4-(HETERO)ARYL-7-(HETERO)ARYL-2-METHYL-5-OXO-1,4,5,6,7,8-HEXAHYDROQUINOLINE-3-CARBOXYLIC ACID DERIVATIVES AS CORONIN-1 MODULATORS

Field of the invention

The present invention relates to immunosuppressive compounds that deplete coronin 1 levels, in particular to coronin 1 promoter inhibitors. Accordingly, the present invention relates to a compound of formula (I), or a pharmaceutically acceptable salt, stereoisomer, diastereoisomer, enantiomer, polymorph, racemic mixture, or solvate thereof. The compound of formula (I) can be used as a medicament, in particular for inhibiting coronin 1 promoter activity in the induction of immunosuppression or in the treatment and/or prevention of a disease or disorder selected from the group consisting of transplant rejection, autoimmune diseases, inflammatory diseases, infectious diseases, and lymphoproliferative disorders. The present invention further relates to a pharmaceutical composition comprising the compound of the present invention and a pharmaceutically acceptable carrier.

Background of the invention

T cell homeostasis is central to the ability of vertebrate organisms to mount an effective immune response. Lymphocyte precursors, originating from the bone marrow, home to the thymus, where negative and positive selection results in the production of CD4 or CD8 single positive T lymphocytes. From the thymus, single positive T lymphocytes seed the peripheral organs, where they cycle for prolonged times between the secondary lymphoid organs and the blood in a naive state. Following infection, T cells become activated by dendritic cells within peripheral lymph nodes which induce massive proliferation of so-called effector T cells. After the infection has been cleared, effector cells have to be eliminated in order to maintain peripheral T cell homeostasis.

The signals that are responsible for the selection, proliferation and survival of T cells rely on stimulation of the T cell receptor by major histocompatibility complex (MHC) molecules that are present on antigen presenting molecules. While in the thymus, positive selection selects those thymocytes recognizing self-MHC molecules, negative selection ensures the elimination of those T cells that strongly recognize self-

peptides in the context of self-MHC. Together, these selection processes within the thymus ensure the generation of naive, non-autoreactive T cells for population of peripheral organs.

Coronin I, also known as coronin 1A, (*coro1a*, CORO1A), IMD8, Coronin-1, Clipin A, P57 or TACO (tryptophan aspartate containing coat protein) is a protein that is transcribed in all cells of the hematopoietic system and neurons (Ferrari, G., et al., Cell, 1999. 97(4): p. 435-47.; Pieters, J., et al., Nat Rev Immunol, 2013. 13(7): p. 510). Coronin I is a member of the WD repeat family of coronin proteins that are widely expressed in the eukaryotic kingdom (Gatfield et al., Mol Biol Cell 2005, 16, 2786-2798; Pieters, J., et al., Nat Rev Immunol, 2013. 13(7): p. 510).

A role of coronin I was suggested for mycobacterial survival within macrophage phagosomes. Coronin 1 has been shown to inhibit endosomal/lysosomal fusion, and to impart non-fusogenic property to specifically mycobacteria containing phagosomes (Ferrari, G., et al., Cell, 1999. **97**(4): p. 435-47.; Jayachandran, R., et al., Cell, 2007. 130(1): p. 37-50.).

Studies analyzing complete coronin 1 knock-out mice have shown that this molecule is an important regulator of naïve T cell homeostasis and it has been linked to immune deficiencies as well as autoimmune disorders (Mueller, P., et al., Nat Immunol, 2008. 9(4): p. 424-31.; Foger, N., et al., Science, 2006. 313(5788): p. 839-42.; Shiow, L.R., et al., Nat Immunol, 2008. 9(11): p. 1307-15.; Haraldsson, M.K., et al., Immunity, 2008. 28(1): p. 40-51.; Siegmund, K., et al., J Immunol, 2011. 186(6): p. 3452-61). T cell-specific coronin 1 knock-out mice were largely resistant to the induction of autoimmunity (Siegmund et al., J. Biol. Chem 2016, 291(42), 22086-22092). Thus, coronin 1 appears to have a predominant T cell-intrinsic role. Furthermore, allografts from MHC mismatched donors were tolerated in coronin 1-deficient mice resulting in long-term survival of transplanted organs along with absence of graft versus host response. Although deletion of coronin 1 results in a state of immunosuppression that results in attenuation of autoimmune responses and allograft rejection, immunity to infectious and foreign antigens are largely maintained in these mice (Pieters et al., Nat Rev Immunol. 2013, 13(7), 510-518; Jayachandran, R., et al., Immunity, 2019. 50(1): p.152-165; Siegmund, K., et al., J Immunol, 2011. 186(6): p. 3452-61).

The presently used immunosuppressants often target proteins that are widely expressed in our body resulting in numerous side effects and toxicity (Rodriguez-Peralvarez, et al., Curr Opin Organ Transplant, 2014. 19(3): p. 253-60). For example, drugs such as calcineurin inhibitors (cyclosporine/FK506), corticosteroids or sirolimus lead to various side-effects and drug-induced toxicity including cancers,

opportunistic infections, hypertension, altered metabolic profile and reduced patient compliance (Dantal, J. and M. Campone, Transplantation, 2016. 100(12): p. 2569-2583.; Ross, K., J Natl Cancer Inst, 2007. 99(6): p. 421-2.).

Coronin 1, though expressed in diverse immune cell subtypes, is especially required for the survival of peripheral T cells (Pieters, J., et al., Nat Rev Immunol, 2013. 13(7): p. 510). In both coronin 1-deficient mice and humans, T cells are depleted in the peripheral lymphoid organs and blood. Despite this T cell deficiency, coronin 1-deficient mice have normal longevity and show no increase in opportunistic infections or spontaneous cancers. However, the absence of coronin 1 induces a prolonged survival of MHC-mismatched organ transplants and resistance towards development of autoimmune disorders (Jayachandran, R., et al., Immunity, 2019. 50: p.1-15.; Siegmund, K., et al., J Immunol, 2011. 186(6): p. 3452-61). These data further support that depletion of coronin 1 levels *in vivo* will induce a state of immunosuppression that will result in prolonged survival of organ transplants, suppression of autoimmune diseases and absence of any major complications with infections or malignancies. Side effects and toxicity are expected to be only minimal, since coronin 1 modulators mainly affect the T cell-specific functionality and survival. Moreover, immunity (including T cell-dependent) against microbial pathogens and cancers is being maintained upon coronin 1 ablation (Jayachandran, R., et al., Immunity, 2019. 50: p.1-15.).

The dihydropyridine scaffold is used as heterocyclic structure in medicine for the treatment of several ailments with several functions including, but not limited to, antihypertensive, antitumor and anticonvulsant activities (selected review: V. K. Sharmaa and S. K. Singh, RSC Adv., 2017, 7, 2682–2732). Most commercially used dihydropyridine containing drugs are either achiral or are used as racemates, few are used as single enantiomers. Asymmetric syntheses of dihydropyridines have been developed but routes towards the related diaryl substituted 4,6,7,8-tetrahydroquinolin-5(1H)-one have not been reported.

Bromodomain Extra Terminal (BET) family of proteins are epigenetic readers comprised of four paralog members (BDR2, BRD3, BRD4 and BRDT) that recognize acetylated N-terminal tails of histones and act as readers of lysine acetylation state and interact with components of the transcriptional and chromatin remodeling machinery. These proteins play a critical role in malignant transformations and immune functioning (Gilan, O., et al., Science, 2020. **368**(6489): p. 387-394. Faivre, E.J., et al., Nature, 2020. **578** (7794): p. 306-310.) and are characterized by the presence two tandem bromodomains, bromodomain 1 (BD1) and bromodomain 2 (BD2), that aid in the docking to acetylated lysine on histones aiding chromatin binding. The BD1 and BD2 domains are highly conserved in evolution and also retain a marked level of homology across the paralogs. Structurally, they are characterized by an evolutionarily conserved

sequence of approximately 110 amino acids that folds itself in to four α-helices (αZ, αA, αB, αC) interconnected by two intervening loops (BC loop and ZA loop) that collectively form a hydrophobic binding cavity for interaction with acetylated lysine of histones. Due to the high level of similarity between the paralogs, selectively targeting one particular BET protein has thus far been elusive, with the earlier reported compounds binding either to both the BD1 and BD2 domains of all the four members (pan-BET inhibitors) or binding to one of the BD domains (either BD1 (pan BD1-selective inhibitors) or BD2 (pan BD2-selective inhibitors)) of all the four BET proteins (Wang, N., et al., Signal Transduct Target Ther, 2021. **6**(1): p. 23. Qi, J. and Y. Shi, Cancer Cell, 2020. **37**(6): p. 764-766.). BRD4 is the most well studied member in the family followed by BRD2 and they have been reported to play an important role in cancer development, embryogenesis, sepsis, immune function and fibrosis. BRD4 and BRD2 gene knock out has resulted in embryonic lethality (Houzelstein, D., et al., Mol Cell Biol, 2002. 22(11): p. 3794-802. Shang, E., et al., Dev Dyn, 2009. 238(4): p. 908-17). However, the role for BRD3 is the least characterized and its major function still remains largely unknown, due to functional redundancy with BRD2 resulting in minimal functional changes (Daneshvar, K., et al., Nat Cell Biol, 2020. 22(10): p. 1211-1222. Stonestrom, A.J., et al., Drug Discov Today Technol, 2016. 19: p. 23-28.).

Summary of the invention

The inventors developed and identified new compounds that deplete coronin 1 in cells, preferably immune cells, by coronin 1 promoter inhibition. Additionally, the absolute configuration of the eutomer was identified thereby separating toxicity of certain compounds from the coronin 1 promotor inhibitory activity. Chiral separation methods and asymmetric synthesis routes for these compounds have been developed. These compounds provide a new approach for inducing immunosuppression, allo-tolerance or prevention and/or treatment of transplant rejection, preferably allograft rejection, autoimmune diseases (selected from the group consisting of (but not limited to) psoriasis, vitiligo, multiple sclerosis, systemic lupus erythematosus, primary sclerosing cholangitis, Hashimoto's thyroiditis, rheumatoid arthritis, myasthenia gravis, diabetes type I or II, disorders secondary to diabetes type I or II, vasculitis, pernicious anaemia, Sjogren syndrome, uveitis, Graves' ophthalmopathy, alopecia areata, allergic asthma, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, myocarditis, hepatitis, and allergic contact dermatitis), inflammatory diseases (selected from the group consisting of (but not limited to) inflammatory bowel disease, Crohn's disease, ulcerative colitis, intrinsic asthma, inflammatory lung injury, inflammatory liver injury, inflammatory glomerular injury, atherosclerosis, osteoarthritis, myositis, polymyositis, cardio vasculopathy, prurigo nodularis, hidradenitis suppurativa, fibrotic disorders, allergic disorders, irritant contact dermatitis, eczematous dermatitis, seborrheic dermatitis, eosinophilic esophagitis, cutaneous

manifestations of immunologically-mediated disorders, inflammatory eye diseases, keratoconjunctivitis, myocardial infarction, stroke, gut ischemia, renal failure, hemorrhage shock, traumatic shock, toxic shock, septic shock and adult respiratory distress syndrome), infectious diseases (selected from the group consisting of (but not limited to) tuberculosis, preferably caused by mycobacteria, *Salmonella* sp. infections, *Helicobacter* sp. infections, retroviral infections, preferably HIV or HTLV, cytomegalo viral infection, *Candida* infection, *Staphylococcus* infections, lympho-choriomeningitis viral infections and viral hepatitis) as well as lymphoproliferative disorders (selected from the group consisting of (but not limited to) T cell lymphoma and T cell leukaemia via coronin 1 depletion).

The present inventors have further identified bromodomain 3 (BRD3) as an upstream regulator of coronin 1 expression and identified new compounds that selectively target bromodomains of BRD3, to inhibit expression of coronin 1. In other words, the compounds of the present invention deplete coronin 1 in cells, preferably immune cells, by inhibiting BRD3 to suppress coronin 1 promoter activity. Thus, these compounds provide a new approach for inducing immunosuppression, allo-tolerance or prevention and/or treatment of transplant rejection, preferably allograft rejection, autoimmune diseases, inflammatory diseases, infectious diseases as well as lymphoproliferative disorders via targeting of BRD3 which leads to coronin 1 depletion. In addition, as BRD3 has been shown to play a role in certain malignant conditions and their metastasis (BRD3-driven *Nu*clear protein in *T*estis (NUT) Midline Carcinoma (NMC), BRD3-driven Ovarian Clear Cell Carcinoma (OCCC)), colorectal carcinoma and rhabdomyosarcoma, these compounds could have potential applications in treating these oncological conditions (Ballenberger, M., et al., Chest, 2022. **161**(1): p. e43-e49. French, C.A., et al., Oncogene, 2008. **27**(15): p. 2237-42. Roberts, T.C., et al., Sci Rep, 2017. **7**(1): p. 6153. Hsu, PL., et al., Sci Adv, 2023. **9**, eade3422.)

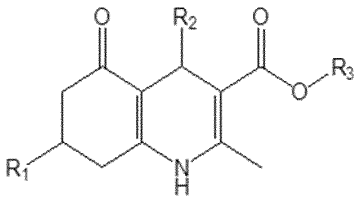
As coronin 1 is needed also for bacterial survival inside macrophages (e.g. for mycobacteria, helicobacter and salmonella) (Jayachandran, R., et al., Cell, 2007. **130**(1): p. 37-50.; Jayachandran, R., et al., Immunity, 2019. **50**: p.1-15.; Zheng, P.Y. and N.L. Jones, Cell Microbiol, 2003. **5**(1): p. 25-40.), reduction of coronin 1 is a method for killing bacteria and treating and/or preventing infections and diseases caused by bacteria, such as tuberculosis, gastric ulcer, gastric cancer etc.

The compounds of the invention have been demonstrated to be effective in imiquimod-induced psoriasis model (see Example 10 and Figure 4), as well as have demonstrated ability to reduce an immune response against an auto antigen, while maintaining the immune response against an infectious antigen, as demonstrated in Example 11 and Figure 5. Furthermore, certain compounds of the invention have

shown superior coronin-1 promotor inhibitor activity in comparison to closely related compounds, as shown in Example 12.

The invention is summarized in the following embodiments.

In a first embodiment, the present invention relates to a compound of formula (I):



(I)

or a pharmaceutically acceptable salt, stereoisomer, diastereoisomer, enantiomer, polymorph, racemic mixture, or solvate thereof, wherein:

R_1 is selected from phenyl, a monocyclic heteroaryl containing at least one N atom (such as pyridyl) and thienyl, wherein said phenyl and said pyridyl are each optionally substituted with one or more optional substituents independently selected from -OH, $-NO_2$, $-NH_2$, -CN, halogen $-C_1$-C_6-alkyl, $-O-C_1$-C_6-alkyl, and $-O-C_1$-C_6-haloalkyl;

R_2 is a bicyclic heteroaryl, optionally substituted with one or more groups selected from R_S, a monocyclic heteroaryl containing at least one N atom, optionally substituted with one or more groups selected from R_S, or naphtalenyl optionally substituted with one or more groups selected from R_S;

R_3 is selected from $-C_1$-C_8-alkyl, $-(C_1$-C_6-alkylene)-S$-C_1$-C_6-alkyl, $-(C_1$-C_6-alkylene)-SO_2-C_1-C_6-alkyl, $-(C_1$-C_6-alkylene)-OH, $-(C_1$-C_6-alkylene)-O$-C_1$-C_6-alkyl, $-(C_2$-C_4-alkylene$-O)_m-H$ wherein m is an integer from 1 to 10 (preferably from 1 to 5, more preferably from 2 to 3, even more preferably 2), $-(C_2$-C_4-alkylene$-O)_m-(C_1$-C_6-alkyl) wherein m is an integer from 1 to 10 (preferably from 1 to 5, more preferably from 2 to 3, even more preferably 2), $-C_1$-C_6-alkylene-cycloalkyl, cycloalkyl, $-C_1$-C_6-alkylene-(oxygen-containing saturated heterocyclyl), oxygen-containing saturated heterocyclyl, $-C_1$-C_6-alkylene-(sulfur-containing saturated heterocyclyl), sulfur-containing saturated heterocyclyl, $-C_1$-C_6-alkylene-(nitrogen-containing saturated heterocyclyl), nitrogen-containing saturated heterocyclyl, $-C_1$-C_6-alkylene-(5 or 6-membered heteroaryl), 5 or 6-membered heteroaryl, $-C_1$-C_6-alkylene-aryl and aryl;

wherein said $-C_1$-C_8-alkyl is optionally substituted with one or more groups selected from Hal and -OH,

wherein said cycloalkyl, the cycloalkyl in the $-C_1$-C_6-alkylene-cycloalkyl, the oxygen-containing saturated heterocyclyl moiety in said $-C_1$-C_6-alkylene-(oxygen-containing saturated heterocyclyl), said oxygen-containing saturated heterocyclyl, the nitrogen-containing saturated heterocyclyl moiety in said $-C_1$-C_6-alkylene-(nitrogen-containing saturated heterocyclyl), said nitrogen-containing saturated heterocyclyl, the

sulfur-containing saturated heterocyclyl moiety in said –C_1-C_6-alkylene-(sulfur-containing saturated heterocyclyl), said sulfur-containing saturated heterocyclyl, the 5 or 6-membered heteroaryl moiety in said –C_1-C_6-alkylene-(5 or 6-membered heteroaryl), said 5 or 6-membered heteroaryl, the aryl moiety in said –C_1-C_6-alkylene-aryl and said aryl are each optionally substituted with one or more groups selected from R_S; and

each R_S is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-OH, -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-OH, -(C_{0-3} alkylene)-NH-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-halo, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-O-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-NO_2, -(C_{0-3} alkylene)-CHO, -(C_{0-3} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-NH-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-N(C_{1-5} alkyl)-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-NH_2, -(C_{0-3} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(O)(NH)(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(O)(N(C_{1-5} alkyl))(C_{1-5} alkyl), -(C_{0-3} alkylene)-N=S(O)(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-P(O)(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-P(O)(O(C_{1-5} alkyl))(O(C_{1-5} alkyl)), -(C_{0-3} alkylene)-P(O)(O(C_{1-5} alkyl))(C_{1-5} alkyl), -(C_{0-3} alkylene)-carbocyclyl, and -(C_{0-3} alkylene)-heterocyclyl, wherein the carbocyclyl moiety in said -(C_{0-3} alkylene)-carbocyclyl and the heterocyclyl moiety in said -(C_{0-3} alkylene)-heterocyclyl are each optionally substituted with one or more groups independently selected from C_{1-4} alkyl, halo, -CN, -NO_2, -OH, -O-(C_{1-4} alkyl), -SH, -S-(C_{1-4} alkyl), -NH_2, -NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)(C_{1-4} alkyl), -COOH, -COO(C_{1-4} alkyl), -$CONH_2$, -CONH(C_{1-4} alkyl), -CON(C_{1-4} alkyl)(C_{1-4} alkyl), -NHCO(C_{1-4} alkyl) and -N(C_{1-4} alkyl)-CO(C_{1-4} alkyl).

In a second embodiment, the present invention relates to a pharmaceutical composition comprising the compound of the present invention or a pharmaceutically acceptable salt, stereoisomer, diastereoisomer, enantiomer, polymorph, racemic mixture, or solvate thereof and a pharmaceutically acceptable carrier.

In a third embodiment, the present invention relates to the compound of the present invention, or a pharmaceutically acceptable salt, stereoisomer, diastereoisomer, enantiomer, polymorph, racemic mixture, or solvate thereof, or the pharmaceutical composition of the present invention, for use as a medicament.

In a fourth embodiment, the present invention relates to the compound of the present invention, or a pharmaceutically acceptable salt, stereoisomer, diastereoisomer, enantiomer, polymorph, racemic mixture, or solvate thereof, or the pharmaceutical composition of the present invention, for use in the induction of immunosuppression or in the treatment and/or prevention of a disease or disorder selected from the group consisting of transplant rejection, autoimmune diseases, inflammatory diseases, infectious diseases, and lymphoproliferative disorders.

In a fifth embodiment, the present invention relates to use of the compound of the present invention or a pharmaceutically acceptable salt, stereoisomer, diastereoisomer, enantiomer, polymorph, racemic mixture, or solvate thereof, in a manufacture of a medicament for the induction of immunosuppression or for the treatment and/or prevention of a disease or disorder selected from the group consisting of transplant rejection, autoimmune diseases, inflammatory diseases, infectious diseases, and lymphoproliferative disorders.

In a sixth embodiment, the present invention relates to method of inducing immunosuppression or method of treating a disease or disorder selected from the group consisting of transplant rejection, autoimmune diseases, inflammatory diseases, infectious diseases, and lymphoproliferative disorders, the method comprising the step of administering the compound of the present invention, or a pharmaceutically acceptable salt, stereoisomer, diastereoisomer, enantiomer, polymorph, racemic mixture, or solvate thereof, to an individual in need thereof. It is to be understood that, preferably, a therapeutically effective dose is to be administered.

Brief description of figures

Invention is further illustrated based on the following Figures. These serve merely illustrative purposes and are not meant to be interpreted as limiting in any way.

FIGURE 1: Principle of the coronin 1 promoter screening assay of the invention: The promoter of a vertebrate (in the present case murine) coronin 1 gene (*coro1a*) was cloned upstream of the coding region

of destabilized green fluorescence protein (GFP). CMV promoter-driven red fluorescence protein (RFP) served as an internal control for non-specific promoter inhibition. These constructs were stably transfected into rat basophil leukemia (RBL) cells and subjected to treatment with small molecule compounds from chemical libraries.

FIGURE 2: Protein Integral Solubility Analysis (PISA) identifies BRD3 as the molecular target: The compounds of the invention, C1PI (coronin-1 promoter inhibitors), target of action has been identified using the PISA procedure in THP-1 (A) or RBL (B) cells. This procedure identified the top target to be BRD3 that gets maximal thermal stabilization with a significantly high p-value in the presence of the C1PI (left panels). In contrast, BRD2 and BRD4 are not significantly stabilized by C1PI (left panels). In the presence of prior art compound ABBV-744 a corresponding level of selectivity for BRD3 over BRD2 and BRD4 is not seen. More specifically, BRD2 and BRD3 are both similarly stabilized in terms of fold change and both significantly high p-value (right panels). Moreover, BRD4 is also stabilized with a significantly high p-value in the presence of prior art compound ABBV-744 (right panels).

As understood herein, ABBV-744 is a compound according to formula:

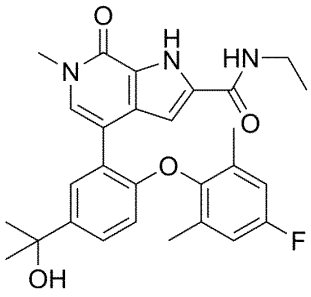


FIGURE 3: (A) Validation of the PISA identified target using an siRNA-based approach: brd3 siRNAs (target specific siRNA) was transfected in to RBL GFP (Rat Basophil Leukemia cell line expressing green fluorescence protein under the coronin 1 promoter) and 72h later, the GFP fluorescence level was assessed using flow cytometry as a measure of reduction in coronin 1 promoter activity. A significant reduction in coronin 1 promoter driven GFP fluorescence upon transfection with target specific siRNA was seen.

(B) Validation of the PISA identified target using a CRISPR/Cas9-based approach: Analysis of coronin 1 and BRD3 protein expression levels as median fluorescence intensity (MFI) by flow cytometry-based analysis of a series of RBL cell line clones that were gene-edited (using CRISPR/Cas9) or not on the brd3 gene.

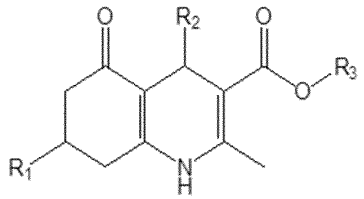
FIGURE 4: (A) In imiquimod-induced psoriasis model, per-oral (PO) compound administration at indicated doses attenuates disease score as assessed on day 7 by PASI score (left panel) and ear thickness (right panel). (B) Assessment of coronin 1 (left panel), inflammatory cytokines IL-17A (middle panel) and TNFα (right panel) from the ears of the mice from imiquimod-induced psoriasis model study by qPCR of healthy, vehicle-treated or C1PI-treated animals on the day of sacrifice (Day 7).

FIGURE 5: Differential suppression immune responses to auto (self) antigen versus infectious antigen by C1PI and reference compounds: OT-II T cells were co-cultured with either OVA-expressing transgenic splenocytes (Act-mOVA) representing autoimmune context or with OT-II splenocytes infected with OVA-expressing Salmonella typhimurium representing infectious context for 4 days and the OT-II T cell proliferation assessed by tritiated-thymidine incorporation in the presence and absence of the indicated compounds (3 μM). Note: The C1PI alone minimally suppress the OT-II T cell immune responses in the infectious context (maintenance of 75% of the response seen with vehicle control) while strongly suppressing OT-II T cell immune responses in the self-antigen/autoimmune context (maintenance of only 20% of the response seen with vehicle control) relative to vehicle unlike the comparator compounds that suppress the OT-II T cell responses equally under both the conditions.

Collectively, the *in vitro* and *in vivo* data shown in Figures 2 to 5 reveal that the C1PI of the present invention preferentially bind to BRD3 (Table 8 shows BD2 preference), confer anti-inflammatory activities, suppress inflammatory cytokines / coronin 1 mRNA expression and induce differential suppression of immune responses to auto (self) antigen versus infectious antigen.

Detailed description of the invention

As mentioned in the foregoing, in one embodiment, the present invention relates to a compound of formula (I):



(I)

or a pharmaceutically acceptable salt, stereoisomer, diastereoisomer, enantiomer, polymorph, racemic mixture, or solvate thereof.

In formula (I), R_1 is selected from phenyl, a monocyclic heteroaryl containing at least one N atom (such as pyridyl, or in other words pyridinyl) and thienyl, wherein said phenyl and said pyridyl are each optionally substituted with one or more optional substituents independently selected from -OH, $-NO_2$, $-NH_2$, -CN, halogen $-C_1$-C_6-alkyl, $-C_1$-C_6-haloalkyl, $-O-C_1$-C_6-alkyl, and $-O-C_1$-C_6-haloalkyl, preferably selected from -OH, $-NO_2$, $-NH_2$, -CN, halogen $-C_1$-C_6-alkyl,$-O-C_1$-C_6-alkyl, and $-O-C_1$-C_6-haloalkyl.

Preferably, R_1 is selected from phenyl and pyridyl, wherein said phenyl and said pyridyl are each optionally substituted with one or more optional substituents independently selected from -OH, $-NO_2$, halogen (preferably chloro or fluoro, more preferably fluoro), $-O-C_1$-C_6-alkyl (such as methoxy) and $-O-C_1$-C_6-haloalkyl (such as trifluoromethoxy), preferably selected from -OH, halogen and $-O-C_1$-C_6-alkyl (such as methoxy), more preferably selected from -OH and $-O-C_1$-C_6-alkyl (such as methoxy).

More preferably, R_1 is phenyl, wherein said phenyl is optionally substituted with one or more$-O-C_1$-C_6-alkyl.

Even more preferably, R_1 is phenyl optionally substituted with methoxy.

Thus, it is preferred that R_1 is selected from 2-methoxyphenyl and phenyl. It is particularly preferred that R_1 is 2-methoxyphenyl.

In one embodiment, R_1 is thienyl. Preferably, in this embodiment, R_1 is thien-2-yl.

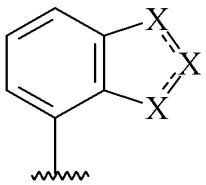
In another embodiment, R_1 is phenyl, wherein said phenyl is optionally substituted with one or more optional substituents independently selected from halogen (preferably chloro) and $-O-C_1$-C_6-alkyl (preferably methoxy), preferably $-O-C_1$-C_6-alkyl (preferably methoxy).

In yet another embodiment, R_1 is pyridinyl, wherein said pyridinyl is optionally substituted with one or more optional substituents independently selected from -OH, halogen and $-O-C_1$-C_6-alkyl (such as methoxy), more preferably selected from -OH and $-O-C_1$-C_6-alkyl (such as methoxy), even more preferably optionally substituted with one or more $-O-C_1$-C_6-alkyl (such as methoxy). In this specific embodiment, it is preferred that pyridinyl is pyridine-4-yl.

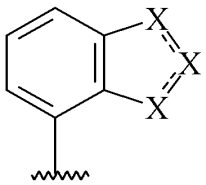
In formula (I), R_2 is a bicyclic heteroaryl, optionally substituted with one or more groups selected from R_S, a monocyclic heteroaryl containing at least one N atom, optionally substituted with one or more groups selected from R_S, or naphtalenyl optionally substituted with one or more groups selected from R_S.

Preferably, R_2 is a bicyclic heteroaryl optionally substituted with one or more groups selected from R_S. More preferably, R_2 is a bicyclic heteroaryl containing at least one N atom optionally substituted with one or more groups selected from R_S. It is further particularly preferred that the bicyclic heteroaryl in R_2 includes a benzene ring fused to a 5 membered heteroaryl ring including at least one N atom, connected to the rest of the molecule through said benzene ring, wherein said phenyl ring and said 5-membered heteroaryl ring are each optionally substituted with one or more groups selected from R_S.

Accordingly, it is preferred that R_2 is of formula:

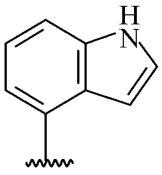
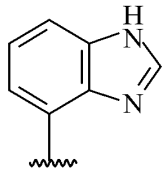
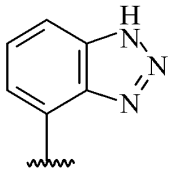


wherein each X is independently selected from CH, O, S, N and NH, provided that at least one X is N or NH, wherein the moiety is further optionally substituted with one or more groups selected from R_S. As it is to be understood herein, the bonds connecting X with each other may be single bonds or double bonds. In particular, bonds connecting together N with N, N with CH or CH with CH are understood to be double bonds. In any other case, such bond is a single bond. It is further particularly preferred that R_2 is of formula:

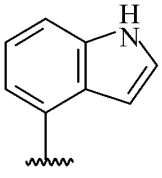


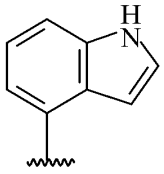
wherein each X is independently selected from CH, O, S, N and NH, provided that at least one X is N or NH, wherein the moiety is further optionally substituted with one or more groups selected from halogen, -CN, -OH, -O-(C_{1-5} alkyl) (preferably methoxy) and C_{1-5} alkyl (preferably methyl). Particularly preferred X are selected from N, NH and CH, provided that at least one X is N or NH.

Thus, accordingly, it is preferred that R_2 is selected from:


, 
, and 
,

wherein each of depicted moieties is optionally substituted with one or more groups selected from R_S, preferably with or more groups selected from halogen, -CN, -OH, -O-(C_{1-5} alkyl) (such as methoxy) and C_{1-5} alkyl (such as methyl).

More preferably, R_2 is  optionally substituted with one or more groups selected from R_S, preferably with or more groups selected from halogen, -CN, -OH, -O-(C_{1-5} alkyl) (such as methoxy) and C_{1-5} alkyl (such as methyl).

It is particularly preferred that R_2 is .

In one embodiment, R_2 is selected from isoquinolin-5-yl, quinolin-5-yl, 1H-indol-4-yl, 1H-benzo[d]imidazol-4-yl, 4-fluoronaphthalen-1-yl, 1H-indol-6-yl, benzofuran-6-yl, benzo[d]oxazol-5-yl, benzo[d]thiazol-5-yl, 1H-indol-5-yl, 1-methyl-1H-indol-3-yl, 1H-pyrrolo[2,3-b]pyridin-4-yl, 7-methyl-1H-indol-4-yl, 7-cyano-1H-indol-4-yl, 7-fluoro-1H-indol-4-yl, 1H-benzo[d][1,2,3]triazol-4-yl. In this embodiment, R_2 is preferably selected from isoquinolin-5-yl, quinolin-5-yl, 1H-indol-4-yl, 1H-benzo[d]imidazol-4-yl. More preferably wherein R_2 is 1H-indol-4-yl.

In another embodiment, R_2 is a monocyclic heteroaryl containing at least one N atom, optionally substituted with one or more groups selected from R_S. Particularly preferred is heteroaryl being pyridinyl (preferably pyridin-2-yl), optionally substituted with one or more groups selected from R_S. Accordingly, it is preferred that R_2 is pyridinyl, preferably pyridine-2-yl, optionally substituted with one or more groups selected from R_S. More preferably, R_2 is pyridinyl, preferably pyridin-2-yl, optionally substituted with one or more groups selected from -OH, -CN, $-NO_2$ and $-NH_2$. Even more preferably, R_2 is pyridinyl, preferably pyridin-2-yl, optionally substituted with one or more groups selected from $-NO_2$ and $-NH_2$. Particularly

preferred R_2 in this specific embodiment is 6-aminopyridin-2-yl or 6-nitropyridin-2-yl, preferably 6-aminopyridin-2-yl,

In again another embodiment, R_2 is naphtalenyl, optionally substituted with one or more groups selected from R_S. Preferably, in this specific embodiment, R_2 is naphtalenyl. More preferably, R_2 is naphtalen-1-yl.

In formula (I), R_3 is selected from –C_1-C_8-alkyl, –(C_1-C_6-alkylene)-S–C_1-C_6-alkyl, –(C_1-C_6-alkylene)-SO_2–C_1-C_6-alkyl, –(C_1-C_6-alkylene)-OH, –(C_1-C_6-alkylene)-O–C_1-C_6-alkyl, –(C_2-C_4-alkylene–O)$_m$–H wherein m is an integer from 1 to 10 (preferably from 1 to 5, more preferably from 2 to 3, even more preferably 2), –(C_2-C_4-alkylene–O)$_m$–(C_1-C_6-alkyl) wherein m is an integer from 1 to 10 (preferably from 1 to 5, more preferably from 2 to 3, even more preferably 2), –C_1-C_6-alkylene-cycloalkyl, cycloalkyl, –C_1-C_6-alkylene-(oxygen-containing saturated heterocyclyl), oxygen-containing saturated heterocyclyl, –C_1-C_6-alkylene-(sulfur-containing saturated heterocyclyl), sulfur-containing saturated heterocyclyl, –C_1-C_6-alkylene-(nitrogen-containing saturated heterocyclyl), nitrogen-containing saturated heterocyclyl, –C_1-C_6-alkylene-(5 or 6-membered heteroaryl), 5 or 6-membered heteroaryl, –C_1-C_6-alkylene-aryl and aryl;
wherein said –C_1-C_8-alkyl is optionally substituted with one or more groups selected from Hal and -OH,
wherein said cycloalkyl, the cycloalkyl in the –C_1-C_6-alkylene-cycloalkyl, the oxygen-containing saturated heterocyclyl moiety in said –C_1-C_6-alkylene-(oxygen-containing saturated heterocyclyl), said oxygen-containing saturated heterocyclyl, the nitrogen-containing saturated heterocyclyl moiety in said –C_1-C_6-alkylene-(nitrogen-containing saturated heterocyclyl), said nitrogen-containing saturated heterocyclyl, the sulfur-containing saturated heterocyclyl moiety in said –C_1-C_6-alkylene-(sulfur-containing saturated heterocyclyl), said sulfur-containing saturated heterocyclyl, the 5 or 6-membered heteroaryl moiety in said –C_1-C_6-alkylene-(5 or 6-membered heteroaryl), said 5 or 6-membered heteroaryl, the aryl moiety in said –C_1-C_6-alkylene-aryl and said aryl are each optionally substituted with one or more groups selected from R_S

As it is understood herein, it is preferred that in R_3, is –(C_1-C_6-alkylene)- is methylene or ethylene, more preferably that –(C_1-C_6-alkylene)- is methylene.

Preferably, R_3 is selected from –C_1-C_8-alkyl, –(C_1-C_6-alkylene)-S–C_1-C_6-alkyl, –(C_1-C_6-alkylene)-SO_2–C_1-C_6-alkyl, –(C_1-C_6-alkylene)-OH, –(C_1-C_6-alkylene)-O–C_1-C_6-alkyl, –(C_2-C_4-alkylene–O)$_m$–H wherein m is an integer from 1 to 10 (preferably from 1 to 5, more preferably from 2 to 3, even more preferably 2), –(C_2-C_4-alkylene–O)$_m$–(C_1-C_6-alkyl) wherein m is an integer from 1 to 10 (preferably from 1 to 5, more preferably from 2 to 3, even more preferably 2), –C_1-C_6-alkylene-cycloalkyl, cycloalkyl, –C_1-C_6-alkylene-

(oxygen-containing saturated heterocyclyl), oxygen-containing saturated heterocyclyl, –C_1-C_6-alkylene-(nitrogen-containing saturated heterocyclyl), nitrogen-containing saturated heterocyclyl, –C_1-C_6-alkylene-(5 or 6-membered heteroaryl), 5 or 6-membered heteroaryl, –C_1-C_6-alkylene-aryl and aryl;

wherein said –C_1-C_8-alkyl is optionally substituted with one or more groups selected from Hal and -OH,

wherein said cycloalkyl, the cycloalkyl in the –C_1-C_6-alkylene-cycloalkyl, the oxygen-containing saturated heterocyclyl moiety in said –C_1-C_6-alkylene-(oxygen-containing saturated heterocyclyl), said oxygen-containing saturated heterocyclyl, the nitrogen-containing saturated heterocyclyl moiety in said –C_1-C_6-alkylene-(nitrogen-containing saturated heterocyclyl), said nitrogen-containing saturated heterocyclyl, the 5 or 6-membered heteroaryl moiety in said –C_1-C_6-alkylene-(5 or 6-membered heteroaryl), said 5 or 6-membered heteroaryl, the aryl moiety in said –C_1-C_6-alkylene-aryl and said aryl are each optionally substituted with one or more groups selected from R_S.

More preferably, R_3 is selected from –C_1-C_8-alkyl, –(C_1-C_6-alkylene)-S–C_1-C_6-alkyl, –(C_1-C_6-alkylene)-SO_2–C_1-C_6-alkyl, –(C_1-C_6-alkylene)-OH, –(C_1-C_6-alkylene)-O–C_1-C_6-alkyl, –(C_2-C_4-alkylene–O)$_m$–H wherein m is an integer from 1 to 10 (preferably from 1 to 5, more preferably from 2 to 3, even more preferably 2), –(C_2-C_4-alkylene–O)$_m$–(C_1-C_6-alkyl) wherein m is an integer from 1 to 10 (preferably from 1 to 5, more preferably from 2 to 3, even more preferably 2), –C_1-C_6-alkylene-cycloalkyl, cycloalkyl, –C_1-C_6-alkylene-(oxygen-containing saturated heterocyclyl), oxygen-containing saturated heterocyclyl, –C_1-C_6-alkylene-(nitrogen-containing saturated heterocyclyl), nitrogen-containing saturated heterocyclyl, –C_1-C_6-alkylene-(5 or 6-membered heteroaryl), 5 or 6-membered heteroaryl, –C_1-C_6-alkylene-aryl and aryl wherein said –C_1-C_8-alkyl is optionally substituted with one or more groups selected from Hal and -OH,

wherein said cycloalkyl, the cycloalkyl in the –C_1-C_6-alkylene-cycloalkyl, the oxygen-containing saturated heterocyclyl moiety in said –C_1-C_6-alkylene-(oxygen-containing saturated heterocyclyl), said oxygen-containing saturated heterocyclyl, are each optionally substituted with one or more C_1-C_6-alkyl, the nitrogen-containing saturated heterocyclyl moiety in said –C_1-C_6-alkylene-(nitrogen-containing saturated heterocyclyl), said nitrogen-containing saturated heterocyclyl, the 5 or 6-membered heteroaryl moiety in said –C_1-C_6-alkylene-(5 or 6-membered heteroaryl), said 5 or 6-membered heteroaryl, the aryl moiety in said –C_1-C_6-alkylene-aryl and said aryl are each optionally substituted with one or more groups selected from R_S.

Even more preferably, R_3 is selected from –C_1-C_8-alkyl, –(C_1-C_6-alkylene)-S–C_1-C_6-alkyl, –(C_1-C_6-alkylene)-OH, –(C_2-C_4-alkylene–O)$_m$–H wherein m is an integer from 1 to 10 (preferably from 1 to 5, more preferably from 2 to 3, even more preferably 2), –(C_1-C_6-alkylene)-O–C_1-C_6-alkyl, –(C_2-C_4-alkylene–O)$_m$–(C_1-C_6-alkyl) wherein m is an integer from 1 to 10 (preferably from 1 to 5, more preferably from 2 to 3,

even more preferably 2), –C_1-C_6-alkylene-cycloalkyl, cycloalkyl, –C_1-C_6-alkylene-(oxygen-containing saturated heterocyclyl) and oxygen-containing saturated heterocyclyl,
wherein said –C_1-C_8-alkyl is optionally substituted with one or more groups selected from Hal and -OH,
wherein said cycloalkyl, the cycloalkyl in the –C_1-C_6-alkylene-cycloalkyl, the oxygen-containing saturated heterocyclyl moiety in said –C_1-C_6-alkylene-(oxygen-containing saturated heterocyclyl) and said oxygen-containing saturated heterocyclyl are each optionally substituted with one or more C_1-C_6-alkyl.

In one embodiment, R_3 is selected from –C_1-C_6-alkylene-(5 or 6-membered heteroaryl), 5 or 6-membered heteroaryl, –C_1-C_6-alkylene-aryl and aryl; wherein the 5 or 6-membered heteroaryl moiety in said –C_1-C_6-alkylene-(5 or 6-membered heteroaryl), said 5 or 6-membered heteroaryl, the aryl moiety in said –C_1-C_6-alkylene-aryl and said aryl are each optionally substituted with one or more groups selected from R_S. Preferably, in this embodiment, R_3 is selected from –C_1-C_6-alkylene-(5 or 6-membered heteroaryl) wherein the 5 or 6-membered heteroaryl moiety in said –C_1-C_6-alkylene-(5 or 6-membered heteroaryl) is optionally substituted with one or more groups selected from R_S. Accordingly, it is preferred that in this embodiment R_3 is selected from isoxazol-3-ylmethyl, 1-methyl-1H-pyrazol-4-ylmethyl, thiazol-5-ylmethyl, oxazol-5-ylmethyl, pyridin-3-ylmethyl, pyridin-2-ylmethyl, pyrimidin-4-ylmethyl, pyrimidin-2-ylmethyl, and 4-(methylsulfonyl)benzyl.

In one alternative embodiment, R_3 is C_{1-8} alkyl wherein said –C_1-C_8-alkyl is optionally substituted with one or more groups selected from Hal and -OH. Preferably, as understood herein, said C_{1-8} alkyl is not substituted. Preferably, R_3 is C_{1-4} alkyl. Particularly suitable R_3 is selected from methyl, ethyl, isopropyl and tert-butyl. Particularly preferred R_3 is methyl (for example methyl-d3, which may also be referred to as -CD_3).

In a further alternative embodiment, R_3 is selected from –C_1-C_6-alkylene-(oxygen-containing saturated heterocyclyl), oxygen-containing saturated heterocyclyl, –C_1-C_6-alkylene-(sulfur-containing saturated heterocyclyl), and sulfur-containing saturated heterocyclyl, wherein the oxygen-containing saturated heterocyclyl moiety in said –C_1-C_6-alkylene-(oxygen-containing saturated heterocyclyl), said oxygen-containing saturated heterocyclyl, the sulfur-containing saturated heterocyclyl moiety in said –C_1-C_6-alkylene-(sulfur-containing saturated heterocyclyl), and said sulfur-containing saturated heterocyclyl are each optionally substituted with one or more groups selected from R_S. Preferably, R_3 is –C_1-C_6-alkylene-(oxygen-containing saturated heterocyclyl), or oxygen-containing saturated heterocyclyl, wherein the oxygen-containing saturated heterocyclyl moiety in said –C_1-C_6-alkylene-(oxygen-containing saturated

heterocyclyl), and said oxygen-containing saturated heterocyclyl, are each optionally substituted with one or more groups selected from R_S.

In a further alternative embodiment, R_3 is selected from $–C_1$-C_8-alkyl, $–(C_1$-C_6-alkylene)-S–C_1-C_6-alkyl, $–(C_1$-C_6-alkylene)-$SO_2–C_1$-C_6-alkyl, $–(C_1$-C_6-alkylene)-OH, $–(C_1$-C_6-alkylene)-O–C_1-C_6-alkyl, $–(C_2$-C_4-alkylene–$O)_m–H$ wherein m is an integer from 1 to 10 (preferably from 1 to 5, more preferably from 2 to 3, even more preferably 2), and $–(C_2$-C_4-alkylene–$O)_m–(C_1$-C_6-alkyl) wherein m is an integer from 1 to 10 (preferably from 1 to 5, more preferably from 2 to 3, even more preferably 2). Preferably, R_3 is selected from $–C_1$-C_8-alkyl,$–(C_1$-C_6-alkylene)-OH, $–(C_1$-C_6-alkylene)-O–C_1-C_6-alkyl, $–(C_2$-C_4-alkylene–$O)_m–H$ wherein m is an integer from 1 to 10 (preferably from 1 to 5, more preferably from 2 to 3, even more preferably 2), and $–(C_2$-C_4-alkylene–$O)_m–(C_1$-C_6-alkyl) wherein m is an integer from 1 to 10 (preferably from 1 to 5, more preferably from 2 to 3, even more preferably 2). More preferably, R_3 is selected from $–C_1$-C_8-alkyl, $–(C_1$-C_6-alkylene)-OH, $–(C_1$-C_6-alkylene)-O–C_1-C_6-alkyl, $–(C_2$-C_4-alkylene–$O)_m–H$ wherein m is an integer from 1 to 10 (preferably from 1 to 5, more preferably from 2 to 3, even more preferably 2), and $–(C_2$-C_4-alkylene–$O)_m–(C_1$-C_6-alkyl) wherein m is an integer from 1 to 10 (preferably from 1 to 5, more preferably from 2 to 3, even more preferably 2). Even more preferably, R_3 is selected from $–C_1$-C_8-alkyl, $–(C_1$-C_6-alkylene)-OH, and $–(C_2$-C_4-alkylene–$O)_m–H$ wherein m is an integer from 1 to 10 (preferably from 1 to 5, more preferably from 2 to 3, even more preferably 2). Again more preferably, R_3 is selected from $–C_1$-C_8-alkyl, and $–(C_1$-C_6-alkylene)-OH. Exemplary R_3 in this specific embodiment is selected from 2-methoxyethyl, 2-hydroxy-2-methylpropyl, and 2-hydroxyethyl. As understood herein, said–C_1-C_8-alkyl is optionally substituted with one or more groups selected from Hal and -OH. Preferably, said $–C_1$-C_8-alkyl is unsubstituted.

In a further alternative embodiment, R_3 is selected from $–C_1$-C_6-alkylene-cycloalkyl, and cycloalkyl, wherein said cycloalkyl, the cycloalkyl in the $–C_1$-C_6-alkylene-cycloalkyl, are each optionally substituted with one or more groups selected from R_S. Preferably, R_3 is selected from $–C_1$-C_6-alkylene-cycloalkyl, and cycloalkyl, wherein said cycloalkyl, the cycloalkyl in the $–C_1$-C_6-alkylene-cycloalkyl, are each optionally substituted with one or more $C_{1\text{-}6}$ alkyl. Preferred R_3 in this specific embodiment is selected from (1-hydroxycyclopropyl)methyl, and cyclopropyl.

In a further alternative embodiment, R_3 is $–C_1$-C_6-alkylene-(nitrogen-containing saturated heterocyclyl), or nitrogen-containing saturated heterocyclyl, wherein the nitrogen-containing saturated heterocyclyl moiety in said $–C_1$-C_6-alkylene-(nitrogen-containing saturated heterocyclyl), and said nitrogen-containing saturated heterocyclyl are each optionally substituted with one or more groups selected from R_S.

Accordingly, if R_3 is nitrogen-containing saturated heterocyclyl, wherein said nitrogen-containing saturated heterocyclyl is optionally substituted with one or more groups selected from R_S, R_3 is preferably selected from (R)-1-(2-fluoroethyl)pyrrolidin-3-yl, (R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl, (S)-4,4-difluoro-1-methylpyrrolidin-3-yl, (R)-1-methylpiperidin-3-yl, (R)-5,5-difluoro-1-methylpiperidin-3-yl, (S)-1-methylpyrrolidin-3-yl, and (R)-1-methyl-5-oxopyrrolidin-3-yl. Alternatively, if R_3 is C_1-C_6-alkylene-(nitrogen-containing saturated heterocyclyl), preferably a methylene-(nitrogen-containing saturated heterocyclyl), wherein the nitrogen-containing saturated heterocyclyl moiety in said –C_1-C_6-alkylene-(nitrogen-containing saturated heterocyclyl) is optionally substituted with one or more groups selected from R_S, R_3 is preferably (1-methyl-1H-pyrazol-4-yl)methyl.

