

CXCR7 receptor modulators

The present invention relates to novel CXCR7 receptor modulators 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 CXCR7 receptor modulators. The invention further relates to the compounds of formula (I) and their use as pharmaceuticals in combination with one or more therapeutic agents and / or radiotherapy in the treatment of cancers, especially in the treatment of malignant glioma, in particular glioblastoma multiforme.

Chemokine receptors are a group of G-protein coupled receptors (GPCRs) that bind peptidic chemokine ligands with high affinity. The predominant function of chemokine receptors is to guide leukocyte trafficking to lymphoid organs and tissues under resting conditions as well as during inflammation, but a role for certain chemokine receptors on non-hematopoietic cells and their progenitors has also been recognized.

Signaling networks and metabolic profiles of cancer cells differ in a microenvironment dependent manner. This is a major reason for lack of therapeutic response of tumors at certain organ sites and of tumor metastases in comparison to primary tumors. CXCL12 (alias stromal cell-derived factor 1, SDF-1; alias Pre-B cell growth stimulating factor, PBSF), a stroma-derived chemo-attractant, exerts anti-apoptotic effects, displays pro-angiogenic properties and plays a key role in seeding circulating tumor cells to metastatic sites. CXCL12 binds and activates two receptors, CXCR7 (alias ACKR3, alias RDC1, alias CMKOR1, alias GPR159) and CXCR4 (alias Fusin, alias Leukocyte-derived seven-transmembrane-domain receptor; LESTR, alias D2S201E, alias seven-transmembrane-segment receptor, alias HM89, alias lipopolysaccharide-associated protein 3; lap3, alias LPS-associated protein 3).

The expression of the CXCL12 receptor CXCR7 correlates with diseases progression in cancer (among others in hormone refractory prostate cancer, in renal cell carcinoma, cervical cancer, papillary thyroid carcinoma, bladder cancer, Ewing's sarcoma, colorectal cancers, lung cancer, meningiomas, MALT lymphoma and in tumors in the brain). CXCR7 is also expressed in hepatocellular carcinoma, breast cancer, osteosarcoma, leukemia, gallbladder cancer, alveolar rhabdomyosarcoma, myeloma, non-small cell lung cancer, oral cancers and pancreas cancer (for review see Sun et al.; CXCL12/CXCR4/CXCR7 Chemokine Axis and Cancer Progression; Cancer Metastasis Rev. 2010, 29(4), 709-722).

CXCR7 silencing and targeting have been shown to reduce tumor growth in experimental disease models as single agents, or in combination with cytotoxic therapies [Wang et al.; The role of CXCR7/RDC1 as a chemokine Receptor for CXCL12/SDF-1 in prostate cancer; Journal of Biochemical Chemistry 2008, 293(7), 4283-4294; Ebsworth et al.; The effect of the CXCR7 inhibitor CCX662 on survival in the ENU rat model of glioblastoma; J Clin Oncol 2012, 30, (suppl; abstr e13580); Zheng et al.; Chemokine receptor CXCR7 regulates the invasion, angiogenesis and tumor growth of human hepatocellular carcinoma cells; Journal of Experimental and Clinical Cancer Research. 2010, 29: 31; Miao et al.; CXCR7 (RDC1) promotes breast and lung tumor growth in vivo and is expressed on tumor associated vasculature; PNAS 2007, 104(40), 15735-15740; Burns et al.; A novel chemokine receptor for SDF-1 and I-TAC involved in cell survival, cell adhesion, and tumor development; Journal of Experimental Medicine 2006, 203(9), 2201-2213; Walters et al.; "Inhibition of CXCR7 extends survival following irradiation of brain tumours in mice and rats", British Journal of Cancer (2014), 1–10 | doi: 10.1038/bjc.2013.830], including among others hepatocellular carcinoma, Kaposi's sarcoma, T cell leukemia, lymphoma, lung carcinomas, breast cancer, rhabdomyosarcoma, prostate cancer, pancreatic cancer and glioblastoma; to alter tumor-associated blood vessels; to reduce tumor cell seeding; to reduce rheumatoid arthritis clinical scores; to decrease the clinical severity of experimental autoimmune encephalomyelitis; to attenuate chronic hypoxia induced pulmonary hypertension, to induce anxiolytic-like behaviour, to trigger an angiocrine response to initiate liver regeneration and resolve fibrosis, and to improve beneficial effects of mesenchymal stem cells based therapies for renal ischemia/reperfusion injury [Cruz-Orengo et al.; CXCR7 influences leukocyte entry into the CNS parenchyma by controlling abluminal CXCL12 abundance during autoimmunity; Journal of Experimental Medicine 2011, 208(2), 327-339; Sartina et al.; Antagonism of CXCR7 attenuates chronic hypoxia-induced pulmonary hypertension; Pediatric Research 2012, 71(6), 682-688; Watanabe et al.; Pathogenic role of CXCR7 in rheumatoid arthritis; Arthritis and Rheumatism 2010, 62(11), 3211-3220; Ding et al, Divergent angiocrine signals from vascular niche balance liver regeneration and fibrosis; Nature 2014; 505(7481):97-102; Ikeda et al, Modulation of Circadian Glucocorticoid Oscillation via Adrenal Opioid-CXCR7 Signaling Alters Emotional Behavior; Cell 2013, 155(6):1323-36].

Recent studies have provided increasing evidence that activation of the CXCL12 pathway is a potential mechanism of tumor resistance to both conventional therapies and biological agents via multiple complementary actions: (i) by directly promoting cancer cell survival, invasion, and the cancer stem and/or tumor-initiating cell phenotype; (ii) by recruiting "distal stroma" (i.e., myeloid bone marrow-derived cells) to indirectly facilitate tumor recurrence and metastasis; and (iii) by promoting angiogenesis directly or in a paracrine manner. Duda DG

- et al (*Clin Cancer Res*; 2011, 17(8); 2074–80) recently discussed preclinical and clinical data that support the potential use of anti-CXCL12 agents including CXCR7 modulators as sensitizers to currently available therapies in cancer treatments. Modulators of the CXCL12 pathway were described to lead to changes of tumor properties, by altering the recruitment of immune and inflammatory infiltrating cells and by inhibiting vasculogenesis (*Brown BJ, Semin Radiat Oncol*; 2013, 23(4); 281-7). Kioi et al (*J clin invest*; 2010, 120(3); 694-705) showed that pharmacologic inhibition of the CXCL12 pathway prevented the influx in tumors of some monocytes and the postirradiation development of functional tumor vasculature resulting in abrogation of tumor regrowth.
- Specifically, the potential role of CXCR7 in brain tumors, malignant glioma and in glioblastoma multiforme is known from the literature. Modulators of the CXCL12 pathway including CXCR7 modulators have been mentioned as potential therapeutic agents for treating brain cancer in combination with chemotherapeutic agents or radiotherapy. For example, Hattermann et al (*Cancer research*, 2010, 70 (8):3299-3308) teach that CXCL12 “stimulation prevented camptothecin- and temozolomide-induced apoptosis and that a CXCR7 antagonist reduced the antiapoptotic effect of CXCL12”. The authors concluded that “CXCR7 is a functional receptor for CXCL12 in astrocytomas/glioblastomas and mediates resistance to drug-induced apoptosis”. Furthermore, Hattermann et al (*Oncology reports*, 27: 1348-1352, 2012) teach that “CXCL12 abrogates the antiproliferative effect of temozolomide”. The authors also teach that this effect could be almost completely abolished by a CXCR7 specific antagonist, “indicating that the anti-apoptotic effect of CXCL12 is mainly mediated via CXCR7”. Ebsworth et al (*Neuro Oncol* (2013) 15 (suppl 3):iii37-iii61. ET-023) teach that a CXCR7 antagonist significantly prolongs survival when administered in combination with radiotherapy in a rat model of glioblastoma. This finding is supported by another study by Ebsworth et al (*J Clin Oncol* 30, 2012 (suppl; abstr e13580) disclosing that *in vivo* inhibition of CXCR7 in concert with radiotherapy results in a significant extension of survival time in another rat model of glioblastoma. In addition, Liu SC et al (*Neuro-Oncology* 2014; 16(1):21-28) teach that inhibition of CXCL12 after irradiation inhibits tumor recurrence in autochthonous brain tumors in rats. Liu SC et al (*Neuro Oncol* (2013) 15 (suppl 3):iii189-iii190. RB-002. doi: 10.1093/neuonc/not188) also teach that inhibition of CXCL12 in a brain metastasis model after irradiation produced a marked inhibition of tumor growth and prolongation of lifespan compared to irradiation alone. Calatozzolo C et al (*Cancer Biology and Therapy* 2011, 11:2, 1-12) teach in *in vitro* experiments that CXCR7 antagonists showed complete inhibition of glioma proliferation.
- CXCR7 is also reported to be expressed in brain metastases (Salmaggi et al, *Cancer Biology and therapy* 2009, 8:17, 1-7). The authors concluded that the CXCL12/CXCR4/CXCR7

pathway could be an interesting target for further researches investigating the role of these molecules in invasion and proliferation of metastatic cells.

Furthermore, CXCL12 depletion sensitizes cancer cells to chemotherapy *in vivo* and CXCL12 treatment blocks colonic carcinoma metastasis. CXCR7 is also a receptor for CXCL11 (alias small inducible cytokine subfamily b, member 11; scyb11, alias interferon-gamma-inducible protein 9; ip9, alias small inducible cytokine subfamily b, member 9b; scyb9b) and therefore modulators of CXCR7 activity can also be used in indications with CXCL11-associated pathology. CXCR7 functions also as a receptor for the opioid peptide BAM22 and its related peptides (peptide E, peptides BAM12, BAM14, BAM18) and therefore modulators of CXCR7 activity possibly may also be used in indications with opioid peptides associated pathologies (Ikeda et al Cell 155, 1323-1336, December 5, 2013). CXCR7 has also been shown to function as a scavenger receptor for CXCL12. Thus, CXCR7 targeting has been shown to alter CXCL12 local concentration leading to a deregulation of the CXCL12 concentration gradient. The biological properties of CXCR7 modulators thus include, but are not limited to, any physiological function and/or cellular function linked and / or controlled by CXCL12 (Duda et al.; CXCL12 (SDF1alpha)-CXCR4/CXCR7 pathway inhibition: an emerging sensitizer for anticancer therapies?; Clin. Cancer Res. 2011 17(8) 2074-2080; Naumann et al.; CXCR7 function as a scavenger for CXCL12 and CXCL11; Plos One 2010, 5(2)e9175).

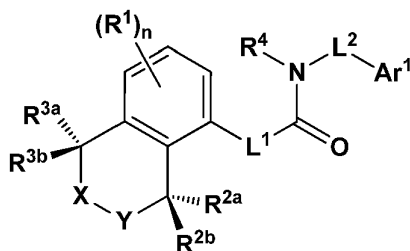
CXCR7 modulation (using small molecules antagonizing CXCL12 binding on CXCR7, or anti-CXCR7 antibodies, or RNA interference techniques to silence CXCR7 expression), CXCL12 modulation of activity/expression, or CXCR7 expression may, thus, be associated with diseases and disorders including cancer, notably carcinomas, leukemias, adenocarcinomas, malignant gliomas, glioblastoma multiforme, brain metastases, multiple myelomas, renal clear cell carcinoma, prostate cancer, pancreatic adenocarcinoma, melanoma, metastatic melanoma, rhabdomyosarcoma, hepatocellular carcinoma, colon tumors, breast cancer, non-small cell lung cancer, oral tumors, adult T-cell leukemia, gallbladder cancer, brain tumors, esophageal cancer, Ewing's sarcoma, bladder cancer, meningiomas, lymphoma, viral-induced tumors, Burkitt's lymphoma, Hodgkin's lymphoma, MALT lymphoma, papillary thyroid carcinoma, cervical cancer, osteosarcoma, lymphoproliferative disease, Kaposi's sarcoma, and choriocarcinoma; primary intra-ocular B-cell lymphoma; inflammation; multiple sclerosis; renal allograft rejection; rheumatoid arthritis; auto-immune encephalomyelitis; demyelinating diseases; systemic lupus erythematosus; osteoarthritis; pulmonary vascular diseases; acute renal failure; ischemia; inflammatory bowel disease; injured central nervous system; HSCs transplantation; cerebral ischemia; pulmonary hypertension; Shiga-toxin-associated hemolytic uremic syndrome; preeclampsia; chronic rhinosinusitis; HIV / AIDS;

atherosclerosis; acute lung injury; asthma; diseases involving CXCR7 and/or CXCL12 and/or CXCL11 mediated metastasis, chemotaxis, cell adhesion, trans-endothelial migration, cell proliferation and/or survival. Further disorders associated with CXCR7 modulation may include proliferative diabetic retinopathy, West Nile virus encephalitis, vascular injury and pulmonary fibrosis. Even further disorders associated with CXCR7 modulation may include hypertension; liver fibrosis; cirrhosis; acute coronary syndrome; stress-related disorders; and diseases involving opioid peptides.

WO2009/076404 discloses certain carboxamide compounds comprising a bicyclic ring, which are antagonists of the chemokine CCR2 receptor. WO1999/042456 and WO2002/046164 disclose certain tetrahydroisoquinoline compounds which are active as positive AMPA receptor modulators, respectively, as estrogen receptor- β ligands.

The present invention provides novel modulators of the CXCR7 receptor which act as CXCR7 receptor agonists and/or as functional antagonists, and may be useful for the prevention or treatment of diseases which respond to the activation of the CXCL12 receptors and/or CXCL11 receptors; including autoimmune disorders (e.g. rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, systemic lupus erythematosus, lupus nephritis, interstitial cystitis, celiac disease), inflammatory diseases (e.g. asthma, chronic obstructive pulmonary disorder, atherosclerosis, myocarditis, sarcoidosis), transplant rejection, hematopoietic stem cell transplantation, fibrosis (e.g. liver cirrhosis), and especially cancer.

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



Formula (I)

wherein

- **X** represents NR^5 , and **Y** represents CHR^Y wherein R^Y represents hydrogen, or (C₁₋₃)alkyl (especially methyl); and
 - **R**^{3a} and **R**^{3b} together with the carbon atom to which they are attached to form a carbonyl group, or
 - two of **R**^{2a}, **R**^{2b}, **R**^{3a} and **R**^{3b} independently represent hydrogen, or (C₁₋₃)alkyl (especially methyl);

and the remaining of R^{2a} , R^{2b} , R^{3a} and R^{3b} represent hydrogen; or

- X represents CHR^X wherein R^X represents hydrogen, or (C_{1-3}) alkyl (especially methyl), and Y represents NR^5 ; and
 - R^{2a} and R^{2b} together with the carbon atom to which they are attached to form a carbonyl group, or
 - two of R^{2a} , R^{2b} , R^{3a} and R^{3b} independently represent hydrogen, or (C_{1-3}) alkyl (especially methyl);

and the remaining of R^{2a} , R^{2b} , R^{3a} and R^{3b} represent hydrogen; or

- X represents NR^5 and Y represents a direct bond; R^{2a} and R^{2b} both represent hydrogen; and R^{3a} and R^{3b} both represent hydrogen; or
- X represents NR^5 , Y represents $-C(O)-$; and R^{2a} , R^{2b} , R^{3a} and R^{3b} all represent hydrogen; or
- X represents $-C(O)-$, Y represents NR^5 ; and R^{2a} , R^{2b} , R^{3a} and R^{3b} all represent hydrogen;

15 R^5 represents

- (C_{1-6}) alkyl;
- (C_{1-4}) alkyl mono-substituted with (C_{1-3}) alkoxy, cyano, vinyl; ethynyl, or (C_{1-3}) alkoxy-carbonyl;
- $-CO-R^{10}$ wherein R^{10} represents (C_{1-5}) alkyl; (C_{1-5}) alkoxy; phenyl; phenyl-oxy-; phenyl- (C_{1-3}) alkyl-; phenyl- (C_{1-3}) alkyl-oxy-; (C_{3-6}) cycloalkyl- (C_{1-3}) alkyl; (C_{3-4}) alkenoxy; (C_{3-4}) alkynoxy; (C_{1-3}) fluoroalkyl; (C_{1-3}) fluoroalkoxy; (C_{1-3}) alkoxy- (C_{2-3}) alkoxy; (C_{1-3}) alkoxy- (C_{1-3}) alkyl; (C_{3-6}) cycloalkyl optionally containing one ring oxygen atom, wherein said cycloalkyl is optionally mono- or di-substituted wherein the substituents independently are fluoro or (C_1) fluoroalkyl; unsubstituted 5-membered heteroaryl (especially furanyl); or $-NR^{10a}R^{10b}$ wherein R^{10a} and R^{10b} independently represent hydrogen, (C_{1-4}) alkyl or (C_{3-6}) cycloalkyl, or R^{10a} and R^{10b} together with the nitrogen to which they are attached to form a 5- to 7-membered saturated ring;
- $-SO_2-R^{11}$ wherein R^{11} represents (C_{1-5}) alkyl or phenyl;
- (C_{2-4}) fluoroalkyl;
- (C_{3-6}) cycloalkyl optionally containing one ring oxygen atom;
- (C_{3-6}) cycloalkyl- (C_{1-3}) alkyl, wherein the (C_{3-6}) cycloalkyl group optionally contains one ring oxygen atom; wherein said cycloalkyl is optionally substituted with one or two methyl substituents;
- phenyl- (C_{0-3}) alkyl-, or 5- or 6-membered heteroaryl- (C_{0-3}) alkyl-, wherein the phenyl or 5- or 6-membered heteroaryl independently is especially unsubstituted, or mono-, or

di-substituted, wherein the substituents are independently selected from (C₁₋₄)alkyl (especially methyl), (C₁₋₄)alkoxy (especially methoxy), halogen, (C₁₋₃)fluoroalkyl (especially trifluoromethyl), (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy), and cyano;

(R¹)_n represents one or two optional substituents (i.e. n represents the integer 0, 1, or 2)

5 independently selected from (C₁₋₄)alkyl (especially methyl), (C₁₋₄)alkoxy (especially methoxy), halogen, (C₁₋₃)fluoroalkyl (especially trifluoromethyl), (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy), and cyano;

L¹ represents a one- or two-membered linker group selected from -NH-CH₂-*, -NR^{16a}-CH₂-* wherein R^{16a} represents (C₁₋₃)alkyl (especially methyl or ethyl); -NH-CHR^{16b}-* wherein R^{16b} represents (C₁₋₃)alkyl (especially methyl); -NH-CR^{16c}R^{16d}-* wherein R^{16c} and R^{16d} together with the carbon to which they are attached to form a (C₃₋₆)cycloalkyl (especially a cyclopropyl) ring; -CH₂-NH-*; -O-CH₂-*; -O-CHR^{17a}-* wherein R^{17a} represents (C₁₋₃)alkyl (especially methyl); -O-CR^{17b}R^{17c}-* wherein R^{17b} and R^{17c} together with the carbon to which they are attached to form a (C₃₋₆)cycloalkyl (especially a cyclobutyl) ring; -CH₂-; -CH₂CH₂-; -CH=CH-; and -CH=C(CH₃)-*; wherein the asterisks indicate the bond with which the group L¹ is attached to the carbonyl group;

L² represents -(C₁₋₄)alkylene- or -(C₃₋₄)alkenylene- (especially a linker group selected from -CH₂-, -CH(CH₃)-, -CH₂-CH₂-, -CH₂-CH₂-CH₂-, *-CH₂-CH=CH-, and *-CH₂-C(CH₃)=CH-, wherein the asterisks indicate the bond with which the group L² is attached to the amide nitrogen atom);

Ar¹ represents phenyl, or 5- or 6-membered heteroaryl (especially pyridinyl); wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from (C₁₋₄)alkyl (especially methyl); (C₁₋₄)alkoxy (especially methoxy); (C₁₋₃)fluoroalkyl (especially trifluoromethyl); (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy); halogen; cyano; or NR^{18a}R^{18b} wherein R^{18a} and R^{18b} independently represent hydrogen or (C₁₋₃)alkyl (especially NR^{18a}R^{18b} represents dimethylamino); and

R⁴ represents

- (C₂₋₆)alkyl;
- (C₂₋₅)alkyl which is mono-substituted with (C₁₋₄)alkoxy, benzyloxy, cyano, or hydroxy; or disubstituted wherein the substituents are independently selected from (C₁₋₃)alkoxy, or hydroxy
- (C₂₋₃)fluoroalkyl which is optionally further substituted with one hydroxy;
- -(C₂₋₄)alkylene-NR⁶R⁷, wherein R⁶ and R⁷ independently represent hydrogen; (C₁₋₄)alkyl; -CO-(C₁₋₄)alkoxy; (C₃₋₅)alkenyl; (C₃₋₄)alkynyl; benzyl; -SO₂-(C₁₋₃)alkyl;

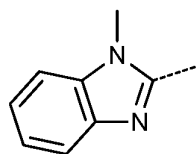
(C₂₋₃)fluoroalkyl; or (C₃₋₆)cycloalkyl or (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl, wherein in the above groups the (C₃₋₆)cycloalkyl group optionally contains one ring oxygen atom, and wherein said (C₃₋₆)cycloalkyl group is optionally substituted with methyl;

- 5 • -(C₁₋₃)alkylene-CO-R⁸, wherein R⁸ represents (C₁₋₄)alkoxy (especially ethoxy); or R⁸ represents NR⁸¹R⁸² wherein R⁸¹ and R⁸² independently represent hydrogen or (C₁₋₄)alkyl, or R⁸¹ and R⁸² together with the nitrogen to which they are attached to form a 4- to 6-membered saturated ring optionally substituted with two fluoro substituents (especially such NR⁸¹R⁸² represents amino, 3,3-difluoroazetidiny);
- 10 • -(C₁₋₃)alkylene-SO₂-R⁹ wherein R⁹ represents (C₁₋₃)alkyl (especially methyl), or amino;
- 10 • (C₃₋₆)cycloalkyl or (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl, wherein the cycloalkyl group is optionally mono-substituted with -CO-(C₁₋₄)alkoxy or hydroxy;
- 15 • (C₄₋₇)heterocyclyl or (C₄₋₇)heterocyclyl-(C₁₋₃)alkyl, wherein in the above groups the (C₄₋₇)heterocyclyl independently contains one or two ring heteroatoms independently selected from nitrogen, sulfur and oxygen; wherein in the above groups said (C₄₋₇)heterocyclyl independently is unsubstituted, or mono-, di-, or tri-substituted wherein the substituents are independently selected from:
 - one oxo substituent attached to a ring carbon atom in alpha position to a ring nitrogen (thus forming together with the nitrogen an amide group, or, in case a ring oxygen is additionally adjacent, a carbamate group, or, in case second ring nitrogen is additionally adjacent, a urea group); and / or
 - 20 ➤ two methyl substituents attached to a ring carbon atom in alpha position to a ring nitrogen atom (thus forming together with the nitrogen a -C(CH₃)₂-N-group); and / or
 - two oxo substituents at a ring sulfur ring atom (thus forming a -SO₂- group); and / or
 - 25 ➤ (C₁₋₄)alkyl (especially methyl) or -CO-(C₁₋₄)alkoxy attached to a ring nitrogen atom having a free valency; and/or
 - two fluoro substituents attached to a ring carbon atom; and/or
 - in case of a (C₄₋₇)heterocyclyl-(C₁₋₃)alkyl group, methyl attached to a ring carbon atom which is attached to the linking (C₁₋₃)alkyl group;
- 30 • 2-oxo-2,3-dihydropyridin-4-yl-(C₁₋₂)alkyl;
- phenyl-(C₁₋₃)alkyl-, or 5- or 6-membered heteroaryl-(C₁₋₃)alkyl-, wherein the phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from (C₁₋₄)alkyl (especially methyl, ethyl), (C₁₋₄)alkoxy (especially methoxy), halogen, (C₁₋₃)fluoroalkyl (especially trifluoromethyl), (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy), and cyano;
- 35

or a pharmaceutically acceptable salt thereof.

The compounds of formula (I) may contain one or more stereogenic or asymmetric centers, such as one or more asymmetric carbon atoms. 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.

- 5 The present invention also includes isotopically labelled, especially ^2H (deuterium) labelled compounds of formula (I) according to embodiments 1) to 33), which compounds are identical to the compounds of formula (I) except that one or more atoms have each been replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Isotopically labelled, especially ^2H (deuterium) labelled
- 10 compounds of formula (I) and salts thereof are within the scope of the present invention. Substitution of hydrogen with the heavier isotope ^2H (deuterium) may lead to greater metabolic stability, resulting e.g. in increased *in-vivo* half-life or reduced dosage requirements, or may lead to reduced inhibition of cytochrome P450 enzymes, resulting e.g. in an improved safety profile. In one embodiment of the invention, the compounds of formula
- 15 (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.
- 20 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 1-methyl-1H-benzimidazol-2-yl group.

- Where the plural form is used for compounds, salts, pharmaceutical compositions, diseases
- 25 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 33) 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
- 30 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 31), 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.

10 The term "halogen" means fluorine, chlorine, or bromine, preferably fluorine or chlorine.

The term "alkyl", used alone or in combination, 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 15 alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, 3-methyl-butyl, 2,2-dimethyl-propyl and 3,3-dimethyl-butyl. For avoidance of any doubt, in case a group is referred to as e.g. propyl or butyl, it is meant to be n-propyl, respectively n-butyl. Preferred are methyl and ethyl. Most preferred is methyl. Examples of (C₂₋₆)alkyl groups as used for R⁴ are ethyl, 3-methyl-butyl and, in addition, 3,3-dimethyl-butyl. Examples of (C₁₋₆)alkyl groups 20 as used for R⁵ are methyl, ethyl, isopropyl, isobutyl, 2,2-dimethyl-propyl, 3,3-dimethyl-butyl, and, in addition, propyl, 1-methyl-propyl, and 1,2-dimethyl-propyl; preferred R⁵ alkyl groups are ethyl, isobutyl and, in addition, propyl. Examples of (C₁₋₅)alkyl groups as used for R¹⁰ are methyl, ethyl, isopropyl, isobutyl, and, in addition, propyl, tert.-butyl, and 2,2-dimethyl-propyl, preferred are methyl and ethyl.

25 Examples of substituted (C₂₋₅)alkyl groups as used for R⁴ are 2-methoxy-ethyl, 2-hydroxy-ethyl, 2-cyano-ethyl, 2-benzyloxy-ethyl, 2-hydroxy-propyl, 2-hydroxy-2-methyl-propyl, 3-hydroxy-3-methyl-butyl, 2-methoxy-ethyl, and 2-hydroxy-3-methoxy-propyl; especially 2-hydroxy-3-methoxy-propyl and 2-hydroxy-2-methyl-propyl. Preferred are (C₂₋₄)alkyl groups mono-substituted with hydroxy, such as especially 2-hydroxy-2-methyl-propyl..

30 The term "-(C_{x-y})alkylene-", used alone or in combination, refers to bivalently bound alkyl group as defined before containing x to y carbon atoms. Preferably, the points of attachment of a -(C_{1-y})alkylene group are in 1,1-diyl, in 1,2-diyl, or in 1,3-diyl arrangement. Preferably, the points of attachment of a -(C_{2-y})alkylene group are in 1,2-diyl or in 1,3-diyl arrangement. For the linker L², examples of -(C₁₋₄)alkylene- groups are methylene, ethylene, ethane-1,1-diyl,

and propylene. For the substituent $-(C_{2-4})\text{alkylene-NR}^6\text{R}^7$ as used for R^4 examples of $-(C_{2-4})\text{alkylene-}$ groups are notably ethylene and propylene, preferred is ethylene.

Examples of $-(C_{1-3})\text{alkylene-CO-R}^8$ groups as used for R^4 are ethoxycarbonyl-methyl, 3-amino-3-oxopropyl, and, in addition, (3,3-difluoroazetidiny)-3-oxo-propyl.

- 5 Examples of $-(C_{1-3})\text{alkylene-SO}_2\text{-R}^9$ groups as used for R^4 are 2-(methane-sulfonyl)-ethyl and 2-(sulfamoyl)-ethyl.

Examples of $-(C_{2-4})\text{alkylene-NR}^6\text{R}^7$ groups as used for R^4 are 2-amino-ethyl, 2-methylamino-ethyl, 2-dimethylamino-ethyl, 2-diethylamino-ethyl, 2-(butylmethylamino)-ethyl, 3-dimethylamino-propyl, and 2-[(*tert.*-butoxycarbonyl)-amino]-ethyl. In addition, further
 10 examples are 2-[(*tert.*-butoxycarbonyl)-methylamino]-ethyl, 2-[(*tert.*-butoxycarbonyl)-ethylamino]-ethyl, 2-ethylamino-ethyl, 2-(ethyl-methylamino)-ethyl, 2-(isopropyl-methylamino)-ethyl, 2-(diisopropylamino)-ethyl, 2-(allyl-methylamino)-ethyl, 2-(methyl-prop-2-ynyl-amino)-ethyl, 2-[(2-fluoroethyl)-methylamino]-ethyl, 2-[(2,2,2-trifluoroethyl)-amino]-ethyl,
 15 2-[methyl-(2,2,2-trifluoroethyl)-amino]-ethyl, 2-[(2-fluoro-1-methylethyl)-methylamino]-ethyl, 2-methanesulfonylamino-ethyl, 2-[(cyclopropyl)-methylamino]-ethyl, 2-[(cyclopropylmethyl)-methylamino]-ethyl, 2-[(cyclobutyl)-methylamino]-ethyl, 2-[(cyclopentyl)-methylamino]-ethyl,
 2-[methyl-(tetrahydrofuran-3-yl)-amino]-ethyl, 2-[ethyl-(3-methyl-oxetan-3-yl-methyl)-amino]-ethyl. Preferred are 2-methylamino-ethyl, 2-dimethylamino-ethyl, and 2-ethylamino-ethyl; especially 2-dimethylamino-ethyl.

- 20 The term "alkoxy", used alone or in combination, refers to an alkyl-O- group wherein the alkyl group is as defined before. The term " $(C_{x-y})\text{alkoxy}$ " (x and y each being an integer) refers to an alkoxy group as defined before containing x to y carbon atoms. For example a $(C_{1-4})\text{alkoxy}$ group means a group of the formula $(C_{1-4})\text{alkyl-O-}$ in which the term " $(C_{1-4})\text{alkyl}$ " has the previously given significance. Examples of alkoxy groups are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec.-butoxy and tert.-butoxy. Preferred are ethoxy
 25 and especially methoxy. Examples of $(C_{1-5})\text{alkoxy}$ groups as used for R^{10} are methoxy, ethoxy, isopropoxy, isobutoxy, tert.-butoxy, 2,2-dimethyl-propoxy, and, in addition, propoxy.

The term "alkenyl", used alone or in combination, refers to a straight or branched hydrocarbon chain containing two to five carbon atoms and one carbon-carbon double bond.

- 30 The term " $(C_{x-y})\text{alkenyl}$ " (x and y each being an integer), refers to an alkenyl group as defined before containing x to y carbon atoms. For example a $(C_{2-5})\text{alkenyl}$ group contains from two to five carbon atoms. Examples of alkenyl groups are vinyl, prop-1-en-1-yl, 2-methylprop-1-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, and especially allyl.

The term "alkynyl", used alone or in combination, refers to a straight or branched hydrocarbon chain containing two to five carbon atoms and one carbon-carbon triple bond. The term "(C_{x-y})alkynyl" (x and y each being an integer), refers to an alkynyl group as defined before containing x to y carbon atoms. For example a (C₂₋₅)alkynyl group contains from two to five carbon atoms. An example of an alkynyl group is prop-2-yn-1-yl.

The term "-(C₃₋₄)alkenylene-", used alone or in combination, refers to bivalently bound alkenyl group as defined before containing three or four carbon atoms. Preferably, the points of attachment of any bivalently bound alkenyl group are in 1,3-diyl arrangement. For the linker L², examples of -(C₁₋₄)alkenylene- groups are *-CH₂-CH=CH-, and *-CH₂-C(CH₃)=CH-, wherein the asterisks indicate the bond with which the group L² is attached to the amide nitrogen atom.

The term "fluoroalkyl" 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. Preferred are (C₁)fluoroalkyl groups such as trifluoromethyl. Examples of (C₂₋₄)fluoroalkyl groups as used for R⁵ are 2,2,2-trifluoroethyl, and, in addition, 2-fluoroethyl and especially 3-fluoropropyl. An example of (C₁₋₃)fluoroalkyl as used for the substituent R¹⁰ is 1,1-difluoroethyl. Examples of optionally substituted (C₂₋₃)fluoroalkyl groups as used for R⁴ are 3,3,3-trifluoro-propyl and 2-hydroxy-3,3,3-trifluoro-propyl.

The term "fluoroalkoxy" refers to an alkoxy group as defined before containing one to three carbon atoms in which one or more (and possibly all) hydrogen atoms have been replaced with fluorine. The term "(C_{x-y})fluoroalkoxy" (x and y each being an integer) refers to a fluoroalkoxy group as defined before containing x to y carbon atoms. For example a (C₁₋₃)fluoroalkoxy group contains from one to three carbon atoms in which one to seven hydrogen atoms have been replaced with fluorine. Representative examples of fluoroalkoxy groups include trifluoromethoxy, difluoromethoxy, 2-fluoroethoxy, 2,2-difluoroethoxy and 2,2,2-trifluoroethoxy. Preferred are (C₁)fluoroalkoxy groups such as trifluoromethoxy and difluoromethoxy.

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

The term "cycloalkyl", used alone or in combination, refers to a saturated monocyclic hydrocarbon ring containing three to six carbon atoms. The term "(C_{x-y})cycloalkyl" (x and y

each being an integer), refers to a cycloalkyl group as defined before containing x to y carbon atoms. For example a (C₃₋₆)cycloalkyl group contains from three to six carbon atoms. Examples of cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. Preferred are cyclopropyl, cyclopentyl and cyclohexyl; especially cyclopropyl.

5 Examples of (C₃₋₆)cycloalkyl groups as used for the group R⁵ are cyclobutyl and cyclopentyl; especially cyclobutyl. In case the (C₃₋₆)cycloalkyl group as used for the group R⁴ is optionally mono-substituted with -CO-(C₁₋₄)alkoxy or hydroxy, an example is 4-hydroxy-cyclohexyl.

The term "(C_{x-y})cycloalkyl-(C_{x-y})alkyl" refers to a (C_{x-y})cycloalkyl group as defined before, which is linked through a (C_{x-y})alkylene group as defined before to the rest of the molecule. A

10 particular example of such groups is cyclopropyl-methyl. Examples of (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl groups as used for the group R⁵ are cyclopropyl-methyl and cyclohexyl-methyl; preferred is cyclopropyl-methyl. An example of (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl groups as used for the group R¹⁰ is cyclohexyl-methyl. An example of (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl groups as used for the group R⁴ is cyclopropyl-methyl. In case the cycloalkyl of a (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl

15 group as used for the group R⁴ is optionally mono-substituted with -CO-(C₁₋₄)alkoxy or hydroxy, examples are (2-(ethoxycarbonyl)cyclopropyl)methyl and, especially (1-hydroxy-cyclopentyl)-methyl.

The term "cycloalkyl optionally containing one ring oxygen atom", used alone or in combination, refers to a cycloalkyl group as defined before. In addition, one ring carbon atom

20 of said cycloalkyl may be replaced by an oxygen atom. Examples of such groups are especially cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl; as well as oxygen containing groups such as oxetanyl, tetrahydrofuranyl, and tetrahydro-2H-pyranyl. As used for the substituent R⁵ (i.e. said cycloalkyl optionally containing one ring oxygen atom is attached to a nitrogen atom) a ring oxygen atom, if

25 present, is preferably separated from said nitrogen atom by at least two ring carbon atoms. Examples of such groups as used for the substituent R⁵ are especially cycloalkyl groups such as cyclobutyl and cyclopentyl; as well as oxetan-3-yl, and tetrahydrofuran-3-yl. Preferred is cyclobutyl. Examples of optionally substituted cycloalkyl optionally containing one ring oxygen atom as used for the group R¹⁰ are cyclopropyl, cyclobutyl, 2-

30 fluorocyclopropyl, 2,2-difluorocyclopropyl, 1-trifluoromethyl-cyclopropyl, and tetrahydrofuran-3-yl. Preferred are 2-fluorocyclopropyl, and 2,2-difluorocyclopropyl.

Examples of optionally substituted (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl groups optionally containing one ring oxygen atom as used for the substituent R⁵ are cyclopropyl-methyl, cyclobutylmethyl, cyclohexyl-methyl, 1-cyclopropyl-ethyl, and (3-methyl-oxetan-3-yl)-methyl;

notably unsubstituted (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl groups as defined herein above, such as especially cyclopropyl-methyl, and cyclobutylmethyl.

- The term "heterocyclyl", used alone or in combination and if not explicitly defined in a more narrow way, refers to a saturated monocyclic hydrocarbon ring containing one or two (especially one) ring heteroatoms independently selected from nitrogen, oxygen and sulfur (especially one or two nitrogen atoms, or one nitrogen atom and one oxygen atom, or one sulfur atom). The term "(C_{x-y})heterocyclyl" refers to such a heterocyclyl group containing x to y ring atoms. Heterocyclyl groups are unsubstituted or substituted as explicitly defined. Examples of heterocyclyl groups as used for the group **R**⁴ are pyrrolidin-3-yl, 1-methyl-pyrrolidin-3-yl, 1-(*tert*.-butoxycarbonyl)-pyrrolidin-3-yl, piperidin-3-yl, 1-methyl-piperidin-3-yl, piperidin-4-yl, 1-methyl-piperidin-4-yl, tetrahydro-pyran-4-yl, and 1,1-dioxo-tetrahydrothiophen-3-yl, and, in addition, 1-(*tert*.-butoxycarbonyl)-piperidin-4-yl. Preferred are 1-methyl-pyrrolidin-3-yl, 1-methyl-piperidin-3-yl, 1-methyl-piperidin-4-yl, and especially pyrrolidin-3-yl.
- The term "(C_{x-y}) heterocyclyl-(C_{x-y})alkyl" refers to a (C_{x-y})heterocyclyl group as defined before, which is linked through a (C_{x-y})alkylene group as defined before to the rest of the molecule. For the (C₄₋₆)heterocyclyl-(C₁₋₃)alkyl groups as used for **R**⁴ examples of -(C₁₋₃)alkylene-groups are especially methylene, and ethylene. Examples of heterocyclyl groups part of such (C₄₋₆)heterocyclyl-(C₁₋₃)alkyl groups as used for the group **R**⁴ are pyrrolidin-1-yl, 1-methyl-pyrrolidin-2-yl, 1-methyl-pyrrolidin-3-yl, 2-oxo-pyrrolidin-1-yl, 1-(*tert*.-butoxycarbonyl)-pyrrolidin-3-yl, 3-(*tert*.-butoxycarbonyl)-2,2-dimethyl-oxazolidin-4-yl, 2-oxo-imidazolidin-1-yl, piperidin-1-yl, 1-methyl-piperidin-2-yl, 1-methyl-piperidin-3-yl, 1-methyl-piperidin-4-yl, morpholin-4-yl, and, in addition 3-methyl-oxetan-3-yl, pyrrolidin-3-yl, [1,4]dioxan-2-yl, piperazin-1-yl, azepan-1-yl, 3,3-difluoroazetidin-1-yl, 3,3-difluoropyrrolidin-1-yl, 3,3-difluoropiperdin-1-yl, 4,4-difluoropiperdin-1-yl, and 1-(*tert*.-butoxycarbonyl)-piperazin-4-yl. Particular examples of (C₄₋₆)heterocyclyl-(C₁₋₃)alkyl groups as used for **R**⁴ are 2-(pyrrolidin-1-yl)-ethyl, 2-(2-oxo-imidazolidin-1-yl)-ethyl, 2-(1-methyl-pyrrolidin-2-yl)-ethyl, 2-(2-oxo-pyrrolidin-1-yl)-ethyl, 2-(morpholin-4-yl)-ethyl, and (3-(*tert*.-butoxycarbonyl)-2,2-dimethyl-oxazolidin-4-yl)-methyl, and, in addition, 3-methyl-oxetan-3-yl-methyl, pyrrolidin-3-yl-methyl, 3-(pyrrolidin-1-yl)-propyl, [1,4]dioxan-2-yl-methyl, 2-(piperazin-1-yl)-ethyl, 2-(piperidin-1-yl)-ethyl, 2-(azepan-1-yl)-ethyl, 2-(3,3-difluoroazetidin-1-yl)-ethyl, 2-(3,3-difluoropyrrolidin-1-yl)-ethyl, 2-(3,3-difluoropiperdin-1-yl)-ethyl, 2-(4,4-difluoropiperdin-1-yl)-ethyl, (1-(*tert*.-butoxycarbonyl)-pyrrolidin-3-yl)-methyl, 2-(1-(*tert*.-butoxycarbonyl)-piperazin-4-yl)-ethyl. Preferred are 2-(pyrrolidin-1-yl)-ethyl, 2-(morpholin-4-yl)-ethyl, [1,4]dioxan-2-yl-methyl, 2-(piperazin-1-yl)-ethyl, and 2-(4,4-difluoropiperdin-1-yl)-ethyl; especially 2-(pyrrolidin-1-yl)-ethyl.

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.

Examples of the substituent **Ar**¹ representing phenyl are especially those which are unsubstituted or mono-, or di-substituted wherein the substituents are independently selected from (C₁₋₄)alkyl; (C₁₋₄)alkoxy; (C₁₋₃)fluoroalkyl; (C₁₋₃)fluoroalkoxy; halogen; and cyano. In a sub-embodiment, the substituents are independently selected from (C₁₋₄)alkyl; (C₁₋₄)alkoxy; (C₁₋₃)fluoroalkyl; and halogen. Particular examples are phenyl, 2-fluoro-phenyl, 3-fluoro-phenyl, 4-fluoro-phenyl, 2,4-difluoro-phenyl, 2-chloro-phenyl, 3-chloro-phenyl, 4-chloro-phenyl, 2-chloro-4-fluoro-phenyl, 2-methyl-phenyl, 3-methyl-phenyl, 4-methyl-phenyl, 2,3-dimethyl-phenyl, 2-methoxy-phenyl, 3-methoxy-phenyl, 4-methoxy-phenyl, 3,4-dimethoxy-phenyl, 2-trifluoromethyl-phenyl, 3-trifluoromethyl-phenyl, 4-trifluoromethyl-phenyl, 4-fluoro-2-trifluoromethyl-phenyl, and, in addition, 2-bromo-phenyl, 3-bromo-phenyl, 4-bromo-phenyl, 2,6-difluoro-phenyl, 2-trifluoromethoxy-phenyl, 3-trifluoromethoxy-phenyl, and 4-trifluoromethoxy-phenyl. Preferred are 2-chloro-phenyl, 2-trifluoromethyl-phenyl, and 2-bromo-phenyl.

The term "aryl-(C_{x-y})alkyl-" refers to an aryl group as defined before; in the particular case of a "phenyl-(C_{x-y})alkyl-" group it refers to a phenyl group, which is linked to the rest of the molecule through a (C_{x-y})alkylene group as defined before (especially through a methylene or ethylene group). The aryl/phenyl group part of aryl/phenyl-(C_{x-y})alkyl- is unsubstituted or substituted as explicitly defined. Examples of phenyl-(C₀₋₃)alkyl- groups as used for the substituent **R**⁵ are benzyl, and phenyl-ethyl. Examples of phenyl-(C₁₋₃)alkyl- groups as used for the substituent **R**⁴ are benzyl, 2-trifluoromethyl-benzyl, and 2-(4-fluoro-phenyl)-ethyl.

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, each independently selected from oxygen, nitrogen and sulfur. Examples of such heteroaryl groups are furanyl, oxazolyl, isoxazolyl, oxadiazolyl, thiophenyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzotriazolyl, benzoxadiazolyl, benzothiadiazolyl, quinolinyl, isoquinolinyl, naphthyridinyl, cinnolinyl, quinoxalinyl, quinoxalyl, phthalazinyl, pyrrolopyridinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, pyrrolopyrazinyl, imidazopyridinyl, imidazopyridazinyl, and imidazothiazolyl. The above-mentioned heteroaryl groups are unsubstituted or substituted as explicitly defined. In case **Ar**¹ represents "5- or 6-membered heteroaryl", the term means the above-mentioned 5- or 6-membered groups. Notably, the term refers to 5-membered

heteroaryl containing at least one nitrogen atom and optionally one further heteroatom selected from nitrogen, oxygen or sulfur; such as especially pyrazolyl, imidazolyl, or thiazolyl; or to 6-membered heteroaryl containing one or two nitrogen atoms; such as pyrimidinyl, pyrazinyl, or pyridinyl; especially pyridinyl. For the substituent Ar^1 , such 5- or 6-membered

5 heteroaryl group is unsubstituted or mono-, or di-substituted wherein the substituents are independently selected from (C_{1-4}) alkyl; (C_{1-4}) alkoxy; (C_{1-3}) fluoroalkyl; (C_{1-3}) fluoroalkoxy; halogen; and cyano. In a sub-embodiment, the substituents are independently selected from (C_{1-4}) alkyl; (C_{1-4}) alkoxy; (C_{1-3}) fluoroalkyl; and halogen; especially (C_{1-4}) alkyl; (C_{1-3}) fluoroalkyl; and halogen. Examples are 1-methyl-imidazol-2-yl, 1-ethyl-1H-pyrazol-3-yl, 4-methyl-thiazol-

10 2-yl, pyridin-2-yl, 3-chloro-pyridin-2-yl, 3-trifluoromethyl-pyridin-2-yl, 6-trifluoromethyl-pyridin-2-yl, and, in addition, thiazol-2-yl, isoxazol-5-yl, 5-methyl-isoxazol-3-yl, 1-methyl-1H-pyrazol-5-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyridin-3-yl, pyridin-4-yl, 3-fluoro-pyridin-2-yl, 5-fluoro-pyridin-2-yl, 3-chloro-pyridin-5-yl, 5-chloro-pyridin-2-yl, 3-bromo-pyridin-2-yl, 3-bromo-pyridin-4-yl, 3-methyl-pyridin-2-yl, 5-methyl-pyridin-2-yl, 6-methyl-pyridin-2-yl, 2-dimethylamino-

15 pyrimidin-5-yl, 5-(4-fluorophenyl-amino)-pyridin-2-yl; preferred are 3-chloro-pyridin-2-yl, 3-trifluoromethyl-pyridin-2-yl, 6-trifluoromethyl-pyridin-2-yl, 3-bromo-pyridin-2-yl, 3-methyl-pyridin-2-yl, 6-methyl-pyridin-2-yl.

The term "heteroaryl- (C_{x-y}) alkyl-" refers to a heteroaryl group as defined before which is linked to the rest of the molecule through a (C_{x-y}) alkylene group as defined before (especially

20 through a methylene or ethylene group). The heteroaryl group part of heteroaryl- (C_{x-y}) alkyl- is unsubstituted or substituted as explicitly defined. Especially it is unsubstituted or mono-substituted with (C_{1-4}) alkyl. Examples of heteroaryl- (C_{1-3}) alkyl- groups as used for the substituent R^4 are (1-methyl-imidazol-2-yl)-methyl, 1-(1-ethyl-1H-pyrazol-3-yl)-ethan-1-yl, (4-methyl-thiazol-2-yl)-methyl, (pyridin-2-yl)-methyl and, in addition, isoxazol-5-ylmethyl.

25 Examples of heteroaryl- (C_{0-3}) alkyl- groups as used for the substituent R^5 are furan-2-yl-methyl and especially the heteroaryl- (C_0) alkyl- groups thiazolyl, pyridinyl, pyrimidinyl; in particular 5-trifluoromethyl-thiazol-2-yl, pyridin-2-yl, and pyrimidin-2-yl.

Further embodiments of the invention are presented hereinafter:

2) A second embodiment relates to compounds according to embodiment 1), wherein

- 30
- X represents NR^5 , and Y represents CHR^Y wherein R^Y represents hydrogen, or (C_{1-3}) alkyl (especially methyl); and
 - R^{3a} and R^{3b} together with the carbon atom to which they are attached to form a carbonyl group, or
 - two of R^{2a} , R^{2b} , R^{3a} and R^{3b} independently represent hydrogen, or (C_{1-3}) alkyl
- 35 (especially methyl);

and the remaining of R^{2a} , R^{2b} , R^{3a} and R^{3b} represent hydrogen; or

- X represents CHR^X wherein R^X represents hydrogen, or (C_{1-3}) alkyl (especially methyl), and Y represents NR^5 ; and
 - R^{2a} and R^{2b} together with the carbon atom to which they are attached to form a carbonyl group, or
 - two of R^{2a} , R^{2b} , R^{3a} and R^{3b} independently represent hydrogen, or (C_{1-3}) alkyl (especially methyl);

and the remaining of R^{2a} , R^{2b} , R^{3a} and R^{3b} represent hydrogen; or

- X represents NR^5 , Y represents $-C(O)-$; and R^{2a} , R^{2b} , R^{3a} and R^{3b} all represent hydrogen; or
- X represents $-C(O)-$, Y represents NR^5 ; and R^{2a} , R^{2b} , R^{3a} and R^{3b} all represent hydrogen;

wherein in first sub-embodiment X represents NR^5 , and in a second sub-embodiment Y represents NR^5 , wherein R^X , R^Y , R^{2a} , R^{2b} , R^{3a} and R^{3b} are as defined above.

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

- X represents NR^5 and:
 - Y represents CH_2 ; and R^{2a} , R^{2b} , R^{3a} and R^{3b} represent hydrogen; or
 - Y represents CHR^Y wherein R^Y represents (C_{1-3}) alkyl (especially methyl); and R^{2a} , R^{2b} , R^{3a} and R^{3b} represent hydrogen; or
 - Y represents CH_2 ; R^{2a} and R^{2b} both represent (C_{1-3}) alkyl (especially methyl); and R^{3a} and R^{3b} both represent hydrogen; or
 - Y represents CH_2 ; R^{2a} and R^{2b} both represent hydrogen; one of R^{3a} and R^{3b} represents (C_{1-3}) alkyl (especially methyl), and the remaining of R^{3a} and R^{3b} represents hydrogen;

or Y represents NR^5 and:

- X represents CH_2 ; and R^{2a} , R^{2b} , R^{3a} and R^{3b} represent hydrogen; or
- X represents CHR^X wherein R^X represents (C_{1-3}) alkyl (especially methyl); and R^{2a} , R^{2b} , R^{3a} and R^{3b} represent hydrogen; or
- X represents CH_2 ; R^{3a} and R^{3b} both represent (C_{1-3}) alkyl (especially methyl); and R^{2a} and R^{2b} both represent hydrogen; or
- X represents CH_2 ; R^{3a} and R^{3b} both represent hydrogen; one of R^{2a} and R^{2b} represents (C_{1-3}) alkyl (especially methyl), and the remaining of R^{2a} and R^{2b} represents hydrogen;

wherein in first sub-embodiment **X** represents NR^5 , and in a second sub-embodiment **Y** represents NR^5 , wherein R^X , R^Y , R^{2a} , R^{2b} , R^{3a} and R^{3b} are as defined above.

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

- **X** represents NR^5 and

- **Y** represents CH_2 ; and R^{2a} , R^{2b} , R^{3a} and R^{3b} represent hydrogen; or
- **Y** represents CH_2 ; R^{2a} and R^{2b} both represent (C_{1-3}) alkyl (especially methyl); and R^{3a} and R^{3b} both represent hydrogen; or
- **Y** represents CH_2 ; R^{2a} and R^{2b} both represent hydrogen; one of R^{3a} and R^{3b} represents (C_{1-3}) alkyl (especially methyl), and the remaining of R^{3a} and R^{3b} represents hydrogen;

- or **Y** represents NR^5 and:

- **X** represents CH_2 ; and R^{2a} , R^{2b} , R^{3a} and R^{3b} represent hydrogen;

wherein in first sub-embodiment **X** represents NR^5 , and in a second sub-embodiment **Y** represents NR^5 , wherein R^{2a} , R^{2b} , R^{3a} and R^{3b} are as defined above.

5) Another embodiment relates to compounds according to any one of embodiments 1) to 4), wherein R^5 represents

- (C_{1-6}) alkyl; [in particular methyl, ethyl, propyl, isopropyl, isobutyl, 1-methyl-propyl, 1,2-dimethyl-propyl, 2,2-dimethyl-propyl, 3,3-dimethyl-butyl];
- (C_{1-4}) alkyl mono-substituted with (C_{1-3}) alkoxy, cyano, vinyl; ethynyl, or (C_{1-3}) alkoxy-carbonyl; [in particular allyl, prop-2-ynyl, cyanomethyl, 2-methoxy-ethyl, 2-methoxy-1-methyl-ethyl, methoxycarbonyl-methyl, ethoxycarbonyl-methyl];
- $-\text{CO}-\text{R}^{10}$ wherein R^{10} represents (C_{1-5}) alkyl; (C_{1-5}) alkoxy; phenyl; phenyl-oxy-; phenyl- (C_{1-3}) alkyl-; phenyl- (C_{1-3}) alkyl-oxy-; (C_{3-6}) cycloalkyl- (C_{1-3}) alkyl; (C_{3-4}) alkenoxy; (C_{3-4}) alkynoxy; (C_{1-3}) fluoroalkyl; (C_{1-3}) fluoroalkoxy; (C_{1-3}) alkoxy- (C_{2-3}) alkoxy; (C_{1-3}) alkoxy- (C_{1-3}) alkyl; (C_{3-6}) cycloalkyl optionally containing one ring oxygen atom, wherein said cycloalkyl is optionally mono- or di-substituted wherein the substituents independently are fluoro or (C_1) fluoroalkyl; unsubstituted 5-membered heteroaryl (especially furanyl); or $-\text{NR}^{10a}\text{R}^{10b}$ wherein R^{10a} and R^{10b} independently represent hydrogen, (C_{1-4}) alkyl or (C_{3-6}) cycloalkyl, or R^{10a} and R^{10b} together with the nitrogen to which they are attached to form a 5- to 7-membered saturated ring; [in particular such $-\text{CO}-\text{R}^{10}$ is methyl-carbonyl, ethyl-carbonyl, propyl-carbonyl, isopropyl-carbonyl, isobutyl-carbonyl, *tert.*-butyl-carbonyl, (2,2-dimethyl-propyl)-carbonyl, methoxymethyl-carbonyl, cyclopropyl-carbonyl, cyclobutyl-carbonyl, (2-fluorocyclopropyl)-carbonyl, (cyclohexyl-methyl)-carbonyl, (2,2-difluorocyclopropyl)-carbonyl, (1-trifluoromethyl-cyclopropyl)-carbonyl, (tetrahydrofuran-3-yl)-carbonyl, (1,1-difluoroethyl)-carbonyl,

- carbamoyl, methylcarbamoyl, ethylcarbamoyl, isopropylcarbamoyl, butyl-carbamoyl, *tert.*-butyl-carbamoyl, cyclohexyl-carbamoyl, dimethylcarbamoyl, (pyrrolidin-1-yl)-carbonyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, isobutoxycarbonyl, *tert.*-butoxycarbonyl, (2,2-dimethyl-propoxy)-carbonyl, allyloxy-carbonyl, prop-2-ynyloxycarbonyl, (2-fluoro-ethoxy)-carbonyl, (2-methoxy-ethoxy)-carbonyl, furan-2-yl-carbonyl, benzoyl, phenoxy-carbonyl, benzyl-carbonyl, benzyloxy-carbonyl];
- $\text{-SO}_2\text{-R}^{11}$ wherein R^{11} represents (C_{1-5}) alkyl or phenyl; [in particular such $\text{-SO}_2\text{-R}^{11}$ is methylsulfonyl, ethylsulfonyl, phenylsulfonyl];
 - (C_{2-4}) fluoroalkyl; [in particular 2-fluoroethyl, 2,2,2-trifluoroethyl, 3-fluoropropyl];
 - (C_{3-6}) cycloalkyl optionally containing one ring oxygen atom; [in particular cyclobutyl, oxetan-3-yl, cyclopentyl, tetrahydrofuran-3-yl];
 - (C_{3-6}) cycloalkyl- (C_{1-3}) alkyl, wherein the (C_{3-6}) cycloalkyl group optionally contains one ring oxygen atom; wherein said cycloalkyl is optionally substituted with one methyl substituent; [in particular such (C_{3-6}) cycloalkyl- (C_{1-3}) alkyl is cyclopropyl-methyl, cyclobutylmethyl, cyclohexyl-methyl, 1-cyclopropyl-ethyl, (3-methyl-oxetan-3-yl)-methyl];
 - phenyl- (C_{0-3}) alkyl-, or 5- or 6-membered heteroaryl- (C_{0-3}) alkyl-, wherein the phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, or mono-, or di-substituted, wherein the substituents are independently selected from (C_{1-4}) alkyl (especially methyl), (C_{1-4}) alkoxy (especially methoxy), halogen, (C_{1-3}) fluoroalkyl (especially trifluoromethyl), (C_{1-3}) fluoroalkoxy (especially trifluoromethoxy), and cyano [in particular unsubstituted phenyl- (C_{1-2}) alkyl-; or thiazolyl, pyridinyl, or pyrimidinyl which are independently unsubstituted or mono-substituted with trifluoromethyl; especially benzyl or phenethyl; or 5-trifluoromethyl-thiazol-2-yl, pyridin-2-yl, or pyrimidin-2-yl];
- 6) Another embodiment relates to compounds according to any one of embodiments 1) to 4), wherein R^5 represents
- (C_{1-6}) alkyl; [in particular methyl, ethyl, propyl, isopropyl, isobutyl, 1-methyl-propyl, 1,2-dimethyl-propyl, 2,2-dimethyl-propyl, 3,3-dimethyl-butyl; especially ethyl, propyl, or isobutyl];
 - (C_{1-4}) alkyl mono-substituted with (C_{1-3}) alkoxy; [in particular 2-methoxy-ethyl];
 - -CO-R^{10} wherein R^{10} represents (C_{1-5}) alkyl; (C_{1-5}) alkoxy; phenyl; phenyl-oxy-; phenyl- (C_{1-3}) alkyl-; phenyl- (C_{1-3}) alkyl-oxy-; (C_{3-6}) cycloalkyl- (C_{1-3}) alkyl; (C_{3-4}) alkenoxo; (C_{3-4}) alkynoxo; (C_{1-3}) fluoroalkyl; (C_{1-3}) fluoroalkoxy; (C_{1-3}) alkoxy- (C_{2-3}) alkoxy; (C_{1-3}) alkoxy- (C_{1-3}) alkyl; (C_{3-6}) cycloalkyl optionally containing one ring oxygen atom,

- wherein said cycloalkyl is optionally mono- or di-substituted wherein the substituents independently are fluoro or (C₁)fluoroalkyl; or -NR^{10a}R^{10b} wherein R^{10a} and R^{10b} independently represent hydrogen, (C₁₋₄)alkyl or (C₃₋₆)cycloalkyl, or R^{10a} and R^{10b} together with the nitrogen to which they are attached to form a 5- to 7-membered saturated ring; [in particular such -CO-R¹⁰ is methyl-carbonyl, ethyl-carbonyl, propyl-carbonyl, isopropyl-carbonyl, isobutyl-carbonyl, *tert*-butyl-carbonyl, (2,2-dimethyl-propyl)-carbonyl, methoxymethyl-carbonyl, cyclopropyl-carbonyl, cyclobutyl-carbonyl, (2-fluorocyclopropyl)-carbonyl, (cyclohexyl-methyl)-carbonyl, (2,2-difluorocyclopropyl)-carbonyl, (1-trifluoromethyl-cyclopropyl)-carbonyl, (tetrahydrofuran-3-yl)-carbonyl (1,1-difluoroethyl)-carbonyl, carbamoyl, methylcarbamoyl, ethylcarbamoyl, isopropylcarbamoyl, butyl-carbamoyl, *tert*-butyl-carbamoyl, cyclohexyl-carbamoyl, dimethylcarbamoyl, (pyrrolidin-1-yl)-carbonyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, isobutoxycarbonyl, *tert*-butoxycarbonyl, (2,2-dimethyl-propoxy)-carbonyl, allyloxy-carbonyl, prop-2-ynyloxycarbonyl, (2-fluoro-ethoxy)-carbonyl, (2-methoxy-ethoxy)-carbonyl, furan-2-yl-carbonyl, benzoyl, phenoxy-carbonyl, benzyl-carbonyl, benzyloxy-carbonyl];
- -SO₂-R¹¹ wherein R¹¹ represents (C₁₋₅)alkyl or phenyl; [in particular such -SO₂-R¹¹ is methylsulfonyl, ethylsulfonyl, phenylsulfonyl];
 - (C₂₋₄)fluoroalkyl; [in particular 2-fluoroethyl, 2,2,2-trifluoroethyl, 3-fluoropropyl];
 - (C₃₋₆)cycloalkyl optionally containing one ring oxygen atom; [in particular cyclobutyl, oxetan-3-yl, cyclopentyl, tetrahydrofuran-3-yl];
 - (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl, wherein the (C₃₋₆)cycloalkyl group optionally contains one ring oxygen atom; wherein said cycloalkyl is optionally substituted with one methyl substituent; [in particular such (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl is cyclopropyl-methyl, cyclobutylmethyl, cyclohexyl-methyl, 1-cyclopropyl-ethyl, (3-methyl-oxetan-3-yl)-methyl];
 - phenyl-(C₁₋₃)alkyl-, wherein the phenyl is unsubstituted [in particular benzyl or phenethyl]; or
 - 5- or 6-membered heteroaryl (especially thiazolyl, pyridinyl, pyrimidinyl) wherein the 5- or 6-membered heteroaryl is unsubstituted, or mono-, or di-substituted, wherein the substituents are independently selected from (C₁₋₄)alkyl (especially methyl), (C₁₋₄)alkoxy (especially methoxy), halogen, (C₁₋₃)fluoroalkyl (especially trifluoromethyl), (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy), and cyano [in particular thiazolyl, pyridinyl, or pyrimidinyl which are independently unsubstituted or mono-substituted with trifluoromethyl; especially 5-trifluoromethyl-thiazol-2-yl, pyridin-2-yl, or pyrimidin-2-yl].

7) Another embodiment relates to compounds according to any one of embodiments 1) to 4), wherein R^5 represents

- (C_{1-6}) alkyl; [in particular methyl, ethyl, propyl, isopropyl, isobutyl, 1-methyl-propyl, 1,2-dimethyl-propyl, 2,2-dimethyl-propyl, 3,3-dimethyl-butyl; especially ethyl, propyl, or isobutyl];
- (C_{1-4}) alkyl mono-substituted with (C_{1-3}) alkoxy [in particular 2-methoxy-ethyl];
- $-CO-R^{10}$ wherein R^{10} represents (C_{1-5}) alkyl; (C_{1-3}) alkoxy- (C_{1-3}) alkyl; or (C_{3-6}) cycloalkyl optionally containing one ring oxygen atom, wherein said cycloalkyl is unsubstituted, or mono- or di-substituted with fluoro; [in particular such $-CO-R^{10}$ is methyl-carbonyl, ethyl-carbonyl, propyl-carbonyl, isopropyl-carbonyl, isobutyl-carbonyl, *tert.*-butyl-carbonyl, (2,2-dimethyl-propyl)-carbonyl, methoxymethyl-carbonyl, cyclopropyl-carbonyl, cyclobutyl-carbonyl, (2-fluorocyclopropyl)-carbonyl, (2,2-difluorocyclopropyl)-carbonyl, (tetrahydrofuran-3-yl)-carbonyl, (1,1-difluoroethyl)-carbonyl; especially methyl-carbonyl, ethyl-carbonyl, methoxymethyl-carbonyl, (2-fluorocyclopropyl)-carbonyl, or (2,2-difluorocyclopropyl)-carbonyl];
- (C_{2-4}) fluoroalkyl; [in particular 2-fluoroethyl, 2,2,2-trifluoroethyl, 3-fluoropropyl; especially 3-fluoropropyl];
- (C_{3-6}) cycloalkyl optionally containing one ring oxygen atom; [in particular cyclobutyl, oxetan-3-yl, cyclopentyl, tetrahydrofuran-3-yl; especially cyclobutyl]; or
- (C_{3-6}) cycloalkyl- (C_{1-3}) alkyl [in particular cyclopropyl-methyl, cyclobutylmethyl, cyclohexyl-methyl, 1-cyclopropyl-ethyl; especially cyclopropyl-methyl, or cyclobutylmethyl].

8) Another embodiment relates to compounds according to any one of embodiments 1) to 7), wherein $(R^1)_n$ represents one optional substituent (i.e. n represents the integer 0, or 1) independently selected from (C_{1-4}) alkyl (especially methyl), (C_{1-4}) alkoxy (especially methoxy), halogen, (C_{1-3}) fluoroalkyl (especially trifluoromethyl), (C_{1-3}) fluoroalkoxy (especially trifluoromethoxy), and cyano; (especially $(R^1)_n$ is absent, or it represents one methyl, methoxy halogen, or trifluoromethyl substituent; preferably $(R^1)_n$ is absent).

9) Another embodiment relates to compounds according to any one of embodiments 1) to 8), wherein L^1 represents a two-membered linker group selected from $-NH-CH_2-^*$, $-NR^{16a}-CH_2-^*$ wherein R^{16a} represents (C_{1-3}) alkyl (especially methyl), $-O-CH_2-^*$, $-CH_2CH_2-$, $-CH=CH-$, and $-CH=C(CH_3)-^*$; wherein the asterisks indicate the bond with which the group L^1 is attached to the carbonyl group.

10) Another embodiment relates to compounds according to any one of embodiments 1) to 8), wherein L^1 represents a two-membered linker group selected from $-NH-CH_2-^*$, $-O-CH_2-^*$,

-CH₂CH₂-, and -CH=CH- (notably **L**¹ represents -NH-CH₂-* or -CH₂CH₂-); wherein the asterisks indicate the bond with which the group **L**¹ is attached to the carbonyl group.

11) Another embodiment relates to compounds according to any one of embodiments 1) to 8), wherein **L**¹ represents -NH-CH₂-* or -CH₂CH₂-; wherein the asterisk indicates the bond with which the group **L**¹ is attached to the carbonyl group.

12) Another embodiment relates to compounds according to any one of embodiments 1) to 11), wherein **L**² represents a linker group selected from -CH₂-, -CH(CH₃)-, -CH₂-CH₂-, -CH₂-CH₂-CH₂-, *-CH₂-CH=CH-, and *-CH₂-C(CH₃)=CH-, wherein the asterisks indicate the bond with which the group **L**² is attached to the amide nitrogen atom.

13) Another embodiment relates to compounds according to any one of embodiments 1) to 11), wherein **L**² represents -(C₁₋₃)alkylene- (notably a linker group selected from -CH₂-, -CH(CH₃)-, -CH₂-CH₂-; especially -CH₂-).

14) Another embodiment relates to compounds according to any one of embodiments 1) to 11), wherein **L**² represents -CH₂-.

15) Another embodiment relates to compounds according to any one of embodiments 1) to 14), wherein **Ar**¹ represents phenyl, or 5- or 6-membered heteroaryl (especially pyridinyl); wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from (C₁₋₄)alkyl (especially methyl); (C₁₋₄)alkoxy (especially methoxy); (C₁₋₃)fluoroalkyl (especially trifluoromethyl); (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy); halogen; cyano; or **NR**^{18a}**R**^{18b} wherein **R**^{18a} and **R**^{18b} independently represent (C₁₋₃)alkyl (especially **NR**^{18a}**R**^{18b} represents dimethylamino); [in particular **Ar**¹ represents phenyl, 2-fluoro-phenyl, 3-fluoro-phenyl, 4-fluoro-phenyl, 2,4-difluoro-phenyl, 2-chloro-phenyl, 3-chloro-phenyl, 4-chloro-phenyl, 2-chloro-4-fluoro-phenyl, 2-methyl-phenyl, 3-methyl-phenyl, 4-methyl-phenyl, 2,3-dimethyl-phenyl, 2-methoxy-phenyl, 3-methoxy-phenyl, 4-methoxy-phenyl, 3,4-dimethoxy-phenyl, 2-trifluoromethyl-phenyl, 3-trifluoromethyl-phenyl, 4-trifluoromethyl-phenyl, 4-fluoro-2-trifluoromethyl-phenyl, 2-bromo-phenyl, 3-bromo-phenyl, 4-bromo-phenyl, 2,6-difluoro-phenyl, 2-trifluoromethoxy-phenyl, 3-trifluoromethoxy-phenyl, 4-trifluoromethoxy-phenyl; or **Ar**¹ represents 1-methyl-imidazol-2-yl, 1-ethyl-1H-pyrazol-3-yl, 4-methyl-thiazol-2-yl, pyridin-2-yl, 3-chloro-pyridin-2-yl, 3-trifluoromethyl-pyridin-2-yl, 6-trifluoromethyl-pyridin-2-yl, thiazol-2-yl, isoxazol-5-yl, 5-methyl-isoxazol-3-yl, 1-methyl-1H-pyrazol-5-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyridin-3-yl, pyridin-4-yl, 3-fluoro-pyridin-2-yl, 5-fluoro-pyridin-2-yl, 3-chloro-pyridin-5-yl, 5-chloro-pyridin-2-yl, 3-bromo-pyridin-2-yl, 3-bromo-pyridin-4-yl, 3-methyl-pyridin-2-yl, 5-methyl-pyridin-2-yl, 6-methyl-pyridin-2-yl, 2-dimethylamino-pyrimidin-5-yl, 5-(4-fluorophenyl-amino)-pyridin-2-yl].

16) Another embodiment relates to compounds according to any one of embodiments 1) to 14), wherein **Ar**¹ represents

- 5 • phenyl which is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from (C₁₋₄)alkyl; (C₁₋₄)alkoxy; (C₁₋₃)fluoroalkyl; (C₁₋₃)fluoroalkoxy; halogen; and cyano (especially mono-substituted with methyl; methoxy; trifluoromethyl, trifluoromethoxy; or halogen); [in particular such **Ar**¹ represents phenyl, 2-fluoro-phenyl, 3-fluoro-phenyl, 4-fluoro-phenyl, 2,4-difluoro-phenyl, 2-chloro-phenyl, 3-chloro-phenyl, 4-chloro-phenyl, 2-chloro-4-fluoro-phenyl, 2-methyl-phenyl, 3-methyl-phenyl, 4-methyl-phenyl, 2,3-dimethyl-phenyl, 2-methoxy-phenyl, 3-methoxy-phenyl, 4-methoxy-phenyl, 3,4-dimethoxy-phenyl, 2-trifluoromethyl-phenyl, 3-trifluoromethyl-phenyl, 4-trifluoromethyl-phenyl, 4-fluoro-2-trifluoromethyl-phenyl, 2-bromo-phenyl, 3-bromo-phenyl, 4-bromo-phenyl, 2,6-difluoro-phenyl, 2-trifluoromethoxy-phenyl, 3-trifluoromethoxy-phenyl, 4-trifluoromethoxy-phenyl; especially 2-chloro-phenyl, 2-bromo-phenyl, 2-trifluoromethyl-phenyl]; or

10 • 6-membered heteroaryl (in particular pyridinyl); which is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from (C₁₋₄)alkyl; (C₁₋₄)alkoxy; (C₁₋₃)fluoroalkyl; (C₁₋₃)fluoroalkoxy; halogen; and cyano (especially mono-substituted with methyl, trifluoromethyl or halogen); [in particular such **Ar**¹ represents pyridin-2-yl, 3-chloro-pyridin-2-yl, 3-trifluoromethyl-pyridin-2-yl, 6-trifluoromethyl-pyridin-2-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyridin-3-yl, pyridin-4-yl, 3-fluoro-pyridin-2-yl, 5-fluoro-pyridin-2-yl, 3-chloro-pyridin-5-yl, 5-chloro-pyridin-2-yl, 3-bromo-pyridin-2-yl, 3-bromo-pyridin-4-yl, 3-methyl-pyridin-2-yl, 5-methyl-pyridin-2-yl, 6-methyl-pyridin-2-yl, 2-dimethylamino-pyrimidin-5-yl, 5-(4-fluorophenyl-amino)-pyridin-2-yl; especially 3-chloro-pyridin-2-yl, 3-trifluoromethyl-pyridin-2-yl, 6-trifluoromethyl-pyridin-2-yl, 3-bromo-pyridin-2-yl, 6-methyl-pyridin-2-yl]; or

15 • 5-membered heteroaryl (in particular imidazolyl, pyrazolyl, thiazolyl or isoxazolyl); which is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from (C₁₋₄)alkyl; (C₁₋₄)alkoxy; (C₁₋₃)fluoroalkyl; (C₁₋₃)fluoroalkoxy; halogen; and cyano (especially mono-substituted with (C₁₋₂)alkyl); [in particular such **Ar**¹ represents 1-methyl-imidazol-2-yl, 1-ethyl-1H-pyrazol-3-yl, 4-methyl-thiazol-2-yl, thiazol-2-yl, isoxazol-5-yl, 5-methyl-isoxazol-3-yl, 1-methyl-1H-pyrazol-5-yl].

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17) Another embodiment relates to compounds according to any one of embodiments 1) to 15), wherein **Ar**¹ represents

- 5 • phenyl which is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from (C₁₋₄)alkyl; (C₁₋₄)alkoxy; (C₁₋₃)fluoroalkyl; (C₁₋₃)fluoroalkoxy; halogen; and cyano (especially mono-substituted with methyl; methoxy; trifluoromethyl, trifluoromethoxy; or halogen); [in particular such **Ar**¹ represents phenyl, 2-fluoro-phenyl, 3-fluoro-phenyl, 4-fluoro-phenyl, 2,4-difluoro-phenyl, 2-chloro-phenyl, 3-chloro-phenyl, 4-chloro-phenyl, 2-chloro-4-fluoro-phenyl, 2-methyl-phenyl, 3-methyl-phenyl, 4-methyl-phenyl, 2,3-dimethyl-phenyl, 2-methoxy-phenyl, 3-methoxy-phenyl, 4-methoxy-phenyl, 3,4-dimethoxy-phenyl, 2-trifluoromethyl-phenyl, 3-trifluoromethyl-phenyl, 4-trifluoromethyl-phenyl, 4-fluoro-2-trifluoromethyl-phenyl, 2-bromo-phenyl, 3-bromo-phenyl, 4-bromo-phenyl, 2,6-difluoro-phenyl, 2-trifluoromethoxy-phenyl, 3-trifluoromethoxy-phenyl, 4-trifluoromethoxy-phenyl; especially 2-chloro-phenyl, 2-bromo-phenyl, 2-trifluoromethyl-phenyl]; or

10 • 6-membered heteroaryl (in particular pyridinyl); which is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from (C₁₋₄)alkyl; (C₁₋₄)alkoxy; (C₁₋₃)fluoroalkyl; (C₁₋₃)fluoroalkoxy; halogen; and cyano (especially mono-substituted with methyl, trifluoromethyl or halogen); [in particular such **Ar**¹ represents pyridin-2-yl, 3-chloro-pyridin-2-yl, 3-trifluoromethyl-pyridin-2-yl, 6-trifluoromethyl-pyridin-2-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyridin-3-yl, pyridin-4-yl, 3-fluoro-pyridin-2-yl, 5-fluoro-pyridin-2-yl, 3-chloro-pyridin-5-yl, 5-chloro-pyridin-2-yl, 3-bromo-pyridin-2-yl, 3-bromo-pyridin-4-yl, 3-methyl-pyridin-2-yl, 5-methyl-pyridin-2-yl, 6-methyl-pyridin-2-yl, 2-dimethylamino-pyrimidin-5-yl, 5-(4-fluorophenyl-amino)-pyridin-2-yl; especially

15 3-chloro-pyridin-2-yl, 3-trifluoromethyl-pyridin-2-yl, 6-trifluoromethyl-pyridin-2-yl, 3-bromo-pyridin-2-yl, 3-methyl-pyridin-2-yl, 6-methyl-pyridin-2-yl].

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18) Another embodiment relates to compounds according to any one of embodiments 1) to 17), wherein **R**⁴ represents

- 30 • (C₂₋₅)alkyl which is mono-substituted with (C₁₋₄)alkoxy, benzyloxy, cyano, or hydroxy; or disubstituted wherein the substituents are independently selected from (C₁₋₃)alkoxy or hydroxy (especially mono-substituted with hydroxy; or disubstituted wherein the substituents are independently methoxy or hydroxy); [in particular such substituted (C₂₋₅)alkyl is 2-methoxy-ethyl, 2-hydroxy-ethyl, 2-hydroxy-propyl, 2-hydroxy-2-methyl-propyl, 3-hydroxy-3-methyl-butyl, 2-methoxy-ethyl, 2-hydroxy-3-methoxy-propyl];

35 • -(C₂₋₄)alkylene-NR⁶R⁷, wherein **R**⁶ and **R**⁷ independently represent hydrogen; (C₁₋₄)alkyl; (C₂₋₃)fluoroalkyl; (C₃₋₆)cycloalkyl; or (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl; [in particular

- such $-(C_{2-4})alkylene-NR^6R^7$ is 2-amino-ethyl, 2-methylamino-ethyl, 2-dimethylamino-ethyl, 2-diethylamino-ethyl, 3-(dimethylamino)-propyl, 2-(butyl-methylamino)-ethyl, 2-ethylamino-ethyl, 2-(ethyl-methylamino)-ethyl, 2-(isopropyl-methylamino)-ethyl, 2-(diisopropylamino)-ethyl, 2-[(2-fluoroethyl)-methylamino]-ethyl, 2-[(2,2,2-trifluoroethyl)-amino]-ethyl, 2-[methyl-(2,2,2-trifluoroethyl)-amino]-ethyl, 2-[(2-fluoro-1-methylethyl)-methylamino]-ethyl, 2-[(cyclopropyl)-methylamino]-ethyl, 2-[(cyclopropylmethyl)-methylamino]-ethyl, 2-[(cyclobutyl)-methylamino]-ethyl, 2-[(cyclopentyl)-methylamino]-ethyl];
- $(C_{3-6})cycloalkyl$ optionally mono-substituted with hydroxy; [in particular cyclopropyl, or 4-hydroxy-cyclohexyl];
 - $(C_{3-6})cycloalkyl-(C_{1-3})alkyl$, wherein the cycloalkyl group is optionally mono-substituted with $-CO-(C_{1-4})alkoxy$ or hydroxy; [in particular cyclopropyl-methyl, (1-hydroxy-cyclopentyl)-methyl, (2-(ethoxycarbonyl)-cyclopropyl)-methyl]; or
 - $(C_{4-7})heterocyclyl$ or $(C_{4-7})heterocyclyl-(C_{1-3})alkyl$, wherein in the above groups the $(C_{4-7})heterocyclyl$ independently contains one or two ring heteroatoms independently selected from nitrogen and oxygen; wherein in the above groups said $(C_{4-7})heterocyclyl$ independently is unsubstituted, or mono-, di-, or tri-substituted wherein the substituents are independently selected from:
 - one oxo substituent attached to a ring carbon atom in alpha position to a ring nitrogen (thus forming together with the nitrogen an amide group, or, in case a ring oxygen is additionally adjacent, a carbamate group, or, in case second ring nitrogen is additionally adjacent, a urea group); and / or
 - two methyl substituents attached to a ring carbon atom in alpha position to a ring nitrogen atom (thus forming together with the nitrogen a $-C(CH_3)_2-N$ -group); and / or
 - $(C_{1-4})alkyl$ (especially methyl) attached to a ring nitrogen atom having a free valency; and/or
 - two fluoro substituents attached to a ring carbon atom; and/or
 - in case of a $(C_{4-7})heterocyclyl-(C_{1-3})alkyl$ group, methyl attached to a ring carbon atom which is attached to the linking $(C_{1-3})alkyl$ group;
- [in particular such $(C_{4-7})heterocyclyl$ is pyrrolidin-3-yl, 1-methyl-pyrrolidin-3-yl, piperidin-3-yl, 1-methyl-piperidin-3-yl, piperidin-4-yl, 1-methyl-piperidin-4-yl, tetrahydro-pyran-4-yl, ; and such $(C_{4-7})heterocyclyl-(C_{1-3})alkyl$ is 2-(pyrrolidin-1-yl)-ethyl, 2-(2-oxo-imidazolidin-1-yl)-ethyl, 2-(1-methyl-pyrrolidin-2-yl)-ethyl, 2-(2-oxo-pyrrolidin-1-yl)-ethyl, 2-(morpholin-4-yl)-ethyl, 3-methyl-oxetan-3-yl-methyl, pyrrolidin-3-yl-methyl, 3-(pyrrolidin-1-yl)-propyl, [1,4]dioxan-2-yl-methyl, 2-(piperazin-1-yl)-ethyl,

2-(piperidin-1-yl)-ethyl, 2-(azepan-1-yl)-ethyl, 2-(3,3-difluoroazetidin-1-yl)-ethyl, 2-(3,3-difluoropyrrolidin-1-yl)-ethyl, 2-(3,3-difluoropiperidin-1-yl)-ethyl, 2-(4,4-difluoropiperidin-1-yl)-ethyl].

