspiro[3.3]heptan-2-yl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	0.91	478.4
1.211	(6R,12aS)-11-((1R*,2R*)-4,4-Difluoro-2-hydroxycyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	0.96	502.3
1.213	(1S,4r)-4-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	1.04	489.4
1.214	(1R,4s)-4-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	1.03	489.4
1.215	(6R,12aS)-11-((1R*,2S*)-4,4-Difluoro-2-hydroxycyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	0.95 and 0.97	502.3
1.218	(6R,12aS)-11-((1R*,3R*)-3-Methoxycyclopentyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	0.98	466.2
1.219	(6R,12aS)-11-((1R*,3R*)-3-Hydroxycyclopentyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	0.87	452.3

1.220	(6R,12aS)-11-((1R*,3S*)-3-Hydroxycyclopentyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	0.90	452.3
1.221	(6R,12aS)-11-((1R*,2S*)-2-Methoxycyclopentyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.04	475.4

Examples 1.223 (1³R,4²S)-6-(4,4-Difluorocyclohexyl)-2⁵-methyl-3-thia-6-aza-1(1,3),4(1,2)-dipyrrolidina-2(1,2)-benzenacyclononaphan-5-one 3,3-dioxide and Example 1.224 (1³S,4²S)-6-(4,4-Difluorocyclohexyl)-2⁵-methyl-3-thia-6-aza-1(1,3),4(1,2)-dipyrrolidina-2(1,2)-benzenacyclononaphan-5-one 3,3-dioxide:

5 ***tert*-Butyl ((4-methyl-2-((RS)-3-vinylpyrrolidin-1-yl)phenyl)sulfonyl)-L-prolinate:** A mixture of *tert*-butyl ((2-fluoro-4-methylphenyl)sulfonyl)-L-prolinate (100 mg, 0.29 mmol, 1 eq), 3-vinylpyrrolidine (68 µL, 0.58 mmol, 2 eq) and DIPEA (0.50 mL, 2.91 mmol, 10 eq) was stirred at 120°C overnight. The mixture was allowed to cool to rt, and was diluted with a few drops of H₂O and DMF, and filtered over a 0.45 µm PTFE filter. The solution was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R= 1.08 min; [M+H]⁺: 421.1.

10 **((4-Methyl-2-((RS)-3-vinylpyrrolidin-1-yl)phenyl)sulfonyl)-L-proline:** Was synthesized using *tert*-butyl ((4-methyl-2-((RS)-3-vinylpyrrolidin-1-yl)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.9 to give the title compound. LC-MS (1): t_R= 0.81 min; [M+H]⁺: 365.3.

(S)-N-Allyl-N-(4,4-difluorocyclohexyl)-1-((4-methyl-2-((RS)-3-vinylpyrrolidin-1-yl)phenyl)sulfonyl)pyrrolidine-2-carboxamide: HATU (137 mg, 0.36 mmol, 1.5 eq) was added to a stirred soln. of ((4-methyl-2-((RS)-3-vinylpyrrolidin-1-yl)phenyl)sulfonyl)-L-proline (189 mg, 0.24 mmol, 1 eq) and DIPEA (0.21 mL, 1.20 mmol, 5 eq) in DMF (2 mL) at rt. After stirring for 5 min, *N*-allyl-4,4-difluorocyclohexan-1-amine (106 mg, 0.17 mmol, 1 eq) in DMF (1 mL) was added, and the mixture was stirred at rt for 2 h. The mixture was diluted with Et₂O, and washed with aq. 0.1M HCl soln., aq. sat. NaHCO₃ soln. and H₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (DCM to 3% MeOH) to give the title compound. LC-MS (1): t_R= 0.98 min; [M+H]⁺: 522.0.

(1³RS,4²S)-6-(4,4-Difluorocyclohexyl)-2⁵-methyl-3-thia-6-aza-1(1,3),4(1,2)-dipyrrolidina-2(1,2)-benzenacyclononaphan-8-en-5-one 3,3-dioxide: A soln. of (S)-N-allyl-N-(4,4-difluorocyclohexyl)-1-((4-methyl-2-((RS)-3-vinylpyrrolidin-1-yl)phenyl)sulfonyl)pyrrolidine-2-carboxamide (80 mg, 0.15 mmol, 1 eq) and Hoveyda-Grubbs Catalyst 2nd Generation (5 mg, 0.01 mmol, 0.05 eq) in DCM (15 mL) was stirred at rt under argon atm for 3 days. The solvent was removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (2): t_R= 1.12 min; [M+H]⁺: 494.4.

(1³R,4²S)-6-(4,4-Difluorocyclohexyl)-2⁵-methyl-3-thia-6-aza-1(1,3),4(1,2)-dipyrrolidina-2(1,2)-benzenacyclononaphan-5-one 3,3-dioxide and (1³S,4²S)-6-(4,4-Difluorocyclohexyl)-2⁵-methyl-3-thia-6-aza-

1(1,3),4(1,2)-dipyrrolidina-2(1,2)-benzenacyclononaphan-5-one 3,3-dioxide: Was synthesized using (1³RS,4²S)-6-(4,4-difluorocyclohexyl)-25-methyl-3-thia-6-aza-1(1,3),4(1,2)-dipyrrolidina-2(1,2)-benzenacyclononaphan-8-en-5-one 3,3-dioxide in analogy to Example 1.6 to give the title compounds. The stereoisomers were separated by basic prep. HPLC to give (13R,42S)-6-(4,4-difluorocyclohexyl)-25-methyl-3-thia-6-aza-1(1,3),4(1,2)-dipyrrolidina-2(1,2)-benzenacyclononaphan-5-one 3,3-dioxide and (13S,42S)-6-(4,4-difluorocyclohexyl)-25-methyl-3-thia-6-aza-1(1,3),4(1,2)-dipyrrolidina-2(1,2)-benzenacyclononaphan-5-one 3,3-dioxide. The stereochemistry at the pyrrolidine ring was attributed arbitrarily. First eluting diastereomer: LC-MS (1): t_R= 1.05 min; [M+H]⁺: 496.0. Second eluting diastereomer: LC-MS (1): t_R= 1.11 min; [M+H]⁺: 496.3.

Example 1.225 (1R,4s)-4-((1²S,5¹R,5³R)-3⁴-Methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile and Example 1.226 (1R,4s)-4-((1²S,5¹S,5³S)-3⁴-Methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile: Were synthesized using *tert*-butyl ((4-methyl-2-(((1R*,3S*)-3-(2-oxoethyl)cyclohexyl)oxy)phenyl)sulfonyl)-L-prolinate and 4-amino-cyclohexanecarbonitrile hydrochloride in analogy to Example 1.124. The residue was purified by acidic prep. HPLC to give (1R,4s)-4-((12S,51R,53R)-34-Methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile and (1R,4s)-4-((12S,51S,53S)-34-Methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile. The stereochemistry at the cyclohexyl ring was attributed arbitrarily. First eluting diastereomer: LC-MS (1): t_R= 1.01; [M+H]⁺: 499.8. Second eluting diastereomer: LC-MS (1): t_R= 1.04; [M+H]⁺: 499.8.

Example 1.227 to Example 1.239 were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.51. LC-MS data of Example 1.227 to Example 1.239 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R (min)	[M+H] ⁺
1.227	(6R,12aS)-11-((1s,4R)-4-Fluoro-4-methylcyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.07	482.2
1.228	(6R,12aS)-11-((1r,4S)-4-Fluoro-4-methylcyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.08	482.2
1.229	(6R,12aS)-11-((S)-6,6-Dimethyltetrahydro-2H-pyran-3-yl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.01	480.0

1.230	(6R,12aS)-11-((R)-6,6-Dimethyltetrahydro-2H-pyran-3-yl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.02	480.3
1.231	(6R,12aS)-11-((S)-2,2-Dimethyltetrahydro-2H-pyran-4-yl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	0.98	480.3
1.232	(6R,12aS)-11-((R)-2,2-Dimethyltetrahydro-2H-pyran-4-yl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	0.99	480.3
1.233	(6R,12aS)-11-((1R,2S)-2-Methoxycyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.11	480.3
1.234	(6R,12aS)-3,6-Dimethyl-11-((2S,4R)-2-methyltetrahydro-2H-pyran-4-yl)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	0.95	465.8
1.235	(6R,12aS)-3,6-Dimethyl-11-((2R,4R)-2-methyltetrahydro-2H-pyran-4-yl)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	0.95	465.8
1.236	(6R,12aS)-3,6-Dimethyl-11-((2S,4S)-2-methyltetrahydro-2H-pyran-4-yl)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	0.96	465.8
1.237	(6R,12aS)-11-((1S,3S)-3-Methoxycyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.04	480.3
1.238	6R,12aS)-11-((1R,3S)-3-Methoxycyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.04	480.2
1.239	(6R,12aS)-11-((1S,3R)-3-Methoxycyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.00	480.3

Example 1.240 (6R,11aS)-10-((1R,2S)-2-Methoxycyclohexyl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide:

Methyl ((2-(((R)-5-((*tert*-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using (S)-5-((*tert*-butyldimethylsilyl)oxy)pentan-2-ol (Bioorg. Med. Chem. Lett. (2008), 18, 175–178)

and methyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 1.23; $[M+H]^+$: 500.0.

Methyl ((2-(((R)-5-hydroxypentan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using methyl ((2-(((R)-5-((*tert*-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.192 to give the title compound. LC-MS (1): t_R = 0.85 min; $[M+H]^+$: 385.8.

Methyl ((4-methyl-2-(((R)-5-oxopentan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate: A soln. of methyl ((2-(((R)-5-hydroxypentan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate (1.00 g, 2.59 mmol, 1 eq) and DIPEA (1.8 mL, 10.40 mmol, 4 eq) in DCM (26 mL) was cooled to 0°C. Sulfur trioxide pyridine complex (1.06 g, 6.49 mmol, 2.5 eq) in DMSO (4.1 mL, 57.10 mmol, 22 eq) was added slowly over 10 min. The mixture was allowed to warm to rt and stirred for 30 min. The mixture was diluted with DCM and brine and the layers were separated through a phase separator. The solvent was removed under reduced pressure and the residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R = 0.90 min; $[M+H]^+$: 384.0.

Methyl ((2-(((R)-5-(((1R,2S)-2-methoxycyclohexyl)amino)pentan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using methyl ((4-methyl-2-(((R)-5-oxopentan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate and (1R,2S)-2-methoxycyclohexanamine hydrochloride in analogy to Example 1.192 to give the title compound. LC-MS (1): t_R = 0.80 min; $[M+H]^+$: 497.2.

Lithium ((2-(((R)-5-(((1R,2S)-2-methoxycyclohexyl)amino)pentan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using methyl ((2-(((R)-5-(((1R,2S)-2-methoxycyclohexyl)amino)pentan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.166 to give the title compound. LC-MS (1): t_R = 0.74 min; $[M+H]^+$: 483.3.

(6R,11aS)-10-(((1R,2S)-2-Methoxycyclohexyl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide: Was synthesized using lithium ((2-(((R)-5-(((1R,2S)-2-methoxycyclohexyl)amino)pentan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.7 to give the title compound. LC-MS (1): t_R = 1.04 min; $[M+H]^+$: 465.0.

Example 1.241 (1R,4s)-4-((6R,11aS)-3,6-Dimethyl-16,16-dioxido-11-oxo-6,7,8,9,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-yl)cyclohexane-1-carbonitrile: Was synthesized using methyl ((4-methyl-2-(((R)-5-oxopentan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate and (1s,4s)-4-aminocyclohexanecarbonitrile hydrochloride in analogy to Example 1.240 to give the title compound. LC-MS (1): t_R = 0.93 min; $[M+H]^+$: 460.1.

Example 1.242 to Example 1.243 were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((6-methyl-2-(((R)-5-oxopentan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.32. LC-MS data of Example 1.242 to Example 1.243 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R (min)	[M+H] ⁺
1.242	(1R*,3S*)-3-((6R,11aS)-3,6-Dimethyl-16,16-dioxido-11-oxo-6,7,8,9,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-yl)cyclohexane-1-carbonitrile	0.96	461.1
1.243	(1R,4s)-4-((6R,11aS)-3,6-Dimethyl-16,16-dioxido-11-oxo-6,7,8,9,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-yl)cyclohexane-1-carbonitrile	0.94	461.3

Example 1.247 (1S,3S)-3-((6R,11aS)-3,6-Dimethyl-16,16-dioxido-11-oxo-6,7,8,9,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-yl)cyclohexane-1-carbonitrile: Was synthesized using *tert*-butyl ((6-methyl-2-(((R)-5-oxopentan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate and (1S,3S)-3-aminocyclohexane-1-carbonitrile 2,2,2-trifluoroacetate in analogy to Example 1.32. LC-MS (1): t_R= 0.95 min; [M+H]⁺: 461.3.

Example 1.248 (6R,11aS,13S)-10-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-13-methoxy-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide:

10 **3-(Benzylthio)-6-methylpyridin-2-ol:** 3-Bromo-6-methylpyridin-2-ol (5.00 g, 25.50 mmol, 1 eq) and XantPhos Pd G2 (1.13 g, 1.28 mmol, 0.05 eq) were dissolved in dioxane (50 mL). DIPEA (8.5 mL, 49.80 mmol, 1.95 eq) was added, followed by benzyl mercaptan (3.3 mL, 28.10 mmol, 1.1 eq). The reaction mixture was stirred at 90°C for 4h. The solvent was partially removed under reduced pressure. The residue was diluted with DCM and washed with aq. sat. NH₄Cl soln. and aq. sat. NaHCO₃ soln. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 20% EtOAc) to give the title compound.

15 LC-MS (1): t_R= 0.77 min; [M+H]⁺: 232.1.

(R)-3-(Benzylthio)-2-((5-((tert-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-6-methylpyridine: 3-(Benzylthio)-6-methylpyridin-2-ol (700 mg, 2.72 mmol, 1 eq) was dissolved in THF (15 mL). The soln. was cooled to 0°C. Then (S)-5-((tert-butyldimethylsilyl)oxy)pentan-2-ol (714 mg, 3.27 mmol, 1.2 eq) and PPh₃ (870 mg, 3.27 mmol, 1.2 eq) were added followed by DEAD (~40% in toluene, 5.5 mL, 5.50 mmol, 2 eq). After the addition, the mixture was allowed to warm up to rt overnight. The reaction mixture was diluted with Et₂O and washed with aq. 0.1M HCl soln., aq. sat. NaHCO₃ soln. and H₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 20% EtOAc) to give the title compound. LC-MS (1): t_R= 1.35 min; [M+H]⁺: 432.3.

25 **(R)-2-((5-((tert-Butyldimethylsilyl)oxy)pentan-2-yl)oxy)-6-methylpyridine-3-sulfonyl chloride:** DCDMH (745 mg, 3.71 mmol, 2 eq) was added to a soln. of (R)-3-(benzylthio)-2-((5-((tert-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-6-methylpyridine (800 mg, 1.85 mmol, 1 eq) in H₂O (0.1 mL) and dioxane (6 mL). The mixture was stirred at rt for 30 min and then poured into aq. sat. NaHCO₃ soln, and extracted with Et₂O and EtOAc. The org. layer was washed

with H₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R=1.09 min; [M+H]⁺: not seen.

(2S,4S)-1-((2-(((R)-5-((*tert*-Butyldimethylsilyl)oxy)pentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-4-

- methoxypyrrolidine-2-carboxylic acid:** (2S,4S)-4-Methoxypyrrolidine-2-carboxylic acid (425 mg, 2.78 mmol, 1 eq) was dissolved in H₂O (1.5 mL) and DMF (1.5 mL). Then NaHCO₃ (311 mg, 3.71 mmol, 2 eq) was added. The soln. was cooled to 0°C. Then a soln. of (R)-2-((5-((*tert*-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-6-methylpyridine-3-sulfonyl chloride (756 mg, 1.85 mmol, 1 eq) in DMF (1 mL) was added. The reaction mixture was warmed to rt and stirred for 10 min. The solvent was removed under reduced pressure. The residue was purified by FC (DCM to 20% MeOH) to give the title compound. LC-MS (1): t_R= 1.14 min; [M+H]⁺: 517.3.

- 10 **Methyl (2S,4S)-1-((2-(((R)-5-((*tert*-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-4-methoxypyrrolidine-2-carboxylate:** (2S,4S)-1-((2-(((R)-5-((*tert*-Butyldimethylsilyl)oxy)pentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-4-methoxypyrrolidine-2-carboxylic acid (236 mg, 0.46 mmol, 1 eq) was dissolved in DCM (5 mL) and MeOH (5 mL). Then trimethylsilyldiazomethane (ca. 10% in Hexanes, ca. 0.6mol/L; 1.0 mL, 0.55 mmol, 1.2 eq) was added. The reaction mixture was stirred at rt for 30 min. The reaction mixture was diluted with DCM and extracted with aq. sat. NaHCO₃ soln. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R= 1.20 min; [M+H]⁺: 531.0.

Methyl (2S,4S)-1-((2-(((R)-5-hydroxypentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-4-methoxypyrrolidine-2-carboxylate:

- 20 Methyl (2S,4S)-1-((2-(((R)-5-((*tert*-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-4-methoxypyrrolidine-2-carboxylate (311 mg, 0.59 mmol, 1 eq) was dissolved in THF (6 mL). Then 1M TBAF soln. in THF (5.9 mL, 5.86 mmol, 10 eq). The reaction mixture was stirred at rt for 30 min. The reaction mixture was diluted with DCM and extracted with aq. sat. NaHCO₃ soln. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R= 0.81 min; [M+H]⁺: 417.2.

- 25 **Methyl (2S,4S)-4-methoxy-1-((6-methyl-2-(((R)-5-oxopentan-2-yl)oxy)pyridin-3-yl)sulfonyl)pyrrolidine-2-carboxylate:** Oxalyl chloride (50 µL, 0.55 mmol, 1.5 eq) was dissolved in DCM (5 mL) and the soln. was cooled to -78°C under argon atm. Then DMSO (70 µL, 0.99 mmol, 2.7 eq) was added dropwise while maintaining a temperature below -70°C. After stirring for another 10 min, a soln. of methyl (2S,4S)-1-((2-(((R)-5-hydroxypentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-4-methoxypyrrolidine-2-carboxylate (153 mg, 0.37 mmol, 1 eq) in DCM (3 mL) was added dropwise. After stirring for another 10 min, TEA (0.26 mL, 1.84 mmol, 5 eq) was added and the reaction mixture was stirred at -78°C for 30 min. Then the soln. was allowed to warm up to rt. The reaction mixture was diluted with DCM and washed with aq. sat. NaHCO₃ soln. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R= 0.87 min; [M+H]⁺: 415.3.

- Methyl (2S,4S)-1-((2-(((R)-5-(((3S,5s)-1,1-difluorospiro[2.3]hexan-5-yl)amino)pentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-4-methoxypyrrolidine-2-carboxylate:** Methyl (2S,4S)-4-methoxy-1-((6-methyl-2-(((R)-5-oxopentan-2-yl)oxy)pyridin-3-yl)sulfonyl)pyrrolidine-2-carboxylate (50 mg, 0.12 mmol, 1 eq) was dissolved in MeOH (1 mL). Then (3s,5s)-1,1-difluorospiro[2.3]hexan-5-amine hydrochloride (31 mg, 0.18 mmol, 1.5 eq) was added and the soln. was stirred at rt for 1h. NaBH(OAc)₃ (51 mg, 0.24 mmol, 2 eq) was then added to the reaction mixture and stirring was continued for 1h. The reaction mixture was diluted with DCM and washed with H₂O. The org. layer was separated and the aq. layer was washed with DCM. The combined org. layers were dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R= 0.77 min; [M+H]⁺: 532.3.
- (2S,4S)-1-((2-(((R)-5-(((3S,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)amino)pentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-4-methoxypyrrolidine-2-carboxylic acid:** Methyl (2S,4S)-1-((2-(((R)-5-(((3S,5s)-1,1-difluorospiro[2.3]hexan-5-yl)amino)pentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-4-methoxypyrrolidine-2-carboxylate (65 mg, 0.12 mmol, 1 eq) was dissolved in THF (1 mL). Then aq. 1M LiOH soln. (2.0 mL, 2.00 mmol, 16.3 eq) was added. The reaction mixture was stirred at rt overnight. The solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R= 0.71 min; [M+H]⁺: 518.2.
- (6R,11aS,13S)-10-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-13-methoxy-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide:** Was synthesized using (2S,4S)-1-((2-(((R)-5-(((3S,5s)-1,1-difluorospiro[2.3]hexan-5-yl)amino)pentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-4-methoxypyrrolidine-2-carboxylic acid in analogy to Example 1.51 to give the title compound. LC-MS (1): t_R= 1.00 min; [M+H]⁺: 500.3.
- Example 1.249 to Example 1.250** were synthesized using the appropriate amine or amine salt derivative and methyl (2S,4S)-4-methoxy-1-((6-methyl-2-(((R)-5-oxopentan-2-yl)oxy)pyridin-3-yl)sulfonyl)pyrrolidine-2-carboxylate and in analogy to Example 1.248. LC-MS data of Example 1.249 to Example 1.250 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
1.249	(6R,11aS,13S)-10-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-13-methoxy-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide	1.04	528.3
1.250	(6R,11aS,13S)-10-(4,4-Difluorocyclohexyl)-13-methoxy-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide	0.99	502.3

Example 1.252 (9aS,13aS,17aR)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,12,13,13a,14,15,16,17,17a-dodecahydrodibenzo[b,k]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-one 5,5-dioxide or

(9aS,13aR,17aS)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,12,13,13a,14,15,16,17,17a-dodecahydrodibenzo[b,k]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-one 5,5-dioxide:

- Ethyl 2-((1R*,2R*)-2-hydroxycyclohexyl)acetate:** 1M L-Selectride soln. in THF (4.0 mL, 4.00 mmol, 1.2 eq) was added dropwise at -78 °C to a stirred soln. of ethyl 2-cyclohexanoneacetate (0.64 mL, 3.42 mmol, 1 eq) in THF (16 mL). The resulting mixture was stirred at -78 °C for 45 min. The reaction was quenched at 0 °C with aq. sat. Rochelle's salt soln. and then diluted with EtOAc. The mixture was vigorously stirred at rt, the layers were separated and the aq. layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 20% EtOAc) to give the title compound.
- 10 **(1R*,2R*)-2-(2-Hydroxyethyl)cyclohexan-1-ol:** 1M LiAlH₄ soln. in THF (1.7 mL, 1.76 mmol, 1.1 eq) was added dropwise, at 0 °C, to a stirred soln. of ethyl 2-((1R*,2R*)-2-hydroxycyclohexyl)acetate (297 mg, 1.59 mmol, 1 eq) in THF (5 mL). The resulting soln. was stirred at 0 °C for 45 min. The reaction mixture was quenched by addition of H₂O, followed by aq. 15% NaOH soln. and H₂O. The reaction mixture was stirred at rt until a fine white precipitate was formed. The reaction mixture was filtered over a pad of Celite and the solvent was removed under reduced
- 15 pressure. The residue was purified by FC (DCM to 5% /MeOH) to give the title compound. ¹H NMR (500 MHz, DMSO) δ: 4.29 (t, *J* = 5.1 Hz, 1 H), 4.17 (d, *J* = 4.2 Hz, 1 H), 3.63-3.65 (m, 1 H), 3.42 (m, 2 H), 1.59-1.64 (m, 1 H), 1.50-1.57 (m, 3 H), 1.42-1.47 (m, 1 H), 1.24-1.39 (m, 5 H), 1.14-1.22 (m, 1 H).

- (1R*,2R*)-2-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)cyclohexan-1-ol:** (1R*,2R*)-2-(2-hydroxyethyl)cyclohexan-1-ol (253 mg, 1.75 mmol, 1 eq) was dissolved in DCM (4 mL). Imidazole (182 mg, 2.63 mmol, 1.5 eq) and DMAP (21 mg, 0.18 mmol, 0.1 eq) were added at rt, then the resulting soln. was cooled to 0 °C and 1M *tert*-butylchlorodiphenylsilane soln. in DCM (8.5 mL, 8.50 mmol, 1.1 eq) diluted in DCM (4 mL) was added slowly dropwise. At the end of the addition, the reaction mixture was partitioned between DCM and aq. 1M HCl soln. The organic layer was washed with brine and separated through a phase separator cartridge. The solvent was removed under reduced pressure. The residue was purified by FC (Hept to 10% EtOAc) to give the title compound. LC-MS
- 20 (1): *t*_R = 1.21 min; [M+H]⁺: 383.2.
- 25

- (RS)-2-Ethylhexyl 3-(((1R*,2S*)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)propanoate:** Was synthesized using (1R*,2R*)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexan-1-ol and *rac*-(R)-2-ethylhexyl 3-((2-hydroxy-4-methylphenyl)sulfonyl)propanoate in analogy to Example 1.124 to give the title compound. LC-MS (1): *t*_R = 1.42 min; [M+H]⁺: 721.1.
- 30

***tert*-Butyl ((2-(((1R*,2S*)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using (RS)-2-ethylhexyl 3-(((1R*,2S*)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)propanoate and *tert*-butyl L-prolinate in analogy to Example 1.124 to give the title compound. LC-MS (1): *t*_R = 1.41 min; [M+H]⁺: 706.5.

tert-Butyl ((2-(((1R*,2S*)-2-(2-hydroxyethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using *tert*-butyl ((2-(((1R*,2S*)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R = 1.04 and 1.06 min; $[M+H]^+$: 467.8.

- 5 **tert-Butyl ((4-methyl-2-(((1R*,2S*)-2-(2-oxoethyl)cyclohexyl)oxy)phenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((2-(((1R*,2S*)-2-(2-hydroxyethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R = 1.11 and 1.12 min; $[M+H]^+$: 466.2.

- tert-Butyl ((2-(((1R*,2S*)-2-(2-((4,4-difluorocyclohexyl)amino)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((4-methyl-2-(((1R*,2S*)-2-(2-oxoethyl)cyclohexyl)oxy)phenyl)sulfonyl)-L-prolinate and 4,4-difluorocyclohexylamine hydrochloride in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R = 0.95 and 0.96 min; $[M+H]^+$: 585.4.

- (2-(((1R*,2S*)-2-(2-((4,4-Difluorocyclohexyl)amino)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-proline hydrochloride:** Was synthesized using *tert*-butyl ((2-(((1R*,2S*)-2-(2-((4,4-difluorocyclohexyl)amino)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.194 to give the title compound. LC-MS (1): t_R = 0.79 and 0.81 min; $[M+H]^+$: 529.3.

- (9aS,13aS,17aR)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,12,13,13a,14,15,16,17,17a-dodecahydridibenzo[b,k]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-one 5,5-dioxide and (9aS,13aR,17aS)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,12,13,13a,14,15,16,17,17a-dodecahydridibenzo[b,k]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-one 5,5-dioxide:** Were synthesized using ((2-(((1R*,2S*)-2-(2-((4,4-difluorocyclohexyl)amino)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-proline hydrochloride in analogy to Example 1.124. The soln. was purified by basic prep. HPLC to give (9aS,13aS,17aR)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,12,13,13a,14,15,16,17,17a-dodecahydridibenzo[b,k]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-one 5,5-dioxide and (9aS,13aR,17aS)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,12,13,13a,14,15,16,17,17a-dodecahydridibenzo[b,k]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-one 5,5-dioxide. The absolute stereochemistry at the cyclohexyl was attributed arbitrarily First eluting diastereomer: LC-MS (1): t_R = 1.12 min; $[M+H]^+$: 511.0. Second eluting diastereomer: LC-MS (1): t_R = 1.13 min; $[M+H]^+$: 511.0.

- Example 1.253 (9aS,13aS,17aS)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,12,13,13a,14,15,16,17,17a-dodecahydridibenzo[b,k]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-one 5,5-dioxide and Example 1.254 (9aS,13aR,17aR)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,12,13,13a,14,15,16,17,17a-dodecahydridibenzo[b,k]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-one 5,5-dioxide:**

- (1R*,2S*)-2-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)cyclohexan-1-ol:** (1R*,2S*)-2-(2-Hydroxyethyl)cyclohexan-1-ol (535 mg, 3.71 mmol, 1 eq) (J. Org. Chem., 2020, 85(2), 758-773) was dissolved in DCM (10 mL). Imidazole (387 mg, 5.56 mmol, 1.5 eq) and DMAP (45 mg, 0.37 mmol, 0.1 eq) were added at rt and the resulting soln. was cooled to 0°C. 1M *t*-Butylchlorodiphenylsilane soln. in DCM (8.5 mL, 8.50 mmol, 1.1 eq) diluted in DCM (7 mL) was added

dropwise. At the end of the addition, the reaction mixture was partitioned between DCM and aq. 1M HCl soln. The organic layer was washed with brine and separated through a phase separator cartridge. The solvent was removed under reduced pressure. The crude residue was purified by FC (Hept to 5% EtOAc) to give the title compound. LC-MS (1): t_R = 1.21 min; $[M+H]^+$: 383.2.

- 5 **(RS)-2-Ethylhexyl 3-((2-(((1S*,2S*)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)propanoate:** Was synthesized using (1R*,2S*)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexan-1-ol and (RS)-2-ethylhexyl 3-((2-hydroxy-4-methylphenyl)sulfonyl)propanoate in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R = 1.42 min; $[M+H]^+$: 721.1.
- 10 ***tert*-Butyl ((2-(((1S*,2S*)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using (RS)-2-ethylhexyl 3-((2-(((1S*,2S*)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)propanoate and *tert*-butyl L-prolinate in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R = 1.41 min; $[M+H]^+$: 706.5.
- 15 ***tert*-Butyl ((2-(((1S*,2S*)-2-(2-hydroxyethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((2-(((1S*,2S*)-2-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R = 1.03 and 1.04 min; $[M+H]^+$: 467.8.
- 20 ***tert*-Butyl ((4-methyl-2-(((1S*,2S*)-2-(2-oxoethyl)cyclohexyl)oxy)phenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((2-(((1S*,2S*)-2-(2-hydroxyethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R = 1.11 and 1.12 min; $[M+H]^+$: 466.2.
- 25 ***tert*-Butyl ((2-(((1S*,2S*)-2-(2-((4,4-difluorocyclohexyl)amino)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((4-methyl-2-(((1S*,2S*)-2-(2-oxoethyl)cyclohexyl)oxy)phenyl)sulfonyl)-L-prolinate and 4,4-difluorocyclohexylamine hydrochloride in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R = 0.94 and 0.95 min; $[M+H]^+$: 585.4.
- 25 **((2-(((1S*,2S*)-2-(2-((4,4-Difluorocyclohexyl)amino)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-proline hydrochloride:** Was synthesized using *tert*-butyl ((2-(((1S*,2S*)-2-(2-((4,4-difluorocyclohexyl)amino)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.194 to give the title compound. LC-MS (1): t_R = 0.80 and 0.81 min; $[M+H]^+$: 529.3.
- 30 **(9aS,13aS,17aS)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,12,13,13a,14,15,16,17,17a-dodecahydrodibenzo[b,k]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-one 5,5-dioxide and (9aS,13aR,17aR)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,12,13,13a,14,15,16,17,17a-dodecahydrodibenzo[b,k]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-one 5,5-dioxide:** Were synthesized using ((2-(((1S*,2S*)-2-(2-((4,4-difluorocyclohexyl)amino)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfonyl)-L-proline hydrochloride in analogy to Example 1.124. The soln. was purified by basic prep.

HPLC to give (9aS,13aS,17aS)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,12,13,13a,14,15,16,17,17a-dodecahydridibenzo[b,k]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-one 5,5-dioxide and (9aS,13aR,17aR)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,12,13,13a,14,15,16,17,17a-dodecahydridibenzo[b,k]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-one 5,5-dioxide. The absolute stereochemistry at the cyclohexyl was attributed arbitrarily. First eluting diastereomer: LC-MS (1): t_R = 1.09 min; $[M+H]^+$: 511.0. Second eluting diastereomer: LC-MS (1): t_R = 1.11 min; $[M+H]^+$: 511.0.

Example 1.256 (1²S,5¹R,5³R)-8-(4,4-Difluorocyclohexyl)-3⁶-methyl-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide and Example 1.257 (1²S,5¹S,5³S)-8-(4,4-Difluorocyclohexyl)-3⁶-methyl-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-

cyclohexanacyclononaphan-9-one 2,2-dioxide:

(RS)-2-Ethylhexyl 3-((2-hydroxy-6-methylpyridin-3-yl)thio)propanoate: 3-Bromo-6-methylpyridin-2-ol (10.0 g, 51.10 mmol, 1 eq) was dissolved in dioxane (511 mL). Xantphos Pd G3 (1.92 mg, 1.92 mmol, 0.04 eq), DIPEA (26.2 mL, 153.00 mmol, 3 eq) and 2-ethylhexyl 3-mercaptopropionate (14.2 mL, 61.30 mmol, 1.2 eq) were added in sequence and the resulting mixture was stirred at 80°C for 1.5h. After cooling to rt, the soln. was diluted with Et₂O and aq. 1M HCl soln. The org. layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 0.99 min; $[M+H]^+$: 326.1.

(RS)-2-Ethylhexyl 3-((2-hydroxy-6-methylpyridin-3-yl)sulfonyl)propanoate: m-CPBA (12.10 g, 54.10 mmol, 2.2 eq) was added portionwise to a stirred soln. of (RS)-2-ethylhexyl 3-((2-hydroxy-6-methylpyridin-3-yl)thio)propanoate (8.33 g, 24.60 mmol, 1 eq) in DCM (97 mL) at 0°C. The resulting suspension was vigorously stirred at rt for 1h. The suspension was filtered and the filtrate was diluted with DCM and washed with aq. sat. NaHCO₃ soln. The org. layer was washed with aq. sat. NaHCO₃ soln. and separated through a phase-separator cartridge. The solvent was removed under reduced pressure. The residue was purified by FC (Hept to 90% EtOAc) to give the title compound. LC-MS (1): t_R = 0.90 min; $[M+H]^+$: 358.1.

(RS)-2-Ethylhexyl 3-(((1R*,3R*)-3-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridin-3-yl)sulfonyl)propanoate: Was synthesized using (RS)-2-ethylhexyl 3-((2-hydroxy-6-methylpyridin-3-yl)sulfonyl)propanoate and (1R*,3S*)-3-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)cyclohexan-1-ol in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R = 1.41 min; $[M+H]^+$: 722.0.

tert-Butyl ((2-(((1R*,3R*)-3-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate: Was synthesized using (RS)-2-ethylhexyl 3-(((1R*,3R*)-3-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridin-3-yl)sulfonyl)propanoate and tert-butyl L-prolinate in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R = 1.39 min; $[M+H]^+$: 707.8.

tert-Butyl ((2-(((1R*,3R*)-3-(2-hydroxyethyl)cyclohexyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate: Was synthesized using tert-Butyl ((2-(((1R*,3R*)-3-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridin-

3-yl)sulfonyl)-L-prolinate in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R = 1.03 min; $[M+H]^+$: 469.2.

5 **tert-Butyl ((6-methyl-2-(((1R*,3S*)-3-(2-oxoethyl)cyclohexyl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((2-(((1R*,3R*)-3-(2-hydroxyethyl)cyclohexyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.124 to give the title compound. LC-MS (2): t_R = 1.17 min; $[M+H]^+$: 467.1.

tert-Butyl ((2-(((1R*,3R*)-3-(2-((4,4-difluorocyclohexyl)amino)ethyl)cyclohexyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate: Was synthesized using *tert*-butyl ((6-methyl-2-(((1R*,3S*)-3-(2-oxoethyl)cyclohexyl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate and 4,4-difluorocyclohexylamine hydrochloride in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R = 0.92 and 0.93 min; $[M+H]^+$: 586.1.

10 **((2-(((1R*,3R*)-3-(2-((4,4-Difluorocyclohexyl)amino)ethyl)cyclohexyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-proline hydrochloride:** Was synthesized using *tert*-butyl ((2-(((1R*,3R*)-3-(2-((4,4-difluorocyclohexyl)amino)ethyl)cyclohexyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.194 to give the title compound. LC-MS (1): t_R = 0.77 and 0.78 min; $[M+H]^+$: 530.0.

15 **(1²S,5¹R,5³R)-8-(4,4-Difluorocyclohexyl)-3⁶-methyl-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide and (1²S,5¹S,5³S)-8-(4,4-Difluorocyclohexyl)-3⁶-methyl-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide:** Were synthesized using ((2-(((1R*,3R*)-3-(2-((4,4-difluorocyclohexyl)amino)ethyl)cyclohexyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-proline hydrochloride in analogy to Example 1.124. The soln. was purified by basic prep. HPLC to give (1²S,5¹R,5³R)-8-(4,4-Difluorocyclohexyl)-3⁶-methyl-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide and (1²S,5¹S,5³S)-8-(4,4-Difluorocyclohexyl)-3⁶-methyl-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide. First eluting diastereomer: LC-MS (1): t_R = 1.11 min; $[M+H]^+$: 512.0. Second eluting diastereomer: LC-MS (1): t_R = 1.15 min; $[M+H]^+$: 512.0.

25 **Example 1.259** 4-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-2,2-dimethylbutanenitrile: Was synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((4-methyl-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.14. LC-MS (1): t_R = 0.87 min; $[M+H]^+$: 462.3.

Example 1.260 (S,Z)-6-(4,4-Difluorocyclohexyl)-2⁵-methyl-3-thia-6-aza-1(3,5)-oxadiazola-4(1,2)-pyrrolidina-2(1,2)-benzenacyclodecaphan-5-one 3,3-dioxide:

30 **Methyl 5-((4,4-difluorocyclohexyl)amino)pentanoate:** 4,4-Difluorocyclohexanone (1.23 g, 8.93 mmol, 1.05 eq) and AcOH (0.5 mL, 8.50 mmol, 1 eq) were added to a soln. of methyl 5-aminopentanoate (1.5 g, 8.50 mmol, 1 eq) in THF (4 mL). After 30 min, NaBH(OAc)₃ (2.79 g, 12.80 mmol, 1.5 eq) was added and the mixture was stirred at rt overnight. The mixture was then diluted with DCM and washed with aq. sat. NaHCO₃ soln. The solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS
35 (1): t_R = 1.04 min; $[M+H]^+$: 350.3.

Methyl 5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentanoate: At 0°C, Boc₂O (1.75 g, 7.94 mmol, 1.1 eq) was added to a soln. of methyl 5-((4,4-difluorocyclohexyl)amino)pentanoate (2.00 g, 7.22 mmol, 1 eq) and TEA (2.5 mL, 18.10 mmol, 2.5 eq) in DCM (50 mL). The mixture was stirred at rt for 3h, then washed with brine. The org. layer was separated, dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 0.50 min; [M+H]⁺: 250.3.

5-((*tert*-Butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentanoic acid: Aq. 1M LiOH soln. (0.48 mL, 0.48 mmol, 1.2 eq) was added to a soln. of methyl 5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentanoate (140 mg, 0.40 mmol, 1 eq) in THF (4 mL). The mixture was stirred at rt for 4h and the solvent removed under reduced pressure. The crude product was used without further purification in the next step. LC-MS (1): t_R = 0.91 min; [M+H]⁺: 336.3.

***tert*-Butyl ((2-cyano-4-methylphenyl)sulfonyl)-L-prolinate:** At 0°C, DIPEA (4.9 mL, 27.80 mmol, 3 eq) and DMAP (114 mg, 0.93 mmol, 0.1 eq) were added to a soln. of 2-cyano-4-methylbenzene-1-sulfonyl chloride (2.00 g, 9.27 mmol, 1 eq) in DCM (10 mL), followed by addition of *tert*-butyl L-prolinate (1.64 g, 9.27 mmol, 1 eq). The mixture was stirred at rt for 1h. After addition of sat. aq. NaHCO₃ soln., the mixture was extracted with DCM, and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 0.98 min; [M+H]⁺: 351.0.

***tert*-Butyl ((2-(N-hydroxycarbamimidoyl)-4-methylphenyl)sulfonyl)-L-prolinate:** Hydroxylamine hydrochloride (130 mg, 1.85 mmol, 1.3 eq) and K₂CO₃ (197 mg, 1.43 mmol, 1 eq) were added to a soln. of *tert*-butyl ((2-cyano-4-methylphenyl)sulfonyl)-L-prolinate (500 mg, 1.43 mmol, 1 eq) in EtOH (10 mL). The mixture was heated to reflux for 1h, cooled to rt, filtered, and the solvent removed under reduced pressure. The product was used in the next step without purification. LC-MS (1): t_R = 0.69 min; [M+H]⁺: 384.3.

***tert*-Butyl ((2-(5-(4-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)butyl)-1,2,4-oxadiazol-3-yl)-4-methylphenyl)sulfonyl)-L-prolinate:** HATU (221 mg, 0.39 mmol, 1.5 eq) was added to a soln. of *tert*-butyl ((2-(N-hydroxycarbamimidoyl)-4-methylphenyl)sulfonyl)-L-prolinate (149 mg, 0.39 mmol, 1 eq) and 5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentanoic acid (130 mg, 0.39 mmol, 1 eq) in DMF (2 mL). The mixture was stirred for 30 min at rt. Tripotassium phosphate (82 mg, 0.39 mmol, 1 eq) was added and the mixture was heated to 115°C for 1 day. The mixture was then cooled, filtered, and the solvent removed partially under reduced pressure. The residue was diluted in EtOAc and washed with H₂O. The org. layer was dried over MgSO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 1.22 min; [M+H]⁺: 683.5.

((2-(5-(4-((4,4-Difluorocyclohexyl)amino)butyl)-1,2,4-oxadiazol-3-yl)-4-methylphenyl)sulfonyl)-L-proline: *tert*-Butyl ((2-(5-(4-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)butyl)-1,2,4-oxadiazol-3-yl)-4-methylphenyl)sulfonyl)-L-prolinate (107 mg, 0.12 mmol, 1 eq) was dissolved in 4M HCl soln. in dioxane (1.5 mL, 2.34 mmol, 20 eq), and the resulting soln. was stirred at rt for 20h. The solvent was removed under reduced

pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R =0.72 min; $[M+H]^+$: 527.3.

(S,Z)-6-(4,4-Difluorocyclohexyl)-2^s-methyl-3-thia-6-aza-1(3,5)-oxadiazola-4(1,2)-pyrrolidina-2(1,2)-benzenacyclodecaphan-5-one 3,3-dioxide: DIPEA (0.16 mL, 0.91 mmol, 8 eq) and HATU (87 mg, 0.23 mmol, 2 eq) were added to a soln. of ((2-(5-(4-((4,4-difluorocyclohexyl)amino)butyl)-1,2,4-oxadiazol-3-yl)-4-methylphenyl)sulfonyl)-L-proline (80 mg, 0.11 mmol, 1 eq) in DMF (2 mL). The mixture was shaken at rt for 15 min. The mixture was purified by acidic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.02 min; $[M+H]^+$: 509.3.

Example 1.261 (S)-6-(4,4-Difluorocyclohexyl)-2^s-methyl-3-thia-6-aza-1(2,5)-oxadiazola-4(1,2)-pyrrolidina-2(1,2)-benzenacyclononaphan-5-one 3,3-dioxide:

***tert*-Butyl 2-(2-bromo-5-methylbenzoyl)hydrazine-1-carboxylate:** 50% Propanephosphonic acid anhydride soln. in DMF (13.5 mL, 0.02 mol, 1.1 eq) was dropwise added to a soln. of 2-bromo-5-methylbenzoic acid (4.60 g, 0.021 mol, 1 eq), *tert*-butyl carbazate (3.05 g, 0.023 mol, 1.1 eq) and DIPEA (8.0 mL, 0.046 mol, 2.2 eq) in DMF (25 mL). The mixture was stirred at rt for 1h. The mixture was partitioned between H₂O and EtOAc. The org. layer was washed with brine, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The crude was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 0.83 min; $[M-tBu+H]^+$: 273.1.

2-Bromo-5-methylbenzohydrazide: *tert*-Butyl 2-(2-bromo-5-methylbenzoyl)hydrazine-1-carboxylate (6.16 g, 18.50 mmol, 1 eq) was dissolved in 3M HCl soln. in cyclopentyl methyl ether (50.0 mL, 1.23 mol, 66 eq). The mixture was stirred at rt for 2h. The solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.52 min; $[M+H]^+$: 229.1.

Benzyl 4-(2-(2-bromo-5-methylbenzoyl)hydrazineyl)-4-oxobutyl)carbamate: HATU (3.90 g, 9.94 mmol, 1.1 eq) was added portionwise to a soln. of *tert*-butyl 2-(2-bromo-5-methylbenzoyl)hydrazine-1-carboxylate (2.40 g, 9.04 mmol, 1 eq), 4-(((benzyloxy)carbonyl)amino)butanoic acid (2.36 g, 9.94 mmol, 1.1 eq), and DIPEA (7.9 mL, 45.20 mmol, 5 eq) in DMF (30 mL), and the resulting mixture was stirred at rt for 2h. Then H₂O was added to the mixture and the resulting precipitate was filtered and dried. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.83 min; $[M+H]^+$: 450.0.

N'-(4-Aminobutanoyl)-2-bromo-5-methylbenzohydrazide: TMSI (1.10 mL, 7.18 mmol, 4 eq) was added dropwise to a soln. of benzyl 4-(2-(2-bromo-5-methylbenzoyl)hydrazineyl)-4-oxobutyl)carbamate (830 mg, 1.80 mmol, 1 eq) in MeCN (50 mL). After the addition, the solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.44 min; $[M+H]^+$: 314.2.

2-Bromo-N'-(4-((4,4-difluorocyclohexyl)amino)butanoyl)-5-methylbenzohydrazide: N'-(4-Aminobutanoyl)-2-bromo-5-methylbenzohydrazide (1.78 g, 3.00 mmol, 1 eq), 4,4-difluorocyclohexanone (457 mg, 3.30 mmol, 1.1 eq) and AcOH (0.17 mL, 3.00 mmol, 1 eq) were dissolved in THF (25 mL). NaBH(OAc)₃ (984 mg, 4.50 mmol, 1.5 eq) was added and the mixture was stirred at rt for 1h. The mixture was partitioned between EtOAc and aq. 1M HCl

soln. The aq. layer was basified using aq. sat. Na_2CO_3 soln. and extracted with EtOAc. The org. layer was washed with brine, dried over MgSO_4 , filtered and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.64 min; $[\text{M}+\text{H}]^+$: 434.0.

- tert*-Butyl (4-(2-(2-bromo-5-methylbenzoyl)hydrazineyl)-4-oxobutyl)(4,4-difluorocyclohexyl)carbamate:** 2M Boc_2O soln. in DCM (0.24 mL, 1.27 mmol, 1.2 eq) was added to a soln. of 2-bromo-N'-((4,4-difluorocyclohexyl)amino)butanoyl)-5-methylbenzohydrazide (580 mg, 1.06 mmol, 1 eq) and TEA (0.37 mL, 2.65 mmol, 2.5 eq) in DCM (25 mL). The resulting mixture was stirred at rt for 3h. The reaction mixture was partitioned between DCM and aq. 1M HCl soln. The org. layer was washed with brine, dried over MgSO_4 , filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 0.97 min; $[\text{M}+\text{H}]^+$: 534.2.

- tert*-Butyl (4-(2-(2-(benzylthio)-5-methylbenzoyl)hydrazineyl)-4-oxobutyl)(4,4-difluorocyclohexyl)carbamate:** Xantphos Pd G3 (21 mg, 0.02 mmol, 0.05 eq) was added to a soln. of 2-bromo-N'-((4,4-difluorocyclohexyl)amino)butanoyl)-5-methylbenzohydrazide (223 mg, 0.41 mmol, 1 eq), benzyl mercaptan (54 μL , 0.45 mmol, 1.1 eq) and DIPEA (0.14 mL, 0.80 mmol, 1.95 eq) in THF (5 mL). The mixture was heated under reflux overnight. The solvent was removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 1.07 min; $[\text{M}+\text{H}]^+$: 576.4.

- tert*-Butyl (3-(5-(2-(benzylthio)-5-methylphenyl)-1,3,4-oxadiazol-2-yl)propyl)(4,4-difluorocyclohexyl)carbamate:** p-Toluenesulfonyl chloride (67 mg, 0.34 mmol, 1.5 eq) was added to a soln. of *tert*-butyl (4-(2-(2-(benzylthio)-5-methylbenzoyl)hydrazineyl)-4-oxobutyl)(4,4-difluorocyclohexyl)carbamate (162 mg, 0.23 mmol, 1 eq) and TEA (88 μL , 0.57 mmol, 2.5 eq) in DCM (10 mL). The mixture was stirred at rt for 1h. The mixture was washed with aq. sat. Na_2CO_3 soln. The org. layer was dried over MgSO_4 , filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 1.20 min; $[\text{M}+\text{H}]^+$: 558.4.

- tert*-Butyl (3-(5-(2-(chlorosulfonyl)-5-methylphenyl)-1,3,4-oxadiazol-2-yl)propyl)(4,4-difluorocyclohexyl)carbamate:** DCDMH (50 mg, 0.25 mmol, 1.5 eq) was added to a soln. of *tert*-butyl (3-(5-(2-(benzylthio)-5-methylphenyl)-1,3,4-oxadiazol-2-yl)propyl)(4,4-difluorocyclohexyl)carbamate (126 mg, 0.17 mmol, 1 eq) in H_2O (0.1 mL) and MeCN (6 mL). The mixture was stirred at rt for 5 min and then poured into aq. sat. NaHCO_3 soln. The org. layer was separated, dried over MgSO_4 , filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 1.13 min; $[\text{M}+\text{H}]^+$: 534.3.

- ((2-(5-(3-((*tert*-Butoxycarbonyl)(4,4-difluorocyclohexyl)amino)propyl)-1,3,4-oxadiazol-2-yl)-4-methylphenyl)sulfonyl)-L-proline:** L-Proline (20 mg, 0.17 mmol, 1.2 eq) in aq. 1M NaOH soln. (1 mL) was added to a soln. of *tert*-butyl (3-(5-(2-(chlorosulfonyl)-5-methylphenyl)-1,3,4-oxadiazol-2-yl)propyl)(4,4-difluorocyclohexyl)carbamate (20 mg, 0.17 mmol, 1.2 eq) in THF (3 mL) and the mixture was stirred at rt for 1h. The mixture was then acidified with aq. 2M HCl soln. and extracted with EtOAc. The combined org. layers were

washed with brine, 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. LC-MS (1): t_R =0.66 min; $[\text{M}+\text{H}]^+$: 613.0.

((2-(5-(3-((4,4-Difluorocyclohexyl)amino)propyl)-1,3,4-oxadiazol-2-yl)-4-methylphenyl)sulfonyl)-L-proline:

((2-(5-(3-((*tert*-Butoxycarbonyl)(4,4-difluorocyclohexyl)amino)propyl)-1,3,4-oxadiazol-2-yl)-4-

- 5 methylphenyl)sulfonyl)-L-proline (13 mg, 0.02 mmol, 1 eq) was dissolved in 4M HCl soln. in dioxane (1 mL), and the resulting soln. was stirred at rt for 1h. The solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R =0.66 min; $[\text{M}+\text{H}]^+$: 512.9.

(S)-6-(4,4-Difluorocyclohexyl)-2⁵-methyl-3-thia-6-aza-1(2,5)-oxadiazola-4(1,2)-pyrrolidina-2(1,2)-

benzenacyclononaphan-5-one 3,3-dioxide: : DIPEA (0.030 mL, 0.18 mmol, 8 eq) and HATU (17 mg, 0.044 mmol,

- 10 2 eq) were added to a soln. of ((2-(5-(3-((4,4-difluorocyclohexyl)amino)propyl)-1,3,4-oxadiazol-2-yl)-4-methylphenyl)sulfonyl)-L-proline (12 mg, 0.022 mmol, 1 eq) in DMF (5 mL). The mixture was stirred at rt for 30 min. The mixture was purified by acidic prep. HPLC to give the title compound. LC-MS (1): t_R =0.92 min; $[\text{M}+\text{H}]^+$: 495.2.

Example 1.262 (4²S,Z)-1⁴-Chloro-6-(4,4-difluorocyclohexyl)-2⁵-methyl-1¹H-3-thia-6-aza-1(3,1)-pyrazola-4(1,2)-pyrrolidina-2(1,2)-benzenacyclononaphan-5-one 3,3-dioxide:

(E)-1-(2-Bromo-5-methylphenyl)-3-(dimethylamino)prop-2-en-1-one: A mixture of 1-(2-bromo-5-methylphenyl)carbonone (2.50 g, 11.70 mmol, 1 eq) and N,N-dimethylformamide dimethyl acetal (7.80 mL, 58.70 mmol, 5 eq) was heated to 120°C for 5h. The solvent was partially removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 0.76 min; $[\text{M}+\text{H}]^+$: 268.2.

- 20 **3-(2-Bromo-5-methylphenyl)-1H-pyrazole:** A soln. of (E)-1-(2-bromo-5-methylphenyl)-3-(dimethylamino)prop-2-en-1-one (3.22 g, 11.80 mmol, 1 eq) and hydrazine hydrate (1.2 mL, 23.50 mmol, 2 eq) in EtOH (50 mL) was heated under reflux for 2h. The solvent was removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 0.86 min; $[\text{M}+\text{H}]^+$: 237.2.

3-(2-Bromo-5-methylphenyl)-1-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-1H-pyrazole: A suspension of 3-(2-bromo-5-methylphenyl)-1H-pyrazole (430 mg, 1.81 mmol, 1 eq), (3-bromopropoxy)-*tert*-butyldimethylsilane (551 mg, 2.18 mmol, 1.2 eq), K_2CO_3 (501 mg, 3.63 mmol, 2 eq) and tetrabutylammonium bromide (12 mg, 0.04 mmol, 0.02 eq) in MeCN (2 mL) was stirred at 100°C for 6h in under microwave heating. After cooling to rt, the inorganic salts were removed by filtration and the solvent was removed under reduced pressure. The residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.25 min; $[\text{M}+\text{H}]^+$: 409.2.

- 25 **3-(3-(2-Bromo-5-methylphenyl)-1H-pyrazol-1-yl)propan-1-ol:** 1M TBAF soln. in THF (0.60 mL, 0.57 mmol, 1.2 eq) was added to a soln. of 3-(2-bromo-5-methylphenyl)-1-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-1H-pyrazole (195 mg, 0.48 mmol, 1 eq) in THF (5 mL). The reaction mixture was stirred at rt for 20 min, then diluted with DCM and washed with H_2O . The org. layer was separated and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 0.84 min; $[\text{M}+\text{H}]^+$: 295.1.

3-(3-(2-Bromo-5-methylphenyl)-1H-pyrazol-1-yl)propanal: Sulfur trioxide pyridine complex (146 mg, 0.41 mmol, 1.1 eq) in DMSO (0.61 mL, 8.57 mmol, 22 eq) was added dropwise to a soln. of 3-(3-(2-bromo-5-methylphenyl)-1H-pyrazol-1-yl)propan-1-ol (115 mg, 0.39 mmol, 1 eq) in DCM (4 mL). After 30 min, the mixture was partitioned between H₂O and DCM. The layers were separated and the aq. layer was extracted with DCM. The combined org. layers were washed with brine, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.78 min; [M+H]⁺: 293.1.

N-(3-(3-(2-Bromo-5-methylphenyl)-1H-pyrazol-1-yl)propyl)-4,4-difluorocyclohexan-1-amine: 4,4-Difluorocyclohexylamine (38 mg, 0.27 mmol, 1 eq) and AcOH (16 mg, 0.27 mmol, 1 eq) were added to a soln. of 3-(3-(2-bromo-5-methylphenyl)-1H-pyrazol-1-yl)propanal (80 mg, 0.27 mmol, 1 eq) in THF (4 mL). After 30 min, NaBH(OAc)₃ (89 mg, 0.41 mmol, 1.5 eq) was added and the mixture was stirred at rt overnight. The mixture was diluted with DCM and washed with aq. sat. NaHCO₃ soln. The org. layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification.

tert-Butyl (3-(3-(2-bromo-5-methylphenyl)-1H-pyrazol-1-yl)propyl)(4,4-difluorocyclohexyl)carbamate: Boc₂O (47 mg, 0.21 mmol, 1.1 eq) was added to a soln. of N-(3-(3-(2-bromo-5-methylphenyl)-1H-pyrazol-1-yl)propyl)-4,4-difluorocyclohexan-1-amine (107 mg, 0.19 mmol, 1 eq) and TEA (68 µL, 0.49 mmol, 2.5 eq) in DCM (10 mL). The resulting mixture was stirred at rt for 48h. The reaction mixture was diluted with DCM and washed with brine. The org. layer was separated, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 1.18 min; [M+H]⁺: 514.1.

tert-Butyl (3-(3-(2-(benzylthio)-5-methylphenyl)-1H-pyrazol-1-yl)propyl)(4,4-difluorocyclohexyl)carbamate: Xantphos Pd G3 (7 mg, 0.008 mmol, 0.05 eq) was added to a soln. of tert-butyl (3-(3-(2-bromo-5-methylphenyl)-1H-pyrazol-1-yl)propyl)(4,4-difluorocyclohexyl)carbamate (80 mg, 0.16 mmol, 1 eq), benzyl mercaptan (20 µL, 0.17 mmol, 1.1 eq) and DIPEA (52 µL, 0.30 mmol, 1.95 eq) in dioxane (1 mL). The mixture was heated to 100°C for 20h. The solvent was removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 1.23 min; [M+H]⁺: 556.2.

tert-Butyl ((2-(1-(3-((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)propyl)-4-chloro-1H-pyrazol-3-yl)-4-methylphenyl)sulfonyl)-L-prolinate: DCDMH (1 mg, 0.072 mmol, 2 eq) was added to a soln. of tert-butyl (3-(3-(2-(benzylthio)-5-methylphenyl)-1H-pyrazol-1-yl)propyl)(4,4-difluorocyclohexyl)carbamate (20 mg, 0.036 mmol, 1 eq) in H₂O (1 µL) and dioxane (0.5 mL). The mixture was stirred at rt for 30 min and then poured into aq. sat. NaHCO₃ soln. The org. layer was separated, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was dissolved in DCM (10 mL) and cooled to 0°C. DIPEA (19 µL, 0.11 mmol, 3 eq) and DMAP (0.44 mg, 0.004 mmol, 0.1 eq) were added at rt followed by L-proline methyl ester hydrochloride (6 mg, 0.036 mmol, 1 eq). The mixture was stirred at rt for 1h. After addition of aq. sat. NaHCO₃ soln., the mixture was extracted with DCM. The org. layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by acidic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.20 min; [M+H]⁺: 667.1.

((2-(4-Chloro-1-(3-((4,4-difluorocyclohexyl)amino)propyl)-1H-pyrazol-3-yl)-4-methylphenyl)sulfonyl)-L-proline: *tert*-Butyl ((2-(1-(3-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)propyl)-4-chloro-1H-pyrazol-3-yl)-4-methylphenyl)sulfonyl)-L-prolinate (12 mg, 0.018 mmol, 1 eq) was dissolved in 4M HCl soln. in dioxane (1.5 mL, 0.36 mmol, 20 eq), and the resulting soln. was stirred at rt for 4h. The solvent was removed volatiles were under
5 reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.70 min; $[M+H]^+$: 511.3.

(4²S,Z)-1⁴-Chloro-6-(4,4-difluorocyclohexyl)-2⁵-methyl-1¹H-3-thia-6-aza-1(3,1)-pyrazola-4(1,2)-pyrrolidina-2(1,2)-benzenacyclonaphan-5-one 3,3-dioxide: DIPEA (18 μ L, 0.10 mmol, 8 eq) and HATU (10 mg, 0.026 mmol, 2 eq) were added to a soln. of ((2-(4-chloro-1-(3-((4,4-difluorocyclohexyl)amino)propyl)-1H-pyrazol-3-yl)-4-methylphenyl)sulfonyl)-L-proline (7 mg, 0.013 mmol, 1 eq) in DMF (2 mL). The mixture was stirred at rt for 15 min.
10 The mixture was purified by acidic prep. HPLC. To give the title compound LC-MS (1): t_R =1.02 min; $[M+H]^+$: 527.3.

Example 1.263 (8R,12aS)-11-(4,4-Difluorocyclohexyl)-3,8-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:

(RS)-5-((*tert*-Butyldiphenylsilyl)oxy)-3-methylpentan-1-ol: A soln. of *tert*-butyldiphenylsilyl chloride (10.1 mL, 39.00 mmol, 1 eq) in DCM (40 mL) was added dropwise at rt to a stirred soln. of 3-methyl-1,5-pentanediol (4.75 g, 39.00 mmol, 1 eq) and imidazole (5.31 g, 78.00 mmol, 2 eq) in DCM (90 mL) at 0°C. The mixture was stirred for 17h while warming up to rt. The mixture was washed with aq. 1M HCl soln. and H₂O. The org. layer was dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 30% EtOAc) to give the title compound. LC-MS (1): t_R = 1.18 min; $[M+H]^+$: 357.3.
15

2-Fluoro-6-methylpyridine-3-sulfonyl chloride: A soln. of 2-fluoro-6-methylpyridin-3-amine (20.00 g, 159.00 mmol, 1 eq) in aq. 32% HCl soln. (250 mL) was cooled to 0°C. A soln. of NaNO₂ (11.80 g, 166.00 mmol, 1.05 eq) in H₂O (30 mL) was added at 0°C to form the corresponding diazonium salt. In a second flask, SOCl₂ (50.2 mL, 682.00 mmol, 4.3 eq) was added dropwise to H₂O (250 mL) at 0°C, followed by CuCl (1.20 g, 11.80 mmol, 0.07 eq)). To the mixture was slowly added the diazonium solution at -10°C. The reaction mixture was stirred for 30 min,
20 then DCM was added. The org. layer was washed with H₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.66 min; $[M+H]^+$: not seen.
25

((2-Fluoro-6-methylpyridin-3-yl)sulfonyl)-L-proline: L-Proline (11.70 g, 101.00 mmol, 0.85 eq) was dissolved in H₂O (220 mL). The reaction mixture was cooled to 4°C and aq. 32% NaOH soln. (22.1 mL, 239.00 mmol, 2.0 eq) was added. A soln. of 2-fluoro-6-methylpyridine-3-sulfonyl chloride (25.00 g, 119.00 mmol, 1 eq) in THF (20 mL) was added dropwise. The mixture was stirred for 1h, and DCM was added. The aq. layer was acidified to pH1 with aq. 2M HCl soln., and extracted again with iPrOAc. The org. layer was washed with H₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.66 min; $[M+H]^+$: 289.1.
30

((2-Methoxy-6-methylpyridin-3-yl)sulfonyl)-L-proline: To a soln. of ((2-fluoro-6-methylpyridin-3-yl)sulfonyl)-L-proline (52.00 g, 0.18 mol, 1 eq) in MeOH (100 mL) was added aq. 25% NaOH soln. (117.00 g, 0.54 mol, 3 eq) in MeOH (100 mL). The mixture was stirred for 15 min, and H₂O was added. The solvents were partially removed under reduced pressure, and the remaining mixture was acidified with aq. 2M HCl soln. The mixture was extracted with iPrOAc. The org. layer was washed with H₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R= 0.70 min; [M+H]⁺: 301.2.

Methyl ((2-hydroxy-6-methylpyridin-3-yl)sulfonyl)-L-prolinate: ((2-Methoxy-6-methylpyridin-3-yl)sulfonyl)-L-proline (29.00 g, 96.60 mmol, 1 eq) was dissolved in 4M HCl soln. in dioxane. The reaction mixture was stirred at 75°C for 6h. The solution was cooled down to rt and MeOH was added. The solvent was removed under reduced pressure. The residue was dissolved in DCM and aq. sat. Na₂CO₃ soln. The org. layer was washed with H₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was taken up in iPrOAc and the mixture was heated to 80°C. After cooling down, the mixture was filtered and the solid was dried under reduced pressure to give the title compound. LC-MS (1): t_R= 0.57 min; [M+H]⁺: 301.2.

Methyl ((2-(((RS)-5-((tert-butylidiphenylsilyl)oxy)-3-methylpentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate: Was synthesized using methyl ((2-hydroxy-6-methylpyridin-3-yl)sulfonyl)-L-prolinate and (RS)-5-((tert-butylidiphenylsilyl)oxy)-3-methylpentan-1-ol in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R= 1.33 min; [M+H]⁺: 639.4.

Methyl ((2-(((R)-5-hydroxy-3-methylpentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate and Methyl ((2-(((S)-5-hydroxy-3-methylpentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate: Were synthesized using methyl ((2-(((RS)-5-((tert-butylidiphenylsilyl)oxy)-3-methylpentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.75. The stereoisomers were separated by prep. chiral SFC (SFC 17 method) to give methyl ((2-(((R)-5-hydroxy-3-methylpentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate (first eluting diastereomer) and methyl ((2-(((S)-5-hydroxy-3-methylpentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate (second eluting diastereomer). First eluting diastereomer: LC-MS (1): t_R= 0.88 min; [M+H]⁺: 401.2. Second eluting diastereomer: LC-MS (1): t_R= 0.88 min; [M+H]⁺: 401.2.

Methyl ((6-methyl-2-(((S)-3-methyl-5-oxopentyl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate: Was synthesized using methyl ((2-(((R)-5-hydroxy-3-methylpentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.7 to give the title compound. LC-MS (1): t_R= 0.94 min; [M+H]⁺: 399.3.

Methyl ((2-(((R)-5-((4,4-difluorocyclohexyl)amino)-3-methylpentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate: Was synthesized using methyl ((6-methyl-2-(((S)-3-methyl-5-oxopentyl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate and 4,4-difluorocyclohexylamine hydrochloride in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R= 0.80 min; [M+H]⁺: 518.3.

((2-(((R)-5-((4,4-Difluorocyclohexyl)amino)-3-methylpentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-proline: Was synthesized using methyl ((2-(((R)-5-((4,4-difluorocyclohexyl)amino)-3-methylpentyl)oxy)-6-methylpyridin-3-

yl)sulfonyl)-L-prolinate in analogy to Example 1.8 to give the title compound. LC-MS (1): t_R = 0.74 min; $[M+H]^+$: 504.3.

5 **(8R,12aS)-11-(4,4-Difluorocyclohexyl)-3,8-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:** Was synthesized using methyl ((2-(((R)-5-((4,4-difluorocyclohexyl)amino)-3-methylpentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-proline in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 1.05 min; $[M+H]^+$: 486.3.

Example 1.264 (8S,12aS)-11-(4,4-Difluorocyclohexyl)-3,8-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:

10 **Methyl ((6-methyl-2-(((R)-3-methyl-5-oxopentyl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate:** Was synthesized using methyl ((2-(((S)-5-hydroxy-3-methylpentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.7 to give the title compound. LC-MS (1): t_R = 0.94 min; $[M+H]^+$: 399.3.

15 **Methyl ((2-(((S)-5-((4,4-difluorocyclohexyl)amino)-3-methylpentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate:** Was synthesized using methyl ((6-methyl-2-(((R)-3-methyl-5-oxopentyl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate and 4,4-difluorocyclohexylamine hydrochloride in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 0.80 min; $[M+H]^+$: 518.3.

((2-(((S)-5-((4,4-Difluorocyclohexyl)amino)-3-methylpentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-proline: Was synthesized using methyl ((2-(((S)-5-((4,4-difluorocyclohexyl)amino)-3-methylpentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.8 to give the title compound. LC-MS (1): t_R = 0.74 min; $[M+H]^+$: 504.3.

20 **(8S,12aS)-11-(4,4-Difluorocyclohexyl)-3,8-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:** Was synthesized using methyl ((2-(((S)-5-((4,4-difluorocyclohexyl)amino)-3-methylpentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-proline in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 1.04 min; $[M+H]^+$: 486.3.

25 **Example 1.266 (1R,3R)-3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile:**

30 ***tert*-Butyl ((1R,3R)-3-carbamoyl-3-methylcyclohexyl)carbamate:** A suspension of (1R,3R)-3-(((*tert*-butoxy)carbonyl)amino)-1-methylcyclohexane-1-carboxylic acid (1.02 g, 3.77 mmol, 1 eq) in DCM (38 mL) was cooled to 0°C. (Diethylamino)sulfur trifluoride (0.63 mL, 4.53 mmol, 1.2 eq) was added dropwise and the resulting soln. was stirred at rt. After 15 min, 7M NH₃ soln. in MeOH (8.00 mL, 56.60 mmol, 15 eq) was added and the mixture was stirred at rt for 1h. H₂O was added, and the solvents were removed under reduced pressure. The residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 0.71 min; $[M+H]^+$: 257.3.

***tert*-Butyl ((1R,3R)-3-cyano-3-methylcyclohexyl)carbamate:** A soln. of *tert*-butyl ((1R,3R)-3-carbamoyl-3-methylcyclohexyl)carbamate (792 mg, 3.09 mmol, 1 eq) in THF (15 mL) was cooled to 0°C. Et₃N (2.10 mL, 14.80

mmol, 4.8 eq) was added, followed by trifluoroacetic anhydride (0.69 mL, 4.94 mmol, 1.6 eq). The mixture was stirred at 0°C for 1h. H₂O and DCM were added. The layers were separated and the org. layer was washed with H₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 40% EtOAc) to give the title compound. LC-MS (1): t_R = 0.89 min; [M+H]⁺: 239.3.

- 5 **(1R,3R)-3-Amino-1-methylcyclohexane-1-carbonitrile hydrochloride**: 4M HCl soln. in dioxane (2.70 mL, 10.60 mmol, 5 eq) was added to a soln. of *tert*-butyl ((1R,3R)-3-cyano-3-methylcyclohexyl)carbamate (503 mg, 2.11 mmol, 1 eq) in DCM (20 mL) at 0°C, and the mixture was stirred overnight while warming up to rt. The solvents were removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.53 min; [M+H]⁺: 139.3.

- 10 ***tert*-Butyl ((2-(((R)-6-(((1R,3R)-3-cyano-3-methylcyclohexyl)amino)hexan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate**: Was synthesized using (1R,3R)-3-amino-1-methylcyclohexane-1-carbonitrile hydrochloride and *tert*-butyl ((4-methyl-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 0.93 min; [M+H]⁺: 561.9.

- ((2-(((R)-6-(((1R,3R)-3-Cyano-3-methylcyclohexyl)amino)hexan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-proline**: Was synthesized using *tert*-butyl ((2-(((R)-6-(((1R,3R)-3-cyano-3-methylcyclohexyl)amino)hexan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.9 to give the title compound. LC-MS (1): t_R = 0.73 min; [M+H]⁺: 506.3.

- (1R,3R)-3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile**: Was synthesized using ((2-(((R)-6-(((1R,3R)-3-cyano-3-methylcyclohexyl)amino)hexan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-proline in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 1.04 min; [M+H]⁺: 488.3.