In formula (I), each R_S is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-OH, -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-OH, -(C_{0-3} alkylene)-NH-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-halo, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-O-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-NO_2, -(C_{0-3} alkylene)-CHO, -(C_{0-3} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-NH-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-N(C_{1-5} alkyl)-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-NH_2, -(C_{0-3} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(O)(NH)(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(O)(N(C_{1-5} alkyl))(C_{1-5} alkyl), -(C_{0-3} alkylene)-N=S(O)(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-P(O)(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-P(O)(O(C_{1-5} alkyl))(O(C_{1-5} alkyl)), -(C_{0-3} alkylene)-P(O)(O(C_{1-5} alkyl))(C_{1-5} alkyl), -(C_{0-3} alkylene)-carbocyclyl, and -(C_{0-3} alkylene)-heterocyclyl, wherein the carbocyclyl moiety in said -(C_{0-3} alkylene)-carbocyclyl and the heterocyclyl moiety in said -(C_{0-3} alkylene)-heterocyclyl are each optionally substituted with one or more groups independently selected from C_{1-4} alkyl, halo, -CN, -NO_2, -OH, -O-(C_{1-4} alkyl), -SH, -S-(C_{1-4} alkyl), -NH_2, -NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)(C_{1-4} alkyl), -COOH, -COO(C_{1-4} alkyl), -$CONH_2$, -CONH(C_{1-4} alkyl), -CON(C_{1-4} alkyl)(C_{1-4} alkyl), -NHCO(C_{1-4} alkyl) and -N(C_{1-4} alkyl)-CO(C_{1-4} alkyl).

Preferably, each R_S is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-OH, -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-OH, -(C_{0-3} alkylene)-NH-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-O-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-NO_2, -(C_{0-3} alkylene)-CHO, -(C_{0-3} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-NH-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-N(C_{1-5} alkyl)-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-NH_2, -(C_{0-3} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-carbocyclyl, and -(C_{0-3} alkylene)-heterocyclyl, wherein the carbocyclyl moiety in said -(C_{0-3} alkylene)-carbocyclyl and the heterocyclyl moiety in said -(C_{0-3} alkylene)-heterocyclyl are each optionally substituted with one or more groups independently selected from C_{1-4} alkyl, halogen, -CN, -NO_2, -OH, -O-(C_{1-4} alkyl), -SH, -S-(C_{1-4} alkyl), -NH_2, -NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)(C_{1-4} alkyl), -COOH, -COO(C_{1-4} alkyl), -$CONH_2$, -CONH(C_{1-4} alkyl), -CON(C_{1-4} alkyl)(C_{1-4} alkyl), -NHCO(C_{1-4} alkyl) and -N(C_{1-4} alkyl)-CO(C_{1-4} alkyl).

More preferably, each R_S is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-OH, -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-OH, -(C_{0-3} alkylene)-NH-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-O-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-NO_2, -(C_{0-3} alkylene)-CHO, -(C_{0-3} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-O-(C_{1-5}

alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-NH-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-N(C_{1-5} alkyl)-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-NH_2, -(C_{0-3} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-(C_{1-5} alkyl), and -(C_{0-3} alkylene)-SO-(C_{1-5} alkyl).

Even more preferably, each R_S is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-OH, -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-OH, -(C_{0-3} alkylene)-NH-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-O(C_{1-5} alkyl), and -(C_{0-3} alkylene)-halogen.

Again more preferably, each R_S is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -OH, -O(C_{1-5} alkyl), -SH, -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), -NH-OH, -N(C_{1-5} alkyl)-OH, -NH-O(C_{1-5} alkyl), -N(C_{1-5} alkyl)-O(C_{1-5} alkyl), and halogen.

Even more preferably, each R_S is independently selected from -OH and halogen.

Preferably, the compound of formula (I) is a compound selected from:

tetrahydro-2H-pyran-4-yl 4-(4-(dimethylamino)naphthalen-1-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (1);

tetrahydro-2H-pyran-4-yl 8'-fluoro-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-[4,4'-biquinoline]-3-carboxylate (2);

tetrahydro-2H-pyran-4-yl 4-(3-acetamidopyridin-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (3);

methyl 4-(1H-indol-4-yl)-2-methyl-5-oxo-7-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4)

tetrahydro-2H-pyran-4-yl 4-(benzofuran-6-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5);

tetrahydro-2H-pyran-4-yl 4-(benzo[d]oxazol-5-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (6);

tetrahydro-2H-pyran-4-yl 4-(benzo[d]thiazol-5-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (7);

tetrahydro-2H-pyran-4-yl 4-(benzo[d]thiazol-6-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (8);

tetrahydro-2H-pyran-4-yl 4-(1H-indol-5-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (9);

tetrahydro-2H-pyran-4-yl 7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-[4,4'-biquinoline]-3-carboxylate (10);

tetrahydro-2H-pyran-4-yl 4-(isoquinolin-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (11);

tetrahydro-2H-pyran-4-yl 4-(4-fluoronaphthalen-1-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (12);

tetrahydro-2H-pyran-4-yl 4-(1H-indol-6-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (13);

tetrahydro-2H-pyran-4-yl 4-(isoquinolin-5-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (14);

tetrahydro-2H-pyran-4-yl 7-(2-methoxyphenyl)-2-methyl-4-(1-methyl-1H-indol-3-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (15);

tetrahydro-2H-pyran-4-yl 7-(2-methoxyphenyl)-2-methyl-5-oxo-4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (16);

tetrahydro-2H-pyran-4-yl 4-(1H-indazol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (17);

tetrahydro-2H-pyran-4-yl 7-(2-methoxyphenyl)-2-methyl-4-(7-methyl-1H-indol-4-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (18);

tetrahydro-2H-pyran-4-yl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (19);

tetrahydro-2H-pyran-4-yl 7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-[4,5'-biquinoline]-3-carboxylate (20);

methyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (21);

tetrahydro-2H-pyran-4-yl 4-(7-cyano-1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (22);

tetrahydro-2H-pyran-4-yl 4-(1H-benzo[d][1,2,3]triazol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (23);

tetrahydro-2H-pyran-4-yl 4-(1H-benzo[d]imidazol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (24);

4-methyltetrahydro-2H-pyran-4-yl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (25);

tert-butyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (26);

benzyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (27);

4-methoxybenzyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (28);

2-nitrobenzyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (29);

(1-methyl-1H-imidazol-5-yl)methyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (30);

oxazol-2-ylmethyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (31);

3-(methylsulfonyl)benzyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (32);

thiazol-5-ylmethyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (33);

8-oxabicyclo[3.2.1]octan-3-yl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (34);

1-methylpyrrolidin-3-yl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (35);

methyl-d3 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (36);

ethyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (37);

isopropyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (38);

cyclopropyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (39);

cyclopropylmethyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (40);

furan-3-ylmethyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (41);

oxazol-5-ylmethyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (42);

isoxazol-5-ylmethyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (43);

(1-methyl-1H-pyrazol-5-yl)methyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (44);

2-(methylsulfonyl)ethyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (45);

isoxazol-3-ylmethyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (46);

pyrimidin-2-ylmethyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (47);

pyrimidin-4-ylmethyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (48);

isothiazol-3-ylmethyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (49);

isothiazol-4-ylmethyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (50);

tetrahydrofuran-3-yl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (51);

(1-methyl-1H-pyrazol-4-yl)methyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (52);

isothiazol-5-ylmethyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (53);

2-(2-methoxyethoxy)ethyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (54);

(1-methyl-1H-pyrazol-3-yl)methyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (55);

2-methoxyethyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (56);

2-hydroxyethyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (57);

(tetrahydrofuran-2-yl)methyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (58);

2-(2-hydroxyethoxy)ethyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (59);

difluoromethyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (60);

pyridin-2-ylmethyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (61);

pyridin-3-ylmethyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (62);

isoxazol-4-ylmethyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (63);

pyridin-4-ylmethyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (64);

1-methylpiperidin-3-yl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (65);

1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (66);

1-methyl-6-oxopiperidin-3-yl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (67);

4,4-difluoro-1-methylpyrrolidin-3-yl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (68);

1-(2,2-difluoroethyl)pyrrolidin-3-yl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (69);

tetrahydro-2H-pyran-4-yl 4-(7-fluoro-1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (70);

1-methyl-5-oxopyrrolidin-3-yl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (71);

5-oxopyrrolidin-3-yl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (72);

4-(methylsulfonyl)benzyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (73);

3-(methylsulfonyl)propyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (74);

4-(methylsulfonyl)butyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (75);

1,1-dioxidotetrahydro-2H-thiopyran-4-yl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (76);

2,2,2-trifluoroethyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (77);

tetrahydro-2H-pyran-4-yl 7-(2-methoxyphenyl)-2-methyl-4-(6-nitropyridin-2-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (78);

5,5-difluoro-1-methylpiperidin-3-yl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (79);

1-(cyanomethyl)pyrrolidin-3-yl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (80);

tetrahydro-2H-pyran-4-yl 4-(2-aminothiazol-5-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (81);

1-(2-fluoroethyl)pyrrolidin-3-yl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (82);

2-hydroxy-2-methylpropyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (83);

(1-hydroxycyclopropyl)methyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (84);

2-hydroxyethyl-1,1,2,2-d4 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (85);

methyl 7-(2-bromophenyl)-4-(1H-indol-4-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (86);

methyl 4-(1H-indol-4-yl)-2-methyl-5-oxo-7-(pyridin-2-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (87);

methyl 7-(2-aminophenyl)-4-(1H-indol-4-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (88);

methyl 4-(6-fluoro-1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (89);

methyl 4-(1H-indol-4-yl)-2-methyl-5-oxo-7-(o-tolyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (90);

methyl 7-(2-hydroxyphenyl)-4-(1H-indol-4-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (91);

tetrahydro-2H-pyran-4-yl 4-(6-aminopyridin-2-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (92); and

methyl 4-(1H-indol-4-yl)-7-(3-methoxypyridin-4-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (93),

or a pharmaceutically acceptable salt thereof.

Further suitable compound of formula (I) is a compound selected from:

2-(2,2,2-trifluoroethyl)-2-azaspiro[3.3]heptan-6-yl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (94);

(6-cyanopyridin-2-yl)methyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (95);

(3S,5R)-5-(methoxycarbonyl)-1-methylpyrrolidin-3-yl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (96);

(S)-2,3-dihydroxypropyl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (97);

1,3-dihydroxypropan-2-yl 4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (98);

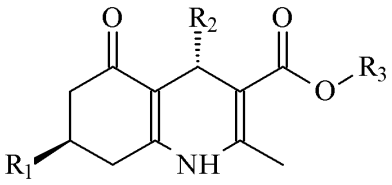
methyl 4-(1H-indol-4-yl)-7-(2-(methoxy-d3)phenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (99);

methyl-d3 -4-(1H-indol-4-yl)-7-(2-(methoxy-d3)phenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (100); and

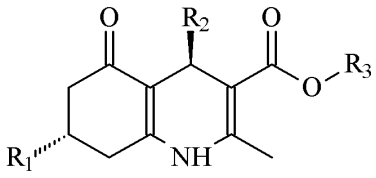
methyl -4-(1H-indol-4-yl)-2-methyl-5-oxo-7-(2-(trifluoromethoxy)phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (101),

or a pharmaceutically acceptable salt thereof.

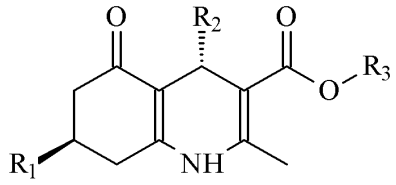
It is to be understood herein, that preferably in the compound of formula (I) R_1 and R_2 substituents are present on the opposite faces of the ring system. Thus, preferably, the compound of formula (I) is a compound of formula:



or a compound of formula:



More preferably, the compound of formula (I) has an absolute configuration of its stereogenic centers as shown in the formula:



Thus, in a further embodiment, the compound of formula (I) is a compound selected from:

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(4-(dimethylamino)naphthalen-1-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (1a);

tetrahydro-2H-pyran-4-yl (4S,7R)-8'-fluoro-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-[4,4'-biquinoline]-3-carboxylate (2a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(3-acetamidopyridin-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (3a);

methyl (4S,7R)-4-(1H-indol-4-yl)-2-methyl-5-oxo-7-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(benzofuran-6-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(benzo[d]oxazol-5-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (6a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(benzo[d]thiazol-5-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (7a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(benzo[d]thiazol-6-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (8a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(1H-indol-5-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (9a);

tetrahydro-2H-pyran-4-yl (4S,7R)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-[4,4'-biquinoline]-3-carboxylate (10a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(isoquinolin-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (11a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(4-fluoronaphthalen-1-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (12a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(1H-indol-6-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (13a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(isoquinolin-5-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (14a);

tetrahydro-2H-pyran-4-yl (4S,7R)-7-(2-methoxyphenyl)-2-methyl-4-(1-methyl-1H-indol-3-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (15a);

tetrahydro-2H-pyran-4-yl (4S,7R)-7-(2-methoxyphenyl)-2-methyl-5-oxo-4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (16a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(1H-indazol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (17a);

tetrahydro-2H-pyran-4-yl (4S,7R)-7-(2-methoxyphenyl)-2-methyl-4-(7-methyl-1H-indol-4-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (18a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (19a);

tetrahydro-2H-pyran-4-yl (4S,7R)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-[4,5'-biquinoline]-3-carboxylate (20a);

methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (21a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(7-cyano-1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (22a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(1H-benzo[d][1,2,3]triazol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (23a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(1H-benzo[d]imidazol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (24a);

4-methyltetrahydro-2H-pyran-4-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (25a);

tert-butyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (26a);

benzyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (27a);

4-methoxybenzyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (28a);

2-nitrobenzyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (29a);

(1-methyl-1H-imidazol-5-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (30a);

oxazol-2-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (31a);

3-(methylsulfonyl)benzyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (32a);

thiazol-5-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (33a);

(1R,3s,5S)-8-oxabicyclo[3.2.1]octan-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (34a);

(1R,3r,5S)-8-oxabicyclo[3.2.1]octan-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (34b);

(S)-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (35a);

methyl-d3 (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (36a);

ethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (37a);

isopropyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (38a);

cyclopropyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (39a);

cyclopropylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (40a);

furan-3-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (41a);

oxazol-5-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (42a);

isoxazol-5-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (43a);

(1-methyl-1H-pyrazol-5-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (44a);

2-(methylsulfonyl)ethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (45a);

isoxazol-3-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (46a);

pyrimidin-2-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (47a);

pyrimidin-4-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (48a);

isothiazol-3-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (49a);

isothiazol-4-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (50a);

(S)-tetrahydrofuran-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (51a);

(R)-tetrahydrofuran-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (51b);

(1-methyl-1H-pyrazol-4-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (52a);

isothiazol-5-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (53a);

2-(2-methoxyethoxy)ethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (54a);

(1-methyl-1H-pyrazol-3-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (55a);

2-methoxyethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (56a);

2-hydroxyethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (57a);

((S)-tetrahydrofuran-2-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (58a);

((R)-tetrahydrofuran-2-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (58b);

2-(2-hydroxyethoxy)ethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (59a);

difluoromethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (60a);

pyridin-2-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (61a);

pyridin-3-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (62a);

isoxazol-4-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (63a);

pyridin-4-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (64a);

(S)-1-methylpiperidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (65a);

(R)-1-methylpiperidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (65b);

(S)-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (66a);

(R)-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (66b);

(S)-1-methyl-6-oxopiperidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (67a);

(S)-4,4-difluoro-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (68a);

(R)-4,4-difluoro-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (68b);

(S)-1-(2,2-difluoroethyl)pyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (69a);

(R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (69b);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(7-fluoro-1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (70a);

(R)-1-methyl-5-oxopyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (71b);

(R)-5-oxopyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (72b);

4-(methylsulfonyl)benzyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (73a);

3-(methylsulfonyl)propyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (74a);

4-(methylsulfonyl)butyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (75a);

1,1-dioxidotetrahydro-2H-thiopyran-4-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (76a);

2,2,2-trifluoroethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (77a);

tetrahydro-2H-pyran-4-yl (4S,7R)-7-(2-methoxyphenyl)-2-methyl-4-(6-nitropyridin-2-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (78a);

(S)-5,5-difluoro-1-methylpiperidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (79a);

(R)-5,5-difluoro-1-methylpiperidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (79b);

(R)-1-(cyanomethyl)pyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (80b);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(2-aminothiazol-5-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (81a);

(R)-1-(2-fluoroethyl)pyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (82b);

2-hydroxy-2-methylpropyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (83a);

(1-hydroxycyclopropyl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (84a);

2-hydroxyethyl-1,1,2,2-d4 (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (85a);

methyl (4S,7R)-7-(2-bromophenyl)-4-(1H-indol-4-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (86a);

methyl (4S,7R)-4-(1H-indol-4-yl)-2-methyl-5-oxo-7-(pyridin-2-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (87a);

methyl (4S,7R)-7-(2-aminophenyl)-4-(1H-indol-4-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (88a);

methyl (4S,7R)-4-(6-fluoro-1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (89a);

methyl (4S,7R)-4-(1H-indol-4-yl)-2-methyl-5-oxo-7-(o-tolyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (90a);

methyl (4S,7R)-7-(2-hydroxyphenyl)-4-(1H-indol-4-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (91a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(6-aminopyridin-2-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (92a); and

methyl (4S,7R)-4-(1H-indol-4-yl)-7-(3-methoxypyridin-4-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (93a),

or a pharmaceutically acceptable salt thereof.

Further suitable compound of formula (I) is a compound selected from

2-(2,2,2-trifluoroethyl)-2-azaspiro[3.3]heptan-6-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (94a);

(6-cyanopyridin-2-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (95a);

(S)-2,3-dihydroxypropyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (97a);

(R)-2,3-dihydroxypropyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (97b);

1,3-dihydroxypropan-2-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (98a);

methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-(methoxy-d3)phenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (99a);

and

methyl (4S,7R)-4-(1H-indol-4-yl)-2-methyl-5-oxo-7-(2-(trifluoromethoxy)phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (101a),

or a pharmaceutically acceptable salt thereof.

Further suitable compound of formula (I) is a compound selected from

(3S,5S)-5-(methoxycarbonyl)-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (96a);

(3R,5S)-5-(methoxycarbonyl)-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (96b);

(3S,5R)-5-(methoxycarbonyl)-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (96c);

(3R,5R)-5-(methoxycarbonyl)-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (96d); and
methyl-d3 (4S,7R)-4-(1H-indol-4-yl)-7-(2-(methoxy-d3)phenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (100a),
or a pharmaceutically acceptable salt thereof.

Further suitable compound of formula (I) is a compound selected from
(R)-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (35b);
(R)-1-methyl-6-oxopiperidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (67b);
(S)-1-methyl-5-oxopyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (71a);
(S)-5-oxopyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (72a);
(S)-1-(cyanomethyl)pyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (80a); and
(S)-1-(2-fluoroethyl)pyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (82a),
or a pharmaceutically acceptable salt thereof.

Further suitable compound of formula (I) is a compound selected from
2-(2,2,2-trifluoroethyl)-2-azaspiro[3.3]heptan-6-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (94a);
(6-cyanopyridin-2-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (95a);
(3S,5S)-5-(methoxycarbonyl)-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (96a);
(3R,5S)-5-(methoxycarbonyl)-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (96b);
(3S,5R)-5-(methoxycarbonyl)-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (96c);

(3R,5R)-5-(methoxycarbonyl)-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (96d);

(S)-2,3-dihydroxypropyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (97a);

(R)-2,3-dihydroxypropyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (97b);

1,3-dihydroxypropan-2-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (98a);

methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-(methoxy-d3)phenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (99a);

methyl-d3 (4S,7R)-4-(1H-indol-4-yl)-7-(2-(methoxy-d3)phenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (100a); and

methyl (4S,7R)-4-(1H-indol-4-yl)-2-methyl-5-oxo-7-(2-(trifluoromethoxy)phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (101a),

or a pharmaceutically acceptable salt thereof.

In one embodiment, the preferred compound of formula (I) is a compound selected from:

2-methoxyethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (56a);

methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (21a);

methyl-d3 (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (36a);

2-hydroxy-2-methylpropyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (83a);

(1-hydroxycyclopropyl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (84a);2-hydroxyethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (57a); and

cyclopropyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (39a),

or a pharmaceutically acceptable salt thereof.

In one embodiment, the preferred compound of formula (I) is

2-hydroxyethyl-1,1,2,2-d4 (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (85a)

or a pharmaceutically acceptable salt thereof.

In a further embodiment, the preferred compound of formula (I) is a compound selected from:

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (19a);

(R)-tetrahydrofuran-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (51b);

(1R,3s,5S)-8-oxabicyclo[3.2.1]octan-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (34a);

(S)-tetrahydrofuran-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (51a);

4-methyltetrahydro-2H-pyran-4-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (25a);

((S)-tetrahydrofuran-2-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (58a);

((R)-tetrahydrofuran-2-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (58b); and

1,1-dioxidotetrahydro-2H-thiopyran-4-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (76a),

or a pharmaceutically acceptable salt thereof.

In a further embodiment, the preferred compound of formula (I) is a compound selected from:

(R)-1-(2-fluoroethyl)pyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (82b);

(R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (69b);

(S)-4,4-difluoro-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (68a);

(R)-1-methylpiperidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (65b);

(R)-5,5-difluoro-1-methylpiperidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (79b);

(S)-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (35a); and

(R)-1-methyl-5-oxopyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (71b),

or a pharmaceutically acceptable salt thereof.

In a further embodiment, the preferred compound of formula (I) is a compound selected from:

isoxazol-3-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (46a);

(1-methyl-1H-pyrazol-4-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (52a);

thiazol-5-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (33a);

oxazol-5-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (42a);

pyridin-3-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (62a);

pyridin-2-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (61a);

pyrimidin-4-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (48a);

pyrimidin-2-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (47a); and

4-(methylsulfonyl)benzyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (73a),

or a pharmaceutically acceptable salt thereof.

Further suitable compound of formula (I) is a compound selected from:

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (19a);

methyl-d3 (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (36a);

2-hydroxyethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (57a);

methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (21a);

2-hydroxy-2-methylpropyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (83a);

(1-hydroxycyclopropyl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (84a);

2-hydroxyethyl-1,1,2,2-d4 (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (85a);

(S)-4,4-difluoro-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (68a); and

(1-methyl-1H-pyrazol-4-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (52a);

or a pharmaceutically acceptable salt thereof

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

The following definitions apply throughout this description, unless indicated specifically to the contrary.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word “comprise”, and variations such as “comprises” and “comprising”, are to be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integer or step.

As used in this specification and the appended claims, the singular forms “a”, “an”, and “the” include plural referents, unless the content clearly dictates otherwise.

The term “about” when used in connection with a numerical value is meant to encompass numerical values within a range having a lower limit that is 0-10% smaller than the indicated numerical value and having an upper limit that is 0-10% larger than the indicated numerical value.

As used herein, the term “alkyl” refers to a monovalent saturated acyclic (i.e., non-cyclic) hydrocarbon group which may be linear or branched. Accordingly, an “alkyl” group does not comprise any carbon-to-carbon double bond or any carbon-to-carbon triple bond. A “C_{1-8} alkyl” denotes an alkyl group having 1 to 8 carbon atoms. Preferred C_{1-8} alkyl is a C_{1-6} alkyl. “C_1-C_6-alkyl”, as used herein, preferably refers to straight chain or branched C_1-C_6-alkyl, which may be, for example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, straight or branched pentyl, straight or branched hexyl. Preferred C_1-C_6-alkyls are C_1-C_4-alkyls, and further preferably C_1-C_3-alkyls. Unless defined otherwise, the term “alkyl” preferably refers to C_{1-4} alkyl, more preferably to methyl or ethyl, and even more preferably to methyl. An alkyl group, in particular methyl group, may be deuterated. For example, a particularly preferred methyl group is -CD_3.

“O–C_1-C_6-alkyl”, as used herein, preferably refers to a “substituted hydroxyl” of the formula (-OR'), wherein R' is a C_1-C_6-alkyl, as defined herein, and the oxygen moiety is directly attached to the parent molecule, and thus the term “O–C_1-C_6-alkyl”, as used herein, refers to straight chain or branched C_1-C_6-alkoxy which may be, for example, methoxy, ethoxy, n-propoxy, isopropoxy, *n*-butoxy, isobutoxy, *sec*-butoxy, *tert*-butoxy, straight or branched pentoxy, straight or branched hexyloxy. Preferred O-C_1-C_6-alkyl are O-C_1-C_4-alkyl.

As used herein, the term “alkenyl” refers to a monovalent unsaturated acyclic hydrocarbon group which may be linear or branched and comprises one or more (e.g., one or two) carbon-to-carbon double bonds while it does not comprise any carbon-to-carbon triple bond. The term “C_{2-6} alkenyl” denotes an alkenyl group having 2 to 6 carbon atoms. Preferred exemplary alkenyl groups are ethenyl, propenyl (e.g., prop-1-en-1-yl, prop-1-en-2-yl, or prop-2-en-1-yl), butenyl, butadienyl (e.g., buta-1,3-dien-1-yl or buta-1,3-dien-2-yl), pentenyl, or pentadienyl (e.g., isoprenyl). Unless defined otherwise, the term “alkenyl” preferably refers to C_{2-4} alkenyl.

As used herein, the term “alkynyl” refers to a monovalent unsaturated acyclic hydrocarbon group which may be linear or branched and comprises one or more (e.g., one or two) carbon-to-carbon triple bonds and optionally one or more (e.g., one or two) carbon-to-carbon double bonds. The term “C_{2-6} alkynyl” denotes an alkynyl group having 2 to 6 carbon atoms. Preferred exemplary alkynyl groups are ethynyl, propynyl (e.g., propargyl), or butynyl. Unless defined otherwise, the term “alkynyl” preferably refers to C_{2-4} alkynyl.

The term “alkylene” preferably refers to an alkanediyl group, i.e. a divalent saturated acyclic hydrocarbon group which may be linear or branched. A “C_{1-6} alkylene” denotes an alkylene group having 1 to 6 carbon atoms. Preferred exemplary alkylene groups are methylene (-CH_2-), ethylene (e.g., -CH_2-CH_2- or -CH(-CH_3)-), propylene (e.g., -CH_2-CH_2-CH_2-, -CH(-CH_2-CH_3)-, -CH_2-CH(-CH_3)-, or -CH(-CH_3)-CH_2-), or butylene (e.g., -CH_2-CH_2-CH_2-CH_2-). Unless defined otherwise, the term “alkylene” preferably refers to C_{2-4} alkylene (including, in particular, linear C_{2-4} alkylene), more preferably to methylene or ethylene, and even more preferably to methylene.

“Halogen”, as used herein, preferably refers to fluorine (fluoro, -F), chlorine (chloro, -Cl), bromine (bromo, -Br), and iodine (iodo, -I). Preferably it refers to fluorine, chlorine or bromine. This also applies, correspondingly, to halogen in combination with other meanings, such as haloalkyl.

The term “cycloalkyl”, as used herein, preferably refers to a saturated hydrocarbon ring group, including monocyclic rings as well as bridged ring, spiro ring and/or fused ring systems (which may be composed, e.g., of two or three rings; such as, e.g., a fused ring system composed of two or three fused rings). “Cycloalkyl” may, e.g., refer to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, decalinyl (i.e., decahydronaphthyl), or adamantyl. Unless defined otherwise, “cycloalkyl” preferably refers to a C_{3-11} cycloalkyl, and more preferably refers to a C_{3-6} cycloalkyl. A particularly preferred “cycloalkyl” is a monocyclic saturated hydrocarbon ring having 3 to 6 ring members (e.g., cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl).

The term “oxygen-containing saturated heterocyclyl”, as used herein, preferably refers to fully saturated 5- to 14-membered ring system group comprising 1 to 2 oxygen atoms and not comprising any other atoms beyond C, H and O. Said heterocyclyl may be a single ring or two or more fused rings wherein at least one ring contains an oxygen atom. Preferably, the term “oxygen-containing saturated heterocyclyl”, as used herein, refers to fully saturated 4- to 7-membered single ring system group comprising 1 to 2 oxygen atoms and not comprising any other atoms beyond C, H and O. Examples of monocyclic oxygen-containing saturated heterocyclyl moieties are given as follows: oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 8-oxabicyclo[3.2.1]octan-3-yl, hexahydrofuro[2,3-b]furan-3-yl and oxepanyl.

The term “nitrogen-containing saturated heterocyclyl”, as used herein preferably refers to fully saturated 5- to 14-membered ring system group comprising 1 to 2 nitrogen atoms and preferably not comprising any other atoms beyond C, H and N. Said heterocyclyl may be a single ring or two or more fused rings wherein at least one ring contains an nitrogen atom. Preferably, the term “nitrogen-containing saturated

heterocyclyl", as used herein, refers to fully saturated 4- to 7-membered single ring system group comprising 1 to 2 nitrogen atoms and not comprising any other atoms beyond C, H and N. Examples of nitrogen-containing saturated heterocyclyl moieties are given as follows: aziridinyl, azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, azepanyl, diazepanyl (e.g., 1,4-diazepanyl), oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, morpholinyl (e.g., morpholin-4-yl), thiomorpholinyl (e.g., thiomorpholin-4-yl), oxazepanyl and 2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl.

The term "sulfur-containing saturated heterocyclyl", as used herein, preferably refers to fully saturated 5- to 14-membered ring system group comprising 1 sulfur atoms and not comprising any other atoms beyond C, H and S. The S atom in the ring may be oxidised, for example in the form of $-SO_2-$ group. Said heterocyclyl may be a single ring or two or more fused rings wherein at least one ring contains an sulfur atom. Preferably, the term "sulfur-containing saturated heterocyclyl", as used herein, refers to fully saturated 4- to 7-membered single ring system group comprising 1 sulfur atoms and not comprising any other atoms beyond C, H and S, wherein the S atom may be oxidised, as indicated herein.

As used herein, the term "carbocyclyl" refers to a hydrocarbon ring group, including monocyclic rings as well as bridged ring, spiro ring and/or fused ring systems (which may be composed, e.g., of two or three rings), wherein said
ring group may be saturated, partially unsaturated (i.e., unsaturated but not aromatic) or aromatic. Unless defined
otherwise, "carbocyclyl" preferably refers to aryl, cycloalkenyl or cycloalkyl.

As used herein, the term "heterocyclyl" refers to a ring group, including monocyclic rings as well as bridged ring, spiro ring and/or fused ring systems (which may be composed, e.g., of two or three rings), wherein said ring group comprises one or more (such as, e.g., one, two, three, or four) ring heteroatoms independently selected from O, S and N, and the remaining ring atoms are carbon atoms, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) may optionally be oxidized, wherein one or more carbon ring atoms may optionally be oxidized (i.e., to form an oxo group), and further wherein said ring group may be saturated, partially unsaturated (i.e., unsaturated but not aromatic) or aromatic. For example, each heteroatom-containing ring comprised in said ring group may contain one or two O atoms and/or one or two S atoms (which may optionally be oxidized) and/or one, two, three or four N atoms (which may optionally be oxidized), provided that the total number of heteroatoms in the corresponding heteroatom-containing ring is 1 to 4 and that there is at least one carbon ring atom (which

may optionally be oxidized) in the corresponding heteroatom-containing ring. Unless defined otherwise, "heterocyclyl" preferably refers to heteroaryl, heterocycloalkenyl or heterocycloalkyl.

As used herein, the term "aryl" refers to an aromatic hydrocarbon ring group, including monocyclic aromatic rings as well as bridged ring and/or fused ring systems containing at least one aromatic ring (e.g., ring systems composed of two or three fused rings, wherein at least one of these fused rings is aromatic; or bridged ring systems composed of two or three rings, wherein at least one of these bridged rings is aromatic). "Aryl" may, e.g., refer to phenyl, naphthyl, dialinyl (i.e., 1,2-dihydronaphthyl), tetralinyl (i.e., 1,2,3,4-tetrahydronaphthyl), indanyl, indenyl (e.g., 1H-indenyl), anthracenyl, phenanthrenyl, 9H-fluorenyl, or azulenyl. Unless defined otherwise, an "aryl" preferably has 6 to 14 ring atoms, more preferably 6 to 10 ring atoms, even more preferably refers to phenyl or naphthyl, and most preferably refers to phenyl.

As used herein, the term "heteroaryl" refers to an aromatic ring group, including monocyclic aromatic rings as well as bridged ring and/or fused ring systems containing at least one aromatic ring (e.g., ring systems composed of two or three fused rings, wherein at least one of these fused rings is aromatic; or bridged ring systems composed of two or three rings, wherein at least one of these bridged rings is aromatic), wherein said aromatic ring group comprises one or more (such as, e.g., one, two, three, or four) ring heteroatoms independently selected from O, S and N, and the remaining ring atoms are carbon atoms, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) may optionally be oxidized, and further wherein one or more carbon ring atoms may optionally be oxidized (i.e., to form an oxo group). For example, each heteroatom-containing ring comprised in said aromatic ring group may contain one or two O atoms and/or one or two S atoms (which may optionally be oxidized) and/or one, two, three or four N atoms (which may optionally be oxidized), provided that the total number of heteroatoms in the corresponding heteroatom-containing ring is 1 to 4 and that there is at least one carbon ring atom (which may optionally be oxidized) in the corresponding heteroatom-containing ring. "Heteroaryl" may, e.g., refer to thienyl (i.e., thiophenyl), benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl (i.e., furanyl), benzofuranyl, isobenzofuranyl, chromanyl, chromenyl (e.g., 2H-1-benzopyranyl or 4H-1-benzopyranyl), isochromenyl (e.g., 1H-2-benzopyranyl), chromonyl, xanthenyl, phenoxathiinyl, pyrrolyl (e.g., 1H-pyrrolyl), imidazolyl, pyrazolyl, pyridyl (i.e., pyridinyl; e.g., 2-pyridyl, 3-pyridyl, or 4-pyridyl), pyrazinyl, pyrimidinyl, pyridazinyl, indolyl (e.g., 3H-indolyl), isoindolyl, indazolyl, indolizinyl, purinyl, quinolyl, isoquinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, cinnolinyl, pteridinyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl (e.g., [1,10]phenanthrolinyl, [1,7]phenanthrolinyl, or [4,7]phenanthrolinyl), phenazinyl, thiazolyl, isothiazolyl,

phenothiazinyl, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl (i.e., furazanyl), or 1,3,4-oxadiazolyl), thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, or 1,3,4-thiadiazolyl), phenoxazinyl, pyrazolo[1,5-a]pyrimidinyl (e.g., pyrazolo[1,5-a]pyrimidin-3-yl), 1,2-benzoisoxazol-3-yl, benzothiazolyl, benzothiadiazolyl, benzoxazolyl, benzisoxazolyl, benzimidazolyl, benzo[b]thiophenyl (i.e., benzothienyl), triazolyl (e.g., 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, or 4H-1,2,4-triazolyl), benzotriazolyl, 1H-tetrazolyl, 2H-tetrazolyl, triazinyl (e.g., 1,2,3-triazinyl, 1,2,4-triazinyl, or 1,3,5-triazinyl), furo[2,3-c]pyridinyl, dihydrofuropyridinyl (e.g., 2,3-dihydrofuro[2,3-c]pyridinyl or 1,3-dihydrofuro[3,4-c]pyridinyl), imidazopyridinyl (e.g., imidazo[1,2-a]pyridinyl or imidazo[3,2-a]pyridinyl), quinazolinyl, thienopyridinyl, tetrahydrothienopyridinyl (e.g., 4,5,6,7-tetrahydrothieno[3,2-c]pyridinyl), dibenzofuranyl, 1,3-benzodioxolyl, benzodioxanyl (e.g., 1,3-benzodioxanyl or 1,4-benzodioxanyl), or coumarinyl. Unless defined otherwise, the term “heteroaryl” preferably refers to a 5 to 14 membered (more preferably 5 to 10 membered) monocyclic ring or fused ring system comprising one or more (e.g., one, two, three or four) ring heteroatoms independently selected from O, S and N, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) are optionally oxidized, and wherein one or more carbon ring atoms are optionally oxidized; even more preferably, a “heteroaryl” refers to a 5 or 6 membered monocyclic ring comprising one or more (e.g., one, two or three) ring heteroatoms independently selected from O, S and N, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) are optionally oxidized, and wherein one or more carbon ring atoms are optionally oxidized.

As used herein, the term “heterocycloalkyl” refers to a saturated ring group, including monocyclic rings as well as bridged ring, spiro ring and/or fused ring systems (which may be composed, e.g., of two or three rings; such as, e.g., a fused ring system composed of two or three fused rings), wherein said ring group contains one or more (such as, e.g., one, two, three, or four) ring heteroatoms independently selected from O, S and N, and the remaining ring atoms are carbon atoms, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) may optionally be oxidized, and further wherein one or more carbon ring atoms may optionally be oxidized (i.e., to form an oxo group). For example, each heteroatom-containing ring comprised in said saturated ring group may contain one or two O atoms and/or one or two S atoms (which may optionally be oxidized) and/or one, two, three or four N atoms (which may optionally be oxidized), provided that the total number of heteroatoms in the corresponding heteroatom-containing ring is 1 to 4 and that there is at least one carbon ring atom (which may optionally be oxidized) in the corresponding heteroatom-containing ring. “Heterocycloalkyl” may, e.g., refer to aziridinyl, azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, azepanyl, diazepanyl (e.g., 1,4-diazepanyl), oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, morpholinyl (e.g., morpholin-4-yl), thiomorpholinyl (e.g., thiomorpholin-4-yl), oxazepanyl, oxiranyl, oxetanyl, tetrahydrofuranyl,

1,3-dioxolanyl, tetrahydropyranyl, 1,4-dioxanyl, oxepanyl, thiiranyl, thietanyl, tetrahydrothiophenyl (i.e., thiolanyl), 1,3-dithiolanyl, thianyl, 1,1-dioxothianyl, thiepanyl, decahydroquinolinyl, decahydroisoquinolinyl, or 2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl. Unless defined otherwise, "heterocycloalkyl" preferably refers to a 3 to 11 membered saturated ring group, which is a monocyclic ring or a fused ring system (e.g., a fused ring system composed of two fused rings), wherein said ring group contains one or more (e.g., one, two, three, or four) ring heteroatoms independently selected from O, S and N, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) are optionally oxidized, and wherein one or more carbon ring atoms are optionally oxidized; more preferably, "heterocycloalkyl" refers to a 5 to 7 membered saturated monocyclic ring group containing one or more (e.g., one, two, or three) ring heteroatoms independently selected from O, S and N, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) are optionally oxidized, and wherein one or more carbon ring atoms are optionally oxidized.

Where a group is said to be optionally substituted, it may carry one or more substituents, such as, e.g., one, two, three or four substituents. It will be understood that the maximum number of substituents is limited by the number of attachment sites available on the substituted moiety. Preferably there are optionally 1-4 substituents, more preferably optionally 1-3 substituents, again more preferably optionally 1 or 2 substituents, and most preferably optionally 1 substituent. Where a group is said to be optionally substituted, and where there are more than one substituent for said optional substitution of said group, said more than one substituent can either be the same or different. As a skilled person will understand, the expression "substituted by" such as in "A is substituted by B" does not mean that B replaces A but that at least one hydrogen atom of A is replaced by at least one group B. The expression "substituted by" is thus equivalent to the expression "substituted with".

Compounds of the invention may have one or more optically active carbon atoms and can thus be present as racemic mixtures, stereoisomers, diastereomers, or enantiomers. All isomeric forms are included in the present invention. The compounds having one or more optically active carbon atoms can be present as an individual stereoisomer, diastereomer, or enantiomer. Alternatively, mixtures thereof can be provided such as racemic mixtures or mixtures containing an excess of one of the stereoisomers, diastereomers, or enantiomers compared to the stereoisomer, diastereomer, or enantiomer having a different orientation at the one or more optically active carbon atoms, preferably the mixtures of the compounds of the invention are characterized by enantiomeric excess of at least 90%, more preferably at least 95%, even more preferably at least 96% of the particular isomer over its enantiomer.

The term "polymorphs" refers to the compounds of the present invention which can exist in two or more crystalline structures. Salts can also be crystalline and may exist as more than one polymorph.

Solvates (including hydrates) as well as anhydrous forms of the salt are also encompassed by the invention. The solvent included in the solvates is not particularly limited and can be any pharmaceutically acceptable solvent. Examples include water as well as C_{1-4} alcohols (such as methanol or ethanol).

"Pharmaceutically acceptable salts" are defined as derivatives of the compounds of the present invention wherein the parent compound is modified by making acid or base salts thereof. Lists of suitable salts can be found in Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing Company, Easton, PA, 1990, p. 1445, the disclosure of which is hereby incorporated by reference.

The term "treating" and/or "treatment" refers to the management and care of a patient having a pathology such as a viral infection or other condition for which administration of one or more therapeutic compounds is indicated for the purpose of combating or alleviating symptoms and complications of those conditions. Treating includes administering one or more formulations of the present invention to prevent the onset of the symptoms or complications, alleviating the symptoms or complications, or eliminating the disease, condition, or disorder. As used herein, "treatment" or "therapy" refer to both therapeutic treatment and prophylactic or preventative measures. The effect may be therapeutic in terms of partially or completely curing a disease or a condition and/or symptoms attributed to the disease or the condition. The term refers to inhibiting the disease or condition, i.e. arresting its development; or ameliorating the disease or condition, i.e. causing regression or reducing symptoms of the disease or condition.

The term "prevention" as used herein refers to means of preventing or delaying the onset of disease or condition and/or symptoms attributed to the disease or condition.

The term "disease" and "disorder" are used interchangeably herein, referring to an abnormal condition, especially an abnormal medical condition such as an illness or injury, wherein a tissue, an organ or an individual is not able to efficiently fulfil its function anymore. Typically, but not necessarily, a disease is associated with specific symptoms or signs indicating the presence of such disease. The presence of such symptoms or signs may thus, be indicative for a tissue, an organ or an individual suffering from a disease. An alteration of these symptoms or signs may be indicative for the progression of such a disease. A progression of a disease is typically characterized by an increase or decrease of such symptoms or signs which may indicate a "worsening" or "bettering" of the disease. The "worsening" of a disease is

characterized by a decreasing ability of a tissue, organ or organism to fulfil its function efficiently, whereas the “bettering” of a disease is typically characterized by an increase in the ability of a tissue, an organ or an individual to fulfil its function efficiently. A tissue, an organ or an individual being at “risk of developing” a disease is in a healthy state but shows potential of a disease emerging. Typically, the risk of developing a disease is associated with early or weak signs or symptoms of such disease. In such case, the onset of the disease may still be prevented by treatment. Examples of a disease include but are not limited to transplant rejection, autoimmune diseases, inflammatory diseases, infectious diseases, and lymphoproliferative disorders.

As used herein, the terms “subject” or “animal” or “patient” or “mammal,” refers to any subject, particularly a mammalian subject, for whom diagnosis, prognosis, prophylaxis or therapy is desired, for example, a human or a domesticated mammal such as a dog, cat or horse or a food animal such as a cow or sheep or pig, preferably to a human.

As used herein, the term “for use” as used in “composition for use in treatment of a disease” shall disclose also the corresponding method of treatment and the corresponding use of a preparation for the manufacture of a medicament for the treatment of a disease.

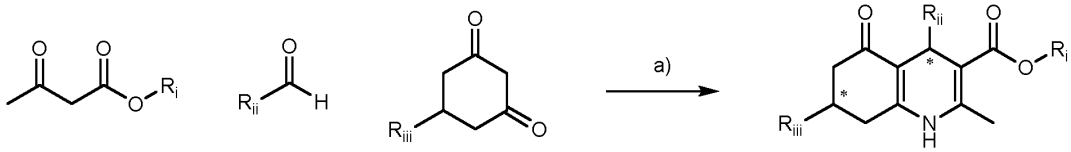
A “therapeutically effective amount” or “effective amount” is the amount of a compound or pharmaceutical composition in accordance with the present invention that will elicit the biological or medical response of a subject, preferably a human subject, that is being sought by the researcher, veterinarian, medical doctor or other clinician. The term “therapeutic administration”, as used herein, should refer to the administration of therapeutically effective amount.

As preferably understood herein, whenever a reference is made to a compound or a pharmaceutically acceptable salt, stereoisomer, diastereoisomer, enantiomer, polymorph, racemic mixture, solvate or isomers and mixtures thereof, preferably a reference is made to a compound or a pharmaceutically acceptable salt, stereoisomer, diastereoisomer, enantiomer, or isomers and mixtures thereof, more preferably a reference is made to a compound or a pharmaceutically acceptable salt, stereoisomer, diastereoisomer, or enantiomer thereof, even more preferably a reference is made to a compound or a pharmaceutically acceptable salt thereof. It is understood that the term "mixtures" covers, but is not limited to, racemic mixtures of the compound or of the pharmaceutically acceptable salt thereof.

As further preferably understood herein, whenever a reference is made to a compound of formula (I), the reference is preferably made to the compound of formula (I) or its pharmaceutically acceptable salt.

Preparation of the compound of formula (I)

The compounds of the present invention are obtainable according to the following scheme of Hantzsch cyclization:



XIV XV XVI I

wherein R_1 to R_3 are defined in formula (I). Further details are given in Example 1.

Asymmetric synthesis of the compounds of the invention can be performed as in, or analogously to, the synthetic method described in the Examples, or as described hereinbelow.

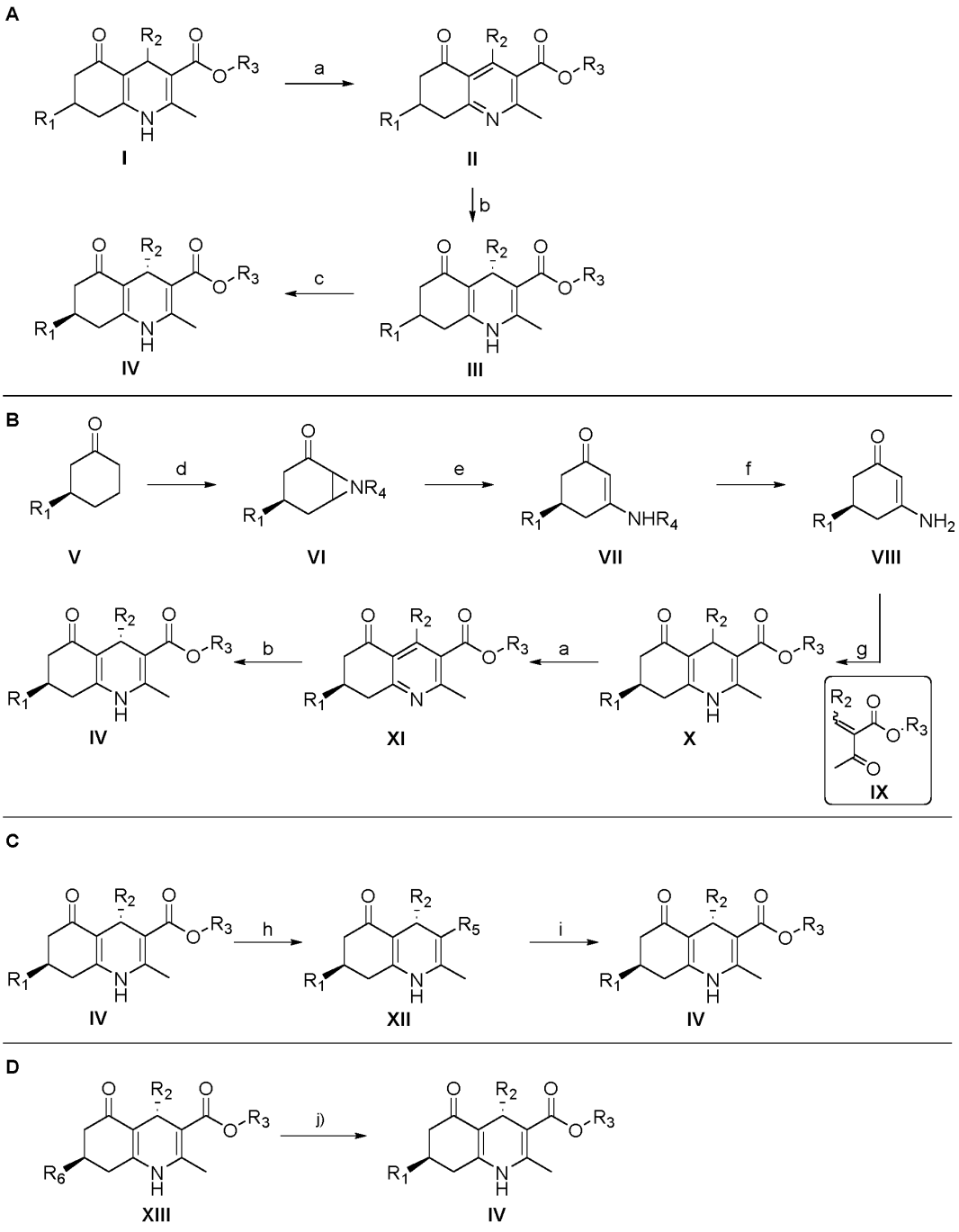
Alternatively, enantiopure compounds can also be obtained by late-stage ester exchange via hydrolysis or hydrogenation and esterification, the synthetic method described in Example 4, or as described hereinbelow.

Alternatively, enantiopure compounds can also be obtained by late-stage cross-coupling reactions, the synthetic method described in Example 6, or as described hereinbelow.

Accordingly, the present invention further relates to the method for preparing the compounds of formula (I), preferably in their enantiopure forms.

For example, the enantiopure compounds according to the present invention can be obtained either via A) diastereoselective synthesis followed by chromatographic separation or B) asymmetric synthesis as are depicted by the following reactions or C) late-stage ester exchange via hydrolysis and esterification or D) late-stage cross-coupling reactions (Scheme 1):

Scheme 1:



wherein R_1 to R_3 are defined in formula (I).