- 19) Another embodiment relates to compounds according to any one of embodiments 1) to 5 17), wherein R^4 represents
- (C_{2-5}) alkyl which is mono-substituted with hydroxy; or disubstituted wherein the substituents are independently methoxy or hydroxy; [in particular such substituted (C_{2-5}) alkyl is 2-methoxy-ethyl, 2-hydroxy-ethyl, 2-hydroxy-propyl, 2-hydroxy-2-methyl-propyl, 3-hydroxy-3-methyl-butyl, 2-methoxy-ethyl, 2-hydroxy-3-methoxy-propyl];
 - 10 • $-(C_{2-4})$ alkylene- NR^6R^7 , wherein R^6 represents hydrogen or (C_{1-4}) alkyl (especially methyl); and R^7 represents (C_{1-4}) alkyl; (C_{2-3}) fluoroalkyl; (C_{3-6}) cycloalkyl; or (C_{3-6}) cycloalkyl- (C_{1-3}) alkyl; [in particular such $-(C_{2-4})$ alkylene- NR^6R^7 is 2-amino-ethyl, 2-methylamino-ethyl, 2-dimethylamino-ethyl, 2-diethylamino-ethyl, 3-(dimethylamino)-propyl, 2-(butyl-methylamino)-ethyl, 2-ethylamino-ethyl, 2-(ethyl-methylamino)-ethyl, 15 2-(isopropyl-methylamino)-ethyl, 2-(diisopropylamino)-ethyl, 2-[(2-fluoroethyl)-methylamino]-ethyl, 2-[(2,2,2-trifluoroethyl)-amino]-ethyl, 2-[methyl-(2,2,2-trifluoroethyl)-amino]-ethyl, 2-[(2-fluoro-1-methylethyl)-methylamino]-ethyl, 2-[(cyclopropyl)-methylamino]-ethyl, 2-[(cyclopropylmethyl)-methylamino]-ethyl, 2-[(cyclobutyl)-methylamino]-ethyl, 2-[(cyclopentyl)-methylamino]-ethyl];
 - 20 • (C_{3-6}) cycloalkyl- (C_{1-3}) alkyl, wherein the cycloalkyl group is optionally mono-substituted with hydroxy; [in particular cyclopropyl-methyl, or (1-hydroxy-cyclopentyl)-methyl];
 - (C_{4-7}) heterocyclyl or (C_{4-7}) heterocyclyl- (C_{1-3}) alkyl, wherein in the above groups the (C_{4-7}) heterocyclyl independently contains one or two ring heteroatoms independently selected from nitrogen and oxygen; wherein in the above groups said 25 (C_{4-7}) heterocyclyl independently is unsubstituted, or mono-, or di-substituted wherein the substituents are independently selected from:
 - one oxo substituent attached to a ring carbon atom in alpha position to a ring nitrogen (thus forming together with the nitrogen an amide group, or, in case a ring oxygen is additionally adjacent, a carbamate group, or, in case second 30 ring nitrogen is additionally adjacent, a urea group); and / or
 - (C_{1-4}) alkyl (especially methyl) attached to a ring nitrogen atom having a free valency; or
 - two fluoro substituents attached to a ring carbon atom;
- [in particular such (C_{4-7}) heterocyclyl is pyrrolidin-3-yl, 1-methyl-pyrrolidin-3-yl, 35 piperidin-3-yl, 1-methyl-piperidin-3-yl, piperidin-4-yl, 1-methyl-piperidin-4-yl, tetrahydro-pyran-4-yl; and such (C_{4-7}) heterocyclyl- (C_{1-3}) alkyl is 2-(pyrrolidin-1-yl)-ethyl,

2-(2-oxo-imidazolidin-1-yl)-ethyl, 2-(1-methyl-pyrrolidin-2-yl)-ethyl, 2-(2-oxo-pyrrolidin-1-yl)-ethyl, 2-(morpholin-4-yl)-ethyl, pyrrolidin-3-yl-methyl, 3-(pyrrolidin-1-yl)-propyl, [1,4]dioxan-2-yl-methyl, 2-(piperazin-1-yl)-ethyl, 2-(piperidin-1-yl)-ethyl, 2-(azepan-1-yl)-ethyl, 2-(3,3-difluoroazetidin-1-yl)-ethyl, 2-(3,3-difluoropyrrolidin-1-yl)-ethyl, 2-(3,3-difluoropiperdin-1-yl)-ethyl, 2-(4,4-difluoropiperdin-1-yl)-ethyl].

20) Another embodiment relates to compounds according to any one of embodiments 1) to 17), wherein R^4 represents

- (C_{2-5}) alkyl which is mono-substituted with hydroxy (in particular 2-methoxy-ethyl, 2-hydroxy-ethyl, 2-hydroxy-propyl, 2-hydroxy-2-methyl-propyl, 3-hydroxy-3-methyl-butyl, 2-methoxy-ethyl, especially 2-hydroxy-2-methyl-propyl];
- (C_{2-5}) alkyl which is disubstituted wherein the substituents are independently methoxy or hydroxy; [in particular 2-hydroxy-3-methoxy-propyl];
- $-(C_{2-4})$ alkylene- NR^6R^7 , wherein R^6 represents hydrogen or (C_{1-4}) alkyl (especially methyl); and R^7 represents (C_{1-4}) alkyl; (C_{2-3}) fluoroalkyl; (C_{3-6}) cycloalkyl; or (C_{3-6}) cycloalkyl- (C_{1-3}) alkyl; [in particular such $-(C_{2-4})$ alkylene- NR^6R^7 is 2-amino-ethyl, 2-methylamino-ethyl, 2-dimethylamino-ethyl, 2-diethylamino-ethyl, 3-(dimethylamino)-propyl, 2-(butyl-methylamino)-ethyl, 2-ethylamino-ethyl, 2-(ethyl-methylamino)-ethyl, 2-(isopropyl-methylamino)-ethyl, 2-(diisopropylamino)-ethyl, 2-[(2-fluoroethyl)-methylamino]-ethyl, 2-[(2,2,2-trifluoroethyl)-amino]-ethyl, 2-[methyl-(2,2,2-trifluoroethyl)-amino]-ethyl, 2-[(2-fluoro-1-methylethyl)-methylamino]-ethyl, 2-[(cyclopropyl)-methylamino]-ethyl, 2-[(cyclopropylmethyl)-methylamino]-ethyl, 2-[(cyclobutyl)-methylamino]-ethyl, 2-[(cyclopentyl)-methylamino]-ethyl; especially 2-methylamino-ethyl, 2-dimethylamino-ethyl, or 2-ethylamino-ethyl];
- (C_{3-6}) cycloalkyl- (C_{1-3}) alkyl, wherein the cycloalkyl group is mono-substituted with hydroxy; [in particular (1-hydroxy-cyclopentyl)-methyl];
- (C_{4-7}) heterocyclyl wherein the (C_{4-7}) heterocyclyl contains one ring heteroatom selected from nitrogen or oxygen; wherein in the above groups said (C_{4-7}) heterocyclyl independently is unsubstituted, or mono-substituted with (C_{1-4}) alkyl (especially methyl) attached to a ring nitrogen atom having a free valency; [in particular pyrrolidin-3-yl, 1-methyl-pyrrolidin-3-yl, piperidin-3-yl, 1-methyl-piperidin-3-yl, piperidin-4-yl, 1-methyl-piperidin-4-yl, or tetrahydro-pyran-4-yl; especially pyrrolidin-3-yl];
- (C_{4-7}) heterocyclyl- (C_{1-3}) alkyl, wherein the (C_{4-7}) heterocyclyl contains one or two ring heteroatoms independently selected from nitrogen and oxygen; wherein in the above groups said (C_{4-7}) heterocyclyl independently is unsubstituted, or mono-, or di-substituted wherein the substituents are selected from:

➤ (C₁₋₄)alkyl (especially methyl) attached to a ring nitrogen atom having a free valency; or

➤ two fluoro substituents attached to a ring carbon atom;

[in particular 2-(pyrrolidin-1-yl)-ethyl, 2-(1-methyl-pyrrolidin-2-yl)-ethyl, 2-(morpholin-4-yl)-ethyl, pyrrolidin-3-yl-methyl, 3-(pyrrolidin-1-yl)-propyl, [1,4]dioxan-2-yl-methyl, 2-(piperazin-1-yl)-ethyl, 2-(piperidin-1-yl)-ethyl, 2-(azepan-1-yl)-ethyl, 2-(3,3-difluoroazetidin-1-yl)-ethyl, 2-(3,3-difluoropyrrolidin-1-yl)-ethyl, 2-(3,3-difluoropiperdin-1-yl)-ethyl, or 2-(4,4-difluoropiperdin-1-yl)-ethyl; especially 2-(pyrrolidin-1-yl)-ethyl, 2-(morpholin-4-yl)-ethyl, pyrrolidin-3-yl-methyl, [1,4]dioxan-2-yl-methyl, 2-(piperazin-1-yl)-ethyl, 2-(4,4-difluoropiperdin-1-yl)-ethyl].

21) Another embodiment relates to compounds according to any one of embodiments 1) to 17), wherein **R**⁴ represents

- 2-methoxy-ethyl, 2-hydroxy-ethyl, 2-hydroxy-propyl, 2-hydroxy-2-methyl-propyl, 3-hydroxy-3-methyl-butyl, or 2-methoxy-ethyl (especially 2-hydroxy-2-methyl-propyl);
- 2-hydroxy-3-methoxy-propyl;
- -(C₂₋₄)alkylene-NR⁶R⁷ selected from 2-amino-ethyl, 2-methylamino-ethyl, 2-dimethylamino-ethyl, 2-diethylamino-ethyl, 3-(dimethylamino)-propyl, 2-(butyl-methylamino)-ethyl, 2-ethylamino-ethyl, 2-(ethyl-methylamino)-ethyl, 2-(isopropyl-methylamino)-ethyl, 2-(diisopropylamino)-ethyl, 2-[(2-fluoroethyl)-methylamino]-ethyl, 2-[(2,2,2-trifluoroethyl)-amino]-ethyl, 2-[methyl-(2,2,2-trifluoroethyl)-amino]-ethyl, 2-[(2-fluoro-1-methylethyl)-methylamino]-ethyl, 2-[(cyclopropyl)-methylamino]-ethyl, 2-[(cyclopropylmethyl)-methylamino]-ethyl, 2-[(cyclobutyl)-methylamino]-ethyl, and 2-[(cyclopentyl)-methylamino]-ethyl; especially 2-methylamino-ethyl, 2-dimethylamino-ethyl, or 2-ethylamino-ethyl;
- (1-hydroxy-cyclopentyl)-methyl;
- (C₄₋₇)heterocyclyl selected from pyrrolidin-3-yl, 1-methyl-pyrrolidin-3-yl, piperidin-3-yl, 1-methyl-piperidin-3-yl, piperidin-4-yl, 1-methyl-piperidin-4-yl, and tetrahydro-pyran-4-yl; especially pyrrolidin-3-yl;
- (C₄₋₇)heterocyclyl-(C₁₋₃)alkyl selected from 2-(pyrrolidin-1-yl)-ethyl, 2-(1-methyl-pyrrolidin-2-yl)-ethyl, 2-(morpholin-4-yl)-ethyl, pyrrolidin-3-yl-methyl, 3-(pyrrolidin-1-yl)-propyl, [1,4]dioxan-2-yl-methyl, 2-(piperazin-1-yl)-ethyl, 2-(piperidin-1-yl)-ethyl, 2-(azepan-1-yl)-ethyl, 2-(3,3-difluoroazetidin-1-yl)-ethyl, 2-(3,3-difluoropyrrolidin-1-yl)-ethyl, 2-(3,3-difluoropiperdin-1-yl)-ethyl, and 2-(4,4-difluoropiperdin-1-yl)-ethyl; especially 2-(pyrrolidin-1-yl)-ethyl, 2-(morpholin-4-yl)-ethyl, pyrrolidin-3-yl-methyl, [1,4]dioxan-2-yl-methyl, 2-(piperazin-1-yl)-ethyl, or 2-(4,4-difluoropiperdin-1-yl)-ethyl.

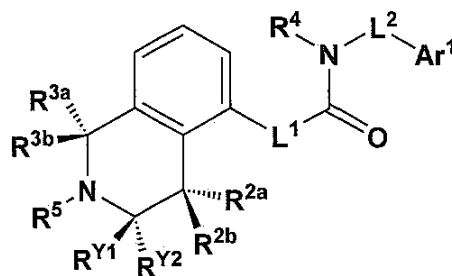
22) The invention, thus, relates to compounds of the formula (I) as defined in embodiment 1), or to such compounds further limited by the characteristics of any one of embodiments 2) to 21), under consideration of their respective dependencies; to pharmaceutically acceptable salts thereof; and to the use of such compounds as medicaments especially in the treatment of disorders relating to a dysfunction of the CXCR7 receptor or its ligands as described herein below. For avoidance of any doubt, especially the following embodiments relating to the compounds of formula (I) are thus possible and intended and herewith specifically disclosed in individualized form:

- 1, 3+1, 4+1, 5+1, 5+3+1, 5+4+1, 6+1, 6+3+1, 6+4+1, 7+1, 7+3+1, 7+4+1, 8+1, 8+3+1, 8+4+1, 8+5+1, 8+5+3+1, 8+5+4+1, 8+6+1, 8+6+3+1, 8+6+4+1, 8+7+1, 8+7+3+1, 8+7+4+1, 10+1, 10+3+1, 10+4+1, 10+5+1, 10+5+3+1, 10+5+4+1, 10+6+1, 10+6+3+1, 10+6+4+1, 10+7+1, 10+7+3+1, 10+7+4+1, 10+8+1, 10+8+3+1, 10+8+4+1, 10+8+5+1, 10+8+5+3+1, 10+8+5+4+1, 10+8+6+1, 10+8+6+3+1, 10+8+6+4+1, 10+8+7+1, 10+8+7+3+1, 10+8+7+4+1, 13+1, 13+3+1, 13+4+1, 13+5+1, 13+5+3+1, 13+5+4+1, 13+6+1, 13+6+3+1, 13+6+4+1, 13+7+1, 13+7+3+1, 13+7+4+1, 13+8+1, 13+8+3+1, 13+8+4+1, 13+8+5+1, 13+8+5+3+1, 13+8+5+4+1, 13+8+6+1, 13+8+6+3+1, 13+8+6+4+1, 13+8+7+1, 13+8+7+3+1, 13+8+7+4+1, 13+10+1, 13+10+3+1, 13+10+4+1, 13+10+5+1, 13+10+5+3+1, 13+10+5+4+1, 13+10+6+1, 13+10+6+3+1, 13+10+6+4+1, 13+10+7+1, 13+10+7+3+1, 13+10+7+4+1, 13+10+8+1, 13+10+8+3+1, 13+10+8+4+1, 13+10+8+5+1, 13+10+8+5+3+1, 13+10+8+5+4+1, 13+10+8+6+1, 13+10+8+6+3+1, 13+10+8+6+4+1, 13+10+8+7+1, 13+10+8+7+3+1, 13+10+8+7+4+1, 17+1, 17+3+1, 17+4+1, 17+5+1, 17+5+3+1, 17+5+4+1, 17+6+1, 17+6+3+1, 17+6+4+1, 17+7+1, 17+7+3+1, 17+7+4+1, 17+8+1, 17+8+3+1, 17+8+4+1, 17+8+5+1, 17+8+5+3+1, 17+8+5+4+1, 17+8+6+1, 17+8+6+3+1, 17+8+6+4+1, 17+8+7+1, 17+8+7+3+1, 17+8+7+4+1, 17+10+1, 17+10+3+1, 17+10+4+1, 17+10+5+1, 17+10+5+3+1, 17+10+5+4+1, 17+10+6+1, 17+10+6+3+1, 17+10+6+4+1, 17+10+7+1, 17+10+7+3+1, 17+10+7+4+1, 17+10+8+1, 17+10+8+3+1, 17+10+8+4+1, 17+10+8+5+1, 17+10+8+5+3+1, 17+10+8+5+4+1, 17+10+8+6+1, 17+10+8+6+3+1, 17+10+8+6+4+1, 17+10+8+7+1, 17+10+8+7+3+1, 17+10+8+7+4+1, 17+13+1, 17+13+3+1, 17+13+4+1, 17+13+5+1, 17+13+5+3+1, 17+13+5+4+1, 17+13+6+1, 17+13+6+3+1, 17+13+6+4+1, 17+13+7+1, 17+13+7+3+1, 17+13+7+4+1, 17+13+8+1, 17+13+8+3+1, 17+13+8+4+1, 17+13+8+5+1, 17+13+8+5+3+1, 17+13+8+5+4+1, 17+13+8+6+1, 17+13+8+6+3+1, 17+13+8+6+4+1, 17+13+8+7+1, 17+13+8+7+3+1, 17+13+8+7+4+1, 17+13+10+1, 17+13+10+3+1, 17+13+10+4+1, 17+13+10+5+1, 17+13+10+5+3+1, 17+13+10+5+4+1, 17+13+10+6+1, 17+13+10+6+3+1, 17+13+10+6+4+1, 17+13+10+7+1, 17+13+10+7+3+1, 17+13+10+7+4+1, 17+13+10+8+1, 17+13+10+8+3+1, 17+13+10+8+4+1, 17+13+10+8+5+1, 17+13+10+8+5+3+1, 17+13+10+8+5+4+1, 17+13+10+8+6+1, 17+13+10+8+6+3+1, 17+13+10+8+6+4+1, 17+13+10+8+7+1, 17+13+10+8+7+3+1, 17+13+10+8+7+4+1, 19+1, 19+3+1, 19+4+1, 19+5+1, 19+5+3+1, 19+5+4+1, 19+6+1, 19+6+3+1, 19+6+4+1, 19+7+1, 19+7+3+1, 19+7+4+1, 19+8+1, 19+8+3+1, 19+8+4+1, 19+8+5+1, 19+8+5+3+1, 19+8+5+4+1, 19+8+6+1, 19+8+6+3+1, 19+8+6+4+1, 19+8+7+1, 19+8+7+3+1, 19+8+7+4+1, 19+10+1, 19+10+3+1, 19+10+4+1, 19+10+5+1, 19+10+5+3+1, 19+10+5+4+1, 19+10+6+1, 19+10+6+3+1, 19+10+6+4+1, 19+10+7+1, 19+10+7+3+1, 19+10+7+4+1, 19+10+8+1, 19+10+8+3+1, 19+10+8+4+1, 19+10+8+5+1,

- 19+10+8+5+3+1, 19+10+8+5+4+1, 19+10+8+6+1, 19+10+8+6+3+1, 19+10+8+6+4+1, 19+10+8+7+1, 19+10+8+7+3+1, 19+10+8+7+4+1, 19+13+1, 19+13+3+1, 19+13+4+1, 19+13+5+1, 19+13+5+3+1, 19+13+5+4+1, 19+13+6+1, 19+13+6+3+1, 19+13+6+4+1, 19+13+7+1, 19+13+7+3+1, 19+13+7+4+1, 19+13+8+1, 19+13+8+3+1, 19+13+8+4+1, 19+13+8+5+1, 19+13+8+5+3+1, 19+13+8+5+4+1,
- 5 19+13+8+6+1, 19+13+8+6+3+1, 19+13+8+6+4+1, 19+13+8+7+1, 19+13+8+7+3+1, 19+13+8+7+4+1, 19+13+10+1, 19+13+10+3+1, 19+13+10+4+1, 19+13+10+5+1, 19+13+10+5+3+1, 19+13+10+5+4+1, 19+13+10+6+1, 19+13+10+6+3+1, 19+13+10+6+4+1, 19+13+10+7+1, 19+13+10+7+3+1, 19+13+10+7+4+1, 19+13+10+8+1, 19+13+10+8+3+1, 19+13+10+8+4+1, 19+13+10+8+5+1, 19+13+10+8+5+3+1, 19+13+10+8+5+4+1, 19+13+10+8+6+1, 19+13+10+8+6+3+1,
- 10 19+13+10+8+6+4+1, 19+13+10+8+7+1, 19+13+10+8+7+3+1, 19+13+10+8+7+4+1, 19+17+1, 19+17+3+1, 19+17+4+1, 19+17+5+1, 19+17+5+3+1, 19+17+5+4+1, 19+17+6+1, 19+17+6+3+1, 19+17+6+4+1, 19+17+7+1, 19+17+7+3+1, 19+17+7+4+1, 19+17+8+1, 19+17+8+3+1, 19+17+8+4+1, 19+17+8+5+1, 19+17+8+5+3+1, 19+17+8+5+4+1, 19+17+8+6+1, 19+17+8+6+3+1, 19+17+8+6+4+1, 19+17+8+7+1, 19+17+8+7+3+1, 19+17+8+7+4+1, 19+17+10+1, 19+17+10+3+1, 19+17+10+4+1,
- 15 19+17+10+5+1, 19+17+10+5+3+1, 19+17+10+5+4+1, 19+17+10+6+1, 19+17+10+6+3+1, 19+17+10+6+4+1, 19+17+10+7+1, 19+17+10+7+3+1, 19+17+10+7+4+1, 19+17+10+8+1, 19+17+10+8+3+1, 19+17+10+8+4+1, 19+17+10+8+5+1, 19+17+10+8+5+3+1, 19+17+10+8+5+4+1, 19+17+10+8+6+1, 19+17+10+8+6+3+1, 19+17+10+8+6+4+1, 19+17+10+8+7+1, 19+17+10+8+7+3+1, 19+17+10+8+7+4+1, 19+17+13+1, 19+17+13+3+1, 19+17+13+4+1,
- 20 19+17+13+5+1, 19+17+13+5+3+1, 19+17+13+5+4+1, 19+17+13+6+1, 19+17+13+6+3+1, 19+17+13+6+4+1, 19+17+13+7+1, 19+17+13+7+3+1, 19+17+13+7+4+1, 19+17+13+8+1, 19+17+13+8+3+1, 19+17+13+8+4+1, 19+17+13+8+5+1, 19+17+13+8+5+3+1, 19+17+13+8+5+4+1, 19+17+13+8+6+1, 19+17+13+8+6+3+1, 19+17+13+8+6+4+1, 19+17+13+8+7+1, 19+17+13+8+7+3+1, 19+17+13+8+7+4+1, 19+17+13+10+1, 19+17+13+10+3+1, 19+17+13+10+4+1,
- 25 19+17+13+10+5+1, 19+17+13+10+5+3+1, 19+17+13+10+5+4+1, 19+17+13+10+6+1, 19+17+13+10+6+3+1, 19+17+13+10+6+4+1, 19+17+13+10+7+1, 19+17+13+10+7+3+1, 19+17+13+10+7+4+1, 19+17+13+10+8+1, 19+17+13+10+8+3+1, 19+17+13+10+8+4+1, 19+17+13+10+8+5+1, 19+17+13+10+8+5+3+1, 19+17+13+10+8+5+4+1, 19+17+13+10+8+6+1, 19+17+13+10+8+6+3+1, 19+17+13+10+8+6+4+1, 19+17+13+10+8+7+1, 19+17+13+10+8+7+3+1,
- 30 19+17+13+10+8+7+4+1, 21+1, 21+3+1, 21+4+1, 21+5+1, 21+5+3+1, 21+5+4+1, 21+6+1, 21+6+3+1, 21+6+4+1, 21+7+1, 21+7+3+1, 21+7+4+1, 21+8+1, 21+8+3+1, 21+8+4+1, 21+8+5+1, 21+8+5+3+1, 21+8+5+4+1, 21+8+6+1, 21+8+6+3+1, 21+8+6+4+1, 21+8+7+1, 21+8+7+3+1, 21+8+7+4+1, 21+10+1, 21+10+3+1, 21+10+4+1, 21+10+5+1, 21+10+5+3+1, 21+10+5+4+1, 21+10+6+1, 21+10+6+3+1, 21+10+6+4+1, 21+10+7+1, 21+10+7+3+1, 21+10+7+4+1, 21+10+8+1, 21+10+8+3+1,
- 35 21+10+8+4+1, 21+10+8+5+1, 21+10+8+5+3+1, 21+10+8+5+4+1, 21+10+8+6+1, 21+10+8+6+3+1, 21+10+8+6+4+1, 21+10+8+7+1, 21+10+8+7+3+1, 21+10+8+7+4+1, 21+13+1, 21+13+3+1, 21+13+4+1, 21+13+5+1, 21+13+5+3+1, 21+13+5+4+1, 21+13+6+1, 21+13+6+3+1, 21+13+6+4+1, 21+13+7+1, 21+13+7+3+1, 21+13+7+4+1, 21+13+8+1, 21+13+8+3+1, 21+13+8+4+1, 21+13+8+5+1, 21+13+8+5+3+1, 21+13+8+5+4+1, 21+13+8+6+1, 21+13+8+6+3+1, 21+13+8+6+4+1, 21+13+8+7+1,
- 40 21+13+8+7+3+1, 21+13+8+7+4+1, 21+13+10+1, 21+13+10+3+1, 21+13+10+4+1, 21+13+10+5+1,

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- 5 21+13+10+8+7+4+1, 21+17+1, 21+17+3+1, 21+17+4+1, 21+17+5+1, 21+17+5+3+1, 21+17+5+4+1,
 21+17+6+1, 21+17+6+3+1, 21+17+6+4+1, 21+17+7+1, 21+17+7+3+1, 21+17+7+4+1, 21+17+8+1,
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- 15 21+17+13+6+1, 21+17+13+6+3+1, 21+17+13+6+4+1, 21+17+13+7+1, 21+17+13+7+3+1,
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 21+17+13+10+3+1, 21+17+13+10+4+1, 21+17+13+10+5+1, 21+17+13+10+5+3+1,
- 20 21+17+13+10+5+4+1, 21+17+13+10+6+1, 21+17+13+10+6+3+1, 21+17+13+10+6+4+1,
 21+17+13+10+7+1, 21+17+13+10+7+3+1, 21+17+13+10+7+4+1, 21+17+13+10+8+1,
 21+17+13+10+8+3+1, 21+17+13+10+8+4+1, 21+17+13+10+8+5+1, 21+17+13+10+8+5+3+1,
 21+17+13+10+8+5+4+1, 21+17+13+10+8+6+1, 21+17+13+10+8+6+3+1, 21+17+13+10+8+6+4+1,
 21+17+13+10+8+7+1, 21+17+13+10+8+7+3+1, 21+17+13+10+8+7+4+1.
- 25 In the list above the numbers refer to the embodiments according to their numbering
 provided hereinabove whereas "+" indicates the dependency from another embodiment. The
 different individualized embodiments are separated by commas. In other words, "17+13+4+1"
 for example refers to embodiment 17) depending on embodiment 13), depending on
 embodiment 4), depending on embodiment 1), i.e. embodiment "17+13+4+1" corresponds to
- 30 the compounds of formula (I) according to embodiment 1) further limited by all the features of
 the embodiments 4), 13), and 17).

23) Another embodiment of the invention relates to compounds of the formula (I) according to embodiment 1) which are also compounds of the formula (II)



Formula (II)

5 wherein

- one of R^{Y1} and R^{Y2} represents hydrogen, or (C_{1-3}) alkyl (especially methyl); and the other represents hydrogen; and
 - R^{3a} and R^{3b} together with the carbon atom to which they are attached to form a carbonyl group, or
 - two of R^{2a} , R^{2b} , R^{3a} and R^{3b} independently represent hydrogen, or (C_{1-3}) alkyl (especially methyl);
- and the remaining of R^{2a} , R^{2b} , R^{3a} and R^{3b} represent hydrogen; or
- R^{Y1} and R^{Y2} together with the carbon to which they are attached to form a carbonyl group; and R^{2a} , R^{2b} , R^{3a} and R^{3b} all represent hydrogen;

15 R^5 represents

- (C_{1-6}) alkyl; [in particular such (C_{1-6}) alkyl is methyl, ethyl, propyl, isopropyl, isobutyl, 1-methyl-propyl, 1,2-dimethyl-propyl, 2,2-dimethyl-propyl, 3,3-dimethyl-butyl];
- (C_{1-4}) alkyl mono-substituted with (C_{1-3}) alkoxy, cyano, vinyl; ethynyl, or (C_{1-3}) alkoxy-carbonyl; [in particular such mono-substituted (C_{1-4}) alkyl is allyl, prop-2-ynyl, cyanomethyl, 2-methoxy-ethyl, 2-methoxy-1-methyl-ethyl, methoxycarbonyl-methyl, ethoxycarbonyl-methyl];
- $-CO-R^{10}$ wherein R^{10} represents (C_{1-5}) alkyl; (C_{1-5}) alkoxy; phenyl; phenyl-oxy-; phenyl- (C_{1-3}) alkyl-; phenyl- (C_{1-3}) alkyl-oxy-; (C_{3-6}) cycloalkyl- (C_{1-3}) alkyl; (C_{3-4}) alkenoxy; (C_{3-4}) alkynoxy; (C_{1-3}) fluoroalkyl; (C_{1-3}) fluoroalkoxy; (C_{1-3}) alkoxy- (C_{2-3}) alkoxy; (C_{1-3}) alkoxy- (C_{1-3}) alkyl; (C_{3-6}) cycloalkyl optionally containing one ring oxygen atom, wherein said cycloalkyl is optionally mono- or di-substituted wherein the substituents independently are fluoro or (C_1) fluoroalkyl; unsubstituted 5-membered heteroaryl (especially furanyl); or $-NR^{10a}R^{10b}$ wherein R^{10a} and R^{10b} independently represent hydrogen, (C_{1-4}) alkyl or (C_{3-6}) cycloalkyl, or R^{10a} and R^{10b} together with the nitrogen to

- which they are attached to form a 5- to 7-membered saturated ring; [in particular such -CO-R¹⁰ is methyl-carbonyl, ethyl-carbonyl, propyl-carbonyl, isopropyl-carbonyl, isobutyl-carbonyl, *tert*.-butyl-carbonyl, (2,2-dimethyl-propyl)-carbonyl, methoxymethyl-carbonyl, cyclopropyl-carbonyl, cyclobutyl-carbonyl, (2-fluorocyclopropyl)-carbonyl, (cyclohexyl-methyl)-carbonyl, (2,2-difluorocyclopropyl)-carbonyl, (1-trifluoromethyl-cyclopropyl)-carbonyl, (tetrahydrofuran-3-yl)-carbonyl, (1,1-difluoroethyl)-carbonyl, carbamoyl, methylcarbamoyl, ethylcarbamoyl, isopropylcarbamoyl, butyl-carbamoyl, *tert*.-butyl-carbamoyl, cyclohexyl-carbamoyl, dimethylcarbamoyl, (pyrrolidin-1-yl)-carbonyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, isobutoxycarbonyl, *tert*.-butoxycarbonyl, (2,2-dimethyl-propoxy)-carbonyl, allyloxy-carbonyl, prop-2-ynyloxycarbonyl, (2-fluoro-ethoxy)-carbonyl, (2-methoxy-ethoxy)-carbonyl, furan-2-yl-carbonyl, benzoyl, phenoxy-carbonyl, benzyl-carbonyl, benzyloxy-carbonyl];
- -SO₂-R¹¹ wherein R¹¹ represents (C₁₋₅)alkyl or phenyl; [in particular such -SO₂-R¹¹ is methylsulfonyl, ethylsulfonyl, phenylsulfonyl];
 - (C₂₋₄)fluoroalkyl; [in particular such (C₂₋₄)fluoroalkyl is 2-fluoroethyl, 2,2,2-trifluoroethyl, 3-fluoropropyl];
 - (C₃₋₆)cycloalkyl optionally containing one ring oxygen atom; [in particular such (C₃₋₆)cycloalkyl is cyclobutyl, oxetan-3-yl, cyclopentyl, tetrahydrofuran-3-yl];
 - (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl, wherein the (C₃₋₆)cycloalkyl group optionally contains one ring oxygen atom; wherein said cycloalkyl is optionally substituted with one or two methyl substituents; [in particular such (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl is cyclopropyl-methyl, cyclobutylmethyl, cyclohexyl-methyl, 1-cyclopropyl-ethyl, (3-methyl-oxetan-3-yl)-methyl];
 - phenyl-(C₀₋₃)alkyl-, or 5- or 6-membered heteroaryl-(C₀₋₃)alkyl-, wherein the phenyl or 5- or 6-membered heteroaryl independently is especially unsubstituted, or mono-, or di-substituted, wherein the substituents are independently selected from (C₁₋₄)alkyl (especially methyl), (C₁₋₄)alkoxy (especially methoxy), halogen, (C₁₋₃)fluoroalkyl (especially trifluoromethyl), (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy), and cyano;
- (R¹)_n represents one or two optional substituents (i.e. n represents the integer 0, 1, or 2) independently selected from (C₁₋₄)alkyl (especially methyl), (C₁₋₄)alkoxy (especially methoxy), halogen, (C₁₋₃)fluoroalkyl (especially trifluoromethyl), (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy), and cyano;
- L¹ represents a one- or two-membered linker group selected from -NH-CH₂-*, -NR^{16a}-CH₂-* wherein R^{16a} represents (C₁₋₃)alkyl (especially methyl or ethyl); -NH-CHR^{16b}-* wherein R^{16b} represents (C₁₋₃)alkyl (especially methyl); -NH-CR^{16c}R^{16d}-* wherein R^{16c} and R^{16d} together

with the carbon to which they are attached to form a (C₃₋₆)cycloalkyl (especially a cyclopropyl) ring; -CH₂-NH-*; -O-CH₂-*; -O-CHR^{17a}-* wherein R^{17a} represents (C₁₋₃)alkyl (especially methyl); -O-CR^{17b}R^{17c}-* wherein R^{17b} and R^{17c} together with the carbon to which they are attached to form a (C₃₋₆)cycloalkyl (especially a cyclobutyl) ring; -CH₂-; -CH₂CH₂-; 5 -CH=CH-; and -CH=C(CH₃)-*; wherein the asterisks indicate the bond with which the group L¹ is attached to the carbonyl group;

L² represents -(C₁₋₄)alkylene- or -(C₃₋₄)alkenylene- (especially a linker group selected from -CH₂-, -CH(CH₃)-, -CH₂-CH₂-, -CH₂-CH₂-CH₂-, *-CH₂-CH=CH-, and *-CH₂-C(CH₃)=CH-, wherein the asterisks indicate the bond with which the group L² is attached to the amide 10 nitrogen atom);

Ar¹ represents phenyl, or 5- or 6-membered heteroaryl (especially pyridinyl); wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from (C₁₋₄)alkyl (especially methyl); (C₁₋₄)alkoxy (especially methoxy); (C₁₋₃)fluoroalkyl (especially trifluoromethyl); (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy); halogen; cyano; or NR^{18a}R^{18b} wherein R^{18a} and R^{18b} 15 independently represent hydrogen or (C₁₋₃)alkyl (especially NR^{18a}R^{18b} represents dimethylamino); [in particular Ar¹ represents phenyl, 2-fluoro-phenyl, 3-fluoro-phenyl, 4-fluoro-phenyl, 2,4-difluoro-phenyl, 2-chloro-phenyl, 3-chloro-phenyl, 4-chloro-phenyl, 2-chloro-4-fluoro-phenyl, 2-methyl-phenyl, 3-methyl-phenyl, 4-methyl-phenyl, 2,3-dimethyl-phenyl, 2-methoxy-phenyl, 3-methoxy-phenyl, 4-methoxy-phenyl, 3,4-dimethoxy-phenyl, 2-trifluoromethyl-phenyl, 3-trifluoromethyl-phenyl, 4-trifluoromethyl-phenyl, 4-fluoro-2-trifluoromethyl-phenyl, 2-bromo-phenyl, 3-bromo-phenyl, 4-bromo-phenyl, 2,6-difluoro-phenyl, 2-trifluoromethoxy-phenyl, 3-trifluoromethoxy-phenyl, 4-trifluoromethoxy-phenyl; or Ar¹ represents 1-methyl-imidazol-2-yl, 1-ethyl-1H-pyrazol-3-yl, 4-methyl-thiazol-2-yl, pyridin-2-yl, 3-chloro-pyridin-2-yl, 3-trifluoromethyl-pyridin-2-yl, 6-trifluoromethyl-pyridin-2-yl, thiazol-2-yl, isoxazol-5-yl, 5-methyl-isoxazol-3-yl, 1-methyl-1H-pyrazol-5-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyridin-3-yl, pyridin-4-yl, 3-fluoro-pyridin-2-yl, 5-fluoro-pyridin-2-yl, 3-chloro-pyridin-5-yl, 5-chloro-pyridin-2-yl, 3-bromo-pyridin-2-yl, 3-bromo-pyridin-4-yl, 3-methyl-pyridin-2-yl, 5-methyl-pyridin-2-yl, 6-methyl-pyridin-2-yl, 2-dimethylamino-pyrimidin-5-yl, 5-(4-fluorophenyl-amino)-pyridin-2-yl]; and 25 30

R⁴ represents

- (C₂₋₆)alkyl [in particular such (C₂₋₆)alkyl is ethyl, 3-methyl-butyl, 3,3-dimethyl-butyl];
- (C₂₋₅)alkyl which is mono-substituted with (C₁₋₄)alkoxy, benzyloxy, cyano, or hydroxy; or disubstituted wherein the substituents are independently selected from (C₁₋₃)alkoxy, or hydroxy; [in particular such substituted (C₂₋₅)alkyl is 2-methoxy-ethyl, 35

2-hydroxy-ethyl, 2-cyano-ethyl, 2-benzyloxy-ethyl, 2-hydroxy-propyl, 2-hydroxy-2-methyl-propyl, 3-hydroxy-3-methyl-butyl, 2-methoxy-ethyl, 2-hydroxy-3-methoxy-propyl];

- 5 • (C₂₋₃)fluoroalkyl which is optionally further substituted with one hydroxy; [in particular such (C₂₋₃)fluoroalkyl is 3,3,3-trifluoro-propyl, 2-hydroxy-3,3,3-trifluoro-propyl];
- 10 • -(C₂₋₄)alkylene-NR⁶R⁷, wherein R⁶ and R⁷ independently represent hydrogen; (C₁₋₄)alkyl; -CO-(C₁₋₄)alkoxy; (C₃₋₅)alkenyl; (C₃₋₄)alkynyl; benzyl; -SO₂-(C₁₋₃)alkyl; (C₂₋₃)fluoroalkyl; or (C₃₋₆)cycloalkyl or (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl, wherein in the above groups the (C₃₋₆)cycloalkyl group optionally contains one ring oxygen atom, and

15 wherein said (C₃₋₆)cycloalkyl group is optionally substituted with methyl; [in particular such -(C₂₋₄)alkylene-NR⁶R⁷ is 2-amino-ethyl, 2-methylamino-ethyl, 2-dimethylamino-ethyl, 2-diethylamino-ethyl, 3-(dimethylamino)-propyl, 2-(butyl-methylamino)-ethyl, 2-[(*tert*.-butoxycarbonyl)-methylamino]-ethyl, 2-[(*tert*.-butoxycarbonyl)-amino]-ethyl, 2-[(*tert*.-butoxycarbonyl)-ethylamino]-ethyl, 2-ethylamino-ethyl, 2-(ethyl-methylamino)-ethyl,

20 2-(isopropyl-methylamino)-ethyl, 2-(diisopropylamino)-ethyl, 2-(allyl-methylamino)-ethyl, 2-(methyl-prop-2-ynyl-amino)-ethyl, 2-[(2-fluoroethyl)-methylamino]-ethyl, 2-[(2,2,2-trifluoroethyl)-amino]-ethyl, 2-[methyl-(2,2,2-trifluoroethyl)-amino]-ethyl, 2-[(2-fluoro-1-methylethyl)-methylamino]-ethyl, 2-methanesulfonylamino-ethyl, 2-[(cyclopropyl)-methylamino]-ethyl, 2-[(cyclopropylmethyl)-methylamino]-ethyl, 2-[(cyclobutyl)-methylamino]-ethyl, 2-[(cyclopentyl)-methylamino]-ethyl, 2-[methyl-(tetrahydrofuran-3-yl)-amino]-ethyl, 2-[ethyl-(3-methyl-oxetan-3-yl-methyl)-amino]-ethyl];
- 25 • -(C₁₋₃)alkylene-CO-R⁸, wherein R⁸ represents (C₁₋₄)alkoxy (especially ethoxy); or R⁸ represents NR⁸¹R⁸² wherein R⁸¹ and R⁸² independently represent hydrogen or (C₁₋₄)alkyl, or R⁸¹ and R⁸² together with the nitrogen to which they are attached to form a 4- to 6-membered saturated ring optionally substituted with two fluoro substituents (especially such NR⁸¹R⁸² represents amino, 3,3-difluoroazetidiny);
- 30 • -(C₁₋₃)alkylene-SO₂-R⁹ wherein R⁹ represents (C₁₋₃)alkyl (especially methyl), or amino;
- 35 • (C₃₋₆)cycloalkyl or (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl, wherein the cycloalkyl group is optionally mono-substituted with -CO-(C₁₋₄)alkoxy or hydroxy; [in particular such (C₃₋₆)cycloalkyl is cyclopropyl, 4-hydroxy-cyclohexyl; and such (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl is cyclopropyl-methyl, (1-hydroxy-cyclopentyl)-methyl, (2-(ethoxycarbonyl)-cyclopropyl)-methyl];
- (C₄₋₇)heterocyclyl or (C₄₋₇)heterocyclyl-(C₁₋₃)alkyl, wherein in the above groups the (C₄₋₇)heterocyclyl independently contains one or two ring heteroatoms independently selected from nitrogen, sulfur and oxygen; wherein in the above groups said

(C₄₋₇)heterocyclyl independently is unsubstituted, or mono-, di-, or tri-substituted wherein the substituents are independently selected from:

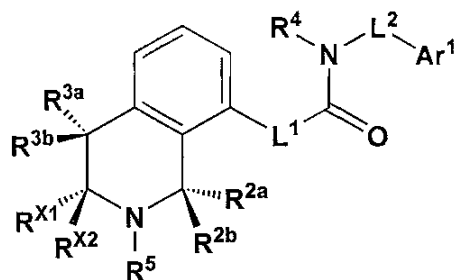
- one oxo substituent attached to a ring carbon atom in alpha position to a ring nitrogen (thus forming together with the nitrogen an amide group, or, in case a ring oxygen is additionally adjacent, a carbamate group, or, in case second ring nitrogen is additionally adjacent, a urea group); and / or
 - two methyl substituents attached to a ring carbon atom in alpha position to a ring nitrogen atom (thus forming together with the nitrogen a -C(CH₃)₂-N-group); and / or
 - two oxo substituents at a ring sulfur ring atom (thus forming a -SO₂- group); and / or
 - (C₁₋₄)alkyl (especially methyl) or -CO-(C₁₋₄)alkoxy attached to a ring nitrogen atom having a free valency; and/or
 - two fluoro substituents attached to a ring carbon atom; and/or
 - in case of a (C₄₋₇)heterocyclyl-(C₁₋₃)alkyl group, methyl attached to a ring carbon atom which is attached to the linking (C₁₋₃)alkyl group;
- [in particular such (C₄₋₇)heterocyclyl is pyrrolidin-3-yl, 1-methyl-pyrrolidin-3-yl, 1-(*tert.*-butoxycarbonyl)-pyrrolidin-3-yl, piperidin-3-yl, 1-methyl-piperidin-3-yl, piperidin-4-yl, 1-methyl-piperidin-4-yl, tetrahydro-pyran-4-yl, 1,1-dioxo-tetrahydrothiophen-3-yl, 1-(*tert.*-butoxycarbonyl)-piperidin-4-yl; and such (C₄₋₇)heterocyclyl-(C₁₋₃)alkyl is 2-(pyrrolidin-1-yl)-ethyl, 2-(2-oxo-imidazolidin-1-yl)-ethyl, 2-(1-methyl-pyrrolidin-2-yl)-ethyl, 2-(2-oxo-pyrrolidin-1-yl)-ethyl, 2-(morpholin-4-yl)-ethyl, 3-(*tert.*-butoxycarbonyl)-2,2-dimethyl-oxazolidin-4-yl-methyl, 3-methyl-oxetan-3-yl-methyl, pyrrolidin-3-yl-methyl, 3-(pyrrolidin-1-yl)-propyl, [1,4]dioxan-2-yl-methyl, 2-(piperazin-1-yl)-ethyl, 2-(piperidin-1-yl)-ethyl, 2-(azepan-1-yl)-ethyl, 2-(3,3-difluoroazetidin-1-yl)-ethyl, 2-(3,3-difluoropyrrolidin-1-yl)-ethyl, 2-(3,3-difluoropiperdin-1-yl)-ethyl, 2-(4,4-difluoropiperdin-1-yl)-ethyl, (1-(*tert.*-butoxycarbonyl)-pyrrolidin-3-yl)-methyl, 2-(1-(*tert.*-butoxycarbonyl)-piperazin-4-yl)-ethyl];
- 2-oxo-2,3-dihydropyridin-4-yl-(C₁₋₂)alkyl;
 - phenyl-(C₁₋₃)alkyl-, or 5- or 6-membered heteroaryl-(C₁₋₃)alkyl-, wherein the phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from (C₁₋₄)alkyl (especially methyl, ethyl), (C₁₋₄)alkoxy (especially methoxy), halogen, (C₁₋₃)fluoroalkyl (especially trifluoromethyl), (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy), and cyano;
- wherein the characteristics disclosed in embodiments 2) to 22) are intended to apply *mutatis mutandis* also to the compounds formula (II) according to embodiment 23); wherein

especially the following embodiments are thus possible and intended and herewith specifically disclosed in individualized form:

23, 23+7, 23+10, 23+10+7, 23+13, 23+13+7, 23+13+10, 23+13+10+7, 23+17, 23+17+7, 23+17, 23+17+13, 23+17+13+7, 23+17+13+10, 23+17+13+10+7, 23+19, 23+19+7, 23+19, 23+19+13, 5 23+19+13+7, 23+19+13+10, 23+19+13+10+7, 23+19+17, 23+19+17+7, 23+19+17, 23+19+17+13, 23+19+17+13+7, 23+19+17+13+10, 23+19+17+13+10+7, 23+21, 23+21+7, 23+21, 23+21+13, 23+21+13+7, 23+21+13+10, 23+21+13+10+7, 23+21+17, 23+21+17+7, 23+21+17, 23+21+17+13, 23+21+17+13+7, 23+21+17+13+10, 23+21+17+13+10+7.

10 In the list above the numbers refer to the embodiments according to their numbering provided hereinabove whereas "+" indicates the limitations as outlined above.

24) Another embodiment of the invention relates to compounds of the formula (I) according to embodiment 1) which are also compounds of the formula (III)



Formula (III)

15 wherein

- one of R^{X1} and R^{X2} represents hydrogen, or (C₁₋₃)alkyl (especially methyl); and the other represents hydrogen; and
 - R^{3a} and R^{3b} together with the carbon atom to which they are attached to form a carbonyl group, or
 - two of R^{2a}, R^{2b}, R^{3a} and R^{3b} independently represent hydrogen, or (C₁₋₃)alkyl (especially methyl);
- and the remaining of R^{2a}, R^{2b}, R^{3a} and R^{3b} represent hydrogen; or
- R^{X1} and R^{X2} together with the carbon to which they are attached to form a carbonyl group; and R^{2a}, R^{2b}, R^{3a} and R^{3b} all represent hydrogen;

25 R⁵ represents

- (C₁₋₆)alkyl; [in particular such (C₁₋₆)alkyl is methyl, ethyl, propyl, isopropyl, isobutyl, 1-methyl-propyl, 1,2-dimethyl-propyl, 2,2-dimethyl-propyl, 3,3-dimethyl-butyl];
- (C₁₋₄)alkyl mono-substituted with (C₁₋₃)alkoxy, cyano, vinyl; ethynyl, or (C₁₋₃)alkoxy-carbonyl; [in particular such mono-substituted (C₁₋₄)alkyl is allyl, prop-2-ynyl,

cyanomethyl, 2-methoxy-ethyl, 2-methoxy-1-methyl-ethyl, methoxycarbonyl-methyl, ethoxycarbonyl-methyl];

- 5 • -CO-R¹⁰ wherein R¹⁰ represents (C₁₋₅)alkyl; (C₁₋₅)alkoxy; phenyl; phenyl-oxy-; phenyl-(C₁₋₃)alkyl-; phenyl-(C₁₋₃)alkyl-oxy-; (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl; (C₃₋₄)alkenoxo; (C₃₋₄)alkynoxo; (C₁₋₃)fluoroalkyl; (C₁₋₃)fluoroalkoxy; (C₁₋₃)alkoxy-(C₂₋₃)alkoxy; (C₁₋₃)alkoxy-(C₁₋₃)alkyl; (C₃₋₆)cycloalkyl optionally containing one ring oxygen atom, wherein said cycloalkyl is optionally mono- or di-substituted wherein the substituents independently are fluoro or (C₁)fluoroalkyl; unsubstituted 5-membered heteroaryl (especially furanyl); or -NR^{10a}R^{10b} wherein R^{10a} and R^{10b} independently represent

10 hydrogen, (C₁₋₄)alkyl or (C₃₋₆)cycloalkyl, or R^{10a} and R^{10b} together with the nitrogen to which they are attached to form a 5- to 7-membered saturated ring; [in particular such -CO-R¹⁰ is methyl-carbonyl, ethyl-carbonyl, propyl-carbonyl, isopropyl-carbonyl, isobutyl-carbonyl, *tert*.-butyl-carbonyl, (2,2-dimethyl-propyl)-carbonyl, methoxymethyl-carbonyl, cyclopropyl-carbonyl, cyclobutyl-carbonyl, (2-fluorocyclopropyl)-carbonyl, (cyclohexyl-methyl)-carbonyl, (2,2-difluorocyclopropyl)-carbonyl, (1-trifluoromethyl-cyclopropyl)-carbonyl, (tetrahydrofuran-3-yl)-carbonyl, (1,1-difluoroethyl)-carbonyl, carbamoyl, methylcarbamoyl, ethylcarbamoyl, isopropylcarbamoyl, butyl-carbamoyl, *tert*.-butyl-carbamoyl, cyclohexyl-carbamoyl, dimethylcarbamoyl, (pyrrolidin-1-yl)-carbonyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, isobutoxycarbonyl, *tert*.-butoxycarbonyl, (2,2-dimethyl-propoxy)-carbonyl, allyloxy-carbonyl, prop-2-ynyloxycarbonyl, (2-fluoro-ethoxy)-carbonyl, (2-methoxy-ethoxy)-carbonyl, furan-2-yl-carbonyl, benzoyl, phenoxy-carbonyl, benzyl-carbonyl, benzyloxy-carbonyl];

15 • -SO₂-R¹¹ wherein R¹¹ represents (C₁₋₅)alkyl or phenyl; [in particular such -SO₂-R¹¹ is methylsulfonyl, ethylsulfonyl, phenylsulfonyl];

20 • (C₂₋₄)fluoroalkyl; [in particular such (C₂₋₄)fluoroalkyl is 2-fluoroethyl, 2,2,2-trifluoroethyl, 3-fluoropropyl];

25 • (C₃₋₆)cycloalkyl optionally containing one ring oxygen atom; [in particular such (C₃₋₆)cycloalkyl is cyclobutyl, oxetan-3-yl, cyclopentyl, tetrahydrofuran-3-yl];

30 • (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl, wherein the (C₃₋₆)cycloalkyl group optionally contains one ring oxygen atom; wherein said cycloalkyl is optionally substituted with one or two methyl substituents; [in particular such (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl is cyclopropyl-methyl, cyclobutylmethyl, cyclohexyl-methyl, 1-cyclopropyl-ethyl, (3-methyl-oxetan-3-yl)-methyl];

35 • phenyl-(C₀₋₃)alkyl-, or 5- or 6-membered heteroaryl-(C₀₋₃)alkyl-, wherein the phenyl or 5- or 6-membered heteroaryl independently is especially unsubstituted, or mono-, or

di-substituted, wherein the substituents are independently selected from (C₁₋₄)alkyl (especially methyl), (C₁₋₄)alkoxy (especially methoxy), halogen, (C₁₋₃)fluoroalkyl (especially trifluoromethyl), (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy), and cyano;

(R¹)_n represents one or two optional substituents (i.e. n represents the integer 0, 1, or 2)

5 independently selected from (C₁₋₄)alkyl (especially methyl), (C₁₋₄)alkoxy (especially methoxy), halogen, (C₁₋₃)fluoroalkyl (especially trifluoromethyl), (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy), and cyano;

L¹ represents a one- or two-membered linker group selected from -NH-CH₂-*, -NR^{16a}-CH₂-* wherein R^{16a} represents (C₁₋₃)alkyl (especially methyl or ethyl); -NH-CHR^{16b}-* wherein R^{16b}

10 represents (C₁₋₃)alkyl (especially methyl); -NH-CR^{16c}R^{16d}-* wherein R^{16c} and R^{16d} together with the carbon to which they are attached to form a (C₃₋₆)cycloalkyl (especially a cyclopropyl) ring; -CH₂-NH-*; -O-CH₂-*; -O-CHR^{17a}-* wherein R^{17a} represents (C₁₋₃)alkyl (especially methyl); -O-CR^{17b}R^{17c}-* wherein R^{17b} and R^{17c} together with the carbon to which they are attached to form a (C₃₋₆)cycloalkyl (especially a cyclobutyl) ring; -CH₂-; -CH₂CH₂-; 15 -CH=CH-; and -CH=C(CH₃)-*; wherein the asterisks indicate the bond with which the group L¹ is attached to the carbonyl group;

L² represents -(C₁₋₄)alkylene- or -(C₃₋₄)alkenylene- (especially a linker group selected from -CH₂-, -CH(CH₃)-, -CH₂-CH₂-, -CH₂-CH₂-CH₂-, *-CH₂-CH=CH-, and *-CH₂-C(CH₃)=CH-, wherein the asterisks indicate the bond with which the group L² is attached to the amide 20 nitrogen atom);

Ar¹ represents phenyl, or 5- or 6-membered heteroaryl (especially pyridinyl); wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from (C₁₋₄)alkyl (especially methyl); (C₁₋₄)alkoxy (especially methoxy); (C₁₋₃)fluoroalkyl (especially trifluoromethyl); (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy); halogen; cyano; or NR^{18a}R^{18b} wherein R^{18a} and R^{18b} 25 independently represent hydrogen or (C₁₋₃)alkyl (especially NR^{18a}R^{18b} represents dimethylamino); [in particular Ar¹ represents phenyl, 2-fluoro-phenyl, 3-fluoro-phenyl, 4-fluoro-phenyl, 2,4-difluoro-phenyl, 2-chloro-phenyl, 3-chloro-phenyl, 4-chloro-phenyl, 2-chloro-4-fluoro-phenyl, 2-methyl-phenyl, 3-methyl-phenyl, 4-methyl-phenyl, 2,3-dimethyl-phenyl, 2-methoxy-phenyl, 3-methoxy-phenyl, 4-methoxy-phenyl, 3,4-dimethoxy-phenyl, 2-trifluoromethyl-phenyl, 3-trifluoromethyl-phenyl, 4-trifluoromethyl-phenyl, 4-fluoro-2-trifluoromethyl-phenyl, 2-bromo-phenyl, 3-bromo-phenyl, 4-bromo-phenyl, 2,6-difluoro-phenyl, 2-trifluoromethoxy-phenyl, 3-trifluoromethoxy-phenyl, 4-trifluoromethoxy-phenyl; or Ar¹ represents 1-methyl-imidazol-2-yl, 1-ethyl-1H-pyrazol-3-yl, 4-methyl-thiazol-2-yl, pyridin- 30 2-yl, 3-chloro-pyridin-2-yl, 3-trifluoromethyl-pyridin-2-yl, 6-trifluoromethyl-pyridin-2-yl, thiazol-

2-yl, isoxazol-5-yl, 5-methyl-isoxazol-3-yl, 1-methyl-1H-pyrazol-5-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyridin-3-yl, pyridin-4-yl, 3-fluoro-pyridin-2-yl, 5-fluoro-pyridin-2-yl, 3-chloro-pyridin-5-yl, 5-chloro-pyridin-2-yl, 3-bromo-pyridin-2-yl, 3-bromo-pyridin-4-yl, 3-methyl-pyridin-2-yl, 5-methyl-pyridin-2-yl, 6-methyl-pyridin-2-yl, 2-dimethylamino-pyrimidin-5-yl, 5-(4-fluorophenyl-amino)-pyridin-2-yl]; and

R^4 represents

- (C_{2-6}) alkyl [in particular such (C_{2-6}) alkyl is ethyl, 3-methyl-butyl, 3,3-dimethyl-butyl];
- (C_{2-5}) alkyl which is mono-substituted with (C_{1-4}) alkoxy, benzyloxy, cyano, or hydroxy; or disubstituted wherein the substituents are independently selected from (C_{1-3}) alkoxy, or hydroxy; [in particular such substituted (C_{2-5}) alkyl is 2-methoxy-ethyl, 2-hydroxy-ethyl, 2-cyano-ethyl, 2-benzyloxy-ethyl, 2-hydroxy-propyl, 2-hydroxy-2-methyl-propyl, 3-hydroxy-3-methyl-butyl, 2-methoxy-ethyl, 2-hydroxy-3-methoxy-propyl];
- (C_{2-3}) fluoroalkyl which is optionally further substituted with one hydroxy; [in particular such (C_{2-3}) fluoroalkyl is 3,3,3-trifluoro-propyl, 2-hydroxy-3,3,3-trifluoro-propyl];
- $-(C_{2-4})$ alkylene- NR^6R^7 , wherein R^6 and R^7 independently represent hydrogen; (C_{1-4}) alkyl; $-CO-(C_{1-4})$ alkoxy; (C_{3-5}) alkenyl; (C_{3-4}) alkynyl; benzyl; $-SO_2-(C_{1-3})$ alkyl; (C_{2-3}) fluoroalkyl; or (C_{3-6}) cycloalkyl or (C_{3-6}) cycloalkyl- (C_{1-3}) alkyl, wherein in the above groups the (C_{3-6}) cycloalkyl group optionally contains one ring oxygen atom, and wherein said (C_{3-6}) cycloalkyl group is optionally substituted with methyl; [in particular such $-(C_{2-4})$ alkylene- NR^6R^7 is 2-amino-ethyl, 2-methylamino-ethyl, 2-dimethylamino-ethyl, 2-diethylamino-ethyl, 3-(dimethylamino)-propyl, 2-(butyl-methylamino)-ethyl, 2-[(*tert*.-butoxycarbonyl)-methylamino]-ethyl, 2-[(*tert*.-butoxycarbonyl)-amino]-ethyl, 2-[(*tert*.-butoxycarbonyl)-ethylamino]-ethyl, 2-ethylamino-ethyl, 2-(ethyl-methylamino)-ethyl, 2-(isopropyl-methylamino)-ethyl, 2-(diisopropylamino)-ethyl, 2-(allyl-methylamino)-ethyl, 2-(methyl-prop-2-ynyl-amino)-ethyl, 2-[(2-fluoroethyl)-methylamino]-ethyl, 2-[(2,2,2-trifluoroethyl)-amino]-ethyl, 2-[methyl-(2,2,2-trifluoroethyl)-amino]-ethyl, 2-[(2-fluoro-1-methylethyl)-methylamino]-ethyl, 2-methanesulfonylamino-ethyl, 2-[(cyclopropyl)-methylamino]-ethyl, 2-[(cyclopropylmethyl)-methylamino]-ethyl, 2-[(cyclobutyl)-methylamino]-ethyl, 2-[(cyclopentyl)-methylamino]-ethyl, 2-[methyl-(tetrahydrofuran-3-yl)-amino]-ethyl, 2-[ethyl-(3-methyl-oxetan-3-yl-methyl)-amino]-ethyl];
- $-(C_{1-3})$ alkylene- $CO-R^8$, wherein R^8 represents (C_{1-4}) alkoxy (especially ethoxy); or R^8 represents $NR^{81}R^{82}$ wherein R^{81} and R^{82} independently represent hydrogen or (C_{1-4}) alkyl, or R^{81} and R^{82} together with the nitrogen to which they are attached to

form a 4- to 6-membered saturated ring optionally substituted with two fluoro substituents (especially such $\text{NR}^{\text{R}1}\text{R}^{\text{R}2}$ represents amino, 3,3-difluoroazetidiny);

- $-(\text{C}_{1-3})\text{alkylene-SO}_2\text{-R}^9$ wherein R^9 represents $(\text{C}_{1-3})\text{alkyl}$ (especially methyl), or amino;
- $(\text{C}_{3-6})\text{cycloalkyl}$ or $(\text{C}_{3-6})\text{cycloalkyl-(C}_{1-3})\text{alkyl}$, wherein the cycloalkyl group is optionally mono-substituted with $-\text{CO-(C}_{1-4})\text{alkoxy}$ or hydroxy; [in particular such $(\text{C}_{3-6})\text{cycloalkyl}$ is cyclopropyl, 4-hydroxy-cyclohexyl; and such $(\text{C}_{3-6})\text{cycloalkyl-(C}_{1-3})\text{alkyl}$ is cyclopropyl-methyl, (1-hydroxy-cyclopentyl)-methyl, (2-(ethoxycarbonyl)-cyclopropyl)-methyl];

- $(\text{C}_{4-7})\text{heterocyclyl}$ or $(\text{C}_{4-7})\text{heterocyclyl-(C}_{1-3})\text{alkyl}$, wherein in the above groups the $(\text{C}_{4-7})\text{heterocyclyl}$ independently contains one or two ring heteroatoms independently selected from nitrogen, sulfur and oxygen; wherein in the above groups said $(\text{C}_{4-7})\text{heterocyclyl}$ independently is unsubstituted, or mono-, di-, or tri-substituted wherein the substituents are independently selected from:

- one oxo substituent attached to a ring carbon atom in alpha position to a ring nitrogen (thus forming together with the nitrogen an amide group, or, in case a ring oxygen is additionally adjacent, a carbamate group, or, in case second ring nitrogen is additionally adjacent, a urea group); and / or
- two methyl substituents attached to a ring carbon atom in alpha position to a ring nitrogen atom (thus forming together with the nitrogen a $-\text{C}(\text{CH}_3)_2\text{-N}$ -group); and / or
- two oxo substituents at a ring sulfur ring atom (thus forming a $-\text{SO}_2\text{-}$ group); and / or
- $(\text{C}_{1-4})\text{alkyl}$ (especially methyl) or $-\text{CO-(C}_{1-4})\text{alkoxy}$ attached to a ring nitrogen atom having a free valency; and/or
- two fluoro substituents attached to a ring carbon atom; and/or
- in case of a $(\text{C}_{4-7})\text{heterocyclyl-(C}_{1-3})\text{alkyl}$ group, methyl attached to a ring carbon atom which is attached to the linking $(\text{C}_{1-3})\text{alkyl}$ group;

[in particular such $(\text{C}_{4-7})\text{heterocyclyl}$ is pyrrolidin-3-yl, 1-methyl-pyrrolidin-3-yl, 1-(*tert.*-butoxycarbonyl)-pyrrolidin-3-yl, piperidin-3-yl, 1-methyl-piperidin-3-yl, piperidin-4-yl, 1-methyl-piperidin-4-yl, tetrahydro-pyran-4-yl, 1,1-dioxo-tetrahydrothiophen-3-yl, 1-(*tert.*-butoxycarbonyl)-piperidin-4-yl; and such $(\text{C}_{4-7})\text{heterocyclyl-(C}_{1-3})\text{alkyl}$ is 2-(pyrrolidin-1-yl)-ethyl, 2-(2-oxo-imidazolidin-1-yl)-ethyl, 2-(1-methyl-pyrrolidin-2-yl)-ethyl, 2-(2-oxo-pyrrolidin-1-yl)-ethyl, 2-(morpholin-4-yl)-ethyl, 3-(*tert.*-butoxycarbonyl)-2,2-dimethyl-oxazolidin-4-yl-methyl, 3-methyl-oxetan-3-yl-methyl, pyrrolidin-3-yl-methyl, 3-(pyrrolidin-1-yl)-propyl, [1,4]dioxan-2-yl-methyl, 2-(piperazin-1-yl)-ethyl, 2-(piperidin-1-yl)-ethyl, 2-(azepan-1-yl)-ethyl, 2-(3,3-difluoroazetid-1-yl)-ethyl, 2-(3,3-

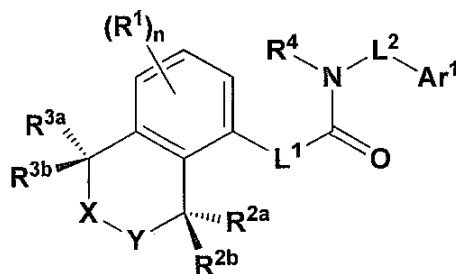
difluoropyrrolidin-1-yl)-ethyl, 2-(3,3-difluoropiperdin-1-yl)-ethyl, 2-(4,4-difluoropiperdin-1-yl)-ethyl, (1-(*tert.*-butoxycarbonyl)-pyrrolidin-3-yl)-methyl, 2-(1-(*tert.*-butoxycarbonyl)-piperazin-4-yl)-ethyl];

- 2-oxo-2,3-dihydropyridin-4-yl-(C₁₋₂)alkyl;
- 5 • phenyl-(C₁₋₃)alkyl-, or 5- or 6-membered heteroaryl-(C₁₋₃)alkyl-, wherein the phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from (C₁₋₄)alkyl (especially methyl, ethyl), (C₁₋₄)alkoxy (especially methoxy), halogen, (C₁₋₃)fluoroalkyl (especially trifluoromethyl), (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy), and cyano;
- 10 wherein the characteristics disclosed in embodiments 2) to 21) are intended to apply *mutatis mutandis* also to the compounds formula (III) according to embodiment 24); wherein especially the following embodiments are thus possible and intended and herewith specifically disclosed in individualized form:

24, 24+7, 24+10, 24+10+7, 24+13, 24+13+7, 24+13+10, 24+13+10+7, 24+17, 24+17+7, 24+17, 24+17+13, 24+17+13+7, 24+17+13+10, 24+17+13+10+7, 24+19, 24+19+7, 24+19, 24+19+13, 24+19+13+7, 24+19+13+10, 24+19+13+10+7, 24+19+17, 24+19+17+7, 24+19+17, 24+19+17+13, 24+19+17+13+7, 24+19+17+13+10, 24+19+17+13+10+7, 24+21, 24+21+7, 24+21, 24+21+13, 24+21+13+7, 24+21+13+10, 24+21+13+10+7, 24+21+17, 24+21+17+7, 24+21+17, 24+21+17+13, 24+21+17+13+7, 24+21+17+13+10, 24+21+17+13+10+7.

- 20 In the list above the numbers refer to the embodiments according to their numbering provided hereinabove whereas "+" indicates the limitations as outlined above.

25) A further embodiment of the invention relates to compounds of the formula (I) which are also compounds of the formula (I_P),



25

Formula (I_P)

wherein

- X represents NR⁵, and Y represents CHR^Y wherein R^Y represents hydrogen, or (C₁₋₃)alkyl (especially methyl); and

- R^{3a} and R^{3b} together with the carbon atom to which they are attached to form a carbonyl group, or
- two of R^{2a} , R^{2b} , R^{3a} and R^{3b} independently represent hydrogen, or (C_{1-3}) alkyl (especially methyl);
- 5 and the remaining of R^{2a} , R^{2b} , R^{3a} and R^{3b} represent hydrogen; or
- X represents CHR^X wherein R^X represents hydrogen, or (C_{1-3}) alkyl (especially methyl), and Y represents NR^5 ; and
 - R^{2a} and R^{2b} together with the carbon atom to which they are attached to form a carbonyl group, or
 - 10 ➤ two of R^{2a} , R^{2b} , R^{3a} and R^{3b} independently represent hydrogen, or (C_{1-3}) alkyl (especially methyl);
 - and the remaining of R^{2a} , R^{2b} , R^{3a} and R^{3b} represent hydrogen; or
- X represents NR^5 and Y represents a direct bond; R^{2a} and R^{2b} both represent hydrogen; and R^{3a} and R^{3b} both represent hydrogen;
- 15 R^5 represents
 - (C_{1-6}) alkyl;
 - $-CO-R^{10}$ wherein R^{10} represents (C_{1-5}) alkyl, (C_{1-5}) alkoxy, phenyl, phenyl-oxy-, phenyl- (C_{1-3}) alkyl-, phenyl- (C_{1-3}) alkyl-oxy-, or (C_{3-6}) cycloalkyl- (C_{1-3}) alkyl,
 - $-SO_2-R^{11}$ wherein R^{11} represents (C_{1-5}) alkyl;
 - 20 • (C_{2-4}) fluoroalkyl;
 - (C_{3-6}) cycloalkyl optionally containing one ring oxygen atom;
 - (C_{3-6}) cycloalkyl- (C_{1-3}) alkyl, wherein the (C_{3-6}) cycloalkyl group optionally contains one ring oxygen atom;
 - phenyl- (C_{1-3}) alkyl-, or 5- or 6-membered heteroaryl- (C_{1-3}) alkyl-, wherein the phenyl or
 - 25 5- or 6-membered heteroaryl independently is especially unsubstituted, or mono-, or di-substituted, wherein the substituents are independently selected from (C_{1-4}) alkyl (especially methyl), (C_{1-4}) alkoxy (especially methoxy), halogen, (C_{1-3}) fluoroalkyl (especially trifluoromethyl), (C_{1-3}) fluoroalkoxy (especially trifluoromethoxy), and cyano;
- $(R^1)_n$ represents one or two optional substituents (i.e. n represents the integer 0, 1, or 2)
- 30 independently selected from (C_{1-4}) alkyl (especially methyl), (C_{1-4}) alkoxy (especially methoxy), halogen, (C_{1-3}) fluoroalkyl (especially trifluoromethyl), (C_{1-3}) fluoroalkoxy (especially trifluoromethoxy), and cyano;
- L^1 represents a one- or two-membered linker group selected from $-NH-CH_2-^*$, $-NR^6-CH_2-^*$ wherein R^6 represents (C_{1-3}) alkyl, $-O-CH_2-^*$, $-CH_2-$, $-CH_2CH_2-$, $-CH=CH-$, and $-CH=C(CH_3)-^*$;

wherein the asterisks indicate the bond with which the group L^1 is attached to the carbonyl group;

L^2 represents $-(C_{1-4})$ alkylene- or $-(C_{3-4})$ alkenylene- (especially a linker group selected from $-CH_2-$, $-CH(CH_3)-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $^*-CH_2-CH=CH-$, and $^*-CH_2-C(CH_3)=CH-$,
 5 wherein the asterisks indicate the bond with which the group L^2 is attached to the amide nitrogen atom);

Ar^1 represents phenyl or 5- or 6-membered heteroaryl; wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from (C_{1-4}) alkyl; (C_{1-4}) alkoxy; (C_{1-3}) fluoroalkyl;
 10 (C_{1-3}) fluoroalkoxy; halogen; and cyano; and

R^4 represents

- (C_{2-6}) alkyl;
- (C_{2-4}) alkyl which is mono-substituted with (C_{1-4}) alkoxy, benzyloxy, cyano, or hydroxy;
- $-(C_{2-4})$ alkylene- NR^6R^7 , wherein R^6 and R^7 independently represent hydrogen, (C_{1-4}) alkyl, or $-CO-(C_{1-4})$ alkoxy;
 15
- $-(C_{1-3})$ alkylene- $CO-R^8$, wherein R^8 represents (C_{1-4}) alkoxy or amino;
- (C_{3-6}) cycloalkyl; or (C_{3-6}) cycloalkyl- (C_{1-3}) alkyl, wherein the cycloalkyl group is optionally mono-substituted with $-CO-(C_{1-4})$ alkoxy;
- (C_{4-6}) heterocyclyl or (C_{4-6}) heterocyclyl- (C_{1-3}) alkyl, wherein in the above groups the
 20 (C_{4-6}) heterocyclyl independently contains one or two ring heteroatoms independently selected from nitrogen, sulfur and oxygen; wherein in the above groups said (C_{4-6}) heterocyclyl independently is unsubstituted, or mono-, di-, or tri-substituted wherein the substituents are independently selected from:
 - one oxo substituent attached to a ring carbon atom in alpha position to a ring
 25 nitrogen (thus forming together with the nitrogen an amide group, or, in case a ring oxygen is additionally adjacent, a carbamate group, or, in case second ring nitrogen is additionally adjacent, a urea group); and / or
 - two methyl substituents attached to a ring carbon atom in alpha position to a ring nitrogen atom (thus forming together with the nitrogen a $-C(CH_3)_2-N$ -
 30 group); and / or
 - two oxo substituents at a ring sulfur ring atom (thus forming a $-SO_2-$ group); and / or
 - (C_{1-4}) alkyl or $-CO-(C_{1-4})$ alkoxy attached to a ring nitrogen atom having a free valency;
- 2-oxo-2,3-dihydropyridin-4-yl- (C_{1-2}) alkyl;
 35

- phenyl-(C₁₋₃)alkyl-, or 5- or 6-membered heteroaryl-(C₁₋₃)alkyl-, wherein the phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from (C₁₋₄)alkyl (especially methyl, ethyl), (C₁₋₄)alkoxy (especially methoxy), halogen, (C₁₋₃)fluoroalkyl (especially trifluoromethyl), (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy), and cyano;

wherein the characteristics disclosed in embodiments 2) to 21) are intended to apply *mutatis mutandis* also to the compounds formula (I_P) according to embodiment 25).

Further disclosed are compounds of formula (I_P) wherein R¹, R^{2a}, R^{2b}, R^{3a}, R^{3b}, L¹, X, Y and Ar¹ as defined in embodiment 25), and wherein R⁴ and L², together with the nitrogen to which they are attached to, form a piperazin-1-yl ring which is substituted in position 2 with Ar¹, and substituted in position 4 with (C₁₋₄)alkyl (especially methyl).

26) Another embodiment relates to compounds according to embodiment 25), and, *mutatis mutandis*, to any one of embodiments 1) to 4) and 8) to 21), wherein R⁵ represents

- (C₁₋₆)alkyl (notably methyl, ethyl, isopropyl, isobutyl, 2,2-dimethyl-propyl or 3,3-dimethyl-butyl; especially ethyl or isobutyl);
- (C₃₋₆)cycloalkyl (especially cyclopentyl); or
- (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl (especially cyclopropyl-methyl).

27) Another embodiment relates to compounds according to embodiments 25) and 26), and, *mutatis mutandis*, to any one of embodiments 1) to 17), wherein R⁴ represents

- (C₂₋₆)alkyl;
- (C₂₋₄)alkyl which is mono-substituted with (C₁₋₄)alkoxy, benzyloxy, cyano, or hydroxy;
- -(C₂₋₄)alkylene-NR⁶R⁷, wherein R⁶ and R⁷ independently represent hydrogen, (C₁₋₄)alkyl, or -CO-(C₁₋₄)alkoxy (notably R⁶ and R⁷ independently represent (C₁₋₃)alkyl, especially both represent methyl);
- -(C₁₋₃)alkylene-CO-R⁸, wherein R⁸ represents (C₁₋₄)alkoxy or amino;
- (C₃₋₆)cycloalkyl (especially cyclopropyl);
- (C₃₋₆)cycloalkyl-CH₂- (especially cyclopropyl-methyl);
- (C₄₋₆)heterocyclyl wherein the (C₄₋₆)heterocyclyl independently contains one ring heteroatom independently selected from nitrogen, sulfur and oxygen; wherein said (C₄₋₆)heterocyclyl is unsubstituted, or mono-, or di-substituted wherein the substituents are independently selected from:
 - two oxo substituents at a ring sulfur ring atom (thus forming a -SO₂- group); or
 - (C₁₋₄)alkyl attached to a ring nitrogen atom having a free valency;

(especially such (C₄₋₆)heterocyclyl is pyrrolidin-3-yl, 1-methyl-pyrrolidin-3-yl, 1-methyl-piperidin-3-yl, 1-methyl-piperidin-4-yl, tetrahydro-pyran-4-yl, or 1,1-dioxo-tetrahydrothiophen-3-yl)

- 5 • (C₄₋₆)heterocyclyl-(C₂₋₃)alkyl, wherein the (C₄₋₆)heterocyclyl contains one ring nitrogen atom and optionally one further nitrogen or oxygen atom; wherein said (C₄₋₆)heterocyclyl is preferably attached to the C₂₋₃)alkyl group at a ring nitrogen atom; wherein said (C₄₋₆)heterocyclyl is unsubstituted, or mono-, or di-substituted wherein the substituents are independently selected from:
 - one oxo substituent attached to a ring carbon atom in alpha position to a ring nitrogen; and / or
 - (C₁₋₄)alkyl attached to a ring nitrogen atom having a free valency;
 (especially the (C₄₋₆)heterocyclyl in a (C₄₋₆)heterocyclyl-(C₂₋₃)alkyl group is pyrrolidin-1-yl, pyrrolidin-2-yl, 1-methyl-pyrrolidin-3-yl, 1-methyl-pyrrolidin-2-yl, 2-oxo-pyrrolidin-1-yl, 2-oxo-imidazolidin-1-yl, piperidin-3-yl, 1-methyl-piperidin-3-yl, piperidin-4-yl, 1-methyl-piperidin-4-yl, or morpholin-4-yl; wherein the (C₁₋₃)alkyl group for the above groups is especially ethylene);
- 15 • phenyl-(C₁₋₃)alkyl- wherein the phenyl is unsubstituted, or mono-substituted, wherein the substituents are independently selected from (C₁₋₄)alkyl (especially methyl), (C₁₋₄)alkoxy (especially methoxy), halogen, (C₁₋₃)fluoroalkyl (especially trifluoromethyl), (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy), and cyano; or
- 20 • 5- or 6-membered heteroaryl-(C₁₋₃)alkyl-, wherein the 5- or 6-membered heteroaryl independently is unsubstituted, or mono-substituted, wherein the substituents are independently selected from (C₁₋₄)alkyl (especially methyl, ethyl), (C₁₋₄)alkoxy (especially methoxy), halogen, (C₁₋₃)fluoroalkyl (especially trifluoromethyl), (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy), and cyano.
- 25

28) Another embodiment relates to compounds according to embodiments 25) and 26), and, *mutatis mutandis*, to any one of embodiments 1) to 17), wherein **R**⁴ represents

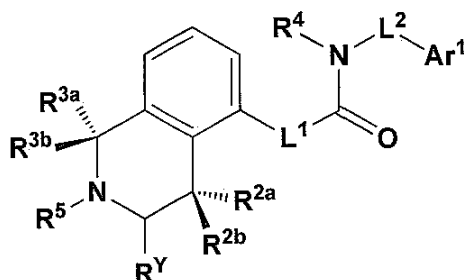
- -(C₂₋₄)alkylene-N**R**⁶**R**⁷, wherein **R**⁶ and **R**⁷ independently represent (C₁₋₃)alkyl (especially dimethylamino-ethyl); or
- 30 • (C₄₋₆)heterocyclyl-CH₂-CH₂-, wherein the (C₄₋₆)heterocyclyl is a group selected from pyrrolidin-1-yl, pyrrolidin-2-yl, 1-methyl-pyrrolidin-3-yl, 1-methyl-pyrrolidin-2-yl, 2-oxo-pyrrolidin-1-yl, 2-oxo-imidazolidin-1-yl, and morpholin-4-yl (especially 2-(pyrrolidin-1-yl)-ethyl).

- 29) The invention, thus, further relates to compounds of the formula (I_P) as defined in embodiment 25), or to such compounds further limited by the characteristics of any one of embodiments 26), 27) and / or 28), and / or, *mutatis mutandis*, limited by the characteristics of any one of embodiments 2) to 21), under consideration of their respective dependencies;
- 5 to pharmaceutically acceptable salts thereof; and to the use of such compounds as medicaments especially in the treatment of disorders relating to a dysfunction of the CXCR7 receptor or its ligands as described herein below. For avoidance of any doubt, especially the following embodiments relating to the compounds of formula (I_P) are thus possible and intended and herewith specifically disclosed in individualized form:
- 10 25+3, 25+4, 25+8+3, 25+8+4, 25+8, 25+8+26+3, 25+8+26+4, 25+8+26, 25+10+3, 25+10+4, 25+10+8+3, 25+10+8+4, 25+10+8, 25+10+8+26+3, 25+10+8+26+4, 25+10+8+26, 25+10, 25+10+26+3, 25+10+26+4, 25+10+26, 25+13+3, 25+13+4, 25+13+8+3, 25+13+8+4, 25+13+8, 25+13+8+26+3, 25+13+8+26+4, 25+13+8+26, 25+13+10+3, 25+13+10+4, 25+13+10+8+3, 25+13+10+8+4, 25+13+10+8, 25+13+10+8+26+3, 25+13+10+8+26+4, 25+13+10+8+26, 25+13+10, 25+13+10+26+3, 25+13+10+26+4, 25+13+10+26, 25+13,
- 15 25+13+26+3, 25+13+26+4, 25+13+26, 25+17+3, 25+17+4, 25+17+8+3, 25+17+8+4, 25+17+8, 25+17+8+26+3, 25+17+8+26+4, 25+17+8+26, 25+17+10+3, 25+17+10+4, 25+17+10+8+3, 25+17+10+8+4, 25+17+10+8, 25+17+10+8+26+3, 25+17+10+8+26+4, 25+17+10+8+26, 25+17+10, 25+17+10+26+3, 25+17+10+26+4, 25+17+10+26, 25+17+13+3, 25+17+13+4, 25+17+13+8+3, 25+17+13+8+4, 25+17+13+8, 25+17+13+8+26+3, 25+17+13+8+26+4, 25+17+13+8+26, 25+17+13+10+3, 25+17+13+10+4, 25+17+13+10+8+3,
- 20 25+17+13+10+8+4, 25+17+13+10+8, 25+17+13+10+8+26+3, 25+17+13+10+8+26+4, 25+17+13+10+8+26, 25+17+13+10, 25+17+13+10+26+3, 25+17+13+10+26+4, 25+17+13+10+26, 25+17+13, 25+17+13+26+3, 25+17+13+26+4, 25+17+13+26, 25+17, 25+17+26+3, 25+17+26+4, 25+17+26, 1+25, 25+26+3, 25+26+4, 25+26, 25+27+3, 25+27+4, 25+27+8+3, 25+27+8+4, 25+27+8, 25+27+8+26+3, 25+27+8+26+4, 25+27+8+26, 25+27+10+3, 25+27+10+4, 25+27+10+8+3, 25+27+10+8+4, 25+27+10+8, 25+27+10+8+26+3,
- 25 25+27+10+8+26+4, 25+27+10+8+26, 25+27+10, 25+27+10+26+3, 25+27+10+26+4, 25+27+10+26, 25+27+13+3, 25+27+13+4, 25+27+13+8+3, 25+27+13+8+4, 25+27+13+8, 25+27+13+8+26+3, 25+27+13+8+26+4, 25+27+13+8+26, 25+27+13+10+3, 25+27+13+10+4, 25+27+13+10+8+3, 25+27+13+10+8+4, 25+27+13+10+8, 25+27+13+10+8+26+3, 25+27+13+10+8+26+4, 25+27+13+10+8+26, 25+27+13+10, 25+27+13+10+26+3, 25+27+13+10+26+4, 25+27+13+10+26, 25+27+13, 25+27+13+26+3,
- 30 25+27+13+26+4, 25+27+13+26, 25+27+17+3, 25+27+17+4, 25+27+17+8+3, 25+27+17+8+4, 25+27+17+8, 25+27+17+8+26+3, 25+27+17+8+26+4, 25+27+17+8+26, 25+27+17+10+3, 25+27+17+10+4, 25+27+17+10+8+3, 25+27+17+10+8+4, 25+27+17+10+8, 25+27+17+10+8+26+3, 25+27+17+10+8+26+4, 25+27+17+10+8+26, 25+27+17+10, 25+27+17+10+26+3, 25+27+17+10+26+4, 25+27+17+10+26, 25+27+17+13+3, 25+27+17+13+4, 25+27+17+13+8+3, 25+27+17+13+8+4, 25+27+17+13+8,
- 35 25+27+17+13+8+26+3, 25+27+17+13+8+26+4, 25+27+17+13+8+26, 25+27+17+13+10+3, 25+27+17+13+10+4, 25+27+17+13+10+8+3, 25+27+17+13+10+8+4, 25+27+17+13+10+8, 25+27+17+13+10+8+26+3,

- 25+27+17+13+10+8+26+4, 25+27+17+13+10+8+26, 25+27+17+13+10, 25+27+17+13+10+26+3,
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 5 25+28+8+26+4, 25+28+8+26, 25+28+10+3, 25+28+10+4, 25+28+10+8+3, 25+28+10+8+4, 25+28+10+8,
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 10 25+28+13+10, 25+28+13+10+26+3, 25+28+13+10+26+4, 25+28+13+10+26, 25+28+13, 25+28+13+26+3,
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 15 25+28+17+13+3, 25+28+17+13+4, 25+28+17+13+8+3, 25+28+17+13+8+4, 25+28+17+13+8,
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 20 25+28+17+13+26, 25+28+17, 25+28+17+26+3, 25+28+17+26+4, 25+28+17+26, 25+28, 25+28+26+3,
 25+28+26+4, 25+28+26.