- Example 1.267 (1S,3S)-3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile**: (1S,3S)-3-Amino-1-methylcyclohexane-1-carbonitrile hydrochloride: Was synthesized using (1S,3S)-3-(((*tert*-butoxy)carbonyl)amino)-1-methylcyclohexane-1-carboxylic acid in analogy to Example 1.266 to give the title compound. LC-MS (1): t_R = 0.53 min; [M+H]⁺: 139.29.

- (1S,3S)-3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile**: Was synthesized using *tert*-butyl ((4-methyl-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate and (1S,3S)-3-amino-1-methylcyclohexane-1-carbonitrile hydrochloride in analogy to Example 1.266 to give the title compound. LC-MS (1): t_R = 1.04 min; [M+H]⁺: 488.2.

Example 1.268 (1R,3S)-3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-

carbonitrile or (1S,3R)-3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile:

(1R*,3S*)-3-Amino-1-methylcyclohexane-1-carbonitrile hydrochloride: Was synthesized using (1R*,3S*)-3-(((tert-butoxy)carbonyl)amino)-1-methylcyclohexane-1-carboxylic acid in analogy to Example 1.266 to give the title compound.

(1R,3S)-3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile and (1S,3R)-3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile : Was synthesized using *tert*-butyl ((4-methyl-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate and (1R*,3S*)-3-amino-1-methylcyclohexane-1-carbonitrile hydrochloride in analogy to Example 1.266. The residue was purified by prep.chiral SFC (SFC 20 method) to give (1R,3S)-3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile and (1S,3R)-3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile. The stereochemistry at the cyclohexyl ring was attributed arbitrarily. First eluting diastereomer: LC-MS (1): t_R = 1.04 min; $[M+H]^+$: 488.2. Second eluting diastereomer: LC-MS (1): t_R = 1.04 min; $[M+H]^+$: 488.2.

Example 1.269 (1R,4s)-4-((6R,12aS)-4-Fluoro-3,6-dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile: Was synthesized using methyl ((3-fluoro-4-methyl-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate 4-amino-1-methyl-cyclohexanecarbonitrile hydrochloride in analogy to Example 1.192 to give the title compound. LC-MS (1): t_R = 1.09 min; $[M+H]^+$: 506.3.

Example 1.270 (9aS,14aR,17aR)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,11,12,13,14,14a,15,17,17a-dodecahydro-10H-benzo[b]furo[3,4-l]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide and **Example 1.271** (9aS,14aS,17aS)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,11,12,13,14,14a,15,17,17a-dodecahydro-10H-benzo[b]furo[3,4-l]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide:

(RS)-2-Ethylhexyl 3-((2-(((3R*,4R*)-4-allyltetrahydrofuran-3-yl)oxy)-4-methylphenyl)sulfonyl)propanoate: Was synthesized using *trans*-4-(prop-2-en-1-yl)oxolan-3-ol and *rac*-(R)-2-ethylhexyl 3-((2-hydroxy-4-methylphenyl)sulfonyl)propanoate in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R = 1.17 min; $[M+H]^+$: 468.1.

tert-Butyl ((2-(((3R*,4R*)-4-allyltetrahydrofuran-3-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using (RS)-2-ethylhexyl 3-((2-(((3R*,4R*)-4-allyltetrahydrofuran-3-yl)oxy)-4-

methylphenyl)sulfonyl)propanoate and *tert*-butyl L-prolinate in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R = 1.07 min; $[M+H]^+$: 452.3.

***tert*-Butyl ((2-(((3*R**,4*R**)-4-(3-hydroxypropyl)tetrahydrofuran-3-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** 1M BH₃ soln. in THF (0.62 mL, 0.62 mmol, 1.2 eq) was added at 0°C to the stirred soln. of *tert*-butyl ((2-(((3*R**,4*R**)-4-allyltetrahydrofuran-3-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate (232 mg, 0.51 mmol, 1 eq) in THF (1 mL). The resulting soln. was then allowed to warm up to rt and stirred for 1h. The reaction mixture was cooled to 0°C and then aq. 4M NaOH soln. (0.13 mL, 0.51 mmol, 1 eq) and aq. 30% (w/w) hydrogen peroxide soln. (53 µL, 0.51 mmol, 1 eq) were added in sequence. The reaction mixture was allowed to warm up to rt and stirred for 2h. The reaction mixture was quenched with aq. sat. Na₂SO₃ soln. and extracted with EtOAc. The org. layer was washed with brine, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 80% EtOAc) to give the title compound. LC-MS (1): t_R = 0.91 min; $[M+H]^+$: 470.1.

***tert*-Butyl ((4-methyl-2-(((3*R**,4*R**)-4-(3-oxopropyl)tetrahydrofuran-3-yl)oxy)phenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((2-(((3*R**,4*R**)-4-(3-hydroxypropyl)tetrahydrofuran-3-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R = 0.97 min; $[M+H]^+$: 468.1.

***tert*-Butyl ((2-(((3*R**,4*R**)-4-(3-((4,4-difluorocyclohexyl)amino)propyl)tetrahydrofuran-3-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((4-methyl-2-(((3*R**,4*R**)-4-(3-oxopropyl)tetrahydrofuran-3-yl)oxy)phenyl)sulfonyl)-L-prolinate and 4,4-difluorocyclohexylamine hydrochloride in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R = 0.86 min; $[M+H]^+$: 587.1.

((2-(((3*R,4*R**)-4-(3-((4,4-Difluorocyclohexyl)amino)propyl)tetrahydrofuran-3-yl)oxy)-4-methylphenyl)sulfonyl)-L-proline hydrochloride:** Was synthesized using *tert*-butyl ((2-(((3*R**,4*R**)-4-(3-((4,4-difluorocyclohexyl)amino)propyl)tetrahydrofuran-3-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.194 to give the title compound. LC-MS (1): t_R = 0.68 and 0.70 min; $[M+H]^+$: 531.0.

(9a*S*,14a*R*,17a*R*)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,11,12,13,14,14a,15,17,17a-dodecahydro-10H-benzo[*b*]furo[3,4-*l*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide and (9a*S*,14a*S*,17a*S*)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,11,12,13,14,14a,15,17,17a-dodecahydro-10H-benzo[*b*]furo[3,4-*l*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide: Were synthesized using ((2-(((3*R**,4*R**)-4-(3-((4,4-difluorocyclohexyl)amino)propyl)tetrahydrofuran-3-yl)oxy)-4-methylphenyl)sulfonyl)-L-proline hydrochloride in analogy to Example 1.124. The residue was purified by basic prep. HPLC to give (9a*S*,14a*R*,17a*R*)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,11,12,13,14,14a,15,17,17a-dodecahydro-10H-benzo[*b*]furo[3,4-*l*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide and (9a*S*,14a*S*,17a*S*)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,11,12,13,14,14a,15,17,17a-dodecahydro-10H-benzo[*b*]furo[3,4-*l*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide. The stereochemistry at the tetrahydrofurane ring was attributed arbitrarily. First eluting diastereomer: LC-MS (1): t_R = 0.95 min; $[M+H]^+$: 513.0. Second eluting diastereomer: LC-MS (1): t_R = 1.01 min; $[M+H]^+$: 513.0.

Example 1.272 (1²S,5¹S,5³S)-8-(4,4-Difluorocyclohexyl)-3⁴-methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclopentanacyclononaphan-9-one 2,2-dioxide and **Example 1.273** (1²S,5¹S,5³S)-8-(4,4-Difluorocyclohexyl)-3⁴-methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclopentanacyclononaphan-9-one 2,2-dioxide:

- 5 **(1R*,3S*)-3-(2-Hydroxyethyl)cyclopentan-1-ol**: 1M LiAlH₄ soln. in THF (3.5 mL, 3.50 mmol, 1.1 eq) was added dropwise at 0°C, to a stirred soln. of methyl 2-(*trans*-3-hydroxycyclopentyl)acetate (500 mg, 3.16 mmol, 1 eq) in THF (10 mL). The resulting soln. was stirred at 0°C for 45 min. The reaction mixture was quenched by addition of H₂O followed by aq. 15% NaOH soln. and H₂O. The reaction mixture was stirred at rt until a fine white suspension was formed. The reaction mixture was filtered over a pad of Celite and the solvent was removed under reduced
- 10 pressure. The residue was purified by FC (DCM to 5% MeOH) to give the title compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ: 4.30-4.32 (m, 2 H), 4.09-4.13 (m, 1 H), 3.38 (m, 2 H), 2.04-2.13 (m, 1 H), 1.75-1.85 (m, 2 H), 1.61-1.67 (m, 1 H), 1.36-1.43 (m, 3 H), 1.19 (ddd, *J*₁ = 5.8 Hz, *J*₂ = 9.5 Hz, *J*₃ = 12.9 Hz, 1 H), 0.99-1.07 (m, 1 H).

- (1R*,3S*)-3-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)cyclopentan-1-ol**: (1R*,3S*)-3-(2-Hydroxyethyl)cyclopentan-1-ol (374 mg, 2.87 mmol, 1 eq) was dissolved in DCM (8 mL). Imidazole (299 mg, 4.31 mmol, 1.5 eq) and DMAP
- 15 (35 mg, 0.29 mmol, 0.1 eq) were added at rt and the resulting soln. was cooled to 0°C. 1M *tert*-Butylchlorodiphenylsilane soln. in DCM (8.5 mL, 8.5 mmol, 1.1 eq) diluted in DCM (5 mL) was added dropwise. After the addition, the reaction mixture was partitioned between DCM and aq. 1M HCl soln. The organic layer was washed with brine and separated through a phase separator cartridge. The solvent was removed under reduced pressure. The residue was purified by FC (Hept to 5% EtOAc) to give the title compound. LC-MS (1): *t*_R = 1.18 min; [M+H]⁺: 369.3.
- 20

- (RS)-2-Ethylhexyl 3-((2-(((1S*,3S*)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopentyl)oxy)-4-methylphenyl)sulfonyl)propanoate**: Was synthesized using (1R*,3S*)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopentan-1-ol and (RS)-2-ethylhexyl 3-((2-hydroxy-4-methylphenyl)sulfonyl)propanoate in analogy to Example 1.124 to give the title compound. LC-MS (1): *t*_R = 1.42 min; [M+H]⁺: 707.3.
- 25

- tert*-Butyl ((2-(((1S*,3S*)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate**: Was synthesized using (RS)-2-ethylhexyl 3-((2-(((1S*,3S*)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopentyl)oxy)-4-methylphenyl)sulfonyl)propanoate and *tert*-butyl L-prolinate in analogy to Example 1.124 to give the title compound. LC-MS (1): *t*_R = 1.39 min; [M+H]⁺: 692.5.

- 30 ***tert*-Butyl ((2-(((1S*,3S*)-3-(2-hydroxyethyl)cyclopentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate**: Was synthesized using *tert*-butyl ((2-(((1S*,3S*)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.124 to give the title compound. LC-MS (1): *t*_R = 1.01 and 1.02 min; [M+H]⁺: 454.1.

- tert-Butyl ((4-methyl-2-(((1S*,3S*)-3-(2-oxoethyl)cyclopentyl)oxy)phenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((2-(((1S*,3S*)-3-(2-hydroxyethyl)cyclopentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.124 to give the title compound. LC-MS (1): *t_R*= 1.07 min; [M+H]⁺: 452.1.
- tert-Butyl ((2-(((1S*,3S*)-3-(2-((4,4-difluorocyclohexyl)amino)ethyl)cyclopentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((4-methyl-2-(((1S*,3S*)-3-(2-oxoethyl)cyclopentyl)oxy)phenyl)sulfonyl)-L-prolinate and 4,4-difluorocyclohexylamine hydrochloride in analogy to Example 1.124 to give the title compound. LC-MS (1): *t_R*= 0.91 and 0.92 min; [M+H]⁺: 571.1.
- ((2-(((1S*,3S*)-3-(2-((4,4-Difluorocyclohexyl)amino)ethyl)cyclopentyl)oxy)-4-methylphenyl)sulfonyl)-L-proline hydrochloride:** Was synthesized using *tert*-butyl ((2-(((1S*,3S*)-3-(2-((4,4-difluorocyclohexyl)amino)ethyl)cyclopentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.194 to give the title compound. LC-MS (1): *t_R*= 0.76 min; [M+H]⁺: 515.0.
- (1²S,5¹S,5³S)-8-(4,4-Difluorocyclohexyl)-3⁴-methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclopentanacyclononaphan-9-one 2,2-dioxide and (1²S,5¹S,5³S)-8-(4,4-Difluorocyclohexyl)-3⁴-methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclopentanacyclononaphan-9-one 2,2-dioxide:** Were synthesized using ((2-(((1S*,3S*)-3-(2-((4,4-difluorocyclohexyl)amino)ethyl)cyclopentyl)oxy)-4-methylphenyl)sulfonyl)-L-proline hydrochloride in analogy to Example 1.124. The residue was purified by basic prep. HPLC to give (1²S,5¹S,5³S)-8-(4,4-difluorocyclohexyl)-3⁴-methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclopentanacyclononaphan-9-one 2,2-dioxide and (1²S,5¹S,5³S)-8-(4,4-Difluorocyclohexyl)-3⁴-methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclopentanacyclononaphan-9-one 2,2-dioxide. The stereochemistry at the cyclopentyl ring was attributed arbitrarily. First eluting diastereomer: LC-MS (1): *t_R*= 1.05 min; [M+H]⁺: 497.0. Second eluting diastereomer: LC-MS (1): *t_R*= 1.08 min; [M+H]⁺: 497.0.
- Example 1.275 to Example 1.277** were synthesized using the appropriate amine or amine salt derivative and methyl ((4-methyl-2-(((R)-5-oxopentan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.240 or *tert*-butyl ((6-methyl-2-(((S)-5-oxopentan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.32. LC-MS data of Example 1.275 to Example 1.277 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	<i>t_R</i>	[M+H] ⁺
1.275	(1S,3S)-3-((6R,11aS)-3,6-Dimethyl-16,16-dioxido-11-oxo-6,7,8,9,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-yl)cyclohexane-1-carbonitrile	0.96	460.2
1.276	(1R,3R)-3-((6R,11aS)-3,6-Dimethyl-16,16-dioxido-11-oxo-6,7,8,9,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-yl)cyclohexane-1-carbonitrile	0.97	460.2

1.277	(1R,3R)-3-((6R,11aS)-3,6-Dimethyl-16,16-dioxido-11-oxo-6,7,8,9,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-yl)cyclohexane-1-carbonitrile	0.98	461.2
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Example 1.278 (6R,12aS,14S)-11-((3S,6r)-1,1-Difluorospiro[2.5]octan-6-yl)-14-methoxy-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide: Was synthesized using (R)-2-((6-((tert-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridine-3-sulfonyl chloride, (2S,4S)-4-methoxypyrrolidine-2-carboxylic acid, and (3s,6s)-1,1-difluorospiro[2.5]octan-6-amine hydrochloride in analogy to Example 1.248 to give the title compound. LC-MS (1): t_R = 1.08 min; $[M+H]^+$: 542.0.

Example 1.279 (9aS,14aR,16aS)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,11,12,13,14,14a,15,16,16a-dodecahydro-10H-benzo[b]cyclobuta[l]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide or (9aS,14aS,16aR)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,11,12,13,14,14a,15,16,16a-dodecahydro-10H-benzo[b]cyclobuta[l]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide:

(RS)-2-(3-(2-oxocyclobutyl)propyl)isoindoline-1,3-dione: 2-(3-Chloropropyl)cyclobutan-1-one (2.27 g, 14.70 mmol, 1 eq) was dissolved in DMF (150 mL) and stirred at rt. Phthalimide, potassium salt (3.37 mg, 18.00 mmol, 1.2 eq) was added dropwise and the reaction mixture was stirred at 80°C for 15h. The reaction mixture was poured into H₂O and extracted with EtOAc. The combined org. layers were washed with brine, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R = 0.86 min; $[M+H]^+$: 258.3.

2-(3-((1R*,2R*)-2-hydroxycyclobutyl)propyl)isoindoline-1,3-dione: (RS)-2-(3-(2-Oxocyclobutyl)propyl)isoindoline-1,3-dione (2.43 g, 8.28 mmol, 1 eq) was dissolved in AcOH (8 mL) and the soln. was stirred at rt. NaBH₃CN (1.10 g, 16.60 mmol, 2 eq) was added and the reaction mixture was stirred at rt for 1.5h. The reaction mixture was slowly poured into aq. sat. NaHCO₃ soln. and solid NaHCO₃ was added until no more gas was formed. The suspension was extracted with EtOAc. The org. layer was washed with brine, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 30% EtOAc) to give the title compound. LC-MS (1): t_R = 0.80 min; $[M+H]^+$: 260.1.

(RS)-2-Ethylhexyl 3-((2-((1R*,2S*)-2-(3-(1,3-dioxoisoindolin-2-yl)propyl)cyclobutoxy)-4-methylphenyl)sulfonyl)propanoate: Was synthesized using 2-(3-((1R*,2R*)-2-hydroxycyclobutyl)propyl)isoindoline-1,3dione and (RS)-2-ethylhexyl 3-((2-hydroxy-4-methylphenyl)sulfonyl)propanoate in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R = 1.26 min; $[M+H]^+$: 598.1.

tert-Butyl ((2-((1R*,2S*)-2-(3-(1,3-dioxoisindolin-2-yl)propyl)cyclobutoxy)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using (RS)-2-ethylhexyl 3-((2-((1R*,2S*)-2-(3-(1,3-dioxoisindolin-2-yl)propyl)cyclobutoxy)-4-methylphenyl)sulfonyl)propanoate and *tert*-butyl L-prolinate in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R = 1.19 min; $[M+H]^+$: 583.0.

- 5 **tert-Butyl ((2-((1R*,2S*)-2-(3-aminopropyl)cyclobutoxy)-4-methylphenyl)sulfonyl)-L-prolinate:** *tert*-Butyl ((2-((1R*,2S*)-2-(3-(1,3-dioxoisindolin-2-yl)propyl)cyclobutoxy)-4-methylphenyl)sulfonyl)-L-prolinate (750 mg, 1.29 mmol, 1 eq) was dissolved in EtOH (13 mL) and the soln. was stirred at rt. Hydrazine monohydrate (0.19 mL, 3.86 mmol, 3 eq) was then added and the reaction mixture was stirred at 60°C for 2h. Hydrazine monohydrate (95 μ L, 1.93 mmol, 1.5 eq) was added again and the reaction mixture was stirred at 60°C for 16h. The reaction mixture
10 was filtered and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.80 and 0.82 min; $[M+H]^+$: 453.1.

- tert-Butyl ((2-((1R*,2S*)-2-(3-((4,4-difluorocyclohexyl)amino)propyl)cyclobutoxy)-4-methylphenyl)sulfonyl)-L-prolinate:** *tert*-Butyl ((2-((1R*,2S*)-2-(3-aminopropyl)cyclobutoxy)-4-methylphenyl)sulfonyl)-L-prolinate (50 mg, 0.10 mmol, 1 eq), 4,4-difluorocyclohexanone (56 mg, 0.41 mmol, 4 eq) and AcOH (23 μ L, 0.41 mmol, 4 eq) were
15 dissolved in MeOH (1 mL) and the reaction mixture was stirred at 70°C for 1h. NaBH(OAc)₃ (108 mg, 0.51 mmol, 5 eq) was added and the reaction mixture was stirred at 70°C for 1h. 4,4-Difluorocyclohexanone (56 mg, 0.41 mmol, 4 eq) and NaBH(OAc)₃ (108 mg, 0.51 mmol, 5 eq) were added again at rt and the reaction mixture was stirred at 70°C for 15h. The reaction mixture was poured onto aq. sat. NaHCO₃ soln. and extracted with EtOAc. The org. layer was washed with brine, dried over MgSO₄, filtered, and the solvent removed under reduced pressure.
20 The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 0.92 and 0.94 min; $[M+H]^+$: 571.1.

- ((2-((1R*,2S*)-2-(3-((4,4-Difluorocyclohexyl)amino)propyl)cyclobutoxy)-4-methylphenyl)sulfonyl)-L-proline hydrochloride:** Was synthesized using *tert*-butyl ((2-((1R*,2S*)-2-(3-((4,4-difluorocyclohexyl)amino)propyl)cyclobutoxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.194 to
25 give the title compound. LC-MS (1): t_R = 0.77 and 0.79 min; $[M+H]^+$: 515.0.

- (9aS,14aR,16aS)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,11,12,13,14,14a,15,16,16a-dodecahydro-10H-benzo[b]cyclobuta[l]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide and (9aS,14aS,16aR)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,11,12,13,14,14a,15,16,16a-dodecahydro-10H-benzo[b]cyclobuta[l]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide:** Were
30 synthesized using ((2-((1R*,2S*)-2-(3-((4,4-difluorocyclohexyl)amino)propyl)cyclobutoxy)-4-methylphenyl)sulfonyl)-L-proline hydrochloride in analogy to Example 1.124. The soln. was purified by basic prep. HPLC to give (9aS,14aR,16aS)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,11,12,13,14,14a,15,16,16a-dodecahydro-10H-benzo[b]cyclobuta[l]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide and (9aS,14aS,16aR)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,11,12,13,14,14a,15,16,16a-dodecahydro-10H-
35 benzo[b]cyclobuta[l]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide. The stereochemistry at

the cyclobutyl ring was attributed arbitrarily. First eluting diastereomer: LC-MS (1): t_R = 1.08 min; $[M+H]^+$: 497.4. Second eluting diastereomer: LC-MS (1): t_R = 1.11 min; $[M+H]^+$: 497.0.

Example 1.280 (S)-6-(4,4-Difluorocyclohexyl)-2⁵-methyl-3-thia-6-aza-1(2,6)-pyridina-4(1,2)-pyrrolidina-2(1,2)-benzenacyclononaphan-5-one 3,3-dioxide:

- 5 ***tert*-Butyl ((4-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)-L-prolinate:** *tert*-Butyl ((2-bromo-4-methylphenyl)sulfonyl)-L-prolinate (1.85 g, 4.58 mmol, 1 eq), $PdCl_2(MeCN)_2$ (24 mg, 0.092 mmol, 0.02 eq) and dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (153 mg, 0.37 mmol, 0.08 eq) were placed in a microwave vial. Dioxane (10 mL), TEA (1.9 mL, 13.70 mmol, 3 eq) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (925 mg, 6.86 mmol, 1.5 eq) were added. The resulting mixture was stirred at 110°C for 1h. The mixture was filtered and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 1.13 min; $[M+H]^+$: 452.3.

- 15 ***tert*-Butyl ((2-(6-chloropyridin-2-yl)-4-methylphenyl)sulfonyl)-L-prolinate:** 2-Bromo-6-chloropyridine (350 mg, 1.78 mmol, 1 eq) and *tert*-butyl ((4-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)-L-prolinate (847 mg, 1.78 mmol, 1.0 eq) were dissolved in EtOH (6 mL), H_2O (3 mL) and toluene (3 mL). Aq. 1M Na_2CO_3 soln. (1.8 mL, 1.78 mmol, 1 eq) and tetrakis(triphenylphosphine)palladium(0) (103 mg, 0.089 mmol, 0.05 eq) were added and the mixture was heated to 90°C for 1h. The mixture was filtered and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 1.09 min; $[M+H]^+$: 437.1.

- 20 ***tert*-Butyl ((2-(6-(3-hydroxyprop-1-yn-1-yl)pyridin-2-yl)-4-methylphenyl)sulfonyl)-L-prolinate:** *tert*-Butyl ((2-(6-chloropyridin-2-yl)-4-methylphenyl)sulfonyl)-L-prolinate (380 mg, 0.87 mmol, 1 eq), propargylalcohol (77 μ L, 1.30 mmol, 1.5 eq) and DIPEA (0.50 mL, 0.088 mmol, 4 eq) were dissolved in MeCN (2 mL) and MeOH (0.5 mL). CuI (17 mg, 0.087 mmol, 0.1 eq) and tetrakis(triphenylphosphine)palladium(0), (100 mg, 0.088 mmol, 0.1 eq) were added and the mixture was heated to 80°C for 2h. The mixture was filtered and the solvent removed under reduced pressure. The residue was purified by basic prep. HPLC. t_R = 0.94 min; $[M+H]^+$: 457.2.

- 25 ***tert*-Butyl ((2-(6-(3-hydroxypropyl)pyridine-2-yl)-4-methylphenyl)sulfonyl)-L-prolinate:** Tris(triphenylphosphine)rhodium(I) chloride (26 mg, 0.029 mmol, 0.1 eq) was added to a soln. of *tert*-butyl ((2-(6-(3-hydroxyprop-1-yn-1-yl)pyridine-2-yl)-4-methylphenyl)sulfonyl)-L-prolinate (130 mg, 0.29 mmol, 1 eq) in THF (5 mL). Under an atm of H_2 , the mixture was heated to 60°C overnight. The solvent was removed under reduced pressure. The residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 0.76 min; $[M+H]^+$: 461.3.

- 30 ***tert*-Butyl ((4-methyl-2-(6-(3-oxopropyl)pyridine-2-yl)phenyl)sulfonyl)-L-prolinate:** At -10°C, sulfur trioxide pyridine complex (73 mg, 0.21 mmol, 1.1 eq) in DMSO (0.5 mL) was added dropwise to a soln. of *tert*-butyl ((2-(6-(3-hydroxypropyl)pyridine-2-yl)-4-methylphenyl)sulfonyl)-L-prolinate (90 mg, 0.20 mmol, 1 eq) in DCM (5 mL). After 30 min, the mixture was partitioned between H_2O and DCM. The layers were separated and the aq. layer was extracted with DCM. The combined org. layers were washed with brine, dried over $MgSO_4$, filtered, and the solvent

removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.78 min; $[M+H]^+$: 459.3.

- tert-Butyl ((2-(6-(3-((4,4-difluorocyclohexyl)amino)propyl)pyridine-2-yl)-4-methylphenyl)sulfonyl)-L-prolinate:** Difluorocyclohexylamine (27 mg, 0.15 mmol, 1 eq) and AcOH (9 μ L, 0.15 mmol, 1 eq) were added to a soln. of *tert*-butyl ((4-methyl-2-(6-(3-oxopropyl)pyridine-2-yl)phenyl)sulfonyl)-L-prolinate (70 mg, 0.15 mmol, 1 eq) in THF (2 mL). After 30 min, NaBH(OAc)₃ (50 mg, 0.23 mmol, 1.5 eq) was added and the mixture was stirred at rt for 4h. The mixture was then diluted with DCM and washed with aq. sat. NaHCO₃ soln. The solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.86 min; $[M+H]^+$: 578.3.
- 5 **(2-(6-(3-((4,4-Difluorocyclohexyl)amino)propyl)pyridine-2-yl)-4-methylphenyl)sulfonyl)-L-proline:** *tert*-Butyl ((2-(6-(3-((4,4-difluorocyclohexyl)amino)propyl)pyridine-2-yl)-4-methylphenyl)sulfonyl)-L-prolinate (25 mg, 0.043 mmol, 1 eq) was dissolved in 4M HCl soln. in dioxane (1 mL), and the resulting soln. was stirred at rt for 4h. The solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.66 min; $[M+H]^+$: 522.3.
- 10 **(S)-6-(4,4-Difluorocyclohexyl)-2⁵-methyl-3-thia-6-aza-1(2,6)-pyridina-4(1,2)-pyrrolidina-2(1,2)-benzenacyclononaphan-5-one 3,3-dioxide:** DIPEA (58 μ L, 0.34 mmol, 8 eq) and HATU (32 mg, 0.08 mmol, 2 eq) were added to a soln. of ((2-(6-(3-((4,4-difluorocyclohexyl)amino)propyl)pyridine-2-yl)-4-methylphenyl)sulfonyl)-L-proline (22 mg, 0.04 mmol, 1 eq) in DMF (2 mL). The mixture was stirred at rt for 15 min. The mixture was purified by acidic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.04 min; $[M+H]^+$: 504.2.
- 15 **Example 1.281 (9aS,14aR,17aR)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,11,12,13,14,14a,16,17,17a-dodecahydro-10H-benzo[b]furo[2,3-l]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide or (9aS,14aS,17aS)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,11,12,13,14,14a,16,17,17a-dodecahydro-10H-benzo[b]furo[2,3-l]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide:**
- (2RS,3SR)-2-Allyltetrahydrofuran-3-ol:** 1M LiAlH₄ soln. in THF (2.20 mL, 2.15 mmol, 1.1 eq) was added dropwise at 0°C to a stirred soln. of 2-(prop-2-en-1-yl)oxolan-3-one (250 mg, 1.98 mmol, 1 eq) in THF (8 mL). The resulting mixture was stirred at 0°C for 40 min. The reaction mixture was quenched at 0°C by addition of aq. sat. Rochelle's salt soln. and diluted with EtOAc. The mixture was vigorously stirred at rt, the layers were separated and the aq. layer was extracted with EtOAc. The combined org. layers were dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. ¹H NMR (500
- 25 MHz, DMSO-*d*₆) δ : 5.82 (m, 2 H), 5.05-5.10 (m, 2 H), 5.00 (m, 2 H), 4.90 (d, J = 4.3 Hz, 1 H), 4.70 (d, J = 4.9 Hz, 1 H), 4.09 (m, 1 H), 3.88 (m, 1 H), 3.83 (q, J = 7.8 Hz, 1 H), 3.77 (m, 1 H), 3.72 (m, 1 H), 3.49-3.60 (m, 3 H).
- 30 **(RS)-2-Ethylhexyl 3-((2-(((2R*,3R*)-2-allyltetrahydrofuran-3-yl)oxy)-4-methylphenyl)sulfonyl)propanoate and (RS)-2-ethylhexyl 3-((2-(((2R*,3S*)-2-allyltetrahydrofuran-3-yl)oxy)-4-methylphenyl)sulfonyl)propanoate:** Were synthesized using (2RS,3SR)-2-allyltetrahydrofuran-3-ol and *rac*-(R)-2-ethylhexyl 3-((2-hydroxy-4-methylphenyl)sulfonyl)propanoate in analogy to Example 1.124. The residue was
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purified by FC (Hept to 20% EtOAc) to give (RS)-2-ethylhexyl 3-((2-(((2R*,3S*)-2-allyltetrahydrofuran-3-yl)oxy)-4-methylphenyl)sulfonyl)propanoate (first eluting diastereomer) and (RS)-2-ethylhexyl 3-((2-(((2R*,3R*)-2-allyltetrahydrofuran-3-yl)oxy)-4-methylphenyl)sulfonyl)propanoate (second eluting diastereomer). First eluting diastereomer: LC-MS (1): t_R = 1.17 min; $[M+H]^+$: 467.1. Second eluting diastereomer: LC-MS (1): t_R = 1.16 min; $[M+H]^+$: 467.4.

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***tert*-Butyl ((2-(((2R*,3R*)-2-allyltetrahydrofuran-3-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using (RS)-2-ethylhexyl 3-((2-(((2S*,3S*)-2-allyltetrahydrofuran-3-yl)oxy)-4-methylphenyl)sulfonyl)propanoate and L-proline *tert*-butyl ester in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R = 1.09 min; $[M+H]^+$: 452.1.

10 ***tert*-Butyl ((2-(((2R*,3R*)-2-(3-hydroxypropyl)tetrahydrofuran-3-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((2-(((2R*,3R*)-2-allyltetrahydrofuran-3-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.270 to give the title compound. LC-MS (1): t_R = 0.93 min; $[M+H]^+$: 470.3.

***tert*-Butyl ((4-methyl-2-(((2R*,3R*)-2-(3-oxopropyl)tetrahydrofuran-3-yl)oxy)phenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((2-(((2S*,3S*)-2-(3-hydroxypropyl)tetrahydrofuran-3-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R = 1.00 min; $[M+H]^+$: 467.8.

***tert*-Butyl ((2-(((2R*,3R*)-2-(3-((4,4-difluorocyclohexyl)amino)propyl)tetrahydrofuran-3-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((4-methyl-2-(((2R*,3R*)-2-(3-oxopropyl)tetrahydrofuran-3-yl)oxy)phenyl)sulfonyl)-L-prolinate and 4,4-difluorocyclohexylamine hydrochloride in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R = 0.88 and 0.89 min; $[M+H]^+$: 587.4.

((2-(((2R*,3R*)-2-(3-((4,4-Difluorocyclohexyl)amino)propyl)tetrahydrofuran-3-yl)oxy)-4-methylphenyl)sulfonyl)-L-proline hydrochloride: Was synthesized using *tert*-butyl ((2-(((2S*,3S*)-2-(3-((4,4-difluorocyclohexyl)amino)propyl)tetrahydrofuran-3-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.194 to give the title compound. LC-MS (1): t_R = 0.71 and 0.73 min; $[M+H]^+$: 531.2.

(9aS,14aR,17aR)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,11,12,13,14,14a,16,17,17a-dodecahydro-10H-benzo[b]furo[2,3-l]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide and (9aS,14aS,17aS)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,11,12,13,14,14a,16,17,17a-dodecahydro-10H-benzo[b]furo[2,3-l]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide: Were synthesized using *tert*-butyl ((2-(((2R*,3R*)-2-(3-((4,4-difluorocyclohexyl)amino)propyl)tetrahydrofuran-3-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.124. The soln. was purified by basic prep. HPLC to give (9aS,14aR,17aR)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,11,12,13,14,14a,16,17,17a-dodecahydro-10H-benzo[b]furo[2,3-l]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide and (9aS,14aS,17aS)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,11,12,13,14,14a,16,17,17a-dodecahydro-10H-benzo[b]furo[2,3-l]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide. The absolute stereochemistry at the

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tetrahydrofuran ring was attributed arbitrarily. First eluting diastereomer: LC-MS (1): t_R= 0.96 min; [M+H]⁺: 513.0.
Second eluting diastereomer: LC-MS (1): t_R= 1.01 min; [M+H]⁺: 513.0.

Example 1.282 to Example 1.286 were synthesized using the appropriate amine or amine salt derivative and methyl ((2-(((R)-5-hydroxy-3-methylpentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.84.

- 5 LC-MS data of Example 1.282 to Example 1.286 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
1.282	(8R,12aS)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,8-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.10	511.4
1.283	3-((8R,12aS)-3,8-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	0.94	488.4
1.284	(1R,4s)-4-((8R,12aS)-3,8-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.99	474.4
1.285	(1R,4s)-4-((8R,12aS)-3,8-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	1.03	488.4
1.286	(8R,12aS)-11-(4-Fluoro-4-methylcyclohexyl)-3,8-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.06	481.2

Example 1.289 to Example 1.294 were synthesized using the appropriate amine or amine salt derivative and methyl ((6-methyl-2-(((S)-3-methyl-5-oxopentyl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.8.

- 10 LC-MS data of Example 1.289 to Example 1.294 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
1.289	(8R,12aS)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,8-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.10	512.4
1.291	(1R,4s)-4-((8R,12aS)-3,8-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.98	475.4

1.292	(1R,4s)-4-((8R,12aS)-3,8-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	1.03	489.4
1.293	(8R,12aS)-11-(4-Fluoro-4-methylcyclohexyl)-3,8-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.07	482.2
1.294	(1R*,3R*)-3-((8R,12aS)-3,8-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.00	475.4

Example 1.296 (S)-5-(4,4-Difluorocyclohexyl)-3-isopropyl-13-methyl-2,3,5,6,7,8,9,10-octahydro-4H-pyrido[2,3-b][1]oxa[4]thia[5,8]diazacyclotridecin-4-one 1,1-dioxide: Was synthesized using *tert*-butyl (2S)-2-amino-3-methylbutanoate hydrochloride and *tert*-butyl (5-((3-(chlorosulfonyl)-6-methylpyridin-2-yl)oxy)pentyl)(4,4-difluorocyclohexyl)carbamate in analogy to Example 1.80 to give the title compound. LC-MS (1): t_R = 1.06 min; $[M+H]^+$: 473.9.

Example 1.297 (S,Z)-5-(4,4-Difluorocyclohexyl)-1⁵-methyl-2-thia-5-aza-1(8,2)-imidazo[1,2-a]pyridina-3(1,2)-pyrrolidinacyclononaphan-4-one 2,2-dioxide:

***tert*-Butyl ((2-amino-6-methylpyridin-3-yl)sulfonyl)-L-prolinate:** Xantphos Pd G3 (438 mg, 0.44 mmol, 0.05 eq) was added to a suspension of *tert*-butyl ((2-chloro-6-methylpyridin-3-yl)sulfonyl)-L-prolinate (3.44 g, 8.77 mmol, 1 eq), benzophenone imine (0.79 mL, 9.65 mmol, 1.1 eq) and Cs_2CO_3 (4.29 g, 13.20 mmol, 1.5 eq) in dioxane (50 mL). The suspension was degassed for 5 min and then heated to 100°C overnight. The mixture was diluted with EtOAc and washed with aq. sat. $NaHCO_3$ soln.. The org. layer was dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude product was dissolved in THF and aq. 2N HCl soln. was added. The reaction mixture was stirred at rt for 40 min. The reaction mixture was partitioned between EtOAc and aq. sat. Na_2CO_3 soln. The org. layer was washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R = 0.75 min; $[M+H]^+$: 342.2.

***tert*-Butyl (4,4-difluorocyclohexyl)(5-methoxyhex-5-en-1-yl)carbamate:** Methyl 5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentanoate (500 mg, 1.43 mmol, 1 eq) was dissolved in THF (10 mL) and the soln. was cooled to -78°C under argon atm.. 0.5M Tebbe's reagent soln. in toluene (3.5 mL, 1.75 mmol, 1.2 eq) was added dropwise. The mixture was stirred at -78°C for 30 min, then slowly warmed up to rt. After 3h, the mixture was carefully diluted with an ice cooled aq. 1M NaOH soln. tBME was added then the mixture was vigorously stirred at rt for 1h. The solid was filtered off and washed with tBME. The layers were separated and the aq. layer was extracted with tBME. The combined org. layers were dried over $MgSO_4$, filtered, and the solvent was removed

under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 1.04 min; $[M+H]^+$: not seen.

***tert*-Butyl (6-bromo-5-oxohexyl)(4,4-difluorocyclohexyl)carbamate:** *tert*-Butyl (4,4-difluorocyclohexyl)(5-methoxyhex-5-en-1-yl)carbamate (480 mg, 1.38 mmol, 1 eq) was dissolved in a mixture of THF (6 mL) and H₂O (1.5 mL). A soln. of NBS (246 mg, 1.38 mmol, 1 eq) in THF (6 mL) was added and the mixture was stirred at rt for 1.5h. The solvent was removed under reduced pressure then the residue was dissolved in EtOAc. The org. layer was dried over MgSO₄, filtered, and the solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 1.08 min; $[M+H]^+$: 414.2.

***tert*-Butyl ((2-(4-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)butyl)-5-methylimidazo[1,2-a]pyridin-8-yl)sulfonyl)-L-proline:** *tert*-Butyl (6-bromo-5-oxohexyl)(4,4-difluorocyclohexyl)carbamate (170 mg, 0.41 mmol, 1 eq) was dissolved in MeCN (5 mL) then *tert*-butyl ((2-amino-6-methylpyridin-3-yl)sulfonyl)-L-proline (153 mg, 0.41 mmol, 1 eq) was added followed by neat NaHCO₃ (69 mg, 0.82 mmol, 2 eq). The reaction mixture was stirred at 85°C overnight. The solvent was removed under reduced pressure. The residue was diluted with DCM and carefully washed with aq. 0.1M HCl soln. The layers were separated by phase separator and the org. layer was removed under reduced pressure. The residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.01 min; $[M+H]^+$: 655.3.

((2-(4-((4,4-Difluorocyclohexyl)amino)butyl)-5-methylimidazo[1,2-a]pyridin-8-yl)sulfonyl)-L-proline: *tert*-Butyl ((2-(4-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)butyl)-5-methylimidazo[1,2-a]pyridin-8-yl)sulfonyl)-L-proline (13 mg, 0.02 mmol, 1 eq) was dissolved in DCM (5 mL). TFA (30 μ L, 0.40 mmol, 20 eq) was added at rt and the resulting mixture was stirred at rt overnight. The solvent was removed under reduced pressure. The crude product was used without further purification in the next step. LC-MS (1): t_R = 0.56 min; $[M+H]^+$: 499.2.

(S,Z)-5-(4,4-Difluorocyclohexyl)-1⁵-methyl-2-thia-5-aza-1(8,2)-imidazo[1,2-a]pyridina-3(1,2)-pyrrolidinacyclononaphan-4-one 2,2-dioxide: At rt, HATU (13.7 mg, 0.04 mmol, 2 eq) and DIPEA (25 μ L, 0.14 mmol, 8 eq) were added to a stirred soln. of ((2-(4-((4,4-difluorocyclohexyl)amino)butyl)-5-methylimidazo[1,2-a]pyridin-8-yl)sulfonyl)-L-proline (9 mg, 0.02 mmol, 1 eq) in DMF (3.2 mL). The soln. was stirred at 60°C for 1h and then was cooled to rt. The soln. was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 0.73 min; $[M+H]^+$: 480.9.

Example 1.298 (S)-3-Butyl-5-(4,4-difluorocyclohexyl)-2,13-dimethyl-2,3,5,6,7,8,9,10-octahydro-4H-pyrido[2,3-b][1]oxa[4]thia[5,8]diazacyclotridecin-4-one 1,1-dioxide:

(S)-3-Butyl-5-(4,4-difluorocyclohexyl)-13-methyl-2,3,5,6,7,8,9,10-octahydro-4H-pyrido[2,3-b][1]oxa[4]thia[5,8]diazacyclotridecin-4-one 1,1-dioxide: Was synthesized using (S)-methyl 2-amino-2-butylacetate hydrochloride and *tert*-butyl (5-((3-(chlorosulfonyl)-6-methylpyridin-2-yl)oxy)pentyl)(4,4-difluorocyclohexyl)carbamate in analogy to Example 1.86 to give the title compound. LC-MS (1): t_R = 1.08 min; $[M+H]^+$: 488.0.

(S)-3-Butyl-5-(4,4-difluorocyclohexyl)-2,13-dimethyl-2,3,5,6,7,8,9,10-octahydro-4H-pyrido[2,3-b][1]oxa[4]thia[5,8]diazacyclotridecin-4-one 1,1-dioxide: Was synthesized using (S)-3-butyl-5-(4,4-difluorocyclohexyl)-13-methyl-2,3,5,6,7,8,9,10-octahydro-4H-pyrido[2,3-b][1]oxa[4]thia[5,8]diazacyclotridecin-4-one 1,1-dioxide and Mel in analogy to Example 1.81 to give the title compound. LC-MS (1): t_R = 1.14 min; $[M+H]^+$: 502.0.

Example 1.299 (S,Z)-5-(4,4-Difluorocyclohexyl)-1⁷-methyl-2-thia-5-aza-1(4,2)-benzo[d]thiazola-3(1,2)-pyrrolidinacyclononaphan-4-one 2,2-dioxide:

tert-Butyl (5-((2-bromo-5-methylphenyl)amino)-5-oxopentyl)carbamate: 5-((tert-Butoxycarbonyl)amino)pentanoic acid (500 mg, 2.23 mmol, 1 eq) and 2-bromo-5-methylaniline (413 mg, 2.23 mmol, 1 eq) were dissolved in DMF (10 mL) then DIPEA (0.95 mL, 5.58 mmol, 2.5 eq) was added. Propylphosphonic anhydride soln. (~50% in DMF, 2.05 mL, 3.35 mmol, 1.5 eq) was added and the mixture was stirred at rt overnight. The soln. was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 0.95 min; $[M+H]^+$: 387.2.

tert-Butyl (5-((2-bromo-5-methylphenyl)amino)-5-thioxopentyl)carbamate: At rt, Lawesson reagent (164 mg, 0.41 mmol, 0.6 eq) was added to a stirred soln. of (tert-butyl (5-((2-bromo-5-methylphenyl)amino)-5-oxopentyl)carbamate (260 mg, 0.68 mmol, 1 eq) in THF (16 mL) and the mixture was stirred at rt overnight. The solvent was removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 0.99 min; $[M+H]^+$: 403.1.

tert-Butyl (4-(4-bromo-7-methylbenzo[d]thiazol-2-yl)butyl)carbamate: A soln. of potassium ferricyanide (692 mg, 2.08 mmol, 3 eq) in H₂O (3.6 mL) was added to a stirred suspension of tert-butyl (5-((2-bromo-5-methylphenyl)amino)-5-thioxopentyl)carbamate (290 mg, 0.69 mmol, 1 eq) in aq. 1.5M NaOH soln. (23 mL) and the mixture was stirred at rt for 3h. EtOAc was added and the aq. layer was separated. The org. layer was washed with brine, dried over MgSO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R = 1.08 min; $[M+H]^+$: 399.1.

tert-Butyl (4-(4-(benzylthio)-7-methylbenzo[d]thiazol-2-yl)butyl)carbamate: Was synthesized using tert-butyl (4-(4-bromo-7-methylbenzo[d]thiazol-2-yl)butyl)carbamate and benzyl mercaptan in analogy to Example 1.262 to give the title compound. LC-MS (1): t_R = 1.17 min; $[M+H]^+$: 443.1.

tert-Butyl (4-(4-(chlorosulfonyl)-7-methylbenzo[d]thiazol-2-yl)butyl)carbamate: Was synthesized using tert-butyl (4-(4-(benzylthio)-7-methylbenzo[d]thiazol-2-yl)butyl)carbamate and DCDMH in analogy to Example 1.261 to give the title compound. LC-MS (1): t_R = 1.09 min; $[M+H]^+$: 419.1.

Methyl ((2-(4-((tert-butoxycarbonyl)amino)butyl)-7-methylbenzo[d]thiazol-4-yl)sulfonyl)-L-prolinate: Was synthesized using tert-butyl (4-(4-(chlorosulfonyl)-7-methylbenzo[d]thiazol-2-yl)butyl)carbamate and L-Proline methyl ester hydrochloride in analogy to Example 1.86 to give the title compound. LC-MS (1): t_R = 1.05 min; $[M+H]^+$: 512.2.

(S,Z)-5-(4,4-Difluorocyclohexyl)-1⁷-methyl-2-thia-5-aza-1(4,2)-benzo[d]thiazola-3(1,2)-

pyrrolidinacyclononaphan-4-one 2,2-dioxide: Was synthesized using methyl ((2-(4-((*tert*-butoxycarbonyl)amino)butyl)-7-methylbenzo[d]thiazol-4-yl)sulfonyl)-L-prolinate and 4,4-difluorocyclohexanone in analogy to Examples 1.166 and 1.167 to give the title compound. LC-MS (1): *t_R*= 1.05 min; [M+H]⁺: 498.0.

- 5 **Example 1.300 (S,Z)-5-(4,4-Difluorocyclohexyl)-1⁷-methyl-2-thia-5-aza-1(4,2)-benzo[d]thiazola-3(1,2)-pyrrolidinacyclodecaphan-4-one 2,2-dioxide:** Was synthesized using 6-((*tert*-butoxycarbonyl)amino)hexanoic acid and 2-bromo-5-methylaniline in analogy to Example 1.299 to give the title compound. LC-MS (1): *t_R*= 1.10 min; [M+H]⁺: 512.3.

- Example 1.301 (3²S,E)-5-(4,4-Difluorocyclohexyl)-1⁴-methyl-1²H-2-thia-5-aza-1(7,2)-indazola-3(1,2)-pyrrolidinacyclononaphan-4-one 2,2-dioxide:**

- tert*-Butyl (S)-2-(allyl(4,4-difluorocyclohexyl)carbamoyl)pyrrolidine-1-carboxylate:** Boc-L-proline (500 mg, 2.30 mmol, 1 eq) was dissolved in DMF (5 mL). DIPEA (1.6 mL, 9.20 mmol, 4 eq) and HATU (962 mg, 2.53 mmol, 1.1 eq) were added followed by N-allyl-4,4-difluorocyclohexan-1-amine (487 mg, 2.30 mmol, 1 eq) and the mixture was stirred at rt overnight. Few drops of formic acid were added and the mixture was filtered over a glass fiber filter.
- 15 The soln. was purified by acidic prep. HPLC to give the title compound. LC-MS (1): *t_R*= 0.97 min; [M+H]⁺: 373.3.

- (S)-N-Allyl-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide hydrochloride:** *tert*-Butyl (S)-2-(allyl(4,4-difluorocyclohexyl)carbamoyl)pyrrolidine-1-carboxylate (782 mg, 2.08 mmol, 1 eq) was dissolved in 4M HCl soln. in dioxane (10 mL, 31.2 mmol, 15 eq) and the resulting soln. was stirred at rt for 1h. The solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): *t_R*= 0.60 min; [M+H]⁺: 273.3.
- 20

7-(Benzylthio)-4-methyl-1H-indazole: Was synthesized using 7-bromo-4-methyl-1H-indazole and benzyl mercaptan in analogy to Example 1.262 to give the title compound. LC-MS (1): *t_R*= 0.98 min; [M+H]⁺: 255.2.

- 2-Allyl-7-(benzylthio)-4-methyl-2H-indazole:** 7-(Benzylthio)-4-methyl-1H-indazole (1.87 g, 7.13 mmol, 1 eq) was dissolved in THF (30mL). N,N-Dicyclohexylmethylamine (3.15 mL, 14.30 mmol, 2 eq) was added followed by allyl bromide (1.25 mL, 14.30 mmol, 2 eq). The reaction mixture was stirred at 60°C overnight. The solvent was removed under reduced pressure. The residue was purified by FC (Hept to 20% EtOAc) to give the title compound. LC-MS (1): *t_R*= 1.05 min; [M+H]⁺: 295.2.
- 25

- 2-Allyl-4-methyl-2H-indazole-7-sulfonyl chloride:** Was synthesized using 2-allyl-7-(benzylthio)-4-methyl-2H-indazole and DCDMH in analogy to Example 1.261 to give the title compound. LC-MS (1): *t_R*= 0.94 min; [M+H]⁺: 271.1.
- 30

(S)-N-Allyl-1-((2-allyl-4-methyl-2H-indazol-7-yl)sulfonyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-

carboxamide: (S)-N-Allyl-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide hydrochloride (237 mg, 0.75 mmol, 1.1 eq) was dissolved in MeCN (10 mL). DIPEA (0.36 mL, 2.05 mmol, 3 eq) and DMAP (8.4 mg, 0.07 mmol, 0.1 eq) were added at rt followed by 2-allyl-4-methyl-2H-indazole-7-sulfonyl chloride (500 mg, 0.68 mmol, 1 eq). The

mixture was stirred at rt for 30 min. The solvent was removed under reduced pressure. The residue was purified by FC (Hept to 70% EtOAc) to give the title compound. LC-MS (1): t_R = 1.04 min; $[M+H]^+$: 507.2.

(3²S,E)-5-(4,4-Difluorocyclohexyl)-1⁴-methyl-1²H-2-thia-5-aza-1(7,2)-indazola-3(1,2)-

pyrrolidinacyclonaphan-4-one 2,2-dioxide: Was synthesized using (S)-N-allyl-1-((2-allyl-4-methyl-2H-indazol-7-yl)sulfonyl)-N-(4,4-difluorocyclohexyl)pyrrolidine-2-carboxamide and Hoveyda-Grubbs Catalyst, 2nd generation in analogy to Example 1.189 to give the title compound. LC-MS (1): t_R = 0.95 min; $[M+H]^+$: 481.2.

Example 1.302 (6R,12aS)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-4,6-propanobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide and Example 1.303 (6S,12aS)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-4,6-propanobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:

tert-Butyl (4,4-difluorocyclohexyl)(5-hydroxyhept-6-en-1-yl)carbamate: To a soln. of *tert*-butyl (4,4-difluorocyclohexyl)(5-oxopentyl)carbamate (990 mg, 2.73 mmol, 1 eq) in MeTHF (15 mL) cooled to 0°C was added dropwise 1M vinylmagnesium bromide soln. in THF (0.37 mL, 2.73 mmol, 1 eq). The mixture was stirred at 0°C for 1h. Aq. sat. NH₄Cl soln. was carefully added. The mixture was extracted with EtOAc. The combined org. layers were washed with brine, dried over MgSO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 60% EtOAc) to give the title compound. LC-MS (1): t_R =1.01; $[M+H]^+$: 348.3.

tert-Butyl ((2-(allyloxy)-4-methylphenyl)sulfonyl)-L-prolinate: *tert*-Butyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate (1.00 g, 2.93 mmol, 1 eq) was dissolved in MeCN (10 mL). K₂CO₃ (1.21 g, 8.79 mmol, 3 eq) was added followed by allyl bromide (0.51 mL, 5.86 mmol, 2 eq). The reaction mixture was stirred at rt for 2h. The mixture was filtered over a glass fiber filter and the solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 1.06 min; $[M+H]^+$: 382.3.

tert-Butyl ((3-allyl-2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate: *tert*-Butyl ((2-(allyloxy)-4-methylphenyl)sulfonyl)-L-prolinate (1.24 g, 3.25 mmol, 1 eq) was dissolved in N,N-dimethylaniline (2.1 mL, 16.30 mmol, 5 eq) and was heated to 150°C overnight. The mixture was diluted with EtOAc and washed with aq. 1M HCl soln. then brine. The org. layer was dried over MgSO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 60% EtOAc) to give the title compound. LC-MS (1): t_R =1.12; $[M+H]^+$: 382.0.

tert-Butyl ((3-allyl-2-((7-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)hept-1-en-3-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: *tert*-Butyl ((3-allyl-2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate (334 mg, 0.88 mmol, 1 eq), *tert*-butyl (4,4-difluorocyclohexyl)(5-hydroxyhept-6-en-1-yl)carbamate (560 mg, 1.32 mmol, 1.5 eq) and PPh₃ polymer-bound, (100-200 mesh, ca. 1.6 mmol/g, 344 mg, 1.31 mmol, 1.5 eq) were suspended in THF (5 mL) and stirred at 0°C. DIAD (0.26 mL, 1.31 mmol, 1.5 eq) was added dropwise and the reaction mixture was stirred at rt for 2h. The mixture was filtered over a glass fiber filter and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R = 1.32 min; $[M+H]^+$: 711.5.

tert-Butyl ((2-(4-((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)butyl)-6-methyl-2,5-dihydrobenzo[b]oxepin-9-yl)sulfonyl)-L-prolinate: *tert-Butyl* ((3-allyl-2-((7-((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)hept-1-en-3-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate (257 mg, 0.27 mmol, 1 eq) was dissolved in THF (15 mL) and Hoveyda-Grubbs Catalyst, 2nd generation (8.8 mg, 0.01 mmol, 0.05 eq) was added.

5 The soln. was degassed for 5 min and was stirred at rt for 30 min. The solvent was removed under reduced pressure. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R = 1.30 min; $[M+H]^+$: 683.5.

tert-Butyl ((2-(4-((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)butyl)-6-methyl-2,3,4,5-tetrahydrobenzo[b]oxepin-9-yl)sulfonyl)-L-prolinate: *tert-Butyl* ((2-(4-((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)butyl)-6-methyl-2,5-dihydrobenzo[b]oxepin-9-yl)sulfonyl)-L-prolinate (110 mg, 0.15 mmol, 1 eq) was dissolved in MeOH (6 mL). The reaction flask was purged with N_2 and 10% Pd/C (10 mg) was added. The reaction mixture was stirred under a H_2 atm at rt for 1h. The mixture was filtered over a glass fiber filter and washed with MeOH. The solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 1.32 min; $[M+H]^+$: 685.5.

15 **((2-(4-((4,4-Difluorocyclohexyl)amino)butyl)-6-methyl-2,3,4,5-tetrahydrobenzo[b]oxepin-9-yl)sulfonyl)-L-proline hydrochloride:** *tert-Butyl* ((2-(4-((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)butyl)-6-methyl-2,3,4,5-tetrahydrobenzo[b]oxepin-9-yl)sulfonyl)-L-prolinate (78 mg, 0.10 mmol, 1 eq) was dissolved in 4M HCl soln. in dioxane (1.97 mL, 56.60 mmol, 592 eq) and the resulting soln. was stirred at rt for 2h. The solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.81 min; $[M+H]^+$: 529.3.

(6R,12aS)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-4,6-propanobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide and (6S,12aS)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-4,6-propanobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide: Were synthesized using ((2-(4-((4,4-difluorocyclohexyl)amino)butyl)-6-methyl-2,3,4,5-tetrahydrobenzo[b]oxepin-9-yl)sulfonyl)-L-proline hydrochloride in analogy to Example 1.7. The crude was purified by acidic prep. HPLC to give the 2 diastereomers. First eluting diastereomer: LC-MS (1): t_R = 1.10 min; $[M+H]^+$: 511.3. Second eluting diastereomer: LC-MS (1): t_R = 1.14 min; $[M+H]^+$: 511.3.

30 **Example 1.320 (S)-5-(4,4-Difluorocyclohexyl)-1⁵-methyl-2-thia-5-aza-1(8,2)-quinolina-3(1,2)-pyrrolidinacyclononaphan-4-one 2,2-dioxide:**

tert-Butyl (4-(8-bromo-5-methylquinolin-2-yl)but-3-yn-1-yl)carbamate: *tert-Butyl* but-3-yn-1-ylcarbamate (606 mg, 3.40 mmol, 1.5 eq), 8-bromo-2-chloro-5-methylquinoline (600 mg, 2.27 mmol, 1 eq) and DIPEA (1.27 mL, 9.07 mmol, 4 eq) were dissolved in MeCN (10 mL) and MeOH (3 mL). The mixture was degassed for 5 min. CuI (44 mg, 0.23 mmol, 0.1 eq) and Pd(PPh₃)₄ (262 mg, 0.23 mmol, 0.1 eq) were added. The mixture was heated to 80°C for 2h. The mixture was filtered over a glass fiber filter and the solvent was removed under reduced pressure. The

residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R =1.06 min; $[M+H]^+$: 389.2.

tert-Butyl (4-(8-bromo-5-methylquinolin-2-yl)butyl)carbamate: Tris(triphenylphosphine)rhodium(I) chloride (95 mg, 0.10 mmol, 0.1 eq) was added to a degassed soln. of *tert*-butyl (4-(8-bromo-5-methylquinolin-2-yl)but-3-yn-1-yl)carbamate (400 mg, 1.03 mmol, 1 eq) in THF (5 mL). Under an atm of H_2 , the mixture was heated to 60°C overnight. The solvent was removed under reduced pressure. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R =1.03 min; $[M+H]^+$: 395.2.

(S)-5-(4,4-Difluorocyclohexyl)-1⁵-methyl-2-thia-5-aza-1(8,2)-quinolina-3(1,2)-pyrrolidinacyclononaphan-4-one 2,2-dioxide: Was synthesized using *tert*-butyl (4-(8-bromo-5-methylquinolin-2-yl)butyl)carbamate and methyl L-prolinate in analogy to Example 1.299 to give the title compound. LC-MS (1): t_R = 1.03 min; $[M+H]^+$: 492.3.

Example 1.324 (S)-5-(4,4-Difluorocyclohexyl)-1⁵-methyl-2-thia-5-aza-1(8,2)-quinolina-3(1,2)-pyrrolidinacyclodecaphan-4-one 2,2-dioxide: Was synthesized using 8-bromo-2-chloro-5-methylquinoline and *tert*-butyl pent-4-yn-1-ylcarbamate in analogy to Example 1.320 to give the title compound. LC-MS (1): t_R = 1.10 min; $[M+H]^+$: 506.3.

Example 1.325 2-(3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclobutyl)acetonitrile: Was synthesized using the appropriate amine or amine salt derivative and methyl ((2-hydroxy-6-methylpyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.14 to give the title compound. LC-MS (2): t_R = 0.99 min; $[M+H]^+$: 474.4.

Example 1.326 (9aS,14aR,17aR)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-2-methyl-7,8,9,9a,11,12,13,14,14a,15,17,17a-dodecahydro-10H-benzo[b]furo[3,4-f]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide and Example 1.327 (9aS,14aS,17aS)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-2-methyl-7,8,9,9a,11,12,13,14,14a,15,17,17a-dodecahydro-10H-benzo[b]furo[3,4-f]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide: Were synthesized using *tert*-butyl ((4-methyl-2-(((3R*,4R*)-4-(3-oxopropyl)tetrahydrofuran-3-yl)oxy)phenyl)sulfonyl)-L-prolinate and (3s,6s)-1,1-difluorospiro[2.5]octan-6-amine hydrochloride in analogy to Examples 1.270 and 1.271. The crude was purified by basic prep. HPLC to give the 2 diastereomers. First eluting diastereomer: LC-MS (1): t_R = 1.00 min; $[M+H]^+$: 539.0. Second eluting diastereomer: LC-MS (1): t_R = 1.06 min; $[M+H]^+$: 539.0.

Example 1.328 and Example 1.329 were synthesized using the appropriate amine salt derivative and methyl ((2-hydroxy-6-methylpyridin-3-yl)sulfonyl)-L-prolinate in analogy to Examples 1.90 and 1.91. LC-MS data of Example 1.328 and Example 1.329 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
1.328	(7S,12aS)-11-(4,4-Difluorocyclohexyl)-3,7-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.07	486.3
1.329	(7S,12aS)-11-((3R,5s)-1,1-difluorospiro[2.3]hexan-5-yl)-3,7-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.08	484.3

Example 1.330 (9aS,14aR,17aR)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-2-methyl-7,8,9,9a,11,12,13,14,14a,15,17,17a-dodecahydro-10H-furo[3,4-f]pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide and Example 1.331 (9aS,14aS,17aS)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-2-methyl-7,8,9,9a,11,12,13,14,14a,15,17,17a-dodecahydro-10H-furo[3,4-f]pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide: Were synthesized using methyl ((2-hydroxy-6-methylpyridin-3-yl)sulfonyl)-L-prolinate and (3s,6s)-1,1-difluorospiro[2.5]octan-6-amine hydrochloride in analogy to Examples 1.270 and 1.271. The crude was purified by acidic prep. HPLC to give the 2 diastereomers. First eluting diastereomer: LC-MS (1): t_R= 1.02 min; [M+H]⁺: 540.0. Second eluting diastereomer: LC-MS (1): t_R= 1.05 min; [M+H]⁺: 540.3.

Example 1.332 (1²S,5²R,5⁴R)-8-(4,4-Difluorocyclohexyl)-3⁴-methyl-5³,5⁴,5⁵,5⁶-tetrahydro-5²H-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-5(4,2)-pyrana-3(1,2)-benzenacyclononaphan-9-one 2,2-dioxide: Was synthesized using methyl 2-(4-oxotetrahydro-2H-pyran-2-yl)acetate and (RS)-2-ethylhexyl 3-((2-hydroxy-4-methylphenyl)sulfonyl)propanoate in analogy to Example 1.252 to give the title compound. LC-MS (1): t_R= 0.94 min; [M+H]⁺: 513.0.

Example 1.333 (1S,3S)-3-((8R,12aS)-3,8-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile: Was synthesized using methyl ((6-methyl-2-(((S)-3-methyl-5-oxopentyl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate and (1S,3S)-3-aminocyclohexane-1-carbonitrile 2,2,2-trifluoroacetate in analogy to Example 1.263 to give the title compound. LC-MS (1): t_R= 0.99 min; [M+H]⁺: 475.1.

Example 1.334 (S,Z)-5-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-1⁵-methyl-2-thia-5-aza-1(8,2)-imidazo[1,2-a]pyridina-3(1,2)-pyrrolidinacyclodecaphan-4-one 2,2-dioxide:

Methyl ((5-methyl-2-(pent-4-en-1-yl)imidazo[1,2-a]pyridin-8-yl)sulfonyl)-L-prolinate: Methyl ((2-amino-6-methylpyridin-3-yl)sulfonyl)-L-prolinate (178 mg, 0.51 mmol, 1 eq) was dissolved in MeOH (5 mL) then 1-bromohept-6-en-2-one (293 mg, 1.53 mmol, 3 eq) was added and the reaction mixture was stirred at 60°C for 48h. The mixture was diluted with DMF and filtered over a glass fiber filter. The soln. was purified by acidic prep. HPLC to give the title compound. LC-MS (1): t_R= 0.75 min; [M+H]⁺: 392.1.

Methyl ((2-(5-hydroxypentyl)-5-methylimidazo[1,2-a]pyridin-8-yl)sulfonyl)-L-prolinate: Was synthesized using methyl ((5-methyl-2-(pent-4-en-1-yl)imidazo[1,2-a]pyridin-8-yl)sulfonyl)-L-prolinate and 1M BH₃.THF complex soln. in analogy to Examples 1.270 to give the title compound. LC-MS (1): t_R= 0.61 min; [M+H]⁺: 410.1.

- Methyl ((5-methyl-2-(5-oxopentyl)imidazo[1,2-a]pyridin-8-yl)sulfonyl)-L-prolinate:** Methyl ((2-(5-hydroxypentyl)-5-methylimidazo[1,2-a]pyridin-8-yl)sulfonyl)-L-prolinate (31 mg, 0.07 mmol, 1 eq) was dissolved in DCM (5 mL). DIPEA (0.05 mL, 0.26 mmol, 4 eq) was added and the mixture was cooled to -10°C. A soln. of PyrSO₃ (28 mg, 0.08 mmol, 1.2 eq) in DMSO (0.11 mL) was added dropwise while maintaining a temperature below -5°C. The reaction mixture was stirred at rt overnight. The reaction mixture was partitioned between H₂O and DCM. The layers were separated through a phase separator cartridge and the solvent was removed under reduced pressure.
- The crude product was used in the next step without further purification. LC-MS (1): t_R= 0.64 min; [M+H]⁺: 408.3.

(S,Z)-5-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-1^s-methyl-2-thia-5-aza-1(8,2)-imidazo[1,2-a]pyridina-3(1,2)-pyrrolidinacyclodecaphan-4-one 2,2-dioxide: Was synthesized using methyl ((5-methyl-2-(5-oxopentyl)imidazo[1,2-a]pyridin-8-yl)sulfonyl)-L-prolinate and (3s,6s)-1,1-difluorospiro[2.5]octan-6-amine hydrochloride in analogy to Example 1.311 to give the title compound. LC-MS (1): t_R= 0.83 min; [M+H]⁺: 521.3.

- Example 1.335 and Example 1.336** were synthesized using the appropriate amine salt derivative and methyl ((3-fluoro-4-methyl-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.192. LC-MS data of Example 1.335 and Example 1.336 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
1.335	(6R,12aS)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-4-fluoro-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.17	528.9
1.336	(1R,4s)-4-((6R,12aS)-4-Fluoro-3,6-dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.05	492.0

- Example 1.337 to Example 1.347** were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((4-methyl-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.108. LC-MS data of Example 1.337 to Example 1.347 are listed in the table below. The LC-MS conditions used were LC-MS (2).

Ex. N°	Name	t _R	[M+H] ⁺
1.337	(1R,3S,6R)-6-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)spiro[2.5]octane-1-carbonitrile	1.07	500.4
1.338	(6R,12aS)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.14	511.3
1.339	(6R,12aS)-11-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.07	483.3
1.342	2-((1R,4s)-4-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexyl)acetonitrile	1.02	488.2
1.344	(1R,4s)-1-Cyclopropyl-4-((6R,12aS)-3,6-dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.08	514.2
1.345	(2S,3aR,5r,6aS)-5-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)octahydropentalene-2-carbonitrile	1.04	500.3
1.346	(2R,3aR,5s,6aS)-5-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)octahydropentalene-2-carbonitrile	1.03	500.3
1.347	(1R,3S)-3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclopentane-1-carbonitrile	0.97	460.2

Example 1.348 (6R,11aS)-3,6-Dimethyl-10-(1,1,2,2-tetrafluorospiro[2.5]octan-6-yl)-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide:

N-Benzyl-4-(difluoromethylene)cyclohexan-1-amine: 4-(Difluoromethylene)cyclohexan-1-one (1.00 g, 6.84 mmol, 1 eq), benzylamine (0.83 mL, 7.53 mmol, 1.1 eq) and AcOH (0.39 mL, 6.84 mmol, 1 eq) were dissolved in THF (38 mL). The mixture was stirred at rt for 30 min then NaBH(OAc)₃ (2.36 g, 8.90 mmol, 1.3 eq) was added. The reaction mixture was stirred at rt for 2h. The reaction mixture was partitioned between aq. 2N HCl soln. and EtOAc. The layers were separated and the org. layer was discarded. The aq. layer was basified using an aq. 25% NaOH soln. until pH ~ 12. The aq. layer was extracted with EtOAc. The combined org. layers were washed with

brine, dried over MgSO_4 , filtered, and the solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.65 min; $[\text{M}+\text{H}]^+$: 238.3.

***tert*-Butyl benzyl(4-(difluoromethylene)cyclohexyl)carbamate:** 2M Boc_2O soln. in DCM (1 mL, 5.27 mmol, 1.2 eq) was added to a soln. of *N*-benzyl-4-(difluoromethylene)cyclohexan-1-amine (1.58 g, 4.39 mmol, 1 eq) and TEA (1.53 mL, 11.00 mmol, 2.5 eq) in DCM (25 mL). The mixture was stirred at rt overnight. 2M Boc_2O soln. in DCM (0.5 mL, 2.64 mmol, 0.6 eq) and TEA (0.8 mL, 5.71 mmol, 1.3 eq) were added again. The mixture was stirred at rt for 2h. The reaction mixture was partitioned between aq. 1M HCl soln. and DCM. The layers were separated and the org. layer was washed with brine twice. The org. layer was separated using a phase separator cartridge and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 50% *t*BME) to give the title compound. LC-MS (1): t_R = 1.17 min; $[\text{M}+\text{H}]^+$: not seen.

***tert*-Butyl benzyl(1,1,2,2-tetrafluorospiro[2.5]octan-6-yl)carbamate:** Trimethyl(trifluoromethyl)silane (1.35 g, 9.19 mmol, 2.5 eq) and NaI (278 mg, 1.84 mmol, 0.5 eq) were added to a soln. of *tert*-butyl benzyl(4-(difluoromethylene)cyclohexyl)carbamate (1.55 g, 3.68 mmol, 1 eq) in THF (25 mL). The mixture was stirred at 70°C overnight. The mixture was filtered over a glass fiber filter and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 10% *t*BME) to give the title compound. LC-MS (1): t_R = 1.18 min; $[\text{M}+\text{H}]^+$: 388.1.

***N*-Benzyl-1,1,2,2-tetrafluorospiro[2.5]octan-6-amine hydrochloride:** *tert*-Butyl benzyl(1,1,2,2-tetrafluorospiro[2.5]octan-6-yl)carbamate (988 mg, 1.91 mmol, 1 eq) was dissolved in 3M HCl soln. in cyclopentyl methyl ether (10 mL, 246 mmol, 128 eq). The mixture was stirred at rt for 1h. The solvent was removed under reduced pressure. The residue was dissolved in formic acid, filtered over a glass fiber filter and was purified by acidic prep. HPLC. Aq. 25% HCl soln. was added and the solvent was removed under reduced pressure to give the title compound. LC-MS (2): t_R = 0.68 min; $[\text{M}+\text{H}]^+$: 288.2.