R_4 is selected from the group consisting of amine protecting groups, most preferably a *tert*-butyloxycarbonyl group. The skilled person is in position to select the correct group for use as R_4.

R_5 is an activated ester equivalent or a carboxylic acid, preferably a carboxylic acid. Said ester equivalents include, but are not limited to carboxylic acid chloride, carboxylic acid bromide and carboxylic acid anhydride. The skilled person is in a position to select the correct group for the use as R_5. Accordingly, R_5 may be selected from carboxylic acid, carboxylic acid chloride, carboxylic acid bromide and carboxylic acid anhydride, preferably R_5 is carboxylic acid.

R_6 is selected from the group consisting of aryl and heteroaryl, wherein said aryl and said heteroaryl each bear a leaving group or are each activated. Said leaving groups include, but are not limited to halogens, triflates, tosylates and other pseudohalides, most preferably halogens. Said activated aryls and heteroaryls include, but are not limited to, boronic acids, boronic esters or boronates of said aryl or heteroaryl, respectively. The skilled person is in position to select the correct group for use as R_6.

The reaction shown can involve the following reaction steps:

Reactions:

a) Conversion of a 1,4-dihydropyridine motive to the corresponding pyridine motive by oxidation;
b) Asymmetric reduction of the pyridine motive via enantioselective partial transfer hydrogenation (chiral phosphoric acid, Hantzsch ester);
c) Separation of the diastereomers via preparative HPLC or flash chromatography;
d) Introduction of alpha, beta unsaturation via silyl enol ether formation followed by oxidation (base, R_3SiX, hypervalent iodine(V)) or selenoxide elimination (RSeX, oxidant) or direct dehydrogenation of cyclohexanones (Pd^{II}, O_2);

followed by aziridine formation via aziridination (*N*-protected-*p*-toluenesulfonamide, bisamine, base);

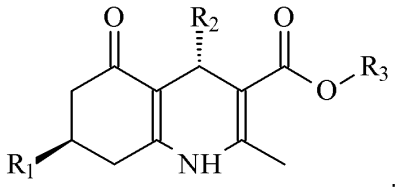
e) Aziridine opening via photochemical irradiation (hv);
f) Optional nitrogen deprotection, unless R_4 is hydrogen;
g) Condensation of intermediates VIII and IX;
h) Ester hydrolysis and optionally formation of active ester equivalent,
i) Esterification; and
j) Cross-coupling reaction.

Suitable reaction conditions for steps a, f - j are known to the skilled person. Alternatively, steps h and i can be replaced by a direct transesterification step.

Alternatively, enantiopure intermediate VIII can be obtained i) via chromatographic separation of racemic VIII, ii) chiral resolution of racemic VIII via formation of diastereomeric salts with enantiopure resolving agents such as carboxylic acids or sulfonic acids, or iii) by addition of a chiral auxiliary, separation and

subsequent removal of the chiral auxiliary. The skilled person is in position to select the correct chromatographic methods, resolving agent or chiral auxiliary.

Accordingly, the present invention further relates to a method of preparing the compound of formula (I), as defined hereinabove, the method comprising the step (b) of asymmetric reduction of the pyridine motive via enantioselective partial transfer hydrogenation. Exemplary methods of the present invention are shown in Scheme 1 A and B. In one embodiment, the method further comprises the step (e) of aziridine opening via photochemical irradiation (hv). Preferably, the compound of formula (I) prepared according to the method of the invention is a compound of formula:



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For the step (b) of asymmetric reduction of the pyridine motive via enantioselective partial transfer hydrogenation, conditions have been adapted from: Org. Lett. 2014, 16, 2982 and ACIE, 2020, 59, 23107.

In one embodiment, the present invention relates to a pharmaceutical composition comprising the compound of the present invention and a pharmaceutically acceptable carrier. The pharmaceutical compositions can be formulated by techniques known to the person skilled in the art, such as the techniques published in “Remington: The Science and Practice of Pharmacy”, Pharmaceutical Press, 22nd edition, which is incorporated herein by reference in its entirety.

In a further preferred embodiment, the present invention relates to the use of a compound of the invention for the manufacture of a medicament for inhibiting coronin 1 expression in the induction of immunosuppression or in the treatment and/or prevention of a disease or disorder selected from the group consisting of transplant rejection, autoimmune diseases, inflammatory diseases, infectious diseases, and lymphoproliferative disorders.

In a further preferred embodiment, the present invention relates to a method for inhibiting coronin 1 expression in the induction of immunosuppression or in the treatment and/or prevention and/or alleviation of symptoms of a disease or disorder selected from the group consisting of transplant rejection, autoimmune diseases, inflammatory diseases, infectious diseases, and lymphoproliferative disorders comprising administering a compound of the invention to a subject in need thereof. In this method, a therapeutically effective amount of the compound of the invention is typically administered.

In a preferred embodiment, a compound of the present invention is used as a medicament for inhibiting coronin 1 expression. In another preferred embodiment, a compound of the present invention is used as a medicament for inhibiting coronin 1 promoter activity. In another preferred embodiment, a compound of the present invention is used as a medicament for depleting coronin 1 in a subject.

In another preferred embodiment, a compound of the invention is used as a medicament for inhibiting coronin 1 expression in the induction of immunosuppression or in the treatment and/or prevention of a disease or disorder selected from transplant rejection, autoimmune diseases, inflammatory diseases, infectious diseases, and lymphoproliferative disorders. In another preferred embodiment, a compound of the invention is used as a medicament for inhibiting coronin 1 expression in the induction of immunosuppression or in the treatment and/or prevention of a disease or disorder selected from the group consisting of transplant rejection, autoimmune diseases, and lymphoproliferative disorders. In another preferred embodiment, a compound of the invention is used as a medicament for inhibiting coronin 1 expression in the treatment and/or prevention of a disease or disorder selected from the group consisting of transplant rejection, autoimmune diseases, inflammatory diseases, infectious diseases, and lymphoproliferative disorders. In another preferred embodiment, a compound of the invention is used as a medicament for inhibiting coronin 1 expression in the treatment and/or prevention of a disease or disorder selected from the group consisting of transplant rejection, autoimmune diseases, and lymphoproliferative disorders. In another preferred embodiment, a compound of the invention is used as a medicament for inhibiting coronin 1 expression in the treatment and/or prevention of transplant rejection and/or lymphoproliferative disorders. In another preferred embodiment, a compound of the invention is used as a medicament for inhibiting coronin 1 expression in the treatment and/or prevention of inflammatory diseases and/or infectious diseases. In another preferred embodiment, a compound of the invention is used as a medicament for inhibiting coronin 1 expression in the induction of immunosuppression. In another preferred embodiment, a compound of the invention is used as a medicament for inhibiting coronin 1 expression in the treatment and/or prevention of transplant rejection. In another preferred embodiment, a compound of the invention is used as a medicament for inhibiting coronin 1 expression in the treatment and/or prevention of autoimmune diseases. In another preferred embodiment, a compound of the invention is used as a medicament for inhibiting coronin 1 expression in the treatment and/or prevention of lymphoproliferative disorders. In another preferred embodiment, a compound of the invention is used as a medicament for inhibiting coronin 1 expression in the treatment and/or prevention of inflammatory diseases. In another preferred embodiment, a compound of the

invention is used as a medicament for inhibiting coronin 1 expression in the treatment and/or prevention of infectious diseases.

In another preferred embodiment, a compound of the invention is used as a medicament in the treatment and/or prevention of a disease or disorder selected from transplant rejection, autoimmune diseases, inflammatory diseases, infectious diseases, and lymphoproliferative disorders. In another preferred embodiment, a compound of the invention is used as a medicament in the treatment and/or prevention of a disease or disorder selected from the group consisting of transplant rejection, autoimmune diseases, and lymphoproliferative disorders. In another preferred embodiment, a compound of the invention is used as a medicament in the treatment and/or prevention of a disease or disorder selected from the group consisting of transplant rejection, autoimmune diseases, inflammatory diseases, infectious diseases, and lymphoproliferative disorders. In another preferred embodiment, a compound of the invention is used as a medicament in the treatment and/or prevention of a disease or disorder selected from the group consisting of transplant rejection, autoimmune diseases, and lymphoproliferative disorders. In another preferred embodiment, a compound of the invention is used as a medicament in the treatment and/or prevention of transplant rejection and/or lymphoproliferative disorders. In another preferred embodiment, a compound of the invention is used as a medicament in the treatment and/or prevention of inflammatory diseases and/or infectious diseases. In another preferred embodiment, a compound of the invention is used as a medicament in the induction of immunosuppression. In another preferred embodiment, a compound of the invention is used as a medicament in the treatment and/or prevention of transplant rejection. In another preferred embodiment, a compound of the invention is used as a medicament in the treatment and/or prevention of autoimmune diseases. In another preferred embodiment, a compound of the invention is used as a medicament in the treatment and/or prevention of lymphoproliferative disorders. In another preferred embodiment, a compound of the invention is used as a medicament in the treatment and/or prevention of inflammatory diseases. In another preferred embodiment, a compound of the invention is used as a medicament in the treatment and/or prevention of infectious diseases.

In preferred embodiment, a compound of the invention is used as a medicament in the induction of immunosuppression or in the treatment and/or prevention of a disease or disorder selected from the group consisting of transplant rejection, autoimmune diseases, inflammatory diseases, infectious diseases, and lymphoproliferative disorders, wherein said disease or disorder to be treated and/or prevented is caused or promoted by coronin 1 expression.

In preferred embodiment, a compound of the invention is used as a medicament in the induction of immunosuppression or in the treatment and/or prevention of a disease or disorder selected from the group consisting of transplant rejection, autoimmune diseases, inflammatory diseases, infectious diseases, and lymphoproliferative disorders, wherein said induction, treatment and/or prevention is based on coronin 1 depletion. In preferred embodiment, a compound of the invention is used as a medicament in the induction of immunosuppression or in the treatment and/or prevention of a disease or disorder selected from the group consisting of transplant rejection, autoimmune diseases, inflammatory diseases, infectious diseases, and lymphoproliferative disorders, wherein said induction, treatment and/or prevention is based on inhibition of coronin 1 expression.

Preferably, said autoimmune disease is selected from the group consisting of psoriasis, vitiligo, multiple sclerosis, systemic lupus erythematosus, Hashimoto's thyroiditis, rheumatoid arthritis, primary sclerosing cholangitis, myasthenia gravis, diabetes type I or II, disorders secondary to diabetes type I or II, vasculitis, pernicious anaemia, Sjogren syndrome, uveitis, Graves' ophthalmopathy, alopecia areata, allergic asthma, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, myocarditis, hepatitis, and allergic contact dermatitis. More preferably, said , said autoimmune disease is selected from the group consisting of psoriasis, multiple sclerosis, systemic lupus erythematosus, Hashimoto's thyroiditis, rheumatoid arthritis, myasthenia gravis, diabetes type I or II, disorders secondary to diabetes type I or II, vasculitis, pernicious anaemia, Sjogren syndrome, uveitis, Graves' ophthalmopathy, alopecia areata, allergic asthma, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, myocarditis, hepatitis, and allergic contact dermatitis.

Preferably, said transplant rejection is selected from the group consisting of acute or chronic rejection of cells, tissue, organ, allografts and xenografts, poor graft functional states, graft versus host disease. Preferably, said transplant rejection is selected from the group consisting of rejection of cardiac transplant, skin transplant, renal transplant, liver transplant, islet transplant, pancreas transplant, lung transplant, bowel transplant, corneal transplant, vascular transplant, adrenal transplant, hair transplant, bone transplant, cartilage transplant and ligamental transplant.

Preferably, said inflammatory disease is selected from the group consisting of inflammatory bowel disease, Crohn's disease, ulcerative colitis, intrinsic asthma, inflammatory lung injury, inflammatory liver injury, inflammatory glomerular injury, atherosclerosis, osteoarthritis, myositis, polymyositis, prurigo nodularis, hidradenitis suppurativa, eosinophilic esophagitis, fibrotic disorders, cardio vasculopathy, allergic disorders, irritant contact dermatitis, eczematous dermatitis, seborrhoeic dermatitis, cutaneous manifestations of immunologically-mediated disorders, inflammatory eye diseases, keratoconjunctivitis,

myocardial infarction, stroke, gut ischemia, renal failure, hemorrhage shock, traumatic shock, toxic shock, septic shock and adult respiratory distress syndrome, preferably consisting of inflammatory bowel disease, Crohn's disease, ulcerative colitis, intrinsic asthma, inflammatory lung injury, inflammatory liver injury, inflammatory glomerular injury, atherosclerosis, osteoarthritis, irritant contact dermatitis, eczematous dermatitis, seborrhoeic dermatitis, cutaneous manifestations of immunologically-mediated disorders, inflammatory eye diseases, keratoconjunctivitis, myocardial infarction, stroke, gut ischemia, renal failure, haemorrhage shock, traumatic shock, toxic shock, septic shock and adult respiratory distress syndrome.

Preferably, said lymphoproliferative disorder is T cell lymphoma or T cell leukaemia.

Preferably, said infectious disease is selected from the group consisting of tuberculosis, preferably caused by mycobacteria, Salmonella sp. infections, Helicobacter sp. infections, retroviral infections, preferably HIV or HTLV, cytomegalo viral infection, candida infection, Staphylococcus infections, lympho-choriomeningitis viral infections and viral hepatitis.

Said Mycobacteria include and preferably are *Mycobacterium tuberculosis, Mycobacterium leprae, Mycobacterium marinum, Mycobacterium bovis, Mycobacterium avium, Mycobacterium intracellulare, Mycobacterium kansasii, Mycobacterium malmoense, Mycobacterium simiae, Mycobacterium szulgai, Mycobacterium xenopi, Mycobacterium scrofulaceum, Mycobacterium abscessus, Mycobacterium chelonae, Mycobacterium haemophilum*, and/or *Mycobacterium ulcerans*.

In a further embodiment, the present invention relates to a compound of formula (I) or a pharmaceutically acceptable salt, stereoisomer, diastereoisomer, enantiomer, polymorph, racemic mixture, solvate or isomers and mixtures thereof, as described hereinabove, for use in the treatment or prevention of a disease that can benefit from BRD3 inhibition, either directly or indirectly via reduced expression of Coronin 1 and/or coronin 1 promoter activity.

The disease that can benefit from BRD3 inhibition (either directly or indirectly via reduced expression of Coronin 1) can preferably be understood as a disease amenable for therapeutic intervention through direct inhibition of BRD3 or via modulation of coronin 1 expression through BRD3 inhibition and/or coronin 1 promoter activity. Preferably, said disease is selected from transplant rejection, autoimmune diseases, inflammatory diseases, infectious diseases, and lymphoproliferative disorders. The recited diseases are as disclosed hereinabove. Furthermore, BRD3-driven diseases are preferably immune inflammatory

diseases, malignant diseases and their metastasis, such as, NMC, OCCC, colorectal carcinoma or rhabdomyosarcoma, preferably NMC, OCCC or rhabdomyosarcoma.

Accordingly, the present invention provides the compound of formula (I) for use in treatment or prevention of transplant rejection, autoimmune diseases, inflammatory diseases, infectious diseases, and lymphoproliferative disorders (as defined herein). The present invention further provides the compound of formula (I) for use in treatment or prevention of NMC, colorectal carcinoma, OCCC or rhabdomyosarcoma and their metastasis, preferably NMC, OCC or rhabdomyosarcoma.

As it is to be understood herein, BRD3 inhibition relates to blocking of the binding site of bromodomains in BRD3, thereby preventing BRD3 from binding its natural ligands (acetylated N-terminal tails of histones and other acetylated transcription factors like GATA-1, RelA, STAT3 etc). Accordingly, the compounds referred to as BRD3-inhibitors can also be referred to as BRD3-blockers, in particular BRD3-bromodomain blockers.

The present inventors have found that, surprisingly, the compounds of the present invention inhibit coronin 1 promoter activity resulting in suppression of the expression of coronin 1, by targeting selectively the bromodomains of BRD3. The target BRD3 is known to drive the development of a highly invasive malignancy in 1/3 of the patients diagnosed to have NUT (Nuclear protein of Testis)-Midline Cancers (NMC) (Kervarrec, T., et al., Reply to: Expanding the Spectrum of Primary Cutaneous Carcinoma With BRD3-NUTM1 Fusion. Am J Surg Pathol, 2021. 45(11): p. 1584-1586). NMC is considered to be one of the most highly aggressive malignancies known with over 80% of the diagnosed patients dying within the first one year. Currently, there exists no specific cure except for surgical resection if detected early prior to significant metastasis or using a therapy with one of the non-selective BET inhibitors or side effect prone chemotherapy for NMC (Shapiro, G.I., et al., Br J Cancer, 2021. 124(4): p. 744-753). The non-selective BET inhibitors also block BRD4 and BRD2, which not only results in toxicity but also induces blanket immunosuppression due to inhibition of BRD4 and BRD2 dependent immune-inflammatory responses. Targeting of BRD3 has been reported to play a critical role in the control of a rare type of gynecological malignancy termed Ovarian Clear Cell Carcinoma (OCCC) (Shigeta, S., et al., Mol Cancer Ther, 2021. 20(4): p. 691-703). As with NMC, the mortality rate of patients with ovarian cancer is the highest among major gynecologic malignancies. The patients with OCCC are often treated with platinum-based chemotherapies causing numerous side effects and toxicity if not for the recently approved PARP inhibitors. Many of these patients become refractory to these therapies and hence there is a dire need for safe and targeted therapy against these cancers. Thus, the present invention relates to the compounds

of the present invention for use in the treatment or prevention of a disease that can benefit from BRD3 inhibition either directly or indirectly via reduced expression of coronin 1 and coronin 1 activity. Preferably, the present invention relates to the compound of the present invention for use in the treatment of prevention of NMC or OCCC, preferably for use in the treatment or prevention of BRD3-driven NMC or BRD3-driven OCCC. Likewise, targeting BRD3 has been shown to play a critical role in eradication of cancer metastasis in a colorectal carcinoma model by being a critical phosphorylated substrate for TYRO3, thereby regulating anti-apoptosis gene expression and epithelial mesenchymal transition (Hsu, PL., et al., Sci Adv, 2023. **9**, eade3422.).

According to the present inventors, exemplary compounds of formula (I) are selective or preferential BRD3-bromodomain inhibitors (blockers). As preferably understood herein, a BRD3-selective (BRD3-preferential) bromodomain blocker is defined as a compound that significantly stabilizes BRD3 and does not significantly stabilize other bromodomain and extra-terminal (BET) family of bromodomain-containing proteins, as determined according to PISA methodology. Preferably, the BRD3-selective bromodomain blocker significantly stabilizes BRD3 and it does not significantly stabilize BRD2 and BRD4, as determined according to PISA methodology. Thermal Proteome Profiling and PISA methodology are techniques well known to the skilled person. Suitable concentration range of compounds for thermal stability profiling are 1 – 6 µM. An exemplary result of a thermal stability profiling using PISA methodology is shown in Fig. 2, and exemplary experimental details of applying such a method are disclosed in Example 9. Preferably, PISA is to be performed at a concentration of the compound at 6 µM using THP-1 or RBL cells (preferably RBL cells).

Preferably, the compound of formula (I), as defined herein, is a selective BRD3-bromodomain inhibitor (BRD3-bromodomain blocker), as defined herein. In other words, the compound of formula (I) preferably binds only to BRD3 and not to other bromodomain and extra-terminal (BET) family of bromodomain-containing proteins, as determined according to PISA methodology.

Further according to the present inventors, it is postulated that the medical applications of the compounds of the present invention which relate to the inhibition/blocking of BRD3 (i.e., the bromodomains of BRD3) are not limited to the compounds of formula (I), as provided herein, but can be practiced with any BRD3-selective bromodomain inhibitor (blocker). Accordingly, the present invention further provides a BRD3-selective bromodomain inhibitor for use in treatment or prevention of transplant rejection, autoimmune diseases, inflammatory diseases, infectious diseases, and lymphoproliferative disorders (as defined herein). The present invention further provides a BRD3-selective bromodomain inhibitor for use in

treatment or prevention of NMC, colorectal carcinoma, OCCC or rhabdomyosarcoma, preferably NMC, OCCC or rhabdomyosarcoma. The exemplary and preferred a BRD3-selective bromodomain inhibitor is a compound of formula (I), as disclosed herein.

In a further aspect of the invention, said compounds of the present invention are used for inhibiting coronin 1 expression *in vitro*, preferably in a cell-based assay. Further, said compounds of the present invention are used for inhibiting coronin 1 promoter activity *in vitro*, preferably in a cell-based assay. Further, said compounds of the present invention are used for depleting coronin 1 *in vitro*, preferably in a cell-based assay. Said cells are preferably vertebrate cells, more preferably mammalian cells, again more preferably mammalian immune cells, again more preferably human, mouse or rat immune cells. Said cells are preferably selected from the group consisting of CD4, CD8 T cells, B cells, neutrophils, macrophages, dendritic cells, Langerhans cells, eosinophils, NK cells, follicular antigen presenting cells, monocytes, neuronal cells, glial cells, or basophil leukemia (RBL) cells, preferably of human, rat and mouse origin.

In a further aspect of the invention, said compounds of the present invention are provided for use for differential suppression of immune responses to auto (self) antigen versus infectious antigen. It is to be understood that the suppression of immune responses to auto (self) antigen is stronger than the suppression of infectious antigen, as determined according to the OT-II model system, as described herein. Accordingly, the compounds of formula (I) are provided for use in suppression of immune responses to auto (self) antigen, wherein said suppression of auto (self) antigen is stronger (wherein the "percent difference" is at least by 20%, preferably at least by 30%, more preferably at least by 50%) than the suppression seen with an infectious antigen as determined according to the OT-II model system. Calculation of "percent difference" is to be performed as follows: The tritiated thymidine incorporation (CPM values) values are normalized against the vehicle treated group which is set to 100%. The relative tritiated thymidine incorporation in an auto (self) antigen context with a particular compound treatment gives X%. The relative tritiated thymidine incorporation in an infectious context with a particular compound treatment gives Y%. The "percent differences" are calculated by Y% - X%., meaning subtracting X% from Y%.

The compounds of formula (I) are selective (or, in other words, preferential) suppressors of immune responses to auto (self) antigens over infectious antigens. As understood herein, preferential suppressors of immune responses to auto (self) antigens over infectious antigens is defined as a compound that has a "percent difference" of at least 20%, more preferably 30% and even more preferably 50%, as determined according to the OT-II model system. The OT-II model system and associated techniques are well known

to the skilled person. Application of the OT-II model system is described in detail in the Examples. Suitable concentration range of compounds for assessing the differential suppression immune responses to auto (self) antigen versus infectious antigen are 1 – 6 µM. An exemplary result of a differential suppression of immune responses to infectious antigen versus auto (self) antigen is shown in Fig. 5, and exemplary experimental details of applying such a method are disclosed in Example 11. Preferably OT-II model system is to be performed at a concentration of the compound at 3 µM.

As preferably understood herein, the compounds of the present invention or the pharmaceutical compositions of the present invention, comprising the compound of the present invention and at least one pharmaceutically acceptable carrier, may be formulated for administration in any way known to the skilled person. Likewise, the compounds of the present invention or the pharmaceutical compositions of the present invention may be administered in accordance with the invention by any route of administration. Accordingly, said route of administration include, but are not limited to, oral (also referred to as peroral, e.g., tablets, capsules, liquids), intravenous, intramuscular, subcutaneous, by inhalation (e.g., aerosols, nebulizers), transdermal (e.g., patches), topical (e.g., creams, ointments), rectal (e.g., suppositories), intraperitoneal, sublingual, buccal, ocular (e.g., eye drops), nasal (e.g., sprays, inhalers), and vaginal. It is further conceivable that the compound of the present invention or the pharmaceutical composition of the present invention may be administered through specialized delivery systems, such as implantable devices, sustained-release formulations, or through the use of nanoparticles or liposomes to improve bioavailability and targeted delivery. It is particularly preferred that the compound of the invention or the pharmaceutical composition of the invention is to be administered perorally.

Typically, a physician will determine the actual dosage which will be most suitable for an individual subject. The specific dose level and frequency of dosage for any particular individual subject may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the individual subject undergoing therapy.

A proposed, yet non-limiting dose of the compounds according to the invention for oral administration to a human (of approximately 70 kg body weight) may be 0.05 to 2000 mg, preferably 0.1 mg to 1000 mg, of the active ingredient per unit dose. The unit dose may be administered, e.g., 1 to 3 times per day. The unit dose may also be administered 1 to 21 times per week. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient/subject as well

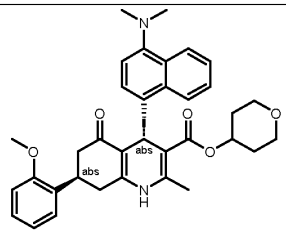
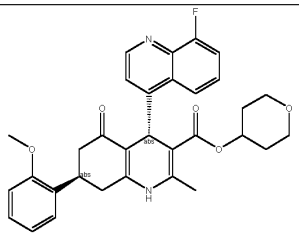
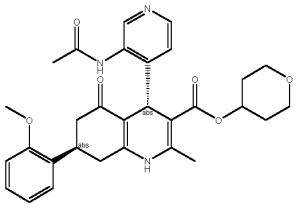
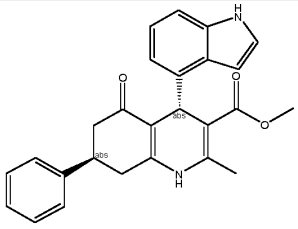
as the severity of the condition to be treated. The precise dose and also the route of administration will ultimately be at the discretion of the attending physician.

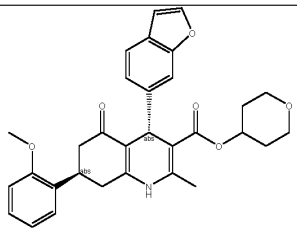
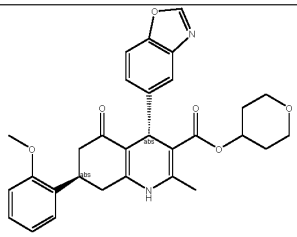
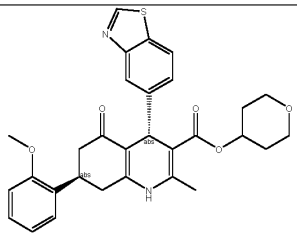
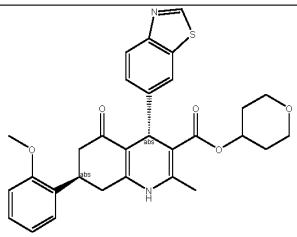
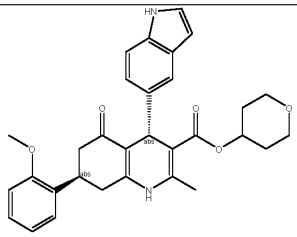
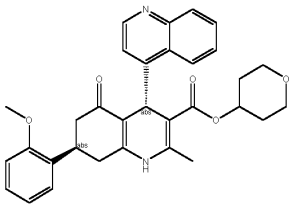
Examples

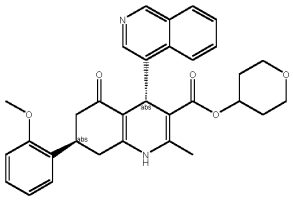
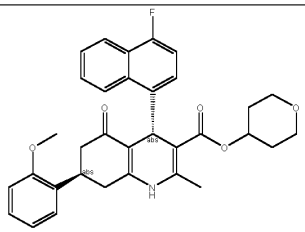
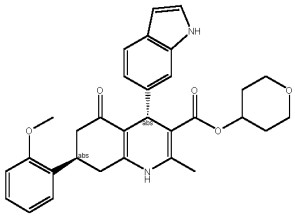
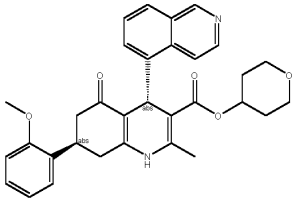
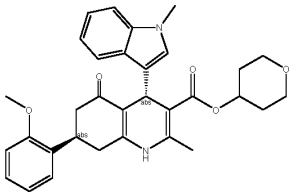
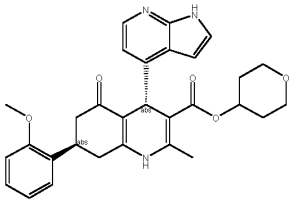
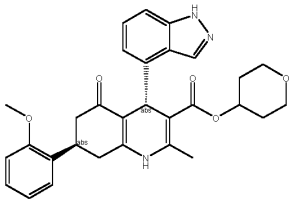
Compounds of the invention that selectively inhibit coronin 1 promoter activity, as determined by the fluorescence-based screening assay.

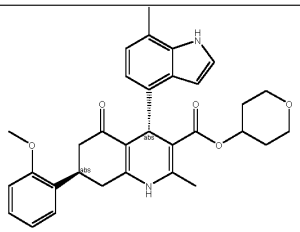
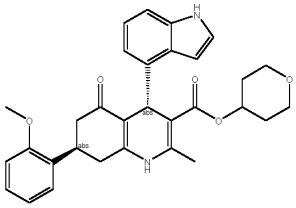
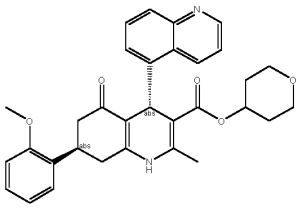
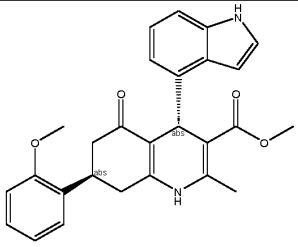
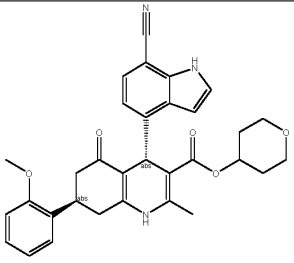
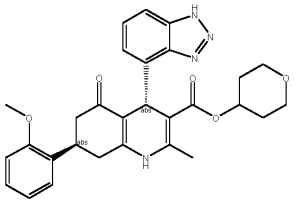
The compounds 1-101 depicted in Table 1 can be synthesized according to the syntheses described in Examples 1-7.

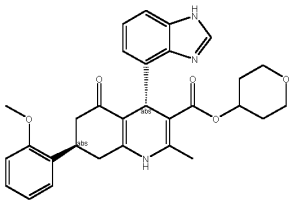
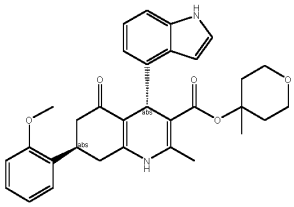
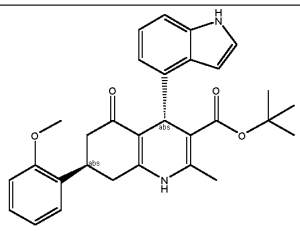
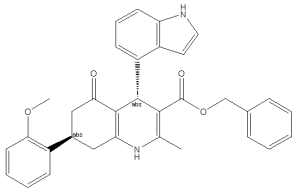
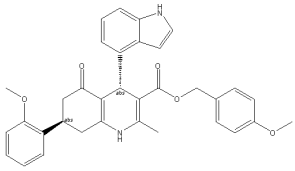
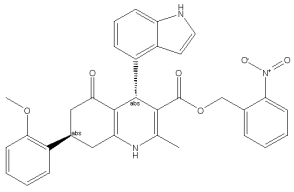
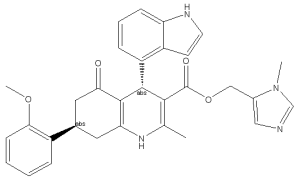
Table 1. Compounds 1-101

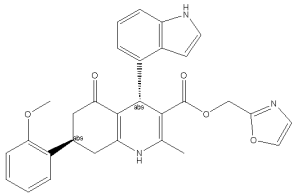
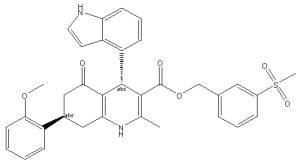
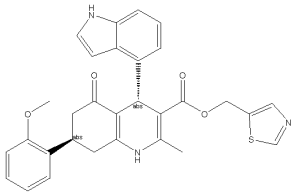
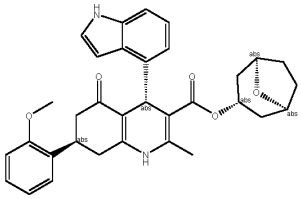
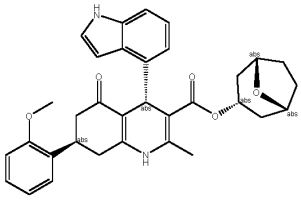
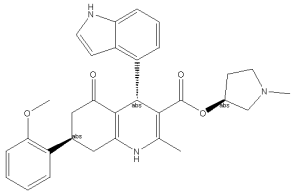
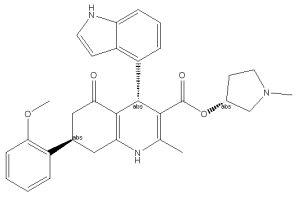
Cpd. No.	Structure	Compound name
1a		tetrahydro-2H-pyran-4-yl (4S,7R)-4-(4-(dimethylamino)naphthalen-1-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (1a)
2a		tetrahydro-2H-pyran-4-yl (4S,7R)-8'-fluoro-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-[4,4'-biquinoline]-3-carboxylate (2a)
3a		tetrahydro-2H-pyran-4-yl (4S,7R)-4-(3-acetamidopyridin-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (3a)
4a		methyl (4S,7R)-4-(1H-indol-4-yl)-2-methyl-5-oxo-7-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4a)

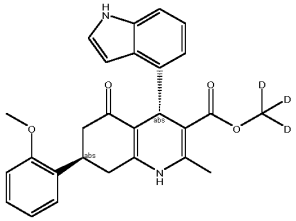
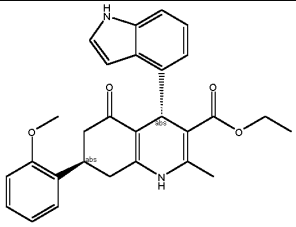
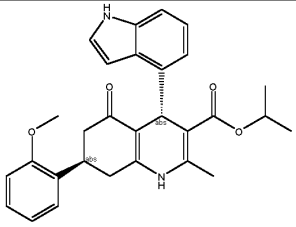
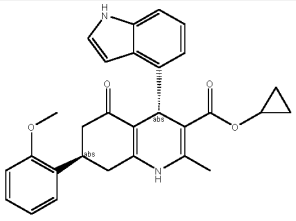
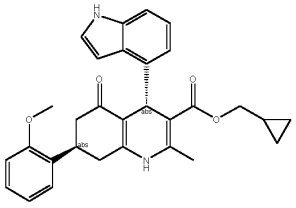
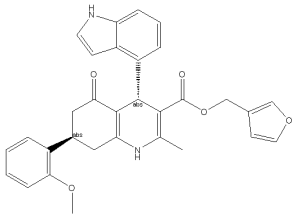
5a		tetrahydro-2H-pyran-4-yl (4S,7R)-4-(benzofuran-6-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5a)
6a		tetrahydro-2H-pyran-4-yl (4S,7R)-4-(benzo[d]oxazol-5-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (6a)
7a		tetrahydro-2H-pyran-4-yl (4S,7R)-4-(benzo[d]thiazol-5-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (7a)
8a		tetrahydro-2H-pyran-4-yl (4S,7R)-4-(benzo[d]thiazol-6-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (8a)
9a		tetrahydro-2H-pyran-4-yl (4S,7R)-4-(1H-indol-5-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (9a)
10a		tetrahydro-2H-pyran-4-yl (4S,7R)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-[4,4'-biquinoline]-3-carboxylate (10a)

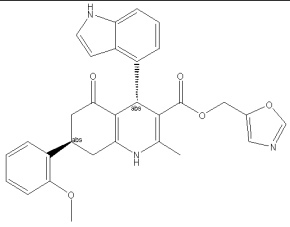
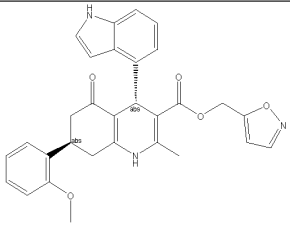
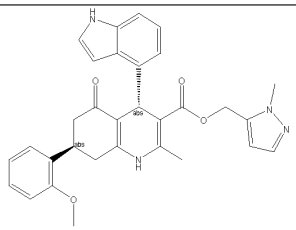
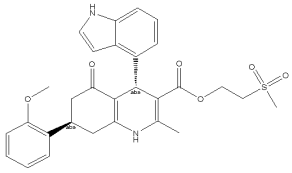
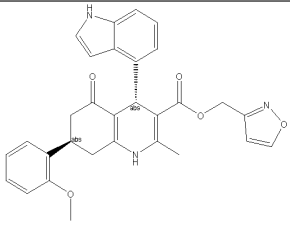
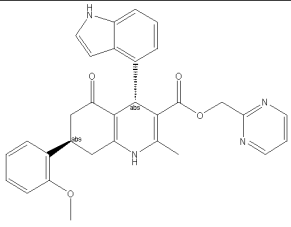
11a		tetrahydro-2H-pyran-4-yl (4S,7R)-4-(isoquinolin-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (11a)
12a		tetrahydro-2H-pyran-4-yl (4S,7R)-4-(4-fluoronaphthalen-1-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (12a)
13a		tetrahydro-2H-pyran-4-yl (4S,7R)-4-(1H-indol-6-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (13a)
14a		tetrahydro-2H-pyran-4-yl (4S,7R)-4-(isoquinolin-5-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (14a)
15a		tetrahydro-2H-pyran-4-yl (4S,7R)-7-(2-methoxyphenyl)-2-methyl-4-(1-methyl-1H-indol-3-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (15a)
16a		tetrahydro-2H-pyran-4-yl (4S,7R)-7-(2-methoxyphenyl)-2-methyl-5-oxo-4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (16a)
17a		tetrahydro-2H-pyran-4-yl (4S,7R)-4-(1H-indazol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (17a)

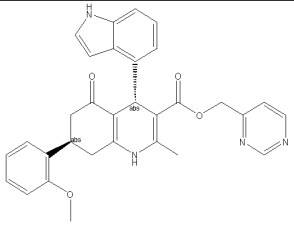
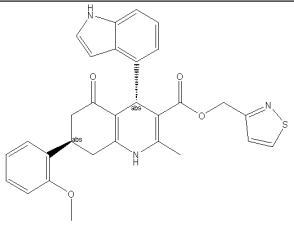
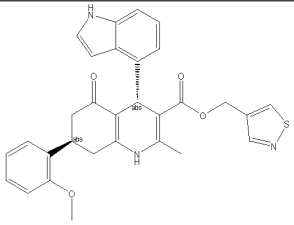
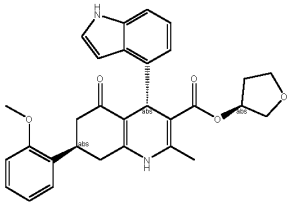
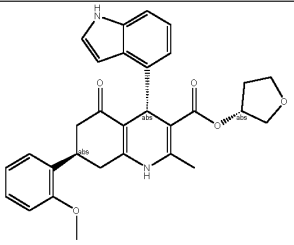
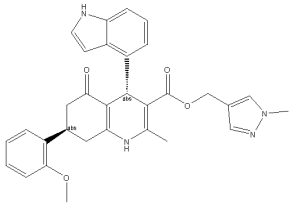
18a		tetrahydro-2H-pyran-4-yl (4S,7R)-7-(2-methoxyphenyl)-2-methyl-4-(7-methyl-1H-indol-4-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (18a)
19a		tetrahydro-2H-pyran-4-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (19a)
20a		tetrahydro-2H-pyran-4-yl (4S,7R)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-[4,5'-biquinoline]-3-carboxylate (20a)
21a		methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (21a)
22a		tetrahydro-2H-pyran-4-yl (4S,7R)-4-(7-cyano-1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (22a)
23a		tetrahydro-2H-pyran-4-yl (4S,7R)-4-(1H-benzo[d][1,2,3]triazol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (23a)

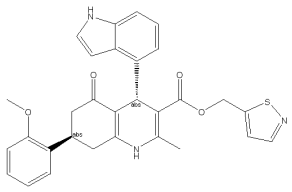
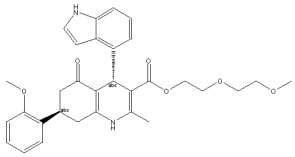
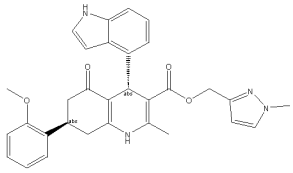
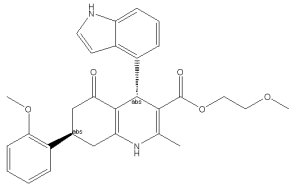
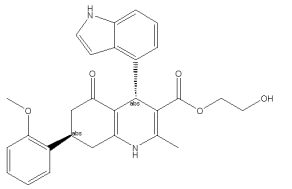
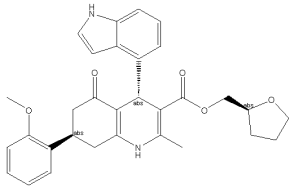
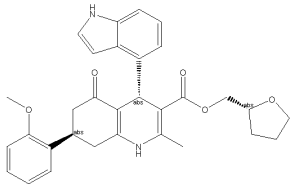
24a		tetrahydro-2H-pyran-4-yl (4S,7R)-4-(1H-benzo[d]imidazol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (24a)
25a		4-methyltetrahydro-2H-pyran-4-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (25a)
26a		tert-butyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (26a)
27a		benzyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (27a)
28a		4-methoxybenzyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (28a)
29a		2-nitrobenzyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (29a)
30a		(1-methyl-1H-imidazol-5-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (30a)

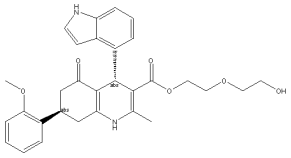
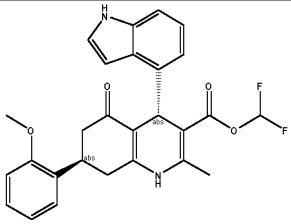
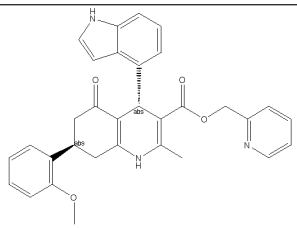
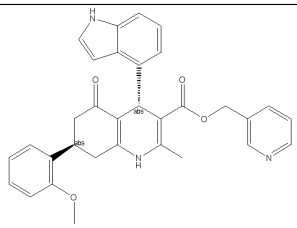
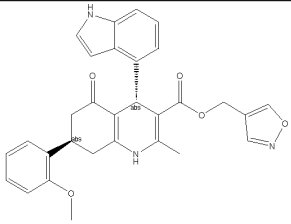
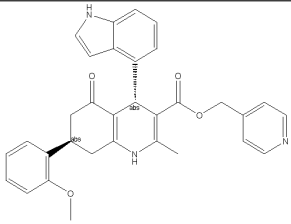
31a		oxazol-2-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (31a)
32a		3-(methylsulfonyl)benzyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (32a)
33a		thiazol-5-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (33a)
34a		(1R,3s,5S)-8-oxabicyclo[3.2.1]octan-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (34a)
34b		(1R,3r,5S)-8-oxabicyclo[3.2.1]octan-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (34b)
35a		(S)-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (35a)
35b		(R)-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (35b)

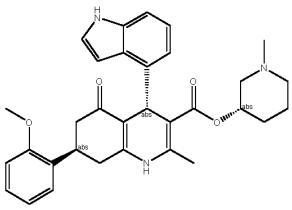
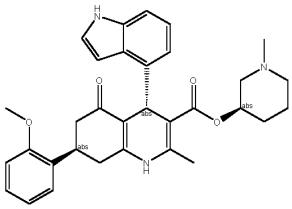
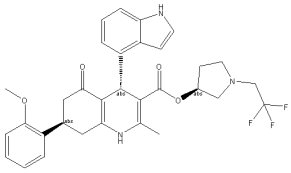
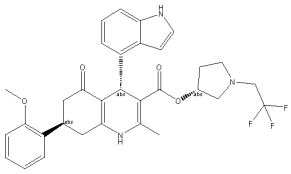
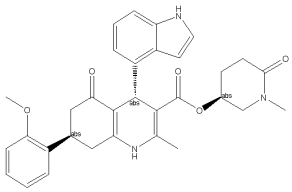
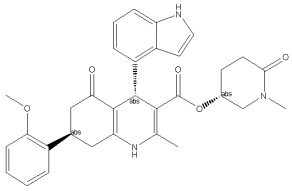
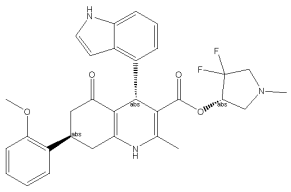
36a		methyl-d3 (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (36a)
37a		ethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (37a)
38a		isopropyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (38a)
39a		cyclopropyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (39a)
40a		cyclopropylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (40a)
41a		furan-3-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (41a)

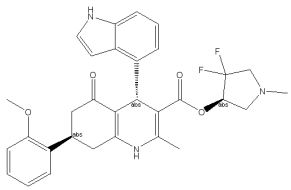
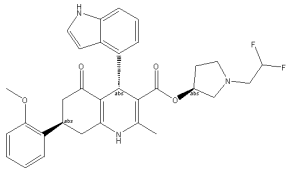
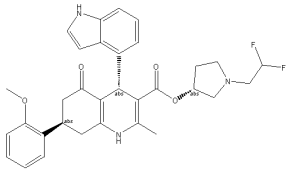
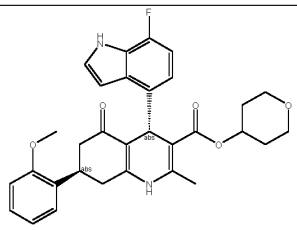
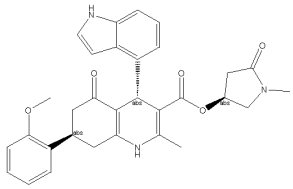
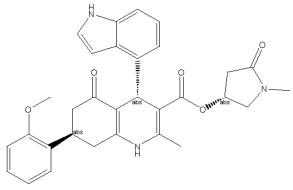
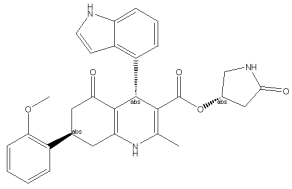
42a		oxazol-5-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (42a)
43a		isoxazol-5-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (43a)
44a		(1-methyl-1H-pyrazol-5-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (44a)
45a		2-(methylsulfonyl)ethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (45a)
46a		isoxazol-3-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (46a)
47a		pyrimidin-2-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (47a)

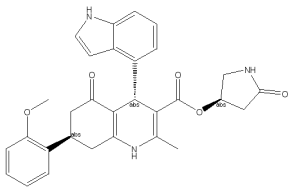
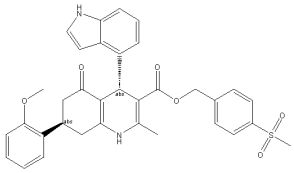
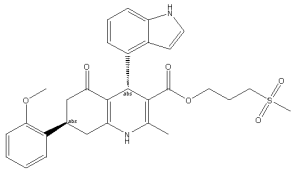
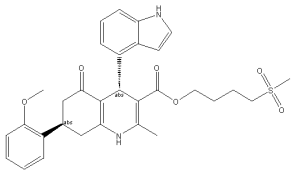
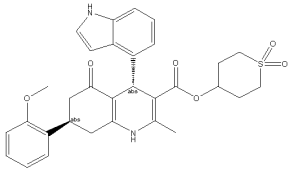
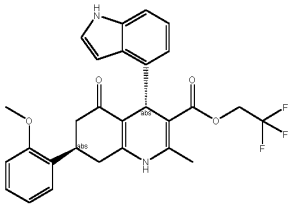
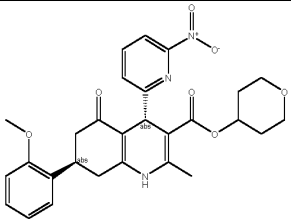
48a		pyrimidin-4-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (48a)
49a		isothiazol-3-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (49a)
50a		isothiazol-4-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (50a)
51a		(S)-tetrahydrofuran-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (51a)
51b		(R)-tetrahydrofuran-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (51b)
52a		(1-methyl-1H-pyrazol-4-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (52a)

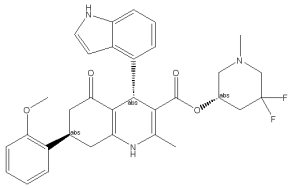
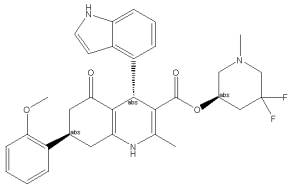
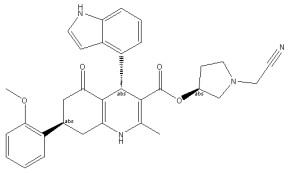
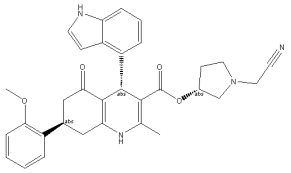
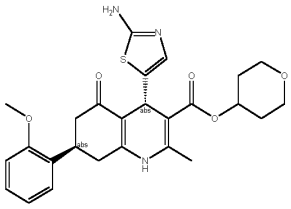
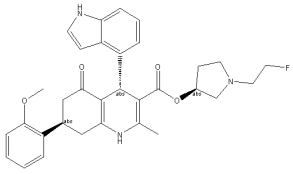
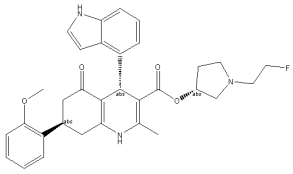
53a		isothiazol-5-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (53a)
54a		2-(2-methoxyethoxy)ethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (54a)
55a		(1-methyl-1H-pyrazol-3-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (55a)
56a		2-methoxyethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (56a)
57a		2-hydroxyethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (57a)
58a		((S)-tetrahydrofuran-2-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (58a)
58b		((R)-tetrahydrofuran-2-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (58b)