In the list above the numbers refer to the embodiments according to their numbering provided hereinabove whereas “+” indicates the dependency from another embodiment. The different individualized embodiments are separated by commas. In other words, “25+17” for example refers to embodiment 17) depending on embodiment 25) (wherein it is understood that the compounds of embodiment 25) are also compounds of formula (I) according to embodiment 1)), i.e. embodiment “25+17” corresponds to the compounds of formula (I) according to embodiment 1) further limited by all the features defining the compounds of formula (I_p) according to embodiment 25), and further limited by all the features of embodiment 17).

30) A further embodiment of the invention relates to compounds of the formula (I) according to embodiment 1) which are also compounds of the formula (II_P)



Formula (II_P)

5 wherein

R^Y represents hydrogen, or (C₁₋₃)alkyl (especially methyl); and

- two of R^{2a} , R^{2b} , R^{3a} and R^{3b} independently represent hydrogen, or (C₁₋₃)alkyl (especially methyl);
- and the remaining of R^{2a} , R^{2b} , R^{3a} and R^{3b} represent hydrogen;

10 R^5 represents

- (C₁₋₆)alkyl;
- -CO- R^{10} wherein R^{10} represents (C₁₋₅)alkyl, (C₁₋₅)alkoxy, phenyl, phenyl-oxy-, phenyl-(C₁₋₃)alkyl-, phenyl-(C₁₋₃)alkyl-oxy-, or (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl,
- -SO₂- R^{11} wherein R^{11} represents (C₁₋₅)alkyl;

15

- (C₂₋₄)fluoroalkyl;
- (C₃₋₆)cycloalkyl optionally containing one ring oxygen atom;
- (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl, wherein the (C₃₋₆)cycloalkyl group optionally contains one ring oxygen atom;
- phenyl-(C₁₋₃)alkyl-, wherein the phenyl-(C₁₋₃)alkyl-is unsubstituted;

20

L^1 represents a two-membered linker group selected from -NH-CH₂*, -NR⁶-CH₂* wherein R^6 represents (C₁₋₃)alkyl, -O-CH₂*, -CH₂CH₂-, -CH=CH-, and -CH=C(CH₃)*; wherein the asterisks indicate the bond with which the group L^1 is attached to the carbonyl group;

L^2 represents -(C₁₋₄)alkylene- or -(C₃₋₄)alkenylene- (especially a linker group selected from -CH₂-, -CH(CH₃)-, -CH₂-CH₂-, -CH₂-CH₂-CH₂-, *-CH₂-CH=CH-, and *-CH₂-C(CH₃)=CH-,

25

wherein the asterisks indicate the bond with which the group L^2 is attached to the amide nitrogen atom);

Ar^1 represents phenyl or 5- or 6-membered heteroaryl; wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono-, di- or tri-substituted, wherein

the substituents are independently selected from (C₁₋₄)alkyl; (C₁₋₄)alkoxy; (C₁₋₃)fluoroalkyl; (C₁₋₃)fluoroalkoxy; halogen; and cyano; and

R⁴ represents

- (C₂₋₆)alkyl;
- 5 • (C₂₋₄)alkyl which is mono-substituted with (C₁₋₄)alkoxy, benzyloxy, cyano, or hydroxy;
- -(C₂₋₄)alkylene-NR⁶R⁷, wherein **R⁶** and **R⁷** independently represent hydrogen, (C₁₋₄)alkyl, or -CO-(C₁₋₄)alkoxy;
- -(C₁₋₃)alkylene-CO-R⁸, wherein **R⁸** represents (C₁₋₄)alkoxy or amino;
- 10 • (C₃₋₆)cycloalkyl; or (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl, wherein the cycloalkyl group is optionally mono-substituted with -CO-(C₁₋₄)alkoxy;
- (C₄₋₆)heterocyclyl or (C₄₋₆)heterocyclyl-(C₁₋₃)alkyl, wherein in the above groups the (C₄₋₆)heterocyclyl independently contains one or two ring heteroatoms independently selected from nitrogen, sulfur and oxygen; wherein in the above groups said (C₄₋₆)heterocyclyl independently is unsubstituted, or mono-, di-, or tri-substituted
- 15 wherein the substituents are independently selected from:
 - one oxo substituent attached to a ring carbon atom in alpha position to a ring nitrogen (thus forming together with the nitrogen an amide group, or, in case a ring oxygen is additionally adjacent, a carbamate group, or, in case second ring nitrogen is additionally adjacent, a urea group); and / or
 - 20 ➤ two methyl substituents attached to a ring carbon atom in alpha position to a ring nitrogen atom (thus forming together with the nitrogen a -C(CH₃)₂-N-group); and / or
 - two oxo substituents at a ring sulfur ring atom (thus forming a -SO₂- group); and / or
 - 25 ➤ (C₁₋₄)alkyl or -CO-(C₁₋₄)alkoxy attached to a ring nitrogen atom having a free valency;
- phenyl-(C₁₋₃)alkyl-, or 5- or 6-membered heteroaryl-(C₁₋₃)alkyl-, wherein the phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from (C₁₋₄)alkyl (especially methyl, ethyl), (C₁₋₄)alkoxy (especially methoxy), halogen, (C₁₋₃)fluoroalkyl (especially trifluoromethyl), (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy), and cyano;
- 30

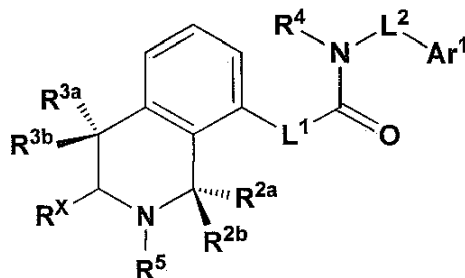
wherein the characteristics disclosed in of any one of embodiments 2) to 29) are intended to apply *mutatis mutandis* also to the compounds formula (II_P) according to embodiment 30); wherein especially the following embodiments are thus possible and intended and herewith

35 specifically disclosed in individualized form:

30+10+26, 30+1+10, 30+13+10+26, 30+13+10, 30+13+26, 30+13, 30+17+10+26, 30+17+10, 30+17+13+10+26, 30+17+13+10, 30+17+13+26, 30+17+13, 30+17+26, 30+17, 30+26, 30+27+10+26, 30+27+10, 30+27+13+10+26, 30+27+13+10, 30+27+13+26, 30+27+13, 30+27+17+10+26, 30+27+17+10, 30+27+17+13+10+26, 30+27+17+13+10, 30+27+17+13+26, 30+27+17+13, 30+27+17+26, 30+27+17, 30+27+26, 30+27, 30+28+10+26, 30+28+10, 30+28+13+10+26, 30+28+13+10, 30+28+13+26, 30+28+13, 30+28+17+10+26, 30+28+17+10, 30+28+17+13+10+26, 30+28+17+13+10, 30+28+17+13+26, 30+28+17+13, 30+28+17+26, 30+28+17, 30+28+26, 30+28, 30.

In the list above the numbers refer to the embodiments according to their numbering provided hereinabove whereas "+" indicates the limitations as outlined above.

- 10 31) A further embodiment of the invention relates to compounds of the formula (I) according to embodiment 1) which are also compounds of the formula (III_P)



Formula (III_P)

wherein

- 15 **R^X** represents hydrogen, or (C₁₋₃)alkyl (especially methyl); and
- **R^{2a}** and **R^{2b}** together with the carbon atom to which they are attached to form a carbonyl group, or
 - two of **R^{2a}**, **R^{2b}**, **R^{3a}** and **R^{3b}** independently represent hydrogen, or (C₁₋₃)alkyl (especially methyl);
- 20 and the remaining of **R^{2a}**, **R^{2b}**, **R^{3a}** and **R^{3b}** represent hydrogen; or
- R⁵** represents
- (C₁₋₆)alkyl;
 - -CO-**R¹⁰** wherein **R¹⁰** represents (C₁₋₅)alkyl, (C₁₋₅)alkoxy, phenyl, phenyl-oxy-, phenyl-(C₁₋₃)alkyl-, phenyl-(C₁₋₃)alkyl-oxy-, or (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl,
 - 25 • -SO₂-**R¹¹** wherein **R¹¹** represents (C₁₋₅)alkyl;
 - (C₂₋₄)fluoroalkyl;
 - (C₃₋₆)cycloalkyl optionally containing one ring oxygen atom;
 - (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl, wherein the (C₃₋₆)cycloalkyl group optionally contains one ring oxygen atom;

- phenyl-(C₁₋₃)alkyl-, wherein the phenyl-(C₁₋₃)alkyl-is unsubstituted;

L¹ represents a two-membered linker group selected from -NH-CH₂-, -NR⁶-CH₂-* wherein **R⁶** represents (C₁₋₃)alkyl, -O-CH₂-, -CH₂CH₂-, -CH=CH-, and -CH=C(CH₃)-*; wherein the asterisks indicate the bond with which the group **L¹** is attached to the carbonyl group;

- 5 **L²** represents -(C₁₋₄)alkylene- or -(C₃₋₄)alkenylene- (especially a linker group selected from -CH₂-, -CH(CH₃)-, -CH₂-CH₂-, -CH₂-CH₂-CH₂-, *-CH₂-CH=CH-, and *-CH₂-C(CH₃)=CH-, wherein the asterisks indicate the bond with which the group **L²** is attached to the amide nitrogen atom);

Ar¹ represents phenyl or 5- or 6-membered heteroaryl; wherein said phenyl or 5- or 6-
10 membered heteroaryl independently is unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from (C₁₋₄)alkyl; (C₁₋₄)alkoxy; (C₁₋₃)fluoroalkyl; (C₁₋₃)fluoroalkoxy; halogen; and cyano; and

R⁴ represents

- (C₂₋₆)alkyl;
- 15 • (C₂₋₄)alkyl which is mono-substituted with (C₁₋₄)alkoxy, benzyloxy, cyano, or hydroxy;
- -(C₂₋₄)alkylene-NR⁶R⁷, wherein **R⁶** and **R⁷** independently represent hydrogen, (C₁₋₄)alkyl, or -CO-(C₁₋₄)alkoxy;
- -(C₁₋₃)alkylene-CO-R⁸, wherein **R⁸** represents (C₁₋₄)alkoxy or amino;
- (C₃₋₆)cycloalkyl; or (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl, wherein the cycloalkyl group is
20 optionally mono-substituted with -CO-(C₁₋₄)alkoxy;
- (C₄₋₆)heterocyclyl or (C₄₋₆)heterocyclyl-(C₁₋₃)alkyl, wherein in the above groups the (C₄₋₆)heterocyclyl independently contains one or two ring heteroatoms independently selected from nitrogen, sulfur and oxygen; wherein in the above groups said (C₄₋₆)heterocyclyl independently is unsubstituted, or mono-, di-, or tri-substituted
25 wherein the substituents are independently selected from:
 - one oxo substituent attached to a ring carbon atom in alpha position to a ring nitrogen (thus forming together with the nitrogen an amide group, or, in case a ring oxygen is additionally adjacent, a carbamate group, or, in case second ring nitrogen is additionally adjacent, a urea group); and / or
 - 30 ➤ two methyl substituents attached to a ring carbon atom in alpha position to a ring nitrogen atom (thus forming together with the nitrogen a -C(CH₃)₂-N-group); and / or
 - two oxo substituents at a ring sulfur ring atom (thus forming a -SO₂- group); and / or

➤ (C₁₋₄)alkyl or -CO-(C₁₋₄)alkoxy attached to a ring nitrogen atom having a free valency;

- phenyl-(C₁₋₃)alkyl-, or 5- or 6-membered heteroaryl-(C₁₋₃)alkyl-, wherein the phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from (C₁₋₄)alkyl (especially methyl, ethyl), (C₁₋₄)alkoxy (especially methoxy), halogen, (C₁₋₃)fluoroalkyl (especially trifluoromethyl), (C₁₋₃)fluoroalkoxy (especially trifluoromethoxy), and cyano;

wherein the characteristics disclosed in of any one of embodiments 2) to 29) are intended to apply *mutatis mutandis* also to the compounds formula (III_P) according to embodiment 31);
 wherein especially the following embodiments are thus possible and intended and herewith specifically disclosed in individualized form:

31+10+26, 31+1+10, 31+13+10+26, 31+13+10, 31+13+26, 31+13, 31+17+10+26, 31+17+10, 31+17+13+10+26, 31+17+13+10, 31+17+13+26, 31+17+13, 31+17+26, 31+17, 31+26, 31+27+10+26, 31+27+10, 31+27+13+10+26, 31+27+13+10, 31+27+13+26, 31+27+13, 31+27+17+10+26, 31+27+17+10, 31+27+17+13+10+26, 31+27+17+13+10, 31+27+17+13+26, 31+27+17+13, 31+27+17+26, 31+27+17, 31+27+26, 31+27, 31+28+10+26, 31+28+10, 31+28+13+10+26, 31+28+13+10, 31+28+13+26, 31+28+13, 31+28+17+10+26, 31+28+17+10, 31+28+17+13+10+26, 31+28+17+13+10, 31+28+17+13+26, 31+28+17+13, 31+28+17+26, 31+28+17, 31+28+26, 31+28, 31.

In the list above the numbers refer to the embodiments according to their numbering provided hereinabove whereas "+" indicates the limitations as outlined above.

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

N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-pyrrolidin-1-yl-ethyl)-acetamide;

N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-

acetamide;

2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-pyrrolidin-1-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;

N-Benzyl-N-(3-dimethylamino-propyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide;

N-(2-Dimethylamino-ethyl)-N-(2-methyl-benzyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-

acetamide;

N-(2-Chloro-benzyl)-N-(2-dimethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide;

N-(2-Dimethylamino-ethyl)-N-(3-fluoro-benzyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide;

- N-(2-Dimethylamino-ethyl)-N-(2-fluoro-benzyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide;
- N-Benzyl-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-acetamide;
- N-Benzyl-N-(2-diethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide;
- 5 N-Benzyl-N-[2-(butyl-methyl-amino)-ethyl]-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide;
- N-Benzyl-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3-trifluoromethyl-benzyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 10 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-phenethyl-acetamide;
- N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3-dimethylamino-propyl)-acetamide;
- 15 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-fluoro-benzyl)-acetamide;
- N-(3-Chloro-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-o-tolyl-ethyl)-acetamide;
- 20 N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-acetamide;
- N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-acetamide;
- N-(2-Chloro-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-acetamide;
- 25 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-fluoro-benzyl)-N-(2-pyrrolidin-1-yl-ethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-((E)-2-methyl-3-phenyl-allyl)-acetamide;
- 30 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(6-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-N-phenethyl-acetamide;
- 35

- N-(2-Chloro-4-fluoro-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2,4-difluoro-benzyl)-N-(2-pyrrolidin-1-yl-ethyl)-acetamide;
- 5 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-N-(3-phenyl-propyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-N-((E)-3-phenyl-allyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(4-fluoro-2-
- 10 trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-[2-(3-trifluoromethyl-phenyl)-ethyl]-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-[2-(2-trifluoromethyl-phenyl)-ethyl]-acetamide;
- 15 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-[1-(2-trifluoromethyl-phenyl)-ethyl]-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-diethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-((E)-2-methyl-3-phenyl-allyl)-N-[2-(1-methyl-
- 20 pyrrolidin-2-yl)-ethyl]-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(2-oxo-pyrrolidin-1-yl)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 25 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-morpholin-4-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Cyano-ethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(tetrahydro-pyran-4-yl)-N-(2-trifluoromethyl-
- 30 benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(4-methyl-thiazol-2-ylmethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 35 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[1-(1-ethyl-1H-pyrazol-3-yl)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide;

- N-(2-Dimethylamino-ethyl)-2-[2-(2,2,2-trifluoro-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-[(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-methyl-amino]-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 5 2-(6-Chloro-2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-6-methoxy-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 5-(((2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-4,4-dimethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester;
- 10 2-(2-Cyclopropylmethyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(1-methyl-piperidin-4-yl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 15 N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide;
- N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide;
- N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-isobutyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide;
- 5-([Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid
- 20 methyl ester;
- N-Benzyl-2-(2-butyryl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- N-(2-Chloro-benzyl)-N-(2-dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide;
- N-(2-Chloro-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- 25 N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(1-methyl-piperidin-3-yl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(1-methyl-piperidin-4-yl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 30 (E)-N-Benzyl-N-(2-dimethylamino-ethyl)-3-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-acrylamide;
- (E)-N-Benzyl-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-acrylamide;
- {Benzyl-[(E)-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-acryloyl]-amino}-acetic acid ethyl ester;
- (E)-N-(2-Chloro-benzyl)-N-(2-dimethylamino-ethyl)-3-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-acrylamide;
- 35 (E)-N-(2-Chloro-benzyl)-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-acrylamide;

- (E)-N-Benzyl-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(1,1-dioxo-tetrahydro-1H-thiophen-3-yl)-acrylamide;
- (E)-N-(2-Dimethylamino-ethyl)-3-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-trifluoromethyl-benzyl)-acrylamide;
- 5 (E)-3-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acrylamide;
- (E)-3-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(1-methyl-piperidin-4-yl)-N-(2-trifluoromethyl-benzyl)-acrylamide;
- (E)-3-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(1-methyl-piperidin-4-yl)-N-(2-trifluoromethyl-benzyl)-acrylamide;
- 10 (E)-3-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-2-methyl-N-(2-trifluoromethyl-benzyl)-acrylamide;
- N-(2-Chloro-benzyl)-N-(2-dimethylamino-ethyl)-3-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-propionamide;
- N-(2-Chloro-benzyl)-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-propionamide;
- 15 N-(2-Dimethylamino-ethyl)-3-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-trifluoromethyl-benzyl)-propionamide;
- 3-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-propionamide;
- 20 3-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(1-methyl-piperidin-4-yl)-N-(2-trifluoromethyl-benzyl)-propionamide;
- N-Benzyl-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-propionamide;
- N-Benzyl-N-(2-dimethylamino-ethyl)-3-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-propionamide;
- N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-N-(3-methyl-butyl)-acetamide;
- 25 N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-N-(2-dimethylamino-ethyl)-acetamide;
- 5-[[Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methoxy]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid methyl ester;
- N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-isobutyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-acetamide;
- N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-acetamide;
- 30 N-(2-Chloro-benzyl)-N-(2-dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-acetamide;
- N-(2-Chloro-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-N-(2-dimethylamino-ethyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 35 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;

- N-(2-Dimethylamino-ethyl)-N-(2-fluoro-benzyl)-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide;
 N-(2-Methylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
 N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-pyrrolidin-3-yl-acetamide;
 5 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
 N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(1-methyl-pyrrolidin-3-yl)-acetamide;
 N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
 N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-isobutyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide;
 10 8-([Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid isopropyl ester;
 N-Benzyl-2-(2-benzyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
 N-Benzyl-2-(2-cyclohexylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
 2-(2-Benzoyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-benzyl-N-(2-dimethylamino-ethyl)-acetamide;
 15 N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-acetamide;
 N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-acetamide;
 N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-N-(2-dimethylamino-ethyl)-acetamide;
 8-([Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methoxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid methyl ester;
 20 N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-isobutyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-acetamide;
 N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-acetamide;
 2-(2-Benzoyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-N-benzyl-N-(2-dimethylamino-ethyl)-acetamide;
 2-((2-Cyclopentyl-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(dimethylamino)ethyl)-N-(2-(trifluoromethyl)benzyl)acetamide;
 25 2-((2-(Cyclopropylmethyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(dimethylamino)ethyl)-N-(2-(trifluoromethyl)benzyl)acetamide; and
 2-((2-(Cyclopropylmethyl)-3-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(dimethylamino)ethyl)-N-(2-(trifluoromethyl)benzyl)acetamide.
- 33) Another embodiment relates to compounds according to embodiment 1) which are
 30 selected from the following compounds:
 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide;
 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3-pyrrolidin-1-yl-propyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
 35 4-[2-[[2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]-(2-trifluoromethyl-benzyl)-amino]-ethyl]-piperazine-1-carboxylic acid tert-butyl ester;

- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-piperidin-1-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Azepan-1-yl-ethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 5 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-diisopropylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-[2-(Cyclopropyl-methyl-amino)-ethyl]-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-trifluoromethoxy-benzyl)-acetamide;
- 10 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(4-hydroxy-cyclohexyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-hydroxy-3-methoxy-propyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 15 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methoxy-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[1,4]dioxan-2-ylmethyl-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethoxy-benzyl)-acetamide;
- 20 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methanesulfonyl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(ethyl-methyl-amino)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 25 N-(2-Bromo-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- N-(3-Bromo-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- N-(3-Bromo-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- 30 N-(4-Bromo-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- N-(3-Bromo-pyridin-4-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- 35 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-hydroxy-propyl)-N-(2-trifluoromethyl-benzyl)-acetamide;

- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-hydroxy-2-methyl-propyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3,3,3-trifluoro-2-hydroxy-propyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 5 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(1-hydroxy-cyclopentylmethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-{2-[(2-fluoro-ethyl)-methyl-amino]-ethyl}-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-[2-(Allyl-methyl-amino)-ethyl]-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 10 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(methyl-prop-2-ynyl-amino)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-thiazol-5-ylmethyl-N-(2-trifluoromethyl-benzyl)-acetamide;
- 15 N-(2-Chloro-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-acetamide;
- N-(3-Chloro-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-isoxazol-5-ylmethyl-N-(2-trifluoromethyl-benzyl)-acetamide;
- 20 N-(3-Chloro-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-hydroxy-2-methyl-propyl)-acetamide;
- 3-[[[2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]-(2-trifluoromethyl-benzyl)-amino]-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester;
- 25 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-methyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-pyridin-2-ylmethyl-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(5-methyl-pyridin-2-ylmethyl)-acetamide;
- 30 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(6-methyl-pyridin-2-ylmethyl)-acetamide;
- N-(5-Chloro-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- 35 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-thiazol-2-ylmethyl-acetamide;

- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(4-methyl-thiazol-2-ylmethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(5-fluoro-pyridin-2-ylmethyl)-acetamide;
- 5 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2,6-difluoro-benzyl)-N-(2-dimethylamino-ethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-fluoro-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3,3-dimethyl-butyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 10 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3,3-dimethyl-butyl)-N-(3-methyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 15 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-{2-[methyl-(2,2,2-trifluoro-ethyl)-amino]-ethyl}-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(3,3-difluoro-piperidin-1-yl)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 20 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(3,3-difluoro-pyrrolidin-1-yl)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(3,3-difluoro-piperidin-1-yl)-ethyl]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 25 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(3,3-difluoro-pyrrolidin-1-yl)-ethyl]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-[2-(2-fluoro-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-8-fluoro-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 30 2-(2-Cyclopropylmethyl-8-fluoro-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-6-methyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 35 N-(3-Chloro-pyridin-2-ylmethyl)-N-(2-dimethylamino-ethyl)-2-[2-((1S*,2S*)-2-fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-acetamide;

- N-[2-[(2-Fluoro-ethyl)-methyl-amino]-ethyl]-2-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(3-Chloro-pyridin-2-ylmethyl)-N-(2-dimethylamino-ethyl)-2-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-acetamide;
- 5 N-(2-Dimethylamino-ethyl)-2-(2-prop-2-ynyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-ethyl-3-oxo-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Ethyl-3-oxo-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 10 N-(2-Dimethylamino-ethyl)-2-(2-isobutyl-3-oxo-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-isobutyl-3-oxo-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 15 2-(2-Isobutyl-3-oxo-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1-oxo-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- (E)-N-(2-Dimethylamino-ethyl)-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-N-(2-trifluoromethyl-benzyl)-acrylamide;
- 20 (E)-N-(2-Dimethylamino-ethyl)-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acrylamide;
- (E)-N-(3-Chloro-pyridin-2-ylmethyl)-N-(2-dimethylamino-ethyl)-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-acrylamide;
- 25 (E)-N-(3-Chloro-pyridin-2-ylmethyl)-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-hydroxy-2-methyl-propyl)-acrylamide;
- (E)-N-(3-Chloro-pyridin-2-ylmethyl)-N-(2-dimethylamino-ethyl)-3-[2-((1R*,2R*)-2-fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-acrylamide;
- (E)-N-(3-Chloro-pyridin-2-ylmethyl)-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-acrylamide;
- 30 (E)-N-(3-Chloro-pyridin-2-ylmethyl)-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-acrylamide;
- N-(2-Dimethylamino-ethyl)-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-N-(2-trifluoromethyl-benzyl)-propionamide;
- 35 N-(2-Dimethylamino-ethyl)-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-propionamide;

- N-[2-(Allyl-methyl-amino)-ethyl]-3-(2-allyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-trifluoromethyl-benzyl)-propionamide;
- 3-(2-Allyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-propionamide;
- 5 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-propionamide;
- N-(2-Dimethylamino-ethyl)-2-[2-(tetrahydro-furan-3-yl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclobutyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 10 N-(2-Dimethylamino-ethyl)-2-[2-(2-methoxy-1-methyl-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-[2-(1,2-dimethyl-propyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 15 2-(2-sec-Butyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-[2-(1-Cyclopropyl-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-[2-(3-methyl-oxetan-3-ylmethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 20 N-(2-Dimethylamino-ethyl)-2-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
- [5-({(2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl}-methyl)-amino]-3,4-dihydro-1H-isoquinolin-2-yl]-acetic acid methyl ester;
- 25 2-(2-Cyclobutylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-[2-(2,2-Difluoro-propionyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-[2-((1R*,2R*)-2-fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 30 2-(2-Cyanomethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-[2-(tetrahydro-furan-3-yl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 35 2-(2-Cyclobutyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;

- 2-(2-Cyclobutylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
[5-({[(2-Dimethylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl]-methyl}-amino)-3,4-dihydro-1H-isoquinolin-2-yl]-acetic acid methyl ester;
- 5 N-(2-Dimethylamino-ethyl)-2-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
N-(2-Dimethylamino-ethyl)-2-(2-pyridin-2-yl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 10 N-(2-Dimethylamino-ethyl)-2-(2-pyrimidin-2-yl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
N-(2-Dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-2-[2-(4-trifluoromethyl-thiazol-2-yl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-acetamide;
- 15 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(R)-1-pyrrolidin-3-ylmethyl-N-(2-trifluoromethyl-benzyl)-acetamide;
2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(S)-1-pyrrolidin-3-ylmethyl-N-(2-trifluoromethyl-benzyl)-acetamide;
- 20 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-pyrrolidin-3-yl-N-(2-trifluoromethyl-benzyl)-acetamide;
2-(2-Cyclopropylmethyl-1-methyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 25 2-(2-Cyclopropanecarbonyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
2-(2-Butyryl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 30 2-(2-Isobutyryl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
2-[2-(2-Methoxy-acetyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 35 2-(2-Cyclobutanecarbonyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
N-(2-Methylamino-ethyl)-2-[2-(3-methyl-butyryl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 35 N-(2-Methylamino-ethyl)-2-[2-(tetrahydro-furan-3-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;

- 5-(((2-Methylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid methyl ester;
- 5-(((2-Methylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid ethyl ester;
- 5 5-(((2-Methylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid prop-2-ynyl ester;
- 5-(((2-Methylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid allyl ester;
- 10 5-(((2-Methylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid 2-fluoro-ethyl ester;
- 5-(((2-Methylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid ethylamide;
- 2-(2-Acetyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 15 N-(2-Methylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Cyclopropanecarbonyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Butyryl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 20 2-(2-Isobutyryl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 2-[2-(2-Methoxy-acetyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-methylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 25 2-(2-Cyclobutanecarbonyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- N-(2-Methylamino-ethyl)-2-[2-(tetrahydro-furan-3-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid methyl ester;
- 30 5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid ethyl ester;
- 5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid prop-2-ynyl ester;
- 35 5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid allyl ester;

- 5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid 2-fluoro-ethyl ester;
- 5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid ethylamide;
- 5 5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid isopropylamide;
- 5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butylamide;
- 10 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(2,2,2-trifluoro-ethylamino)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Bromo-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-acetamide;
- N-(3-Chloro-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-acetamide;
- 15 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-piperazin-1-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-ethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 20 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-piperidin-4-yl-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-pyrrolidin-3-ylmethyl-N-(2-trifluoromethyl-benzyl)-acetamide;
- 25 N-(2-Amino-ethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Acetyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 30 N-(2-Chloro-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-acetamide;
- N-[2-(Cyclobutyl-methyl-amino)-ethyl]-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 35 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-{2-[methyl-(tetrahydro-furan-3-yl)-amino]-ethyl}-N-(2-trifluoromethyl-benzyl)-acetamide;

- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(isopropyl-methyl-amino)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-[2-(Cyclopropylmethyl-methyl-amino)-ethyl]-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 5 N-[2-(Cyclopentyl-methyl-amino)-ethyl]-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-{2-[(2-fluoro-1-methyl-ethyl)-methyl-amino]-ethyl}-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-{ethyl-(3-methyl-oxetan-3-ylmethyl)-amino-ethyl}-N-(2-trifluoromethyl-benzyl)-acetamide;
- 10 3-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-yl)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-propionamide;
- N-(3-Chloro-pyridin-2-ylmethyl)-2-(2-cyclobutyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- 15 N-(3-Bromo-pyridin-2-ylmethyl)-2-(2-cyclobutyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- N-[2-(Allyl-methyl-amino)-ethyl]-2-(2-allyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Allyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethoxy-benzyl)-acetamide;
- 20 2-(2-Allyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-{2-[(2-fluoro-ethyl)-methyl-amino]-ethyl}-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Allyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 25 N-[2-(Allyl-methyl-amino)-ethyl]-3-(2-allyl-1,2,3,4-tetrahydro-isoquinolin-8-yl)-N-(2-trifluoromethyl-benzyl)-propionamide;
- 3-(2-Allyl-1,2,3,4-tetrahydro-isoquinolin-8-yl)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-propionamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 30 N-[2-(Cyclopropyl-methyl-amino)-ethyl]-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-trifluoromethoxy-benzyl)-acetamide;
- 35 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethoxy-benzyl)-acetamide;

- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 5 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-[2-(3,3-difluoro-piperidin-1-yl)-ethyl]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-[2-(3,3-difluoro-pyrrolidin-1-yl)-ethyl]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-[2-(3,3-difluoro-azetidin-1-yl)-2-oxo-ethyl]-N-
- 10 (2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-[2-(3,3-difluoro-azetidin-1-yl)-2-oxo-ethyl]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- N-(3-Chloro-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- 15 N-(3-Bromo-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- 2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-Benzyl-N-(2-diethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide;
- 20 N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-fluoro-benzyl)-acetamide;
- 2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(1-methyl-piperidin-4-yl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-methyl-benzyl)-acetamide;
- N-(2-Chloro-benzyl)-N-(2-dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide;
- 25 N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(3-trifluoromethyl-benzyl)-acetamide;
- N-Benzyl-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-acetamide;
- N-Benzyl-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-acetamide;
- N-(3-Chloro-pyridin-2-ylmethyl)-N-(2-dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-
- 30 acetamide;
- N-(2-Diethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(1-methyl-piperidin-3-yl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 35 N-(2,6-Difluoro-benzyl)-N-(2-dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide;

- N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(3-methyl-pyridin-2-ylmethyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(6-methyl-pyridin-2-ylmethyl)-acetamide;
- 5 N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(3-fluoro-pyridin-2-ylmethyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(6-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 10 N-(2-Dimethylamino-ethyl)-2-(2-methanesulfonyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 8-(((2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid dimethylamide;
- 15 8-(((2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid methylamide;
- (E)-N-(2-Dimethylamino-ethyl)-3-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-yl)-N-(2-trifluoromethyl-benzyl)-acrylamide;
- N-(2-Dimethylamino-ethyl)-2-[2-(2-dimethyl-propionyl)-1,2,3,4-tetrahydro-isoquinolin-8-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 20 2-(2-Benzoyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 8-(((2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid isopropyl ester;
- 25 2-(2-Cyclohexylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-propyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 30 N-(2-Dimethylamino-ethyl)-2-(2-isobutyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 35 2-(2-Cyclopropanecarbonyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;

- N-(2-Dimethylamino-ethyl)-2-[2-(pyrrolidine-1-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-8-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-[2-(2,2-dimethyl-propyl)-1,2,3,4-tetrahydro-isoquinolin-8-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 5 N-(2-Dimethylamino-ethyl)-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 10 N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-((R)-2-Cyclopropylmethyl-1-methyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 15 2-((S)-2-Cyclopropylmethyl-1-methyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-[2-((1R,2R)-2-fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-[2-((1S,2S)-2-fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 20 3-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylmethyl)-1-(2-dimethylamino-ethyl)-1-(2-trifluoromethyl-benzyl)-urea;
- 2-[2-(2,2-Difluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 25 N-(2-Dimethylamino-ethyl)-2-[2-(furan-2-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-propyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide.

The compounds of formula (I) according to embodiments 1) to 33) and their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical compositions for enteral (such especially oral) or parenteral administration (including topical application or inhalation).

In another aspect, there is provided a pharmaceutical composition comprising, as active principle, a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.

In a further aspect, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, for use as a medicament.

In yet another aspect, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament, for the prevention or treatment of diseases or disorders selected from the group consisting of:

5 cancers selected from carcinomas, leukemias, adenocarcinomas, malignant glioma, glioblastoma multiforme, brain metastases, multiple myelomas, renal clear cell carcinoma, prostate cancer, pancreatic adenocarcinoma, melanoma, metastatic melanoma, hepatocellular carcinoma, colon tumors, breast cancer, non-small cell lung cancer, colorectal

10 cancer, brain tumors, Ewing's sarcoma, lymphoma, Burkitt's lymphoma, Hodgkin's lymphoma, adult T-cell leukemia, lymphoproliferative disease, Kaposi's sarcoma, and choriocarcinoma;

 autoimmune disorders selected from multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, lupus nephritis, interstitial

15 cystitis, celiac disease, auto-immune encephalomyelitis, demyelinating diseases, osteoarthritis, and type I diabetes;

 inflammatory diseases selected from asthma, chronic obstructive pulmonary disorder, atherosclerosis, myocarditis, sarcoidosis, and chronic rhinosinusitis;

 transplant rejectionselected from renal allograft rejection, cardiac allograft rejection,

20 and graft-versus-host diseases brought about by hematopoietic stem cell transplantation; and fibrosis selected from liver fibrosis, liver cirrhosis, and idiopathic pulmonary fibrosis.

In another aspect, there is provided a use of an effective amount of the compound of formula (I) as disclosed herein, or of a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a tumor, wherein said effective amount leads to a change of the

25 properties of said tumor, wherein said change of tumor properties is expressed by an altered recruitment of immune and inflammatory infiltrating cells and/or by an inhibition of tumor vasculogenesis, and wherein said change of tumor properties is achieved by modulating the CXCL12 receptor pathway.

In yet another aspect, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament, for the prevention or treatment of cancers selected from carcinomas, leukemias, adenocarcinomas, malignant glioma, glioblastoma multiforme, brain metastases, multiple myelomas, renal clear cell carcinoma, prostate cancer, pancreatic adenocarcinoma, melanoma, metastatic melanoma, hepatocellular carcinoma, colon tumors, breast cancer, non-small cell lung cancer, colorectal cancer, brain tumors, Ewing's sarcoma, lymphoma, Burkitt's lymphoma, Hodgkin's lymphoma, adult T-cell leukemia, lymphoproliferative disease, Kaposi's sarcoma, and choriocarcinoma; wherein said compound is optionally used in combination with one or more chemotherapy agents and / or radiotherapy and / or targeted therapy.

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.

- 5 The present invention also relates to a method for the prevention 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 33).

In a preferred embodiment of the invention, the administered amount is comprised between 1 mg and 1000 mg per day, particularly between 5 mg and 500 mg per day, more particularly
10 between 25 mg and 400 mg per day, especially between 50 mg and 200 mg per day.

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
15 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. In the particular case of temperatures, the term "about" placed before a temperature "Y" refers
20 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.

For avoidance of any doubt, if compounds are described as useful for the prevention or treatment of certain diseases, such compounds are likewise suitable for use in the preparation of a medicament for the prevention or treatment of said diseases.

- 25 The compounds of formula (I) according to embodiments 1) to 33) are useful for the prevention or treatment of disorders relating to a dysfunction of the CXCR7 receptor or its ligands, i.e. relating to a dysfunction of the CXCR7 receptor, or dysfunction of ligands signalling through CXCR7, or dysfunction of CXCR7 ligands (CXCL12 and CXCL11) signalling through their other receptors (CXCR4 and CXCR3).

- 30 Diseases or disorders relating to the CXCR7 receptor or its ligands are especially selected from:

- cancers (notably carcinomas, leukemias, adenocarcinomas, malignant glioma, glioblastoma multiforme, brain metastases, multiple myelomas, renal clear cell carcinoma, prostate cancer, pancreatic adenocarcinoma, melanoma, metastatic

- melanoma, hepatocellular carcinoma, colon tumors, breast cancer, non-small cell lung cancer, colorectal cancer, brain tumors, Ewing's sarcoma, lymphoma, Burkitt's lymphoma, Hodgkin's lymphoma, adult T-cell leukemia, lymphoproliferative disease, and Kaposi's sarcoma; as well as choriocarcinoma; especially malignant glioma, glioblastoma multiforme, brain metastases, pancreatic adenocarcinoma, lymphoma, Burkitt's lymphoma, and Hodgkin's lymphoma) ;
- inflammatory diseases (notably asthma, chronic obstructive pulmonary disorder, atherosclerosis, myocarditis, and sarcoidosis; as well as chronic rhinosinusitis; especially chronic rhinosinusitis, asthma, and atherosclerosis);
 - autoimmune disorders (notably multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, lupus nephritis, interstitial cystitis, and celiac disease; as well as auto-immune encephalomyelitis, demyelinating diseases, osteoarthritis, and type I diabetes; especially multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, and auto-immune encephalomyelitis);
 - transplant rejection (notably renal allograft rejection, cardiac allograft rejection, and graft-versus-host diseases brought about by hematopoietic stem cell transplantation); and
 - fibrosis (notably liver fibrosis, liver cirrhosis, and idiopathic pulmonary fibrosis; especially liver cirrhosis).
- Notably such diseases or disorders relating to the CXCR7 receptor or its ligands are cancers and autoimmune disorders.
- In addition, further diseases or disorders relating to the CXCR7 receptor or its ligands are diseases involving CXCR7 and / or CXCL12 and / or CXCL11 mediated metastasis, chemotaxis, cell adhesion, trans-endothelial migration, cell proliferation and/or survival.
- In addition, further diseases or disorders relating to the CXCR7 receptor or its ligands are pulmonary vascular diseases; acute renal failure; ischemia including cerebral ischemia; injured central nervous system; HSCs transplantation; pulmonary hypertension; Shiga-toxin-associated hemolytic uremic syndrome; preeclampsia; and HIV / AIDS. Even further diseases and disorder relating to the CXCR7 receptor or its ligands are proliferative diabetic retinopathy; West Nile virus encephalitis; acute coronary syndrome; hypertension; vascular injury; angiogenesis; and brain and neuronal dysfunctions (such as inflammatory components of Alzheimer's disease); stress-related disorders (such as anxiety, depression, and posttraumatic stress disorder); and diseases involving opioid receptors. In a sub-embodiment, such a further particular disease or disorder relating to the CXCR7 receptor or its ligands is especially pulmonary hypertension.

In addition, further particular diseases or disorders relating to a dysfunction of the CXCR7 receptor or its ligands are selected from the group consisting of kidney dysfunction; nasal polyposis; cardiac allograft rejection; cardiac dysfunction; atherosclerosis; asthma; glomerulonephritis; contact dermatitis; inflammatory bowel disease; colitis; psoriasis; and
5 reperfusion injury.

In addition, further particular diseases or disorders relating to a dysfunction of the CXCR7 receptor or its ligands are hematopoietic stem cell mobilizations.

The term "cancer" refers to all sorts of cancers such as carcinomas, leukemias, adenocarcinomas, malignant glioma, glioblastoma multiforme, brain metastases, multiple
10 myelomas, renal clear cell carcinoma, prostate cancer, pancreatic adenocarcinoma, melanoma, metastatic melanoma, rhabdomyosarcoma, hepatocellular carcinoma, colon tumors, breast cancer, non-small cell lung cancer, oral tumors, colorectal cancer, gallbladder cancer, brain tumors, Ewing's sarcoma, bladder cancer, meningioma, lymphoma, viral-induced tumors, Burkitt's lymphoma, Hodgkin's lymphoma, adult T-cell leukemia,
15 lymphoproliferative disease, Kaposi's sarcoma, MALT lymphoma, papillary thyroid carcinoma, cervical cancer, and osteosarcoma; primary intra-ocular B-cell lymphoma; and diseases involving CXCR7 and/or CXCL12 and/or CXCL11 mediated metastasis. In addition, cancer furthermore comprises mesotheliomas, ovarian cancer, head and neck cancer, small cell lung cancer, esophageal cancer, stomach cancer, hepatobiliary cancer, cancer of the
20 small intestine, rectal cancer, kidney cancer, penile cancer, urethral cancer, testicular cancer, vaginal cancer, uterine cancer, thyroid cancer, parathyroid cancer, adrenal cancer, pancreatic endocrine cancer, carcinoid cancer, bone cancer, skin cancer, retinoblastomas, non-Hodgkin's lymphoma, multicentric Castleman's disease or AIDS-associated cancer, primary effusion lymphoma, and neuroectodermal tumors. The term furthermore comprises
25 choriocarcinoma. Preferably the term refers to carcinomas, leukemias, adenocarcinomas, malignant glioma, glioblastoma multiforme, brain metastases, multiple myelomas, renal clear cell carcinoma, prostate cancer, pancreatic adenocarcinoma, melanoma, metastatic melanoma, hepatocellular carcinoma, colon tumors, breast cancer, non-small cell lung cancer, colorectal cancer, brain tumors, Ewing's sarcoma, lymphoma, Burkitt's lymphoma,
30 Hodgkin's lymphoma, adult T-cell leukemia, lymphoproliferative disease, and Kaposi's sarcoma; especially to malignant glioma, glioblastoma multiforme, brain metastases, pancreatic adenocarcinoma, lymphoma, Burkitt's lymphoma, and Hodgkin's lymphoma.

The term "autoimmune disorders" refers to diseases and disorders comprising rheumatoid arthritis (RA); multiple sclerosis (MS); autoimmune encephalomyelitis; and inflammatory
35 bowel disease (IBD, especially comprising Crohn's disease and ulcerative colitis). In addition,

autoimmune diseases further comprise disorders such as systemic lupus erythematosus (SLE); psoriasis; psoriatic arthritis; lupus nephritis; interstitial cystitis; celiac disease; antiphospholipid syndrome; thyroiditis such as Hashimoto's thyroiditis; lymphocytic thyroiditis; myasthenia gravis; type I diabetes; uveitis; episcleritis; scleritis; Kawasaki's disease; uveo-retinitis; posterior uveitis; uveitis associated with Behcet's disease; uveomeningitis syndrome; allergic encephalomyelitis; atopic diseases such as rhinitis, conjunctivitis, dermatitis; and post-infectious autoimmune diseases including rheumatic fever and post-infectious glomerulonephritis. The term further comprises auto-immune encephalomyelitis; demyelinating diseases; osteoarthritis. In a sub-embodiment, autoimmune disorders include especially rheumatoid arthritis (RA); multiple sclerosis (MS); and inflammatory bowel disease (comprising Crohn's disease and ulcerative colitis); as well as systemic lupus erythematosus (SLE); lupus nephritis; interstitial cystitis; celiac disease; and type I diabetes; as well as in addition auto-immune encephalomyelitis; demyelinating diseases; and osteoarthritis.

The term "inflammatory diseases" refers to diseases and disorders comprising especially chronic rhinitis as well as asthma, chronic obstructive pulmonary disorder (COPD), atherosclerosis, myocarditis, dry eye disease, sarcoidosis, and inflammatory myopathies, as well as acute lung injury.

The term "transplant rejection" refers to diseases and disorders comprising rejection of transplanted organs such as kidney, liver, heart, lung, pancreas, cornea, and skin; graft-versus-host diseases brought about by (hematopoietic) stem cell transplantation; chronic allograft rejection and chronic allograft vasculopathy.

Fibrosis may be defined as comprising especially liver cirrhosis, as well as idiopathic pulmonary fibrosis, renal fibrosis, endomyocardial fibrosis, and arthrofibrosis. The term further comprises liver fibrosis.

The compounds of formula (I) as defined in embodiments 1) to 33) are in particular useful as therapeutic agents for the prevention or treatment of a cancer. They can be used as single therapeutic agents or in combination with one or more chemotherapy agents and / or radiotherapy and / or targeted therapy. In a sub-embodiment, when a compound of formula (I) is used for the prevention or treatment of a cancer in combination with one or more chemotherapy agents and / or radiotherapy, such cancer is especially a malignant glioma, in particular a glioblastoma multiforme. Such combined treatment may be effected simultaneously, separately, or over a period of time.

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

- a compound of formula (I) as defined in embodiments 1) to 33);
- and one or more cytotoxic chemotherapy agents.

5 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) as defined in embodiments 1) to 33);

- and instructions how to use said pharmaceutical composition for the prevention or the
10 treatment of a cancer (especially of a malignant glioma, in particular of a glioblastoma multiforme), in combination with chemotherapy and / or radiotherapy and / or targeted therapy.

The terms "radiotherapy" or "radiation therapy" or "radiation oncology", refer to the medical use of ionizing radiation in the prevention (adjuvant therapy) and / or treatment of cancer;

15 including external and internal radiotherapy.

The term "targeted therapy" refers to the prevention (adjuvant therapy) and / or treatment of cancer with one or more anti-neoplastic agents such as small molecules or antibodies which attack specific types of cancer cells with less harm to normal cells. Some targeted therapies block the action of certain enzymes, proteins, or other molecules involved in the growth and
20 spread of cancer cells. Other types of targeted therapies help the immune system kill cancer cells (immunotherapies); or deliver toxic substances directly to cancer cells and kill them.

The term "chemotherapy" refers to the treatment of cancer with one or more cytotoxic anti-neoplastic agents ("cytotoxic chemotherapy agents"). Chemotherapy is often used in conjunction with other cancer treatments, such as radiation therapy or surgery. The term
25 especially refers to conventional chemotherapeutic agents which act by killing cells that divide rapidly, one of the main properties of most cancer cells. Chemotherapy may use one drug at a time (single-agent chemotherapy) or several drugs at once (combination chemotherapy or polychemotherapy). Chemotherapy using drugs that convert to cytotoxic activity only upon light exposure is called photochemotherapy or photodynamic therapy.

30 The term "cytotoxic chemotherapy agent" or "chemotherapy agent" as used herein refers to an active anti-neoplastic agent inducing apoptosis or necrotic cell death. When used in combination with the compounds of formula (I), the term especially refers to conventional cytotoxic chemotherapy agents such as:

- a) alkylating agents (for example mechlorethamine, chlorambucil, cyclophosphamide, ifosfamide, streptozocin, carmustine, lomustine, melphalan, busulfan, dacarbazine, temozolomide, thiotepa or altretamine);
- b) platinum drugs (for example cisplatin, carboplatin or oxaliplatin);
- 5 c) antimetabolite drugs (for example 5-fluorouracil, capecitabine, 6-mercaptopurine, methotrexate, gemcitabine, cytarabine, fludarabine or pemetrexed);
- d) anti-tumor antibiotics (for example daunorubicin, doxorubicin, epirubicin, idarubicin, actinomycin-D, bleomycin, mitomycin-C or mitoxantrone);
- e) mitotic inhibitors (for example paclitaxel, docetaxel, ixabepilone, vinblastine, vincristine, 10 vinorelbine, vindesine or estramustine); or
- f) topoisomerase inhibitors (for example etoposide, teniposide, topotecan, irinotecan, diflomotecan or elomotecan).

When used in combination with the compounds of formula (I), preferred cytotoxic chemotherapy agents are the above-mentioned alkylating agents (notably mechlorethamine, chlorambucil, cyclophosphamide, ifosfamide, streptozocin, carmustine, lomustine, 15 melphalan, busulfan, dacarbazine, 3-methyl-(triazene-1-yl)imidazole-4-carboxamide (MTIC) and prodrugs thereof such as especially temozolomide, thiotepa, altretamine; or pharmaceutically acceptable salts of these compounds; in particular temozolomide); and mitotic inhibitors (notably paclitaxel, docetaxel, ixabepilone, vinblastine, vincristine, 20 vinorelbine, vindesine, estramustine; or pharmaceutically acceptable salts of these compounds; in particular paclitaxel). Most preferred cytotoxic chemotherapy agents to be used in combination with the compounds of formula (I) or (II) are those routinely used in the treatment of glioblastoma multiforme, in particular temozolomide. Equally preferred is radiotherapy.

25 Chemotherapy may be given with a curative intent or it may aim to prolong life or to palliate symptoms.

- a) Combined modality chemotherapy is the use of drugs with other cancer treatments, such as radiation therapy or surgery.
- b) Induction chemotherapy is the first line treatment of cancer with a chemotherapeutic 30 drug. This type of chemotherapy is used for curative intent.
- c) Consolidation chemotherapy is the given after remission in order to prolong the overall disease free time and improve overall survival. The drug that is administered is the same as the drug that achieved remission.
- d) Intensification chemotherapy is identical to consolidation chemotherapy but a different 35 drug than the induction chemotherapy is used.

- e) Combination chemotherapy involves treating a patient with a number of different drugs simultaneously. The drugs differ in their mechanism and side effects. The biggest advantage is minimising the chances of resistance developing to any one agent. Also, the drugs can often be used at lower doses, reducing toxicity.
- 5 f) Neoadjuvant chemotherapy is given prior to a local treatment such as surgery, and is designed to shrink the primary tumor. It is also given to cancers with a high risk of micrometastatic disease.
- g) Adjuvant chemotherapy is given after a local treatment (radiotherapy or surgery). It can be used when there is little evidence of cancer present, but there is risk of recurrence. It is also useful in killing any cancerous cells that have spread to other parts of the body. These micrometastases can be treated with adjuvant chemotherapy and can reduce relapse rates caused by these disseminated cells.
- 10 h) Maintenance chemotherapy is a repeated low-dose treatment to prolong remission.
- i) Salvage chemotherapy or palliative chemotherapy is given without curative intent, but simply to decrease tumor load and increase life expectancy. For these regimens, a better toxicity profile is generally expected.
- 15

When combined with the compounds of formula (I), preventive or curative forms of chemotherapy (or *mutatis mutandis*: radiotherapy) such as those listed under a), b) c), d), e), and especially g) and / or h) above are preferred.

- 20 "Simultaneously" or "simultaneous", when referring to an administration type, means in the present application that the administration type concerned consists in the administration of two or more active ingredients by the same route and at the same time.

- "Separately" or "separate", when referring to an administration type, means in the present application that the administration type concerned consists in the administration of two or more active ingredients at approximately the same time by at least two different routes. For example when used in combination with radiotherapy, the present CXCR7 modulators would be used "separately".
- 25

- By administration "over a period of time" is meant in the present application the administration of two or more active ingredients / or of one or more active ingredients in combination with radiotherapy treatment, at different times. In a sub-embodiment, the term refers to an administration method according to which the entire administration of one of the active ingredients and / or of the radiotherapy treatment, is completed before the administration of the other / the others begins. In this way it is possible to administer one of the active ingredients / to use radiotherapy, for several months before administering the other
- 30

active ingredient or ingredients. Administration "over a period of time" encompasses situations wherein the active ingredients are not given with the same periodicity (e.g. wherein one active ingredient is given once a day and another is given once a week).

Administration "over a period of time" also encompasses situations wherein the CXCR7 modulators of formula (I) would be used in a treatment that starts after an initial chemotherapeutic or radiotherapeutic treatment (for example an induction chemotherapy), optionally in combination with a further / an ongoing chemotherapeutic or radiotherapeutic treatment (for example in combination with a consolidation chemotherapy, an intensification chemotherapy, an adjuvant chemotherapy, or a maintenance chemotherapy; or radiotherapeutic equivalents thereof); wherein such further / ongoing chemotherapeutic or radiotherapeutic treatment would be simultaneously, separately, or over a period of time in the sense of "not given with the same periodicity".

The compounds of formula (I) as defined in embodiments 1) to 33) are also useful in a method of treating tumors comprising administering an effective amount of the compound of formula (I) wherein said administration leads to a change of tumor properties, and wherein said modification is achieved by modulating the CXCL12 receptor pathway; wherein said treatment may optionally be effected in combination with a conventional chemotherapeutic or radiotherapeutic treatment (in which case the tumor is notably a malignant glioma, in particular a glioblastoma multiforme). Such combined treatment may be effected simultaneously, separately, or over a period of time.

The compounds of formula (I) as defined in embodiments 1) to 33) are also useful in a method of modulating an immune response comprising the administration of an effective amount of the compound of formula (I) wherein said effective amount modulates an inflammatory disease and wherein said response is mediated by the CXCL12 receptor pathway.

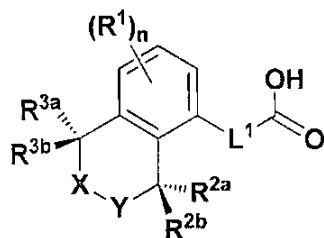
Besides, any preferences and (sub-)embodiments indicated for the compounds of formula (I) (whether for the compounds themselves, salts thereof, compositions containing the compounds or salts thereof, or uses of the compounds or salts thereof, etc.) apply *mutatis mutandis* to compounds of formula (II),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

Preparation of compounds of Formula (I)

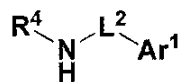
An embodiment of the invention is a process for the preparation of compounds of Formula (I). Compounds according to Formula (I) of the present invention can be prepared from commercially available or well known starting materials according to the methods described in the experimental part, by analogous methods; or according to the general sequence of reactions outlined below, wherein R^1 , R^{2a} , R^{2b} , R^{3a} , R^{3b} , R^4 , L^1 , L^2 , X , Y and Ar^1 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 R^1 , R^{2a} , R^{2b} , R^{3a} , R^{3b} , R^4 , L^1 , L^2 , X , Y and Ar^1 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*.

Amide coupling as last step

Generally examples of Formula (I) are obtained from a carboxylic acid precursor of Structure 1 and an amine of Structure 2 using HATU or another amide coupling reagent in a solvent such as DCM or DMF at room temperature or 0°C in the presence of a base like TEA or DIPEA.



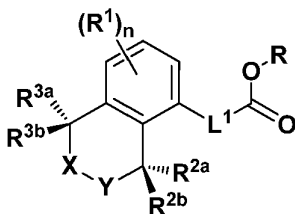
Structure 1



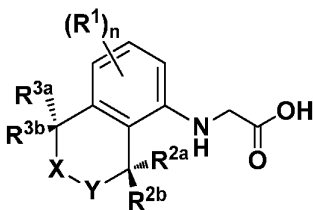
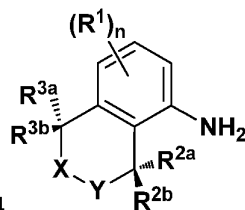
Structure 2

Preparation of compounds of Structure 1

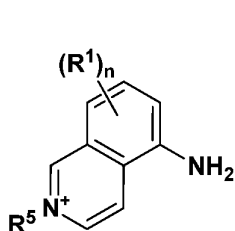
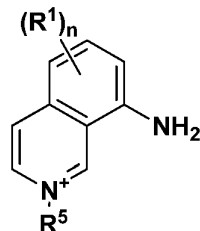
Compounds of Structure 1 are made by ester cleavage of a compound of Structure 3 in which R represents a *tert*-Butyl, Ethyl, Methyl group or the like. In a typical reaction a compound of Structure 3 is stirred with a base such as aq. NaOH soln. or aq. LiOH soln. in a solvent such as EtOH, MeOH or THF at room temperature or reflux. In an alternative method, in particular if R is a *tert*-butyl group a compound of Structure 3 is stirred in DCM at room temperature in the presence of TFA to give a compound of Structure 1.

**Structure 3**

Compounds of Structure 4 which represent a particular case of compounds of Structure 1 can be made by reaction of a compound of Structure 5 with glyoxylic acid monohydrate in presence of NaBH_3CN in a solvent such as MeOH or the like.

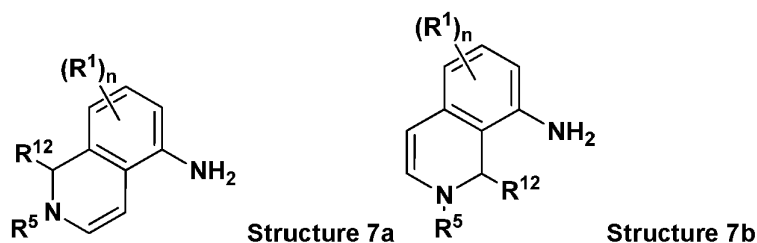
**Structure 4****Structure 5**

In a particular case wherein R^{2a} , R^{2b} , R^{3a} and R^{3b} represent H, compounds of Structure 5 can be synthesized from the corresponding 5- or 8-aminoisoquinoline derivatives via a two steps sequence. Thus a 5- or 8-aminoisoquinoline is then reacted with a reagent of type R^5LG wherein LG represents a leaving group such as Cl, Br, I, OMs or the like in an alkylation reaction well known by a person skilled in the art. In such a reaction a 5- or 8-aminoisoquinoline is dissolved in a solvent such as MeCN, dioxane, DMF or the like in presence of a reagent of type R^5LG and a base such as TEA, DIPEA, K_2CO_3 or the like at room temperature, or at elevated temperature up to reflux to yield a compound of Structure 6a or a compound of Structure 6b respectively. In the next step a compound of Structure 6a or a compound of Structure 6b is reduced by NaBH_4 or Pd/C or the likes in a solvent such as MeOH, EtOH containing or not water and AcOH to yield a compound of Structure 5. In some instances the transformation from a compound of Structure 6a or 6b to a compound of Structure 4 can be made in a one pot – two steps reaction sequence using palladium on charcoal as a catalyst under a pressure of hydrogen gas from 1 to 10 bar.

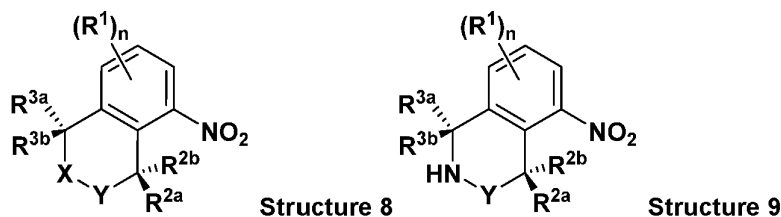
**Structure 6a****Structure 6b**

In a particular case compounds of Structure 5 wherein $\text{X}=\text{NR}^5$ and either one of R^{3a} or R^{3b} but not both represents an alkyl group and respectively wherein $\text{Y}=\text{NR}^5$ and either one of R^{2a} or R^{2b} but not both represents an alkyl group, a compound of Structure 6a or 6b respectively

can be reacted with a Grignard reagent of type $R^{12}MgCl$ or $R^{12}MgBr$ in a solvent such as ether or THF to give a compound of Structure 7a and 7b respectively. These compounds can then be reduced in a solvent such as MeOH or EtOH with a reducing agent such as $NaBH_4$ at room temperature to give special cases of compounds of Structure 5. In this particular case R^{12} represents one of R^{3a} , R^{3b} , R^{2a} or R^{2b} .



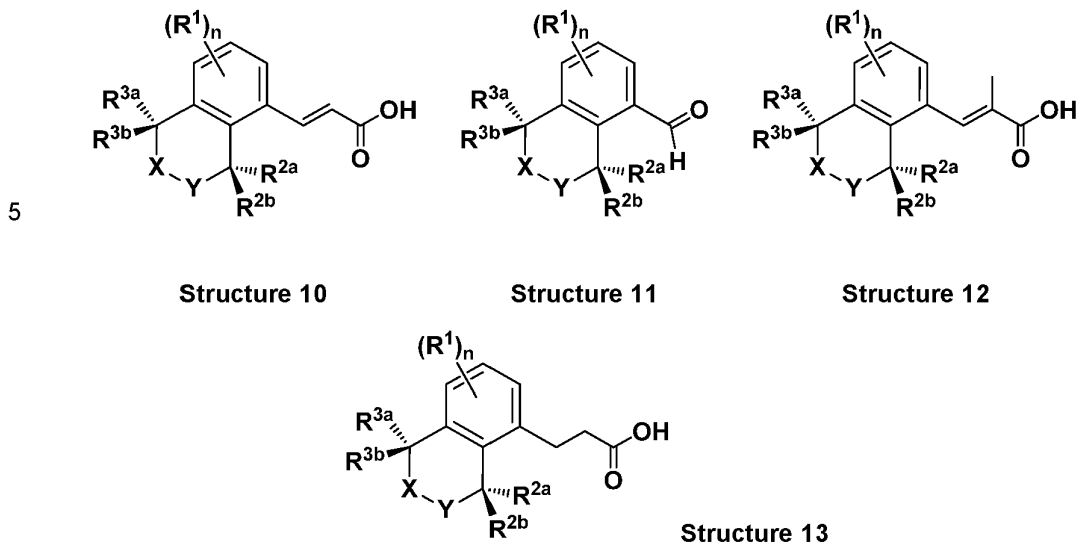
In a particular case a compound of Structure 5 can be made from a compound of Structure 8. In a typical experiment a compound of Structure 8 is reduced with Pd/C in a solvent such as EtOH, THF, EtOAc or the like at RT in presence of H_2 or with the help of an H-Cube® hydrogen generator. Alternatively a compound of Structure 5 can be obtained from a compound of Structure 8 by reaction with $SnCl_2$ in a solvent such as DMF or EtOH well known by a person skilled in the art.



A compound of Structure 8 is commercially available or can be obtained from a compound of Structure 9 by reductive amination using an aldehyde or a ketone of type $R^{13}R^{14}CO$ and a reducing agent such as $NaBH(OAc)_3$, $NaBH_4$ or $NaBH_3CN$ or the like in a solvent such as MeOH, EtOH, DCM, or the like. In this case R^5 corresponds to $R^{13}R^{14}CH$. In case X represents NBoc, a compound of Structure 8 can be obtained from a compound of Structure 9 by reaction with Boc anhydride in THF, DCM or water in a presence or absence of a base.

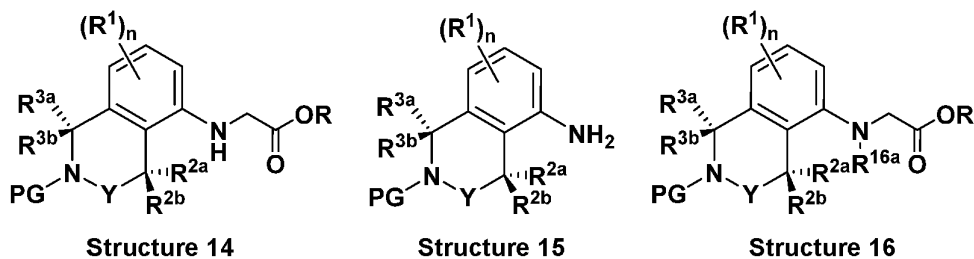
Compounds of Structure 10 which represent a particular case of compounds of Structure 1 can be made by Knoevenagel condensation / decarboxylation sequence of a starting material of Structure 11 with malonic acid in a mixture of pyridine and piperidine used as solvents in a reaction well known by a person skilled in the art. Similarly compounds of Structure 12 which represent a particular case of compounds of Structure 1 can be made by Perkin condensation of a starting material of Structure 11 using propionic anhydride and NaOAc without any solvent at temperature between 150 and 200°C. Compounds of Structure 13 which represent a particular case of compounds of Structure 1 can be made by catalytic

hydrogenation of compounds of Structure 10. In a typical experiment well known by a person skilled in the art a compound of Structure 10 is dissolved in MeOH, EtOH or the like in presence or absence of AcOH, then Pd / C is added and the resulting suspension stirred vigorously under an atmosphere of H₂.



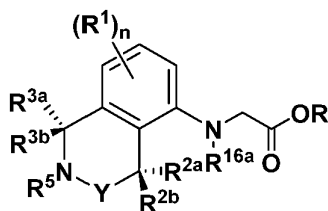
Preparation of compounds of Structure 3

- 10 In case R⁵ represents a group (PG) such as a Boc or a Cbz group then compounds of Structure 14 which are a particular case of compounds of Structure 3 can be made from compounds of Structure 15 which are a particular case of compounds of Structure 5 and are described in the literature or commercially available. Thus a compound of Structure 15 is reacted with an alkylbromoacetate such as ethylbromoacetate in a solvent such as acetonitrile, in presence of a base such as TEA or DIPEA at room temperature.
- 15

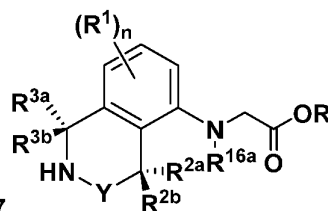


- Compound of Structure 14 can be substituted to form the corresponding compound of Structure 16 which are also particular cases of compounds of Structure 3 by reaction with an aldehyde of type R¹⁵CHO in a solvent such as DCM in presence of AcOH and a reducing agent such as NaBH(OAc)₃. In this case R^{16a} corresponds to the group R¹⁵CH₂.
- 20 In case R⁵ represents an alkyl, halogenoalkyl, cycloalkyl or cycloalkylalkyl group then a compound of Structure 17 which is a particular case of compounds of Structure 3 can be

made in a two-step procedure from a compound of Structure 16. Hence a compound of Structure 16 dissolved in a solvent such as DCM or the like is reacted with TFA or with a solution of HCl in dioxane at room temperature to give a compound of Structure 18 or its corresponding HCl or TFA salt. The compound of structure 18 is then reacted with an reagent of type R^5LG wherein LG represents a leaving group such as Cl, Br, I, OMs, OTf or the like in an alkylation reaction well known by a person skilled in the art. In such a reaction a compound of Structure 18 is dissolved in a solvent such as MeCN, dioxane, DMF or the like in presence of a reagent of type R^5LG and a base such as TEA, DIPEA, K_2CO_3 or the like at room temperature, or at elevated temperature up to reflux. A compound of Structure 18 can also be reacted with an aldehyde or a ketone of type $R^{13}R^{14}C=O$ in a solvent such as MeOH, EtOH and a reducing agent such as $NaBH_4$, $NaBH(OAc)_3$, $NaBH_3CN$ or the like at room temperature. In this case a compound of Structure 17 wherein R^5 corresponds to $R^{13}R^{14}CH$ is obtained.

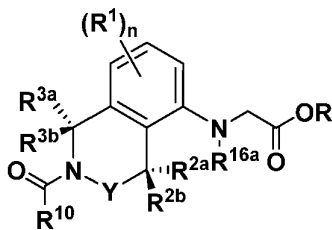


Structure 17

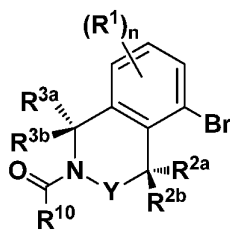


Structure 18

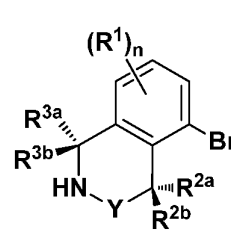
A compound of Structure 19 which is a particular case of compounds of Structure 3 can be made from a compound of Structure 18. In a typical reaction procedure, a compound of Structure 18 is dissolved in a solvent such as DCM, THF or water is reacted with acid chloride or chloroformate $R^{10}COCl$ and a base such as NaOH, K_2CO_3 , TEA or DIPEA at $0^\circ C$ to room temperature, according to a procedure known to a person skilled in the art. Compounds of Structure 17 wherein R^{16a} represents H can also be made from compounds of Structure 20 following a Buchwald-Hartwig type reaction wherein a compound of Structure 20 is reacted with a glycine alkyl ester hydrochloride salt in the presence of a base such as K_2CO_3 , Cs_2CO_3 , $tBuOK$ and ligand such as BINAP or the like and a palladium reagent such as $Pd_2(dba)_3$, $Pd(PPh_3)_4$ or the like in a solvent such as toluene, dioxane or DMF at a temperature between 60 and $120^\circ C$.



Structure 19



Structure 20



Structure 21

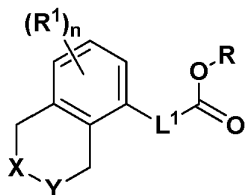
Compounds of Structure 20 can be obtained by reaction of a starting material of Structure 21 dissolved in a solvent such as DCM, THF or water with an acid chloride or chloroformate $R^{10}COCl$ and a base such as NaOH, K_2CO_3 , TEA or DIPEA at $0^\circ C$ to room temperature, according to a procedure known to a person skilled in the art.

- 5 Following another procedure, compounds of Structure 22. Which are a particular case of compounds of Structure 3, can be made from compounds of Structure 23a or 23b. In such a procedure a compound of Structure 23a or 23b is allowed to react with a reagent of type R^5LG wherein LG represents a leaving group such as Cl, Br, I, OMs or the like in an alkylation reaction well known by a person skilled in the art. In such a reaction a compound
- 10 of Structure 23a or 23b is dissolved in a solvent such as MeCN, dioxane, DMF or the like in presence of a reagent of type R^5LG and a base such as TEA, DIPEA, K_2CO_3 or the like at room temperature, or at elevated temperature up to reflux to yield a compound of Structure 24a or 24b. Then a compound of Structure 24a or 24b is reduced by $NaBH_4$ in a solvent such as MeOH or EtOH in the presence or the absence of water. Alternatively this last step can be
- 15 carried out in the presence of H_2 with a metal catalyst, especially with Pd / C.

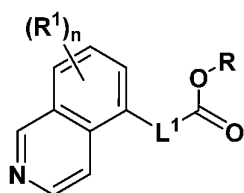
Following yet another procedure, the two steps described for the synthesis of a compound of Structure 22 from a compound of Structure 23a or 23b can be inverted. In a first step a compound of Structure 23a or 23b can be reduced by use of PtO_2 in a solvent such as AcOH or EtOH in presence of an acid under catalytic hydrogenation conditions to yield a compound

20 of Structure 25a or 25b respectively. Then a compound of Structure 25a or 25b can be reacted with:

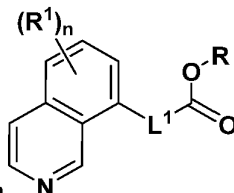
- an aldehyde or a ketone of type $R^{13}R^{14}CO$ and a reducing agent such as $NaBH(OAc)_3$, $NaBH_4$ or $NaBH_3CN$ or the like in a solvent such as MeOH, EtOH, DCM, or the like. In this case R^5 corresponds to $R^{13}R^{14}CH$
- 25 • a carboxylic acid of type $R^{10}C(O)OH$ in a solvent such as DMF or DCM or a mixture of both with a coupling reagent such as HATU or the like with or without a base such as DIPEA or TEA at a temperature between $0^\circ C$ and RT. In this case a compound of Structure 22 wherein R^5 corresponds to $R^{10}CO$ is obtained.



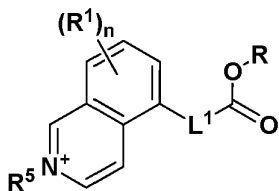
Structure 22



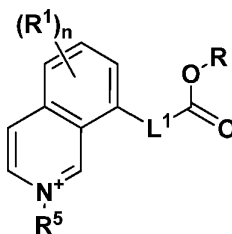
Structure 23a



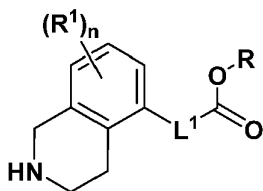
Structure 23b



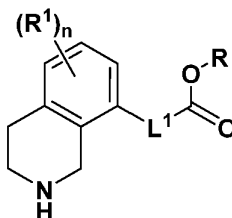
Structure 24a



Structure 24b

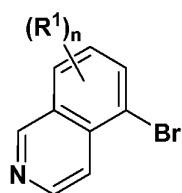


Structure 25a

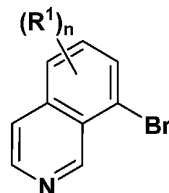


Structure 25b

- Compounds of Structure 23a or 23b are easily accessible from known procedures or are commercially available. In a particular case wherein L^1 represents $-NHCH_2-$, $-NHCHR^{16a}-$ or $-NHCHR^{16b}R^{16c}-$, compounds of Structure 23a or 23b can be obtained by reaction of a compound of Structure 26a or 26b respectively following a Buchwald-Hartwig type reaction wherein a starting material of Structure 27 is reacted with a glycine alkyl ester hydrochloride salt in the presence of a base such as K_2CO_3 , Cs_2CO_3 , $tBuOK$ and ligand such as BINAP or the like and a palladium reagent such as $Pd_2(dba)_3$, $Pd(PPh_3)_4$ or the like in a solvent such as toluene, dioxane or DMF at a temperature between 60 and 120°C.



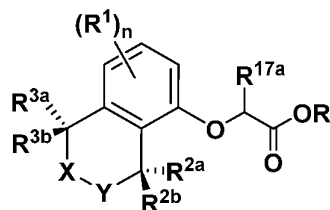
Structure 26a



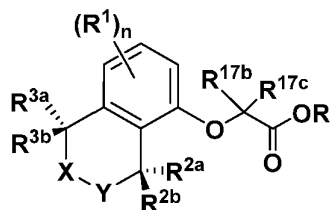
Structure 26b

- Compounds of Structure 27a and 27b which are a particular case of compounds of Structure 3 can be obtained from commercially available compounds of Structure 28. In an alkylation reaction well known to a person skilled in the art, a starting material of Structure 28 is dissolved in acetone, MeCN, THF or the like and reacted at a temperature between 40 and 80°C with a reagent of type $R^{17a}CH(Br)CO_2R$ or $R^{17b}R^{17c}C(Br)CO_2R$ respectively in

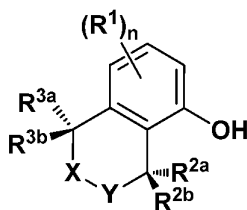
presence of a base such as TEA, DIPEA, or K_2CO_3 or the like to yield a compound of Structure 27.



Structure 27a



Structure 27b

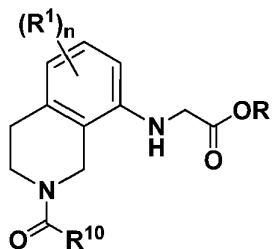


Structure 28

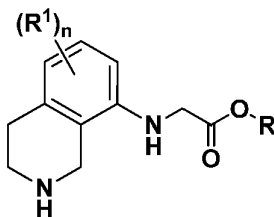
5

Compounds of Structure 29 which are a particular case of compounds of Structure 22 and as such a particular case of compounds of Structure 3 can be made from compounds of Structure 30. Typically a compound of Structure 30 is dissolved in DCM or THF and reacted with:

- 10 • one equivalent of an aldehyde or a ketone of type $R^{13}R^{14}C=O$ in a solvent such as MeOH, EtOH with addition of water and a reducing agent such as $NaBH_4$, $NaBH(OAc)_3$, $NaBH_3CN$ or the like at room temperature with or without addition of a dehydrating agent such as $ZnCl_2$. In this case a compound of Structure 29 wherein R^5 corresponds to $R^{13}R^{14}CH$ is obtained.
- 15 • an acetyl chloride or a chloroformate of type $R^{10}C(O)Cl$, alternatively an anhydride of type $R^{10}C(O)OC(O)R^{10}$ in a solvent such as DCM or THF or the like with a base such as TEA or DIPEA at a temperature between $0^\circ C$ and room temperature. Or alternatively a carboxylic acid of type $R^{10}C(O)OH$ in a solvent such as DMF, DCM or a mixture of both with a coupling reagent such as HATU and the like and a base such as TEA or DIPEA. In this case a compound of Structure 29 wherein R^5 corresponds to $R^{10}CO$ is obtained.
- 20 • a reagent of type R^5LG wherein LG represents a leaving group such as a Br or Cl atom, a methanesulfonate or a trifluoromethanesulfonate group in a solvent such as DMF, MeCN or THF with a base such as TEA or DIPEA or the like.

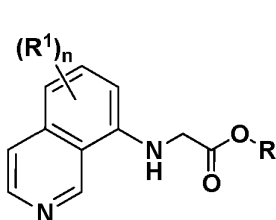


Structure 29

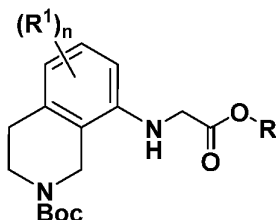


Structure 30

Compounds of Structure 30 can be made from compounds of Structure 31 by a reduction reaction following a method already described for the synthesis of compounds of Structure 25a and 25b from compounds of Structure 23a or 23b respectively. Compounds of Structure 31 are a particular case of compounds of Structure 23a and 23b and are made following the method described for their syntheses. Alternatively compounds of Structure 30 or salts thereof can be made from the corresponding compounds of Structure 32 according to a Boc cleavage reaction wherein a compound of Structure 32 is dissolved in DCM and reacted with TFA or HCl soln. in dioxane. Compounds of Structure 32 are a particular case of compounds of Structure 29.



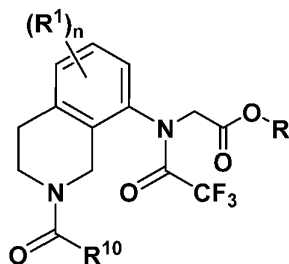
Structure 31



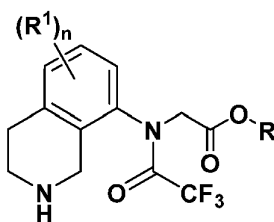
Structure 32

Compounds of Structure 29 can alternatively be made from compounds of Structure 32 over 4 steps. First a compound of Structure 32 is protected on the anilinic N-atom by a TFA amide formation following a reaction wherein a compound of Structure 32 is dissolved in DCM together with a base such as TEA or DIPEA followed by trifluoroacetic anhydride at 0°C to room temperature to yield a compound of Structure 35. The Boc protecting group of a compound of Structure 35 is then removed in DCM or dioxane or a mixture of both by reaction with TFA or HCl soln. in dioxane to give a compound of Structure 34 or a salt thereof. A compound of Structure 33 is then obtained from a compound of Structure 34 by a reaction analogous to the formation of a compound of Structure 29 from a compound of Structure 30. In the last step, the compound of Structure 33 obtained is reacted in a mixture of MeOH or EtOH and water with a base such as K₂CO₃, Na₂CO₃ or the like at elevated temperature between 50 and 100°C to give a compound of Structure 29 following a method of deprotection of trifluoroacetamide well known from a person skilled in the art.