1,1,2,2-Tetrafluorospiro[2.5]octan-6-amine hydrochloride: *N*-Benzyl-1,1,2,2-tetrafluorospiro[2.5]octan-6-amine hydrochloride (484 mg, 1.44 mmol, 1 eq) was dissolved in a mixture of aq. 2M HCl soln. (2 mL) and AcOH (5 mL). The reaction flask was purged with N_2 for 5 min and 10% Pd/C (100 mg, 0.09 mmol, 0.07 eq) was added. The reaction was stirred at 70°C under H_2 atm overnight. The mixture was filtered over a glass fiber filter and the solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.51 min; $[\text{M}+\text{H}]^+$: 198.2.

Methyl ((6-methyl-2-(((*R*)-5-oxopentan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate: Was synthesized using methyl ((2-hydroxy-6-methylpyridin-3-yl)sulfonyl)-L-prolinate and (*S*)-5-((*tert*-butyldimethylsilyl)oxy)pentan-2-ol in analogy to Example 1.263 to give the title compound. LC-MS (1): t_R = 0.92 min; $[\text{M}+\text{H}]^+$: 385.1.

(6*R*,11*aS*)-3,6-Dimethyl-10-(1,1,2,2-tetrafluorospiro[2.5]octan-6-yl)-7,8,9,10,11*a*,12,13,14-octahydropyrido[2,3-*b*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclododecin-11(6*H*)-one 16,16-dioxide: Was synthesized using methyl ((6-methyl-2-(((*R*)-5-oxopentan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate and 1,1,2,2-

tetrafluorospiro[2.5]octan-6-amine hydrochloride in analogy to Example 1.84 to give the title compound. LC-MS (4): t_R= 1.19 min; [M+H]⁺: 534.2.

Example 1.349 (6R,11aS)-10-((1RS,3RS,6SR)-7,7-Difluorobicyclo[4.1.0]heptan-3-yl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-*b*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclododecin-11(6*H*)-one 16,16-dioxide: Was synthesized using methyl ((6-methyl-2-(((R)-5-oxopentan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate and rel-(1*S*,3*S*,6*R*)-7,7-difluoronorcaran-3-amine hydrochloride in analogy to Example 1.84 to give the title compound. LC-MS (1): t_R= 1.06 min; [M+H]⁺: 484.2.

Example 1.350 and Example 1.351 were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.51. LC-MS data of Example 1.350 and Example 1.351 are listed in the table below. The LC-MS conditions used were LC-MS (4).

Ex. N°	Name	t _R	[M+H] ⁺
1.350	(6R,12aS)-3,6-Dimethyl-11-((1,1,2,2-tetrafluorospiro[2.5]octan-6-yl)-6,7,8,9,10,11,12a,13,14,15-decahydro-12 <i>H</i> -pyrido[2,3- <i>b</i>]pyrrolo[1,2- <i>e</i>][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.23	548.2
1.351	(6R,12aS)-11-((1RS,3RS,6SR)-7,7-Difluorobicyclo[4.1.0]heptan-3-yl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12 <i>H</i> -pyrido[2,3- <i>b</i>]pyrrolo[1,2- <i>e</i>][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.17	498.1

Example 1.352 to Example 1.354 were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl-((4-methyl-2-((5-oxopentyl)oxy)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.7. LC-MS data of Example 1.352 to Example 1.354 are listed in the table below. The LC-MS conditions used were LC-MS (4).

Ex. N°	Name	t _R	[M+H] ⁺
1.352	(<i>S</i>)-11-((3 <i>R</i> ,6 <i>s</i>)-1,1-Difluorospiro[2.5]octan-6-yl)-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12 <i>H</i> -benzo[<i>b</i>]pyrrolo[1,2- <i>e</i>][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.09	497.2
1.353	(1 <i>R</i> ,4 <i>s</i>)-4-((<i>S</i>)-3-Methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6 <i>H</i> -benzo[<i>b</i>]pyrrolo[1,2- <i>e</i>][1]oxa[4]thia[5,8]diazacyclotridecin-11(12 <i>H</i>)-yl)cyclohexane-1-carbonitrile	0.92	460.3
1.354	(1 <i>R</i> ,4 <i>s</i>)-1-Methyl-4-((<i>S</i>)-3-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6 <i>H</i> -benzo[<i>b</i>]pyrrolo[1,2- <i>e</i>][1]oxa[4]thia[5,8]diazacyclotridecin-11(12 <i>H</i>)-yl)cyclohexane-1-carbonitrile	0.98	474.3

Example 1.355 to Example 1.359 were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((4-methyl-2-(((1*R**,3*S**)-3-(2-oxoethyl)cyclohexyl)oxy)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.124. LC-MS data of Example 1.355 to Example 1.359 are listed in the table below. The LC-MS conditions used were LC-MS (2).

Ex. N°	Name	t _R	[M+H] ⁺
1.355	(1 ² S,5 ¹ R*,5 ³ R*)-8-((3 <i>R</i> ,5 <i>s</i>)-1,1-Difluorospiro[2.3]hexan-5-yl)-3 ⁴ -methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide	1.15 and 1.22	509.1
1.356	(1 ² S,5 ¹ R*,5 ³ R*)-8-((3 <i>R</i> ,6 <i>s</i>)-1,1-Difluorospiro[2.5]octan-6-yl)-3 ⁴ -methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide	1.21 and 1.27	537.1
1.357	(1 <i>R</i> ,4 <i>s</i>)-1-Methyl-4-((1 ² S,5 ¹ R*,5 ³ R*)-3 ⁴ -methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile	1.09 and 1.16	514.1
1.358	(1 ² S,5 ¹ R*,5 ³ R*)-8-((3 <i>R</i> ,5 <i>s</i>)-1,1-Difluorospiro[2.3]hexan-5-yl)-3 ⁶ -methyl-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide	1.22 and 1.27	510.1
1.359	(1 ² S,5 ¹ R*,5 ³ R*)-8-((3 <i>R</i> ,6 <i>s</i>)-1,1-Difluorospiro[2.5]octan-6-yl)-3 ⁶ -methyl-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide	1.28 and 1.33	538.1

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Example 1.360 (6*R*,12*aS*)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,13,14,15,16-decahydrodipyrido[2,3-*b*:1',2'-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-12(12*aH*)-one 18,18-dioxide:

(*RS*)-2-Ethylhexyl 3-((2-(((*R*)-hex-5-en-2-yl)oxy)-6-methylpyridin-3-yl)thio)propanoate: (*RS*)-2-Ethylhexyl 3-((2-hydroxy-6-methylpyridin-3-yl)thio)propanoate (13.64 g, 41.90 mmol, 1 eq) was dissolved in THF (510 mL) and the soln. was cooled to 0°C. (*S*)-Hex-5-en-2-ol (5.04 g, 50.30 mmol, 1.2 eq) and PPh₃ (16.65 g, 62.90 mmol, 1.5 eq) were added followed by a dropwise addition of ~40% DEAD soln. in toluene (62.7 mL, 137 mmol, 3.3 eq). The mixture was allowed to warm up to rt and was stirred for 1h. The reaction mixture was diluted with Et₂O and washed with brine. The org. layer was dried over Na₂SO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 25% EtOAc) to give the title compound. LC-MS (1): t_R= 1.30 min; [M+H]⁺: 408.4.

(*RS*)-2-Ethylhexyl 3-((2-(((*R*)-6-hydroxyhexan-2-yl)oxy)-6-methylpyridin-3-yl)thio)propanoate: Was synthesized using (*RS*)-2-ethylhexyl 3-((2-(((*R*)-hex-5-en-2-yl)oxy)-6-methylpyridin-3-yl)thio)propanoate and 1M

BH₃.THF complex soln. in analogy to Example 1.270 to give the title compound. LC-MS (1): t_R= 1.20 min; [M+H]⁺: 426.4.

(RS)-2-Ethylhexyl 3-((2-(((R)-6-((*tert*-butyldiphenylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridin-3-yl)thio)propanoate: Was synthesized using (RS)-2-ethylhexyl 3-((2-(((R)-6-hydroxyhexan-2-yl)oxy)-6-methylpyridin-3-yl)thio)propanoate and *tert*-butyldiphenylsilyl chloride in analogy to Example 1.263 to give the title compound. LC-MS (1): t_R= 1.49 min; [M+H]⁺: 664.6.

(RS)-2-Ethylhexyl 3-((2-(((R)-6-((*tert*-butyldiphenylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)propanoate: Was synthesized using (RS)-2-ethylhexyl 3-((2-(((R)-6-((*tert*-butyldiphenylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridin-3-yl)thio)propanoate and mCPBA in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R= 1.45 min; [M+H]⁺: 696.1.

Methyl (S)-1-((2-(((R)-6-hydroxyhexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)piperidine-2-carboxylate: Was synthesized using (RS)-2-ethylhexyl 3-((2-(((R)-6-((*tert*-butyldiphenylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)propanoate and methyl (S)-piperidine-2-carboxylate hydrochloride soln. in THF in analogy to Examples 1.256 to give the title compound. LC-MS (1): t_R= 0.96 min; [M+H]⁺: 415.1.

Methyl (S)-1-((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)piperidine-2-carboxylate: Was synthesized using methyl (S)-1-((2-(((R)-6-hydroxyhexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)piperidine-2-carboxylate and oxalyl chloride in analogy to Example 1.51 to give the title compound. LC-MS (1): t_R= 1.01 min; [M+H]⁺: 413.1.

(6R,12aS)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,13,14,15,16-decahydrodiprido[2,3-*b*:1',2'-e][1]oxa[4]thia[5,8]diazacyclotridecin-12(12aH)-one 18,18-dioxide: Was synthesized using methyl (S)-1-((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)piperidine-2-carboxylate and 4,4-difluorocyclohexan-1-amine in analogy to Example 1.263 to give the title compound. LC-MS (1): t_R= 1.14 min; [M+H]⁺: 500.0.

Example 1.363 to Example 1.368 were synthesized using the appropriate amine or amine salt derivative and the appropriate aldehyde in analogy to Example 1.240. LC-MS data of Example 1.363 to Example 1.373 are listed in the table below. The LC-MS conditions used were LC-MS (4).

Ex. N°	Name	t _R	[M+H] ⁺
1.363	(6R,11aS)-10-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide	1.1	497.2
1.364	(6R,11aS)-10-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide	1.04	469.3
1.365	(1R,4s)-4-((6R,11aS)-3,6-Dimethyl-16,16-dioxido-11-oxo-6,7,8,9,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-yl)-1-methylcyclohexane-1-carbonitrile	0.99	474.3
1.366	(1R,4s)-4-((6R,11aS)-3,6-Dimethyl-16,16-dioxido-11-oxo-6,7,8,9,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-yl)-1-methylcyclohexane-1-carbonitrile	1.01	475.3
1.367	(1R,4s)-4-((S)-3-Methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.93	461.3
1.368	(1R,4s)-1-Methyl-4-((S)-3-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.99	475.4

Example 1.369 (1S,3S)-3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile:

- 5 **tert-Butyl ((1S,3S)-3-cyano-3-methylcyclohexyl)carbamate:** Was synthesized using (1S,3S)-3-(((tert-butoxy)carbonyl)amino)-1-methylcyclohexane-1-carboxylic acid in analogy to Example 1.143 to give the title compound. LC-MS (1): t_R= 0.88 min; [M+H]⁺: 239.4.

- 10 **(1S,3S)-3-Cyano-3-methylcyclohexan-1-ammonium hydrochloride:** 4M HCl soln. in dioxane (1.38 mL, 5.5 mmol, 5 eq) was added to a solution of *tert*-butyl ((1S,3S)-3-cyano-3-methylcyclohexyl)carbamate (262 mg, 1.1 mmol, 1 eq) in DCM (10 mL) at 0 °C and the mixture was stirred at rt overnight. 4M HCl in dioxane soln. (1.38 mL, 5.5 mmol, 5 eq) was added again and the mixture was stirred for 1h. The solvent was removed under reduced pressure to give the title compound. LC-MS (1): t_R= 0.53 min; [M+H]⁺: 139.3.

- 15 **(1S,3S)-3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile:** Was synthesized using *tert*-butyl ((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate and (1S,3S)-

3-cyano-3-methylcyclohexan-1-ammonium hydrochloride in analogy to Example 1.240 to give the title compound. LC-MS (4): t_R = 1.07 min; $[M+H]^+$: 489.0.

Example 1.370 to Example 1.371 were synthesized using the appropriate amine or amine salt derivative and the appropriate aldehyde in analogy to Example 1.240. LC-MS data of Example 1.370 to Example 1.371 are listed in the table below. The LC-MS conditions used were LC-MS (4).

1.370	(1S,3S)-3-((8R,12aS)-3,8-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	1.07	489.1
1.371	(8R,12aS)-11-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-3,8-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.12	484.0

Example 1.372 (1R,3R)-3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile:

10 (1R,3R)-3-Cyano-3-methylcyclohexan-1-ammonium hydrochloride: Was synthesized using *tert*-butyl ((1R,3R)-3-cyano-3-methylcyclohexyl)carbamate in analogy to Example 1.369 to give the title compound. LC-MS (1): t_R = 0.53 min; $[M+H]^+$: 139.3.

(1R,3R)-3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile: Was synthesized using *tert*-butyl ((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate and (1R,3R)-3-cyano-3-methylcyclohexan-1-ammonium hydrochloride in analogy to Example 1.51 to give the title compound. LC-MS (4): t_R = 1.07 min; $[M+H]^+$: 489.1.

Example 1.373 (1R,3R)-3-((8R,12aS)-3,8-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile: Was synthesized using methyl ((6-methyl-2-(((S)-3-methyl-5-oxopentyl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate and (1R,3R)-3-cyano-3-methylcyclohexan-1-ammonium hydrochloride in analogy to Example 1.263 to give the title compound. LC-MS (4): t_R = 1.07 min; $[M+H]^+$: 489.1

Example 1.374 (1³R,5²S)-7-(4,4-Difluorocyclohexyl)-3⁵-methyl-2-oxa-4-thia-7-aza-1(3,1)-piperidina-5(1,2)-pyrrolidina-3(1,2)-benzenacyclononaphan-6-one 4,4-dioxide:

25 *tert*-Butyl (R)-3-(2-(((S)-2-(methoxycarbonyl)pyrrolidin-1-yl)sulfonyl)-5-methylphenoxy)piperidine-1-carboxylate: Was synthesized using methyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate and *tert*-butyl (S)-3-hydroxypiperidine-1-carboxylate in analogy to Example 1.84 to give the title compound. LC-MS (1): t_R = 1.04 min; $[M+H]^+$: 483.1.

Methyl ((4-methyl-2-(((R)-piperidin-3-yl)oxy)phenyl)sulfonyl)-L-prolinate hydrochloride: *tert*-butyl (R)-3-(2-(((S)-2-(methoxycarbonyl)pyrrolidin-1-yl)sulfonyl)-5-methylphenoxy)piperidine-1-carboxylate (348 mg, 0.72 mmol, 1 eq) was dissolved in 4M HCl soln. in dioxane (7 mL). The reaction mixture was stirred at rt for 2h. The solvent was removed under reduced pressure. The crude product was used in the next step without further purification.

5 LC-MS (2): t_R = 0.81 min; $[M+H]^+$: 383.3.

Methyl ((2-(((R)-1-(2-((*tert*-butoxycarbonyl)amino)ethyl)piperidin-3-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate: *tert*-Butyl (2-bromoethyl)carbamate (221 mg, 0.94 mmol, 1.3 eq) was added at rt to a stirred suspension of methyl ((4-methyl-2-(((R)-piperidin-3-yl)oxy)phenyl)sulfonyl)-L-prolinate hydrochloride (302 mg, 0.72 mmol, 1 eq) and K_2CO_3 (398 mg, 2.88 mmol, 4 eq) in MeCN (7.5 mL). The mixture was stirred at 55°C overnight. The mixture

10 was partitioned between H_2O and EtOAc and the org. layer was washed twice with brine, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 80% EtOAc) to give the title compound. LC-MS (1): t_R = 0.79 min; $[M+H]^+$: 526.3.

Methyl ((2-(((R)-1-(2-aminoethyl)piperidin-3-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate hydrochloride: Methyl ((2-(((R)-1-(2-((*tert*-butoxycarbonyl)amino)ethyl)piperidin-3-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate

15 (228 mg, 0.43 mmol, 1 eq) was dissolved in a 4M HCl soln. in dioxane (4 mL). The reaction mixture was stirred at rt overnight. The solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (2): t_R = 0.84 min; $[M+H]^+$: 426.2.

(1³R,5²S)-7-(4,4-Difluorocyclohexyl)-3⁵-methyl-2-oxa-4-thia-7-aza-1(3,1)-piperidina-5(1,2)-pyrrolidina-3(1,2)-benzenacyclononaphan-6-one 4,4-dioxide: Was synthesized using methyl ((2-(((R)-1-(2-aminoethyl)piperidin-3-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate hydrochloride and 4,4-difluorocyclohexan-1-one in analogy to

20 Examples 1.166 to give the title compound. LC-MS (1): t_R = 0.75 min; $[M+H]^+$: 512.2.

Example 1.375 (1²S,5²S,5⁴R)-8-(4,4-difluorocyclohexyl)-3⁴-methyl-5²,5³,5⁴,5⁵-tetrahydro-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-5(4,2)-furana-3(1,2)-benzenacyclononaphan-9-one 2,2-dioxide:

(RS)-4-((*tert*-Butyldiphenylsilyl)oxy)dihydrofuran-2(3H)-one: Was synthesized using (RS)-4-hydroxydihydrofuran-2(3H)-one and *tert*-butyldiphenylsilyl chloride in analogy to Example 1.263 to give the title

25 compound. LC-MS (1): t_R = 1.13 min; $[M+H]^+$: 341.1.

(2R*,4S*)-4-((*tert*-Butyldiphenylsilyl)oxy)tetrahydrofuran-2-yl acetate: A 1M Diisobutylaluminum hydride soln. in DCM (6.5 mL, 6.5 mmol, 1.1 eq) was added dropwise over 15 min at -78°C, to a stirred soln. of (RS)-4-((*tert*-butyldiphenylsilyl)oxy)dihydrofuran-2(3H)-one (2.00 g, 5.87 mmol, 1 eq) in DCM (36 mL). The mixture was stirred

30 at -78°C for 2h45. 1M Diisobutylaluminum hydride soln. (2 mL) was added at -78°C and the mixture was stirred at -78°C for 40 min. Pyridine (1.40 mL, 17.6 mmol, 3 eq), DMAP (804 mg, 6.45 mmol, 1.1 eq) and acetic anhydride (2.20 mL, 23.5 mmol, 4 eq) were then added in sequence. The resulting mixture was stirred at -78°C for 2h then slowly let warming up to rt overnight. The reaction mixture was quenched by addition of aq. sat. NH_4Cl soln.. The mixture was stirred at rt for 30 min then the layers were separated. The org. layer was washed with aq. 0.5M

35 $NaHSO_3$, aq. sat. $NaHCO_3$ and brine. The org. layer was separated through a phase separator cartridge and the

solvent was removed under reduced pressure. The residue was purified by FC (Hept to 10% EtOAc) to give the title compound. LC-MS (1): t_R = 1.19 min; $[M+H]^+$: not seen.

5 **(((3R*,5S*)-5-Allyltetrahydrofuran-3-yl)oxy)(tert-butyl)diphenylsilane:** A soln. of $SnBr_4$ (1.11 g, 2.50 mmol, 1.2 eq) in DCM (3 mL) was added over 15 min at $-78^\circ C$ to a stirred soln. of (2R*,4S*)-4-((tert-butyl)diphenylsilyl)oxy)tetrahydrofuran-2-yl acetate (800 mg, 2.08 mmol, 1 eq) and allyltrimethylsilane (1.40 mL, 8.32 mmol, 4 eq) in DCM (28 mL). The reaction mixture was stirred at $-78^\circ C$ for 1h then at rt for 2h30. The mixture was partitioned between DCM and aq. sat. Na_2CO_3 . The org. layer was separated and was washed with brine. The org. layer was separated through a phase separator cartridge and the solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 1.24 min; $[M+H]^+$:
10 not seen.

(3R*,5S*)-5-Allyltetrahydrofuran-3-ol: Was synthesized using (((3R*,5S*)-5-allyltetrahydrofuran-3-yl)oxy)(tert-butyl)diphenylsilane and 1M TBAF soln. in THF in analogy to Example 1.75 to give the title compound.

15 **(3R*,5R*)-5-Allyltetrahydrofuran-3-yl 4-nitrobenzoate:** (3R*,5S*)-5-Allyltetrahydrofuran-3-ol (169 mg, 1.32 mmol, 1 eq), 4-nitrobenzoic acid (450 mg, 2.64 mmol, 2 eq) and PPh_3 polymer-bound, (100-200 mesh, ca. 1.6 mmol/g, 1.67 g) were suspended in THF (13 mL) and stirred at $0^\circ C$. DIAD (0.56 mL, 2.77 mmol, 2.1 eq) was added dropwise and the reaction mixture was stirred at rt overnight. The reaction mixture was filtered, washed with DCM followed by MeOH and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 10% EtOAc) to give the title compound. LC-MS (1): t_R = 0.97 min; $[M+H]^+$: not seen.

20 **(3R*,5R*)-5-Allyltetrahydrofuran-3-ol:** H_2O (1.4 mL), THF (5.7 mL) and K_2CO_3 (162 mg, 1.15 mmol, 1.1 eq) were added sequentially at rt to a soln. of (3R*,5R*)-5-allyltetrahydrofuran-3-yl 4-nitrobenzoate (290 mg, 1.04 mmol, 1 eq) in MeOH (11 mL). The reaction mixture was stirred at rt for 1h30. The mixture was partitioned between EtOAc and aq. 1M NaOH soln.. The org. layer was separated and was washed with brine. The org. layer was dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 30% EtOAc) to give the title compound.

25 **tert-Butyl ((2-(((3R*,5S*)-5-allyltetrahydrofuran-3-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using (3R*,5R*)-5-allyltetrahydrofuran-3-ol and tert-butyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 1.09 min; $[M+H]^+$: 452.0.

30 **tert-Butyl ((4-methyl-2-(((3R*,5R*)-5-(2-oxoethyl)tetrahydrofuran-3-yl)oxy)phenyl)sulfonyl)-L-prolinate:** A soln. of 2.5 wt.% OsO_4 in $tBuOH$ (0.10 mL, 0.01 mmol, 0.02 eq) was added at rt to a stirred soln. of tert-butyl ((2-(((3R*,5S*)-5-allyltetrahydrofuran-3-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate (145 mg, 0.32 mmol, 1 eq) in THF (2.3 mL) and H_2O (2.3 mL). After few min, $NaIO_4$ (173 mg, 0.80 mmol, 2.5 eq) was added in small portions over 10 min. The mixture was stirred at rt overnight. The white solid was filtered off and washed with EtOAc. The filtrate was washed with aq. sat. $NaHCO_3$ soln. and brine, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.97
35 min; $[M+H]^+$: 454.0.

(1²S,5²S,5⁴R)-8-(4,4-Difluorocyclohexyl)-3⁴-methyl-5²,5³,5⁴,5⁵-tetrahydro-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-5(4,2)-furana-3(1,2)-benzenacyclononaphan-9-one 2,2-dioxide: Was synthesized using *tert*-butyl ((4-methyl-2-(((3R*,5R*)-5-(2-oxoethyl)tetrahydrofuran-3-yl)oxy)phenyl)sulfonyl)-L-prolinate and 4,4-difluorocyclohexan-1-amine hydrochloride in analogy to Example 1.281 to give the title compound. LC-MS (1): t_R= 0.92 min; [M+H]⁺: 499.2.

Example 1.376 (3aS,10R)-5-(4,4-Difluorocyclohexyl)-10,13-dimethyl-1,2,5,6,7,8,9,10-octahydrooxazolo[3,2-e]pyrido[2,3-b][1]oxa[4]thia[5,8]diazacyclotridecin-4(3aH)-one 16,16-dioxide:

Ethyl (S)-3-((*tert*-butyldiphenylsilyl)oxy)butanoate: Was synthesized using ethyl (S)-3-hydroxybutanoate and *tert*-butyldiphenylsilyl chloride in analogy to Example 1.263 to give the title compound. LC-MS (1): t_R= 1.26 min; [M+H]⁺: 371.1.

(S)-3-((*tert*-Butyldiphenylsilyl)oxy)-N-methoxy-N-methylbutanamide: Ethyl (S)-3-((*tert*-butyldiphenylsilyl)oxy)butanoate (146.0 g, 394 mmol, 1 eq) and N,O-dimethylhydroxylamine hydrochloride (61.1 g, 611 mmol, 1.6 eq) were suspended in MeTHF (800 mL). The mixture was cooled to -25°C then a 2M isopropylmagnesium chloride soln. in THF (584 mL, 1180 mmol, 3 eq) was added dropwise while maintaining a temperature below -15°C. The reaction mixture was stirred at -25°C for 15 min. The mixture was quenched with cold aq. 20% citric acid soln.. The layers were separated and the org. layer was washed with H₂O, dried over MgSO₄, filtered, and the solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R= 1.17 min; [M+H]⁺: 386.0.

(S)-3-((*tert*-Butyldiphenylsilyl)oxy)butanal: A 25% Diisobutylaluminum hydride soln. in toluene (235 mL, 350 mmol, 1.8 eq) was added dropwise at -78°C, to a stirred soln. of (S)-3-((*tert*-butyldiphenylsilyl)oxy)-N-methoxy-N-methylbutanamide (75.00 g, 195 mmol, 1 eq) in MeTHF (400 mL). The internal temperature was kept below -60°C during the addition. The mixture was stirred at -78°C for 40 min. The mixture was quenched at -78°C with AcOH (9 mL, 156 mmol, 0.8 eq) then was warmed up to 10°C. Aq. 20% citric acid soln. was carefully added and the mixture was stirred at 60°C for 30 min then was cooled to rt. The layers were separated and the org. layer was washed with H₂O, dried over MgSO₄, filtered, and the solvent was removed under reduced pressure. The crude product was used in the next step without further purification.

Ethyl (S,E)-5-((*tert*-butyldiphenylsilyl)oxy)hex-2-enoate: Triethylphosphonoacetate (60.00 mL, 294 mmol, 1.5 eq) and DBU (44.00 mL, 294 mmol, 1.5 eq) were added to a suspension of LiCl (12.60 g, 294 mmol, 1.5 eq) in MeCN (70 mL). The reaction mixture was stirred at rt for 10 min then was cooled down to 0°C. A soln. of (S)-3-((*tert*-butyldiphenylsilyl)oxy)butanal (64.00 g, 196 mmol, 1 eq) in MeCN (30 mL) was added dropwise while maintaining a temperature below 10°C. The mixture was stirred at 0°C for 1h. The mixture was quenched with H₂O and extracted with tBME. The combined org. layers were washed with aq. 20% citric acid soln., brine, dried over MgSO₄, filtered, and the solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R=1.29; [M+H]⁺: 397.2.

Ethyl (S)-5-((*tert*-butyldiphenylsilyl)oxy)hexanoate: Was synthesized using ethyl (S,E)-5-((*tert*-butyldiphenylsilyl)oxy)hex-2-enoate and Pd/C in analogy to Example 1.75 to give the title compound. LC-MS (1): t_R = 1.30 min; $[M+H]^+$: 399.2.

5 **(S)-5-((*tert*-Butyldiphenylsilyl)oxy)hexan-1-ol:** Was synthesized using ethyl (S)-5-((*tert*-butyldiphenylsilyl)oxy)hexanoate and $LiAlH_4$ in analogy to Example 1.252 to give the title compound. LC-MS (1): t_R = 1.21 min; $[M+H]^+$: 357.2.

(S)-5-((*tert*-Butyldiphenylsilyl)oxy)hexanal: Was synthesized using (S)-5-((*tert*-butyldiphenylsilyl)oxy)hexan-1-ol and oxalyl chloride in analogy to Example 1.37 to give the title compound. LC-MS (1): t_R = 1.24 min; $[M+H]^+$: 355.1.

10 ***tert*-Butyl (S)-(4,4-difluorocyclohexyl)(5-hydroxyhexyl)carbamate:** Was synthesized using (S)-5-((*tert*-butyldiphenylsilyl)oxy)hexanal and 4,4-difluorocyclohexan-1-amine hydrochloride in analogy to Example 1.75 to give the title compound. LC-MS (1): t_R = 0.99 min; $[M+H]^+$: 336.2.

15 **(RS)-2-Ethylhexyl 3-((2-(((R)-6-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)propanoate:** Was synthesized using (RS)-2-ethylhexyl 3-((2-hydroxy-6-methylpyridin-3-yl)thio)propanoate and *tert*-butyl (S)-(4,4-difluorocyclohexyl)(5-hydroxyhexyl)carbamate in analogy to Example 1.360 to give the title compound. LC-MS (1): t_R = 1.33 min; $[M+H]^+$: 675.1.

***tert*-Butyl (R)-(4,4-difluorocyclohexyl)(5-((3-(N-(2-hydroxyethyl)sulfamoyl)-6-methylpyridin-2-yl)oxy)hexyl)carbamate:** Was synthesized using (RS)-2-Ethylhexyl 3-((2-(((R)-6-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)propanoate and ethanolamine in analogy to Examples 1.124 and 1.125 to give the title compound. LC-MS (1): t_R = 1.09 min; $[M+H]^+$: 550.1.

20 ***tert*-Butyl (4,4-difluorocyclohexyl)((5R)-5-((6-methyl-3-((2-vinyloxazolidin-3-yl)sulfonyl)pyridin-2-yl)oxy)hexyl)carbamate:** A microwave vial was charged with *tert*-butyl (R)-(4,4-difluorocyclohexyl)(5-((3-(N-(2-hydroxyethyl)sulfamoyl)-6-methylpyridin-2-yl)oxy)hexyl)carbamate (251 mg, 0.44 mmol, 1 eq), 4Å molecular sieves (47.4 mg, 0.44 mmol, 1 eq) and pyridinium *p*-toluenesulfonate (33.4 mg, 0.13 mmol, 0.3 eq). A soln. of acrolein diethyl acetal (0.21 mL, 1.32 mmol, 3 eq) in 1,2-dichloroethane (5 mL) was added and the capped vial was put in
25 a heating block at 90°C for 2 h. The mixture was allowed to cool to rt and was diluted with DCM and aq. sat. $NaHCO_3$ soln. The layers were separated through a phase separation cartridge. The org. layer was dried under reduced pressure. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R = 1.22 min; $[M+H]^+$: 588.1.

30 ***tert*-Butyl (4,4-difluorocyclohexyl)((5R)-5-((3-((2-formyloxazolidin-3-yl)sulfonyl)-6-methylpyridin-2-yl)oxy)hexyl)carbamate:** To a solution of *tert*-butyl (4,4-difluorocyclohexyl)((5R)-5-((6-methyl-3-((2-vinyloxazolidin-3-yl)sulfonyl)pyridin-2-yl)oxy)hexyl)carbamate (290 mg, 0.493 mmol, 1 eq) in THF (3 mL) and water (0.25 mL) were added 2,6-lutidine (0.116 mL, 0.987 mmol, 2 eq) and 50% wt 4-methylmorpholine-N-oxide soln. in H_2O (0.205 mL, 0.987 mmol, 2 eq) were added and the reaction mixture was cooled to 0°C. A 2.5% wt. OsO_4 soln. in *tert*-butanol (1.86 mL, 0.148 mmol, 0.3001 eq) was added dropwise. After 45 min. the reaction mixture was

allowed to warm to rt and the mixture was stirred for 3 hours. The reaction mixture was quenched with Na₂SO₃ solution. The solution turned brown. The mixture was extracted three times with EtOAc. The comb. org. layers were dried over MgSO₄, filtered, and the solvent was removed under reduced pressure. The residue was dissolved in THF (3 mL) and water (0.25 mL) and NaIO₄ (426 mg, 1.97 mmol, 4 eq) was added. The reaction mixture stirred overnight. The reaction mixture was filtered and the filtrate was extracted with EtOAc. The comb. org. layers were dried over MgSO₄, filtered, and the solvent was removed under reduced pressure to give the title compound. LC-MS (2): t_R= 1.14 min; [M+H]⁺: 590.3.

3-((2-(((R)-6-((*tert*-Butoxycarbonyl)(4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)oxazolidine-2-carboxylic acid: A soln. of sodium phosphate monobasic monohydrate (412 mg, 2.96 mmol, 6 eq) and sodium chlorite (334 mg, 2.96 mmol, 6 eq) in H₂O (0.84 mL) was added to a soln. of *tert*-butyl (4,4-difluorocyclohexyl)((5R)-5-((3-((2-formyloxazolidin-3-yl)sulfonyl)-6-methylpyridin-2-yl)oxy)hexyl)carbamate (529 mg, 0.49 mmol, 1 eq) and 2-methyl-2-butene (2.2 mL, 19.7 mmol, 40 eq) in THF (1.8 mL) and anhyd. *t*BuOH (1.8 mL). The resulting suspension was stirred at rt for 2h before the addition of sodium phosphate monobasic monohydrate (412 mg, 2.96 mmol, 6 eq) and sodium chlorite (334 mg, 2.96 mmol, 6 eq) in H₂O (0.84 mL). The mixture was stirred at rt overnight. The reaction mixture was diluted with EtOAc and washed with brine. The layers were separated and the org. layer was dried over MgSO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) and by basic prep. HPLC to give the title compound. LC-MS (1): t_R= 1.10; [M+H]⁺: 606.0.

3-((2-(((R)-6-((4,4-Difluorocyclohexyl)amino)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)oxazolidine-2-carboxylic acid: Was synthesized using 3-((2-(((R)-6-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)oxazolidine-2-carboxylic acid in analogy to Example 1.75 to give the title compound. LC-MS (1): t_R= 0.74; [M+H]⁺: 506.0.

(3aS,10R)-5-(4,4-Difluorocyclohexyl)-10,13-dimethyl-1,2,5,6,7,8,9,10-octahydrooxazolo[3,2-*e*]pyrido[2,3-*b*][1]oxa[4]thia[5,8]diazacyclotridecin-4(3aH)-one 16,16-dioxide: Was synthesized using 3-((2-(((R)-6-((4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)oxazolidine-2-carboxylic acid in analogy to Example 1.75 to give the title compound. LC-MS (1): t_R= 1.07 min; [M+H]⁺: 488.0.

Example 1.377 (9aS,14aR,17aR)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,12,13,14,14a,15,16,17,17a-dodecahydrocyclopenta[*f*]pyrido[2,3-*b*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-10(11H)-one 5,5-dioxide:

(1R*,2S*)-2-Allylcyclopentan-1-ol: CuCl (121 mg, 1.19 mmol, 0.1 eq) was suspended in THF (14 mL). The suspension was cooled to 0°C and a 1M allyl magnesium bromide soln. in Et₂O (23.2 mL, 23.20 mmol, 1.95 eq) was added. The mixture was stirred at 0°C for 10 min. A soln. of 1,2-epoxycyclopentane (1.00 g, 11.90 mmol, 1 eq) in THF (0.5 mL) was added dropwise. The mixture was warmed to rt and stirred for 2h. The reaction mixture was poured into aq. sat. NH₄Cl soln. and was extracted with Et₂O. The combined org. layers were dried over

MgSO₄, filtered, and the solvent was removed under reduced pressure. The crude product was used in the next step without further purification.

- 5 **(RS)-2-Ethylhexyl 3-((2-hydroxy-6-methylpyridin-3-yl)sulfonyl)propanoate:** Was synthesized using rac-(R)-2-ethylhexyl 3-((2-(((1R,2R)-2-allylcyclopentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)propanoate and (1R*,2S*)-2-Allylcyclopentan-1-ol in analogy to Example 1.256 to give the title compound. LC-MS (1): t_R= 1.28 min; [M+H]⁺: 466.1.

Methyl ((2-(((1R*,2R*)-2-allylcyclopentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate: Was synthesized using (RS)-2-ethylhexyl 3-((2-hydroxy-6-methylpyridin-3-yl)sulfonyl)propanoate and L-Proline methyl ester hydrochloride in analogy to Example 1.256 to give the title compound. LC-MS (1): t_R= 1.11 min; [M+H]⁺: 409.1.

- 10 **Methyl ((2-(((1R*,2R*)-2-(3-hydroxypropyl)cyclopentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate:** Was synthesized using methyl ((2-(((1R*,2R*)-2-allylcyclopentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate in analogy to Examples 1.270 and 1.271 to give the title compound. LC-MS (1): t_R= 0.95 min; [M+H]⁺: 427.1.

- 15 **Methyl ((6-methyl-2-(((1R*,2R*)-2-(3-oxopropyl)cyclopentyl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate:** Was synthesized using methyl ((2-(((1R*,2R*)-2-(3-hydroxypropyl)cyclopentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate in analogy to Examples 1.270 and 1.271 to give the title compound. LC-MS (1): t_R= 1.01 min; [M+H]⁺: 425.1.

- 20 **Methyl ((2-(((1R*,2R*)-2-(3-((4,4-difluorocyclohexyl)amino)propyl)cyclopentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate:** Was synthesized using methyl ((6-methyl-2-(((1R*,2R*)-2-(3-oxopropyl)cyclopentyl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate and 4,4-difluorocyclohexan-1-amine hydrochloride in analogy to Examples 1.270 and 1.271 to give the title compound. LC-MS (1): t_R= 0.86 and 0.87 min; [M+H]⁺: 544.0.

Lithium ((2-(((1R*,2R*)-2-(3-((4,4-difluorocyclohexyl)amino)propyl)cyclopentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate: Was synthesized using methyl ((2-(((1R*,2R*)-2-(3-((4,4-difluorocyclohexyl)amino)propyl)cyclopentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.166 to give the title compound.

- 25 **(9aS,14aR,17aR)-11-(4,4-Difluorocyclohexyl)-2-methyl-7,8,9,9a,12,13,14,14a,15,16,17,17a-dodecahydrocyclopenta[*f*]pyrido[2,3-*b*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-10(11*H*)-one 5,5-dioxide:** Was synthesized using lithium ((2-(((1R*,2R*)-2-(3-((4,4-difluorocyclohexyl)amino)propyl)cyclopentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.166 to give the title compound. LC-MS (1): t_R= 1.11 min; [M+H]⁺: 512.0.

- 30 **Example 1.378 to Example 1.380** were synthesized using the appropriate amine or amine salt derivative and methyl ((3-fluoro-4-methyl-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.192. LC-MS data of Example 1.378 to Example 1.380 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
1.378	(6R,12aS)-11-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-4-fluoro-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12 <i>H</i> -benzo[<i>b</i>]pyrrolo[1,2- <i>e</i>][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.12	501.0
1.379	(1R,3R)-3-((6R,12aS)-4-Fluoro-3,6-dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6 <i>H</i> -benzo[<i>b</i>]pyrrolo[1,2- <i>e</i>][1]oxa[4]thia[5,8]diazacyclotridecin-11(12 <i>H</i>)-yl)-1-methylcyclohexane-1-carbonitrile	1.10	506.0
1.380	(1S,3S)-3-((6R,12aS)-4-Fluoro-3,6-dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6 <i>H</i> -benzo[<i>b</i>]pyrrolo[1,2- <i>e</i>][1]oxa[4]thia[5,8]diazacyclotridecin-11(12 <i>H</i>)-yl)-1-methylcyclohexane-1-carbonitrile	1.10	506.0

- Example 1.381 (9a*S*,14a*R*,17a*R*)-2-Methyl-11-(1,1,2,2-tetrafluorospiro[2.5]octan-6-yl)-7,8,9,9a,11,12,13,14,14a,15,17,17a-dodecahydro-10*H*-furo[3,4-*l*]pyrido[2,3-*b*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide and Example 1.382 (9a*S*,14a*S*,17a*S*)-2-Methyl-11-(1,1,2,2-tetrafluorospiro[2.5]octan-6-yl)-7,8,9,9a,11,12,13,14,14a,15,17,17a-dodecahydro-10*H*-furo[3,4-*l*]pyrido[2,3-*b*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide:**
- Methyl ((2-(((3*R*^{*},4*R*^{*})-4-allyltetrahydrofuran-3-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate:** Was synthesized using methyl ((2-hydroxy-6-methylpyridin-3-yl)sulfonyl)-L-prolinate and trans-4-(prop-2-en-1-yl)oxolan-3-ol in analogy to Example 1.263 to give the title compound. LC-MS (1): t_R= 0.98 min; [M+H]⁺: 411.2.
- Methyl ((2-(((3*R*^{*},4*R*^{*})-4-(3-hydroxypropyl)tetrahydrofuran-3-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate:** Was synthesized using methyl ((2-(((3*R*^{*},4*R*^{*})-4-allyltetrahydrofuran-3-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate in analogy to Examples 1.270 and 1.271 to give the title compound. LC-MS (1): t_R= 0.79 min; [M+H]⁺: 429.2.
- Methyl ((6-methyl-2-(((3*RS*,4*RS*)-4-(3-oxopropyl)tetrahydrofuran-3-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate:** Was synthesized using methyl ((2-(((3*R*^{*},4*R*^{*})-4-(3-hydroxypropyl)tetrahydrofuran-3-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R= 0.85 min; [M+H]⁺: 427.2.
- (9a*S*,14a*R*,17a*R*)-2-Methyl-11-(1,1,2,2-tetrafluorospiro[2.5]octan-6-yl)-7,8,9,9a,11,12,13,14,14a,15,17,17a-dodecahydro-10*H*-furo[3,4-*l*]pyrido[2,3-*b*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide and (9a*S*,14a*S*,17a*S*)-2-Methyl-11-(1,1,2,2-tetrafluorospiro[2.5]octan-6-yl)-7,8,9,9a,11,12,13,14,14a,15,17,17a-dodecahydro-10*H*-furo[3,4-*l*]pyrido[2,3-*b*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide:** Were synthesized using methyl ((6-methyl-2-(((3*RS*,4*RS*)-4-(3-oxopropyl)tetrahydrofuran-3-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate and 1,1,2,2-

tetrafluorospiro[2.5]octan-6-amine hydrochloride in analogy to Example 1.377. The crude was purified by acidic prep. HPLC to give the 2 diastereomers. First eluting diastereomer: LC-MS (1): t_R = 1.06 min; $[M+H]^+$: 576.2. Second eluting diastereomer: LC-MS (1): t_R = 1.09 min; $[M+H]^+$: 576.2.

Example 1.383 (3aS,10RS)-5-(4,4-Difluorocyclohexyl)-10,13-dimethyl-1,2,3,3a,6,9,10,11-octahydrobenzo[*l*]pyrrolo[1,2-*b*][1]thia[2,5,11]triazacyclotridecin-4(5*H*)-one 16,16-dioxide: Was synthesized using pent-4-en-2-amine hydrochloride and *tert*-butyl ((2-fluoro-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.189 to give the title compound. LC-MS (1): t_R = 1.08 min; $[M+H]^+$: 482.0.

Example 1.384 (1*R*,4*s*)-4-((*S*)-7,7-Difluoro-3-methyl-17,17-dioxido-12-oxo-7,8,9,10,12*a*,13,14,15-octahydro-6*H*-benzo[*b*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-11(12*H*)-yl)cyclohexane-1-carbonitrile:
10 *tert*-Butyl 4,4-difluoro-5-hydroxypentanoate: A soln. of 5-(*tert*-butyl) 1-ethyl 2,2-difluoropentanedioate (4.00 g, 15.20 mmol, 1 eq) in EtOH (21 mL) was added dropwise to a suspension of NaBH₄ (705 mg, 18.30 mmol, 1.2 eq) in EtOH (21 mL). The internal temperature was kept below 15°C during the addition and the reaction mixture was stirred at 15°C for 1h. The reaction mixture was partitioned between EtOAc and aq. 5% citric acid soln. The org. layer was washed with brine, dried over MgSO₄, filtered, and the solvent was removed under reduced pressure.
15 The residue was purified by FC (Hept to 15% EtOAc) to give the title compound.

***tert*-Butyl 4,4-difluoro-5-((tetrahydro-2*H*-pyran-2-yl)oxy)pentanoate:** *tert*-Butyl 4,4-difluoro-5-hydroxypentanoate (2.78 g, 13.20 mmol, 1 eq) and 4-methylbenzene-1-sulfonic acid (120 mg, 0.66 mmol, 0.05 eq) were dissolved in DCM (10 mL) and the mixture was cooled down to -10°C. 3,4-Dihydro-2*H*-pyrane (3.7 mL, 39.70 mmol, 3 eq) was added and the reaction mixture was stirred at rt for 72h. The mixture was poured into aq. sat. NaHCO₃ soln. and was extracted with DCM. The combined org. layers were washed with brine, dried over MgSO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 10% EtOAc) to give the title compound. LC-MS (1): t_R = 1.02; $[M+H]^+$: 295.1.

4,4-Difluoro-5-((tetrahydro-2*H*-pyran-2-yl)oxy)pentan-1-ol: 1*M* LiAlH₄ soln. in THF (10.8 mL, 10.8 mmol, 1.2 eq) was added dropwise at 0°C to a stirred soln. of *tert*-butyl 4,4-difluoro-5-((tetrahydro-2*H*-pyran-2-yl)oxy)pentanoate (2.65 g, 8.99 mmol, 1 eq) in THF (55 mL). The resulting soln. was stirred at 0°C for 1h40. The reaction mixture was quenched by addition of H₂O followed by aq. 15% NaOH soln. and H₂O. The reaction mixture was stirred at rt until a white suspension was formed. The reaction mixture was filtered over a pad of Celite, washed with EtOAc and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 30% EtOAc) to give the title compound.

30 *tert*-Butyl((4,4-difluoro-5-((tetrahydro-2*H*-pyran-2-yl)oxy)pentyl)oxy)diphenylsilane: Was synthesized using 4,4-difluoro-5-((tetrahydro-2*H*-pyran-2-yl)oxy)pentan-1-ol and *tert*-butyldiphenylsilyl chloride in analogy to Example 1.263 to give the title compound. LC-MS (1): t_R = 1.30 min; $[M+H]^+$: 463.1.

5-((*tert*-Butyldiphenylsilyl)oxy)-2,2-difluoropentan-1-ol: Pyridinium *p*-toluenesulfonate (24.6 mg, 0.10 mmol, 0.05 eq) was added to a soln. of *tert*-butyl((4,4-difluoro-5-((tetrahydro-2*H*-pyran-2-yl)oxy)pentyl)oxy)diphenylsilane (896 mg, 1.94 mmol, 1 eq) in EtOH (8 mL). The reaction mixture was stirred at 60°C for 1h30. The mixture was poured into aq. sat. NaHCO₃ soln. and was extracted with EtOAc. The combined org. layers were washed with

brine, dried over MgSO_4 , filtered and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 10% EtOAc) to give the title compound. LC-MS (1): t_R = 1.15 min; $[\text{M}+\text{H}]^+$: 379.1.

5 **5-((*tert*-Butyldiphenylsilyl)oxy)-2,2-difluoropentyl methanesulfonate:** Trifluoromethanesulfonic anhydride (0.31 mL, 1.76 mmol, 1.1 eq) was added dropwise at 0°C to a stirred soln. of 5-((*tert*-butyldiphenylsilyl)oxy)-2,2-difluoropentanol (607 mg, 1.60 mmol, 1 eq) and 2,6-lutidine (0.38 mL, 3.21 mmol, 2 eq) in DCM (8 mL). The reaction mixture was stirred at 0°C for 15 min. The solvent was removed under reduced pressure and the crude product was used in the next step without further purification. LC-MS (1): t_R = 1.29 min; $[\text{M}+\text{H}]^+$: not seen.

***tert*-Butyl ((2-((5-((*tert*-butyldiphenylsilyl)oxy)-2,2-difluoropentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** *tert*-Butyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate (601 mg, 1.76 mmol, 1.1 eq) was dissolved in MeCN (16 mL). K_2CO_3 (670 mg, 4.80 mmol, 3 eq) was added followed by 5-((*tert*-butyldiphenylsilyl)oxy)-2,2-difluoropentyl methanesulfonate (1.54 g, 1.60 mmol, 1 eq). The reaction mixture was stirred at 60°C overnight. The mixture was filtered and the solvent was removed under reduced pressure. The residue was partitioned between EtOAc and brine. The org. layer was separated, dried over MgSO_4 , filtered and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 15% EtOAc) to give the title compound. LC-MS (1): t_R = 1.36 min; $[\text{M}+\text{H}]^+$: 702.0.

***tert*-Butyl ((2-((2,2-difluoro-5-hydroxypentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((2-((5-((*tert*-butyldiphenylsilyl)oxy)-2,2-difluoropentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.192 to give the title compound. LC-MS (1): t_R = 0.99 min; $[\text{M}+\text{H}]^+$: 464.0.

20 ***tert*-Butyl ((2-((2,2-difluoro-5-oxopentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((2-((2,2-difluoro-5-hydroxypentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate and PyrSO_3 in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R = 1.04 min; $[\text{M}+\text{H}]^+$: 462.0.

(1*R*,4*s*)-4-((*S*)-7,7-Difluoro-3-methyl-17,17-dioxido-12-oxo-7,8,9,10,12*a*,13,14,15-octahydro-6*H*-

25 **benzo[*b*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-11(12*H*)-yl)cyclohexane-1-carbonitrile:** Was synthesized using *tert*-butyl ((2-((2,2-difluoro-5-oxopentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate and (1*s*,4*s*)-4-aminocyclohexanecarbonitrile hydrochloride in analogy to Example 1.7 to give the title compound. LC-MS (1): t_R = 0.97 min; $[\text{M}+\text{H}]^+$: 496.0.

30 **Example 1.385 and Example 1.386** were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((2-((2,2-difluoro-5-oxopentyl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.384. LC-MS data of Example 1.385 and Example 1.386 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
1.385	(1R,4s)-4-((S)-7,7-Difluoro-3-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	1.01	510.0
1.386	(1S,3S)-3-((S)-7,7-Difluoro-3-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.98	496.0

Example 1.387 (1²S,5¹R,5³R)-8-((S)-6,6-Dimethyltetrahydro-2H-pyran-3-yl)-3⁶-methyl-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide or (1²S,5¹R,5³R)-8-((R)-6,6-Dimethyltetrahydro-2H-pyran-3-yl)-3⁶-methyl-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide :

Benzyl (S)-(6,6-dimethyltetrahydro-2H-pyran-3-yl)carbamate or **Benzyl (R)-(6,6-dimethyltetrahydro-2H-pyran-3-yl)carbamate** : Benzyl chloroformate (6.6 mL, 44.20 mmol, 1.2 eq) was added dropwise to a suspension of 6,6-dimethyltetrahydro-2H-pyran-3-amine (5.00 g, 36.8 mmol, 1 eq) and Na₂CO₃ (7.81 g, 73.70 mmol, 2 eq) in DCM (122 mL) and H₂O (122 mL). The mixture was stirred at rt for 3h. The layers were separated, the org. layer was washed with H₂O, dried over MgSO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by basic prep. HPLC then separated by SFC (SFC 21 method, first eluting enantiomer) to give the title compound. LC-MS (1): t_R= 0.90 min; [M+H]⁺: 264.2.

(S)-6,6-Dimethyl-tetrahydro-pyran-3-ylamine or **(R)-6,6-Dimethyl-tetrahydro-pyran-3-ylamine**: Benzyl (S)-(6,6-dimethyltetrahydro-2H-pyran-3-yl)carbamate or benzyl (R)-(6,6-dimethyltetrahydro-2H-pyran-3-yl)carbamate (1000 mg, 3.8 mmol, 1 eq) was dissolved in MeOH (40 mL). The solution was flushed several times with N₂ before wet Pd/C (10% Pd basis, 404 mg, 0.38 mmol, 0.1 eq) was added. The mixture was stirred under H₂ atmosphere for 1.5 h. The reaction mixture was filtered and the solvent was removed under reduced pressure to give the title compound. LC-MS (1): t_R= 0.32 min; [M+H]⁺: 130.2.

(1²S,5¹R,5³R)-8-((S)-6,6-Dimethyltetrahydro-2H-pyran-3-yl)-3⁶-methyl-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide or **(1²S,5¹R,5³R)-8-((R)-6,6-Dimethyltetrahydro-2H-pyran-3-yl)-3⁶-methyl-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide**: Was synthesized using *tert*-butyl ((6-methyl-2-(((1R*,3S*)-3-(2-oxoethyl)cyclohexyl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate and (S)-6,6-dimethyl-tetrahydro-pyran-3-ylamine hydrochloride in analogy to Examples 1.256 and 1.257. The diastereomeric mixture was separated by acidic prep. HPLC to give the title compound (first eluting diastereomer). LC-MS (1): t_R= 1.09 min; [M+H]⁺: 506.0.

Example 1.388 to **Example 1.392** were synthesized using the appropriate amine or amine salt derivative and methyl ((6-methyl-2-(((1R*,2R*)-2-(3-oxopropyl)cyclopentyl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate in analogy to

Example 1.377. LC-MS data of Example 1.388 to Example 1.392 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
1.388	(1R,4s)-4-((9aS,14aR,17aR)-2-Methyl-5,5-dioxido-10-oxo-8,9,9a,10,12,13,14,14a,15,16,17,17a-dodecahydrocyclopenta[<i>f</i>]pyrido[2,3- <i>b</i>]pyrrolo[1,2- <i>e</i>][1]oxa[4]thia[5,8]diazacyclotridecin-11(7 <i>H</i>)-yl)cyclohexane-1-carbonitrile	1.05	501.0
1.389	(1R,4s)-4-((9aS,14aS,17aS)-2-Methyl-5,5-dioxido-10-oxo-8,9,9a,10,12,13,14,14a,15,16,17,17a-dodecahydrocyclopenta[<i>f</i>]pyrido[2,3- <i>b</i>]pyrrolo[1,2- <i>e</i>][1]oxa[4]thia[5,8]diazacyclotridecin-11(7 <i>H</i>)-yl)cyclohexane-1-carbonitrile	1.07	501.0
1.390	(1S,4r)-1-Methyl-4-((9aS,14aR,17aR)-2-methyl-5,5-dioxido-10-oxo-8,9,9a,10,12,13,14,14a,15,16,17,17a-dodecahydrocyclopenta[<i>f</i>]pyrido[2,3- <i>b</i>]pyrrolo[1,2- <i>e</i>][1]oxa[4]thia[5,8]diazacyclotridecin-11(7 <i>H</i>)-yl)cyclohexane-1-carbonitrile	1.09	515.0
1.391	(1S,4r)-1-Methyl-4-((9aS,14aS,17aS)-2-methyl-5,5-dioxido-10-oxo-8,9,9a,10,12,13,14,14a,15,16,17,17a-dodecahydrocyclopenta[<i>f</i>]pyrido[2,3- <i>b</i>]pyrrolo[1,2- <i>e</i>][1]oxa[4]thia[5,8]diazacyclotridecin-11(7 <i>H</i>)-yl)cyclohexane-1-carbonitrile	1.11	515.0
1.392	(9aS,14aR,17aR)-11-((S)-6,6-Dimethyltetrahydro-2 <i>H</i> -pyran-3-yl)-2-methyl-7,8,9,9a,12,13,14,14a,15,16,17,17a-dodecahydrocyclopenta[<i>f</i>]pyrido[2,3- <i>b</i>]pyrrolo[1,2- <i>e</i>][1]oxa[4]thia[5,8]diazacyclotridecin-10(11 <i>H</i>)-one 5,5-dioxide	1.08	506.0

5 **Example 1.393 to Example 1.395** were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((4-methyl-2-(((1R*,3S*)-3-(2-oxoethyl)cyclohexyl)oxy)phenyl)sulfonyl)-L-prolinate in analogy to Examples 1.124 and 1.125. LC-MS data of Example 1.393 to Example 1.395 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
1.393	(1R,4s)-1-Methyl-4-(((1 ² S,5 ¹ R,5 ³ R)-3 ⁴ -methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclonaphane-8-yl)cyclohexane-1-carbonitrile	1.07	514.0
1.394	(1R,4s)-1-methyl-4-(((1 ² S,5 ¹ R,5 ³ S)-3 ⁴ -Methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclonaphane-8-yl)cyclohexane-1-carbonitrile	1.10	514.1
1.395	(1S,3S)-3-(((1 ² S,5 ¹ R,5 ³ R)-3 ⁴ -Methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclonaphane-8-yl)cyclohexane-1-carbonitrile	1.04	499.8

Example 1.396 to Example 1.398 were synthesized using 6-aminospiro[2.5]octane-1-carbonitrile hydrochloride and *tert*-butyl ((4-methyl-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.108. The diastereomers were separated by chiral SFC (SFC 21 method). LC-MS data of Example 1.396 to Example 5 1.398 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
1.396	(1R,3S,6R)-6-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6 <i>H</i> -benzo[<i>b</i>]pyrrolo[1,2- <i>e</i>][1]oxa[4]thia[5,8]diazacyclotridecin-11(12 <i>H</i>)-yl)spiro[2.5]octane-1-carbonitrile	1.02	500.2
1.397	(1S,3S,6S)-6-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6 <i>H</i> -benzo[<i>b</i>]pyrrolo[1,2- <i>e</i>][1]oxa[4]thia[5,8]diazacyclotridecin-11(12 <i>H</i>)-yl)spiro[2.5]octane-1-carbonitrile	1.03	500.2
1.398	(1S,3R,6R)-6-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6 <i>H</i> -benzo[<i>b</i>]pyrrolo[1,2- <i>e</i>][1]oxa[4]thia[5,8]diazacyclotridecin-11(12 <i>H</i>)-yl)spiro[2.5]octane-1-carbonitrile	1.02	500.2

Example 1.399 (1³RS,4²S)-6-((3R,5*s*)-1,1-Difluorospiro[2.3]hexan-5-yl)-2⁵-methyl-3-thia-6-aza-1(1,3),4(1,2)-dipyrrolidina-2(1,2)-benzenacyclonaphan-5-one 3,3-dioxide:
***tert*-Butyl ((2-(3-allylpyrrolidin-1-yl)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl 10 ((2-fluoro-4-methylphenyl)sulfonyl)-L-prolinate and 3-(prop-2-en-1-yl)pyrrolidine hydrochloride in analogy to Example 1.189 to give the title compound. LC-MS (1): t_R= 1.09 min; [M+H]⁺: 435.4.

tert-Butyl ((2-((RS)-3-(3-hydroxypropyl)pyrrolidin-1-yl)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using *tert*-butyl ((2-(3-allylpyrrolidin-1-yl)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.270 and 1.271 to give the title compound. LC-MS (1): t_R = 0.88 and 0.89 min; $[M+H]^+$: 453.4.

tert-Butyl ((4-methyl-2-((RS)-3-(3-oxopropyl)pyrrolidin-1-yl)phenyl)sulfonyl)-L-prolinate: Was synthesized using *tert*-butyl ((2-((RS)-3-(3-hydroxypropyl)pyrrolidin-1-yl)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.270 and 1.271 to give the title compound. LC-MS (1): t_R = 0.98 min; $[M+H]^+$: 451.3.

(1³RS,4²S)-6-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-2⁶-methyl-3-thia-6-aza-1(1,3),4(1,2)-dipyrrolidina-2(1,2)-benzenacyclononaphan-5-one 3,3-dioxide: Was synthesized using *tert*-butyl ((4-methyl-2-((RS)-3-(3-oxopropyl)pyrrolidin-1-yl)phenyl)sulfonyl)-L-prolinate and (3s,5s)-1,1-difluorospiro[2.3]hexan-5-amine hydrochloride in analogy to Example 1.270 to give the title compound. LC-MS (2): t_R = 1.05 and 1.07 min; $[M+H]^+$: 485.1.

Example 1.400 (1S,3S)-3-((1²S,5¹RS,5³RS)-3⁴-Methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclopentanacyclononaphane-8-yl)cyclohexane-1-carbonitrile: Was synthesized using *tert*-butyl ((4-methyl-2-(((1R*,3S*)-3-(2-oxoethyl)cyclopentyl)oxy)phenyl)sulfonyl)-L-prolinate and (1S,3S)-3-aminocyclohexane-1-carbonitrile 2,2,2-trifluoroacetate in analogy to Examples 1.272 and 1.273 to give the title compound. LC-MS (2): t_R = 1.00 min; $[M+H]^+$: 486.3.

Example 1.401 (1²S,5²S,5⁴R)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3⁴-methyl-5²,5³,5⁴,5⁵-tetrahydro-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-5(4,2)-furana-3(1,2)-benzenacyclononaphan-9-one 2,2-dioxide and Example 1.402 (1²S,5²R,5⁴S)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3⁴-methyl-5²,5³,5⁴,5⁵-tetrahydro-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-5(4,2)-furana-3(1,2)-benzenacyclononaphan-9-one 2,2-dioxide: Were synthesized using *tert*-butyl ((4-methyl-2-(((3R*,5R*)-5-(2-oxoethyl)tetrahydrofuran-3-yl)oxy)phenyl)sulfonyl)-L-prolinate and (3s,6s)-1,1-difluorospiro[2.5]octan-6-amine hydrochloride in analogy to Example 1.375. The crude was purified by basic prep. HPLC and FC (Hept to 80% EtOAc) to give the 2 diastereomers. First eluting diastereomer: LC-MS (1): t_R = 0.99 min; $[M+H]^+$: 525.2. Second eluting diastereomer: LC-MS (1): t_R = 1.01 min; $[M+H]^+$: 525.0.

Example 1.403 (9aS,14aR,17aR)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-1-fluoro-2-methyl-7,8,9,9a,11,12,13,14,14a,15,17,17a-dodecahydro-10H-benzo[b]furo[3,4-*l*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide and Example 1.404 (9aS,14aS,17aS)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-1-fluoro-2-methyl-7,8,9,9a,11,12,13,14,14a,15,17,17a-dodecahydro-10H-benzo[b]furo[3,4-*l*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide:

(RS)-2-Ethylhexyl 3-((3-fluoro-2-hydroxy-4-methylphenyl)sulfonyl)propanoate: Was synthesized using 6-bromo-2-fluoro-3-methylphenol and (RS)-2-ethylhexyl 3-mercaptopropanoate in analogy to Examples 1.124 and 1.125 to give the title compound. LC-MS (1): t_R = 1.06 min; $[M+H]^+$: 375.1.

(RS)-2-Ethylhexyl 3-((2-(((3R,4R)-4-allyltetrahydrofuran-3-yl)oxy)-3-fluoro-4-methylphenyl)sulfonyl)propanoate: Was synthesized using (RS)-2-ethylhexyl 3-((3-fluoro-2-hydroxy-4-

methylphenyl)sulfonyl)propanoate and *trans*-4-(prop-2-en-1-yl)oxolan-3-ol in analogy to Example 1.377 to give the title compound. LC-MS (1): t_R = 1.22 min; $[M+H]^+$: 485.2.

tert-Butyl ((3-fluoro-4-methyl-2-(((3R*,4R*)-4-(3-oxopropyl)tetrahydrofuran-3-yl)oxy)phenyl)sulfonyl)-L-prolinate: Was synthesized using *trans*-4-(prop-2-en-1-yl)oxolan-3-ol and (RS)-2-ethylhexyl 3-((3-fluoro-2-hydroxy-4-methylphenyl)sulfonyl)propanoate in analogy to Examples 1.270 and 1.271 to give the title compound. LC-MS (1): t_R = 1.02 min; $[M+H]^+$: 486.0.

(9aS,14aR,17aR)-11-((3R,6S)-1,1-Difluorospiro[2.5]octan-6-yl)-1-fluoro-2-methyl-7,8,9,9a,11,12,13,14,14a,15,17,17a-dodecahydro-10H-benzo[b]furo[3,4-*f*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide and (9aS,14aS,17aS)-11-((3R,6S)-1,1-Difluorospiro[2.5]octan-6-yl)-1-fluoro-2-methyl-7,8,9,9a,11,12,13,14,14a,15,17,17a-dodecahydro-10H-benzo[b]furo[3,4-*f*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-10-one 5,5-dioxide: Were synthesized using *tert*-butyl ((3-fluoro-4-methyl-2-(((3R*,4R*)-4-(3-oxopropyl)tetrahydrofuran-3-yl)oxy)phenyl)sulfonyl)-L-prolinate and (3S,6S)-1,1-difluorospiro[2.5]octan-6-amine hydrochloride in analogy to Examples 1.270 and 1.271. The crude was purified by FC (Hept to 30% EtOAc) to give the 2 diastereomers. First eluting diastereomer: LC-MS (1): t_R = 1.09 min; $[M+H]^+$: 557.3. Second eluting diastereomer: LC-MS (1): t_R = 1.10 min; $[M+H]^+$: 557.2.

Example 1.405 (1²S,5²R*,5⁴R*)-8-(4,4-Difluorocyclohexyl)-3³-fluoro-3⁴-methyl-5³,5⁴,5⁵,5⁶-tetrahydro-5²H-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-5(4,2)-pyrana-3(1,2)-benzenacyclononaphan-9-one 2,2-dioxide: Was synthesized using methyl 2-(4-oxotetrahydro-2H-pyran-2-yl)acetate and (RS)-2-ethylhexyl 3-((3-fluoro-2-hydroxy-4-methylphenyl)sulfonyl)propanoate in analogy to Example 1.332 to give the title compound. LC-MS (1): t_R = 1.07 min; $[M+H]^+$: 531.2.

Example 1.406 (1S,3S)-3-((9aS,14aR,17aR)-2-Methyl-5,5-dioxido-10-oxo-8,9,9a,10,12,13,14,14a,15,16,17,17a-dodecahydrocyclopenta[*f*]pyrido[2,3-*b*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-11(7H)-yl)cyclohexane-1-carbonitrile and Example 1.407 (1S,3S)-3-((9aS,14aS,17aS)-2-Methyl-5,5-dioxido-10-oxo-8,9,9a,10,12,13,14,14a,15,16,17,17a-dodecahydrocyclopenta[*f*]pyrido[2,3-*b*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-11(7H)-yl)cyclohexane-1-carbonitrile: Were synthesized using methyl ((6-methyl-2-(((1R*,2R*)-2-(3-oxopropyl)cyclopentyl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate and (1S,3S)-3-aminocyclohexane-1-carbonitrile hydrochloride in analogy to Example 1.377. The crude was purified by basic prep. HPLC to give the title compounds. First eluting diastereomer: LC-MS (1): t_R = 1.06 min; $[M+H]^+$: 501.0. Second eluting diastereomer: LC-MS (1): t_R = 1.07 min; $[M+H]^+$: 501.0.

Example 1.408 to Example 1.415 were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((6-methyl-2-(((1R*,3S*)-3-(2-oxoethyl)cyclohexyl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate in analogy to Examples 1.256 and 1.257. LC-MS data of Example 1.407 to Example 1.415 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
1.408	(1R,4s)-4-((1 ² S,5 ¹ R,5 ³ R)-3 ⁶ -Methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile	1.05	501.0
1.409	(1R,4s)-4-((1 ² S,5 ¹ S,5 ³ S)-3 ⁶ -Methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile	1.08	501.0
1.410	(1R,4s)-1-Methyl-4-((1 ² S,5 ¹ R,5 ³ R)-3 ⁶ -methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile	1.09	514.9
1.411	(1R,4s)-1-Methyl-4-((1 ² S,5 ¹ S,5 ³ S)-3 ⁶ -methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile	1.12	515.0
1.412	(1S,3S)-1-methyl-3-((1 ² S,5 ¹ R,5 ³ R)-3 ⁶ -methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile	1.10	515.0
1.413	(1S,3S)-1-methyl-3-((1 ² S,5 ¹ S,5 ³ S)-3 ⁶ -methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile	1.13	515.0
1.414	(1S,3S)-3-((1 ² S,5 ¹ R,5 ³ R)-3 ⁶ -methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile	1.06	501.0
1.415	(1S,3S)-3-((1 ² S,5 ¹ S,5 ³ S)-3 ⁶ -methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile	1.09	501.0

Example 1.416 (1R,4s)-4-((S)-7,7-Difluoro-3-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile:
Methyl ((2-((2,2-difluoro-5-oxopentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate: Was synthesized using methyl ((2-hydroxy-6-methylpyridin-3-yl)sulfonyl)-L-prolinate and 5-((*tert*-butyldiphenylsilyl)oxy)-2,2-difluoropentyl methanesulfonate in analogy to Example 1.384 to give the title compound. LC-MS (1): t_R= 0.92 min; [M+H]⁺: 421.0.

(1R,4s)-4-((S)-7,7-Difluoro-3-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile: Was synthesized using methyl ((2-((2,2-difluoro-5-oxopentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate and (1s,4s)-4-aminocyclohexanecarbonitrile hydrochloride in analogy to Example 1.263 to give the title compound. LC-MS (1): t_R= 0.97 min; [M+H]⁺: 497.0.

Example 1.417 and **Example 1.418** were synthesized using the appropriate amine or amine salt derivative and methyl ((2-((2,2-difluoro-5-oxopentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.416. LC-MS data of Example 1.x and Example 1.x are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
1.417	(1S,4r)-4-((S)-7,7-Difluoro-3-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	1.01	511.0
1.418	(1S,3S)-3-((S)-7,7-Difluoro-3-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.98	497.0

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Example 1.425 to **Example 1.429** were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((4-methyl-2-((RS)-3-(3-oxopropyl)pyrrolidin-1-yl)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.399. LC-MS data of Example 1.425 to Example 1.429 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
1.425	(1R,4s)-1-Methyl-4-((1 ³ R,4 ² S)-2 ⁵ -methyl-3,3-dioxido-5-oxo-3-thia-6-aza-1(1,3),4(1,2)-dipyrrolidina-2(1,2)-benzenacyclononaphane-6-yl)cyclohexane-1-carbonitrile	1.08	499.0
1.428	(1 ³ S,4 ² S)-6-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-2 ⁵ -methyl-3-thia-6-aza-1(1,3),4(1,2)-dipyrrolidina-2(1,2)-benzenacyclononaphan-5-one 3,3-dioxide	1.15	522.0
1.429	(1 ³ R,4 ² S)-6-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-2 ⁵ -methyl-3-thia-6-aza-1(1,3),4(1,2)-dipyrrolidina-2(1,2)-benzenacyclononaphan-5-one 3,3-dioxide	1.15	522.0

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Example 1.430 (1S,3S)-3-((6R,12aS)-4-Fluoro-3,6-dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile: Was synthesized using methyl ((3-fluoro-4-methyl-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate and (1S,3S)-3-aminocyclohexane-1-carbonitrile 2,2,2-trifluoroacetate in analogy to Example 1.192 to give the title compound. LC-MS (1): t_R= 1.06 min; [M+H]⁺: 492.2.