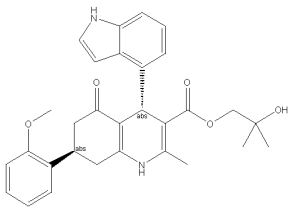
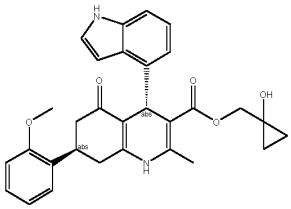
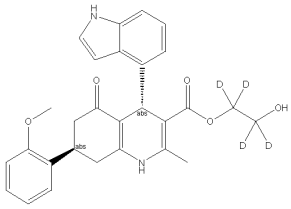
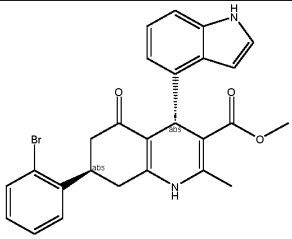
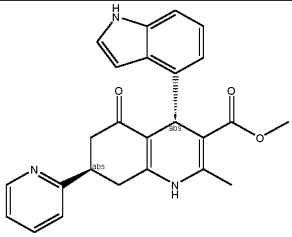
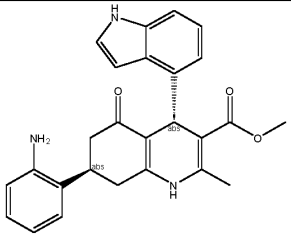
59a		2-(2-hydroxyethoxy)ethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (59a)
60a		difluoromethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (60a)
61a		pyridin-2-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (61a)
62a		pyridin-3-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (62a)
63a		isoxazol-4-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (63a)
64a		pyridin-4-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (64a)

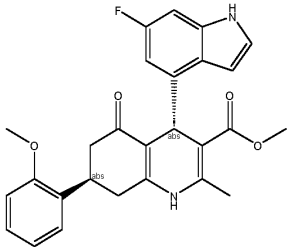
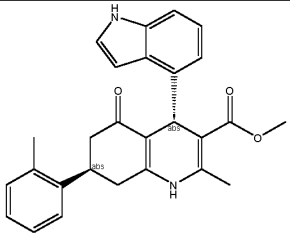
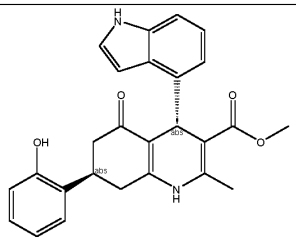
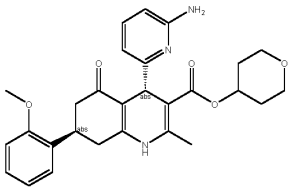
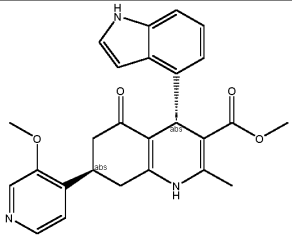
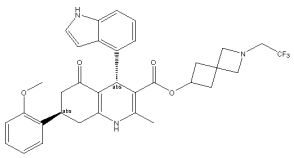
65a		(S)-1-methylpiperidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (65a)
65b		(R)-1-methylpiperidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (65b)
66a		(S)-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (66a)
66b		(R)-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (66b)
67a		(S)-1-methyl-6-oxopiperidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (67a)
67b		(R)-1-methyl-6-oxopiperidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (67b)
68a		(S)-4,4-difluoro-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (68a)

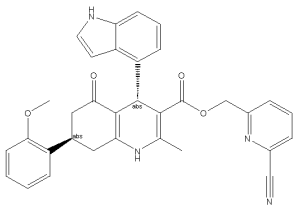
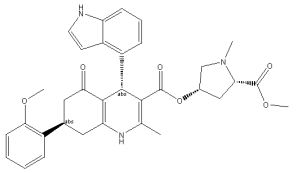
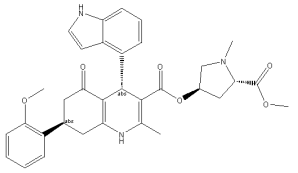
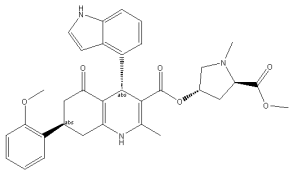
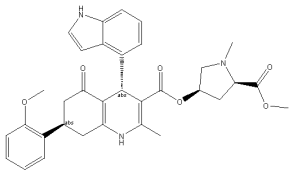
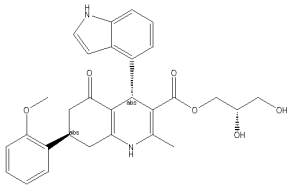
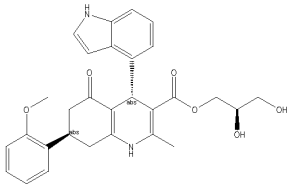
68b		(R)-4,4-difluoro-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (68b)
69a		(S)-1-(2,2-difluoroethyl)pyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (69a)
69b		(R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (69b)
70a		tetrahydro-2H-pyran-4-yl (4S,7R)-4-(7-fluoro-1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (70a)
71a		(S)-1-methyl-5-oxopyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (71a)
71b		(R)-1-methyl-5-oxopyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (71b)
72a		(S)-5-oxopyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (72a)

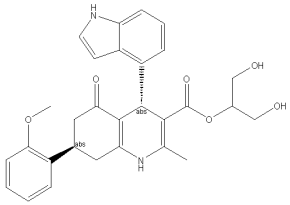
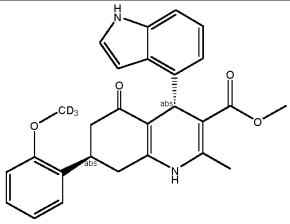
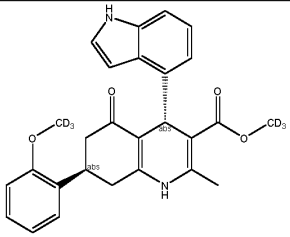
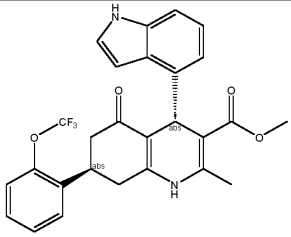
72b		(R)-5-oxopyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (72b)
73a		4-(methylsulfonyl)benzyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (73a)
74a		3-(methylsulfonyl)propyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (74a)
75a		4-(methylsulfonyl)butyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (75a)
76a		1,1-dioxidotetrahydro-2H-thiopyran-4-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (76a)
77a		2,2,2-trifluoroethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (77a)
78a		tetrahydro-2H-pyran-4-yl (4S,7R)-7-(2-methoxyphenyl)-2-methyl-4-(6-nitropyridin-2-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (78a)

79a		(S)-5,5-difluoro-1-methylpiperidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (79a)
79b		(R)-5,5-difluoro-1-methylpiperidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (79b)
80a		(S)-1-(cyanomethyl)pyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (80a)
80b		(R)-1-(cyanomethyl)pyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (80b)
81a		tetrahydro-2H-pyran-4-yl (4S,7R)-4-(2-aminothiazol-5-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (81a)
82a		(S)-1-(2-fluoroethyl)pyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (82a)
82b		(R)-1-(2-fluoroethyl)pyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (82b)

83a		2-hydroxy-2-methylpropyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (83a)
84a		(1-hydroxycyclopropyl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (84a)
85a		2-hydroxyethyl-1,1,2,2-d4 (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (85a)
86a		methyl (4S,7R)-7-(2-bromophenyl)-4-(1H-indol-4-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (86a)
87a		methyl (4S,7R)-4-(1H-indol-4-yl)-2-methyl-5-oxo-7-(pyridin-2-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (87a)
88a		methyl (4S,7R)-7-(2-aminophenyl)-4-(1H-indol-4-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (88a)

89a		methyl (4S,7R)-4-(6-fluoro-1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (89a)
90a		methyl (4S,7R)-4-(1H-indol-4-yl)-2-methyl-5-oxo-7-(o-tolyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (90a)
91a		methyl (4S,7R)-7-(2-hydroxyphenyl)-4-(1H-indol-4-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (91a)
92a		tetrahydro-2H-pyran-4-yl (4S,7R)-4-(6-aminopyridin-2-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (92a)
93a		methyl (4S,7R)-4-(1H-indol-4-yl)-7-(3-methoxypyridin-4-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (93a)
94a		2-(2,2,2-trifluoroethyl)-2-azaspiro[3.3]heptan-6-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (94a)

95a		(6-cyanopyridin-2-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (95a)
96a		(3S,5S)-5-(methoxycarbonyl)-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (96a)
96b		(3R,5S)-5-(methoxycarbonyl)-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (96b)
96c		(3S,5R)-5-(methoxycarbonyl)-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (96c)
96d		(3R,5R)-5-(methoxycarbonyl)-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (96d)
97a		(S)-2,3-dihydroxypropyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (97a)
97b		(R)-2,3-dihydroxypropyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (97b)

98a		1,3-dihydroxypropan-2-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (98a)
99a		methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-(methoxy-d3)phenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (99a)
100a		methyl-d3 (4S,7R)-4-(1H-indol-4-yl)-7-(2-(methoxy-d3)phenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (100a)
101a		methyl (4S,7R)-4-(1H-indol-4-yl)-2-methyl-5-oxo-7-(2-(trifluoromethoxy)phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (101a)

General Information for Examples:

MS UPLC Method:

A2: Column Acquity UPLC CSH C18 (2.1x50mm) 1.7µm, Eluent A = H_2O + 0.02 % HCOOH - Eluent B = CH_3CN + 0.02% HCOOH - Gradient: 2% B to 98% B in 2.4 min - Flow rate = 0.8 mL/min

A3: Column Acquity UPLC CSH C18 (2.1x50mm) 1.7µm, Eluent A = H_2O + 0.02 % HCOOH - Eluent B = CH_3CN + 0.02% HCOOH - Gradient: 2% B to 98% B in 1.5 min - Flow rate = 0.8 mL/min

A20 Column Acquity UPLC CSH C18 (2.1x100mm) 1.7µm, Eluent A = H_2O + 0.02 % HCOOH - Eluent B = CH_3CN + 0.02% HCOOH - Gradient: 2% B to 98% B in 15 min - Flow rate = 0.7 mL/min

A21 Column Acquity UPLC CSH C18 (2.1x50mm) 1.7µm, Eluent A = H_2O + 0.02 % HCOOH - Eluent B = CH_3CN + 0.02% HCOOH - Gradient: 2% B to 98% B in 4 min - Flow rate = 1.0 mL/min

For mixtures of diastereomers the major peak is reported, unless otherwise indicated.

Chiral UPLC Methods:

C1: Column Chiralpack IC 250x4.6mm 6 µm, Eluent 60:40 CO_2/MeOH, Flow rate = 2.4 mL/min, Pressure 104 bar

C2: Column Chiralpack AD 250x4.6mm 5 µm, Eluent 70:30 CO_2/*i*PrOH, Flow rate = 2.4 mL/min, Pressure 104 bar

C3: Column Chiralpack IB 250x4.6mm 5 µm, Eluent 60:40 CO_2/MeOH, Flow rate = 2.4 mL/min, Pressure 104 bar

C4: Column Chiralcel OJ 250x4.6mm 5 µm, Eluent 60:40 CO_2/MeOH, Flow rate = 2.4 mL/min, Pressure 104 bar

C5: Column Chiralpack IB 250x4.6mm 5 µm, Eluent 60:40 CO_2/MeOH+0.5% diisopropylamide, Flow rate = 2.4 mL/min, Pressure 104 bar

C6: Column Chiralpack IB 250x4.6mm 5 µm, Eluent 70:30 CO_2/MeOH+0.5% diisopropylamide, Flow rate = 2.4 mL/min, Pressure 104 bar

C7: Column Chiralpack IA 250x4.6mm 5 µm, Eluent 60:40 CO_2/MeOH, Flow rate = 2.4 mL/min, Pressure 104 bar

NMR spectroscopy:

Chemical shifts (δ) are reported in ppm with the residual solvent signal as internal standard. The data is reported as (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, coupling constant(s), integration). For mixtures of diastereomers the spectroscopic signals of the mixtures were reported unless otherwise noted.

Reaction conditions:

Experimental descriptions of reaction conditions are reported as example procedures for a subset of compounds and compounds that were obtained using an analogous procedure. The skilled person is in position to determine the appropriate reaction times, work-up and purification conditions for each individual compound.

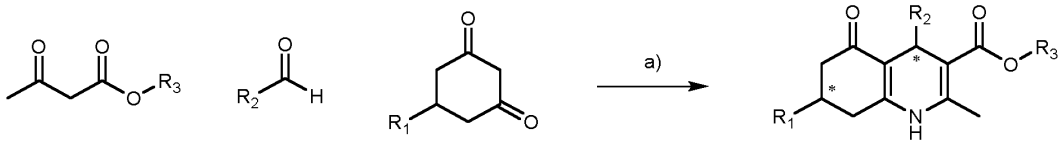
Abbreviations:

ACN	acetonitrile
AcOH	acetic acid
Boc	tert-butyloxycarbonyl or tert-butoxycarbonyl
Cpd.	compound
d	day
DCM	dichloromethane

DMF	dimethylformamide
DMSO	dimethyl sulfoxide
equiv	equivalents
EtOAc	ethyl acetate
EtOH	ethanol
IBX*MPO	2-Iodoxybenzoic acid * 4-methoxypyridine N-oxide
h	hour
*i*Pr	*iso*-propyl
M	molar
MeTHF	2-methyltetrahydrofuran
min	minutes
MS	mass spectrometry
NMR	nuclear magnetic resonance
prep.	preparative
RBF	round bottom flask
RT	room temperature
Rt	retention time
*t*Bu	*tert*-butyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TRIP	3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate
UPLC	Ultra-performance liquid chromatography

EXAMPLE 1

Synthesis of racemic scaffolds for evaluation:

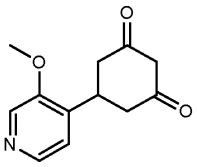


XIV XV XVI I

General scheme for the synthesis of racemic scaffolds using a modified Hantzsch dihydropyridine synthesis giving direct access to racemic 4,7-substituted 4,6,7,8-tetrahydroquinolin-5(1H)-ones (I).

Procedures preparing non-commercial diketones for a:

5-(3-methoxy-4-pyridyl)cyclohexane-1,3-dione:



Step i) To a stirred solution of 3-methoxypyridine-4-carbaldehyde (400 mg, 2.83 mmol) in water (1.5 mL) and acetone (0.80 mL) was added sodium hydroxide (8.0 mg, 0.20 mmol). The mixture was stirred at RT overnight. Then all solvents were removed under vacuum. EtOAc and water were added, and the aqueous phase was extracted twice with EtOAc. The organic phase was dried with Na2SO4, filtered and concentrated under vacuum to give (*E*)-4-(3-methoxy-4-pyridyl)but-3-en-2-one.

M/z = 178 [M+H]+, Rt = 1.45 min (Method A2)

Step ii) To a stirred solution of diethyl propanedioate (241 µL, 1.56 mmol) in ethanol (2.0 mL) at 0 °C was added slowly sodium ethoxide (580 µL, 1.55 mmol) in ethanol (2.0 mL). The mixture was stirred 5 min at 0 °C. Then was added (*E*)-4-(3-methoxy-4-pyridyl)but-3-en-2-one (275 mg, 0.466 mmol). The mixture was stirred at 60 °C 1 h 30 min. The mixture was concentrated under vacuum. Then EtOAc, water and saturated aqueous solution of $NaHCO_3$ were added. The organic phase was washed with water. The aqueous phase was recovered and acidified with acetic acid until pH 4. The aqueous phase was extracted twice with EtOAc, the organic phase was dried with Na_2SO_4, filtered, and concentrated under vacuum to give ethyl 2-(3-methoxy-4-pyridyl)-4,6-dioxo-cyclohexanecarboxylate.

M/z = 292 [M+H]+, Rt = 1.47 min (Method A2)

Step iii) To a stirred solution of ethyl 2-(3-methoxy-4-pyridyl)-4,6-dioxo-cyclohexanecarboxylate (120 mg, 0.41 mmol) and sodium hydroxide (50.0 µL, 1.70 mmol) in water (0.48 mL). The reaction mixture was stirred at 50°C overnight. Then the mixture was cooled and sulfuric acid (112 µL, 2.09 mmol) was added until an acidic pH. The reaction mixture was stirred at RT 45 min. DCM and water were added and the aqueous phase was recovered. The aqueous phase was basified with $NaHCO_3$ until pH 8. Then the aqueous phase was extracted twice with EtOAc, the organic phase was dried with Na_2SO_4, filtered, and concentrated under vacuum to give the title compound.

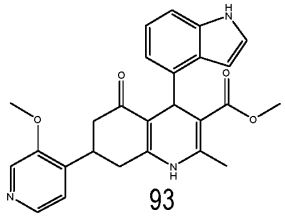
M/z = 220 [M+H]+, Rt = 0.38 min (Method A2)

Example Procedure a1: 93

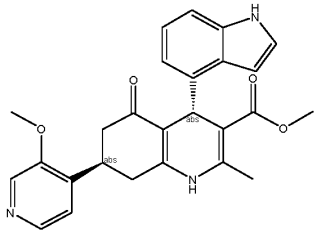
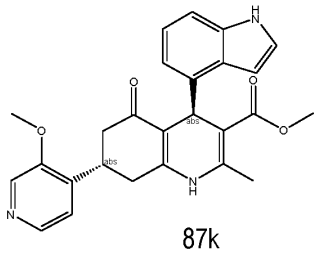
To a stirred solution of 5-(3-methoxy-4-pyridyl)cyclohexane-1,3-dione (90.0 mg, 0.41 mmol) in ethanol (2.0 mL) was added methyl 3-oxobutanoate (50.0 µL, 0.440 mmol), (2*S*)-pyrrolidine-2-carboxylic acid (10.0 mg, 0.084 mmol), 1H-indole-4-carbaldehyde (51.0 µL, 0.44 mmol) and ammonium acetate (49.0 mg, 0.62 mmol). The reaction mixture was stirred 1 h 30 min at 80 °C. The reaction mixture was concentrated under vacuum, water and ethyl acetate were added, the phases separated, and the aqueous

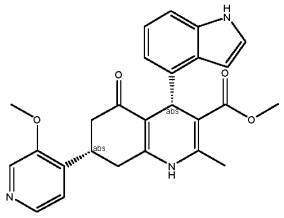
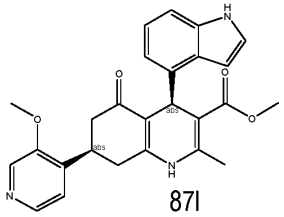
phase was extracted with ethyl acetate. The combined organic layers were washed with water, dried using a phase separator and concentrated under vacuum. The crude material was purified by Flash chromatography on silica gel using a gradient of acetone in toluene from 10% to 50%. The desired fractions were combined and concentrated under vacuum to give the title compound.

The following compounds were obtained using this protocol:

Structure Cpd. No.	NMR Mixture of 2 diastereomers	MS
 93	(50/50): 1H NMR (600 MHz, DMSO-d6) δ 10.95 – 10.74 (m, 1H), 9.41 – 9.07 (m, 1H), 8.31 – 8.22 (m, 1H), 8.22 – 7.78 (m, 1H), 7.32 – 7.30 (m, 1H), 7.26 – 7.19 (m, 1H), 7.16 – 7.10 (m, 1H), 6.94 – 6.84 (m, 1H), 6.81 – 6.67 (m, 1H), 6.61 – 6.51 (m, 1H), 5.49 – 5.09 (m, 1H), 3.91 – 3.82 (m, 3H), 3.68 – 3.63 (m, 1H), 3.47 – 3.40 (m, 3H), 2.92 – 2.61 (m, 2H), 2.48 – 2.18 (m, 5H)	M/z = 444 [M+H]+, Rt = 1.04/1.08 min (Method A21)

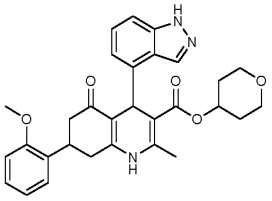
The following compounds were obtained using this protocol and subsequently separated by Flash chromatography (see below for analytic):

Structure Cpd. No.	NMR	MS
 and  87k	Mixture of 2 *anti*-isomers (50/50): 1H NMR (500 MHz, DMSO-d6) δ 10.89 (s, 1H), 9.27 (s, 1H), 8.55 – 8.52 (m, 1H), 7.78 – 7.72 (m, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.28 – 7.24 (m, 2H), 7.15 (dt, J = 8.0, 0.9 Hz, 1H), 6.93 (t, J = 7.6 Hz, 1H), 6.82 (dd, J = 7.4, 0.9 Hz, 1H), 6.60 (ddd, J = 3.1, 2.1, 0.9 Hz, 1H), 5.33 (s, 1H), 3.46 (s, 3H), 3.30 – 3.22 (m, 1H), 2.91 (dd, J = 17.1, 11.6 Hz, 1H), 2.81 – 2.75 (m, 1H), 2.56 (dd, J = 16.5, 12.9 Hz, 1H), 2.38 – 2.32 (m, 1H), 2.27 (s, 3H)	M/z = 414 [M+H]+, Rt = 1.3 min (Method A21)

 and  87l	Mixture of 2 *syn*-isomers (50/50): 1H NMR (500 MHz, DMSO-d6) δ 10.82 (s, 1H), 9.16 (s, 1H), 8.46 (dd, J = 5.2, 2.2 Hz, 1H), 7.59 (td, J = 7.7, 1.9 Hz, 1H), 7.22 – 7.18 (m, 3H), 7.09 (dt, J = 8.0, 0.9 Hz, 1H), 6.83 – 6.79 (m, 1H), 6.61 (dd, J = 7.4, 0.9 Hz, 1H), 6.50 (ddd, J = 3.1, 2.0, 0.9 Hz, 1H), 5.26 (s, 1H), 3.64 – 3.52 (m, 1H), 3.46 (s, 3H), 3.02 (dd, J = 16.6, 8.3 Hz, 1H), 2.83 (dd, J = 16.5, 5.0 Hz, 1H), 2.50 – 2.48 (m, 2H), 2.22 (s, 3H)	M/z = 414 [M+H]+, Rt = 1.17 min (Method A21)

Example Procedure a2:

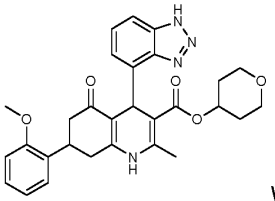
tetrahydro-2H-pyran-4-yl 4-(1H-indazol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (17):



A 6ml vial was successively charged with tetrahydropyran-4-yl 3-oxobutanoate (70 mg, 0.38 mmol), 5-(2-methoxyphenyl)cyclohexane-1,3-dione (75%, 100 mg, 0.34 mmol), 1H-indazole-4-carbaldehyde (50 mg, 0.344 mmol), ammonium acetate (98%, 41 mg, 0.52 mmol) and (2*S*)-pyrrolidine-2-carboxylic acid (4.0 mg, 0.034 mmol) in ethanol (0.3 mL). The reaction mixture was stirred at RT for 5 h. A precipitate was observed. The suspension was filtered, washed with ethanol and dried under vacuum to afford the title compound.

Mixture of 2 diastereomers (75/25) 1H NMR (DMSO-d6) δ: 12.83 (d, J = 31.3 Hz, 1H), 9.30 (d, J = 43.5 Hz, 1H), 8.11 (d, J = 29.1 Hz, 1H), 7.33 – 7.10 (m, 4H), 6.94 (dd, J = 16.9, 7.9 Hz, 3H), 5.33 (d, J = 17.4 Hz, 1H), 4.68 (t, J = 4.1, 4.1 Hz, 1H), 3.75 (d, J = 21.9 Hz, 3H), 3.65 (s, 1H), 3.43 (d, J = 12.5 Hz, 1H), 3.35 (s, 2H), 3.22 (d, J = 8.5 Hz, 1H), 2.89 – 2.54 (m, 2H), 2.34 (d, J = 8.7 Hz, 4H), 2.21 (d, J = 15.2 Hz, 1H), 1.74 (s, 1H), 1.45 (d, J = 9.0 Hz, 2H), 1.06 (d, J = 9.3 Hz, 1H)

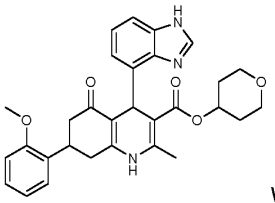
tetrahydro-2H-pyran-4-yl 4-(1H-benzo[d][1,2,3]triazol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (23):



was obtained via the aforementioned protocol.

Mixture of 2 diastereomers (27/73) 1H NMR (400 MHz, DMSO-d6) δ 15.71 (s, 1H), 9.25 (d, J = 30.3 Hz, 1H), 7.74 (dd, J = 17.8, 8.2 Hz, 1H), 7.30 – 7.10 (m, 5H), 7.00 – 6.83 (m, 3H), 4.54 (tt, J = 8.8, 4.1 Hz, 1H), 3.78 (s, 1H), 3.74 (s, 3H), 3.52 (dt, J = 11.6, 4.3 Hz, 2H), 3.26 – 3.16 (m, 1H), 3.08 (ddd, J = 11.7, 9.8, 2.8 Hz, 1H), 2.61 – 2.52 (m, 1H), 2.36 (d, J = 6.1 Hz, 3H), 2.25 – 2.14 (m, 1H), 1.72 – 1.62 (m, 1H), 1.37 (qd, J = 9.3, 4.8 Hz, 1H), 1.01 – 0.89 (m, 1H), 0.67 – 0.57 (m, 1H)

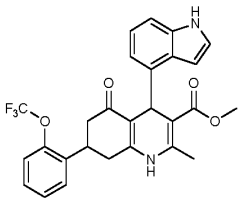
tetrahydro-2H-pyran-4-yl 4-(1H-benzo[d]imidazol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (24):



was obtained via the aforementioned protocol.

Mixture of 2 diastereomers (27/73) 1H NMR (400 MHz, DMSO-d6) δ 12.13 (d, J = 8.6 Hz, 1H), 9.26 (d, J = 44.6 Hz, 1H), 8.14 (d, J = 14.3 Hz, 1H), 7.43 – 7.34 (m, 1H), 7.27 (dd, J = 7.6, 1.7 Hz, 1H), 7.23 – 7.11 (m, 2H), 7.08 – 7.04 (m, 1H), 7.01 – 6.89 (m, 4H), 5.25 (d, J = 10.8 Hz, 1H), 4.68 – 4.55 (m, 1H), 3.70 (s, 1H), 3.57 – 3.42 (m, 2H), 3.43 – 3.34 (m, 2H), 3.17 – 3.01 (m, 1H), 2.86 – 2.52 (m, 4H), 2.25 (dt, J = 13.9, 6.1 Hz, 2H), 1.69 (d, J = 13.3 Hz, 1H), 1.48 – 1.34 (m, 1H), 1.14 (s, 1H), 0.85 (dd, J = 8.6, 4.2 Hz, 1H)

methyl 4-(1H-indol-4-yl)-2-methyl-5-oxo-7-(2-(trifluoromethoxy)phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (101):

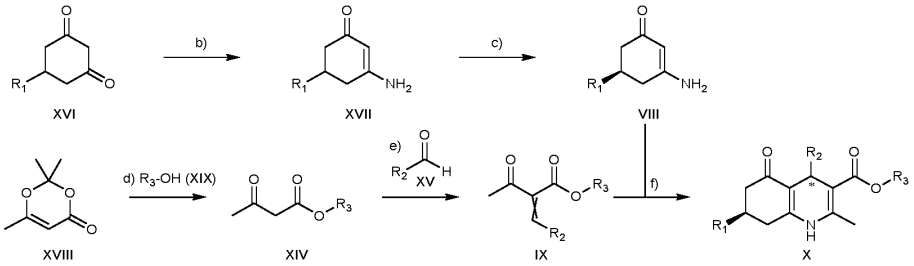


was obtained via the aforementioned protocol.

Mixture of 2 diastereomers (20/80) 1H NMR (400 MHz, DMSO-d6) δ 10.88 (d, J = 25.2 Hz, 1H), 9.22 (d, J = 45.4 Hz, 1H), 7.66 (dd, J = 7.0, 2.5 Hz, 1H), 7.50 – 7.29 (m, 3H), 7.29 – 7.07 (m, 2H), 7.00 – 6.50 (m, 3H), 5.30 (d, J = 12.2 Hz, 1H), 3.45 (d, J = 9.7 Hz, 3H), 3.38 (d, J = 12.8 Hz, 1H), 2.97 – 2.57 (m, 3H), 2.25 (d, J = 2.7 Hz, 3H), 2.15 (d, J = 16.5 Hz, 1H)

EXAMPLE 2

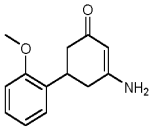
Synthesis of (4*RS*,7*R*)-configurated scaffolds for evaluation



General scheme for the synthesis of (4*RS*,7*R*)-configurated scaffolds using enaminone (VIII) as an enantiopure building block. Condensation of enaminone (VII) with intermediate (IX) obtained from aldol-type condensation of aldehyde (XV) with β-keto ester (XIV) gives (4*RS*,7*R*)-configurated 4,7-substituted 4,6,7,8-tetrahydroquinolin-5(1H)-ones (X).

Example Procedure b:

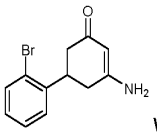
3-amino-5-(2-methoxyphenyl)cyclohex-2-en-1-one:



A 1L RBF was successively charged with 5-(2-methoxyphenyl)cyclohexane-1,3-dione (82%, 43.4 g, 0.163 mol) and ammonium acetate (98%, 15.2 g, 0.193 mol) in ethanol (234 mL) at RT. The reaction mixture was stirred at 85 °C for 3 h. The mixture was concentrated under vacuum. A solution of saturated aqueous $NaHCO_3$ solution and then EtOAc were added. The suspension was filtered, washed with H_2O and dried under vacuum to give a first batch of title compound. The phases in filtrate were separated and the aqueous phase was extracted with ethyl acetate. The combined organic layers were dried over hydrophobic paper and concentrated under vacuum to afford a second batch of the title compound.

1H NMR (400 MHz, DMSO-d6) δ 7.27 – 7.17 (m, 2H), 6.98 (dd, J = 8.0, 1.1 Hz, 1H), 6.91 (td, J = 7.4, 1.1 Hz, 1H), 4.98 (d, J = 0.9 Hz, 1H), 3.79 (s, 3H), 3.50 (tt, J = 11.5, 4.3 Hz, 1H), 2.59 – 2.51 (m, 1H), 2.45 – 2.29 (m, 2H), 2.14 (ddd, J = 15.8, 4.3, 1.4 Hz, 1H) + 2H hidden (NH2)

3-amino-5-(2-bromophenyl)cyclohex-2-en-1-one:



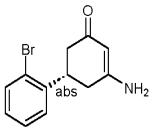
was obtained via the aforementioned protocol.

1H NMR (400 MHz, DMSO-d6) δ 7.62 (dd, J = 8.0, 1.3 Hz, 1H), 7.49 (dd, J = 7.9, 1.7 Hz, 1H), 7.38 (td, J = 7.6, 1.3 Hz, 1H), 7.23 – 7.16 (m, 1H), 5.02 (d, J = 0.9 Hz, 1H), 3.55 (tt, J = 11.4, 4.3 Hz, 1H), 2.64 – 2.54 (m, 1H), 2.49 – 2.34 (m, 2H), 2.25 – 2.15 (m, 1H)

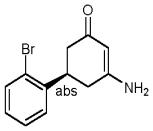
Example Procedure c:

(5*R*)-3-amino-5-(2-bomophenyl)cyclohex-2-en-1-one and (5*S*)-3-amino-5-(2-bromophenyl)cyclohex-2-en-1-one:

3-amino-5-(2-bromophenyl)cyclohex-2-en-1-one was submitted to chiral separation. Column Chiralpack AD-G 250x20mm 5 µm, Eluent 60:40 CO_2/MeOH, Flow rate = 50mL/min, Pressure 100 bar



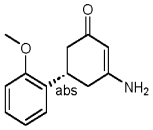
The 1st isomer isolated that corresponded to (5*R*)-3-amino-5-(2-bromophenyl)cyclohex-2-en-1-one showed a retention time of 3.4 min using UPLC method C7.



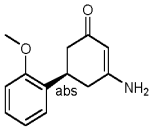
The 2nd isomer isolated that corresponded to (5*S*)-3-amino-5-(2-bromophenyl)cyclohex-2-en-1-one showed a retention time of 4.6 min using UPLC method C7.

(5*R*)-3-amino-5-(2-methoxyphenyl)cyclohex-2-en-1-one and (5*S*)-3-amino-5-(2-methoxyphenyl)cyclohex-2-en-1-one:

3-amino-5-(2-methoxyphenyl)cyclohex-2-en-1-one was submitted to chiral separation. Column Chiralpack IC 300x76.6mm 20 µm, Eluent ACN + 0.5% diisopropylamide, Flow rate = 275mL/min

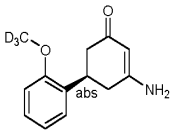


The 1st isomer isolated that corresponded to (5*S*)-3-amino-5-(2-methoxyphenyl)cyclohex-2-en-1-one showed a retention time of 16.6 min.



The 2nd isomer isolated that corresponded to (5*R*)-3-amino-5-(2-methoxyphenyl)cyclohex-2-en-1-one showed a retention time of 21.2 min.

(*R*)-5-amino-2'-(methoxy-d3)-1,6-dihydro-[1,1'-biphenyl]-3(2H)-one:

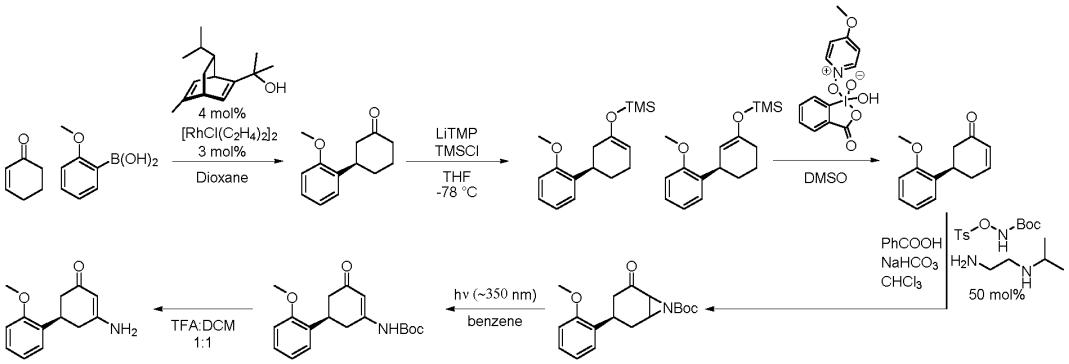


In a sealed tube, to a stirred solution of (5*R*)-3-amino-5-(2-bromophenyl)cyclohex-2-en-1-one (62.5 mg, 0.23 mmol) in methanol-d3 (0.80 mL, 19.8 mmol) and anhydrous toluene (0.80 mL) was added cesium carbonate (112 mg, 0.34 mmol). The reaction mixture was degassed with argon for 5 minutes and diacetoxypalladium (10.3 mg, 0.045 mmol) and di-tert-butyl[2',4',6'-tri(propan-2-yl)biphenyl-2-yl]phosphane (39.1 mg, 0.09 mmol) were added. The reaction mixture was heated at 80°C for 16h.

The reaction mixture was cooled down to rt and concentrated under reduced pressure. The crude material was purified by Flash chromatography on silica gel using a gradient of MeOH in DCM from 2% to 10%. Fractions were combined and concentrated to afford the title compound.

M/z = 221 [M+H]+, Rt = 0.54 min (Method A3)

Alternatively (5*R*)-3-amino-5-(2-methoxyphenyl)cyclohex-2-en-1-one can be obtained via:



Step i) A solution of $[RhCl(C_2H_4)_2]_2$ (152 mg, 0.39 mmol, 0.03 equiv, prepared from $RhCl_3$ x H_2O according to: https://doi.org/10.1002/047084289X.rn01715) and 2-((1*R*,4*R*,7*R*)-7-isopropyl-5-methylbicyclo[2.2.2]octa-2,5-dien-2-yl)propan-2-ol (115 mg, 0.52 mmol, 0.04 equiv) in 1,4-dioxane (22 mL) was stirred for 5 min at room temperature. The synthesis of the ligand and this exact transformation has been described in "Org. Lett. 2008, 10, 19, 4387–4389". 1.5 M aq. KOH (4.3 mL, 6.5 mmol, 0.5 equiv) was added, and the resulting solution was stirred at room temperature for an additional 5 min. (2-methoxyphenyl)boronic acid (2.96 g, 19.5 mmol, 1.50 equiv) and cyclohexenone (1.26 mL, 13.0 mmol, 1.00 equiv) were added to it with additional 1,4-dioxane (21 mL, 0.3 M overall), and the resulting mixture was stirred at room temperature overnight (15 h). The reaction mixture was directly passed through a pad of silica gel with Et_2O, and the solvent was removed under vacuum. The residue was purified via flash silica gel column chromatography (hexane:EtOAc = 4:1) to afford (*R*)-3-(2-methoxyphenyl)cyclohexan-1-one.^{1}H NMR and HR-MS (ESI) data is in accordance with literature spectra.

Chiral HPLC: Daicel Chiralpak OD-H, hexane:^{i}PrOH = 97:3, 1 mL/min, t_R (major) = 11.2 min; t_R (minor) = 9.7 min, e.r. = 97:3 (94% ee).

Step ii) To a solution of 2,2,6,6-tetramethylpiperidine (2.28 mL, 13.4 mmol, 1.07 equiv) in THF (88 mL) was added a 1.43 M hexane solution of *n*-BuLi (11 mL, 16.8 mmol, 1.34 equiv) at 4 °C (ice-water bath). After stirring for 1 h at the same temperature, the reaction mixture was cooled to –78 °C. TMSCl (2.22 mL, 17.5 mmol, 1.4 equiv) was then added, followed by addition of a solution of (*R*)-3-(2-methoxyphenyl)cyclohexan-1-one (2.55 g, 12.5 mmol, 1.00 equiv) in THF (88 mL, overall 0.07 M). After stirring for 2 h at the same temperature, the reaction mixture was quenched by addition of saturated $NaHCO_3$ aqueous solution, extracted with Et_2O, dried over Na_2SO_4, and concentrated to afford crude silyl-enol ether, which was used for the next step without further purification.

Step iii) The silyl-enol ether was dissolved in a minimal amount of DMSO and the IBX•MPO complex (52.8 mL, 0.4 M in DMSO, 21.1 mmol, 2.00 equiv) was added at room temperature and the solution was left to stir until completion was observed via TLC. Upon completion, the reaction mixture was diluted with aqueous $NaHCO_3$ and extracted with diethyl ether. The combined organic phases were washed with saturated aqueous $NaHCO_3$, water, and brine. After drying ($MgSO_4$), the solvent was removed *in vacuo* to yield the crude product, which was purified via flash column chromatography (hexane:EtOAc = 9:1) to afford (*R*)-2'-methoxy-1,6-dihydro-[1,1'-biphenyl]-3(2H)-one.

^{1}H NMR (400 MHz, $CDCl_3$) **δ**: 7.24 (ddd, J = 8.1, 7.4, 1.8 Hz, 1H), 7.18 (dd, J = 7.6, 1.7 Hz, 1H), 7.10 – 7.04 (m, 1H), 6.95 (td, J = 7.5, 1.2 Hz, 1H), 6.89 (dd, J = 8.2, 1.1 Hz, 1H), 6.16 – 6.06 (m, 1H), 3.83 (s, 3H), 3.78 – 3.66 (m, 1H), 2.82 – 2.54 (m, 4H).

Step iv) To a stirred solution of benzoic acid (246 mg, 2.01 mmol, 1.00 equiv), sodium bicarbonate (846 mg, 10.1 mmol, 5.00 equiv), *tert*-butyl (tosyloxy)carbamate (579 mg, 2.01 mmo, 1.00 equivl) in $CHCl_3$ (15 mL), N,N-dimethylethane-1,2-diamine (0.13 mL, 1.01 mmol, 0.5 equiv) was added at room temperature, under nitrogen atmosphere. (*R*)-2'-methoxy-1,6-dihydro-[1,1'-biphenyl]-3(2H)-one (489 g, 2.42 mmol, 1.20 equiv) in $CHCl_3$ (5 mL) was added in one portion and the resulting mixture was stirred at room temperature overnight (15 h). Water was added and the aqueous solution was extracted with $CHCl_3$ and the combined organic layers were washed once with saturated brine, dried over $NaSO_4$ and concentrated *in vacuo*. The resulting oily residue was purified by column chromatography (hexane:EtOAc = 4:1) to afford *tert*-butyl (4*R*)-4-(2-methoxyphenyl)-2-oxo-7-azabicyclo[4.1.0]heptane-7-carboxylate.

^{1}H NMR (400 MHz, $CDCl_3$) **δ**: 7.24 – 7.16 (m, 1H), 7.15 – 7.05 (m, 1H), 6.97 – 6.81 (m, 2H), 3.81 (s, 3H), 3.77 – 3.51 (m, 1H), 3.24 – 3.09 (m, 1H), 3.05 – 2.62 (m, 2H), 2.48 – 2.05 (m, 3H), 1.48 (s, 9H).

Chiral HPLC: Daicel Chiralpak OD-R, H_2O:ACN +0.1% FA = 1:1, 1 mL/min, t_R (D1, major) = 32.3 min; t_R (D1, minor) = 28.5 min; t_R (D2, major) = 19.1 min; t_R (D2, minor) = 23.7 min, e.r. = 97:3 (94% ee).

Step v) tert-butyl (4*R*)-4-(2-methoxyphenyl)-2-oxo-7-azabicyclo[4.1.0]heptane-7-carboxylate (78% pure, enone impurity, 132 mg, 0.32 mmol, 1.00 equiv) was split into two 20 mL heat-dried Schlenk tubes and degassed benzene (19 mL, 0.008M) was added to both. The vessels were transferred to a UV reactor and were irradiated for 5 h at ~350 nm. The solutions were combined and concentrated under reduced pressure. The crude residue was purified via column chromatography (hexane:EtOAc = 3:2) to afford *tert*-butyl (*R*)-(2'-methoxy-5-oxo-1,2,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)carbamate.

^{1}H NMR (400 MHz, $CDCl_3$) **δ**: 7.26 – 7.20 (m, 1H), 7.15 (dd, J = 7.6, 1.7 Hz, 1H), 6.93 (td, J = 7.5, 1.1 Hz, 1H), 6.88 (dd, J = 8.2, 1.1 Hz, 1H), 6.55 (br s, 1H), 6.44 (d, J = 1.6 Hz, 1H), 3.81 (s, 3H), 3.78 – 3.65 (m, 1H), 2.84 – 2.51 (m, 5H), 1.48 (s, 9H).

Chiral HPLC: Daicel Chiralpak OD-R, H_2O:ACN +0.1% FA = 1:1, 1 mL/min, t_R (major) = 15.5 min; t_R (minor) = 18.1 min, e.r. = 98:2 (96% ee).

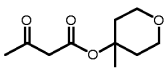
Step vi) *tert*-butyl (*R*)-(2'-methoxy-5-oxo-1,2,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)carbamate (81.0 mg, 0.25 mmol, 1.00 equiv) was loaded into a 10 mL flask coupled with a magnetic stirring bar and was dissolved in a 1:1 mixture of DCM:TFA (2.2 mL, 0.2 M). The solution was stirred at room temperature for 1 h and the solvent was removed under reduced pressure. The residue was redissolved in ethyl acetate and washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated under reduced pressure to yield the title compound, which can be employed in the next step without further purification.

1H NMR (400 MHz, DMSO-d6) **δ** 7.27 – 7.17 (m, 2H), 7.04 – 6.41 (m, 4H), 4.98 (d, J = 0.9 Hz, 1H), 3.79 (s, 3H), 3.50 (tt, J = 11.4, 4.3 Hz, 1H), 2.59 – 2.51 (m, 1H), 2.45 – 2.29 (m, 2H), 2.14 (ddd, J =16.0, 4.4, 1.4 Hz, 1H).

(5*S*)-3-amino-5-(2-methoxyphenyl)cyclohex-2-en-1-one can also be obtained accordingly, using the appropriate isomer of the catalyst.

Example Procedure d:

4-methyltetrahydro-2H-pyran-4-yl 3-oxobutanoate:

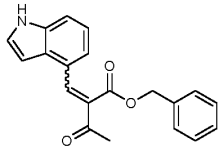


In a vial, 2,2,6-trimethyl-4H-1,3-dioxin-4-one (187 µL, 1.34 mmol) was dissolved in toluene (400 µL). Then 4-methyloxan-4-ol (155 mg, 1.34 mmol) was added. The reaction mixture was stirred at 120 °C for 4 h. The reaction mixture was concentrated under reduced pressure to obtain the title compound. The product was used as a crude in the next step.

1H NMR (DMSO-d6) δ: 3.66 – 3.48 (m, 6H), 2.18 (s, 3H), 2.04 – 1.94 (m, 2H), 1.64 (ddd, J = 14.4, 10.1, 4.9 Hz, 2H), 1.48 (s, 3H)

Example Procedure e1:

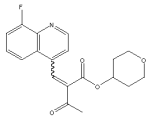
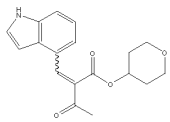
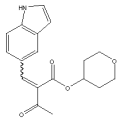
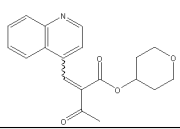
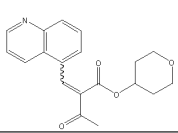
benzyl 2-((1H-indol-4-yl)methylene)-3-oxobutanoate:

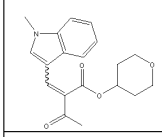
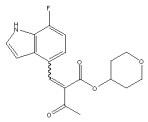
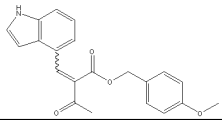
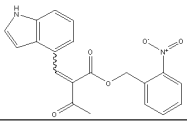
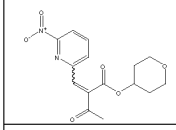
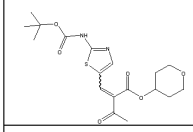
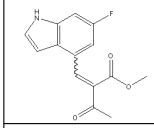
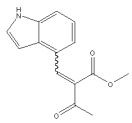
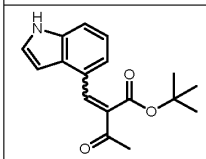
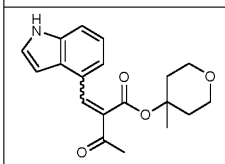


A round bottomed flask was successively charged with (2*S*)-pyrrolidine-2-carboxylic acid (2.31 g, 20.1 mmol), benzyl 3-oxobutanoate (17 mL, 0.100 mol) and 1H-indole-4-carbaldehyde (10.0 g, 66.8 mmol) in ethanol (80 mL). Molecular sieves 4A was added. The reaction mixture was stirred at 40°C overnight. The mixture was evaporated. The crude material was purified by Flash chromatography on silica gel using a gradient of ethyl acetate in cyclohexane from 0% to 50%. Fractions were combined and concentrated to afford the title compound.