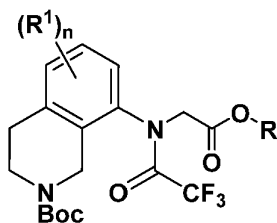
88



Structure 33



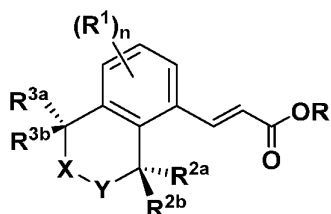
Structure 34



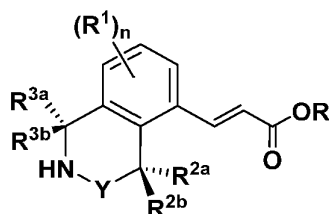
Structure 35

Compounds of Structure 36 which are particular cases of compounds of Structure 3 can be made from compounds of Structure 39 (which are a particular case of compounds of Structure 10) in three steps. Hence a compound of Structure 39 can be esterified to give a compound of Structure 38 by reaction with ethyl iodide in a solvent such as MeCN with a base such as Cs₂CO₃ or the like at a temperature above RT for example 55°C. A compound a Structure 37 can be obtained from a compound of Structure 38 by a classical Boc cleavage reaction well known by a person skilled in the art. Finally a compound of Structure 36 is obtained after reaction with:

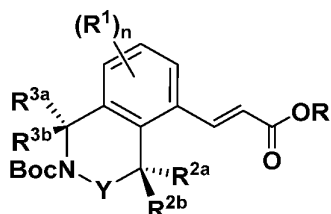
- a reagent of type R⁵LG wherein LG represents a leaving group such as a Br or Cl atom, a methanesulfonate or a trifluoromethanesulfonate group in a solvent such as DMF, MeCN or THF with a base such as TEA or DIPEA or the like.
- one equivalent of an aldehyde or a ketone of type R¹³R¹⁴C=O in a solvent such as MeOH, EtOH with addition of water and a reducing agent such as NaBH₄, NaBH(OAc)₃, NaBH₃CN or the like at room temperature with or without addition of a dehydrating agent such as ZnCl₂. In this case a compound of Structure 36 respectively wherein R⁵ corresponds to R¹³R¹⁴CH is obtained.
- a carboxylic acid of type R¹⁰C(O)OH in a solvent such as DMF, DCM or a mixture of both with a coupling reagent such as HATU and the like and a base such as TEA or DIPEA. In this case a compound of Structure 36 respectively wherein R⁵ corresponds to R¹⁰CO is obtained.



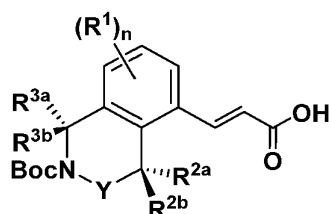
Structure 36



Structure 37

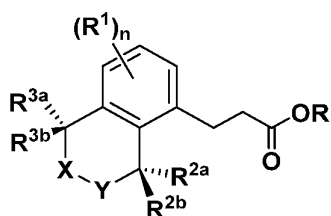


Structure 38

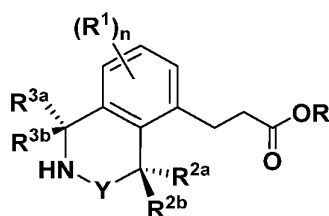


Structure 39

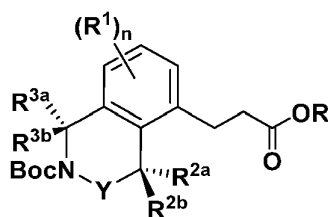
- 5 In analogy, compounds of Structure 40 which are particular cases of compounds of Structure 3 can be made from compounds of Structure 38. Hence a compound of Structure 38 can be reduced with palladium on charcoal in a catalytic hydrogenation reaction procedure well known by a person skilled in the art to give a compound of Structure 42. A compound a
- 10 Structure 41 can be obtained from a compound of Structure 42 by a classical Boc cleavage reaction with TFA or HCl soln. in dioxane in a solvent such as DCM or dioxane. Finally a compound of Structure 40 is obtained after reaction with a reagent of type R⁵LG wherein LG represents a leaving group such as a Br or Cl atom, a methanesulfonate or a trifluoromethanesulfonate group in a solvent such as DMF, MeCN or THF with a base such as TEA or DIPEA or the like.



Structure 40

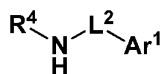


Structure 41



Structure 42

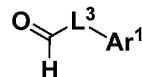
Synthesis of compounds of Structure 2



Structure 2

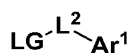


Structure 43



Structure 44

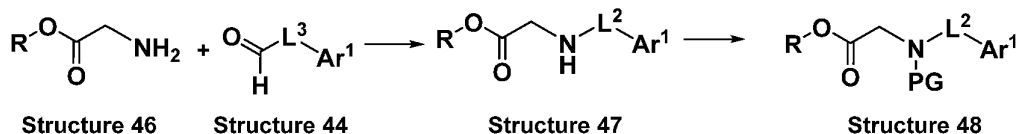
Compounds of Structure 2 are commercially available or are made by condensation of a
 5 primary amine of Structure 43 with an aldehyde of Structure 44 in a typical reductive
 amination reaction with a reducing agent such as $\text{NaBH}(\text{OAc})_3$, NaBH_3CN or NaBH_4 in a
 solvent such as THF, DCM, MeOH, water or the like at temperatures between 0°C and
 reflux, preferentially at room temperature. In this case L^2 corresponds to $-\text{CH}_2-\text{L}^3$.



Structure 45

10

Compounds of Structure 2 can also be obtained by condensation of an amine of Structure 43
 and a compound of Structure 45 with LG = halogen like Cl, Br or I in a solvent such as EtOH,
 MeOH, THF, or dioxane at temperatures between 0°C and reflux, preferentially at refluxing
 temperature in the presence of NaI in the case of LG = halogen like Cl or Br.

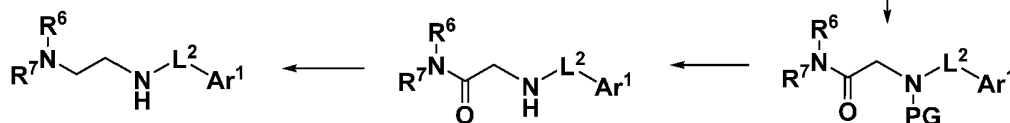


Structure 46

Structure 44

Structure 47

Structure 48



Structure 51

Structure 50

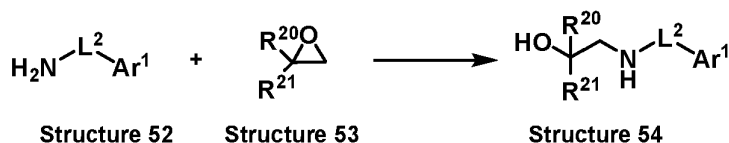
Structure 49

15

Reaction Scheme A

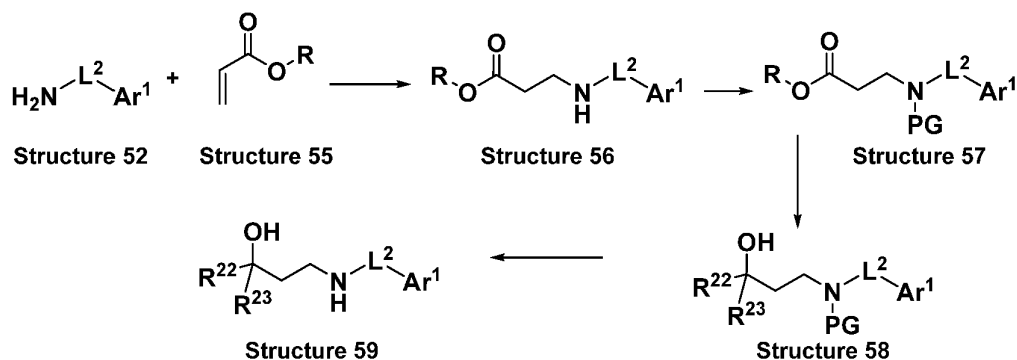
Compounds of Structure 51 which represents a particular case of compounds of Structure 2
 may alternatively be prepared as illustrated in reaction Scheme A. An aminoester of
 Structure 46 is alkylated by treatment with an aldehyde of Structure 44 in a typical reductive
 20 amination reaction with a reducing agent such as $\text{NaBH}(\text{OAc})_3$, NaBH_3CN or NaBH_4 in a
 solvent such as THF, DCM, MeOH, water or the like at temperatures between 0°C and
 reflux, preferentially at room temperature. The aminoester of Structure 47 can be protected
 by treatment with di-*tert*-butyl dicarbonate in the presence of a base like DIPEA or TEA in a
 solvent like DCM, AcOEt, dioxane or THF to give the N-protected amine of Structure 48.
 25 Transformation of the ester of Structure 48 into the amide of Structure 49 involves treatment

of the N-protected amine of Structure 48 with the *in situ* prepared dimethylaluminum amide resulting from the reaction of a trialkyl aluminium compound like trimethyl aluminium with an amine HNR^6R^7 in a solvent like toluene, DCM or DCE at temperatures between RT and reflux. During this reaction the N-protecting group can be spontaneously cleaved or it as to be removed by treatment with an acid like hydrochloric acid or trifluoroacetic acid in a solvent like MeOH or dioxane. An amine of Structure 50 can be directly used for the preparation of compounds of Structure 1 as it represents a particular case of compounds of Structure 2. Otherwise, reduction of the amide group of a compound of Structure 50 by treatment with a reducing agent like diborane in THF at temperatures between RT and reflux deliver compounds of Structure 51.



Reaction Scheme B

Compounds of Structure 54 which are particular compounds of Structure 2 can also be obtained as illustrated in reaction Scheme B. Thus, by condensation of an amine of Structure 52 and a mono or disubstituted epoxide of Structure 53 in a polar aprotic solvent like MeCN in the presence of calcium trifluoromethanesulfonate at room temperature.



Reaction Scheme C

Compounds of Structure 59 which are particular examples of compounds of Structure 2 may alternatively be prepared as illustrated in reaction Scheme C. An amine of Structure 52 is alkylated by treatment with an acryl ester of Structure 55 in a typical Michael addition reaction in a solvent such as MeOH or EtOH or the like at temperatures between 0°C and reflux, preferentially at room temperature. The aminoester of Structure 56 can be protected by treatment with di-*tert*-butyl dicarbonate in the presence of a base like DIPEA or TEA in a solvent like DCM, AcOEt, dioxane or THF to give the N-protected amino ester of Structure

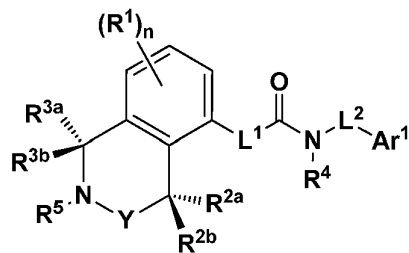
57. Transformation of the protected amino ester of Structure 57 into the amino alcohol of Structure 58 involves treatment of the N-protected amine of Structure 57 with an organometallic species like an alkyl magnesium halogenide or alkyl lithium like methyl lithium in a solvent like diethyl ether, THF or dioxane at temperatures between -78°C and room temperature. The protected amide of Structure 58 is then Boc-protected by treatment with an acid, preferentially 4M HCl in dioxane or with TFA in DCM to give the corresponding amine of Structure 59.

Alkylation, acylation, urea formation, carbamoylation (event- TFA amide cleavage) as last step

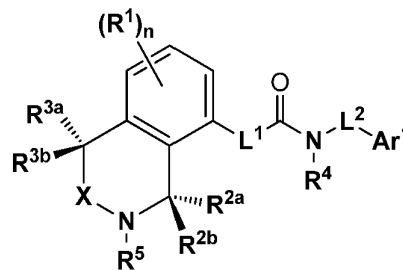
- 10 Compounds of Structure 60a or 60b which represent particular cases of compounds of Formula (I) can be obtained directly from compounds of Structure 61a or 61b respectively.

Thus a compound of Structure 61a or 61b is reacted in the first step with either:

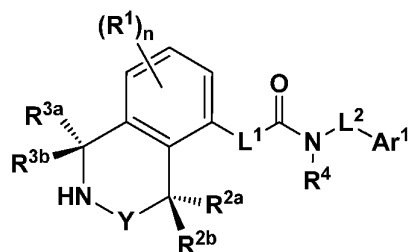
- one equivalent of an aldehyde or a ketone of type $R^{13}R^{14}C=O$ in a solvent such as MeOH, EtOH with addition of water and a reducing agent such as $NaBH_4$, $NaBH(OAc)_3$, $NaBH_3CN$ or the like at room temperature with or without addition of a dehydrating agent such as $ZnCl_2$. In this case a compound of Structure 60a or 60b respectively wherein R^5 corresponds to $R^{13}R^{14}CH$ is obtained.
- an acetyl chloride or a chloroformate of type $R^{10}C(O)Cl$ in a solvent such as DCM or THF or the like with a base such as TEA or DIPEA at a temperature between 0°C and room temperature. Or alternatively a carboxylic acid of type $R^{10}C(O)OH$ in a solvent such as DMF, DCM or a mixture of both with a coupling reagent such as HATU and the like and a base such as TEA or DIPEA. In this case a compound of Structure 60a or 60b respectively wherein R^5 corresponds to $R^{10}CO$ is obtained.
- an isocyanate of type $R^{24}NCO$ wherein R^{24} represents an alkyl group such as ethyl, in a solvent such as DCM with a base such as TEA or DIPEA at a temperature between 0°C and room temperature. In this case a compound of Structure 60a or 60b respectively wherein R^5 corresponds to $R^{10}CO$, wherein R^{10} represents $R^{10a}R^{10b}N$ wherein R^{10a} represents R^{24} and R^{10b} represents H is obtained.
- a sulfonyl chloride of type $R^{11}SO_2Cl$ in a solvent such as DCM with a base such as TEA or DIPEA a compound of Structure 60a or 60b respectively is obtained with R^5 corresponding to $R^{11}SO_2$.
- a reagent of type R^5LG wherein LG represents a leaving group such as a Br or Cl atom, a methanesulfonate or a trifluoromethanesulfonate group in a solvent such as DMF, MeCN or THF with a base such as TEA or DIPEA or the like.



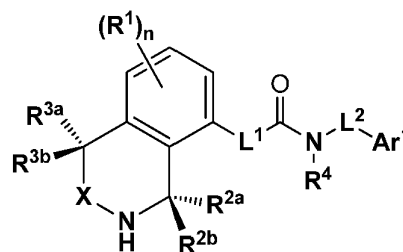
Structure 60a



Structure 60b



Structure 61a

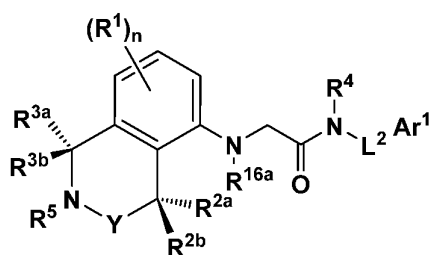


Structure 61b

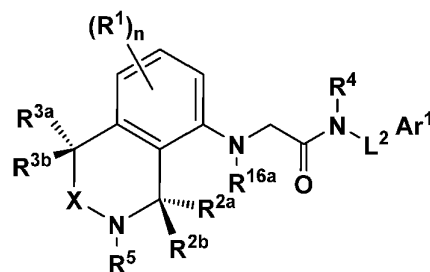
5

In case R^{16a} is not H, compounds of Structure 62a or 62b which are a particular case of compounds of Formula (I) can be prepared from compounds of Structure 63a and 63b respectively which are particular cases of compounds of Structure 61a and 61b respectively. Following a typical procedure, a compound of Structure 62a or 62b can be obtained by reaction of a compound of Structure 63a or 63b respectively with several equivalents of an aldehyde or a ketone of type $R^{13}R^{14}C=O$ in a solvent such as MeOH, EtOH with addition of water and a reducing agent such as $NaBH_4$, $NaBH(OAc)_3$, $NaBH_3CN$ or the like at room temperature. In this case a compound of Structure 62a or 62b wherein R^5 is equal to R^{16a} corresponding to $R^{13}R^{14}CH$ is obtained.

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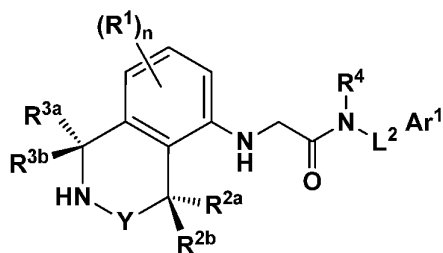


Structure 62a

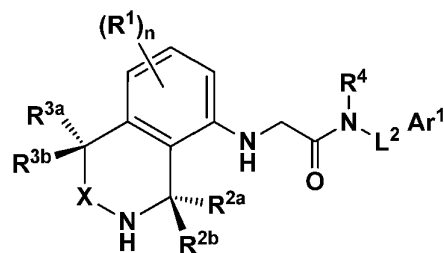


Structure 62b

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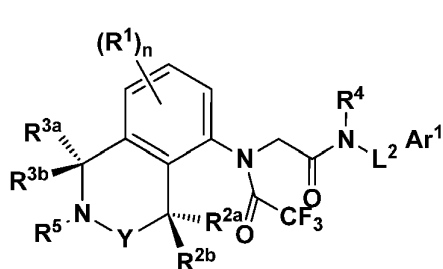


Structure 63a

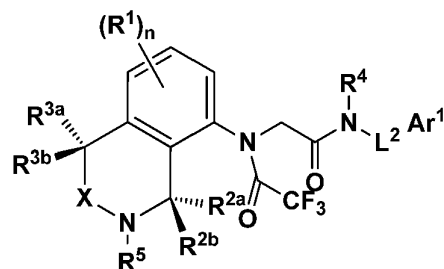


Structure 63b

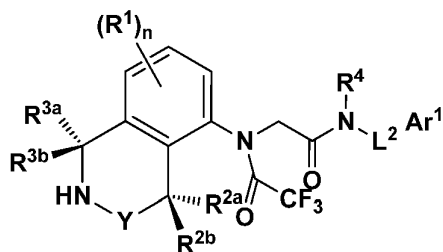
In case R^{16a} is equal to H, a compound of Structure 62a or 62b can be obtained in a two steps procedure from a compound of Structure 65a or 65b respectively.



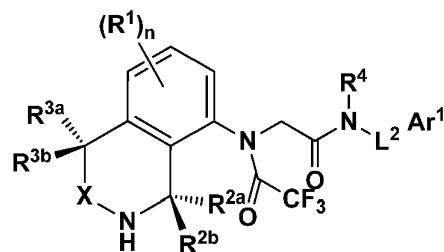
Structure 64a



Structure 64b



Structure 65a



Structure 65b

Thus a compound of Structure 65a or 65b is reacted in the first step with either:

- 10 • an aldehyde or a ketone of type $R^{13}R^{14}C=O$ in a solvent such as MeOH, EtOH with addition of water and a reducing agent such as $NaBH_4$, $NaBH(OAc)_3$, $NaBH_3CN$ or the like at room temperature, adding or not $ZnCl_2$ as a dehydrating agent. In this case a compound of Structure 64a or 64b respectively wherein R^5 corresponds to $R^{13}R^{14}CH$ is obtained.
- 15 • an acetyl chloride or a chloroformate of type $R^{10}C(O)Cl$ in a solvent such as DCM or THF or the like with a base such as TEA or DIPEA at a temperature between $0^\circ C$ and room temperature. Or alternatively a carboxylic acid of type $R^{10}C(O)OH$ in a solvent such as DMF, DCM or a mixture of both with a coupling reagent such as HATU and

the like and a base such as TEA or DIPEA. In this case a compound of Structure 64a or 64b respectively wherein R^5 corresponds to $R^{10}CO$ is obtained

- a sulfonyl chloride of type $R^{11}SO_2Cl$ in a solvent such as DCM with a base such as TEA or DIPEA a compound of Structure 64a or 64b respectively is obtained with R^5 corresponding to $R^{11}SO_2$.
- a reagent of type $R^{10a}R^{10b}NC(O)Cl$ in a solvent such as DCM with a base such as TEA or DIPEA or alternatively a reagent of type $R^{17}R^{18}NC(O)O(pNO_2Ph)$ made in situ from the reaction of an amine hydrochloride of type $R^{10a}R^{10b}NH HCl$ and 4-nitrophenylchloroformate in DCM in the presence of a base such as Na_2CO_3 or $NaHCO_3$, a compound of Structure 64a or 64b respectively is obtained with R^5 corresponding to $R^{10}CO$ wherein R^{10} corresponds to $R^{10a}R^{10b}N$
- a reagent of type R^5LG wherein LG represents a leaving group such as a I, Br or Cl atom, a methanesulfonate or a trifluoromethanesulfonate group and R^5 an alkyl residue in a solvent such as DMF, toluene, MeCN or THF with a base such as TEA or DIPEA or the like.
- a reagent of type R^5LG wherein LG represents a leaving group such as a I, Br or Cl atom, a methanesulfonate or a trifluoromethanesulfonate group and R^5 an aromatic or heteroaromatic residue in a solvent such as toluene, dioxane or DMF, a palladium catalyst such as $Pd_2(dba)_3$ and a ligand such as DavePhos or the like with a base such as sodium tert-butoxide or the like

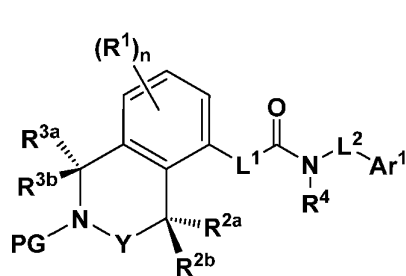
In the second step, the compound of Structure 64a or 64b obtained from the first step is reacted in a mixture of MeOH or EtOH and water with a base such as K_2CO_3 , Na_2CO_3 or the like at elevated temperature between 50 and 100°C to give a compound of Structure 62a or 62b respectively wherein R^{16a} represents H, following a method of deprotection of trifluoroacetamide well known from a person skilled in the art.

Preparation of compounds of Structure 61a and 61b (and compounds of structure 63a and 63b)

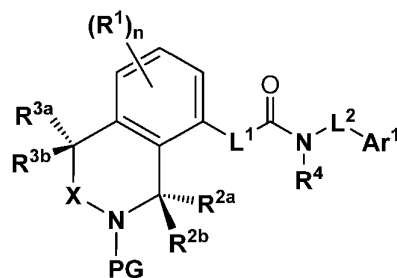
Compounds of Structure 61a and 61b and salts thereof and compounds of Structure 63a and 63b and salt thereof which are particular cases of compounds of Structure 61a and 61b are made from compounds of Structure 66a and 66b respectively wherein PG represents a Boc group or a benzyloxycarbonyl group. In case PG represents a Boc group, in a typical experiment, a compound of Structure 66a or 66b is diluted in a solvent such as DCM and TFA is added. The resulting mixture is allowed to stir at a temperature between 0°C to 40°C. Alternatively a compound of Structure 66a or 66b is diluted in dioxane, THF or the like and HCl solution in dioxane, THF or ether is added to form a compound of Structure 61a or 61b respectively. In case PG represents a benzyloxycarbonyl group and L^1 does not represent –

C=C-, a compound of Structure 66a or 66b respectively is dissolved in EtOAc and catalytically reduced by hydrogen in presence of palladium on charcoal to give a compound of Structure 61a or 61b respectively following a deprotection reaction condition well known by a person skilled in the art.

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Structure 66a



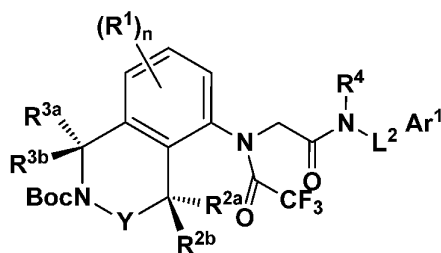
Structure 66b

Compounds of Structure 66a or 66b can be but are not necessarily special cases of compounds of Formula (I) and can be obtained from compounds of Structure 1 wherein X = NBoc or Y = NBoc respectively or X=NCbz or Y=NCbz respectively following an amide coupling experiment described for the preparation of compounds of Formula (I) from compounds of Structure 1.

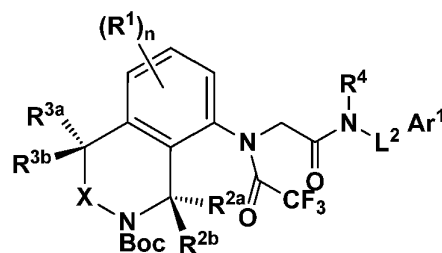
Preparation of compounds of Structure 65a and 65b

Compounds of Structure 65a and 65b are made from compounds a Structure 67a and 67b respectively which are a particular case of compounds of Structure 42a and 42b respectively following a typical reaction of Boc deprotection already described for the preparation of compounds of Structure 61a and 61b respectively from compounds of Structure 66a or 66b respectively.

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Structure 67a



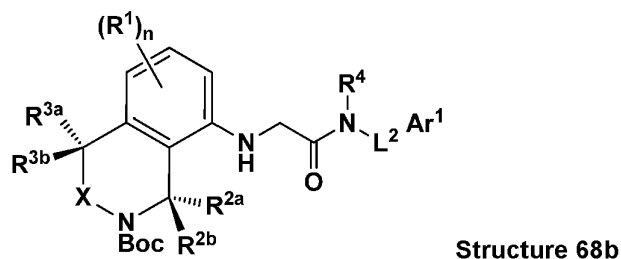
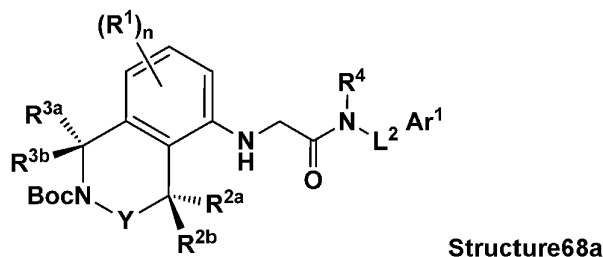
Structure 67b

Compounds of Structure 67a and 67b can be obtained from compounds of Structure 68a or 68b respectively. In a typical experiment, well known to a person skilled in the art, a compound of Structure 68a or 68b is dissolved in DCM together with a base such as TEA or DIPEA followed by trifluoroacetic anhydride at 0°C to room temperature. Compounds of Structure 68a or 68b are special cases of compounds of Structure 66a and 66b respectively

25

and as such can be but not necessarily special cases of compounds of Formula (I), and can be obtained from compounds of Structure 1 wherein X = NBoc or Y = NBoc respectively following an amide coupling experiment described for the preparation of compounds of Formula (I) from compounds of Structure 1.

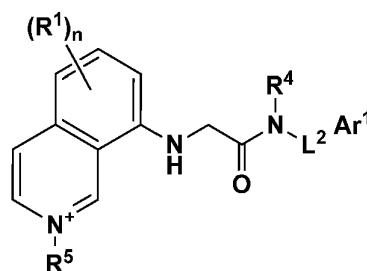
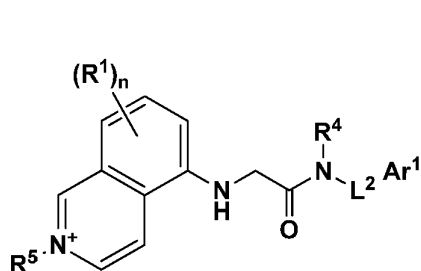
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Last two steps: quinoline alkylation followed by a reduction

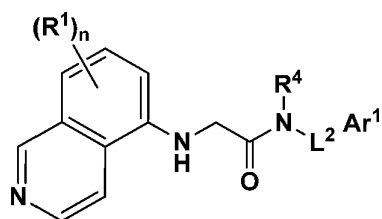
Compounds of Formula (I) can also be obtained from compounds of formula 69a and 69b. In a typical procedure a compound of structure 69a or 69b is stirred in MeOH or EtOH with NaBH₄ at room temperature to give the corresponding compound of Formula (I).

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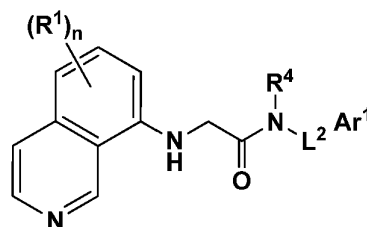


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Compounds of structure 69a and 69b can be made from compounds of Structure 70a and 70b respectively. In such a procedure, compounds of Structure 70a and 70b respectively are reacted with a reagent of type R⁵LG wherein LG represents a leaving group such as Cl, Br, I, OMs in a solvent such as MeCN, dioxane, DMF or the like in presence of a reagent of type R⁵LG and a base such as TEA, DIPEA, K₂CO₃ or the like at room temperature, or at elevated temperature up to reflux.

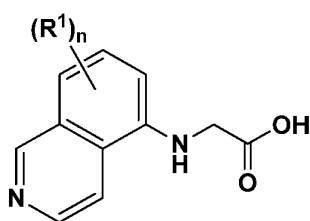


Structure 70a

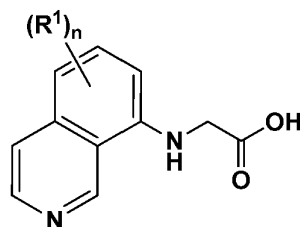


Structure 077b

Compounds of Structure 70a and 70b can be obtained from compounds of Structure 71a and 71b by reaction with an amine of Structure 2 using HATU or another amide coupling reagent in a solvent such as DCM or DMF at room temperature or 0°C in the presence of a base like TEA or DIPEA.



Structure 71a

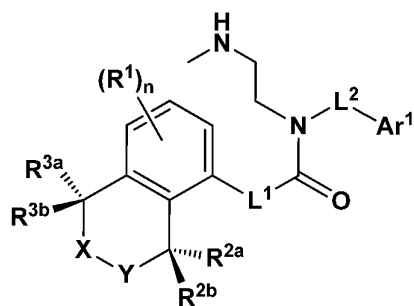


Structure 71b

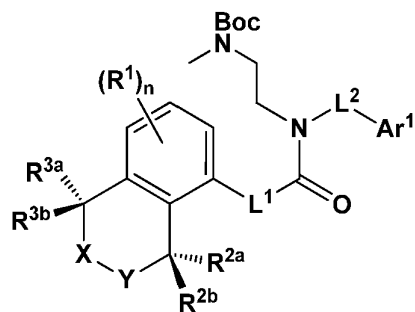
Compounds of Structure 71a and 71b are prepared by reaction of a commercially available 5-amino or 8-aminoisoquinoline respectively with glyoxylic acid hydrate in a solvent such as MeCN or the like with a reducing agent such as NaBH₃CN or the like at room temperature.

Special cases modification of side chain

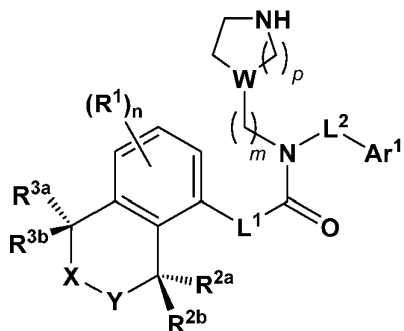
In certain particular cases a compound of Structure 72 which is a particular case of compounds of Formula (I) can be obtained from a compound of Structure 73 which can be but is not necessarily a particular case of compound of Formula (I). In a typical experiment a compound of Structure 73 is dissolved in DCM or dioxane and HCl soln. in dioxane or EtOAc or TFA or the like is added at a temperature between 0°C and room temperature. Compounds of Structure 73 are made according to methods described for the synthesis of compounds of Formula(I). Similarly a compound of Structure 74 wherein W represents N or CH, m is 0 or 1 and p is 1 or 2 can be obtained from a compound of Structure 75 wherein W represents N or CH, m is 0 or 1 and p is 1 or 2 which can be but is not necessarily a particular case of compounds of Formula (I) by the same reaction procedure.



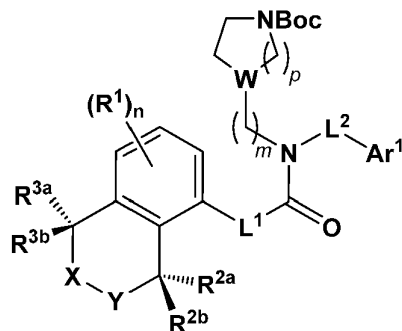
Structure 72



Structure 73

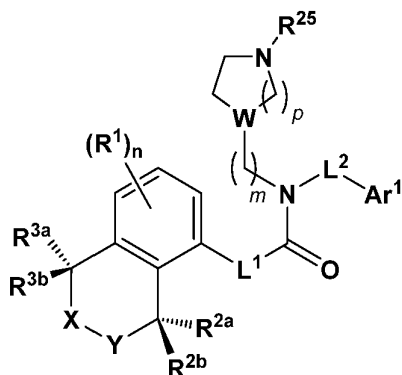


Structure 74

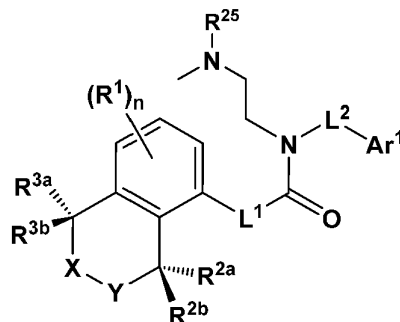


Structure 75

- 5 Compounds of Structure 75 can be made according to methods described for the synthesis of compounds of Formula(I). Finally a compound of Structure 76 or a compound of Structure 77 which are particular cases of compounds of Formula(I) can be prepared starting from a compound of Structure 74 or a compound of Structure 72 respectively by a typical reductive-amination reaction procedure wherein a compound of Structure 74 is dissolved in MeOH,
- 10 EtOH or the like and reacted with formaldehyde (in this case R^{25} represents a methyl group), an aldehyde or a ketone of type $R^{26}R^{27}CO$ (in this case R^{25} represents $R^{26}R^{27}CH-$) and a reducing agent such as $NaBH_4$, $NaBH_3CN$ or $NaBH(OAc)_3$ or the like with or without addition of an acid such as acetic acid and with or without the addition of a dehydrating agent like $ZnCl_2$ or molecular sieve.

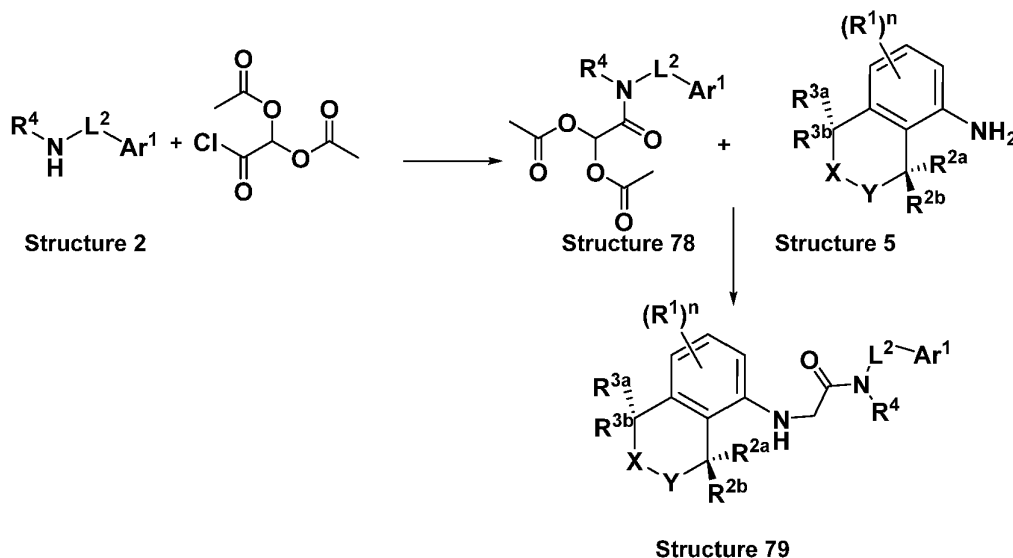


Structure 76



Structure 77

Alternative preparation of compounds of Formula (I)



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Reaction Scheme D

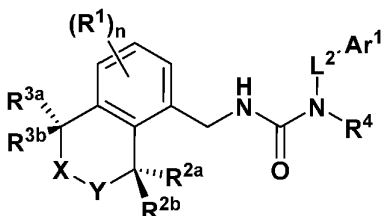
In a particular case wherein R^{2a} , R^{2b} , R^{3a} and R^{3b} represent H, compounds of Structure 79 which is a particular case of compounds of Formula(I) can be alternatively prepared as illustrated in reaction Scheme D from the corresponding 5- or 8-aminoisoquinoline derivatives via a two step sequence. Thus an amine of Structure 2 is reacted with diacetoxyacetyl chloride (McCaully, R., J. U.S. Patent 3,896,170, 1975) in DCM in the presence of a base like KHCO_3 , K_2CO_3 , NEt_3 or DIPEA at temperatures between -10°C and room temperature to give the diacetoxy amide of Structure 78 as a masked glyoxamide derivative. This crude intermediate of Structure 78 is condensed with an aniline of Structure 5 in a solvent like DCM, THF, MeOH or EtOH at temperatures between RT and reflux temperature in the presence of a catalytic amount of an acid like TFA or AcOH to deliver the intermediate imine which is directly treated with a reducing agent such as $\text{NaBH}(\text{OAc})_3$,

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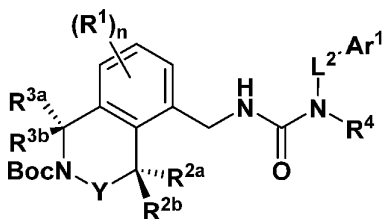
NaBH₃CN or NaBH₄ at temperatures between 0°C and reflux, preferentially at room temperature to yield compounds of Structure 70 which are a particular case of compounds of Formula (I).

Special case with L₁C(O)N being a urea function

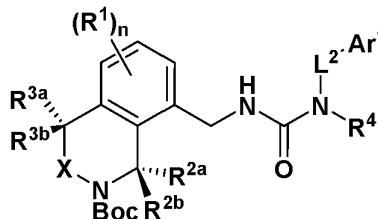
- 5 In a particular case compounds of Structure 80 which are particular cases of compounds of Formula(I) are made from compounds of Structure 81a or Structure 81b respectively. In a typical procedure a compound of Structure 81a or 81b respectively is dissolved in DCM or dioxane or a mixture of both and reacted with HCl soln. in dioxane or TFA in a Boc cleavage reaction procedure well known by a person skilled in the art. This affords a compound of
- 10 Structure 82a or 82b respectively or a salt thereof.



Structure 80

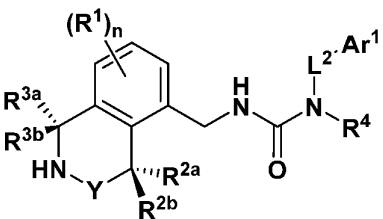


Structure 81a

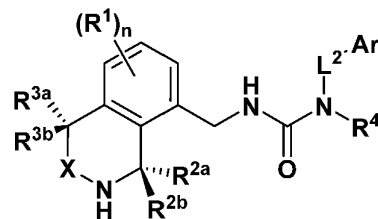


Structure 81b

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Structure 82a



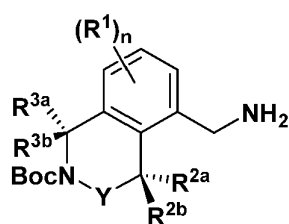
Structure 82b

- Then a compound of Structure 82a or 82b respectively is reacted with one equivalent of an aldehyde or a ketone of type R¹³R¹⁴C=O in a solvent such as MeOH, EtOH and a reducing agent such as NaBH₄, NaBH(OAc)₃, NaBH₃CN or the like at room temperature with or
- 20

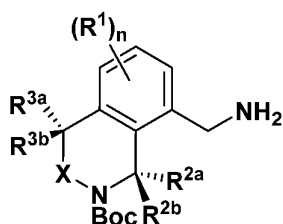
without addition of a dehydrating agent such as ZnCl_2 . In this case a compound of Structure 80 respectively wherein R^5 corresponds to $\text{R}^{13}\text{R}^{14}\text{CH}$ is obtained.

Compounds of Structure 81a or 81b respectively are made by reaction of a compound of Structure 82a or 82b respectively in water in presence of carbonyldiimidazole at 0°C to room

5 temperature with an amine of Structure 2.



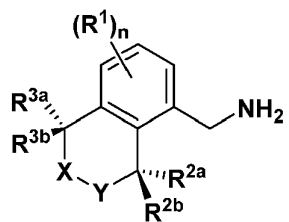
Structure 83a



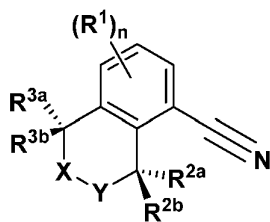
Structure 83b

Compounds of Structure 83a and 83b are either commercially available or made according to procedures well known by a person skilled in the art.

Compounds of Structure 80 can also be made directly from compounds of Structure 84 via
10 the method described for the synthesis of compounds of Structure 81a and 81b from compounds of Structure 83a and 83b. Compounds of Structure 84 can be made from compounds of Structure 85 by a reduction with procedure using CoCl_2 in the presence of NaBH_4 or another reducing agent in a solvent such as methanol at a temperature between RT and reflux.



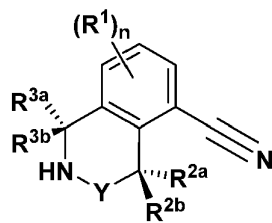
Structure 84



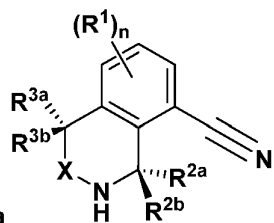
Structure 85

15

Compounds of Structure 85 can be made from a compound of Structure 86a or 86b which are commercially available or easily accessible via an alkylation method well known from a person skilled in the art.



Structure 86a



Structure 86b

20

Experimental Part**I. Chemistry**

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

In case a Example compound's or Precursor's name is preceeded with the mention rac- this means this Example compound or Precursor is obtained as a racemic mixture of two enantiomers.

LC-MS conditions

Method LC-A: Agilent 1100 series with mass spectrometry detection (MS: Finnigan single quadrupole). Column: Zorbax SB-aq (3.5 μ m, 4.6 x 50 mm). Conditions: MeCN [eluent A]; water + 0.04% TFA [eluent B]. Gradient: 95% B $\rightarrow$ 5% B over 1.5 min (flow: 4.5 mL/min). Detection: UV/Vis + MS.

Method LC-B: Agilent 1100 series with mass spectrometry detection (MS: Finnigan single quadrupole). Column: Waters Atlantis T3 (5 μ m, 4.6 x 30 mm). Conditions: MeCN [eluent A]; water + 0.04% TFA [eluent B]. Gradient: 95% B $\rightarrow$ 5% B over 1.5 min (flow: 4.5 mL/min). Detection: UV/Vis + MS.

Method LC-C: Waters Acquity Binary, Solvent Manager, MS: Waters SQ Detector, DAD: Acquity UPLC PDA Detector, ELSD: Acquity UPLC ELSD. Column: Acquity UPLC BEH C18 1.7 μ m 2.1x50 mm from Waters, thermostated in the Acquity UPLC Column Manager at 60°C. Conditions: MeCN+0.045% TFA [eluent A]; water + 0.05% TFA [eluent B]. Method: Gradient: 98% B $\rightarrow$ 2% B over 2.0 min. Flow: 1.2 mL/min. Detection: UV 214nm and ELSD, and MS, t_R is given in min.

Method LC-F: Waters Acquity Binary, Solvent Manager, MS: Waters SQ Detector, DAD: Acquity UPLC PDA Detector, ELSD: Acquity UPLC ELSD. Column: Acquity UPLC BEH C18 1.7 μ m 2.1x50 mm from Waters, thermostated in the Acquity UPLC Column Manager at 60°C. Conditions: MeCN+0.045% formic acid [eluent A]; water + 0.05% formic acid [eluent B]. Method: Gradient: 98% B $\rightarrow$ 2% B over 2.0 min. Flow: 1.0 mL/min. Detection: UV 214nm and ELSD, and MS, t_R is given in min.

Method LC-F1: Waters Acquity Binary, Solvent Manager, MS: Waters SQ Detector, DAD: Acquity UPLC PDA Detector, ELSD: Acquity UPLC ELSD. Column: ACQUITY UPLC HSS T3 C18 1.8 μ m 2.1x50 mm from Waters, thermostated in the Acquity UPLC Column Manager at 60°C. Conditions: MeCN+0.045% formic acid [eluent A]; water + 0.05% formic acid [eluent B]. Method: Gradient: 98% B $\rightarrow$ 2% B over 2.0 min. Flow: 1.0 mL/min.

Detection: UV 214nm and ELSD, and MS, t_R is given in min.

Methods LC-G and LC-H: Dionex ultimate 3000 system, MS: Thermo MSQ MS, DAD: Dionex 3000 Ultimate, ELSD: PolymerLab ELS 2100, Column: Accucore C18 2.6 μ m 2.1x50 mm, thermostated in TCC-3000 column compartment at 40°C. Conditions: MeCN [eluent A]; water + 0.05% NH₄OH + 2% MeCN [eluent B]. Method: Gradient: 95% B $\rightarrow$ 5% B over 1.2 min (**LC-G**) or 2 min (**LC-H**). Flow: 1.2 mL/min.

Detection: UV 214nm and ELSD, and MS, t_R is given in min.

Preparative HPLC with basic conditions

Method LC-D: Column: Waters XBridge (10 μ m, 75 x 30 mm). Conditions: MeCN [eluent A]; water + 0.5% NH₄OH (25% aq.) [eluent B]; Gradient see **Table 1** (flow: 75 mL/min), the starting percentage of Eluent A (x) is determined depending on the polarity of the compound to purify. Detection: UV/Vis + MS

Table 1

t (min)	0	0.01	4.0	6.0	6.2	6.6
Eluent A (%)	x	x	95	95	x	x
Eluent B (%)	100-x	100-x	5	5	100-x	100-x

Preparative HPLC with acidic conditions

Method LC-E: Column: Waters Atlantis T3 (10 μ m, 75 x 30 mm). Conditions: MeCN [eluent A]; water + 0.5% formic acid [eluent B]; Gradient see **Table 2** (flow: 75 mL/min), the starting percentage of Eluent A (x) is determined depending on the polarity of the compound to purify. Detection: UV/Vis + MS

Table 2

t (min)	0	0.01	4.0	6.0	6.2	6.6
Eluent A (%)	x	x	95	95	x	x
Eluent B (%)	100-x	100-x	5	5	100-x	100-x

Chiral preparative and analytical HPLC conditions

Method LC-K: Binary Pump, Dionex HPG-3200SD, Autosampler: Dionex WPS-3000, Column compartment: Dionex TCC-3200, Diode array detector: Dionex DAD-3000, Degaser:

Dionex SRD-3400, Column: ChiralPak AD-H 250 x 4.6 mm ID, 5 µm. Conditions: Isocratic, Eluent (heptane / EtOH / DIPEA 80:20:0.5); flow: 0.8 mL/min. Detection: UV/Vis

Method LC-L: Binary Pump, Dionex HPG-3200SD, Autosampler: Dionex WPS-3000, Column compartment: Dionex TCC-3200, Diode array detector: Dionex DAD-3000, Degaser:

- 5 Dionex SRD-3400, Column: Column: ChiralPak IA-H 250 x 20 mm ID, 5 µm. Conditions: Isocratic, Eluent (EtOH / MeCN / DIPEA 90:10:0.1); flow: 1 mL/min. Detection: UV/Vis

Abbreviations (as used hereinbefore or hereinafter):

	AcOH	acetic acid
	aq.	aqueous
10	Ar	argon
	BINAP	racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
	BSA	bovine serum albumin
	DABCO	1,4-diazabicyclo[2.2.2]octane
	DCC	N,N'-dicyclohexylcarbodiimide
15	DCE	1,2-dichloroethane
	DCM	dichloromethane
	deion.	deionized
	DIPEA	diisopropyl-ethylamine, Hünig's base, ethyl-diisopropylamine
	dioxane	1,4-dioxane
20	DMAP	4-dimethylaminopyridine
	DMF	dimethylformamide
	DMSO	dimethylsulfoxide
	eq.	equivalent(s)
	Ether	diethyl ether
25	EtOAc	ethyl acetate
	EtOH	ethanol
	g	gram(s)
	h	hour(s)
	HATU	2-(7-aza-1 <i>H</i> -benzotriazole-1-yl)-1,1,3,3-tetramethyluronium
30		hexafluorophosphate
	HPLC	high performance liquid chromatography
	HV	high vacuum conditions
	LC-MS	liquid chromatography – mass spectrometry
	MeCN	acetonitrile
35	Mel	methyl iodide
	MeOH	methanol

	mg	milligram(s)
	mL	milliliter(s)
	mmol	millimole(s)
	min	minute(s)
5	N	normality of a solution
	MS	mass spectroscopy
	NaBH(OAc) ₃	sodium triacetoxymethylborohydride
	NaOAc	sodium acetate
	NMR	nuclear magnetic resonance spectroscopy
10	OAc	acetate
	Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium(0)
	prep.	preparative
	rac	racemic
	RT	room temperature
15	s	second(s)
	sat.	saturated
	soln.	solution
	T	temperature
	TBME	<i>tert</i> -butyl methyl ether
20	TEA	triethylamine
	TFA	trifluoroacetic acid
	TFAA	trifluoroacetic acid anhydride
	THF	tetrahydrofuran
	<i>t</i> _R	retention time
25	X-Phos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

Example 1:**N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-acetamide**

- 30 To a solution of (2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-acetic acid **Precursor A1** (44 mg, 0.143 mmol), *N*-benzyl-*N*',*N*'-dimethylethane-1,2-diamine **Amine 7** (30.7 mg, 0.172 mmol) and HATU (55 mg, 0.145 mmol) in 1 mL DCM cooled to 0°C is added DIPEA (22.7 mg, 0.145 mmol). The reaction mixture is allowed to stir at RT for 1 h. Water is added and the resulting organic phase is washed with sat. aq. NaHCO₃ soln. and brine then
- 35 dried over MgSO₄, filtered and evaporated under reduced pressure. The crude residue is purified by prep. HPLC (Method D) to yield the title compound as a yellow solid. LC-C: *t*_R =

0.55 min; $[M+H]^+ = 406.4$; 1H -NMR ($CDCl_3$), 60:40 mixture of two rotamers, δ : 7.38 (m, 1 H), 7.31 (m, 3 H), 7.20 (d, $J = 7.1$ Hz, 1 H), 7.12 (m, 1 H), 7.05 (m, 1 H), 6.98 (d, $J = 7.4$ Hz, 1 H), 4.69 (s, 0.8 H), 4.55 (s, 1.2 H), 3.75 (m, 2.8 H), 3.63 (s, 1.2 H), 3.55 (t, $J = 6.8$ Hz, 1.2 H), 3.31 (t, $J = 7.2$ Hz, 0.8 H), 2.88 (m, 0.8 H), 2.83 (m, 2 H), 2.68 (m, 1.2 H), 2.53 (t, $J = 6.9$ Hz, 1.2 H), 2.44 (m, 2 H), 2.37 (t, $J = 7.3$ Hz, 0.8 H), 2.27 (m, 3.6 H), 2.19 (s, 2.4 H), 0.99 (m, 1 H), 0.59 (m, 2 H), 0.20 (m, 2 H)

Examples 2–7 listed in **Table 3** are prepared applying the method described for **Example 1** using the corresponding **Precursor** and **Amine** respectively.

Table 3: Examples 2–7

Example	Compound	t_R [min] (LC-C)	MS Data m/z $[M+H]^+$
2	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-N-phenethyl-acetamide	0.58	420.4
3	N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-pyrrolidin-1-yl-ethyl)-acetamide	0.56	432.4
4	rac-N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-acetamide	0.58	446.4
5	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.56	475.4
6	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.63	474.4
7	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-pyrrolidin-1-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.65	500.4

Example 8:

5-([Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

To a solution of 5-(carboxymethyl-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester **Precursor B1** (1.4 g, 4.57 mmol), *N*-benzyl-*N*',*N*'-dimethylethane-1,2-diamine **Amine 7** (0.81 g, 4.57 mmol) and HATU (2.09 g, 5.49 mmol) in 15 mL DCM cooled to 0°C is added DIPEA (1.18 g, 9.14 mmol). The reaction mixture is allowed to stir at RT for 1 h. Water is added and the resulting organic phase is washed with sat. aq. $NaHCO_3$ soln. and brine then dried over $MgSO_4$, filtered and evaporated under reduced pressure. Flash-chromatography on silica-gel (Eluent: EtOAc 100% then EtOAc / MeOH 80:20) yields the title compound as a yellow oil.

LC-B: $t_R = 0.72$ min; $[M+H]^+ = 467.1$

Examples 9 – 65, 90, 211-251, 295-308 and 315 listed in **Table 4** are prepared applying the method described for **Example 8** using the corresponding **Precursor** and **Amine** respectively.

5 **Table 4: Examples 9 – 65, 90, 211-251, 295-308 / 315**

Example	Compound	t_R [min] (LC-C)	MS Data m/z $[M+H]^+$
9	5-({[Benzyl-(3-methyl-butyl)-carbamoyl]-methyl}-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	1.44	466.4
10	5-({[(1-Methyl-piperidin-4-yl)-(2-trifluoromethyl-benzyl)-carbamoyl]-methyl}-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	1.01	561.5
11	rac-5-({[(1-Methyl-piperidin-3-yl)-(2-trifluoromethyl-benzyl)-carbamoyl]-methyl}-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	1.03	561.5
12	N-Benzyl-N-(3-methyl-butyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	1.24	422.4
13	N-Benzyl-N-(3-dimethylamino-propyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.74	437.4
14	N-(2-Dimethylamino-ethyl)-N-(3-methyl-benzyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.78	437.5
15	N-(2-Dimethylamino-ethyl)-N-(2-methyl-benzyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.77	437.4
16	N-(2-Dimethylamino-ethyl)-N-(4-methyl-benzyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.78	437.4
17	N-(2-Dimethylamino-ethyl)-N-phenethyl-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.76	437.4
18	N-(3-Chloro-benzyl)-N-(2-dimethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.78	457.4
19	N-(4-Chloro-benzyl)-N-(2-dimethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.8	457.4

20	N-(2-Chloro-benzyl)-N-(2-dimethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.77	457.4
21	N-(2-Dimethylamino-ethyl)-N-(3-fluoro-benzyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.74	441.4
22	N-(2-Dimethylamino-ethyl)-N-(4-fluoro-benzyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.75	441.4
23	N-(2-Dimethylamino-ethyl)-N-(2-fluoro-benzyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.73	441.4
24	N-Benzyl-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-acetamide	0.75	449.4
25	N-Benzyl-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-pyridin-2-ylmethyl-acetamide	0.95	443.4
26	N-Benzyl-N-(1-methyl-1 <i>H</i> -imidazol-2-ylmethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.71	446.4
27	N-Benzyl-N-(2-diethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.76	451.4
28	N-(2-Dimethylamino-ethyl)-N-(2-methoxy-benzyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.76	453.4
29	N-(2-Dimethylamino-ethyl)-N-(3-methoxy-benzyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.74	453.4
30	N-(2-Dimethylamino-ethyl)-N-(4-methoxy-benzyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.73	453.4
31	N-Benzyl-N-[2-(butyl-methyl-amino)-ethyl]-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.81	465.5
32	rac-N-Benzyl-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.76	463.4
33	N-(2-Dimethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3-trifluoromethyl-benzyl)-acetamide	0.82	491.4
34	N-(2-Dimethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(4-trifluoromethyl-benzyl)-acetamide	0.83	491.4

35	N-(2-Dimethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	0.81	491.4
36	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-phenethyl-acetamide	0.61	435.4
37	N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3-dimethylamino-propyl)-acetamide	0.59	435.5
38	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-fluoro-benzyl)-acetamide	0.58	439.4
39	N-(3-Chloro-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide	0.54	456.4
40	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-o-tolyl-ethyl)-acetamide	0.65	449.5
41	N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-acetamide	0.59	447.4
42	rac-N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-acetamide	0.61	461.5
43	N-(2-Chloro-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-acetamide	0.63	481.4
44	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-fluoro-benzyl)-N-(2-pyrrolidin-1-yl-ethyl)-acetamide	0.6	465.4
45	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-((E)-2-methyl-3-phenyl-allyl)-acetamide	0.69	461.5
46	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(6-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.61	490.4
47	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.59	490.4

48	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3-methyl-butyl)-N-(2-trifluoromethyl-benzyl)-acetamide	1.09	488.4
49	rac-2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-N-phenethyl-acetamide	0.65	475.5
50	N-(2-Chloro-4-fluoro-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-acetamide	0.65	499.4
51	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2,4-difluoro-benzyl)-N-(2-pyrrolidin-1-yl-ethyl)-acetamide	0.62	483.4
52	rac-2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-N-(3-phenyl-propyl)-acetamide	0.70	489.5
53	rac-2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-N-((E)-3-phenyl-allyl)-acetamide	0.68	487.5
54	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(4-fluoro-2-trifluoromethyl-benzyl)-acetamide	0.68	507.4
55	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-[2-(3-trifluoromethyl-phenyl)-ethyl]-acetamide	0.71	503.4
56	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-[2-(4-trifluoromethyl-phenyl)-ethyl]-acetamide	0.71	503.4
57	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-[2-(2-trifluoromethyl-phenyl)-ethyl]-acetamide	0.70	503.5
58	rac-2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-[1-(2-trifluoromethyl-phenyl)-ethyl]-acetamide	0.68	503.4
59	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(3,4-dimethoxy-phenyl)-ethyl]-N-(2-dimethylamino-ethyl)-acetamide	0.58	495.5

60	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-diethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.68	517.4
61	rac-2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-((E)-2-methyl-3-phenyl-allyl)-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-acetamide	0.72	501.4
62	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.67	515.4
63	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(2-oxo-pyrrolidin-1-yl)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide	0.82	529.4
64	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-morpholin-4-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.66	531.5
65	rac-3-{Benzyl-[2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]-amino}-pyrrolidine-1-carboxylic acid <i>tert</i> -butyl ester	0.96	519.5
90	5-{{{[2-(Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl]-methyl}-amino]-4,4-dimethyl-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	1.08	563.5
211	rac-2-((2-(Cyclopropylmethyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(dimethylamino)ethyl)-N-(2-(trifluoromethyl)benzyl)acetamide	0.68	503.1
212	rac-2-((2-(Cyclopropylmethyl)-3-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(dimethylamino)ethyl)-N-(2-(trifluoromethyl)benzyl)acetamide	0.67	503.4
Example No	Example name	<i>t_R</i> [min] (LC-F) unless otherwise indicated	MS Data m/z [M+H] ⁺
213	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide	0.53	529.4

214	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3-pyrrolidin-1-yl-propyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.53	529.4
215	{2-[[2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]-(3-trifluoromethyl-pyridin-2-ylmethyl)-amino]-ethyl}-methyl-carbamic acid <i>tert</i> -butyl ester	0.86	576.4
216	4-{2-[[2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]-(2-trifluoromethyl-benzyl)-amino]-ethyl}-piperazine-1-carboxylic acid <i>tert</i> -butyl ester	0.69	630.4
217	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-piperidin-1-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.52	529.4
218	N-(2-Azepan-1-yl-ethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	0.54	543.4
219	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-diisopropylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.55	545.4
220	N-[2-(Cyclopropyl-methyl-amino)-ethyl]-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	0.54	515.4
221	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-trifluoromethoxy-benzyl)-acetamide	0.53	505.3
222	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(4-hydroxy-cyclohexyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.75	516.4
223	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-hydroxy-3-methoxy-propyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.74	506.3
224	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-N-(3,3,3-trifluoro-propyl)-acetamide	0.89	514.3
225	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methoxy-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.81	476.4

226	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[1,4]dioxan-2-ylmethyl-N-(2-trifluoromethyl-benzyl)-acetamide	0.79	518.3
227	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethoxy-benzyl)-acetamide	0.52	505.4
228	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(4-trifluoromethoxy-benzyl)-acetamide	0.54	505.3
229	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methanesulfonyl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.71	524.3
230	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methanesulfonylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.71	539.3
231	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(ethyl-methyl-amino)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide	0.5	503.4
232	{2-[[2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]-(2-trifluoromethyl-benzyl)-amino]-ethyl}-ethyl-carbamic acid <i>tert</i> -butyl ester	0.97	589.4
233	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-sulfamoyl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.68	525.3
234	N-(2-Bromo-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide	0.47	499.2
235	(2-[(2-Bromo-benzyl)-[2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]-amino]-ethyl)-methyl-carbamic acid <i>tert</i> -butyl ester	0.91	585.3
236	N-(3-Bromo-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide	0.41	500.3
237	N-(3-Bromo-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide	0.48	499.2

238	N-(4-Bromo-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide	0.49	499.3
239	N-(3-Bromo-pyridin-4-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide	0.37	500.2
240	rac-2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-hydroxy-propyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.74	476.4
241	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-hydroxy-2-methyl-propyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.77	490.4
242	rac-2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3,3,3-trifluoro-2-hydroxy-propyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.83	530.3
243	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(1-hydroxy-cyclopentylmethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.85	516.4
244	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-2-[(2-fluoro-ethyl)-methyl-amino]-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.52	521.4
245	N-[2-(Allyl-methyl-amino)-ethyl]-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	0.52	515.4
246	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(methyl-prop-2-ynyl-amino)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide	0.58	513.4
247	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-thiazol-5-ylmethyl-N-(2-trifluoromethyl-benzyl)-acetamide	0.76	515.3
248	N-(2-Chloro-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-acetamide	0.59	531.3
249	N-(3-Chloro-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-acetamide	0.47	532.4

250	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-isoxazol-5-ylmethyl-N-(2-trifluoromethyl-benzyl)-acetamide	0.77 (LC-A)	489.21
251	N-(3-Chloro-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-hydroxy-2-methyl-propyl)-acetamide	0.64	457.3
295	N-(2-Chloro-benzyl)-2-(2-cyclopropylmethyl-7-trifluoromethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide	0.56	523.3
296	2-(2-Cyclopropylmethyl-7-trifluoromethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.59	557.3
297	{2-[[2-(2-Methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-acetyl]-(2-trifluoromethyl-benzyl)-amino]-ethyl}-methyl-carbamic acid <i>tert</i> -butyl ester	0.91	579.4
298	N-(3,3-Dimethyl-butyl)-2-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(3-methyl-pyridin-2-ylmethyl)-acetamide	0.73	453.4
299	N-(2-Hydroxy-3-methoxy-propyl)-2-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide	0.70	510.3
300	N-[2-(4,4-Difluoro-piperidin-1-yl)-ethyl]-2-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.49	570.3
301	N-(2-Hydroxy-2-methyl-propyl)-2-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide	0.73	494.3
302	N-{2-[(2-Fluoro-ethyl)-methyl-amino]-ethyl}-2-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide	0.49	525.3
303	2-[2-(2-Methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(3-methyl-oxetan-3-ylmethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.75	506.3
304	N-(3-Hydroxy-3-methyl-butyl)-2-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide	0.76	508.4

305	N-(3-Chloro-pyridin-2-ylmethyl)-N-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-2-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-acetamide	0.44	536.3
306	N-(3-Chloro-pyridin-2-ylmethyl)-N-(2-dimethylamino-ethyl)-2-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-acetamide	0.37	460.3
307	N-(3-Chloro-pyridin-2-ylmethyl)-N-(2-hydroxy-2-methyl-propyl)-2-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-acetamide	0.6	461.3
308	N-(2-Dimethylamino-ethyl)-2-(2-prop-2-ynyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	0.49	473.3
315	2-(2-Cyclopropylmethyl-1-oxo-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.74	503.3

Examples 211a

(S)- or (R)-2-((2-(Cyclopropylmethyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(dimethylamino)ethyl)-N-(2-(trifluoromethyl)benzyl)acetamide

- 5 LC-K: t_R = 6.95 min, ^1H NMR (400 MHz, DMSO, 2:1 mixture of rotamers) δ : 7.76 (m, 1 H), 7.65 (m, 1 H), 7.50 (m, 1 H), 7.35 (m, 1 H), 6.99 (m, 0.66 H), 6.90 (t, J = 7.8 Hz, 0.33 H), 6.42 (m, 1.66 H), 6.20 (m, 0.33 H), 4.96 (m, 1 H), 4.89 (s, 0.66 H), 4.79 (s, 1.33 H), 4.19 (m, 1.33 H), 3.86 (m, 1.66 H), 3.50 (m, 1.33 H), 3.41 (t, J = 6.7 Hz, 0.66 H), 3.03 (m, 1 H), 2.90 (m, 1 H), 2.23-2.49 (m, 5 H), 2.16 (m, 6 H), 1.21 (m, 3 H), 0.87 (m, 1 H), 0.47 (dd, J_1 = 1.7 Hz, J_2 = 8.0 Hz, 2 H), 0.10 (m, 2 H) ,
- 10 and **Example 211b**

(R)- or (S)-2-((2-(Cyclopropylmethyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(dimethylamino)ethyl)-N-(2-(trifluoromethyl)benzyl)acetamide

LC-K: t_R = 9.01 min; are obtained using chiral prep. HPLC conditions (LC-K) for the racemic

- 15 **Example 211.**

Precursor A1

2-(2-(Cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)acetic acid

- To a solution of (2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-acetic acid *tert*-butyl ester **Precursor A2** (0.34 g, 1.13 mmol) in 8 mL DCM is added TFA (0.97 mL, 12.6 mmol). The reaction mixture is allowed to stir at RT for 24 h and is diluted with 1 mL toluene. The
- 20

solvents are evaporated under reduced pressure to yield 0.276 g (99%) of the title compound as a yellow solid which is used without further purification.

LC-A: t_R = 0.48 min; $[M+H]^+$ = 246.12

Precursor A2

5 **(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-acetic acid *tert*-butyl ester**

A solution of 5-*tert*-butoxycarbonylmethyl-2-cyclopropylmethyl-isoquinolinium bromide **Precursor A3** (450 mg, 1.19 mmol) in 5 mL MeOH and 0.5 mL deion. water cooled to 0°C is treated portionwise with NaBH₄ (60 mg, 1.59 mmol) over 15 min. The reaction mixture is stirred at 0°C for 1 h and at RT for 1 h. The solvent is evaporated under reduced pressure.

10 The residue is partitioned between 20 mL DCM and 20 mL sat. aq. NaHCO₃. The water layer is extracted twice with 10 mL DCM. The combined organic layers are dried over MgSO₄ and evaporated under reduced pressure. The residue is dried under HV overnight to yield 344 mg (96%) of the title compound as an orange oil. LC-A: t_R = 0.69 min; $[M+H]^+$ = 302.21

Precursor A3

15 **5-*tert*-Butoxycarbonylmethyl-2-cyclopropylmethyl-isoquinolinium bromide**

To a solution of isoquinolin-5-yl-acetic acid *tert*-butyl ester [Bioorg. and Med. Chem. Letters, 2011, 21, 1838-1843] (0.313 g, 1.29 mmol) in 2 mL MeCN is added bromomethyl-cyclopropane (0.21 g, 1.56 mmol). The reaction mixture is heated under reflux for 8 h. The mixture is allowed to cool to RT and the solvent is evaporated under reduced pressure. The oily residue is triturated with 5 mL ether. The resulting solid is filtered over a sintered funnel then washed with ether and dried under HV. This yields 0.457 g (94%) of the sub-title compound as a light yellow solid. LC-A: t_R = 0.69 min; $[M+H]^+$ = 297.98

Precursor B1

25 **5-(Carboxymethyl-amino)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester**

To a solution of 5-(ethoxycarbonylmethyl-amino)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester **Precursor D1** (6.9 g, 20.8 mmol) in 150 mL THF is added 1M aq. LiOH sol. (125 mL, 125 mmol). The reaction mixture is allowed to stir at RT for 2 h and is acidified with 2N aq. HCl sol. to pH=4. The resulting aq. phase is extracted twice with EtOAc. The combined organic phase is washed with brine, dried over MgSO₄, filtered and evaporated under reduced pressure to yield 5.6 g (88%) of the title compound as a white solid which is used without further purification.

LC-B: t_R = 0.78 min; $[M+H]^+$ = 467.1; ¹H-NMR (d₆-DMSO) δ : 11.52-13.03 (bs, 1 H), 6.98 (t, J = 7.8 Hz, 1 H), 6.43 (d, J = 7.6 Hz, 1 H), 6.25 (d, J = 7.9 Hz, 1 H), 4.42 (bs, 2 H), 3.83 (s, 2 H), 3.59 (t, J = 5.4 Hz, 2 H), 2.47 (t, J = 5.9 Hz, 2 H), 1.43 (s, 9 H).

Precursor B2 (2-Propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetic acid LC-B: $t_R = 0.55$ min; $[M+H]^+ = 263.2$, **Precursor B8 5-(Carboxymethyl-amino)-4,4-dimethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester** LC-A: $t_R = 0.88$ min; $[M+H]^+ = 335.2$ and **Precursor B18 *rac*-[2-((1S*,2S*)-2-Fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-acetic acid** LC-A: $t_R = 0.62$ min; $[M+H]^+ = 293.2$ are prepared applying the method described for **Precursor B1** from **Precursor C2**, **Precursor C8** and **Precursor C18** respectively.

Precursor B3

(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetic acid

10 a) 5-Amino-2-cyclopropylmethyl-isoquinolinium bromide

5-Aminoisoquinoline (6 g, 41.6 mmol) is suspended in 30 mL MeCN and bromomethylcyclopropane (5.6 g, 41.6 mmol) is added. The reaction mixture is heated at 85°C for 2.5 h then stirred at RT overnight. Then bromomethylcyclopropane (1 g, 7.4 mmol) is added and the mixture is heated at 85°C for 5 h. The mixture is allowed to cool to RT and
15 the resulting solid is filtered over a sintered funnel then washed with ether and dried under HV. This yields 10.58 g (91%) of the sub-title compound as a yellow solid.

LC-A: $t_R = 0.49$ min; $[M]^+ = 199.2$ (Mass of cation)

b) 2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamine

To a solution of 5-amino-2-cyclopropylmethyl-isoquinolinium bromide (500 mg, 1.79 mmol) in a mixture of 30 mL MeOH and 2 mL water cooled to 0°C is added portionwise NaBH₄ (339 mg, 8.95 mmol) over 10 min. The resulting mixture is allowed to stir at 0°C for 1 h then at RT overnight. The solvent is evaporated under reduced pressure. The residue is partitioned between DCM and sat. aq. NaHCO₃ soln. The resulting aq. layer is extracted twice with DCM. The combined organic layers are dried over MgSO₄, filtered and evaporated under
20 reduced pressure. This yields 316 mg (100%) of the sub-title compound as a red gum which is used without further purification.

LC-A: $t_R = 0.36$ min; $[M+H]^+ = 203.2$

c) A solution of 2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamine (300 mg, 1.48 mmol) in 15 mL MeOH is cooled to 0°C in an ice-bath. Glyoxylic acid monohydrate (320 mg, 3.48 mmol), TEA (299 mg, 2.97 mmol) are added followed by NaBH₃CN (103 mg, 1.63 mmol). The resulting mixture is allowed to stir at 0°C for 30 min then at RT for 4 h. Water is slowly added and the volatiles are removed under reduced pressure. The crude solid is suspended in acetone, sonicated, triturated and then filtered over a sintered funnel. The acetone filtrate is evaporated under reduced pressure and dried under HV to yield 405 mg
30 (100%) of the title compound as a yellow solid which is used without further purification.

LC-A: $t_R = 0.50$ min; $[M+H]^+ = 261.3$

Alternatively to the steps b) and c):

- d) To a solution of 5-amino-2-cyclopropylmethyl-isoquinolinium bromide (35 g, 0.125 mol) and glyoxylic acid monohydrate (13.8 g, 0.15 mol) in 500 mL MeOH in an autoclave is added Pearlman's catalyst (3.34 g, 6.27 mmol). The resulting mixture is put under 10 bar of H₂ and allowed to stir at RT overnight. The solvent crude mixture is filtered and the filtrate rinsed with MeOH. The organic phase is evaporated under reduced pressure. The residue is recrystallized from TBME to yield 32 g (100%) of the title compound as beige solid.

- Precursor B20 ((2-(2-Methoxyethyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)acetic acid**, LC-A: $t_R = 0.65$ min; $[M+H]^+ = 265.4$ is prepared applying the method described for **Precursor B3** using 2-methoxyethylbromide following Steps a) to give 5-amino-2-(2-methoxyethyl)isoquinolin-2-ium bromide LC-A: $t_R = 0.44$ min; $[M]^+ = 203.3$ (Mass of cation) and then step d). **Precursor B21 ((2-Propargyl-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)acetic acid**, LC-A: $t_R = 0.45$ min; $[M+H]^+ = 245.2$ is prepared applying the method described for **Precursor B3** using propargyl bromide following Steps a) to give 5-amino-2-(prop-2-yn-1-yl)isoquinolin-2-ium bromide LC-A: $t_R = 0.41$ min; $[M]^+ = 183.2$ (Mass of cation) then step b) to give 2-(prop-2-yn-1-yl)-1,2,3,4-tetrahydroisoquinolin-5-amine LC-A: $t_R = 0.28$ min; $[M+H]^+ = 187.3$ and then step c).

Precursor B24

(2-Cyclopropylmethyl-1-oxo-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetic acid

- To a solution of 5-amino-2-cyclopropylmethyl-3,4-dihydro-2*H*-isoquinolin-1-one hydrochloride **Precursor C24** (92mg, 0.425 mmol) in 3 mL MeOH is added glyoxylic acid (12.6 mg, 0.17 mmol), NaBH₃CN (32.1 mg, 0.51 mmol), AcOH (102 mg, 1.7 mmol) and NaOAc (70 mg, 0.851 mmol). The reaction mixture is allowed to stir at RT overnight. Then glyoxylic acid (12.6 mg, 0.17 mmol) is added each 2 hours for three times. Water is then added and the volatiles are removed under reduced pressure. The crude residue (120 mg) is used as such in the next step.

LC-A: $t_R = 0.64$ min; $[M+H]^+ = 275.2$

Precursor B10

- rac-2-((2-(Cyclopropylmethyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)acetic acid**

a) *rac-2-(Cyclopropylmethyl)-1-methyl-1,2-dihydroisoquinolin-5-amine*

- To a solution of the above mentioned 5-amino-2-cyclopropylmethyl-isoquinolinium bromide (500 mg, 2.38 mmol) in 5 mL THF cooled to 0°C is added MeMgCl 3M soln. in THF (1.5 mL, 4.5 mmol). The resulting brown solution is allowed to warm up to RT and is stirred at this temperature for 2 h. The solution is then poured onto sat. aq. NH₄Cl soln. and the resulting aq. phase is extracted three times with ether. The combined organic phase is dried over

MgSO₄ and the solvent removed under reduced pressure. This yields 410 mg (80%) of a crude orange oil which is used without further purification in the next step.

LC-A: $t_R = 0.48$ min; $[M+H]^+ = 215.1$

b) *rac-2-(Cyclopropylmethyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-amine*

- 5 A solution of the above mentioned *rac-2-(cyclopropylmethyl)-1-methyl-1,2-dihydroisoquinolin-5-amine* (410 mg, 1.53 mmol) in 6 mL MeOH is cooled to 0°C and NaBH₄ (64 mg, 1.68 mmol) is added. The resulting suspension is allowed to stir at 0°C for 30 min. The solvents are removed under reduced pressure and the residue is partitioned between sat. aq. NaHCO₃ soln. and DCM. The resulting aq. phase is extracted twice with DCM. The combined
10 organic phase is dried over MgSO₄ and the solvent removed under reduced pressure. This yields quantitatively 354 mg of the sub-title compound as light brown oil which is used as such in the next step.

LC-A: $t_R = 0.43$ min; $[M+H]^+ = 217.1$

- c) A solution of *rac-2-(cyclopropylmethyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-amine*
15 (354 mg, 1.46 mmol) in 10 ml MeOH is cooled to 0°C in an ice-bath. Glyoxylic acid monohydrate (268 mg, 2.91 mmol), TEA (295 mg, 2.91 mmol) are added followed by NaBH₃CN (229 mg, 3.64 mmol). The resulting mixture is allowed to stir at 0°C for 1 h then at RT for 2 h. Water is slowly added and the volatiles are removed under reduced pressure. The crude solid is suspended in acetone, sonicated and triturated then filtered over a
20 sintered funnel. Evaporation of the acetone solution yields 554 mg of the title compound as a yellow solid which is used without further purification.

LC-A: $t_R = 0.53$ min; $[M+H]^+ = 275.1$

Precursor B11

- rac-2-((2-(Cyclopropylmethyl)-3-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)acetic acid***
25

a) *rac-2-(cyclopropylmethyl)-3-methyl-5-nitro-1,2,3,4-tetrahydroisoquinoline*

- To a solution of *rac-3-methyl-5-nitro-1,2,3,4-tetrahydroisoquinoline* (624 mg, 3.18 mmol) in 8 mL DCM are added cyclopropane carboxaldehyde (245 mg, 3.5 mmol) and DIPEA (617 mg, 4.77 mmol) and the reaction mixture is stirred at RT for 1 h. NaBH(OAc)₃ (1011 mg, 4.77
30 mmol) is then added and the resulting mixture is allowed to stir at RT for 1 h. The mixture is diluted with water and DCM. The resulting aq. phase is extracted twice with DCM. The combined organic phase is washed with brine and dried over MgSO₄. The solvent is evaporated under reduced pressure to yield 708 mg (90%) of the sub-title compound as a brown oil which is used as such in the next step.

- 35 LC-A: $t_R = 0.56$ min; $[M+H]^+ = 247.1$

b) *rac*-2-(Cyclopropylmethyl)-3-methyl-1,2,3,4-tetrahydroisoquinolin-5-amine

To a degassed solution of *rac*-2-(cyclopropylmethyl)-3-methyl-5-nitro-1,2,3,4-tetrahydroisoquinoline (705 mg, 2.66 mmol) in 50 mL MeOH is added 10% Pd / C mixture (70 mg, 0.066 mmol) and the well stirred suspension is put under an atmospheric pressure of H₂ for 3 h. The mixture is filtered over Celite and washed three times with MeOH. The solvent is removed under reduced pressure. Flash-chromatography on silica-gel (Eluent: DCM / MeOH 100:0 to 90:10) yields 483 mg (84%) of the sub-title compound as yellow oil.
LC-A: *t_R* = 0.42 min; [M+H]⁺ = 217.3

c) A solution of *rac*-2-(cyclopropylmethyl)-3-methyl-1,2,3,4-tetrahydroisoquinolin-5-amine (483 mg, 1.92 mmol) in 10 mL MeOH is cooled to 0°C in an ice-bath. Glyoxylic acid monohydrate (353 mg, 3.84 mmol), TEA (389 mg, 3.84 mmol) are added followed by NaBH₃CN (302 mg, 4.8 mmol). The resulting mixture is allowed to stir at 0°C for 30 min then at RT for 2.5 h. Water is slowly added and the volatiles are removed under reduced pressure. The crude solid is suspended in acetone, sonicated and triturated then filtered over a sintered funnel. The acetone filtrate is evaporated under reduced pressure to yield 410 mg (78%) of the title compound as a yellow oil which is used without further purification.
LC-A: *t_R* = 0.52 min; [M+H]⁺ = 275.2

Precursor B19**((2-(Cyclopropylmethyl)-7-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)acetic acid**

a) 2-(Cyclopropylmethyl)-5-nitro-7-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline
To a solution of 7-(trifluoromethyl)-1,2,3,4-tetrahydro-5-nitroisoquinoline hydrochloride (300 mg, 1.06 mmol) in 3 mL DCM at RT are added cyclopropanecarboxaldehyde (0.095 mL, 1.27 mmol) and DIPEA (0.273 mL, 1.59 mmol). The reaction mixture is stirred for 1 h then NaBH(OAc)₃ (337 mg, 1.59 mmol) is added. The reaction mixture is allowed to stirred for 2 h at RT and is diluted with water and DCM. The resulting aq. phase is extracted twice with DCM. The combined organic phase is washed with brine and dried over MgSO₄. The solvent is evaporated under reduced pressure to yield quantitatively 331 mg of the sub-title compound as a brown oil which is used as such in the next step.
LC-A: *t_R* = 0.65 min; [M+H]⁺ = 301.5

b) 2-(Cyclopropylmethyl)-7-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinolin-5-amine

To a degassed solution of 2-(cyclopropylmethyl)-5-nitro-7-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline (319 mg, 1.06 mmol) in 30 mL MeOH is added 10% Pd/C mixture (32 mg) and the well stirred suspension is put under atmospheric pressure of H₂ for 5 h. The mixture is filtered over Celite and washed three times with MeOH. The solvent is removed

under reduced pressure to yield quantitatively 289 mg of the crude sub-title compound as brown solid which is used as such in the next step.

LC-A: $t_R = 0.61$ min; $[M+H]^+ = 217.2$

- 5 c) A solution of 2-(cyclopropylmethyl)-7-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinolin-5-amine (285 mg, 0.84 mmol) in 5 mL MeOH is cooled to 0°C in an ice-bath. Glyoxylic acid monohydrate (332 mg, 3.61 mmol), TEA (171 mg, 1.69 mmol) are added followed by NaBH₃CN (151 mg, 2.4 mmol). The resulting mixture is allowed to stir at 0°C for 30 min then at RT for 2 h. Glyoxylic acid monohydrate (100 mg) and NaBH₃CN (30 mg) are added and the resulting mixture is allowed to stir at RT for 4 h. Glyoxylic acid monohydrate (50 mg) is added and the resulting mixture is allowed to stir at RT for 2 h. Water is slowly added and the volatiles are removed under reduced pressure. The crude solid is suspended in acetone, sonicated and triturated then filtered over a sintered funnel. The acetone filtrate is evaporated under reduced pressure to yield 664 mg of the crude title compound as an orange oil which is used without further purification in the next step.

- 15 LC-A: $t_R = 0.61$ min; $[M+H]^+ = 329.3$

Precursor B25

(2-((Benzyloxy)carbonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)aminoacetic acid

- To a solution of 5-amino-3,4-dihydroisoquinoline-2(1*H*)-carboxylic acid benzyl ester ester [J. Med. Chem. **1990**, 33(2), 596-600] (517 mg, 1.1 mmol) in 5 mL MeOH cooled to 0°C is added glyoxylic acid 50% in water soln. (0.151 mL, 1.1 mmol) then NaBH₃CN (104 mg, 1.65 mmol) and the resulting reaction mixture is allowed to stir at RT for 1 h. It is then poured in water and the resulting aq. phase is extracted three times with DCM. The combined organic phase is washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure to yield the title compound as a yellow oil.