15

Example 1.431 to **Example 1.434** were synthesized using pentane-1,5-diol and the appropriate amine or amine salt derivative in analogy to Example 1.192. LC-MS data of Example 1.431 to Example 1.434 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
1.431	(S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-4-fluoro-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.14	514.9
1.432	(1R,4s)-4-((S)-4-Fluoro-3-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	1.06	492.0
1.433	(1R,4s)-4-((S)-4-Fluoro-3-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.02	478.0
1.434	(1S,3S)-3-((S)-4-Fluoro-3-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.03	478.0

Example 1.435 (S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrrolo[1,2-b][1]thia[2,5]diazacyclotridecin-12(5H)-one 17,17-dioxide:

Methyl ((6-methyl-2-(((trifluoromethyl)sulfonyl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate:

- 5 Trifluoromethanesulfonic anhydride (0.17 mL, 1.00 mmol, 1.5 eq) was added dropwise at 0°C to a stirred soln. of methyl ((2-hydroxy-6-methylpyridin-3-yl)sulfonyl)-L-prolinate (200 mg, 0.67 mmol, 1 eq) and anh. pyridine (0.22 mL, 2.66 mmol, 4 eq) in DCM (3 mL). The reaction mixture was stirred at 0°C for 2h then was partitioned between aq. sat. NH₄Cl and DCM. The org. layer was separated using a phase separator cartridge and the solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R= 1.01 min; [M+H]⁺: 432.9.

Methyl ((2-(6-hydroxyhex-1-yn-1-yl)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate: Was synthesized using methyl ((6-methyl-2-(((trifluoromethyl)sulfonyl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate and hex-5-yn-1-ol in analogy to Example 1.78 to give the title compound. LC-MS (1): t_R= 0.74 min; [M+H]⁺: 381.05.

- 15 **Methyl ((2-(6-hydroxyhexyl)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate:** Was synthesized using methyl ((2-(6-hydroxyhex-1-yn-1-yl)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.78 to give the title compound. LC-MS (1): t_R= 0.73 min; [M+H]⁺: 385.1.

Methyl ((6-methyl-2-(6-oxohexyl)pyridin-3-yl)sulfonyl)-L-prolinate: Was synthesized using methyl ((2-(6-hydroxyhexyl)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate and PyrSO₃ in analogy to Example 1.311 to give the title compound. LC-MS (1): t_R= 0.79 min; [M+H]⁺: 383.1.

- 20 **(S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrrolo[1,2-b][1]thia[2,5]diazacyclotridecin-12(5H)-one 17,17-dioxide:** Was synthesized using methyl ((6-

methyl-2-(6-oxohexyl)pyridin-3-yl)sulfonyl)-L-prolinate and (3s,6s)-1,1-difluorospiro[2.5]octan-6-amine hydrochloride in analogy to Example 1.84 to give the title compound. LC-MS (1): t_R= 0.97 min; [M+H]⁺: 496.0.

Example 1.438 (1R,4s)-1-Methyl-4-((S)-3-methyl-17,17-dioxido-12-oxo-5,6,7,8,9,10,12a,13,14,15-decahydropyrido[2,3-l]pyrrolo[1,2-b][1]thia[2,5]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile:

- 5 Was synthesized using methyl ((6-methyl-2-(6-oxohexyl)pyridin-3-yl)sulfonyl)-L-prolinate and *cis*-4-amino-1-methyl-cyclohexanecarbonitrile hydrochloride in analogy to Example 1.435 to give the title compound. LC-MS (1): t_R= 0.88 min; [M+H]⁺: 473.1.

- Example 1.439 to Example 1.446** were synthesized using the appropriate amine or amine salt derivative and *tert*-butyl ((4-methyl-2-(((1R*,3S*)-3-(2-oxoethyl)cyclopentyl)oxy)phenyl)sulfonyl)-L-prolinate in analogy to Examples 1.272 and 1.273. LC-MS data of Example 1.439 to Example 1.446 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
1.439	(1 ² S,5 ¹ R,5 ³ R)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3 ⁴ -methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclopentanacyclononaphan-9-one 2,2-dioxide	1.09	523.0
1.440	(1 ² S,5 ¹ S,5 ³ S)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3 ⁴ -methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclopentanacyclononaphan-9-one 2,2-dioxide	1.11	523.0
1.441	(1R,4s)-4-((1 ² S,5 ¹ R,5 ³ R)-3 ⁴ -Methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclopentanacyclononaphane-8-yl)cyclohexane-1-carbonitrile	0.97	486.0
1.442	(1R,4s)-4-((1 ² S,5 ¹ S,5 ³ S)-3 ⁴ -Methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclopentanacyclononaphane-8-yl)cyclohexane-1-carbonitrile	1.00	486.0
1.443	(1 ² S,5 ¹ R,5 ³ R)-8-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-3 ⁴ -methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclopentanacyclononaphan-9-one 2,2-dioxide	1.04	495.0
1.444	(1 ² S,5 ¹ S,5 ³ S)-8-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-3 ⁴ -methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclopentanacyclononaphan-9-one 2,2-dioxide	1.07	495.0
1.445	(1R,4s)-1-Methyl-4-((1 ² S,5 ¹ R,5 ³ R)-3 ⁴ -methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclopentanacyclononaphane-8-yl)cyclohexane-1-carbonitrile	1.01	500.0

1.446	(1R,4s)-1-Methyl-4-((1 ² S,5 ¹ S,5 ³ S)-3 ⁴ -methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclopentanacyclononaphane-8-yl)cyclohexane-1-carbonitrile	1.04	500.0
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- Example 1.447** (1S,3S)-3-((1²S,5¹R,5³R)-3⁶-Methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclopentanacyclononaphane-8-yl)cyclohexane-1-carbonitrile and **Example 1.448** (1S,3S)-3-((1²S,5¹S,5³S)-3⁶-Methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclopentanacyclononaphane-8-yl)cyclohexane-1-carbonitrile:
- Methyl ((2-(((1R*,3R*)-3-(2-((tert-butylidiphenylsilyl)oxy)ethyl)cyclopentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate:** Was synthesized using methyl ((2-hydroxy-6-methylpyridin-3-yl)sulfonyl)-L-prolinate and (1R*,3S*)-3-(2-((tert-butylidiphenylsilyl)oxy)ethyl)cyclopentan-1-ol in analogy to Example 1.263 to give the title compound. LC-MS (1): t_R= 1.36 min; [M+H]⁺: 651.1.
- Methyl ((2-(((1R*,3R*)-3-(2-hydroxyethyl)cyclopentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate:** Was synthesized using methyl ((2-(((1R*,3R*)-3-(2-((tert-butylidiphenylsilyl)oxy)ethyl)cyclopentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.263 to give the title compound. LC-MS (1): t_R= 0.89 min; [M+H]⁺: 413.1.
- Methyl ((6-methyl-2-(((1R*,3R*)-3-(2-oxoethyl)cyclopentyl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate:** Was synthesized using methyl ((2-(((1R*,3R*)-3-(2-hydroxyethyl)cyclopentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate in analogy to Example 1.311 to give the title compound. LC-MS (1): t_R= 0.95 min; [M+H]⁺: 411.2.
- (1S,3S)-3-((1²S,5¹R,5³R)-3⁶-Methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclopentanacyclononaphane-8-yl)cyclohexane-1-carbonitrile and (1S,3S)-3-((1²S,5¹S,5³S)-3⁶-Methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclopentanacyclononaphane-8-yl)cyclohexane-1-carbonitrile: Were synthesized using methyl ((6-methyl-2-(((1R*,3R*)-3-(2-oxoethyl)cyclopentyl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate and (1S,3S)-3-aminocyclohexane-1-carbonitrile 2,2,2-trifluoroacetate in analogy to Example 1.377. The crude was purified by basic prep. HPLC to give the 2 diastereomers. First eluting diastereomer: LC-MS (1): t_R= 0.99 min; [M+H]⁺: 487.0. Second eluting diastereomer: LC-MS (1): t_R= 1.01 min; [M+H]⁺: 487.0.
- Example 1.449 to Example 1.458** were synthesized using the appropriate amine or amine salt derivative and methyl ((6-methyl-2-(((1R*,3S*)-3-(2-oxoethyl)cyclopentyl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate in analogy to Examples 1.447 and 1.448. LC-MS data of Example 1.449 to Example 1.458 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
1.449	(1 ² S,5 ¹ R,5 ³ R)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3 ⁶ -methyl-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclopentanacyclononaphan-9-one 2,2-dioxide	1.12	524.2
1.450	(1 ² S,5 ¹ S,5 ³ S)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3 ⁶ -methyl-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclopentanacyclononaphan-9-one 2,2-dioxide	1.15	524.2
1.451	(1R,4s)-4-((1 ² S,5 ¹ R,5 ³ R)-3 ⁶ -Methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclopentanacyclononaphane-8-yl)cyclohexane-1-carbonitrile	1.00	487.2
1.452	(1R,4s)-4-((1 ² S,5 ¹ S,5 ³ S)-3 ⁶ -Methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclopentanacyclononaphane-8-yl)cyclohexane-1-carbonitrile	1.03	487.2
1.453	(1 ² S,5 ¹ R,5 ³ R)-8-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-3 ⁶ -methyl-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclopentanacyclononaphan-9-one 2,2-dioxide	1.08	496.2
1.454	(1 ² S,5 ¹ S,5 ³ S)-8-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-3 ⁶ -methyl-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclopentanacyclononaphan-9-one 2,2-dioxide	1.11	496.1
1.455	(1R,4s)-1-Methyl-4-((1 ² S,5 ¹ R,5 ³ R)-3 ⁶ -methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclopentanacyclononaphane-8-yl)cyclohexane-1-carbonitrile	1.05	501.2
1.456	(1R,4s)-1-Methyl-4-((1 ² S,5 ¹ S,5 ³ S)-3 ⁶ -methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclopentanacyclononaphane-8-yl)cyclohexane-1-carbonitrile	1.07	501.2
1.457	(1 ² S,5 ¹ R,5 ³ R)-8-(4,4-Difluorocyclohexyl)-3 ⁶ -methyl-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclopentanacyclononaphan-9-one 2,2-dioxide	1.07	498.0
1.458	(1 ² S,5 ¹ S,5 ³ S)-8-(4,4-Difluorocyclohexyl)-3 ⁶ -methyl-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclopentanacyclononaphan-9-one 2,2-dioxide	1.10	498.0

Example 1.459 (1²S,5²S,5⁴R)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3⁶-methyl-5²,5³,5⁴,5⁵-tetrahydro-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(4,2)-furanacyclononaphan-9-one 2,2-dioxide and

Example 1.460 (1²S,5²R,5⁴S)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3⁶-methyl-5²,5³,5⁴,5⁵-tetrahydro-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(4,2)-furanacyclononaphan-9-one 2,2-dioxide:

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Methyl ((2-(((3R*,5S*)-5-allyltetrahydrofuran-3-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate: Was synthesized using methyl ((2-hydroxy-6-methylpyridin-3-yl)sulfonyl)-L-prolinate and (3R*,5R*)-5-

allyltetrahydrofuran-3-ol in analogy to Examples 1.381 and 1.382 to give the title compound. LC-MS (1): t_R = 0.99 min; $[M+H]^+$: 411.2.

Methyl ((6-methyl-2-(((3R*,5R*)-5-(2-oxoethyl)tetrahydrofuran-3-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate:

Was synthesized using methyl ((2-(((3R*,5S*)-5-allyltetrahydrofuran-3-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-prolinate in analogy to Examples 1.90 and 1.91 to give the title compound. LC-MS (1): t_R = 0.82 min; $[M+H]^+$: 413.0.

(1²S,5²S,5⁴R)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3⁶-methyl-5²,5³,5⁴,5⁵-tetrahydro-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(4,2)-furanacyclononaphan-9-one 2,2-dioxide and (1²S,5²R,5⁴S)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3⁶-methyl-5²,5³,5⁴,5⁵-tetrahydro-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(4,2)-furanacyclononaphan-9-one 2,2-dioxide: Were synthesized using methyl ((6-methyl-2-(((3R*,5R*)-5-(2-oxoethyl)tetrahydrofuran-3-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate and (3r,6r)-1,1-difluorospiro[2.5]octan-6-amine hydrochloride in analogy to Examples 1.381 and 1.382. The crude was purified by basic prep. HPLC to give the 2 diastereomers. First eluting diastereomer: LC-MS (1): t_R = 0.99 min; $[M+H]^+$: 526.2. Second eluting diastereomer: LC-MS (1): t_R = 1.02 min; $[M+H]^+$: 526.2.

Example 1.461 (1²S,5²S,5⁴R)-8-(4,4-Difluorocyclohexyl)-3⁶-methyl-5²,5³,5⁴,5⁵-tetrahydro-4-oxa-2-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(4,2)-furanacyclononaphan-9-one 2,2-dioxide: Was synthesized using methyl ((6-methyl-2-(((3R*,5R*)-5-(2-oxoethyl)tetrahydrofuran-3-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate and 4,4-difluorocyclohexan-1-amine in analogy to Examples 1.459 and 1.460 to give the title compound. LC-MS (1): t_R = 0.94 min; $[M+H]^+$: 500.0.

Example 1.462 (3S,10R)-5-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,10,13-trimethyl-2,3,5,6,7,8,9,10-octahydro-4H-pyrido[2,3-b][1]oxa[4]thia[5,8]diazacyclotridecin-4-one 1,1-dioxide:

Methyl ((2-(((R)-6-((tert-butylidiphenylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-alaninate: Was synthesized using (RS)-2-ethylhexyl 3-((2-(((R)-6-((tert-butylidiphenylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)propanoate and L-alanine methyl ester hydrochloride in analogy to Example 1.360 to give the title compound. LC-MS (1): t_R = 1.30 min; $[M+H]^+$: 613.0.

Methyl ((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-alaninate: Was synthesized using (RS)-2-ethylhexyl 3-((2-(((R)-6-((tert-butylidiphenylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)propanoate and L-alanine methyl ester hydrochloride in analogy to Example 1.360 to give the title compound. LC-MS (1): t_R = 0.89 min; $[M+H]^+$: 373.0.

Methyl ((2-(((R)-6-hydroxyhexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)-L-alaninate: Was synthesized using methyl ((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-alaninate in analogy to Example 1.360 to give the title compound. LC-MS (1): t_R = 0.84 min; $[M+H]^+$: Not seen.

(3S,10R)-5-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,10,13-trimethyl-2,3,5,6,7,8,9,10-octahydro-4H-pyrido[2,3-b][1]oxa[4]thia[5,8]diazacyclotridecin-4-one 1,1-dioxide: Was synthesized using methyl ((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-alaninate and (3s,6s)-1,1-difluorospiro[2.5]octan-6-amine hydrochloride in analogy to Example 1.360 to give the title compound. LC-MS (1): t_R = 1.10 min; $[M+H]^+$: 486.0.

Example 1.463 (1R,4s)-1-Methyl-4-((3S,10R)-3,10,13-trimethyl-1,1-dioxido-4-oxo-3,4,7,8,9,10-hexahydro-2H-pyrido[2,3-b][1]oxa[4]thia[5,8]diazacyclotridecin-5(6H)-yl)cyclohexane-1-carbonitrile: Was synthesized using methyl ((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-alaninate and *cis*-4-amino-1-methylcyclohexanecarbonitrile hydrochloride in analogy to Example 1.462 to give the title compound. LC-MS (1): t_R = 1.02 min; $[M+H]^+$: 463.0.

Example 1.464 (1²S,5²S,5⁴R)-8-(4,4-Difluorocyclohexyl)-3³-fluoro-3⁴-methyl-5²,5³,5⁴,5⁵-tetrahydro-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-5(4,2)-furana-3(1,2)-benzenacyclononaphan-9-one 2,2-dioxide and Example 1.465 (1²S,5²R,5⁴S)-8-(4,4-Difluorocyclohexyl)-3³-fluoro-3⁴-methyl-5²,5³,5⁴,5⁵-tetrahydro-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-5(4,2)-furana-3(1,2)-benzenacyclononaphan-9-one 2,2-dioxide:

Methyl ((2-(((3R*,5S*)-5-allyltetrahydrofuran-3-yl)oxy)-3-fluoro-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using methyl ((3-fluoro-2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate and (3R*,5R*)-5-allyltetrahydrofuran-3-ol in analogy to Examples 1.459 and 1.460 to give the title compound. LC-MS (1): t_R = 1.03 min; $[M+H]^+$: 428.2.

Methyl ((3-fluoro-4-methyl-2-(((3R*,5R*)-5-(2-oxoethyl)tetrahydrofuran-3-yl)oxy)phenyl)sulfonyl)-L-prolinate: Was synthesized using methyl ((2-(((3R*,5S*)-5-allyltetrahydrofuran-3-yl)oxy)-3-fluoro-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Examples 1.459 and 1.460 to give the title compound. LC-MS (1): t_R = 0.88 min; $[M+H]^+$: 430.0.

(1²S,5²S,5⁴R)-8-(4,4-Difluorocyclohexyl)-3³-fluoro-3⁴-methyl-5²,5³,5⁴,5⁵-tetrahydro-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-5(4,2)-furana-3(1,2)-benzenacyclononaphan-9-one 2,2-dioxide and (1²S,5²R,5⁴S)-8-(4,4-Difluorocyclohexyl)-3³-fluoro-3⁴-methyl-5²,5³,5⁴,5⁵-tetrahydro-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-5(4,2)-furana-3(1,2)-benzenacyclononaphan-9-one 2,2-dioxide: Were synthesized using methyl ((3-fluoro-4-methyl-2-(((3R*,5R*)-5-(2-oxoethyl)tetrahydrofuran-3-yl)oxy)phenyl)sulfonyl)-L-prolinate and 4,4-difluorocyclohexan-1-amine hydrochloride in analogy to Example 1.461. The crude was purified by basic prep. HPLC and FC (Hept to 50% EtOAc) to give the 2 diastereomers. First eluting diastereomer: LC-MS (1): t_R = 0.98 min; $[M+H]^+$: 517.1. Second eluting diastereomer: LC-MS (1): t_R = 1.01 min; $[M+H]^+$: 517.2.

Example 1.466 (3S,10R)-5-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-2,3,10,13-tetramethyl-2,3,5,6,7,8,9,10-octahydro-4H-pyrido[2,3-b][1]oxa[4]thia[5,8]diazacyclotridecin-4-one 1,1-dioxide: Was synthesized using (3S,10R)-5-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-3,10,13-trimethyl-2,3,5,6,7,8,9,10-octahydro-4H-pyrido[2,3-b][1]oxa[4]thia[5,8]diazacyclotridecin-4-one 1,1-dioxide in analogy to Example 1.81 to give the title compound. LC-MS (1): t_R = 1.16 min; $[M+H]^+$: 499.7.

Example 1.469: Was synthesized using the appropriate amine or amine salt derivative, methyl ((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-alaninate, and MeI (or CD₃I) in analogy to Example 1.466 to give the title compound. LC-MS (1): t_R = 1.08 min; $[M+H]^+$: 477.0.

Example 1.472 (6R,11aS)-10-(4,4-Difluorocyclohexyl)-4-fluoro-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide:

- Methyl ((2-(((R)-5-((tert-butylidimethylsilyl)oxy)pentan-2-yl)oxy)-3-fluoro-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using methyl ((3-fluoro-2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate and and (S)-5-((tert-butylidimethylsilyl)oxy)pentan-2-ol in analogy to Example 1.240 to give the title compound. LC-MS (1): t_R = 1.29 min; $[M+H]^+$: 518.5.
- 5 **Methyl ((3-fluoro-2-(((R)-5-hydroxypentan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using methyl ((2-(((R)-5-((tert-butylidimethylsilyl)oxy)pentan-2-yl)oxy)-3-fluoro-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.240 to give the title compound. LC-MS (1): t_R = 090 min; $[M+H]^+$: 404.3.
- Methyl ((3-fluoro-4-methyl-2-(((R)-5-oxopentan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate:** Was synthesized using methyl ((3-fluoro-2-(((R)-5-hydroxypentan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example
- 10 1.240 to give the title compound. LC-MS (1): t_R = 0.96 min; $[M+H]^+$: 402.0.
- (6R,11aS)-10-(4,4-Difluorocyclohexyl)-4-fluoro-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide:** Was synthesized using methyl ((3-fluoro-4-methyl-2-(((R)-5-oxopentan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate and 4,4-difluorocyclohexan-1-amine hydrochloride in analogy to Example 1.240 to give the title compound. LC-MS (1): t_R =
- 15 1.07 min; $[M+H]^+$: 489.0.
- Example 1.473 to Example 1.477** were synthesized using the appropriate amine or amine salt derivative and methyl ((3-fluoro-4-methyl-2-(((R)-5-oxopentan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.240. LC-MS data of Example 1.473 to Example 1.477 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
1.473	(6R,11aS)-10-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-4-fluoro-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide	1.12	515.0
1.475	(1R,4s)-4-((6R,11aS)-4-Fluoro-3,6-dimethyl-16,16-dioxido-11-oxo-6,7,8,9,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-yl)cyclohexane-1-carbonitrile	1.00	478.0
1.476	(1R,4s)-4-((6R,11aS)-4-Fluoro-3,6-dimethyl-16,16-dioxido-11-oxo-6,7,8,9,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-yl)-1-methylcyclohexane-1-carbonitrile	1.05	492.0
1.477	(1S,3S)-3-((6R,11aS)-4-Fluoro-3,6-dimethyl-16,16-dioxido-11-oxo-6,7,8,9,11a,12,13,14-octahydrobenzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-yl)cyclohexane-1-carbonitrile	1.02	478.0

Example 1.478 (S)-5-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-13-methyl-1,2,3,3a,6,7,8,9,10,11-decahydrobenzo[*l*]pyrrolo[1,2-*b*][1]thia[2,5]diazacyclotridecin-4(5*H*)-one 16,16-dioxide:

Methyl ((2-bromo-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using (S)-Methyl pyrrolidine-2-carboxylate hydrochloride and 2-bromo-4-methylbenzene-1-sulfonyl chloride in analogy to Example 1.9 to give the title compound. LC-MS (1): t_R = 0.93 min; $[M+H]^+$: 362.1.

Methyl ((2-(6-hydroxyhex-1-yn-1-yl)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using methyl ((2-bromo-4-methylphenyl)sulfonyl)-L-prolinate and hex-5-yn-1-ol in analogy to Example 1.434 to give the title compound. LC-MS (1): t_R = 0.88 min; $[M+H]^+$: 380.4.

Methyl ((2-(6-hydroxyhexyl)-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using methyl ((2-(6-hydroxyhex-1-yn-1-yl)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.434 to give the title compound. LC-MS (1): t_R = 0.94 min; $[M+H]^+$: 384.4.

Methyl ((4-methyl-2-(6-oxohexyl)phenyl)sulfonyl)-L-prolinate: Was synthesized using methyl ((2-bromo-4-methylphenyl)sulfonyl)-L-prolinate and hex-5-yn-1-ol in analogy to Example 1.434 to give the title compound. LC-MS (1): t_R = 0.99 min; $[M+H]^+$: 382.4.

(S)-5-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-13-methyl-1,2,3,3a,6,7,8,9,10,11-decahydrobenzo[*l*]pyrrolo[1,2-*b*][1]thia[2,5]diazacyclotridecin-4(5*H*)-one 16,16-dioxide: Was synthesized using methyl ((4-methyl-2-(6-oxohexyl)phenyl)sulfonyl)-L-prolinate and (3s,6s)-1,1-difluorospiro[2.5]octan-6-amine hydrochloride in analogy to Example 1.434 to give the title compound. LC-MS (1): t_R = 1.16 min; $[M+H]^+$: 495.0.

Example 1.480 (1R,4s)-4-((S)-13-Methyl-16,16-dioxido-4-oxo-2,3,3a,4,6,7,8,9,10,11-decahydrobenzo[*l*]pyrrolo[1,2-*b*][1]thia[2,5]diazacyclotridecin-5(1*H*)-yl)cyclohexane-1-carbonitrile: Was synthesized using the appropriate amine or amine salt derivative and methyl ((4-methyl-2-(6-oxohexyl)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.478. LC-MS (1): t_R = 1.04 min; $[M+H]^+$: 458.0.

Example 1.482 (1²S,5¹R,5³R)-8-((S)-6,6-Dimethyltetrahydro-2*H*-pyran-3-yl)-3³-fluoro-3⁴-methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide and Example 1.483 (1²S,5¹S,5³S)-8-((S)-6,6-Dimethyltetrahydro-2*H*-pyran-3-yl)-3³-fluoro-3⁴-methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide:

Methyl ((3-fluoro-4-methyl-2-(((1R*,3S*)-3-(2-oxoethyl)cyclohexyl)oxy)phenyl)sulfonyl)-L-prolinate: Was synthesized using methyl ((3-fluoro-2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate and (1R*,3S*)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexan-1-ol in analogy to Example 1.192 to give the title compound. LC-MS (1): t_R = 1.03 min; $[M+H]^+$: 442.0.

(1²S,5¹R,5³R)-8-((S)-6,6-Dimethyltetrahydro-2*H*-pyran-3-yl)-3³-fluoro-3⁴-methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide and (1²S,5¹S,5³S)-8-((S)-6,6-Dimethyltetrahydro-2*H*-pyran-3-yl)-3³-fluoro-3⁴-methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide: Were synthesized using methyl ((3-fluoro-4-methyl-2-(((1R*,3S*)-3-(2-oxoethyl)cyclohexyl)oxy)phenyl)sulfonyl)-L-prolinate and (S)-6,6-dimethyl-tetrahydro-

pyran-3-ylamine hydrochloride in analogy to Example 1.192. The crude was purified by basic prep. HPLC to give the 2 diastereomers. First eluting diastereomer: LC-MS (1): t_R = 1.12 min; $[M+H]^+$: 523.0. Second eluting diastereomer: LC-MS (1): t_R = 1.17 min; $[M+H]^+$: 523.0.

Example 1.484 (9aS,14aR,17aR)-11-((S)-6,6-Dimethyltetrahydro-2H-pyran-3-yl)-1-fluoro-2-methyl-7,8,9,9a,12,13,14,14a,15,16,17,17a-dodecahydrobenzo[b]cyclopenta[*f*]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10(11*H*)-one 5,5-dioxide and Example 1.485 (9aS,14aS,17aS)-11-((S)-6,6-Dimethyltetrahydro-2H-pyran-3-yl)-1-fluoro-2-methyl-7,8,9,9a,12,13,14,14a,15,16,17,17a-dodecahydrobenzo[b]cyclopenta[*f*]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10(11*H*)-one 5,5-dioxide: Were synthesized using methyl ((3-fluoro-2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate, (1*R**,2*S**)-2-allylcyclopentan-1-ol and (S)-6,6-dimethyl-tetrahydro-pyran-3-ylamine hydrochloride in analogy to Examples 1.381 and 1.382. The crude was purified by basic prep. HPLC to give the 2 diastereomers. First eluting diastereomer: LC-MS (1): t_R = 1.12 min; $[M+H]^+$: 523.0. Second eluting diastereomer: LC-MS (1): t_R = 1.15 min; $[M+H]^+$: 523.0.

Example 1.487 (6R,12aS)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3-fluoro-6-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:

Methyl ((4-fluoro-2-hydroxyphenyl)sulfonyl)-L-prolinate: Was synthesized using 2-bromo-4-fluorobenzenesulfonyl chloride and L-proline methyl ester in analogy to Example 1.39 to give the title compound. LC-MS (1): t_R = 0.78 min; $[M+H]^+$: 304.0.

Methyl ((4-fluoro-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate: Was synthesized using methyl ((4-fluoro-2-hydroxyphenyl)sulfonyl)-L-prolinate and (S)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-ol in analogy to Example 1.192 to give the title compound. LC-MS (1): t_R = 0.92 min; $[M+H]^+$: 402.1.

(6R,12aS)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3-fluoro-6-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide: Was synthesized using methyl ((4-fluoro-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate and (3*S*,6*S*)-1,1-difluorospiro[2.5]octan-6-amine hydrochloride in analogy to Example 1.192 to give the title compound. LC-MS (1): t_R = 1.08 min; $[M+H]^+$: 515.2.

Example 1.488 to Example 1.489 were synthesized using the appropriate amine or amine salt derivative and methyl ((4-fluoro-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.487. LC-MS data of Example 1.488 to Example 1.489 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
1.488	(1R,4s)-4-((6R,12aS)-3-Fluoro-6-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	1.00	492.2
1.489	(1R,4s)-4-((6R,12aS)-3-Fluoro-6-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.96	478.1

Example 1.493 to **Example 1.497** were synthesized using 2-bromo-4-chlorobenzenesulfonyl chloride, L-proline methyl ester and the appropriate amine or amine salt derivative in analogy to Example 1.487 or methyl ((4-methyl-2-(6-oxohexyl)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.478 . LC-MS data of Example 1.493 to Example 1.497 are listed in the table below. The LC-MS conditions used were LC-MS (1).

5

Ex. N°	Name	t _R	[M+H] ⁺
1.493	(6R,12aS)-3-Chloro-11-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-6-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.12	530.9
1.494	(1R,4s)-4-((6R,12aS)-3-Chloro-6-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	1.04	508.0
1.495	(1R,4s)-4-((6R,12aS)-3-Chloro-6-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.00	494.0
1.496	(1S,3S)-3-((6R,12aS)-3-Chloro-6-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.01	494.0
1.497	(1R,4s)-1-Methyl-4-((S)-13-methyl-16,16-dioxido-4-oxo-2,3,3a,4,6,7,8,9,10,11-decahydrobenzo[f]pyrrolo[1,2-b][1]thia[2,5]diazacyclotridecin-5(1H)-yl)cyclohexane-1-carbonitrile	1.08	472.2

Example 1.501 (6R,12aS)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-6-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide: Was synthesized using 2-bromobenzenesulfonyl chloride, L-proline methyl ester and the appropriate amine or amine salt derivative in analogy to Example 1.487. LC-MS (1): t_R= 1.08 min; [M+H]⁺: 496.9.

10

Example 1.504 (1R,4s)-4-((8R,12aS)-4-Fluoro-3,8-dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile:

(S)-6-((tert-Butyldiphenylsilyl)oxy)-4-methylhexan-1-ol: (S)-6-((tert-Butyldiphenylsilyl)oxy)-4-methylhexanal (J. Org. Chem. 2020, 85(17), 11549-11559) (17.34 g, 47.00 mmol, 1 eq) was dissolved in MeOH (150 mL) and THF (150 mL). The soln. was cooled to 0°C then NaBH₄ (5.33 g, 141 mmol, 3 eq) was added. The reaction mixture was stirred at rt for 2h. Aq. sat. NH₄Cl soln. was added and the mixture was stirred at rt for 10 min. The mixture was then extracted with EtOAc. The combined org. layers were washed with brine, dried over MgSO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R= 1.21 min; [M+H]⁺: 371.3.

(S)-6-((tert-Butyldiphenylsilyl)oxy)-4-methylhexyl methanesulfonate: (S)-6-((tert-Butyldiphenylsilyl)oxy)-4-methylhexan-1-ol (16.35 g, 44.10 mmol, 1 eq) was dissolved in DCM (300 mL) and was stirred at 0°C. TEA (13.6 mL, 97.10 mmol, 2.2 eq) and methanesulfonyl chloride (4.45 mL, 57.40 mmol, 1.3 eq) were added and the reaction mixture was stirred at rt for 1h. The reaction mixture was partitioned between aq. sat. NaHCO₃ soln. and DCM. The org. layer was separated and the solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R= 1.24 min; [M+H]⁺: 449.1.

(S)-tert-Butyl((6-iodo-3-methylhexyl)oxy)diphenylsilane: NaI (13.36 g, 88.3 mmol, 2 eq) was added to a soln. of (S)-6-((tert-butylidiphenylsilyl)oxy)-4-methylhexyl methanesulfonate (19.80 g, 44.1 mmol, 1 eq) in acetone (300 mL). The mixture was stirred at 60°C overnight. The mixture was cooled to rt and diluted with Et₂O. The precipitate was filtered and the solvent was removed under reduced pressure. The residue was dissolved in Et₂O then was washed with aq. sat. Na₂S₂O₃ and brine. The org. layer was dried over MgSO₄ and the solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R= 1.35 min; [M+H]⁺: 481.8.

(S)-tert-Butyl((3-methylhex-5-en-1-yl)oxy)diphenylsilane: Potassium *tert*-butoxide (14.09 g, 119 mmol, 3 eq) was added in one portion to a soln. of (S)-tert-butyl((6-iodo-3-methylhexyl)oxy)diphenylsilane (19.10 g, 39.80 mmol, 1 eq) in THF (200 mL). The mixture was stirred at rt for 1h then partitioned between cold H₂O and EtOAc. The org. layer was washed with aq. sat. NaHCO₃ soln., brine, dried over MgSO₄, and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 20% EtOAc) to give the title compound. LC-MS (1): t_R= 1.34 min; [M+H]⁺: 353.2.

(4R)-6-((tert-Butyldiphenylsilyl)oxy)-4-methylhexane-1,2-diol: Was synthesized using (S)-tert-butyl((3-methylhex-5-en-1-yl)oxy)diphenylsilane and AD-mix-α in analogy to Example 1.504 (Step 2) to give the title compound. LC-MS (1): t_R= 1.10 min; [M+H]⁺: 387.3.

(R)-5-((tert-Butyldiphenylsilyl)oxy)-3-methylpentanal: Was synthesized using (4R)-6-((tert-butylidiphenylsilyl)oxy)-4-methylhexane-1,2-diol and NaIO₄ in analogy to Example 1.504 (Step 3) to give the title compound. LC-MS (1): t_R= 1.24 min; [M+H]⁺: 355.2.

(S)-5-((*tert*-Butyldiphenylsilyl)oxy)-3-methylpentan-1-ol: Was synthesized using (R)-5-((*tert*-butyldiphenylsilyl)oxy)-3-methylpentanal and NaBH₄ in analogy to Example 1.503 to give the title compound. LC-MS (1): t_R= 1.19 min; [M+H]⁺: 357.3.

5 **Methyl ((3-fluoro-4-methyl-2-(((S)-3-methyl-5-oxopentyl)oxy)phenyl)sulfonyl)-L-prolinate:** Was synthesized using methyl ((3-fluoro-2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate and (S)-5-((*tert*-butyldiphenylsilyl)oxy)-3-methylpentan-1-ol in analogy to Example 1.84 to give the title compound. LC-MS (1): t_R= 1.02 min; [M+H]⁺: 416.2.

10 **(1R,4s)-4-((8R,12aS)-4-Fluoro-3,8-dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile:** Was synthesized using methyl ((3-fluoro-4-methyl-2-(((S)-3-methyl-5-oxopentyl)oxy)phenyl)sulfonyl)-L-prolinate and *cis*-4-amino-1-methyl-cyclohexanecarbonitrile hydrochloride in analogy to Example 1.84 to give the title compound. LC-MS (2): t_R= 1.14 min; [M+H]⁺: 506.0.

15 **Example 1.505 (8R,12aS)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-4-fluoro-3,8-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:** Was synthesized using methyl ((3-fluoro-4-methyl-2-(((S)-3-methyl-5-oxopentyl)oxy)phenyl)sulfonyl)-L-prolinate and (3s,6s)-1,1-difluorospiro[2.5]octan-6-amine in analogy to Example 1.504 to give the title compound. LC-MS (1): t_R= 1.18 min; [M+H]⁺: 529.2.

20 **Example 1.507 (S)-5-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-12-fluoro-13-methyl-1,2,3,3a,6,7,8,9,10,11-decahydrobenzo[b]pyrrolo[1,2-b][1]thia[2,5]diazacyclotridecin-4(5H)-one 16,16-dioxide:** **6-(2-Fluoro-3-methyl-6-nitrophenyl)hex-5-yn-1-ol:** Was synthesized using 2-bromo-3-fluoro-4-methyl-1-nitrobenzene and hex-5-yn-1-ol in analogy to Example 1.435 to give the title compound. LC-MS (1): t_R= 0.90 min; [M+H]⁺: 252.2.

25 **6-(6-Amino-2-fluoro-3-methylphenyl)hexan-1-ol:** A suspension of 6-(2-fluoro-3-methyl-6-nitrophenyl)hex-5-yn-1-ol (6.24 g, 24.80 mmol, 1 eq), NH₄Cl (6.68 g, 124 mmol, 5 eq) and iron powder (70 mesh, 7.01 g, 124 mmol, 5 eq) in EtOH (40 mL) and H₂O (20 mL) was stirred at 90°C for 20h. The reaction mixture was allowed to cool to rt, filtered, and the cake washed with EtOH. The solvent was removed under reduced pressure and the residue was partitioned between aq. sat. NaHCO₃ soln. and DCM. The layers were separated and the aq. layer was extracted with DCM. The combined org. layers were washed with brine, dried over MgSO₄, filtered, and the solvent was removed under reduced pressure. The residue was dissolved in EtOH (100 mL) and Pd/C (640 mg) was added. The reaction was stirred at rt under a H₂ atm for 20 h. The mixture was filtered through Celite and the solvent was removed under reduced pressure. The crude product was purified by FC (Hept to 80% EtOAc) to give the title compound. LC-MS (1): t_R= 0.68 min; [M+H]⁺: 226.2.

30 **6-(2-Fluoro-6-iodo-3-methylphenyl)hexan-1-ol:** Toluene-4-sulfonic acid monohydrate (11.16 g, 57.80 mmol, 3 eq) was added portionwise at 0°C to a soln. of 6-(6-amino-2-fluoro-3-methylphenyl)hexan-1-ol (4.34 g, 19.30 mmol, 1 eq) in MeCN (70 mL). The thick suspension was stirred at rt for 15 min then a soln. of NaNO₂ (2.55 g, 36.60 mmol, 1.9 eq) in H₂O (8 mL) was added dropwise at 0°C. The reaction mixture was stirred at 0°C for 40 min then

a soln. of KI (8.08 g, 48.2 mmol, 2.5 eq) in H₂O (8 mL) was added dropwise. The cooling bath was removed and the mixture was stirred at rt for 1 h. The solvent was removed under reduced pressure then the residue was dissolved in H₂O and extracted with EtOAc. The combined org. layers were washed with brine, dried over MgSO₄ and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R= 1.06 min; [M+H]⁺: not seen.

5

6-(6-(Benzylthio)-2-fluoro-3-methylphenyl)hexan-1-ol: Was synthesized using 6-(2-fluoro-6-iodo-3-methylphenyl)hexan-1-ol and benzyl mercaptan in analogy to Example 1.146 to give the title compound. LC-MS (1): t_R= 1.13 min; [M+H]⁺: 333.1.

Benzyl(2-(6-(benzyloxy)hexyl)-3-fluoro-4-methylphenyl)sulfane:

6-(6-(benzylthio)-2-fluoro-3-

10 methylphenyl)hexan-1-ol (2.53 g, 7.61 mmol, 1 eq) was dissolved in toluene (30 mL). Aq. 50% NaOH soln. (5 mL) was added followed by tributylmethylammonium chloride (183 mg, 0.76 mmol, 0.1 eq) and benzyl bromide (1.1 mL, 9.13 mmol, 1.2 eq) in sequence. The mixture was heated to 70°C and was stirred overnight. The mixture was cooled down to rt and the solvent was removed under reduced pressure. The residue was partitioned between aq. sat. NaHCO₃ soln. and DCM. The org. layer was separated and the aq. layer was extracted with DCM. The
15 combined org. layers were washed with H₂O, brine, dried over MgSO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R= 1.30 min; [M+H]⁺: 423.2.

2-(6-(Benzyloxy)hexyl)-3-fluoro-4-methylbenzenesulfonyl chloride: Was synthesized using benzyl(2-(6-(benzyloxy)hexyl)-3-fluoro-4-methylphenyl)sulfane in analogy to Example 1.146 to give the title compound. LC-MS
20 (1): t_R= 1.25 min; [M+H]⁺: 399.2.

Methyl ((2-(6-(benzyloxy)hexyl)-3-fluoro-4-methylphenyl)sulfonyl)-L-prolinate: Was synthesized using 2-(6-(benzyloxy)hexyl)-3-fluoro-4-methylbenzenesulfonyl chloride and methyl L-prolinate hydrochloride in analogy to Example 1.146 to give the title compound. LC-MS (1): t_R= 1.18 min; [M+H]⁺: 492.1.

Methyl ((3-fluoro-2-(6-hydroxyhexyl)-4-methylphenyl)sulfonyl)-L-prolinate: Methyl ((2-(6-(benzyloxy)hexyl)-3-fluoro-4-methylphenyl)sulfonyl)-L-prolinate (630 mg, 1.28 mmol, 1 eq) was dissolved in MeOH (50 mL) and 20%
25 wt. Pd(OH)₂ on carbon (180 mg, 0.26 mmol, 0.2 eq) was added. The reaction was stirred at rt, under H₂ atm, for 20 h. The mixture was filtered through Celite and the solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R= 0.96 min; [M+H]⁺: 402.1.

Methyl ((3-fluoro-4-methyl-2-(6-oxohexyl)phenyl)sulfonyl)-L-prolinate: Was synthesized using methyl ((3-fluoro-2-(6-hydroxyhexyl)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.435 to give the title
30 compound. LC-MS (1): t_R= 1.01 min; [M+H]⁺: 400.2.

(S)-5-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-12-fluoro-13-methyl-1,2,3,3a,6,7,8,9,10,11-

decahydrobenzo[*l*]pyrrolo[1,2-*b*][1]thia[2,5]diazacyclotridecin-4(5*H*)-one 16,16-dioxide: Was synthesized using methyl ((3-fluoro-4-methyl-2-(6-oxohexyl)phenyl)sulfonyl)-L-prolinate and (3s,6s)-1,1-difluorospiro[2.5]octan-6-amine hydrochloride in analogy to Example 1.435 to give the title compound. LC-MS (1): t_R= 1.17 min; [M+H]⁺:
35 513.1.

Example 1.508 to **Example 1.509** were synthesized using the appropriate amine or amine salt derivative and methyl ((3-fluoro-4-methyl-2-(6-oxohexyl)phenyl)sulfonyl)-L-prolinate in analogy to Example 1.507. LC-MS data of Example 1.508 to Example 1.509 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
1.508	(1R,4s)-4-((S)-12-Fluoro-13-methyl-16,16-dioxido-4-oxo-2,3,3a,4,6,7,8,9,10,11-decahydrobenzo[<i>f</i>]pyrrolo[1,2- <i>b</i>][1]thia[2,5]diazacyclotridecin-5(1 <i>H</i>)-yl)cyclohexane-1-carbonitrile	1.06	476.1
1.509	(1R,4s)-4-((S)-12-Fluoro-13-methyl-16,16-dioxido-4-oxo-2,3,3a,4,6,7,8,9,10,11-decahydrobenzo[<i>f</i>]pyrrolo[1,2- <i>b</i>][1]thia[2,5]diazacyclotridecin-5(1 <i>H</i>)-yl)-1-methylcyclohexane-1-carbonitrile	1.10	490.2

- 5 **Example 1.512 (1R,4s)-4-((6R,12aS)-4-Fluoro-3-methoxy-6-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6*H*-benzo[*b*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-11(12*H*)-yl)-1-methylcyclohexane-1-carbonitrile:**

(S)-((6-(Benzyloxy)hexan-2-yl)oxy)(*tert*-butyl)diphenylsilane: Was synthesized using (S)-5-((*tert*-butyldiphenylsilyl)oxy)hexan-1-ol and benzyl bromide in analogy to Example 1.506 to give the title compound. LC-MS (1): t_R = 1.38 min; [M+H]⁺: 447.1.

(S)-6-(Benzyloxy)hexan-2-ol: Was synthesized using (S)-((6-(benzyloxy)hexan-2-yl)oxy)(*tert*-butyl)diphenylsilane and a 1M TBAF soln. in THF in analogy to Example 1.192 to give the title compound. LC-MS (1): t_R = 0.84 min; [M+H]⁺: 209.2.

6-(Benzylothio)-2-fluoro-3-methoxyphenol: Was synthesized using 4-bromo-2-fluoro-3-hydroxyanisole and benzyl mercaptan in analogy to Example 1.146 to give the title compound. LC-MS (1): t_R = 0.95 min; [M+H]⁺: not seen.

(R)-Benzyl(2-((6-(benzyloxy)hexan-2-yl)oxy)-3-fluoro-4-methoxyphenyl)sulfane: Was synthesized using 6-(benzylothio)-2-fluoro-3-methoxyphenol and (S)-6-(Benzyloxy)hexan-2-ol in analogy to Example 1.64 to give the title compound. LC-MS (1): t_R = 1.24 min; [M+H]⁺: 455.1.

***tert*-Butyl ((2-(((R)-6-(benzyloxy)hexan-2-yl)oxy)-3-fluoro-4-methoxyphenyl)sulfonyl)-L-prolinate:** Was synthesized using (R)-benzyl(2-((6-(benzyloxy)hexan-2-yl)oxy)-3-fluoro-4-methoxyphenyl)sulfane and *tert*-butyl L-prolinate in analogy to Example 1.51 to give the title compound. LC-MS (1): t_R = 1.22 min; [M+H]⁺: 566.2.

***tert*-Butyl ((3-fluoro-2-(((R)-6-hydroxyhexan-2-yl)oxy)-4-methoxyphenyl)sulfonyl)-L-prolinate:** Was synthesized using *tert*-butyl ((2-(((R)-6-(benzyloxy)hexan-2-yl)oxy)-3-fluoro-4-methoxyphenyl)sulfonyl)-L-prolinate and 20% wt. Pd(OH)₂ on carbon in analogy to Example 1.507 to give the title compound. LC-MS (1): t_R = 1.00 min; [M+H]⁺: 476.1.

tert-Butyl ((3-fluoro-4-methoxy-2-((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate: Was synthesized using *tert*-butyl ((3-fluoro-2-((R)-6-hydroxyhexan-2-yl)oxy)-4-methoxyphenyl)sulfonyl)-L-prolinate and oxalyl chloride in analogy to Example 1.51 to give the title compound. LC-MS (1): t_R = 1.05 min; $[M+H]^+$: 474.1.

- 5 **(1R,4s)-4-((6R,12aS)-4-Fluoro-3-methoxy-6-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile:** Was synthesized using *tert*-butyl ((3-fluoro-4-methoxy-2-((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate and 4-amino-1-methyl-cyclohexanecarbonitrile hydrochloride in analogy to Example 1.7 to give the title compound. LC-MS (1): t_R = 1.03 min; $[M+H]^+$: 522.2.

- 10 **Example 1.514 (6R,12aS)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,4-difluoro-6-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:**

(RS)-2-Ethylhexyl 3-((3,4-difluoro-2-methoxyphenyl)sulfonyl)propanoate: Was synthesized using 1-bromo-3,4-difluoro-2-methoxybenzene and 2-ethylhexyl 3-mercaptopropionate in analogy to Examples 1.124 and 1.125 to give the title compound. LC-MS (1): t_R = 1.13 min; $[M+H]^+$: 393.2.

- 15 **((3,4-Difluoro-2-methoxyphenyl)sulfonyl)-L-proline:** Was synthesized using (RS)-2-ethylhexyl 3-((3,4-difluoro-2-methoxyphenyl)sulfonyl)propanoate and L-proline in analogy to Examples 1.124 and 1.125 to give the title compound. LC-MS (1): t_R = 0.78 min; $[M+H]^+$: 322.0.

- 20 **Methyl ((3,4-difluoro-2-hydroxyphenyl)sulfonyl)-L-prolinate:** Was synthesized using ((3,4-difluoro-2-methoxyphenyl)sulfonyl)-L-proline and BBr_3 in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 0.79 min; $[M+H]^+$: 322.0.

Methyl ((3,4-difluoro-2-((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate: Was synthesized using methyl ((3,4-difluoro-2-hydroxyphenyl)sulfonyl)-L-prolinate and (S)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-ol in analogy to Example 1.192 to give the title compound. LC-MS (1): t_R = 0.96 min; $[M+H]^+$: 420.0.

- 25 **(6R,12aS)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,4-difluoro-6-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:** Was synthesized using methyl ((3,4-difluoro-2-((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate and (3s,6s)-1,1-difluorospiro[2.5]octan-6-amine hydrochloride in analogy to Example 1.192 to give the title compound. LC-MS (1): t_R = 1.12 min; $[M+H]^+$: 533.1.

- 30 **Example 1.517 (1aR,4aS,16aS)-3-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-12-methyl-1a,2,3,4a,5,6,7,15,16,16a-decahydrobenzo[b]cyclopropa[*j*]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-4(1H)-one 9,9-dioxide:**

(R)-tert-Butyl(oxiran-2-ylmethoxy)diphenylsilane: Was synthesized using (S)-(-)-glycidol and *tert*-butyldiphenylsilyl chloride in analogy to Example 1.263 to give the title compound. LC-MS (1): t_R = 1.18 min; $[M+H]^+$: not seen.

- Ethyl (1R,2R)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclopropane-1-carboxylate:** Was synthesized using (*R*)-*tert*-butyl(oxiran-2-ylmethoxy)diphenylsilane and triethylphosphonoacetate in analogy to Example 1.75 to give the title compound. LC-MS (1): t_R = 1.26 min; $[M+H]^+$: 383.1.
- ((1R,2R)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)cyclopropyl)methanol :** Was synthesized using ethyl (1R,2R)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclopropane-1-carboxylate in analogy to Example 1.79 to give the title compound. LC-MS (1): t_R = 1.14 min; $[M+H]^+$: 341.0.
- (1R,2R)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)cyclopropane-1-carbaldehyde:** Was synthesized using ((1R,2R)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclopropyl)methanol in analogy to Example 1.240 to give the title compound. LC-MS (1): t_R = 1.20 min; $[M+H]^+$: 339.0.
- tert*-Butyldiphenyl(((1R,2S)-2-vinylcyclopropyl)methoxy)silane:** 2M *n*-BuLi soln. in cyclohexane (1.2 mL, 2.40 mmol, 1.4 eq) was added dropwise at -78°C to a suspension of methyl triphenylphosphonium bromide (857 mg, 2.40 mmol, 1.4 eq) in THF (6 mL). The reaction mixture was stirred at -78°C for 30 min then at 0°C for 45 min before cooling again to -78°C. A soln. of (1R,2R)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclopropane-1-carbaldehyde (583 mg, 1.72 mmol, 1 eq) in THF (2.2 mL) was quickly added and the reaction mixture was allowed to warm to rt over 2h. MeOH (0.9 mL) was added then the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 30% EtOAc) to give the title compound. LC-MS (1): t_R = 1.29 min; $[M+H]^+$: 337.1.
- 2-((1S,2R)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)cyclopropyl)ethan-1-ol:** Was synthesized using *tert*-butyldiphenyl(((1R,2S)-2-vinylcyclopropyl)methoxy)silane in analogy to Examples 1.270 and 1.271 to give the title compound. LC-MS (1): t_R = 1.17 min; $[M+H]^+$: 355.0.
- Methyl ((2-(2-((1S,2R)-2-formylcyclopropyl)ethoxy)-4-methylphenyl)sulfonyl)-L-prolinate:** Was synthesized using 2-((1S,2R)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclopropyl)ethan-1-ol and methyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.150 to give the title compound. LC-MS (1): t_R = 0.92 min; $[M+H]^+$: 396.0.
- (1aR,4aS,16aS)-3-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-12-methyl-1a,2,3,4a,5,6,7,15,16,16a-decahydrobenzo[b]cyclopropa[j]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-4(1H)-one 9,9-dioxide:** Was synthesized using methyl ((2-(2-((1S,2R)-2-formylcyclopropyl)ethoxy)-4-methylphenyl)sulfonyl)-L-prolinate and (3s,6s)-1,1-difluorospiro[2.5]octan-6-amine hydrochloride in analogy to Example 1.150 to give the title compound. LC-MS (1): t_R = 1.09 min; $[M+H]^+$: 509.0.
- Example 1.518 (1R,4s)-1-Methyl-4-((1aR,4aS,16aS)-12-methyl-9,9-dioxido-4-oxo-1,1a,2,4a,5,6,7,15,16,16a-decahydrobenzo[b]cyclopropa[j]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-3(4H)-yl)cyclohexane-1-carbonitrile:** Was synthesized using methyl ((2-(2-((1S,2R)-2-formylcyclopropyl)ethoxy)-4-methylphenyl)sulfonyl)-L-prolinate and cis-4-amino-1-methyl-cyclohexanecarbonitrile hydrochloride in analogy to Example 1.517 to give the title compound. LC-MS (1): t_R = 1.01 min; $[M+H]^+$: 485.8.

Example 1.522 (1R,4s)-4-((4aS,11R)-11,14-Dimethyl-17,17-dioxido-5-oxo-1,2,4a,5,8,9,10,11-octahydro-4H-[1,4]oxazino[4,3-e]pyrido[2,3-b][1]oxa[4]thia[5,8]diazacyclotridecin-6(7H)-yl)-1-methylcyclohexane-1-carbonitrile:

(R)-2-((6-(Benzyloxy)hexan-2-yl)oxy)-3-(benzylthio)-6-methylpyridine: Was synthesized using 3-bromo-6-methylpyridin-2-ol and (S)-6-(benzyloxy)hexan-2-ol in analogy to Example 1.512 to give the title compound. LC-MS (1): t_R = 1.25 min; $[M+H]^+$: 422.1.

Methyl (S)-4-((2-(((R)-6-(benzyloxy)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)morpholine-3-carboxylate: Was synthesized using (R)-2-((6-(Benzyloxy)hexan-2-yl)oxy)-3-(benzylthio)-6-methylpyridine and (S)-methyl morpholine-3-carboxylate in analogy to Example 1.512 to give the title compound. LC-MS (1): t_R = 1.12 min; $[M+H]^+$: 507.1.

Methyl (S)-4-((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)morpholine-3-carboxylate: Was synthesized using methyl (S)-4-((2-(((R)-6-(benzyloxy)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)morpholine-3-carboxylate in analogy to Example 1.507 to give the title compound. LC-MS (1): t_R = 0.91 min; $[M+H]^+$: 415.1.

(1R,4s)-4-((4aS,11R)-11,14-Dimethyl-17,17-dioxido-5-oxo-1,2,4a,5,8,9,10,11-octahydro-4H-[1,4]oxazino[4,3-e]pyrido[2,3-b][1]oxa[4]thia[5,8]diazacyclotridecin-6(7H)-yl)-1-methylcyclohexane-1-carbonitrile: Was synthesized using methyl (S)-4-((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)morpholine-3-carboxylate and cis-4-amino-1-methyl-cyclohexanecarbonitrile hydrochloride in analogy to Example 1.507 to give the title compound. LC-MS (1): t_R = 1.00 min; $[M+H]^+$: 505.2.

Example 1.527 (1³RS,4²S)-6-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-2⁵-methyl-3-thia-6-aza-1(1,3),4(1,2)-dipyrrolidina-2(1,2)-benzenacyclooctaphan-5-one 3,3-dioxide:

Methyl ((4-methyl-2-((RS)-3-(2-oxoethyl)pyrrolidin-1-yl)phenyl)sulfonyl)-L-prolinate: Was synthesized using (RS)-3-(2-(benzyloxy)ethyl)pyrrolidine 2,2,2-trifluoroacetate and methyl ((2-fluoro-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.525 to give the title compound. LC-MS (1): t_R = 0.86 min; $[M+H]^+$: 395.2.

(1³RS,4²S)-6-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-2⁵-methyl-3-thia-6-aza-1(1,3),4(1,2)-dipyrrolidina-2(1,2)-benzenacyclooctaphan-5-one 3,3-dioxide: Was synthesized using methyl ((4-methyl-2-((RS)-3-(2-oxoethyl)pyrrolidin-1-yl)phenyl)sulfonyl)-L-prolinate and (3s,6s)-1,1-difluorospiro[2.5]octan-6-amine hydrochloride in analogy to Example 1.525 to give the title diastereomers. LC-MS (1): t_R = 1.05 and 1.08 min; $[M+H]^+$: 508.2.

Example 1.529 (1R,4s)-4-((4aS,11R)-11,14-Dimethyl-17,17-dioxido-5-oxo-2,3,4a,5,8,9,10,11-octahydro-1H-benzo[b][1,3]oxazino[3,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-6(7H)-yl)-1-methylcyclohexane-1-carbonitrile:

(S)-Hex-5-en-2-ol: CuBr (7.60 g, 52.00 mmol, 0.1 eq) was suspended in THF (30 mL). The suspension was cooled to 0°C and 1M allyl magnesium bromide in Et₂O (625.0 mL, 625.00 mmol, 1.25 eq) was added. The mixture was stirred at 0°C for 45 min. (S)-(-)-Propylene oxide (29.30 g, 0.50 mmol, 1 eq) was added dropwise. The reaction mixture was warmed to rt and stirred for 2h. Aq. sat. NH₄Cl soln. was added dropwise, followed by aq. 32% HCl soln. to adjust the pH to 1. H₂O was added and the emulsion was stirred for 1h and filtered. The layers were

separated and the org. layer was washed with H₂O, dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification.

(S)-((Hex-5-en-2-yloxy)methyl)benzene: (S)-Hex-5-en-2-ol (5.00 g, 49.90 mmol, 1 eq) was added dropwise to a stirred suspension of NaH (60% dispersion in oil, 3.45 g, 86.20 mmol, 1.7 eq) in THF (80 mL). The reaction mixture was stirred for 15 min, then benzyl bromide (8.60 mL, 70.90 mmol, 1.4 eq) was added dropwise, followed by tetrabutylammonium iodide (2.88 g, 7.73 mmol, 0.15 eq). The reaction was heated under for 2h30. The reaction was cooled to rt, and aq. sat. NH₄Cl soln. was added. The aq. layer was extracted with tBME. The combined org. layers were dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.85 min; [M+H]⁺: not seen.

(S)-5-(Benzyloxy)hexan-1-ol: 1M BH₃ soln. in THF (60.0 mL, 60.0 mmol, 1.2 eq) was added at 0°C to a stirred soln. of (S)-((hex-5-en-2-yloxy)methyl)benzene (9.50 g, 49.90 mmol, 1 eq) in THF (110 mL). The resulting soln. was warmed up to rt and stirred for 1h. The reaction mixture was cooled to 0°C and aq. 5M NaOH soln. (11.1 mL, 52.40 mmol, 1.05 eq) and aq. 30% (w/w) hydrogen peroxide soln. (10.0 mL, 97.90 mmol, 2 eq) were added in sequence. The reaction mixture was warmed up to rt and stirred for 2h. The reaction mixture was quenched with aq. sat. Na₂SO₃ soln. and extracted with DCM. The org. layer was washed with brine, dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 0.83 min; [M+H]⁺: 209.3.

(S)-((5-(Benzyloxy)hexyl)oxy)(tert-butyl)diphenylsilane: (S)-5-(Benzyloxy)hexan-1-ol (4.00 g, 19.20 mmol, 1 eq) was dissolved in DCM (40 mL). The soln. was cooled to 0°C and imidazole (1.45 g, 21.10 mmol, 1.1 eq) was added, followed by tert-butyl(chloro)diphenylsilane (5.60 mL, 21.10 mmol, 1.1 eq). The reaction mixture was warmed to rt and stirred for 1h. The mixture was diluted with DCM and aq. 5% citric acid soln. was added. The org. layer was washed with H₂O, dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 10% EtOAc) to give the title compound. LC-MS (1): t_R = 1.34 min; [M+H]⁺: 447.3.

(S)-6-((tert-Butyldiphenylsilyl)oxy)hexan-2-ol: (S)-((5-(Benzyloxy)hexyl)oxy)(tert-butyl)diphenylsilane (8.58 g, 19.20 mmol, 1 eq) was dissolved in MeOH (200 mL). Pd(OH)₂/C (2.70 g, 3.84 mmol, 0.2 eq) was added and the reaction mixture was flushed with N₂ and stirred under H₂ atm. at rt for 5h. The reaction mixture was filtered through 0.45 μm PTFE filter, washed with MeOH and the solvents were removed under reduced pressure. The crude product was used in the next step without further purification.

(R)-((5-(2-Bromo-5-methylphenoxy)hexyl)oxy)(tert-butyl)diphenylsilane: Was synthesized using 2-Bromo-5-methylphenol and (S)-6-((tert-butylidiphenylsilyl)oxy)hexan-2-ol in analogy to Example 1.64 to give the title compound. LC-MS (1): t_R = 1.37 min; [M+H]⁺: 527.2.

(RS)-2-Ethylhexyl 3-(((R)-6-((tert-butylidiphenylsilyl)oxy)hexan-2-yl)oxy)-4-methylphenylsulfonyl)propanoate: Was synthesized using (R)-((5-(2-bromo-5-methylphenoxy)hexyl)oxy)(tert-butyl)diphenylsilane and 2-ethylhexyl 3-mercaptopropionate in analogy to Examples 1.124 and 1.125 to give the title compound. LC-MS (1): t_R = 1.43 min; [M+H]⁺: 695.4.

(R)-2-((6-(((tert-Butyldiphenylsilyl)oxy)hexan-2-yl)oxy)-N-(3-hydroxypropyl)-4-methylbenzenesulfonamide:

Was synthesized using (RS)-2-ethylhexyl 3-((2-(((R)-6-((tert-butyldiphenylsilyl)oxy)hexan-2-yl)oxy)-4-methylphenyl)sulfonyl)propanoate and 3-amino-1-propanol in analogy to Example 1.376 to give the title compound. LC-MS (1): t_R = 1.24 min; $[M+H]^+$: 584.3.

- 5 **Ethyl (RS)-3-((2-(((R)-6-((tert-butyldiphenylsilyl)oxy)hexan-2-yl)oxy)-4-methylphenyl)sulfonyl)-1,3-oxazinane-2-carboxylate:** Ethyl diethoxyacetate (0.43 mL, 2.33 mmol, 1.5 eq) and camphor-10-sulfonic acid (423 mg, 1.78 mmol, 1.15 eq) were added to a soln. of (R)-2-((6-((tert-butyldiphenylsilyl)oxy)hexan-2-yl)oxy)-N-(3-hydroxypropyl)-4-methylbenzenesulfonamide (906 mg, 1.55 mmol, 1 eq) in toluene (20 mL). The reaction mixture was refluxed for 16h. The soln. was cooled down to 0°C and aq. sat. NaHCO_3 was added. The mixture was
- 10 extracted with DCM. The combined org. layers were dried over MgSO_4 and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 20% EtOAc) to give the title compound. LC-MS (1): t_R = 1.35 min; $[M+H]^+$: 668.3.

Ethyl (RS)-3-((4-methyl-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-1,3-oxazinane-2-carboxylate: Was synthesized using ethyl (RS)-3-((2-(((R)-6-((tert-butyldiphenylsilyl)oxy)hexan-2-yl)oxy)-4-methylphenyl)sulfonyl)-1,3-oxazinane-2-carboxylate in analogy to Example 1.360 to give the title compound. LC-MS (1): t_R = 0.99 min; $[M+H]^+$: 428.2.

(1R,4s)-4-((4aS,11R)-11,14-Dimethyl-17,17-dioxido-5-oxo-2,3,4a,5,8,9,10,11-octahydro-1H-**benzo[*b*][1,3]oxazino[3,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-6(7*H*)-yl)-1-methylcyclohexane-1-**

carbonitrile: Was synthesized using ethyl (RS)-3-((4-methyl-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-1,3-oxazinane-2-carboxylate and *cis*-4-amino-1-methyl-cyclohexanecarbonitrile hydrochloride in analogy to Example 1.360. The mixture was separated by chiral SFC (SFC 9 method) to give the title compound (second eluting diastereomer). LC-MS (3): t_R = 1.24 min; $[M+H]^+$: 504.5.

Example 1.532 to Example 1.555 were synthesized using the appropriate amine or amine salt derivative and the appropriate aldehyde in analogy to Examples reported herein before. LC-MS data of Example 1.532 to Example 1.555 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
1.532	(1S,3S)-3-((1 ² S,5 ¹ R*,5 ³ R*)-3 ³ -Fluoro-3 ⁴ -methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile	1.11	518.2	1
1.533	(S)-5-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-11-fluoro-12-methyl-1,2,3,3a,5,6,7,8,9,10-decahydro-4 <i>H</i> -benzo[<i>k</i>]pyrrolo[1,2- <i>b</i>][1]thia[2,5]diazacyclododecin-4-one 15,15-dioxide	1.12	499.1	1

1.534	(1 ² S,5 ¹ R*,5 ³ R*)-8-(4,4-Difluorocyclohexyl)-3 ³ -fluoro-3 ⁴ -methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide	1.16	529.2	1
1.535	(1R,4s)-4-((S)-11-Fluoro-12-methyl-15,15-dioxido-4-oxo-2,3,3a,4,7,8,9,10-octahydro-1H-benzo[k]pyrrolo[1,2-b][1]thia[2,5]diazacyclododecin-5(6H)-yl)-1-methylcyclohexane-1-carbonitrile	1.05	476.2	1
1.536	(1 ² S,5 ¹ R*,5 ³ R*)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3 ³ -fluoro-3 ⁴ -methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide	1.21	555.2	1
1.537	(1 ² S,5 ¹ R,5 ³ R)-8-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-3 ³ -fluoro-3 ⁴ -methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide	1.13	527.2	1
1.538	(1 ² S,5 ¹ S,5 ³ S)-8-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-3 ³ -fluoro-3 ⁴ -methyl-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide	1.16	527.2	1
1.539	(1R,4s)-4-((1 ² S,5 ¹ R,5 ³ R)-3 ³ -Fluoro-3 ⁴ -methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile	1.06	518.2	1
1.540	(1R,4s)-4-((1 ² S,5 ¹ S,5 ³ S)-3 ³ -Fluoro-3 ⁴ -methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile	1.11	518.2	1
1.541	(1R,4s)-4-((1 ² S,5 ¹ R,5 ³ R)-3 ³ -Fluoro-3 ⁴ -methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphane-8-yl)-1-methylcyclohexane-1-carbonitrile	1.10	532.1	1
1.542	(1R,4s)-4-((1 ² S,5 ¹ S,5 ³ S)-3 ³ -Fluoro-3 ⁴ -methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphane-8-yl)-1-methylcyclohexane-1-carbonitrile	1.14	532.1	1

1.543	(1R,4s)-4-((6R,12aS)-3,4-Difluoro-6-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.01	496.1	1
1.544	(1R,4s)-4-((S)-12-Methyl-15,15-dioxido-4-oxo-2,3,3a,4,7,8,9,10-octahydro-1H-benzo[k]pyrrolo[1,2-b][1]thia[2,5]diazacyclododecin-5(6H)-yl)cyclohexane-1-carbonitrile	0.97	444.2	1
1.545	(1S,3S)-3-((S)-12-Methyl-15,15-dioxido-4-oxo-2,3,3a,4,7,8,9,10-octahydro-1H-benzo[k]pyrrolo[1,2-b][1]thia[2,5]diazacyclododecin-5(6H)-yl)cyclohexane-1-carbonitrile	0.98	444.2	1
1.547	(1R,4s)-4-((3S,10R)-3,10,13-Trimethyl-1,1-dioxido-4-oxo-3,4,7,8,9,10-hexahydro-2H-benzo[b][1]oxa[4]thia[5,8]diazacyclotridecin-5(6H)-yl)cyclohexane-1-carbonitrile: Methyl ((4-methyl-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-alaninate	0.94	448.0	1
1.548	(1R,4s)-1-Methyl-4-((3S,10R)-3,10,13-trimethyl-1,1-dioxido-4-oxo-3,4,7,8,9,10-hexahydro-2H-benzo[b][1]oxa[4]thia[5,8]diazacyclotridecin-5(6H)-yl)cyclohexane-1-carbonitrile	0.99	462.0	1
1.551	(1R,4s)-4-((3S,10R)-2,3,10,13-Tetramethyl-1,1-dioxido-4-oxo-3,4,7,8,9,10-hexahydro-2H-benzo[b][1]oxa[4]thia[5,8]diazacyclotridecin-5(6H)-yl)cyclohexane-1-carbonitrile	1.00	462.0	1
1.554	(3S,10R)-5-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-2,3,10,13-tetramethyl-2,3,5,6,7,8,9,10-octahydro-4H-benzo[b][1]oxa[4]thia[5,8]diazacyclotridecin-4-one 1,1-dioxide	1.12	499.1	1

Example 1.556 (6R,8R,12aS)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6,8-trimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:

- 5 **(2RS,4R)-6-((tert-Butyldiphenylsilyl)oxy)-4-methylhexan-2-ol:** A soln. of 3M MeMgCl in THF (2.7 mL, 8.09 mmol, 1.2 eq) was added dropwise at 0°C to a soln. of (R)-5-((tert-butyldiphenylsilyl)oxy)-3-methylpentanal (2.39

g, 6.74 mmol, 1 eq) in THF (18 mL). The reaction mixture was stirred at 0°C for 2h then was partitioned between EtOAc and aq. sat. NH₄Cl soln. The layers were separated and the aq. layer was extracted with EtOAc. The combined org. layers were dried over MgSO₄ and filtered. The solvent was removed under reduced pressure and the residue was purified by FC (Hept to 30% EtOAc) to give the title compound. LC-MS (1): t_R= 1.23 min; [M+H]⁺: 371.1.

5

Methyl ((4-methyl-2-(((2RS,4S)-4-methyl-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate: Was synthesized using methyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate and (2RS,4R)-6-((*tert*-butyldiphenylsilyl)oxy)-4-methylhexan-2-ol in analogy to Example 1.499 to give the title compound. LC-MS (1): t_R= 0.99 min; [M+H]⁺: 412.3.

(6R,8R,12aS)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6,8-trimethyl-6,7,8,9,10,11,12a,13,14,15-

10 **decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:** Was synthesized using methyl ((4-methyl-2-(((2RS,4S)-4-methyl-6-oxohexan-2-yl)oxy)phenyl)sulfonyl)-L-prolinate and (3s,6s)-1,1-difluorospiro[2.5]octan-6-amine hydrochloride in analogy to Example 1.84 to give the title compound. LC-MS (1): t_R= 1.12 min; [M+H]⁺: 525.1.

Example 1.558 to Example 1.594 were synthesized using the appropriate amine or amine salt derivative and the appropriate scaffolds in analogy to Examples reported herein before. LC-MS data of Example 1.558 to Example 1.594 are listed in the table below. The LC-MS conditions used were LC-MS (1).