M/z = 320 [M+H]+, Rt = 0.87/0.92 min (Method A3)

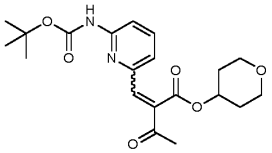
The following compounds were obtained using this protocol:

Structure	Name	MS
	tetrahydro-2H-pyran-4-yl 2-((8-fluoroquinolin-4-yl)methylene)-3-oxobutanoate	M/z = 344 [M+H]+, Rt = 0.71/0.75 min (Method A3)
	tetrahydro-2H-pyran-4-yl 2-((1H-indol-4-yl)methylene)-3-oxobutanoate	M/z = 314 [M+H]+, Rt = 0.75/0.79 min (Method A3)
	tetrahydro-2H-pyran-4-yl 2-((1H-indol-5-yl)methylene)-3-oxobutanoate	M/z = 314 [M+H]+, Rt = 0.75/0.79 min (Method A3)
	tetrahydro-2H-pyran-4-yl 3-oxo-2-(quinolin-4-ylmethylene)butanoate	M/z = 326 [M+H]+, Rt = 0.57/0.59 min (Method A3)
	tetrahydro-2H-pyran-4-yl 3-oxo-2-(quinolin-5-ylmethylene)butanoate	M/z = 326 [M+H]+, Rt = 0.53 /0.55 min (Method A3)

	tetrahydro-2H-pyran-4-yl 2-((1-methyl-1H-indol-3-yl)methylene)-3-oxobutanoate	M/z = 328 [M+H]+, Rt = 0.87 min (Method A3)
	tetrahydro-2H-pyran-4-yl 2-((7-fluoro-1H-indol-4-yl)methylene)-3-oxobutanoate	M/z = 332 [M+H]+, Rt = 1.28/1.37 min (Method A3)
	4-methoxybenzyl 2-((1H-indol-4-yl)methylene)-3-oxobutanoate	M/z = 372 [M+Na]+, Rt = 0.87/0.92 min (Method A3)
	2-nitrobenzyl 2-((1H-indol-4-yl)methylene)-3-oxobutanoate	M/z = 365 [M+H]+, Rt = 0.87/0.91 min (Method A3)
	tetrahydro-2H-pyran-4-yl 2-((6-nitropyridin-2-yl)methylene)-3-oxobutanoate	M/z = 321 [M+H]+, Rt = 0.69/0.74 min (Method A3)
	tetrahydro-2H-pyran-4-yl 2-((2-((tert-butoxycarbonyl)amino)thiazol-5-yl)methylene)-3-oxobutanoate	M/z = 341 [M-*t*Bu+H]+, Rt = 0.83/0.87 min (Method A3)
	methyl 2-((6-fluoro-1H-indol-4-yl)methylene)-3-oxobutanoate	M/z = 262 [M+H]+, Rt = 0.76/0.79 min (Method A3)
	methyl 2-((1H-indol-4-yl)methylene)-3-oxobutanoate	M/z = 244 [M+H]+, Rt = 0.72/0.75 min (Method A3)
	tert-butyl 2-((1H-indol-4-yl)methylene)-3-oxobutanoate	M/z = 308 [M+Na]+, Rt = 0.88/0.94 min (Method A3)
	4-methyltetrahydro-2H-pyran-4-yl 2-((1H-indol-4-yl)methylene)-3-oxobutanoate	M/z = 350 [M+Na]+, Rt = 0.78/0.82 min (Method A3)

Example Procedure e2:

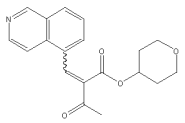
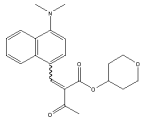
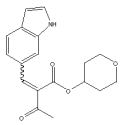
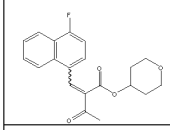
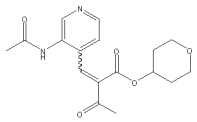
tetrahydro-2H-pyran-4-yl 2-((6-((tert-butoxycarbonyl)amino)pyridin-2-yl)methylene)-3-oxobutanoate:

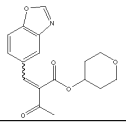
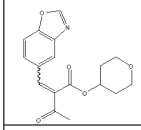
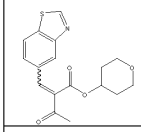
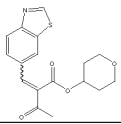
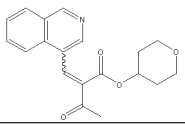
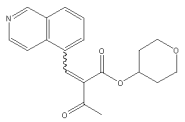
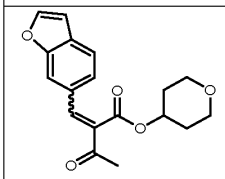


To a stirred solution of tert-butyl N-(6-formylpyridin-2-yl)carbamate (100 mg, 0.44 mmol) in anhydrous ethanol (2.0 mL), at RT were added Activated molecular sieves 4A (100 mg) and tetrahydropyran-4-yl 3-oxobutanoate (101 mg, 0.44 mmol). The reaction mixture was stirred at RT for 1 d. The solvent was removed under reduced pressure. To the mixture was added DCM then the mixture was filtered and washed with DCM. The organic phase was washed with brine, dried through a separator phase and solvent was removed under reduced pressure to give the crude product. The product was purified by flash chromatography on silica gel (solid injection onto dicalite) using a gradient of heptane / EtOAc, from 100:0 to 40:60, product elution started at 15% solvent B and 40% solvent B). Desired fractions were combined, and solvent was removed under reduced pressure to afford the title compound.

M/z = 391 [M+H]+, Rt = 0.87/0.92 min (Method A3)

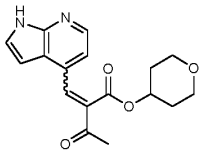
The following compounds were obtained using this protocol:

Structure	Name	MS
	tetrahydro-2H-pyran-4-yl 2-(isoquinolin-5-ylmethylene)-3-oxobutanoate	M/z = 326 [M+H]+, Rt = 0.60/0.65 min (Method A3)
	tetrahydro-2H-pyran-4-yl 2-((4-(dimethylamino)naphthalen-1-yl)methylene)-3-oxobutanoate	M/z = 368 [M+H]+, Rt = 0.83 min (Method A3)
	tetrahydro-2H-pyran-4-yl 2-((1H-indol-6-yl)methylene)-3-oxobutanoate	M/z = 314 [M+H]+, Rt = 0.78 min (Method A3)
	tetrahydro-2H-pyran-4-yl 2-((4-fluoronaphthalen-1-yl)methylene)-3-oxobutanoate	M/z = 343 [M+H]+, Rt = 0.94/0.99 min (Method A3)
	tetrahydro-2H-pyran-4-yl 2-((3-acetamidopyridin-4-yl)methylene)-3-oxobutanoate	M/z = 333 [M+H]+, Rt = 0.47 min (Method A3)

	tetrahydro-2H-pyran-4-yl 2-(benzo[d]oxazol-5-ylmethylene)-3-oxobutanoate	M/z = 316 [M+H]+, Rt = 0.71/0.74 min (Method A3)
	tetrahydro-2H-pyran-4-yl 2-(benzo[d]thiazol-5-ylmethylene)-3-oxobutanoate	M/z = 332 [M+H]+, Rt = 0.74/0.78 min (Method A3)
	tetrahydro-2H-pyran-4-yl 2-(benzo[d]thiazol-6-ylmethylene)-3-oxobutanoate	M/z = 332 [M+H]+, Rt = 0.75/0.78 min (Method A3)
	tetrahydro-2H-pyran-4-yl 2-(isoquinolin-4-ylmethylene)-3-oxobutanoate	M/z = 326 [M+H]+, Rt = 0.56 min (Method A3)
	tetrahydro-2H-pyran-4-yl 2-((7-methyl-1H-indol-4-yl)methylene)-3-oxobutanoate	M/z = 328 [M+H]+, Rt = 0.79 min (Method A3)
	tetrahydro-2H-pyran-4-yl 2-(isoquinolin-5-ylmethylene)-3-oxobutanoate	M/z = 326 [M+H]+, Rt = 0.60/0.65 min (Method A3)
	tetrahydro-2H-pyran-4-yl 2-(benzofuran-6-ylmethylene)-3-oxobutanoate	M/z = 315 [M+H]+, Rt = 0.82/0.87 min (Method A3)

Example Procedure e3:

tetrahydro-2H-pyran-4-yl 2-((1H-pyrrolo[2,3-b]pyridin-4-yl)methylene)-3-oxobutanoate:



A vial was successively charged with (2*S*)-pyrrolidine-2-carboxylic acid (34.7 mg, 0.3 mmol), tetrahydropyran-4-yl 3-oxobutanoate (206 mg, 1.11 mmol) and tetrahydropyran-4-yl 3-oxobutanoate (206 mg, 1.11 mmol) in 2-propanol-anhydrous (2.0 mL). Molecular sieves 4A was added. The reaction mixture was stirred at RT overnight. The reaction was concentrated and the crude material was purified by Flash

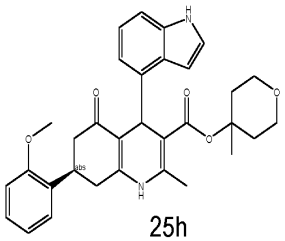
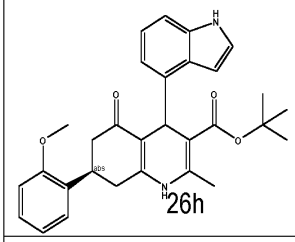
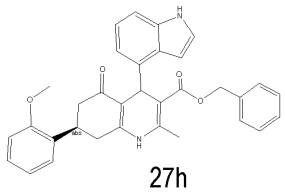
chromatography on silica gel using a gradient of ethyl acetate/EtOH (3/1) in heptane from 0% to 100%. Fractions were combined and concentrated to afford the title compound.

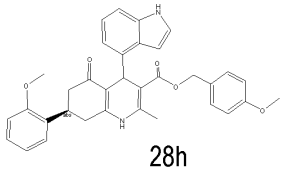
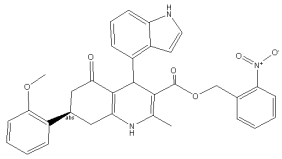
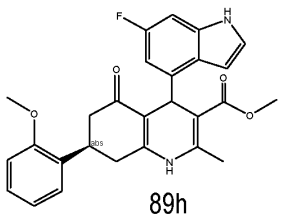
M/z = 315 [M+H]+, Rt = 0.66/0.69 min (Method A3)

Example Procedure f1: 27h

A vial was successively charged with (5*R*)-3-amino-5-(2-methoxyphenyl)cyclohex-2-en-1-one (4.00 g, 18.4 mmol), molecular sieves 4A and benzyl 2-((1H-indol-4-yl)methylene)-3-oxobutanoate (10.8 g, 22.4 mmol) in anhydrous DMF (20.0 mL). The reaction mixture was stirred at 130 °C overnight. The reaction was concentrated. The crude material was purified by Flash chromatography on silica using a gradient of acetone in toluene from 0% to 30%. Fractions were combined and evaporated to afford the title compound.

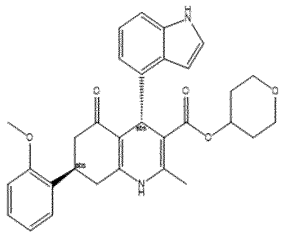
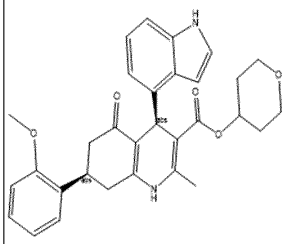
The following compounds were obtained using this protocol:

Structure Cpd. No.	NMR Mixture of 2 diastereomers	MS
 25h	(50/50) 1H NMR (DMSO-d6) δ: 10.85 (d, J = 29.6 Hz, 1H), 9.13 (d, J = 49.4 Hz, 1H), 7.31 – 7.08 (m, 4H), 7.03 – 6.53 (m, 6H), 5.27 (d, J = 20.3 Hz, 1H), 3.75 (d, J = 24.3 Hz, 3H), 3.70 – 3.17 (m, 3H), 3.15 – 2.57 (m, 3H), 2.46 – 2.31 (m, 2H), 2.27 (d, J = 13.4 Hz, 3H), 2.03 – 1.79 (m, 2H), 1.49 (dd, J = 11.5, 7.2 Hz, 2H), 1.18 (d, J = 3.9 Hz, 3H)	M/z = 528 [M+H]+, Rt = 0.87 min (Method A3)
 26h	(50/50) 1H NMR (500 MHz, DMSO-d6) δ 10.85 (d, J = 35.0 Hz, 1H), 9.06 (d, J = 60.5 Hz, 1H), 7.33 – 6.82 (m, 8H), 6.80 – 6.65 (m, 1H), 6.58 (dddd, J = 24.4, 3.1, 2.0, 0.9 Hz, 1H), 5.23 (d, J = 19.9 Hz, 1H), 3.76 (d, J = 28.4 Hz, 4H), 2.86 – 2.57 (m, 2H), 2.48 – 2.27 (m, 2H), 2.23 (dd, J = 13.0, 0.6 Hz, 3H), 1.24 (d, J = 4.0 Hz, 9H).	M/z = 485 [M+H]+, Rt = 1.67 min (Method A21)
 27h	(47/53) 1H NMR (DMSO-d6, 600 MHz) δ 10.6-11.0 (m, 1H), 9.0-9.4 (m, 1H), 7.0-7.3 (m, 9H), 6.6-7.0 (m, 4H), 6.5-6.6 (m, 1H), 5.35 (s, 1H), 4.8-5.0 (m, 2H), 3.7-3.8 (m, 3H), 3.6-3.7 (m, 1H), 2.6-2.9 (m, 2H), 2.1-2.5 (m, 5H)	M/z = 519 [M+H]+, Rt = 0.94 min (Method A3)

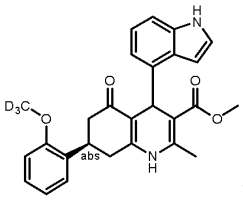
 28h	(50/50) 1H NMR (DMSO-d6, 600 MHz): δ 10.79-10.91 (m, 1H), 9.09-9.29 (m, 1H), 7.11-7.27 (m, 3H), 7.04-7.09 (m, 2H), 6.99-7.02 (m, 1H), 6.88-6.98 (m, 2H), 6.80-6.86 (m, 2H), 6.69-6.79 (m, 1H), 6.66 (td, J = 7.4, 1.1 Hz, 1H), 6.49-6.57 (m, 1H), 5.16-5.34 (m, 1H), 4.90 (dd, J = 12.3, 9.5 Hz, 1H), 4.79 (dd, J = 15.7, 12.2 Hz, 1H), 3.71-3.77 (m, 6H), 3.61-3.68 (m, 1H), 2.81 (dd, J = 17.0, 11.9 Hz, 1H), 2.69-2.73 (m, 1H), 2.30-2.45 (m, 2H), 2.23-2.29 (m, 3H)	M/z = 549 [M+H]+, Rt = 2.47 min (Method A21)
 29h	1H NMR (600 MHz, DMSO-d6) δ 10.74 - 10.95 (m, 1 H) 9.15 - 9.47 (m, 1 H) 8.04 (dt, 1 H) 7.45 - 7.54 (m, 1 H) 7.36 (dtd, 1 H) 7.21 - 7.30 (m, 1 H) 7.15 - 7.20 (m, 1 H) 7.10 - 7.15 (m, 1 H) 7.00 (dd, 1 H) 6.90 - 6.97 (m, 2 H) 6.87 (d, 1 H) 6.80 - 6.85 (m, 1 H) 6.64 - 6.78 (m, 1 H) 6.52 - 6.64 (m, 1 H) 5.33 (s, 1 H) 5.16 - 5.33 (m, 2 H) 3.71 - 3.80 (m, 3 H) 3.32 - 3.70 (m, 1 H) 2.55 - 2.87 (m, 2 H) 2.37 - 2.48 (m, 1 H) 2.31 (d, 3 H) 2.16 - 2.25 (m, 1 H)	M/z = 564 [M+H]+, Rt = 8.37 min (Method A20)
 89h	1H NMR (500 MHz, DMSO-d6) δ 11.11 – 10.81 (m, 1H), 9.51 – 9.00 (m, 1H), 7.36 – 6.35 (m, 8H), 5.29 (d, J = 19.4 Hz, 1H), 3.84 – 3.72 (m, 3H), 3.71 – 3.62 (m, 1H), 3.46 (d, J = 5.6 Hz, 3H), 2.92 – 2.60 (m, 2H), 2.56 – 2.13 (m, 5H)	M/z = 461 [M+H]+, Rt = 2.12/2.15 min (Method A21)

The following compounds were obtained using this protocol and subsequently separated by prep. UPLC (see below for analytic):

Structure Cpd. No.	**NMR**	**MS / prep. UPLC**

 19a	1H NMR (600 MHz, DMSO-d6) δ 10.89 - 10.85 (m, 1H), 9.24 (s, 1H), 7.27 (dd, J = 7.6, 1.6 Hz, 1H), 7.25 - 7.24 (m, 1H), 7.23 - 7.20 (m, 1H), 7.15 (dt, J = 8.0, 0.9 Hz, 1H), 6.97 - 6.90 (m, 3H), 6.84 (dd, J = 7.4, 0.8 Hz, 1H), 6.62 (ddd, J = 3.1, 2.1, 0.7 Hz, 1H), 5.31 (s, 1H), 4.67 (tt, J = 8.5, 4.2 Hz, 1H), 3.72 (s, 3H), 3.69 - 3.48 (m, 2H), 3.38 - 3.32 (m, 2H), 3.28 - 3.23 (m, 1H), 2.81 (dd, J = 17.0, 11.9 Hz, 1H), 2.62 - 2.56 (m, 1H), 2.47 - 2.37 (m, 1H), 2.30 (s, 3H), 2.19 (ddd, J = 16.3, 3.8, 1.5 Hz, 1H), 1.83 - 1.43 (m, 3H), 1.16 (dtd, J = 13.0, 8.8, 4.1 Hz, 1H)	M/z = 513 [M+H]+, Rt = 2.13 min (Method A21) / Rt = 4.91 min (Method C1)
 19g	1H NMR (600 MHz, DMSO-d6) δ 10.81 - 10.78 (m, 1H), 9.12 (s, 1H), 7.21 (t, J = 2.8 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.11 (dt, J = 8.1, 0.9 Hz, 1H), 7.00 (dd, J = 7.6, 1.6 Hz, 1H), 6.93 (dd, J = 8.4, 1.0 Hz, 1H), 6.87 (t, J = 7.5 Hz, 1H), 6.78 (dd, J = 7.3, 0.7 Hz, 1H), 6.66 (td, J = 7.5, 1.0 Hz, 1H), 6.57 (ddd, J = 3.0, 2.1, 0.9 Hz, 1H), 5.26 (s, 1H), 4.67 (tt, J = 8.6, 4.2 Hz, 1H), 3.77 (s, 3H), 3.73 - 3.53 (m, 3H), 3.38 - 3.33 (m, 1H), 3.29 - 3.24 (m, 1H), 2.74 - 2.65 (m, 2H), 2.41 - 2.29 (m, 2H), 2.28 (s, 3H), 1.81 - 1.44 (m, 3H), 1.21 - 1.14 (m, 1H)	M/z = 513 [M+H]+, Rt = 2.11 min (Method A21) / Rt = 7.34 min (Method C1)

methyl (7*R*)-4-(1H-indol-4-yl)-7-(2-(methoxy-d3)phenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (99h):



was obtained via the aforementioned protocol employing (*R*)-5-amino-2'-(methoxy-d3)-1,6-dihydro-[1,1'-biphenyl]-3(2H)-one.

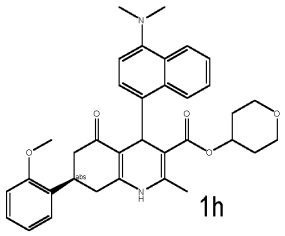
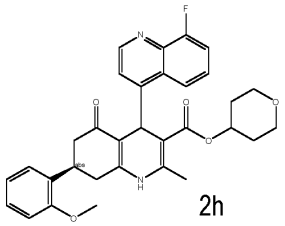
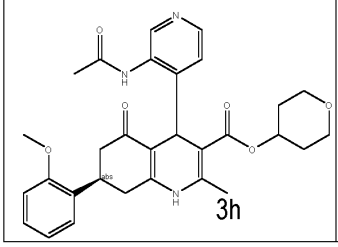
M/z = 446 [M+H]+, Rt = 0.82 min (Method A3)

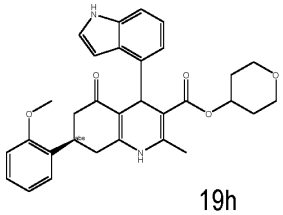
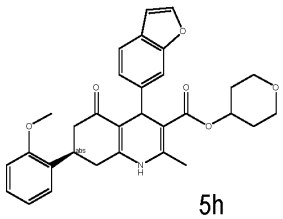
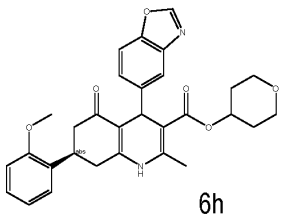
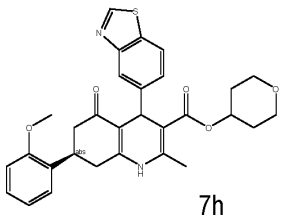
Example Procedure f2: 5h

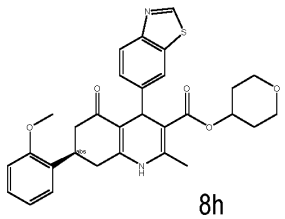
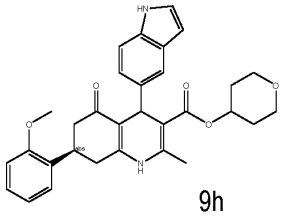
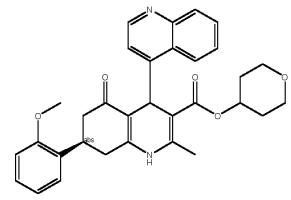
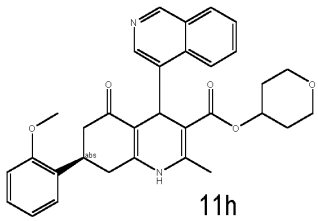
A 1ml vial was successively charged with (5*R*)-3-amino-5-(2-methoxyphenyl)cyclohex-2-en-1-one (50 mg, 0.23 mmol), and tetrahydropyran-4-yl 2-(benzofuran-6-ylmethylene)-3-oxo-butanoate (118.0 mg, 0.33

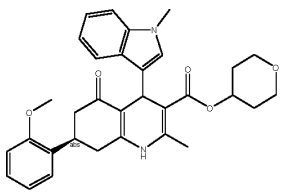
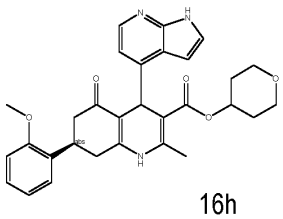
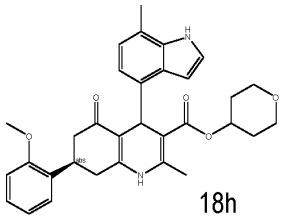
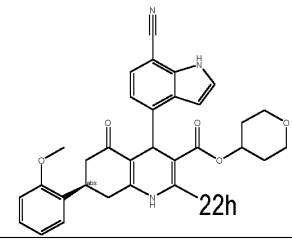
mmol) in DMF (0.25 mL). Molecular sieves were added. The reaction mixture was stirred at 100 °C overnight. The reaction mixture was filtered through a PTFE filter. The filtrate was purified by reverse-phase flash chromatography using a gradient of acetonitrile in water from 20% to 70% (neutral). Fractions were combined and evaporated to afford the title compound.

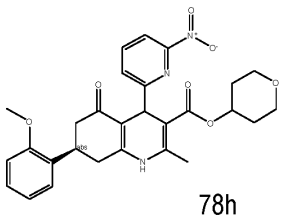
The following compounds were obtained using this protocol:

Structure Cpd. No.	NMR Mixture of 2 diastereomers	MS
 1h	(50/50) 1H NMR (DMSO-d6, 500 MHz) δ 9.1-9.3 (m, 1H), 8.6-8.8 (m, 1H), 8.0-8.2 (m, 1H), 7.4-7.6 (m, 2H), 6.6-7.3 (m, 6H), 5.5-5.7 (m, 1H), 4.5-4.7 (m, 1H), 3.7-3.8 (m, 3H), 3.3-3.7 (m, 3H), 3.1-3.3 (m, 2H), 2.6-2.9 (m, 8H), 2.3-2.4 (m, 3H), 2.1-2.6 (m, 2H), 0.7-1.8 (m, 4H)	M/z = 567 [M+H]+, Rt = 2.2 min (Method A21)
 2h	(50/50) 1H NMR (DMSO-d6, 600 MHz) δ 9.3-9.5 (m, 1H), 8.7-8.9 (m, 1H), 8.5-8.7 (m, 1H), 7.5-7.7 (m, 2H), 7.3-7.5 (m, 1H), 6.6-7.3 (m, 4H), 5.5-5.7 (m, 1H), 4.6-4.6 (m, 1H), 3.7-3.8 (m, 3H), 3.3-3.7 (m, 5H), 3.1-3.3 (m, 2H), 2.6-2.9 (m, 2H), 2.3-2.4 (m, 4H), 1.6-1.8 (m, 1H), 1.37 (ddd, 1H, J =3.5, 6.2, 12.9 Hz), 1.2-1.2 (m, 1H), 0.6-0.8 (m, 1H)	M/z = 543 [M+H]+, Rt = 2.02 min (Method A21)
 3h	(50/50) 1H NMR (500 MHz, DMSO-d6) δ 10.66 – 10.22 (m, 1H), 9.84 – 9.46 (m, 1H), 9.08 – 8.65 (m, 1H), 8.34 – 7.86 (m, 1H), 7.47 – 6.37 (m, 5H), 5.00 (d, J = 9.6 Hz, 1H), 4.79 – 4.56 (m, 1H), 3.78 (d, J = 15.5 Hz, 3H), 3.32 (s, 5H), 2.89 – 2.55 (m, 4H), 2.43 (d, J = 5.8 Hz, 3H), 2.21 (d, J = 11.5 Hz, 3H), 1.83 – 1.66 (m, 1H), 1.52 – 1.35 (m, 2H), 1.18 – 0.92 (m, 1H)	M/z = 533 [M+H]+, Rt = 1.54 min (Method A21)

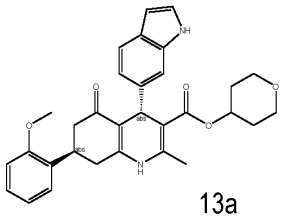
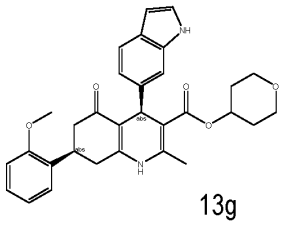
 19h	(50/50) 1H NMR (600 MHz, DMSO-d6) δ 10.72 - 10.91 (m, 1 H) 9.02 - 9.34 (m, 1 H) 7.25 (s, 1 H) 7.19 - 7.23 (m, 1 H) 7.12 - 7.17 (m, 1 H) 6.99 - 7.12 (m, 1 H) 6.94 - 6.97 (m, 1 H) 6.91 - 6.93 (m, 1 H) 6.82 - 6.89 (m, 1 H) 6.64 - 6.81 (m, 1 H) 6.54 - 6.64 (m, 1 H) 5.23 - 5.35 (m, 1 H) 4.67 (td, J =8.66, 4.40 Hz, 1 H) 3.71 - 3.79 (m, 3 H) 3.44 - 3.71 (m, 3 H) 3.34 - 3.39 (m, 1 H) 3.22 - 3.29 (m, 1 H) 2.55 - 2.87 (m, 2 H) 2.30 - 2.47 (m, 2 H) 2.28 (s, 3 H) 1.48 - 1.79 (m, 2 H) 1.01 - 1.47 (m, 2 H)	M/z = 513 [M+H]+, Rt = 2.09 min (Method A21)
 5h	(50/50) 1H NMR (DMSO-d6, 600 MHz) δ 9.1-9.3 (m, 1H), 7.9-7.9 (m, 1H), 7.4-7.5 (m, 1H), 6.8-6.9 (m, 1H), 6.5-7.3 (m, 6H), 5.0-5.1 (m, 1H), 4.7-4.9 (m, 1H), 3.7-3.8 (m, 4H), 3.3-3.7 (m, 4H), 2.6-2.8 (m, 2H), 2.3-2.4 (m, 3H), 2.2-2.6 (m, 2H), 1.2-1.9 (m, 4H)	M/z = 514 [M+H]+, Rt = 2.35 min (Method A21)
 6h	(50/50) 1H NMR (DMSO-d6, 600 MHz) δ 9.1-9.3 (m, 1H), 8.5-8.7 (m, 1H), 7.4-7.7 (m, 2H), 6.5-7.4 (m, 5H), 5.0-5.1 (m, 1H), 4.7-4.8 (m, 1H), 3.7-3.8 (m, 4H), 3.2-3.7 (m, 4H), 2.74 (d, 2H, J =6.9 Hz), 2.3-2.4 (m, 3H), 2.2-2.6 (m, 2H), 1.2-1.9 (m, 4H)	M/z = 515 [M+H]+, Rt = 2.03 min (Method A21)
 7h	(50/50) 1H NMR (DMSO-d6, 600 MHz) δ 9.30 (s, 1H), 9.21 (s, 1H), 7.9-8.1 (m, 1H), 7.7-7.9 (m, 1H), 6.57 (t, 5H, J =7.4 Hz), 5.0-5.2 (m, 1H), 4.78 (dt, 1H, J =4.0, 7.8 Hz), 3.2-3.8 (m, 8H), 2.75 (d, 2H, J =6.7 Hz), 2.2-2.5 (m, 5H), 1.8-1.9 (m, 1H), 1.61 (dt, 1H, J =4.1, 8.6 Hz), 1.5-1.6 (m, 1H), 1.30 (tdd, 1H, J =4.1, 8.4, 12.6 Hz)	M/z = 531 [M+H]+, Rt = 2.11 min (Method A21)

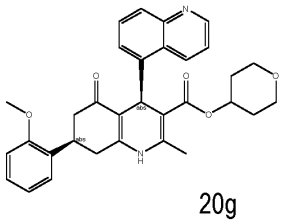
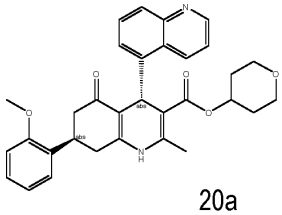
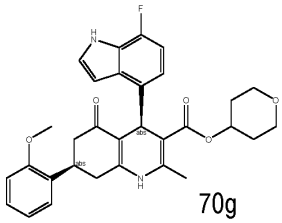
 8h	(50/50) 1H NMR (DMSO-d6, 500 MHz) δ 9.1-9.3 (m, 2H), 7.8-8.0 (m, 2H), 7.4-7.5 (m, 1H), 6.5-7.3 (m, 4H), 5.0-5.2 (m, 1H), 4.7-4.8 (m, 1H), 3.7-3.9 (m, 3H), 3.2-3.7 (m, 5H), 2.6-2.9 (m, 2H), 2.3-2.4 (m, 3H), 2.2-2.6 (m, 2H), 1.1-1.9 (m, 4H)	M/z = 531 [M+H]+, Rt = 2.12 min (Method A21)
 9h	(50/50) 1H NMR (DMSO-d6, 500 MHz) δ 10.6-11.1 (m, 1H), 8.8-9.3 (m, 1H), 6.6-7.4 (m, 9H), 6.2-6.4 (m, 1H), 4.9-5.1 (m, 1H), 4.7-4.9 (m, 1H), 3.3-3.8 (m, 7H), 2.6-2.8 (m, 2H), 2.3-2.4 (m, 3H), 2.2-2.6 (m, 2H), 1.2-1.9 (m, 4H)	M/z = 513 [M+H]+, Rt = 7.2 min (Method A21)
 10h	(50/50) 1H NMR (DMSO-d6, 500 MHz) δ 9.3-9.5 (m, 1H), 8.7-8.9 (m, 2H), 7.9-8.0 (m, 1H), 7.7-7.8 (m, 1H), 7.6-7.7 (m, 1H), 6.5-7.4 (m, 5H), 5.6-5.8 (m, 1H), 4.5-4.7 (m, 1H), 3.7-3.9 (m, 3H), 3.3-3.7 (m, 3H), 3.1-3.3 (m, 2H), 2.6-3.0 (m, 2H), 2.5-2.6 (m, 1H), 2.1-2.5 (m, 4H), 1.3-1.8 (m, 2H), 0.6-1.2 (m, 2H)	M/z = 526 [M+H]+, Rt = 1.59 min (Method A21)
 11h	(45/55) 1H NMR (500 MHz, DMSO-d6) δ 0.68 - 1.27 (m, 2 H) 1.35 - 1.75 (m, 2 H) 2.15 - 2.58 (m, 5 H) 2.66 - 2.88 (m, 2 H) 3.12 - 3.30 (m, 2 H) 3.34 - 3.72 (m, 3 H) 3.72 - 3.81 (m, 3 H) 4.55 - 4.68 (m, 1 H) 5.51 - 5.67 (m, 1 H) 6.62 (t, J =7.57 Hz, 1 H) 6.86 - 7.02 (m, 2 H) 7.11 - 7.30 (m, 2 H) 7.64 (dt, J =15.20, 7.54 Hz, 1 H) 7.76 - 7.87 (m, 1 H) 8.02 (dd, J =18.39, 8.13 Hz, 1 H) 8.25 - 8.40 (m, 1 H) 8.58 - 8.76 (m, 1 H) 9.01 - 9.13 (m, 1 H) 9.29 - 9.49 (m, 1 H)	M/z = 525 [M+H]+, Rt = 1.52 min (Method A21)

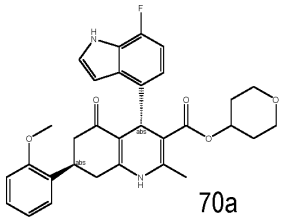
 15h	(53/47) 1H NMR (600 MHz, DMSO-d6) δ 9.08 - 9.29 (m, 1 H) 7.58 - 7.68 (m, 1 H) 7.29 (s, 1 H) 7.10 - 7.23 (m, 1 H) 7.03 - 7.09 (m, 1 H) 6.93 - 7.01 (m, 3 H) 6.79 (s, 1 H) 6.56 - 6.64 (m, 1 H) 5.13 - 5.24 (m, 1 H) 4.71 - 4.82 (m, 1 H) 3.72 - 3.79 (m, 3 H) 3.64 - 3.72 (m, 3 H) 3.31 - 3.63 (m, 5 H) 2.57 - 2.84 (m, 2 H) 2.34 - 2.48 (m, 1 H) 2.31 (d, J =12.32 Hz, 3 H) 2.17 - 2.26 (m, 1 H) 1.58 - 1.85 (m, 2 H) 1.26 - 1.57 (m, 2 H)	M/z = 550 [M+Na]+, Rt = 2.65 min (Method A21)
 16h	(48/52) 1H NMR (500 MHz, DMSO-d6) δ 11.54 - 11.21 (m, 1H), 9.49 - 9.17 (m, 1H), 8.09 - 7.95 (m, 1H), 7.42 - 7.30 (m, 1H), 7.29 - 6.96 (m, 2H), 6.96 - 6.58 (m, 3H), 6.58 - 6.49 (m, 1H), 5.34 - 5.23 (m, 1H), 4.76 - 4.62 (m, 1H), 3.83 - 3.72 (m, 3H), 3.72 - 3.34 (m, 4H), 3.30 - 3.25 (m, 1H), 2.91 - 2.56 (m, 2H), 2.49 - 2.15 (m, 5H), 1.87 - 1.06 (m, 4H)	M/z = 514 [M+H]+, Rt = 1.49 min (Method A21)
 18h	(47/53) 1H NMR (500 MHz, DMSO-d6) δ 10.62 - 10.89 (m, 1 H) 9.03 - 9.32 (m, 1 H) 7.25 - 7.31 (m, 1 H) 7.21 - 7.25 (m, 1 H) 7.17 - 7.21 (m, 1 H) 6.95 - 7.07 (m, 1 H) 6.89 - 6.95 (m, 1 H) 6.69 - 6.77 (m, 1 H) 6.66 - 6.69 (m, 1 H) 6.55 - 6.64 (m, 1 H) 5.15 - 5.37 (m, 1 H) 4.68 (dt, J =8.44, 4.28 Hz, 1 H) 3.72 - 3.82 (m, 3 H) 3.54 - 3.71 (m, 2 H) 3.32 - 3.41 (m, 2 H) 3.25 - 3.31 (m, 1 H) 2.54 - 2.87 (m, 2 H) 2.22 - 2.47 (m, 8 H) 1.09 - 1.89 (m, 4 H)	M/z = 527 [M+H]+, Rt = 2.22 min (Method A21)
 22h	(50/50) 1H NMR (DMSO-d6, 600 MHz): δ 11.32-12.06 (m, 1H), 9.00-9.88 (m, 1H), 7.33-7.52 (m, 2H), 6.54-7.29 (m, 6H), 5.27-5.43 (m, 1H), 4.56-4.81 (m, 1H), 3.70-3.80 (m, 3H), 3.18-3.69 (m, 5H), 2.57-2.87 (m, 2H), 2.35-2.48 (m, 1H), 2.32 (d, J = 13.8 Hz, 3H), 2.13-2.23 (m, 1H), 1.01-1.77 (m, 4H)	M/z = 538 [M+H]+, Rt = 2.17 min (Method A21)

 78h	(55/45) 1H NMR (600 MHz, DMSO-d6) δ 9.32 (d, J = 10.9 Hz, 1H), 8.28 - 6.33 (m, 7H), 5.26 - 5.10 (m, 1H), 4.86 - 4.74 (m, 1H), 3.85 - 3.75 (m, 3H), 3.75 - 3.32 (m, 6H), 2.85 - 2.57 (m, 2H), 2.46 (d, J = 7.8 Hz, 1H), 2.37 - 2.20 (m, 3H), 1.85 - 1.76 (m, 1H), 1.64 - 1.45 (m, 2H), 1.38 - 1.24 (m, 1H)	M/z = 520 [M+H]+, Rt = 2.17 min (Method A21)

In analogy the following compounds were synthesized and subsequently separated by prep. UPLC (see below for analytic):

Structure Cpd. No.	**NMR**	**MS / prep. UPLC**
 13a	1H NMR (600 MHz, DMSO-d6) δ 1.30 - 1.85 (m, 4 H) 2.25 (dd, J =16.29, 2.64 Hz, 1 H) 2.34 (s, 3 H) 2.50 - 2.56 (m, 1 H) 2.57 - 2.64 (m, 1 H) 2.78 (dd, J =17.02, 11.88 Hz, 1 H) 3.31 - 3.60 (m, 4 H) 3.70 - 3.77 (m, 4 H) 4.78 (tt, J =8.09, 4.02 Hz, 1 H) 5.03 (s, 1 H) 6.27 - 6.32 (m, 1 H) 6.88 - 6.95 (m, 2 H) 6.97 (d, J =8.22 Hz, 1 H) 7.17 - 7.25 (m, 3 H) 7.28 (dd, J =7.63, 1.47 Hz, 1 H) 7.35 (d, J =8.07 Hz, 1 H) 9.16 (s, 1 H) 10.88 (s, 1 H)	M/z = 513 [M+H]+, Rt = 2.21 min (Method A21) / Rt = 2.35 min (Method C4)
 13g	1H NMR (500 MHz, DMSO-d6) δ 10.84 (s, 1H), 9.07 (s, 1H), 7.29 (d, J = 8.1 Hz, 1H), 7.22 (t, J = 2.7 Hz, 1H), 7.18 (s, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.01 (dd, J = 7.6, 1.2 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 6.85 (dd, J = 8.1, 1.4 Hz, 1H), 6.67 (t, J = 7.4 Hz, 1H), 6.30 - 6.28 (m, 1H), 4.99 (s, 1H), 4.78 (tt, J = 8.2, 4.0 Hz, 1H), 3.80 - 3.78 (m, 3H), 3.78 - 3.34 (m, 5H), 2.72 (d, J = 6.9 Hz, 2H), 2.48 - 2.34 (m, 2H), 2.33 (s, 3H), 1.88 - 1.34 (m, 4H)	M/z = 514 [M+H]+, Rt = 2.18 min (Method A21) / Rt = 2.96 min (Method C4)

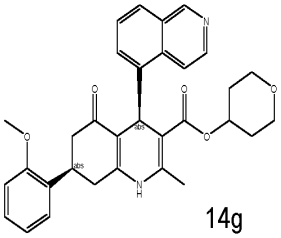
 20g	1H NMR (DMSO-d6, 500 MHz): δ 9.25 (s, 1H), 9.09 (d, J = 8.4 Hz, 1H), 8.84 (dd, J = 4.1, 1.6 Hz, 1H), 7.77 (d, J = 8.3 Hz, 1H), 7.60 (dd, J = 8.3, 7.4 Hz, 1H), 7.56 (dd, J = 8.8, 4.1 Hz, 1H), 7.37 (dd, J = 7.3, 1.1 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 6.93 (d, J = 7.5 Hz, 1H), 6.86 (dd, J = 7.6, 1.6 Hz, 1H), 6.65 (t, J = 7.3 Hz, 1H), 5.60 (s, 1H), 4.59 (tt, J = 9.1, 4.4 Hz, 1H), 3.78 (s, 3H), 3.60-3.70 (m, 2H), 3.44 (dt, J = 11.7, 4.3 Hz, 1H), 3.23-3.29 (m, 1H), 3.11-3.19 (m, 1H), 2.72-2.84 (m, 2H), 2.30-2.44 (m, 5H), 1.67-1.73 (m, 1H), 1.33-1.42 (m, 1H), 1.13-1.20 (m, 1H), 0.70 (dtd, J = 13.1, 9.6, 4.0 Hz, 1H)	M/z = 525 [M+H]+, Rt = 1.54 min (Method A21) / Rt = 4.57 min (Method C5)
 20a	1H NMR (DMSO-d6, 500 MHz): δ 9.36 (s, 1H), 9.18 (d, J = 7.6 Hz, 1H), 8.86 (dd, J = 4.0, 1.6 Hz, 1H), 7.82 (d, J = 8.3 Hz, 1H), 7.69 (dd, J = 8.4, 7.3 Hz, 1H), 7.59 (dd, J = 8.8, 4.1 Hz, 1H), 7.47 (dd, J = 7.3, 1.2 Hz, 1H), 7.27 (dd, J = 7.6, 1.6 Hz, 1H), 7.20-7.25 (m, 1H), 6.97 (dd, J = 8.3, 1.0 Hz, 1H), 6.93 (td, J = 7.5, 1.1 Hz, 1H), 5.65 (s, 1H), 4.60 (tt, J = 9.0, 4.3 Hz, 1H), 3.73 (s, 3H), 3.61 (dt, J = 11.7, 4.3 Hz, 1H), 3.33-3.45 (m, 2H), 3.23-3.29 (m, 1H), 3.12-3.18 (m, 1H), 2.85 (dd, J = 17.0, 11.8 Hz, 1H), 2.63-2.69 (m, 1H), 2.51-2.52 (m, 1H), 2.39 (s, 3H), 2.16-2.20 (m, 1H), 1.67-1.72 (m, 1H), 1.33-1.40 (m, 1H), 1.14-1.20 (m, 1H), 0.67-0.74 (m, 1H)	M/z = 525 [M+H]+, Rt = 1.6 min (Method A21) / Rt = 6.17 min (Method C5)
 70g	1H NMR (600 MHz, DMSO-d6) δ 11.27 (s, 1H), 9.15 (s, 1H), 7.29 - 7.27 (m, 1H), 7.14 (t, 1H), 6.96 (dd, 1H), 6.93 (dd, 1H), 6.69 (s, 1H), 6.72 - 6.68 (m, 1H), 6.65 - 6.62 (m, 2H), 5.23 (s, 1H), 4.67 (tt, 1H), 3.77 (s, 3H), 3.71 - 3.33 (m, 4H), 3.29 - 3.24 (m, 1H), 2.74 - 2.65 (m, 2H), 2.43 - 2.31 (m, 2H), 2.29 (s, 3H), 1.79 - 1.41 (m, 3H), 1.14 (br d, 1H)	M/z = 531 [M+H]+, Rt = 2.17 min (Method A21) / Rt = 5.50 min (Method C6)

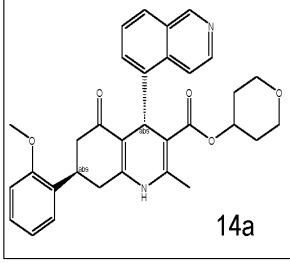
 70a	1H NMR (600 MHz, DMSO-d6) δ 11.35 (s, 1H), 9.27 (s, 1H), 7.33 - 7.32 (m, 1H), 7.27 (dd, 1H), 7.21 (ddd, 1H), 6.96 (dd, 1H), 6.92 (td, 1H), 6.77 (d, 1H), 6.76 (s, 1H), 6.70 (td, 1H), 5.28 (s, 1H), 4.68 (tt, 1H), 3.72 (s, 3H), 3.68 - 3.48 (m, 2H), 3.37 - 3.32 (m, 2H), 3.30 - 3.24 (m, 1H), 2.81 (dd, 1H), 2.62 - 2.57 (m, 1H), 2.45 (dd, 1H), 2.31 (s, 3H), 2.19 (ddd, 1H), 1.79 - 1.44 (m, 3H), 1.17 - 1.10 (m, 1H)	M/z = 531 [M+H]+, Rt = 2.2 min (Method A21) / Rt = 6.96 min (Method C6)

Example Procedure f3: 14g and 14a

A 1ml vial was successively charged with (5*R*)-3-amino-5-(2-methoxyphenyl)cyclohex-2-en-1-one (42 mg, 0.19 mmol) and tetrahydropyran-4-yl 2-(5-isoquinolylmethylene)-3-oxo-butanoate (63.0 mg, 0.19 mmol) in Ethanol (0.20 mL). The reaction mixture was stirred at 80 °C overnight. The reaction was concentrated. The crude was purified by reverse-phase flash chromatography using a gradient of acetonitrile in water from 0% to 50% (neutral). Fractions were combined, evaporated and submitted to chiral separation to give 14g and 14a.

The following compounds were obtained using this protocol and subsequently separated by prep. UPLC (see below for analytic):

Structure **Cpd. No.**	**NMR**	**MS / prep. UPLC**
 14g	1H NMR (500 MHz, DMSO-d6) δ 9.27 (s, 1 H) 9.19 (s, 1 H) 8.48 - 8.53 (m, 1 H) 8.44 - 8.48 (m, 1 H) 7.87 (dd, J =6.19, 3.06 Hz, 1 H) 7.41 - 7.65 (m, 2 H) 7.01 - 7.23 (m, 1 H) 6.93 (d, J =8.13 Hz, 1 H) 6.85 (dd, J =7.63, 1.50 Hz, 1 H) 6.63 (t, J =7.44 Hz, 1 H) 5.57 (s, 1 H) 4.59 (dt, J =9.16, 4.74 Hz, 1 H) 3.78 (s, 3 H) 3.45 (dt, J =11.51, 4.19 Hz, 3 H) 3.11 - 3.28 (m, 2 H) 2.70 - 2.88 (m, 2 H) 2.37 - 2.44 (m, 2 H) 2.35 (s, 3 H) 1.32 - 1.79 (m, 2 H) 0.59 - 1.22 (m, 2 H)	M/z = 525 [M+H]+, Rt = 1.7 min (Method A21) / Rt = 5.46 min (Method C2)

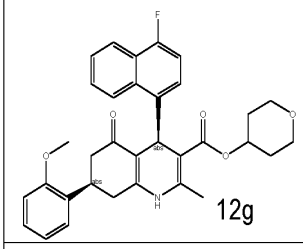
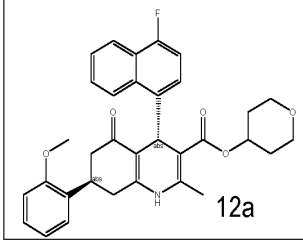
 14a	1H NMR (600 MHz, DMSO-d6) δ 9.37 (s, 1H), 9.21 (s, 1H), 8.56 - 8.52 (m, 2H), 7.91 (d, J = 6.7 Hz, 1H), 7.67 - 7.60 (m, 2H), 7.26 (dd, J = 7.6, 1.6 Hz, 1H), 7.21 (td, J = 7.8, 1.6 Hz, 1H), 6.96 (dd, J = 8.4, 0.9 Hz, 1H), 6.92 (td, J = 7.5, 1.0 Hz, 1H), 5.61 (s, 1H), 4.59 (tt, J = 9.1, 4.3 Hz, 1H), 3.72 (s, 3H), 3.60 (dt, J = 11.6, 4.4 Hz, 1H), 3.42 - 3.34 (m, 2H), 3.29 - 3.23 (m, 1H), 3.17 - 3.12 (m, 1H), 2.84 (dd, J = 17.1, 11.8 Hz, 1H), 2.68 - 2.60 (m, 1H), 2.54 - 2.51 (m, 1H), 2.37 (s, 3H), 2.20 - 2.15 (m, 1H), 1.73 - 1.33 (m, 2H), 1.20 - 0.66 (m, 2H)	M/z = 525 [M+H]+, Rt = 1.99 min (Method A21) / Rt = 9.65 min (Method C2)

Example Procedure f4: 12g and 12a

A 1 ml vial was successively charged with (5*R*)-3-amino-5-(2-methoxyphenyl)cyclohex-2-en-1-one (60 mg, 0.276 mmol), (2*S*)-pyrrolidine-2-carboxylic acid (6.36 mg, 0.06 mmol) and tetrahydropyran-4-yl 2-[(4-fluoro-1-naphthyl)methylene]-3-oxo-butanoate (99.5 mg, 0.28 mmol) in ethanol (0.3 mL). The reaction mixture was stirred at 80 °C overnight. The reaction mixture was concentrated. The crude material was purified by Flash chromatography on silica gel using a gradient of acetone in toluene from 0% to 30%. Fractions were combined and evaporated. The crude was purified by preparative HPLC using a gradient of acetonitrile in water from 20% to 80% (0.005% trifluoroacetic acid in water). Fractions were combined and quenched with carbonate supported. The mixture was filtered and concentrated. After prep UPLC 12g and 12a were obtained.