- 25 LC-A: $t_R = 0.81$ min; $[M+H]^+ = 381.1$

Precursor D1

5-(Ethoxycarbonylmethyl-amino)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester

- To a solution of 5-amino-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (6 g, 0.0242 mol) in 60 mL MeCN is added DIPEA (3.07 g, 24.2 mmol). The mixture is stirred 10 min at RT then ethylbromoacetate (4.04 g, 24.2 mmol) is added. The reaction is stirred for 6 h at reflux. After cooling, the mixture is poured into water and the resulting aq. phase is extracted twice with DCM. The combined organic phase is washed with sat. aq. NaHCO₃ soln. and brine then dried over MgSO₄, filtered and evaporated under reduced pressure.
- 35 Flash-chromatography on silica-gel (gradient of EtOAc / heptane from 5:95 to 40:60) yields 6.9 g (86%) of the title compound as a light yellow oil.

LC-B: $t_R = 0.96$ min; $[M+H]^+ = 335.1$; $^1\text{H-NMR}$ (d_6 -DMSO) δ : 7.12 (d, $J = 7.5$ Hz, $J = 8.0$ Hz, 1 H), 6.60 (d, $J = 7.5$ Hz, 1 H), 6.41 (d, $J = 8.0$ Hz, 1 H), 4.57 (s, 2 H), 4.28 (q, $J = 7.1$ Hz, 2 H), 3.95 (s, 2 H), 3.74 (t, $J = 5.9$ Hz, 2 H), 2.62 (t, $J = 5.9$ Hz, 2 H), 1.50 (s, 9 H), 1.33 (t, $J = 7.1$ Hz, 3 H)

5 Precursor C8

5-(Ethoxycarbonylmethyl-amino)-4,4-dimethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester LC-A: $t_R = 1.00$ min; $[M+H]^+ = 363.2$ is prepared applying the method described for **Precursor D1** from commercially available 5-amino-4,4-dimethyl-3,4-dihydroisoquinoline-2(1H)-carboxylic acid *tert*-butyl ester.

10 Precursor C2

(2-Propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetic acid ethyl ester

a) 1-(5-Bromo-3,4-dihydro-1H-isoquinolin-2-yl)-propan-1-one

To a solution of 5-bromo-1,2,3,4-tetrahydroisoquinoline [J. Med. Chem., **2012**, 55(17), 7746 - 7758] (8.4 g, 39.4 mmol) in 250 mL DCM is added TEA (3.98 g, 39.4 mmol). The resulting solution is allowed to stir for 10 min at RT. Propionylchloride (3.62 g, 39.4 mmol) is added dropwise and the resulting solution is allowed to stir at RT for 1.5 h. The mixture is then poured into water. The phases are separated and the organic phase is washed with sat. aq. NaHCO_3 soln. and brine then dried over MgSO_4 , filtered and the solvent removed under reduced pressure. Flash-chromatography on silica-gel (Eluent: EtOAc / heptane / DCM 1:5:5) yields 7.15 g (68%) of the sub-title compound as a light orange oil.

LC-B: $t_R = 0.80$ min; $[M+H]^+ = 267.9$

b) A mixture of 1-(5-bromo-3,4-dihydro-1H-isoquinolin-2-yl)-propan-1-one (4 g, 13.4 mmol), glycine ester hydrochloride (2.5 g 16.1 mmol), Cs_2CO_3 (10.5 g, 32.2 mmol), rac-BINAP (0.67 g, 1.08 mmol) and $\text{Pd}_2(\text{dba})_3$ (0.49 g, 0.54 mmol) in 80 mL toluene is stirred at 90°C for 24 h then at 100°C for 29 h. After cooling the solvent is removed under reduced pressure. The residue is taken up in EtOAc. Water and sat. aq. NaHCO_3 soln. are added and the phases are separated. The resulting aq. phase is extracted twice with EtOAc. The combined organic phase is washed with water and brine then dried over Na_2SO_4 , filtered and evaporated under reduced pressure. Flash-chromatography on silica-gel (gradient of EtOAc / DCM / heptane 4:5:5 to 5:5:5) yields 1.8 g (46%) of the title compound as a yellow-orange oil.

LC-B: $t_R = 0.96$ min; $[M+H]^+ = 335.1$; $^1\text{H NMR}$ (d_6 -DMSO) δ : 7.12 (d, $J = 7.5$ Hz, $J = 8.0$ Hz, 1 H), 6.60 (d, $J = 7.5$ Hz, 1 H), 6.41 (d, $J = 8.0$ Hz, 1 H), 4.57 (s, 2 H), 4.28 (q, $J = 7.1$ Hz, 2 H), 3.95 (s, 2 H), 3.74 (t, $J = 5.9$ Hz, 2 H), 2.62 (t, $J = 5.9$ Hz, 2 H), 1.50 (s, 9 H), 1.33 (t, $J = 7.1$ Hz, 3 H)

35 Precursor C24

5-Amino-2-cyclopropylmethyl-3,4-dihydro-2H-isoquinolin-1-one hydrochloride

a) 5-Bromo-2-cyclopropylmethyl-3,4-dihydro-2H-isoquinolin-1-one

To a solution of 5-bromo-1,2,3,4-tetrahydroisoquinolin-1-one [CAS#: 1109230-25-2] (500 mg, 2.21 mmol) in 20 mL DMF cooled to 0°C is added 60% dispersion NaH in mineral oil (79.6 mg, 3.32 mmol). After gas evolution ceased bromomethylcyclopropane (299 mg, 2.21 mmol) is added and the resulting suspension is allowed to stir overnight at RT. Then another 60% dispersion NaH in mineral oil (79.6 mg, 3.32 mmol) and bromomethylcyclopropane (299 mg, 2.21 mmol) are added and the mixture is allowed to stir at RT for 3 h. The mixture is filtered and the remaining solid rinsed with DMF. The DMF is removed under reduced pressure and HV. Purification of the crude residue by HPLC (Method D) yields 209 mg (34%) of the sub-title compound as a yellow solid. LC-A: t_R = 0.86 min; $[M+H]^+$ = 282.0

b) (2-Cyclopropylmethyl-1-oxo-1,2,3,4-tetrahydro-isoquinolin-5-yl)-carbamic acid tert-butyl ester

To a solution of 5-bromo-2-cyclopropylmethyl-3,4-dihydro-2H-isoquinolin-1-one (30 mg, 0.107 mmol) in 4 mL dioxane are added *tert*-butyl carbamate (12.5 mg, 0.107 mmol), Pd₂(dba)₃ (7.4 mg, 0.00803 mmol), X-Phos (7.7 mg, 0.0161 mmol) and sodium *tert*-butoxide (15.4 mg, 0.161 mmol). The resulting reaction mixture is allowed to heat at 100°C for 3 h. After cooling the mixture is diluted in DCM and the resulting organic phase washed twice with water, dried over MgSO₄, filtered and evaporated. Purification of the residue by preparative HPLC (Method D) yields 23 mg (68%) of the sub-title compound as a yellow solid. LC-A: t_R = 0.83 min; $[M+H]^+$ = 317.2

c) To a solution of (2-cyclopropylmethyl-1-oxo-1,2,3,4-tetrahydro-isoquinolin-5-yl)-carbamic acid *tert*-butyl ester (23 mg, 0.0727 mmol, 1 eq) in 3 mL MeOH is added 1.25M HCl soln. in MeOH (0.23 mL, 0.291 mmol) at 0°C. The reaction mixture is stirred overnight at 50°C.

The solvent is removed under reduced pressure to give quantitatively the title compound as a light yellow solid.

LC-A: t_R = 0.53 min; $[M+H]^+$ = 217.2

Example 70:**rac-N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(1,1-dioxo-tetrahydro-1H-thiophen-3-yl)-acetamide**

To a solution of crude (2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetic acid **Precursor B3** (made from **Precursor C3** as described below) (100 mg, 0.297 mmol), N-benzyl-N-(1,1-dioxido-tetrahydrothien-3-yl)amine **Amine 31** (78 g, 0.297 mmol) in 2 mL DMF are added HATU (136 mg, 0.357 mmol) and DIPEA (94.2 mg, 0.743 mmol). The reaction mixture is allowed to stir at RT for 1 h. Water is added and the aq. phase is extracted twice with DCM. The resulting organic phase is washed with sat. aq NaHCO₃ soln. and brine then

dried over MgSO_4 , filtered and evaporated under reduced pressure. The crude residue is purified by prep. HPLC (Method E) to yield the title compound as a yellow solid.

LC-A: $t_R = 0.68$ min; $[\text{M}+\text{H}]^+ = 468.0$; $^1\text{H-NMR}$ (d_6 -DMSO) $T = 80^\circ\text{C}$ δ 9.63 (m, 1 H), 7.38 (m, 2 H), 7.30 (m, 3 H), 7.11 (m, 1 H), 6.52 (m, 2 H), 4.74 (m, 3 H), 4.48 (m, 1 H), 4.32 (m, 1 H), 4.09 (m, 2 H), 3.84 (m, 1 H), 3.41 (m, 1 H), 3.31 (m, 1 H), 3.00-3.16 (m, 5 H), 2.83 (m, 2 H), 2.31 (m, 2 H), 1.20 (m, 1 H), 0.72 (m, 2 H), 0.45 (m, 2 H).

rac-N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(1,1-dioxo-tetrahydro-1H-thiophen-3-yl)-acetamide hydrochloride

Pure example 70 is dissolved in EtOH. Then 1.25M HCl soln. in EtOH (2 eq.) is added and the resulting soln. is allowed to stir at RT for 10 min. The volatiles are then removed under reduced pressure and the resulting crude hydrochloride dried under HV to yield the title compound.

Examples 66–69 / 71-72 / 74-89 / 91 / 252-294 / 309-314 / 575-577 listed in **Table 5** are prepared applying the method described for **Example 70** using the corresponding **Precursor** and **Amine** respectively.

Table 5: Examples 66–69 / 71-72 / 74-89 / 91 / 252-294 / 309-314 / 575-577

Example No	Example name	t_R [min] (LC-C)	MS Data m/z $[\text{M}+\text{H}]^+$
66	N-(2-Chloro-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-ethyl-acetamide	0.89	412.4
67	N-Benzyl-N-(2-cyano-ethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.75	403.4
68	3-{Benzyl-[2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]-amino}-propionamide	0.65	421.4
69	N-Cyclopropyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2,3-dimethyl-benzyl)-acetamide	0.95	418.4
71	{Benzyl-[2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]-amino}-acetic acid ethyl ester	0.84	436.4
72	N-(2-Cyano-ethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	0.85	471.4
74	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(tetrahydro-pyran-4-yl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.89	502.4

75	N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(4-fluoro-phenyl)-ethyl]-acetamide	0.99	472.4
76	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.65	489.4
77	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(4-methyl-thiazol-2-ylmethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.95	529.3
78	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-oxo-2,3-dihydro-pyridin-4-ylmethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.76	525.4
79	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(2-oxo-imidazolidin-1-yl)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide	0.78	530.4
80	rac-2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[1-(1-ethyl-1 <i>H</i> -pyrazol-3-yl)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide	0.97	540.4
81	rac- <i>trans</i> -2-[[[2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]-(2-trifluoromethyl-benzyl)-amino]-methyl]-cyclopropanecarboxylic acid ethyl ester	0.98	544.4
82	N-(2-Benzoyloxy-ethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	1.06	552.4
83	{2-[[[2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]-(2-trifluoromethyl-benzyl)-amino]-ethyl]-methyl-carbamic acid <i>tert</i> -butyl ester	1.03	575.5
84	(<i>R</i>)-4-[[[2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]-(2-trifluoromethyl-benzyl)-amino]-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid <i>tert</i> -butyl ester	1.11	631.6
85	N-Benzyl-N-(2-dimethylamino-ethyl)-2-[2-(2,2,2-trifluoro-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-acetamide	0.76	449.4

86	N-(2-Dimethylamino-ethyl)-2-[2-(2,2,2-trifluoro-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide	0.85	517.4
87	2-[(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-methyl-amino]-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.66	503.4
88	2-(6-Chloro-2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.68	523.4
89	2-(2-Cyclopropylmethyl-6-methoxy-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.65	519.5
91	2-(2-Cyclopropylmethyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.7	517.5
Example No	Example name	t_R [min] (LC-F) unless otherwise indicated	MS Data m/z [M+H]⁺
252	4-[[2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]-(2-trifluoromethyl-benzyl)-amino]-piperidine-1-carboxylic acid <i>tert</i> -butyl ester	0.96	601.4
253	3-[[2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]-(2-trifluoromethyl-benzyl)-amino]-methyl]-pyrrolidine-1-carboxylic acid <i>tert</i> -butyl ester	0.95	601.4
254	3-[[2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]-(2-trifluoromethyl-benzyl)-amino]-pyrrolidine-1-carboxylic acid <i>tert</i> -butyl ester	0.93	587.4
255	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-pyrimidin-4-ylmethyl-acetamide	0.61 (LC-F1)	423.3
256	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-methyl-pyridin-2-ylmethyl)-acetamide	0.38	436.4

257	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-pyridin-2-ylmethyl-acetamide	0.35	422.4
258	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(5-methyl-pyridin-2-ylmethyl)-acetamide	0.39	436.4
259	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(6-methyl-pyridin-2-ylmethyl)-acetamide	0.38	436.4
260	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-pyrimidin-2-ylmethyl-acetamide	0.39 (LC-F1)	423.4
261	N-(5-Chloro-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide	0.42	456.3
262	N-(5-Chloro-pyridin-3-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide	0.38	456.3
263	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-pyridin-3-ylmethyl-acetamide	0.61 (LC-F1)	423.3
264	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-methyl-2H-pyrazol-3-ylmethyl)-acetamide	0.40 (LC-F1)	425.4
265	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-thiazol-2-ylmethyl-acetamide	0.34	428.3
266	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(4-methyl-thiazol-2-ylmethyl)-acetamide	0.38	442.3
267	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(5-fluoro-pyridin-2-ylmethyl)-acetamide	0.37	440.4
268	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-pyridin-4-ylmethyl-acetamide	0.46 (LC-F1)	422.3

269	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(5-methyl-isoxazol-3-ylmethyl)-acetamide	0.36	426.3
270	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2,6-difluoro-benzyl)-N-(2-dimethylamino-ethyl)-acetamide	0.43	457.3
271	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-fluoro-pyridin-2-ylmethyl)-acetamide	0.36	440.4
272	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-dimethylamino-pyrimidin-5-ylmethyl)-acetamide	0.66 (LC-F1)	466.4
273	{2-[[2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]-(2-trifluoromethyl-benzyl)-amino]-ethyl}-carbamic acid <i>tert</i> -butyl ester	0.89	561.3
274	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3,3-dimethyl-butyl)-N-(2-trifluoromethyl-benzyl)-acetamide	1.00	502.4
275	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3,3-dimethyl-butyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.93	503.4
276	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3,3-dimethyl-butyl)-N-(3-methyl-pyridin-2-ylmethyl)-acetamide	0.77	449.4
277	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide	0.64	565.3
278	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-{2-[methyl-(2,2,2-trifluoro-ethyl)-amino]-ethyl}-N-(2-trifluoromethyl-benzyl)-acetamide	0.92	557.3
279	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.52	566.4
280	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-[methyl-(2,2,2-trifluoro-ethyl)-amino]-ethyl]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.85	558.3

281	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(3,3-difluoro-piperidin-1-yl)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide	0.79	565.4
282	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(3,3-difluoro-pyrrolidin-1-yl)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide	0.76	551.3
283	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(3,3-difluoro-piperidin-1-yl)-ethyl]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.61	566.4
284	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(3,3-difluoro-pyrrolidin-1-yl)-ethyl]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.60	552.3
285	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-[5-(4-fluoro-phenylamino)-pyridin-2-ylmethyl]-acetamide	0.51	531.4
286	N-(2-Dimethylamino-ethyl)-2-[2-(2-fluoro-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide	0.45	481.3
287	2-(8-Chloro-2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.56	523.3
288	2-(2-Cyclopropylmethyl-8-fluoro-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.51	507.3
289	2-(2-Cyclopropylmethyl-8-fluoro-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.45	508.3
290	2-(2-Cyclopropylmethyl-6-methyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.51	503.4
291	(S)-2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-propionamide	0.51	503.4
292	1-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-cyclopropanecarboxylic acid (2-dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-amide	0.42	515.3

293	rac-N-(3-Chloro-pyridin-2-ylmethyl)-N-(2-dimethylamino-ethyl)-2-[2-((1S*,2S*)-2-fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-acetamide	0.60	488.3
294	rac-N-(3-Chloro-pyridin-2-ylmethyl)-N-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-2-[2-((1S*,2S*)-2-fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-acetamide	0.68	564.3
309	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-3-oxo-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	0.72	477.3
310	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-3-oxo-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.65	478.3
311	2-(2-Ethyl-3-oxo-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.74	503.3
312	N-(2-Dimethylamino-ethyl)-2-(2-isobutyl-3-oxo-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	0.83	505.4
313	N-(2-Dimethylamino-ethyl)-2-(2-isobutyl-3-oxo-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.76	506.3
314	2-(2-Isobutyl-3-oxo-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.85	531.4
Example No	Example name	t_R [min] (LC-A)	MS Data m/z [M+H]⁺
575	N-(3-Bromo-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide	0.58	530.1
576	N-(3-Bromo-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-hydroxy-2-methyl-propyl)-acetamide	0.72	531.2
577	N-(2-Chloro-benzyl)-2-(2-cyclopropylmethyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide	0.62	483.2

Example 73

N-(2-Amino-ethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(4-trifluoromethyl-benzyl)-acetamide is made applying the method described for **Example**

- 5 **70** using the corresponding **Precursor B3** and **Amine 71** respectively. The solid obtained is dissolved in EtOH. Then 1.25M HCl soln. in EtOH (2 eq.) is added and the resulting soln. is allowed to stir at RT for 10 min. The volatiles are then removed under reduced pressure and the resulting crude dihydrochloride dried under HV to yield the title compound. LC-A: t_R = 0.60 min; $[M+H]^+$ = 461.1

10 **Precursor B3'**

(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetic acid

- To a solution of (2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetic acid ethyl ester **Precursor C3** (2.65 g, 8.27 mmol) in 10 ml THF is added 1M aq. LiOH sol. (14.3 mL, 14.3 mmol). The reaction mixture is allowed to stir at RT overnight. The resulting yellow
15 soln. is acidified by adding 7 mL 2N aq. HCl soln. The volatiles are evaporated under reduced pressure then under HV to yield the title compound as the hydrochloride as a yellow solid which contains 1.6 equivalent of LiCl. This mixture is used without further purification in the next step.

- LC-A: t_R = 0.50 min; $[M+H]^+$ = 261.1. $^1\text{H-NMR}$ (d_6 -DMSO) δ : 7.04 (t, J = 7.8 Hz, 1 H), 6.46 (d, J = 7.6 Hz, 1 H), 6.32 (d, J = 8.1 Hz, 1 H), 4.27 (s, 2 H), 3.84 (s, 3 H), 3.46 (s, 3 H), 3.01 (d, J = 7.0 Hz, 2 H), 2.79 (s, 2 H), 1.22 (m, 1 H), 0.65 (m, 2 H), 0.42 (d, J = 4.6 Hz, 2 H)
20

- Precursors B4'-B7' / B9' / B12'-B17' / B22'-B23'** listed in **Table 6** are prepared applying the above method described for **Precursor B3'** using the corresponding **Precursor** as starting material. As for the case of **Precursor B3'**, **Precursors B4'-B7' / B9' / B12'-B17' / B22'-B23'** are obtained as a mixture with LiCl and are obtained as their hydrochloride salt if
25 they bear a basic nitrogen atom

Table 6: Precursor B4'-B7' / B9' / B12'-B17' / B22'-B23'

Precursor	Example name	t_R [min] (LC-A)	MS Data m/z $[M+H]^+$
B4'	[2-(2,2,2-Trifluoro-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-acetic acid	0.57	289.1
B5'	(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl(methyl)amino)-acetic acid	0.47	275.1

B6'	(2-Cyclopropylmethyl-6-chloro-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetic acid	0.54	295.11
B7'	(2-Cyclopropylmethyl-6-methoxy-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetic acid	0.47	291.1
B9'	(2-Cyclopropylmethyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetic acid	0.56	289.3
B12'	(2-(2-Fluoroethyl)-1,2,3,4-tetrahydroisoquinolin-5-ylamino)-acetic acid	0.42	253.2
B13'	(8-Chloro-2-(cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinolin-5-ylamino)acetic acid	0.57	295.2
B14'	(8-Fluoro-2-(cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinolin-5-ylamino)acetic acid	0.51	279.3
B15'	(2-(Cyclopropylmethyl)-6-methyl-1,2,3,4-tetrahydroisoquinolin-5-ylamino)-acetic acid	0.51	275.1
B16'	(S)-2-(2-(Cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinolin-5-ylamino)-propionic acid	0.53	275.2
B17'	1-((2-(Cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)cyclopropane-1-carboxylic acid	0.56	287.3
B22'	(2-ethyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-5-yl)aminoacetic acid	0.59	249.2
B23'	(2-isobutyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-5-yl)aminoacetic acid	nd	nd

Precursor C3**(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetic acid ethyl ester****a) (1,2,3,4-Tetrahydro-isoquinolin-5-ylamino)-acetic acid ethyl ester hydrochloride**

- 5 To a solution of 5-(ethoxycarbonylmethyl-amino)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester **Precursor D1** (20 g, 51.4 mmol) in 150 mL dioxane is added dropwise 77 mL 4*N* HCl soln. in dioxane. The resulting mixture is allowed to stir at RT overnight. The solvent is coevaporated twice with DCM under reduced pressure. The solid residue is

trituated in ether, filtered and dried under HV. This yields quantitatively the subtitle compound as a beige solid.

LC-A: $t_R = 0.52$ min; $[M+H]^+ = 235.1$

- b) To a solution of (1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetic acid ethyl ester hydrochloride (12.7 g, 42.2 mmol) in 100 mL DCM is added at RT cyclopropanecarboxaldehyde (3.66 g, 3.9 mL) and DIPEA (10.9 g, 84.4 mmol). The resulting yellow solution is allowed to stir for 1 h at RT. Then $\text{NaBH}(\text{OAc})_3$ (13.4 g, 63.3 mmol) is added in small portions and the resulting mixture is allowed to stir at RT for 1 h. Sat. aq. NaHCO_3 soln. is slowly added and the resulting aq. phase is extracted three times with DCM.
- 10 The combined organic phase is washed with sat. aq. NaHCO_3 soln. and with brine then dried over MgSO_4 , filtered and the solvent removed under reduced pressure. Flash-chromatography on silica-gel (Eluent: gradient of EtOAc / heptane / MeOH 50:50:0 to 100:0:0 to 90:0:10) yields 7.1 g (58%) of the title compound as a yellow solid.

- LC-A: $t_R = 0.62$ min; $[M+H]^+ = 289.2$. $^1\text{H-NMR}$ (CDCl_3) δ : 7.07 (t, $J = 7.7$ Hz, 1 H), 6.54 (d, $J = 7.6$ Hz, 1 H), 6.36 (d, $J = 7.9$ Hz, 1 H), 4.28 (q, $J = 7.1$ Hz, 2 H), 4.19 (t, $J = 5.0$ Hz, 1 H), 3.95 (d, $J = 5.2$ Hz, 2 H), 3.71 (s, 2 H), 2.91 (t, $J = 6.1$ Hz, 2 H), 2.67 (t, $J = 6.0$ Hz, 2 H), 2.45 (d, $J = 6.6$ Hz, 2 H), 1.33 (t, $J = 7.1$ Hz, 3 H), 1.01 (m, 1 H), 0.59 (m, 2 H), 0.21 (m, 2 H)
- 15

Precursor C4

- [2-(2,2,2-Trifluoro-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-acetic acid ethyl ester**
- 20

- To a solution of (1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetic acid ethyl ester hydrochloride (**Precursor C3** step a) (200 mg, 0.739 mmol) in 3 mL toluene is added TEA (149.5 mg, 2.95 mmol). The resulting solution is allowed to stir for 10 min at RT. Then 2,2,2-trifluoroethyltrifluoromethanesulfonate (171 mg, 0.739 mmol) is added in and the resulting mixture is allowed to stir at RT for 2 h then at reflux for 2 h. TEA (149.5 mg, 2.95 mmol) and 2,2,2-trifluoroethyltrifluoromethanesulfonate (171 mg, 0.739 mmol) are added again and the resulting suspension is allowed to stir at reflux for 2 h then at RT overnight. After cooling the reaction mixture is poured onto water. The resulting aq. phase is extracted twice with DCM. The combined organic phase is washed with sat. aq. NaHCO_3 soln. and with brine then dried over MgSO_4 , filtered and the solvent removed under reduced pressure. Flash-chromatography on silica-gel (gradient of EtOAc / heptane 5:95 to 100:0) yields 114 mg (49%) of the title compound as a yellow oil.
- 25
- 30

LC-A: $t_R = 0.77$ min; $[M+H]^+ = 317.1$

Precursor C12

- (2-(2-Fluoroethyl)-1,2,3,4-tetrahydroisoquinolin-5-ylamino)-acetic acid ethyl ester**
- 35

To a solution of (1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetic acid ethyl ester hydrochloride (**Precursor C3** step a) (100 mg, 0.32 mmol) in 1 mL DMF is added DIPEA (62 mg, 0.48 mmol). The resulting solution is allowed to stir for 10 min at RT. Then 1-bromo-2-fluoroethane (41 mg, 0.32 mmol) is added and the resulting mixture is allowed to stir at RT overnight. The reaction mixture is poured onto water and the resulting aq. phase is extracted three times with EtOAc. The combined organic phase is washed with sat. aq. NaHCO₃ soln. and with brine then dried over MgSO₄, filtered and the solvent removed under reduced pressure to yield 64 mg (71%) of the title compound as a brown oil which is used without purification in the next step.

LC-A: $t_R = 0.56$ min; $[M+H]^+ = 281.3$

Precursor C18

rac-[2-((1S*,2S*)-2-Fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-acetic acid ethyl ester

To a solution of (1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetic acid ethyl ester hydrochloride (**Precursor C3** step a) (1 g, 3.69 mmol) and cis-2-fluoro-cyclopropanecarboxylic acid (384 mg, 3.69 mmol) in 20 mL DMF is added HATU (1.69 g, 4.43 mmol) then DIPEA (1.19g, 9.23 mmol). The brown solution is stirred for overnight at RT. Sat. aq. NaHCO₃ soln. is added and the resulting aq. phase is extracted twice with EtOAc. The combined organic phase is washed with brine, dried over MgSO₄, filtered and the solvent evaporated under reduced pressure. Flash-chromatography on silica-gel (gradient of EtOAc / heptane 50:50 to 100:0) yields 747 mg (63%) of the title compound as a yellow oil.

LC-A: $t_R = 0.77$ min; $[M+H]^+ = 321.2$

Precursor C5

(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl(methyl)amino)-acetic acid ethyl ester

a) tert-Butyl 5-((2-ethoxy-2-oxoethyl)(methyl)amino)-3,4-dihydroisoquinoline-2(1H)-carboxylate

A solution of 5-(ethoxycarbonylmethyl-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester **Precursor D1** (100 g, 0.3 mmol), formaldehyde (49.9 mg, 0.59 mmol) and AcOH (36 mg, 0.59 mmol) in 2 mL DCM is stirred at RT for 1 h. Then NaBH(OAc)₃ (190 mg, 0.897 mmol) is added and the resulting mixture is allowed to stir at RT for 1 h. It is then poured onto water and the resulting aq. phase is extracted twice with DCM. The combined organic phase is washed with brine dried over MgSO₄, filtered and evaporated under reduced pressure. This yields 100 mg (96%) of the sub-title compound which is used as such in the next step.

LC-A: $t_R = 0.56$ min; $[M+H]^+ = 249.1$; 1H -NMR ($CDCl_3$) δ : 7.17 (t, $J = 7.8$ Hz, 1 H), 7.01 (d, $J = 8.0$ Hz, 1 H), 6.84 (m, 1 H), 4.58 (s, 2 H), 4.20 (q, $J = 7.2$ Hz, 2 H), 3.72 (s, 2 H), 3.60 (d, $J = 0.8$ Hz, 2 H), 2.81-2.92 (m, 5 H), 1.52 (s, 9 H), 1.28 (t, $J = 7.1$ Hz, 3 H)

b) 2-(Methyl(1,2,3,4-tetrahydroisoquinolin-5-yl)amino)acetic acid ethyl ester

- 5 To a solution of *tert*-butyl 5-((2-ethoxy-2-oxoethyl)(methyl)amino)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (100 mg, 0.248 mmol) in 2 mL DCM is added 0.5 mL TFA. The resulting yellowish solution is stirred at RT for 1.5 h then poured into water. The resulting aq. phase is made basic with sat. aq. $NaHCO_3$ soln. then extracted twice with DCM. The organic phase is washed with brine then dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to yield 61 mg (99%) of the sub-title compound which is used as such in the next step.

LC-A: $t_R = 0.95$ min; $[M+H]^+ = 349.2$

- c) To a solution of 2-(methyl(1,2,3,4-tetrahydroisoquinolin-5-yl)amino)acetic acid ethyl ester (61 mg, 0.214 mmol) in 2 mL DMF is added K_2CO_3 (29.5 mg, 0.214 mmol). The resulting mixture is allowed to stir for 20 min at RT. Then bromomethylcyclopropane (28.9 mg, 0.214 mmol) is added and the resulting yellow mixture is allowed to stir at RT for 2 h. The mixture is poured into water and the resulting aq. phase is extracted three times with EtOAc. The combined organic phase is washed with sat. aq. $NaHCO_3$ soln., with brine then dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Drying under HV yields 59 mg (91%) of the title compound as a yellow oil.

LC-A: $t_R = 0.64$ min; $[M+H]^+ = 303.2$

Precursor C6

(6-Chloro-2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetic acid ethyl ester

- 25 a) (6-Chloro-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetic acid ethyl ester

To a solution of 6-chloro-5-(ethoxycarbonylmethyl-amino)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester **Precursor D6** (215 mg, 0.583 mmol) in 4 mL DCM is added 1 mL TFA. The resulting yellowish solution is stirred at RT for 1 h then poured into water. The resulting aq. phase is made basic with sat. aq. $NaHCO_3$ soln. then extracted twice with DCM.

- 30 The organic phase is washed with brine then dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to yield 149 mg (95%) of the sub-title compound used as such in the next step.

LC-A: $t_R = 0.58$ min; $[M+H]^+ = 269.1$

- b) To a solution of (6-chloro-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetic acid ethyl ester (145 mg, 0.54 mmol) in 4 mL DMF is added K_2CO_3 (74.6 mg, 0.54 mmol). The resulting mixture is allowed to stir for 20 min at RT. Then bromomethylcyclopropane (72.8 mg, 0.54

mmol) is added and the resulting yellow mixture is allowed to stir at RT for 4.5 h. The mixture is poured onto water and the resulting aq. phase is extracted three times with DCM. The combined organic phase is washed with sat. aq. NaHCO₃ soln. and with brine then dried over MgSO₄, filtered and the solvent removed under reduced pressure. Flash-chromatography on silica-gel (Eluent: gradient of EtOAc / heptane 5:95 to 100:0) yields 145 mg (83%) of the title compound as a yellow oil.

LC-A: t_R = 0.65 min; $[M+H]^+$ = 323.1

Precursors C7 / C9 and C13-C15 listed in **Table 7** are prepared applying the above method described for **Precursor C6** using the corresponding **Precursors D7 / C8** and **D13-D15** respectively as starting material.

Table 7: Precursor C7 / C9 and C13-C15

Precursor	Example name	t_R [min] (LC-A)	MS Data m/z $[M+H]^+$
C7	(2-Cyclopropylmethyl-6-methoxy-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetic acid ethyl ester	0.61	319.2
C9	(2-Cyclopropylmethyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetic acid ethyl ester	0.68	317.2
C13	(8-Chloro-2-(cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinolin-5-ylamino) acetic acid ethyl ester	0.67	323.2
C14	(8-Fluoro-2-(cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinolin-5-ylamino) acetic acid ethyl ester	0.62	307.3
C15	(6-Methyl-2-(cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinolin-5-ylamino) acetic acid ethyl ester	0.64	303.2

Precursor D6 6-Chloro-5-(ethoxycarbonylmethyl-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester, LC-A: t_R = 0.97 min; $[M+H]^+$ = 369.0, **Precursor D7 6-Methoxy-5-(ethoxycarbonylmethyl-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester**, LC-A: t_R = 0.91 min; $[M+H]^+$ = 365.1 and **Precursor D15 6-Methyl-5-(ethoxycarbonylmethyl-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester**, LC-A: t_R = 0.95 min; $[M+H]^+$ = 349.2 are made according to the procedure described for the synthesis of **Precursor D1** using the appropriate starting materials.

Precursor D13

8-Chloro-5-(ethoxycarbonylmethyl-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

a) 8-chloro-5-nitro-1,2,3,4-tetrahydroisoquinoline

To a solution of 8-chloro-5-nitroisoquinoline (630 mg, 3.02 mmol) in 7 mL AcOH cooled to 0°C in an ice-bath is added NaBH₄ (685 mg, 18.1 mmol). The resulting mixture is stirred at 0°C for 30 min then poured into ice-cold water. Sat. aq. NH₃ soln. is added and the resulting aq. phase is extracted twice with DCM. The organic phase is washed with brine then dried over MgSO₄, filtered and the solvent removed under reduced pressure to yield 520 mg (81%) of the sub-title compound used as such in the next step.

LC-A: $t_R = 0.45$ min; $[M+H]^+ = 213.1$

b) *tert*-Butyl 8-chloro-5-nitro-3,4-dihydroisoquinoline-2(1H)-carboxylate

To a solution of 8-chloro-5-nitro-1,2,3,4-tetrahydroisoquinoline (520 mg, 2.23 mmol) in a mixture of 5 mL THF and 10 mL is added NaOH (356 mg, 8.9 mmol) and Boc₂O (729 mg, 3.34 mmol). The resulting mixture is stirred at RT 2 h then poured into water. The resulting aq. phase is extracted twice with EtOAc. The organic phase is washed with brine then dried over MgSO₄, filtered and the solvent removed under reduced pressure. Flash-chromatography on silica-gel: (Eluent: Hept. / EtOAc 95:5 to 60:40) yields 503 mg (72%) of the sub-title compound as a yellow solid.

LC-A: $t_R = 0.97$ min; $[M+H]^+ =$ n.d.; ¹H NMR (CDCl₃), δ : 7.84 (d, $J = 8.7$ Hz, 1 H), 7.43 (d, $J = 8.7$ Hz, 1 H), 4.68 (bs, 2 H), 3.66 (t, $J = 5.8$ Hz, 2 H), 3.13 (t, $J = 5.8$ Hz, 2 H), 1.54 (m, 9 H)

c) *tert*-Butyl 5-amino-8-chloro-3,4-dihydroisoquinoline-2(1H)-carboxylate

To a solution of *tert*-butyl 8-chloro-5-nitro-3,4-dihydroisoquinoline-2(1H)-carboxylate (300 mg, 0.873 mmol) in 15 mL EtOH is added SnCl₂·2H₂O (591 mg, 2.62 mmol). The resulting mixture is heated at 70°C for 2 h then stirred at RT overnight. The mixture is poured into water then put to pH=8-9 with sat. aq. NaHCO₃ soln. and extracted three times with DCM. The combined organic phase is washed with water and brine then dried over MgSO₄ and concentrated *in vacuo*. Flash-chromatography on silica-gel: (Eluent: Hept. / EtOAc 95:5 to 60:40) yields 198 mg (80%) of the sub-title compound as an orange solid.

LC-A: $t_R = 0.92$ min; $[M-tBu+MeCN]^+ = 268.0$; ¹H-NMR (400 MHz, CDCl₃) δ : 7.06 (d, $J = 8.4$ Hz, 1 H), 6.56 (d, $J = 8.4$ Hz, 1 H), 4.56 (s, 2 H), 3.71 (t, $J = 5.8$ Hz, 2 H), 3.63 (bs, 2 H), 2.56 (t, $J = 5.8$ Hz, 2 H), 1.52 (s, 9 H).

d) To a solution of *tert*-butyl 5-amino-8-chloro-3,4-dihydroisoquinoline-2(1H)-carboxylate (198 mg, 0.7 mmol) in 3 mL MeCN is added DIPEA (109 mg, 0.84 mmol). The mixture is stirred at RT for 10 min and ethyl bromoacetate (170 mg, 1.02 mmol) is added. The solution is stirred at reflux for 1 h and then allowed to cool down to RT. The mixture is poured into water and

extracted twice with DCM. The combined organic phase is washed with sat. aq. NaHCO₃ soln. and brine then dried over MgSO₄ and concentrated *in vacuo*.

Flash-chromatography on silica-gel: (Eluent: Hept. / EtOAc 95:5 to 60:40) yields 90 mg (35%) of the title compound as a yellow oil.

- 5 LC-A: t_R = 0.98 min; $[M-tBu+MeCN]^+$ = 354.0

Precursor D14

8-Fluoro-5-(ethoxycarbonylmethyl-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic

acid *tert*-butyl ester is made according to the procedure described for the synthesis of **Precursor D13** starting from 8-fluoro-5-nitro-1,2,3,4-tetrahydroisoquinoline and following

- 10 steps b), c) and d) cited above.

LC-A: t_R = 0.95 min; $[M+H]^+$ = 353.1.; ¹H-NMR (400 MHz, d₆-DMSO) δ : 6.86 (dd, $J_1 = J_2 = 9.0$ Hz, 1 H), 6.25 (dd, $J_1 = 4.6$ Hz, $J_2 = 9.0$ Hz, 1 H), 5.30 (m, 1 H), 4.45 (s, 2 H), 4.11 (q, $J = 7.1$ Hz, 2 H), 3.91 (d, $J = 6.3$ Hz, 2 H), 3.60 (t, $J = 5.4$ Hz, 2 H), 1.43 (m, 11 H), 1.19 (t, $J = 7.1$ Hz, 4 H)

- 15 **Precursor C16**

2-(S)-(2-(Cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinolin-5-ylamino)-propionic acid ethyl ester

a) 2-(S)-isoquinolin-5-ylaminopropionic acid ethyl ester

- To a solution of 5-bromoisoquinoline (300 mg, 1.41 mmol), L-ethyl 2-aminopropanoate hydrochloride (217 mg, 1.41 mmol), Cs₂CO₃ (1105 mg, 3.39 mmol), Brettphos (75.9 mg, 0.141 mmol) and Pd₂(dba)₃ (65 mg, 0.0707 mmol) in a microwave tube is added under inert atmosphere 3 mL degassed toluene. The mixture is irradiated under microwaves at 140°C for 30min then at 150°C for 30min. Subsequently Cs₂CO₃ (460mg), Brettphos (30mg) and Pd₂(dba)₃ (30mg) are added again and the resulting mixture is irradiated at 150°C for 30min.
- 25 The brownish suspension is diluted in EtOAc and sat. aq. NaHCO₃ soln. is added. The organic layer is separated and the aq. layer is extracted twice with EtOAc. The combined organic layers are washed with water and brine, dried over MgSO₄, filtered and evaporated. Flash-chromatography on silica-gel: (Eluent: Hept. / EtOAc 95:5 to 20:80 to 0:100) yields 137 mg (40%) of the sub-title compound as a yellow oil.

- 30 LC-A: t_R = 0.58 min; $[M+H]^+$ = 246.3

b) 2-(S)-(1,2,3,4-Tetrahydroisoquinolin-5-ylamino)-propionic acid ethyl ester

A solution of 2-(S)-isoquinolin-5-ylaminopropionic acid ethyl ester (136 mg, 0.418 mmol) in 8 mL AcOH is purged three times with Argon then PtO₂ (28.4 mg, 0.125 mmol) is carefully added and the resulting dark mixture is stirred under H₂ atmosphere at RT for 5 h. It is then

filtered over Celite, and the filter cake rinsed with AcOH. Evaporation of the solvent *in vacuo* yields 198 mg of the sub-title compound as a brown oil which is use as such in the next step.

- c) To a solution of 198 mg of 2-(S)-(1,2,3,4-tetrahydroisoquinolin-5-ylamino)-propionic from step b) dissolved in 4 mL DMF is added K₂CO₃ (132 mg, 0.96 mmol). The resulting
5 yellow suspension is allowed to stir at RT for 10 min. Then (bromomethyl)cyclopropane (64 mg, 0.474 mmol) is added and the reaction mixture is allowed to stir at RT overnight. It is then poured into water and the resulting aq. phase is extracted three times with DCM. The combined organic phase is washed with sat. aq. NaHCO₃ sol., then with brine, dried over MgSO₄, filtered and evaporated under reduced pressure. Flash-chromatography on silica-
10 gel: (Eluent: Hept. / EtOAc 95:5 to 20:80 to 0:100) yields 118 mg (58%) of the title compound as a yellow oil.

LC-A: t_R = 0.64 min; [M+H]⁺ = 303.3; ¹H-NMR (400 MHz, CDCl₃) δ : 7.04 (t, J = 7.8 Hz, 1 H), 6.52 (d, J = 7.8 Hz, 1 H), 6.41 (d, J = 7.8 Hz, 1 H), 4.20 (m, 3 H), 4.06 (d, J = 8.1 Hz, 1 H), 3.71 (s, 2 H), 2.91 (t, J = 6.0 Hz, 2 H), 2.66 (m, 2 H), 2.45 (d, J = 6.5 Hz, 2 H), 1.51 (d, J =
15 6.8 Hz, 3 H), 1.28 (t, J = 7.1 Hz, 4 H), 1.01 (m, 2 H), 0.59 (m, 2 H), 0.21 (m, 2 H).

Precursor C17

- 1-((2-(Cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)cyclopropane-1-carboxylic acid ethyl ester** is made according to the procedure described for the synthesis of **Precursor C16** using 1-amino-cyclopropyl-1-carboxylic acid ethyl ester hydrochloride
20 instead of L-ethyl 2-aminopropanoate hydrochloride in step a)

LC-A: t_R = 0.67 min; [M+H]⁺ = 315.3

Precursor C22

(2-Ethyl-3-oxo-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetic acid ethyl ester

a) 5-bromo-2-ethyl-1,4-dihydro-2H-isoquinolin-3-one

- [Org. Process R&D **2010**, 14, 1, 227] To a solution of ethyl 2-bromophenylacetamide
25 [1150114-52-1] (10.85g, 44.8 mmol) in 46.1 mL Eaton's reagent is added paraformaldehyde (1.7 g, 53.8 mmol) and the resulting mixture is heated to 80°C. for 2.5 h. After cooling the reaction mixture is diluted with water and basified with 50% aq. NaOH soln. to pH=8. The resulting aq. Phase is extracted three times with EtOAc. The combined organic phase is
30 washed with brine, then dried over MgSO₄, filtered and the solvent removed under reduced pressure. Flash-chromatography on silica-gel: (Eluent: Hept. / EtOAc 90:10 to 50:50) yields 3.475 g (31%) of the sub-title compound as a white solid.

LC-A: t_R = 0.75 min; [M+H]⁺ = 254.0; ¹H-NMR (400 MHz, CDCl₃) δ : 7.53 (dd, J_1 = 2.5 Hz, J_2 = 6.5 Hz, 1 H), 7.15 (m, 2 H), 4.54 (s, 2 H), 3.71 (t, J = 1.6 Hz, 2 H), 3.62 (q, J = 7.2 Hz, 2 H),
35 1.24 (t, J = 7.2 Hz, 3 H)

b) 5-(Benzhydrylidene-amino)-2-ethyl-1,4-dihydro-2H-isoquinolin-3-one

To a solution of 5-bromo-2-ethyl-1,4-dihydro-2H-isoquinolin-3-one (3475 mg, 13.7 mmol) in 50 mL degassed toluene are added Pd₂(dba)₃ (977 mg, 1.07 mmol), BINAP (1873 mg, 3.01 mmol) and 0.5M KHMDs soln. in toluene (54.6 mL, 27.3 mmol) followed by benzophenone imine (7665 mg, 41 mmol) and the resulting reaction mixture is allowed to stir at 120°C for 1.25 h. After cooling, sat. aq. NH₄Cl soln. and water (1:1) are added and the resulting aq. phase is extracted with DCM. The combined organic phase is washed with sat. aq. NaHCO₃ soln. and brine then dried over MgSO₄, filtered and the solvent removed under reduced pressure. Flash-chromatography on silica-gel: (Eluent: Hept. / EtOAc 95:5 to 70:30 then change of eluents: Hept. /EtOAc/TEA 9 : 1 : 0.1 to 70 : 30 : 0.1) yields 762 mg (16%) of the sub-title compound as an orange solid.

LC-A: t_R = 0.92 min; [M+H]⁺ = 355.2

c) 5-Amino-2-ethyl-1,4-dihydro-2H-isoquinolin-3-one

To a solution of 5-(benzhydrylidene-amino)-2-ethyl-1,4-dihydro-2H-isoquinolin-3-one (762 mg, 2.15 mmol) in 20 mL MeOH is added sodium acetate (423 mg, 5.16 mmol) and hydroxylamine hydrochloride (270 mg, 3.89 mmol). The resulting reaction mixture is stirred at RT for 45 min. 1N aq. NaOH soln. is added and the resulting aq. phase is extracted twice with DCM. The combined organic phase is washed with brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The resulting crude sub-title compound (500 mg) is used as such in the next step.

LC-A: t_R = 0.61 min; [M+H]⁺ = 191.34

d) To a solution of 5-amino-2-ethyl-1,4-dihydro-2H-isoquinolin-3-one (409 mg, 2.15 mmol) and DIPEA (556 mg, 4.3 mmol) in 8 mL anhydrous dioxane is heated at 60°C. Ethyl bromoacetate (395 mg, 2.36 mmol) is added slowly. The resulting reaction mixture is shaken at 60°C for 3.5 h. Then ethyl bromoacetate (72.6 mg, 0.436 mmol) is added again and further stirred at 60°C. After 5 h ethyl bromoacetate (36 mg, 0.218 mmol) is added again and the resulting mixture stirred at 60°C overnight. After cooling, the mixture is concentrated to dryness then partitioned between EtOAc and water. The resulting organic layer is washed with brine, dried over MgSO₄, filtered and concentrated to dryness. The crude residue is purified by prep. HPLC (Method D) to yield 285 mg (48%) of the title compound as a yellow solid.

LC-A: t_R = 0.74 min; [M+H]⁺ = 277.16; ¹H-NMR (400 MHz, CDCl₃) δ : 7.17 (t, J = 7.9 Hz, 1 H), 6.63 (d, J = 7.6 Hz, 1 H), 6.44 (d, J = 8.1 Hz, 1 H), 4.53 (s, 2 H), 4.29 (q, J = 7.1 Hz, 2 H), 3.95 (s, 2 H), 3.61 (q, J = 7.1 Hz, 2 H), 3.45 (s, 2 H), 1.33 (t, J = 7.1 Hz, 3 H), 1.24 (t, J = 7.1 Hz, 3 H)

Precursor C23**(2-Isobutyl-3-oxo-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetic acid ethyl ester**

Is made according to the procedure described for the synthesis of Precursor C22 using the corresponding starting material. LC-B: t_R = 0.75 min; $[M+H]^+$ = 305.1; 1H -NMR (400 MHz, $CDCl_3$) δ : 7.16 (t, J_1 = 7.6 Hz, J_2 = 8.1 Hz 1 H), 6.61 (d, J = 7.6 Hz, 1 H), 6.44 (d, J = 8.1 Hz, 1 H), 4.49 (s, 2 H), 4.29 (q, J = 7.1 Hz, 2 H), 3.95 (s, 2 H), 3.47 (s, 2 H), 3.39 (d, J = 7.6 Hz, 2 H), 2.10 (m, 1 H), 1.33 (t, J = 7.1 Hz, 3 H), 0.96 (d, J = 6.7 Hz, 6 H)

Example 92:

5-((E)-2-[(2-Chloro-benzyl)-ethyl-carbamoyl]-vinyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

To a solution of 5-((E)-2-carboxy-vinyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester **Precursor E1** (50 mg, 0.165 mmol), (2-chloro-benzyl)-ethyl-amine **Amine 1** (27.8 mg, 0.165 mmol) and HATU (75.2 mg, 0.412 mmol) in 1 mL DCM is added DIPEA (53.3 mg, 0.412 mmol). The reaction mixture is allowed to stir at RT for 1 h. Water is added and the resulting organic phase is washed with sat. aq $NaHCO_3$ soln. and brine then dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude residue is purified by prep. HPLC (Method E) to yield the title compound as a yellow oil.

LC-A: t_R = 1.03 min; $[M+H]^+$ = 455.3; 1H -NMR (d_6 -DMSO): 60:40 mixture of rotamers δ 7.82-7.68 (m, 1.6 H), 7.45 (m, 1.4H), 7.31-7.08 (m, 5.6 H), 6.83 (d, J =14.0 Hz), 4.84 (s, 0.8 H), 4.68 (s, 1.2 H), 4.50 (m, 2H), 2.84 (bs, 1.2H), 2.74 (bs, 0.8 H), 1.41 (s, 9H), 1.14 (bs, 1.8H), 1.06 (bs, 1.2). Some peaks are missing due to irradiation of residual water peak.

Examples 93-101 / 316-350 listed in **Table 8** are prepared applying the method described for **Example 92** using the corresponding **Precursor** and **Amine** respectively.

Table 8: Examples 93–101 / 316-350

Example No	Example name	t_R [min] (LC-C)	MS Data m/z $[M+H]^+$
93	5-((E)-2-[Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-vinyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.96	464.4
94	5-((E)-2-(Benzyl-ethoxycarbonylmethyl-carbamoyl)-vinyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	1.28	479.4
95	5-((E)-2-[Benzyl-(1,1-dioxo-tetrahydro-1 <i>H</i> -thiophen-3-yl)-carbamoyl]-vinyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	1.18	511.3

96	5-((E)-2-[(1-Methyl-piperidin-4-yl)-(2-trifluoromethyl-benzyl)-carbamoyl]-vinyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	1.02	558.5
97	5-((E)-2-[(2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl]-propenyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	1.03	546.5
98	5-{2-[(2-Chloro-benzyl)-(2-dimethylamino-ethyl)-carbamoyl]-ethyl}-3,4-dihydro-1H-isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.99	500.4
99	5-{2-[(2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl]-ethyl}-3,4-dihydro-1H-isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	1.02	534.4
100	5-{2-[(1-Methyl-piperidin-4-yl)-(2-trifluoromethyl-benzyl)-carbamoyl]-ethyl}-3,4-dihydro-1H-isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	1.01	560.4
101	5-[[Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methoxy]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.93	468.4
Example No	Example name	t_R [min] (LC-F)	MS Data m/z [M+H] ⁺
316	(E)-N-Benzyl-N-(1,1-dioxo-tetrahydro-1H-thiophen-3-yl)-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-acrylamide	0.61	469.3
317	(E)-N-(2-Dimethylamino-ethyl)-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-N-(2-trifluoromethyl-benzyl)-acrylamide	0.47	490.3
318	(E)-N-(2-Dimethylamino-ethyl)-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acrylamide	0.4	491.3
319	{2-[(E)-3-[2-(2-Methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-acryloyl]-(2-trifluoromethyl-benzyl)-amino}-ethyl}-methyl-carbamic acid <i>tert</i> -butyl ester	0.9	576.3
320	(E)-N-(3,3-Dimethyl-butyl)-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-N-(3-methyl-pyridin-2-ylmethyl)-acrylamide	0.71	450.4
321	(E)-N-(2-Hydroxy-3-methoxy-propyl)-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-N-(2-trifluoromethyl-benzyl)-acrylamide	0.71	507.3
322	(E)-N-[2-(4,4-Difluoro-piperidin-1-yl)-ethyl]-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acrylamide	0.49	567.3

323	(E)-N-(2-Hydroxy-2-methyl-propyl)-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-N-(2-trifluoromethyl-benzyl)-acrylamide	0.74	491.3
324	(E)-3-[2-(2-Methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-N-(3-methyl-oxetan-3-ylmethyl)-N-(2-trifluoromethyl-benzyl)-acrylamide	0.75	503.3
325	(E)-N-(3-Hydroxy-3-methyl-butyl)-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-N-(2-trifluoromethyl-benzyl)-acrylamide	0.76	505.3
326	(E)-N-(3-Chloro-pyridin-2-ylmethyl)-N-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-acrylamide	0.44	533.3
327	(E)-N-(3-Chloro-pyridin-2-ylmethyl)-N-(2-dimethylamino-ethyl)-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-acrylamide	0.37	457.3
328	(E)-N-(3-Chloro-pyridin-2-ylmethyl)-N-(2-hydroxy-2-methyl-propyl)-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-acrylamide	0.6	458.3
329	(E)-N-(3-Chloro-pyridin-2-ylmethyl)-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-hydroxy-2-methyl-propyl)-acrylamide	0.63	454.3
330	rac-(E)-N-(3-Chloro-pyridin-2-ylmethyl)-N-(2-dimethylamino-ethyl)-3-[2-((1 <i>R</i> *,2 <i>R</i> *)-2-fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-acrylamide	0.62	485.3
331	rac-(E)-N-(3-Chloro-pyridin-2-ylmethyl)-3-[2-((1 <i>R</i> *,2 <i>R</i> *)-2-fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-N-(2-hydroxy-2-methyl-propyl)-acrylamide	0.97	486.3
332	rac-(E)-N-(3-Chloro-pyridin-2-ylmethyl)-N-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-3-[2-((1 <i>R</i> *,2 <i>R</i> *)-2-fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-acrylamide	0.69	561.3
333	(E)-N-(3-Chloro-pyridin-2-ylmethyl)-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-acrylamide	0.39	453.3
334	(E)-N-(3-Chloro-pyridin-2-ylmethyl)-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-acrylamide	0.47	529.3
335	N-(2-Dimethylamino-ethyl)-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-N-(2-trifluoromethyl-benzyl)-propionamide	0.46	492.3

336	N-(2-Dimethylamino-ethyl)-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-propionamide	0.4	493.4
337	{2-[[3-[2-(2-Methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-propionyl]-(2-trifluoromethyl-benzyl)-amino]-ethyl}-methyl-carbamic acid <i>tert</i> -butyl ester	0.9	578.4
338	N-(3,3-Dimethyl-butyl)-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-N-(3-methyl-pyridin-2-ylmethyl)-propionamide	0.69	452.4
339	N-(2-Hydroxy-3-methoxy-propyl)-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-N-(2-trifluoromethyl-benzyl)-propionamide	0.7	509.4
340	N-[2-(4,4-Difluoro-piperidin-1-yl)-ethyl]-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-propionamide	0.48	569.4
341	N-(2-Hydroxy-2-methyl-propyl)-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-N-(2-trifluoromethyl-benzyl)-propionamide	0.73	493.4
342	N-{2-[(2-Fluoro-ethyl)-methyl-amino]-ethyl}-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-N-(2-trifluoromethyl-benzyl)-propionamide	0.48	524.3
343	3-[2-(2-Methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-N-(3-methyl-oxetan-3-ylmethyl)-N-(2-trifluoromethyl-benzyl)-propionamide	0.75	505.3
344	N-(3-Hydroxy-3-methyl-butyl)-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-N-(2-trifluoromethyl-benzyl)-propionamide	0.75	507.4
345	N-(3-Chloro-pyridin-2-ylmethyl)-N-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-propionamide	0.44	535.3
346	N-(3-Chloro-pyridin-2-ylmethyl)-N-(2-dimethylamino-ethyl)-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-propionamide	0.37	459.3
347	N-(3-Chloro-pyridin-2-ylmethyl)-N-(2-hydroxy-2-methyl-propyl)-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-propionamide	0.6	460.3
348	N-[2-(Allyl-methyl-amino)-ethyl]-3-(2-allyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-trifluoromethyl-benzyl)-propionamide	0.5	500.3

349	3-(2-Allyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-propionamide	0.47	474.4
350	rac-2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-propionamide	0.49	504.4

Precursor E1**5-((E)-2-Carboxy-vinyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester**

To a solution of malonic acid (104 mg, 0.995 mmol) in a mixture of 0.02 mL piperidine and 2 mL pyridine is added 5-formyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (100 mg, 0.383 mmol) the resulting yellow solution is allowed to stir at reflux for 2.5 h. After cooling the reaction mixture is poured onto DCM and the resulting organic phase is washed with water, 1M aq. HCl soln. then brine. It is then dried over MgSO₄, filtered and evaporated under reduced pressure to yield 115 mg (99%) of the title compound as a yellow solid which is used as such in the next step.

LC-B: $t_R = 0.84$ min; $[M + H]^+ = 304.2$; ¹H-NMR (CDCl₃): δ 8.07 (d, $J = 15.8$ Hz, 1 H), 7.51 (d, $J = 7.6$ Hz, 1 H), 7.25 (m, 1 H), 7.19 (m, 1 H), 6.41 (d, $J = 15.8$ Hz, 1 H), 4.62 (s, 2 H), 3.71 (t, $J = 6.0$ Hz, 2 H), 2.98 (t, $J = 6.0$ Hz, 2 H), 1.52 (s, 9 H)

Precursor E2**5-((E)-2-Carboxy-propenyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester**

A solution of 5-formyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (400 mg, 1.53 mmol), propionic anhydride (4040 mg, 31 mmol) and NaOAc (126 mg, 1.53 mmol) is heated under microwave irradiation at 180°C for 5 h. After cooling the reaction mixture is poured onto DCM and the resulting organic phase is washed with water, 1M aq. HCl soln. then brine. It is then dried over MgSO₄, filtered and evaporated under reduced pressure. The crude residue is purified by prep. HPLC (Method E) to yield 14 mg (3%) of the title compound as a yellow oil.

LC-A: $t_R = 1.00$ min; $[M + H]^+ =$ n.d.

Precursor E3**(E)-3-(2-(2-methoxyethyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)acrylic acid**

a) (E)-5-(3-Ethoxy-3-oxoprop-1-en-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylic acid *tert*-butyl ester

To a solution of 5-((E)-2-carboxy-vinyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester **Precursor E1** (5.32 g, 17.5 mmol) dissolved in 100 mL MeCN are added Cs₂CO₃ (5.71 g, 17.5 mmol) and ethyl iodide (2.74 g, 17.5 mmol). The resulting suspension is

allowed to stir at 55°C for 5 h. It is allowed to cool down to room temperature the poured into water. The resulting aq. phase is extracted three times with DCM. The combined organic phase is washed with water and brine then dried over MgSO₄, filtered and the solvent evaporated under reduced pressure to yield 5.39 g (93%) of the sub-title compound as a yellow oil. LC-A: t_R = 0.82 min; [M+H]⁺ = n.d. ¹H-NMR (400 MHz, d₆-DMSO) δ : 7.86 (d, J = 15.9 Hz, 1 H), 7.62 (t, J = 4.8 Hz, 1 H), 7.24 (m, 2 H), 6.51 (d, J = 15.9 Hz, 1 H), 4.51 (s, 2 H), 4.20 (q, J = 7.1 Hz, 2 H), 3.58 (t, J = 5.8 Hz, 2 H), 2.87 (t, J = 5.9 Hz, 2 H), 1.43 (s, 9 H), 1.27 (t, J = 7.1 Hz, 3 H)

b) (E)-3-(1,2,3,4-Tetrahydroisoquinolin-5-yl)acrylic acid ethyl ester hydrochloride

- 10 To a solution of (E)-5-(3-ethoxy-3-oxoprop-1-en-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylic acid *tert*-butyl ester (2.9 g, 8.75 mmol) in 20 mL DCM is added dropwise 4N HCl soln. in dioxane (6.6 mL, 26.3 mmol). The resulting solution is allowed to stir at RT for 2 h. The solvent is the removed under reduced pressure, the residue is taken up in DCM and evaporated again under reduced pressure, then under HV to yield quantitatively 2.38 g of the sub-title compound as a yellow solid.

LC-A: t_R = 0.57 min; [M+H]⁺ = 232.3

c) (E)-3-(2-(2-Methoxyethyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)acrylic acid ethyl ester

- 20 To a solution of (E)-3-(1,2,3,4-tetrahydroisoquinolin-5-yl)acrylic acid ethyl ester hydrochloride (2.38g, 8.89 mmol) in 30 mL DMF is added K₂CO₃ (2.46 g, 17.6 mmol) and 2-bromoethylmethylether (1.24 g, 8.89 mmol) and the resulting suspension is allowed to stir at 65°C for 5 h. After cooling, water is added and the resulting aq. phase is extracted twice with EtOAc. The combined organic phase is washed with sat. aq. NaHCO₃ soln. and brine then dried over MgSO₄, filtered and the solvent evaporated under reduced pressure. Flash-chromatography on silica-gel: (Eluent: Hept. / EtOAc 70:30 to 40:60) yields 1.6 g (62%) of the sub-title compound as a yellow oil.

LC-A: t_R = 0.61 min; [M+H]⁺ = 290.0; ¹H-NMR (400 MHz, d₆-DMSO) δ : 7.83 (d, J = 15.9 Hz, 1 H), 7.58 (d, J = 7.4 Hz, 1 H), 7.15 (m, 2 H), 6.50 (d, J = 15.9 Hz, 1 H), 4.20 (q, J = 7.1 Hz, 2 H), 3.60 (s, 2 H), 3.52 (t, J = 5.8 Hz, 2 H), 3.26 (s, 3 H), 2.87 (t, J = 5.8 Hz, 2 H), 2.74 (t, J = 5.7 Hz, 2 H), 2.64 (t, J = 5.8 Hz, 2 H), 1.26 (t, J = 7.1 Hz, 3 H)

- 30 d) To a solution of (E)-3-(2-(2-methoxyethyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)acrylic acid ethyl ester (1.6 g, 5.5 mmol) in 20 mL THF is added at RT 1M LiOH aq. soln. (11.1 mL, 11.1 mmol). The reaction mixture is stirred overnight at RT. and is then acidified to pH = 4 with 1M aq. HCl soln. to afford 1.77 g of the title compound (93%) after evaporation of the volatiles followed by a second evaporation after addition of DCM and drying under HV.

LC-A: t_R = 0.48 min; $[M+H]^+$ = 262.4; 1H -NMR (400 MHz, d_6 -DMSO) δ : 7.75 (d, J = 15.8 Hz, 1 H), 7.63 (d, J = 7.6 Hz, 1 H), 7.23 (m, 2 H), 6.47 (d, J = 15.8 Hz, 1 H), 4.12 (s, 2 H), 3.71 (d, J = 4.3 Hz, 2 H), 3.30 (s, 3 H), 3.25 (m, 2 H), 3.09 (m, 4 H).

Precursor E4

5 **rac-(E)-3-[2-((1*S**,2*S**)-2-Fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-acrylic acid**

a) rac-(E)-3-[2-((1*S**,2*S**)-2-Fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-acrylic acid ethyl ester

To a solution of (E)-3-(1,2,3,4-tetrahydroisoquinolin-5-yl)acrylic acid ethyl ester
 10 hydrochloride (800 mg, 2.99 mmol) and *cis*-2-fluoro-cyclopropanecarboxylic acid (311 mg, 2.99 mmol) in 8 mL DMF are added HATU (1363 mg, 3.59 mmol) then DIPEA (965 mg, 7.47 mmol). The yellow solution is stirred for 1.5 h at RT. Water is then added and the resulting aq. phase is extracted twice with DCM. The combined organic phase is washed with sat. aq. $NaHCO_3$ soln. and brine then dried over $MgSO_4$ and the solvent is removed under reduced
 15 pressure. Flash-chromatography on silica-gel: (Eluent: Hept. / EtOAc 70:30 to 20:80) yields 864 mg (91%) of the sub-title compound as a yellow oil.

LC-A: t_R = 0.83 min; $[M+H]^+$ = 318.1

b) The title compound is obtained as a white foam in 80% yield following the procedure describe for **Precursor E3** step d) starting from (E)-3-(2-(*cis*-2-fluorocyclopropane-1-
 20 carbonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)acrylic acid ethyl ester.

LC-A: t_R = 0.68 min; $[M+H]^+$ = 290.0

Precursor E5

(E)-3-(2-(cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)acrylic acid

a) (E)-3-(2-(Cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)acrylic acid ethyl ester

To a solution of (E)-3-(1,2,3,4-tetrahydroisoquinolin-5-yl)acrylic acid ethyl ester
 25 hydrochloride (800 mg, 2.99 mmol) dissolved in 8 mL DCM (**Precursor E3** step b) is added cyclopropanecarboxaldehyde (419 mg, 5.98 mmol) and DIPEA (772 mg, 5.98 mmol). The yellow suspension is allowed to stir for 10 min at RT, then $NaBH(OAc)_3$ is added and the resulting mixture is allowed to stir at RT for 1.5 h. Water is then added and the resulting aq.
 30 phase is extracted three times with DCM. The combined organic phase is washed with sat. aq. $NaHCO_3$ soln. and brine then dried over $MgSO_4$ and the solvent is removed under reduced pressure. Flash-chromatography on silica-gel: (Eluent: Hept. / EtOAc 70:30 to 20:80) yields 593 mg (70%) of the sub-title compound as a yellow solid.

LC-A: t_R = 0.63 min; $[M+H]^+$ = 286.1; 1H -NMR (400 MHz, d_6 -DMSO) δ : 8.02 (d, J = 15.9 Hz, 1 H), 7.76 (d, J = 7.2 Hz, 1 H), 7.35 (m, 2 H), 6.68 (d, J = 15.9 Hz, 1 H), 4.38 (q, J = 7.1 Hz, 2
 35 H).

H), 3.81 (s, 2 H), 3.07 (t, $J = 5.8$ Hz, 2 H), 2.93 (t, $J = 5.8$ Hz, 2 H), 2.53 (d, $J = 6.6$ Hz, 2 H), 1.45 (t, $J = 7.1$ Hz, 3 H), 1.10 (m, 1 H), 0.69 (m, 2 H), 0.33 (m, 2 H).

- b) The title compound is obtained as a white foam in 91% yield following the procedure describe for **Precursor E3** step d) starting from (E)-3-(2-(cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)acrylic acid ethyl ester.

LC-A: $t_R = 0.52$ min; $[M+H]^+ = 258.1$

Precursor F1

5-(2-Carboxy-ethyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

- To a solution of 5-((E)-2-carboxy-vinyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester **Precursor E1** (500 mg, 1.52 mmol) in 15 mL MeOH and palladium on charcoal 10% (80.7 mg, 0.076 mmol) is stirred under a positive atmosphere of H_2 for 2 h. The mixture is put under inert Ar atmosphere then filtered over celite. The solid celite cake is washed twice with MeOH. Evaporation of the solvent under reduced pressure yields 459 mg (91%) of the title compound as a white solid.

- LC-A: $t_R = 0.83$ min; $[M+H]^+ = 306.1$; 1H -NMR ($CDCl_3$): δ 7.17 (t, $J = 7.5$ Hz, 1 H), 7.09 (m, 1 H), 7.02 (d, $J = 7.5$ Hz, 1 H), 4.60 (s, 2 H), 3.69 (t, $J = 5.8$ Hz, 2 H), 3.50 (s, 1 H), 2.96 (m, 2 H), 2.83 (t, $J = 5.8$ Hz, 2 H), 2.66 (m, 2 H), 1.51 (s, 9 H)

Precursor F2

3-(2-(2-Methoxyethyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)propanoic acid

- a) 5-(3-Ethoxy-3-oxopropyl)-3,4-dihydroisoquinoline-2(1H)-carboxylic acid *tert*-butyl ester

- To a solution of (E)-5-(3-ethoxy-3-oxoprop-1-en-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylic acid *tert*-butyl ester (**Precursor E3** step a) (3 g, 9.05 mmol) dissolved in degassed 40 mL MeOH is added 10% Pd / C (482 mg, 0.45 mmol). The resulting suspension is allowed to stir under hydrogen at RT for 3 h. The crude suspension is filtered over Celite and the filter cake is rinsed twice with MeOH. Evaporation of the solvent under reduced pressure yields 2.86 g (95%) of the sub-title compound as a yellow oil.

LC-A: $t_R = 0.97$ min; $[M+H]^+ = n.d.$; 1H -NMR (400 MHz, d_6 -DMSO) δ : 7.11 (m, 1 H), 7.03 (m, 2 H), 4.48 (s, 2 H), 4.05 (q, $J = 7.1$ Hz, 2 H), 3.56 (t, $J = 5.9$ Hz, 2 H), 2.82 (t, $J = 7.7$ Hz, 2 H), 2.74 (t, $J = 5.9$ Hz, 2 H), 2.55 (t, $J = 7.7$ Hz, 2 H), 1.43 (s, 9 H), 1.16 (t, $J = 7.1$ Hz, 3 H)

- b) 3-(1,2,3,4-Tetrahydroisoquinolin-5-yl)propionic acid ethyl ester hydrochloride

- To a solution of (E)-5-(3-ethoxy-3-oxopropyl)-3,4-dihydroisoquinoline-2(1H)-carboxylic acid *tert*-butyl ester (2.86 g, 8.58 mmol) in 20 mL DCM is added dropwise 4N HCl soln. in dioxane (6.4 mL, 25.7 mmol). The resulting solution is allowed to stir at RT for 2 h. The solvent is the removed under reduced pressure, the residue is taken up in DCM and evaporated again under reduced pressure, then under HV to yield quantitatively 2.30 g of the sub-title compound as a yellow solid.

LC-A: $t_R = 0.55$ min; $[M+H]^+ = 234.2$

c) 3-(2-(2-Methoxyethyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)propionic acid ethyl ester

To a solution of (E)-3-(1,2,3,4-tetrahydroisoquinolin-5-yl)propionic acid ethyl ester hydrochloride (2.30g, 8.53 mmol) in 30 mL DMF is added K_2CO_3 (2.36 g, 17.1 mmol) and 2-bromoethylmethylether (1.194 g, 8.53 mmol) and the resulting suspension is allowed to stir at 65°C for 5 h. After cooling, water is added and the resulting aq. phase is extracted twice with EtOAc. The combined organic phase is washed with sat. aq. $NaHCO_3$ soln. and brine then dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. Flash-chromatography on silica-gel: (Eluent: Hept. / EtOAc 70:30 to 40:60 to 0:100) yields 1.13 g (46%) of the sub-title compound as a yellow oil.

LC-A: $t_R = 0.60$ min; $[M+H]^+ = 292.3$; 1H -NMR (400 MHz, d_6 -DMSO) δ : 7.04 (m, 1 H), 6.98 (m, 1 H), 6.89 (d, $J = 7.2$ Hz, 1 H), 4.05 (q, $J = 7.1$ Hz, 2 H), 3.52 (s, 2 H), 3.52 (t, $J = 5.9$ Hz, 2 H), 3.26 (s, 3 H), 2.77 (d, $J = 8.0$ Hz, 2 H), 2.72 (m, 4 H), 2.62 (t, $J = 5.8$ Hz, 2 H), 2.55 (t, $J = 8.0$ Hz, 2 H), 1.17 (t, $J = 7.1$ Hz, 3 H)

d) To a solution of 3-(2-(2-methoxyethyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)propionic acid ethyl ester (1.13 g, 3.88 mmol) in 20 mL THF is added at RT 1M LiOH aq. soln. (7.8 mL, 7.8 mmol). The reaction mixture is stirred overnight at RT and is then acidified to pH = 4 with 1M aq. HCl soln. to afford the 1.38 g of the title compound as the hydrochloride containing 1 equivalent LiCl (100%) after evaporation of the volatiles followed by a second evaporation after addition of DCM and drying under HV.

LC-A: $t_R = 0.48$ min; $[M+H]^+ = 264.4$

Precursor F3

3-(2-Allyl-1,2,3,4-tetrahydroisoquinolin-5-yl)propanoic acid is made according to the procedure described for **3-(2-(2-methoxyethyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)propanoic acid Precursor F2** (steps c and d) starting from 3-(1,2,3,4-tetrahydroisoquinolin-5-yl)propionic acid ethyl ester hydrochloride using allylbromide instead of 2-bromoethylmethylether and MeCN instead of DMF.

LC-A: $t_R = 0.48$ min; $[M+H]^+ = 246.2$

Precursor G1

5-Carboxymethoxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester

To a solution of 5-ethoxycarbonylmethoxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester **Precursor H1** (640 mg, 1.72 mmol) in 8 mL THF is added 1M aq. LiOH sol. (6.43 mL, 6.43 mmol). The reaction mixture is allowed to stir at RT for 1 h and is acidified with 1N aq. HCl sol. The resulting aq. phase is extracted twice with DCM. The combined organic phase is washed with brine then dried over $MgSO_4$, filtered and evaporated under reduced

pressure to yield quantitatively the title compound as a light yellow solid which is used without further purification.

LC-B: $t_R = 0.80$ min; $[M+H]^+ = 308.0$. 1H -NMR ($CDCl_3$) δ : 7.15 (t, $J = 7.9$ Hz, 1 H), 6.79 (d, $J = 7.7$ Hz, 1 H), 6.63 (d, $J = 8.1$ Hz, 1 H), 4.69 (s, 2 H), 4.58 (s, 2 H), 3.66 (t, $J = 5.8$ Hz, 2 H),
 5 2.86 (t, $J = 5.8$ Hz, 2 H), 1.51 (s, 9 H)

Precursor G2

rac-2-((2-(*tert*-Butoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)oxy)propanoic acid,

LC-B: $t_R = 0.84$ min; $[M+H]^+ = 307.3$, 1H -NMR (400 MHz, d_6 -DMSO) δ : 13.00 (m, 1 H), 7.11 (dd, $J_1 = 8.1$ Hz, $J_2 = 7.7$ Hz, 1 H), 6.76 (d, $J = 7.7$ Hz, 1 H), 6.65 (d, $J = 8.1$ Hz, 1 H), 4.82
 10 (q, $J = 6.7$ Hz, 1 H), 4.48 (s, 2 H), 3.55 (m, 2 H), 2.68 (m, 2 H), 1.52 (d, $J = 6.8$ Hz, 3 H), 1.43 (s, 9 H), is prepared applying the method described for **Precursor G1** using NaOH instead of LiOH.

Precursor H1

5-Ethoxycarbonylmethoxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester
 15

To a solution of 5-hydroxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester [Tetrahedron **2006**, 62(29), 6869 - 6875] (500 mg, 2.01 mmol) in 8 mL acetone are added K_2CO_3 (416 mg, 3.01 mmol) and ethyl bromoacetate (335 mg, 2.01 mmol). The reaction mixture is allowed to stir at 80°C for 1 h. After cooling, the mixture is poured onto water. The
 20 resulting aq. phase is extracted twice with DCM. The combined organic phase is washed with brine dried over $MgSO_4$, filtered and evaporated under reduced pressure to yield 640 mg (95%) of the title compound as a yellow oil which is used without further purification.

LC-B: $t_R = 0.98$ min; $[M+H]^+ = 336.0$. 1H -NMR ($CDCl_3$) δ : 7.13 (t, $J = 7.9$ Hz, 1 H), 6.78 (d, $J = 7.7$ Hz, 1 H), 6.59 (d, $J = 8.1$ Hz, 1 H), 4.65 (s, 2 H), 4.58 (s, 2 H), 4.28 (q, $J = 7.1$ Hz, 2 H),
 25 3.66 (t, $J = 5.8$ Hz, 2 H), 2.87 (t, $J = 5.8$ Hz, 2 H), 1.51 (s, 9 H), 1.32 (t, $J = 7.1$ Hz, 3 H)

Precursor H2

rac-5-((1-Ethoxy-1-oxopropan-2-yl)oxy)-3,4-dihydroisoquinoline-2(1*H*)-carboxylic acid

***tert*-butyl ester**, LC-A: $t_R = 0.98$ min; $[M-tBu+MeCN]^+ = 335.1$, 1H -NMR (400 MHz, d_6 -DMSO) δ : 7.11 (dd, $J_1 = 8.2$ Hz, $J_2 = 7.6$ Hz, 1 H), 6.78 (d, $J = 7.6$ Hz, 1 H), 6.67 (d, $J = 8.2$ Hz, 1 H),
 30 4.94 (q, $J = 6.8$ Hz, 1 H), 4.48 (bs, 2 H), 4.13 (q, $J = 7.2$ Hz, 2 H), 3.50-3.61 (m, 2 H), 2.69 (m, 2 H), 1.52 (d, $J = 6.7$ Hz, 3 H), 1.35 (s, 9 H), 1.17 (t, $J = 7.2$ Hz, 3 H), is prepared applying the method described for **Precursor H1** using ethyl 2-bromopropionate instead of ethylbromacetate.

Example 102

35 **N-Benzyl-N-(2-dimethylamino-ethyl)-2-[ethyl-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-amino]-acetamide**

To a solution of N-benzyl-N-(2-(dimethylamino)ethyl)-2-((1,2,3,4-tetrahydroisoquinolin-5-yl)amino)acetamide dihydrochloride **Precursor J1** (27 mg, 0.063 mmol) in 0.2 mL MeOH and 0.1 mL water is added acetaldehyde (3.3 mg, 0.076 mmol) and NaBH₃CN (11.9 mg, 0.19 mmol). The resulting mixture is allowed to stir at RT for 1 h. It is then poured onto sat. aq. NaHCO₃ soln. and the resulting aq. phase is extracted three times with DCM. The combined organic phase is washed with brine, dried over MgSO₄, filtered and evaporated under reduced pressure. The crude residue is purified by prep. HPLC (Method E) to yield the title compound as a colourless oil.

LC-B: t_R = 0.46 min; [M+H]⁺ = 423.1

10 Example 210

2-((2-Cyclopentyl-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(dimethylamino)ethyl)-N-(2-(trifluoromethyl)benzyl)acetamide

To a solution of N-(2-trifluoromethyl)benzyl-N-(2-(dimethylamino)ethyl)-2-((1,2,3,4-tetrahydroisoquinolin-5-yl)amino)acetamide dihydrochloride **Precursor J2** (100 mg, 0.181 mmol) in 2 mL MeOH is added successively cyclopentanone (90 mg, 5.9 mmol), NaBH₃CN (39.9 mg, 3.5 mmol) and ZnCl₂ (144 mg, 1.06 mmol) and the resulting mixture is allowed to stir at RT overnight. Water is added and the resulting aq. phase is extracted twice with DCM. The combined organic phase is washed with sat. aq. NaHCO₃ soln. and brine, dried over MgSO₄ filtered and evaporated under reduced pressure. The crude residue is purified by prep. HPLC (Method D) to yield the title compound as a colourless oil.

LC-B: t_R = 0.61 min; [M+H]⁺ = 503.1

Examples 351-356 / 365-367 listed in **Table 9** are prepared applying one of the methods described for **Example 210**, using the corresponding Precursor and the corresponding ketone respectively.

25 Table 9: Examples 351-356 / 365-367

Example No	Example name	t_R [min] (LC-F) unless otherwise indicated	MS Data m/z [M+H] ⁺
351	rac-N-(2-Dimethylamino-ethyl)-2-[2-(tetrahydro-furan-3-yl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide	0.45	505.3
352	2-(2-Cyclobutyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.49	489.4

353	N-(2-Dimethylamino-ethyl)-2-(2-oxetan-3-yl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	0.47	491.3
354	rac-N-(2-Dimethylamino-ethyl)-2-[2-(2-methoxy-1-methyl-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide	0.49	507.4
355	rac-N-(2-Dimethylamino-ethyl)-2-[2-(1,2-dimethyl-propyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide	0.63 (LC-A)	505.3
356	rac-2-(2-sec-Butyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.5	491.4
365	rac-N-(2-Dimethylamino-ethyl)-2-[2-(tetrahydro-furan-3-yl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.39	506.3
366	2-(2-Cyclobutyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.42	490.3
367	N-(2-Dimethylamino-ethyl)-2-(2-oxetan-3-yl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.4	492.3

Example 105 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(1-methyl-piperidin-4-yl)-N-(2-trifluoromethyl-benzyl)-acetamide

To a solution of N-(1-methyl-piperidin-4-yl)-2-(1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide dihydrochloride **Precursor J4** (33 mg, 0.058 mmol) in 0.5 mL MeOH are added cyclopropanecarboxaldehyde (4.9 mg, 0.071 mmol) and NaBH₃CN (9.3 mg, 0.147 mmol) and 0.5 mL water. The resulting mixture is allowed to stir at RT for 3 h. It is then diluted with DCM, sat. aq. NaHCO₃ soln. and water. The phases are separated and the resulting aq. phase is extracted twice with DCM. The combined organic phase is dried over MgSO₄, filtered and evaporated under reduced pressure. The crude residue is purified by prep. HPLC (Method D) to yield the title compound as a yellow oil.

LC-A: t_R = 0.62 min; $[M+H]^+$ = 515.1

Examples 91 / 357-358 listed in **Table 10** are prepared applying one of the methods described for **Example 105**, using the corresponding Precursor and the corresponding aldehyde or ketone respectively.

Table 10: Examples 91 / 357-358

Example No	Example name	t_R [min] (Method)	MS Data m/z [M+H] ⁺
91	2-(2-Cyclopropylmethyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.63 (A)	517.2
357	2-[2-(1-Cyclopropyl-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.52 (G)	503.4
358	N-(2-Dimethylamino-ethyl)-2-[2-(3-methyl-oxetan-3-ylmethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide	0.46 (G)	519.4

Example 103**N-(2-Dimethylamino-ethyl)-2-(2-ethanesulfonyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide**

To a solution of N-(2-trifluoromethyl)benzyl-N-(2-(dimethylamino)ethyl)-2-((1,2,3,4-tetrahydroisoquinolin-5-yl)amino)acetamide dihydrochloride **Precursor J2** (145 mg, 0.197 mmol) in 3 mL DCM are added DIPEA (25.4 mg, 0.197 mmol) and ethanesulfonylchloride (25.3 mg, 0.197 mmol). The resulting mixture is allowed to stir at RT for 1 h then poured onto water. The resulting aq. phase is extracted twice with DCM. The combined organic phase is washed with sat. aq. NaHCO₃ soln. and brine, dried over MgSO₄, filtered and evaporated under reduced pressure. The crude residue is purified by prep. HPLC (Method E) to yield the title compound formic acid salt as a brown foam.