15

Ex. N°	Name	t _R	[M+H] ⁺	LC-MS conditions
1.558	(1R,3R)-3-((3S,10R)-12-Fluoro-3,10,13-trimethyl-1,1-dioxido-4-oxo-3,4,7,8,9,10-hexahydro-2H-benzo[b][1]oxa[4]thia[5,8]diazacyclotridecin-5(6H)-yl)cyclohexane-1-carbonitrile	1.04	466.0	1
1.559	(1S,4r)-1-Methyl-4-((6R,8R,12aS)-3,6,8-trimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.08	502.1	1
1.560	(1S,4r)-1-Methyl-4-((6S,8R,12aS)-3,6,8-trimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.10	502.1	1
1.579	(1R,4s)-4-((3S,10R)-12-Fluoro-2,3,10,13-tetramethyl-1,1-dioxido-4-oxo-3,4,7,8,9,10-hexahydro-2H-benzo[b][1]oxa[4]thia[5,8]diazacyclotridecin-5(6H)-yl)-1-methylcyclohexane-1-carbonitrile	1.16	494.1	1

1.581	(1R,4s)-1-Methyl-4-((1 ³ R,4 ² S)-2 ⁵ -methyl-3,3-dioxido-5-oxo-3-thia-6-aza-1(1,3),4(1,2)-dipyrrolidina-2(1,2)-benzenacyclooctaphane-6-yl)cyclohexane-1-carbonitrile	1.00	485.1	1
1.582	(1R,4s)-1-methyl-4-((1 ³ S,4 ² S)-2 ⁵ -methyl-3,3-dioxido-5-oxo-3-thia-6-aza-1(1,3),4(1,2)-dipyrrolidina-2(1,2)-benzenacyclooctaphane-6-yl)cyclohexane-1-carbonitrile	1.03	485.1	1
1.590	(6R,12aS)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3-methoxy-6-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.06	527.0	1
1.591	(1R,4s)-4-((6R,12aS)-3-Methoxy-6-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	0.98	504.2	1
1.592	(1R,4s)-4-((6R,12aS)-3-Methoxy-6-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.94	490.0	1
1.593	(1S,3S)-3-((6R,12aS)-3-Methoxy-6-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.95	490.0	1
1.594	(1R,4s)-1-methyl-4-((9aS,13aS,14aR)-2-methyl-5,5-dioxido-10-oxo-8,9,9a,10,12,13,13a,14,14a,15-decahydrobenzo[b]cyclopropa[k]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(7H)-yl)cyclohexane-1-carbonitrile	1.10	485.9	1

Example 1.595 (1R,4s)-4-((1aR,4aS,15R,16aS)-12,15-Dimethyl-9,9-dioxido-4-oxo-1,1a,2,4a,5,6,7,15,16,16a-decahydrobenzo[b]cyclopropa[j]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-3(4H)-yl)-1-methylcyclohexane-1-carbonitrile and **Example 1.596** (1R,4s)-4-((1aR,4aS,15S,16aS)-12,15-Dimethyl-9,9-dioxido-4-oxo-1,1a,2,4a,5,6,7,15,16,16a-decahydrobenzo[b]cyclopropa[j]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-3(4H)-yl)-1-methylcyclohexane-1-carbonitrile:

2-((1S,2R)-2-(((tert-Butyldiphenylsilyl)oxy)methyl)cyclopropyl)acetaldehyde: Was synthesized using 2-((1S,2R)-2-(((tert-butyl)diphenylsilyl)oxy)methyl)cyclopropyl)ethan-1-ol and PyrSO₃ in analogy to Example 1.240 to give the title compound. LC-MS (1): t_R= 1.20 min; [M+H]⁺: 353.1.

(RS)-1-(((1S,2R)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)cyclopropyl)propan-2-ol): Was synthesized using 2-(((1S,2R)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclopropyl)acetaldehyde in analogy to Example 1.556 to give the title compound. LC-MS (1): t_R = 1.19 min; $[M+H]^+$: 369.1.

Methyl ((2-(((RS)-1-(((1S,2R)-2-formylcyclopropyl)propan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate:

- 5 Was synthesized using (RS)-1-(((1S,2R)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclopropyl)propan-2-ol and methyl ((2-hydroxy-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.517 to give the title compound. LC-MS (1): t_R = 1.00 min; $[M+H]^+$: 410.0.

(1R,4s)-4-((1aR,4aS,15R,16aS)-12,15-Dimethyl-9,9-dioxido-4-oxo-1,1a,2,4a,5,6,7,15,16,16a-decahydrobenzo[b]cyclopropa[7]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-3(4H)-yl)-1-

- 10 **methylcyclohexane-1-carbonitrile and (1R,4s)-4-((1aR,4aS,15S,16aS)-12,15-Dimethyl-9,9-dioxido-4-oxo-1,1a,2,4a,5,6,7,15,16,16a-decahydrobenzo[b]cyclopropa[7]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-3(4H)-yl)-1-methylcyclohexane-1-carbonitrile:** Were synthesized using methyl ((2-(((RS)-1-(((1S,2R)-2-formylcyclopropyl)propan-2-yl)oxy)-4-methylphenyl)sulfonyl)-L-prolinate and cis-4-amino-1-methyl-cyclohexanecarbonitrile hydrochloride in analogy to Example 1.517. The mixture was purified by SFC (SFC 25 method) to give the 2 diastereomers. First eluting diastereomer: LC-MS (1): t_R = 1.11 min; $[M+H]^+$: 500.1. Second eluting diastereomer: LC-MS (1): t_R = 1.11 min; $[M+H]^+$: 500.1.

Example 1.599 (1R,4s)-1-Methyl-4-((4²S,E)-2⁵-methyl-3,3-dioxido-5-oxo-1¹H-3-thia-6-aza-1(3,1)-pyrazola-4(1,2)-pyrrolidina-2(1,2)-benzenacyclononaphane-6-yl)cyclohexane-1-carbonitrile:

Methyl ((4-methyl-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)phenyl)sulfonyl)-L-prolinate: 1-(2-

- 20 Tetrahydropyranyl)-1H-pyrazole-5-boronic acid pinacol ester (5.05 g, 18.00 mmol, 1.2 eq), methyl ((2-bromo-4-methylphenyl)sulfonyl)-L-prolinate (5.43 g, 15.00 mmol, 1.0 eq) and Na_2CO_3 (3.50 g, 33.00 mmol, 2.2 eq) were dissolved in dioxane (80 mL) and H_2O (20 mL). $Pd(PPh_3)_4$ (866 mg, 0.75 mmol, 0.05 eq) was added and the mixture was heated to 100°C overnight. The mixture was filtered and the filtrate was poured into H_2O . The mixture was extracted with EtOAc. The combined org. layer were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by FC (Hept to 20% EtOAc) to give the title compound. LC-MS (1): t_R = 0.97 min; $[M+H]^+$: 434.0.

- 25 **Methyl ((4-methyl-2-(1H-pyrazol-3-yl)phenyl)sulfonyl)-L-prolinate:** 4M HCl soln. in dioxane (11.5 mL, 45.70 mmol, 5 eq) was added to a soln. of methyl ((4-methyl-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)phenyl)sulfonyl)-L-prolinate (3.96 g, 9.13 mmol, 1 eq) in MeOH (50 mL) at 0°C. The mixture was stirred for 2h at rt. The solvent was removed under reduced pressure and the residue was partitioned between aq. sat. $NaHCO_3$ and EtOAc. The layers were separated. The org. layer was dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.83 min; $[M+H]^+$: 350.0.

- 30 **Methyl ((2-(1-(but-3-en-1-yl)-1H-pyrazol-3-yl)-4-methylphenyl)sulfonyl)-L-prolinate:** Cs_2CO_3 (3.85 g, 11.80 mmol, 1.5 eq) was added to a soln. of methyl ((4-methyl-2-(1H-pyrazol-3-yl)phenyl)sulfonyl)-L-prolinate (2.75 g, 7.87 mmol, 1 eq) and bromobutene (1.2 mL, 11.80 mmol, 1.5 eq) in DMF (50 mL). The reaction mixture was stirred

at 60°C for 2h. The suspension was cooled to rt and was filtered off through a Celite pad. The solvent was removed under reduced pressure and the residue was partitioned between aq. 10% NaHSO₄ soln. and DCM. The layers were separated. The solvent was removed under reduced pressure and the residue was purified by FC (Hept to 20% EtOAc) to give the title compound. LC-MS (1): t_R= 1.00 min; [M+H]⁺: 404.0.

- 5 **Methyl ((4-methyl-2-(1-(3-oxopropyl)-1H-pyrazol-3-yl)phenyl)sulfonyl)-L-prolinate:** Was synthesized using methyl ((2-(1-(but-3-en-1-yl)-1H-pyrazol-3-yl)-4-methylphenyl)sulfonyl)-L-prolinate in analogy to Example 1.503 to give the title compound. LC-MS (1): t_R= 0.86 min; [M+H]⁺: 406.0.

- (1R,4s)-1-Methyl-4-((4²S,E)-2⁵-methyl-3,3-dioxido-5-oxo-1¹H-3-thia-6-aza-1(3,1)-pyrazola-4(1,2)-pyrrolidina-2(1,2)-benzenacyclononaphane-6-yl)cyclohexane-1-carbonitrile: Was synthesized using methyl ((4-methyl-2-(1-(3-oxopropyl)-1H-pyrazol-3-yl)phenyl)sulfonyl)-L-prolinate and cis-4-amino-1-methyl-cyclohexanecarbonitrile hydrochloride in analogy to Example 1.84 to give the title compound. LC-MS (1): t_R= 0.95 min; [M+H]⁺: 496.1.

Example 1.600 (6R,12aS)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3-methoxy-6-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:

- 15 **(RS)-2-Ethylhexyl 3-((2-(((R)-6-((tert-butylidimethylsilyl)oxy)hexan-2-yl)oxy)-6-methoxypyridin-3-yl)sulfonyl)propanoate:** Was synthesized using 3-bromo-6-methoxypyridin-2-ol and (S)-6-((tert-butylidimethylsilyl)oxy)hexan-2-ol in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R= 1.36 min; [M+H]⁺: 588.3.

- tert-Butyl ((6-methoxy-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate:** Was synthesized using (RS)-2-ethylhexyl 3-((2-(((R)-6-((tert-butylidimethylsilyl)oxy)hexan-2-yl)oxy)-6-methoxypyridin-3-yl)sulfonyl)propanoate and L-proline tert-butyl ester hydrochloride in analogy to Example 1.124 to give the title compound. LC-MS (1): t_R= 1.05 min; [M+H]⁺: 457.2.

- (6R,12aS)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3-methoxy-6-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide:** Was synthesized using tert-butyl ((6-methoxy-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate and (3s,6s)-1,1-difluorospiro[2.5]octan-6-amine hydrochloride in analogy to Example 1.22 to give the title compound. LC-MS (1): t_R= 1.09 min; [M+H]⁺: 528.2.

Example 1.601 (1R,4s)-4-((6R,12aS)-3-Methoxy-6-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-

- 30 **methylcyclohexane-1-carbonitrile:** Was synthesized using tert-butyl ((6-methoxy-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)-L-prolinate and cis-4-amino-1-methyl-cyclohexanecarbonitrile hydrochloride in analogy to Example 1.22 to give the title compound. LC-MS (1): t_R= 1.02 min; [M+H]⁺: 505.2.

Example 1.605 (1²S,5¹R,5³R)-8-(4,4-Difluorocyclohexyl)-3⁴-methyl-4-oxa-2-thia-8-aza-1(1,2)-piperidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide:

Methyl 2-((1S,3S)-3-hydroxycyclohexyl)acetate: Was synthesized using methyl (S)-2-(3-oxocyclohexyl)acetate (Chemistry - A European Journal (2020), 26(55), 12528-12532) and L-selectride in analogy to Examples 1.124 and 1.125 to give the title compound. LC-MS (1): t_R = 1.24 min; $[M+H]^+$: not seen.

(1S,3R)-3-(2-Hydroxyethyl)cyclohexan-1-ol: Was synthesized using methyl 2-((1S,3S)-3-hydroxycyclohexyl)acetate and $LiAlH_4$ in analogy to Examples 1.124 and 1.125 to give the title compound.

(1S,3R)-3-(2-((tert-Butyldiphenylsilyl)oxy)ethyl)cyclohexan-1-ol: Was synthesized using (1S,3R)-3-(2-hydroxyethyl)cyclohexan-1-ol and *tert*-butyl(chloro)diphenylsilane in analogy to Examples 1.124 and 1.125 to give the title compound. LC-MS (1): t_R = 1.24 min; $[M+H]^+$: not seen.

Methyl (S)-1-((5-chloro-2-methoxy-4-methylphenyl)sulfonyl)piperidine-2-carboxylate: Was synthesized using 5-chloro-2-methoxy-4-methylbenzenesulfonyl chloride and (S)-piperidine-2-carboxylic acid methyl ester hydrochloride in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 0.99 min; $[M+H]^+$: 362.1.

Methyl (S)-1-((5-chloro-2-hydroxy-4-methylphenyl)sulfonyl)piperidine-2-carboxylate: Was synthesized using methyl (S)-1-((5-chloro-2-methoxy-4-methylphenyl)sulfonyl)piperidine-2-carboxylate and BBr_3 in analogy to Example 1.1 to give the title compound. LC-MS (1): t_R = 0.91 min; $[M+H]^+$: 348.1.

Methyl (S)-1-((2-hydroxy-4-methylphenyl)sulfonyl)piperidine-2-carboxylate: To a solution of methyl (S)-1-((5-chloro-2-hydroxy-4-methylphenyl)sulfonyl)piperidine-2-carboxylate (4.34 g, 12.5 mmol, 1 eq) in MeOH (18.5 mL) was added NaOAc (2.07 g, 25 mmol, 2 eq) and $Pd(OH)_2/C$ (20 wt. %, wet, 877 mg, 1.25 mmol, 0.1 eq). The reaction was stirred at 50°C for 5h under a H_2 atmosphere. The reaction mixture was filtered, rinsed with MeOH and the solvent removed under reduced pressure. The residue was dissolved in EtOAc and aq. sat. $NaHCO_3$ soln. The org layers were 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. LC-MS (1): t_R = 0.86 min; $[M+H]^+$: 314.1.

Methyl (S)-1-((4-methyl-2-(((1R,3S)-3-(2-oxoethyl)cyclohexyl)oxy)phenyl)sulfonyl)piperidine-2-carboxylate: Was synthesized using methyl (S)-1-((2-hydroxy-4-methylphenyl)sulfonyl)piperidine-2-carboxylate and (1S,3R)-3-(2-((tert-butyldiphenylsilyl)oxy)ethyl)cyclohexan-1-ol in analogy to Examples 1.482 and 1.483 to give the title compound. LC-MS (1): t_R = 1.04 min; $[M+H]^+$: 438.2.

(1²S,5¹R,5³R)-8-(4,4-Difluorocyclohexyl)-3⁴-methyl-4-oxa-2-thia-8-aza-1(1,2)-piperidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2,2-dioxide: Was synthesized using methyl (S)-1-((4-methyl-2-(((1R,3S)-3-(2-oxoethyl)cyclohexyl)oxy)phenyl)sulfonyl)piperidine-2-carboxylate and 4,4-difluorocyclohexan-1-amine in analogy to Examples 1.482 and 1.483 to give the title compound. LC-MS (2): t_R = 1.26 min; $[M+H]^+$: 525.3.

Example 1.608 to Example 1.610 were synthesized using the appropriate amine or amine salt derivative 3-bromo-2-hydroxypyridine and (S)-6-((tert-butyldimethylsilyl)oxy)hexan-2-ol in analogy to Example 1.51. LC-MS data of Example 1.608 and Example 1.610 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
1.608	(6R,12aS)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-6-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.04	475.2
1.609	(1R,4s)-1-methyl-4-((6R,12aS)-6-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.96	475.2
1.610	(1R,4s)-4-((6R,12aS)-6-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.91	461.2

Example 1.614 to **Example 1.629** were synthesized using the appropriate amine or amine salt derivative and the appropriate scaffolds in analogy to Examples reported herein before. LC-MS data of Example 1.614 to Example 1.629 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
1.614	(4 ² S,Z)-1 ⁴ -Chloro-6-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-2 ⁵ -methyl-1 ¹ H-3-thia-6-aza-1(3,1)-pyrazola-4(1,2)-pyrrolidina-2(1,2)-benzenacyclononaphan-5-one 3,3-dioxide	1.10	553.0	1
1.615	(6R,12aS,14S)-11-(4,4-Difluorocyclohexyl)-3,6,14-trimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.06	500.0	1
1.617	(6S,8R,12aS)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6,8-trimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.16	526.1	1
1.618	(6R,8R,12aS)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6,8-trimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.16	526.1	1
1.619	(1R,4s)-1-Methyl-4-((6S,8R,12aS)-3,6,8-trimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.08	503.1	1

1.620	(1R,4s)-1-Methyl-4-((6R,8R,12aS)-3,6,8-trimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.09	503.1	1
1.629	(1R,4s)-4-((1aR,4aS,16aS)-12-Methyl-9,9-dioxido-4-oxo-1,1a,2,4a,5,6,7,15,16,16a-decahydrobenzo[b]cyclopropa[j]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-3(4H)-yl)cyclohexane-1-carbonitrile	0.98	472.1	1

Example 1.630 (1R,4s)-4-((4²S,Z)-1⁴-fluoro-2⁵-methyl-3,3-dioxido-5-oxo-1¹H-3-thia-6-aza-1(3,1)-pyrazola-4(1,2)-pyrrolidina-2(1,2)-benzenacyclononaphane-6-yl)-1-methylcyclohexane-1-carbonitrile: 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (336 mg, 0.92 mmol, 3 eq) was added to a soln. of (1R,4s)-1-methyl-4-((4²S,E)-2⁵-methyl-3,3-dioxido-5-oxo-1¹H-3-thia-6-aza-1(3,1)-pyrazola-4(1,2)-pyrrolidina-2(1,2)-benzenacyclononaphane-6-yl)cyclohexane-1-carbonitrile (152 mg, 0.31 mmol, 1 eq) in MeCN (5 mL). The mixture was stirred at 80°C for 2h. The solvent was removed under reduced pressure and the residue was purified by acidic prep. HPLC to give the title compound. LC-MS (1): t_R= 0.99 min; [M+H]⁺: 513.9.

Example 1.631 to Example 1.712 were synthesized using the appropriate amine or amine salt derivative and the appropriate scaffolds in analogy to Examples reported herein before. LC-MS data of Example 1.631 to Example 1.712 are listed in the table below.

Ex. N°	Name	t _R	[M+H] ⁺	LC-MS conditions
1.631	(1R,4s)-4-((8R,12aS)-4-Fluoro-3,8-dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.08	492.1	1
1.633	(6R,12aS)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-14,14-difluoro-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.12	547.7	1
1.634	(1R,4s)-4-((6R,12aS)-14,14-Difluoro-3,6-dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	1.05	525.0	1

1.635	(1R,4s)-4-((3S,10R)-2-Ethyl-3,10,13-trimethyl-1,1-dioxido-4-oxo-3,4,7,8,9,10-hexahydro-2H-pyrido[2,3-b][1]oxa[4]thia[5,8]diazacyclotridecin-5(6H)-yl)-1-methylcyclohexane-1-carbonitrile	1.18	491.3	1
1.638	(3 ¹ R,3 ³ R,8S)-6-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-1 ⁶ ,8,9-trimethyl-2-oxa-10-thia-6,9-diaza-1(2,3)-pyridina-3(1,3)-cyclohexanacyclodecaphan-7-one 10,10-dioxide: Methyl N-((2-hydroxy-6-methylpyridin-3-yl)sulfonyl)-N-methyl-L-alaninate	1.32	526.3	2
1.639	(1R,4s)-1-Methyl-4-((3 ¹ R,3 ³ R,8S)-1 ⁶ ,8,9-trimethyl-10,10-dioxido-7-oxo-2-oxa-10-thia-6,9-diaza-1(2,3)-pyridina-3(1,3)-cyclohexanacyclodecaphane-6-yl)cyclohexane-1-carbonitrile	1.20	503.3	1
1.641	(6R,12aS)-11-((1s,4R)-4-Ethynylcyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.06	474.2	1
1.642	(1 ³ R,4 ² S)-6-(4,4-Difluorocyclohexyl)-2 ⁶ -methyl-3-thia-6-aza-2(2,3)-pyridina-1(1,3),4(1,2)-dipyrrolidinacyclononaphan-5-one 3,3-dioxide	1.08	497.1	1
1.643	(1R,4s)-1-Methyl-4-((1 ³ R,4 ² S)-2 ⁶ -methyl-3,3-dioxido-5-oxo-3-thia-6-aza-2(2,3)-pyridina-1(1,3),4(1,2)-dipyrrolidinacyclononaphane-6-yl)cyclohexane-1-carbonitrile	0.99	500.0	1
1.644	(1 ³ R,4 ² S)-6-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-2 ⁶ -methyl-3-thia-6-aza-2(2,3)-pyridina-1(1,3),4(1,2)-dipyrrolidinacyclononaphan-5-one 3,3-dioxide	1.07	523.0	1
1.645	(1 ³ R,4 ² S)-6-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-2 ⁶ -methyl-3-thia-6-aza-2(2,3)-pyridina-1(1,3),4(1,2)-dipyrrolidinacyclononaphan-5-one 3,3-dioxide	1.03	495.0	1
1.646	(1 ³ R,4 ² S)-6-((S)-6,6-Dimethyltetrahydro-2H-pyran-3-yl)-2 ⁶ -methyl-3-thia-6-aza-2(2,3)-pyridina-1(1,3),4(1,2)-dipyrrolidinacyclononaphan-5-one 3,3-dioxide	0.98	491.0	1
1.647	(1S,4r)-4-((1 ³ R,4 ² S)-2 ⁶ -Methyl-3,3-dioxido-5-oxo-3-thia-6-aza-2(2,3)-pyridina-1(1,3),4(1,2)-dipyrrolidinacyclononaphane-6-yl)cyclohexane-1-carbonitrile	0.94	486.1	1

1.650	(6R,12aS)-11-((RS)-3,3-dimethylcyclopentyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.12	464.3	1
1.651	(1R,4s)-4-((4 ² S,E)-2 ⁶ -Fluoro-2 ⁵ -methyl-3,3-dioxido-5-oxo-1 ¹ H-3-thia-6-aza-1(3,1)-pyrazola-4(1,2)-pyrrolidina-2(1,2)-benzenacyclononaphane-6-yl)-1-methylcyclohexane-1-carbonitrile	0.95	514.0	1
1.652	(1R,4s)-4-((4 ² S,Z)-1 ⁴ -Chloro-2 ⁶ -fluoro-2 ⁵ -methyl-3,3-dioxido-5-oxo-1 ¹ H-3-thia-6-aza-1(3,1)-pyrazola-4(1,2)-pyrrolidina-2(1,2)-benzenacyclononaphane-6-yl)-1-methylcyclohexane-1-carbonitrile	1.01	547.8	1
1.653	(1R,4s)-1-Cyclopropyl-4-((6R,12aS)-3,6-dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.10	515.4	1
1.654	(1S,3R)-3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclopentane-1-carbonitrile	1.01	475.1	1
1.655	(1S,4s)-1-Methyl-4-((R)-2,10,13-trimethyl-1,1-dioxido-4-oxo-3,4,7,8,9,10-hexahydro-2H-pyrido[2,3-b][1]oxa[4]thia[5,8]diazacyclotridecin-5(6H)-yl)cyclohexane-1-carbonitrile	1.02	463.3	1
1.657	4-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-ethylcyclohexane-1-carbonitrile	0.97	503.0	1
1.658	4-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-(ethyl-d5)cyclohexane-1-carbonitrile	0.97	503.0	1
1.659	4-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-(methyl-d3)cyclohexane-1-carbonitrile	1.03	492.1	1

1.660	4-((6R,12aS)-4-Fluoro-3,6-dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-(methyl-d3)cyclohexane-1-carbonitrile	1.08	509.1	1
1.661	(1R,4s)-4-((S)-8-Cyclopropyl-3-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8,11]triazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	0.76	515.0	1
1.662	(1R,4s)-1-Methyl-4-((6R,12aS,15S)-3,6,15-trimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.07	503.1	1
1.663	(6R,12aS,15S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6,15-trimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.15	526.1	1
1.664	(1R,4s)-4-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-6,7,9,10,12a,13,14,15-octahydropyrido[2,3-e]pyrrolo[1,2-h][1,4]dioxo[7]thia[8,11]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	0.95	491.1	1
1.665	(1R,4s)-4-((6S,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-6,7,9,10,12a,13,14,15-octahydropyrido[2,3-e]pyrrolo[1,2-h][1,4]dioxo[7]thia[8,11]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	0.99	491.2	1
1.666	(1R,4s)-4-((6R,12aS)-3-Chloro-4-fluoro-6-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	1.10	526.0	1
1.667	(1R,4s)-4-((3aS,9S)-9,12-Dimethyl-15,15-dioxido-4-oxo-2,3,3a,4,7,8,9,10-octahydro-1H-benzo[k]pyrrolo[1,2-b][1]thia[2,5]diazacyclododecin-5(6H)-yl)-1-methylcyclohexane-1-carbonitrile	1.25	472.4	1
1.668	(1R,4s)-1-Methyl-4-((8RS,12aS)-3-methyl-17,17-dioxido-12-oxo-8-(trifluoromethyl)-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.01	542.0	1

1.669	(1R,4s)-4-((3 ¹ R,3 ³ R,8S)-1 ⁶ ,8-Dimethyl-10,10-dioxido-7-oxo-2-oxa-10-thia-6,9-diaza-1(2,3)-pyridina-3(1,3)-cyclohexanacyclodecaphane-6-yl)-1-methylcyclohexane-1-carbonitrile	1.06	489.3	1
1.671	(1R,4s)-1-Methyl-4-((6S,12aS)-3-methyl-17,17-dioxido-12-oxo-6-(trifluoromethyl)-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.00	542.0	1
1.672	(1R,4s)-1-Methyl-4-((6S,12aS)-3-methyl-17,17-dioxido-12-oxo-6-(trifluoromethyl)-7,8,9,10,12a,13,14,15-octahydro-6H-pyrrolo[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.02	543.0	1
1.673	(6S,12aS)-11-(4,4-Difluorocyclohexyl)-3-methyl-6-(trifluoromethyl)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.04	540.0	1
1.674	(1R,4s)-1-Methyl-4-((6S,12aS)-3-methyl-17,17-dioxido-12-oxo-8-(trifluoromethyl)-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.01	542.0	1
1.675	(1R,4s)-1-Methyl-4-((8R,12aS)-3-methyl-17,17-dioxido-12-oxo-8-(trifluoromethyl)-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.01	542.0	1
1.676	(1R,4s)-4-((3 ¹ R,3 ³ R,8S)-1 ⁶ -Fluoro-15,8,9-trimethyl-10,10-dioxido-7-oxo-2-oxa-10-thia-6,9-diaza-1(1,2)-benzena-3(1,3)-cyclohexanacyclodecaphane-6-yl)-1-methylcyclohexane-1-carbonitrile	1.13	520.1	1
1.677	(1R,4s)-1-Methyl-4-((6R,12aS)-3-methyl-17,17-dioxido-12-oxo-6-(trifluoromethyl)-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.04	542.0	1
1.679	(1S,4s)-1-Methyl-4-((3 ¹ R,3 ³ R)-1 ⁶ -methyl-10,10-dioxido-7-oxo-2-oxa-10-thia-6,9-diaza-1(2,3)-pyridina-3(1,3)-cyclohexanacyclodecaphane-6-yl)cyclohexane-1-carbonitrile	1.04	475.4	1

1.680	(1S,4s)-4-((3 ¹ R,3 ³ R)-1 ⁶ ,9-dimethyl-10,10-dioxido-7-oxo-2-oxa-10-thia-6,9-diaza-1(2,3)-pyridina-3(1,3)-cyclohexanacyclodecaphane-6-yl)-1-methylcyclohexane-1-carbonitrile	1.09	489.4	1
1.681	(1R,4s)-4-((6S,12aS)-8-Cyclopropyl-3,6-dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8,11]triazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	0.81	529.0	1
1.682	(1R,4s)-1-Methyl-4-((6R,12aS)-3,6,15,15-tetramethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	1.28	516.8	1
1.683	2-((R)-3-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)pyrrolidin-1-yl)acetonitrile	0.77	475.0	1
1.684	(S,Z)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3-methyl-6,7,10,11,12a,13,14,15-octahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide	1.05	496.0	1
1.685	(1R,4s)-1-Methyl-4-((S,Z)-3-methyl-17,17-dioxido-12-oxo-7,10,12a,13,14,15-hexahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.96	473.1	1
1.689	(6R,12aS)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-6,7,10,11,12a,13,14,15-octahydropyrido[2,3-e]pyrrolo[1,2-h][1,4]dioxo[7]thia[8,11]diazacyclotridecin-12(9H)-one 17,17-dioxide	1.04	514.2	1
1.690	(6S,12aS)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-6,7,10,11,12a,13,14,15-octahydropyrido[2,3-e]pyrrolo[1,2-h][1,4]dioxo[7]thia[8,11]diazacyclotridecin-12(9H)-one 17,17-dioxide	1.07	514.2	1
1.691	(1R,4s)-4-((S)-8-Cyclopropyl-3-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8,11]triazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	0.74	516.0	1

1.692	(S)-8-Cyclopropyl-11-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8,11]triazacyclotridecin-12-one 17,17-dioxide	0.83	539.0	1
1.693	(1R,4s)-4-((6R,12aS)-4-Fluoro-6-methyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	1.05	492.3	1
1.700	(1R,4s)-4-((1 ² S,5 ¹ R,5 ³ S)-3 ³ -Fluoro-3 ⁴ -methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclopentanacyclononaphane-8-yl)-1-methylcyclohexane-1-carbonitrile	1.10	518.4	1
1.701	(1R,4s)-4-((1 ² S,5 ¹ S,5 ³ R)-3 ³ -Fluoro-3 ⁴ -methyl-2,2-dioxido-9-oxo-4-oxa-2-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclopentanacyclononaphane-8-yl)-1-methylcyclohexane-1-carbonitrile	1.14	518.4	1
1.703	(3 ¹ R,3 ³ S,8S)-6-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-1 ⁶ ,8,9-trimethyl-2-oxa-10-thia-6,9-diaza-1(2,3)-pyridina-3(1,3)-cyclopentanacyclodecaphan-7-one 10,10-dioxide	1.15	512.4	1
1.707	(1R,4s)-4-((6R,12aS)-6-Ethyl-3-methyl-17,17-dioxido-12-oxo-6,7,9,10,12a,13,14,15-octahydropyrido[2,3-e]pyrrolo[1,2-h][1,4]dioxo[7]thia[8,11]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	0.99	505.0	1
1.710	(1R,4s)-1-Methyl-4-((9aS,14aS,17aR)-2-methyl-5,5-dioxido-10-oxo-8,9,9a,10,12,13,14a,16,17,17a-decahydro-15H-cyclopenta[b]pyrido[2,3-e]pyrrolo[1,2-h][1,4]dioxo[7]thia[8,11]diazacyclotridecin-11(7H)-yl)cyclohexane-1-carbonitrile	0.99	517.0	1
1.711	(6R,11aS)-3-Bromo-10-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-6-methyl-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide	1.12	562.1	1

1.712	(9aS,14aS,17aR)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-2-methyl-7,8,9,9a,12,13,14a,16,17,17a-decahydro-15H-cyclopenta[b]pyrido[2,3-e]pyrrolo[1,2-h][1,4]dioxo[7]thia[8,11]diazacyclotridecin-10(11H)-one 5,5-dioxide	1.08	540.3	1
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Methods for the preparation of sulfonimidamide (SIA) compounds (Examples 2.x)

Example 2.1 (12aS)-11-(4,4-Difluorocyclohexyl)-3-methyl-17-(methylimino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide:

- 5 **(RS)-2-Ethylhexyl 3-((2-((5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)thio)propanoate:** (RS)-2-Ethylhexyl 3-((2-hydroxy-4-methylphenyl)thio)propanoate (500 mg, 1.54 mmol, 1 eq) was dissolved in THF (15 mL). The soln. was cooled to 0°C. Then *tert*-butyl (4,4-difluorocyclohexyl)(5-hydroxypentyl)carbamate (594 mg, 1.85 mmol, 1.2 eq) and PPh₃ (492 mg, 1.85 mmol, 1.2 eq) were added followed by DEAD (~40% in toluene, 1.5 mL, 3.08 mmol, 2 eq). After the addition, the mixture was allowed to warm up to rt and stirred for 2h. The reaction mixture was diluted with Et₂O and washed with aq. 0.1M HCl soln., aq. sat. NaHCO₃ soln. and H₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 20% EtOAc) to give the title compound. LC-MS (1): t_R= 1.36 min; [M+H]⁺: 627.8.

- 15 ***tert*-Butyl (4,4-difluorocyclohexyl)(5-(2-mercapto-5-methylphenoxy)pentyl)carbamate:** (RS)-2-Ethylhexyl 3-((2-((5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)thio)propanoate (683 mg, 1.09 mmol, 1 eq) was dissolved in MeOH (11 mL). Then 25 wt.% NaOMe soln. in MeOH (1.20 mL, 5.44 mmol, 5 eq) was added. The reaction mixture was stirred at 60°C for 3h. The reaction was cooled to rt and the 3/4 of the solvent was removed under reduced pressure. The remaining soln. was dissolved in Et₂O and washed with aq. 1M HCl soln. and H₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 30% EtOAc) to give the title compound. LC-MS (1): t_R= 1.23 min; [M+H]⁺: 444.0.

- 25 **Methyl 2-((5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-4-methylbenzenesulfinate:** *tert*-Butyl (4,4-difluorocyclohexyl)(5-(2-mercapto-5-methylphenoxy)pentyl)carbamate (203 mg, 0.46 mmol, 1 eq) was dissolved in DCM/MeOH 1:1 (9 mL). *N*-bromosuccinimide (173 mg, 0.96 mmol, 2.1 eq) was added at 0°C under argon atm. The reaction mixture was stirred at 0°C for 2 min, after which the reaction was immediately quenched using cold aq. sat. NaHCO₃ soln. Et₂O was added and the aq. layer was separated. The org. layer was washed with H₂O, dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 25% EtOAc) to give the title compound. LC-MS (1): t_R= 1.17 min; [M+H]⁺: 490.0.

- 30 ***tert*-Butyl (5-(2-(aminosulfinyl)-5-methylphenoxy)pentyl)(4,4-difluorocyclohexyl)carbamate:** Methyl 2-((5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-4-methylbenzenesulfinate (161 mg, 0.33 mmol, 1

eq) was dissolved in THF (4 mL). Then 1M LiHMDS soln. in THF (1.00 mL, 1.00 mmol, 3 eq) was added dropwise at -78°C under argon atm. The reaction mixture was stirred -78°C for 20 min, then slowly warmed up to rt. The reaction mixture was quenched with aq. sat. NH₄Cl soln. and stirred vigorously for 15 min. EtOAc was added and the org. layer was washed with H₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R= 1.06 min; [M+H]⁺: 475.0.

tert-Butyl (5-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)sulfinyl)-5-methylphenoxy)pentyl)(4,4-difluorocyclohexyl)carbamate: *tert*-Butyl (5-(2-(aminosulfinyl)-5-methylphenoxy)pentyl)(4,4-difluorocyclohexyl)carbamate (70 mg, 0.15 mmol, 1 eq) was dissolved in THF (2 mL). Then 1M LiHMDS soln. in THF (0.3 mL, 0.30 mmol, 2 eq) was added dropwise at 0°C under argon atm. The reaction mixture was stirred at 0°C for 30 min. Then a soln. of (9H-fluoren-9-yl)methyl carbonochloridate (43 mg, 0.16 mmol, 1.1 eq) in THF (1 mL) was added dropwise. The reaction mixture was stirred at 0°C for 30 min. Et₂O was added and the org. layer was washed with aq. 0.1M HCl soln., aq. sat. NaHCO₃ soln. and H₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R= 1.23 min; [M+H]⁺: 696.9.

tert-Butyl (N-((((9H-fluoren-9-yl)methoxy)carbonyl)-2-((((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenylsulfonimidoyl)-L-prolinate: *tert*-Butyl (5-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)sulfinyl)-5-methylphenoxy)pentyl)(4,4-difluorocyclohexyl)carbamate (40 mg, 0.057 mmol, 1 eq) was dissolved in DCM (1 mL). Then *t*BuOCl (9 mg, 0.086 mmol, 1.5 eq) was added at 0°C under argon atm. The reaction mixture was stirred at 0°C for 20 min. Then a soln. of *tert*-butyl *L*-prolinate (15 mg, 0.087 mmol, 1.5 eq) and DIPEA (0.03 mL, 0.17 mmol, 3 eq) in DCM (1 mL) was added dropwise. The reaction mixture was warmed to rt and stirred for 20 min. Et₂O was added and the org. layer and washed with 0.1M HCl soln., aq. sat. NaHCO₃ soln. and H₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R= 1.33 min; [M+H]⁺: 866.4.

(N-((((9H-Fluoren-9-yl)methoxy)carbonyl)-2-((((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenylsulfonimidoyl)-L-proline: *tert*-Butyl (N-((((9H-fluoren-9-yl)methoxy)carbonyl)-2-((((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenylsulfonimidoyl)-L-prolinate (30 mg, 0.035 mmol, 1 eq) was dissolved in DCM (1 mL). Then TFA (0.3 mL, 3.50 mmol, 100 eq) was added. The reaction mixture was stirred at rt for 4h. Toluene (10 mL) was added and the solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R= 0.92 and 0.93 min; [M+H]⁺: 710.2.

(9H-Fluoren-9-yl)methyl ((12a*S*)-11-(4,4-difluorocyclohexyl)-3-methyl-17-oxido-12-oxo-7,8,9,10,11,12,12a,13,14,15-decahydro-6H-17λ⁴-benzo[*b*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-17-ylidene)carbamate: (N-((((9H-Fluoren-9-yl)methoxy)carbonyl)-2-((((tert-butoxycarbonyl)(4,4-

5 difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenylsulfonimidoyl)-L-proline (32 mg, 0.039 mmol, 1 eq) in DMF (5 mL) was added dropwise using a syringe pump to a soln. of DIPEA (0.05 mL, 0.31 mmol, 8 eq) and HATU (59 mg, 0.16 mmol, 4 eq) in DMF (5 mL). The reaction mixture was stirred at rt for 10 min. Et₂O was added and the org. layer was washed with aq. 0.1M HCl soln. and H₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 1.17 and 1.18 min; [M+H]⁺: 692.0.

10 **(12aS)-11-(4,4-Difluorocyclohexyl)-17-imino-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide:** (9H-Fluoren-9-yl)methyl ((12aS)-11-(4,4-difluorocyclohexyl)-3-methyl-17-oxido-12-oxo-7,8,9,10,11,12,12a,13,14,15-decahydro-6H-17λ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-17-ylidene)carbamate (18 mg, 0.027 mmol, 1 eq) was dissolved in MeCN (1 mL). Then DBU (4 μL, 0.027 mmol, 1 eq) was added. The reaction mixture was stirred at rt for 10 min. EtOAc was added and the org. layer was washed with aq. 0.1M HCl soln. and H₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (DCM to 10% MeOH) to give the title compound. LC-MS (1): t_R = 0.87 and 0.89 min; [M+H]⁺: 469.8.

15 **(12aS)-11-(4,4-Difluorocyclohexyl)-3-methyl-17-(methylimino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide:** (12aS)-11-(4,4-Difluorocyclohexyl)-17-imino-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide (10 mg, 0.021 mmol, 1 eq) was dissolved in DMF (0.5 mL). Then NaH (60% in mineral oil, 2 mg, 0.043 mmol, 2 eq) was added. The reaction mixture was stirred at rt for 30 min. Then MeI (7 μL, 0.11 mmol, 5 eq) was added. The reaction mixture was stirred at rt for 10 min. The reaction was quenched with a few drops of H₂O. The mixture was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 0.86 min; [M+H]⁺: 484.0.

25 **Example 2.2 (12aS,17R)-11-(4,4-Difluorocyclohexyl)-17-imino-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide and Example 2.3 (12aS,17S)-11-(4,4-Difluorocyclohexyl)-17-imino-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide:**

30 (12aS)-11-(4,4-Difluorocyclohexyl)-17-imino-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide was purified by FC (DCM to 5% MeOH) to give (12aS,17S)-11-(4,4-difluorocyclohexyl)-17-imino-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide (first eluting diastereomer) and (12aS,17R)-11-(4,4-difluorocyclohexyl)-17-imino-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide (second eluting diastereomer). First eluting diastereomer: LC-MS (1): t_R = 0.90 min; [M+H]⁺: 469.8. Second eluting diastereomer: LC-MS (1): t_R = 0.87 min; [M+H]⁺: 469.8.

Example 2.4 (12aS,17S)-11-(4,4-Difluorocyclohexyl)-3-methyl-17-(methylimino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide: Was synthesized using (12aS,17S)-11-(4,4-difluorocyclohexyl)-17-imino-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide (first eluting diastereomer) in analogy to Example 2.1 to give the title compound. LC-MS (1): t_R = 0.85 min; $[M+H]^+$: 484.0.

Example 2.5 (6R,12aS,17S)-11-(4,4-Difluorocyclohexyl)-17-imino-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide:

***tert*-Butyl ((2-(((R)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfinyl)carbamate:** (R)-3-Bromo-2-((6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridine (1.84 g, 4.57 mmol, 1 eq) was dissolved in THF (35 mL). The soln. was cooled to -78°C under argon atm. Then 1.6M *n*-BuLi soln. in hexanes (5.50 mL, 5.50 mmol, 1.2 eq) was added dropwise. The reaction mixture was stirred at -78°C for 30 min, then a soln. of *tert*-butyl (oxo- λ^4 -sulfaneylidene)carbamate (J. Am. Chem. Soc. (2004), 126 (40), 12740–12741) (1.12 g, 6.86 mmol, 1.5 eq) in THF (10 mL) was added dropwise. The reaction mixture was stirred at -78°C for 30 min. The reaction was quenched with H₂O and allowed to warm up to rt. The reaction mixture was diluted with Et₂O and washed with H₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 55% EtOAc) to give the title compound. LC-MS (1): t_R = 1.24 min; $[M+H]^+$: 487.1.

Methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((R)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate and Methyl ((R)-N-(*tert*-butoxycarbonyl)-2-(((R)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate: *tert*-Butyl ((2-(((R)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfinyl)carbamate (1.01 g, 2.07 mmol, 1 eq) was dissolved in DCM (30 mL). The soln. was cooled to 0°C under argon atm. Then *t*BuOCl (563 mg, 5.19 mmol, 2.5 eq) was added. The reaction mixture was stirred at 0°C for 20 min. Then a soln. of methyl *L*-prolinate hydrochloride (521 mg, 3.11 mmol, 1.5 eq) and DIPEA (1.4 mL, 8.30 mmol, 4 eq) in DCM (10 mL) was added dropwise. The soln. was stirred at rt for 10 min. The reaction mixture was diluted with Et₂O and washed with aq. 1M HCl soln., aq. sat. NaHCO₃ soln. and H₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 40% EtOAc) to give methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((R)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate (first eluting diastereomer) and methyl ((R)-N-(*tert*-butoxycarbonyl)-2-(((R)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate (second eluting diastereomer). First eluting diastereomer: LC-MS (1): t_R = 1.30 min; $[M+H]^+$: 614.4. Second eluting diastereomer: LC-MS (1): t_R = 1.30 min; $[M+H]^+$: 614.4

Methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((R)-6-hydroxyhexan-2-yl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate: Methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((R)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate (first eluting diastereomer) (376 mg, 0.43 mmol, 1 eq) was dissolved in THF (4 mL). Then 1M TBAF soln. in THF (1.70 mL, 1.70 mmol, 4 eq) was added. The reaction mixture was stirred

at rt for 1h. The reaction mixture was diluted with EtOAc and Et₂O and washed with H₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R= 0.96 min; [M+H]⁺: 500.2.

- Methyl ((S)-N-(*tert*-butoxycarbonyl)-6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridine-3-sulfonimidoyl)-L-prolinate:** Oxalyl chloride (43 µL, 0.50 mmol, 1.5 eq) was dissolved in DCM (3 mL) and the soln. was cooled to -78°C under argon atm. Then DMSO (63 µL, 0.89 mmol, 2.7 eq) was added dropwise while maintaining a temperature below -70°C. After stirring for another 10 min, a soln. of methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((R)-6-hydroxyhexan-2-yl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate (206 mg, 0.33 mmol, 1 eq) in DCM (2 mL) was added dropwise. After stirring for another 10 min, TEA (0.23 mL, 1.65 mmol, 5 eq) was added and the reaction mixture was stirred at -78°C for 30 min. Then the soln. was allowed to warm up to rt. The reaction mixture was diluted with Et₂O and washed with aq. 1M HCl soln., aq. sat. NaHCO₃ soln. and H₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 60% EtOAc) to give the title compound. LC-MS (1): t_R= 1.02 min; [M+H]⁺: 498.0.

- Methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((R)-6-((4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate:** Methyl ((S)-N-(*tert*-butoxycarbonyl)-6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridine-3-sulfonimidoyl)-L-prolinate (30 mg, 0.06 mmol, 1 eq) was dissolved in MeOH (1 mL). Then 4,4-difluorocyclohexan-1-amine (83 µL, 0.066 mmol, 1.1 eq) was added and the soln. was stirred at rt for 3h. NaBH₄ (2.7 mg, 0.072 mmol, 1.2 eq) was then added to the reaction mixture and stirring was continued for 10 min. The reaction mixture was diluted with DCM and washed with H₂O. The org. layer was separated and the aq. layer was washed with DCM. The combined org. layers were dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R= 0.90 min; [M+H]⁺: 617.4.

- ((S)-N-(*tert*-Butoxycarbonyl)-2-(((R)-6-((4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-proline:** Methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((R)-6-((4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate (34 mg, 0.056 mmol, 1 eq) was dissolved in THF (1 mL). Then aq. 1M LiOH soln. (0.56 mL, 0.56 mmol, 10 eq) was added. The reaction mixture was stirred at rt for 45 min. Aq. 1M HCl soln. was added. The reaction mixture was diluted with DCM and washed H₂O. The org. layer was separated and the aq. layer was washed with DCM. The combined org. layers were dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure to give the title compound. LC-MS (1): t_R= 0.83 min; [M+H]⁺: 603.4.

- tert*-Butyl ((6R,12aS,17S)-11-(4,4-difluorocyclohexyl)-3,6-dimethyl-17-oxido-12-oxo-7,8,9,10,11,12,12a,13,14,15-decahydro-6H-17λ⁴-pyrido[2,3-*b*]pyrrolo[1,2-*e*][1]oxa[4]thia[5,8]diazacyclotridecin-17-ylidene)carbamate:** Was synthesized using ((S)-N-(*tert*-butoxycarbonyl)-2-(((R)-6-((4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-proline in analogy to Example 2.1 to give the title compound. LC-MS (1): t_R= 1.10 min; [M+H]⁺: 585.4.

(6R,12aS,17S)-11-(4,4-Difluorocyclohexyl)-17-imino-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide: *tert*-Butyl ((6R,12aS,17S)-11-(4,4-difluorocyclohexyl)-3,6-dimethyl-17-oxido-12-oxo-7,8,9,10,11,12,12a,13,14,15-decahydro-6H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-17-ylidene)carbamate (20 mg, 0.035 mmol, 1 eq) was dissolved in MeCN (1 mL). Then TMSI (13 μ L, 0.087 mmol, 2.5 eq) was added. The reaction mixture was stirred at rt for 5 min. The reaction was quenched with aq. sat. NaHCO₃ soln. and extracted with DCM. The solvent was removed under reduced pressure. The residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R= 0.95 min; [M+H]⁺: 485.3.

Example 2.6 (6R,12aS,17R)-11-(4,4-Difluorocyclohexyl)-17-imino-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide: Was synthesized using methyl ((R)-N-(*tert*-butoxycarbonyl)-2-(((R)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate and 4,4-difluorocyclohexylamine hydrochloride in analogy to Example 2.5 to give the title compound. LC-MS (1): t_R= 0.97 min; [M+H]⁺: 485.3.

Example 2.7 (6R,12aS,17S)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-17-(methylimino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide: Was synthesized using (6R,12aS,17S)-11-(4,4-difluorocyclohexyl)-17-imino-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide in analogy to Example 2.1 to give the title compound. LC-MS (1): t_R= 0.93 min; [M+H]⁺: 499.0.

Example 2.8 (6R,12aS,17R)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-17-(methylimino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide: Was synthesized using ((6R,12aS,17R)-11-(4,4-difluorocyclohexyl)-17-imino-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide in analogy to Example 2.1 to give the title compound. LC-MS (1): t_R= 0.95 min; [M+H]⁺: 499.0.

Example 2.9 to Example 2.16 were synthesized using the appropriate amine or amine salt derivative and methyl ((S)-N-(*tert*-butoxycarbonyl)-6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridine-3-sulfonimidoyl)-L-prolinate or methyl ((R)-N-(*tert*-butoxycarbonyl)-6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridine-3-sulfonimidoyl)-L-prolinate in analogy to Example 2.5. LC-MS data of Example 2.9 to Example 2.16 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
2.9	(6R,12aS,17S)-11-((3R,5s)-1,1-difluorospiro[2.3]hexan-5-yl)-17-imino-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide	0.96	483.0

2.10	(6R,12aS,17S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-17-imino-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ ⁴ -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide	1.01	511.0
2.11	(6R,12aS,17R)-11-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-17-imino-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ ⁴ -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide	0.98	483.0
2.12	(6R,12aS,17R)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-17-imino-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ ⁴ -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide	1.03	511.0
2.13	(6R,12aS,17S)-11-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-3,6-dimethyl-17-(methylimino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ ⁴ -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide	0.92	497.0
2.14	(6R,12aS,17S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-17-(methylimino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ ⁴ -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide	0.98	525.4
2.16	(6R,12aS,17R)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-17-(methylimino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ ⁴ -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide	1.0	525.0

Example 2.26 to Example 2.42 were synthesized using 2-bromo-5-methylphenol, (S)-5-((*tert*-butyldimethylsilyl)oxy)pentan-2-ol (Bioorg. Med. Chem. Lett. (2008), 18, 175–178) or (R)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-ol and the appropriate amine or amine salt derivative in analogy to Example 2.5. LC-MS data of Example 2.26 to Example 2.42 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
2.26	(6R,11aS,16S)-10-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-16-imino-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydro-16H-16λ ⁴ -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16-oxide	0.94	496.2
2.28	(6R,11aS,16R)-10-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-16-imino-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydro-16H-16λ ⁴ -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16-oxide	0.96	496.3

2.30	(6R,11aS,16S)-10-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-16-(methylimino)-7,8,9,10,11a,12,13,14-octahydro-16H-16 λ^4 -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16-oxide	0.09	510.3
2.32	(6R,11aS,16R)-10-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-16-(methylimino)-7,8,9,10,11a,12,13,14-octahydro-16H-16 λ^4 -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16-oxide	0.92	510.3
2.34	(6R,12aS,17S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-17-imino-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide	0.92	510.0
2.36	(6R,12aS,17R)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-17-imino-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide	0.96	510.0
2.38	(6R,12aS,17S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-17-(methylimino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide	0.91	524.0
2.39	(6R,12aS,17S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-17-((methyl-d3)imino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide	0.91	524.0
2.41	(6R,12aS,17R)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-17-(methylimino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide	0.93	524.0
2.42	(6R,12aS,17R)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-17-((methyl-d3)imino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide	0.93	524.0

Example 2.43 (6R,12aS,17R)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-4-fluoro-17-imino-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide:

- 5 (R)-((5-(6-Bromo-2-fluoro-3-methylphenoxy)hexyl)oxy)(*tert*-butyl)dimethylsilane: Was synthesized using 2-Fluoro-3-methyl-6-bromophenol and (S)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-ol in analogy to Example 1.528 to give the title compound. LC-MS (1): t_R = 1.37 min; $[M+H]^+$: 419.0.

(6R,12aS,17R)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-4-fluoro-17-imino-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide: Was synthesized using (R)-((5-(6-bromo-2-fluoro-3-methylphenoxy)hexyl)oxy)(*tert*-butyl)dimethylsilane and (3s,6s)-1,1-difluorospiro[2.5]octan-6-amine hydrochloride in analogy to Example 2.5 to give the title compound. LC-MS (1): t_R = 1.10 min; $[M+H]^+$: 528.0.

Example 2.44 (1²S,5¹S,5³S,2S)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-2-imino-3⁶-methyl-2 λ^6 -4-oxa-2 λ^6 -thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide:
3-Bromo-2-(((1R*,3R*)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridine: Was synthesized using (1S*,3R*)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexan-1-ol and 3-bromo-6-methylpyridin-2-ol in analogy to Example 1.51 to give the title compound. LC-MS (1): t_R = 1.48 min; $[M+H]^+$: 552.0.

***tert*-Butyl ((RS)-2-(((1S,3S)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridin-3-yl)sulfinyl)carbamate and *tert*-Butyl ((RS)-2-(((1R,3R)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridin-3-yl)sulfinyl)carbamate:** 3-Bromo-2-(((1R*,3R*)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridine (3.12 g, 5.65 mmol, 1 eq) was dissolved in THF (40 mL). The soln. was cooled to -78°C under argon atmosphere. Then 1.9M PhLi soln. in Bu₂O (3.6 mL, 6.77 mmol, 1.2 eq) was added dropwise. The reaction mixture was stirred at -78°C for 30 min, then a soln. of *tert*-butyl (oxo- λ^4 -sulfaneylidene)carbamate (1.11 g, 6.77 mmol, 1.2 eq) in THF (10 mL) was added dropwise. The reaction mixture was stirred at -78°C for 1.5h. The reaction was quenched with H₂O and allowed to warm up to rt. The solution was diluted with EtOAc and washed with H₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 30% EtOAc) to give *tert*-butyl ((RS)-2-(((1S,3S)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridin-3-yl)sulfinyl)carbamate (first eluting diastereomer) and *tert*-butyl ((RS)-2-(((1R,3R)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridin-3-yl)sulfinyl)carbamate (second eluting diastereomer). The stereochemistry at the cyclohexyl ring was attributed arbitrarily. First eluting diastereomer: LC-MS (1): t_R = 1.36 min; $[M+H]^+$: 637.4. Second eluting diastereomer: LC-MS (1): t_R = 1.35 min; $[M+H]^+$: 637.4.

Methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((1S,3S)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate and Methyl ((R)-N-(*tert*-butoxycarbonyl)-2-(((1S,3S)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate: Were synthesized using *tert*-butyl ((RS)-2-(((1S,3S)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridin-3-yl)sulfinyl)carbamate (first eluting diastereomer) and methyl L-prolinate hydrochloride in analogy to Example 2.5. The diastereomers were separated by FC (Hept to 40% EtOAc) to give methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((1S,3S)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate (first eluting diastereomer) and methyl ((R)-N-(*tert*-butoxycarbonyl)-2-(((1S,3S)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate (second eluting

diastereomer). First eluting diastereomer: LC-MS (1): t_R = 1.39 min; $[M+H]^+$: 764.1. Second eluting diastereomer: LC-MS (1): t_R = 1.39 min; $[M+H]^+$: 764.1.

Methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((1R,3R)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate and Methyl ((R)-N-(*tert*-butoxycarbonyl)-2-(((1R,3R)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate: Were synthesized using ((RS)-2-(((1R,3R)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridin-3-yl)sulfinyl)carbamate (second eluting diastereomer) and methyl L-prolinate hydrochloride in analogy to Example 2.5. The diastereomers were separated by FC (Hept to 40% EtOAc) to give methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((1R,3R)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate (first eluting diastereomer) and methyl ((R)-N-(*tert*-butoxycarbonyl)-2-(((1R,3R)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate (second eluting diastereomer). First eluting diastereomer: LC-MS (1): t_R = 1.40 min; $[M+H]^+$: 764.1. Second eluting diastereomer: LC-MS (1): t_R = 1.40 min; $[M+H]^+$: 764.1.

(1²S,5¹S,5³S,2S)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-2-imino-3⁶-methyl-2λ⁶-4-oxa-2 λ⁶-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide: Was synthesized using ((S)-N-(*tert*-butoxycarbonyl)-2-(((1S,3S)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate (first eluting diastereomer) and (3s,6s)-1,1-difluorospiro[2.5]octan-6-amine hydrochloride in analogy to Example 2.5 to give the title compound. LC-MS (1): t_R = 1.09 min; $[M+H]^+$: 537.0.

Example 2.45 to Example 2.50 were synthesized using methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((1S,3S)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate or methyl ((R)-N-(*tert*-butoxycarbonyl)-2-(((1S,3S)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate or ((S)-N-(*tert*-butoxycarbonyl)-2-(((1R,3R)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate or methyl ((R)-N-(*tert*-butoxycarbonyl)-2-(((1R,3R)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate and the appropriate amine or amine salt derivative in analogy to Example 2.44. LC-MS data of Example 2.45 to Example 2.50 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t_R	$[M+H]^+$
2.45	(1 ² S,5 ¹ S,5 ³ S,2R)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-2-imino-3 ⁶ -methyl-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide	1.10	537.0
2.46	(1 ² S,5 ¹ S,5 ³ S,2R)-8-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-2-imino-3 ⁶ -methyl-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide	0.86	509.0

2.47	(1 ² S,5 ¹ R,5 ³ R,2S)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-2-imino-3 ⁶ -methyl-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide	1.08	537.0
2.48	(1 ² S,5 ¹ R,5 ³ R,2S)-8-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-2-imino-3 ⁶ -methyl-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide	1.03	509.0
2.49	(1R,4s)-4-((1 ² S,5 ¹ S,5 ³ S,2S)-2-Imino-3 ⁶ -methyl-2-oxido-9-oxo-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphane-8-yl)-1-methylcyclohexane-1-carbonitrile	1.01	514.1
2.50	(1R,4s)-4-((1 ² S,5 ¹ R,5 ³ R,2R)-2-Imino-3 ⁶ -methyl-2-oxido-9-oxo-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphane-8-yl)-1-methylcyclohexane-1-carbonitrile	1.02	514.1

- Example 2.51 (1R,4s)-4-((1²S,5¹R,5³R,2S)-2-Imino-3⁶-methyl-2-oxido-9-oxo-2λ⁶-4-oxa-2λ⁶-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphane-8-yl)-1-methylcyclohexane-1-carbonitrile:**
***tert*-Butyl (RS)-((2-(benzyloxy)-6-methylpyridin-3-yl)sulfinyl)carbamate:** Was synthesized using 2-(benzyloxy)-
 5 3-bromo-6-methylpyridine and *tert*-butyl (oxo-λ4-sulfaneylidene)carbamate in analogy to Example 2.5 to give the title compound. LC-MS (1): *t_R*= 1.00 min; [M+H]⁺: 363.0.

- Methyl ((S)-2-(benzyloxy)-N-(*tert*-butoxycarbonyl)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate and Methyl ((R)-2-(benzyloxy)-N-(*tert*-butoxycarbonyl)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate:** Were synthesized using *tert*-butyl (RS)-((2-(benzyloxy)-6-methylpyridin-3-yl)sulfinyl)carbamate in analogy to Example
 10 2.5. The diastereomers were separated by FC (Hept/EtOAc 8:2 to 6:4) to give methyl ((S)-2-(benzyloxy)-N-(*tert*-butoxycarbonyl)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate (first eluting diastereomer) and ((R)-2-(benzyloxy)-N-(*tert*-butoxycarbonyl)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate (second eluting diastereomer). First eluting diastereomer: LC-MS (1): *t_R*= 1.07 min; [M+H]⁺: 490.31. Second eluting diastereomer: LC-MS (1): *t_R*= 1.06 min; [M+H]⁺: 490.3.
- 15 **Methyl ((S)-N-(*tert*-butoxycarbonyl)-2-hydroxy-6-methylpyridine-3-sulfonimidoyl)-L-prolinate:** Pd(OH)₂/C (20% wt, 12.3 g, 0.0175 mol, 0.25 eq) was added to a solution of give methyl ((S)-2-(benzyloxy)-N-(*tert*-butoxycarbonyl)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate (first eluting diastereomer) (34.2 g, 0.070 mol, 1 eq) in EtOAc (570 mL, 5.8 mol, 82.91 eq). The mixture was evacuated and purged with N₂ three times and with H₂ and stirred at rt under H₂ atmosphere for 2 h. The mixture was filtered through a Celite pad and the solvent removed
 20 under reduced pressure. The residue was redissolved in EtOAc (500 mL) and Pd(OH)₂ (20% wt, 8 g, 0.0113 mol, 0.163 eq) were added and the mixture was stirred for 1.5 h under H₂ atmosphere. The mixture was filtered through a Celite pad and the solvent removed under reduced pressure to give the title compound. LC-MS (1): *t_R*= 0.71 min; [M+H]⁺: 400.1.

Methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((1R,3R)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate: Was synthesized using methyl ((S)-N-(*tert*-butoxycarbonyl)-2-hydroxy-6-methylpyridine-3-sulfonimidoyl)-L-prolinate and (1S,3R)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexan-1-ol in analogy to Example 1.51 to give the title compound. LC-MS (1): t_R = 1.37 min; $[M+H]^+$: 764.6.

Methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((1R,3R)-3-(2-hydroxyethyl)cyclohexyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate: Was synthesized using methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((1R,3R)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate in analogy to Example 2.44 to give the title compound. LC-MS (1): t_R = 1.00 min; $[M+H]^+$: 526.1.

10 Methyl ((S)-N-(*tert*-butoxycarbonyl)-6-methyl-2-(((1R,3S)-3-(2-oxoethyl)cyclohexyl)oxy)pyridine-3-sulfonimidoyl)-L-prolinate: Was synthesized using methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((1R,3R)-3-(2-hydroxyethyl)cyclohexyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate in analogy to Example 2.5 to give the title compound. LC-MS (1): t_R = 1.09 min; $[M+H]^+$: 524.2.

Methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((1R,3R)-3-(2-(((1S,4S)-4-cyano-4-methylcyclohexyl)amino)ethyl)cyclohexyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate: Was synthesized using methyl ((S)-N-(*tert*-butoxycarbonyl)-6-methyl-2-(((1R,3S)-3-(2-oxoethyl)cyclohexyl)oxy)pyridine-3-sulfonimidoyl)-L-prolinate and *cis*-4-amino-1-methyl-cyclohexanecarbonitrile hydrochloride in analogy to Example 2.5 to give the title compound. LC-MS (1): t_R = 0.87 min; $[M+H]^+$: 646.4.

20 ((S)-N-(*tert*-butoxycarbonyl)-2-(((1R,3R)-3-(2-(((1S,4S)-4-cyano-4-methylcyclohexyl)amino)ethyl)cyclohexyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-proline: Was synthesized using methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((1R,3R)-3-(2-(((1S,4S)-4-cyano-4-methylcyclohexyl)amino)ethyl)cyclohexyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate in analogy to Example 2.5 to give the title compound. LC-MS (1): t_R = 0.82 min; $[M+H]^+$: 632.5.

***tert*-Butyl ((1²S,5¹R,5³R,2S)-8-((1S,4R)-4-cyano-4-methylcyclohexyl)-3⁶-methyl-2-oxido-9-oxo-2 λ^6 -4-oxa-2 λ^6 -thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphane-2-ylidene)carbamate:** Was synthesized using ((S)-N-(*tert*-butoxycarbonyl)-2-(((1R,3R)-3-(2-(((1S,4S)-4-cyano-4-methylcyclohexyl)amino)ethyl)cyclohexyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-proline in analogy to Example 2.5 to give the title compound. LC-MS (1): t_R = 1.15 min; $[M+H]^+$: 614.1.

30 (1R,4s)-4-((1²S,5¹R,5³R,2S)-2-Imino-3⁶-methyl-2-oxido-9-oxo-2 λ^6 -4-oxa-2 λ^6 -thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphane-8-yl)-1-methylcyclohexane-1-carbonitrile: Was synthesized using *tert*-butyl ((1²S,5¹R,5³R,2S)-8-((1S,4R)-4-cyano-4-methylcyclohexyl)-3⁶-methyl-2-oxido-9-oxo-2 λ^6 -4-oxa-2 λ^6 -thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphane-2-ylidene)carbamate in analogy to Example 2.5 to give the title compound. LC-MS (1): t_R = 1.01 min; $[M+H]^+$: 514.1.

Example 2.52 (1R,4s)-4-((1²S,5¹S,5³S,2R)-2-Imino-3⁶-methyl-2-oxido-9-oxo-2λ⁶-4-oxa-2λ⁶-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphane-8-yl)-1-methylcyclohexane-1-carbonitrile:
Was synthesized using methyl ((R)-N-(*tert*-butoxycarbonyl)-2-(((1S,3S)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate and *cis*-4-amino-1-methyl-cyclohexanecarbonitrile hydrochloride in analogy to Example 2.51 to give the title compound. LC-MS (1): t_R= 1.01 min; [M+H]⁺: 514.0.

Example 2.53 to **Example 2.59** were synthesized using the appropriate precursor and MeI in analogy to Example 2.1. LC-MS data of Example 2.53 to Example 2.59 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
2.53	(1 ² S,5 ¹ S,5 ³ S,2S)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3 ⁶ -methyl-2-(methylimino)-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide	1.06	551.1
2.54	(1R,4s)-1-Methyl-4-((1 ² S,5 ¹ S,5 ³ S,2S)-3 ⁶ -methyl-2-(methylimino)-2-oxido-9-oxo-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile	0.98	528.1
2.55	(1 ² S,5 ¹ R,5 ³ R,2R)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3 ⁶ -methyl-2-(methylimino)-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide	1.08	551.0
2.56	(1 ² S,5 ¹ R,5 ³ R,2R)-8-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-3 ⁶ -methyl-2-(methylimino)-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide	1.05	523.0
2.57	(1R,4s)-1-Methyl-4-((1 ² S,5 ¹ R,5 ³ R,2R)-3 ⁶ -methyl-2-(methylimino)-2-oxido-9-oxo-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile	1.01	528.1
2.58	(1 ² S,5 ¹ R,5 ³ R,2S)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3 ⁶ -methyl-2-(methylimino)-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide	1.05	551.1
2.59	(1 ² S,5 ¹ R,5 ³ R,2S)-8-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-3 ⁶ -methyl-2-(methylimino)-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide	1.01	523.0

Example 2.60 (1R,4s)-1-Methyl-4-((1²S,5¹R,5³R,2S)-3⁶-methyl-2-(methylimino)-2-oxido-9-oxo-2λ⁶-4-oxa-2λ⁶-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile: Was synthesized using (1R,4s)-4-((1²S,5¹R,5³R,2S)-2-imino-3⁶-methyl-2-oxido-9-oxo-2λ⁶-4-oxa-2λ⁶-thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphane-8-yl)-1-methylcyclohexane-1-carbonitrile (Example 2.51) and Mel in analogy to Example 2.1 to give the title compound. LC-MS (1): t_R= 0.97 min; [M+H]⁺: 528.0.

Example 2.61 and **Example 2.62** were synthesized using methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((1R,3R)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate or methyl ((R)-N-(*tert*-butoxycarbonyl)-2-(((1R,3R)-3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate and 4,4-difluorocyclohexan-1-amine in analogy to Example 2.44. LC-MS data of Example 2.61 and Example 2.62 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
2.61	(1 ² S,5 ¹ R,5 ³ R,2R)-8-(4,4-Difluorocyclohexyl)-2-imino-3 ⁶ -methyl-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide	1.04	511.0
2.62	(1 ² S,5 ¹ R,5 ³ R,2S)-8-(4,4-Difluorocyclohexyl)-2-imino-3 ⁶ -methyl-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide	1.02	511.0

Example 2.63 and **Example 2.64** were synthesized using the appropriate precursor and Mel in analogy to Example 2.1. LC-MS data of Example 2.63 and Example 2.64 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
2.63	(1 ² S,5 ¹ R,5 ³ R,2S)-8-(4,4-Difluorocyclohexyl)-3 ⁶ -methyl-2-(methylimino)-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide	1.00	525.0
2.64	(6R,12aS,17S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-4-fluoro-3,6-dimethyl-17-(methylimino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ ⁴ -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide	1.02	542.3

Example 2.65 (6R,12aS,17S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-4-fluoro-17-imino-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide: Was synthesized using (R)-((5-(6-bromo-2-fluoro-3-methylphenoxy)hexyl)oxy)(*tert*-butyl)dimethylsilane and methyl L-prolinate hydrochloride in analogy to Example 5 2.43 to give the title compound. LC-MS (1): t_R = 1.05 min; $[M+H]^+$: 528.0.

Example 2.66 (6R,11aS,16S)-10-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-16-imino-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydro-16H-16 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16-oxide: (R)-3-Bromo-2-((5-((*tert*-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-6-methylpyridine: Was synthesized using 3-bromo-6-methylpyridin-2-ol and (S)-5-((*tert*-butyldimethylsilyl)oxy)pentan-2-ol in analogy to Example 1.51 to give the title compound. LC-MS (1): t_R = 1.32 min; $[M+H]^+$: 388.2.

tert-Butyl ((2-(((R)-5-((*tert*-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfinyl)carbamate: Was synthesized using (R)-3-bromo-2-((5-((*tert*-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-6-methylpyridine and *tert*-butyl (oxo- λ^4 -sulfaneylidene)carbamate in analogy to Example 2.5 to give the title compound. LC-MS (1): t_R = 1.23 and 1.24 min; $[M+H]^+$: 473.3.

Methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((R)-5-((*tert*-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate and Methyl ((R)-N-(*tert*-butoxycarbonyl)-2-(((R)-5-((*tert*-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate: Were synthesized using *tert*-butyl ((2-(((R)-5-((*tert*-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-6-methylpyridin-3-yl)sulfinyl)carbamate and L-proline methyl ester hydrochloride in analogy to Example 2.5. The residue was purified by FC (Hept to 40% EtOAc) to give methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((R)-5-((*tert*-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate (first eluting diastereomer) and methyl ((R)-N-(*tert*-butoxycarbonyl)-2-(((R)-5-((*tert*-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate (second eluting diastereomer). First eluting diastereomer: LC-MS (1): t_R = 1.30 min; $[M+H]^+$: 600.4. Second eluting diastereomer: LC-MS (1): t_R = 1.29 min; $[M+H]^+$: 600.4.

Methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((R)-5-hydroxypentan-2-yl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate: Was synthesized using ((S)-N-(*tert*-butoxycarbonyl)-2-(((R)-5-((*tert*-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate (first eluting diastereomer) in analogy to Example 2.4 to give the title compound. LC-MS (1): t_R = 0.93 min; $[M+H]^+$: 486.3.

Methyl ((S)-N-(*tert*-butoxycarbonyl)-6-methyl-2-(((R)-5-oxopentan-2-yl)oxy)pyridine-3-sulfonimidoyl)-L-prolinate: Was synthesized using methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((R)-5-hydroxypentan-2-yl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate in analogy to Example 2.5 to give the title compound. LC-MS (1): t_R = 0.98 min; $[M+H]^+$: 483.8.

(6R,11aS,16S)-10-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-16-imino-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydro-16H-16 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16-oxide:

Was synthesized using methyl ((S)-N-(*tert*-butoxycarbonyl)-6-methyl-2-(((R)-5-oxopentan-2-yl)oxy)pyridine-3-sulfonimidoyl)-L-prolinate and (3s,6s)-1,1-difluorospiro[2.5]octan-6-amine hydrochloride in analogy to Example 2.5 to give the title compound. LC-MS (1): t_R = 0.99 min; [M+H]⁺: 496.9.

Example 2.67 (6R,11aS,16R)-10-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-16-imino-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydro-16H-16 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16-oxide:

Methyl ((R)-N-(*tert*-butoxycarbonyl)-6-methyl-2-(((R)-5-oxopentan-2-yl)oxy)pyridine-3-sulfonimidoyl)-L-prolinate: Was synthesized using methyl ((R)-N-(*tert*-butoxycarbonyl)-2-(((R)-5-((*tert*-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate (second eluting diastereomer) in analogy to Example 2.5 to give the title compound: LC-MS (1): t_R = 0.97 min; [M+H]⁺: 483.8.

(6R,11aS,16R)-10-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-16-imino-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydro-16H-16 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16-oxide:

Was synthesized using methyl ((R)-N-(*tert*-butoxycarbonyl)-6-methyl-2-(((R)-5-oxopentan-2-yl)oxy)pyridine-3-sulfonimidoyl)-L-prolinate and (3s,6s)-1,1-difluorospiro[2.5]octan-6-amine hydrochloride in analogy to Example 2.4 to give the title compound. LC-MS (1): t_R = 1.00 min; [M+H]⁺: 496.9.

Example 2.68 (6R,11aS,16R)-10-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-16-imino-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydro-16H-16 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16-oxide:

Was synthesized using methyl ((R)-N-(*tert*-butoxycarbonyl)-6-methyl-2-(((R)-5-oxopentan-2-yl)oxy)pyridine-3-sulfonimidoyl)-L-prolinate and (3s,5s)-1,1-difluorospiro[2.3]hexan-5-amine hydrochloride in analogy to Example 2.5 to give the title compound. LC-MS (1): t_R = 0.94 min; [M+H]⁺: 469.0

Example 2.69 (6R,11aS,16S)-10-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-16-(methylimino)-7,8,9,10,11a,12,13,14-octahydro-16H-16 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16-oxide:

Was synthesized using (6R,11aS,16S)-10-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-16-imino-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydro-16H-16 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16-oxide and MeI in analogy to Example 2.5 to give the title compound. LC-MS (1): t_R = 0.97 min; [M+H]⁺: 511.0.

Example 2.70 (6R,11aS,16S)-10-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-3,6-dimethyl-16-(methylimino)-7,8,9,10,11a,12,13,14-octahydro-16H-16 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16-oxide:

was synthesized using methyl ((S)-N-(*tert*-butoxycarbonyl)-6-methyl-2-(((R)-5-oxopentan-2-yl)oxy)pyridine-3-sulfonimidoyl)-L-prolinate and (3s,5s)-1,1-difluorospiro[2.3]hexan-5-amine hydrochloride in analogy to Example 2.5 to give the title compound. LC-MS (1): t_R = 0.92 min; [M+H]⁺: 483.0.

Example 2.71 (1R,4s)-4-((6R,12aS,17S)-4-Fluoro-17-imino-3,6-dimethyl-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile: Was synthesized using (R)-((5-(6-bromo-2-fluoro-3-methylphenoxy)hexyl)oxy)(*tert*-butyl)dimethylsilane and *cis*-4-amino-1-methyl-cyclohexanecarbonitrile hydrochloride in analogy to Example 2.5 to give the title compound. LC-MS (1): t_R= 0.98 min; [M+H]⁺: 505.2.

Example 2.72 (6R,11aS,16S)-10-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-16-(methylimino)-7,8,9,10,11a,12,13,14-octahydro-16H-16λ⁴-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16-oxide: Was synthesized using (1R,4s)-4-((6R,12aS,17S)-4-fluoro-17-imino-3,6-dimethyl-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile and MeI in analogy to Example 2.4 to give the title compound. LC-MS (1): t_R= 0.93 min; [M+H]⁺: 519.3.

Example 2.73 to Example 2.75 were synthesized using the appropriate amine or amine salt derivative and 3-bromo-2-((5-((*tert*-butyldimethylsilyl)oxy)pentyl)oxy)-6-methylpyridine in analogy to Example 2.5. LC-MS data of Example 2.73 to Example 2.75 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
2.73	(12aS,17R)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-17-imino-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ ⁴ -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide	0.97	496.9
2.75	(12aS,17S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-17-imino-3-methyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ ⁴ -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide	1.01	497.0

Example 2.76 (1R,4s)-4-((6R,11aS,16S)-16-Imino-3,6-dimethyl-16-oxido-11-oxo-6,7,8,9,11a,12,13,14-octahydro-16H-16λ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-yl)cyclohexane-1-carbonitrile:

(R)-((4-(2-Bromo-5-methylphenoxy)pentyl)oxy)(*tert*-butyl)dimethylsilane: Was synthesized using (S)-5-((*tert*-butyldimethylsilyl)oxy)pentan-2-ol and 2-bromo-5-methylphenol in analogy to Example 2.5 to give the title compound. LC-MS (1): t_R= 1.31 min; [M+H]⁺: 389.3.

***tert*-Butyl ((2-(((R)-5-((*tert*-butyldimethylsilyl)oxy)pentan-2-yl)oxy)-4-methylphenyl)sulfinyl)carbamate:** Was synthesized using (R)-((4-(2-bromo-5-methylphenoxy)pentyl)oxy)(*tert*-butyl)dimethylsilane and *tert*-butyl (oxo-λ⁴-sulfaneylidene)carbamate in analogy to Example 2.5 to give the title compound. LC-MS (1): t_R= 1.22 and 1.23 min; [M+H]⁺: 472.3.

Methyl ((S)-N-(tert-butoxycarbonyl)-2-(((R)-5-((tert-butylidimethylsilyl)oxy)pentan-2-yl)oxy)-4-methylphenylsulfonimidoyl)-L-prolinate and Methyl ((R)-N-(tert-butoxycarbonyl)-2-(((R)-5-((tert-butylidimethylsilyl)oxy)pentan-2-yl)oxy)-4-methylphenylsulfonimidoyl)-L-prolinate: Was synthesized using *tert*-butyl ((2-(((R)-5-((tert-butylidimethylsilyl)oxy)pentan-2-yl)oxy)-4-methylphenyl)sulfinyl)carbamate and L-proline methyl ester hydrochloride in analogy to Example 2.5. The residue was purified by FC (Hept to 50% EtOAc) to give methyl ((S)-N-(tert-butoxycarbonyl)-2-(((R)-5-((tert-butylidimethylsilyl)oxy)pentan-2-yl)oxy)-4-methylphenylsulfonimidoyl)-L-prolinate (first eluting diastereomer) and methyl ((R)-N-(tert-butoxycarbonyl)-2-(((R)-5-((tert-butylidimethylsilyl)oxy)pentan-2-yl)oxy)-4-methylphenylsulfonimidoyl)-L-prolinate (second eluting diastereoisomer). First eluting diastereomer: LC-MS (1): t_R = 1.25 min; $[M+H]^+$: 599.1. Second eluting diastereomer: LC-MS (1): t_R = 1.25 min; $[M+H]^+$: 599.1.

Methyl ((S)-N-(tert-butoxycarbonyl)-2-(((R)-5-hydroxypentan-2-yl)oxy)-4-methylphenylsulfonimidoyl)-L-prolinate: Was synthesized using methyl ((S)-N-(tert-butoxycarbonyl)-2-(((R)-5-((tert-butylidimethylsilyl)oxy)pentan-2-yl)oxy)-4-methylphenylsulfonimidoyl)-L-prolinate (first eluting diastereomer) in analogy to Example 2.5 to give the title compound. LC-MS (1): t_R = 0.92 min; $[M+H]^+$: 485.3.

Methyl ((S)-N-(tert-butoxycarbonyl)-4-methyl-2-(((R)-5-oxopentan-2-yl)oxy)phenylsulfonimidoyl)-L-prolinate: Was synthesized using methyl ((S)-N-(tert-butoxycarbonyl)-2-(((R)-5-hydroxypentan-2-yl)oxy)-4-methylphenylsulfonimidoyl)-L-prolinate in analogy to Example 2.5 to give the title compound. LC-MS (1): t_R = 0.96 min; $[M+H]^+$: 483.0.

(1R,4s)-4-((6R,11aS,16S)-16-Imino-3,6-dimethyl-16-oxido-11-oxo-6,7,8,9,11a,12,13,14-octahydro-16H-16 λ ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-yl)cyclohexane-1-carbonitrile: Was synthesized using methyl ((S)-N-(tert-butoxycarbonyl)-4-methyl-2-(((R)-5-oxopentan-2-yl)oxy)phenylsulfonimidoyl)-L-prolinate and (1s,4s)-4-aminocyclohexanecarbonitrile hydrochloride in analogy to Example 2.5 to give the title compound. LC-MS (1): t_R = 0.81 min; $[M+H]^+$: 459.1.

Example 2.77 (1R,4s)-4-((6R,11aS,16R)-16-Imino-3,6-dimethyl-16-oxido-11-oxo-6,7,8,9,11a,12,13,14-octahydro-16H-16 λ ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-yl)cyclohexane-1-carbonitrile:

Methyl ((R)-N-(tert-butoxycarbonyl)-2-(((R)-5-hydroxypentan-2-yl)oxy)-4-methylphenylsulfonimidoyl)-L-prolinate: Was synthesized using methyl ((R)-N-(tert-butoxycarbonyl)-2-(((R)-5-((tert-butylidimethylsilyl)oxy)pentan-2-yl)oxy)-4-methylphenylsulfonimidoyl)-L-prolinate (second eluting diastereoisomer) in analogy to Example 2.5 to give the title compound. LC-MS (1): t_R = 0.91 min; $[M+H]^+$: 485.0.

Methyl ((R)-N-(tert-butoxycarbonyl)-4-methyl-2-(((R)-5-oxopentan-2-yl)oxy)phenylsulfonimidoyl)-L-prolinate: Was synthesized using methyl ((R)-N-(tert-butoxycarbonyl)-2-(((R)-5-hydroxypentan-2-yl)oxy)-4-methylphenylsulfonimidoyl)-L-prolinate in analogy to Example 2.5. LC-MS (1): t_R = 0.95 min; $[M+H]^+$: 483.0.

(1R,4s)-4-((6R,11aS,16R)-16-Imino-3,6-dimethyl-16-oxido-11-oxo-6,7,8,9,11a,12,13,14-octahydro-16H-16λ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-yl)cyclohexane-1-carbonitrile: Was synthesized using methyl ((R)-N-(*tert*-butoxycarbonyl)-4-methyl-2-(((R)-5-oxopentan-2-yl)oxy)phenylsulfonimidoyl)-L-prolinate in analogy to Example 2.5 to give the title compound. LC-MS (1): t_R= 0.83 min; [M+H]⁺: 459.2.

Example 2.78 to Example 2.95 were synthesized using the appropriate scaffold and the appropriate amine or amine salt derivative in analogy to the examples reported herein before. LC-MS data of Example 2.78 to Example 2.95 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
2.78	(1R,4s)-4-((6R,11aS,16S)-16-Imino-3,6-dimethyl-16-oxido-11-oxo-6,7,8,9,11a,12,13,14-octahydro-16H-16λ ⁴ -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-yl)-1-methylcyclohexane-1-carbonitrile	0.86	473.1
2.79	(1R,4s)-4-((6R,11aS,16R)-16-Imino-3,6-dimethyl-16-oxido-11-oxo-6,7,8,9,11a,12,13,14-octahydro-16H-16λ ⁴ -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-yl)-1-methylcyclohexane-1-carbonitrile	0.88	473.2
2.80	(1R,4s)-4-((6R,11aS,16S)-3,6-Dimethyl-16-(methylimino)-16-oxido-11-oxo-6,7,8,9,11a,12,13,14-octahydro-16H-16λ ⁴ -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-yl)cyclohexane-1-carbonitrile	0.78	473.1
2.81	(1R,4s)-4-((6R,11aS,16S)-3,6-Dimethyl-16-(methylimino)-16-oxido-11-oxo-6,7,8,9,11a,12,13,14-octahydro-16H-16λ ⁴ -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-yl)-1-methylcyclohexane-1-carbonitrile	0.82	487.0
2.82	(1R,4s)-4-((6R,11aS,16R)-3,6-Dimethyl-16-(methylimino)-16-oxido-11-oxo-6,7,8,9,11a,12,13,14-octahydro-16H-16λ ⁴ -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-10(11H)-yl)-1-methylcyclohexane-1-carbonitrile	0.84	487.0
2.83	(1R,4s)-4-((6R,12aS,17S)-17-Imino-3,6-dimethyl-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ ⁴ -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	0.92	488.2
2.84	(1R,4s)-4-((6R,12aS,17S)-17-Imino-3,6-dimethyl-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ ⁴ -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.88	474.2

2.85	(1S,3S)-3-((6R,12aS,17S)-17-Imino-3,6-dimethyl-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.89	474.2
2.86	(1R,4s)-4-((6R,12aS,17S)-17-Imino-3,6-dimethyl-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17 λ^4 -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	0.86	487.2
2.87	(1R,4s)-4-((6R,12aS,17S)-17-Imino-3,6-dimethyl-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17 λ^4 -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.82	473.2
2.88	(1S,3S)-3-((6R,12aS,17S)-17-Imino-3,6-dimethyl-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17 λ^4 -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.83	473.2
2.89	(1R,4s)-4-((6R,12aS,17S)-3,6-Dimethyl-17-(methylimino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	0.90	502.2
2.90	(1S,3S)-3-((6R,12aS,17S)-3,6-Dimethyl-17-(methylimino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.87	488.2
2.92	(1R,4s)-4-((6R,12aS,17S)-3,6-Dimethyl-17-(methylimino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17 λ^4 -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	0.85	501.2
2.93	(1S,3S)-3-((6R,12aS,17S)-3,6-Dimethyl-17-(methylimino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17 λ^4 -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.82	487.2
2.94	(1R,4s)-4-((6R,12aS,17S)-3,6-Dimethyl-17-(methylimino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.85	488.2
2.95	(1R,4s)-4-((6R,12aS,17S)-3,6-Dimethyl-17-(methylimino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17 λ^4 -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.80	487.2

Example 2.96 (8R,12aS,17S)-11-(4,4-Difluorocyclohexyl)-3,8-dimethyl-17-(methylimino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide:

(S)-3-Bromo-2-((5-((*tert*-butyldiphenylsilyl)oxy)-3-methylpentyl)oxy)-6-methylpyridine: Was synthesized using (S)-5-((*tert*-butyldiphenylsilyl)oxy)-3-methylpentan-1-ol and 3-bromo-6-methylpyridin-2-ol in analogy to example 1.51 to give the title compound. LC-MS (1): t_R = 1.41 min; $[M+H]^+$: 526.0.

***tert*-Butyl ((2-(((S)-5-((*tert*-butyldiphenylsilyl)oxy)-3-methylpentyl)oxy)-6-methylpyridin-3-yl)sulfinyl)carbamate:** Was synthesized using (S)-3-bromo-2-((5-((*tert*-butyldiphenylsilyl)oxy)-3-methylpentyl)oxy)-6-methylpyridine and *tert*-butyl (oxo- λ 4-sulfaneylidene)carbamate in analogy to Example 2.5 to give the title compound. LC-MS (1): t_R = 1.34; $[M+H]^+$: 611.0.

Methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((S)-5-((*tert*-butyldiphenylsilyl)oxy)-3-methylpentyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate and Methyl ((R)-N-(*tert*-butoxycarbonyl)-2-(((S)-5-((*tert*-butyldiphenylsilyl)oxy)-3-methylpentyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate: Were synthesized using *tert*-butyl ((2-(((S)-5-((*tert*-butyldiphenylsilyl)oxy)-3-methylpentyl)oxy)-6-methylpyridin-3-yl)sulfinyl)carbamate and L-proline methyl ester hydrochloride in analogy to Example 2.5. The residue was purified by FC (Hept to 40% EtOAc) to give methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((S)-5-((*tert*-butyldiphenylsilyl)oxy)-3-methylpentyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate (first eluting diastereomer) and methyl ((R)-N-(*tert*-butoxycarbonyl)-2-(((S)-5-((*tert*-butyldiphenylsilyl)oxy)-3-methylpentyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate (second eluting diastereoisomer). First eluting diastereomer: LC-MS (1): t_R = 1.37 min; $[M+H]^+$: 738.0. Second eluting diastereomer: LC-MS (1): t_R = 1.37 min; $[M+H]^+$: 738.0.

Methyl (N-(*tert*-butoxycarbonyl)-2-(((R)-5-hydroxy-3-methylpentyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate: Was synthesized using methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((S)-5-((*tert*-butyldiphenylsilyl)oxy)-3-methylpentyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate (first eluting diastereomer) in analogy to Example 2.5 to give the title compound. LC-MS (1): t_R = 0.96 min; $[M+H]^+$: 500.0.

Methyl (N-(*tert*-butoxycarbonyl)-6-methyl-2-(((S)-3-methyl-5-oxopentyl)oxy)pyridine-3-sulfonimidoyl)-L-prolinate: Was synthesized using methyl (N-(*tert*-butoxycarbonyl)-2-(((R)-5-hydroxy-3-methylpentyl)oxy)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate in analogy to example 2.5 to give the title compound. LC-MS (1): t_R = 1.01 min; $[M+H]^+$: 498.1.

(8R,12aS,17S)-11-(4,4-Difluorocyclohexyl)-3,8-dimethyl-17-(methylimino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide: Was synthesized using methyl (N-(*tert*-butoxycarbonyl)-6-methyl-2-(((S)-3-methyl-5-oxopentyl)oxy)pyridine-3-sulfonimidoyl)-L-prolinate and 4,4-difluorocyclohexylamine hydrochloride in analogy to Example 2.5 to give the title compound. LC-MS (1): t_R = 0.95 min; $[M+H]^+$: 499.0.

Example 2.97 to Example 2.109 were synthesized using the appropriate scaffold and the appropriate amine or amine salt derivative in analogy to the examples reported herein before. LC-MS data of Example 2.97 to Example 2.109 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
2.97	(8R,12aS,17S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-17-imino-3,8-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ ⁴ -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide	1.01	511.1
2.98	(1R,4s)-4-((6R,12aS,17S)-4-Fluoro-17-imino-3,6-dimethyl-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ ⁴ -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.92	491.2
2.99	(8R,12aS,17S)-11-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-17-imino-3,8-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ ⁴ -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide	0.97	483.1
2.100	(1R,4s)-4-((8R,12aS,17S)-17-Imino-3,8-dimethyl-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ ⁴ -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.88	474.2
2.101	(1R,4s)-4-((8R,12aS,17S)-17-Imino-3,8-dimethyl-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ ⁴ -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	0.93	488.2
2.102	(8R,12aS,17S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,8-dimethyl-17-(methylimino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ ⁴ -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide	0.99	525.1
2.103	(8R,12aS,17S)-11-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-3,8-dimethyl-17-(methylimino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ ⁴ -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide	0.96	497.0
2.104	(1R,4s)-4-((8R,12aS,17S)-3,8-Dimethyl-17-(methylimino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ ⁴ -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	0.92	501.8
2.105	(1R,4s)-4-((8R,12aS,17S)-17-Imino-3,8-dimethyl-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ ⁴ -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	0.91	487.1

2.106	(1R,4s)-4-((8R,12aS,17S)-17-Imino-3,8-dimethyl-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ ⁴ -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	0.98	510.1
2.107	(1R,4s)-4-((8R,12aS,17S)-3,8-Dimethyl-17-(methylinimo)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ ⁴ -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	0.91	501.1
2.108	(8R,12aS,17S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,8-dimethyl-17-(methylinimo)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ ⁴ -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide	0.98	524.1
2.109	(1R,4s)-4-((8R,12aS,17S)-3,8-Dimethyl-17-(methylinimo)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ ⁴ -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.91	488.1

Example 2.110 (1R,4s)-4-((8R,12aS,17S)-4-Fluoro-3,8-dimethyl-17-(methylinimo)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile: Was synthesized using 2-fluoro-3-methyl-6-bromophenol, (S)-5-((*tert*-butyldiphenylsilyl)oxy)-3-methylpentan-1-ol, the appropriate amine or amine salt derivative in analogy to Example 2.5. The mixture was purified by acidic prep. HPLC to give the title compound (first eluting diastereomer). LC-MS (1): *t_R* = 1.08 min; [M+H]⁺: 519.1.

Example 2.111 (1³R,4²S,3S)-6-(4,4-Difluorocyclohexyl)-2⁶-methyl-3-(methylinimo)-3λ⁶-3 λ⁶-thia-6-aza-2(2,3)-pyridina-1(1,3),4(1,2)-dipyrrolidinacyclononaphan-5-one 3-oxide:

***tert*-Butyl ((2-chloro-6-methylpyridin-3-yl)sulfinyl)carbamate:** Was synthesized using 5-bromo-6-chloro-2-picoline and *tert*-butyl (oxo-λ⁴-sulfaneylidene)carbamate in analogy to Example 2.5 to give the title compound. LC-MS (1): *t_R* = 0.79 min; [M+H]⁺: 291.1.

Methyl ((S)-N-(*tert*-butoxycarbonyl)-2-chloro-6-methylpyridine-3-sulfonimidoyl)-L-prolinate and Methyl ((R)-N-(*tert*-butoxycarbonyl)-2-chloro-6-methylpyridine-3-sulfonimidoyl)-L-prolinate: Were synthesized using *tert*-butyl ((2-chloro-6-methylpyridin-3-yl)sulfinyl)carbamate and methyl *L*-prolinate hydrochloride in analogy to Example 2.5. The diastereomers were separated by FC (Hept to 35% EtOAc) to give methyl ((S)-N-(*tert*-butoxycarbonyl)-2-chloro-6-methylpyridine-3-sulfonimidoyl)-L-prolinate (first eluting diastereomer) and methyl ((R)-N-(*tert*-butoxycarbonyl)-2-chloro-6-methylpyridine-3-sulfonimidoyl)-L-prolinate (second eluting diastereomer). First eluting diastereomer: LC-MS (1): *t_R* = 0.91 min; [M+H]⁺: 418.0. Second eluting diastereomer: LC-MS (1): *t_R* = 0.91 min; [M+H]⁺: 418.0.

Methyl ((S)-N-(*tert*-butoxycarbonyl)-2-((R)-3-(3-hydroxypropyl)pyrrolidin-1-yl)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate: A mixture of methyl ((S)-N-(*tert*-butoxycarbonyl)-2-chloro-6-methylpyridine-3-sulfonimidoyl)-L-prolinate (first eluting diastereomer) (1.00 g, 2.39 mmol, 1 eq), (*R*)-3-(pyrrolidin-3-yl)propan-1-ol hydrochloride (700 mg, 4.23 mmol, 1.77 eq) and DIPEA (2 mL, 12.00 mmol, 5 eq) was stirred at 120°C for 3h30.

5 The mixture was partitioned between EtOAc and brine. The org. layer was separated, dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R= 0.90 min; [M+H]⁺: 511.2.

Methyl ((S)-N-(*tert*-butoxycarbonyl)-6-methyl-2-((R)-3-(3-oxopropyl)pyrrolidin-1-yl)pyridine-3-sulfonimidoyl)-L-prolinate: Was synthesized using methyl ((S)-N-(*tert*-butoxycarbonyl)-2-((R)-3-(3-hydroxypropyl)pyrrolidin-1-yl)-6-methylpyridine-3-sulfonimidoyl)-L-prolinate in analogy to Example 2.5 to give the title compound. LC-MS (1): t_R= 0.97 min; [M+H]⁺: 509.2.

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(1³R,4²S,3S)-6-(4,4-Difluorocyclohexyl)-2⁶-methyl-3-(methylimino)-3λ⁶-3 λ⁶-thia-6-aza-2(2,3)-pyridina-1(1,3),4(1,2)-dipyrrolidinacyclononaphan-5-one 3-oxide: Was synthesized using methyl methyl ((S)-N-(*tert*-butoxycarbonyl)-6-methyl-2-((R)-3-(3-oxopropyl)pyrrolidin-1-yl)pyridine-3-sulfonimidoyl)-L-prolinate and 4,4-difluorocyclohexan-1-amine hydrochloride in analogy to Example 2.5 to give the title compound. LC-MS (2): t_R= 0.93 min; [M+H]⁺: 510.3.

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Example 2.112 (1²S,5¹R,5³R,2R)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-2-imino-3⁴-methyl-2λ⁶-4-oxa-2λ⁶-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide:

(2-(((1R,3R)-3-(2-Bromo-5-methylphenoxy)cyclohexyl)ethoxy)(*tert*-butyl)diphenylsilane: Was synthesized using 2-bromo-5-methylphenol and (1S,3R)-3-(2-(((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexan-1-ol in analogy to example 2.5 to give the title compound. LC-MS (1): t_R= 0.97 min; [M+H]⁺: 536.0.

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***tert*-Butyl ((2-(((1R,3R)-3-(2-(((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfinyl)carbamate:** Was synthesized using (2-(((1R,3R)-3-(2-Bromo-5-methylphenoxy)cyclohexyl)ethoxy)(*tert*-butyl)diphenylsilane and *tert*-butyl (oxo-λ⁴-sulfaneylidene)carbamate in analogy to Example 2.5 to give the title compound. LC-MS (1): t_R= 1.31 and 1.32 min; [M+H]⁺: 636.3.

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Methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((1R,3R)-3-(2-(((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-4-methylphenylsulfonimidoyl)-L-prolinate and Methyl ((R)-N-(*tert*-butoxycarbonyl)-2-(((1R,3R)-3-(2-(((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-4-methylphenylsulfonimidoyl)-L-prolinate: Was synthesized using *tert*-butyl ((2-(((1R,3R)-3-(2-(((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-4-methylphenyl)sulfinyl)carbamate and methyl L-prolinate hydrochloride in analogy to Example 2.5. The diastereomers were separated by FC (Hept to 50% EtOAc) to give methyl methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((1R,3R)-3-(2-(((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-4-methylphenylsulfonimidoyl)-L-prolinate (first eluting diastereomer) and methyl ((R)-N-(*tert*-butoxycarbonyl)-2-(((1R,3R)-3-(2-(((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-4-methylphenylsulfonimidoyl)-L-prolinate (second eluting

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diastereomer). First eluting diastereomer: LC-MS (1): *t_R*= 1.35 min; [M+H]⁺: 763.35. Second eluting diastereomer: LC-MS (1): *t_R*= 0.91 min; [M+H]⁺: 763.35.

Methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((1R,3R)-3-(2-hydroxyethyl)cyclohexyl)oxy)-4-methylphenylsulfonimidoyl)-L-prolinate: Was synthesized using methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((1R,3R)-3-(2-(((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-4-methylphenylsulfonimidoyl)-L-prolinate in analogy to Example 2.4 to give the title compound. LC-MS (1): *t_R*= 0.98 min; [M+H]⁺: 525.22.

Methyl ((S)-N-(*tert*-butoxycarbonyl)-4-methyl-2-(((1R,3S)-3-(2-oxoethyl)cyclohexyl)oxy)phenylsulfonimidoyl)-L-prolinate: Was synthesized using methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((1R,3R)-3-(2-hydroxyethyl)cyclohexyl)oxy)-4-methylphenylsulfonimidoyl)-L-prolinate in analogy to Example 2.5 to give the title compound. LC-MS (1): *t_R*= 1.03 min; [M+H]⁺: 522.95.

(1²S,5¹R,5³R,2R)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-2-imino-3⁴-methyl-2λ⁶-4-oxa-2λ⁶-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide: Was synthesized using methyl ((S)-N-(*tert*-butoxycarbonyl)-4-methyl-2-(((1R,3S)-3-(2-oxoethyl)cyclohexyl)oxy)phenylsulfonimidoyl)-L-prolinate and (3s,6s)-1,1-difluorospiro[2.5]octan-6-amine hydrochloride in analogy to Example 2.5 to give the title compound. LC-MS (1): *t_R*= 0.97 min; [M+H]⁺: 536.0.

Example 2.113 (1²S,5¹R,5³R,2S)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-2-imino-3⁴-methyl-2λ⁶-4-oxa-2λ⁶-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide: Was synthesized ((R)-N-(*tert*-butoxycarbonyl)-2-(((1R,3R)-3-(2-(((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclohexyl)oxy)-4-methylphenylsulfonimidoyl)-L-prolinate (second eluting diastereomer) in analogy to Example 2.112 to give the title compound. LC-MS (1): *t_R*= 0.98 min; [M+H]⁺: 536.0.

Example 2.114 to Example 2.135 were synthesized using the appropriate aldehyde and the appropriate amine or amine salt derivative in analogy to the examples reported herein before. LC-MS data of Example 2.113 to Example 2.135 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	<i>t_R</i>	[M+H] ⁺
2.114	(1R,4s)-4-((12aS,17S)-17-Imino-3-methyl-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ ⁴ -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	0.88	474.1
2.115	(12aS,17S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3-methyl-17-(methylimino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ ⁴ -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide	0.95	511.0
2.116	(1R,4s)-1-Methyl-4-((12aS,17S)-3-methyl-17-(methylimino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ ⁴ -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.87	488.1

2.117	(1 ² S,5 ¹ R,5 ³ R,2S)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3 ⁴ -methyl-2-(methylimino)-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide	0.94	550.0
2.118	(1 ² S,5 ¹ R,5 ³ R,2R)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3 ⁴ -methyl-2-(methylimino)-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide	0.97	550.0
2.120	(1R,4s)-4-((6R,12aS,17S)-4-Fluoro-3,6-dimethyl-17-(methylimino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ ⁴ -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.90	505.2
2.121	(1S,3S)-3-((6R,12aS,17S)-4-Fluoro-3,6-dimethyl-17-(methylimino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ ⁴ -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.91	505.2
2.122	(1 ³ R,4 ² S,3S)-6-(4,4-Difluorocyclohexyl)-2 ⁵ -methyl-3-(methylimino)-3λ ⁶ -3λ ⁶ -thia-6-aza-1(1,3),4(1,2)-dipyrrolidina-2(1,2)-benzenacyclononaphan-5-one 3-oxide	0.88	509.4
2.123	(1S,3S)-3-((6R,12aS,17S)-4-Fluoro-17-imino-3,6-dimethyl-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ ⁴ -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.94	491.2
2.125	(1 ³ R,4 ² S,3S)-6-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-2 ⁵ -methyl-3-(methylimino)-3λ ⁶ -3λ ⁶ -thia-6-aza-1(1,3),4(1,2)-dipyrrolidina-2(1,2)-benzenacyclononaphan-5-one 3-oxide	0.92	535.4
2.126	(1 ³ R,4 ² S,3S)-6-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-2 ⁵ -methyl-3-(methylimino)-3λ ⁶ -3λ ⁶ -thia-6-aza-1(1,3),4(1,2)-dipyrrolidina-2(1,2)-benzenacyclononaphan-5-one 3-oxide	0.87	507.4
2.127	(1R,4s)-1-Methyl-4-((1 ³ R,4 ² S,3S)-2 ⁵ -methyl-3-(methylimino)-3-oxido-5-oxo-3λ ⁶ -3λ ⁶ -thia-6-aza-1(1,3),4(1,2)-dipyrrolidina-2(1,2)-benzenacyclononaphane-6-yl)cyclohexane-1-carbonitrile	0.85	512.4
2.128	(1 ² S,5 ¹ R,5 ³ R,2S)-8-(4,4-Difluorocyclohexyl)-3 ⁴ -methyl-2-(methylimino)-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide	0.92	524.0
2.129	(1 ² S,5 ¹ R,5 ³ R,2S)-8-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-3 ⁴ -methyl-2-(methylimino)-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide	0.92	522.0
2.130	(1R,4s)-1-Methyl-4-((1 ² S,5 ¹ R,5 ³ R,2S)-3 ⁴ -methyl-2-(methylimino)-2-oxido-9-oxo-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile	0.89	527.1

2.131	(1 ² S,5 ¹ R,5 ³ R,2S)-8-(4,4-Difluorocyclohexyl)-2-imino-3 ⁴ -methyl-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide	0.94	510.0
2.132	(1 ² S,5 ¹ R,5 ³ R,2S)-8-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-2-imino-3 ⁴ -methyl-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide	0.95	508.0
2.133	(1R,4s)-4-((1 ² S,5 ¹ R,5 ³ R,2S)-2-Imino-3 ⁴ -methyl-2-oxido-9-oxo-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphane-8-yl)-1-methylcyclohexane-1-carbonitrile	0.92	513.1
2.134	(1R,4s)-4-((1 ² S,5 ¹ R,5 ³ R,2S)-2-Imino-3 ⁴ -methyl-2-oxido-9-oxo-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile	0.88	499.0
2.135	(1S,3S)-3-((1 ² S,5 ¹ R,5 ³ R,2S)-2-Imino-3 ⁴ -methyl-2-oxido-9-oxo-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile	0.88	499.0

Example 2.136 (6R,8R,12aS,17S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6,8-trimethyl-17-(methylimino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide:

5 **Methyl ((S)-2-(benzyloxy)-N-(*tert*-butoxycarbonyl)-4-methylphenylsulfonimidoyl)-L-prolinate and Methyl ((R)-2-(benzyloxy)-N-(*tert*-butoxycarbonyl)-4-methylphenylsulfonimidoyl)-L-prolinate:** Were synthesized using 3-(benzyloxy)-4-bromotoluene and *tert*-butyl (oxo-λ⁴-sulfaneylidene)carbamate in analogy to Example 2.5. The diastereomers were separated by FC (Hept to 30% EtOAc) to give methyl ((S)-2-(benzyloxy)-N-(*tert*-butoxycarbonyl)-4-methylphenylsulfonimidoyl)-L-prolinate (first eluting diastereomer) and methyl ((R)-2-(benzyloxy)-N-(*tert*-butoxycarbonyl)-4-methylphenylsulfonimidoyl)-L-prolinate (second eluting diastereomer). First
10 eluting diastereomer: LC-MS (1): t_R= 1.09 min; [M+H]⁺: 489.0. Second eluting diastereomer: LC-MS (1): t_R= 1.09 min; [M+H]⁺: 489.0.

Methyl ((S)-N-(*tert*-butoxycarbonyl)-2-hydroxy-4-methylphenylsulfonimidoyl)-L-prolinate: Methyl ((S)-2-(benzyloxy)-N-(*tert*-butoxycarbonyl)-4-methylphenylsulfonimidoyl)-L-prolinate (first eluting diastereomer) (1.02 g,
15 2.09 mmol, 1 eq) was dissolved in THF (20 mL). The reaction flask was purged with N₂ and 10% Pd/C (102 mg) was added. The reaction mixture was stirred under a H₂ atm at rt for 1h. The mixture was filtered over a glass fiber filter and washed with a mixture of MeOH and THF. The solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R= 1.00 min; [M+H]⁺: 399.1.

Methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((2RS,4R)-6-((*tert*-butyldiphenylsilyl)oxy)-4-methylhexan-2-yl)oxy)-4-methylphenylsulfonimidoyl)-L-prolinate: Was synthesized using methyl ((S)-N-(*tert*-butoxycarbonyl)-2-hydroxy-

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4-methylphenylsulfonimidoyl)-L-prolinate and (2RS,4R)-6-((*tert*-butyldiphenylsilyl)oxy)-4-methylhexan-2-ol in analogy to Example 2.5 to give the title compound. LC-MS (1): *t*_R= 1.40 min; [M+H]⁺: 751.1.

Methyl (N-(*tert*-butoxycarbonyl)-2-(((2RS,4R)-6-hydroxy-4-methylhexan-2-yl)oxy)-4-methylphenylsulfonimidoyl)-L-prolinate: Was synthesized using methyl ((S)-N-(*tert*-butoxycarbonyl)-2-(((2RS,4R)-6-((*tert*-butyldiphenylsilyl)oxy)-4-methylhexan-2-yl)oxy)-4-methylphenylsulfonimidoyl)-L-prolinate in analogy to Example 2.5 to give the title compound. LC-MS (1): *t*_R= 1.00 and 1.02 min; [M+H]⁺: 513.1.

Methyl (N-(*tert*-butoxycarbonyl)-4-methyl-2-(((2S,4S)-4-methyl-6-oxohexan-2-yl)oxy)phenylsulfonimidoyl)-L-prolinate: Was synthesized using methyl (N-(*tert*-butoxycarbonyl)-2-(((2RS,4R)-6-hydroxy-4-methylhexan-2-yl)oxy)-4-methylphenylsulfonimidoyl)-L-prolinate in analogy to Example 2.5 to give the title compound: LC-MS (1): *t*_R= 1.06; [M+H]⁺: 511.1.

(6R,8R,12aS,17S)-11-(((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-3,6,8-trimethyl-17-(methylimino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide: Was synthesized using methyl (N-(*tert*-butoxycarbonyl)-4-methyl-2-(((2S,4S)-4-methyl-6-oxohexan-2-yl)oxy)phenylsulfonimidoyl)-L-prolinate and (3s,6s)-1,1-difluorospiro[2.5]octan-6-amine hydrochloride in analogy to Example 2.5. The diastereomers were separated by prep. chiral SFC (SFC 26 method, second eluting diastereomer) to give the title compound. LC-MS (1): *t*_R= 0.96 min; [M+H]⁺: 538.2.

Example 2.137 (1R,4s)-1-Methyl-4-((6R,8R,12aS,17S)-3,6,8-trimethyl-17-(methylimino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile: Was synthesized using methyl (N-(*tert*-butoxycarbonyl)-4-methyl-2-(((2S,4S)-4-methyl-6-oxohexan-2-yl)oxy)phenylsulfonimidoyl)-L-prolinate and *cis*-4-amino-1-methylcyclohexanecarbonitrile hydrochloride in analogy to Example 2.136. The diastereomers were separated by prep. chiral SFC (SFC 27 method, second eluting diastereomer) to give the title compound. LC-MS (3): *t*_R= 1.07 min; [M+H]⁺: 515.5.

Example 2.138 to Example 2.175 were synthesized using the appropriate amine or amine salt derivative and the appropriate scaffolds in analogy to Examples reported herein before. LC-MS data of Example 2.138 to Example 2.175 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	<i>t</i> _R	[M+H] ⁺
2.138	(6R,12aS,17S)-11-(((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-17-((methyl-d3)imino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ ⁴ -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide	0.97	525.1

2.139	(1R,4s)-4-((6R,12aS,17S)-3,6-Dimethyl-17-((methyl-d3)imino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	0.90	502.2
2.140	(1R,4s)-4-((6R,12aS,17S)-3,6-Dimethyl-17-((methyl-d3)imino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17 λ^4 -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	0.85	501.2
2.141	(1R,4s)-4-((8R,12aS,17S)-3,8-Dimethyl-17-((methyl-d3)imino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17 λ^4 -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	0.91	501.1
2.142	(1R,4s)-4-((1aR,4aS,9S,16aS)-9-Imino-12-methyl-9-oxido-4-oxo-1,1a,2,4a,5,6,7,15,16,16a-decahydro-9H-9 λ^4 -benzo[b]cyclopropa[j]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-3(4H)-yl)-1-methylcyclohexane-1-carbonitrile	0.87	485.1
2.143	(1S,3S)-3-((1 2 S,5 1 R,5 3 R,2S)-3 4 -Methyl-2-(methylimino)-2-oxido-9-oxo-2 λ^6 -4-oxa-2 λ^6 -thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile	0.87	513.1
2.144	(1 2 S,5 1 R,5 3 R,2S)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3 3 -fluoro-2-imino-3 4 -methyl-2 λ^6 -4-oxa-2 λ^6 -thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide	1.08	554.0
2.145	(1 2 S,5 1 R,5 3 R,2S)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3 3 -fluoro-3 4 -methyl-2-(methylimino)-2 λ^6 -4-oxa-2 λ^6 -thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide	1.05	568.0
2.146	(5S,9aS,12aR,13aS)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-5-imino-2-methyl-7,8,9,9a,12,12a,13,13a,14,15-decahydro-5H-5 λ^4 -cyclopropa[j]pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-10(11H)-one 5-oxide	0.97	509.0
2.147	(1R,4s)-4-((5S,9aS,12aR,13aS)-5-Imino-2-methyl-5-oxido-10-oxo-8,9,9a,10,12,12a,13,13a,14,15-decahydro-5H-5 λ^4 -cyclopropa[j]pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(7H)-yl)-1-methylcyclohexane-1-carbonitrile	0.89	486.0

2.148	(1aR,4aS,9R,16aS)-3-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-9-imino-12-methyl-1a,2,3,4a,5,6,7,15,16,16a-decahydro-9H-9λ ⁴ -benzo[b]cyclopropa[j]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-4(1H)-one 9-oxide	0.96	508.0
2.149	(1 ² S,5 ¹ R,5 ³ R,2S)-8-(4,4-Difluorocyclohexyl)-3 ³ -fluoro-2-imino-3 ⁴ -methyl-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide	1.03	528.0
2.150	(1 ² S,5 ¹ R,5 ³ R,2R)-8-(4,4-Difluorocyclohexyl)-3 ³ -fluoro-2-imino-3 ⁴ -methyl-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide	1.08	528.1
2.151	(1 ² S,5 ¹ R,5 ³ R,2S)-8-(4,4-Difluorocyclohexyl)-3 ³ -fluoro-3 ⁴ -methyl-2-(methylimino)-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide	1.0	542.1
2.152	(6R,12aS,17S)-17-(Cyclopropylimino)-11-((3R,6s)-1,1-difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ ⁴ -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide	1.12	551.4
2.153	N-((6R,12aS,17S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-17-oxido-12-oxo-7,8,9,10,11,12,12a,13,14,15-decahydro-6H-17λ ⁴ -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-17-ylidene)cyanamide	1.11	536.0
2.154	(1R,4s)-4-((1 ² S,5 ¹ R,5 ³ R,2S)-3 ³ -Fluoro-2-imino-3 ⁴ -methyl-2-oxido-9-oxo-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphane-8-yl)-1-methylcyclohexane-1-carbonitrile	1.0	531.1
2.155	(1R,4s)-4-((1 ² S,5 ¹ R,5 ³ R,2S)-3 ³ -Fluoro-3 ⁴ -methyl-2-(methylimino)-2-oxido-9-oxo-2λ ⁶ -4-oxa-2λ ⁶ -thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphane-8-yl)-1-methylcyclohexane-1-carbonitrile	0.98	545.1
2.160	(1R,4s)-1-Methyl-4-((6S,8R,12aS,17S)-3,6,8-trimethyl-17-(methylimino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ ⁴ -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.97	476.2

2.161	(1R,4s)-1-Methyl-4-((6R,8R,12aS,17S)-3,6,8-trimethyl-17-(methylimino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-carbonitrile	0.99	546.4
2.162	(1R,4s)-1-methyl-4-((1S,3S,8R)-2,3,8,13-Tetramethyl-1-(methylimino)-1-oxido-4-oxo-1,2,3,4,7,8,9,10-octahydro-1 λ^4 -benzo[b][1]oxa[4]thia[5,8]diazacyclotridecin-5(6H)-yl)cyclohexane-1-carbonitrile	1.18	564.4
2.163	(1S,3S,8R)-5-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-1-imino-2,3,8,13-tetramethyl-2,3,5,6,7,8,9,10-octahydro-1 λ^4 -pyrido[2,3-b][1]oxa[4]thia[5,8]diazacyclotridecin-4(1H)-one 1-oxide	1.1	567.4
2.164	(1R,4s)-4-((1S,3S,8R)-1-Imino-2,3,8,13-tetramethyl-1-oxido-4-oxo-1,2,3,4,7,8,9,10-octahydro-1 λ^4 -pyrido[2,3-b][1]oxa[4]thia[5,8]diazacyclotridecin-5(6H)-yl)-1-methylcyclohexane-1-carbonitrile	1.01	589.1
2.167	(1R,4s)-4-((6R,12aS,17S)-17-((2-Methoxyethyl)imino)-3,6-dimethyl-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	1.0	501.9
2.168	(1R,4s)-4-((6R,12aS,17S)-3,6-Dimethyl-17-oxido-12-oxo-17-(phenylimino)-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	0.97	525.1
2.169	(6R,12aS,17S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-17-(oxetan-3-ylimino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide	0.9	502.2
2.170	(6R,12aS,17S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-17-(pyrimidin-2-ylimino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide	0.85	501.2
2.171	(1R,3S,10R)-5-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-2,3,10,13-tetramethyl-1-(methylimino)-2,3,5,6,7,8,9,10-octahydro-1 λ^4 -benzo[b][1]oxa[4]thia[5,8]diazacyclotridecin-4(1H)-one 1-oxide	0.91	501.1

2.173	(1R,4s)-4-((6R,12aS,15S,17S)-17-Imino-3,6,15-trimethyl-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	0.87	513.1
2.175	(1R,4s)-4-((6R,12aS,15S,17R)-17-Imino-3,6,15-trimethyl-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	1.05	568.0

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

Example 3.1 (12aR*,15aS*)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,13,14,15,15a-decahydrobenzo[b]cyclopenta[e][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one 16,16-dioxide:

- 5 **Methyl (1RS,2SR)-2-((2-bromo-4-methylphenyl)thio)cyclopentane-1-carboxylate:** 2-Bromo-4-methylbenzenethiol (5.0 g, 23.40 mmol, 1 eq) and methyl 1-cyclopentenecarboxylic acid (5.90 mL, 46.80 mmol, 2 eq) were dissolved in piperidine (15 mL). The reaction mixture was stirred at 70°C for 1h. The reaction mixture was cooled to rt. Aq. 1M HCl soln. was added to the reaction mixture, followed by EtOAc. The layers were separated, and the aq. layer was extracted with EtOAc. The org. layers were dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R = 1.11 min; [M+H]⁺: 331.0.

- 15 **Methyl (1RS,2SR)-2-((2-bromo-4-methylphenyl)sulfonyl)cyclopentane-1-carboxylate:** Methyl (1RS,2SR)-2-((2-bromo-4-methylphenyl)thio)cyclopentane-1-carboxylate (4.31 g, 13.10 mmol, 1 eq) was dissolved in DCM (30 mL). Then NaHCO₃ (3.31 g, 39.30 mmol, 3 eq) and m-CPBA (8.80 g, 39.30 mmol, 3 eq) were added portionwise at 0°C. The reaction mixture was stirred at 0°C for 2h. Aq. 1M NaOH soln. was added to the reaction mixture, followed by DCM. The biphasic mixture was stirred until all solid dissolved. The org. layer was separated, and the aq. layer was extracted with DCM. The combined org. layers were dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.94 min; [M+H]⁺: 361.0.

- 20 **Methyl (1RS,2SR)-2-((4-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)cyclopentane-1-carboxylate:** Methyl (1RS,2SR)-2-((2-bromo-4-methylphenyl)sulfonyl)cyclopentane-1-carboxylate (1.35 g, 3.74 mmol, 1 eq) was dissolved in dioxane (16 mL). Then PdCl₂(MeCN)₂ (20 mg, 0.075 mmol, 0.02 eq) and SPhos (61 mg, 0.15 mmol, 0.04 eq) were added. The flask was sealed and evacuated under vacuum then filled back with N₂. Then TEA (1.6 mL, 11.20 mmol, 3 eq) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.9 mL, 5.61 mmol, 1.5 eq) were added. The reaction mixture was stirred at 100°C overnight. The crude mixture was filtered and the remaining solid was rinsed with dioxane. Sat. aq. NaHCO₃ soln. was added to the mother liquor and the aq. layer was extracted with DCM. The combined org. layers
- 25

were washed with brine. The org. layer was dried over MgSO_4 , filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R = 1.03 min; $[\text{M}+\text{H}]^+$: 409.2.

Methyl (1RS,2SR)-2-((2-hydroxy-4-methylphenyl)sulfonyl)cyclopentane-1-carboxylate: Methyl (1RS,2SR)-2-((4-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)cyclopentane-1-carboxylate (1.07 g, 2.62 mmol, 1 eq) was dissolved in THF (10 mL). Then aq. 30% (w/w) hydrogen peroxide soln. (0.5 mL, 5.25 mmol, 2 eq) and aq. 1M NaOH soln. (2.50 mL, 5.90 mmol, 2.2 eq) were successively added at 0°C. The mixture was stirred at 0°C for 1h. Aq. 1M HCl soln. was added to the reaction mixture, followed by EtOAc. The combined org. layers were washed with brine, dried over MgSO_4 , filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 40% EtOAc) to give the title compound. LC-MS (1): t_R = 0.80 min; $[\text{M}+\text{H}]^+$: 299.2.

Methyl (1RS,2SR)-2-((2-((5-((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)sulfonyl)cyclopentane-1-carboxylate: Methyl (1RS,2SR)-2-((2-hydroxy-4-methylphenyl)sulfonyl)cyclopentane-1-carboxylate (620 mg, 2.08 mmol, 1 eq) was dissolved in THF (16 mL). The soln. was cooled to 0°C. Then *tert*-butyl (4,4-difluorocyclohexyl)(5-hydroxypentyl)carbamate (935 mg, 2.91 mmol, 1.4 eq) and PPh_3 (661 mg, 2.49 mmol, 1.2 eq) were added followed by DEAD (~40% in toluene, 1.9 mL, 4.16 mmol, 2 eq). After the addition, the mixture was allowed to warm up to rt and stirred for 1h. The solvent was removed under reduced pressure. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R = 1.18 min; $[\text{M}+\text{H}]^+$: 602.3.

Methyl (1RS,2SR)-2-((2-((5-((4,4-difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)sulfonyl)cyclopentane-1-carboxylate: Methyl (1RS,2SR)-2-((2-((5-((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)sulfonyl)cyclopentane-1-carboxylate (1.06 g, 1.76 mmol, 1 eq) was dissolved in DCM (5 mL). Aq. 4M HCl soln. in dioxane (1.80 mL, 7.04 mmol, 4 eq) was added at 0°C. The reaction mixture was stirred at rt overnight. The solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.83 min; $[\text{M}+\text{H}]^+$: 502.2.

(1R*,2S*)-2-((2-((5-((4,4-Difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)sulfonyl)cyclopentane-1-carboxylic acid: Methyl (1RS,2SR)-2-((2-((5-((4,4-difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)sulfonyl)cyclopentane-1-carboxylate (1.06 g, 2.10 mmol, 1 eq) was dissolved in THF (25 mL). Then aq. 1M LiOH soln. (6.30 mL, 6.31 mmol, 3 eq) was added dropwise. The reaction mixture was stirred at rt for 1h. Aq. 1M HCl was added. The reaction mixture was diluted with DCM and washed H_2O . The org. layer was separated and the aq. layer was washed with EtOAc. The org. layers were combined, dried over Na_2SO_4 , filtered, and the solvent removed under reduced pressure to give the title compound. LC-MS (1): t_R = 0.76 min; $[\text{M}+\text{H}]^+$: 488.2.

(12aR*,15aS*)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,13,14,15,15a-decahydrobenzo[b]cyclopenta[e][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one 16,16-dioxide: (1R*,2S*)-2-((2-((5-((4,4-Difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)sulfonyl)cyclopentane-1-carboxylic acid (1.0 g, 2.05 mmol, 1 eq) was dissolved in DMF (100 mL). This soln. was added dropwise using a syringe pump to a soln.

of DIPEA (1.10 mL, 6.15 mmol, 3 eq) and HATU (1.17 g, 3.08 mmol, 1.5 eq) in DMF (20 mL). The reaction mixture was stirred at rt for 1h. EtOAc and H₂O were added. The layers were separated and the aq. layer was extracted with EtOAc. The combined org. layers were washed with brine, dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R= 1.04 min; [M+H]⁺: 470.0.

Example 3.2 (12aS,15aR)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,13,14,15,15a-decahydrocyclopenta[e]pyrido[2,3-b][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one 16,16-dioxide:

(1RS,2SR)-2-((2-Fluoro-6-methylpyridin-3-yl)thio)cyclopentane-1-carboxylic acid: 3-Bromo-2-fluoro-6-picoline (140 mg, 0.72 mmol, 1 eq) was dissolved in dioxane (7 mL). Then XantPhos Pd G2 (64 mg, 0.072 mmol, 0.1 eq), DIPEA (0.25 mL, 1.44 mmol, 2 eq) and (1RS,2SR)-2-mercaptocyclopentane-1-carboxylic acid (122 mg, 0.79 mmol, 1.1 eq) were added. The reaction mixture was stirred at 110°C for 4h. After cooling to rt, the reaction mixture was diluted with EtOAc and washed with aq. 0.1M HCl soln. and H₂O. The org. layer was washed with brine, dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 10% EtOAc) to give the title compound. LC-MS (1): t_R= 0.79 and 0.82 min; [M+H]⁺: 256.2.

(1RS,2SR)-2-((2-Fluoro-6-methylpyridin-3-yl)sulfonyl)cyclopentane-1-carboxylic acid: (1RS,2SR)-2-((2-Fluoro-6-methylpyridin-3-yl)thio)cyclopentane-1-carboxylic acid (204 mg, 0.80 mmol, 1 eq) was dissolved in DCM (8 mL). Then NaHCO₃ (201 mg, 2.40 mmol, 3 eq) and m-CPBA (537 mg, 2.40 mmol, 3 eq) were added at rt. The reaction mixture was stirred at rt for 2h. The reaction mixture was diluted with DCM and washed with aq. 0.1M HCl soln. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (DCM to 10% MeOH) to give the title compound. LC-MS (1): t_R= 0.66 and 0.69 min; [M+H]⁺: 288.1.

Methyl (1RS,2SR)-2-((2-hydroxy-6-methylpyridin-3-yl)sulfonyl)cyclopentane-1-carboxylate: (1RS,2SR)-2-((2-Fluoro-6-methylpyridin-3-yl)sulfonyl)cyclopentane-1-carboxylic acid (209 mg, 0.52 mmol, 1 eq) was suspended in aq. 6M HCl soln. (5 mL). The reaction mixture was stirred at 100°C (sealed tube) overnight. The reaction mixture was cooled to rt and the solvent was removed under reduced pressure. The residue was suspended in MeOH (7 mL) and H₂SO₄ (1 mol%) was added. The reaction mixture was stirred under reflux for 3h. Then the solvent was removed under reduced pressure and the residue was dissolved in DCM. The org. layer was washed with H₂O, dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R= 0.62 min; [M+H]⁺: 300.0.

Methyl (1RS,2SR)-2-((2-((5-((tert-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)cyclopentane-1-carboxylate: Was synthesized using methyl (1RS,2SR)-2-((2-hydroxy-6-methylpyridin-3-yl)sulfonyl)cyclopentane-1-carboxylate and *tert*-butyl (4,4-difluorocyclohexyl)(5-hydroxypentyl)carbamate in analogy to Example 3.1 to give the title compound. LC-MS (1): t_R= 1.19 min; [M+H]⁺: 603.0.

(1R*,2S*)-2-((2-((5-((*tert*-Butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)cyclopentane-1-carboxylic acid: Was synthesized using methyl (1RS,2SR)-2-((2-((5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)cyclopentane-1-carboxylate in analogy to Example 1.8 to give the title compound. LC-MS (1): t_R = 1.10 min; $[M+H]^+$: 589.0.

- 5 **(1R*,2S*)-2-((2-((5-((4,4-Difluorocyclohexyl)amino)pentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)cyclopentane-1-carboxylic acid:** Was synthesized using (1R*,2S*)-2-((2-((5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)cyclopentane-1-carboxylic acid in analogy to Example 3.1 to give the title compound. LC-MS (1): t_R = 0.74 min; $[M+H]^+$: 489.0.

- (12aS,15aR)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,13,14,15,15a-decahydrocyclopenta[e]pyrido[2,3-b][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one 16,16-dioxide:** Was synthesized using (1R*,2S*)-2-((2-((5-((4,4-difluorocyclohexyl)amino)pentyl)oxy)-6-methylpyridin-3-yl)sulfonyl)cyclopentane-1-carboxylic acid in analogy to Example 3.1. The mixture of stereoisomers was purified by prep. chiral SFC (SFC 4 method) to give (12aS,15aR)-11-(4,4-difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,13,14,15,15a-decahydrocyclopenta[e]pyrido[2,3-b][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one 16,16-dioxide (first eluting diastereomer) and (12aR,15aS)-11-(4,4-difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,13,14,15,15a-decahydrocyclopenta[e]pyrido[2,3-b][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one 16,16-dioxide (second eluting diastereomer). First eluting diastereomer: LC-MS (1): t_R = 1.06 min; $[M+H]^+$: 471.2. Second eluting diastereomer: LC-MS (1): t_R = 1.06 min; $[M+H]^+$: 471.2.

- Example 3.3 (6R,12aS,15aR)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,13,14,15,15a-decahydrobenzo[b]cyclopenta[e][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one 16,16-dioxide:**

- (1RS,2RS)-2-((2-Hydroxy-4-methylphenyl)thio)cyclopentane-1-carboxylic acid:** 2-Iodo-5-methyl-phenol (253 mg, 1.05 mmol, 1 eq) and XantPhos Pd G2 (93 mg, 0.11 mmol, 0.1 eq) were charged into a microwave vial. Then a solution of 2-sulfanylcyclopentane-1-carboxylic acid (185 mg, 1.21 mmol, 1.15 eq) in dioxane (4.0 mL) was added, followed by DIPEA (0.36 mL, 2.10 mmol, 2 eq). The brown mixture was degassed by a N_2 during 5 min, and the reaction mixture was stirred at 160°C for 10 min. EtOAc was added and the org. layer was washed with aq. 1M HCl soln., dried over Na_2SO_4 , filtered, and the solvent removed under reduced pressure. The residue was purified by FC (DCM to 10% MeOH) to give the title compound. LC-MS (1): t_R = 0.84 min; $[M+H]^+$: not seen.

- Methyl (1RS,2RS)-2-((2-hydroxy-4-methylphenyl)thio)cyclopentane-1-carboxylate: (S)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-ol:** (1RS,2RS)-2-((2-Hydroxy-4-methylphenyl)thio)cyclopentane-1-carboxylic acid (320 mg, 1.27 mmol, 1 eq) was dissolved in MeOH (4 mL). H_2SO_4 (4 μ L, 0.063 mmol, 0.05 eq) was added and the reaction mixture was stirred under reflux for 72h. The soln. was diluted with EtOAc and washed with H_2O . The org. layer was dried over Na_2SO_4 , filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.97 min; $[M+H]^+$: not seen.

- Methyl (1RS,2RS)-2-((2-(((R)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-4-methylphenyl)thio)cyclopentane-1-carboxylate:** Methyl (1RS,2RS)-2-((2-hydroxy-4-

methylphenylthio)cyclopentane-1-carboxylate (230 mg, 0.86 mmol, 1 eq) was dissolved in THF (7 mL). The soln. was cooled to 0°C. Then (S)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-ol (211 mg, 0.91 mmol, 1.05 eq) and PPh₃ polymer-bound (100-200 mesh, ca. 1.6 mmol/g, 700 mg, 2.68 mmol, 3.1 eq) were added followed by DEAD (~40% in toluene, 0.50 mL, 1.04 mmol, 1.2 eq). After the addition, the mixture was allowed to warm up to rt and stirred for 17h. (S)-6-((*tert*-Butyldimethylsilyl)oxy)hexan-2-ol (42 mg, 0.18 mmol, 0.2 eq) and PPh₃ polymer-bound (100-200 mesh, ca. 1.6 mmol/g, 100 mg, 0.38 mmol, 0.44 eq) were added again followed by DEAD (~40% in toluene, 0.10 mL, 0.10 mmol, 0.12 eq). The reaction mixture was stirred for 2h. The soln. was diluted with Et₂O and washed with aq. 1M HCl., aq. sat. NaHCO₃ soln. and H₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 1.35 min and 1.36 min; [M+H]⁺: 481.0.

Methyl (1R_S,2R_S)-2-((2-(((R)-6-hydroxyhexan-2-yl)oxy)-4-methylphenyl)thio)cyclopentane-1-carboxylate: Methyl (1R_S,2R_S)-2-((2-(((R)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-4-methylphenyl)thio)cyclopentane-1-carboxylate (310 mg, 0.65 mmol, 1 eq) was dissolved in THF (5 mL). 1M TBAF soln. in THF (1.3 mL, 1.29 mmol, 2 eq) was added and the reaction mixture was stirred at rt overnight. The mixture was diluted with Et₂O and the org. layer was washed with H₂O, dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 1.04 min; [M+H]⁺: 367.1.

Methyl (1R*,2S*)-2-((4-methyl-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)thio)cyclopentane-1-carboxylate: A soln. of oxalyl chloride (0.12 mL, 1.39 mmol, 1.5 eq) in DCM (7 mL) was cooled to -78°C. DMSO (0.18 mL, 2.50 mmol, 2.7 eq) was added dropwise while maintaining the temperature below -70°C. After stirring for another 10 min, a soln. of methyl (1R_S,2R_S)-2-((2-(((R)-6-hydroxyhexan-2-yl)oxy)-4-methylphenyl)thio)cyclopentane-1-carboxylate (340 mg, 0.93 mmol, 1 eq) in DCM (2 mL) was added dropwise keeping the temperature below -70°C. After 10 min stirring, TEA (0.65 mL, 4.64 mmol, 5 eq) was added and the soln. was stirred at -78°C for 30 min. Then the reaction mixture was allowed to warm up to rt. After 1h, the mixture was diluted with Et₂O and washed with aq. 1M HCl soln., aq. sat. NaHCO₃ soln., and H₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 1.10 min; [M+H]⁺: 365.1.

Methyl (1R*,2S*)-2-((2-(((R)-6-((4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-4-methylphenyl)thio)cyclopentane-1-carboxylate: Methyl (1R*,2S*)-2-((4-methyl-2-(((R)-6-oxohexan-2-yl)oxy)phenyl)thio)cyclopentane-1-carboxylate (251 mg, 0.69 mmol, 1 eq) was dissolved in MeOH (7 mL). 4,4-Difluorocyclohexan-1-amine (102 mg, 0.72 mmol, 1.05 eq) was added followed by NaBH(OAc)₃ (200 mg, 0.895 mmol, 1.3 eq). The reaction mixture was stirred at rt for 17h. Then 4,4-difluorocyclohexan-1-amine (20 mg, 0.14 mmol, 0.2 eq) and NaBH(OAc)₃ (46 mg, 0.33 mmol, 0.3 eq) were added again. The reaction mixture was stirred at rt for 1h. Aq. sat. NaHCO₃ soln. was added and the aq. layer was extracted with EtOAc. The org. layer was washed

with H₂O, dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 70% EtOAc) to give the title compound. LC-MS (1): t_R = 0.92 min; [M+H]⁺: 484.2.

- (1R*,2S*)-2-((2-(((R)-6-((4,4-Difluorocyclohexyl)amino)hexan-2-yl)oxy)-4-methylphenyl)thio)cyclopentane-1-carboxylic acid:** Methyl (1R*,2S*)-2-((2-(((R)-6-((4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-4-methylphenyl)thio)cyclopentane-1-carboxylate (257 mg, 0.53 mmol, 1 eq) was dissolved in THF (10 mL). Aq. 1M LiOH soln. (10.6 mL, 10.60 mmol, 20 eq) was added and the reaction mixture was stirred at rt overnight. The reaction was quenched with aq. 1M HCl soln. and the aq. layer was extracted with DCM. The combined org. layers were dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 0.87 min; [M+H]⁺: 470.0.
- (6R,12aS,15aR)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,13,14,15,15a-decahydrobenzo[b]cyclopenta[e][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one and (6R,12aR,15aS)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,13,14,15,15a-decahydrobenzo[b]cyclopenta[e][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one:** (1R*,2S*)-2-((2-(((R)-6-((4,4-Difluorocyclohexyl)amino)hexan-2-yl)oxy)-4-methylphenyl)thio)cyclopentane-1-carboxylic acid (243 mg, 0.52 mmol, 1 eq) was dissolved in MeCN (75 mL). This soln. was added dropwise to a soln. of DIPEA (0.53 mL, 3.10 mmol, 6 eq) and HATU (590 mg, 1.55 mmol, 3 eq) in MeCN (30 mL). The reaction mixture was stirred at rt for 3h. The reaction was diluted with EtOAc and washed with aq. 1M HCl soln. The combined org. layers were dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by basic prep. HPLC to give (6R,12aS,15aR)-11-(4,4-difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,13,14,15,15a-decahydrobenzo[b]cyclopenta[e][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one (first eluting diastereomer) and (6R,12aR,15aS)-11-(4,4-difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,13,14,15,15a-decahydrobenzo[b]cyclopenta[e][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one (second eluting diastereomer). First eluting diastereomer: LC-MS (1): t_R = 1.19 min; [M+H]⁺: 451.8. Second eluting diastereomer: LC-MS (1): t_R = 1.21 min; [M+H]⁺: 451.8.
- (6R,12aS,15aR)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,13,14,15,15a-decahydrobenzo[b]cyclopenta[e][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one 16,16-dioxide:** (6R,12aR,15aS)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,13,14,15,15a-decahydrobenzo[b]cyclopenta[e][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one (25 mg, 0.053 mmol, 1 eq) was dissolved in DCM (1 mL). The soln. was cooled to 0°C and m-CBPA (30 mg, 0.13 mmol, 2.5 eq) was added. The reaction mixture was warmed up to rt and stirred for 3h. The solvent was removed under reduced pressure and the residue was purified by basic prep. HPLC to give the title compound. LC-MS (1): t_R = 1.10 min; [M+H]⁺: 483.9.

Example 3.4 (6R,12aS,15aR)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,13,14,15,15a-decahydrocyclopenta[e]pyrido[2,3-b][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one 16,16-dioxide:

- (RS)-2-Ethylhexyl 3-((2-(((R)-6-((*tert*-butyldiphenylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridin-3-yl)thio)propanoate:** (RS)-2-Ethylhexyl 3-((2-hydroxy-6-methylpyridin-3-yl)thio)propanoate (3.39 g, 10.40 mmol, 1

eq) was dissolved in THF (130 mL). The soln. was cooled to 0°C. Then (S)-6-((*tert*-butyldiphenylsilyl)oxy)hexan-2-ol (4.50 g, 12.50 mmol, 1.2 eq) and PPh₃ (4.13 g, 15.60 mmol, 1.5 eq) were added followed by DEAD (~40% in toluene, 7.2 mL, 15.60 mmol, 1.5 eq). After the addition, the mixture was allowed to warm up to rt and stirred for 2h. (RS)-2-Ethylhexyl 3-((2-hydroxy-6-methylpyridin-3-yl)thio)propanoate (500 mg, 1.53 mmol, 0.15 eq) was added again the reaction mixture was stirred overnight. The reaction mixture was diluted with Et₂O and washed with brine. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 20% EtOAc) to give the title compound. LC-MS (1): t_R = 1.47 min; [M+H]⁺: 664.5.

Potassium (R)-2-((6-((*tert*-butyldiphenylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridine-3-thiolate: (RS)-2-Ethylhexyl 3-((2-(((R)-6-((*tert*-butyldiphenylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridin-3-yl)thio)propanoate (5.00 g, 7.53 mmol, 1 eq) was dissolved in THF (100 mL). The reaction mixture was cooled to -78°C. 1M Potassium *tert*-butoxide solution soln. in THF (11.3 mL, 11.30 mmol, 1.5 eq) was added dropwise at -78°C. The reaction was stirred at -78°C for 1h, then quenched with aq. 1M HCl soln. The mixture was warmed to rt and the solvent were partially removed under reduced pressure. The residue was dissolved in EtOAc. The org. layer was washed with aq. 1M HCl soln., dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R = 1.36 min; [M+H]⁺: 480.3

Methyl (1RS,2RS)-2-((2-(((R)-6-((*tert*-butyldiphenylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridin-3-yl)thio)cyclopentane-1-carboxylate: Potassium (R)-2-((6-((*tert*-butyldiphenylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridine-3-thiolate (4.26 g, 8.22 mmol, 1 eq) and methyl cyclopent-1-ene-1-carboxylate (2.18 g, 16.40 mmol, 2 eq) were dissolved in piperidine (1 mL). The reaction mixture was stirred at rt overnight. The mixture was poured onto a ice cooled mixture of aq. 1M HCl soln. and EtOAc. The org. layer was washed with aq. 1M HCl soln. and brine, and the aq. layer was extracted with EtOAc. The combined org. layers were washed with brine, dried over Na₂SO₄ and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 25% EtOAc) to give the title compound. LC-MS (1): t_R = 1.40 min; [M+H]⁺: 606.4.

Methyl (1RS,2RS)-2-((2-(((R)-6-((*tert*-butyldiphenylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)cyclopentane-1-carboxylate: Methyl (1RS,2RS)-2-((2-(((R)-6-((*tert*-butyldiphenylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridin-3-yl)thio)cyclopentane-1-carboxylate (3.71 g, 3.67 mmol, 1 eq) was dissolved in DCM (60 mL). The soln. was cooled to 0°C and m-CPBA (3.80 g, 11.00 mmol, 3 eq) was added. The reaction mixture was warmed to rt and stirred for 35 min. Aq. 1M NaOH soln. and DCM were added and the biphasic mixture was stirred until complete dissolution of the solid. The aq. layer was extracted with DCM. The org. layer was washed with H₂O and brine, dried over Na₂SO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by FC (Hept to 20% EtOAc) to give the title compound. LC-MS (1): t_R = 1.33 min; [M+H]⁺: 638.5.

Methyl (1RS,2RS)-2-((2-(((R)-6-hydroxyhexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)cyclopentane-1-carboxylate: Methyl (1RS,2RS)-2-((2-(((R)-6-((*tert*-butyldiphenylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)cyclopentane-1-carboxylate (1.75 g, 1.51 mmol, 1 eq) was dissolved in THF (15 mL), and 1M TBAF sln. in THF (2.3 mL, 2.32 mmol, 1.5 eq) was added. The reaction mixture was stirred at rt for 4h. Aq. sat. NaHCO₃ soln.

and EtOAc were added. The org. layer was washed with brine, dried over Na₂SO₄, filtered and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 60% EtOAc) to give the title compound. LC-MS (1): t_R= 0.90 min and 0.91 min; [M+H]⁺: 400.3.