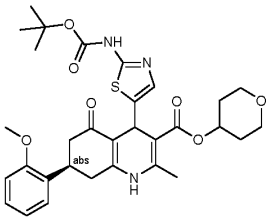
In analogy the following compounds were synthesized and subsequently separated by prep. UPLC (see below for analytic):

Structure	**Cpd. No.**	**NMR**	**MS / prep. UPLC**

 12g	1H NMR (600 MHz, DMSO-d6) δ 9.22 (s, 1 H) 8.74 (br d, J =8.66 Hz, 1 H) 7.94 (d, J =8.36 Hz, 1 H) 7.62 (ddd, J =8.40, 6.93, 1.10 Hz, 1 H) 7.51 - 7.58 (m, 1 H) 7.20 - 7.26 (m, 1 H) 7.17 (dd, J =10.34, 8.14 Hz, 1 H) 7.13 (d, J =8.22 Hz, 1 H) 6.92 (d, J =8.22 Hz, 1 H) 6.87 (dd, J =7.63, 1.32 Hz, 1 H) 6.65 (t, J =7.48 Hz, 1 H) 5.59 (s, 1 H) 4.59 (dt, J =9.02, 4.73 Hz, 1 H) 3.77 (s, 3 H) 3.65 - 3.69 (m, 1 H) 3.35 - 3.65 (m, 2 H) 3.07 - 3.28 (m, 2 H) 2.68 - 2.89 (m, 2 H) 2.36 - 2.44 (m, 2 H) 2.34 (s, 3 H) 1.40 (br d, J =9.10 Hz, 2 H) 0.64 - 1.21 (m, 2 H)	M/z = 542 [M+H]+, Rt = 2.56 min (Method A21) / Rt = 3.26 min (Method C3)
 12a	1H NMR (600 MHz, DMSO-d6) δ 9.33 (s, 1 H) 8.83 (d, J =8.66 Hz, 1 H) 7.97 (d, J =8.36 Hz, 1 H) 7.66 (ddd, J =8.51, 6.97, 1.25 Hz, 1 H) 7.54 - 7.61 (m, 1 H) 7.34 (dd, J =8.14, 5.65 Hz, 1 H) 7.24 - 7.29 (m, 2 H) 7.21 (td, J =7.81, 1.69 Hz, 1 H) 6.96 (d, J =7.63 Hz, 1 H) 6.93 (s, 1 H) 5.64 (s, 1 H) 4.60 (dt, J =8.95, 4.62 Hz, 1 H) 3.72 (s, 3 H) 3.39 - 3.64 (m, 2 H) 3.33 - 3.38 (m, 1 H) 3.09 - 3.28 (m, 2 H) 2.82 (d, J =11.74 Hz, 1 H) 2.64 (ddd, J =16.98, 4.07, 1.25 Hz, 1 H) 2.50 - 2.54 (m, 1 H) 2.36 (s, 3 H) 2.10 - 2.25 (m, 1 H) 1.10 - 1.75 (m, 3 H) 0.72 (dtd, J =13.11, 9.33, 9.33, 4.18 Hz, 1 H)	M/z = 542 [M+H]+, Rt = 2.61 min (Method A21) / Rt = 4.16 min (Method C3)

Example Procedure f5: towards 81h and 92h

tetrahydro-2H-pyran-4-yl (7*R*)-4-(2-((tert-butoxycarbonyl)amino)thiazol-5-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate:

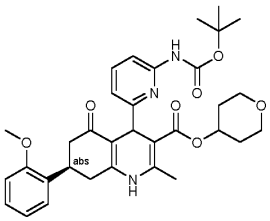


To a stirred solution of tetrahydro-2H-pyran-4-yl 2-((2-((tert-butoxycarbonyl)amino)thiazol-5-yl)methylene)-3-oxobutanoate (180 mg, 0.42 mmol) in DMF (2.0 mL), at RT were added Activated molecular sieves 4A (180 mg) and (5*R*)-3-amino-5-(2-methoxyphenyl)cyclohex-2-en-1-one (109 mg, 0.50

mmol). The reaction mixture was heated to 80 °C and stirred at 80 °C for 2 d. The mixture was cooled down to RT, filtered, washed with DCM and solvent was removed under reduced pressure to give the crude product. Product was purified by flash chromatography on silica gel (solid injection onto dicalite) using a gradient of Heptane / EtOAc, from 100:0 to 50:50, product elution started at 30% solvent B). Desired fractions were combined, and solvent was removed under reduced pressure to afford the title compound.

M/z = 596 [M+H]+, Rt = 0.88/0.89 min (Method A3)

tetrahydro-2H-pyran-4-yl (7*R*)-4-(6-((tert-butoxycarbonyl)amino)pyridin-2-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate:



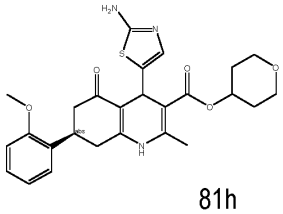
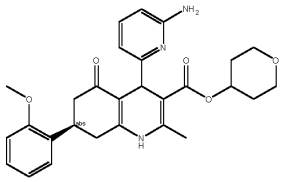
Was obtained via the aforementioned protocol.

M/z = 590 [M+H]+, Rt = 0.81 min (Method A3)

Example Procedure Boc-deprotection: 92h

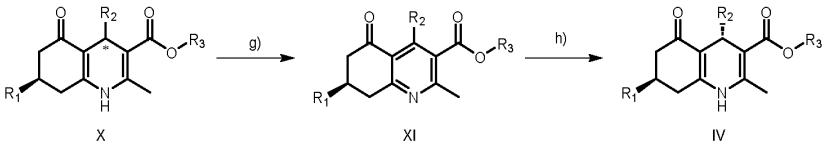
To a stirred solution of tetrahydro-2H-pyran-4-yl (7*R*)-4-(6-((tert-butoxycarbonyl)amino)pyridin-2-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (27.0 mg, 0.023 mmol) in DCM (1.5 mL), at RT was 4 M hydrogen chloride (286 µL, 1.14 mmol). The reaction mixture was stirred at RT for 1 d. To the mixture was added 4 M hydrogen chloride (114 µL, 0.458 mmol) and the reaction was stirred at RT for 3 h. Solvent was removed under reduced pressure to give the crude product. The product was purified by flash chromatography on silica gel (C18) using a gradient of water / ACN, from 90:10 to 0:100, product elution started at 40% solvent B). Desired fractions were combined, and solvent was removed under reduced pressure to afford the title compound.

Structure	Cpd. No.	NMR Mixture of 2 diastereomers	MS

 81h	(55/45) 1H NMR (600 MHz, DMSO-d6) δ 9.35 – 9.21 (m, 1H), 7.29 – 7.12 (m, 2H), 7.02 – 6.97 (m, 1H), 6.96 – 6.81 (m, 1H), 6.63 (br s, 2H), 6.47 – 6.30 (m, 1H), 5.00 – 4.87 (m, 2H), 3.80 (d, J = 2.2 Hz, 3H), 3.78 – 3.58 (m, 2H), 3.55 – 3.42 (m, 3H), 2.79 – 2.57 (m, 3H), 2.47 – 2.32 (m, 1H), 2.29 (d, J = 1.5 Hz, 3H), 1.87 – 1.74 (m, 2H), 1.58 – 1.47 (m, 2H)	M/z = 496 [M+H]+, Rt = 3.95/4.10 min (Method A20)
 92h	(40/60) 1H NMR (600 MHz, DMSO-d6) δ 9.08 – 8.82 (m, 1H), 7.30 – 7.24 (m, 1H), 7.24 – 7.20 (m, 1H), 7.20 – 7.14 (m, 1H), 7.01 – 6.95 (m, 1H), 6.95 – 6.79 (m, 1H), 6.47 – 6.29 (m, 1H), 6.23 – 6.10 (m, 1H), 5.53 – 5.38 (m, 2H), 4.96 – 4.86 (m, 1H), 4.86 – 4.78 (m, 1H), 3.81 – 3.79 (m, 3H), 3.78 – 3.64 (m, 2H), 3.63 – 3.49 (m, 1H), 3.49 – 3.38 (m, 2H), 2.75 – 2.66 (m, 1H), 2.60 – 2.52 (m, 1H), 2.45 – 2.40 (m, 1H), 2.32 – 2.28 (m, 1H), 2.26 (d, J = 6.7 Hz, 3H), 1.53 (s, 4H)	M/z = 490 [M+H]+, Rt = 1.18/1.22 min (Method A21)

EXAMPLE 3

Synthesis of stereo defined scaffolds for evaluation

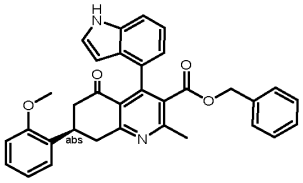


X XI IV

General scheme for the synthesis of stereo defined scaffolds building on (4*RS*,7*R*)-configurated 4,7-substituted 4,6,7,8-tetrahydroquinolin-5(1H)-ones (X) that in two-step procedure of oxidation and subsequent asymmetric transfer hydrogenation can be converted to (4*S*,7*R*)-configurated 4,7-substituted 4,6,7,8-tetrahydroquinolin-5(1H)-ones (IV).

Example Procedure g:

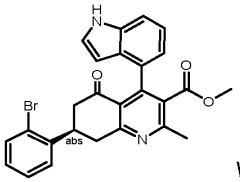
benzyl (7*R*)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate:



In a RBF, at 0 °C, 27h (6.70 g, 11.8 mmol) was dissolved in anhydrous DCM (60.0 mL) and 4,5-dichloro-3,6-dioxo-cyclohexa-1,4-diene-1,2-dicarbonitrile (2.70 g, 11.8 mmol) was added. The reaction was then stirred at 0 °C for 1 h. The reaction mixture was filtered, the solid was washed with DCM and the filtrate was concentrated under reduced pressure to obtain a brown residue. The crude material was purified by Flash chromatography on silica using a gradient of Acetone in toluene from 0% to 20%. Fractions were combined and evaporated to afford the title compound.

1H NMR (400 MHz, DMSO-d6) δ 11.14 (dd, J = 8.0, 2.6 Hz, 1H), 7.44 – 6.66 (m, 13H), 5.92 (dddd, J = 24.2, 3.1, 2.0, 0.9 Hz, 1H), 4.91 – 4.55 (m, 2H), 3.81 (d, J = 2.9 Hz, 4H), 3.52 – 3.32 (m, 2H), 3.11 – 2.79 (m, 1H), 2.70 – 2.52 (m, 1H), 2.50 (td, J = 4.2, 2.3 Hz, 3H)

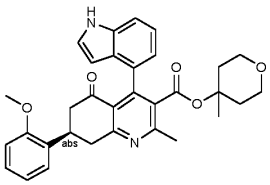
methyl (7*R*)-7-(2-bromophenyl)-4-(1H-indol-4-yl)-2-methyl-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate:



Was obtained via the aforementioned protocol.

1H NMR (400 MHz, DMSO-d6) δ 11.10 (d, J = 10.0 Hz, 1H), 7.67 (ddd, J = 8.0, 2.7, 1.3 Hz, 1H), 7.53 (ddd, J = 17.1, 7.8, 1.7 Hz, 1H), 7.48 – 7.33 (m, 2H), 7.30 – 7.10 (m, 2H), 7.09 (ddd, J = 8.1, 7.1, 2.5 Hz, 1H), 6.78 – 6.69 (m, 1H), 5.98 – 5.90 (m, 1H), 3.98 – 3.80 (m, 1H), 3.50 (dt, J = 16.7, 10.7 Hz, 1H), 3.33 (d, J = 10.3 Hz, 4H), 3.24 – 2.82 (m, 1H), 2.77 – 2.54 (m, 1H), 2.53 (s, 3H)

4-methyltetrahydro-2H-pyran-4-yl (7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate:

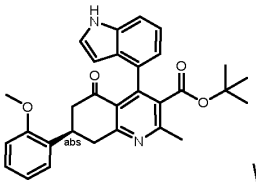


Was obtained via the aforementioned protocol.

1H NMR(DMSO, 500 MHz): δ (ppm) 11.08 (d, J=5.3 Hz, 1H), 7.39 (dq, J=8.2, 1.0 Hz, 1H), 7.25 (tdd, J=8.7, 5.2, 2.5 Hz, 3H), 7.10 – 6.99 (m, 2H), 6.99 – 6.92 (m, 1H), 6.70 (ddd, J=17.7, 7.1, 0.9 Hz, 1H), 5.90

(dddd, J=30.8, 3.0, 2.0, 1.0 Hz, 1H), 3.82 (d, J=2.2 Hz, 4H), 3.55 – 3.29 (m, 3H), 3.21 (dt, J=11.7, 4.2 Hz, 1H), 2.93 (ddd, J=64.3, 15.9, 12.0 Hz, 2H), 2.81 – 2.52 (m, 5H), 1.62 (d, J=12.7Hz, 1H), 1.37 (ddt, J=14.4, 10.2, 5.2 Hz, 1H), 1.23 (d, J=11.6 Hz, 2H), 0.91 (d, J=7.3 Hz, 3H)

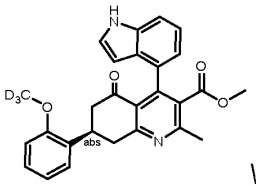
tert-butyl (7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate:



Was obtained via the aforementioned protocol.

1H NMR (500 MHz, DMSO-d6) δ 11.06 (dt, J = 7.7, 2.3 Hz, 1H), 7.38 (ddt, J = 8.2, 1.9, 0.9 Hz, 1H), 7.32 – 7.21 (m, 3H), 7.12 – 7.01 (m, 2H), 6.95 (tdd, J = 7.5, 2.1, 1.1 Hz, 1H), 6.69 (ddd, J = 15.3, 7.1, 0.9 Hz, 1H), 5.89 (dddd, J = 31.3, 3.0, 1.9, 0.9 Hz, 1H), 3.82 (d, J = 2.4 Hz, 4H), 3.48 – 3.27 (m, 6H), 2.93 (ddd, J = 57.7, 16.0, 12.0 Hz, 1H), 2.65 – 2.54 (m, 1H), 2.52 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 8.4 Hz, 9H)

methyl (7*R*)-4-(1H-indol-4-yl)-7-(2-(methoxy-d3)phenyl)-2-methyl-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate:



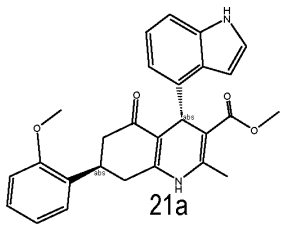
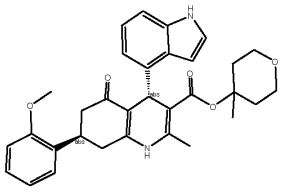
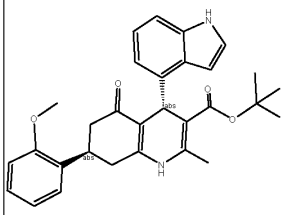
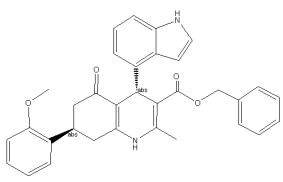
Was obtained via the aforementioned protocol.

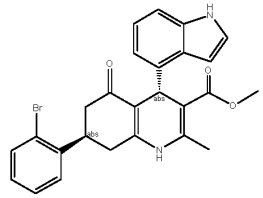
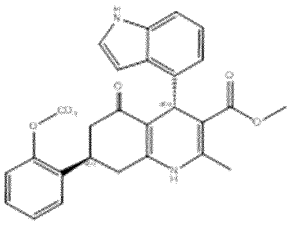
M/z = 444 [M+H]+, Rt = 0.9 min (Method A3)

Example Procedure h: 27a

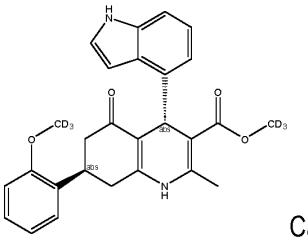
In a vial, benzyl (7*R*)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate (2.60 g, 4.98 mmol) was dissolved in DCM-anhydrous (25.0 mL). Then, diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (95%, 2.66 g, 9.97 mmol) and *S*-TRIP (97%, 155 mg, 0.20 mmol) were added. The reaction mixture was stirred at 40 °C overnight. Then additional diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1330 mg, 4.98 mmol) *S*-TRIP (76.6 mg, 0.010 mmol) were added, and the reaction was stirred at 40 °C overnight again. The reaction mixture was filtered and the solid was lightly washed with dichloromethane. The solid was dried under vacuum and the crude was purified by Flash chromatography on silica gel using a gradient of acetone in toluene from 0% to 25%. Fractions were combined and evaporated to afford the title compound.

The following compounds were obtained using this protocol:

Structure Cpd. No.	NMR	MS
 21a	1H NMR (DMSO-d6, 500 MHz): δ 10.91 (s, 1H), 9.25 (s, 1H), 7.29 (dd, J = 7.6, 1.7 Hz, 1H), 7.26 (t, J = 2.8 Hz, 1H), 7.20-7.24 (m, 1H), 7.16 (d, J = 8.0 Hz, 1H), 6.91-6.98 (m, 3H), 6.82 (d, J = 7.4 Hz, 1H), 6.61 (t, J = 2.6 Hz, 1H), 5.33 (s, 1H), 3.74 (s, 3H), 3.45 (s, 3H), 3.33-3.41 (m, 1H), 2.84 (dd, J = 16.9, 11.9 Hz, 1H), 2.62 (dd, J = 17.1, 2.9 Hz, 1H), 2.43-2.49 (m, 1H), 2.28 (s, 3H), 2.16-2.24 (m, 1H)	M/z = 443 [M+H]+, Rt = 2.09 min (Method A21)
 25a	1H NMR (DMSO-d6, 600 MHz): δ 10.87 (t, J = 2.1 Hz, 1H), 9.17 (s, 1H), 7.27 (dd, J = 7.6, 1.6 Hz, 1H), 7.19-7.24 (m, 2H), 7.16 (dt, J = 8.1, 0.9 Hz, 1H), 6.90-6.96 (m, 3H), 6.82 (dd, J = 7.4, 0.8 Hz, 1H), 6.66 (ddd, J = 3.0, 2.1, 0.9 Hz, 1H), 5.30 (s, 1H), 3.71 (s, 3H), 3.19-3.50 (m, 4H), 3.01 (br d, J = 1.6 Hz, 1H), 2.79 (dd, J = 16.9, 12.0 Hz, 1H), 2.54-2.60 (m, 1H), 2.45 (dd, J = 16.4, 13.4 Hz, 1H), 2.29 (s, 3H), 2.16-2.22 (m, 1H), 1.78-1.99 (m, 2H), 1.40-1.53 (m, 2H), 1.18 (s, 3H)	M/z = 527 [M+H]+, Rt = 7.47 min (Method A21)
 26a	1H NMR (DMSO-d6, 600 MHz): δ 10.87 (s, 1H), 9.10 (s, 1H), 7.27 (dd, J = 7.6, 1.6 Hz, 1H), 7.23-7.25 (m, 1H), 7.19-7.23 (m, 1H), 7.15 (dt, J = 8.0, 0.9 Hz, 1H), 6.90-6.99 (m, 3H), 6.84 (dd, J = 7.4, 0.8 Hz, 1H), 6.59 (ddd, J = 3.1, 2.1, 0.9 Hz, 1H), 5.24 (s, 1H), 3.72 (s, 3H), 3.31-3.37 (m, 1H), 2.80 (dd, J = 16.9, 12.0 Hz, 1H), 2.59 (ddd, J = 17.0, 4.3, 1.6 Hz, 1H), 2.43 (dd, J = 16.4, 13.1 Hz, 1H), 2.23 (s, 3H), 2.15-2.20 (m, 1H), 1.23 (s, 9H)	M/z = 485 [M+H]+, Rt = 2.46 min (Method A21)
 27a	1H NMR (DMSO-d6, 500 MHz): δ 10.91 (t, J = 2.2 Hz, 1H), 9.29 (s, 1H), 7.17-7.29 (m, 7H), 7.06-7.10 (m, 2H), 6.91-6.98 (m, 3H), 6.81 (dd, J = 7.4, 0.9 Hz, 1H), 6.60 (ddd, J = 3.1, 2.1, 0.8 Hz, 1H), 5.36 (s, 1H), 4.89-4.99 (m, 2H), 3.73 (s, 3H), 3.33-3.41 (m, 1H), 2.83 (dd, J = 17.0, 12.0 Hz, 1H), 2.56-2.66 (m, 1H), 2.43-2.49 (m, 1H), 2.31 (s, 3H), 2.17-2.23 (m, 1H)	M/z = 519 [M+H]+, Rt = 2.5 min (Method A21)

 86a	1H NMR (600 MHz, DMSO-d6) δ 10.89 (t, J = 2.1 Hz, 1H), 9.28 (s, 1H), 7.60 (dd, J = 7.9, 1.3 Hz, 1H), 7.52 (dd, J = 7.9, 1.8 Hz, 1H), 7.40 (td, J = 7.6, 1.3 Hz, 1H), 7.26 (dd, J = 3.2, 2.4 Hz, 1H), 7.21 – 7.18 (m, 1H), 7.15 (dt, J = 8.0, 1.0 Hz, 1H), 6.93 (t, J = 7.6 Hz, 1H), 6.82 (dd, J = 7.3, 1.0 Hz, 1H), 6.58 (ddd, J = 3.2, 2.1, 1.0 Hz, 1H), 5.32 (s, 1H), 3.51 – 3.39 (m, 4H), 2.80 (dd, J = 17.0, 11.7 Hz, 1H), 2.73 – 2.68 (m, 1H), 2.63 – 2.57 (m, 1H), 2.26 (s, 3H), 2.26 – 2.22 (m, 1H)	M/z = 491 [M+H]+, Rt = 2.16 min (Method A21)
 99a	1H NMR (600 MHz, DMSO-d6) δ 10.89 (s, 1H), 9.24 (s, 1H), 7.27 (dd, J = 7.6, 1.6 Hz, 1H), 7.26 – 7.24 (m, 1H), 7.23 – 7.19 (m, 1H), 7.18 – 7.13 (m, 1H), 6.97 – 6.90 (m, 3H), 6.81 (dd, J = 7.3, 0.7 Hz, 1H), 6.60 (ddd, J = 3.0, 2.1, 0.9 Hz, 1H), 5.32 (s,1H), 3.44 (s, 3H), 3.40 – 3.32 (m, 1H), 2.82 (dd, J = 17.0, 11.9 Hz, 1H), 2.65 – 2.58 (m, 1H), 2.46 (dd, J = 16.3, 13.1 Hz, 1H), 2.27 (s, 3H), 2.19 (ddd, J = 16.3, 3.9, 1.3 Hz, 1H)	M/z = 446 [M+H]+, Rt = 2.35 min (Method A21)

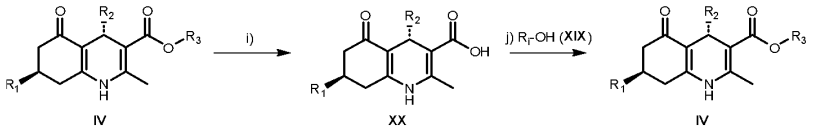
methyl-d3 (4*S*,7*R*)-4-(1H-indol-4-yl)-7-(2-(methoxy-d3)phenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (100a):



Can be made via the aforementioned protocol. M/z = 449 [M+H]+,

EXAMPLE 4

Late-stage derivatization of stereo defined scaffolds for evaluation

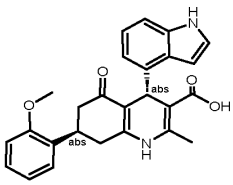


IV XX IV

General scheme for the late-stage derivatization of stereo defined 4,7-substituted 4,6,7,8-tetrahydroquinolin-5(1H)-ones (IV) employing the free carboxylic acid XX as intermediate towards a diverse set of esters.

Example Procedure i:

(4*S*,7*R*)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid:

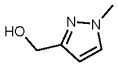


A 250ml round-bottomed flask charged with 27a (3.65 g, 6.83 mmol) in THF (60.0 mL). Then palladium (727 mg, 0.683 mmol) was added. The reaction mixture was stirred under a hydrogen atmosphere at RT for 3 h. The reaction mixture was filtered through a pad of celite, and the filtrate was concentrated under vacuum to afford the title compound.

1H NMR (400 MHz, DMSO-d6) δ 11.52 (s, 1H), 10.88 (t, J = 2.2 Hz, 1H), 9.13 (s, 1H), 7.32 – 7.12 (m, 4H), 6.99 – 6.90 (m, 3H), 6.81 (dd, J = 7.4, 1.0 Hz, 1H), 6.66 – 6.63 (m, 1H), 5.30 (s, 1H), 3.73 (s, 3H), 3.35 (dd, J = 12.8, 4.0 Hz, 1H), 2.82 (dd, J = 17.0, 12.0 Hz, 1H), 2.64 – 2.55 (m, 1H), 2.48 – 2.41 (m, 1H), 2.28 (s, 3H), 2.24 – 2.07 (m, 1H)

Procedures preparing non-commercial alcohols for j:

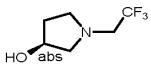
(1-methyl-1H-pyrazol-3-yl)methanol:



A round-bottomed flask was successively charged with 1-methyl-1H-pyrazole-3-carbaldehyde (100 mg, 0.91 mmol) and Sodium borohydride (545 mg, 1.36 mmol) in ethanol (6.0 mL). The reaction mixture was stirred at RT for 1 h. The reaction mixture was filtered, and the filtrate was concentrated under vacuum to afford the title compound.

1H NMR (400 MHz, CDCl3) δ 7.29 (d, J = 2.2 Hz, 1H), 6.22 (d, J = 2.2 Hz, 1H), 4.66 (d, J = 6.0 Hz, 2H), 3.86 (s, 3H), 2.43 (t, J = 6.0, 6.0 Hz, 1H)

(*S*)-1-(2,2,2-trifluoroethyl)pyrrolidin-3-ol:

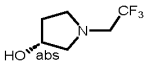


A vial was successively charged with (3*S*)-pyrrolidin-3-ol (250 mg, 2.81 mmol), triethylamine (0.784 mL, 5.62 mmol) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (0.512 mL, 3.37 mmol) in DCM-Anhydrous (25.0 mL). The reaction was stirred at RT for 2 h. Water was added. The phases were separated, and the

aqueous phase was extracted with dichloromethane. The combined organic layers were dried using a phase separator and concentrated under vacuum to afford the title compound.

1H NMR (400 MHz, MeOD-d4) δ 4.35 (ddd, J = 10.3, 6.3, 3.1 Hz, 1H), 3.19 (q, J = 9.9 Hz, 2H), 2.99 (dd, J = 10.3, 5.9 Hz, 1H), 2.92 (dt, J = 9.1, 7.3 Hz, 1H), 2.74 (td, J = 8.5, 5.3 Hz, 1H), 2.67 (dd, J = 10.2, 3.2 Hz, 1H), 2.21 – 2.00 (m, 1H), 1.76 (ddd, J = 13.3, 6.8, 4.2 Hz, 1H)

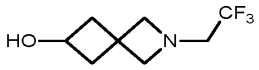
(*R*)-1-(2,2,2-trifluoroethyl)pyrrolidin-3-ol:



Was obtained via the aforementioned protocol.

1H NMR (400 MHz, MeOD-d4) δ 4.35 (ddd, J = 10.3, 6.3, 3.2 Hz, 1H), 3.19 (qd, J = 9.8, 0.8 Hz, 2H), 2.99 (dd, J = 10.3, 5.8 Hz, 1H), 2.92 (dt, J = 9.0, 7.3 Hz, 1H), 2.74 (td, J = 8.5, 5.3 Hz, 1H), 2.67 (dd, J = 10.3, 3.1 Hz, 1H), 2.22 – 2.02 (m, 1H), 1.75 (dddd, J = 13.1, 7.9, 5.2, 3.1 Hz, 1H)

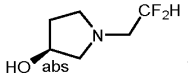
2-(2,2,2-trifluoroethyl)-2-azaspiro[3.3]heptan-6-ol:



Was obtained via the aforementioned protocol.

1H NMR (400 MHz, DMSO-d6) δ 4.93 (d, J = 6.2 Hz, 1H), 3.91 (td, J = 7.3, 6.3 Hz, 1H), 3.25 (d, J = 17.0 Hz, 4H), 3.09 (q, J = 10.2 Hz, 2H), 2.32 (ddt, J = 9.1, 7.0, 2.6 Hz, 2H), 1.92 – 1.81 (m, 2H)

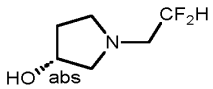
(*S*)-1-(2,2-difluoroethyl)pyrrolidin-3-ol:



Was obtained via the aforementioned protocol employing 2,2-difluoroethyl trifluoromethanesulfonate.

1H NMR (400 MHz, Methanol-d4) δ 5.95 (tt, J = 56.0, 4.3 Hz, 1H), 4.35 (ddd, J = 10.5, 6.2, 3.1 Hz, 1H), 3.02 – 2.83 (m, 4H), 2.65 (ddd, J = 16.3, 9.4, 4.3 Hz, 2H), 2.13 (dq, J = 13.7, 7.3 Hz, 1H), 1.74 (dddd, J = 13.4, 8.2, 5.5, 3.0 Hz, 1H)

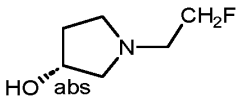
(*R*)-1-(2,2-difluoroethyl)pyrrolidin-3-ol:



Was obtained via the aforementioned protocol employing 2,2-difluoroethyl trifluoromethanesulfonate.

1H NMR (400 MHz, DMSO-d6) δ 5.14 (tt, J = 55.9, 4.3 Hz, 1H), 3.54 (ddd, J = 10.4, 6.2, 3.1 Hz, 1H), 2.18 – 2.02 (m, 4H), 1.85 (ddd, J = 16.1, 9.4, 4.4 Hz, 2H), 1.32 (ddd, J = 15.2, 13.8, 7.3 Hz, 1H), 0.93 (dddd, J = 13.3, 8.1, 5.5, 3.0 Hz, 1H)

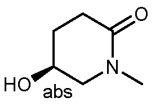
(*R*)-1-(2-fluoroethyl)pyrrolidin-3-ol:



A vial was successively charged with (3*R*)-pyrrolidin-3-ol (0.278 mL, 3.27 mmol) and N-ethyl-N-isopropyl-propan-2-amine (1.14 mL, 6.54 mmol) in acetonitrile (15.0 mL). Then a solution of 1-fluoro-2-iodo-ethane (755 mg, 4.25 mmol) in acetonitrile (5.0 mL) was added. The reaction was stirred at 55°C overnight. Water was added. The phases were separated, and the aqueous phase was extracted with dichloromethane/methanol (90/10). The combined organic layers were dried using a phase separator and concentrated under vacuum to afford the title compound.

1H NMR (400 MHz, Methanol-d4) δ 4.69 (d, J = 4.9 Hz, 1H), 4.57 (t, J = 4.8 Hz, 1H), 4.43 (ddd, J = 9.8, 5.8, 2.9 Hz, 1H), 3.17 – 2.94 (m, 4H), 2.87 (ddd, J = 10.1, 8.4, 5.2 Hz, 1H), 2.80 (dd, J = 11.0, 3.0 Hz, 1H), 2.19 (ddt, J = 14.2, 8.2, 7.2 Hz, 1H), 1.89 – 1.75 (m, 1H).

(*S*)-5-hydroxy-1-methylpiperidin-2-one:



Step i) To a stirred solution of (5*S*)-5-hydroxypiperidin-2-one (300 mg, 2.55 mmol), N,N-dimethylpyridin-4-amine (63.0 mg, 0.51 mmol and triethylamine (0.392 mL, 2.81 mmol) in 2-methyltetrahydrofuran-anhydrous (8.5 mL) at 0 °C, benzoyl chloride (0.326 mL, 2.81 mmol) was added dropwise. The reaction was stirred at RT for 2 h. The reaction mixture was concentrated to dryness. The crude material was purified by Flash chromatography on silica gel using a gradient of EtOAc/EtOH (3/1) in cyclohexane from 0% to 50%. Fractions were combined and evaporated to afford [(3*S*)-6-oxo-3-piperidyl] benzoate.

1H NMR (400 MHz, DMSO-d6) δ 8.01 – 7.90 (m, 2H), 7.72 – 7.63 (m, 1H), 7.58 – 7.50 (m, 2H), 7.47 (s, 1H), 5.28 (p, J = 3.7 Hz, 1H), 3.52 (ddd, J = 13.5, 3.7, 1.5 Hz, 1H), 3.37 – 3.28 (m, 1H), 2.44 – 2.31 (m, 1H), 2.25 (dt, J = 17.6, 5.5 Hz, 1H), 2.15 – 2.02 (m, 2H)

Step ii) To a stirred solution of [(3*S*)-6-oxo-3-piperidyl] benzoate (110 mg, 0.502 mmol) in DMF-anhydrous (4.6 mL) at 0 °C under nitrogen, sodium hydride (44.1 mg, 1.10 mmol) was added slowly, followed by iodomethane (250 µL, 4.01 mmol). The reaction was stirred at 0°C for 2 h. The reaction was poured into a solution a 1N HCl. Ethyl acetate was added. The phases were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic layers were dried using a phase separator and concentrated under vacuum. The crude material was purified by Flash chromatography on silica gel using

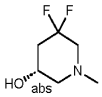
a gradient of EtOAc/EtOH (3/1) in cyclohexane from 0% to 80%. Fractions were combined and evaporated to [(3*S*)-1-methyl-6-oxo-3-piperidyl] benzoate.

1H NMR (400 MHz, DMSO-d6) δ 8.01 – 7.94 (m, 2H), 7.72 – 7.63 (m, 1H), 7.59 – 7.49 (m, 2H), 5.39 – 5.31 (m, 1H), 3.69 (dd, J = 13.4, 3.9 Hz, 1H), 3.44 (ddd, J = 13.5, 3.5, 1.5 Hz, 1H), 2.83 (s, 3H), 2.48 – 2.38 (m, 1H), 2.31 (dt, J = 17.4, 5.5 Hz, 1H), 2.15 – 2.00 (m, 2H)

Step iii) To a stirred solution of [(3*S*)-1-methyl-6-oxo-3-piperidyl] benzoate (130 mg, 0.541 mmol) in methanol-anhydrous (5.4 mL) at RT was added 0.5M sodium methanolate (0.54 mL, 0.27 mmol). The reaction mixture was stirred at RT for 2 h. To this reaction was added Amberlite IRC120 until pH 7. The reaction mixture was filtered, and the resin was washed with methanol. The filtrate was evaporated to afford the title compound.

1H NMR (400 MHz, Chloroform-d) δ 4.16 (dtd, J = 9.6, 4.6, 3.3 Hz, 1H), 3.52 – 3.42 (m, 1H), 3.25 (ddd, J = 12.5, 5.0, 1.2 Hz, 1H), 2.92 (s, 3H), 2.59 (ddd, J = 17.9, 8.5, 6.6 Hz, 1H), 2.36 (dt, J = 17.8, 6.4 Hz, 2H), 2.05 – 1.84 (m, 2H)

(*R*)-5,5-difluoro-1-methylpiperidin-3-ol:



Step i) To a stirred solution of tert-butyl (5*R*)-3,3-difluoro-5-hydroxypiperidine-1-carboxylate (200 mg, 0.843 mmol) in 1,4-Dioxane (4.0 mL) at RT was added 4 M hydrogen chloride (2.11 mL, 8.43 mmol). The reaction was stirred at RT overnight. The reaction mixture was concentrated to dryness to afford the expected HCl salt.

1H NMR (400 MHz, DMSO-d6) δ 9.77 (s, 2H), 5.72 (s, 1H), 4.02 (tt, J = 7.9, 3.8 Hz, 1H), 3.65 – 3.38 (m, 2H), 3.17 (dd, J = 12.3, 3.6 Hz, 1H), 2.86 (dd, J = 12.3, 8.0 Hz, 1H), 2.36 (qd, J = 13.3, 4.4 Hz, 1H), 2.09 (tdd, J = 15.0, 13.5, 8.3 Hz, 1H)

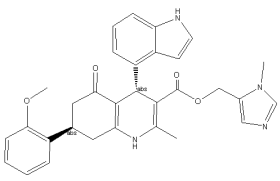
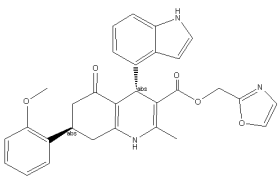
Step ii) To a stirred solution of (3*R*)-5,5-difluoropiperidin-3-ol*hydrochloride (150 mg, 0.82 mmol) and PARAFORMALDEHYDE (123 mg, 4.10 mmol) in anhydrous methanol (8.2 mL) at RT under nitrogen was added cyanoborohydride supported (1.54 g, 2.46 mmol). The reaction was stirred at 40°C for 2 h. Then a few drops of AcOH were added and the reaction was stirred at 40°C overnight. The resin was filtered and washed with dichloromethane and methanol. The filtrate was evaporated to dryness to afford the title compound.

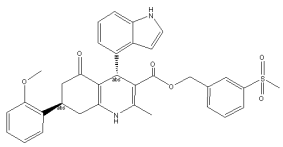
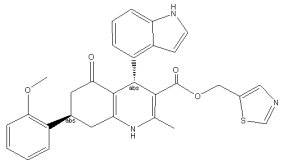
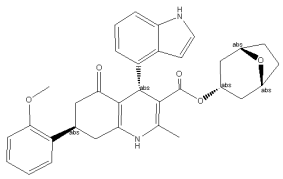
1H NMR (400 MHz, DMSO-d6) δ 5.04 (s, 1H), 3.67 (dq, J = 9.8, 4.9 Hz, 1H), 2.87 (dddt, J = 11.9, 9.6, 5.5, 2.0 Hz, 1H), 2.80 (ddd, J = 10.8, 4.1, 2.1 Hz, 1H), 2.23 (s, 4H), 2.22 – 2.11 (m, 1H), 1.86 – 1.78 (m, 1H), 1.66 – 1.48 (m, 1H)

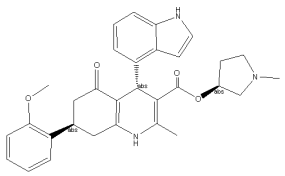
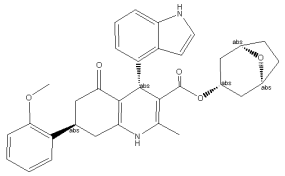
Example Procedure j1: 34a/34b

To a stirred solution of (4*S*,7*R*)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid (40.0 mg, 0.075 mmol) in acetonitrile-anhydrous (0.75 mL) at RT were added 8-oxabicyclo[3.2.1]octan-3-ol (39.5 mg, 0.30 mmol), pyridine (24 µL, 0.3 mmol) and propylphosphonic anhydride in DMF 50% w/w (216 µL, 0.3 mmol). The reaction mixture was heated to 40 °C and stirred for 1 h. Water and ethyl acetate were added, the phases separated, and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with water, dried using a phase separator and concentrated under vacuum. The crude was purified by reverse-phase flash chromatography using a gradient of acetonitrile in water from 30% to 70% (neutral). Fractions were combined and lyophilized to afford two batches corresponding to the two isomers 34b and 34a

The following compounds were obtained using this protocol:

Structure Cpd. No.	NMR	MS
 30a	1H NMR (DMSO-d6, 600 MHz) δ 10.88 (t, 1H, J =1.9 Hz), 9.29 (s, 1H), 7.52 (s, 1H), 7.26 (dd, 1H, J =1.5, 7.7 Hz), 7.21 (ddd, 1H, J =1.7, 7.4, 8.2 Hz), 7.2-7.2 (m, 1H), 7.14 (td, 1H, J =0.9, 8.0 Hz), 6.95 (dd, 1H, J =1.0, 8.3 Hz), 6.92 (dt, 1H, J =1.0, 7.5 Hz), 6.9-6.9 (m, 1H), 6.85 (d, 1H, J =1.0 Hz), 6.71 (dd, 1H, J =0.8, 7.4 Hz), 6.47 (ddd, 1H, J =0.8, 2.1, 3.1 Hz), 5.24 (s, 1H), 4.8-5.0 (m, 2H), 3.71 (s, 3H), 3.30 (s, 1H), 3.17 (s, 3H), 2.80 (dd, 1H, J =12.0, 16.9 Hz), 2.6-2.6 (m, 1H), 2.43 (dd, 1H, J =13.2, 16.4 Hz), 2.30 (s, 3H), 2.1-2.2 (m, 1H)	M/z = 523 [M+H]+, Rt = 1.29 min (Method A21)
 31a	1H NMR (DMSO-d6, 500 MHz): δ 10.73-11.07 (m, 1H), 9.37 (s, 1H), 8.11 (d, J = 0.9 Hz, 1H), 7.28 (dd, J = 7.6, 1.6 Hz, 1H), 7.19-7.25 (m, 3H), 7.15 (dt, J = 8.0, 0.9 Hz, 1H), 6.97 (dd, J = 8.3, 0.9 Hz, 1H), 6.94 (td, J = 7.5, 1.0 Hz, 1H), 6.89 (t, J = 7.4 Hz, 1H), 6.77 (dd, J = 7.4, 0.8 Hz, 1H), 6.48 (ddd, J = 3.1, 2.0, 0.9 Hz, 1H), 5.29 (s, 1H), 5.06 (d, J = 13.8 Hz, 1H), 4.94 (d, J = 13.6 Hz, 1H), 3.73 (s, 3H), 3.35 (br d, J = 12.1 Hz, 1H), 2.85 (dd, J = 17.0, 11.8 Hz, 1H), 2.59-2.68 (m, 1H), 2.46 (dd, J = 16.3, 13.1 Hz, 1H), 2.30 (s, 3H), 2.15-2.23 (m, 1H)	M/z = 510 [M+H]+, Rt = 2.03 min (Method A21)

 32a	1H NMR (DMSO-d6, 500 MHz): δ 10.81-10.99 (m, 1H), 9.33 (s, 1H), 7.81 (d, J = 0.8 Hz, 2H), 7.47 (td, J = 7.6, 0.7 Hz, 1H), 7.28 (dd, J = 7.7, 1.6 Hz, 1H), 7.20-7.26 (m, 3H), 7.18 (dt, J = 8.0, 0.9 Hz, 1H), 6.90-6.99 (m, 3H), 6.82 (dd, J = 7.3, 0.8 Hz, 1H), 6.57 (ddd, J = 3.1, 2.1, 0.9 Hz, 1H), 5.36 (s, 1H), 5.05 (d, J = 1.3 Hz, 2H), 3.73 (s, 3H), 3.32-3.42 (m, 1H), 3.19 (s, 3H), 2.84 (dd, J = 17.0, 11.9 Hz, 1H), 2.56-2.67 (m, 1H), 2.41-2.50 (m, 1H), 2.32 (s, 3H), 2.20 (dd, J = 16.3, 2.7 Hz, 1H)	M/z = 597 [M+H]+, Rt = 2.19 min (Method A21)
 33a	1H NMR (DMSO-d6, 500 MHz) δ 10.90 (s, 1H), 9.33 (s, 1H), 9.04 (d, 1H, J =0.6 Hz), 7.77 (d, 1H, J =0.6 Hz), 7.27 (dd, 1H, J =1.6, 7.6 Hz), 7.2-7.3 (m, 2H), 7.15 (d, 1H, J =8.0 Hz), 6.8-7.0 (m, 3H), 6.79 (dd, 1H, J =0.6, 7.3 Hz), 6.55 (t, 1H, J =2.1 Hz), 5.29 (s, 1H), 5.1-5.3 (m, 2H), 3.73 (s, 3H), 3.3-3.4 (m, 1H), 2.83 (dd, 1H, J =11.9, 16.9 Hz), 2.6-2.7 (m, 1H), 2.45 (dd, 1H, J =13.1, 16.3 Hz), 2.29 (s, 3H), 2.1-2.2 (m, 1H)	M/z = 526 [M+H]+, Rt = 6.95 min (Method A20)
 34b	1H NMR (600 MHz, DMSO-d6) δ 10.90 (s, 1 H) 9.26 (s, 1 H) 7.27 (dd, J =7.63, 1.61 Hz, 1 H) 7.23 - 7.25 (m, 1 H) 7.21 (ddd, J =8.18, 7.45, 1.69 Hz, 1 H) 7.14 - 7.17 (m, 1 H) 6.94 - 6.96 (m, 1 H) 6.93 - 6.94 (m, 1 H) 6.90 - 6.93 (m, 1 H) 6.83 (dd, J =7.34, 0.73 Hz, 1 H) 6.66 (ddd, J =3.04, 2.09, 0.88 Hz, 1 H) 5.40 (s, 1 H) 4.68 (t, J =5.14 Hz, 1 H) 4.18 (br s, 1 H) 4.11 - 4.14 (m, 1 H) 3.71 (s, 3 H) 3.26 - 3.30 (m, 1 H) 2.80 (dd, J =17.02, 12.18 Hz, 1 H) 2.54 - 2.59 (m, 1 H) 2.44 - 2.49 (m, 1 H) 2.32 (s, 3 H) 2.20 (ddd, J =16.43, 3.81, 1.47 Hz, 1 H) 1.94 - 2.03 (m, 1 H) 1.87 (dt, J =14.89, 4.73 Hz, 2 H) 1.57 - 1.74 (m, 3 H) 1.35 - 1.52 (m, 2 H)	M/z = 539 [M+H]+, Rt = 7.28 min (Method A20)

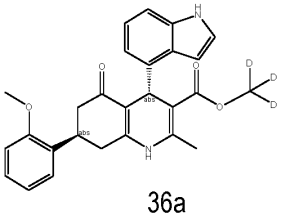
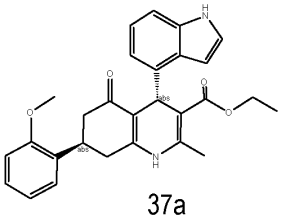
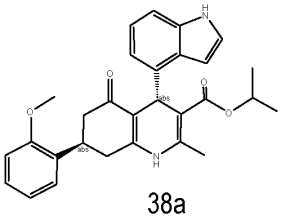
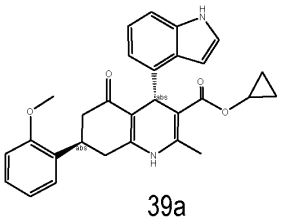
 35a	1H NMR (DMSO-d6, 500 MHz): δ 10.89 (t, J = 2.1 Hz, 1H), 9.23 (s, 1H), 7.20-7.29 (m, 3H), 7.16 (dt, J = 8.0, 1.0 Hz, 1H), 6.92-6.98 (m, 3H), 6.86 (dd, J = 7.4, 1.0 Hz, 1H), 6.61 (ddd, J = 3.1, 2.1, 0.9 Hz, 1H), 5.29 (s, 1H), 4.87-4.92 (m, 1H), 3.73 (s, 3H), 3.33-3.38 (m, 1H), 2.83 (dd, J = 17.0, 11.8 Hz, 1H), 2.58-2.67 (m, 2H), 2.35-2.48 (m, 3H), 2.28 (s, 3H), 2.17-2.27 (m, 5H), 1.83-1.90 (m, 1H), 1.35 (dddd, J = 13.5, 7.8, 5.3, 2.9 Hz, 1H)	M/z = 512 [M+H]+, Rt = 1.26 min (Method A21)
 34a	1H NMR (600 MHz, DMSO-d6) δ 10.86 (t, J =2.05 Hz, 1 H) 9.21 (s, 1 H) 7.27 (dd, J =7.63, 1.61 Hz, 1 H) 7.24 - 7.25 (m, 1 H) 7.21 (ddd, J =8.22, 7.41, 1.69 Hz, 1 H) 7.14 (dt, J =8.03, 0.90 Hz, 1 H) 6.95 (dd, J =8.36, 1.03 Hz, 1 H) 6.93 (s, 1 H) 6.91 - 6.93 (m, 1 H) 6.82 (dd, J =7.34, 0.88 Hz, 1 H) 6.57 (ddd, J =3.08, 2.05, 0.88 Hz, 1 H) 5.24 (s, 1 H) 4.73 - 4.94 (m, 1 H) 4.29 - 4.33 (m, 1 H) 4.21 (br d, J =3.08 Hz, 1 H) 3.72 (s, 3 H) 3.31 - 3.36 (m, 1 H) 2.75 - 2.89 (m, 1 H) 2.56 - 2.63 (m, 1 H) 2.43 (dd, J =16.36, 13.13 Hz, 1 H) 2.27 (s, 3 H) 2.13 - 2.22 (m, 1 H) 1.74 - 1.81 (m, 2 H) 1.61 - 1.73 (m, 2 H) 1.41 - 1.60 (m, 3 H) 1.14 - 1.27 (m, 1 H)	M/z = 539 [M+H]+, Rt = 2.24 min (Method A21)

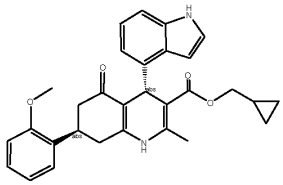
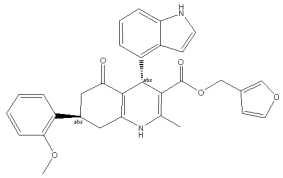
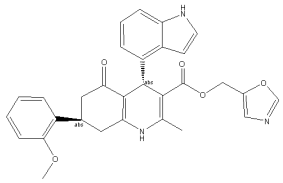
Example Procedure j2: 53a

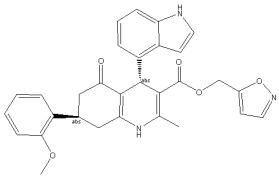
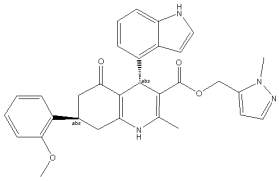
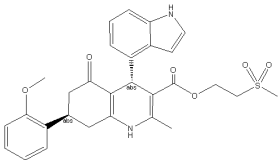
To a stirred suspension of (4*S*,7*R*)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid (40.0 mg, 0.075 mmol) in DCM-anhydrous (0.75 mL) at RT were added successively (1,2-thiazol-5-yl)methanol (35.8 mg, 0.30 mmol), pyridine (24 µL, 0.30 mmol) and propylphosphonic anhydride in DMF 50% w/w (216 µL, 0.3 mmol). The reaction mixture was heated to 40 °C and stirred for 1 h. Water and ethyl acetate were added, the phases separated, and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with water, dried using a phase separator and concentrated under vacuum. The crude material was purified by Flash chromatography on silica gel using a gradient of acetone in toluene from 0% to 40%. Fractions were combined and evaporated to afford the title compound.