LC-A: t_R = 0.74 min; [M+H]⁺ = 527.2

Example 359**N-(2-(dimethylamino)ethyl)-2-((2-(2-methoxyethyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(trifluoromethyl)benzyl)acetamide**

To a solution of N-(2-trifluoromethyl)benzyl-N-(2-(dimethylamino)ethyl)-2-((1,2,3,4-tetrahydroisoquinolin-5-yl)amino)acetamide dihydrochloride **Precursor J2** (500 mg, 0.907 mmol) in 10 mL DMF are added K₂CO₃ (251 mg, 1.81 mmol) and 2-bromoethylmethylether (126 mg, 0.907 mmol). The resulting mixture is allowed to stir at RT overnight then at 65°C for 5 h. It is then poured onto water. The resulting aq. phase is extracted twice with DCM. The combined organic phase is washed with sat. aq. NaHCO₃ soln. and brine, dried over MgSO₄, filtered and evaporated under reduced pressure. The crude residue is purified by prep. HPLC (Method D) to yield the title compound as a yellow oil.

LC-A: t_R = 0.58 min; [M+H]⁺ = 493.2

Examples 360-361 / 368-371 listed in **Table 11** are prepared applying one of the methods described for **Example 359** using the corresponding Precursor and the corresponding alkyl bromide respectively.

5 **Table 11: Examples 360-361 / 368-371**

Example No	Example name	t_R [min] (LC-F) unless otherwise indicated	MS Data m/z [M+H] ⁺
360	[5-({[(2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl]-methyl}-amino)-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-acetic acid methyl ester	0.5	507.3
361	2-(2-Cyclobutylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.54	503.4
368	2-(2-Cyclobutylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.47	504.4
369	[5-({[(2-Dimethylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl]-methyl}-amino)-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-acetic acid ethyl ester	0.47	522.3
370	[5-({[(2-Dimethylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl]-methyl}-amino)-3,4-dihydro-1 <i>H</i> -isoquinolin-2-yl]-acetic acid methyl ester	0.74 (LC-F1)	508.3
371	N-(2-Dimethylamino-ethyl)-2-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.4	494.3

Example 362

2-[2-(2,2-Difluoro-propionyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide

- 10 To a solution of N-(2-trifluoromethyl)benzyl-N-(2-(dimethylamino)ethyl)-2-((1,2,3,4-tetrahydroisoquinolin-5-yl)amino)acetamide dihydrochloride **Precursor J2** (104 mg, 0.178 mmol) in 2 mL DMF are added 2,2-difluoropropionic acid (19.6 mg, 0.178 mmol), HATU (81.4 mg, 0.214 mmol) and DIPEA (57 mg, 0.446 mmol). The resulting mixture is allowed to stir at RT for 2 h. Water is added and the resulting aq. phase is extracted twice with EtOAc. The

combined organic phase is washed with sat. aq. NaHCO_3 soln. and brine, dried over MgSO_4 , filtered and evaporated under reduced pressure. The crude residue is purified by prep. HPLC (Method D) to yield the title compound as a yellow oil.

LC-A: $t_R = 0.78$ min; $[\text{M}+\text{H}]^+ = 527.3$

5

Examples 363 / 372 / 570-572 listed in **Table 12** are prepared applying one of the methods described for **Example 362** using the corresponding **Precursor** and the corresponding carboxylic acid respectively.

Table 12: Examples 363 / 372 / 570-572

Example No	Example name	t_R [min] (LC-A)	MS Data m/z $[\text{M}+\text{H}]^+$
363	rac-N-(2-Dimethylamino-ethyl)-2-[2-((1R*,2R*)-2-fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide	0.71	521.4
372	rac-2-[2-((1S*,2S*)-2-Fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(1-hydroxy-cyclopentylmethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.93	548.2
570	rac-2-[2-(2,2-Difluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.75	539.4
571	N-(2-Dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-2-[2-(1-trifluoromethyl-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-acetamide	0.78	571.4
572	N-(2-Dimethylamino-ethyl)-2-[2-(furan-2-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide	0.74	529.2

10

Examples 363a

N-(2-Dimethylamino-ethyl)-2-[2-((1R*,2R*)-2-fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide

LC-L: $t_R = 4.71$ min

15

Example 363b

N-(2-Dimethylamino-ethyl)-2-[2-((1S*,2S*)-2-fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide

LC-L: $t_R = 6.47$ min

Are obtained by separation using preparative HPLC conditions (Method-L) of the racemic **Example 363**.

Reference example 104

5 **rac-2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-1-(4-methyl-2-phenyl-piperazin-1-yl)-ethanone**

a) *N*-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-2,2,2-trifluoro-*N*-[2-(4-methyl-2-phenyl-piperazin-1-yl)-2-oxo-ethyl]-acetamide

To a solution of rac-2,2,2-trifluoro-*N*-[2-(4-methyl-2-phenyl-piperazin-1-yl)-2-oxo-ethyl]-*N*-(1,2,3,4-tetrahydro-isoquinolin-5-yl)-acetamide dihydrochloride **Precursor J3** (167 mg, 0.311 mmol) and cyclopropanecarboxaldehyde (21.8 mg, 0.311 mmol) in 1.5 mL MeOH and 0.75 mL water is added NaBH₃CN (48.9 mg, 0.778 mmol) and the resulting mixture is stirred at RT overnight. Sat. aq. NaHCO₃ soln. is added and the resulting aq. phase is extracted twice with DCM. The combined organic phase is evaporated under reduced pressure and dried under HV. The crude sub-title product is used as such in the next step.

b) To a solution of *N*-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-2,2,2-trifluoro-*N*-[2-(4-methyl-2-phenyl-piperazin-1-yl)-2-oxo-ethyl]-acetamide (160 mg, 0.283 mmol) in 1.5 mL MeOH and 0.5 mL water is added K₂CO₃ (235 mg, 1.7 mmol) and the resulting yellow solution is stirred at 60°C for 2 h. Sat. aq. NaHCO₃ soln. is added and the resulting aq. phase is extracted twice with DCM. The combined organic phase is evaporated under reduced pressure. The crude is purified by prep. HPLC (Method E).

LC-A: *t*_R = 0.50 min; [M+H]⁺ = 419.2

Example 108

25 **2-(2-Acetyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-*N*-benzyl-*N*-(2-dimethylamino-ethyl)-acetamide**

a) *N*-(2-Acetyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-*N*-(2-(benzyl(2-dimethylamino)ethyl)amino)-2-oxoethyl)-2,2,2-trifluoroacetamide

To a solution of *N*-{[benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl}-2,2,2-trifluoro-*N*-(1,2,3,4-tetrahydro-isoquinolin-5-yl)-acetamide dihydrochloride **Precursor J5** (120 mg, 0.179 mmol) in 2 mL DCM is added TEA (72.6 mg, 0.717 mmol) and the resulting mixture is stirred at RT for 10 min. Then acetylchloride (15.5 mg, 0.197 mmol) is added and the resulting solution is allowed to stir at RT overnight. Sat. aq. NaHCO₃ soln. and water are added and the resulting aq. phase is extracted twice with DCM. The combined organic phase is evaporated under reduced pressure and dried under HV. The crude sub-title product is used as such in the next step.

LC-B: t_R = 0.57 min; $[M+H]^+$ = 505.0

- b) To a solution of *N*-(2-acetyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-*N*-(2-(benzyl(2-(dimethylamino)ethyl)amino)-2-oxoethyl)-2,2,2-trifluoroacetamide (90.2 mg, 0.179 mmol) in 1.5 mL MeOH and 0.5 mL water is added K_2CO_3 (99 mg, 0.72 mmol) and the resulting yellow solution is stirred at 65°C for 4 h then at RT overnight. Sat. aq. $NaHCO_3$ soln. and water are added and the resulting aq. phase is extracted twice with DCM. The combined organic phase is evaporated under reduced pressure. The crude is purified by prep. HPLC (Method E). This yields the title compound as a colorless oil.

LC-B: t_R = 0.55 min; $[M+H]^+$ = 409.1

10 Example 113

5-([Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl)-amino)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid methyl ester

a) 5-([Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl)-(2,2,2-trifluoro-acetyl)-amino]-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid methyl ester

- 15 To a solution of *N*-{[benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl}-2,2,2-trifluoro-*N*-(1,2,3,4-tetrahydro-isoquinolin-5-yl)-acetamide dihydrochloride **Precursor J5** (120 mg, 0.179 mmol) in 2 mL DCM is added TEA (72.6 mg, 0.717 mmol) and the resulting mixture is stirred at RT for 10 min. Then methylchloroformate (18.6 mg, 0.197 mmol) is added and the resulting solution is allowed to stir at RT overnight. After cooling, sat. aq. $NaHCO_3$ soln. and water are added and the resulting aq. phase is extracted twice with DCM. The combined organic phase is evaporated under reduced pressure and dried under HV. The crude sub-
- 20 title product is used as such in the next step.

LC-B: t_R = 0.64 min; $[M+H]^+$ = 521.2

- b) To a solution of methyl 5-([benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl)-(2,2,2-trifluoro-acetyl)-amino]-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid methyl ester (93.2 mg, 0.179 mmol) in 1.5 mL MeOH and 0.75 mL water is added K_2CO_3 (99 mg, 0.72 mmol) and the resulting yellow solution is stirred at 65°C overnight. After cooling, water is added and the resulting aq. phase is extracted twice with DCM. The combined organic phase is evaporated under reduced pressure. The crude residue is purified by prep. HPLC (Method E). This yields
- 25 the title compound as a colorless oil.

LC-B: t_R = 0.61 min; $[M+H]^+$ = 425.1

- Examples 105-107 / 109-112 / 114-138** listed in **Table 13** are prepared applying one of the methods described for **Reference example 104**, **Example 108** or **Example 113**, using the
- 35 corresponding **Precursor** and the corresponding aldehyde, ketone, carboxylic acid chloride or chloroformate respectively.

Table 13: Examples 105-107 / 109-112 / 114-138

Example No	Example name	t _R [min] (LC-C)	MS Data m/z [M+H] ⁺
105	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(1-methyl-piperidin-4-yl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.65	515.4
106	N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.51	381.4
107	N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.53	395.4
109	N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.55	409.5
110	N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide	0.58	421.4
111	N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.73	423.4
112	N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-isobutyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.6	423.5
114	N-Benzyl-2-(2-butyryl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide	0.78	437.4
115	N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-isobutyryl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.78	437.5
116	N-Benzyl-N-(2-dimethylamino-ethyl)-2-[2-(2,2-dimethyl-propyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-acetamide	0.62	437.5
117	5-({[Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl}-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid ethyl ester	0.83	439.4
118	N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-furan-2-ylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.59	447.4
119	N-Benzyl-N-(2-dimethylamino-ethyl)-2-[2-(3-methyl-butyryl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-acetamide	0.83	451.4
120	N-Benzyl-N-(2-dimethylamino-ethyl)-2-[2-(3,3-dimethyl-butyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-acetamide	0.69	451.5
121	5-({[Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl}-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid isopropyl ester	0.89	453.4

122	5-({[Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl}-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid isobutyl ester	0.95	467.4
123	N-Benzyl-2-(2-benzyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide	0.64	457.4
124	N-Benzyl-2-(2-cyclohexylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide	0.7	463.5
125	2-(2-Benzoyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-benzyl-N-(2-dimethylamino-ethyl)-acetamide	0.82	471.4
126	N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-phenethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	nd	nd
127	5-({[Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl}-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid 2,2-dimethyl-propyl ester	0.99	481.5
128	N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-phenylacetyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.84	485.4
129	N-Benzyl-2-[2-(2-cyclohexyl-acetyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-dimethylamino-ethyl)-acetamide	0.95	491.5
130	5-({[Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl}-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid phenyl ester	0.92	487.4
131	5-({[Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl}-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid benzyl ester	0.95	501.4
132	N-Benzyl-N-(3-methyl-butyl)-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.87	380.4
133	N-(2-Chloro-benzyl)-N-(2-dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide	0.57	429.4
134	N-(2-Chloro-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide	0.62	455.4
135	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	0.61	463.4
136	rac-2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(1-methyl-piperidin-3-yl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.68	515.5
137	2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(1-methyl-piperidin-4-yl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.61	489.4

Example 364**2-(2-Cyanomethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide**

To a solution of N-[(2-dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl]-methyl}-
 5 2,2,2-trifluoro-N-(1,2,3,4-tetrahydro-isoquinolin-5-yl)-acetamide dihydrochloride **Precursor J8** (100 mg, 0.143 mmol) dissolved in 2 mL MeCN is added chloroacetonitrile (11 mg, 0.143 mmol) and sodium *tert*-butoxide (27.4 mg, 0.285 mmol) and resulting mixture is allowed to stir at RT for 5 h. The solvent is evaporated under reduced pressure and the residue is taken up in DCM and sat. aq. NaHCO₃ solution. The resulting aq. phase is extracted twice with
 10 DCM. The combined organic phase evaporated to dryness. The crude residue is purified by prep. HPLC (Method D). This yields the title compound as a colorless oil.

LC-A: $t_R = 0.68$ min; $[M+H]^+ = 474.0$

Example 373**N-(2-Dimethylamino-ethyl)-2-(2-phenyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide**

To a solution of N-[(2-dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl]-methyl}-
 2,2,2-trifluoro-N-(1,2,3,4-tetrahydro-isoquinolin-5-yl)-acetamide dihydrochloride **Precursor J8** (100 mg, 0.143 mmol) dissolved in 2 mL toluene is added iodobenzene (35.6 mg, 0.171 mmol), Pd₂(dba)₃ (3.92 mg, 0.0043 mmol) DavePhos (5.05mg, 0.0128 mmol) and sodium
 20 *tert*-butoxide (27.4 mg, 0.285 mmol) and resulting mixture is allowed to stir at 80°C overnight. The solvent is evaporated under reduced pressure and the residue is taken up in DCM and sat. aq. NaHCO₃ solution. The resulting aq. phase is extracted twice with DCM. The combined organic phase evaporated to dryness. The crude residue is purified by prep. HPLC (Method D). This yields the title compound as a colorless oil.

25 LC-A: $t_R = 0.90$ min; $[M+H]^+ = 511.3$

Examples 374-376 listed in **Table 14** are prepared applying one of the methods described for **Example 373**, using the corresponding heteroaryl iodide respectively.

Table 14: Examples 374-376

Example No	Example name	t_R [min] (LC-F)	MS Data m/z $[M+H]^+$
374	N-(2-Dimethylamino-ethyl)-2-(2-pyridin-2-yl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	0.58	512.3
375	N-(2-Dimethylamino-ethyl)-2-(2-pyrimidin-2-yl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	0.81	513.3

376	N-(2-Dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-2-[2-(4-trifluoromethyl-thiazol-2-yl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-acetamide	0.96	586.3
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Precursor J1**N-Benzyl-N-(2-dimethylamino-ethyl)-2-(1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide dihydrochloride**

- 5 To a solution of 5-({[benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl}-amino)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester **Example 8** (580 mg, 1.24 mmol) in 4 mL DCM is added 0.62 mL 4N HCl in dioxane soln. The resulting mixture is allowed to stir at RT for 1.5 h at which time a white precipitate has formed. The solid is filtered and dried under HV. (It is sensitive to moisture and turns into a yellow oil rapidly after opening of the flask to
- 10 air). This yields 390 mg (71%) of the title compound as a yellow oil.

LC-B: $t_R = 0.43$ min; $[M+H]^+ = 367.2$

Precursors J4 / J11-J13 listed in **Table 15** are prepared applying the above method described for **Precursor J1** using the corresponding precursors (**Example 10**, **Example 90**, **Precursor K12**, **Precursor K13**) respectively as starting material.

15

Table 15: Precursor J4 / J11-J13

Precursor	Precursor name	t_R [min] (LC-A)	MS Data m/z [M+H] ⁺
J4	N-(1-Methyl-piperidin-4-yl)-2-(1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide dihydrochloride	0.56	461.0
J11	N-(2-Dimethylamino-ethyl)-2-(4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide dihydrochloride	0.58	463.1
J12	N-(2-Dimethylamino-ethyl)-2-(1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-pyridin-3-ylmethyl)-acetamide dihydrochloride	0.52	436.1
J13	N-((1-hydroxycyclopentyl)methyl)-2-((1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(trifluoromethyl)benzyl)acetamide hydrochloride	0.73	462.2

Precursor J2**N-(2-trifluoromethyl)benzyl-N-(2-(dimethylamino)ethyl)-2-((1,2,3,4-tetrahydroisoquinolin-5-yl)amino)acetamide dihydrochloride**

To a solution of 5-(((2-dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbonyl)-methyl)-amino)-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester **Precursor K2** (150 mg, 0.236 mmol) in 2 mL DCM is 0.5 mL TFA. The resulting yellow solution is allowed to stir at RT for 1.5 h. The mixture is poured onto water and basified with sat. aq. NaHCO₃ soln. The resulting aq. phase is extracted twice with EtOAc. The combined organic phase is washed with brine, dried over MgSO₄, filtered and evaporated under reduced pressure. This yields the title compound as a brown oil which is used as such in the next step.

LC-B: $t_R = 0.56$ min; $[M+H]^+ = 435.1$

Precursor J3**rac-2,2,2-Trifluoro-N-[2-(4-methyl-2-phenyl-piperazin-1-yl)-2-oxo-ethyl]-N-(1,2,3,4-tetrahydro-isoquinolin-5-yl)-acetamide dihydrochloride**

a) 5-[[2-(4-Methyl-2-phenyl-piperazin-1-yl)-2-oxo-ethyl]-(2,2,2-trifluoro-acetyl)-amino]-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester

To a solution of rac-5-[2-(4-methyl-2-phenyl-piperazin-1-yl)-2-oxo-ethylamino]-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester **Precursor K3** (100 mg, 0.202 mmol) in 4 mL DCM is added TEA (123 mg, 1.21 mmol) and the solution is allowed to stir at RT for 10 min. Then TFAA (170 mg, 0.809 mmol) is added dropwise slowly and the resulting yellow solution is allowed to stir at RT for 45min. Sat. aq. NaHCO₃ soln. is added and the resulting aq. phase is extracted twice with DCM. The combined organic phase is evaporated under reduced pressure to give 151 mg of the crude sub-title compound as a yellow oil.

LC-A: $t_R = 0.79$ min; $[M+H]^+ = 561.0$

b) To a solution of 5-[[2-(4-methyl-2-phenyl-piperazin-1-yl)-2-oxo-ethyl]-(2,2,2-trifluoro-acetyl)-amino]-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (151 mg of crude, 0.202 mmol) in 3 mL dioxane is added 4N HCl soln. in 1.5 mL dioxane and allowed to stir at RT overnight. The solvent is evaporated under reduced pressure, the remainder of dioxane is coevaporated twice with DCM. After drying under HV this yields 159 mg of the title compound which is used as such in the next step.

LC-B: $t_R = 0.48$ min; $[M+H]^+ = 496.98$

Precursors J5-J10 listed in **Table 16** are prepared applying the method described for **Precursor J3** using the corresponding **Precursor** or **Example** as starting material.

Table 16: Precursor J5-J10

Precursor	Precursor name	t_R [min] (Method)	MS Data m/z [M+H] ⁺
J5	N-[[Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl]-2,2,2-trifluoro-N-(1,2,3,4-tetrahydro-isoquinolin-5-yl)-acetamide dihydrochloride	0.44 (B)	463.1
J6	N-[[Benzyl-(3-methyl-butyl)-carbamoyl]-methyl]-2,2,2-trifluoro-N-(1,2,3,4-tetrahydro-isoquinolin-5-yl)-acetamide hydrochloride	0.72 (B)	463.2
J7	N-[[[2-Chloro-benzyl)-(2-dimethylamino-ethyl)-carbamoyl]-methyl]-2,2,2-trifluoro-N-(1,2,3,4-tetrahydro-isoquinolin-5-yl)-acetamide dihydrochloride	0.48 (B)	496.98
J8	N-[[[2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl]-methyl]-2,2,2-trifluoro-N-(1,2,3,4-tetrahydro-isoquinolin-5-yl)-acetamide dihydrochloride	0.51 (B)	530.99
J9	rac-2,2,2-Trifluoro-N-[[[1-methyl-piperidin-3-yl)-(2-trifluoromethyl-benzyl)-carbamoyl]-methyl]-N-(1,2,3,4-tetrahydro-isoquinolin-5-yl)-acetamide dihydrochloride	0.59 (A)	557.2
J10	2,2,2-Trifluoro-N-[[[1-methyl-piperidin-4-yl)-(2-trifluoromethyl-benzyl)-carbamoyl]-methyl]-N-(1,2,3,4-tetrahydro-isoquinolin-5-yl)-acetamide dihydrochloride	0.59 (A)	557.1

Precursor J14**Methyl-{2-[[2-(1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]-(2-trifluoromethyl-benzyl)-amino]-ethyl}-carbamic acid *tert*-butyl ester**

- 5 To a solution of 5-((2-((2-((*tert*-butoxycarbonyl)(methylamino)ethyl)(2-(trifluoromethyl)benzyl)amino)-2-oxoethyl)amino)-3,4-dihydroisoquinoline-2(1*H*)-carboxylic acid benzyl ester **Precursor K14** (56% purity, 2.24 g, 1.92 mmol) in degassed 20 mL EtOAc is added 0.5 g 10% Pd / C and the resulting suspension is allowed to stir at RT under an atmosphere of H₂ overnight. Then 0.2 g 10% Pd / C are added and the resulting suspension
- 10 is allowed to stir at RT under an atmosphere of H₂ for 4 days. The mixture is then filtered over Celite, the filter cake is rinsed three times with EtOAc. The combined organic phase is concentrated in vacuo to yield quantitatively 1.07g of the title compound as a yellow oil.
- LC-A: t_R = 0.78 min; [M+H]⁺ = 521.4

15 Precursor J15

Methyl-{2-[[2-(1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]-(3-trifluoromethyl-pyridin-2-ylmethyl)-amino]-ethyl}-carbamic acid *tert*-butyl ester, LC-A: $t_R = 0.74$ min; $[M+H]^+ = 522.3$, is prepared according to the procedure described for **Precursor J14** using **Precursor K15** as starting material.

5

Precursors K2-K3 / K7 / K12-K15 listed in **Table 17** are prepared applying the method described for the synthesis of **Example 8** from **precursor B1** using the corresponding **Precursor B1, B8 or B25** and the corresponding **Amine**.

10 **Table 17: Precursor K2-K3 / K7 / K12-K15**

Precursor	Precursor name	t_R [min] (LC-A)	MS Data m/z $[M+H]^+$
K2	5-({[(2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl]-methyl}-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.81	535.3
K3	rac-5-[2-(4-Methyl-2-phenyl-piperazin-1-yl)-2-oxo-ethylamino]-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.73	465.2
K7	5-({[(2-Chloro-benzyl)-(2-dimethylamino-ethyl)-carbamoyl]-methyl}-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.74	501
K12	5-({[(2-Dimethylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl]-methyl}-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.78	536.3
K13	5-((2-(((1-hydroxycyclopentyl)methyl)(2-(trifluoromethyl)benzyl)amino)-2-oxoethyl)amino)-3,4-dihydroisoquinoline-2(1 <i>H</i>)-carboxylic acid <i>tert</i> -butyl ester	1.03	561.9
K14	5-((2-((2-((<i>tert</i> -butoxycarbonyl)(methyl)amino)ethyl)(2-(trifluoromethyl)benzyl)amino)-2-oxoethyl)amino)-3,4-dihydroisoquinoline-2(1 <i>H</i>)-carboxylic acid benzyl ester	1.08	655.4
K15	5-((2-((2-((<i>tert</i> -butoxycarbonyl)(methyl)amino)ethyl)((3-(trifluoromethyl)pyridin-2-yl)methyl)amino)-2-oxoethyl)amino)-3,4-dihydroisoquinoline-2(1 <i>H</i>)-carboxylic acid benzyl ester	1.04	656.0

Example 138

(E)-N-Benzyl-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-hydroxyethyl)-acrylamide

To a solution of (E)-N-benzyl-N-(2-hydroxyethyl)-3-(1,2,3,4-tetrahydroisoquinolin-5-yl)acrylamide hydrochloride **Precursor L1** (45 mg, 0.136 mmol) and
5 cyclopropanecarboxaldehyde (9.6 mg, 0.136 mmol) in 0.5 mL water and 1 mL MeOH is added NaBH₃CN (21.4 mg, 0.34 mmol). The resulting mixture is allowed to stir at RT for 1 h. Sat. aq. NaHCO₃ soln. is added and the resulting aq. phase is extracted twice with DCM. The solvent is evaporated under reduced pressure. The crude is purified by prep. HPLC (Method E). The solid obtained is dissolved in a large excess of 1.25 HCl soln. in EtOH and the
10 resulting solution is allowed to stir at RT for 10 min. The solvent is then removed under reduced pressure and the crude product is dried under HV. This yields the title compound hydrochloride as a yellow oil.

LC-A: t_R = 0.64 min; $[M+H]^+$ = 391.4

Example 162

15 **N-Benzyl-N-(2-dimethylamino-ethyl)-3-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-propionamide**

To a solution of N-benzyl-N-(2-dimethylamino-ethyl)-3-(1,2,3,4-tetrahydro-isoquinolin-5-yl)-propionamide dihydrochloride **Precursor O4** (40 mg, 0.082 mmol) in 2 mL DCM is added TEA (33.2 mg, 0.328 mmol) followed by propionyl chloride (8.36 mg, 0.09 mmol). The
20 resulting yellow mixture is allowed to stir at RT for 1.5 h. Sat. aq. NaHCO₃ soln. is added and the resulting aq. phase is extracted twice with DCM. The solvent is evaporated under reduced pressure. The crude residue is purified by prep. HPLC (Method D). This yields the title compound as a colorless oil.

LC-B: t_R = 0.58 min; $[M+H]^+$ = 422.0

25 **Example 167**

5-[[Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methoxy]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid methyl ester

To a solution of N-benzyl-N-(2-dimethylamino-ethyl)-2-(1,2,3,4-tetrahydro-isoquinolin-5-yl)oxy)-acetamide dihydrochloride **Precursor Q2** (50 mg, 0.09 mmol) in 0.5 mL DCM is added
30 TEA (36.8 mg, 0.36 mmol) followed by methylchloroformate (9.44 mg, 0.1 mmol). The resulting yellow mixture is allowed to stir at RT for 1 h. Sat. aq. NaHCO₃ soln. is added and the resulting aq. phase is extracted twice with DCM. The solvent is evaporated under reduced pressure. The crude is purified by prep. HPLC (Method E). This yields the title compound as a yellow oil.

35 LC-B: t_R = 0.61 min; $[M+H]^+$ = 426.2

Examples 139–161 / 163-166 / 168-174 / 454 listed in **Table 18** are prepared applying one of the methods described for **Example 138**, **Example 162** or **Example 167** respectively using the corresponding **Precursor** and the corresponding aldehyde, ketone, carboxylic acid chloride or chloroformate respectively.

5 **Table 18: Examples 139–161 / 163-166 / 168-174 / 454**

Example No	Example name	t_R [min] (LC-C) unless otherwise indicated	MS Data m/z [M+H] ⁺
139	(E)-N-(2-Chloro-benzyl)-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-ethyl-acrylamide	0.89	409.3
141	(E)-N-Cyclopropyl-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2,3-dimethyl-benzyl)-acrylamide	0.94	415.4
142	(E)-N-Benzyl-N-(2-dimethylamino-ethyl)-3-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-acrylamide	0.52	378.3
143	(E)-N-Benzyl-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-acrylamide	0.58	418.5
144	{Benzyl-[(E)-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-acryloyl]-amino}-acetic acid ethyl ester	0.84	433.4
145	(E)-N-(2-Chloro-benzyl)-N-(2-dimethylamino-ethyl)-3-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-acrylamide	0.57	426.4
146	(E)-N-(2-Chloro-benzyl)-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-acrylamide	0.61	452.4
147	(E)-N-Benzyl-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(1,1-dioxo-tetrahydro-1H-thiophen-3-yl)-acrylamide	0.72	465.4
148	(E)-N-Benzyl-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-[2-(4-fluoro-phenyl)-ethyl]-acrylamide	0.97	469.4
149	(E)-N-(2-Dimethylamino-ethyl)-3-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-trifluoromethyl-benzyl)-acrylamide	0.62	460.4
150	(E)-3-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acrylamide	0.65	486.4
151	(E)-3-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(1-methyl-piperidin-4-yl)-N-(2-trifluoromethyl-benzyl)-acrylamide	0.6	486.4

152	(E)-3-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(1-methyl-piperidin-4-yl)-N-(2-trifluoromethyl-benzyl)-acrylamide	0.65	512.4
Reference example 153	rac-(E)-3-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-1-(4-methyl-2-phenyl-piperazin-1-yl)-propenone	0.51	416.4
154	(E)-3-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-2-methyl-N-(2-trifluoromethyl-benzyl)-acrylamide	0.65	500.3
155	N-(2-Chloro-benzyl)-N-(2-dimethylamino-ethyl)-3-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-propionamide	0.57	428.4
156	N-(2-Chloro-benzyl)-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-propionamide	0.62	454.3
157	N-(2-Dimethylamino-ethyl)-3-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-trifluoromethyl-benzyl)-propionamide	0.61	462.4
158	3-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-propionamide	0.65	488.4
159	3-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(1-methyl-piperidin-4-yl)-N-(2-trifluoromethyl-benzyl)-propionamide	0.6	488.4
160	3-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(1-methyl-piperidin-4-yl)-N-(2-trifluoromethyl-benzyl)-propionamide	0.64	514.4
161	N-Benzyl-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-propionamide	0.57	420.5
163	N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-N-(3-methyl-butyl)-acetamide	0.97	421.4
164	N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-acetamide	0.49	382.4
165	N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-acetamide	0.51	396.4
166	N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-N-(2-dimethylamino-ethyl)-acetamide	0.56	422.4
168	N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-isobutyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-acetamide	0.57	424.4
169	N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-acetamide	0.71	424.4
170	N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-isobutyryl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-acetamide	0.76	438.5

171	N-(2-Chloro-benzyl)-N-(2-dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-acetamide	0.55	430.3
172	N-(2-Chloro-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-N-(2-dimethylamino-ethyl)-acetamide	0.59	456.4
173	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-N-(2-trifluoromethyl-benzyl)-acetamide	0.59	464.4
174	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.63	490.4
454	3-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-yl)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-propionamide	0.49 (LC-A)	488.0

Example 140**(E)-N-Benzyl-N-(2-carbamoyl-ethyl)-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-**

isoquinolin-5-yl)-acrylamide dihydrochloride is prepared applying the method described for **Example 138**, using the corresponding **Precursor L3** and cyclopropanecarboxaldehyde. The solid obtained is dissolved in a large excess of 1.25 HCl soln. in EtOH and the resulting solution is allowed to stir at RT for 10 min. The solvent is then removed under reduced pressure and the crude product is dried under HV. This yields the title compound as a yellow oil.

LC-A: $t_R = 0.62$ min; $[M+H]^+ = 418.1$.

Precursor L1**(E)-N-Benzyl-N-(2-dimethylamino-ethyl)-3-(1,2,3,4-tetrahydro-isoquinolin-5-yl)-acrylamide**

To a solution of 5-[(E)-2-[benzyl-(2-hydroxy-ethyl)-carbamoyl]-vinyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester **Precursor M1** (43 mg, 0.098 mmol) in 2 mL dioxane is added 0.34 ml 4M HCl soln. in dioxane. The resulting soln. is allowed to stir at RT overnight. Evaporation of the volatiles under reduced pressure yields quantitatively the crude title compound as a white solid which is used as such in the next step.

LC-B: $t_R = 0.49$ min; $[M+H]^+ = 337.3$

Precursors L2-L13 listed in **Table 19** are prepared applying the method described for **Precursor L1** using the corresponding **Precursor** or **Example** as starting material.

Table 19: Precursor L2-L13

Precursor	Precursor name	t_R [min] (Method)	MS Data m/z $[M+H]^+$
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L2	(E)-N-(2-Chlorobenzyl)-N-ethyl-3-(1,2,3,4-tetrahydroisoquinolin-5-yl)acrylamide hydrochloride	0.69 (A)	355.2
L3	(E)-N-Benzyl-N-(2-cyanoethyl)-3-(1,2,3,4-tetrahydroisoquinolin-5-yl)acrylamide hydrochloride	0.63 (A)	346.3
L4	(E)-N-Cyclopropyl-N-(2,3-dimethylbenzyl)-3-(1,2,3,4-tetrahydroisoquinolin-5-yl)acrylamide hydrochloride	0.73 (A)	461.4
L5	(E)-N-Benzyl-N-(2-(dimethylamino)ethyl)-3-(1,2,3,4-tetrahydroisoquinolin-5-yl)acrylamide hydrochloride	0.44 (B)	364.1
L6	(E)-Ethyl 2-(N-benzyl-3-(1,2,3,4-tetrahydroisoquinolin-5-yl)acrylamido)acetate hydrochloride	0.68 (A)	379.3
L7	(E)-N-(2-Chlorobenzyl)-N-(2-(dimethylamino)ethyl)-3-(1,2,3,4-tetrahydroisoquinolin-5-yl)acrylamide dihydrochloride	0.47 (B)	398
L8	(E)-N-Benzyl-N-(1,1-dioxidotetrahydrothiophen-3-yl)-3-(1,2,3,4-tetrahydroisoquinolin-5-yl)acrylamide hydrochloride	0.62 (A)	411.3
L9	(E)-N-Benzyl-N-(4-fluorophenethyl)-3-(1,2,3,4-tetrahydroisoquinolin-5-yl)acrylamide hydrochloride	0.76 (A)	415.4
L10	(E)-N-(2-(Dimethylamino)ethyl)-3-(1,2,3,4-tetrahydroisoquinolin-5-yl)-N-(2-(trifluoromethyl)benzyl)acrylamide dihydrochloride	0.49 (B)	432
L11	(E)-N-(1-Methylpiperidin-4-yl)-3-(1,2,3,4-tetrahydroisoquinolin-5-yl)-N-(2-(trifluoromethyl)benzyl)acrylamide dihydrochloride	0.55 (A)	458.1
L12	rac-(E)-1-(4-Methyl-2-phenylpiperazin-1-yl)-3-(1,2,3,4-tetrahydroisoquinolin-5-yl)prop-2-en-1-one dihydrochloride	0.44 (A)	362.2
L13	(E)-N-(2-(Dimethylamino)ethyl)-2-methyl-3-(1,2,3,4-tetrahydroisoquinolin-5-yl)-N-(2-(trifluoromethyl)benzyl)acrylamide dihydrochloride	0.55 (A)	446.1

Precursor O1**N-(2-Chloro-benzyl)-N-(2-dimethylamino-ethyl)-3-(1,2,3,4-tetrahydro-isoquinolin-5-yl)-propionamide dihydrochloride**

- 5 To a solution of 5-{2-[(2-chloro-benzyl)-(2-dimethylamino-ethyl)-carbonyl]-ethyl}-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester **Example 98** (85 mg, 0.161 mmol)

in 2 mL dioxane is added 0.141 ml 4M HCl soln. in dioxane. The resulting soln. is allowed to stir at RT overnight. Evaporation of the volatiles under reduced pressure yields 78 mg (100%) of the compound as a yellow solid which is used as such in the next step.

LC-A: $t_R = 0.52$ min; $[M+H]^+ = 400.2$

- 5 **Precursors O2-O4** listed in **Table 20** are prepared applying the method described for **Precursor O1** using the corresponding **Precursor** or **Example** as starting material.

Table 20: Precursor O2-O4

Precursor	Precursor name	t_R [min] (Method)	MS Data m/z $[M+H]^+$
O2	N-(2-Dimethylamino-ethyl)-3-(1,2,3,4-tetrahydro-isoquinolin-5-yl)- N-(2-trifluoromethyl-benzyl)-propionamide dihydrochloride	0.54 (A)	433.9
O3	N-(1-Methyl-piperidin-4-yl)-3-(1,2,3,4-tetrahydro-isoquinolin-5-yl)- N-(2-trifluoromethyl-benzyl)-propionamide dihydrochloride	0.54 (A)	460.2
O4	N-Benzyl-N-(2-dimethylamino-ethyl)-3-(1,2,3,4-tetrahydro- isoquinolin-5-yl)-propionamide dihydrochloride	0.43 (B)	366.1

Precursor Q1

- 10 **N-Benzyl-N-(3-methyl-butyl)-2-(1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-acetamide hydrochloride**

To a solution of 5-[[benzyl-(3-methyl-butyl)-carbamoyl]-methoxy]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester **Precursor R1** (90 mg, 0.187 mmol) in 2 mL dioxane is added 0.655 ml 4M HCl soln. in dioxane. The resulting soln. is allowed to stir 5 h at RT. Evaporation of the volatiles under reduced pressure yields 78 mg (100%) of the compound as a white solid which is used as such in the next step.

LC-B: $t_R = 0.69$ min; $[M+H]^+ = 367.1$

Precursors Q2-Q4 listed in **Table 21** are prepared applying the method described for **Precursor Q1** using the corresponding **Precursor** or **Example** as starting material.

- 20 **Table 21: Precursor Q2-Q4**

Precursor	Precursor name	t_R [min] (Method)	MS Data m/z $[M+H]^+$
Q2	N-Benzyl-N-(2-dimethylamino-ethyl)-2-(1,2,3,4-tetrahydro- isoquinolin-5-yloxy)-acetamide dihydrochloride	0.41 (B)	368.1

Q3	N-(2-Chloro-benzyl)-N-(2-dimethylamino-ethyl)-2-(1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-acetamide dihydrochloride	0.45 (B)	401.7
Q4	N-(2-Dimethylamino-ethyl)-2-(1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-N-(2-trifluoromethyl-benzyl)-acetamide dihydrochloride	0.47 (B)	436

Precursors M1-R4 listed in **Table 22** are prepared applying the method described for the synthesis of **Example 92** from **precursor E1** using the corresponding **Precursor** and the corresponding **Amine**.

5 **Table 22: Precursor M1-R4**

Precursor	Precursor name	t_R [min] (Method)	MS Data m/z [M+H]⁺
M1	5-((E)-2-[Benzyl-(2-hydroxy-ethyl)-carbamoyl]-vinyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.90 (A)	437.3
M3	5-((E)-2-[Benzyl-(2-cyano-ethyl)-carbamoyl]-vinyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.96 (A)	446.1
M4	5-((E)-2-[Cyclopropyl-(2,3-dimethyl-benzyl)-carbamoyl]-vinyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	1.06 (A)	461.4
M7	5-((E)-2-[(2-Chloro-benzyl)-(2-dimethylamino-ethyl)-carbamoyl]-vinyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.75 (B)	497.8
M9	5-((E)-2-[Benzyl-[2-(4-fluoro-phenyl)-ethyl]-carbamoyl]-vinyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	1.06 (A)	515.4
M10	5-((E)-2-[(2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl]-vinyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.76 (B)	532.1
M12	rac-5-[(E)-3-(4-Methyl-2-phenyl-piperazin-1-yl)-3-oxo-propenyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.74 (A)	462.3
P4	5-[2-[Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-ethyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.72 (B)	465.8

R1	5-[[Benzyl-(3-methyl-butyl)-carbamoyl]-methoxy]-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	1.14 (B)	467
R3	5-[[{(2-Chloro-benzyl)-(2-dimethylamino-ethyl)-carbamoyl]-methoxy]-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.73 (B)	502.3
R4	5-[[{(2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl]-methoxy]-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.75 (B)	536.1

Example 175**N-Benzyl-N-cyclopropylmethyl-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide**

- 5 To a solution of N-benzyl-N-(cyclopropylmethyl)-2-(isoquinolin-5-ylamino)acetamide **Precursor S1** (226 mg, 0.65 mmol) in 1 mL MeCN is added iodomethane (95 mg, 0.67 mmol). The mixture is allowed to stir at RT for 3 h. The volatiles are evaporated under reduced pressure and the crude product is dissolved in 2 mL MeOH before NaBH₄ (49 mg, 1.3 mmol) is added. The colour changes from yellow to colorless and the resulting solution is
- 10 allowed to stir at RT for 1 h. Sat. aq. NaHCO₃ and water are added and the resulting aq. phase is extracted three times with DCM with a phase separator. The organic phases are combined and the solvent is removed under reduced pressure. The crude residue is dissolved in 2 mL EtOH and DABCO (875 mg, 7.8 mmol) is added. The resulting solution is heated at reflux for 1 h. After evaporation of the volatiles under reduced pressure, the crude
- 15 residue is purified by prep. HPLC (Method E).
LC-C: *t_R* = 0.83 min; [M+H]⁺ = 364.4

Example 177**N-(2-Dimethylamino-ethyl)-N-(2-fluoro-benzyl)-2-(2-methyl-1,2,3,4-tetrahydro-**

isoquinolin-5-ylamino)-acetamide LC-C: *t_R* = 0.52 min; [M+H]⁺ = 399.4 is made from N-(2-(dimethylamino)ethyl)-N-(2-fluorobenzyl)-2-(isoquinolin-5-ylamino)acetamide **Precursor S2**

20 according to the procedure described for the synthesis of **Example 175**.

Precursor S1**N-Benzyl-N-(cyclopropylmethyl)-2-(isoquinolin-5-ylamino)acetamide**

- To a solution of 2-(isoquinolin-5-ylamino)acetic acid **Precursor T1** (202 mg, 1 mmol)
- 25 dissolved in 2 mL DMF is added benzyl-cyclopropylmethyl-amine **Amine 4** (161 mg, 1 mmol), DIPEA (388 mg, 3 mmol) and HATU (380 mg, 1 mmol). The resulting solution is allowed to stir at RT overnight. Sat. aq. NaHCO₃ and water are added and the resulting aq.

phase is extracted three times with DCM with a phase separator. The organic phases are combined and the solvent is removed under reduced pressure. Flash-chromatography on silica-gel: (Eluent: (DCM / MeOH) 95:5 + 2% aq. NH₃ soln.) yields 226 mg (65%) of the title compound.

- 5 ¹H-NMR (CD₃OD), 50:50 mixture of two rotamers, δ : 9.07 (m, 1 H), 8.36 (d, J = 6.1 Hz, 0.5 H), 8.33 (d, J = 6.1 Hz, 1 H), 7.96 (d, J = 6.1 Hz, 0.5 H), 7.89 (d, J = 6.1 Hz, 0.5 H), 7.52 (t, J = 8.0 Hz, 0.5 H), 7.44 (t, J = 8.0 Hz, 1 H), 7.37 (m, 2 H), 7.29 (m, 4 H), 6.82 (d, J = 7.6 Hz, 0.5 H), 6.62 (d, J = 7.6 Hz, 0.5 H), 4.86 (s, 1 H), 4.82 (s, 1 H), 4.31 (s, 1 H), 4.18 (s, 1 H), 3.39 (d, J = 7.0 Hz, 1 H), 3.34 (m, 1 H), 2.82 (s), 1.06 (m, 1 H), 0.58 (m, 1 H), 0.50 (m, 1 H),
10 0.26 (m, 2 H)

Precursor S2

N-(2-(Dimethylamino)ethyl)-N-(2-fluorobenzyl)-2-(isoquinolin-5-ylamino)acetamide

is made according to the procedure described for the synthesis of **Precursor S1** using **Precursor T1** and **Amine 20** as starting materials.

- 15 **Precursor T1**

2-(Isoquinolin-5-ylamino)acetic acid

- To a solution of 5-isoquinoline (1g, 6.94 mmol) in 15 mL MeCN cooled to 0°C is added 1.54 mL 50% glyoxylic acid soln. in water and NaBH₃CN (872 mg, 13.9 mmol). The mixture is allowed to warm up to RT and is stirred at this temperature overnight. Then MeCN is
20 evaporated under reduced pressure, the residue is taken up in water (pH=9). The resulting aq. phase is extracted with ether. The aq. phase is then acidified with 1N HCl soln. and the solvent is evaporated under reduced pressure. The residue is dissolved with MeOH and eluted on a SiliaBond® SCX acid column. It is released with ammonia. After evaporation, the crude is dissolved in 1N HCl aq. soln. and heated up at 85°C for 2 h. Evaporation of the
25 volatiles to dryness and under HV yields 820 mg (58%) of the title compound as a white solid.

¹H-NMR (d₆-DMSO) δ : 9.59 (s, 1 H), 8.64 (d, J = 6.8 Hz, 1 H), 8.48 (dd, J_1 = 6.9 Hz, J_2 = 0.6 Hz, 1 H), 7.86 (t, J = 8.1 Hz, 1 H), 7.75 (m, 1 H), 7.13 (d, J = 7.8 Hz, 1 H), 4.23 (s, 2 H)

Example 179

- 30 **2-(2-Cyclopropylmethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide**

- To a solution of {2-[[2-(2-cyclopropylmethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]- (2-trifluoromethyl-benzyl)-amino]-ethyl}-methyl-carbamic acid *tert*-butyl ester **Example 83** (30 mg, 0.052 mmol) in 1 mL DCM is added 0.15 mL TFA. The resulting yellow solution is
35 allowed to stir at RT for 30 min then poured onto water. The resulting aq. phase is basified to pH=8-9 with sat. aq. NaHCO₃ soln. then extracted twice with DCM. The combined organic

phase is washed with brine then dried over MgSO_4 , filtered and evaporated under reduced pressure. After drying under HV, pure title compound is obtained as a yellow foam.

LC-A: $t_R = 0.60$ min; $[\text{M}+\text{H}]^+ = 475.2$

- Example 177** N-(2-Methylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide, LC-A: $t_R = 0.70$ min; $[\text{M}+\text{H}]^+ = 477.2$ and **Example 178** rac-N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-pyrrolidin-3-yl-acetamide, LC-A: $t_R = 0.55$ min; $[\text{M}+\text{H}]^+ = 419.1$ are prepared applying the method described for **Example 179** from **Precursor U1** and **Example 65** respectively.

Example 385

2-(2-Cyclopropanecarbonyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide

- To a solution of *tert*-butyl 2-(2-((2-(cyclopropanecarbonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(trifluoromethyl)benzyl)acetamido)ethyl)(methyl)carbamate **Precursor U11** (58.9 mg, 0.1 mmol) in 1 mL DCM and 0.5 mL MeOH is added 0.5 mL 4N HCl soln. in dioxane (2 mmol). The resulting yellow solution is allowed to stir at RT for 30 min then the volatiles are removed under reduced pressure and the residue dried under HV. The crude residue is purified by prep. HPLC (Method D).

LC-F: $t_R = 0.74$ min; $[\text{M}+\text{H}]^+ = 489.3$

- In some case, the hydrochloride salt of the title compound obtained after evaporation of the volatiles does not need further purification. In some other instances 4M HCl in MeOH is added to the preparative HPLC fractions in order to obtain after drying the title compound as an hydrochloride salt.

- Examples 377-384 / 386-433 / 435-446** listed in **Table 23** are prepared applying one of the methods described for **Example 179** or **Example 385** respectively using the corresponding **Precursor** or **Example compound**.

Table 23: Examples 377-384 / 386-433 / 435-446

Example No	Example name	t_R [min] (LC-FF) unless otherwise indicated	MS Data m/z $[\text{M}+\text{H}]^+$
377	N-Benzyl-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-piperidin-4-yl-acetamide	0.39	407.3

378	rac-N-Benzyl-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-pyrrolidin-3-yl-acetamide	0.39	393.3
379	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(R)-1-pyrrolidin-3-ylmethyl-N-(2-trifluoromethyl-benzyl)-acetamide	0.52	501.4
380	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(S)-1-pyrrolidin-3-ylmethyl-N-(2-trifluoromethyl-benzyl)-acetamide	0.52	501.4
381	rac-2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-pyrrolidin-3-yl-N-(2-trifluoromethyl-benzyl)-acetamide	0.5	487.3
382	rac-2-(2-Cyclopropylmethyl-1-methyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.52	489.4
383	2-(2-Isobutyl-3-oxo-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.83	491.3
384	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.49	475.3
386	2-(2-Butyryl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.76	491.3
387	2-(2-Isobutyryl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.76	491.4
3388	2-[2-(2-Methoxy-acetyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.67	493.3
389	2-(2-Cyclobutanecarbonyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.79	503.3
390	2-[2-(2,2-Dimethyl-propionyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.82	505.3
391	N-(2-Methylamino-ethyl)-2-[2-(3-methyl-butyryl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide	0.81	505.3
392	rac-N-(2-Methylamino-ethyl)-2-[2-(tetrahydro-furan-3-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide	0.69	519.3
393	2-[2-(3,3-Dimethyl-butyryl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.85	519.4
394	5-([[(2-Methylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl]-methyl]-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid methyl ester	0.76	479.3

395	5-(((2-Methylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid ethyl ester	0.81	493.3
396	5-(((2-Methylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid prop-2-ynyl ester	0.8	503.3
397	5-(((2-Methylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid allyl ester	0.84	505.3
398	5-(((2-Methylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid propyl ester	0.87	507.3
399	5-(((2-Methylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid isopropyl ester	0.86	507.3
400	5-(((2-Methylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid 2-fluoro-ethyl ester	0.78	511.3
401	5-(((2-Methylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid isobutyl ester	0.91	521.4
402	5-(((2-Methylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid 2,2-dimethyl-propyl ester	0.94	535.4
403	5-(((2-Methylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid ethylamide	0.69	492.3
404	5-(((2-Methylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid isopropylamide	0.74	506.4
405	5-(((2-Methylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid butylamide	0.8	520.4
406	5-(((2-Methylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butylamide	0.81	520.4

407	5-(((2-Methylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid cyclohexylamide	0.85	546.4
408	2-(2-Acetyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.6	464.3
409	N-(2-Methylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.65	478.3
410	2-(2-Cyclopropanecarbonyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.67	490.3
411	2-(2-Butyryl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.69	492.3
412	2-(2-Isobutyryl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.69	492.4
413	2-[2-(2-Methoxy-acetyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-methylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.97 (LC-F1)	494.3
414	2-(2-Cyclobutanecarbonyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.72	504.3
415	2-[2-(2,2-Dimethyl-propionyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-methylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.75	506.4
416	N-(2-Methylamino-ethyl)-2-[2-(3-methyl-butyryl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.74	506.4
417	rac-N-(2-Methylamino-ethyl)-2-[2-(tetrahydro-furan-3-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.63	520.3
418	2-[2-(3,3-Dimethyl-butyryl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-methylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.79	520.4
419	5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid methyl ester	0.69	480.3

420	5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid ethyl ester	0.74	494.3
421	5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid prop-2-ynyl ester	0.73	504.3
422	5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid allyl ester	0.77	506.3
423	5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid propyl ester	0.8	508.3
424	5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid isopropyl ester	0.8	508.3
425	5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid 2-fluoro-ethyl ester	0.7	512.3
426	5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid isobutyl ester	0.85	522.4
427	5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid 2-methoxy-ethyl ester	0.69	524.3
428	5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid 2,2-dimethyl-propyl ester	0.89	536.4
429	5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid ethylamide	0.62	493.3
430	5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid isopropylamide	0.67	507.3
431	5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid butylamide	0.73	521.4

432	5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butylamide	0.74	521.4
433	5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid cyclohexylamide	0.78	547.4
435	N-(2-Bromo-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-acetamide	0.47	485.3
436	N-(3-Chloro-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-acetamide	0.39	442.3
437	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.43	476.3
438	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-piperazin-1-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.51	530.4
439	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-ethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.5	489.4
440	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-piperidin-4-yl-N-(2-trifluoromethyl-benzyl)-acetamide	0.49	501.3
441	rac-2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-pyrrolidin-3-ylmethyl-N-(2-trifluoromethyl-benzyl)-acetamide	0.52	501.4
442	N-(2-Amino-ethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	0.49	461.4
443	N-Benzyl-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-methylamino-ethyl)-acetamide	0.38	381.2
444	2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.46	449.3
445	2-(2-Acetyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.67	463.3
446	N-(2-Chloro-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-acetamide	0.46	441.3

Example 434

2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(2,2,2-trifluoro-ethylamino)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide

To a solution of 2-((2-(cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-((4-methoxybenzyl)(2,2,2-trifluoroethyl)amino)ethyl)-N-(2-(trifluoromethyl)benzyl)acetamide

Precursor U60 (164 mg, 0.247 mmol) and 0.5 mL AcOH in 5 mL MeOH is added 10% Pd / C (26.3 mg, 0.0247 mmol). The suspension is stirred under H₂ atmosphere for 8 h. The crude mixture is then filtered and the concentrated under reduced pressure. The crude residue is purified by prep. HPLC (Method D). LC-F: t_R = 0.84 min; $[M+H]^+$ = 543.3

Precursor U1

Methyl-{2-[[2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]-(2-trifluoromethyl-benzyl)-amino]-ethyl}-carbamic acid *tert*-butyl ester LC-A: t_R = 1.00 min; $[M+H]^+$ = 576.8 is prepared according to the method described for the synthesis of **Example 8** using **Precursor B2** and **Amine 73** as starting materials.

Precursor U10

***tert*-Butyl (2-(2-((2-acetyl-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(trifluoromethyl)benzyl)acetamido)ethyl)(methyl)carbamate**

To a solution of acetyl chloride (7.85 mg, 0.1 mmol) in 1 mL DCM is added TEA (10.1 mg, 0.1 mmol) and methyl-{2-[[2-(1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]-(2-trifluoromethyl-benzyl)-amino]-ethyl}-carbamic acid *tert*-butyl ester **Precursor J14** (54.2 mg, 0.1 mmol). The resulting mixture is allowed to stir at RT for 1.5 h. The obtained solution of title compound, LC-G: t_R = 1.11 min; $[M+H]^+$ = 563.2, is used as such in the next step.

Precursor U20

Methyl 5-((2-((2-((*tert*-butoxycarbonyl)(methyl)amino)ethyl)(2-(trifluoromethyl)benzyl)amino)-2-oxoethyl)amino)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate

To a solution of methyl chloroformate (10.5 mg, 0.11 mmol) in 1 mL DCM is added TEA (10.1 mg, 0.1 mmol) and methyl-{2-[[2-(1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]-(2-trifluoromethyl-benzyl)-amino]-ethyl}-carbamic acid *tert*-butyl ester **Precursor J14** (54.2 mg, 0.1 mmol). The resulting mixture is allowed to stir at RT for 1.5 h. The obtained solution of title compound, LC-G: t_R = 1.21 min; $[M+H]^+$ = 519.2, is used as such in the next step.

Precursor U29

***tert*-Butyl (2-(2-((2-(Ethylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(trifluoromethyl)benzyl)acetamido)ethyl)(methyl)carbamate**

To a solution of ethyl isocyanate (8.2 mg, 0.11 mmol) in 1 mL DCM is added TEA (10.1 mg, 0.1 mmol) and methyl-{2-[[2-(1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]-(2-trifluoromethyl-benzyl)-amino]-ethyl}-carbamic acid *tert*-butyl ester **Precursor J14** (54.2 mg, 0.1 mmol). The resulting mixture is allowed to stir at RT for 1.5 h. The obtained solution of title compound, LC-G: t_R = 1.11 min; $[M+H]^+$ = 592.2, is used as such in the next step.

Precursors U2-U9 / U11-U19 / U21-U28 / U30-U63 listed in Table 24 are prepared applying one of the methods described for the synthesis of Precursor U1 from precursor B2 and amine 73 or Precursor U10, Precursor U20 and Precursor U29 from Precursor J14 using the corresponding reagents.

5 Table 24: Precursors U2-U9 / U11-U19 / U21-U28 / U30-U63

Precursor	Precursor name	t_R [min] (Method)	MS Data m/z [M+H] ⁺
U2	4-{Benzyl-[2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetyl]-amino}-piperidine-1-carboxylic acid <i>tert</i> -butyl ester	1.8 (H)	507.2
U3	3-{Benzyl-[2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetyl]-amino}-pyrrolidine-1-carboxylic acid <i>tert</i> -butyl ester	1.75 (H)	493.2
U9	<i>tert</i> -Butyl (2-(2-((2-(cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)amino)-N-(2-(trifluoromethyl)benzyl)acetamido)ethyl)(methyl)carbamate	0.83 (A)	575.1
U4	(S)-3-[[[2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]-(2-trifluoromethyl-benzyl)-amino]-methyl]-pyrrolidine-1-carboxylic acid <i>tert</i> -butyl ester	0.86 (A)	601.3
U5	(R)-3-[[[2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]-(2-trifluoromethyl-benzyl)-amino]-methyl]-pyrrolidine-1-carboxylic acid <i>tert</i> -butyl ester	0.86 (A)	601.3
U6	rac-3-[[2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]-(2-trifluoromethyl-benzyl)-amino]-pyrrolidine-1-carboxylic acid <i>tert</i> -butyl ester	0.85 (A)	587.3
U7	rac- <i>tert</i> -Butyl (2-(2-((2-(cyclopropylmethyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(trifluoromethyl)benzyl)acetamido)ethyl)(methyl)carbamate	0.87 (A)	589.3
U8	<i>tert</i> -Butyl (2-(2-((2-(isobutyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(trifluoromethyl)benzyl)acetamido)ethyl)(methyl)carbamate	0.98 (B)	591.1
U11	<i>tert</i> -Butyl (2-(2-((2-(cyclopropanecarbonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(trifluoromethyl)benzyl)acetamido)ethyl)(methyl)carbamate	1.2 (G)	589.2

U12	<i>tert</i> -Butyl (2-(2-((2-butyryl-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(trifluoromethyl)benzyl)acetamido)ethyl)(methyl)carbamate	1.23 (G)	591.2
U13	<i>tert</i> -Butyl (2-(2-((2-isobutyryl-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(trifluoromethyl)benzyl)acetamido)ethyl)(methyl)carbamate	1.23 (G)	591.2
U14	<i>tert</i> -Butyl (2-(2-((2-(2-methoxyacetyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(trifluoromethyl)benzyl)acetamido)ethyl)(methyl)carbamate	1.14 (G)	593.2
U15	<i>tert</i> -Butyl (2-(2-((2-(cyclobutanecarbonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(trifluoromethyl)benzyl)acetamido)ethyl)(methyl)carbamate	1.24 (G)	603.2
U16	<i>tert</i> -Butyl methyl(2-(2-((2-pivaloyl-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(trifluoromethyl)benzyl)acetamido)ethyl)carbamate	1.28 (G)	605.2
U17	<i>tert</i> -Butyl methyl(2-(2-((2-(3-methylbutanoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(trifluoromethyl)benzyl)acetamido)ethyl)carbamate	1.26 (G)	605.2
U18	<i>tert</i> -Butyl (S)-methyl(2-(2-((2-(tetrahydrofuran-3-carbonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(trifluoromethyl)benzyl)acetamido)ethyl)carbamate	1.15 (G)	619.2
U19	<i>tert</i> -Butyl (2-(2-((2-(3,3-dimethylbutanoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(trifluoromethyl)benzyl)acetamido)ethyl)(methyl)carbamate	1.3 (G)	619.3
U21	Ethyl 5-((2-((2-((<i>tert</i> -butoxycarbonyl)(methyl)amino)ethyl)(2-(trifluoromethyl)benzyl)amino)-2-oxoethyl)amino)-3,4-dihydroisoquinoline-2(1 <i>H</i>)-carboxylate	1.29 (G)	593.2
U22	Prop-2-yn-1-yl 5-((2-((2-((<i>tert</i> -butoxycarbonyl)(methyl)amino)ethyl)(2-(trifluoromethyl)benzyl)amino)-2-oxoethyl)amino)-3,4-dihydroisoquinoline-2(1 <i>H</i>)-carboxylate	1.26 (G)	603.2
U23	Allyl 5-((2-((2-((<i>tert</i> -butoxycarbonyl)(methyl)amino)ethyl)(2-(trifluoromethyl)benzyl)amino)-2-oxoethyl)amino)-3,4-dihydroisoquinoline-2(1 <i>H</i>)-carboxylate	1.30 (G)	605.2
U24	Propyl 5-((2-((2-((<i>tert</i> -butoxycarbonyl)(methyl)amino)ethyl)(2-(trifluoromethyl)benzyl)amino)-2-oxoethyl)amino)-3,4-dihydroisoquinoline-2(1 <i>H</i>)-carboxylate	1.33 (G)	607.2

U25	Isopropyl 5-((2-((2-((<i>tert</i> -butoxycarbonyl)(methyl)amino)ethyl)(2-(trifluoromethyl)benzyl)amino)-2-oxoethyl)amino)-3,4-dihydroisoquinoline-2(1 <i>H</i>)-carboxylate	1.33 (G)	607.2
U26	2-Fluoroethyl 5-((2-((2-((<i>tert</i> -butoxycarbonyl)(methyl)amino)ethyl)(2-(trifluoromethyl)benzyl)amino)-2-oxoethyl)amino)-3,4-dihydroisoquinoline-2(1 <i>H</i>)-carboxylate	1.24 (G)	611.2
U27	Isobutyl 5-((2-((2-((<i>tert</i> -butoxycarbonyl)(methyl)amino)ethyl)(2-(trifluoromethyl)benzyl)amino)-2-oxoethyl)amino)-3,4-dihydroisoquinoline-2(1 <i>H</i>)-carboxylate	1.37 (G)	621.2
U28	Neopentyl 5-((2-((2-((<i>tert</i> -butoxycarbonyl)(methyl)amino)ethyl)(2-(trifluoromethyl)benzyl)amino)-2-oxoethyl)amino)-3,4-dihydroisoquinoline-2(1 <i>H</i>)-carboxylate	1.40 (G)	635.3
U30	<i>tert</i> -Butyl (2-(2-((2-(Isopropylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(trifluoromethyl)benzyl)acetamido)ethyl)(methyl)carbamate	1.19 (G)	606.2
U31	<i>tert</i> -Butyl (2-(2-((2-(Butylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(trifluoromethyl)benzyl)acetamido)ethyl)(methyl)carbamate	1.23 (G)	620.2
U32	<i>tert</i> -Butyl (2-(2-((2-((<i>tert</i> -Butylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(trifluoromethyl)benzyl)acetamido)ethyl)(methyl)carbamate	1.26 (G)	620.3
U33	<i>tert</i> -Butyl (2-(2-((2-(Cyclohexylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(trifluoromethyl)benzyl)acetamido)ethyl)(methyl)carbamate	1.27 (G)	646.0
U34	<i>tert</i> -Butyl (2-(2-((2-Acetyl-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-((3-(trifluoromethyl)pyridin-2-yl)methyl)acetamido)ethyl)(methyl)carbamate	1.01 (G)	564.2
U35	<i>tert</i> -Butyl methyl(2-(2-((2-propionyl-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-((3-(trifluoromethyl)pyridin-2-yl)methyl)acetamido)ethyl)carbamate	1.07 (G)	578.2
U36	<i>tert</i> -Butyl (2-(2-((2-(cyclopropanecarbonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-((3-(trifluoromethyl)pyridin-2-yl)methyl)acetamido)ethyl)(methyl)carbamate	1.04 (G)	590.4

U37	<i>tert</i> -Butyl (2-(2-((2-butyryl-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-((3-(trifluoromethyl)pyridin-2-yl)methyl)acetamido)ethyl)(methyl)carbamate	1.11 (G)	592.1
U38	<i>tert</i> -Butyl (2-(2-((2-isobutyryl-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-((3-(trifluoromethyl)pyridin-2-yl)methyl)acetamido)ethyl)(methyl)carbamate	1.11 (G)	592.1
U39	<i>tert</i> -Butyl (2-(2-((2-(2-methoxyacetyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-((3-(trifluoromethyl)pyridin-2-yl)methyl)acetamido)ethyl)(methyl)carbamate	1.02 (G)	594.1
U40	<i>tert</i> -Butyl (2-(2-((2-(cyclobutanecarbonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-((3-(trifluoromethyl)pyridin-2-yl)methyl)acetamido)ethyl)(methyl)carbamate	1.09 (G)	645.1
U41	<i>tert</i> -Butyl methyl(2-(2-((2-pivaloyl-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-((3-(trifluoromethyl)pyridin-2-yl)methyl)acetamido)ethyl)carbamate	1.16 (G)	605.8
U42	<i>tert</i> -Butyl methyl(2-(2-((2-(3-methylbutanoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-((3-(trifluoromethyl)pyridin-2-yl)methyl)acetamido)ethyl)carbamate	1.13 (G)	606.8
U43	<i>tert</i> -Butyl methyl(2-(2-((2-(tetrahydrofuran-3-carbonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-((3-(trifluoromethyl)pyridin-2-yl)methyl)acetamido)ethyl)carbamate	1.03 (G)	620.1
U44	<i>tert</i> -butyl (2-(2-((2-(3,3-dimethylbutanoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-((3-(trifluoromethyl)pyridin-2-yl)methyl)acetamido)ethyl)(methyl)carbamate	1.20 (G)	620.2
U45	Methyl 5-((2-((2-((<i>tert</i> -butoxycarbonyl)(methyl)amino)ethyl)((3-(trifluoromethyl)pyridin-2-yl)methyl)amino)-2-oxoethyl)amino)-3,4-dihydroisoquinoline-2(1 <i>H</i>)-carboxylate	1.12 (G)	580.2
U46	Ethyl 5-((2-((2-((<i>tert</i> -butoxycarbonyl)(methyl)amino)ethyl)((3-(trifluoromethyl)pyridin-2-yl)methyl)amino)-2-oxoethyl)amino)-3,4-dihydroisoquinoline-2(1 <i>H</i>)-carboxylate	1.17 (G)	594.1
U47	Propyl 5-((2-((2-((<i>tert</i> -butoxycarbonyl)(methyl)amino)ethyl)((3-(trifluoromethyl)pyridin-2-yl)methyl)amino)-2-oxoethyl)amino)-3,4-dihydroisoquinoline-2(1 <i>H</i>)-carboxylate	1.15 (G)	604.1
U48	Allyl 5-((2-((2-((<i>tert</i> -butoxycarbonyl)(methyl)amino)ethyl)((3-(trifluoromethyl)pyridin-2-yl)methyl)amino)-2-oxoethyl)amino)-3,4-dihydroisoquinoline-2(1 <i>H</i>)-carboxylate	1.20 (G)	623.1

U49	Propyl 5-((2-((2-((<i>tert</i> -butoxycarbonyl)(methyl)amino)ethyl)((3-(trifluoromethyl)pyridin-2-yl)methyl)amino)-2-oxoethyl)amino)-3,4-dihydroisoquinoline-2(1 <i>H</i>)-carboxylate	1.23 (G)	608.2
U50	Isopropyl 5-((2-((2-((<i>tert</i> -butoxycarbonyl)(methyl)amino)ethyl)((3-(trifluoromethyl)pyridin-2-yl)methyl)amino)-2-oxoethyl)amino)-3,4-dihydroisoquinoline-2(1 <i>H</i>)-carboxylate	1.21 (G)	608.1
U51	2-Fluoroethyl 5-((2-((2-((<i>tert</i> -butoxycarbonyl)(methyl)amino)ethyl)((3-(trifluoromethyl)pyridin-2-yl)methyl)amino)-2-oxoethyl)amino)-3,4-dihydroisoquinoline-2(1 <i>H</i>)-carboxylate	1.13 (G)	612.1
U52	Isobutyl 5-((2-((2-((<i>tert</i> -butoxycarbonyl)(methyl)amino)ethyl)((3-(trifluoromethyl)pyridin-2-yl)methyl)amino)-2-oxoethyl)amino)-3,4-dihydroisoquinoline-2(1 <i>H</i>)-carboxylate	1.27 (G)	639.2
U53	2-Methoxyethyl 5-((2-((2-((<i>tert</i> -butoxycarbonyl)(methyl)amino)ethyl)((3-(trifluoromethyl)pyridin-2-yl)methyl)amino)-2-oxoethyl)amino)-3,4-dihydroisoquinoline-2(1 <i>H</i>)-carboxylate	1.11 (G)	624.1
U54	Neopentyl 5-((2-((2-((<i>tert</i> -butoxycarbonyl)(methyl)amino)ethyl)((3-(trifluoromethyl)pyridin-2-yl)methyl)amino)-2-oxoethyl)amino)-3,4-dihydroisoquinoline-2(1 <i>H</i>)-carboxylate	1.27 (G)	n.d.
U55	<i>tert</i> -Butyl (2-(2-((2-(ethylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-((3-(trifluoromethyl)pyridin-2-yl)methyl)acetamido)ethyl)(methyl)carbamate	1.03 (G)	593.2
U56	<i>tert</i> -Butyl (2-(2-((2-(isopropylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-((3-(trifluoromethyl)pyridin-2-yl)methyl)acetamido)ethyl)(methyl)carbamate	1.06 (G)	607.2
U57	<i>tert</i> -Butyl (2-(2-((2-(butylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-((3-(trifluoromethyl)pyridin-2-yl)methyl)acetamido)ethyl)(methyl)carbamate	1.09 (G)	621.1
U58	<i>tert</i> -Butyl (2-(2-((2-(<i>tert</i> -butylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-((3-(trifluoromethyl)pyridin-2-yl)methyl)acetamido)ethyl)(methyl)carbamate	1.15 (G)	621.0
U59	<i>tert</i> -Butyl (2-(2-((2-(cyclohexylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-((3-(trifluoromethyl)pyridin-2-yl)methyl)acetamido)ethyl)(methyl)carbamate	1.17 (G)	664.2

U60	2-((2-(Cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-((4-methoxybenzyl)(2,2,2-trifluoroethyl)amino)ethyl)-N-(2-(trifluoromethyl)benzyl)acetamide	0.90 (A)	662.9
U61	2-((2-(Cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-((4-methoxybenzyl)(2,2,2-trifluoroethyl)amino)ethyl)-N-(2-(trifluoromethyl)benzyl)acetamide	0.82 (A)	586.9
U62	<i>tert</i> -Butyl (2-(N-(2-chlorobenzyl)-2-((2-(cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)acetamido)ethyl)(methyl)carbamate	0.82 (A)	541.3
U63	<i>tert</i> -Butyl (2-(N-((3-chloropyridin-2-yl)methyl)-2-((2-(cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)acetamido)ethyl)(methyl)carbamate	0.77 (A)	542.2

Example 180**rac-N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(1-methyl-pyrrolidin-3-yl)-acetamide**

- 5 To a solution of N-benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-pyrrolidin-3-yl-acetamide **Example 178** (12 mg, 0.0287 mmol) in 0.5 mL MeOH is added one drop of 36.5% formaldehyde soln. in water (20 mg, 0.243 mmol) then NaBH₄ (2 mg, 0.0529 mmol) and the resulting soln. is allowed to stir at RT for 1 h. The solvent is removed under reduced pressure, the residue is partitioned between sat. aq. NaHCO₃ soln. and DCM. The
- 10 resulting aq. phase is extracted twice with DCM. The combined organic phase is dried over MgSO₄, filtered and the solvent removed under reduced pressure. Purification of the crude residue by prep. HPLC (Method D) yields the title compound as a white solid.
- LC-A: *t_R* = 0.56 min; [M+H]⁺ = 433.1

Example 447

- 15 **N-[2-(Cyclobutyl-methyl-amino)-ethyl]-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide**

- To a solution of the dihydrochloride salt of N-[2-(cyclobutyl-methyl-amino)-ethyl]-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide **Example 179** (50 mg, 0.089 mmol) in 1 mL MeOH is added cyclobutanone (31
- 20 mg, 0.443 mmol), ZnCl₂ (24.1 mg, 0.177 mmol) and NaBH₃CN (19.5 mg, 0.31 mmol). The resulting yellow mixture is allowed to stir at RT overnight. Water is added and the resulting organic phase is extracted three times with DCM. The combined organic phase is washed with sat. aq. NaHCO₃ soln. dried over MgSO₄, filtered and the solvent removed under

reduced pressure. Purification of the crude residue by prep. HPLC (Method D) yields the title compound as a yellow oil.

LC-A: $t_R = 0.63$ min; $[M+H]^+ = 529.1$

- Examples 448-453** listed in **Table 25** are prepared applying the method described for **Example 447** using the corresponding **Example compound** and ketone respectively.

Table 25: Examples 448-453

Example No	Example name	t_R [min] (LC-F)	MS Data m/z $[M+H]^+$
448	rac-2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-{2-[methyl-(tetrahydro-furan-3-yl)-amino]-ethyl}-N-(2-trifluoromethyl-benzyl)-acetamide	0.52	545.4
449	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(isopropyl-methyl-amino)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide	0.52	517.4
450	N-[2-(Cyclopropylmethyl-methyl-amino)-ethyl]-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	0.54	529.4
451	N-[2-(Cyclopentyl-methyl-amino)-ethyl]-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	0.55	543.4
452	rac-2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-{2-[(2-fluoro-1-methyl-ethyl)-methyl-amino]-ethyl}-N-(2-trifluoromethyl-benzyl)-acetamide	0.53	535.4
453	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-[ethyl-(3-methyl-oxetan-3-ylmethyl)-amino]-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide	0.55	573.4

Example 181

- 8-({[Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl}-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester**

- To a solution of 8-(carboxymethyl-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester **Precursor V1** (884 mg, 2.42 mmol) in 20 mL DCM are added N-benzyl-N',N'-dimethylethane-1,2-diamine **Amine 7** (432 mg, 2.42 mmol), HATU (1106 mg, 2.91 mmol) and DIPEA (783 mg, 6.06 mmol). The resulting brown suspension is allowed to stir at RT for 1 h. The organic phase is washed with water, sat. aq. NaHCO_3 and brine successively then

dried over MgSO_4 , filtered and evaporated under reduced pressure. Flash-chromatography on silica-gel (Eluent: gradient of DCM / MeOH 100:0 to 80:20) yields the title compound as a brown oil.

LC-B: $t_R = 0.73$ min; $[M+H]^+ = 467.08$

- 5 **Examples 182-184 / 455-543** listed in **Table 26** are prepared applying the method described for **Example 181** using the corresponding **Precursor** and **Amine** respectively.

Table 26: Examples 182-184 / 455-543

Example No	Example name	t_R [min] (LC-C)	MS Data m/z $[M+H]^+$
182	N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide	0.53	381.4
183	N-Benzyl-N-(3-methyl-butyl)-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide	0.95	380.4
184	N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-methyl-1-oxo-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide	0.78	395.4
Example No	Example name	t_R [min] (LC-F) unless indicated otherwise	MS Data m/z $[M+H]^+$
455	N-(3-Chloro-pyridin-2-ylmethyl)-2-(2-cyclobutyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-acetamide	0.39	456.3
456	N-(3-Bromo-pyridin-2-ylmethyl)-2-(2-cyclobutyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-acetamide	0.4	500.3
457	N-(3-Chloro-pyridin-2-ylmethyl)-2-(2-cyclobutyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-hydroxy-2-methyl-propyl)-acetamide	0.64	457.3
458	N-(3-Bromo-pyridin-2-ylmethyl)-2-(2-cyclobutyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-hydroxy-2-methyl-propyl)-acetamide	0.65	501.2
459	rac-N-(3-Chloro-pyridin-2-ylmethyl)-N-(2-dimethylamino-ethyl)-2-[2-((1R*,2R*)-2-fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-8-ylamino]-acetamide	0.64	488.3

460	rac-N-(3-Bromo-pyridin-2-ylmethyl)-N-(2-dimethylamino-ethyl)-2-[2-((1R*,2R*)-2-fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-8-ylamino]-acetamide	0.66	532.2
461	rac-N-(3-Bromo-pyridin-2-ylmethyl)-2-[2-((1R*,2R*)-2-fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-8-ylamino]-N-(2-hydroxy-2-methyl-propyl)-acetamide	1.03	533.2
463	N-[2-(Allyl-methyl-amino)-ethyl]-2-(2-allyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	0.51	501.3
464	2-(2-Allyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethoxy-benzyl)-acetamide	0.5	491.3
465	2-(2-Allyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-{2-[(2-fluoro-ethyl)-methyl-amino]-ethyl}-N-(2-trifluoromethyl-benzyl)-acetamide	0.5	507.3
466	2-(2-Allyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.48	475.4
467	N-[2-(Allyl-methyl-amino)-ethyl]-3-(2-allyl-1,2,3,4-tetrahydro-isoquinolin-8-yl)-N-(2-trifluoromethyl-benzyl)-propionamide	0.51	500.3
468	3-(2-Allyl-1,2,3,4-tetrahydro-isoquinolin-8-yl)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-propionamide	0.48	474.4
475	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.49	489.3
476	N-[2-(Cyclopropyl-methyl-amino)-ethyl]-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	0.54	515.4
471	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-trifluoromethoxy-benzyl)-acetamide	0.53	505.4
472	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethoxy-benzyl)-acetamide	0.52	505.4

473	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)- N-(2-dimethylamino-ethyl)-N-(4-trifluoromethoxy-benzyl)- acetamide	0.54	505.3
474	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)- N-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-N-(2-trifluoromethyl- benzyl)-acetamide	0.65	565.4
475	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)- N-[2-[methyl-(2,2,2-trifluoro-ethyl)-amino]-ethyl]-N-(2- trifluoromethyl-benzyl)-acetamide	0.92	557.3
476	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)- N-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-N-(3-trifluoromethyl-pyridin- 2-ylmethyl)-acetamide	0.52	566.4
477	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)- N-[2-[methyl-(2,2,2-trifluoro-ethyl)-amino]-ethyl]-N-(3- trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.86	558.3
478	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)- N-[2-(3,3-difluoro-piperidin-1-yl)-ethyl]-N-(2-trifluoromethyl- benzyl)-acetamide	0.81	565.3
479	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)- N-[2-(3,3-difluoro-pyrrolidin-1-yl)-ethyl]-N-(2-trifluoromethyl- benzyl)-acetamide	0.78	551.3
480	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)- N-[2-(3,3-difluoro-piperidin-1-yl)-ethyl]-N-(3-trifluoromethyl-pyridin- 2-ylmethyl)-acetamide	0.62	566.4
481	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)- N-[2-(3,3-difluoro-pyrrolidin-1-yl)-ethyl]-N-(3-trifluoromethyl- pyridin-2-ylmethyl)-acetamide	0.61	552.3
482	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)- N-[2-(3,3-difluoro-azetidin-1-yl)-2-oxo-ethyl]-N-(2-trifluoromethyl- benzyl)-acetamide	0.78	551.3
483	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)- N-[2-(3,3-difluoro-azetidin-1-yl)-2-oxo-ethyl]-N-(3-trifluoromethyl- pyridin-2-ylmethyl)-acetamide	0.69	552.3

484	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-[2-(3,3-difluoro-azetidin-1-yl)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide	0.75	537.3
485	N-(3-Chloro-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-acetamide	0.4	456.3
486	N-(3-Bromo-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-acetamide	0.41	500.3
487	N-(3-Chloro-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-hydroxy-2-methyl-propyl)-acetamide	0.64	457.3
488	N-(3-Bromo-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-hydroxy-2-methyl-propyl)-acetamide	0.66	501.2
489	2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.47	489.3
490	N-Benzyl-N-(2-diethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide	1.73 (LC-H)	423.1
491	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-fluoro-benzyl)-acetamide	0.39	413.3
492	2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(1-methyl-piperidin-4-yl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.46	489.4
493	(2-(Benzyl-[2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetyl]-amino)-ethyl)-methyl-carbamic acid <i>tert</i> -butyl ester	0.82	481.4
494	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-methyl-benzyl)-acetamide	0.42	409.3
495	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(3-methyl-benzyl)-acetamide	0.43	409.4
496	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(4-methyl-benzyl)-acetamide	0.43	409.4

497	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-methoxy-benzyl)-acetamide	0.42	425.4
498	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(3-methoxy-benzyl)-acetamide	0.4	425.4
499	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(4-methoxy-benzyl)-acetamide	0.4	425.4
500	N-(2-Chloro-benzyl)-N-(2-dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide	0.43	429.3
501	N-(3-Chloro-benzyl)-N-(2-dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide	0.44	429.3
502	N-(4-Chloro-benzyl)-N-(2-dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide	0.44	429.3
503	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(3-fluoro-benzyl)-acetamide	0.40	413.3
504	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(4-fluoro-benzyl)-acetamide	0.40	413.3
505	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(3-trifluoromethyl-benzyl)-acetamide	0.47	463.3
506	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(4-trifluoromethyl-benzyl)-acetamide	0.48	463.3
507	N-Benzyl-N-(3-dimethylamino-propyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide	0.40	409.4
508	rac-N-Benzyl-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-acetamide	0.42	435.4
509	N-Benzyl-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-acetamide	0.40	421.3
510	2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-morpholin-4-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.48	505.3
511	N-(3-Chloro-pyridin-2-ylmethyl)-N-(2-dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide	0.36	430.3
512	rac-N-Benzyl-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(1-methyl-pyrrolidin-3-yl)-acetamide	0.39	407.3

513	2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(3-methyl-butyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.94	462.4
514	N-(2-Diethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	0.48	491.4
515	{2-[[2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetyl]-(2-trifluoromethyl-benzyl)-amino]-ethyl}-methyl-carbamic acid <i>tert</i> -butyl ester	0.90	549.4
516	N-(2-Cyano-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	0.71	445.3
517	2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-[2-(2-oxo-pyrrolidin-1-yl)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide	0.7	503.3
518	rac-2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(1-methyl-piperidin-3-yl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.49	489.3
519	2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(tetrahydro-pyran-4-yl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.75	476.3
520	2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(4-methyl-thiazol-2-ylmethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.82	503.3
521	rac-N-[1-(1-Ethyl-1 <i>H</i> -pyrazol-3-yl)-ethyl]-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	0.85	514.4
522	rac-N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-[1-(2-trifluoromethyl-phenyl)-ethyl]-acetamide	0.49	477.4
523	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(4-fluoro-2-trifluoromethyl-benzyl)-acetamide	0.48	481.3
524	N-(2,6-Difluoro-benzyl)-N-(2-dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide	0.39	431.4
525	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(3-methyl-pyridin-2-ylmethyl)-acetamide	0.35	410.4
526	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(6-methyl-pyridin-2-ylmethyl)-acetamide	0.35	410.4

527	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(5-methyl-pyridin-2-ylmethyl)-acetamide	0.35	410.4
528	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(3-fluoro-pyridin-2-ylmethyl)-acetamide	0.33	414.3
529	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(5-fluoro-pyridin-2-ylmethyl)-acetamide	0.34	414.3
530	N-(5-Chloro-pyridin-2-ylmethyl)-N-(2-dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide	0.38	430.3
531	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.39	464.3
532	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(6-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.42	464.3
533	N-(5-Chloro-pyridin-3-ylmethyl)-N-(2-dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide	0.35	430.3
534	N-(2-Dimethylamino-ethyl)-N-(2-dimethylamino-pyrimidin-5-ylmethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide	0.56 (LC-F1)	440.4
535	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(5-methyl-isoxazol-3-ylmethyl)-acetamide	0.41 (LC-F1)	400.3
536	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(4-methyl-thiazol-2-ylmethyl)-acetamide	0.35	416.3
537	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-o-tolyl-ethyl)-acetamide	0.46	423.4
538	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-[2-(2-trifluoromethyl-phenyl)-ethyl]-acetamide	0.5	477.4
539	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-[2-(3-trifluoromethyl-phenyl)-ethyl]-acetamide	0.51	477.4

540	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-pyridin-2-ylmethyl-acetamide	0.65	396.3
541	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-thiazol-2-ylmethyl-acetamide	0.63	402.3
542	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-phenethyl-acetamide	0.42	409.4
543	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-3-oxo-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	0.66	477.3

Precursor V1**8-(Carboxymethyl-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester**

- 5 To a solution of 8-(ethoxycarbonylmethyl-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester **Precursor W1** (2.24 g, 5.02 mmol) in 60 mL THF is added 10.8 mL (10.8 mmol) 1M aq. LiOH soln. The resulting mixture is allowed to stir at RT for 1 h. The organic solvent is removed under reduced pressure and the resulting aq. mixture is diluted with water. The resulting aq. phase is extracted twice with DCM. Then the aq. phase is made
- 10 acidic (pH=3) via addition of 1N aq. HCl soln. and the resulting aq. phase is extracted twice with DCM. The combined organic phase is washed with brine, dried over MgSO₄, filtered then the solvent is removed under reduced pressure to yield 825 mg (54%) of the title compound which is used as such in the next step.