Methyl (1R,2RS)-2-((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)cyclopentane-1-

- 5 **carboxylate:** Methyl (1R,2RS)-2-((2-(((R)-6-hydroxyhexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)cyclopentane-1-carboxylate (500 mg, 1.14 mmol, 1 eq) was dissolved in DCM (5 mL). Aq. 5% NaHCO₃ soln. (10 mL), KBr (151 mg, 1.25 mmol, 1.1 eq), and TEMPO (14 mg, 0.085 mmol, 0.02 eq) were added consecutively. The reaction mixture was stirred at rt, and aq. 10% NaOCl soln. (5 mL) was added. The reaction mixture was stirred at rt for 20 min, then quenched with aq. sat. Na₂S₂O₃ soln. The aq. layer was extracted with DCM. The org. layer was washed with brine, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R= 0.96 min; [M+H]⁺: 398.3.

Methyl (1R,2RS)-2-((2-(((R)-6-((4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-6-methylpyridin-3-

- 15 **yl)sulfonyl)cyclopentane-1-carboxylate:** 4,4-Difluorocyclohexan-1-amine (122 mg, 0.88 mmol, 1 eq) was dissolved in MeOH (4 mL). Methyl (1R,2RS)-2-((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)sulfonyl)cyclopentane-1-carboxylate (424 mg, 0.88 mmol, 1 eq) and AcOH (50 µL, 0.88 mmol, 1 eq) were added and the reaction mixture was stirred at rt for 30 min. NaBH(CN)₃ (293 mg, 1.31 mmol, 1.5 eq) was added and the the reaction mixture was stirred rt for 1h. The reaction was poured onto aq. sat. Na₂CO₃ soln. and extracted with EtOAc. The org. layer was washed with H₂O, dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R= 0.82 min and 0.83 min; [M+H]⁺: 517.2.

(1R,2S)-2-((2-(((R)-6-((4,4-Difluorocyclohexyl)amino)hexan-2-yl)oxy)-6-methylpyridin-3-

- 25 **yl)sulfonyl)cyclopentane-1-carboxylic acid and (1S,2R)-2-((2-(((R)-6-((4,4-Difluorocyclohexyl)amino)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)cyclopentane-1-carboxylic:** Methyl (1R,2RS)-2-((2-(((R)-6-((4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)cyclopentane-1-carboxylate (548 mg, 1.06 mmol, 1 eq) was dissolved in THF (10 mL). Aq. 1M LiOH (4.2 mL, 4.24 mmol, 4 eq) was added and the reaction mixture was stirred at rt for 2.5h. The mixture was quenched with citric acid until pH= 4. The aq. layer was extracted with DCM. The combined org. layers were dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by basic prep. HPLC to give (1R,2S)-2-((2-(((R)-6-((4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)cyclopentane-1-carboxylic acid (first eluting diastereomer) and (1S,2R)-2-((2-(((R)-6-((4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)cyclopentane-1-carboxylic acid (second eluting diastereomer). First eluting diastereomer: LC-MS (1): t_R= 0.75 min; [M+H]⁺: 503.3. Second eluting diastereomer: LC-MS (1): t_R= 0.77 min; [M+H]⁺: 503.4.

(6R,12aS,15aR)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,13,14,15,15a-

- 35 **decahydrocyclopenta[e]pyrido[2,3-b][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one 16,16-dioxide:** (1S,2R)-2-((2-(((R)-6-((4,4-Difluorocyclohexyl)amino)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)cyclopentane-1-

- carboxylic acid (176 mg, 0.34 mmol, 1 eq) in MeCN (25 mL) was added dropwise to a soln. of DIPEA (0.35 mL, 2.02 mmol, 6 eq) and HATU (320 mg, 0.84 mmol, 2.5 eq) in MeCN (10 mL). The reaction mixture was stirred at rt for 30 min. Et₂O and H₂O were added and the aq. layer was extracted with Et₂O. The combined org. layers were dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 70% EtOAc) to give the title compound. LC-MS (1): t_R = 1.10 min; [M+H]⁺: 485.3.

Example 3.5 (6R,12aR,15aS)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,13,14,15,15a-decahydrocyclopenta[e]pyrido[2,3-b][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one 16,16-dioxide: Was synthesized using (1R,2S)-2-((2-(((R)-6-((4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-6-methylpyridin-3-yl)sulfonyl)cyclopentane-1-carboxylic acid in analogy to Example 3.4. LC-MS (1): t_R = 1.08 min; [M+H]⁺: 485.3.

- Example 3.6 (6S,12aR,15aS)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,13,14,15,15a-decahydrocyclopenta[e]pyrido[2,3-b][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one 16,16-dioxide and Example 3.7 (6S,12aS,15aR)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,13,14,15,15a-decahydrocyclopenta[e]pyrido[2,3-b][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one 16,16-dioxide:** Was synthesized using (R)-(+)-propylene oxide in analogy to Example 3.4 to give the title compound. The stereoisomers were separated by prep. chiral separation (SFC 6 method) to give (6S,12aR,15aS)-11-(4,4-difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,13,14,15,15a-decahydrocyclopenta[e]pyrido[2,3-b][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one 16,16-dioxide (first eluting diastereomer) and (6S,12aS,15aR)-11-(4,4-difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,13,14,15,15a-decahydrocyclopenta[e]pyrido[2,3-b][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one 16,16-dioxide (second eluting diastereomer). First eluting diastereomer: LC-MS (1): t_R = 1.10 min; [M+H]⁺: 484.9. Second eluting diastereomer: LC-MS (1): t_R = 1.10 min; [M+H]⁺: 484.9.

Methods for the preparation of sulfoximine compounds (Examples 4.x)

Example 4.1 (12aS,15aR,16S)-11-(4,4-Difluorocyclohexyl)-16-imino-3-methyl-6,7,8,9,10,11,12a,13,14,15,15a,16-dodecahydro-12H-16λ⁴-benzo[b]cyclopenta[e][1]oxa[4]thia[8]azacyclotridecin-12-one 16-oxide:

- (1RS,2SR)-2-((2-Hydroxy-4-methylphenyl)thio)cyclopentane-1-carboxylic acid:** 2-Bromo-5-methylphenol (500 mg, 2.62 mmol, 1 eq) was dissolved in dioxane (8 mL). Then (1R,2S)-2-mercaptocyclopentane-1-carboxylic acid (444 mg, 2.88 mmol, 1.1 eq), DIPEA (0.9 mL, 5.24 mmol, 2 eq) and XantPhos Pd G2 (233 mg, 0.26 mmol, 0.1 eq) were added. The reaction mixture was stirred at 80°C for 3h. The solvent was removed under reduced pressure. The residue was purified by FC (DCM to 10% MeOH) to give the title compound. LC-MS (1): t_R = 0.84 min; [M+H]⁺: not seen.

Methyl (1RS,2SR)-2-((2-hydroxy-4-methylphenyl)thio)cyclopentane-1-carboxylate: (1RS,2SR)-2-((2-Hydroxy-4-methylphenyl)thio)cyclopentane-1-carboxylic acid (510 mg, 2.02 mmol, 1 eq) was dissolved in MeOH (10 mL). Then H₂SO₄ (1 mol%) was added. The reaction mixture was stirred at reflux overnight. The reaction mixture was cooled to rt and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc and

washed with H₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R= 0.96 min; [M+H]⁺: not seen.

Methyl (1R,2SR)-2-((2-((5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)thio)cyclopentane-1-carboxylate: Methyl (1R,2SR)-2-((2-hydroxy-4-methylphenyl)thio)cyclopentane-1-carboxylate (344 mg, 1.29 mmol, 1 eq) was dissolved in THF (13 mL). The soln. was cooled to 0°C. Then *tert*-butyl (4,4-difluorocyclohexyl)(5-hydroxypentyl)carbamate (554 mg, 1.72 mmol, 1.3 eq) and PPh₃ (413 mg, 1.55 mmol, 1.2 eq) were added followed by DEAD (~40% in toluene, 1.25 mL, 2.58 mmol, 2 eq). After the addition, the mixture was allowed to warm up to rt and stirred for 2h. The solvent was removed under reduced pressure. The residue was purified by FC (Hept to 50% EtOAc) to give the title compound. LC-MS (1): t_R= 1.26 and 1.27 min; [M+H]⁺: 570.5.

Methyl (1R,2SR)-2-((2-((5-((4,4-difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)thio)cyclopentane-1-carboxylate: Methyl (1R,2SR)-2-((2-((5-((*tert*-butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)thio)cyclopentane-1-carboxylate (1.18 g, 2.07 mmol, 1 eq) was dissolved in DCM (10 mL), TFA (1.0 mL, 13.1 mmol, 6.3 eq) was added and the reaction mixture was stirred at rt overnight. The solvent was removed under reduced pressure. The residue was dissolved in toluene and the solvent was removed under reduced pressure. The crude product was used in the next step without further purification. LC-MS (1): t_R= 0.90 min; [M+H]⁺: 470.1.

(1R*,2S*)-2-((2-((5-((*tert*-Butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)thio)cyclopentane-1-carboxylic acid: Methyl (1R,2SR)-2-((2-((5-((4,4-difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)thio)cyclopentane-1-carboxylate (475 mg, 0.83 mmol, 1 eq) was dissolved in THF (4 mL). Then aq. 1M LiOH soln. (5.40 mL, 5.42 mmol, 6.5 eq) was added. The reaction mixture was stirred at rt for 5h. Aq. 1M HCl was added. The reaction mixture was diluted with EtOAc. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure to give the title compound. LC-MS (1): t_R= 1.19 min; [M+H]⁺: 556.3.

(1R*,2S*)-2-((2-((5-((4,4-Difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)thio)cyclopentane-1-carboxylic acid: (1R*,2S*)-2-((2-((5-((*tert*-Butoxycarbonyl)(4,4-difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)thio)cyclopentane-1-carboxylic acid (459 mg, 0.83 mmol, 1 eq) was dissolved in dioxane (2 mL). Then aq. 4M HCl soln. in dioxane (2.10 mL, 8.26 mmol, 10 eq) was added. The reaction mixture was stirred at rt for 4h. The solvent was removed under reduced pressure to give the title compound. LC-MS (1): t_R= 0.76 min; [M+H]⁺: 488.2.

(12aR*,15aS*)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,13,14,15,15a-decahydrobenzo[b]cyclopenta[e][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one: (1R*,2S*)-2-((2-((5-((4,4-Difluorocyclohexyl)amino)pentyl)oxy)-4-methylphenyl)thio)cyclopentane-1-carboxylic acid (486 mg, 0.99 mmol, 1 eq) was dissolved in DMF (30 mL). This soln. was added dropwise using a syringe pump to a soln. of DIPEA (1.4

mL, 7.9 mmol, 8 eq) and HATU (1.5 g, 3.95 mmol, 4 eq) in DMF (10 mL). The reaction mixture was stirred at rt for 10 min. Et₂O was added and the org. layer was washed with aq. 1M HCl soln. and H₂O. The org. layer was dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by FC (Hept to 80% EtOAc) to give the title compound. LC-MS (1): t_R = 1.06 min; [M+H]⁺: 470.2.

- 5 **(12aR*,15aS*,16S)-11-(4,4-Difluorocyclohexyl)-16-imino-3-methyl-6,7,8,9,10,11,12a,13,14,15,15a,16-dodecahydro-12H-16λ⁴-benzo[b]cyclopenta[e][1]oxa[4]thia[8]azacyclotridecin-12-one 16-oxide:**
(12aR*,15aS*)-11-(4,4-Difluorocyclohexyl)-3-methyl-6,7,8,9,10,11,13,14,15,15a-decahydrobenzo[b]cyclopenta[e][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one (197 mg, 0.45 mmol, 1 eq) was dissolved in MeOH (4.5 mL). Then (diacetoxyiodo)benzene (370 mg, 1.13 mmol, 2.5 eq) and ammonium carbamate (70.3 mg, 0.90 mmol, 2 eq) were added. The reaction mixture was stirred at rt for 1h. The solvent was removed under reduced pressure. The residue was purified by FC (DCM to 5% MeOH) to give (12aR*,15aS*,16R)-11-(4,4-difluorocyclohexyl)-16-imino-3-methyl-6,7,8,9,10,11,12a,13,14,15,15a,16-dodecahydro-12H-16λ⁴-benzo[b]cyclopenta[e][1]oxa[4]thia[8]azacyclotridecin-12-one 16-oxide (first eluting diastereomer) and (12aR*,15aS*,16S)-11-(4,4-difluorocyclohexyl)-16-imino-3-methyl-6,7,8,9,10,11,12a,13,14,15,15a,16-dodecahydro-12H-16λ⁴-benzo[b]cyclopenta[e][1]oxa[4]thia[8]azacyclotridecin-12-one 16-oxide (second eluting diastereomer). The stereochemistry at the cyclopentyl sulfoximine ring was attributed arbitrarily. First eluting diastereomer: LC-MS (1): t_R = 0.88 min; [M+H]⁺: 469.1. Second eluting diastereomer: LC-MS (1): t_R = 0.87 min; [M+H]⁺: 469.0.

- 20 **(12aS,15aR,16S)-11-(4,4-Difluorocyclohexyl)-16-imino-3-methyl-6,7,8,9,10,11,12a,13,14,15,15a,16-dodecahydro-12H-16λ⁴-benzo[b]cyclopenta[e][1]oxa[4]thia[8]azacyclotridecin-12-one 16-oxide and (12aR,15aS,16S)-11-(4,4-difluorocyclohexyl)-16-imino-3-methyl-6,7,8,9,10,11,12a,13,14,15,15a,16-dodecahydro-12H-16λ⁴-benzo[b]cyclopenta[e][1]oxa[4]thia[8]azacyclotridecin-12-one 16-oxide :**
(12aR*,15aS*,16S)-11-(4,4-Difluorocyclohexyl)-16-imino-3-methyl-6,7,8,9,10,11,12a,13,14,15,15a,16-dodecahydro-12H-16λ⁴-benzo[b]cyclopenta[e][1]oxa[4]thia[8]azacyclotridecin-12-one 16-oxide was purified by prep. chiral SFC (SFC 7 method) to give (12aR,15aS,16S)-11-(4,4-difluorocyclohexyl)-16-imino-3-methyl-6,7,8,9,10,11,12a,13,14,15,15a,16-dodecahydro-12H-16λ⁴-benzo[b]cyclopenta[e][1]oxa[4]thia[8]azacyclotridecin-12-one 16-oxide (first eluting diastereomer) and (12aS,15aR,16S)-11-(4,4-difluorocyclohexyl)-16-imino-3-methyl-6,7,8,9,10,11,12a,13,14,15,15a,16-dodecahydro-12H-16λ⁴-benzo[b]cyclopenta[e][1]oxa[4]thia[8]azacyclotridecin-12-one 16-oxide (second eluting diastereomer). First eluting diastereomer: LC-MS (1): t_R = 0.87 min; [M+H]⁺: 469.0.
30 Second eluting diastereomer: LC-MS (1): t_R = 0.86 min; [M+H]⁺: 469.0.

Example 4.2 (6R,12aS,15aR,16S)-11-(4,4-Difluorocyclohexyl)-16-imino-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15,15a,16-dodecahydro-12H-16 λ⁴-cyclopenta[e]pyrido[2,3-b][1]oxa[4]thia[8]azacyclotridecin-12-one 16-oxide:

- 35 **Methyl (1RS,2RS)-2-((2-hydroxy-6-methylpyridin-3-yl)thio)cyclopentane-1-carboxylate:** (1RS,2SR)-2-((2-Fluoro-6-methylpyridin-3-yl)thio)cyclopentane-1-carboxylic acid (2.63 g, 10.3 mmol, 1 eq) was suspended in aq.

6M HCl soln. (25 mL). The reaction mixture was stirred at 100°C overnight. The reaction mixture was cooled to rt and the solvent was removed under reduced pressure. The residue was suspended in MeOH (130 mL) and the reaction mixture was stirred at 80°C overnight. The solvent was removed under reduced pressure and the residue was purified by FC (Hept to 100% EtOAc) to give the title compound. LC-MS (1): t_R = 0.71 min; $[M+H]^+$: 268.1.

- 5 **Methyl (1RS,2RS)-2-((2-(((R)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridin-3-yl)thio)cyclopentane-1-carboxylate:** Was synthesized using methyl (1RS,2RS)-2-((2-hydroxy-6-methylpyridin-3-yl)thio)cyclopentane-1-carboxylate and (S)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-ol in analogy to Example 4.1 to give the title compound. LC-MS (1): t_R = 1.40 min; $[M+H]^+$: 481.8.

- Methyl (1RS,2RS)-2-((2-(((R)-6-hydroxyhexan-2-yl)oxy)-6-methylpyridin-3-yl)thio)cyclopentane-1-carboxylate:** Was synthesized using methyl (1RS,2RS)-2-((2-(((R)-6-((*tert*-butyldimethylsilyl)oxy)hexan-2-yl)oxy)-6-methylpyridin-3-yl)thio)cyclopentane-1-carboxylate in analogy to Example 4.1 to give the title compound. LC-MS (1): t_R = 1.09 min; $[M+H]^+$: 368.1.

- Methyl (1RS,2RS)-2-((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)thio)cyclopentane-1-carboxylate:** Was synthesized using methyl (1RS,2RS)-2-((2-(((R)-6-hydroxyhexan-2-yl)oxy)-6-methylpyridin-3-yl)thio)cyclopentane-1-carboxylate in analogy to Example 4.1 to give the title compound. LC-MS (1): t_R = 1.06 min; $[M+H]^+$: 366.1.

- Methyl (1R*,2S*)-2-((2-(((R)-6-((4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-6-methylpyridin-3-yl)thio)cyclopentane-1-carboxylate:** Was synthesized using methyl (1RS,2RS)-2-((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)thio)cyclopentane-1-carboxylate and 4,4-difluorocyclohexylamine hydrochloride in analogy to Example 3.3 to give the title compound. LC-MS (1): t_R = 0.89 min; $[M+H]^+$: 485.1.

- (6R,12aR*,15aS*)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,13,14,15,15a-decahydrocyclopenta[e]pyrido[2,3-b][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one:** Was synthesized using methyl (1R*,2S*)-2-((2-(((R)-6-((4,4-difluorocyclohexyl)amino)hexan-2-yl)oxy)-6-methylpyridin-3-yl)thio)cyclopentane-1-carboxylate in analogy to Example 3.3 to give the title compound LC-MS (1): t_R = 1.17 and 1.19 min; $[M+H]^+$: 453.1.

- (6R,12aS,15aR,16S)-11-(4,4-Difluorocyclohexyl)-16-imino-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15,15a,16-dodecahydro-12H-16 λ^4 -cyclopenta[e]pyrido[2,3-b][1]oxa[4]thia[8]azacyclotridecin-12-one 16-oxide:** Was synthesized using (6R,12aR*,15aS*)-11-(4,4-difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,13,14,15,15a-decahydrocyclopenta[e]pyrido[2,3-b][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one and ammonium carbamate in analogy to Example 4.1. The residue was purified by prep. chiral SFC (SFC 34 method, fourth eluting diastereoisomer) to give the title compound. LC-MS (1): t_R = 0.94 min; $[M+H]^+$: 484.1.

Example 4.3 to Example 4.6 were synthesized using the appropriate amine or amine salt derivative and methyl (1RS,2RS)-2-((6-methyl-2-(((R)-6-oxohexan-2-yl)oxy)pyridin-3-yl)thio)cyclopentane-1-carboxylate in analogy to

Example 4.2. LC-MS data of Example 4.3 to Example 4.6 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
4.3	(6R, 12aS, 15aR, 16R)-11-((3R,6s)-1, 1-Difluorospiro[2.5]octan-6-yl)-16-imino-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15,15a,16-dodecahydro-12H-16λ ⁴ -cyclopenta[e]pyrido[2,3-b][1]oxa[4]thia[8]azacyclotridecin-12-one 16-oxide	1.01	510.0
4.4	(6R, 12aS, 15aR, 16S)-11-((3R,6s)-1, 1-Difluorospiro[2.5]octan-6-yl)-16-imino-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15,15a,16-dodecahydro-12H-16λ ⁴ -cyclopenta[e]pyrido[2,3-b][1]oxa[4]thia[8]azacyclotridecin-12-one 16-oxide	0.98	510.0
4.6	(1R,4s)-4-((6R, 12aS, 15aR, 16S)-16-Imino-3,6-dimethyl-16-oxido-12-oxo-7,8,9,10,12a,13,14,15,15a,16-decahydro-6H-16λ ⁴ -cyclopenta[e]pyrido[2,3-b][1]oxa[4]thia[8]azacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	0.91	487.1

5 **Example 4.7 to Example 4.10** were synthesized using the appropriate precursor and Mel in analogy to Example 2.1. LC-MS data of Example 4.7 to Example 4.10 are listed in the table below. The LC-MS conditions used were LC-MS (1).

Ex. N°	Name	t _R	[M+H] ⁺
4.7	(6R, 12aS, 15aR, 16S)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-16-(methylimino)-6,7,8,9,10,11,12a,13,14,15,15a,16-dodecahydro-12H-16λ ⁴ -cyclopenta[e]pyrido[2,3-b][1]oxa[4]thia[8]azacyclotridecin-12-one 16-oxide	0.92	497.8
4.8	(6R, 12aS, 15aR, 16S)-11-((3R,6s)-1, 1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-16-(methylimino)-6,7,8,9,10,11,12a,13,14,15,15a,16-dodecahydro-12H-16λ ⁴ -cyclopenta[e]pyrido[2,3-b][1]oxa[4]thia[8]azacyclotridecin-12-one 16-oxide	0.96	524.1
4.9	(1R,4s)-4-((6R, 12aS, 15aR, 16S)-3,6-Dimethyl-16-(methylimino)-16-oxido-12-oxo-7,8,9,10,12a,13,14,15,15a,16-decahydro-6H-16λ ⁴ -cyclopenta[e]pyrido[2,3-b][1]oxa[4]thia[8]azacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	0.89	501.1

4.10	(1R,4s)-4-((6R,12aS,15aR,16R)-3,6-Dimethyl-16-(methylimino)-16-oxido-12-oxo-7,8,9,10,12a,13,14,15,15a,16-decahydro-6H-16 λ^4 -cyclopenta[e]pyrido[2,3-b][1]oxa[4]thia[8]azacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile	0.92	501.1
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II-Biological assays

IP1 accumulation assay

- 5 Agonistic activity on the human orexin-2 receptor (hOX₂R) 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 (hOX₂R), 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% CO₂. 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 soln. 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).
- 10 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 soln.s, 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 soln. in H₂O, diluted to 4-times its final concentration in Stimulation buffer supplemented with 0.2% BSA.
- 15 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% CO₂. The assay is terminated by addition of lysis buffer containing IP1-detection reagents according to the kit's instructions. After 1 h lysis at rt, 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).

25 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 (EC₅₀) 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).

EC₅₀ 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 EC₅₀ 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. EC₅₀ and Emax values from several measurements are given as median values.

Agonistic activities of example compounds on hOX₂R are displayed in Table 1.

Table 1

Ex. Number	EC50 [nM]	Emax %	Ex. Number	EC50 [nM]	Emax %	Ex. Number	EC50 [nM]	Emax %
1.1	50	100	1.215	70	110	1.432	0.4	110
1.2	500	100	1.218	70	110	1.433	0.4	100
1.3	3	95	1.219	400	110	1.434	2	92
1.4	60	90	1.220	200	110	1.435	7	100
1.6	20	110	1.221	50	89	1.438	4	91
1.5	100	100	1.223	1	100	1.439	0.1	100
1.7	30	100	1.224	3	120	1.440	1	98
1.8	300	97	1.225	0.1	100	1.441	0.02	100
1.9	60	100	1.226	1	98	1.442	0.1	100
1.10	100	110	1.227	10	110	1.443	0.3	100
1.11	9	120	1.228	10	110	1.444	4	91
1.12	30	99	1.229	30	100	1.445	0.01	100
1.13	3	100	1.230	90	100	1.446	0.2	98
1.14	20	98	1.231	100	100	1.447	1	100
1.15	2	96	1.232	80	100	1.448	1	100
1.18	20	90	1.233	20	100	1.449	0.05	100
1.19	10	100	1.234	100	88	1.450	0.1	99
1.20	200	90	1.235	200	110	1.451	0.02	100
1.21	60	110	1.236	50	98	1.452	0.1	100
1.22	40	100	1.237	100	110	1.453	0.3	96
1.23	400	94	1.238	30	100	1.454	2	95
1.24	50	110	1.239	400	110	1.455	0.01	100

1.25	200	94	1.240	100	67	1.456	0.04	98
1.26	80	99	1.241	1	110	1.457	0.3	100
1.27	100	100	1.242	40	90	1.458	2	97
1.28	300	93	1.243	2	100	1.459	0.2	100
1.29	300	100	1.247	5	100	1.460	1	99
1.30	100	95	1.248	30	110	1.461	1	100
1.31	200	99	1.249	7	89	1.462	6	99
1.32	8	100	1.250	40	110	1.463	3	100
1.33	200	110	1.252	200	88	1.464	1	100
1.34	200	95	1.253	70	96	1.465	4	93
1.35	60	100	1.254	400	84	1.466	1	100
1.36	2	100	1.256	0.4	110	1.469	0.2	100
1.37	80	96	1.257	20	110	1.472	4	98
1.38	100	110	1.259	20	100	1.473	1	100
1.39	300	98	1.260	300	75	1.475	0.2	100
1.40	0.4	100	1.261	400	98	1.476	0.3	100
1.41	8	97	1.262	80	86	1.477	0.2	99
1.42	60	100	1.263	4	110	1.478	2	85
1.43	50	100	1.264	100	100	1.480	0.4	110
1.44	60	90	1.266	5	110	1.482	1	100
1.45	300	95	1.267	2	100	1.483	3	110
1.46	200	100	1.268	10	100	1.484	1	89
1.48	1	100	1.269	0.3	110	1.485	6	97
1.49	300	110	1.270	300	90	1.487	1	97
1.50	30	110	1.271	60	95	1.488	1	100
1.51	1	100	1.272	7	110	1.489	2	110
1.52	0.3	110	1.273	1	110	1.493	2	87
1.53	10	97	1.275	1	110	1.494	0.3	100
1.54	30	100	1.276	60	95	1.495	1	100
1.55	80	97	1.277	60	110	1.496	2	100
1.56	8	88	1.278	1	100	1.497	2	110
1.57	<0.1	100	1.279	200	100	1.501	3	100
1.58	20	100	1.280	80	51	1.504	1	100
1.59	8	100	1.281	100	110	1.505	10	94
1.60	50	100	1.282	0.2	99	1.507	2	94

1.61	10	98	1.283	5	110	1.508	1	97
1.62	40	100	1.284	0.4	100	1.509	0.3	97
1.63	30	99	1.285	0.1	100	1.512	8	110
1.64	200	84	1.286	10	95	1.514	10	100
1.65	10	94	1.289	<0.1	100	1.517	1	100
1.66	200	110	1.291	0.2	100	1.518	<0.3	98
1.67	20	98	1.292	<0.1	100	1.522	6	95
1.68	70	110	1.293	5	98	1.527	2	100
1.69	2	110	1.294	9	93	1.529	0.4	100
1.70	70	100	1.296	400	45	1.532	1	110
1.71	20	96	1.297	90	100	1.533	3	94
1.72	40	99	1.298	30	21	1.534	7	110
1.73	1	100	1.299	50	100	1.535	4	83
1.74	60	110	1.300	5	110	1.536	1	110
1.75	10	110	1.301	400	98	1.537	0.3	98
1.76	300	90	1.302	50	100	1.538	9	100
1.77	400	100	1.303	50	110	1.539	0.1	100
1.78	400	94	1.320	80	110	1.540	0.4	100
1.79	500	65	1.324	200	93	1.541	0.03	100
1.80	100	98	1.325	50	100	1.542	0.3	96
1.81	300	91	1.326	2	100	1.543	3	100
1.82	3	97	1.327	4	100	1.544	8	100
1.83	200	100	1.328	10	92	1.545	3	100
1.84	4	100	1.329	10	110	1.547	2	100
1.85	100	100	1.330	1	100	1.548	6	89
1.86	70	100	1.331	10	85	1.551	1	100
1.87	100	94	1.332	1	100	1.554	1	99
1.88	100	97	1.333	6	94	1.556	2	91
1.89	10	91	1.334	1	110	1.558	1	100
1.90	300	95	1.335	1	110	1.559	<0.1	100
1.91	200	81	1.336	0.3	110	1.560	6	92
1.92	300	95	1.337	0.4	100	1.579	1	110
1.93	100	92	1.338	0.2	98	1.581	1	100
1.94	60	53	1.339	9	92	1.582	3	95
1.95	4	100	1.342	2	93	1.590	3	110

1.96	20	99	1.344	1	110	1.591	1	110
1.97	100	94	1.345	5	110	1.592	2	110
1.98	1	110	1.346	2	98	1.593	4	100
1.99	3	110	1.347	2	120	1.594	6	110
1.100	20	100	1.348	0.3	100	1.595	0.1	98
1.101	400	50	1.349	2	96	1.596	1	97
1.102	10	100	1.350	0.3	100	1.599	10	110
1.103	20	110	1.351	1	100	1.600	3	110
1.104	30	110	1.352	2	100	1.601	3	110
1.105	1	100	1.353	2	110	1.605	4	95
1.107	200	88	1.354	1	110	1.608	4	95
1.108	80	110	1.355	1	110	1.609	1	99
1.109	10	110	1.356	<0.1	100	1.610	6	98
1.110	20	110	1.357	0.1	98	1.615	1	100
1.112	20	100	1.358	0.3	110	1.617	10	100
1.113	200	110	1.359	0.2	99	1.618	1	100
1.118	30	100	1.360	2	91	1.619	4	98
1.119	1	100	1.363	0.2	110	1.620	0.3	100
1.120	3	100	1.364	5	110	1.629	2	110
1.121	5	93	1.365	1	100	1.631	5	93
1.122	4	110	1.366	1	100	1.633	3	89
1.123	60	110	1.367	2	100	1.634	1	100
1.124	1	110	1.368	1	110	1.635	0.1	100
1.125	20	100	1.369	0.4	98	1.638	0.2	99
1.126	30	97	1.370	4	120	1.639	<0.1	100
1.127	200	100	1.371	1	110	1.641	4	95
1.128	20	98	1.372	1	100	1.642	0.3	100
1.129	80	58	1.373	1	100	1.643	<0.1	100
1.130	100	93	1.374	10	86	1.644	<0.1	100
1.131	300	100	1.375	5	110	1.645	1	100
1.132	90	94	1.376	10	94	1.646	4	95
1.133	200	110	1.377	1	110	1.647	0.1	100
1.134	100	110	1.378	5	110	1.650	7	91
1.135	20	93	1.379	1	91	1.653	0.2	110
1.136	30	94	1.380	0.3	100	1.654	0.3	100

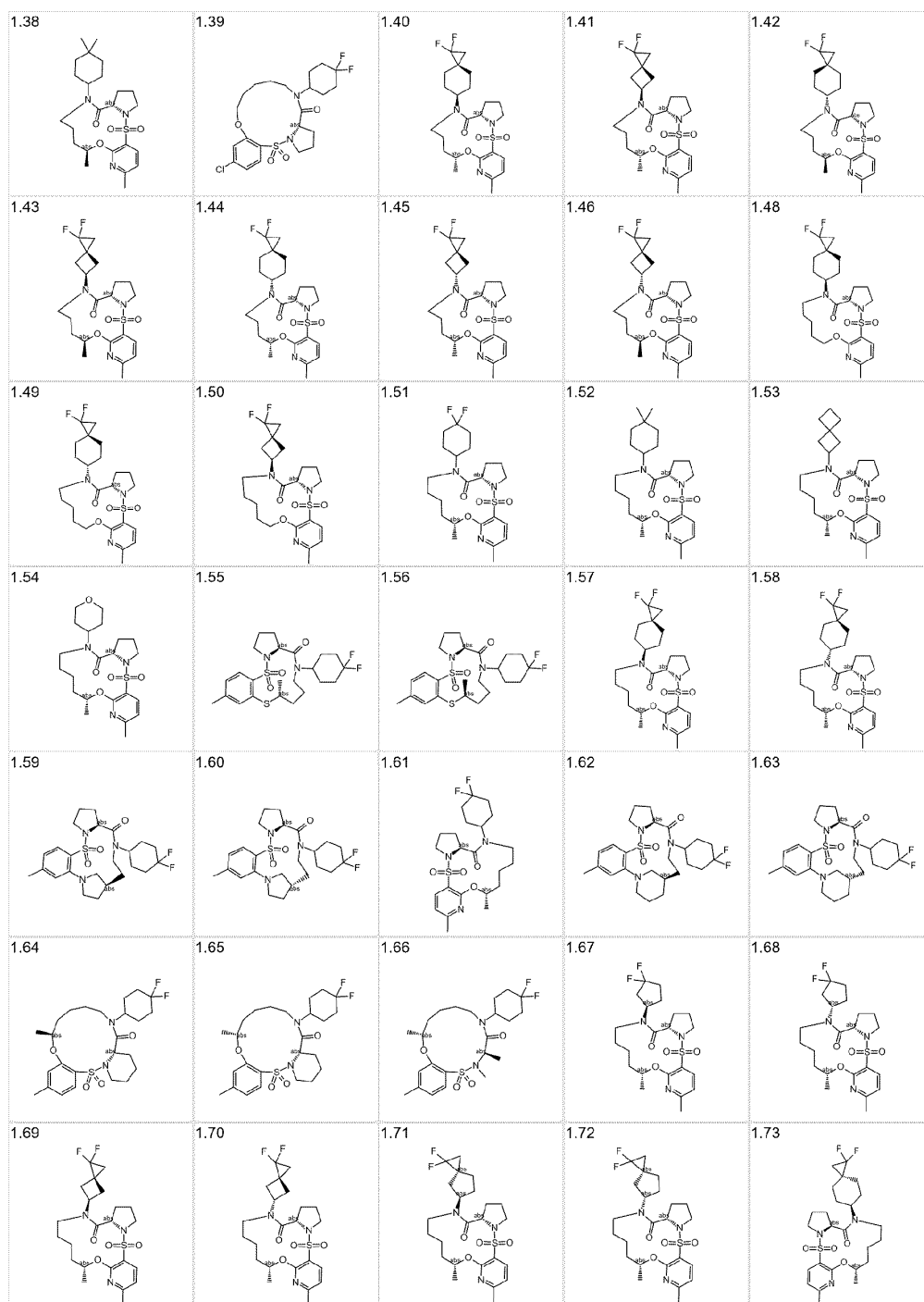
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1.140	40	100	1.385	6	94	1.659	1	100
1.141	<0.1	99	1.386	10	97	1.660	1	98
1.142	200	100	1.387	0.3	100	1.661	1	100
1.143	1	100	1.388	<0.1	97	1.662	0.3	100
1.144	50	100	1.389	2	100	1.663	2	100
1.145	0.5	100	1.390	0.1	100	1.664	6	97
1.146	200	120	1.391	1	98	1.665	9	86
1.149	20	110	1.392	2	100	1.666	1	100
1.150	400	120	1.393	0.02	100	1.667	2	110
1.162	0.3	100	1.394	1	110	1.668	3	98
1.166	5	91	1.395	1	100	1.669	0.3	110
1.167	200	90	1.396	0.2	100	1.671	0.3	110
1.168	20	81	1.397	4	100	1.672	<0.1	110
1.173	9	100	1.398	1	100	1.673	2	110
1.177	30	120	1.399	1	99	1.674	3	110
1.178	3	100	1.400	4	95	1.675	1	100
1.179	40	100	1.401	1	99	1.676	0.1	100
1.183	200	100	1.402	3	100	1.677	0.4	94
1.184	20	97	1.403	1	100	1.679	1	100
1.185	10	100	1.404	10	100	1.680	<0.2	100
1.188	300	80	1.405	4	110	1.681	8	97
1.189	100	100	1.406	0.4	98	1.682	10	91
1.190	500	87	1.407	9	100	1.683	4	100
1.191	20	110	1.408	0.03	110	1.684	8	97
1.192	10	99	1.409	1	98	1.685	3	97
1.193	1	100	1.410	0.02	100	1.689	1	110
1.194	100	81	1.411	1	100	1.690	5	100
1.196	500	95	1.412	1	99	1.691	1	100
1.197	50	100	1.413	10	93	1.692	1	100
1.202	2	100	1.414	0.5	100	1.693	8	94
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1.204	9	130	1.416	2	96	1.701	0.4	100

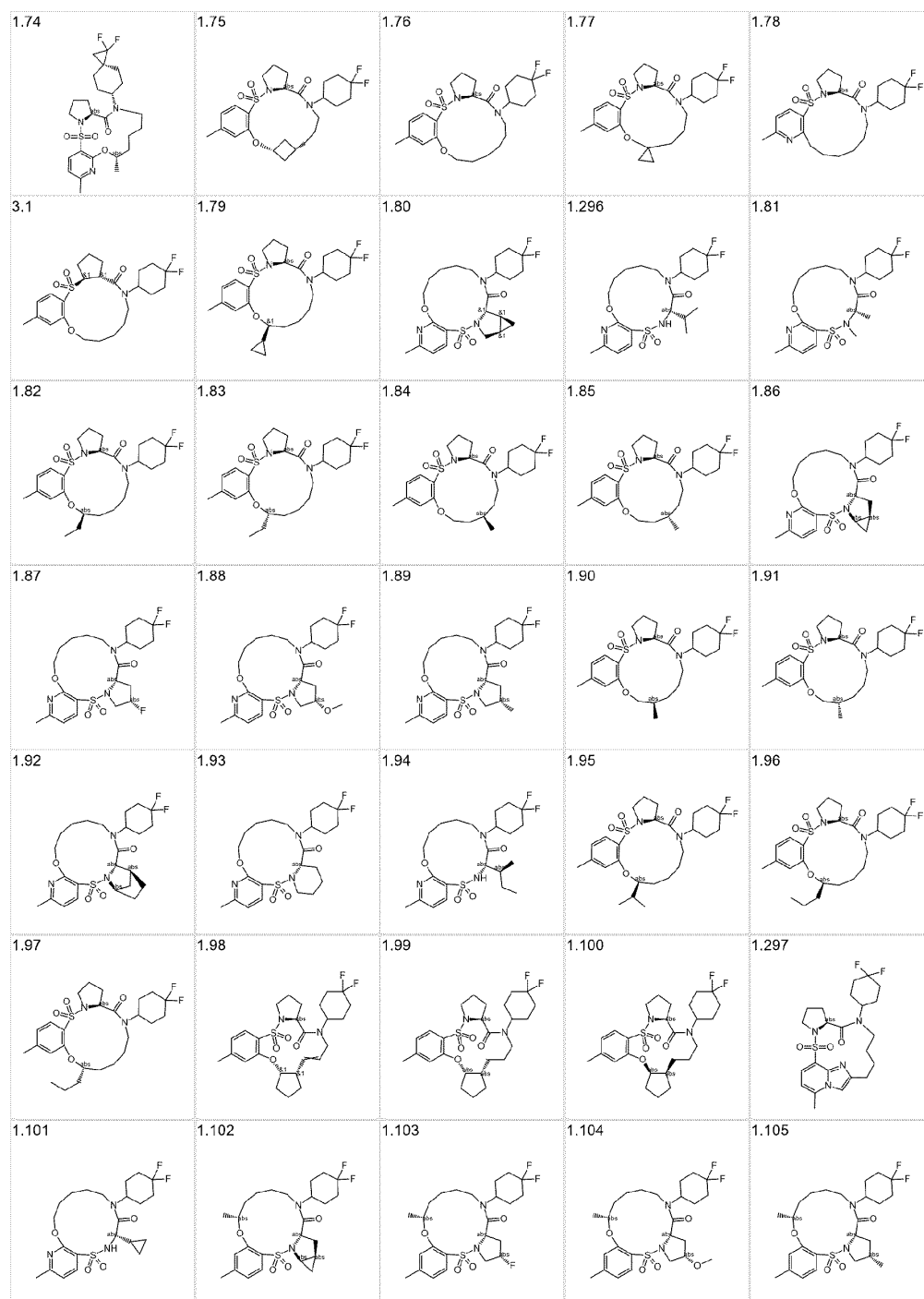
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1.208	60	95	1.418	2	120	1.707	1	97
1.209	20	120	1.425	<0.1	110	1.710	1	100
1.210	100	110	1.428	0.04	100	1.711	1	100
1.211	4	100	1.429	0.3	110	1.712	0.4	100
1.213	1	96	1.430	0.1	100			
1.214	0.1	100	1.431	1	97			
2.1	300	110	2.67	1	110	2.120	1	95
2.2	300	90	2.69	1	100	2.121	6	100
2.3	300	98	2.70	7	110	2.122	1	100
2.4	300	93	2.71	2	97	2.123	2	99
2.5	8	88	2.72	1	100	2.124	4	99
2.6	9	99	2.73	10	99	2.125	0.01	100
2.7	3	110	2.75	6	99	2.126	1	99
2.8	50	97	2.76	6	96	2.127	0.04	110
2.9	5	98	2.77	2	97	2.128	3	110
2.10	0.5	100	2.78	3	96	2.129	1	91
2.11	5	100	2.79	1	100	2.130	0.1	100
2.12	0.2	100	2.80	2	110	2.131	4	120
2.13	4	100	2.81	2	110	2.132	3	89
2.14	0.3	100	2.82	4	100	2.133	<0.1	100
2.16	3	100	2.83	0.1	100	2.134	<0.1	100
2.26	3	100	2.84	0.2	100	2.135	6	97
2.28	5	120	2.85	1	100	2.136	8	96
2.30	2	120	2.86	1	100	2.137	3	100
2.32	20	110	2.87	1	110	2.138	0.2	100
2.34	2	100	2.88	3	91	2.139	0.1	100
2.36	1	110	2.89	<0.1	100	2.140	0.4	100
2.38	1	100	2.90	1	100	2.141	1	100
2.39	1	120	2.92	1	100	2.142	2	97
2.41	3	92	2.93	2	120	2.143	8	90
2.42	2	110	2.94	0.3	100	2.144	0.4	100
2.43	8	98	2.95	0.5	110	2.145	0.2	100
2.44	5	100	2.96	8	110	2.146	1	99

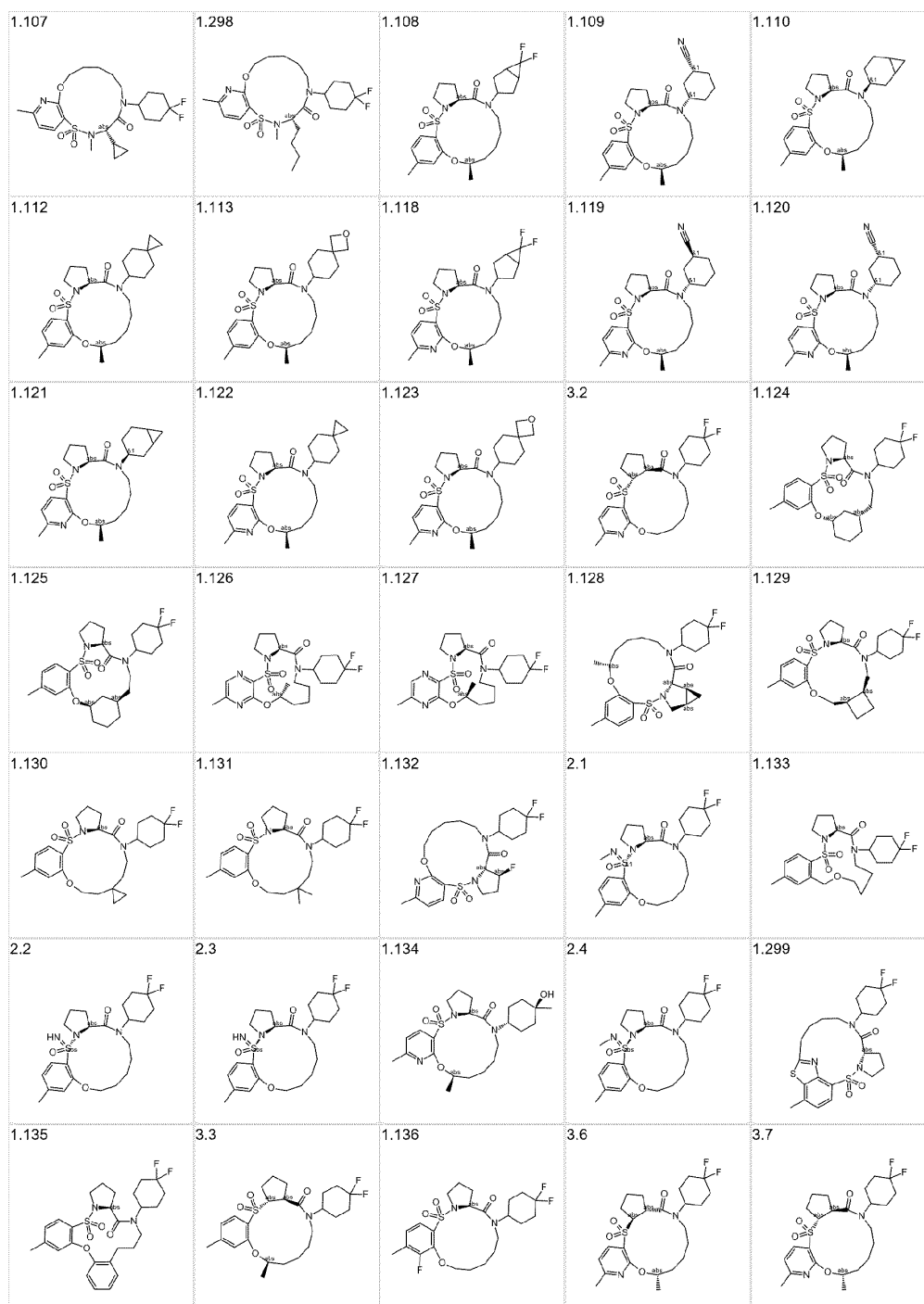
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2.47	0.1	98	2.99	7	99	2.149	2	96
2.48	1	97	2.100	1	95	2.150	2	99
2.49	4	100	2.101	0.5	100	2.151	1	93
2.50	0.04	110	2.102	0.3	100	2.152	0.2	97
2.51	0.05	100	2.103	4	100	2.153	0.2	100
2.52	7	82	2.104	0.3	99	2.154	0.1	110
2.53	7	100	2.105	1	100	2.155	<0.1	110
2.54	5	92	2.106	1	100	2.160	8	100
2.55	2	94	2.107	0.5	100	2.161	1	100
2.56	10	94	2.108	1	100	2.162	2	100
2.57	1	86	2.109	0.4	100	2.163	8	92
2.58	<0.1	110	2.110	10	110	2.164	4	80
2.59	0.3	110	2.111	3	95	2.167	9	93
2.60	<0.1	100	2.112	0.3	110	2.168	2	96
2.61	2	97	2.113	<0.2	110	2.169	2	91
2.62	1	100	2.114	2	100	2.170	2	95
2.63	1	110	2.115	3	99	2.171	9	97
2.64	4	97	2.116	2	84	2.173	1	95
2.65	3	100	2.117	<0.2	97	2.175	1	100
2.66	1	110	2.118	4	90			
3.1	100	95	4.1	300	110	4.9	1	94
3.2	10	100	4.2	3	96	4.10	9	100
3.3	80	100	4.3	1	100			
3.4	1	110	4.4	1	99			
3.5	10	100	4.6	<0.2	93			
3.6	500	90	4.7	10	97			
3.7	300	98	4.8	1	99			

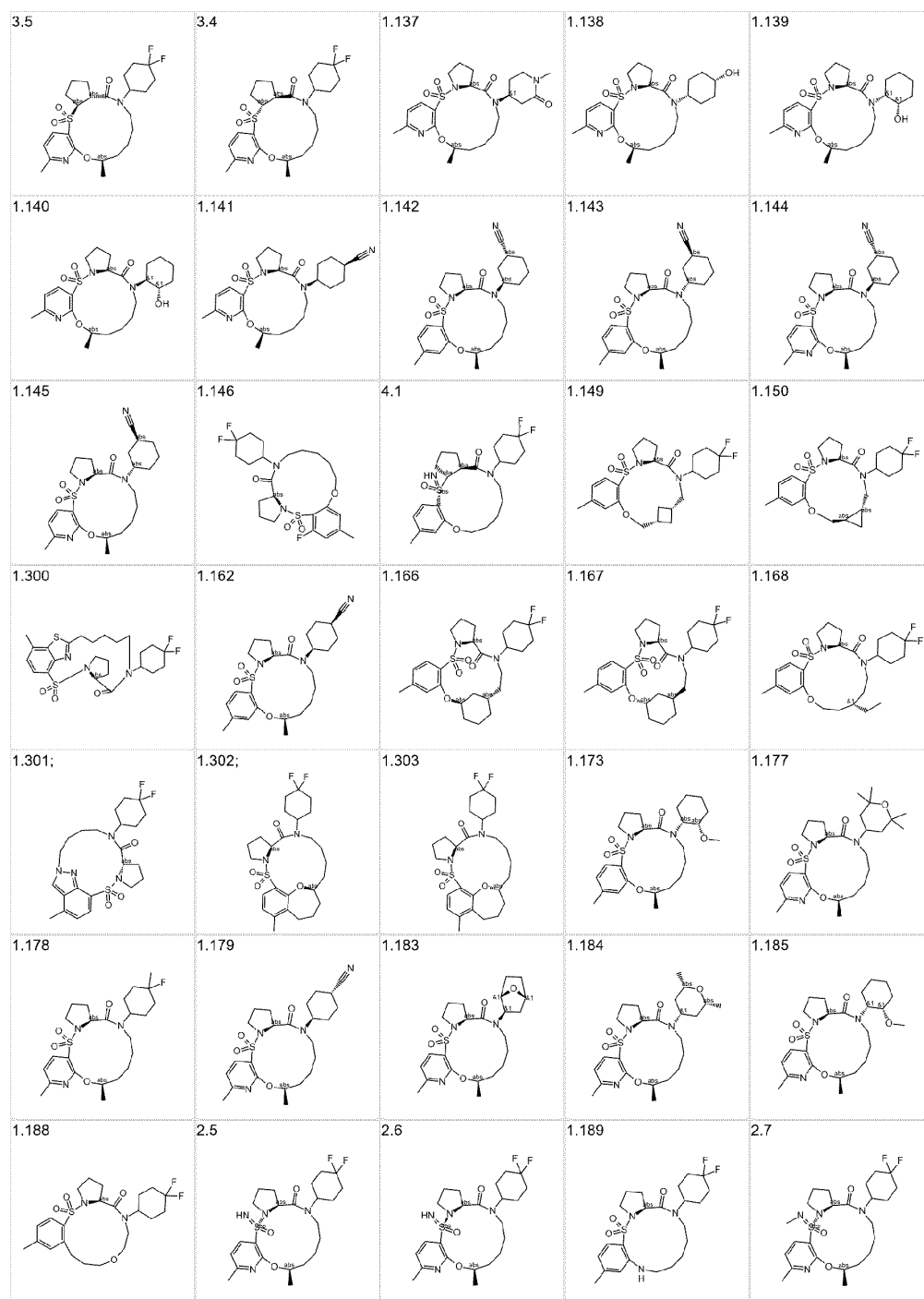
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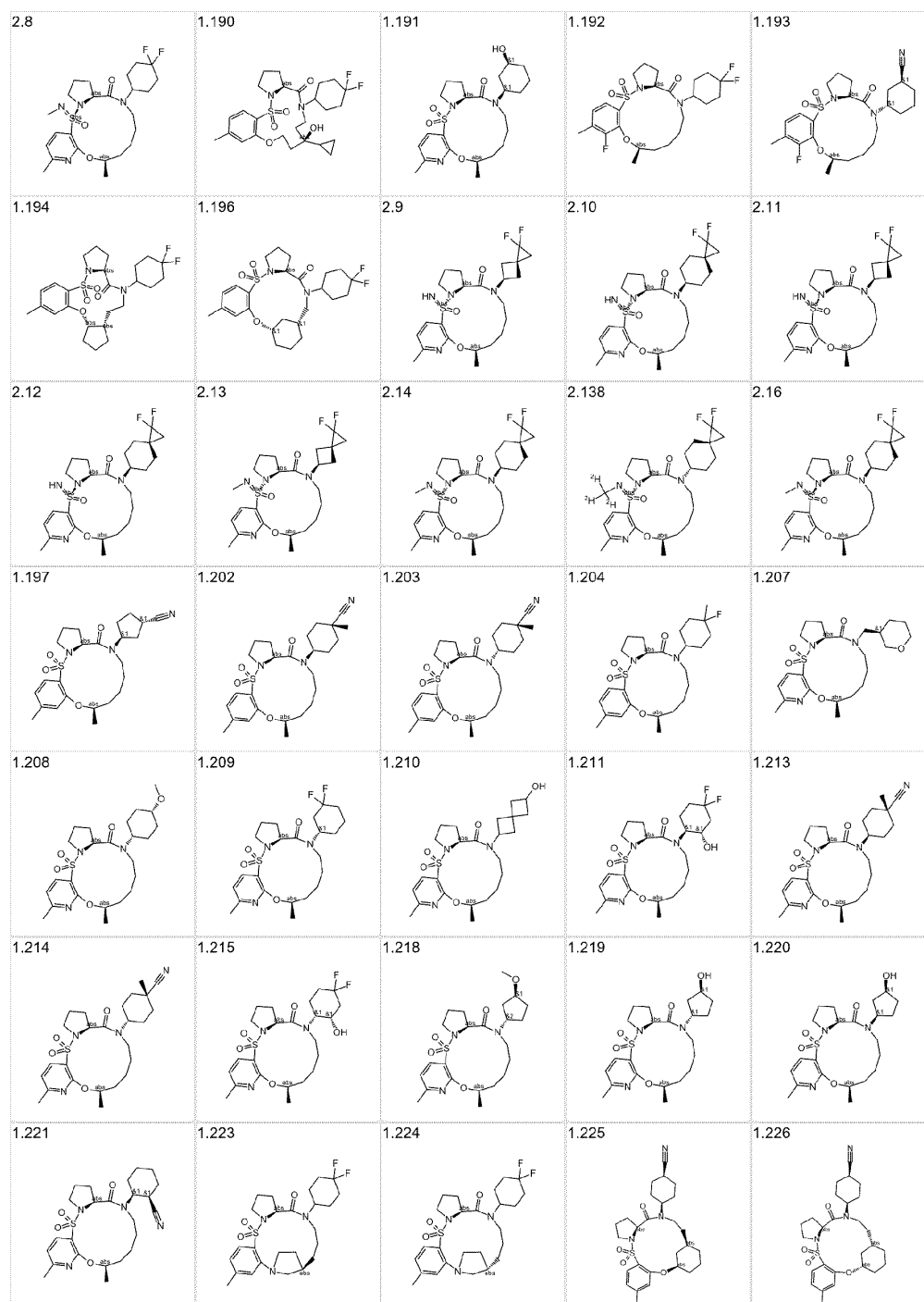
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1.18	1.19	1.20	1.21	1.22
1.23	1.24	1.25	1.26	1.27
1.28	1.29	1.30	1.31	1.32
1.33	1.34	1.35	1.36	1.37