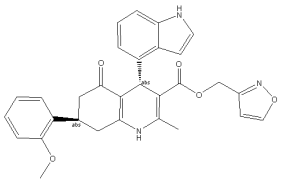
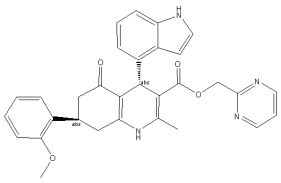
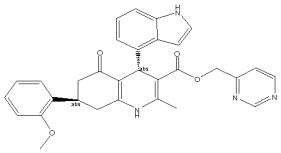
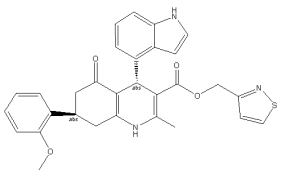
The following compounds were obtained using this protocol:

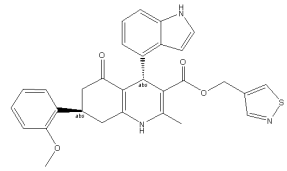
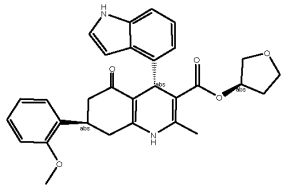
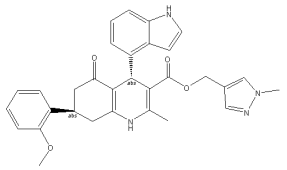
Structure	**Cpd. No.**	**NMR**	**MS**

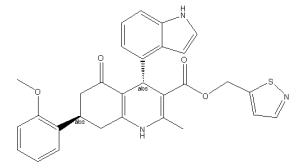
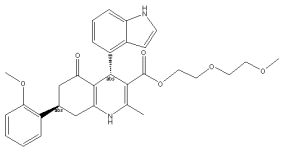
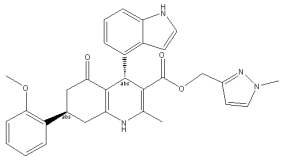
 36a	1H NMR (DMSO-d6, 600 MHz) δ 10.89 (s, 1H), 9.23 (s, 1H), 7.28 (dd, 1H, J =1.6, 7.6 Hz), 7.2-7.3 (m, 1H), 7.21 (ddd, 1H, J =1.8, 7.4, 8.1 Hz), 7.15 (td, 1H, J =0.9, 8.0 Hz), 6.9-7.0 (m, 3H), 6.81 (dd, 1H, J =0.8, 7.3 Hz), 6.60 (ddd, 1H, J =0.9, 2.1, 3.1 Hz), 5.32 (s, 1H), 3.73 (s, 3H), 3.36 (tt, 1H, J =4.0, 12.5 Hz), 2.82 (dd, 1H, J =11.9, 17.0 Hz), 2.61 (ddd, 1H, J =1.5, 4.2, 17.0 Hz), 2.46 (dd, 1H, J =13.1, 16.4 Hz), 2.27 (s, 3H), 2.2-2.2 (m, 1H)	M/z = 446 [M+H]+, Rt = 2.35 min (Method A21)
 37a	1H NMR (DMSO-d6, 600 MHz) δ 10.88 (s, 1H), 9.21 (s, 1H), 7.27 (dd, 1H, J =1.6, 7.6 Hz), 7.2-7.3 (m, 1H), 7.21 (ddd, 1H, J =1.7, 7.4, 8.2 Hz), 7.1-7.2 (m, 1H), 6.9-7.0 (m, 3H), 6.83 (dd, 1H, J =0.9, 7.3 Hz), 6.59 (ddd, 1H, J =0.9, 2.1, 3.0 Hz), 5.31 (s, 1H), 3.8-4.0 (m, 2H), 3.73 (s, 3H), 3.3-3.4 (m, 1H), 2.82 (dd, 1H, J =12.0, 17.0 Hz), 2.6-2.7 (m, 1H), 2.45 (dd, 1H, J =13.1, 16.4 Hz), 2.27 (s, 3H), 2.1-2.2 (m, 1H), 1.05 (t, 3H, J =7.1 Hz)	M/z = 457 [M+H]+, Rt = 2.21 min (Method A21)
 38a	1H NMR (DMSO-d6, 600 MHz): δ 10.64-11.04 (m, 1H), 9.18 (s, 1H), 7.27 (dd, J = 7.7, 1.7 Hz, 1H), 7.23-7.25 (m, 1H), 7.21 (ddd, J = 8.1, 7.4, 1.8 Hz, 1H), 7.14 (dt, J = 8.0, 0.9 Hz, 1H), 6.96 (dd, J = 8.4, 1.0 Hz, 1H), 6.90-6.94 (m, 2H), 6.84 (dd, J = 7.3, 0.9 Hz, 1H), 6.59 (ddd, J = 3.1, 2.1, 0.9 Hz, 1H), 5.28 (s, 1H), 4.70 (spt, J = 6.2 Hz, 1H), 3.72 (s, 3H), 3.34 (tt, J = 13.0, 4.0 Hz, 1H), 2.81 (dd, J = 16.9, 12.0 Hz, 1H), 2.60 (ddd, J = 16.9, 4.2, 1.6 Hz, 1H), 2.43 (dd, J = 16.4, 13.1 Hz, 1H), 2.27 (s, 3H), 2.14-2.21 (m, 1H), 1.13 (d, J = 6.2 Hz, 3H), 0.85 (d, J = 6.2 Hz, 3H)	M/z = 471 [M+H]+, Rt = 2.34 min (Method A21)
 39a	1H NMR (DMSO-d6, 600 MHz): δ 10.88 (t, J = 2.1 Hz, 1H), 9.24 (s, 1H), 7.24-7.27 (m, 2H), 7.21 (ddd, J = 8.2, 7.4, 1.8 Hz, 1H), 7.15 (dt, J = 8.0, 0.9 Hz, 1H), 6.91-6.96 (m, 3H), 6.79 (dd, J = 7.3, 1.0 Hz, 1H), 6.56 (ddd, J = 3.1, 2.1, 1.0 Hz, 1H), 5.18 (s, 1H), 3.89-3.92 (m, 1H), 3.72 (s, 3H), 3.31-3.36 (m, 1H), 2.82 (dd, J = 16.9, 11.9 Hz, 1H), 2.56-2.62 (m, 1H), 2.38-2.47 (m, 1H), 2.27 (s, 3H), 2.15-2.20 (m, 1H), 0.51-0.57 (m, 2H), 0.39-0.45 (m, 1H), 0.02-0.07 (m, 1H)	M/z = 469 [M+H]+, Rt = 2.24 min (Method A21)

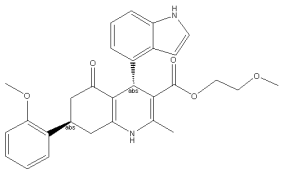
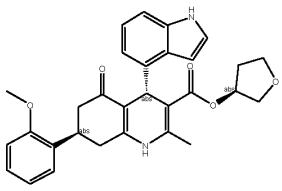
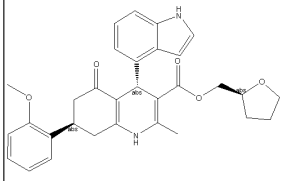
 40a	1H NMR (600 MHz, DMSO-d6) δ 10.97 – 10.75 (m, 1H), 9.22 (s, 1H), 7.28 (dd, J = 7.6, 1.6 Hz, 1H), 7.25 – 7.18 (m, 2H), 7.16 – 7.09 (m, 1H), 7.02 – 6.90 (m, 3H), 6.86 (dd, J = 7.4, 1.0 Hz, 1H), 6.60 (dt, J = 2.1, 1.1 Hz, 1H), 5.33 (s, 1H), 3.78 – 3.70 (m, 4H), 3.67 – 3.60 (m, 1H), 3.36 (tt, J = 12.5, 4.0 Hz, 1H), 2.83 (dd, J = 17.0, 11.9 Hz, 1H), 2.62 (ddd, J = 17.0, 4.1, 1.6 Hz, 1H), 2.45 (dd, J = 16.4, 13.1 Hz, 1H), 2.27 (s, 3H), 2.22 – 2.15 (m, 1H), 1.01 – 0.91 (m, 1H), 0.50 – 0.34 (m, 2H), 0.18 – 0.07 (m, 2H)	M/z = 483 [M+H]+, Rt = 2.37 min (Method A21)
 41a	1H NMR (500 MHz, DMSO-d6) δ 10.69 - 11.16 (m, 1 H) 9.27 (s, 1 H) 7.58 (t, J =1.69 Hz, 1 H) 7.42 - 7.44 (m, 1 H) 7.28 (dd, J =7.63, 1.63 Hz, 1 H) 7.19 - 7.26 (m, 2 H) 7.17 (d, J =8.00 Hz, 1 H) 6.95 - 6.99 (m, 1 H) 6.89 - 6.95 (m, 2 H) 6.81 (dd, J =7.32, 0.69 Hz, 1 H) 6.57 - 6.60 (m, 1 H) 6.29 - 6.31 (m, 1 H) 5.32 (s, 1 H) 4.72 - 4.87 (m, 2 H) 3.73 (s, 3 H) 3.33 - 3.42 (m, 1 H) 2.76 - 2.92 (m, 1 H) 2.56 - 2.67 (m, 1 H) 2.39 - 2.49 (m, 1 H) 2.29 (s, 3 H) 2.09 - 2.25 (m, 1 H)	M/z = 509 [M+H]+, Rt = 7.85 min (Method A20)
 42a	1H NMR (600 MHz, DMSO-d6) δ 10.87 (t, J = 2.0 Hz, 1H), 9.32 (s, 1H), 8.33 (s, 1H), 7.27 (dd, J = 7.7, 1.7 Hz, 1H), 7.23 - 7.19 (m, 2H), 7.14 (dt, J = 8.0, 0.9 Hz, 1H), 7.01 (s, 1H), 6.97 - 6.87 (m, 3H), 6.75 (dd, J = 7.4, 0.8 Hz, 1H), 6.47 (ddd, J = 3.1, 2.1, 0.9 Hz, 1H), 5.26 (s, 1H), 4.98 (qd, J = 13.6, 0.7 Hz, 2H), 3.72 (s, 3H), 3.35 (tt, J = 12.5, 4.0 Hz, 1H), 3.31 (s, 11H), 2.83 (dd, J = 17.0, 11.9 Hz, 1H), 2.64 - 2.59 (m, 1H), 2.44 (dd, J = 17.0, 13.1 Hz, 1H), 2.27 (s, 3H), 2.21 - 2.16 (m, 1H)	M/z = 510 [M+H]+, Rt = 6.72 min (Method A20)

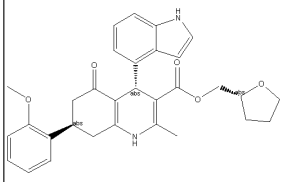
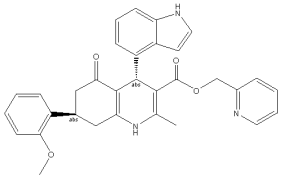
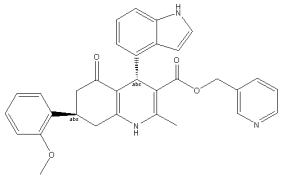
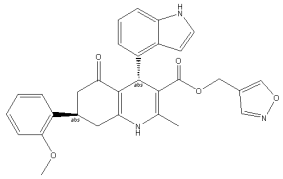
 43a	1H NMR (DMSO-d6, 600 MHz): δ 10.89 (dd, J = 2.1, 2.0 Hz, 1H), 9.36 (s, 1H), 8.47 (d, J = 1.8 Hz, 1H), 7.27 (dd, J = 7.6, 1.6 Hz, 1H), 7.19-7.24 (m, 2H), 7.16 (ddd, J = 8.0, 1.0, 1,0 Hz, 1H), 6.96 (dd, J = 8.4, 1.0 Hz, 1H), 6.93 (td, J = 7.5, 1.0 Hz, 1H), 6.91 (dd, J = 8.0, 7.4 Hz, 1H), 6.79 (dd, J = 7.4, 1.0 Hz, 1H), 6.53 (ddd, J = 3.1, 2.1, 1.0 Hz, 1H), 6.11 (dt, J = 1.8, 0.7, 0.7 Hz, 1H), 5.30 (s, 1H), 5.11 (dd, J = 13.9, 0.7 Hz, 1H), 5.06 (dd, J = 13.9, 0.7 Hz, 1H), 3.72 (s, 3H), 3.35 (dddd, J = 13.2, 11.9, 4.1, 4.0 Hz, 1H), 2.83 (dd, J = 17.1, 11.9 Hz, 1H), 2.61 (ddd, J = 17.1, 4.1, 1.5 Hz, 1H), 2.45 (dd, J = 16.4, 13.2 Hz, 1H), 2.29 (s, 3H), 2.16-2.24 (m, 1H)	M/z = 510 [M+H]+, Rt = 7.11 min (Method A20)
 44a	1H NMR (DMSO-d6, 600 MHz): δ 10.89 (t, J = 2.1 Hz, 1H), 9.32 (s, 1H), 7.29 (d, J = 1.8 Hz, 1H), 7.26 (dd, J = 7.7, 1.7 Hz, 1H), 7.19-7.22 (m, 2H), 7.15 (dt, J = 8.0, 1.0 Hz, 1H), 6.94-6.97 (m, 1H), 6.90-6.94 (m, 1H), 6.89 (dd, J = 8.1, 7.3 Hz, 1H), 6.73 (dd, J = 7.4, 1.0 Hz, 1H), 6.50 (ddd, J = 3.1, 2.0, 0.9 Hz, 1H), 6.12 (d, J = 1.8 Hz, 1H), 5.27 (s, 1H), 4.93-5.00 (m, 2H), 3.71 (s, 3H), 3.45 (s, 3H), 3.31-3.35 (m, 1H), 2.81 (dd, J = 17.1, 12.0 Hz, 1H), 2.56-2.63 (m, 1H), 2.44 (dd, J = 16.5, 13.1 Hz, 1H), 2.30 (s, 3H), 2.16-2.21 (m, 1H)	M/z = 523 [M+H]+, Rt = 6.9 min (Method A20)
 45a	1H NMR (500 MHz, DMSO-d6) δ 10.92 (s, 1 H) 9.32 (s, 1 H) 7.26 - 7.29 (m, 2 H) 7.22 (t, 1 H) 7.15 - 7.18 (m, 1 H) 6.92 - 6.98 (m, 3 H) 6.85 (dd, 1 H) 6.65 - 6.67 (m, 1 H) 5.31 (s, 1 H) 4.26 (ddd, 1 H) 4.18 (ddd, 1 H) 3.73 (s, 3 H) 3.36 - 3.39 (m, 1 H) 3.24 - 3.31 (m, 2 H) 2.83 (dd, 1 H) 2.71 (s, 3 H) 2.57 - 2.65 (m, 1 H) 2.43 - 2.49 (m, 1 H) 2.32 (s, 3 H) 2.20 (dd, 1 H)	M/z = 535 [M+H]+, Rt = 1.91 min (Method A21)

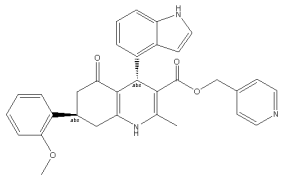
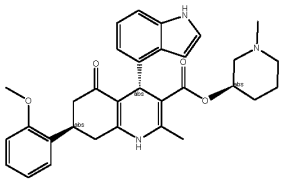
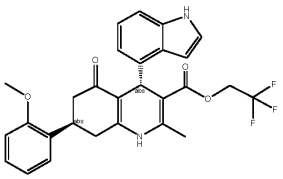
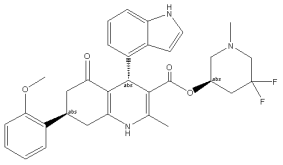
 46a	1H NMR (500 MHz, DMSO-d6) δ 10.91 (s, 1 H) 9.35 (s, 1 H) 8.81 (d, 1 H) 7.28 (dd, 1 H) 7.20 - 7.25 (m, 2 H) 7.16 - 7.19 (m, 1 H) 6.91 - 6.98 (m, 3 H) 6.82 (dd, 1 H) 6.57 (td, 1 H) 6.07 (d, 1 H) 5.32 (s, 1 H) 5.02 (s, 2 H) 3.73 (s, 3 H) 3.32 - 3.39 (m, 1 H) 2.79 - 2.89 (m, 1 H) 2.59 - 2.65 (m, 1 H) 2.42 - 2.49 (m, 1 H) 2.31 (s, 3 H) 2.20 (dd, 1 H)	M/z = 510 [M+H]+, Rt = 2.14 min (Method A21)
 47a	1H NMR (DMSO-d6, 500 MHz): δ 10.87 (t, J = 2.1 Hz, 1H), 9.30 (s, 1H), 8.76 (d, J = 4.9 Hz, 2H), 7.42 (t, J = 4.9 Hz, 1H), 7.29 (dd, J = 7.6, 1.8 Hz, 1H), 7.21-7.25 (m, 1H), 7.18-7.20 (m, 1H), 7.15 (dt, J = 8.0, 1.0 Hz, 1H), 6.89-6.98 (m, 3H), 6.82 (dd, J = 7.4, 1.0 Hz, 1H), 6.55 (ddd, J = 3.1, 2.0, 0.9 Hz, 1H), 5.39 (s, 1H), 5.15 (d, J = 14.4 Hz, 1H), 5.00 (d, J = 14.3 Hz, 1H), 3.74 (s, 3H), 3.33-3.41 (m, 1H), 2.86 (dd, J = 16.9, 11.8 Hz, 1H), 2.64 (ddd, J = 17.0, 4.2, 1.4 Hz, 1H), 2.44-2.49 (m, 1H), 2.32 (s, 3H), 2.19-2.24 (m, 1H)	M/z = 521 [M+H]+, Rt = 1.94 min (Method A21)
 48a	1H NMR (DMSO-d6, 500 MHz): δ 10.91 (t, J = 2.1 Hz, 1H), 9.38 (s, 1H), 9.03 (d, J = 1.4 Hz, 1H), 8.40 (d, J = 5.3 Hz, 1H), 7.29 (dd, J = 7.6, 1.8 Hz, 1H), 7.20-7.25 (m, 3H), 6.92-6.99 (m, 3H), 6.88 (dd, J = 7.3, 0.9 Hz, 1H), 6.65 (ddd, J = 3.2, 2.1, 0.9 Hz, 1H), 6.43 (dd, J = 5.2, 1.4 Hz, 1H), 5.42 (s, 1H), 5.09 (d, J = 15.4 Hz, 1H), 4.94 (d, J = 15.3 Hz, 1H), 3.74 (s, 3H), 3.33-3.40 (m, 1H), 2.85 (dd, J = 17.1, 11.8 Hz, 1H), 2.63 (ddd, J = 17.0, 4.1, 1.6 Hz, 1H), 2.45-2.50 (m, 1H), 2.35 (s, 3H), 2.20-2.26 (m, 1H)	M/z = 521 [M+H]+, Rt = 1.99 min (Method A21)
 49a	1H NMR (500 MHz, DMSO-d6) δ 10.90 (s, 1 H) 9.34 (s, 1 H) 8.92 (d, J =4.63 Hz, 1 H) 7.28 (dd, J =7.69, 1.44 Hz, 1 H) 7.20 - 7.25 (m, 2 H) 7.17 (d, J =8.00 Hz, 1 H) 6.97 (d, J =8.25 Hz, 1 H) 6.93 - 6.95 (m, 1 H) 6.90 - 6.93 (m, 1 H) 6.83 (d, J =4.63 Hz, 1 H) 6.79 - 6.82 (m, 1 H) 6.57 (t, J =2.13 Hz, 1 H) 5.35 (s, 1 H) 5.06 (d, J =1.25 Hz, 2 H) 3.73 (s, 3 H) 3.38 - 3.42 (m, 1 H) 2.84 (dd, J =17.20, 11.82 Hz, 1 H) 2.59 - 2.66 (m, 1 H) 2.42 - 2.48 (m, 1 H) 2.31 (s, 3 H) 2.20 (dd, J =16.38, 2.63 Hz, 1 H)	M/z = 526 [M+H]+, Rt = 7.43 min (Method A20)

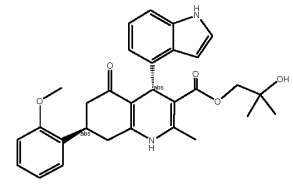
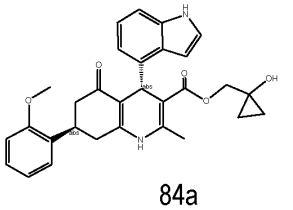
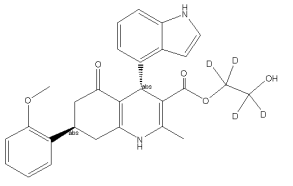
 50a	1H NMR (500 MHz, DMSO-d6) δ 10.91 (s, 1 H) 9.31 (s, 1 H) 8.60 (s, 1 H) 8.26 (s, 1 H) 7.28 (dd, J =7.57, 1.56 Hz, 1 H) 7.20 - 7.25 (m, 2 H) 7.17 (d, J =8.00 Hz, 1 H) 6.96 (d, J =8.25 Hz, 1 H) 6.93 (s, 1 H) 6.89 - 6.93 (m, 1 H) 6.79 (d, J =7.25 Hz, 1 H) 6.57 (t, J =2.13 Hz, 1 H) 5.32 (s, 1 H) 4.96 - 5.14 (m, 2 H) 3.73 (s, 3 H) 3.35 - 3.44 (m, 1 H) 2.83 (dd, J =16.95, 11.94 Hz, 1 H) 2.58 - 2.66 (m, 1 H) 2.46 (dd, J =16.45, 13.07 Hz, 1 H) 2.30 (s, 3 H) 2.20 (dd, J =16.70, 3.06 Hz, 1 H)	M/z = 526 [M+H]+, Rt = 7.35 min (Method A20)
 51b	1H NMR (DMSO-d6, 500 MHz): δ 10.90 (t, J = 2.2 Hz, 1H), 9.27 (s, 1H), 7.20-7.29 (m, 3H), 7.16 (dt, J = 8.0, 0.9 Hz, 1H), 6.92-6.98 (m, 3H), 6.85 (dd, J = 7.3, 0.9 Hz, 1H), 6.60 (ddd, J = 3.1, 2.1, 0.8 Hz, 1H), 5.28 (s, 1H), 5.03 (ddt, J = 6.6, 4.5, 2.1 Hz, 1H), 3.73 (s, 3H), 3.56-3.69 (m, 3H), 3.33-3.38 (m, 1H), 3.25 (dd, J = 9.9, 2.1 Hz, 1H), 2.83 (dd, J = 17.0, 11.9 Hz, 1H), 2.61 (ddd, J = 17.0, 4.2, 1.4 Hz, 1H), 2.45 (dd, J = 16.4, 13.1 Hz, 1H), 2.29 (s, 3H), 2.17-2.23 (m, 1H), 2.02 (dtd, J = 13.5, 8.4, 6.5 Hz, 1H), 1.79-1.85 (m, 1H)	M/z = 499 [M+H]+, Rt = 2.06 min (Method A21)
 52a	1H NMR (DMSO-d6, 600 MHz): δ 10.90 (br s, 1H), 9.23 (s, 1H), 7.34 (s, 1H), 7.26 (dd, J = 7.6, 1.5 Hz, 1H), 7.25 (t, J = 2.8 Hz, 1H), 7.23 (s, 1H), 7.19-7.23 (m, 1H), 7.16 (d, J = 8.1 Hz, 1H), 6.94-6.98 (m, 1H), 6.89-6.94 (m, 2H), 6.75-6.81 (m, 1H), 6.55-6.59 (m, 1H), 5.28 (s, 1H), 4.73-4.84 (m, 2H), 3.74 (s, 3H), 3.72 (s, 3H), 3.31-3.38 (m, 1H), 2.81 (dd, J = 17.0, 11.9 Hz, 1H), 2.56-2.64 (m, 1H), 2.44 (dd, J = 16.4, 13.1 Hz, 1H), 2.26 (s, 3H), 2.15-2.22 (m, 1H)	M/z = 523 [M+H]+, Rt = 2.02 min (Method A21)

 53a	1H NMR (DMSO-d6, 500 MHz): δ 10.91 (t, J = 2.2 Hz, 1H), 9.37 (s, 1H), 8.40 (d, J = 1.6 Hz, 1H), 7.28 (dd, J = 7.7, 1.7 Hz, 1H), 7.23-7.25 (m, 1H), 7.20-7.23 (m, 1H), 7.17 (dt, J = 8.0, 1.0 Hz, 1H), 7.14-7.15 (m, 1H), 6.91-6.98 (m, 3H), 6.83 (dd, J = 7.4, 1.0 Hz, 1H), 6.60 (ddd, J = 3.1, 2.1, 0.9 Hz, 1H), 5.34 (s, 1H), 5.28 (s, 2H), 3.73 (s, 3H), 3.32-3.39 (m, 1H), 2.84 (dd, J = 17.0, 11.9 Hz, 1H), 2.59-2.65 (m, 1H), 2.43-2.49 (m, 1H), 2.30-2.34 (m, 3H), 2.18-2.24 (m, 1H)	M/z = 526 [M+H]+, Rt = 2.21 min (Method A21)
 54a	1H NMR (DMSO-d6, 500 MHz): δ 10.89 (t, J = 2.1 Hz, 1H), 9.25 (s, 1H), 7.20-7.30 (m, 3H), 7.16 (dt, J = 8.0, 0.9 Hz, 1H), 6.91-6.98 (m, 3H), 6.85 (dd, J = 7.4, 1.0 Hz, 1H), 6.63 (ddd, J = 3.1, 2.0, 0.9 Hz, 1H), 5.32 (s, 1H), 3.90-4.01 (m, 2H), 3.74 (s, 3H), 3.34-3.51 (m, 6H), 3.24-3.25 (m, 1H), 3.24 (s, 3H), 2.84 (dd, J = 16.9, 11.8 Hz, 1H), 2.59-2.65 (m, 1H), 2.43-2.49 (m, 1H), 2.29 (s, 3H), 2.17-2.23 (m, 1H)	M/z = 531 [M+H]+, Rt = 2.08 min (Method A21)
 55a	1H NMR (DMSO-d6, 500 MHz): δ 10.90 (t, J = 2.1 Hz, 1H), 9.26 (s, 1H), 7.59 (d, J = 2.3 Hz, 1H), 7.28 (dd, J = 7.6, 1.8 Hz, 1H), 7.23-7.24 (m, 1H), 7.20-7.23 (m, 1H), 7.16 (dt, J = 8.0, 0.9 Hz, 1H), 6.90-6.98 (m, 3H), 6.79 (dd, J = 7.4, 0.9 Hz, 1H), 6.55 (ddd, J = 3.1, 2.0, 0.9 Hz, 1H), 6.02 (d, J = 2.3 Hz, 1H), 5.30 (s, 1H), 4.92 (d, J = 12.4 Hz, 1H), 4.76 (d, J = 12.4 Hz, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 3.32-3.39 (m, 1H), 2.83 (dd, J = 16.9, 11.8 Hz, 1H), 2.59-2.65 (m, 1H), 2.45 (dd, J = 16.4, 13.1 Hz, 1H), 2.17-2.31 (m, 4H)	M/z = 523 [M+H]+, Rt = 2.04 min (Method A21)

 56a	1H NMR (500 MHz, DMSO-d6) δ 10.89 (s, 1 H) 9.25 (s, 1 H) 7.28 (dd, J =7.69, 1.69 Hz, 1 H) 7.25 - 7.27 (m, 1 H) 7.19 - 7.25 (m, 1 H) 7.16 (d, J =8.00 Hz, 1 H) 6.96 - 6.99 (m, 1 H) 6.94 - 6.96 (m, 1 H) 6.91 - 6.94 (m, 1 H) 6.85 (dd, J =7.32, 0.81 Hz, 1 H) 6.61 (ddd, J =3.10, 2.03, 0.75 Hz, 1 H) 5.32 (s, 1 H) 3.97 - 4.05 (m, 1 H) 3.88 - 3.95 (m, 1 H) 3.74 (s, 3 H) 3.39 - 3.45 (m, 2 H) 3.33 - 3.39 (m, 1 H) 3.21 (s, 3 H) 2.84 (dd, J =16.95, 11.82 Hz, 1 H) 2.57 - 2.69 (m, 1 H) 2.46 (dd, J =16.32, 13.07 Hz, 1 H) 2.28 (s, 3 H) 2.15 - 2.24 (m, 1 H)	M/z = 487 [M+H]+, Rt = 2.08 min (Method A21)
 51a	1H NMR (500 MHz, DMSO-d6) δ 10.90 (s, 1 H) 9.27 (s, 1 H) 7.27 - 7.30 (m, 1 H) 7.25 - 7.27 (m, 1 H) 7.19 - 7.24 (m, 1 H) 7.16 (d, J =8.00 Hz, 1 H) 6.96 - 6.98 (m, 1 H) 6.94 - 6.96 (m, 1 H) 6.93 (d, J =1.63 Hz, 1 H) 6.85 (dd, J =7.32, 0.81 Hz, 1 H) 6.60 (td, J =2.03, 0.94 Hz, 1 H) 5.28 (s, 1 H) 4.94 - 5.12 (m, 1 H) 3.73 (s, 4 H) 3.61 - 3.67 (m, 2 H) 3.58 (dd, J =9.88, 1.38 Hz, 1 H) 3.34 (br s, 1 H) 2.83 (dd, J =16.95, 11.94 Hz, 1 H) 2.56 - 2.66 (m, 1 H) 2.45 (dd, J =16.38, 13.13 Hz, 1 H) 2.30 (s, 3 H) 2.14 - 2.25 (m, 1 H) 1.87 (dd, J =13.32, 6.44 Hz, 1 H) 1.42 - 1.55 (m, 1 H)	M/z = 499 [M+H]+, Rt = 2.05 min (Method A21)
 58a	1H NMR (500 MHz, DMSO-d6) δ 10.89 (s, 1 H) 9.26 (s, 1 H) 7.28 (dd, J =7.63, 1.63 Hz, 1 H) 7.24 - 7.26 (m, 1 H) 7.20 - 7.24 (m, 1 H) 7.13 - 7.18 (m, 1 H) 6.90 - 6.99 (m, 3 H) 6.85 (dd, J =7.32, 0.81 Hz, 1 H) 6.64 (td, J =2.03, 0.94 Hz, 1 H) 5.33 (s, 1 H) 3.86 - 3.95 (m, 1 H) 3.81 - 3.86 (m, 1 H) 3.80 (s, 1 H) 3.73 (s, 3 H) 3.54 - 3.66 (m, 2 H) 3.35 (s, 1 H) 2.83 (dd, J =16.95, 11.82 Hz, 1 H) 2.61 (ddd, J =16.92, 3.97, 1.13 Hz, 1 H) 2.46 (dd, J =16.38, 13.13 Hz, 1 H) 2.30 (s, 3 H) 2.14 - 2.24 (m, 1 H) 1.61 - 1.75 (m, 3 H) 1.27 - 1.38 (m, 1 H)	M/z = 513 [M+H]+, Rt = 2.18 min (Method A21)

 58b	1H NMR (500 MHz, DMSO-d6) δ 10.90 (s, 1 H) 9.27 (s, 1 H) 7.27 - 7.30 (m, 1 H) 7.24 - 7.26 (m, 1 H) 7.19 - 7.24 (m, 1 H) 7.16 (d, J =8.00 Hz, 1 H) 6.97 (dd, J =8.38, 0.88 Hz, 1 H) 6.90 - 6.95 (m, 2 H) 6.84 (dd, J =7.32, 0.81 Hz, 1 H) 6.64 (ddd, J =3.03, 2.09, 0.75 Hz, 1 H) 5.34 (s, 1 H) 3.85 (d, J =10.38 Hz, 2 H) 3.78 (s, 1 H) 3.73 (s, 3 H) 3.66 - 3.72 (m, 1 H) 3.55 - 3.65 (m, 1 H) 3.32 - 3.39 (m, 1 H) 2.83 (dd, J =16.95, 11.94 Hz, 1 H) 2.58 - 2.66 (m, 1 H) 2.42 - 2.48 (m, 1 H) 2.30 (s, 3 H) 2.15 - 2.25 (m, 1 H) 1.64 - 1.86 (m, 3 H) 1.33 - 1.52 (m, 1 H)	M/z = 513 [M+H]+, Rt = 2.18 min (Method A21)
 61a	1H NMR (DMSO-d6, 500 MHz) δ 10.90 (s, 1H), 9.34 (s, 1H), 8.3-8.6 (m, 1H), 7.53 (dt, 1H, J =1.8, 7.7 Hz), 7.29 (dd, 1H, J =1.6, 7.6 Hz), 7.2-7.3 (m, 4H), 6.9-7.0 (m, 3H), 6.8-6.9 (m, 1H), 6.70 (d, 1H, J =7.9 Hz), 6.62 (ddd, 1H, J =0.8, 2.1, 3.0 Hz), 5.41 (s, 1H), 4.9-5.1 (m, 2H), 3.73 (s, 3H), 3.3-3.4 (m, 1H), 2.84 (dd, 1H, J =11.9, 16.9 Hz), 2.6-2.7 (m, 1H), 2.4-2.5 (m, 1H), 2.33 (s, 3H), 2.2-2.3 (m, 1H)	M/z = 520 [M+H]+, Rt = 1.97 min (Method A21)
 62a	1H NMR (500 MHz, DMSO-d6) δ 10.90 (s, 1H), 9.32 (s, 1H), 8.46 (dd, J = 4.8, 1.8 Hz, 1H), 8.37 (d, J = 1.8 Hz, 1H), 7.35 (dt, J = 8.0, 1.9 Hz, 1H), 7.29 - 7.15 (m, 6H), 6.97 - 6.90 (m, 3H), 6.79 (dd, J = 7.3, 0.8 Hz, 1H), 6.57 - 6.55 (m, 1H), 5.33 (s, 1H), 4.97 (s, 2H), 3.73 (s, 3H), 3.38 - 3.32 (m, 1H), 2.83 (dd, J = 17.1, 11.9 Hz, 1H), 2.64 - 2.58 (m, 1H), 2.49 - 2.42 (m, 1H), 2.31 (s, 3H), 2.20 (dd, J = 16.6, 2.8 Hz, 1H)	M/z = 520 [M+H]+, Rt = 1.72 min (Method A21)
 63a	1H NMR (DMSO-d6, 600 MHz): δ 10.91 (t, J = 2.1 Hz, 1H), 9.29 (s, 1H), 8.58 (t, J = 0.7 Hz, 1H), 8.21 (s, 1H), 7.27 (dd, J = 7.6, 1.8 Hz, 1H), 7.23-7.24 (m, 1H), 7.19-7.23 (m, 1H), 7.16 (d, J = 7.8 Hz, 1H), 6.90-6.96 (m, 3H), 6.79 (dd, J = 7.3, 1.0 Hz, 1H), 6.57 (ddd, J = 3.1, 2.1, 1.0 Hz, 1H), 5.29 (s, 1H), 4.88-4.90 (m, 1H), 4.79-4.82 (m, 1H), 3.72 (s, 3H), 3.31-3.37 (m, 1H), 2.82 (dd, J = 17.1, 12.0 Hz, 1H), 2.58-2.63 (m, 1H), 2.38-2.47 (m, 1H), 2.26-2.30 (m, 3H), 2.17-2.21 (m, 1H)	M/z = 510 [M+H]+, Rt = 2.13 min (Method A21)

 64a	1H NMR (DMSO-d6, 600 MHz) δ 10.7-11.0 (m, 1H), 9.34 (s, 1H), 8.2-8.5 (m, 2H), 7.28 (dd, 1H, J =1.6, 7.6 Hz), 7.2-7.3 (m, 3H), 6.9-7.0 (m, 3H), 6.8-6.9 (m, 3H), 6.64 (ddd, 1H, J =0.9, 2.1, 3.1 Hz), 5.40 (s, 1H), 4.9-5.1 (m, 2H), 3.72 (s, 3H), 3.3-3.4 (m, 1H), 2.83 (dd, 1H, J =11.9, 17.0 Hz), 2.60 (ddd, 1H, J =1.5, 4.2, 17.1 Hz), 2.4-2.5 (m, 1H), 2.33 (s, 3H), 2.2-2.3 (m, 1H)	M/z = 520 [M+H]+, Rt = 1.61 min (Method A21)
 65b	1H NMR (DMSO-d6, 600 MHz): δ 10.88 (s, 1H), 9.22 (s, 1H), 7.20-7.28 (m, 3H), 7.12-7.18 (m, 1H), 6.91-6.97 (m, 3H), 6.86 (d, J = 7.1 Hz, 1H), 6.57-6.60 (m, 1H), 5.28 (s, 1H), 4.51 (tt, J = 8.6, 4.1 Hz, 1H), 3.72 (s, 3H), 3.32-3.38 (m, 1H), 2.82 (dd, J = 16.9, 12.0 Hz, 1H), 2.57-2.64 (m, 1H), 2.36-2.47 (m, 2H), 2.25-2.30 (m, 4H), 2.15-2.21 (m, 1H), 2.06 (s, 3H), 1.87-1.96 (m, 1H), 1.59-1.73 (m, 3H), 1.33-1.47 (m, 1H), 1.21-1.30 (m, 1H)	M/z = 526 [M+H]+, Rt = 1.31 min (Method A21)
 77a	1H NMR (500 MHz, DMSO-d6) δ 10.92 (t, J = 2.2 Hz, 1H), 9.48 (s, 1H), 7.29 - 7.21 (m, 3H), 7.17 (dt, J = 8.0, 1.0 Hz, 1H), 6.98 - 6.92 (m, 3H), 6.85 (dd, J = 7.4, 1.0 Hz, 1H), 6.56 (ddd, J = 3.1, 2.1, 0.9 Hz, 1H), 5.31 (s, 1H), 4.62 (dq, J = 13.1, 9.2 Hz, 1H), 4.46 (dq, J = 13.0, 9.1 Hz, 1H), 3.73 (s, 3H), 3.38 - 3.32 (m, 1H), 2.85 (dd, J = 16.9, 11.9 Hz, 1H), 2.66 - 2.59 (m, 1H), 2.49 - 2.44 (m, 1H), 2.32 (s, 3H), 2.21 (ddd, J = 16.4, 3.9, 1.6 Hz, 1H)	M/z = 511 [M+H]+, Rt = 2.38 min (Method A21)
 79b	1H NMR (500 MHz, DMSO-d6) δ 10.90 (t, J = 2.1 Hz, 1H), 9.28 (s, 1H), 7.30 - 7.25 (m, 2H), 7.26 - 7.20 (m, 1H), 7.17 (dt, J = 8.0, 0.9 Hz, 1H), 7.00 - 6.91 (m, 3H), 6.88 (dd, J = 7.3, 0.9 Hz, 1H), 6.60 (ddd, J = 3.0, 2.0, 0.8 Hz, 1H), 5.27 (s, 1H), 4.67 (tt, J = 8.5, 4.5 Hz, 1H), 3.73 (s, 3H), 3.39 - 3.33 (m, 1H), 2.83 (dd, J = 16.9, 11.8 Hz, 1H), 2.77 - 2.67 (m, 1H), 2.66 - 2.56 (m, 1H), 2.49 - 2.36 (m, 2H), 2.35 - 2.23 (m, 5H), 2.23 - 2.15 (m, 4H), 1.96 - 1.81 (m, 2H)	M/z = 562 [M+H]+, Rt = 1.84 min (Method A21)

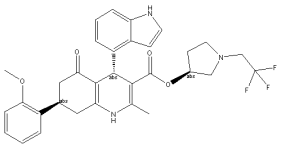
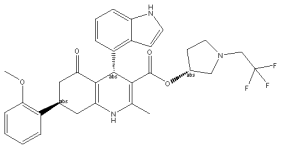
 83a	1H NMR (600 MHz, DMSO-d6) δ 10.88 (t, J = 2.0 Hz, 1H), 9.26 (s, 1H), 7.27 (dd, J = 7.7, 1.7 Hz, 1H), 7.24 – 7.23 (m, 1H), 7.21 (ddd, J = 8.2, 7.4, 1.7 Hz, 1H), 7.15 (dt, J = 8.0, 0.9 Hz, 1H), 6.98 – 6.89 (m, 3H), 6.84 (dd, J = 7.4, 0.8 Hz, 1H), 6.66 (ddd, J = 3.2, 2.1, 0.9 Hz, 1H), 5.35 (s, 1H), 4.26 (s, 1H), 3.71 (s, 3H), 3.68 (d, J = 10.7 Hz, 1H), 3.59 (d, J = 10.7 Hz, 1H), 3.36 – 3.27 (m, 1H), 2.81 (dd, J = 16.9, 12.0 Hz, 1H), 2.58 (ddd, J = 17.1, 4.1, 1.5 Hz, 1H), 2.46 (dd, J = 16.4, 13.2 Hz, 1H), 2.33 (s, 3H), 2.24 – 2.16 (m, 1H), 0.99 (s, 3H), 0.89 (s, 3H)	M/z = 501 [M+H]+, Rt = 2.03 min (Method A21)
 84a	1H NMR (600 MHz, DMSO-d6) δ 10.88 (t, 1H), 9.21 (s, 1H), 7.29 - 7.20 (m, 3H), 7.15 (dt, 1H), 6.97 - 6.91 (m, 3H), 6.89 - 6.87 (m, 1H), 6.62 (ddd, 1H), 5.36 (s, 1H), 5.22 (s, 1H), 4.06 (dd, 1H), 3.73 (s, 3H), 3.72 - 3.69 (m, 1H), 3.39 - 3.33 (m, 1H), 2.83 (dd, 1H), 2.64 - 2.59 (m, 1H), 2.45 (dd, 1H), 2.29 (s, 3H), 2.26 - 2.16 (m, 1H), 0.61 - 0.52 (m, 2H), 0.46 - 0.39 (m, 2H)	M/z = 499 [M+H]+, Rt = 2 min (Method A21)
 85a	1H NMR (600 MHz, DMSO-d6) δ 11.10 – 10.62 (m, 1H), 9.21 (s, 1H), 7.28 (dd, J = 7.6, 1.8 Hz, 1H), 7.26 – 7.24 (m, 1H), 7.23 – 7.19 (m, 1H), 7.15 (dt, J = 8.0, 0.9 Hz, 1H), 6.98 – 6.95 (m, 1H), 6.93 (d, J = 7.3 Hz, 2H), 6.85 (dd, J = 7.4, 0.8 Hz, 1H), 6.63 – 6.60 (m, 1H), 5.33 (s, 1H), 4.56 (s, 1H), 3.73 (s, 3H), 3.40 – 3.33 (m, 1H), 2.81 (br d, J = 11.9 Hz, 1H), 2.69 – 2.55 (m, 1H), 2.45 (dd, J = 16.4, 13.1 Hz, 1H), 2.28 (s, 3H), 2.23 – 2.15 (m, 1H)	M/z = 477 [M+H]+, Rt = 1.82 min (Method A21)

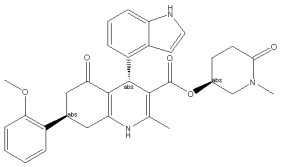
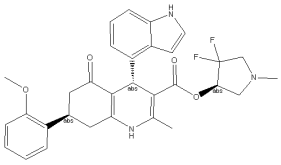
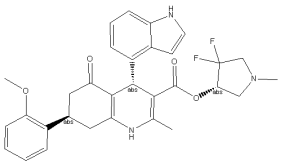
Example Procedure j3: 69a

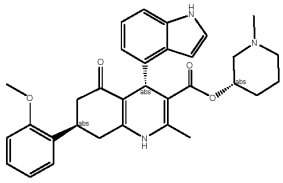
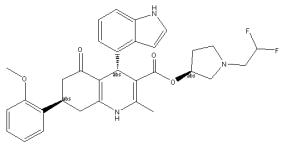
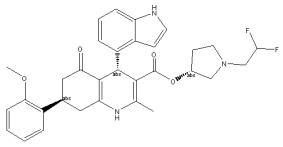
To a stirred solution of (4*S*,7*R*)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid (50.0 mg, 0.082 mmol) in DCM (0.82 mL) at RT were added (3*S*)-1-(2,2-difluoroethyl)pyrrolidin-3-ol (52.0 mg, 0.33 mmol), pyridine (26.4 µL, 0.33 mmol) and propylphosphonic anhydride in MeTHF 50% w/w (0.193 mL, 0.33 mmol). The reaction mixture was heated to 40 °C and stirred for 2 h. Water and ethyl acetate were added. The phases were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with water, dried using a phase separator and concentrated under vacuum. The crude material was purified by Flash

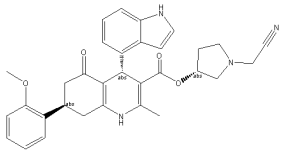
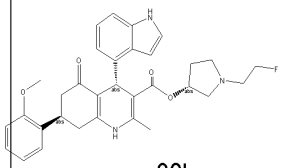
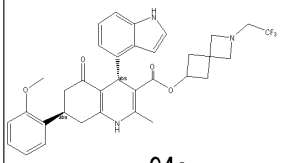
chromatography on silica gel using a gradient of acetone in toluene from 0% to 30%. Fractions were combined and evaporated to afford the title compound.