LC-B: $t_R = 0.80$ min; $[M+H]^+ = 307.12$

15

Precursor V2'

- (2-Methyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetic acid hydrochloride is made according to the Method described for the synthesis of **Precursor B3'**. In this particular case, 1 equivalent LiOH is used and the crude HCl salt of **Precursor V2'** is obtained by direct
- 20 addition of an excess 1M aq. HCl soln. the reaction mixture and evaporating the solution to dryness then drying the crude residue under HV. In this case a mixture of the hydrochloride salt of Precursor V2' with 1 equivalent LiCl is obtained.

LC-B: $t_R = 0.36$ min; $[M+H]^+ = 221.2$

- 25 **Precursor V4'** (2-Cyclobutyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetic acid hydrochloride, LC-A: $t_R = 0.50$ min; $[M+H]^+ = 261.4$, ¹H-NMR (400 MHz, d₆-DMSO) δ : 6.92 (dd, $J_1 = 7.9$ Hz, $J_2 = 7.5$ Hz, 1 H), 6.33 (d, $J = 7.5$ Hz, 1 H), 6.20 (d, $J = 7.9$ Hz, 1 H), 4.69

(m, 1 H), 3.24 (d, $J = 3.6$ Hz, 2 H), 3.17 (s, 2 H), 2.94 (t, $J = 7.4$ Hz, 1 H), 2.71 (t, $J = 5.4$ Hz, 2 H), 2.50 (m, 2 H), 2.10 (m, 2 H), 1.88 (m, 2 H), 1.69 (m, 2 H), **Precursor V5'** (2-(2-cis-fluorocyclopropane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino acetic acid hydrochloride, LC-A: $t_R = 0.65$ min; $[M+H]^+ = 293.4$ and **Precursor V9'** (2-ethyl-3-oxo-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetic acid, LC-A: $t_R = 0.58$ min; $[M+H]^+ = 249.1$ are prepared applying the methods described for the synthesis of **Precursor V2** from **Precursor W2** using **Precursor W4**, **Precursor W5** and **Precursor W9** respectively.

Precursor V3

10 2-((2-Methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-8-yl)amino)acetic acid

a) 8-Amino-2-methyl-3,4-dihydro-2H-isoquinolin-1-one

A solution of 2-methyl-8-nitro-3,4-dihydro-2H-isoquinolin-1-one hydrochloride [Synthesis **2007**, (7), 981 - 983] in 6 mL EtOAc and 0.6 mL EtOH is submitted to hydrogenation conditions in an H-Cube apparatus with Pd / C cartridge (5% Pd, 30°C, full H_2 mode, 15 1ml/min). Evaporation of the solvent under reduced pressure yields 61 mg (100%) of the sub-title compound as a light yellow solid.

LC-B: $t_R = 0.45$ min; $[M+H]^+ = 177.3$

b) 8-Amino-2-methyl-3,4-dihydro-2H-isoquinolin-1-one 61 mg (0.346 mmol) is reacted in the same conditions as for the synthesis of **Precursor B24** to yield 51 mg (63%) of the title 20 compound as yellow solid.

LC-B: $t_R = 0.60$ min; $[M+H]^+ = 234.9$; 1H -NMR ($CDCl_3$) δ : 7.23 (t, $J = 7.8$ Hz, 1 H), 6.46 (d, $J = 7.3$ Hz, 1 H), 6.42 (d, $J = 8.5$ Hz, 1 H), 4.02 (s, 2 H), 3.52 (t, $J = 6.6$ Hz, 2 H), 3.14 (s, 3 H), 2.93 (t, $J = 6.6$ Hz, 2 H)

25 **Precursor V6'**

(2-Allyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetic acid hydrochloride

To a solution of N-(2-allyl-1,2,3,4-tetrahydroisoquinolin-8-yl)-N-(2,2,2-trifluoroacetyl)aminoacetic acid ethyl ester **Precursor W6** (1.15g, 2.77 mmol) in 10 mL THF is added a soln. of LiOH (128 mg, 1.94 mmol) in 4 mL water. The resulting mixture is 30 allowed to stir at RT for 4 h. Then LiOH (47 mg, 1.11 mmol) dissolved in 1 mL water is added again. The resulting mixture is allowed to stir at RT for 1 h. Then LiOH (58 mg, 1.39 mmol) dissolved in 1 mL water is added again. The resulting mixture is allowed to stir at RT overnight. Then LiOH (82 mg, 1.94 mmol) dissolved in 1 mL water is added again. The resulting mixture is allowed to stir at RT for 2 h. Then 2M HCl aq. soln. is added (4 mL, 8.03 35 mmol) and the reaction mixture is evaporated until dryness. This yield the title compound as a mixture with excess LiCl as a white solid. LC-A: $t_R = 0.50$ min; $[M+H]^+ = 264.1$

Precursor V7' (2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetic acid hydrochloride LC-A: $t_R = 0.50$ min; $[M+H]^+ = 261.2$, and **Precursor V8'** (2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetic acid hydrochloride, LC-A: $t_R = 0.45$ min; $[M+H]^+ = 235.2$ are prepared applying the methods described for the synthesis of **Precursor V6** from **Precursor W6** using **Precursor W7** and **Precursor W8** respectively.

Precursor W1

8-(Ethoxycarbonylmethyl-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester

a) 2-(Isoquinolin-8-ylamino)acetic acid ethyl ester

To a round bottomed flask containing 8-bromoisoquinoline (3g, 14.4 mmol) are added Cs_2CO_3 (13.2 g, 40.4 mmol), glycine ethyl ester hydrochloride (2.21g, 15.9 mmol), BINAP (449 mg, 0.72 mmol) and $Pd_2(dba)_3$ (0.397 g, 0.433 mmol) followed by 50 mL toluene. The resulting brown suspension is allowed to stir at 80°C for 2 h, at 50°C overnight then at 110°C for 9 h.

After cooling the suspension is filtered over Celite. The celite cake is rinsed three times with EtOAc. The combined organic phase is washed with brine, dried over Na_2SO_4 and filtered. Evaporation of the solvents *in vacuo* yields 4.64 g of a brown oil. Flash-chromatography on silica-gel (Eluent: gradient of heptane / EtOAc 90:10 to 0:100) yields 2.33 g (70%) of the sub-title compound as yellow solid.

LC-B: $t_R = 0.47$ min; $[M+H]^+ = 231.2$; 1H -NMR ($CDCl_3$) δ : 9.41 (s, 1 H), 8.52 (d, $J = 5.7$ Hz, 1 H), 7.58 (d, $J = 5.7$ Hz, 1 H), 7.53 (t, $J = 7.9$ Hz, 1 H), 7.20 (d, $J = 8.2$ Hz, 1 H), 6.54 (d, $J = 7.7$ Hz, 1 H), 5.49 (s, 1 H), 4.34 (q, $J = 7.1$ Hz, 2 H), 4.09 (d, $J = 4.9$ Hz, 2 H), 1.36 (t, $J = 7.1$ Hz, 3 H)

b) (1,2,3,4-Tetrahydro-isoquinolin-8-ylamino)-acetic acid ethyl ester

To a solution of 2-(isoquinolin-8-ylamino)acetic acid ethyl ester (2.3 g, 9.89 mmol) in 200 mL AcOH purged under Ar atmosphere is added PtO_2 (606 mg, 2.67 mmol). The flask is put under an atmosphere of H_2 . The crude suspension is allowed to stir at RT overnight. Then the solids are removed over celite and the celite cake is washed twice with AcOH. The combined organic phase is evaporated to dryness under reduced pressure. Toluene is added to the dry residue and the solvent is removed under reduced pressure once again. The crude solid obtained is dried under HV. This yields 3.45 g (145%) of the sub-title compound still containing AcOH.

LC-B: $t_R = 0.49$ min; $[M+H]^+ = 235.2$

- c) To a solution of (1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetic acid ethyl ester (3.45 g, 9.57 mmol) in 100 mL DCM are added TEA (1.45g, 14.4 mmol) and di-*tert*-butyl-dicarbonate (2.09 g, 9.57 mmol). The resulting brown solution is allowed to stir for 2.5 h at RT. The organic phase is washed with sat. aq. NaHCO₃ soln. and brine, dried over MgSO₄, filtered
5 then evaporated under reduced pressure. This yields after drying under HV 2.24 g (70%) of the title compound as a brown oil which is used as such in the next step.

LC-B: t_R = 0.98 min; $[M+H]^+$ = 335.2

Precursor W2

10 (2-Methyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetic acid ethyl ester

a) 8-(Ethoxycarbonylmethyl-amino)-2-methyl-isoquinolinium iodide

- To a solution of 2-(isoquinolin-8-ylamino)acetic acid ethyl ester (130 mg, 0.565 mmol) made according to the method described for the synthesis of **Precursor W1** Step a) in 2 mL acetone is added MeI (185 mg, 1.3 mmol). The yellow orange suspension is allowed to stir
15 for 4 h at RT. The yellow solid formed is filtered, rinsed with acetone and dried under HV. This yields 120 mg (59%) of the sub-title compound as a yellow solid.

LC-B: t_R = 0.47 min; $[M+H]^+$ = 245.2; ¹H-NMR (CDCl₃) δ : 11.30 (s, 1 H), 8.15 (m, 1 H), 7.93 (m, 1 H), 7.87 (m, 2 H), 7.20 (d, J = 7.8 Hz, 1 H), 6.69 (d, J = 8.3 Hz, 1 H), 4.54 (s, 3 H), 4.26 (m, 4 H), 1.32 (t, J = 7.1 Hz, 3 H)

- b) To a solution of 8-(ethoxycarbonylmethyl-amino)-2-methyl-isoquinolinium iodide (120 mg, 0.322 mmol) in 3 mL MeOH and 0.5 mL water cooled to 0°C is added NaBH₄ (71 mg, 1.87 mmol). The resulting mixture is allowed to stir at RT overnight. The MeOH is then removed under reduced pressure and the remainder is poured into water. The resulting aq. phase is extracted twice with DCM. The combined organic phase is washed with brine then dried over
20 MgSO₄, filtered and evaporated under reduced pressure. This organic phase contains no product. The aq. phase is extracted again twice with EtOAc. The resulting combined organic phase is washed with brine then dried over MgSO₄, filtered and evaporated under reduced pressure. This yields 71 mg (89%) of the title compound as yellow oil.

LC-B: t_R = 0.48 min; $[M+H]^+$ = 249.3.

- 30 This compound partially contains (2-methyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetic acid methyl ester LC-B: t_R = 0.43 min; $[M+H]^+$ = 235.2

Precursor W4

(2-Cyclobutyl-1,2,3,4-tetrahydroisoquinolin-8-yl)amino acetic acid methyl ester

- 35 To a solution of (1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetic acid ethyl ester (**Precursor W1** step b) (225 mg, 0.96 mmol) in 5 mL MeOH is added cyclobutanone (337 mg, 4.8 mmol),

ZnCl₂ (393 mg, 2.88 mmol) and NaBH₃CN (181 mg, 2.88 mmol). The resulting yellow mixture is allowed to stir at RT for 3 days. Water is added and the resulting organic phase is extracted twice with DCM. The combined organic phase is washed with sat. aq. NaHCO₃ soln. and brine dried over MgSO₄, filtered and the solvent removed under reduced pressure.

- 5 The title compound (80%) obtained as a yellow oil is used as such in the next step without further purification.

Precursor W5

(2-(2-cis-Fluorocyclopropane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-5-yl)amino

10 **acetic acid ethyl ester**

To a solution of (1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetic acid ethyl ester (**Precursor W1** step b) (330 mg, 1 mmol) in 4 mL DCM is added cis-2-fluoro-cyclopropanecarboxylic acid (104 mg, 1 mmol), HATU (457 mg, 1.2 mmol) then DIPEA (324 mg, 2.5 mmol). The resulting yellow solution is stirred at rt for 1.5 h. The crude mixture is poured into sat. aq. NaHCO₃

15 soln. and the resulting aq. phase is extracted twice with DCM. The organic phase is washed with brine, dried over MgSO₄, filtered and evaporated.

LC-A: t_R = 0.79 min; $[M+H]^+$ = 321.2

Precursor W6

20 **N-(2-allyl-1,2,3,4-tetrahydroisoquinolin-8-yl)-N-(2,2,2-trifluoroacetyl)aminoacetic acid ethyl ester**

To a solution of N-(1,2,3,4-tetrahydroisoquinolin-8-yl)-N-(2,2,2-trifluoroacetyl)aminoacetic acid ethyl ester **Precursor AD1** (1 g, 2.73 mmol), K₂CO₃ (0.471 g, 3.41 mmol) in 20 mL MeCN is added allylbromide (167 mg, 1.36 mol) and the reaction mixture is stirred at RT for

25 16 h. The white suspension is filtered off and the white solid is washed with EtOAc. The filtrate is concentrated to dryness under reduced pressure. Flash-chromatography on silica-gel (Eluent: gradient of heptane / EtOAc 80:20) yields 425 mg (42%) of the sub-title compound as yellow oil.

LC-A: t_R = 0.65 min; $[M+H]^+$ = 371.0

30

Precursor W7

N-(2-cyclopropylmethyl-1,2,3,4-tetrahydroisoquinolin-8-yl)-N-(2,2,2-trifluoroacetyl)aminoacetic acid ethyl ester

- To a solution of N-(1,2,3,4-tetrahydroisoquinolin-8-yl)-N-(2,2,2-trifluoroacetyl)aminoacetic acid ethyl ester **Precursor AD1** (1097 mg, 2.99 mmol) in 20mL DCM is added
- 35

cyclopropanecarboxaldehyde (231 mg, 3.29 mmol), DIPEA (773 mg, 5.98 mmol), and NaBH(OAc)₃ (761 mg, 3.59 mmol). The resulting reaction mixture is stirred at RT for 1 h.

- 10 mL DCM and 15 mL sat. aq. NaHCO₃ soln. are added and the resulting aq. phase is extracted twice with DCM, dried over MgSO₄, filtered and evaporated to dryness under reduced pressure. Flash-chromatography on silica-gel (Eluent: gradient of DCM / MeOH 100:0 to 90:10) yields the title compound as a yellow oil.

LC-A: t_R = 0.67 min; $[M+H]^+$ = 385.1

Precursor W8

- 10 **N-(2-Ethyl-1,2,3,4-tetrahydroisoquinolin-8-yl)-N-(2,2,2-trifluoroacetyl)aminoacetic acid ethyl ester**, LC-A: t_R = 0.65 min; $[M+H]^+$ = 359.2 is prepared applying the methods described for the synthesis of **Precursor W7** from **Precursor AD1** using acetaldehyde as reagent.

Precursor W9

- 15 **(2-Ethyl-3-oxo-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetic acid ethyl ester** is made following the method described for the synthesis of **Precursor C22** step d) using 8-amino-2-ethyl-1,4-dihydro-2H-isoquinolin-3-one instead of 5-amino-2-ethyl-1,4-dihydro-2H-isoquinolin-3-one as starting material.

- 20 **8-amino-2-ethyl-1,4-dihydro-2H-isoquinolin-3-one**

a) (2-Bromo-6-nitro-benzyl)-ethyl-amine

- To a solution of 2-bromo-6-nitrobenzaldehyde (2.5 g, 10.9 mmol) in 40 mL MeOH at RT is added 2M ethylamine soln. in THF (5.5 mL, 10.9 mmol) and the resulting mixture is stirred at RT for 30min, then NaBH₄ (473 mg, 12.5 mmol) is slowly added at 5°C and the mixture is stirred at RT for 21 h. Then NaBH₄ (150 mg, 3.97 mmol) and 2M ethylamine soln. in THF (0.8 mL, 1.6 mmol) are added. After an additional 2.5 h at RT, water is added and the MeOH is removed under reduced pressure. The aqueous layer is extracted three times with EtOAc. The combined organic layers is dried over MgSO₄, filtered and concentrated to dryness. Flash-chromatography on silica-gel (Eluent: Hept. / EtOAc 95:5 to 70:30) yields 305 mg (11%) of the sub-title compound as an orange oil.

LC-A: t_R = 0.45 min; $[M+H]^+$ = 258.9; ¹H-NMR (400 MHz, CDCl₃) δ : 7.33 (t, J = 8.1 Hz, 1 H), 7.80 (d, J = 8.1 Hz, 1 H), 7.86 (d, J = 8.0 Hz, 1 H), 4.15 (s, 1 H), 2.82 (q, J = 7.1 Hz, 1 H), 1.20 (t, J = 7.1 Hz, 2 H)

b) (2-Bromo-6-nitro-benzyl)-ethyl-carbamic acid tert-butyl ester

- 35 To a solution of (2-bromo-6-nitro-benzyl)-ethyl-amine (305 mg, 1.18 mmol) in dry DCM (10 mL) is added TEA (182 mg, 1.78 mmol) and di-*tert*-butyl dicarbonate (257 mg, 1.18 mmol).

The resulting mixture is stirred at RT for 3 h. It is then washed with sat. aq. NaHCO_3 soln. followed by brine then dried over MgSO_4 , filtered and evaporated. Flash-chromatography on silica-gel (Eluent: Hept. / EtOAc 90:10 to 75:25) yields 329 mg (78%) of the sub-title compound as a yellow oil.

- 5 LC-A: $t_R = 0.97$ min; $[\text{M}+\text{H}]^+ = 359.1$; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 7.80 (d, $J = 8.0$ Hz, 1 H), 7.59 (d, $J = 8.0$ Hz, 1 H), 7.30 (m, 1 H), 4.82 (s, 2 H), 3.12 (bs, 2 H), 1.42 (bs, 9 H), 1.05 (t, $J = 7.0$ Hz, 3 H)

c) {2-[(tert-Butoxycarbonyl-ethyl-amino)-methyl]-3-nitro-phenyl}-acetic acid tert-butyl ester

- 2-tert-Butoxy-2-oxoethylzinc chloride (0.5M in diethyl ether soln.) (3.3 mL, 1.63 mmol) is added to a mixture of (2-bromo-6-nitro-benzyl)-ethyl-carbamic acid tert-butyl ester_ (325 mg, 0.905 mmol), $\text{Pd}_2(\text{dba})_3$ (26 mg, 0.0452 mmol) and 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (17.8 mg, 0.0452 mmol) in dry 5 mL dioxane under argon atmosphere. The reaction mixture is heated at 50°C for 16 h. After cooling another 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (18 mg, 0.0457 mmol), $\text{Pd}_2(\text{dba})_3$ (26 mg, 0.0452 mmol) and 2-tert-butoxy-2-oxoethylzinc chloride (0.5M in diethyl ether) (1.7 mL, 0.815 mmol) are added. The reaction mixture is allowed to stir at 50°C for 5 h then at 80°C for 19 h. After cooling 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (18 mg, 0.0457 mmol), $\text{Pd}_2(\text{dba})_3$ (26 mg, 0.0452 mmol, 0.05 eq) and 2-tert-butoxy-2-oxoethylzinc chloride (0.5M in diethyl ether) (1.7 mL, 0.815 mmol) are added and the resulting reaction mixture is heated at 80°C for 4 h. the solvents are removed under reduced pressure. Flash-chromatography on silica-gel (Eluent: Hept. / EtOAc / TEA 95 : 5 : 0.1) yields 57 mg (16%) of the sub-title compound as a yellow oil.

LC-A: $t_R = 1.03$ min; $[\text{M}+\text{H}]^+ = 395.2$

d) 2-Ethyl-8-nitro-1,4-dihydro-2H-isoquinolin-3-one

- 25 {2-[(tert-Butoxycarbonyl-ethyl-amino)-methyl]-3-nitro-phenyl}-acetic acid tert-butyl ester (55mg, 0.139 mmol) is dissolved in 1 mL of TFA/DCM (2:1) mixture cooled to 0°C . The resulting solution is allowed to stir for 1 h at 0°C then 5 h at RT. The solvents are removed under reduced pressure without heating. The crude residue is dissolved 3 times with DCM and the solvent each time evaporated under reduced pressure. The crude residue is dissolved in 1 mL pyridine, DCC (83.4 mg, 0.404 mmol) and DMAP (51.4 mg, 0.421 mmol) are added. The resulting mixture is allowed to stir at RT for 1.5 h. Water is added and the resulting aq. Phase is extracted twice with EtOAc. The combined organic phase is washed with brine, dried over MgSO_4 , filtered and the solvents evaporated under reduced pressure. Flash-chromatography on silica-gel (Eluent: DCM / MeOH 100 : 0 to 95 : 5) yields 30 mg (100%) of the sub-title compound as a yellow solid.

LC-A: $t_R = 0.70$ min; $[M+MeCN]^+ = 262.1$

e) To a solution of 2-ethyl-8-nitro-1,4-dihydro-2H-isoquinolin-3-one (30 mg, 0.136 mmol) in 1 mL acetone is added sat. aq. NH_4Cl soln. The reaction mixture is cooled to $0^\circ C$ and Zn dust (92 mg, 23 mmol) is added slowly. The reaction mixture is allowed to stir at RT for 1 h.

5 EtOAc is added as well as anhydrous sodium sulfate (1g). The resulting suspension is stirred for 15 min then filtered over Celite and rinsed with EtOAc then EtOAc / MeOH (9:1). The solvent is removed under reduced pressure to yield pure title compound as a yellowish solid.

LC-A: $t_R = 0.440$ min; $[M+MeCN]^+ = 232.1$

10 Precursor AD1

N-(1,2,3,4-tetrahydroisoquinolin-8-yl)-N-(2,2,2-trifluoroacetyl)aminoacetic acid ethyl ester hydrochloride

a) 8-(N-(2-ethoxy-2-oxoethyl)-2,2,2-trifluoroacetamido)-3,4-dihydroisoquinoline-2(1H)-carboxylic acid tert-butyl ester

15 To a solution of 8-(ethoxycarbonylmethyl-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester **Precursor W1** (1.6 mg, 4.78 mmol) in 20 mL DCM is added TEA (4.84 g, 47.8 mmol) and the resulting mixture is allowed to stir at RT for 5 min. Then TFAA (4.56 g, 21.5 mmol) is added dropwise and the resulting mixture is allowed to stir at RT for 30 min. Sat. aq. $NaHCO_3$ soln. is added and the resulting aq. phase is extracted twice with DCM.

20 The combined organic phase is dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford the sub-title compound as a yellow oil which still contains TEA but is used as such in the next step.

LC-A: $t_R = 0.98$ min; $[M+H]^+ = 431.0$

b) To a solution of crude 8-(N-(2-ethoxy-2-oxoethyl)-2,2,2-trifluoroacetamido)-3,4-dihydroisoquinoline-2(1H)-carboxylic acid tert-butyl ester (2.6 g, 4.78 mmol) in 15 mL DCM is added dropwise 4N HCl in dioxane soln. (8.5 mL, 33.5 mmol) and the mixture is allowed to stir at RT for 30 min then at $60^\circ C$ for 2 h. After cooling all volatiles are removed under reduced pressure to yield the sub-title compound as a yellow solid.

LC-A: $t_R = 0.61$ min; $[M+H]^+ = 332.1$ **Example 185**

30 **N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide**

a) N-([Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl)-2,2,2-trifluoro-N-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-yl)-acetamide

To a solution of N-([benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl)-2,2,2-trifluoro-N-(1,2,3,4-tetrahydro-isoquinolin-8-yl)-acetamide dihydrochloride **Precursor X1** (50 mg, 0.084 mmol) in 0.5 mL MeOH and 0.25 mL water is added acetaldehyde (7.9 mg, 0.179 mmol) and

35

the resulting solution is allowed to stir at RT for 10 min. Then NaBH₃CN (29.3 mg, 0.467 mmol) is added and the mixture is allowed to stir at RT overnight. Then acetaldehyde (7.9 mg, 0.179 mmol) is added again and the resulting solution is allowed to stir again 3 h at RT. The mixture is poured onto sat. aq. NaHCO₃ soln. and the resulting aq. phase is extracted
5 twice with DCM. The combined organic phase is evaporated to dryness which yields the crude sub-title compound as a yellow solid which is used as such in the next step.

LC-B: t_R = 0.48 min; $[M+H]^+$ = 491.2

b) To a solution of N-[[benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl]-2,2,2-trifluoro-N-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-yl)-acetamide (41.2 mg, 0.084 mmol) in 1 mL MeOH
10 is added 0.5 mL water and K₂CO₃ (69.7 mg, 0.504 mmol) and the resulting mixture is stirred at 65°C for 4 h. After cooling the mixture is diluted with water and the resulting aq. phase is extracted twice with DCM. The combined organic phase is evaporated to dryness and the crude residue purified by prep. HPLC (Method E) to yield the title compound as a yellow oil.

LC-A: t_R = 0.46 min; $[M+H]^+$ = 395.3

15

Example 188

N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide

a) N-[[Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl]-2,2,2-trifluoro-N-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-8-yl)-acetamide
20

To a solution of N-[[benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl]-2,2,2-trifluoro-N-(1,2,3,4-tetrahydro-isoquinolin-8-yl)-acetamide dihydrochloride **Precursor X1** (50 mg, 0.084 mmol) in 0.6 mL DCM are added TEA (34 mg, 0.336 mmol) and propionyl chloride (8.5 mg, 0.092 mmol) and the resulting yellow solution is allowed to stir at RT for 1 h. The mixture is
25 poured onto sat. aq. NaHCO₃ soln. and the resulting aq. phase is extracted twice with DCM. The combined organic phase is evaporated to dryness which yields the crude sub-title compound as a yellow solid which is used as such in the next step.

LC-B: t_R = 0.63 min; $[M+H]^+$ = 519.1

b) The crude N-[[benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl]-2,2,2-trifluoro-N-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-8-yl)-acetamide from step a) is submitted to the conditions of the preparation of **Example 185** step b) to yield the title compound as a yellow oil.

LC-B: t_R = 0.61 min; $[M+H]^+$ = 423.1

35 **Example 190**

8-([Benzy-(2-dimethylamino-ethyl)-carbamoyl]-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid methyl ester

a) 8-([Benzy-(2-dimethylamino-ethyl)-carbamoyl]-methyl)-(2,2,2-trifluoro-acetyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester

- 5 To a solution of N-([benzy-(2-dimethylamino-ethyl)-carbamoyl]-methyl)-2,2,2-trifluoro-N-(1,2,3,4-tetrahydro-isoquinolin-8-yl)-acetamide dihydrochloride **Precursor X1** (50 mg, 0.084 mmol) in 0.6 mL DCM are added TEA (34 mg, 0.336 mmol) and methyl chloroformate (8.7 mg, 0.092 mmol) and the resulting yellow solution is allowed to stir at RT for 2 h. The mixture is poured onto sat. aq. NaHCO₃ soln. and the resulting aq. phase is extracted twice with
- 10 DCM. The combined organic phase is evaporated to dryness which yields the crude sub-title compound as a yellow solid which is used as such in the next step.

LC-B: t_R = 0.65 min; $[M+H]^+$ = 521.1

- b) The crude methyl 8-([benzy-(2-dimethylamino-ethyl)-carbamoyl]-methyl)-(2,2,2-trifluoro-acetyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester from step a) is
- 15 submitted to the conditions of the preparation of **Example 185** step b) to yield the title compound as a yellow oil.

LC-B: t_R = 0.64 min; $[M+H]^+$ = 425.1

Example 544

N-(2-Dimethylamino-ethyl)-2-(2-methanesulfonyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide

- a) N-(2-((2-(dimethylamino)ethyl)(2-(trifluoromethyl)benzyl)amino)-2-oxoethyl)-2,2,2-trifluoro-N-(2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)acetamide

- To a solution of N-([benzy-(2-dimethylamino-ethyl)-carbamoyl]-methyl)-2,2,2-trifluoro-N-(1,2,3,4-tetrahydro-isoquinolin-8-yl)-acetamide dihydrochloride **Precursor X1** (20 mg, 0.035 mmol) in 1 mL DCM are added methanesulfonyl chloride (4 mg, 0.035 mmol), pyridine (2.8 mg, 0.035 mmol) and DMAP (0.43 mg, 0.0035 mmol) and the resulting yellow solution is allowed to stir at RT overnight, then methanesulfonyl chloride (4 mg, 0.035 mmol), pyridine (2.8 mg, 0.035 mmol) and DMAP (0.43 mg, 0.0035 mmol) are added again and the mixture stirred at RT for 24 h. The mixture is poured onto sat. aq. NaHCO₃ soln. and the resulting
- 25 aq. phase is extracted twice with DCM. The combined organic phase is evaporated to dryness which yields the crude sub-title compound as a yellow solid which is used as such in the next step.

LC-B: t_R = 0.76 min; $[M+H]^+$ = 609.2

- b) The crude N-(2-((2-(dimethylamino)ethyl)(2-(trifluoromethyl)benzyl)amino)-2-oxoethyl)-2,2,2-trifluoro-N-(2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)acetamide from step a)
- 35

is submitted to the conditions of the preparation of **Example 185** step b) to yield the title compound as a yellow oil.

LC-B: $t_R = 0.72$ min; $[M+H]^+ = 513.0$

Examples 186-187 / 189 / 191-200 / 545 / 548-557 / 559-560 / 563-567 listed in **Table 27**

- 5 are prepared applying one of the methods described for **Example 185**, **Example 188**, **Example 190**, **Example 544** respectively using the corresponding **Precursor** and the corresponding aldehyde, ketone, carboxylic acid chloride or chloroformate respectively.

Table 27: Examples 186-187 / 189 / 191-200 / 545 / 548-557 / 559-560 / 563-567

Example No	Example name	t_R [min] (LC-C)	MS Data m/z $[M+H]^+$
186	N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide	0.56	409.4
187	N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-acetamide	0.58	421.4
189	N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-isobutyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide	0.6	423.5
191	N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-isobutyryl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide	0.82	437.5
192	8-({[Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl}-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid isopropyl ester	0.92	453.4
193	N-Benzyl-2-(2-benzyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-acetamide	0.63	457.4
194	N-Benzyl-2-(2-cyclohexylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-acetamide	0.68	463.5
195	2-(2-Benzoyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-benzyl-N-(2-dimethylamino-ethyl)-acetamide	0.87	471.4
196	N-(2-Chloro-benzyl)-N-(2-dimethylamino-ethyl)-2-(2-ethyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide	0.57	457.4
197	N-(2-Chloro-benzyl)-2-(2-cyclopropylmethyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-acetamide	0.63	483.4
198	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	0.62	491.4

199	2-(2-Cyclopropylmethyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.67	517.5
200	2-(2-Cyclopropylmethyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(1-methyl-piperidin-4-yl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.67	543.4
Example No	Example name	t_R [min] (LC-F)	MS Data m/z [M+H] ⁺
545	2-(2-Benzenesulfonyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.88	575.3
548	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-N-(2-trifluoromethyl-benzyl)-propionamide	0.45	478.3
549	1-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-cyclobutanecarboxylic acid (2-dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-amide	0.42	504.3
550	(E)-N-(2-Dimethylamino-ethyl)-3-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-yl)-N-(2-trifluoromethyl-benzyl)-acrylamide	0.46	460.3
551	N-(2-Dimethylamino-ethyl)-2-[2-(2,2-dimethyl-propionyl)-1,2,3,4-tetrahydro-isoquinolin-8-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide	0.87	519.4
552	2-(2-Benzoyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.86	539.3
553	8-({[(2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl]-methyl}-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid isopropyl ester	0.89	521.4
554	2-(2-Cyclohexylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.59	531.4
555	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	0.46	463.3
556	N-(2-Dimethylamino-ethyl)-2-(2-propyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	0.48	477.4

557	N-(2-Dimethylamino-ethyl)-2-(2-isobutyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	0.51	491.4
559	N-(2-Dimethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	0.77	491.3
560	2-(2-Cyclopropanecarbonyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.78	503.3
563	N-(2-Dimethylamino-ethyl)-2-[2-(2,2-dimethyl-propyl)-1,2,3,4-tetrahydro-isoquinolin-8-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide	0.54	505.4
564	N-(2-Dimethylamino-ethyl)-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide	0.45	449.4
565	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide	0.51	515.4
566	2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide	0.43	490.4
567	N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-N-(2-trifluoromethyl-benzyl)-acetamide	0.43	464.3

Example 546**8-({[(2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl]-methyl}-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid dimethylamide**

- 5 a) 8-(N-(2-((2-(dimethylamino)ethyl)(2-(trifluoromethyl)benzyl)amino)-2-oxoethyl)-2,2,2-trifluoroacetamido)-N,N-dimethyl-3,4-dihydroisoquinoline-2(1H)-carboxamide

To a solution of N-[[benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl]-2,2,2-trifluoro-N-(1,2,3,4-tetrahydro-isoquinolin-8-yl)-acetamide dihydrochloride **Precursor X1** (20 mg, 0.035 mmol) in 0.5 mL DCM are added dimethylcarbamoyl chloride (6 mg, 0.0564 mmol) and TEA (5.7 mg, 0.0564 mmol) and the resulting yellow solution is allowed to stir at RT overnight. The mixture is poured onto sat. aq. NaHCO₃ soln. and the resulting aq. phase is extracted twice with DCM. The combined organic phase is evaporated to dryness which yields quantitatively the sub-title compound as a yellow solid which is used as such in the next step.

- 15 LC-B: $t_R = 0.77$ min; $[M+H]^+ = 602.4$

b) 8-(N-(2-((2-(dimethylamino)ethyl)(2-(trifluoromethyl)benzyl)amino)-2-oxoethyl)-2,2,2-trifluoroacetamido)-N,N-dimethyl-3,4-dihydroisoquinoline-2(1H)-carboxamide from step a) is submitted to the conditions of the preparation of **Example 185** step b) to yield the title compound as a yellow oil.

5 LC-B: $t_R = 0.72$ min; $[M+H]^+ = 506.3$

Example 547

8-([[(2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl]-methyl]-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid methylamide

a) 8-(N-(2-((2-(Dimethylamino)ethyl)(2-(trifluoromethyl)benzyl)amino)-2-oxoethyl)-2,2,2-trifluoroacetamido)-N-methyl-3,4-dihydroisoquinoline-2(1H)-carboxamide

To a solution of methylamine hydrochloride (3.81 mg, 0.0564 mmol) in 0.5 ml MeCN at RT are added Na_2CO_3 (10.4 mg, 0.123 mmol) and 4-nitrophenyl chloroformate (9.24 mg, 0.0459 mmol). The mixture is stirred at RT overnight. Then methylamine hydrochloride (3.81 mg, 0.0564 mmol, 1.6 eq) and Na_2CO_3 (10.4 mg, 0.123 mmol, 3.5 eq) are added and the mixture stirred at RT for 4 h. Then N-([benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl)-2,2,2-trifluoro-N-(1,2,3,4-tetrahydro-isoquinolin-8-yl)-acetamide dihydrochloride **Precursor X1** (20 mg, 0.035 mmol) in 0.5 ml MeCN and TEA (0.00737 ml, 0.0529 mmol, 1.5 eq) are added dropwise and the reaction mixture is allowed to stir at RT for 4 h. Water is then added and the resulting aq. phase is extracted with EtOAc. The combined organic layers are dried over MgSO_4 , filtered and concentrated under reduced pressure. The crude sub-title compound is used without further purification

LC-B: $t_R = 0.73$ min; $[M+H]^+ = 588.2$

b) 8-(N-(2-((2-(dimethylamino)ethyl)(2-(trifluoromethyl)benzyl)amino)-2-oxoethyl)-2,2,2-trifluoroacetamido)-N-methyl-3,4-dihydroisoquinoline-2(1H)-carboxamide from step a) is submitted to the conditions of the preparation of **Example 185** step b) to yield the title compound as a yellow oil.

LC-B: $t_R = 0.69$ min; $[M+H]^+ = 492.3$

Examples 561-562 listed in **Table 28** are prepared applying the method described for **Example 547 Precursor X6** and the corresponding amine respectively.

Table 28: Examples 561-562

Example No	Example name	t_R [min] (LC-F)	MS Data m/z $[M+H]^+$
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561	N-(2-Dimethylamino-ethyl)-2-[2-(pyrrolidine-1-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-8-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide	0.83	532.4
562	8-([[(2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl]-methyl]-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid amide	0.68	478.3

Example 558**N-(2-Dimethylamino-ethyl)-2-[2-(2,2,2-trifluoro-ethyl)-1,2,3,4-tetrahydro-isoquinolin-8-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide**

- 5 To a solution of N-([[(2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl]-methyl]-2,2,2-trifluoro-N-(1,2,3,4-tetrahydro-isoquinolin-8-yl)-acetamide dihydrochloride **Precursor X6** in (75 mg, 0.132 mmol) in 5 mL toluene is added TEA (53.5 mg, 0.529 mmol) and the resulting solution is allowed to stir 10 min at RT then 2,2,2-trifluoroethyl trifluoromethanesulfonate (60.4 mg, 0.265 mmol) is added and the resulting mixture is
- 10 allowed to stir at RT over night then TEA (53.5 mg, 0.529 mmol) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (60.4 mg, 0.265 mmol) and the reaction mixture is allowed to stir at RT for 72 h. Water is added and the resulting aq. Phase is extracted with DCM. The combined organic layers are washed with sat. aq. NaHCO₃ soln., dried over MgSO₄, filtered and concentrated. The crude is dissolved in 5 mL MeOH and K₂CO₃ (108 mg, 0.78 mmol)
- 15 and water are added and the resulting mixture is allowed to stir at 65°C overnight. The mixture is then diluted with a small amount of water, then DCM is added and the phases separated. The combined organic layers are dried over Na₂SO₄, filtered and concentrated. The crude residue is purified by prep. HPLC (Method E) to yield the title compound as an orange solid.
- 20 LC-A: $t_R = 0.78$ min; $[M+H]^+ = 517.2$.

Precursor X1**N-([Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl)-2,2,2-trifluoro-N-(1,2,3,4-tetrahydro-isoquinolin-8-yl)-acetamide dihydrochloride**

- a) 8-([[(Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl)-(2,2,2-trifluoro-acetyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester
- 25

- To a solution of 8-([[(benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester **Example 181** (723 mg, 1.22 mmol) in 15 mL DCM is added TEA (1.34 g, 13.4 mmol) and the resulting solution is allowed to stir at RT for 5 min. Then TFAA (1.18 g, 5.66 mmol) is slowly added dropwise and the resulting brown
- 30 soln. is allowed to stir at RT for 1 h. The solution is washed twice with water then with brine. The solvent is removed under reduced pressure and the crude residue purified by fast

filtration on a silica-gel pad (Eluent : EtOAc 100% then EtOAc / MeOH / ammonia 8:2:0.2) to yield 508 mg (74%) of the sub-title compound as yellow foam.

LC-B: t_R = 0.75 min; $[M+H]^+$ = 563.1

- b) To a solution of 8-[[benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl]-(2,2,2-trifluoro-acetyl)-amino]-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (592 mg, 1.05 mmol) in 8 mL dioxane is added 3.7 mL 4*N* HCl soln. in dioxane (14.8 mmol). The resulting solution is allowed to stir at RT for 1 h. The volatiles are removed under reduced pressure. The residue is taken coevaporated twice with DCM. Finally the solid residue is dried under HV. This yields quantitatively 572 mg of the title compound as very hygroscopic light yellow foam which turns to an oil on standing.

LC-B: t_R = 0.45 min; $[M+H]^+$ = 463.0

Precursors X2-X4 / X6-X8 listed in **Table 29** are prepared applying the method described for **Precursor X1** using the corresponding **Precursor Y2-Y4 / Y6-Y8** respectively

Table 29: Precursors X2-X4 / X6-X8

Precursor	Precursor name	t_R [min] (LC-A)	MS Data m/z $[M+H]^+$
X2	N-[[[2-Chloro-benzyl]-(2-dimethylamino-ethyl)-carbamoyl]-methyl]-N-(4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-8-yl)-2,2,2-trifluoro-acetamide dihydrochloride	0.59	525.3
X3	N-[[[2-Dimethylamino-ethyl]-(2-trifluoromethyl-benzyl)-carbamoyl]-methyl]-N-(4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-8-yl)-2,2,2-trifluoro-acetamide dihydrochloride	0.61	559.3
X4	N-(4,4-Dimethyl-1,2,3,4-tetrahydro-isoquinolin-8-yl)-2,2,2-trifluoro-N-[[[1-methyl-piperidin-4-yl]-(2-trifluoromethyl-benzyl)-carbamoyl]-methyl]-acetamide dihydrochloride	0.62	585.4
X6	N-[[[2-Dimethylamino-ethyl]-(2-trifluoromethyl-benzyl)-carbamoyl]-methyl]-2,2,2-trifluoro-N-(1,2,3,4-tetrahydro-isoquinolin-8-yl)-acetamide dihydrochloride	0.58	531.4
X7	2,2,2-Trifluoro-N-[[[2-pyrrolidin-1-yl-ethyl]-(2-trifluoromethyl-benzyl)-carbamoyl]-methyl]-N-(1,2,3,4-tetrahydro-isoquinolin-8-yl)-acetamide dihydrochloride	0.61	557.2
X8	N-[[[2-Dimethylamino-ethyl]-(3-trifluoromethyl-pyridin-2-yl)-methyl]-carbamoyl]-methyl]-2,2,2-trifluoro-N-(1,2,3,4-tetrahydro-isoquinolin-8-yl)-acetamide dihydrochloride	0.54	532.4

Precursors Y2-Y4 / Y6-Y8 listed in **Table 30** are prepared applying the method described for **Example 181** using **Precursor V1** or **Precursor V4** and the corresponding **Amine** respectively.

Table 30: Precursors Y2-Y4 / Y6-Y8

Precursor	Precursor name	t_R [min] (LC-A)	MS Data m/z [M+H] ⁺
Y2	8-(((2-Chloro-benzyl)-(2-dimethylamino-ethyl)-carbamoyl)-methyl)-amino)-4,4-dimethyl-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.82	529
Y3	8-(((2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-4,4-dimethyl-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.84	563.2
Y4	4,4-Dimethyl-8-(((1-methyl-piperidin-4-yl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.83	589.2
Y6	8-(((2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.82	535.4
Y7	8-(((2-Pyrrolidin-1-yl-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.85	561.1
Y8	8-(((2-Dimethylamino-ethyl)-((3-trifluoromethyl-pyridin-2-yl)-methyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.80	536.4

Precursor V4

8-(Carboxymethyl-amino)-4,4-dimethyl-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester LC-A: t_R = 0.81 min; [M+H]⁺ = 335.3; ¹H-NMR (CDCl₃) δ : 6.96 (d, J = 8.2 Hz, 1 H), 6.77 (s, 1 H), 6.64 (dd, J_1 = 8.2 Hz, J_2 = 1.9 Hz, 1 H), 5.22-6.12 (bs, 1 H), 4.55 (m, 2 H), 4.01 (s, 2 H), 3.40 (bs, 2 H), 1.51 (s, 9 H), 1.26 (s, 6 H) is made according to the Method described for the synthesis of **Precursor V1** starting from **Precursor W10**.

Precursor W10**8-(Ethoxycarbonylmethyl-amino)-4,4-dimethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester**

To a solution of 8-amino-4,4-dimethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (400 mg, 1.45 mmol) in 5 mL MeCN is added DIPEA (187 mg, 1.45 mmol) and the mixture is stirred at RT for 15 min. Then ethylbromoacetate (242 mg, 1.45 mmol) is added and the resulting soln. is allowed to stir at 60°C for 2 h then at RT overnight. The mixture is then poured onto water, the resulting aq. phase is extracted twice with DCM. The combined organic phase is washed with sat. aq. NaHCO₃ soln. then with brine. It is dried over MgSO₄, filtered and the solvent is evaporated under reduced pressure. The crude residue is purified by fast filtration on a silica-gel pad (Eluent: EtOAc / heptane 1:4) to yield 385 mg (73%) of the title compound as yellow oil.

LC-A: t_R = 0.96 min; $[M+H]^+$ = 363.3; ¹H-NMR (CDCl₃) δ : 6.93 (d, J = 7.7 Hz, 1 H), 6.61 (s, 1 H), 6.51 (dd, J_1 = 8.2 Hz, J_2 = 1.5 Hz, 1 H), 4.54 (d, J = 9.1 Hz, 2 H), 4.27 (q, J = 7.1 Hz, 2 H), 3.92 (s, 2 H), 3.40 (s, 2 H), 1.50 (s, 9 H), 1.32 (t, J = 7.2 Hz, 3 H), 1.26 (s, 6 H)

Example 201**N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-acetamide**

To a solution of N-benzyl-N-(2-dimethylamino-ethyl)-2-(1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-acetamide dihydrochloride **Precursor X5** (50 mg, 0.114 mmol) and formaldehyde (8.5 mg, 0.284 mmol) in 0.25 mL water and 0.5 mL MeOH is added NaBH₃CN (17.8 mg, 0.284 mmol) and the resulting mixture is stirred at RT for 1 h. Sat. aq. NaHCO₃ soln. is added and the resulting aq. phase is extracted twice with DCM. The combined organic phase is evaporated under reduced pressure. The crude residue is purified by prep. HPLC (Method D) to yield the title compound as a yellow oil.

LC-B: t_R = 0.43 min; $[M+H]^+$ = 382.1

Examples 202-203 / 205 listed in **Table 31** are prepared applying one of the methods described for **Example 201** using **Precursor X5** and the corresponding aldehyde respectively.

Table 31: Examples 202-203 / 205

Example No	Example name	t_R [min] (LC-C)	MS Data m/z $[M+H]^+$
202	8-[[Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methoxy]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid methyl ester	0.52	396.4

203	N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-isobutyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-acetamide	0.56	422.4
205	2-(2-Benzoyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-N-benzyl-N-(2-dimethylamino-ethyl)-acetamide	0.57	424.4

Example 204**8-[[Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methoxy]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid methyl ester**

- 5 To a solution of N-benzyl-N-(2-dimethylamino-ethyl)-2-(1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-acetamide dihydrochloride **Precursor X5** (50 mg, 0.114 mmol) in 1 mL DCM are added TEA (46 mg, 0.454 mmol) and methylchloroformate (10.7 mg, 0.114 mmol) and the resulting mixture is stirred at RT for 1 h. Sat. aq. NaHCO₃ soln. is added and the resulting aq. phase is extracted twice with DCM. The combined organic phase is evaporated under
- 10 reduced pressure. The crude residue is purified by prep. HPLC (Method D) to yield the title compound as a yellow oil.

LC-B: $t_R = 0.63$ min; $[M+H]^+ = 426.4$

Example 206**N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-acetamide**

- 15 To a solution of N-benzyl-N-(2-dimethylamino-ethyl)-2-(1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-acetamide dihydrochloride **Precursor X5** (50 mg, 0.114 mmol) in 1 mL DCM are added TEA (46 mg, 0.454 mmol) and propionyl chloride (11.6 mg, 0.114 mmol) and the resulting mixture is stirred at RT for 1 h. Sat. aq. NaHCO₃ soln. is added and the resulting aq. phase is extracted twice with DCM. The combined organic phase is evaporated under
- 20 reduced pressure. The crude residue is purified by prep. HPLC (Method D) to yield the title compound as a colorless oil.

LC-B: $t_R = 0.60$ min; $[M+H]^+ = 424.3$

Example 207 2-(2-Benzoyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-N-benzyl-N-(2-

- 25 **dimethylamino-ethyl)-acetamide** LC-B: $t_R = 0.67$ min; $[M+H]^+ = 472.3$ is prepared according to the Method described for the preparation of **Example 206** using benzoylchloride in place of propionylchloride.

Precursor X5**N-Benzyl-N-(2-dimethylamino-ethyl)-2-(1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-**

- 30 **acetamide dihydrochloride**

To a solution of 8-[[benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methoxy]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester **Precursor Y5** (509 mg, 1.09 mmol) in 8 mL

dioxane is added 3.82 mL (15.3 mmol) 4N HCl soln. in dioxane. The resulting yellowish soln. is allowed to stir at RT for 2 h. The volatiles are removed under reduced pressure, the residue is taken up in DCM and the solvent is removed under reduced pressure. This last procedure is repeated three times. This yields 480 mg (100%) of the title compound as a light yellow solid.

LC-B: $t_R = 0.43$ min; $[M+H]^+ = 368.1$

Precursors X9 / X12–X14 listed in **Table 32** are prepared applying the method described for **Precursor X5** using the corresponding **Precursors Y9 / Y12–Y14** respectively.

Table 32: Precursors X9 / X12–X14

Precursor	Precursor name	t_R [min] (LC-A)	MS Data m/z $[M+H]^+$
X9	N-(2-(dimethylamino)ethyl)-2-((1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-N-(2-(trifluoromethyl)benzyl)acetamide dihydrochloride	0.55	436.3
X12	rac-N-(2-(dimethylamino)ethyl)-2-((1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-N-(2-(trifluoromethyl)benzyl)propanamide dihydrochloride	0.56	450.2
X13	N-(2-(dimethylamino)ethyl)-1-((1,2,3,4-tetrahydroisoquinolin-8-yl)oxy)-N-(2-(trifluoromethyl)benzyl)cyclobutane-1-carboxamide dihydrochloride	0.53	476.4
X14	(E)-N-(2-(dimethylamino)ethyl)-3-(1,2,3,4-tetrahydroisoquinolin-8-yl)-N-(2-(trifluoromethyl)benzyl)acrylamide dihydrochloride	0.57	432.2

Precursor Y5

8-[[Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methoxy]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

To a solution of 8-carboxymethoxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester **Precursor V11** (400 mg, 1.3 mmol), N-benzyl-N',N'-dimethylethane-1,2-diamine **Amine 7** (232 mg, 1.3 mmol) and HATU (594 mmol, 1.56 mmol) in 8 mL DCM is added DIPEA (421 mg, 3.25 mmol). The resulting yellow suspension is allowed to stir at RT for 2 h. Then sat. aq. NaHCO₃ soln. is added and the resulting aq. phase is extracted twice with DCM. The combined organic phase is washed with brine and dried over MgSO₄, filtered then evaporated under reduced pressure. Flash-chromatography on silica-gel (Eluent: DCM / MeOH from 100:0 to 80:20) yields 509mg (84%) of the title compound as a yellow oil.

LC-B: $t_R = 0.73$ min; $[M+H]^+ = 468.1$

Precursors Y9 / Y12–Y14 listed in **Table 33** are prepared applying the method described for **Precursor Y5** using the corresponding **Precursors V11–V14** respectively.

5 **Table 33: Precursors Y9 / Y12–Y14**

Precursor	Precursor name	t_R [min] (Method LC-A)	MS Data m/z $[M+H]^+$
Y9	8-{{[(2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl]-methoxy}-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.82	536.4
Y12	rac-8-{1-[(2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl]-ethoxy}-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.83	550.4
Y13	8-{1-[(2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl]-cyclobutoxy}-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.85	576.4
Y14	8-{{(E)-2-[(2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl]-vinyl}-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.84	532.2

Precursor V11

8-Carboxymethoxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester

To a solution of 8-ethoxycarbonylmethoxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester **Precursor W11** (1.39 g, 3.85 mmol) in 50 mL THF is added 1M LiOH soln. in water (20.8 mL, 20.8 mmol). The reaction mixture is allowed to stir at RT for 2.5 h. Then 2M HCl aq. soln. is added until pH=4 and the resulting acidic aq. phase is extracted twice with EtOAc. The combined organic phase is washed with brine then dried over MgSO₄ and filtered. Evaporation of the solvent under reduced pressure and drying under HV yields 1.21 g (100%) of the title compound as a yellow solid which is used as such in the next step.

LC-B: $t_R = 0.82$ min; $[M+H]^+ = 308.1$; ¹H-NMR (CDCl₃) δ : 7.37-7.51 (bs, 1 H), 7.13 (t, $J = 7.9$ Hz, 1 H), 6.81 (d, $J = 7.6$ Hz, 1 H), 6.62 (d, $J = 8.1$ Hz, 1 H), 4.67 (m, 4 H), 3.65 (t, $J = 5.4$ Hz, 2 H), 2.83 (t, $J = 5.6$ Hz, 2 H), 1.51 (s, 9 H)

20 **Precursors V12–V13** listed in **Table 34** are prepared applying the method described for **Precursor V11** using the corresponding **Precursors W12–W13** respectively.

Table 34: Precursors V12–V13

Precursor	Precursor name	t_R [min] (Method LC-A)	MS Data m/z [M+H] ⁺
V12	rac-8-(1-Carboxy-ethoxy)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.85	322.1
V13	8-(1-Carboxy-cyclobutoxy)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.90	348.2

Precursor W11**8-Ethoxycarbonylmethoxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester**

To a soln. of 8-hydroxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester [Bioorg. & Med. Chem. Letters **2006**, 16(13), 3415 - 3418] (300 mg, 1.2 mmol) in 5 mL acetone are added K₂CO₃ (249 mg, 1.8 mmol) and ethylbromoacetate (201 mg, 1.2 mmol). The resulting mixture is allowed to stir at 70°C for 2 h. After cooling, it is poured onto water. The resulting aq. phase is extracted twice with DCM. The combined organic phase is washed with brine then dried over MgSO₄ and filtered. Evaporation of the solvent under reduced pressure and drying under HV yields quantitatively the title compound as a yellow oil which is used as such in the next step.

LC-B: t_R = 0.98 min; [M+H]⁺ = 336.1; ¹H-NMR δ : 7.13 (t, J = 7.9 Hz, 1 H), 6.78 (d, J = 7.7 Hz, 1 H), 6.59 (d, J = 8.1 Hz, 1 H), 4.65 (s, 2 H), 4.58 (s, 2 H), 4.28 (m, 2 H), 3.66 (t, J = 5.7 Hz, 2 H), 2.87 (t, J = 5.8 Hz, 2 H), 1.51 (s, 9 H), 1.32 (t, J = 7.1 Hz, 4 H)

Precursors W12–W13 listed in **Table 35** are prepared applying the method described for **Precursor W11** using the corresponding starting material respectively.

Table 35: Precursors W12–W13

Precursor	Precursor name	t_R [min] (Method LC-A)	MS Data m/z [M+H] ⁺
W12	rac-8-(1-Ethoxycarbonyl-ethoxy)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	0.99	350.2
W13	8-(1-Ethoxycarbonyl-cyclobutoxy)-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester	1.02	376.3

Precursor V14**8-((E)-2-Carboxy-vinyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester**

Is made according to the method described for the synthesis of **Precursor E1** using 8-formyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester instead of 5-formyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester.

LC-A: $t_R = 0.85$ min; $[M-tBu+MeCN]^+ = 289.2$

1H -NMR (400 MHz, $CDCl_3$) δ : 8.01 (d, $J = 15.7$ Hz, 1 H), 7.49 (m, 1 H), 7.23 (m, 2 H), 6.40 (d, $J = 15.7$ Hz, 1 H), 4.75 (s, 2 H), 3.68 (t, $J = 5.8$ Hz, 2 H), 2.90 (t, $J = 5.8$ Hz, 2 H), 1.53 (m, 9 H)

10 Example 208**N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-methyl-2,3-dihydro-1H-isoindol-4-ylamino)-acetamide**

a) *N*-{[Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl}-2,2,2-trifluoro-N-(2-methyl-2,3-dihydro-1H-isoindol-4-yl)-acetamide

15 To a solution of N-{[benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl}-N-(2,3-dihydro-1H-isoindol-4-yl)-2,2,2-trifluoro-acetamide dihydrochloride **Precursor Z1** (50 mg, 0.0853 mmol) and formaldehyde (2.6 mg, 0.0853 mmol) in 1 mL MeOH and 0.25 mL water is added $NaBH_3CN$ (13.4 mg, 0.213 mmol). The resulting mixture is allowed to stir at RT for 1 h. Sat. aq. $NaHCO_3$ soln. is added and the resulting aq. phase is extracted twice with DCM. The organic phase is evaporated under reduced pressure to yield 29 mg (73%) of the crude sub-

20 title compound as a yellow oil.

b) To a solution of N-{[benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl}-2,2,2-trifluoro-N-(2-methyl-2,3-dihydro-1H-isoindol-4-yl)-acetamide (24.6 mg, 0.0531 mmol) in 1 mL MeOH and 0.5 mL water is added K_2CO_3 (44 mg, 0.319 mmol). The resulting mixture is allowed to stir at 65°C for 2 h then at RT overnight. After cooling, sat. aq. $NaHCO_3$ soln. is added and the resulting aq. phase is extracted twice with DCM. The organic phase is evaporated under reduced pressure and the crude residue is purified by prep. HPLC (Method D) to yield the

25 title compound as a yellow oil.

LC-B: $t_R = 0.43$ min; $[M+H]^+ = 367.1$

30 Example 209**N-Benzyl-2-(2-cyclopropylmethyl-2,3-dihydro-1H-isoindol-4-ylamino)-N-(2-**

dimethylamino-ethyl)-acetamide LC-B: $t_R = 0.47$ min; $[M+H]^+ = 407.1$ is prepared according to the Method described for the preparation of **Example 208** using **Precursor Z1** and cyclopropanecarboxaldehyde as starting materials.

35 Precursor Z1

N-([Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl)-N-(2,3-dihydro-1H-isoindol-4-yl)-2,2,2-trifluoro-acetamide dihydrochloride

a) 4-([Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl)-(2,2,2-trifluoro-acetyl)-amino]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester

- 5 To a solution of 4-([benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl)-amino)-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester **Precursor AA1** (270 mg, 0.495 mmol) in 5 mL DCM is added TEA (200 mg, 1.98 mmol) and the resulting mixture is stirred at 5 min at RT then TFAA (208 mg, 0.99 mmol) is added and the resulting mixture is allowed to stir at RT for 1 h. The organic phase is washed with water and brine. The organic phase is dried over
10 MgSO₄, filtered and the solvent removed under reduced pressure to give 214 mg (79%) of the subtitle compound as a yellow oil.

LC-B: $t_R = 0.75$ min; $[M+H]^+ = 549.0$

- b) To a solution of 4-([benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl)-(2,2,2-trifluoro-acetyl)-amino]-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester (210 mg, 0.383 mmol)
15 in 5 mL dioxane is added 1.34 mL 4N HCl soln. in dioxane. The resulting brown suspension is allowed to stir at RT overnight. The solvent is coevaporated twice with EtOAc. After drying under HV, this yields 228 mg (114%) of the title compounds still containing some dioxane. It is used as such in the next step.

LC-B: $t_R = 0.48$ min; $[M+H]^+ = 448.9$

20 **Precursor AA1**

4-([Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl)-amino)-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester

- To a solution of 4-(carboxymethyl-amino)-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester **Precursor AB1** (300 mg, 1.03 mmol) and *N*-benzyl-*N*',*N*'-dimethylethane-1,2-diamine
25 **Amine 7** (183 mg, 1.03 mmol) and HATU (468 mg, 1.03 mmol) in 5 mL DCM is added DIPEA (332 mg, 2.57 mmol). The reaction mixture is allowed to stir at RT for 1 h. Sat. aq. NaHCO₃ soln. is added and the resulting aq. phase is extracted twice with DCM. The combined organic phase is evaporated under reduced pressure. Flash-chromatography on silica-gel (Eluent: EtOAc / MeOH 100:0 to 80:20) yields 339 mg (73%) of the title compound
30 as a yellow oil.

LC-B: $t_R = 0.73$ min; $[M+H]^+ = 453.1$

Precursor AB1

4-(Carboxymethyl-amino)-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester

- To a solution of 4-(ethoxycarbonylmethyl-amino)-1,3-dihydro-isoindole-2-carboxylic acid *tert*-
35 butyl ester **Precursor AC1** (1.09 g, 3.06 mmol) in 50 mL THF is added 18.4 mL (18.4 mmol) 1N aq. LiOH soln. the resulting mixture is allowed to stir at RT overnight. The mixture is

acidified to pH=4 with 2N aq. HCl soln. and the resulting aq. phase is extracted twice with DCM. The combined organic phase is washed with water and brine, dried over MgSO_4 , filtered and evaporated to yield 833 mg (93%) of the title compound as a purple solid which is used as such in the next step.

- 5 LC-B: $t_R = 0.77$ min; $[\text{M}+\text{H}]^+ = 293.0$; $^1\text{H-NMR}$ (d_6 -DMSO) δ : 7.06 (t, $J = 7.7$ Hz, 1 H), 6.56 (t, $J = 6.7$ Hz, 1 H), 6.30 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.3$ Hz, 1 H), 4.52 (d, $J = 10.5$ Hz, 2 H), 4.42 (d, $J = 11.4$ Hz, 2 H), 3.82 (s, 2 H), 1.47 (d, $J = 5.4$ Hz, 9 H)

Precursor AC1

10 4-(Ethoxycarbonylmethyl-amino)-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester

a) 4-Amino-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester

- To a solution of 4-amino-isoindoline [J. Pharm. Sci. **1964**, 53, 981] (500 mg, 3.73 mmol) in 10 mL dioxane is added 1N aq. NaOH soln. (3.73 mL, 3.73 mmol) and di-*tert*-butyl-di-carbonate (813 mg, 3.73 mmol) and the resulting mixture is allowed to stir at RT for 1 h. The reaction mixture is poured onto water and the resulting aq. phase is extracted twice with EtOAc. The combined organic phase is washed with sat. aq. NaHCO_3 soln., brine then dried over MgSO_4 . It is then filtered and the solvent is removed under reduced pressure. After drying under HV the 769 mg (88%) from the sub-title compound are obtained. It is used as such in the next step.

- 20 LC-B: $t_R = 0.69$ min; $[\text{M-tert-Bu}+\text{MeCN}]^+ = 220.1$

b) To a solution of 4-amino-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester (769 mg, 3.02 mmol) in 10 mL MeCN are added DIPEA (585 mg, 4.53 mmol) and ethyl bromoacetate (504 mg, 3.02 mmol). The resulting mixture is allowed to stir at 60°C for 17 h. After cooling the mixture is poured onto water and the resulting aq. phase is extracted twice with DCM.

- 25 The combined organic phase is washed with water and brine. It is dried over MgSO_4 , filtered and the solvent removed under reduced pressure. This yields quantitatively the title compound as a brown oil which is used as such in the next step.

LC-B: $t_R = 0.94$ min; $[\text{M}+\text{MeCN}]^+ = 321.1$

Example 568

30 3-(2-Cyclopropylmethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylmethyl)-1-(2-dimethylamino-ethyl)-1-(2-trifluoromethyl-benzyl)-urea

A solution of 1-(2-dimethylamino-ethyl)-3-(1,2,3,4-tetrahydro-isoquinolin-5-ylmethyl)-1-(2-trifluoromethyl-benzyl)-urea **Precursor AD1** (89 mg, 0.18 mmol) and cyclopropanecarboxaldehyde (12.6 mg, 0.18 mmol) in MeOH 1 mL and water 0.5 mL is allowed to stir at RT for 5 min. Then NaBH_3CN (28.3 mg, 0.45 mmol) is added and the resulting mixture is allowed to stir at RT for 1 h. It is then poured into sat. aq. NaHCO_3 soln.

and the resulting aq. phase is extracted twice with DCM. The combined organic phase is washed with brine, dried over MgSO_4 , filtered and evaporated. The crude residue is purified by prep. HPLC (Method E) to yield the title compound as a yellow oil.

LC-A: $t_R = 0.58$ min; $[\text{M}+\text{H}]^+ = 486.3$

5 **Precursor AE1**

1-(2-Dimethylamino-ethyl)-3-(1,2,3,4-tetrahydro-isoquinolin-5-ylmethyl)-1-(2-trifluoromethyl-benzyl)-urea

To a solution of 5-[3-(2-dimethylamino-ethyl)-3-(2-trifluoromethyl-benzyl)-ureidomethyl]-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester **Precursor AF1** (170 mg, 0.197 mmol) in 5 mL DCM is added 0.5 mL TFA. The yellowish solution is stirred overnight at RT. The reaction mixture is then poured into water. The resulting aq. phase is then basified (pH=8-9) with sat. aq. NaHCO_3 soln. and extracted twice with DCM. The combined organic phase are washed with brine, dried over MgSO_4 , filtered and concentrated. This yields quantitatively the title compound as a yellow oil.

15 LC-A: $t_R = 0.54$ min; $[\text{M}+\text{H}]^+ = 435.2$

Precursor AF1

5-[3-(2-Dimethylamino-ethyl)-3-(2-trifluoromethyl-benzyl)-ureidomethyl]-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester

To a solution of 5-aminomethyl-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester [CAS # 1196156-49-6] (150 mg, 0.549 mmol) in 0.5 mL water cooled to 0°C is added CDI (125 mg, 0.768 mmol). The resulting suspension is allowed to warm to RT over 1 h then *N,N*-Dimethyl-*N'*-(2-trifluoromethyl-benzyl)-ethane-1,2-diamine **Amine 45** (189 mg, 0.768 mmol) is added and the reaction is allowed to stir overnight at RT. The mixture is then diluted in DCM and the layers are separated. The aq. phase is extracted twice with DCM. The combined organic phase is washed with water and brine then dried over MgSO_4 , filtered and the solvent removed under reduced pressure. Flash-chromatography on silica-gel (Eluent: Hept. / EtOAc 95:5 to 60:40) yields 128 mg (44%) of the title compound as a yellow oil.

LC-A: $t_R = 0.80$ min; $[\text{M}+\text{H}]^+ = 535.6$

Example 569

30 **3-(2-Cyclopropylmethyl)-1,2,3,4-tetrahydro-isoquinolin-8-ylmethyl)-1-(2-dimethylamino-ethyl)-1-(2-trifluoromethyl-benzyl)-urea**

a) 2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinoline-8-carbonitrile

To a solution of 1,2,3,4-tetrahydroisoquinoline-8-carbonitrile hydrochloride (500 mg, 2.57 mmol) in 8 mL DCM is added at RT, cyclopropanecarboxaldehyde (180 mg, 2.57 mmol) and DIPEA (398 mg, 3.08 mmol). The solution is stirred for 10 min then $\text{NaBH}(\text{OAc})_3$ (1089 mg, 5.14 mmol) is added. The reaction mixture is allowed to stir at RT for 2 h, it is then poured

into water and the resulting aq. phase is extracted twice with DCM. Evaporation of the solvent in vacuo yields 540 mg (99%) of the sub-title compound as a yellow oil which is used as such in the next step.

LC-B: t_R = 0.49 min; $[M+H]^+$ = 213.4

5 b) (2-(Cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)methanamine

To a solution of CoCl_2 (258 mg, 1.98 mmol) in 10 mL MeOH is added dropwise at RT a solution of 2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinoline-8-carbonitrile (540 mg, 1.65 mmol) in 5 mL MeOH. The resulting purple solution is stirred for 10min then cooled at 0°C with an ice bath. NaBH_4 (313 mg, 8.27 mmol) is then slowly added portionwise and the
10 resulting black suspension is stirred for 1 h at 0°C then at RT overnight. The solution is cooled again to 0°C and another 100 mg of CoCl_2 and 100mg of NaBH_4 are added again and the stirring is continued for 6 h at RT. To the black suspension is added sat. aq. NH_4Cl soln. and this biphasic mixture is allowed to stir for 30min at RT. It is then basified to pH=12 by addition of 25% NH_4OH soln. in water. The resulting aq. phase is extracted three times
15 with DCM and the combined organic phases are washed with NaCl then dried over MgSO_4 , filtered and evaporated. Flash-chromatography on silica-gel (Eluent: DCM / MeOH from 100:0 to 80:20) yields 75 mg (21%) of the sub-title compound as a brown oil.

LC-A: t_R = 0.27 min; $[M+H]^+$ = 217.3

c) The title compound is obtained from (2-(cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinolin-8-yl)methanamine (75 mg, 0.239 mmol) and **Amine 45** using the method described for the
20 synthesis of **Precursor AF1** to yield the title compound as a brown oil.

LC-A: t_R = 0.59 min; $[M+H]^+$ = 489.5

Example 573:

25 **N-(2-Dimethylamino-ethyl)-2-(2-propyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide**

a) *Acetic acid acetoxy-[(2-dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl]-methyl ester*

A solution of freshly distilled diacetoxyacetyl chloride (McCaully, R. J. U.S. Patent 3,896,170, 1975) (1.42 g, 6.81 mmol) in 5 mL DCM is added dropwise to a suspension of N,N-dimethyl-N'-(2-trifluoromethyl-benzyl)-ethane-1,2-diamine (1.29 g, 5.24 mmol) and KHCO_3 (2.622 g, 26.2 mmol) in 5 mL DCM at -10°C over 15 min. The reaction mixture is allowed to stir at rt for
30 1 h. 20 mL water is added. The layers are separated. The aqueous layer is extracted twice with 20 mL DCM. The combined organic phase is washed with 25 mL sat. aq. NaHCO_3 soln. and 25 mL brine then dried over MgSO_4 , filtered and evaporated under reduced pressure to
35 deliver 2.05 g of the sub-title compound as a light yellow oil; LC-A: t_R = 0.63 min; $[M+H]^+$ = 405.10

b) A solution of acetic acid acetoxyl-[(2-dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl]-methyl ester (552 mg, 1.23 mmol), acetic acid (3.8 mg, 0.06 mmol) and 2-propyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamine (140 mg, 0.737 mmol) in 10 mL MeOH is allowed to stir at 40°C for 18 h. The reaction mixture is allowed to cool down to rt and treated with
 5 NaBH₃CN (77.2 mg, 1.23 mmol), stirred for 1.5 h, and treated again with NaBH₃CN (38.6 mg, 0.62 mmol) for 18 h. The reaction mixture is quenched with 3 mL water and evaporated under reduced pressure. The residue is partitioned between 20 mL 1 N aq. NaOH sol. and 20 mL DCM. The layers are separated. The aqueous layer are extracted twice with 20 mL DCM. The combined organic layer is washed with 25 mL brine then dried over MgSO₄. The
 10 crude residue is purified by prep. HPLC (Method D) to yield 0.221 g of the title compound as a yellow solid. LC-C: t_R = 0.58 min; [M+H]⁺ = 477.12

Example 574:

N-(2-Dimethylamino-ethyl)-2-[2-(3-fluoro-propyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide, LC-C: t_R = 0.58 min; [M+H]⁺ = 496.10 is
 15 prepared according to the method described for **Example 573** from 2-(3-fluoro-propyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamine

2-Propyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamine is obtained according to **reaction B3 Step a)** described above using 5-aminoisoquinoline and 1-iodopropane to prepare the intermediate 5-amino-2-propyl-isoquinolin-2-ium iodide which is reduced according to
 20 reaction **reaction B3 Step b)** to yield the title compound as a reddish oil. LC-A: t_R = 0.34 min; [M+H]⁺ = 191.27

2-(3-Fluoro-propyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamine is obtained according to **reaction B3 Step a)** described above using 5-aminoisoquinoline and 1-fluoro-3-iodopropane to prepare the intermediate 5-amino-2-(3-fluoropropyl)-isoquinolin-2-ium iodide which is
 25 reduced according to reaction **reaction B3 Step b)** to yield the title compound as a reddish oil. LC-A: t_R = 0.28 min; [M+H]⁺ = 209.19

Amine building blocks

Amines 1-162 are either commercially available or are prepared following one of the
 30 methods described below:

Amine 22

Method A

N'-(3-Chloro-pyridin-2-ylmethyl)-N,N-dimethyl-ethane-1,2-diamine

To a solution of 3-chloro-2-formylpyridine (1.5 g, 10.6 mmol) in 25 mL DCM are added 2-dimethylamino-ethylamine (1.27 mL, 11.7 mmol) and DIPEA (3.6 mL, 21.2 mmol). The
 35 resulting solution is treated portionswise with NaBH(OAc)₃ (3.37 g, 15.9 mmol) and allowed

to stir for 18 h at RT. The reaction mixture is diluted with 10 mL DCM and washed with 25 mL aq. sat. NaHCO_3 solution. The aqueous phase is extracted twice with 20 mL DCM. The combined organic phase is washed with 70 mL brine, dried over MgSO_4 , filtered and evaporated under reduced pressure. This yields the title compound (1.6g, 71%) as a colourless liquid. LC-A: $t_R = 0.20$ min; $[\text{M}+\text{H}]^+ = 214.17$

Amine 50

Method B

N,N-Dimethyl-*N'*-[2-(3-trifluoromethyl-phenyl)-ethyl]-ethane-1,2-diamine

To a solution of 3-(trifluoromethyl)phenethyl bromide (1.34 mL, 7.9 mmol) in 20 mL EtOH is added NaI (3.58 g, 23.9 mmol). The suspension is refluxed for 1 h. The mixture is cooled to RT then a solution of 2-dimethylamino-ethylamine (4.32 mL, 39.5 mmol) in 15 mL EtOH is added dropwise. The mixture is stirred at RT for 2 h then refluxed overnight. The mixture is cooled to RT and EtOH is evaporated. 50 mL DCM is added and the white solid is filtered off. The mother liquid is washed with 50 mL water then the aqueous phase is extracted twice with 25 mL DCM. The combined organic layer is dried over MgSO_4 , filtered and concentrated. Flash-chromatography on silica-gel (EtOAc / MeOH / TEA 80 : 18 : 2) yields 0.84 g (41%) of the title compound as a light orange oil. LC-B: $t_R = 0.50$ min; $[\text{M}+\text{H}]^+ = 261.22$

Amine 128

Method C

[2-(3,3-Difluoro-azetidin-1-yl)-2-oxo-ethyl]-*N*-(2-trifluoromethyl-benzyl)-amine

a) (2-Trifluoromethyl-benzylamino)-acetic acid ethyl ester

To a solution of 2-(trifluoromethyl)benzaldehyde (0.379 mL, 2.87 mmol) in 30 mL DCM at RT are added glycine ethyl ester hydrochloride (401 mg, 2.87 mmol), DIPEA (0.949 mL, 5.74 mmol) and sodium triacetoxyborohydride (913 mg, 4.31 mmol) and the mixture is stirred at RT overnight then under reflux for 6 h. The mixture is cooled to RT then washed with 30 mL sat. aq. NaHCO_3 . The combined organic layer is dried over Na_2SO_4 , filtered and concentrated. Flash-chromatography on silica-gel (heptane / EtOAc 1:0 to 4:1) yields 0.35 g of the title compound as a colourless oil.

LC-A: $t_R = 0.56$ min; $[\text{M}+\text{H}]^+ = 262.12$

b) N-(tert-Butoxycarbonyl)-(2-trifluoromethyl-benzylamino)-acetic acid ethyl ester

To a solution of (2-trifluoromethyl-benzylamino)-acetic acid ethyl ester (290 mg, 1.11 mmol) in 10 mL DCM at RT is added TEA (0.232 mL, 1.67 mmol) followed by di-*tert*-butyl dicarbonate (242 mg, 1.11 mmol). The mixture is stirred at RT for 72 h. The reaction mixture is washed with 10 mL sat. aq. NaHCO_3 , followed by 10 mL brine, then dried over Na_2SO_4 , filtered and evaporated to yield 0.395 g of the title compound as a colourless oil.

LC-A: $t_R = 0.99$ min; $[\text{M}+\text{H}-\text{C}(\text{CH}_3)]^+ = 305.93$

- c) A 2M solution of trimethylaluminum in toluene (1.18 mL, 2.35 mmol) is added at 0°C to a solution of 3,3-difluoroazetidine hydrochloride (244 mg, 1.88 mmol) in 5 mL DCE then the mixture is stirred at RT for 45min. A solution of N--(tert-butoxycarbonyl)-(2-trifluoromethyl-benzylamino)-acetic acid ethyl ester (340 mg, 0.941 mmol,) in 5 mL DCE is added and the reaction mixture is stirred at 85°C for 2 h. The mixture is cooled to 0°C and diluted with 10 mL DCM. 20 mL sat. aq. NaHCO₃ soln. is slowly added. The aq. layer is extracted twice with 20 mL DCM and the combined organic layer is dried over MgSO₄, filtered and concentrated. Flash-chromatography on silica-gel (Hept. / EtOAc 4:1 to 0:1) yields 0.188 g of the title compound as a yellowish oil. LC-A: t_R = 0.55 min; [M+H]⁺ = 309.04

10 Amine 130

Method D

[2-(3,3-Difluoro-azetidin-1-yl)-ethyl]-(2-trifluoromethyl-benzyl)-amine

- A solution of sodium borohydride (225 mg, 5.94 mmol) in 5 mL THF is cooled to 0°C then a solution of iodine (603 mg, 2.37 mmol) in 5 mL THF is added dropwise at 0°C. After completion of the addition, a solution of [2-(3,3-difluoro-azetidin-1-yl)-2-oxo-ethyl]-N-(2-trifluoromethyl-benzyl)-amine (183 mg, 0.594 mmol) in 5 mL THF is slowly added to the colorless BH₃ solution and the reaction mixture is then warmed up to RT and stirred at RT overnight then at 70°C in a sealed tube for 3 h. The reaction mixture is cooled to 0°C and 25 mL water is added. The mixture is then extracted twice with 25 mL EtOAc. The combined organic layer is dried over Na₂SO₄, filtered and concentrated.
- The crude residue is then dissolved in 8 mL MeOH in a sealed tube, treated with 4 M HCl in 3 mL dioxane and shaken at 50°C for 6 h. The mixture is then cooled to RT and concentrated. The residue is dissolved in 25 mL EtOAc and washed twice with 25 mL sat. aq. NaHCO₃. The organic layer is dried over Na₂SO₄, filtered and concentrated. Flash-chromatography on silica-gel (Hept. / EtOAc 4:1 to 3:2) yields 0.161 g of the title compound as a light yellowish oil. LC-B: t_R = 0.59 min; [M+H]⁺ = 295.06

Amine 142

Method E

rac-1-(2-Trifluoromethyl-benzylamino)-propan-2-ol

- To a solution of 2-(trifluoromethyl)benzylamine (500 mg, 2.85 mmol) and rac-propylene oxide (0.2 mL, 2.85 mmol) in 10 mL MeCN is added at RT at once calcium trifluoromethanesulfonate (483 mg, 1.43 mmol). The yellow solution is stirred for 2 h at RT. MeCN is evaporated then 25 mL water is added and the mixture is extracted three times with 10 mL EtOAc. The combined organic phase is washed with brine, dried over MgSO₄, filtered and evaporated. Flash-chromatography on silica-gel (Eluent: DCM/(TEA 0.4% in MeOH)

99:1 to 95:5) yields 0.504 g of the title compound as a yellowish oil. LC-A: t_R = 0.49 min; $[M+H]^+$ = 234.24

Amine 152

Method F

5 2-Methyl-4-(2-trifluoromethyl-benzylamino)-butan-2-ol

a) Ethyl 3-((2-(trifluoromethyl)benzyl)amino)propanoate

A solution of 2-trifluorobenzylamine (500 mg, 2.85 mmol) and ethyl acrylate (0.31 mL, 2.85 mmol) in 5 mL EtOH is stirred at RT overnight. 25 mL water is added and the aq. solution is extracted twice with 20 mL DCM. The combined organic layer is washed with 25 mL brine,
10 dried over $MgSO_4$, filtered and evaporated. Flash-chromatography on silica-gel (Eluent: Hept. / EtOAc 1:1 to 1:4) yields 0.731 g of the title compound as a colourless oil. LC-A: t_R = 0.58 min; $[M+H]^+$ = 276.31

b) Ethyl 3-((tert-butoxycarbonyl)(2-(trifluoromethyl)benzyl)amino)propanoate

A solution of ethyl 3-((2-trifluoromethyl-benzyl)amino)propanoate (430 mg, 1.5 mmol) in 5 mL
15 THF is treated with di-tert-butyl dicarbonate (635 mg, 3 mmol) and stirred at RT overnight. 2-Dimethylamino-ethylamine (264 mg, 3 mmol) is added and the stirring is continued for 15 min at RT. 25 mL sat. aq. NH_4Cl soln. is added and the residual aq. solution is extracted twice with 25 mL DCM. The combined organic layer is washed with 25 mL brine, dried over $MgSO_4$, filtered and evaporated. Flash-chromatography on silica-gel (Eluent: heptane /
20 EtOAc 19:1 to 4:1) yields 0.491 g of the title compound as a colourless oil. LC-A: t_R = 1.01 min; $[M+H]^+$ = 376.25

c) tert-Butyl (3-hydroxy-3-methylbutyl)(2-(trifluoromethyl)benzyl)carbamate

A solution of ethyl 3-((tert-butoxycarbonyl)(2-trifluoromethyl-benzyl)amino)propanoate (491 mg, 1.3 mmol) in 4 mL THF is added over 20 min at -78°C under argon to a solution of 1.6 M methyl lithium in diethylether (2.28 mL, 3.65 mmol). The resulting brownish solution is stirred
25 for 1.5 h then quenched by the addition of 25 mL water. The mixture is extracted twice with 25 mL EtOAc. The combined organic layer is washed with 25 mL sat. aq. $NaHCO_3$, dried over $MgSO_4$, filtered and evaporated. Flash-chromatography on silica-gel (Eluent: Hept. / EtOAc 19:1 to 0:1) yields 0.253 g of the title compound as a colourless oil. LC-A: t_R = 0.94
30 min; $[M+H]^+$ = 362.23

d) 2-methyl-4-((2-(trifluoromethyl)benzyl)amino)butan-2-ol

A solution of tert-butyl (3-hydroxy-3-methylbutyl)(2-(trifluoromethyl)benzyl)carbamate (253 mg, 0.7 mmol) in 5 mL DCM is treated with 4 N HCl solution in dioxane (0.332 mL, 2.1 mmol) and stirred at RT for 1 h. The reaction mixture is treated with 25 mL sat. aq. $NaHCO_3$

and extracted twice with 25 mL DCM. The organic layers are washed with 25 mL sat. aq. NaHCO_3 , dried over MgSO_4 , filtered and evaporated to yield 0.178 g of the title compound as a brownish oil. LC-A: $t_R = 0.56$ min; $[\text{M}+\text{H}]^+ = 262.31$

- 5 Amines listed in **Table 36** below are commercially available or are prepared by applying either one of the above-mentioned methods A, B, C, D, E or F using commercially available starting materials or building blocks whose synthesis is described after table 36. Prepared amines are characterized by their LC- data.