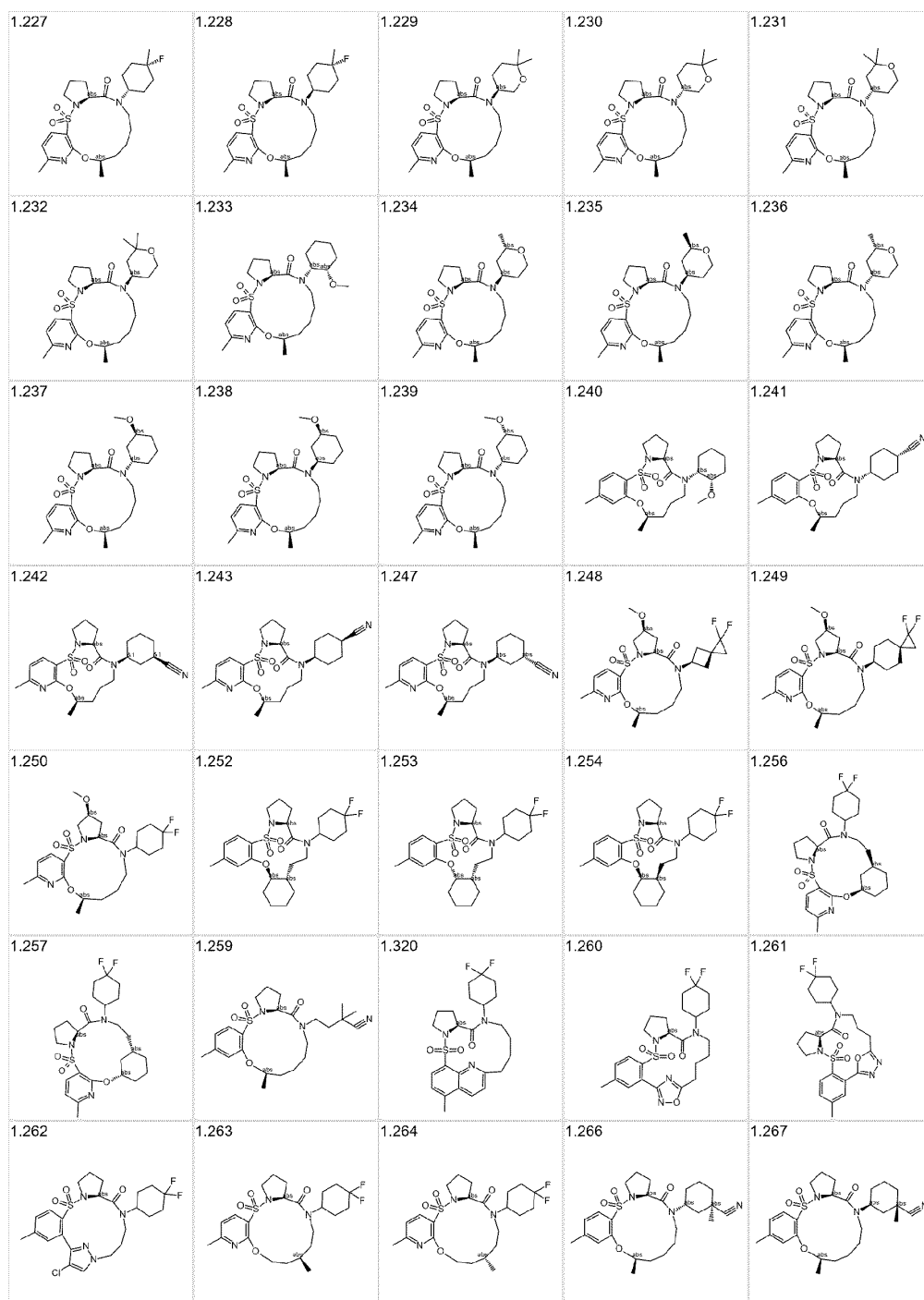


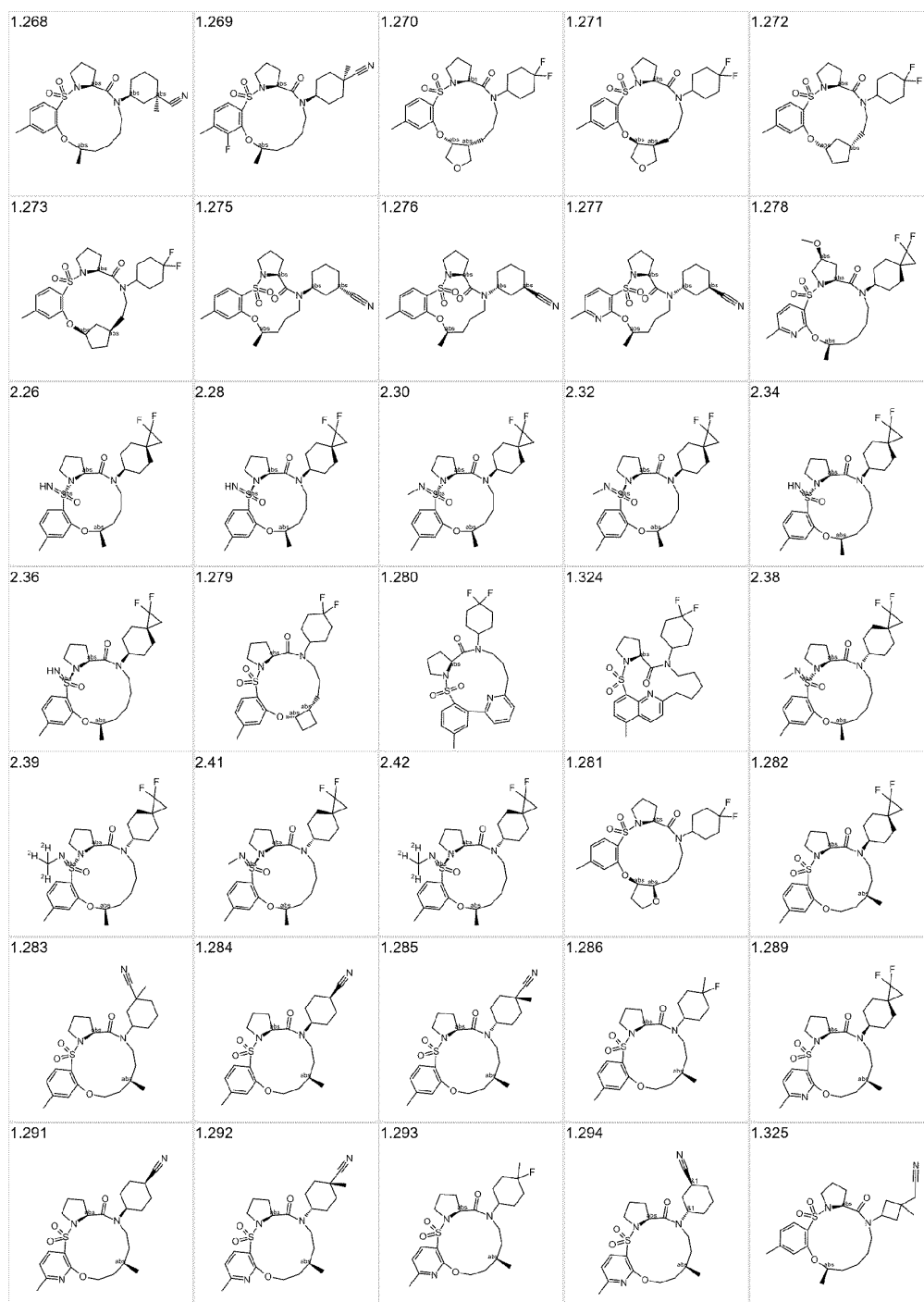


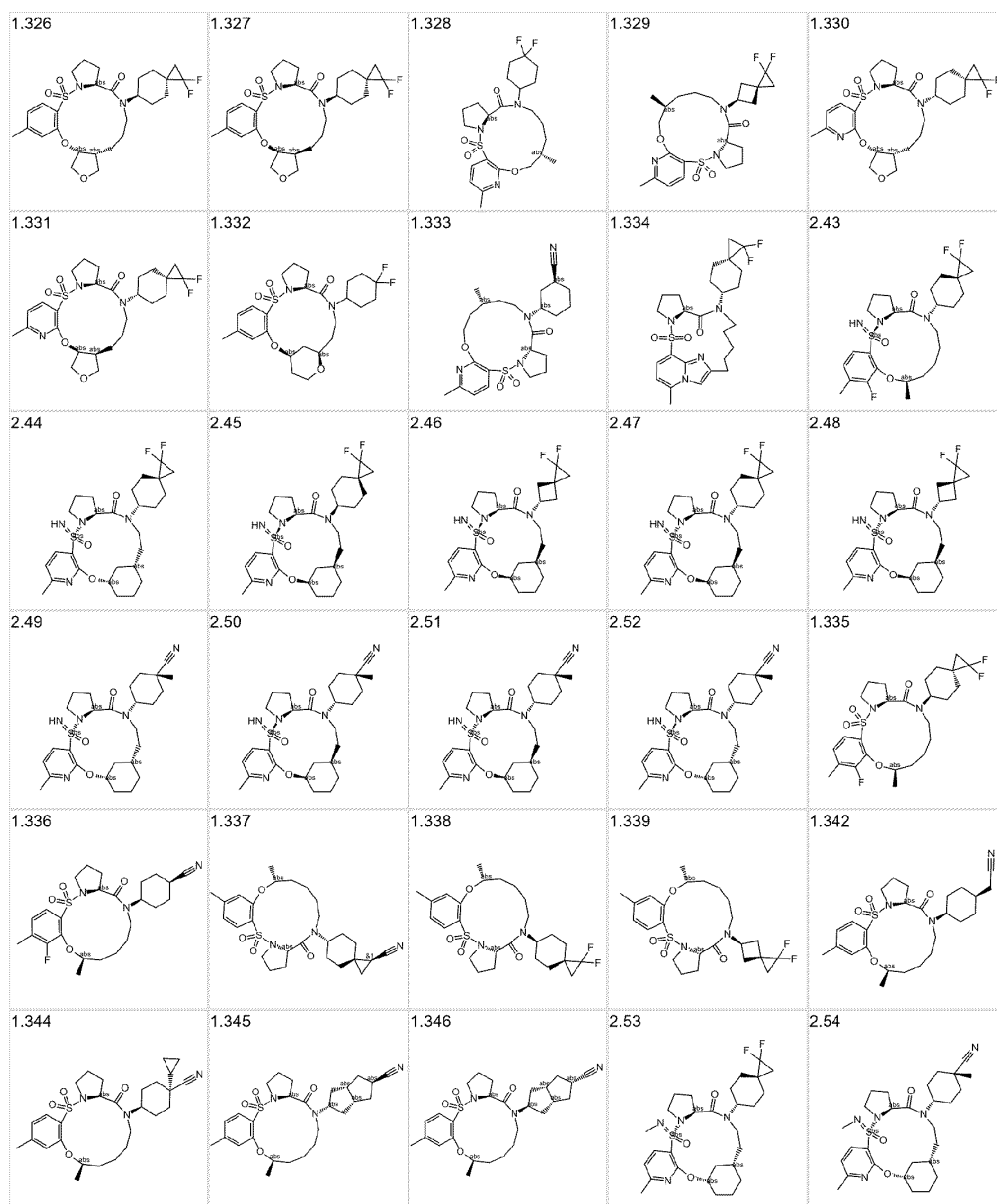


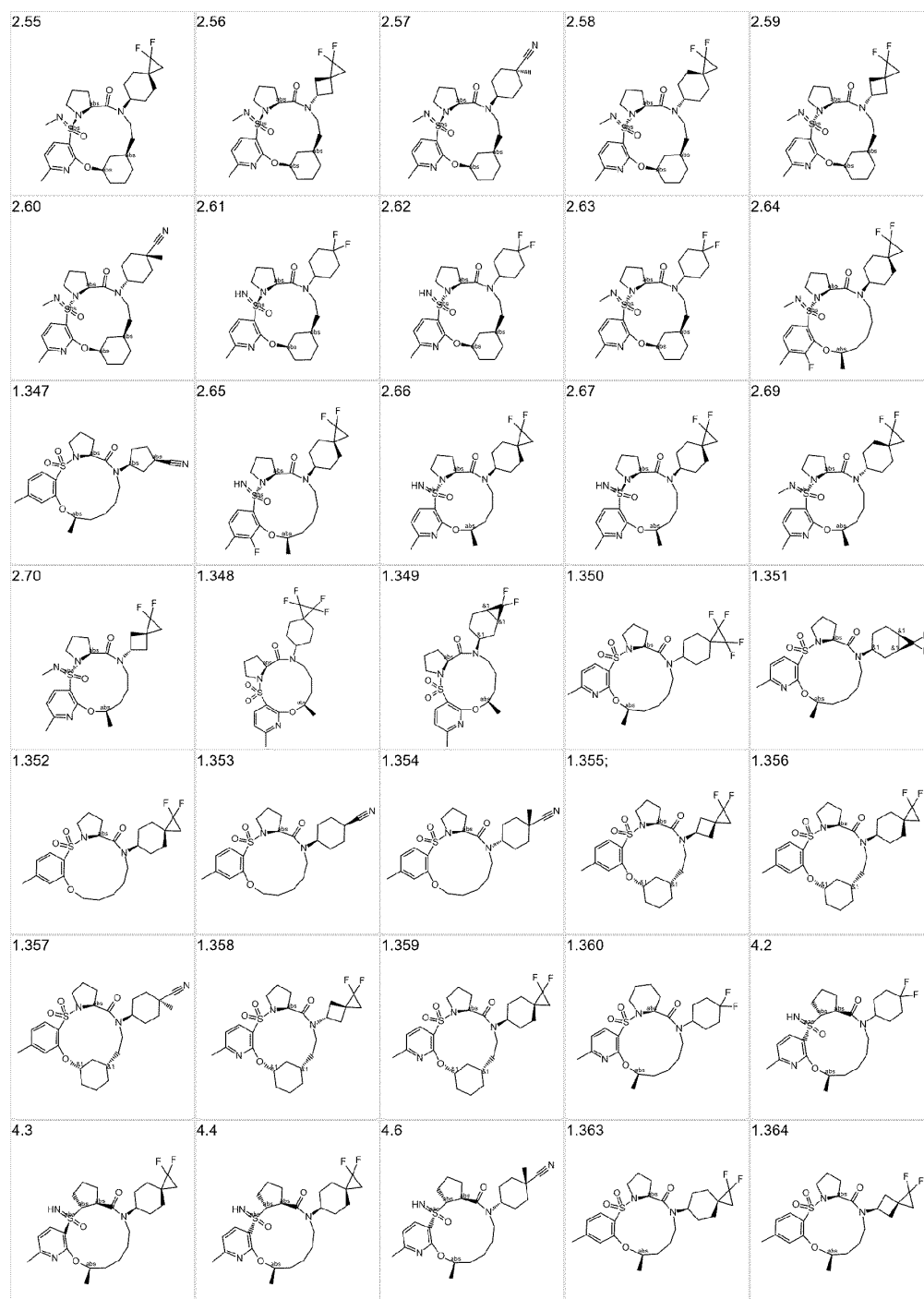


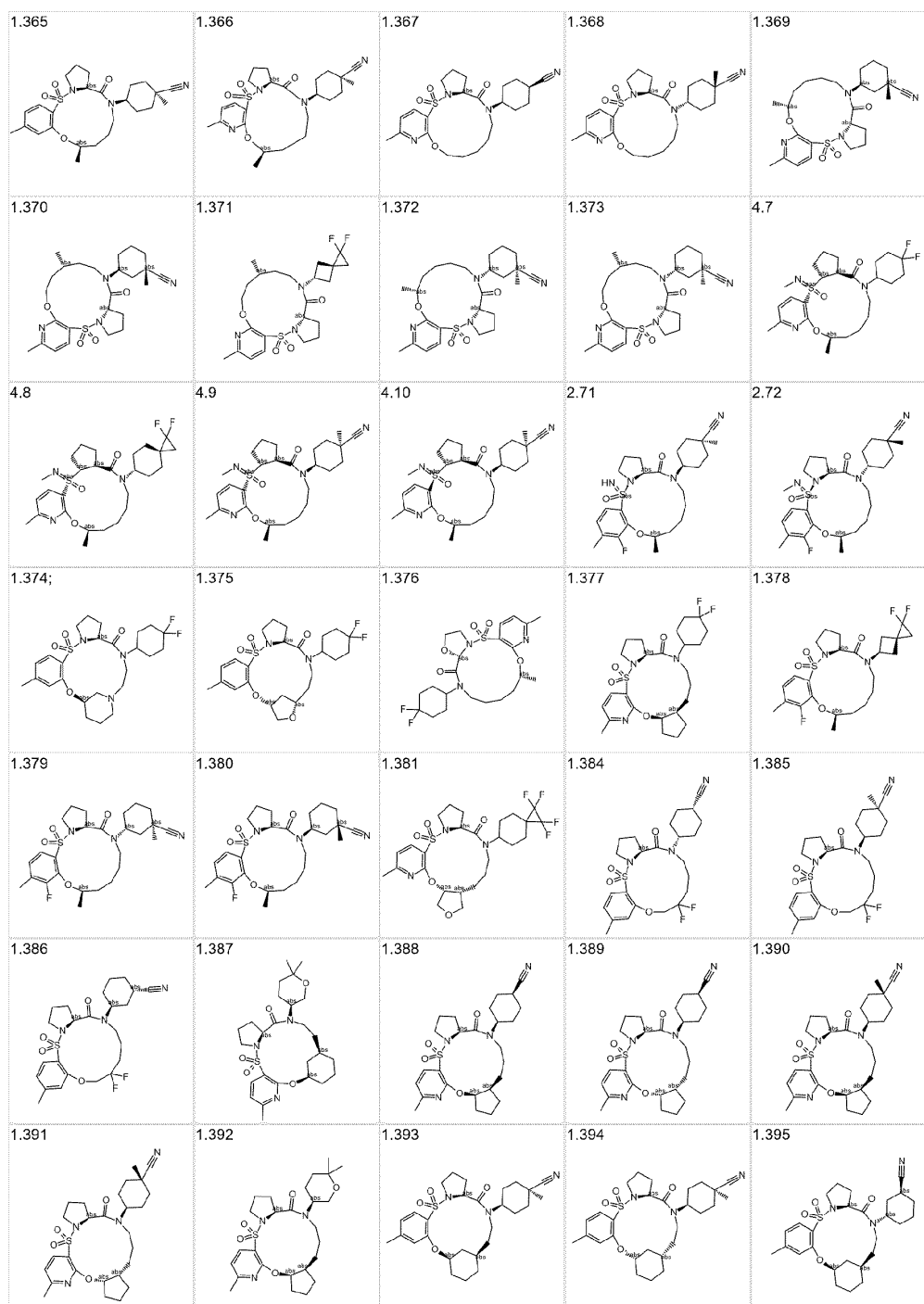


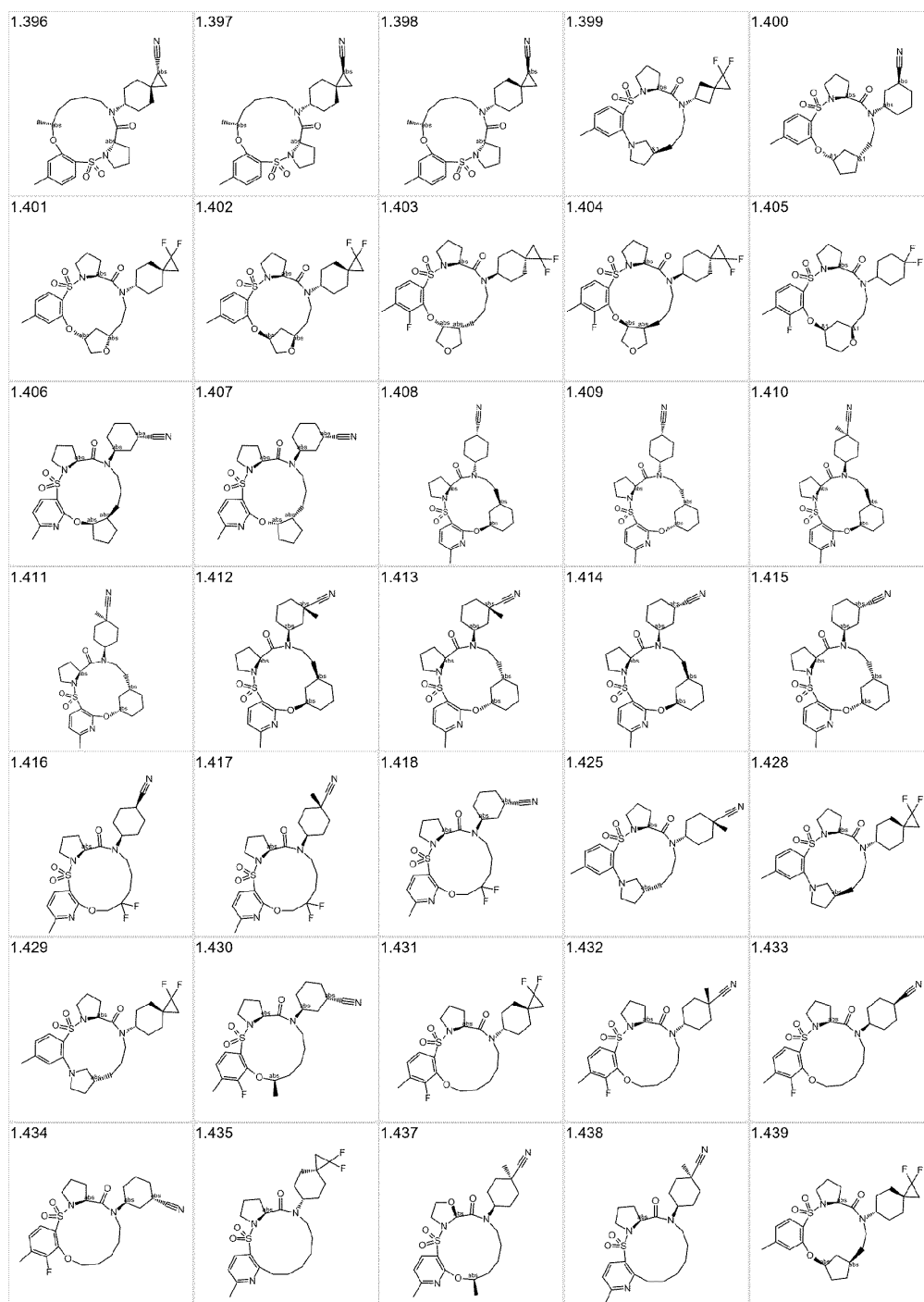


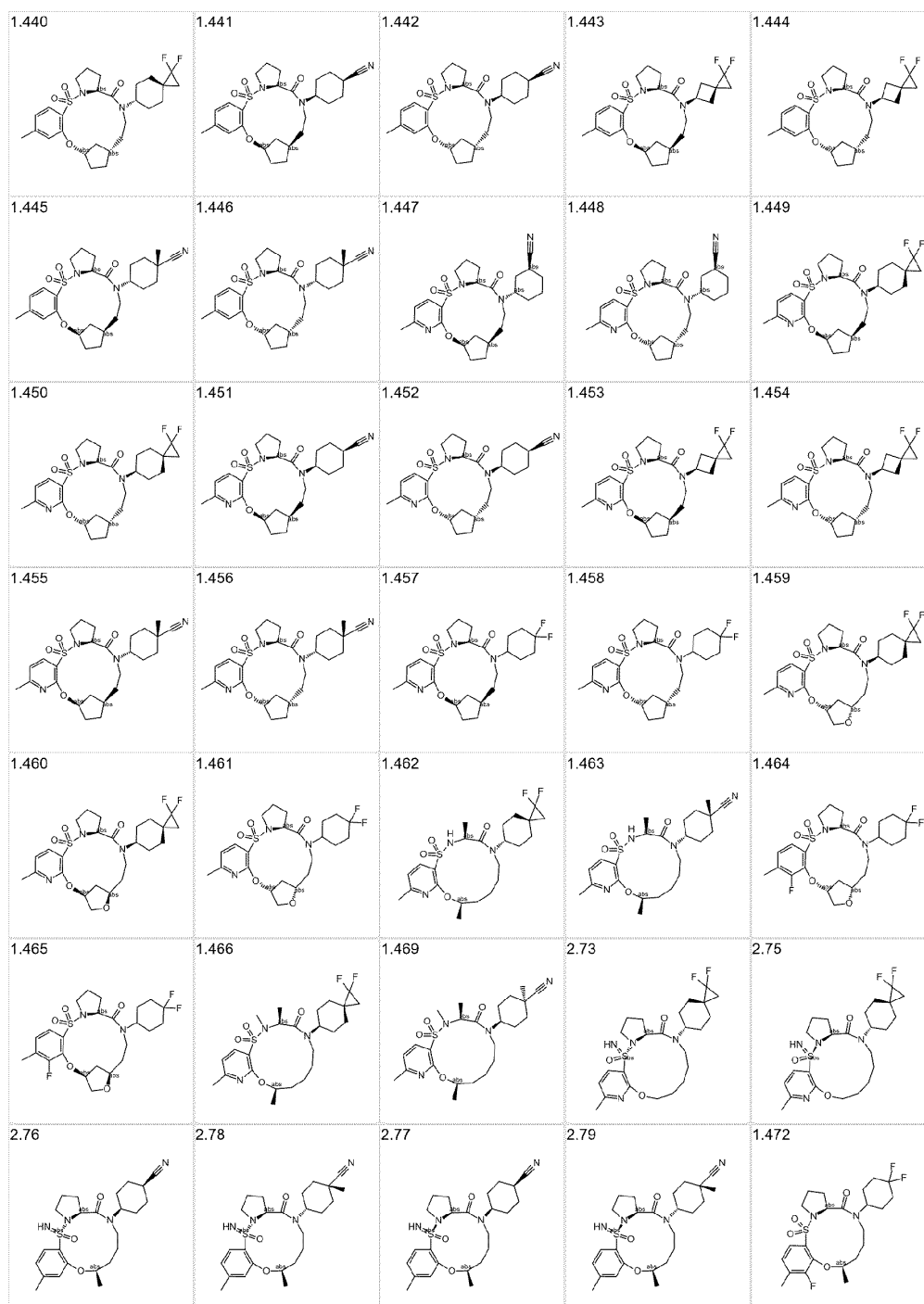


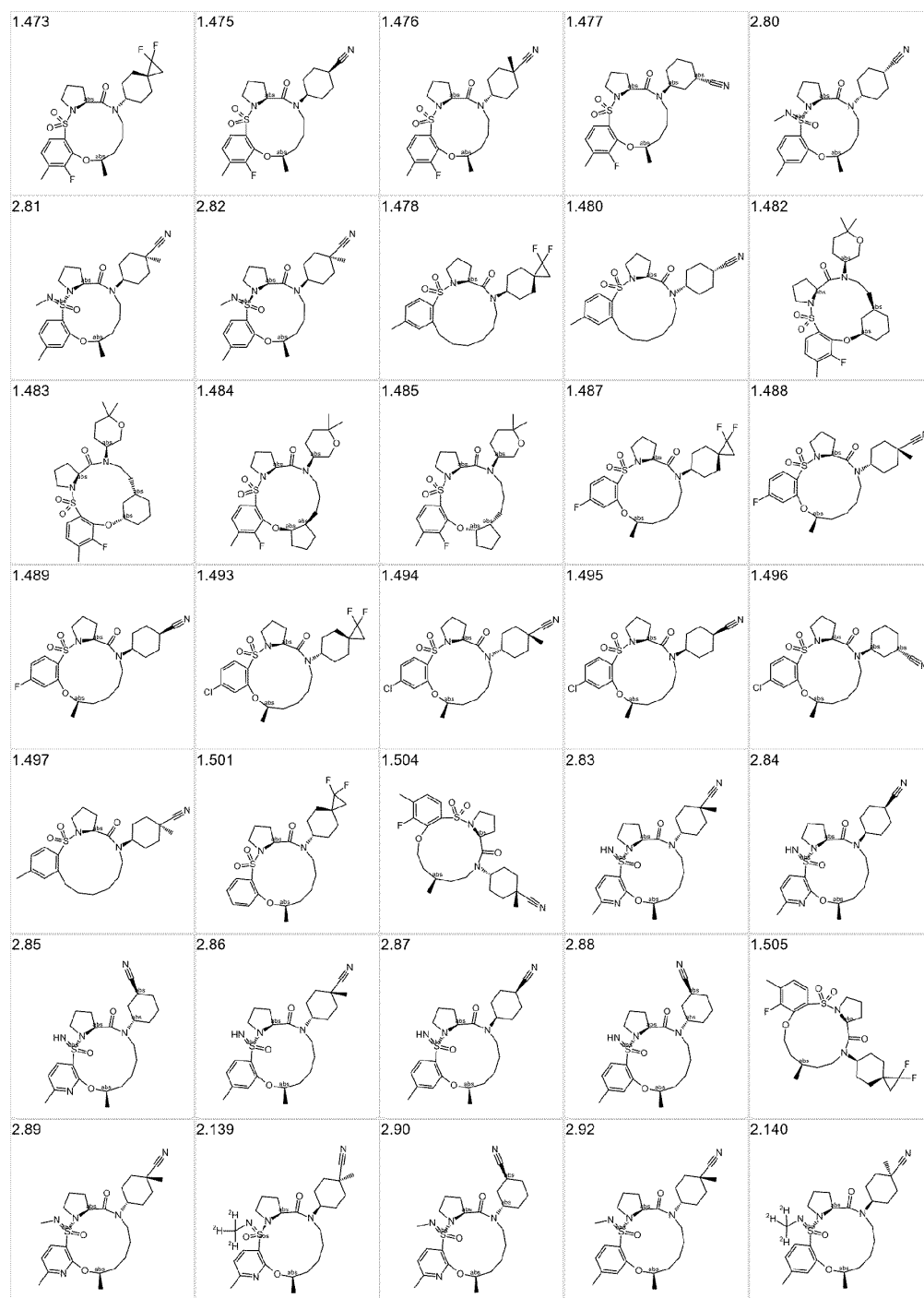


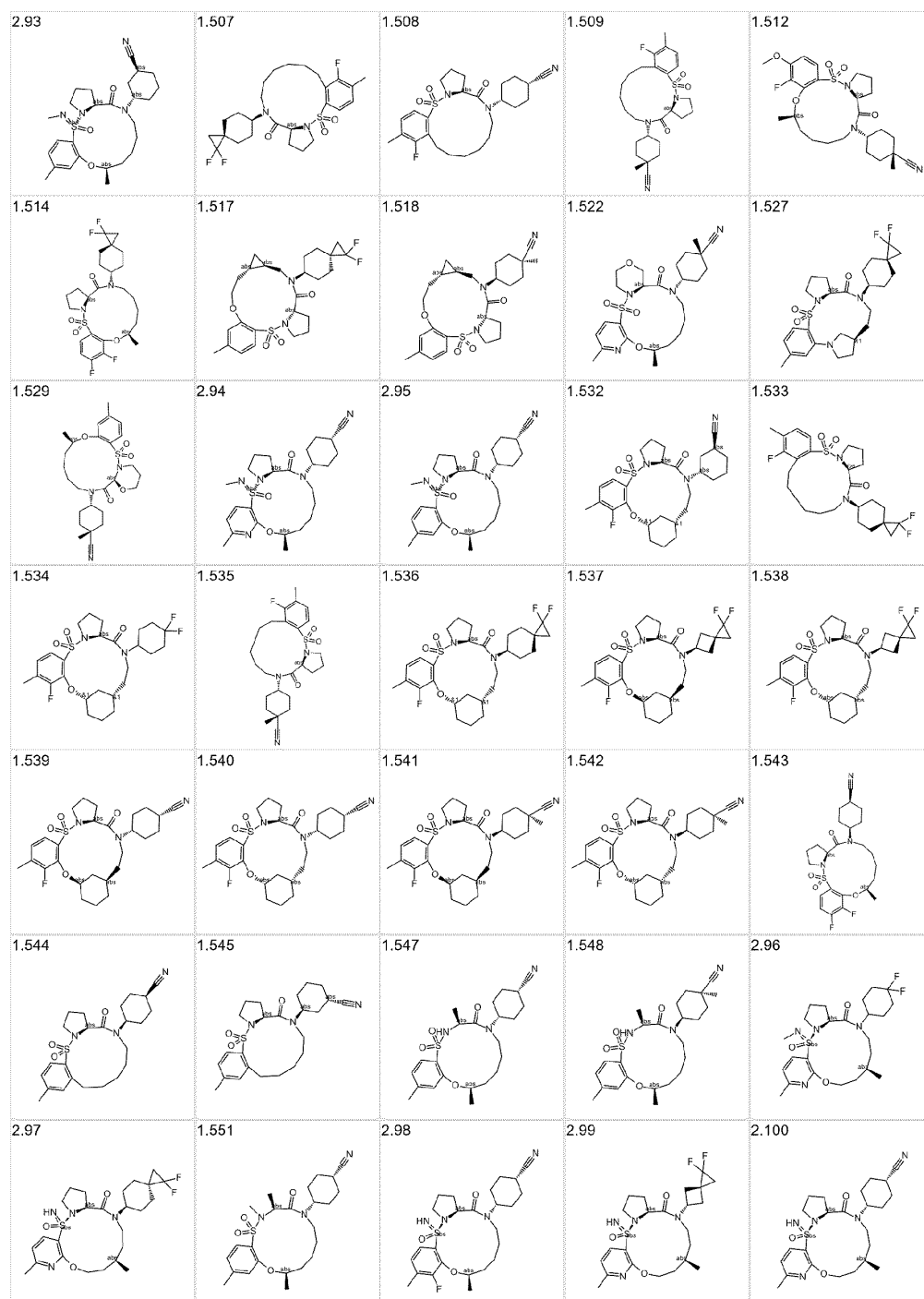


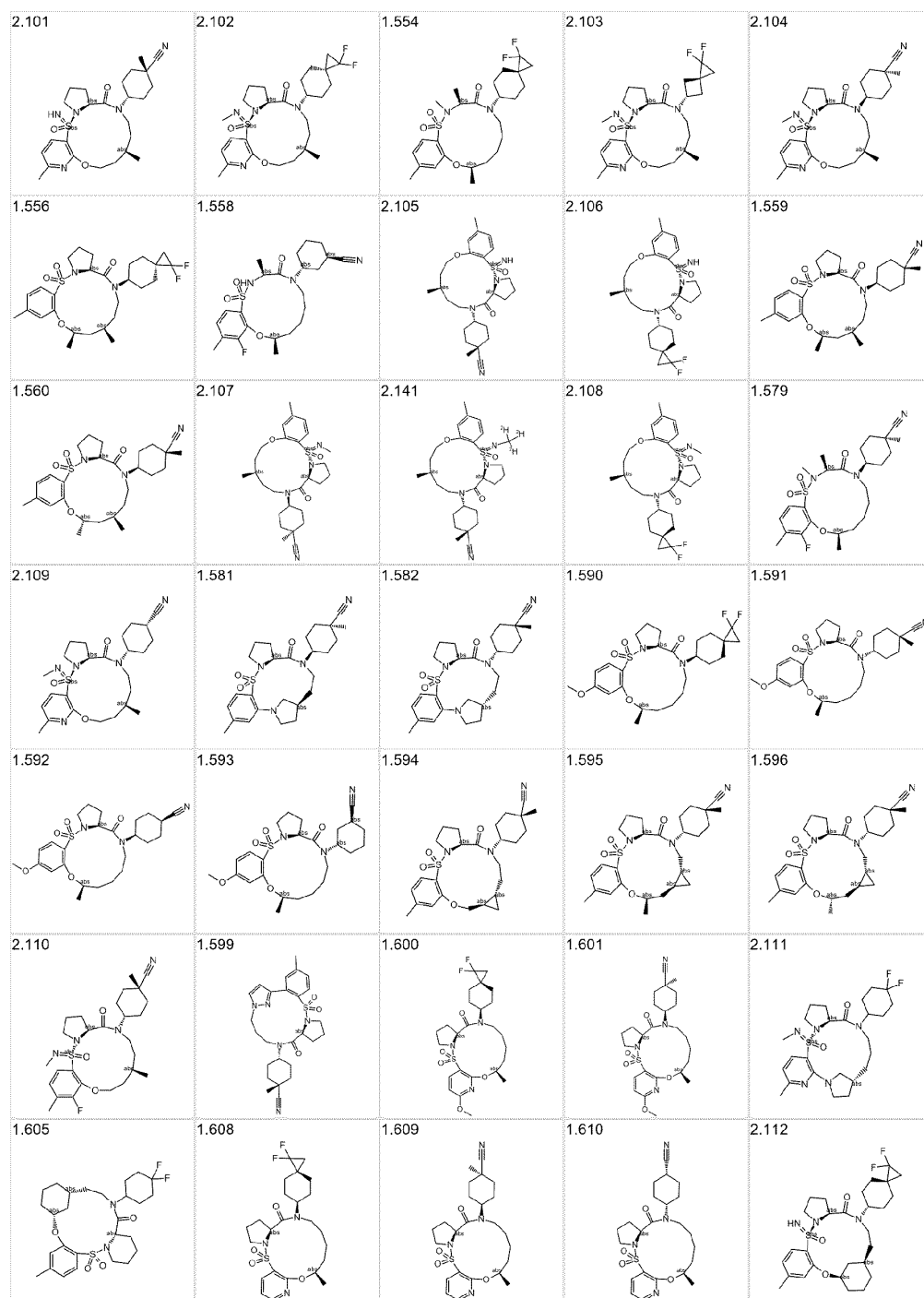


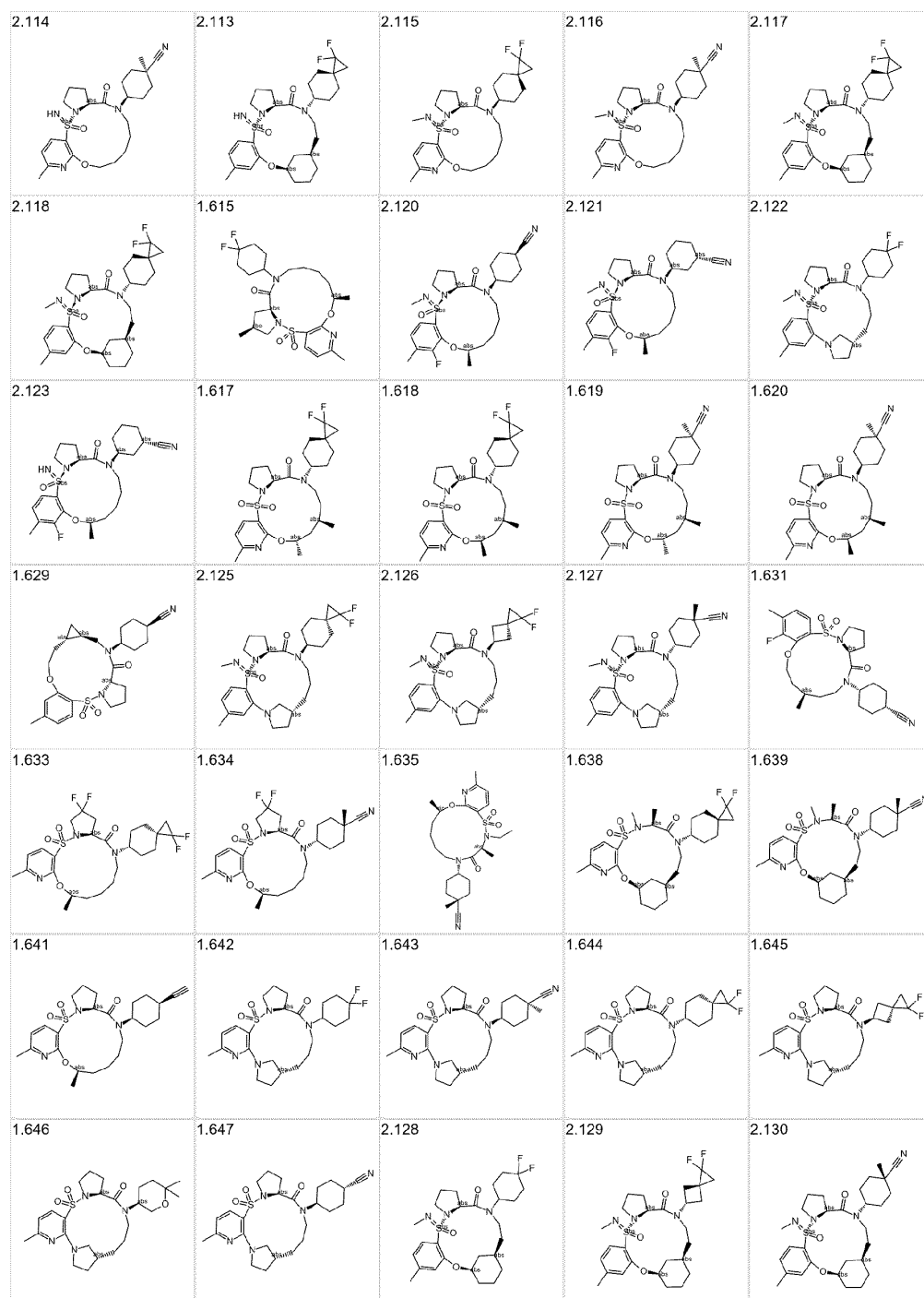


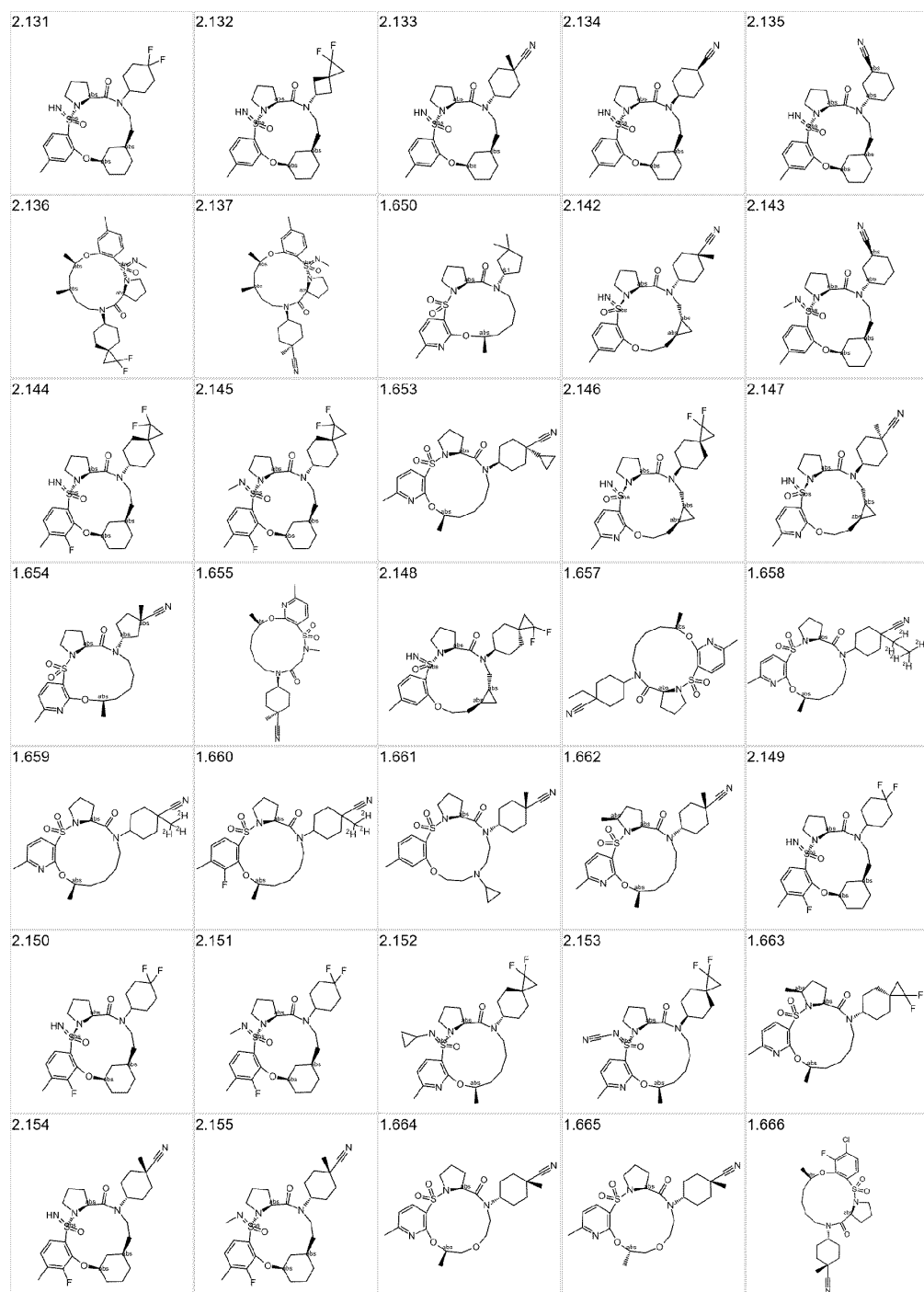


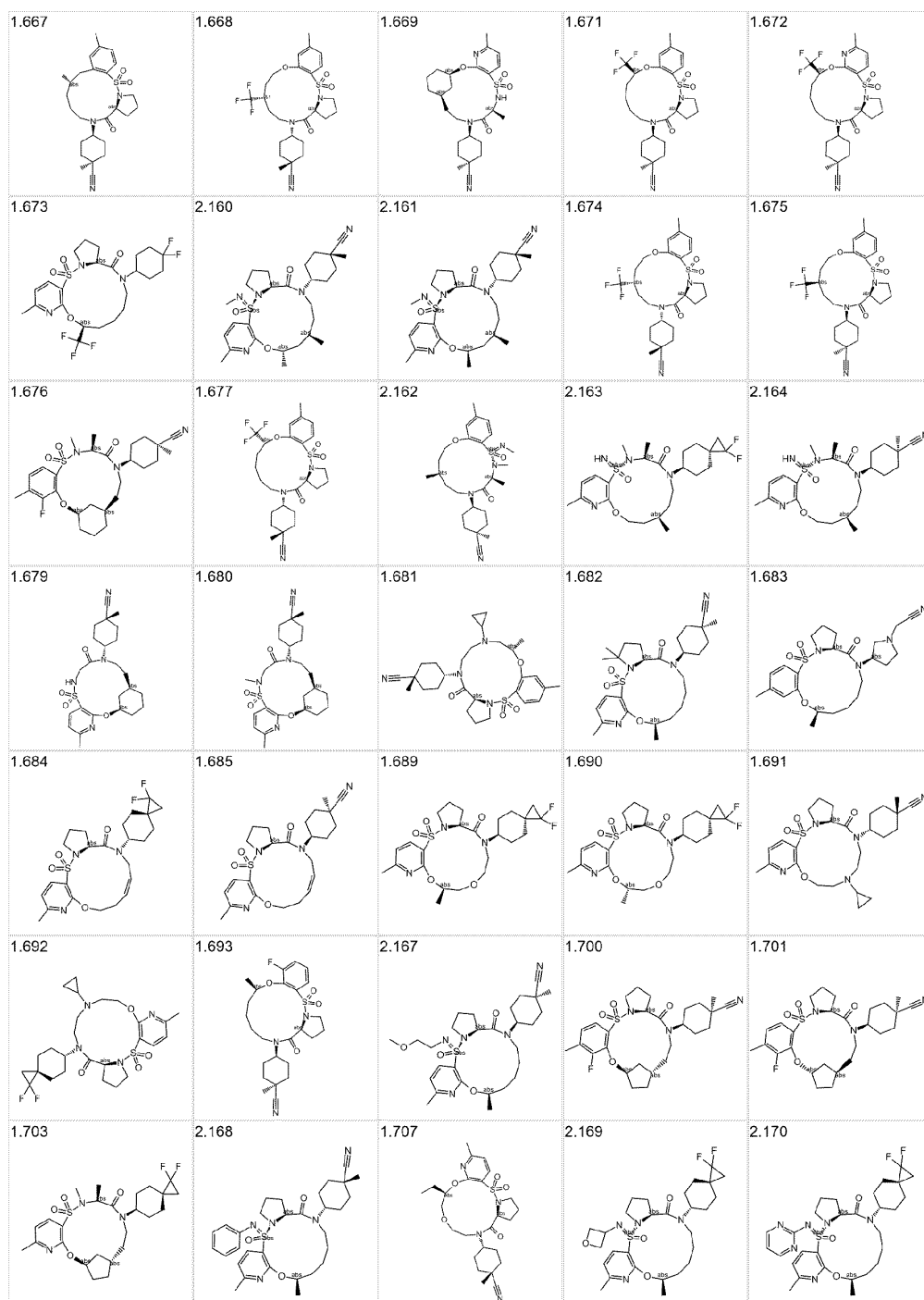


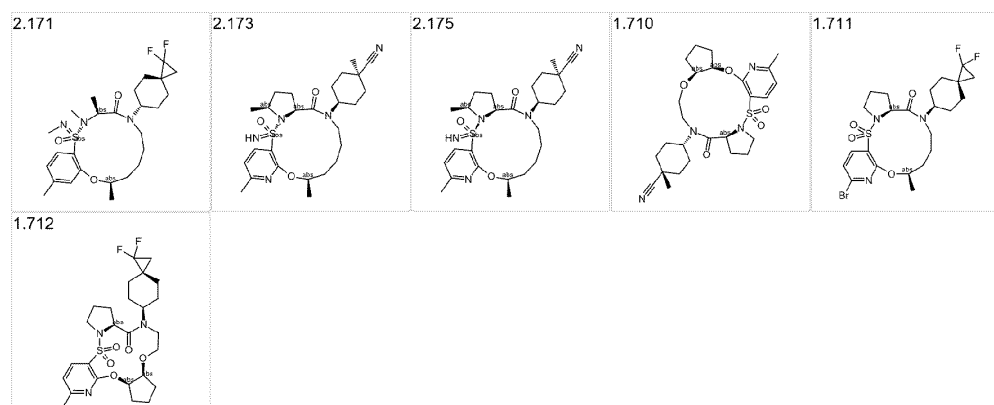








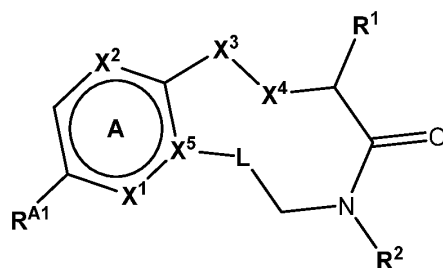




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Claims

1. A compound of Formula (I)



Formula (I)

5

wherein

❖ **Ring A** is a 6-membered aromatic ring, wherein:

- **R^{A1}** represents hydrogen, (C₁₋₃)alkyl, (C₁₋₃)alkoxy, halogen, monocyclic (C₃₋₄)cycloalkyl, or (C₁)fluoroalkyl;
- **X¹** represents independently N or CR^{A3}, wherein **R^{A3}** represents hydrogen, halogen, (C₁₋₃)alkyl, or (C₁₋₃)alkoxy;
- **X²** represents independently N or CR^{A2}, wherein **R^{A2}** represents hydrogen or halogen; and
- **X⁵** represents C;

10

and **L** represents:

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- linker group **L¹**, wherein the backbone of said linker group **L¹** is linear and consists of a total of 3 to 6 backbone atoms; wherein said backbone atoms are independently selected from 3 to 6 carbon atoms and 0 to 2 heteroatoms independently selected from O, N or S; wherein said backbone is saturated or partially unsaturated; wherein said backbone is unsubstituted, or mono-, di- or tri-substituted; wherein the substituents are independently selected from the group consisting of:

20

- (C₁₋₆)alkyl;
- (C₃₋₆)cycloalkan-1,1-diyl;
- (C₃₋₆)cycloalkyl;
- hydroxy;
- halogen; and
- (C₁₋₃)fluoroalkyl;

25

- or linker group **L²**, wherein the backbone of said linker group **L²** consists of a total of 4 to 6 backbone atoms; wherein said backbone atoms are independently selected from 3 to 5 carbon atoms and 1 or 2 heteroatoms independently selected from O, N or S; wherein said backbone is saturated or partially unsaturated; wherein 2 or 3 adjacent atoms of said backbone atoms are contained in a 3- to 6-membered saturated, partially unsaturated or aromatic cyclic moiety

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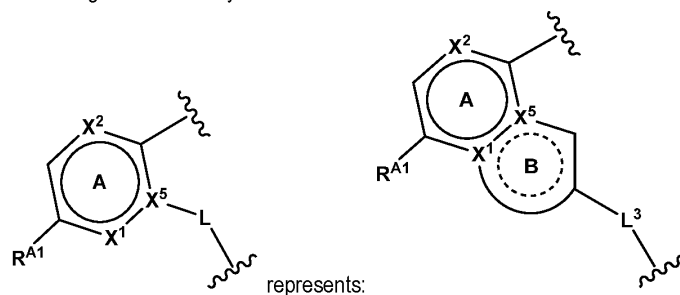
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comprising a total of 0 to 3 heteroatoms independently selected from O, N or S; wherein L^2 is unsubstituted, or mono- or di-substituted; wherein the substituents are independently selected from the group consisting of:

- (C_{1-3}) alkyl; and
- halogen;

5

❖ or the fragment formed by



Formula (I-B)

wherein

10

➤ **Ring A** represents a 6-membered aromatic ring, wherein:

- X^2 represents CH or N; and
- R^{A1} represents independently hydrogen, (C_{1-3}) alkyl, (C_{1-3}) alkoxy, halogen, monocyclic (C_{3-4}) cycloalkyl, or (C_1) fluoroalkyl;

15

and **Ring B** represents a 5- to 7-membered heterocyclic ring; wherein said **Ring B** including ring atoms X^1 and X^5 contains a total of 1 or 2 ring heteroatoms; wherein said heteroatoms are independently selected from N, O, or S;

➤ **Ring A** represents a 6-membered aromatic ring, wherein:

- X^2 represents CH or N; and
- R^{A1} represents independently hydrogen, (C_{1-3}) alkyl, (C_{1-3}) alkoxy, halogen, monocyclic (C_{3-4}) cycloalkyl, or (C_1) fluoroalkyl;

20

and **Ring B** represents a 5-membered heteroaromatic ring; wherein said **Ring B** including ring atoms X^1 and X^5 contains a total of 1 to 3 ring heteroatoms; wherein said heteroatoms are independently selected from N, O, or S; or

➤ **Ring A** represents a 6-membered aromatic ring, wherein:

- X^2 represents CH or N; and
- R^{A1} represents independently hydrogen, (C_{1-3}) alkyl, (C_{1-3}) alkoxy, halogen, monocyclic (C_{3-4}) cycloalkyl, or (C_1) fluoroalkyl;

25

and **Ring B** represents a 6-membered heteroaromatic ring; wherein said **Ring B** including ring atoms X^1 and X^5 contains a total of 1 or 2 ring heteroatoms; wherein said ring heteroatoms are

30

N;

and L^3 represents:

- a linear linker group; wherein L^3 consists of a total of 3 or 4 backbone atoms; wherein said backbone atoms are independently selected from 3 or 4 carbon atoms and 0 or 1 heteroatom independently selected from O, N or S; wherein said backbone is saturated or mono-unsaturated; wherein said backbone is unsubstituted or mono-substituted with (C_{1-3}) alkyl; or halogen;

X^3 represents SO_2 or $S(=O)(=NR^3)$, wherein R^3 represents hydrogen, (C_{1-3}) alkyl, monocyclic (C_{3-6}) cycloalkyl, or phenyl;

X^4 represents:

- NR^{N1} ; wherein:

- R^{N1} represents hydrogen or (C_{1-3}) alkyl; and
- R^1 represents (C_{1-5}) alkyl or $-(CH_2)_n-(C_{3-4})$ cycloalkyl wherein n independently represents the integer 0 or 1;

- NR^{N1} ; wherein R^1 and R^{N1} together form a ring comprising X^4 , herein **Ring E**, wherein said **Ring E** represents:

- a 4- to 6-membered saturated monocyclic heterocycloalkan-diyl comprising X^4 and zero or one ring oxygen 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, phenyl, and cyano; or
- a 6- to 8-membered saturated spiro, fused, or bridged bicyclic heterocycloalkan-diyl comprising X^4 ;

- or $CHRC^1$; wherein R^1 and R^{C1} together form a ring comprising X^4 , herein **Ring F**, wherein said **Ring F** represents a monocyclic (C_{5-6}) cycloalkan-diyl or a monocyclic 5- or 6-membered heterocycloalkan-diyl comprising one ring oxygen atom; and

R^2 represents:

- 3-cyano-3,3-dimethylpropyl;
- $-(CH_2)_m-(\text{Ring D})$, wherein m is the integer 0 or 1, and **Ring D** represents:
 - a saturated monocyclic (C_{4-7}) cycloalkyl; wherein said (C_{4-7}) cycloalkyl is unsubstituted, mono-, di-, or tri-substituted; wherein the substituents are independently selected from the group consisting of:
 - (C_{1-3}) alkyl; wherein said (C_{1-3}) alkyl independently is unsubstituted or mono-substituted with cyano;
 - halogen;
 - (C_{1-3}) fluoroalkyl;
 - (C_{1-3}) alkoxy;
 - (C_{3-4}) cycloalkyl;

- carbamoyl;
 - hydroxy;
 - cyano; and
 - (C₂₋₃)alkynyl;
 - 5
 - a saturated bicyclic (C₅₋₈)spirocycloalkyl; wherein said (C₅₋₈)spirocycloalkyl is unsubstituted, or mono-, di-, tri- or tetra-substituted; wherein the substituents are independently selected from the group consisting of: halogen, cyano, and hydroxy;
 - a saturated fused or bridged bicyclic (C₅₋₈)cycloalkyl; wherein said bicyclic (C₅₋₈)cycloalkyl is unsubstituted, or mono- or di-substituted; wherein the substituents are independently selected
 - 10
 - from the group consisting of: (C₁₋₃)fluoroalkyl, halogen, cyano, and carbamoyl;
 - a 5- or 6-membered saturated monocyclic heterocycle comprising one ring heteroatomic group selected from O, NR^{N2}, S, or SO₂; wherein R^{N2} represents (C₁₋₃)alkyl or cyanomethyl; wherein said heterocycle is unsubstituted, or mono-, di-, tri-, or tetra-substituted; wherein the substituents are independently selected from the group consisting of: (C₁₋₃)alkyl, halogen, (C₁₋₃)fluoroalkyl, and oxo;
 - 15
 - a 9-membered saturated spiro bicyclic heterocycle comprising one ring oxygen atom; or
 - a 7-membered saturated fused or bridged bicyclic heterocycle comprising one ring oxygen atom;
- or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein:

- 20 **Ring A** is a 6-membered aromatic ring, wherein:
- R^{A1} represents hydrogen, (C₁₋₃)alkyl, (C₁₋₃)alkoxy, halogen, monocyclic (C₃₋₄)cycloalkyl, or (C₁)fluoroalkyl;
 - X¹ represents independently N or CR^{A3}, wherein R^{A3} represents hydrogen, halogen, (C₁₋₃)alkyl, or (C₁₋₃)alkoxy;
 - 25 ➤ X² represents independently N or CR^{A2}, wherein R^{A2} represents hydrogen or halogen; and
 - X⁵ represents C;

and **L** represents:

- linker group **L**¹, wherein the backbone of said linker group **L**¹ is linear and consists of a total of 3 to 6 backbone atoms; wherein said backbone atoms are independently selected from 3 to 6 carbon atoms
- 30 and 0 to 2 heteroatoms independently selected from O, N or S; wherein said backbone is saturated or partially unsaturated; wherein said backbone is unsubstituted, or mono-, di- or tri-substituted; wherein the substituents are independently selected from the group consisting of: (C₁₋₆)alkyl; (C₃₋₆)cycloalkan-1,1-diyl; (C₃₋₆)cycloalkyl; hydroxy; halogen, and (C₁₋₃)fluoroalkyl;
- or linker group **L**², wherein the backbone of said linker group **L**² consists of a total of 4 to 6 backbone
- 35 atoms; wherein said backbone atoms are independently selected from 3 to 5 carbon atoms and 1 or 2 heteroatom independently selected from O, N or S; wherein said backbone is saturated or partially

unsaturated; wherein 2 or 3 adjacent atoms of said backbone atoms are contained in a 3- to 6-membered saturated, partially unsaturated or aromatic cyclic moiety comprising a total of 0 to 3 heteroatoms independently selected from O, N or S; wherein **L**² is unsubstituted, or mono- or di-substituted; wherein the substituents are independently selected from (C₁₋₃)alkyl or halogen;

5 or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 2, wherein

❖ **L** represents linker group **L**¹ and the backbone of linker group **L**¹ is selected from the group consisting of:

*-O-(CH₂)₂-, *-O-(CH₂)₃-, -(CH₂)₄-, *-S-(CH₂)₃-, *-O-(CH₂)₄-, -(CH₂)₃-O-(CH₂)₃-, *(CH₂)₃-O-(CH₂)₂-, -(CH₂)₅-,
 10 , *-NH-(CH₂)₂-CH=CH-, *-NH-(CH₂)₄-, *-CH=CH-(CH₂)₃-, *-O-(CH₂)₂-CH=CH-, *-O-(CH₂)₂-O-(CH₂)₂-, *-O-(CH₂)₅-, and *-O-(CH₂)₂-NH-(CH₂)₂-, wherein the asterisks indicate the attachment point of linker group **L**¹ to **Ring A**; wherein said backbone is unsubstituted, or mono- or di-substituted; wherein the substituents are independently selected from the group consisting of: (C₁₋₆)alkyl, (C₃₋₆)cycloalkan-1,1-diyl, (C₃₋₆)cycloalkyl, hydroxy, halogen, and (C₁₋₃)fluoroalkyl; or

❖ **L** represents linker group **L**² and the backbone of linker group **L**² is selected from the group consisting of:

➤ *-O-(CH₂)-(cyclic moiety)-, *-O-(cyclic moiety)-(CH₂)-, *-O-(cyclic moiety)-CH=CH-, *-O-(cyclic moiety)-(CH₂)₂-; wherein independently the cyclic moiety of such linker group **L**² represents:

○ (C₃₋₆)cycloalkan-1,2-diyl;
 ○ phen-1,2-diyl; or
 ○ 5- or 6-membered heterocycloalkan-diyl; wherein said heterocycloalkan-diyl is linked to the
 20 rest of the molecule via two of its ring atoms that are in ortho position relative to one another;
 or

➤ *-(cyclic moiety)-(CH₂)-, *-(cyclic moiety)-(CH₂)₂-, *-(cyclic moiety)-CH=CH-, *-(cyclic moiety)-(CH₂)₃-,
 *-O-(cyclic moiety)-, *-O-(cyclic moiety)-(CH₂)-, and *-O-(CH₂)-(cyclic moiety)-; wherein independently the cyclic moiety of such linker group **L**² represents:

○ (C₃₋₆)cycloalkan-1,3-diyl;
 ○ 5- or 6-membered heterocycloalkan-diyl; wherein said heterocycloalkan-diyl is linked to the
 rest of the molecule via two of its ring atoms that are in meta position relative to one another;
 ○ 5- or 6-membered heteroaryl-diyl; wherein said heteroaryl-diyl is linked to the rest of the
 25 molecule via two of its ring atoms that are in meta position relative to one another;

30 wherein the asterisks indicate the attachment point of linker group **L**² to **Ring A**;

wherein said **L**² is unsubstituted, or mono- or di-substituted; wherein the substituents are independently selected from the group consisting of: (C₁₋₃)alkyl and halogen;

or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 2, wherein

35 **L** represents linker group **L**¹; said linker group **L**¹ independently is:

- 5 **O-CH(CH3)-CH2-; **O-CH2-CH2-CH2-; **O-CH(CH3)-CH2-CH2-; **O-cyclopropan-1,1-diyl-CH2-CH2-; -CH2-CH2-CH2-CH2-; **S-CH(CH3)-CH2-CH2-; -CH2-CH2-CH2-CH2-CH2-; **CH=CH-CH2-CH2-CH2-; **O-CH2-CH2-CH2-CH2-; **O-CH(CH3)-CH2-CH2-CH2-; **O-CH(ethyl)-CH2-CH2-CH2-; **O-CH(n-propyl)-CH2-CH2-CH2-; **O-CH(isopropyl)-CH2-CH2-CH2-; **O-CH(cyclopropyl)-CH2-CH2-CH2-; **O-CH2-CH(CH3)-CH2-CH2-; **O-CH2-CH2-CH(CH3)-CH2-; **O-CH2-CH2-CH(ethyl)-CH2-; **O-CH2-CF2-CH2-CH2-; **O-CH2-CH2-C(CH3)2-CH2-; **O-CH2-CH2-cyclopropan-1,1-diyl-CH2-; **O-CH2-CH2-C(hydroxy)(cyclopropyl)-CH2-; **O-CH2-CH2-CH2-CH(CH3)-; **O-CH(CH3)-CH2-CH=CH-; **CH2-O-CH2-CH2-CH2-; **CH2-CH2-CH2-O-CH2-; **O-CH(CH3)-CH2-O-CH2-; **NH-CH2-CH2-CH2-CH2-; **N(CH3)-CH2-CH2-CH2-CH2-; **N(CH3)-CH2-CH2-CH=CH-; **NH-CH(CH3)-CH2-CH=CH-; **NH-CH(CH3)-CH2-CH2-CH2-; or **O-CH2-CH2-CH2-CH2-CH2-; **O-CH(ethyl)-CH2-O-CH2-; **O-CH(CH3)-CH2-CH(CH3)-CH2-; **O-CH2-CH2-N(cyclopropyl)-CH2-; **O-CH(CH3)-CH2-N(cyclopropyl)-CH2-; **O-CH(CF3)-CH2-CH2-CH2-; **O-CH2-CH2-CH(CF3)-CH2-; **O-CH2-CH2-N(2,2,2-trifluoroethyl)-CH2-; or **O-CH2-CH2-CH=CH-;

L represents linker group L²; said linker group L² independently is:

- 15 **-(pyrrolidin-1*,3-diyl)-CH2-; **-(piperidin-1*,3-diyl)-CH2-; **O-CH2-(cyclopropan-1,2-diyl)-; **O-CH2-(cyclobutan-1,2-diyl)-; **O-(cyclopentan-1,2-diyl)-CH2-; **O-(cyclohexan-1,2-diyl)-CH2-; **O-(cyclohexan-1,3-diyl)-; **O-(cyclohexan-1,3-diyl)-CH2-; **-(pyrrolidin-1*,3-diyl)-CH2-CH2-; **O-(cyclopentan-1,2-diyl)-CH=CH-; **O-(cyclopentan-1,3-diyl)-CH2-; **O-(cyclopentan-1,2-diyl)-CH2-CH2-; **O-CH2-(cyclobutan-1,3-diyl)-; **O-(tetrahydrofuran-3,4-diyl)-CH2-CH2-; **-(4-chloro-pyrazol-1,3*-diyl)-CH2-CH2-; **O-(tetrahydrofuran-2,3*-diyl)-CH2-CH2-; **O-(cyclobutan-1,2-diyl)-CH2-CH2-; **O-CH2-CH2-(cyclopropan-1,2-diyl)-; **O-([1,3,4]oxadiazol-2,5-diyl)-CH2-; **O-(phen-1,2-diyl)-CH2-CH2-; **-(pyridin-2,6-diyl)-CH2-CH2-; **-([1,2,4]oxadiazol-3*,5-diyl)-CH2-CH2-CH2-; **O-(cyclobutan-1,3-diyl)-CH2-CH2-; **O-(tetrahydrofuran-2,4*-diyl)-CH2-; **O-(tetrahydropyran-2,4*-diyl)-CH2-; **O-(piperidin-1,3*-diyl)-CH2-; **O-CH2-(cyclopentan-1,3-diyl)-; **O-(tetrahydropyran-3,5-diyl)-CH2-; or **O-(cyclohexan-1,2-diyl)-CH2-;
- 20 CH2-; **O-CH2-(cyclopropan-1,2-diyl)-CH2-; **O-CH(CH3)-CH2-(cyclopropan-1,2-diyl)-; **-(pyrazol-1,3*-diyl)-CH2-CH2-; or **O-(cyclopentan-1,2-diyl)-O-CH2-;
- 25 CH2-; **O-CH2-(cyclopropan-1,2-diyl)-CH2-; **O-CH(CH3)-CH2-(cyclopropan-1,2-diyl)-; **-(pyrazol-1,3*-diyl)-CH2-CH2-; or **O-(cyclopentan-1,2-diyl)-O-CH2-;

wherein the double asterisks indicate the attachment point of the linker group L¹, respectively L² to Ring A; and, where applicable, the single asterisks indicate the attachment point of (i) the linker oxygen atom which is attached to Ring A, or (ii) of Ring A, as the case may be;

- 30 or a pharmaceutically acceptable salt thereof.

5. A compound according to any of claims 1 to 4, wherein X³ represents SO₂ or S(=O)(=NR³), wherein R³ represents hydrogen or (C₁₋₃)alkyl;

or a pharmaceutically acceptable salt thereof.

6. A compound according to any of claims 1 to 5, wherein X⁴ represents CHR^{C1}, and R¹ and R^{C1} together form a ring comprising X⁴, herein Ring F, wherein Ring F represents a monocyclic (C₅₋₆)cycloalkan-diyl;
- 35

or a pharmaceutically acceptable salt thereof.

7. A compound according to any of claims 1 to 5, wherein X^4 represents NR^{N1} , and R^1 and R^{N1} together form a ring comprising X^4 , herein **Ring E**; wherein said **Ring E** represents:

- a 5- or 6-membered saturated monocyclic heterocycloalkan-diyl comprising X^4 and zero or one ring oxygen atom; wherein said heterocycloalkan-diyl is unsubstituted or mono-substituted; wherein the substituents are independently selected from the group consisting of: (C_{1-3}) alkyl, halogen, and (C_{1-3}) alkoxy; or
- a 6- or 7-membered saturated fused or bridged bicyclic heterocycloalkan-diyl comprising X^4 ;

or a pharmaceutically acceptable salt thereof.

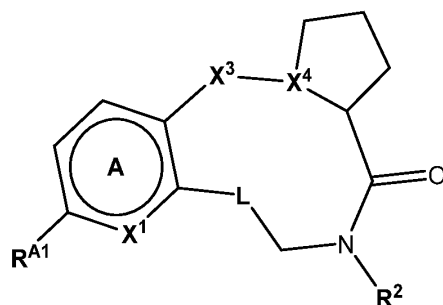
8. A compound according to any of claims 1 to 7, wherein R^2 represents:

- 3-cyano-3,3-dimethylpropyl;
- $-(CH_2)_m-$ (**Ring D**), wherein m is the integer 0 or 1, and **Ring D** represents:
 - a saturated monocyclic (C_{4-7}) cycloalkyl; wherein said (C_{4-7}) cycloalkyl is mono-, di-, or tri-substituted; wherein the substituents are independently selected from the group consisting of:
 - (C_{1-3}) alkyl; wherein said (C_{1-3}) alkyl is unsubstituted or mono-substituted with cyano;
 - halogen;
 - (C_{1-3}) alkoxy;
 - (C_{3-4}) cycloalkyl;
 - hydroxy; and
 - cyano;
 - a saturated bicyclic (C_{5-8}) spirocycloalkyl; wherein said (C_{5-8}) spirocycloalkyl is unsubstituted, or mono-, di-, tri- or tetra-substituted; wherein the substituents are independently selected from the group consisting of: halogen, cyano, and hydroxy;
 - a saturated fused or bridged bicyclic (C_{5-8}) cycloalkyl; wherein said bicyclic (C_{5-8}) cycloalkyl is unsubstituted, or mono- or di-substituted; wherein the substituents are independently selected from the group consisting of: (C_{1-3}) fluoroalkyl, halogen, and cyano;
 - a 5- or 6-membered saturated monocyclic heterocycle comprising one ring heteroatomic group selected from O, NR^{N2} , or SO_2 ; wherein R^{N2} represents (C_{1-3}) alkyl; wherein said heterocycle is unsubstituted, or mono-, di-, tri-, or tetra-substituted; wherein the substituents are independently selected from the group consisting of: (C_{1-3}) alkyl and oxo;
 - a 9-membered saturated spiro bicyclic heterocycle comprising one ring oxygen atom; or
 - a 7-membered saturated fused or bridged bicyclic heterocycle comprising one ring oxygen atom;

or a pharmaceutically acceptable salt thereof.

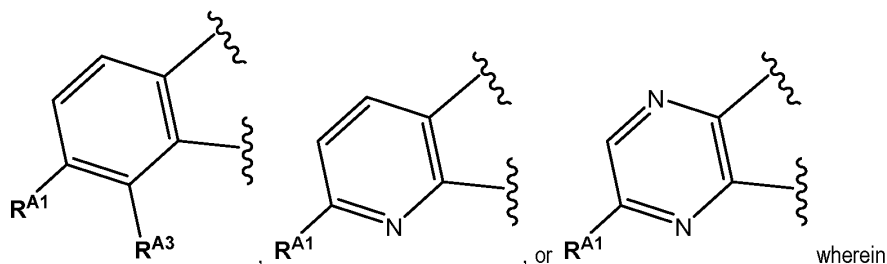
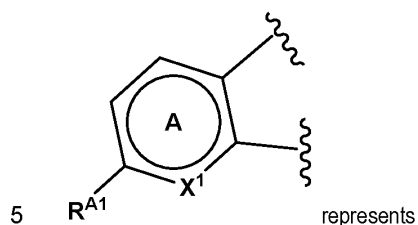
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9. A compound according to claim 1 which is a compound of Formula (IV)



Formula (IV)

wherein the fragment



- R^{A1} independently represents hydrogen, (C_{1-3}) alkyl, (C_{1-3}) alkoxy, or halogen; and
- R^{A3} , if present, independently represents hydrogen, halogen, or (C_{1-3}) alkyl;

L represents:

- 10
- linker group L^1 wherein such linker group L^1 independently is:
 - **O-CH(CH₃)-CH₂-; **O-CH₂-CH₂-CH₂-; **O-CH(CH₃)-CH₂-CH₂-; **O-cyclopropan-1,1-diyl-CH₂-CH₂-; -CH₂-CH₂-CH₂-CH₂-; **S-CH(CH₃)-CH₂-CH₂-; -CH₂-CH₂-CH₂-CH₂-CH₂-; **CH=CH-CH₂-CH₂-CH₂-; **O-CH₂-CH₂-CH₂-CH₂-CH₂-; **O-CH(CH₃)-CH₂-CH₂-CH₂-; **O-CH(ethyl)-CH₂-CH₂-CH₂-; **O-CH(n-propyl)-CH₂-CH₂-CH₂-; **O-CH(isopropyl)-CH₂-CH₂-CH₂-; **O-CH(cyclopropyl)-CH₂-CH₂-CH₂-; **O-CH₂-CH(CH₃)-CH₂-CH₂-; **O-CH₂-CH₂-CH(CH₃)-CH₂-; **O-CH₂-CH₂-CH(ethyl)-CH₂-; **O-CH₂-CF₂-CH₂-CH₂-; **O-CH₂-CH₂-C(CH₃)₂-CH₂-; **O-CH₂-CH₂-cyclopropan-1,1-diyl-CH₂-; **O-CH₂-CH₂-C(hydroxy)(cyclopropyl)-CH₂-; **O-CH₂-CH₂-CH₂-CH(CH₃)-; **O-CH(CH₃)-CH₂-CH=CH-; **CH₂-O-CH₂-CH₂-CH₂-; **CH₂-CH₂-CH₂-O-CH₂-; **O-CH(CH₃)-CH₂-O-CH₂-; **NH-CH₂-CH₂-CH₂-CH₂-; **N(CH₃)-CH₂-CH₂-CH₂-CH₂-; **N(CH₃)-CH₂-CH₂-CH=CH-; **NH-CH(CH₃)-CH₂-CH₂-CH₂-; or **O-CH₂-CH₂-CH₂-CH₂-CH₂-; **O-CH(ethyl)-CH₂-O-CH₂-; **O-CH₂-CF₂-CH₂-CH₂-; **O-CH(CH₃)-CH₂-CH(CH₃)-CH₂-; **O-CH₂-CH₂-N(cyclopropyl)-CH₂-; **O-CH(CH₃)-
- 15
- 20

CH₂-N(cyclopropyl)-CH₂-; **O-CH(CF₃)-CH₂-CH₂-CH₂-; **O-CH₂-CH₂-CH(CF₃)-CH₂-; or **O-CH₂-CH₂-N(2,2,2-trifluoroethyl)-CH₂-;

wherein the double asterisks indicate the attachment point of said linker group **L**¹ to **Ring A**;

or

- 5 • linker group **L**²; wherein such linker group **L**² independently is:
- **-(pyrrolidin-1*,3-diyl)-CH₂-; **-(piperidin-1*,3-diyl)-CH₂-; **O-CH₂-(cyclopropan-1,2-diyl)-; **O-CH₂-(cyclobutan-1,2-diyl)-; **O-(cyclopentan-1,2-diyl)-CH₂-; **O-(cyclohexan-1,2-diyl)-CH₂-; **O-(cyclohexan-1,3-diyl)-; **O-(cyclohexan-1,3-diyl)-CH₂-; **-(pyrrolidin-1*,3-diyl)-CH₂-CH₂-; **O-(cyclopentan-1,2-diyl)-CH=CH-; **O-(cyclopentan-1,3-diyl)-CH₂-; **O-(cyclopentan-1,2-diyl)-CH₂-CH₂-; **O-CH₂-(cyclobutan-1,3-diyl)-;
- 10 **O-(tetrahydrofuran-3,4-diyl)-CH₂-CH₂-; **-(4-chloro-pyrazol-1,3*-diyl)-CH₂-CH₂-; **O-(tetrahydrofuran-2,3*-diyl)-CH₂-CH₂-; **O-(cyclobutan-1,2-diyl)-CH₂-CH₂-; **O-CH₂-CH₂-(cyclopropan-1,2-diyl)-; **O-([1,3,4]oxadiazol-2,5-diyl)-CH₂-; **O-(phen-1,2-diyl)-CH₂-CH₂-; **-(pyridin-2,6-diyl)-CH₂-CH₂-; **-([1,2,4]oxadiazol-3*,5-diyl)-CH₂-CH₂-CH₂-; **O-(cyclobutan-1,3-diyl)-CH₂-CH₂-; **O-(tetrahydrofuran-2,4*-diyl)-CH₂-; **O-(tetrahydropyran-2,4*-diyl)-CH₂-; **O-(piperidin-1,3*-diyl)-CH₂-; **O-CH₂-(cyclopentan-1,3-diyl)-;
- 15 **O-(tetrahydropyran-3,5-diyl)-CH₂-; **O-(cyclohexan-1,2-diyl)-CH₂-CH₂-; **O-CH₂-(cyclopropan-1,2-diyl)-CH₂-; **O-CH(CH₃)-CH₂-(cyclopropan-1,2-diyl)-; **-(pyrazol-1,3*-diyl)-CH₂-CH₂-; or **O-(cyclopentan-1,2-diyl)-O-CH₂-;

wherein the double asterisks indicate the attachment point of linker group **L**² to **Ring A**; and, where applicable, the single asterisks indicate the attachment point of (i) the linker oxygen atom which is attached to **Ring A**, or

- 20 (ii) of **Ring A**, as the case may be;

X³ represents SO₂ or S(=O)(=NR³), wherein **R**³ represents hydrogen or methyl;

X⁴ represents N or CH; and

R² represents:

- cyclopentyl or cyclohexyl; wherein said cyclopentyl or cyclohexyl independently is mono-, or di-substituted; wherein the substituents are independently selected from the group consisting of (C₁₋₃)alkyl, halogen, and cyano; or
- 25 ➤ a saturated bicyclic (C₆₋₈)spirocycloalkyl; wherein said (C₆₋₈)spirocycloalkyl is unsubstituted, or di-substituted with fluoro;

or a pharmaceutically acceptable salt thereof.

- 30 10. A compound according to claim 1, which is selected from the following compounds:

(6R,12aS,15aR)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,13,14,15,15a-

decahydrocyclopenta[e]pyrido[2,3-b][1]oxa[4]thia[8]azacyclotridecin-12(12aH)-one 16,16-dioxide;

(6R,12aS,17S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-17-imino-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-

decahydro-12H,17H-17λ⁴-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide;

- (6R,12aS,17S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-17-(methylimino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide;
- (6R,11aS)-10-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-7,8,9,10,11a,12,13,14-octahydropyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclododecin-11(6H)-one 16,16-dioxide;
- 5 (6R,12aS)-11-(4,4-Difluorocyclohexyl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide;
- (6R,12aS)-11-((3R,5s)-1,1-Difluorospiro[2.3]hexan-5-yl)-3,6-dimethyl-6,7,8,9,10,11,12a,13,14,15-decahydro-12H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17,17-dioxide;
- 10 (1R,4s)-4-((6R,12aS)-3,6-Dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile; or
- (1R,4s)-4-((6R,12aS)-4-Fluoro-3,6-dimethyl-17,17-dioxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile;
- (6R,12aS,17S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-17-(methylimino)-
- 15 6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide;
- (6R,12aS,17S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-17-((methyl-d3)imino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17 λ^4 -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide;
- 20 (1 2 S,5 1 S,5 3 S,2R)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-2-imino-3 6 -methyl-2 λ^6 -4-oxa-2 λ^6 -thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide;
- (1 2 S,5 1 R,5 3 R,2S)-8-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-2-imino-3 6 -methyl-2 λ^6 -4-oxa-2 λ^6 -thia-8-aza-3(3,2)-pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphan-9-one 2-oxide
- (1R,4s)-1-Methyl-4-((1 2 S,5 1 R,5 3 R,2S)-3 6 -methyl-2-(methylimino)-2-oxido-9-oxo-2 λ^6 -4-oxa-2 λ^6 -thia-8-aza-3(3,2)-
- 25 pyridina-1(1,2)-pyrrolidina-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile;
- (1R,4s)-4-((6R,12aS,17S)-3,6-Dimethyl-17-(methylimino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17 λ^4 -pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile;
- (1R,4s)-4-((6R,12aS,17S)-3,6-Dimethyl-17-(methylimino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-
- 30 6H,17H-17 λ^4 -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile;
- (1R,4s)-4-((8R,12aS,17S)-3,8-Dimethyl-17-(methylimino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17 λ^4 -benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile;

- (1R,4s)-1-Methyl-4-((1²S,5¹R,5³R,2S)-3⁴-methyl-2-(methylimino)-2-oxido-9-oxo-2λ⁶-4-oxa-2λ⁶-thia-8-aza-1(1,2)-pyrrolidina-3(1,2)-benzena-5(1,3)-cyclohexanacyclononaphane-8-yl)cyclohexane-1-carbonitrile;
- (1R,4s)-1-Methyl-4-((6R,8R,12aS,17S)-3,6,8-trimethyl-17-(methylimino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-
- 5 carbonitrile;
- (6R,12aS,17S)-11-((3R,6s)-1,1-Difluorospiro[2.5]octan-6-yl)-3,6-dimethyl-17-((methyl-d3)imino)-6,7,8,9,10,11,12a,13,14,15-decahydro-12H,17H-17λ⁴-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-12-one 17-oxide;
- (1R,4s)-4-((6R,12aS,17S)-3,6-Dimethyl-17-((methyl-d3)imino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-
- 10 6H,17H-17λ⁴-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile;
- (1R,4s)-4-((6R,12aS,17S)-3,6-Dimethyl-17-((methyl-d3)imino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile;
- 15 (1R,4s)-4-((8R,12aS,17S)-3,8-Dimethyl-17-((methyl-d3)imino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ⁴-benzo[b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile;
- (1R,4s)-1-Methyl-4-((6R,8R,12aS,17S)-3,6,8-trimethyl-17-(methylimino)-17-oxido-12-oxo-7,8,9,10,12a,13,14,15-octahydro-6H,17H-17λ⁴-pyrido[2,3-b]pyrrolo[1,2-e][1]oxa[4]thia[5,8]diazacyclotridecin-11(12H)-yl)cyclohexane-1-
- 20 carbonitrile; or
- (1R,4s)-4-((6R,12aS)-6-Ethyl-3-methyl-17,17-dioxido-12-oxo-6,7,9,10,12a,13,14,15-octahydropyrido[2,3-e]pyrrolo[1,2-h][1,4]dioxo[7]thia[8,11]diazacyclotridecin-11(12H)-yl)-1-methylcyclohexane-1-carbonitrile;
- or a pharmaceutically acceptable salt thereof.
11. A pharmaceutical composition comprising, as active principle, one or more compounds according to any one
- 25 of claims 1 to 10, or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.
12. A compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, for use as a medicament.
13. A compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, for use in improving wakefulness.
- 30 14. A compound according to any one of claims 1 to 10, 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;
- 35

- 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;
- 5 • for use in the treatment of eating disorders, obesity, neuropsychiatric disorders, pain, inflammation, or cognitive impairments associated with diminished wakefulness; or
- for the use in treatment of fatigue including:
 - improving symptoms of fatigue accompanied by poor concentration and memory;
 - improving symptoms of chronic fatigue associated with cancer or chemotherapy;
 - 10 ○ improving symptoms of chronic fatigue associated with infections, (chronic) inflammatory diseases, autoimmune diseases or neurological diseases;
 - treatment of chronic fatigue associated with myalgic encephalomyelitis/chronic fatigue syndrome;
- for use in improving symptoms of cognitive impairment including age-related cognitive disorders;
- for use in the treatment of attention deficit including attention-deficit hyperactivity disorder; or
- 15 • for use in the treatment of mood disorders associated with reduced hedonic drive including depression, schizophrenia, or addiction.
- 15. Use of a compound of Formula (I) as defined in any one of claims 1 to 10, or of a pharmaceutically acceptable salt thereof, in the preparation of a medicament for improving wakefulness.
- 16. A method for improving wakefulness comprising administering to a subject in need thereof an effective amount
- 20 of a compound of Formula (I) as defined in any one of claims 1 to 10, or of a pharmaceutically acceptable salt thereof.