Table 36

Amine No	Compound name
1	(2-Chloro-benzyl)-ethyl-amine
2	2-Benzylamino-ethanol
3	3-(Benzylamino)propanenitrile
4	Benzyl-cyclopropylmethyl-amine
5	1-Methyl-3-phenylpiperazine
6	Cyclopropyl-(2,3-dimethyl-benzyl)-amine
7	N-Benzyl-N',N'-dimethylethane-1,2-diamine
8	3-Benzylamino-propionamide
9	Benzyl-(3-methyl-butyl)-amine
10	N'-Benzyl-N,N-dimethylpropane-1,3-diamine
11	N,N-Dimethyl-N'-phenethyl-ethane-1,2-diamine
12	N,N-Dimethyl-N'-(3-methyl-benzyl)-ethane-1,2-diamine
13	N,N-Dimethyl-N'-(4-methylbenzyl)ethane-1,2-diamine
14	N,N-Dimethyl-N'-(2-methylbenzyl)ethane-1,2-diamine
15	[(4-Chlorophenyl)methyl][2-(dimethylamino)ethyl]amine
16	N'-(3-Chloro-benzyl)-N,N-dimethyl-ethane-1,2-diamine
17	N'-(2-Chlorobenzyl)-N,N-dimethylethane-1,2-diamine
18	N'-(4-Fluoro-benzyl)-N,N-dimethyl-ethane-1,2-diamine
19	N'-(3-Fluoro-benzyl)-N,N-dimethyl-ethane-1,2-diamine
20	N'-(2-Fluoro-benzyl)-N,N-dimethyl-ethane-1,2-diamine
21	Benzylamino-acetic acid ethyl ester
22	N'-(3-Chloro-pyridin-2-ylmethyl)-N,N-dimethyl-ethane-1,2-diamine
23	<i>tert</i> -Butyl 3-(benzylamino)pyrrolidine-1-carboxylate LC-A: $t_R = 0.52$ min; $[\text{M}+\text{H}]^+ = 277.2$

24	N,N-Dimethyl-N'-(2-o-tolyl-ethyl)-ethane-1,2-diamine
25	Benzyl[2-(diethylamino)ethyl]amine
26	N'-(4-Methoxy-benzyl)-N,N-dimethyl-ethane-1,2-diamine
27	N'-(3-Methoxy-benzyl)-N,N-dimethyl-ethane-1,2-diamine
28	N'-(2-Methoxy-benzyl)-N,N-dimethyl-ethane-1,2-diamine
29	Benzyl-pyridin-2-ylmethyl-amine
30	Benzyl-(2-pyrrolidin-1-yl-ethyl)-amine
31	N-Benzyl-N-(1,1-dioxidotetrahydrothien-3-yl)amine
32	Benzyl-(1-methyl-1 <i>H</i> -imidazol-2-ylmethyl)-amine
33	N'-Benzyl-N-butyl-N-methyl-ethane-1,2-diamine
34	N,N-Dimethyl-N'-((E)-2-methyl-3-phenyl-allyl)-ethane-1,2-diamine LC-A: $t_R = 0.47$ min; $[M+H]^+ = 219.5$
35	3-(2-Trifluoromethyl-benzylamino)-propionitrile
36	N-Benzyl-2-(1-methylpyrrolidin-2-yl)ethanamine LC-A: $t_R = 0.31$ min; $[M+H]^+ = 219.5$
37	(2-Chloro-benzyl)-(2-pyrrolidin-1-yl-ethyl)-amine
38	(2-Fluoro-benzyl)-(2-pyrrolidin-1-yl-ethyl)-amine
39	2-(1-Methylpyrrolidin-2-yl)-N-phenylethanamine
40	(2-Chloro-4-fluoro-benzyl)-(2-pyrrolidin-1-yl-ethyl)-amine
41	(2,4-Difluoro-benzyl)-(2-pyrrolidin-1-yl-ethyl)-amine
42	N-Benzyl-N-[2-(4-fluorophenyl)ethyl]amine
43	N,N-Dimethyl-N'-(3-trifluoromethyl-benzyl)-ethane-1,2-diamine
44	N,N-Dimethyl-N'-(4-trifluoromethyl-benzyl)-ethane-1,2-diamine
45	N,N-Dimethyl-N'-(2-trifluoromethyl-benzyl)-ethane-1,2-diamine
46	(3-Methyl-butyl)-(2-trifluoromethyl-benzyl)-amine
47	N,N-Dimethyl-N'-(6-trifluoromethyl-pyridin-2-ylmethyl)-ethane-1,2-diamine LC-A: $t_R = 0.30$ min; $[M+H]^+ = 248.1$
48	N,N-Dimethyl-N'-(3-trifluoromethyl-pyridin-2-ylmethyl)-ethane-1,2-diamine LC-A: $t_R = 0.25$ min; $[M+H]^+ = 248.1$
49	N'-(4-Fluoro-2-trifluoromethyl-benzyl)-N,N-dimethyl-ethane-1,2-diamine LC-A: t_R $= 0.42$ min; $[M+H]^+ = 265.1$
50	N,N-Dimethyl-N'-[2-(3-trifluoromethyl-phenyl)-ethyl]-ethane-1,2-diamine
51	N,N-Dimethyl-N'-[2-(4-trifluoromethyl-phenyl)-ethyl]-ethane-1,2-diamine LC-A: $t_R = 0.46$ min; $[M+H]^+ = 261.1$

52	N,N-Dimethyl-N'-[2-(2-trifluoromethyl-phenyl)-ethyl]-ethane-1,2-diamine LC-A: $t_R = 0.48$ min; $[M+H]^+ = 261.1$
53	N,N-dimethyl-N'-{1-[2-(trifluoromethyl)phenyl]ethyl}ethane-1,2-diamine
54	[2-(3,4-Dimethoxyphenyl)ethyl][2-(dimethylamino)ethyl]amine
55	(E)-N-(2-(1-Methylpyrrolidin-2-yl)ethyl)-3-phenylprop-2-en-1-amine
56	N-(2-(1-methylpyrrolidin-2-yl)ethyl)-3-phenylpropan-1-amine LC-A: $t_R = 0.41$ min; $[M+H]^+ = 247.3$
57	(E)-2-methyl-N-(2-(1-methylpyrrolidin-2-yl)ethyl)-3-phenylprop-2-en-1-amine LC-A: $t_R = 0.57$ min; $[M+H]^+ = 259.1$
58	(Tetrahydro-pyran-4-yl)-(2-trifluoromethyl-benzyl)-amine
59	(4-Methyl-thiazol-2-ylmethyl)-(2-trifluoromethyl-benzyl)-amine
60	(2-Pyrrolidin-1-yl-ethyl)-(2-trifluoromethyl-benzyl)-amine
61	(1-Methyl-piperidin-4-yl)-(2-trifluoromethyl-benzyl)-amine
62	1-Methyl-N-(2-(trifluoromethyl)benzyl)piperidin-3-amine
63	N,N-Diethyl-N'-(2-trifluoromethyl-benzyl)-ethane-1,2-diamine
64	<i>tert</i> -Butyl 3-(benzylamino)pyrrolidine-1-carboxylate
65	4-[(2-Trifluoromethyl-benzylamino)-methyl]-3 <i>H</i> -pyridin-2-one LC-A: $t_R = 0.49$ min; $[M+H]^+ = 283.6$
66	1-[2-(2-Trifluoromethyl-benzylamino)-ethyl]-pyrrolidin-2-one LC-A: $t_R = 0.51$ min; $[M+H]^+ = 287.2$
67	(2-Morpholin-4-yl-ethyl)-(2-trifluoromethyl-benzyl)-amine
68	1-[2-(2-Trifluoromethyl-benzylamino)-ethyl]-imidazolidin-2-one LC-A: $t_R = 0.51$ min; $[M+H]^+ = 288.6$
69	Ethyl 2-(((2-(trifluoromethyl)benzyl)amino)methyl)cyclopropanecarboxylate LC-A: $t_R = 0.63$ min; $[M+H]^+ = 302.1$
70	1-(1-Ethyl-1 <i>H</i> -pyrazol-3-yl)-N-(2-(trifluoromethyl)benzyl)ethanamine LC-A: $t_R = 0.63$ min; $[M+H]^+ = 298.5$
71	[2-(4-Trifluoromethyl-benzylamino)-ethyl]-carbamic acid <i>tert</i> -butyl ester LC-A: $t_R = 0.78$ min; $[M+H]^+ = 319.1$
72	(2-Benzyloxy-ethyl)-(2-trifluoromethyl-benzyl)-amine LC-A: $t_R = 0.70$ min; $[M+H]^+ = 310.1$
73	Methyl-[2-(2-trifluoromethyl-benzylamino)-ethyl]-carbamic acid <i>tert</i> -butyl ester LC-A: $t_R = 0.70$ min; $[M+H]^+ = 333.2$

74	<i>tert</i> -Butyl 2,2-dimethyl-4-(((2-(trifluoromethyl)benzyl)amino)methyl)oxazolidine-3-carboxylate LC-A: $t_R = 0.77$ min; $[M+H]^+ = 389.0$
75	rac-[2-(1-Methyl-pyrrolidin-2-yl)-ethyl]-(2-trifluoromethyl-benzyl)-amine LC-A: $t_R = 0.43$ min; $[M+H]^+ = 287.17$
76	(3-Pyrrolidin-1-yl-propyl)-(2-trifluoromethyl-benzyl)-amine LC-A: $t_R = 0.43$ min; $[M+H]^+ = 287.18$
77	(2-Benzylamino-ethyl)-methyl-carbamic acid <i>tert</i> -butyl ester LC-A: $t_R = 0.75$ min; $[M+H]^+ = 265.2$
78	4-Benzylamino-piperidine-1-carboxylic acid <i>tert</i> -butyl ester LC-A: $t_R = 0.71$ min; $[M+H]^+ = 291.12$
79	Methyl-{2-[(3-trifluoromethyl-pyridin-2-ylmethyl)-amino]-ethyl}-carbamic acid <i>tert</i> -butyl ester LC-A: $t_R = 0.61$ min; $[M+H]^+ = 334.23$
80	4-(2-Trifluoromethyl-benzylamino)-piperidine-1-carboxylic acid <i>tert</i> -butyl ester LC-A: $t_R = 0.72$ min; $[M+H]^+ = 359.18$
81	rac- 3-[(2-Trifluoromethyl-benzylamino)-methyl]-pyrrolidine-1-carboxylic acid <i>tert</i> -butyl ester LC-A: $t_R = 0.70$ min; $[M+H]^+ = 359.16$
82	rac-3-(2-Trifluoromethyl-benzylamino)-pyrrolidine-1-carboxylic acid <i>tert</i> -butyl ester LC-A: $t_R = 0.66$ min; $[M+H]^+ = 345.23$
83	N,N-Dimethyl-N'-pyrimidin-4-ylmethyl-ethane-1,2-diamine LC-G: $t_R = 0.54$ min; $[M+H]^+ = 181.3$
84	N,N-Dimethyl-N'-(3-methyl-pyridin-2-ylmethyl)-ethane-1,2-diamine LC-G: $t_R = 1.19$ min; $[M+H]^+ = 194.2$
85	N,N-Dimethyl-N'-pyridin-2-ylmethyl-ethane-1,2-diamine LC-G: $t_R = 0.90$ min; $[M+H]^+ = 180.3$
86	N,N-Dimethyl-N'-(5-methyl-pyridin-2-ylmethyl)-ethane-1,2-diamine LC-G: $t_R = 1.13$ min; $[M+H]^+ = 194.3$
87	N,N-Dimethyl-N'-(6-methyl-pyridin-2-ylmethyl)-ethane-1,2-diamine LC-G: $t_R = 1.0$ min; $[M+H]^+ = 194.2$
88	N,N-Dimethyl-N'-pyrimidin-2-ylmethyl-ethane-1,2-diamine LC-G: $t_R = 0.61$ min; $[M+H]^+ = 181.2$
89	N'-(5-Chloro-pyridin-2-ylmethyl)-N,N-dimethyl-ethane-1,2-diamine LC-G: $t_R = 1.18$ min; $[M+H]^+ = 214.2$

90	N'-(5-Chloro-pyridin-3-ylmethyl)-N,N-dimethyl-ethane-1,2-diamine LC-G: $t_R = 1.08$ min; $[M+H]^+ = 214.2$
91	N,N-Dimethyl-N'-pyridin-3-ylmethyl-ethane-1,2-diamine LC-G: $t_R = 0.63$ min; $[M+H]^+ = 180.3$
92	N,N-Dimethyl-N'-(2-methyl-2H-pyrazol-3-ylmethyl)-ethane-1,2-diamine LC-G: $t_R = 0.61$ min; $[M+H]^+ = 183.3$
93	N,N-Dimethyl-N'-thiazol-2-ylmethyl-ethane-1,2-diamine LC-G: $t_R = 0.73$ min; $[M+H]^+ = 186.2$
94	N,N-Dimethyl-N'-(4-methyl-thiazol-2-ylmethyl)-ethane-1,2-diamine LC-G: $t_R = 0.90$ min; $[M+H]^+ = 200.2$
95	N'-(5-Fluoro-pyridin-2-ylmethyl)-N,N-dimethyl-ethane-1,2-diamine LC-G: $t_R = 0.90$ min; $[M+H]^+ = 198.2$
96	N,N-Dimethyl-N'-pyridin-4-ylmethyl-ethane-1,2-diamine LC-G: $t_R = 0.60$ min; $[M+H]^+ = 180.3$
97	N,N-Dimethyl-N'-(5-methyl-isoxazol-3-ylmethyl)-ethane-1,2-diamine LC-G: $t_R = 0.77$ min; $[M+H]^+ = 184.3$
98	N'-(2,6-Difluoro-benzyl)-N,N-dimethyl-ethane-1,2-diamine LC-G: $t_R = 1.12$ min; $[M+H]^+ = 215.2$
99	N'-(3-Fluoro-pyridin-2-ylmethyl)-N,N-dimethyl-ethane-1,2-diamine LC-G: $t_R = 0.83$ min; $[M+H]^+ = 198.2$
100	N-(2-Dimethylamino-pyrimidin-5-ylmethyl)-N',N'-dimethyl-ethane-1,2-diamine LC-G: $t_R = 0.92$ min; $[M+H]^+ = 224.2$
101	[2-(2-Trifluoromethyl-benzylamino)-ethyl]-carbamic acid tert-butyl ester LC-A: $t_R = 0.65$ min; $[M+H]^+ = 319.08$
102	(S)-3-[(2-Trifluoromethyl-benzylamino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester LC-A: $t_R = 0.70$ min; $[M+H]^+ = 359.27$
103	(R)-3-[(2-Trifluoromethyl-benzylamino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester LC-A: $t_R = 0.70$ min; $[M+H]^+ = 359.23$
104	(3,3-Dimethyl-butyl)-(2-trifluoromethyl-benzyl)-amine LC-A: $t_R = 0.69$ min; $[M+H]^+ = 260.22$
105	(3,3-Dimethyl-butyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-amine LC-A: $t_R = 0.64$ min; $[M+H]^+ = 261.22$
106	(3,3-Dimethyl-butyl)-(3-methyl-pyridin-2-ylmethyl)-amine LC-A: $t_R = 0.59$ min; $[M+H]^+ = 207.27$

107	4-[2-(2-Trifluoromethyl-benzylamino)-ethyl]-piperazine-1-carboxylic acid tert-butyl ester LC-A: $t_R = 0.61$ min; $[M+H]^+ = 388.26$
108	(2-Piperidin-1-yl-ethyl)-(2-trifluoromethyl-benzyl)-amine LC-A: $t_R = 0.43$ min; $[M+H]^+ = 287.31$
109	(2-Azepan-1-yl-ethyl)-(2-trifluoromethyl-benzyl)-amine LC-A: $t_R = 0.47$ min; $[M+H]^+ = 301.23$
110	N,N-Diisopropyl-N'-(2-trifluoromethyl-benzyl)-ethane-1,2-diamine LC-A: $t_R = 0.46$ min; $[M+H]^+ = 303.22$
111	N-Cyclopropyl-N-methyl-N'-(2-trifluoromethyl-benzyl)-ethane-1,2-diamine LC-A: $t_R = 0.42$ min; $[M+H]^+ = 273.17$
112	N,N-Dimethyl-N'-(3-trifluoromethoxy-benzyl)-ethane-1,2-diamine LC-A: $t_R = 0.41$ min; $[M+H]^+ = 263.14$
113	4-(2-Trifluoromethyl-benzylamino)-cyclohexanol LC-A: $t_R = 0.50$ min; $[M+H]^+ = 274.02$
114	1-Methoxy-3-(2-trifluoromethyl-benzylamino)-propan-2-ol LC-A: $t_R = 0.51$ min; $[M+H]^+ = 264.14$
115	(2-Trifluoromethyl-benzyl)-(3,3,3-trifluoro-propyl)-amine LC-A: $t_R = 0.59$ min; $[M+H]^+ = 272.26$
116	(2-Methoxy-ethyl)-(2-trifluoromethyl-benzyl)-amine LC-A: $t_R = 0.52$ min; $[M+H]^+ = 234.2$
117	[1,4]Dioxan-2-ylmethyl-(2-trifluoromethyl-benzyl)-amine LC-A: $t_R = 0.53$ min; $[M+H]^+ = 276.75$
118	N,N-Dimethyl-N'-(2-trifluoromethoxy-benzyl)-ethane-1,2-diamine LC-A: $t_R = 0.37$ min; $[M+H]^+ = 263.16$
119	N,N-Dimethyl-N'-(4-trifluoromethoxy-benzyl)-ethane-1,2-diamine LC-A: $t_R = 0.42$ min; $[M+H]^+ = 263.15$
120	[2-(4,4-Difluoro-piperidin-1-yl)-ethyl]-(2-trifluoromethyl-benzyl)-amine LC-A: $t_R = 0.57$ min; $[M+H]^+ = 323.06$
121	N-Methyl-N-(2,2,2-trifluoro-ethyl)-N'-(2-trifluoromethyl-benzyl)-ethane-1,2-diamine LC-A: $t_R = 0.65$ min; $[M+H]^+ = 315.08$
122	[2-(4,4-Difluoro-piperidin-1-yl)-ethyl]-(3-trifluoromethyl-pyridin-2-ylmethyl)-amine LC-A: $t_R = 0.48$ min; $[M+H]^+ = 324.09$

123	N-Methyl-N-(2,2,2-trifluoro-ethyl)-N'-(3-trifluoromethyl-pyridin-2-ylmethyl)-ethane-1,2-diamine LC-A: $t_R = 0.61$ min; $[M+H]^+ = 317.2$
124	[2-(3,3-Difluoro-piperidin-1-yl)-ethyl]-(2-trifluoromethyl-benzyl)-amine LC-A: $t_R = 0.64$ min; $[M+H]^+ = 323.06$
125	[2-(3,3-Difluoro-pyrrolidin-1-yl)-ethyl]-(2-trifluoromethyl-benzyl)-amine LC-A: $t_R = 0.62$ min; $[M+H]^+ = 309.07$
126	[2-(3,3-Difluoro-piperidin-1-yl)-ethyl]-(3-trifluoromethyl-pyridin-2-ylmethyl)-amine LC-A: $t_R = 0.58$ min; $[M+H]^+ = 324.08$
127	[2-(3,3-Difluoro-pyrrolidin-1-yl)-ethyl]-(3-trifluoromethyl-pyridin-2-ylmethyl)-amine LC-A: $t_R = 0.56$ min; $[M+H]^+ = 310.07$
128	[2-(3,3-difluoro-azetidin-1-yl)-2-oxo-ethyl]-N-(2-trifluoromethyl-benzyl)-amine LC-A: $t_R = 0.55$ min; $[M+H]^+ = 309.04$
129	[2-(3,3-difluoro-azetidin-1-yl)-2-oxo-ethyl]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-amine LC-A: $t_R = 0.51$ min; $[M+H]^+ = 310.02$
130	[2-(3,3-Difluoro-azetidin-1-yl)-ethyl]-(2-trifluoromethyl-benzyl)-amine LC-A: $t_R = 0.59$ min; $[M+H]^+ = 295.06$
131	(2-Methanesulfonyl-ethyl)-(2-trifluoromethyl-benzyl)-amine LC-A: $t_R = 0.51$ min; $[M+H]^+ = 282.09$
132	N-[2-(2-Trifluoromethyl-benzylamino)-ethyl]-methanesulfonamide LC-A: $t_R = 0.50$ min; $[M+H]^+ = 297.25$
133	N-Ethyl-N-methyl-N'-(2-trifluoromethyl-benzyl)-ethane-1,2-diamine LC-A: $t_R = 0.40$ min; $[M+H]^+ = 261.31$
134	Ethyl-[2-(2-trifluoromethyl-benzylamino)-ethyl]-carbamic acid tert-butyl ester LC-A: $t_R = 0.72$ min; $[M+H]^+ = 347.30$
135	2-(2-Trifluoromethyl-benzylamino)-ethanesulfonic acid amide LC-A: $t_R = 0.46$ min; $[M+H]^+ = 283.22$
136	N'-(2-Bromo-benzyl)-N,N-dimethyl-ethane-1,2-diamine LC-A: $t_R = 0.31$ min; $[M+H]^+ = 259.01$
137	[2-(2-Bromo-benzylamino)-ethyl]-methyl-carbamic acid tert-butyl ester LC-A: $t_R = 0.66$ min; $[M+H]^+ = 343.02$
138	N'-(3-Bromo-pyridin-2-ylmethyl)-N,N-dimethyl-ethane-1,2-diamine LC-A: $t_R = 0.21$ min; $[M+H]^+ = 260.06$
139	N'-(3-Bromo-benzyl)-N,N-dimethyl-ethane-1,2-diamine LC-A: $t_R = 0.36$ min; $[M+H]^+ = 257.05$

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140	N'-(4-Bromo-benzyl)-N,N-dimethyl-ethane-1,2-diamine LC-A: $t_R = 0.36$ min; $[M+H]^+ = 257.05$
141	N'-(3-Bromo-pyridin-4-ylmethyl)-N,N-dimethyl-ethane-1,2-diamine LC-A: $t_R = 0.22$ min; $[M+H]^+ = 258.06$
142	rac-1-(2-Trifluoromethyl-benzylamino)-propan-2-ol LC-A: $t_R = 0.49$ min; $[M+H]^+ = 234.23$
143	2-Methyl-1-(2-trifluoromethyl-benzylamino)-propan-2-ol LC-A: $t_R = 0.52$ min; $[M+H]^+ = 248.25$
144	rac-1,1,1-Trifluoro-3-(2-trifluoromethyl-benzylamino)-propan-2-ol LC-A: $t_R = 0.59$ min; $[M+H]^+ = 288.21$
145	1-[(2-Trifluoromethyl-benzylamino)-methyl]-cyclopentanol LC-A: $t_R = 0.58$ min; $[M+H]^+ = 274.06$
146	N-(4-methoxybenzyl)-N-(2,2,2-trifluoroethyl)-N'-(2-(trifluoromethyl)benzyl)ethane-1,2-diamine LC-A: $t_R = 0.79$ min; $[M+H]^+ = 421.19$
147	Allyl-(3-methyl-pyridin-2-ylmethyl)-amine LC-A: $t_R = 0.39$ min; $[M+H]^+ = 163.12$
148	N-Allyl-N-methyl-N'-(2-trifluoromethyl-benzyl)-ethane-1,2-diamine LC-A: $t_R = 0.43$ min; $[M+H]^+ = 273.14$
149	N-(2-Fluoro-ethyl)-N-methyl-N'-(2-trifluoromethyl-benzyl)-ethane-1,2-diamine LC-A: $t_R = 0.42$ min; $[M+H]^+ = 279.10$
150	(3-Methyl-oxetan-3-ylmethyl)-(2-trifluoromethyl-benzyl)-amine LC-A: $t_R = 0.52$ min; $[M+H]^+ = 260.28$
151	N-Methyl-N-prop-2-ynyl-N'-(2-trifluoromethyl-benzyl)-ethane-1,2-diamine LC-A: $t_R = 0.47$ min; $[M+H]^+ = 271.12$
152	2-Methyl-4-(2-trifluoromethyl-benzylamino)-butan-2-ol LC-A: $t_R = 0.56$ min; $[M+H]^+ = 262.31$
153	[2-(2-Chloro-benzylamino)-ethyl]-methyl-carbamic acid tert-butyl ester LC-A: $t_R = 0.75$ min; $[M+H]^+ = 299.27$
154	{2-[(3-Chloro-pyridin-2-ylmethyl)-amino]-ethyl}-methyl-carbamic acid tert-butyl ester LC-A: $t_R = 0.59$ min; $[M+H]^+ = 300.27$
155	Thiazol-5-ylmethyl-(2-trifluoromethyl-benzyl)-amine LC-A: $t_R = 0.52$ min; $[M+H]^+ = 273.19$
156	(2-Chloro-benzyl)-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-amine LC-A: $t_R = 0.50$ min; $[M+H]^+ = 289.25$

157	Ethyl-[2-(2-trifluoromethyl-benzylamino)-ethyl]-carbamic acid tert-butyl ester LC-A: $t_R = 0.72$ min; $[M+H]^+ = 347.30$
158	N-[5-(4-Fluoro-phenylamino)-pyridin-2-ylmethyl]-N',N'-dimethyl-ethane-1,2-diamine LC-A: $t_R = 0.47$ min; $[M+H]^+ = 289.09$
159	(3-Chloro-pyridin-2-ylmethyl)-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-amine LC-A: $t_R = 0.42$ min; $[M+H]^+ = 290.05$
160	Isoxazol-5-ylmethyl-(2-trifluoromethyl-benzyl)-amine LC-A: $t_R = 0.52$ min; $[M+H]^+ = 257.24$
161	1-[(3-Chloro-pyridin-2-ylmethyl)-amino]-2-methyl-propan-2-ol LC-A: $t_R = 0.41$ min; $[M+H]^+ = 215.32$
162	1-[(3-Bromo-pyridin-2-ylmethyl)-amino]-2-methyl-propan-2-ol LC-A: $t_R = 0.43$ min; $[M+H]^+ = 259.26$

Building blocks

5-(4-Fluoro-phenylamino)-pyridine-2-carbaldehyde

a) (6-[1,3]Dioxolan-2-yl-pyridin-3-yl)-(4-fluoro-phenyl)-amine

- 5 A suspension of 5-bromo-2-[1,3]dioxolan-2-yl-pyridine (6.8 g, 29.6 mmol), 4-fluoroaniline (3.94 g, 35.5 mmol); Pd₂dba₃ (1.35 g, 1.48 mmol), XPhos (1.41 g, 2.96 mmol) and NaOtBu (3.98 g, 41.4 mmol) in 100 mL dioxane is heated to 100°C for 5 h. The mixture is cooled to RT and diluted with 100 mL EtOAc and filtered through a pad of celite. The resulting solution is washed with 100 mL of 10% aq. NaHCO₃ soln. and 100 mL brine. The organic layer is
- 10 dried over MgSO₄ and evaporated under reduced pressure. Flash-chromatography on silica-gel (Eluent: Hept. / EtOAc 1:1 to 1:2) yields the title compound (6.8 g, 88%) as a beige solid. LC-A: $t_R = 0.60$ min; $[M+H]^+ = 261.06$

b) 5-(4-Fluoro-phenylamino)-pyridine-2-carbaldehyde

- A solution of (6-[1,3]dioxolan-2-yl-pyridin-3-yl)-(4-fluoro-phenyl)-amine 7.001a (3.5 g, 13.4 mmol) in 180 mL THF is treated with water (9 mL, 27.5 mmol) and p-toluenesulfonic acid (3.84 g, 20.2 mmol) under argon and stirred at 50°C for 3 h. The mixture is cooled down to RT, poured on 100 mL aq. sat. NaHCO₃ soln. and extracted three times with 100 mL EtOAc. The combined organic layers are washed with 100 mL brine and dried over MgSO₄, filtered and concentrated under reduced pressure to deliver the crude title compound (2.9 g, 100%)
- 20 as a beige solid
LC-A: $t_R = 0.75$ min; $[M+H]^+ = 217.18$

II. Biological Assays

In vitro assay

The CXCL12 receptor and CXCR7 agonistic activities of the compounds of formula (I) are determined in accordance with the following experimental method.

- 5 The assay is using the PathHunterTM CHO-K1 CXCR7 b-arrestin cell line from DiscoverX. The system is based on the Enzyme Fragment Complementation Technology. Two complementing fragments of the b-galactosidase enzyme are expressed within stably transfected cells. The larger portion of b-gal, termed EA for Enzyme Acceptor, is fused to the C-terminus of b-arrestin 2. The smaller fragment, termed ProLinkTM tag, is fused to CXCR7 at
10 the C-terminus. Upon activation, b-arrestin is recruited which forces the interaction of ProLink and EA, allowing complementation of the two fragments of b-gal and the formation of a functional enzyme which is capable of hydrolysing the substrate and generating a chemiluminescent signal.

- CHO-K1 CXCR7 b-arrestin cells are detached from culture dishes with a cell dissociation
15 buffer (Invitrogen, #13151-014) and collected in growing medium (F12 HAMS 90 %(v/v) /FCS 10%(v/v), Penicilin/streptomycin 1 %(v/v)). 5000 cells per well (in 20 µl) are seeded in a 384 well plate (white-walled, clear bottom; BD Falcon # 353274). The plate is incubated at 37°C / 5% CO₂ for 24 hours. Medium is then replaced by 20 µl OPTIMEM (Invitrogen #31985) for 3 to 4 hours. Test compounds are dissolved at 10mM in DMSO and serially diluted in DMSO to
20 200X of the final concentration for dose response curves. Compounds are then diluted 1:33.3 in HBSS1X. 5µl / well of HBSS1X / 20mM HEPES / 0.2% BSA are added to the assay plate followed by addition of 5µl / well of diluted compounds. CXCL12 (Peprotech #300-28A) may be used as a reference agonist. The plate is incubated for 90 minutes at 37°C. 12 µl of detection reagent (Path Hunter Detection Kit, DiscoverX, #93-0001) is transferred to the
25 assay plate and to the plate is incubated for 1 hour at room temperature. Luminescent signal is read in a microplate reader (FLUOstar Optima, bmg). The calculated EC₅₀ values may fluctuate depending on the daily cellular assay performance. Fluctuations of this kind are known to those skilled in the art. Average EC₅₀ values from several measurements are given as geometric mean values.

Agonistic activities of exemplified compounds are displayed in **Table 37**:

Table 37

Example Number	CXCR7 EC50 (nM)	Example Number	CXCR7 EC50 (nM)	Example Number	CXCR7 EC50 (nM)	Example Number	CXCR7 EC50 (nM)
1	79	147	16	291	92	435	7
2	144	148	54	292	103	436	9
3	42	149	0.6	293	20	437	5
4	47	150	1	294	237	438	15
5	187	151	34	295	411	439	3
6	60	152	8	296	430	440	15
7	32	Reference example 153	285	297	461	441	5
8	230	154	29	298	114	442	10
9	451	155	17	299	291	443	147
10	337	156	1	300	96	444	15
11	52	157	9	301	208	445	11
12	194	158	2	302	27	446	4
13	37	159	72	303	246	447	1
14	53	160	15	304	311	448	2
15	15	161	4	305	230	449	1
16	63	162	46	306	39	450	1
17	135	163	17	307	423	451	1
18	61	164	84	308	28	452	4
19	102	165	61	309	24	453	6
20	11	166	6	310	78	454	3
21	39	167	39	311	24	455	10
22	80	168	20	312	37	456	8
23	16	169	42	313	31	457	232

24	28	170	74	314	23	458	109
25	309	171	18	315	5	459	59
26	442	172	2	316	370	460	85
27	19	173	5	317	5	461	420
28	63	174	0.8	318	7	463	16
29	174	175	339	319	443	464	36
30	283	176	26	320	154	465	39
31	13	177	14	321	244	466	13
32	28	178	25	322	119	467	14
33	16	179	3	323	182	468	10
34	132	180	8	324	243	469	5
35	4	181	117	325	334	470	15
36	25	182	69	326	184	471	21
37	4	183	140	327	20	472	21
38	3	184	270	328	293	473	102
39	4	185	79	329	23	474	47
40	44	186	91	330	11	475	121
41	5	187	34	331	314	476	15
42	5	188	71	332	96	477	63
43	2	189	37	333	2	478	92
44	3	190	110	334	13	479	78
45	8	191	59	335	23	480	28
46	3	192	38	336	47	481	41
47	2	193	48	337	429	482	32
48	52	194	13	338	279	483	33
49	16	195	12	339	457	484	79
50	6	196	264	340	277	485	8
51	3	197	257	341	397	486	5
52	17	198	388	342	110	487	100

53	23	199	255	343	415	488	91
54	7	200	235	344	438	489	7
55	43	201	27	345	400	490	21
56	70	202	23	346	73	491	21
57	24	203	8	347	445	492	41
58	16	204	40	348	13	493	249
59	147	205	13	349	12	494	28
60	1	206	26	350	32	495	63
61	5	207	5	351	34	496	79
62	1	208	248	352	4	497	77
63	19	209	51	353	85	498	118
64	8	210	5	354	11	499	245
65	150	211	2	355	10	500	31
66	168	211a	1	356	6	501	54
67	115	211b	6	357	4	502	113
68	330	212	6	358	26	503	65
69	418	213	2	359	9	504	93
70	189	214	3	360	30	505	42
71	326	215	108	361	6	506	155
72	28	216	34	362	21	507	74
73	66	217	2	363	3	508	34
74	49	218	2	363a	6	509	36
75	137	219	3	363b	5	510	109
76	2	220	3	364	44	511	29
77	46	221	9	365	35	512	56
78	376	222	27	366	2	513	377
79	135	223	10	367	115	514	6
80	47	224	52	368	3	515	382
81	126	225	29	369	92	516	181

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82	158	226	13	370	40	517	302
83	88	227	6	371	16	518	9
84	272	228	117	372	271	519	250
85	187	229	38	373	67	520	188
86	23	230	81	374	5	521	269
87	3	231	1	375	6	522	140
88	11	232	162	376	27	523	58
89	8	233	72	377	276	524	27
90	32	234	3	378	321	525	41
91	1	235	107	379	3	526	44
92	413	236	3	380	6	527	162
93	88	237	5	381	9	528	42
94	452	238	43	382	8	529	174
95	432	239	23	383	51	530	174
96	249	240	15	384	4	531	6
97	365	241	8	385	7	532	30
98	224	242	24	386	12	533	359
99	177	243	8	387	12	534	395
100	376	244	3	388	13	535	355
101	148	245	3	389	20	536	92
102	370	246	14	390	83	537	217
103	97	247	29	391	49	538	155
Reference example 104	233	248	32	392	30	539	115
105	9	249	12	393	110	540	220
106	100	250	31	394	9	541	175
107	43	251	24	395	32	542	113
108	52	252	426	396	38	543	84
109	73	253	42	397	35	544	34

110	14	254	161	398	82	545	80
111	32	255	390	399	64	546	8
112	40	256	11	400	31	547	15
113	26	257	29	401	250	548	133
114	36	258	27	402	198	549	257
115	54	259	5	403	24	550	2
116	96	260	125	404	60	551	35
117	79	261	47	405	257	552	4
118	126	262	62	406	80	553	14
119	87	263	127	407	326	554	5
120	154	264	374	408	10	555	6
121	101	265	48	409	8	556	8
122	337	266	16	410	5	557	5
123	120	267	33	411	15	558	59
124	52	268	350	412	20	559	13
125	240	269	54	413	8	560	5
126	249	270	7	414	37	561	7
127	395	271	10	415	178	562	100
128	290	272	230	416	86	563	26
129	449	273	144	417	15	564	17
130	390	274	179	418	148	565	4
131	450	275	43	419	6	566	3
132	130	276	17	420	21	567	4
133	20	277	28	421	29	568	29
134	2	278	79	422	33	569	26
135	9	279	8	423	79	570	14
136	1	280	28	424	60	571	86
137	45	281	43	425	27	572	5
138	55	282	47	426	74	573	3

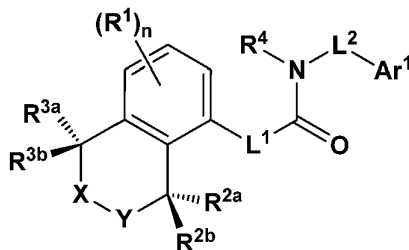
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139	55	283	11	427	106	574	6
140	54	284	18	428	120	575	0.9
141	98	285	408	429	7	576	6
142	23	286	37	430	9	577	0.9
143	3	287	150	431	120		
144	22	288	23	432	42		
145	8	289	16	433	166		
146	2	290	5	434	20		

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Claims

1. A compound of formula (I)



Formula (I)

5 wherein

- **X** represents NR^5 , and **Y** represents CHR^Y wherein R^Y represents hydrogen, or (C_{1-3}) alkyl; and
 - R^{3a} and R^{3b} together with the carbon atom to which they are attached to form a carbonyl group, or
 - two of R^{2a} , R^{2b} , R^{3a} and R^{3b} independently represent hydrogen, or (C_{1-3}) alkyl; and the remaining of R^{2a} , R^{2b} , R^{3a} and R^{3b} represent hydrogen; or
- **X** represents CHR^X wherein R^X represents hydrogen, or (C_{1-3}) alkyl, and **Y** represents NR^5 ; and
 - R^{2a} and R^{2b} together with the carbon atom to which they are attached to form a carbonyl group, or
 - two of R^{2a} , R^{2b} , R^{3a} and R^{3b} independently represent hydrogen, or (C_{1-3}) alkyl; and the remaining of R^{2a} , R^{2b} , R^{3a} and R^{3b} represent hydrogen; or
- **X** represents NR^5 and **Y** represents a direct bond; R^{2a} and R^{2b} both represent hydrogen; and R^{3a} and R^{3b} both represent hydrogen; or
- **X** represents NR^5 , **Y** represents $-\text{C}(\text{O})-$; and R^{2a} , R^{2b} , R^{3a} and R^{3b} all represent hydrogen; or
- **X** represents $-\text{C}(\text{O})-$, **Y** represents NR^5 ; and R^{2a} , R^{2b} , R^{3a} and R^{3b} all represent hydrogen;

 R^5 represents

- (C_{1-6}) alkyl;
- (C_{1-4}) alkyl mono-substituted with (C_{1-3}) alkoxy, cyano, vinyl; ethynyl, or (C_{1-3}) alkoxy-carbonyl;
- $-\text{CO}-\text{R}^{10}$ wherein R^{10} represents (C_{1-5}) alkyl; (C_{1-5}) alkoxy; phenyl; phenyl-oxy-; phenyl- (C_{1-3}) alkyl-; phenyl- (C_{1-3}) alkyl-oxy-; (C_{3-6}) cycloalkyl- (C_{1-3}) alkyl; (C_{3-4}) alkenoxyl;

- (C₃₋₄)alkynoxy; (C₁₋₃)fluoroalkyl; (C₁₋₃)fluoroalkoxy; (C₁₋₃)alkoxy-(C₂₋₃)alkoxy; (C₁₋₃)alkoxy-(C₁₋₃)alkyl; (C₃₋₆)cycloalkyl optionally containing one ring oxygen atom, wherein said cycloalkyl is optionally mono- or di-substituted wherein the substituents independently are fluoro or (C₁)fluoroalkyl; unsubstituted 5-membered heteroaryl; or
- 5 -NR^{10a}R^{10b} wherein R^{10a} and R^{10b} independently represent hydrogen, (C₁₋₄)alkyl or (C₃₋₆)cycloalkyl, or R^{10a} and R^{10b} together with the nitrogen to which they are attached to form a 5- to 7-membered saturated ring;
- -SO₂-R¹¹ wherein R¹¹ represents (C₁₋₅)alkyl or phenyl;
 - (C₂₋₄)fluoroalkyl;
- 10 • (C₃₋₆)cycloalkyl optionally containing one ring oxygen atom;
- (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl, wherein the (C₃₋₆)cycloalkyl group optionally contains one ring oxygen atom; wherein said cycloalkyl is optionally substituted with one or two methyl substituents;
- 15 • phenyl-(C₀₋₃)alkyl-, or 5- or 6-membered heteroaryl-(C₀₋₃)alkyl-, wherein the phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, or mono-, or di-substituted, wherein the substituents are independently selected from (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, (C₁₋₃)fluoroalkyl, (C₁₋₃)fluoroalkoxy, and cyano;
- (R¹)_n represents one or two optional substituents independently selected from (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, (C₁₋₃)fluoroalkyl, (C₁₋₃)fluoroalkoxy, and cyano;
- 20 L¹ represents a one- or two-membered linker group selected from -NH-CH₂-*, -NR^{16a}-CH₂-* wherein R^{16a} represents (C₁₋₃)alkyl; -NH-CHR^{16b}-* wherein R^{16b} represents (C₁₋₃)alkyl; -NH-CR^{16c}R^{16d}-* wherein R^{16c} and R^{16d} together with the carbon to which they are attached to form a (C₃₋₆)cycloalkyl ring; -CH₂-NH-*; -O-CH₂-*; -O-CHR^{17a}-* wherein R^{17a} represents (C₁₋₃)alkyl; -O-CR^{17b}R^{17c}-* wherein R^{17b} and R^{17c} together with the carbon to which they are
- 25 attached to form a (C₃₋₆)cycloalkyl ring; -CH₂-; -CH₂CH₂-; -CH=CH-; and -CH=C(CH₃)-*; wherein the asterisks indicate the bond with which the group L¹ is attached to the carbonyl group;
- L² represents -(C₁₋₄)alkylene- or -(C₃₋₄)alkenylene-;
- Ar¹ represents phenyl, or 5- or 6-membered heteroaryl; wherein said phenyl or 5- or 6-
- 30 membered heteroaryl independently is unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from (C₁₋₄)alkyl; (C₁₋₄)alkoxy; (C₁₋₃)fluoroalkyl; (C₁₋₃)fluoroalkoxy; halogen; cyano; or NR^{18a}R^{18b} wherein R^{18a} and R^{18b} independently represent hydrogen or (C₁₋₃)alkyl; and

R^4 represents

- (C_{2-6}) alkyl;
- (C_{2-5}) alkyl which is mono-substituted with (C_{1-4}) alkoxy, benzyloxy, cyano, or hydroxy; or disubstituted wherein the substituents are independently selected from (C_{1-3}) alkoxy, or hydroxy
- (C_{2-3}) fluoroalkyl which is optionally further substituted with one hydroxy;
- $-(C_{2-4})$ alkylene- NR^6R^7 , wherein R^6 and R^7 independently represent hydrogen; (C_{1-4}) alkyl; $-CO-(C_{1-4})$ alkoxy; (C_{3-5}) alkenyl; (C_{3-4}) alkynyl; benzyl; $-SO_2-(C_{1-3})$ alkyl; (C_{2-3}) fluoroalkyl; or (C_{3-6}) cycloalkyl or (C_{3-6}) cycloalkyl- (C_{1-3}) alkyl, wherein in the above groups the (C_{3-6}) cycloalkyl group optionally contains one ring oxygen atom, and wherein said (C_{3-6}) cycloalkyl group is optionally substituted with methyl;
- $-(C_{1-3})$ alkylene- $CO-R^8$, wherein R^8 represents (C_{1-4}) alkoxy; or R^8 represents $NR^{81}R^{82}$ wherein R^{81} and R^{82} independently represent hydrogen or (C_{1-4}) alkyl, or R^{81} and R^{82} together with the nitrogen to which they are attached to form a 4- to 6-membered saturated ring optionally substituted with two fluoro substituents;
- $-(C_{1-3})$ alkylene- SO_2-R^9 wherein R^9 represents (C_{1-3}) alkyl, or amino;
- (C_{3-6}) cycloalkyl or (C_{3-6}) cycloalkyl- (C_{1-3}) alkyl, wherein the cycloalkyl group is optionally mono-substituted with $-CO-(C_{1-4})$ alkoxy or hydroxy;
- (C_{4-7}) heterocyclyl or (C_{4-7}) heterocyclyl- (C_{1-3}) alkyl, wherein in the above groups the (C_{4-7}) heterocyclyl independently contains one or two ring heteroatoms independently selected from nitrogen, sulfur and oxygen; wherein in the above groups said (C_{4-7}) heterocyclyl independently is unsubstituted, or mono-, di-, or tri-substituted wherein the substituents are independently selected from:
 - one oxo substituent attached to a ring carbon atom in alpha position to a ring nitrogen; and / or
 - two methyl substituents attached to a ring carbon atom in alpha position to a ring nitrogen atom; and / or
 - two oxo substituents at a ring sulfur ring atom; and / or
 - (C_{1-4}) alkyl or $-CO-(C_{1-4})$ alkoxy attached to a ring nitrogen atom having a free valency; and/or
 - two fluoro substituents attached to a ring carbon atom; and/or
 - in case of a (C_{4-7}) heterocyclyl- (C_{1-3}) alkyl group, methyl attached to a ring carbon atom which is attached to the linking (C_{1-3}) alkyl group;
- 2-oxo-2,3-dihydropyridin-4-yl- (C_{1-2}) alkyl;
- phenyl- (C_{1-3}) alkyl-, or 5- or 6-membered heteroaryl- (C_{1-3}) alkyl-, wherein the phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono-, or di-substituted,

wherein the substituents are independently selected from (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, (C₁₋₃)fluoroalkyl, (C₁₋₃)fluoroalkoxy, and cyano;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1; wherein

5 • X represents NR⁵ and:

- Y represents CH₂; and R^{2a}, R^{2b} R^{3a} and R^{3b} represent hydrogen; or
- Y represents CHR^Y wherein R^Y represents (C₁₋₃)alkyl; and R^{2a}, R^{2b} R^{3a} and R^{3b} represent hydrogen; or
- Y represents CH₂; R^{2a} and R^{2b} both represent (C₁₋₃)alkyl; and R^{3a} and R^{3b} both represent hydrogen; or
- Y represents CH₂; R^{2a} and R^{2b} both represent hydrogen; one of R^{3a} and R^{3b} represents (C₁₋₃)alkyl, and the remaining of R^{3a} and R^{3b} represents hydrogen;

• or Y represents NR⁵ and:

- X represents CH₂; and R^{2a}, R^{2b} R^{3a} and R^{3b} represent hydrogen; or
- X represents CHR^X wherein R^X represents (C₁₋₃)alkyl; and R^{2a}, R^{2b} R^{3a} and R^{3b} represent hydrogen; or
- X represents CH₂; R^{3a} and R^{3b} both represent (C₁₋₃)alkyl; and R^{2a} and R^{2b} both represent hydrogen; or
- X represents CH₂; R^{3a} and R^{3b} both represent hydrogen; one of R^{2a} and R^{2b} represents (C₁₋₃)alkyl, and the remaining of R^{2a} and R^{2b} represents hydrogen;

or a pharmaceutically acceptable salt thereof.

3. A compound according to claims 1 or 2; wherein R⁵ represents

- (C₁₋₆)alkyl;
- (C₁₋₄)alkyl mono-substituted with (C₁₋₃)alkoxy;
- -CO-R¹⁰ wherein R¹⁰ represents (C₁₋₅)alkyl; (C₁₋₅)alkoxy; phenyl; phenyl-oxy-; phenyl-(C₁₋₃)alkyl-; phenyl-(C₁₋₃)alkyl-oxy-; (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl; (C₃₋₄)alkenoxy; (C₃₋₄)alkynoxy; (C₁₋₃)fluoroalkyl; (C₁₋₃)fluoroalkoxy; (C₁₋₃)alkoxy-(C₂₋₃)alkoxy; (C₁₋₃)alkoxy-(C₁₋₃)alkyl; (C₃₋₆)cycloalkyl optionally containing one ring oxygen atom, wherein said cycloalkyl is optionally mono- or di-substituted wherein the substituents independently are fluoro or (C₁)fluoroalkyl; or -NR^{10a}R^{10b} wherein R^{10a} and R^{10b} independently represent hydrogen, (C₁₋₄)alkyl or (C₃₋₆)cycloalkyl, or R^{10a} and R^{10b} together with the nitrogen to which they are attached to form a 5- to 7-membered saturated ring;
- -SO₂-R¹¹ wherein R¹¹ represents (C₁₋₅)alkyl or phenyl;

- (C₂₋₄)fluoroalkyl;
- (C₃₋₆)cycloalkyl optionally containing one ring oxygen atom;
- (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl, wherein the (C₃₋₆)cycloalkyl group optionally contains one ring oxygen atom; wherein said cycloalkyl is optionally substituted with one methyl substituent;
- phenyl-(C₁₋₃)alkyl-, wherein the phenyl is unsubstituted; or
- 5- or 6-membered heteroaryl wherein the 5- or 6-membered heteroaryl is unsubstituted, or mono-, or di-substituted, wherein the substituents are independently selected from (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, (C₁₋₃)fluoroalkyl, (C₁₋₃)fluoroalkoxy, and cyano;

or a pharmaceutically acceptable salt thereof.

4. A compound according to claims 1 or 2; wherein **R**⁵ represents

- (C₁₋₆)alkyl;
- (C₁₋₄)alkyl mono-substituted with (C₁₋₃)alkoxy;
- -CO-**R**¹⁰ wherein **R**¹⁰ represents (C₁₋₅)alkyl; (C₁₋₃)alkoxy-(C₁₋₃)alkyl; or (C₃₋₆)cycloalkyl optionally containing one ring oxygen atom, wherein said cycloalkyl is unsubstituted, or mono- or di-substituted with fluoro;
- (C₂₋₄)fluoroalkyl;
- (C₃₋₆)cycloalkyl optionally containing one ring oxygen atom; or
- (C₃₋₆)cycloalkyl-(C₁₋₃)alkyl;

or a pharmaceutically acceptable salt thereof.

5. A compound according to any one of claims 1 to 4; wherein (**R**¹)_n represents one optional substituent independently selected from (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, (C₁₋₃)fluoroalkyl, (C₁₋₃)fluoroalkoxy, and cyano;

or a pharmaceutically acceptable salt thereof.

6. A compound according to any one of claims 1 to 5; wherein **L**¹ represents a two-membered linker group selected from -NH-CH₂*, -O-CH₂*, -CH₂CH₂-, and -CH=CH-; wherein the asterisks indicate the bond with which the group **L**¹ is attached to the carbonyl group;

or a pharmaceutically acceptable salt thereof.

7. A compound according to any one of claims 1 to 6; wherein **L**² represents -CH₂-;

or a pharmaceutically acceptable salt thereof.

8. A compound according to any one of claims 1 to 7; wherein Ar^1 represents

- phenyl which is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from (C_{1-4}) alkyl; (C_{1-4}) alkoxy; (C_{1-3}) fluoroalkyl; (C_{1-3}) fluoroalkoxy; halogen; and cyano; or
- 5 • 6-membered heteroaryl; which is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from (C_{1-4}) alkyl; (C_{1-4}) alkoxy; (C_{1-3}) fluoroalkyl; (C_{1-3}) fluoroalkoxy; halogen; and cyano;

or a pharmaceutically acceptable salt thereof.

9. A compound according to any one of claims 1 to 8; wherein R^4 represents

- 10 • (C_{2-5}) alkyl which is mono-substituted with hydroxy; or disubstituted wherein the substituents are independently methoxy or hydroxy;
- $-(\text{C}_{2-4})$ alkylene- NR^6R^7 , wherein R^6 represents hydrogen or (C_{1-4}) alkyl; and R^7 represents (C_{1-4}) alkyl; (C_{2-3}) fluoroalkyl; (C_{3-6}) cycloalkyl; or (C_{3-6}) cycloalkyl- (C_{1-3}) alkyl;
- 15 • (C_{3-6}) cycloalkyl- (C_{1-3}) alkyl, wherein the cycloalkyl group is optionally mono-substituted with hydroxy;
- (C_{4-7}) heterocyclyl or (C_{4-7}) heterocyclyl- (C_{1-3}) alkyl, wherein in the above groups the (C_{4-7}) heterocyclyl independently contains one or two ring heteroatoms independently selected from nitrogen and oxygen; wherein in the above groups said (C_{4-7}) heterocyclyl independently is unsubstituted, or mono-, or di-substituted wherein
- 20 the substituents are independently selected from:
 - one oxo substituent attached to a ring carbon atom in alpha position to a ring nitrogen; and / or
 - (C_{1-4}) alkyl attached to a ring nitrogen atom having a free valency; or
 - two fluoro substituents attached to a ring carbon atom;

25 or a pharmaceutically acceptable salt thereof.

10. A compound according to any one of claims 1 to 8; wherein R^4 represents

- 2-methoxy-ethyl, 2-hydroxy-ethyl, 2-hydroxy-propyl, 2-hydroxy-2-methyl-propyl, 3-hydroxy-3-methyl-butyl, or 2-methoxy-ethyl;
- 2-hydroxy-3-methoxy-propyl;
- 30 • $-(\text{C}_{2-4})$ alkylene- NR^6R^7 selected from 2-amino-ethyl, 2-methylamino-ethyl, 2-dimethylamino-ethyl, 2-diethylamino-ethyl, 3-(dimethylamino)-propyl, 2-(butyl-methylamino)-ethyl, 2-ethylamino-ethyl, 2-(ethyl-methylamino)-ethyl, 2-(isopropyl-methylamino)-ethyl, 2-(diisopropylamino)-ethyl, 2-[(2-fluoroethyl)-methylamino]-ethyl, 2-[(2,2,2-trifluoroethyl)-amino]-ethyl, 2-[methyl-(2,2,2-trifluoroethyl)-amino]-ethyl, 2-
- 35 [(2-fluoro-1-methylethyl)-methylamino]-ethyl, 2-[(cyclopropyl)-methylamino]-ethyl, 2-

[(cyclopropylmethyl)-methylamino]-ethyl, 2-[(cyclobutyl)-methylamino]-ethyl, and 2-[(cyclopentyl)-methylamino]-ethyl;

- (1-hydroxy-cyclopentyl)-methyl;
- (C₄₋₇)heterocyclyl selected from pyrrolidin-3-yl, 1-methyl-pyrrolidin-3-yl, piperidin-3-yl, 1-methyl-piperidin-3-yl, piperidin-4-yl, 1-methyl-piperidin-4-yl, and tetrahydro-pyran-4-yl;
- (C₄₋₇)heterocyclyl-(C₁₋₃)alkyl selected from 2-(pyrrolidin-1-yl)-ethyl, 2-(1-methyl-pyrrolidin-2-yl)-ethyl, 2-(morpholin-4-yl)-ethyl, pyrrolidin-3-yl-methyl, 3-(pyrrolidin-1-yl)-propyl, [1,4]dioxan-2-yl-methyl, 2-(piperazin-1-yl)-ethyl, 2-(piperidin-1-yl)-ethyl, 2-(azepan-1-yl)-ethyl, 2-(3,3-difluoroazetidin-1-yl)-ethyl, 2-(3,3-difluoropyrrolidin-1-yl)-ethyl, 2-(3,3-difluoropiperdin-1-yl)-ethyl, and 2-(4,4-difluoropiperdin-1-yl)-ethyl;

or a pharmaceutically acceptable salt thereof.

11. A compound according to claim 1 selected from the group consisting of:

- N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-pyrrolidin-1-yl-ethyl)-acetamide;
- 15 N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-pyrrolidin-1-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-Benzyl-N-(3-dimethylamino-propyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide;
- 20 N-(2-Dimethylamino-ethyl)-N-(2-methyl-benzyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide;
- N-(2-Chloro-benzyl)-N-(2-dimethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide;
- N-(2-Dimethylamino-ethyl)-N-(3-fluoro-benzyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide;
- 25 N-(2-Dimethylamino-ethyl)-N-(2-fluoro-benzyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide;
- N-Benzyl-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-acetamide;
- N-Benzyl-N-(2-diethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide;
- 30 N-Benzyl-N-[2-(butyl-methyl-amino)-ethyl]-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide;
- N-Benzyl-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3-trifluoromethyl-benzyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 35 acetamide;

- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-phenethyl-acetamide;
- N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3-dimethylamino-propyl)-acetamide;
- 5 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-fluoro-benzyl)-acetamide;
- N-(3-Chloro-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-o-tolyl-ethyl)-acetamide;
- 10 N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-acetamide;
- N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-acetamide;
- N-(2-Chloro-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-acetamide;
- 15 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-fluoro-benzyl)-N-(2-pyrrolidin-1-yl-ethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-((E)-2-methyl-3-phenyl-allyl)-acetamide;
- 20 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(6-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-N-phenethyl-acetamide;
- 25 N-(2-Chloro-4-fluoro-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2,4-difluoro-benzyl)-N-(2-pyrrolidin-1-yl-ethyl)-acetamide;
- 30 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-N-(3-phenyl-propyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-N-((E)-3-phenyl-allyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(4-fluoro-2-trifluoromethyl-benzyl)-acetamide;
- 35

- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-[2-(3-trifluoromethyl-phenyl)-ethyl]-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-[2-(2-trifluoromethyl-phenyl)-ethyl]-acetamide;
- 5 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-[1-(2-trifluoromethyl-phenyl)-ethyl]-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-diethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-((E)-2-methyl-3-phenyl-allyl)-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-acetamide;
- 10 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(2-oxo-pyrrolidin-1-yl)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 15 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-morpholin-4-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Cyano-ethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(tetrahydro-pyran-4-yl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 20 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(4-methyl-thiazol-2-ylmethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 25 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[1-(1-ethyl-1H-pyrazol-3-yl)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-[2-(2,2,2-trifluoro-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-[(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-methyl-amino]-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 30 2-(6-Chloro-2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-6-methoxy-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 35 5-(((2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-4,4-dimethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester;

- 2-(2-Cyclopropylmethyl-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(1-methyl-piperidin-4-yl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 5 N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide;
N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide;
N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-isobutyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide;
5-({[Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methyl}-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid
- 10 methyl ester;
N-Benzyl-2-(2-butyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
N-(2-Chloro-benzyl)-N-(2-dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide;
N-(2-Chloro-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- 15 N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(1-methyl-piperidin-3-yl)-N-(2-trifluoromethyl-benzyl)-acetamide;
2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(1-methyl-piperidin-4-yl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 20 (E)-N-Benzyl-N-(2-dimethylamino-ethyl)-3-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-acrylamide;
(E)-N-Benzyl-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-acrylamide;
{Benzyl-[(E)-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-acryloyl]-amino}-acetic acid ethyl ester;
(E)-N-(2-Chloro-benzyl)-N-(2-dimethylamino-ethyl)-3-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-acrylamide;
- 25 (E)-N-(2-Chloro-benzyl)-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-acrylamide;
(E)-N-Benzyl-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(1,1-dioxo-tetrahydro-1H-thiophen-3-yl)-acrylamide;
(E)-N-(2-Dimethylamino-ethyl)-3-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-trifluoromethyl-benzyl)-acrylamide;
- 30 (E)-3-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acrylamide;
(E)-3-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(1-methyl-piperidin-4-yl)-N-(2-trifluoromethyl-benzyl)-acrylamide;
- 35 (E)-3-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(1-methyl-piperidin-4-yl)-N-(2-trifluoromethyl-benzyl)-acrylamide;

- (E)-3-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-2-methyl-N-(2-trifluoromethyl-benzyl)-acrylamide;
- N-(2-Chloro-benzyl)-N-(2-dimethylamino-ethyl)-3-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-propionamide;
- N-(2-Chloro-benzyl)-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-
- 5 propionamide;
- N-(2-Dimethylamino-ethyl)-3-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-trifluoromethyl-benzyl)-propionamide;
- 3-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-propionamide;
- 10 3-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(1-methyl-piperidin-4-yl)-N-(2-trifluoromethyl-benzyl)-propionamide;
- N-Benzyl-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-propionamide;
- N-Benzyl-N-(2-dimethylamino-ethyl)-3-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-propionamide;
- N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-N-(3-methyl-butyl)-acetamide;
- 15 N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-N-(2-dimethylamino-ethyl)-acetamide;
- 5-[[Benzyl-(2-dimethylamino-ethyl)-carbamoyl]-methoxy]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid methyl ester;
- N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-isobutyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-acetamide;
- N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-acetamide;
- 20 N-(2-Chloro-benzyl)-N-(2-dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-acetamide;
- N-(2-Chloro-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-N-(2-dimethylamino-ethyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 25 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-N-(2-fluoro-benzyl)-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetamide;
- N-(2-Methylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 30 N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-pyrrolidin-3-yl-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(1-methyl-pyrrolidin-3-yl)-acetamide;
- N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- 35 N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-isobutyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide;

- 8-([Benzy-(2-dimethylamino-ethyl)-carbamoyl]-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid isopropyl ester;
- N-Benzyl-2-(2-benzyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- N-Benzyl-2-(2-cyclohexylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- 5 2-(2-Benzoyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-benzyl-N-(2-dimethylamino-ethyl)-acetamide;
- N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-acetamide;
- N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-acetamide;
- N-Benzyl-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-N-(2-dimethylamino-ethyl)-acetamide;
- 8-([Benzy-(2-dimethylamino-ethyl)-carbamoyl]-methoxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid methyl ester;
- 10 N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-isobutyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-acetamide;
- N-Benzyl-N-(2-dimethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-acetamide;
- 2-(2-Benzoyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-N-benzyl-N-(2-dimethylamino-ethyl)-acetamide;
- 2-((2-Cyclopentyl-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(dimethylamino)ethyl)-N-(2-
- 15 (trifluoromethyl)benzyl)acetamide;
- 2-((2-(Cyclopropylmethyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(dimethylamino)ethyl)-N-(2-(trifluoromethyl)benzyl)acetamide; and
- 2-((2-(Cyclopropylmethyl)-3-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)amino)-N-(2-(dimethylamino)ethyl)-N-(2-(trifluoromethyl)benzyl)acetamide;
- 20 or a pharmaceutically acceptable salt thereof.
- 12.** A compound according to claim 1 selected from the group consisting of:
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3-pyrrolidin-1-yl-propyl)-N-(2-trifluoromethyl-
- 25 benzyl)-acetamide;
- 4-{2-[[2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]-(2-trifluoromethyl-benzyl)-amino]-ethyl}-piperazine-1-carboxylic acid tert-butyl ester;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-piperidin-1-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 30 N-(2-Azepan-1-yl-ethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-diisopropylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-[2-(Cyclopropyl-methyl-amino)-ethyl]-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-
- 35 trifluoromethyl-benzyl)-acetamide;

- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-trifluoromethoxy-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(4-hydroxy-cyclohexyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 5 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-hydroxy-3-methoxy-propyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methoxy-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[1,4]dioxan-2-ylmethyl-N-(2-trifluoromethyl-benzyl)-acetamide;
- 10 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethoxy-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methanesulfonyl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 15 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(ethyl-methyl-amino)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Bromo-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- N-(3-Bromo-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- 20 N-(3-Bromo-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- N-(4-Bromo-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- 25 N-(3-Bromo-pyridin-4-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-hydroxy-propyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-hydroxy-2-methyl-propyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 30 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3,3,3-trifluoro-2-hydroxy-propyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(1-hydroxy-cyclopentylmethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 35 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-{2-[(2-fluoro-ethyl)-methyl-amino]-ethyl}-N-(2-trifluoromethyl-benzyl)-acetamide;

- N-[2-(Allyl-methyl-amino)-ethyl]-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(methyl-prop-2-ynyl-amino)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 5 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-thiazol-5-ylmethyl-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Chloro-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-acetamide;
- N-(3-Chloro-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-acetamide;
- 10 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-isoxazol-5-ylmethyl-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(3-Chloro-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-hydroxy-2-methyl-propyl)-acetamide;
- 15 3-[[[2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-acetyl]-(2-trifluoromethyl-benzyl)-amino]-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-methyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-pyridin-2-ylmethyl-
- 20 acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(5-methyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(6-methyl-pyridin-2-ylmethyl)-acetamide;
- 25 N-(5-Chloro-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-thiazol-2-ylmethyl-
- acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(4-methyl-thiazol-
- 30 2-ylmethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(5-fluoro-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2,6-difluoro-benzyl)-N-(2-dimethylamino-ethyl)-acetamide;
- 35 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-fluoro-pyridin-2-ylmethyl)-acetamide;

- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3,3-dimethyl-butyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3,3-dimethyl-butyl)-N-(3-methyl-pyridin-2-ylmethyl)-acetamide;
- 5 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-{2-[methyl-(2,2,2-trifluoro-ethyl)-amino]-ethyl}-
- 10 N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(3,3-difluoro-piperidin-1-yl)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(3,3-difluoro-pyrrolidin-1-yl)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 15 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(3,3-difluoro-piperidin-1-yl)-ethyl]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(3,3-difluoro-pyrrolidin-1-yl)-ethyl]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-[2-(2-fluoro-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-
- 20 benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-8-fluoro-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-8-fluoro-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 25 2-(2-Cyclopropylmethyl-6-methyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(3-Chloro-pyridin-2-ylmethyl)-N-(2-dimethylamino-ethyl)-2-[2-((1S*,2S*)-2-fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-acetamide;
- N-[2-[(2-Fluoro-ethyl)-methyl-amino]-ethyl]-2-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-
- 30 trifluoromethyl-benzyl)-acetamide;
- N-(3-Chloro-pyridin-2-ylmethyl)-N-(2-dimethylamino-ethyl)-2-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-prop-2-ynyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 35 N-(2-Dimethylamino-ethyl)-2-(2-ethyl-3-oxo-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;

- 2-(2-Ethyl-3-oxo-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-isobutyl-3-oxo-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 5 N-(2-Dimethylamino-ethyl)-2-(2-isobutyl-3-oxo-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Isobutyl-3-oxo-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1-oxo-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 10 (E)-N-(2-Dimethylamino-ethyl)-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-N-(2-trifluoromethyl-benzyl)-acrylamide;
- (E)-N-(2-Dimethylamino-ethyl)-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acrylamide;
- 15 (E)-N-(3-Chloro-pyridin-2-ylmethyl)-N-(2-dimethylamino-ethyl)-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-acrylamide;
- (E)-N-(3-Chloro-pyridin-2-ylmethyl)-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-hydroxy-2-methyl-propyl)-acrylamide;
- (E)-N-(3-Chloro-pyridin-2-ylmethyl)-N-(2-dimethylamino-ethyl)-3-[2-((1R*,2R*)-2-fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-acrylamide;
- 20 (E)-N-(3-Chloro-pyridin-2-ylmethyl)-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-acrylamide;
- (E)-N-(3-Chloro-pyridin-2-ylmethyl)-3-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-acrylamide;
- 25 N-(2-Dimethylamino-ethyl)-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-N-(2-trifluoromethyl-benzyl)-propionamide;
- N-(2-Dimethylamino-ethyl)-3-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-propionamide;
- N-[2-(Allyl-methyl-amino)-ethyl]-3-(2-allyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-trifluoromethyl-benzyl)-propionamide;
- 30 3-(2-Allyl-1,2,3,4-tetrahydro-isoquinolin-5-yl)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-propionamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-yloxy)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-propionamide;
- 35 N-(2-Dimethylamino-ethyl)-2-[2-(tetrahydro-furan-3-yl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;

- 2-(2-Cyclobutyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-[2-(2-methoxy-1-methyl-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 5 N-(2-Dimethylamino-ethyl)-2-[2-(1,2-dimethyl-propyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-sec-Butyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-[2-(1-Cyclopropyl-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 10 N-(2-Dimethylamino-ethyl)-2-[2-(3-methyl-oxetan-3-ylmethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 15 [5-(((2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino]-3,4-dihydro-1H-isoquinolin-2-yl]-acetic acid methyl ester;
- 2-(2-Cyclobutylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-[2-(2,2-Difluoro-propionyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 20 N-(2-Dimethylamino-ethyl)-2-[2-((1R*,2R*)-2-fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyanomethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 25 N-(2-Dimethylamino-ethyl)-2-[2-(tetrahydro-furan-3-yl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Cyclobutyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Cyclobutylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 30 [5-(((2-Dimethylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino]-3,4-dihydro-1H-isoquinolin-2-yl]-acetic acid methyl ester;
- N-(2-Dimethylamino-ethyl)-2-[2-(2-methoxy-ethyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 35 N-(2-Dimethylamino-ethyl)-2-(2-pyridin-2-yl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;

- N-(2-Dimethylamino-ethyl)-2-(2-pyrimidin-2-yl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-2-[2-(4-trifluoromethyl-thiazol-2-yl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-acetamide;
- 5 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(R)-1-pyrrolidin-3-ylmethyl-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(S)-1-pyrrolidin-3-ylmethyl-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-pyrrolidin-3-yl-N-(2-trifluoromethyl-benzyl)-acetamide;
- 10 2-(2-Cyclopropylmethyl-1-methyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 15 2-(2-Cyclopropanecarbonyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Butyryl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Isobutyryl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 20 2-[2-(2-Methoxy-acetyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclobutanecarbonyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 25 N-(2-Methylamino-ethyl)-2-[2-(3-methyl-butyryl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Methylamino-ethyl)-2-[2-(tetrahydro-furan-3-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 5-(((2-Methylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid methyl ester;
- 30 5-(((2-Methylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid ethyl ester;
- 5-(((2-Methylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid prop-2-ynyl ester;
- 35 5-(((2-Methylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid allyl ester;

- 5-(((2-Methylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid 2-fluoro-ethyl ester;
- 5-(((2-Methylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid ethylamide;
- 5 2-(2-Acetyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- N-(2-Methylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Cyclopropanecarbonyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 10 2-(2-Butyryl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Isobutyryl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 15 2-[2-(2-Methoxy-acetyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-methylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Cyclobutanecarbonyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- N-(2-Methylamino-ethyl)-2-[2-(tetrahydro-furan-3-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 20 5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid methyl ester;
- 5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid ethyl ester;
- 25 5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid prop-2-ynyl ester;
- 5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid allyl ester;
- 5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid 2-fluoro-ethyl ester;
- 30 5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid ethylamide;
- 5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid isopropylamide;
- 35 5-(((2-Methylamino-ethyl)-(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butylamide;

- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(2,2,2-trifluoro-ethylamino)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Bromo-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-acetamide;
- 5 N-(3-Chloro-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-piperazin-1-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 10 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-ethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-piperidin-4-yl-N-(2-trifluoromethyl-benzyl)-acetamide;
- 15 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-pyrrolidin-3-ylmethyl-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Amino-ethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 20 2-(2-Acetyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Chloro-benzyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-methylamino-ethyl)-acetamide;
- 25 N-[2-(Cyclobutyl-methyl-amino)-ethyl]-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-{2-[methyl-(tetrahydro-furan-3-yl)-amino]-ethyl}-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-[2-(isopropyl-methyl-amino)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 30 N-[2-(Cyclopropylmethyl-methyl-amino)-ethyl]-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-[2-(Cyclopentyl-methyl-amino)-ethyl]-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 35 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-{2-[(2-fluoro-1-methyl-ethyl)-methyl-amino]-ethyl}-N-(2-trifluoromethyl-benzyl)-acetamide;

- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-{2-[ethyl-(3-methyl-oxetan-3-ylmethyl)-amino]-ethyl}-N-(2-trifluoromethyl-benzyl)-acetamide;
- 3-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-yl)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-propionamide;
- 5 N-(3-Chloro-pyridin-2-ylmethyl)-2-(2-cyclobutyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- N-(3-Bromo-pyridin-2-ylmethyl)-2-(2-cyclobutyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- N-[2-(Allyl-methyl-amino)-ethyl]-2-(2-allyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 10 2-(2-Allyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethoxy-benzyl)-acetamide;
- 2-(2-Allyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-{2-[(2-fluoro-ethyl)-methyl-amino]-ethyl}-N-(2-trifluoromethyl-benzyl)-acetamide;
- 15 2-(2-Allyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-[2-(Allyl-methyl-amino)-ethyl]-3-(2-allyl-1,2,3,4-tetrahydro-isoquinolin-8-yl)-N-(2-trifluoromethyl-benzyl)-propionamide;
- 3-(2-Allyl-1,2,3,4-tetrahydro-isoquinolin-8-yl)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-propionamide;
- 20 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-[2-(Cyclopropyl-methyl-amino)-ethyl]-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 25 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-trifluoromethoxy-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethoxy-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 30 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-[2-(4,4-difluoro-piperidin-1-yl)-ethyl]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-[2-(3,3-difluoro-piperidin-1-yl)-ethyl]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 35 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-[2-(3,3-difluoro-pyrrolidin-1-yl)-ethyl]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;

- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-[2-(3,3-difluoro-azetidin-1-yl)-2-oxo-ethyl]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-[2-(3,3-difluoro-azetidin-1-yl)-2-oxo-ethyl]-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- 5 N-(3-Chloro-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- N-(3-Bromo-pyridin-2-ylmethyl)-2-(2-cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-acetamide;
- 2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 10 N-Benzyl-N-(2-diethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-fluoro-benzyl)-acetamide;
- 2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(1-methyl-piperidin-4-yl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 15 N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-methyl-benzyl)-acetamide;
- N-(2-Chloro-benzyl)-N-(2-dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(3-trifluoromethyl-benzyl)-acetamide;
- N-Benzyl-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-acetamide;
- 20 N-Benzyl-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-acetamide;
- N-(3-Chloro-pyridin-2-ylmethyl)-N-(2-dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide;
- N-(2-Diethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 25 2-(2-Ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(1-methyl-piperidin-3-yl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2,6-Difluoro-benzyl)-N-(2-dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(3-methyl-pyridin-2-ylmethyl)-acetamide;
- 30 N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(6-methyl-pyridin-2-ylmethyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(3-fluoro-pyridin-2-ylmethyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
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- N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(6-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-methanesulfonyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 5 8-(((2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid dimethylamide;
- 8-(((2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid methylamide;
- (E)-N-(2-Dimethylamino-ethyl)-3-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-yl)-N-(2-trifluoromethyl-benzyl)-
- 10 acrylamide;
- N-(2-Dimethylamino-ethyl)-2-[2-(2,2-dimethyl-propionyl)-1,2,3,4-tetrahydro-isoquinolin-8-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Benzoyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 15 8-(((2-Dimethylamino-ethyl)-(2-trifluoromethyl-benzyl)-carbamoyl)-methyl)-amino)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid isopropyl ester;
- 2-(2-Cyclohexylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-
- 20 acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-propyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-isobutyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 25 N-(2-Dimethylamino-ethyl)-2-(2-propionyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 2-(2-Cyclopropanecarbonyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-[2-(pyrrolidine-1-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-8-ylamino]-N-(2-
- 30 trifluoromethyl-benzyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-[2-(2,2-dimethyl-propyl)-1,2,3,4-tetrahydro-isoquinolin-8-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
- N-(2-Dimethylamino-ethyl)-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 35 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-pyrrolidin-1-yl-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;

- 2-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ylamino)-N-(2-dimethylamino-ethyl)-N-(3-trifluoromethyl-pyridin-2-ylmethyl)-acetamide;
 N-(2-Dimethylamino-ethyl)-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-8-yloxy)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 5 2-((R)-2-Cyclopropylmethyl-1-methyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
 2-((S)-2-Cyclopropylmethyl-1-methyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
 N-(2-Dimethylamino-ethyl)-2-[2-((1R,2R)-2-fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
- 10 N-(2-Dimethylamino-ethyl)-2-[2-((1S,2S)-2-fluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
 3-(2-Cyclopropylmethyl-1,2,3,4-tetrahydro-isoquinolin-5-ylmethyl)-1-(2-dimethylamino-ethyl)-1-(2-trifluoromethyl-benzyl)-urea;
- 15 2-[2-(2,2-Difluoro-cyclopropanecarbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-dimethylamino-ethyl)-N-(2-trifluoromethyl-benzyl)-acetamide;
 N-(2-Dimethylamino-ethyl)-2-[2-(furan-2-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-ylamino]-N-(2-trifluoromethyl-benzyl)-acetamide;
 N-(2-Dimethylamino-ethyl)-2-(2-propyl-1,2,3,4-tetrahydro-isoquinolin-5-ylamino)-N-(2-trifluoromethyl-benzyl)-acetamide;
- 20 or a pharmaceutically acceptable salt thereof.

- 13.** A pharmaceutical composition comprising, as active principle, a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.
- 25 **14.** A compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, for use as a medicament.
- 15.** Use of a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament, for the prevention or treatment of diseases or disorders selected from the group consisting of:
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 - cancers selected from carcinomas, leukemias, adenocarcinomas, malignant glioma, glioblastoma multiforme, brain metastases, multiple myelomas, renal clear cell carcinoma, prostate cancer, pancreatic adenocarcinoma, melanoma, metastatic melanoma, hepatocellular carcinoma, colon tumors, breast cancer, non-small cell lung cancer, colorectal cancer, brain tumors, Ewing's sarcoma, lymphoma, Burkitt's

- lymphoma, Hodgkin's lymphoma, adult T-cell leukemia, lymphoproliferative disease, Kaposi's sarcoma, and choriocarcinoma;
- autoimmune disorders selected from multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, lupus nephritis, interstitial cystitis, celiac disease, auto-immune encephalomyelitis, demyelinating diseases, osteoarthritis, and type I diabetes;
- inflammatory diseases selected from asthma, chronic obstructive pulmonary disorder, atherosclerosis, myocarditis, sarcoidosis, and chronic rhinosinusitis;
- transplant rejection selected from renal allograft rejection, cardiac allograft rejection, and graft-versus-host diseases brought about by hematopoietic stem cell transplantation; and
- fibrosis selected from liver fibrosis, liver cirrhosis, and idiopathic pulmonary fibrosis.

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16. Use of an effective amount of the compound of formula (I) according to claims 1 or 12, or of a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a tumor, wherein said effective amount leads to a change of the properties of said tumor, wherein said change of tumor properties is expressed by an altered recruitment of immune
5 and inflammatory infiltrating cells and/or by an inhibition of tumor vasculogenesis, and wherein said change of tumor properties is achieved by modulating the CXCL12 receptor pathway.

17. Use of a compound according to any one of claims 1 to 12, or a pharmaceutically
10 acceptable salt thereof in the manufacture of a medicament, for the prevention or treatment of cancers selected from carcinomas, leukemias, adenocarcinomas, malignant glioma, glioblastoma multiforme, brain metastases, multiple myelomas, renal clear cell carcinoma, prostate cancer, pancreatic adenocarcinoma, melanoma, metastatic melanoma, hepatocellular carcinoma, colon tumors, breast cancer, non-small cell lung cancer, colorectal
15 cancer, brain tumors, Ewing's sarcoma, lymphoma, Burkitt's lymphoma, Hodgkin's lymphoma, adult T-cell leukemia, lymphoproliferative disease, Kaposi's sarcoma, and choriocarcinoma; wherein said compound is optionally used in combination with one or more chemotherapy agents and / or radiotherapy and / or targeted therapy.