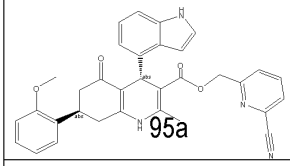
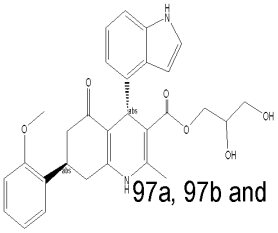
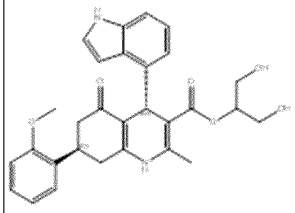
The following compounds were obtained using this protocol:

Structure Cpd. No.	NMR	MS
 66a	1H NMR (600 MHz, DMSO-d6) δ 11.05 - 10.71 (m, 1H), 9.24 (s, 1H), 7.27 (dd, J = 7.6, 1.6 Hz, 1H), 7.25 - 7.23 (m, 1H), 7.21 (ddd, J = 8.4, 7.3, 1.8 Hz, 1H), 7.15 (dt, J = 7.9, 0.8 Hz, 1H), 6.96 (dd, J = 8.4, 0.9 Hz, 1H), 6.95 - 6.91 (m, 2H), 6.85 (dd, J = 7.3, 0.8 Hz, 1H), 6.65 - 6.59 (m, 1H), 5.27 (s, 1H), 4.89 (ddt, J = 7.6, 6.1, 2.9 Hz, 1H), 3.72 (s, 3H), 3.38 - 3.31 (m, 1H), 3.19 (qd, J = 10.2, 2.1 Hz, 2H), 2.98 (dd, J = 10.6, 6.1 Hz, 1H), 2.81 (dd, J = 17.0, 11.9 Hz, 1H), 2.65 - 2.52 (m, 4H), 2.44 (dd, J = 16.4, 13.1 Hz, 1H), 2.28 (s, 3H), 2.23 - 2.14 (m, 1H), 1.84 (dq, J = 13.6, 7.6 Hz, 1H), 1.39 - 1.31 (m, 1H)	M/z = 580 [M+H]+, Rt = 2.65 min (Method A21)
 66b	1H NMR (600 MHz, DMSO-d6) δ 10.90 (t, J = 2.1 Hz, 1H), 9.24 (s, 1H), 7.27 (dd, J = 7.7, 1.7 Hz, 1H), 7.24 (dd, J = 3.0, 2.0 Hz, 1H), 7.21 (ddd, J = 8.6, 7.4, 1.7 Hz, 1H), 7.15 (dt, J = 8.0, 0.9 Hz, 1H), 6.95 (dd, J = 8.6, 1.2 Hz, 1H), 6.94 - 6.91 (m, 2H), 6.84 (dd, J = 7.4, 0.9 Hz, 1H), 6.64 (ddd, J = 3.0, 2.1, 0.9 Hz, 1H), 5.27 (s, 1H), 4.90 (ddt, J = 7.2, 5.9, 2.8 Hz, 1H), 3.72 (s, 3H), 3.36 - 3.31 (m, 1H), 3.05 - 2.91 (m, 2H), 2.87 - 2.76 (m, 2H), 2.64 - 2.56 (m, 3H), 2.44 (dd, J = 16.4, 13.1 Hz, 1H), 2.29 (s, 3H), 2.23 - 2.14 (m, 2H), 2.01 (dtd, J = 13.7, 7.5, 7.2 Hz, 1H), 1.74 - 1.62 (m, 1H)	M/z = 580 [M+H]+, Rt = 2.34 min (Method A21)

 67a	1H NMR (600 MHz, DMSO-d6) δ 10.89 (t, J = 2.2 Hz, 1H), 9.30 (s, 1H), 7.26 (dd, J = 7.7, 1.7 Hz, 1H), 7.24 - 7.20 (m, 2H), 7.15 (dt, J = 8.0, 1.0 Hz, 1H), 6.97 - 6.94 (m, 1H), 6.94 - 6.90 (m, 2H), 6.82 (dd, J = 7.3, 1.0 Hz, 1H), 6.56 (ddd, J = 3.1, 2.1, 1.0 Hz, 1H), 5.27 (s, 1H), 4.90 - 4.86 (m, 1H), 3.72 (s, 3H), 3.48 (dd, J = 13.1, 4.3 Hz, 1H), 3.35 - 3.31 (m, 1H), 3.21 (ddd, J = 13.1, 3.9, 1.5 Hz, 1H), 2.81 (dd, J = 16.9, 12.0 Hz, 1H), 2.76 (s, 3H), 2.64 - 2.56 (m, 1H), 2.44 (dd, J = 16.4, 13.1 Hz, 1H), 2.30 - 2.26 (m, 3H), 2.19 (ddd, J = 16.4, 3.9, 1.6 Hz, 1H), 2.08 - 1.98 (m, 2H), 1.76 - 1.71 (m, 1H), 1.61 - 1.55 (m, 1H)	M/z = 540 [M+H]+, Rt = 1.86 min (Method A21)
 68b	1H NMR (500 MHz, DMSO-d6) δ 10.91 (s, 1H), 9.39 (s, 1H), 7.29 - 7.26 (m, 2H), 7.24 - 7.20 (m, 1H), 7.17 (d, J = 8.0 Hz, 1H), 6.98 - 6.92 (m, 3H), 6.87 (dd, J = 7.3, 0.9 Hz, 1H), 6.62 - 6.60 (m, 1H), 5.29 (s, 1H), 4.94 - 4.88 (m, 1H), 3.73 (s, 3H), 3.37 - 3.32 (m, 1H), 2.98 (ddd, J = 14.1, 10.8, 7.9 Hz, 1H), 2.88 - 2.70 (m, 3H), 2.65 - 2.58 (m, 1H), 2.49 - 2.42 (m, 1H), 2.32 (s, 3H), 2.23 - 2.18 (m, 4H), 2.10 (dt, J = 10.1, 5.3 Hz, 1H)	M/z = 548 [M+H]+, Rt = 1.66 min (Method A21)
 68a	1H NMR (500 MHz, DMSO-d6) δ 10.88 (t, J = 2.2 Hz, 1H), 9.36 (s, 1H), 7.29 - 7.21 (m, 3H), 7.15 (dt, J = 8.0, 1.0 Hz, 1H), 6.98 - 6.91 (m, 3H), 6.85 (dd, J = 7.3, 1.1 Hz, 1H), 6.62 (ddd, J = 3.1, 2.1, 0.9 Hz, 1H), 5.30 (s, 1H), 4.99 - 4.93 (m, 1H), 3.73 (s, 3H), 3.38 - 3.33 (m, 1H), 3.14 (dd, J = 10.1, 7.1 Hz, 1H), 2.95 - 2.81 (m, 2H), 2.65 - 2.59 (m, 1H), 2.47 - 2.33 (m, 3H), 2.31 (s, 3H), 2.23 (s, 3H), 2.22 - 2.18 (m, 1H)	M/z = 548 [M+H]+, Rt = 1.6 min (Method A21)

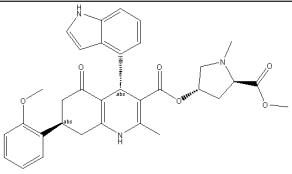
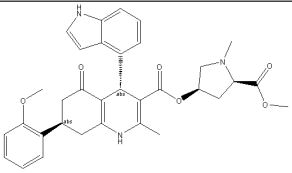
 65a	1H NMR (600 MHz, DMSO-d6) δ 10.88 (t, J = 2.2 Hz, 1H), 9.22 (s, 1H), 7.28 - 7.20 (m, 3H), 7.15 (dt, J = 8.0, 1.0 Hz, 1H), 6.97 - 6.91 (m, 3H), 6.85 (dd, J = 7.5, 1.0 Hz, 1H), 6.57 (ddd, J = 3.2, 2.1, 1.0 Hz, 1H), 5.27 (s, 1H), 4.49 (tt, J = 8.6, 4.1 Hz, 1H), 3.72 (s, 3H), 3.36 - 3.32 (m, 1H), 2.81 (dd, J = 16.9, 12.0 Hz, 1H), 2.64 - 2.57 (m, 2H), 2.48 - 2.37 (m, 2H), 2.28 (s, 3H), 2.26 - 2.17 (m, 1H), 2.12 (s, 3H), 2.02 - 1.91 (m, 2H), 1.62 - 1.54 (m, 1H), 1.45 - 1.31 (m, 2H), 1.06 - 0.96 (m, 1H)	M/z = 526 [M+H]+, Rt = 1.77 min (Method A21)
 69a	1H NMR (600 MHz, DMSO-d6) δ 10.88 (t, J = 1.9 Hz, 1H), 9.24 (s, 1H), 7.28 - 7.20 (m, 3H), 7.15 (dt, J = 7.9, 0.9 Hz, 1H), 6.97 - 6.91 (m, 3H), 6.85 (dd, J = 7.3, 0.9 Hz, 1H), 6.61 (ddd, J = 3.0, 2.1, 0.9 Hz, 1H), 6.07 (tt, J = 55.8, 4.3 Hz, 1H), 5.27 (s, 1H), 4.89 - 4.85 (m, 1H), 3.72 (s, 3H), 3.44 - 3.32 (m, 1H), 2.89 - 2.76 (m, 4H), 2.62 - 2.51 (m, 3H), 2.47 - 2.41 (m, 2H), 2.28 (s, 3H), 2.21 - 2.17 (m, 1H), 1.87 - 1.80 (m, 1H), 1.35 (dddd, J = 13.3, 7.8, 5.1, 2.8 Hz, 1H)	M/z = 562 [M+H]+, Rt = 1.51 min (Method A21)
 69b	1H NMR (600 MHz, DMSO-d6) δ 10.89 (s, 1H), 9.24 (s, 1H), 7.27 (dd, J = 7.7, 1.5 Hz, 1H), 7.25 - 7.23 (m, 1H), 7.23 - 7.19 (m, 1H), 7.16 (d, J = 8.1 Hz, 1H), 6.96 (dd, J = 8.5, 1.0 Hz, 1H), 6.95 - 6.91 (m, 2H), 6.84 (dd, J = 7.3, 0.7 Hz, 1H), 6.62 (t, J = 1.0 Hz, 1H), 6.15 - 5.87 (m, 1H), 5.27 (s, 1H), 4.95 - 4.84 (m, 1H), 3.72 (s, 3H), 3.33 (br s, 1H), 2.82 (dd, J = 16.9, 12.0 Hz, 1H), 2.72 (dd, J = 10.6, 6.2 Hz, 1H), 2.70 - 2.65 (m, 1H), 2.65 - 2.62 (m, 1H), 2.61 - 2.56 (m, 1H), 2.56 - 2.51 (m, 2H), 2.44 (dd, J = 16.4, 13.1 Hz, 1H), 2.28 (s, 3H), 2.23 - 2.16 (m, 1H), 2.11 (dd, J = 10.5, 3.0 Hz, 1H), 2.02 (dd, J = 13.6, 7.4 Hz, 1H), 1.71 - 1.59 (m, 1H)	M/z = 562 [M+H]+, Rt = 1.49 min (Method A21)

 80b	1H NMR (500 MHz, DMSO-d6) δ 10.90 (s, 1H), 9.26 (s, 1H), 7.30 – 7.25 (m, 2H), 7.25 – 7.19 (m, 1H), 7.16 (d, J = 8.0 Hz, 1H), 6.99 – 6.90 (m, 3H), 6.86 (dd, J = 7.3, 0.8 Hz, 1H), 6.63 – 6.57 (m, 1H), 5.28 (s, 1H), 4.97 – 4.89 (m, 1H), 3.76 – 3.69 (m, 5H), 3.36 – 3.33 (m, 1H), 2.83 (dd, J = 16.9, 11.9 Hz, 1H), 2.71 – 2.57 (m, 3H), 2.49 – 2.41 (m, 2H), 2.34 (dd, J = 10.3, 2.9 Hz, 1H), 2.28 (s, 3H), 2.24 – 2.09 (m, 2H), 1.74 – 1.64 (m, 1H)	M/z = 537 [M+H]+, Rt = 2.03 min (Method A21)
 82b	1H NMR (500 MHz, DMSO-d6) δ 10.89 (t, J = 2.2 Hz, 1H), 9.24 (s, 1H), 7.29 – 7.20 (m, 3H), 7.16 (dt, J = 7.9, 1.0 Hz, 1H), 6.99 – 6.91 (m, 3H), 6.86 (dd, J = 7.4, 1.0 Hz, 1H), 6.62 (ddd, J = 3.2, 2.1, 0.9 Hz, 1H), 5.28 (s, 1H), 4.91 – 4.87 (m, 1H), 4.51 (t, J = 5.3 Hz, 1H), 4.41 (t, J = 5.2 Hz, 1H), 3.73 (s, 3H), 3.38 – 3.33 (m, 1H), 2.83 (dd, J = 16.9, 11.8 Hz, 1H), 2.65 – 2.52 (m, 5H), 2.49 – 2.39 (m, 2H), 2.29 (s, 3H), 2.22 – 2.01 (m, 3H), 1.64 (dddd, J = 13.4, 7.8, 5.2, 2.9 Hz, 1H)	M/z = 544 [M+H]+, Rt = 1.3 min (Method A21)
 94a	1H NMR (600 MHz, DMSO-d6) δ 10.88 (t, J = 2.1 Hz, 1H), 9.21 (s, 1H), 7.29 – 7.26 (m, 1H), 7.26 – 7.23 (m, 1H), 7.23 – 7.18 (m, 1H), 7.17 – 7.11 (m, 1H), 6.98 – 6.88 (m, 3H), 6.83 (dd, J = 7.3, 0.9 Hz, 1H), 6.62 (ddd, J = 3.2, 2.1, 0.9 Hz, 1H), 5.27 (s, 1H), 4.62 (quin, J = 7.1 Hz, 1H), 3.72 (s, 3H), 3.38 – 3.32 (m, 1H), 3.27 – 3.21 (m, 2H), 3.20 – 3.10 (m, 2H), 3.06 (q, J = 10.2 Hz, 2H), 2.81 (dd, J = 17.0, 11.9 Hz, 1H), 2.60 (ddd, J = 17.1, 4.1, 1.5 Hz, 1H), 2.48 – 2.33 (m, 2H), 2.26 (s, 3H), 2.21 – 2.15 (m, 2H), 2.08 (dd, J = 12.0, 7.0 Hz, 1H), 1.55 (dd, J = 12.2, 6.9 Hz, 1H)	M/z = 606 [M+H]+, Rt = 1.9 min (Method A21)

 95a	1H NMR (600 MHz, DMSO-d6) δ 10.89 (s, 1H), 9.36 (s, 1H), 7.87 (dd, J = 7.6, 1.0 Hz, 1H), 7.71 (t, J = 7.8 Hz, 1H), 7.28 (dd, J = 7.7, 1.7 Hz, 1H), 7.24 – 7.16 (m, 3H), 6.98 – 6.89 (m, 3H), 6.83 (ddd, J = 7.7, 3.5, 1.0 Hz, 2H), 6.59 (ddd, J = 3.1, 2.1, 0.9 Hz, 1H), 5.37 (s, 1H), 5.15 – 4.88 (m, 2H), 3.72 (s, 3H), 3.38 – 3.31 (m, 1H), 2.84 (dd, J = 17.0, 11.9 Hz, 1H), 2.66 – 2.57 (m, 1H), 2.49 – 2.42 (m, 1H), 2.33 (s, 3H), 2.25 – 2.15 (m, 1H)	M/z = 545 [M+H]+, Rt = 2.27 min (Method A21)
 97a, 97b and  98	Mixture of 2 diastereomers and the symmetric secondary alcohol product (45/45/10) 1H NMR (600 MHz, DMSO-d6) δ 10.89 (dt, J = 5.9, 2.1 Hz, 1H), 9.22 (d, J = 2.8 Hz, 1H), 7.27 (dd, J = 7.6, 1.4 Hz, 1H), 7.25 – 7.18 (m, 2H), 7.15 (ddt, J = 8.0, 1.7, 0.9 Hz, 1H), 6.96 (dd, J = 8.3, 1.0 Hz, 1H), 6.93 (t, J = 7.6 Hz, 2H), 6.88 – 6.80 (m, 1H), 6.66 – 6.55 (m, 1H), 5.32 (d, J = 5.6 Hz, 1H), 4.74 – 4.60 (m, 1H), 4.53 – 4.45 (m, 1H), 3.93 (dd, J = 11.1, 5.2 Hz, 1H), 3.85 – 3.76 (m, 1H), 3.73 (s, 3H), 3.63 – 3.53 (m, 1H), 3.38 – 3.32 (m, 2H), 3.26 – 3.18 (m, 1H), 2.89 – 2.77 (m, 1H), 2.65 – 2.56 (m, 1H), 2.45 (ddd, J = 16.3, 13.2, 1.2 Hz, 1H), 2.34 – 2.25 (m, 3H), 2.22 – 2.13 (m, 1H)	M/z = 503 [M+H]+, Rt = 1.71 min (Method A21)

The following compounds can be made using this protocol:

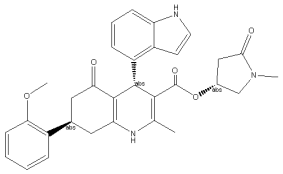
Structure **Cpd. No.**	**MS**
96a	M/z = 570 [M+H]+
96b	M/z = 570 [M+H]+

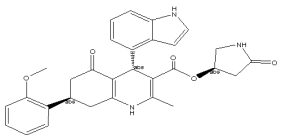
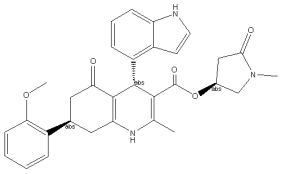
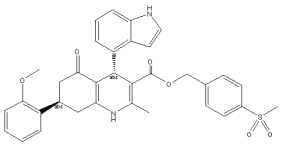
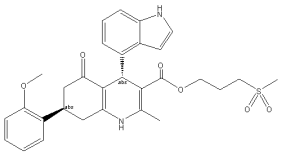
 96c	M/z = 570 [M+H]+
 96d	M/z = 570 [M+H]+

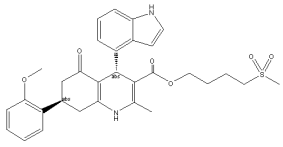
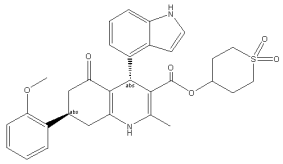
Example Procedure j4: 73a

To a stirred suspension of (4*S*,7*R*)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid (40 mg, 0.075 mmol) and (4-(methylsulfonyl)phenyl)methanol (0.22 mmol, 3eq) in DCM-anhydrous (0.80 mL) at RT were added successively pyridine (18 µL, 0.22 mmol) and propylphosphonic anhydride in DMF 50% w/w (132 µL, 0.22 mmol). The reaction mixture was stirred at 40 °C for 2 h. Water was added, and the two phases were separated. The combined organic layers were dried using a phase separator and concentrated under vacuum. The crude was purified by prep-HPLC using acetonitrile/water (0.1% COOH). Fractions were combined and lyophilized to afford the title compound.

The following compounds were obtained using this protocol:

Structure Cpd. No.	**NMR**	**MS**
 71b	1H NMR (500 MHz, DMSO-d6) δ 10.91 (s, 1H), 9.30 (s, 1H), 7.30 - 7.25 (m, 2H), 7.22 (td, J = 7.8, 1.6 Hz, 1H), 7.17 (d, J = 8.1 Hz, 1H), 7.00 - 6.90 (m, 3H), 6.84 - 6.79 (m, 1H), 6.55 (t, J = 2.1 Hz, 1H), 5.24 (s, 1H), 5.11 - 5.02 (m, 1H), 3.73 (s, 3H), 3.44 (dd, J = 11.1, 5.9 Hz, 1H), 3.38 - 3.32 (m, 1H), 2.83 (dd, J = 17.1, 11.8 Hz, 1H), 2.69 - 2.57 (m, 6H), 2.44 (dd, J = 16.4, 13.1 Hz, 1H), 2.28 (s, 3H), 2.23 - 2.12 (m, 2H)	M/z = 526 [M+H]+, Rt = 1.84 min (Method A21)

 72b	1H NMR (500 MHz, DMSO-d6) δ 10.91 (s, 1H), 9.29 (s, 1H), 7.67 (s, 1H), 7.29 - 7.20 (m, 3H), 7.16 (d, 1H), 6.98 - 6.92 (m, 3H), 6.84 (dd, 1H), 6.56 (t, 1H), 5.26 (s, 1H), 5.12 - 5.08 (m, 1H), 3.73 (s, 3H), 3.39 - 3.34 (m, 2H), 2.86 - 2.76 (m, 2H), 2.65 - 2.53 (m, 2H), 2.45 (dd, 1H), 2.28 (s, 3H), 2.20 (dd, 1H), 2.07 - 1.99 (m, 1H)	M/z = 512 [M+H]+, Rt = 1.75 min (Method A21)
 71a	1H NMR (500 MHz, DMSO-d6) δ 10.90 (s, 1H), 9.30 (s, 1H), 7.29 - 7.20 (m, 3H), 7.16 (d, 1H), 6.98 - 6.91 (m, 3H), 6.82 (dd, 1H), 6.56 (dd, 1H), 5.24 (s, 1H), 5.03 - 4.99 (m, 1H), 3.73 (s, 3H), 3.64 (dd, 1H), 3.38 - 3.32 (m, 1H), 3.23 (dd, 1H), 2.83 (dd, 1H), 2.72 (s, 3H), 2.65 - 2.56 (m, 1H), 2.48 - 2.41 (m, 2H), 2.29 (s, 3H), 2.20 (dd, 1H), 1.83 (dd, 1H)	M/z = 526 [M+H]+, Rt = 1.86 min (Method A21)
 73a	1H NMR (600 MHz, DMSO-d6) δ 10.92 (t, J = 2.1 Hz, 1H), 9.33 (s, 1H), 7.69 (d, J = 8.5 Hz, 2H), 7.27 (dd, J = 7.6, 1.6 Hz, 1H), 7.24 - 7.19 (m, 3H), 7.14 (d, J = 8.5 Hz, 2H), 6.98 - 6.90 (m, 3H), 6.83 (dd, J = 7.4, 0.8 Hz, 1H), 6.62 (ddd, J = 3.1, 2.1, 0.9 Hz, 1H), 5.38 (s, 1H), 5.12 - 4.96 (m, 2H), 3.72 (s, 3H), 3.38 - 3.32 (m, 1H), 3.18 (s, 3H), 2.82 (dd, J = 17.1, 12.0 Hz, 1H), 2.60 (ddd, J = 17.1, 4.1, 1.5 Hz, 1H), 2.49 - 2.43 (m, 1H), 2.32 (s, 3H), 2.20 (ddd, J = 16.4, 3.8, 1.4 Hz, 1H)	M/z = 597 [M+H]+, Rt = 2.2 min (Method A21)
 74a	1H NMR (500 MHz, DMSO-d6) δ 10.92 (t, J = 2.2 Hz, 1H), 9.29 (s, 1H), 7.29 - 7.20 (m, 3H), 7.17 (dt, J = 8.0, 0.9 Hz, 1H), 6.98 - 6.92 (m, 3H), 6.85 (dd, J = 7.4, 1.0 Hz, 1H), 6.64 (ddd, J = 3.1, 2.0, 0.9 Hz, 1H), 5.30 (s, 1H), 4.00 - 3.89 (m, 2H), 3.73 (s, 3H), 3.37 - 3.32 (m, 1H), 2.85 (s, 3H), 2.84 - 2.70 (m, 3H), 2.65 - 2.54 (m, 1H), 2.49 - 2.43 (m, 1H), 2.32 (s, 3H), 2.23 - 2.17 (m, 1H), 1.87 - 1.81 (m, 2H)	M/z = 549 [M+H]+, Rt = 1.93 min (Method A21)

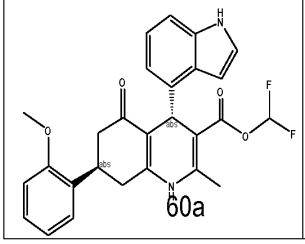
 75a	1H NMR (500 MHz, DMSO-d6) δ 10.90 (t, J = 2.1 Hz, 1H), 9.25 (s, 1H), 7.29 - 7.20 (m, 3H), 7.16 (dt, J = 8.0, 0.9 Hz, 1H), 6.99 - 6.92 (m, 3H), 6.85 (dd, J = 7.4, 1.0 Hz, 1H), 6.62 (ddd, J = 3.1, 2.0, 0.9 Hz, 1H), 5.31 (s, 1H), 3.92 - 3.79 (m, 2H), 3.73 (s, 3H), 3.38 - 3.32 (m, 1H), 3.00 (t, J = 7.4 Hz, 2H), 2.88 (s, 3H), 2.83 (dd, J = 17.0, 11.9 Hz, 1H), 2.65 - 2.53 (m, 1H), 2.49 - 2.43 (m, 1H), 2.30 (s, 3H), 2.22 - 2.17 (m, 1H), 1.60 - 1.50 (m, 4H)	M/z = 563 [M+H]+, Rt = 1.98 min (Method A21)
 76a	1H NMR (500 MHz, DMSO-d6) δ 10.94 (t, J = 2.2 Hz, 1H), 9.33 (s, 1H), 7.29 - 7.16 (m, 4H), 6.97 - 6.91 (m, 3H), 6.86 (dd, J = 7.4, 1.0 Hz, 1H), 6.66 (ddd, J = 3.1, 2.1, 0.9 Hz, 1H), 5.31 (s, 1H), 4.82 - 4.79 (m, 1H), 3.72 (s, 3H), 3.35 - 3.32 (m, 1H), 3.07 - 2.99 (m, 1H), 2.97 - 2.91 (m, 1H), 2.85 - 2.76 (m, 2H), 2.64 - 2.53 (m, 1H), 2.47 - 2.36 (m, 2H), 2.35 (s, 3H), 2.24 - 2.19 (m, 1H), 2.10 - 2.02 (m, 2H), 1.84 - 1.65 (m, 2H)	M/z = 561 [M+H]+, Rt = 1.97 min (Method A21)

Example Procedure j5: 60a

A vial was successively charged with potassium hydroxide (10.4 mg, 0.19 mmol) and (4*S*,7*R*)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid (30.0 mg, 0.056 mmol) in acetonitrile (0.30 mL) and water (60.0 µL). The reaction mixture was stirred at RT for 1 h 30 min. Then [bromo(difluoro)methyl]-trimethyl-silane (22.2 µL, 0.140 mmol) was added and the reaction was stirred for 1 h. dichloromethane and water were added. The phases were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with water, dried using a phase separator and concentrated under vacuum. The crude material was purified by Flash chromatography on silica gel using a gradient of acetone in toluene from 0% to 50%. Fractions were combined and evaporated to afford the title compound.

The following compounds were obtained using this protocol:

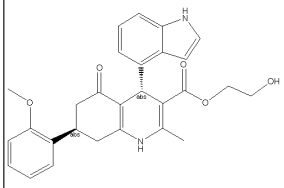
Structure Cpd. No.	**NMR**	**MS**

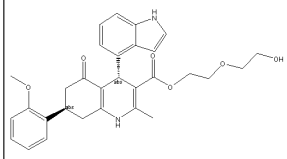
 60a	1H NMR (DMSO-d6, 600 MHz): δ 10.94 (t, J = 2.1 Hz, 1H), 9.71 (s, 1H), 7.26-7.29 (m, 2H), 7.20-7.24 (m, 1H), 7.17-7.19 (m, 1H), 7.24 (t, J = 143.9 Hz, 1H), 6.91-6.98 (m, 3H), 6.84 (dd, J = 7.4, 1.0 Hz, 1H), 6.56 (ddd, J = 3.2, 2.1, 0.9 Hz, 1H), 5.25 (s, 1H), 3.71-3.74 (m, 3H), 3.32-3.38 (m, 1H), 2.86 (dd, J = 17.1, 11.7 Hz, 1H), 2.58-2.68 (m, 1H), 2.51-2.54 (m, 1H), 2.35 (s, 3H), 2.22 (ddd, J = 16.5, 3.9, 1.5 Hz, 1H)	M/z = 479 [M+H]+, Rt = 2.32 min (Method A21)

Example Procedure j6: 57a

To a stirred solution of (4*S*,7*R*)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid (200 mg, 0.33 mmol) in DCM (3 mL) at RT were added 2-[tert-butyl(dimethyl)silyl]oxyethanol (262 µL, 1.31 mmol), pyridine (106 µL, 1.31 mmol) and propylphosphonic anhydride in MeTHF 50% w/w (770 µL, 1.31 mmol). The reaction mixture was heated to 40 °C and stirred for 1 h and left stirred at RT for 72 h. Water and ethyl acetate were added. The phases were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with water, dried using a phase separator and concentrated under vacuum. The crude was purified by Flash chromatography on silica gel using a gradient of acetone in toluene from 5% to 60%. Fractions were combined and evaporated. This batch was purified by reverse-phase flash chromatography using a gradient of acetonitrile in water from 20% to 80% (neutral). Fractions were isolated and evaporated to afford the title compound.

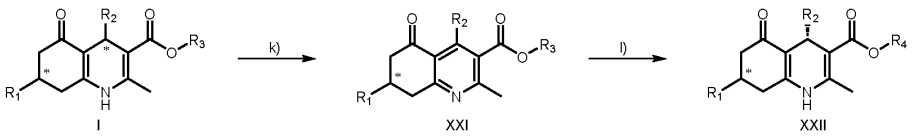
The following compounds were obtained using this protocol:

Structure Cpd. No.	**NMR**	**MS**
 57a	1H NMR (DMSO-d6, 600 MHz): δ 10.88 (t, J = 1.9 Hz, 1H), 9.21 (s, 1H), 7.28 (dd, J = 7.6, 1.7 Hz, 1H), 7.23-7.25 (m, 1H), 7.21 (ddd, J = 8.3, 7.4, 1.7 Hz, 1H), 7.15 (ddd, J = 8.0, 0.9, 0.8 Hz, 1H), 6.96 (dd, J = 8.3, 1.0 Hz, 1H), 6.90-6.95 (m, 2H), 6.85 (dd, J = 7.4, 0.8 Hz, 1H), 6.61 (ddd, J = 3.1, 1.9, 0.9 Hz, 1H), 5.32 (s, 1H), 4.61 (t, J = 5.5 Hz, 1H), 3.92 (ddd, J = 11.3, 6.5, 4.9 Hz, 1H), 3.74-3.80 (m, 1H), 3.73 (s, 3H), 3.41-3.53 (m, 2H), 3.36 (tt, J = 12.5, 4.0 Hz, 1H), 2.83 (dd, J = 17.0, 11.9 Hz, 1H), 2.58-2.65 (m, 1H), 2.45 (dd, J = 16.4, 13.1 Hz, 1H), 2.27 (s, 3H), 2.16-2.22 (m, 1H)	M/z = 473 [M+H]+, Rt = 1.84 min (Method A21)

 59a	1H NMR (DMSO-d6, 600 MHz): δ 10.88 (t, J = 2.0 Hz, 1H), 9.24 (s, 1H), 7.27 (dd, J = 7.6, 1.7 Hz, 1H), 7.23-7.25 (m, 1H), 7.21 (ddd, J = 8.3, 7.4, 1.7 Hz, 1H), 7.15 (dt, J = 8.0, 0.9 Hz, 1H), 6.96 (dd, J = 8.3, 1.0 Hz, 1H), 6.90-6.95 (m, 2H), 6.84 (dd, J = 7.3, 0.9 Hz, 1H), 6.61 (ddd, J = 3.1, 2.0, 0.9 Hz, 1H), 5.31 (s, 1H), 4.56 (t, J = 5.6 Hz, 1H), 3.96-4.01 (m, 1H), 3.88-3.96 (m, 1H), 3.73 (s, 3H), 3.44-3.53 (m, 4H), 3.32-3.40 (m, 3H), 2.83 (dd, J = 17.0, 11.9 Hz, 1H), 2.61 (ddd, J = 17.0, 4.1, 1.5 Hz, 1H), 2.45 (dd, J = 16.4, 13.1 Hz, 1H), 2.28 (s, 3H), 2.16-2.22 (m, 1H)	M/z = 517 [M+H]+, Rt = 1.85 min (Method A21)

EXAMPLE 5

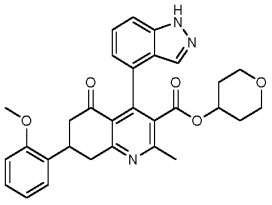
Synthesis of (4*S*,7*RS*)-configurated scaffolds for evaluation



General scheme for the synthesis of stereo defined scaffolds building on racemic 4,7-substituted 4,6,7,8-tetrahydroquinolin-5(1H)-ones (I) that in two-step procedure of oxidation and subsequent asymmetric transfer hydrogenation can be converted to (4*S*,7*RS*)-configurated 4,7-substituted 4,6,7,8-tetrahydroquinolin-5(1H)-ones (XXII).

Example Procedure k:

<u>tetrahydro-2H-pyran-4-yl 4-(1H-indazol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate:</u>

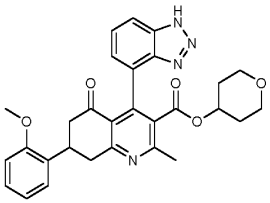


In a RBF, at 0 °C, tetrahydro-2H-pyran-4-yl 4-(1H-indazol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (50.0 mg, 0.093 mmol) was dissolved in DCM-anhydrous (0.92 mL) and 4,5-dichloro-3,6-dioxo-cyclohexa-1,4-diene-1,2-dicarbonitrile (21.0 mg, 0.09 mmol) was added. The reaction was then stirred at 0 °C for 1 h. The reaction mixture was filtered, the solid was washed with DCM and the filtrate was concentrated under reduced pressure. The crude material was

purified by Flash chromatography on silica gel using a gradient of acetone in toluene from 0% to 30%. Fractions were combined and evaporated to afford the title compound.

1H NMR (400 MHz, DMSO-d6) δ 13.06 (s, 1H), 7.70 – 7.47 (m, 2H), 7.31 (ddd, J = 8.5, 7.0, 3.1 Hz, 1H), 7.28 – 7.12 (m, 2H), 7.03 (d, J = 8.3 Hz, 1H), 7.01 – 6.91 (m, 1H), 6.79 (dd, J = 24.5, 6.9 Hz, 1H), 4.70 – 4.59 (m, 1H), 3.82 (d, J = 3.5 Hz, 4H), 3.53 – 3.35 (m, 4H), 3.13 (q, J = 4.3 Hz, 2H), 2.98 (ddd, J = 59.8, 16.0, 12.1 Hz, 1H), 2.69 – 2.57 (m, 1H), 2.55 (d, J = 2.4 Hz, 3H), 1.56 – 1.19 (m, 2H), 1.19 – 1.01 (m, 1H), 0.68 – 0.46 (m, 1H)

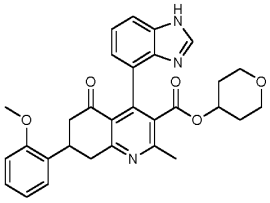
tetrahydro-2H-pyran-4-yl 4-(1H-benzo[d][1,2,3]triazol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate:



was obtained via the aforementioned protocol.

1H NMR (400 MHz, DMSO-d6) δ 15.84 – 15.29 (m, 1H), 7.90 (d, J = 105.2 Hz, 1H), 7.54 – 6.84 (m, 7H),4.66 (s, 1H), 3.83 (d, J = 10.2 Hz, 4H), 3.48 (s, 2H), 3.04 (d, J = 51.4 Hz, 3H), 2.58 (d, J = 3.0 Hz, 4H), 1.58 (s, 1H), 1.16 (s, 2H), 0.46 (d, J = 44.8 Hz, 1H)

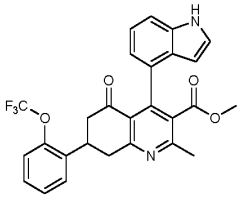
tetrahydro-2H-pyran-4-yl 4-(1H-benzo[d]imidazol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate:



was obtained via the aforementioned protocol.

1H NMR (400 MHz, DMSO-d6) δ 8.87 (s, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.42 (dd, J = 7.7, 2.0 Hz, 2H), 7.30 – 7.24 (m, 2H), 7.12 (s, 1H), 7.09 – 7.05 (m, 1H), 5.46 (tt, J = 9.0, 4.2 Hz, 1H), 4.68 (dt, J = 7.9, 4.2 Hz, 1H), 4.27 – 4.11 (m, 1H), 3.84 (s, 3H), 3.61 – 3.54 (m, 2H), 3.15 – 3.08 (m, 2H), 2.55 (d, J = 4.5 Hz, 3H), 2.15 – 2.01 (m, 2H), 1.79 – 1.54 (m, 3H), 1.26 – 1.14 (m, 2H)

methyl 4-(1H-indol-4-yl)-2-methyl-5-oxo-7-(2-(trifluoromethoxy)phenyl)-5,6,7,8-tetrahydroquinoline-3-carboxylate:



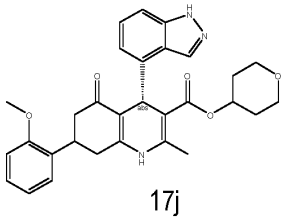
was obtained via the aforementioned protocol.

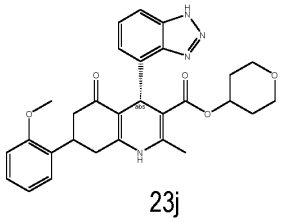
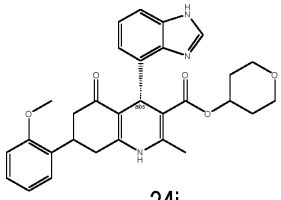
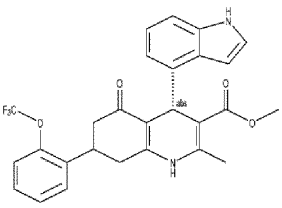
1H NMR (400 MHz, DMSO-d6) δ 11.10 (d, J = 11.3 Hz, 1H), 7.78 – 7.62 (m, 1H), 7.56 – 7.34 (m, 4H), 7.28 – 7.05 (m, 2H), 6.80 – 6.69 (m, 1H), 5.94 (dddd, J = 10.6, 3.1, 2.0, 0.9 Hz, 1H), 3.96 – 3.77 (m, 1H), 3.55 (td, J = 16.3, 11.6 Hz, 1H), 3.34 (d, J = 10.0 Hz, 3H), 3.30 – 2.83 (m, 2H), 2.65 – 2.43 (m, 4H)

Example Procedure I: 23j

To a stirred solution of tetrahydropyran-4-yl 4-(1H-benzotriazol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-7,8-dihydro-6H-quinoline-3-carboxylate (85.0 mg, 0.16 mmol) in DCM-anhydrous (1.6 mL) at RT were added *S*-TRIP (5.0 mg, 6.57 µmol) and diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (87.5 mg, 0.33 mmol). The reaction mixture was heated to 45 °C and stirred overnight. To the mixture was added again diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (87.5 mg, 0.33 mmol) then the reaction was further heated to 55 °C and stirred for 4 h. The mixture was cooled down to RT and solvent was removed under reduced pressure to afford the crude product. The Product was purified by flash chromatography on silica gel (solid injection onto dicalite) using a gradient of Toluene / Acetone (95:0 to 0:100, product elution started at 30% solvent B). Desired fractions were combined, and solvent was removed under reduced pressure. This batch was dissolved in MeOH and was added water. The mixture was freeze dried to afford the title compound.

The following compounds were obtained using this protocol:

Structure Cpd. No.	NMR Mixture of 2 diastereomers	MS
 17j	(50/50)1H NMR (DMSO-d6, 500 MHz): δ 12.71-12.98 (m, 1H), 9.18-9.40 (m, 1H), 8.05-8.19 (m, 1H), 7.09-7.34 (m, 4H), 6.54-7.03 (m, 4H), 5.30-5.38 (m, 1H), 4.69 (td, J = 8.7, 4.3 Hz, 1H), 3.78 (s, 2H), 3.73 (s, 1H), 3.61-3.71 (m, 2H), 3.35-3.51 (m, 2H), 3.21-3.29 (m, 1H), 2.61-2.89 (m, 2H), 2.32-2.41 (m, 4H), 1.73-1.79 (m, 1H), 1.39-1.50 (m, 2H), 1.03-1.10 (m, 1H)	M/z = 514 [M+H]+, Rt = 1.93 min (Method A21)

 23j	(50/50) 1H NMR (500 MHz, DMSO-d6) δ 9.21 (br s, 1 H) 7.63 - 7.85 (m, 1 H) 7.27 (dd, J =7.63, 1.63 Hz, 1 H) 7.20 - 7.26 (m, 1 H) 7.05 - 7.20 (m, 2 H) 6.86 - 6.99 (m, 2 H) 5.23 - 5.53 (m, 1 H) 4.43 - 4.77 (m, 1 H) 3.72 - 3.81 (m, 3 H) 3.63 - 3.71 (m, 1 H) 3.35 - 3.61 (m, 2 H) 3.01 - 3.27 (m, 2 H) 2.63 - 2.88 (m, 2 H) 2.37 (br dd, J =3.81, 1.81 Hz, 5 H) 1.34 - 1.76 (m, 2 H) 1.00 (d, J =6.75 Hz, 2 H)	M/z = 515 [M+H]+, Rt = 1.99 min (Method A21)
 24j	(58/26+9/7) 1H NMR (DMSO-d6, 600 MHz): δ 12.10 (br s, 1H), 9.31 (s, 1H), 8.15 (s, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.27 (dd, J = 7.7, 1.7 Hz, 1H), 7.22 (td, J = 7.8, 1.7 Hz, 1H), 7.03-7.08 (m, 1H), 6.95-6.97 (m, 1H), 6.89-6.94 (m, 2H), 5.26 (s, 1H), 4.60 (ddt, J = 12.7, 8.5, 4.5 Hz, 1H), 3.73 (s, 2H), 3.36-3.44 (m, 1H), 3.25-3.29 (m, 2H), 3.18-3.22 (m, 1H), 3.09-3.14 (m, 1H), 2.68-2.83 (m, 2H), 2.51-2.65 (m, 2H), 2.39 (s, 2H), 2.20-2.29 (m, 1H), 1.63-1.83 (m, 2H), 1.35-1.49 (m, 2H), 1.27-1.32 (m, 1H) additionally to the diastereomers minor 2 conformers were observed	M/z = 514 [M+H]+, Rt = 1.33 min (Method A21)
 101j	(mixture of diastereoisomers) 1H NMR (500 MHz, DMSO-d6) δ 10.94 – 10.81 (m, 1H), 9.36 – 8.96 (m, 1H), 7.69 – 7.06 (m, 6H), 6.96 – 6.87 (m, 1H), 6.87 – 6.72 (m, 1H), 6.57 – 6.49 (m, 1H), 5.35 – 5.23 (m, 1H), 3.49 – 3.42 (m, 3H), 3.72 – 3.32 (m, 1H),2.89 – 2.78 (m, 1H), 2.77 – 2.57 (m, 1.5H), 2.47 – 2.33 (m, 1H), 2.26 – 2.22 (m, 3H), 2.17 – 2.10 (m, 0.5H)	M/z = 497 [M+H]+, Rt = 2.25 min (Method A21)

EXAMPLE 6

Alternative late-stage derivatization of stereo defined scaffolds for evaluation



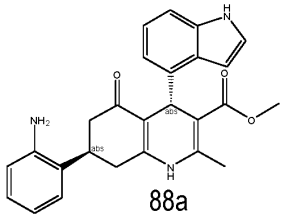
XIII IV

General scheme for the late-stage derivatization of stereo defined 4,7-substituted 4,6,7,8-tetrahydroquinolin-5(1H)-ones (IV) employing haloaromatics as intermediate towards a diverse set of compounds.

Example Procedure m1: 88a

To a stirred solution of 86a (40.0 mg, 0.08 mmol) in anhydrous DMSO (0.81 mL) at RT under argon were added successively cesium carbonate (80.4 mg, 0.24 mmol), sodium azide (21.0 mg, 0.32 mmol), copper(I) iodide (16.2 mg, 0.08 mmol) and (2*S*)-pyrrolidine-2-carboxylic acid (4.8 mg, 0.04 mmol). The reaction was degassed under vacuum and refilled with argon 3 times. The reaction was stirred at 80°C overnight and then at 100 °C for 3 h. The reaction was quenched with $NaHCO_3$. Ethyl acetate was added. The phases were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic layers were dried using a phase separator and concentrated under vacuum. The crude was purified by reverse-phase flash chromatography using a gradient of acetonitrile in water from 20% to 80% (neutral). Fractions were combined and lyophilized to afford the title compound.

The following compounds were obtained using this protocol:

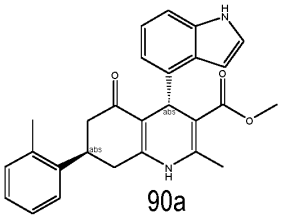
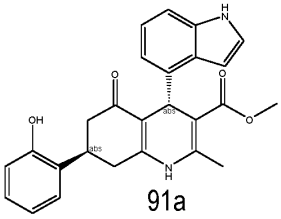
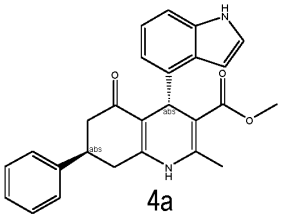
Structure Cpd. No.	NMR	MS
 88a	1H NMR (600 MHz, DMSO-d6) δ 10.84 (s, 1H), 9.17 (s, 1H), 7.26 – 7.20 (m, 1H), 7.13 (dt, J = 8.0, 0.9 Hz, 1H), 7.08 (dd, J = 7.8, 1.3 Hz, 1H), 6.96 – 6.92 (m, 1H), 6.89 (td, J = 7.6, 1.5 Hz, 1H), 6.84 (dd, J = 7.5, 0.9 Hz, 1H), 6.65 (ddd, J = 3.0, 2.1, 0.9 Hz, 1H), 6.62 (dd, J = 7.9, 1.3 Hz, 1H), 6.55 (td, J = 7.4, 1.2 Hz, 1H), 5.33 (s, 1H), 4.86 (s, 2H), 3.44 (s, 3H), 3.27 – 3.18 (m, 1H), 2.75 – 2.61 (m, 2H), 2.44 (dd, J = 16.4, 12.6 Hz, 1H), 2.28 – 2.18 (m, 4H)	M/z = 428 [M+H]+, Rt = 1.69 min (Method A21)

Example Procedure m2: 90a, 91a and 4a

In a sealed tube, to a stirred solution of 86a (79.2 mg, 0.16 mmol) in water (0.40 mL) and 1,4-dioxane (0.80 mL) was added cesium carbonate (80.4 mg, 0.24 mmol). The reaction mixture was degassed with argon for 5 minutes and palladium(II) acetate (7.4 mg, 0.032 mmol), di-tert-butyl[2',4',6'-tri(propan-2-yl)biphenyl-2-yl]phosphane (27.9 mg, 0.065 mmol) and 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (67.6 µL, 0.24 mmol) were added. The reaction mixture was heated at 95 °C for 16 h. The reaction mixture was cooled down to RT and concentrated under reduced pressure. The crude was purified by flash column chromatography eluting Acetone in Toluene from 10 to 50%. Desired fractions were concentrated under reduced pressure to give 90a. From the same reaction 91a and 4a could be isolated as well.

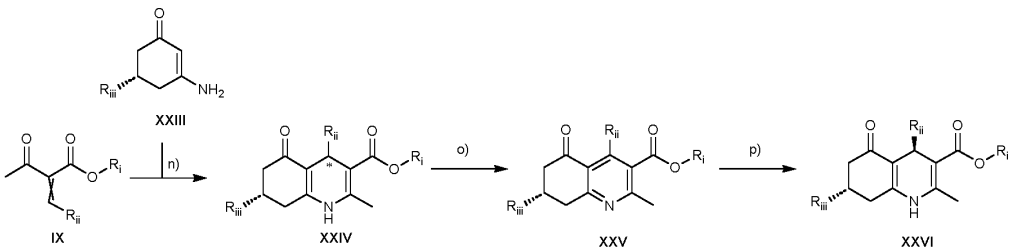
The following compounds were obtained using this protocol:

Structure Cpd. No.	NMR	MS

 90a	1H NMR (600 MHz, DMSO-d6) δ 10.88 (s, 1H), 9.21 (s, 1H), 7.37 (d, J = 7.0 Hz, 1H), 7.27 – 7.22 (m, 1H), 7.21 – 7.07 (m, 4H), 6.96 – 6.90 (m, 1H), 6.83 (dd, J = 7.4, 0.8 Hz, 1H), 6.60 (ddd, J = 3.1, 2.1, 0.9 Hz, 1H), 5.33 (s, 1H), 3.45 (s, 3H), 3.29 – 3.21 (m, 1H), 2.78 (dd, J = 17.2, 11.7 Hz, 1H), 2.60 (ddd, J = 17.2, 4.3, 1.6 Hz, 1H), 2.58 – 2.51 (m, 1H), 2.26 (s, 3H), 2.22 – 2.12 (m, 4H)	M/z = 427 [M+H]+, Rt = 2.11 min (Method A21)
 91a	1H NMR (600 MHz, DMSO-d6) δ 10.88 (t, J = 2.1 Hz, 1H), 9.45 (s, 1H), 9.22 (s, 1H), 7.25 – 7.23 (m, 1H), 7.19 – 7.13 (m, 2H), 7.05 – 7.00 (m, 1H), 6.95 – 6.91 (m, 1H), 6.82 – 6.74 (m, 3H), 6.60 (ddd, J = 3.1, 2.0, 0.9 Hz, 1H), 5.32 (s, 1H), 3.46 – 3.43 (m, 3H), 3.35 – 3.31 (m, 1H), 2.78 (dd, J = 17.0, 11.9 Hz, 1H), 2.67 – 2.60 (m, 1H), 2.49 – 2.46 (m, 1H), 2.27 (s, 3H), 2.24 – 2.15 (m, 1H)	M/z = 429 [M+H]+, Rt = 1.81 min (Method A21)
 4a	1H NMR (600 MHz, DMSO-d6) δ 10.87 (s, 1H), 9.24 (s, 1H), 7.34 – 7.28 (m, 4H), 7.25 – 7.24 (m, 1H), 7.23 – 7.20 (m, 1H), 7.14 (dt, J = 8.0, 0.9 Hz, 1H), 6.96 – 6.89 (m, 1H), 6.81 (dd, J = 7.3, 0.9 Hz, 1H), 6.60 (ddd, J = 3.1, 2.0, 0.9 Hz, 1H), 5.33 (s, 1H), 3.45 (s, 3H), 3.12 – 3.02 (m, 1H), 2.82 (dd, J = 17.1, 11.8 Hz, 1H), 2.70 – 2.62 (m, 1H), 2.56 – 2.50 (m, 1H), 2.30 – 2.22 (m, 4H)	M/z = 413 [M+H]+, Rt = 2.01 min (Method A21)

EXAMPLE 7

Synthesis other stereoisomers scaffolds for evaluation

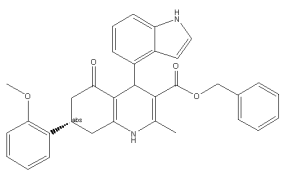


Analogous to the previous examples other stereoisomers of the 4,7-substituted 4,6,7,8-tetrahydroquinolin-5(1H)-ones (XXIV) and the enantiopure compound XXVI can be synthesized.

Example Procedure n: 27i

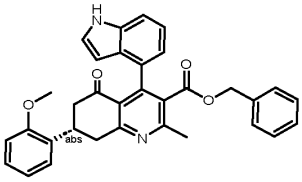
A 1ml vial was successively charged with (5*S*)-3-amino-5-(2-methoxyphenyl)cyclohex-2-en-1-one (100 mg, 0.460 mmol), molecular sieves 4A and benzyl 2-(1H-indol-4-ylmethylene)-3-oxo-butanoate (267 mg, 0.55 mmol) in DMF-Anhydrous (0.5 mL). The reaction mixture was stirred at 130 °C overnight. The reaction was concentrated. The crude material was purified by Flash chromatography on silica gel using a gradient of acetone in toluene from 0% to 30%. Fractions were combined and evaporated to afford the title compound.

The following compounds were obtained using this protocol:

Structure Cpd. No.	NMR Mixture of 2 diastereomers	MS
 27i	(47/53)1H NMR (DMSO-d6, 500 MHz) δ 10.7-11.0 (m, 1H), 9.0-9.4 (m, 1H), 6.3-7.4 (m, 14H), 5.2-5.4 (m, 1H), 4.7-5.0 (m, 2H), 3.7-3.8 (m, 3H), 3.3-3.7 (m, 1H), 2.6-2.9 (m, 2H), 2.1-2.5 (m, 5H)	M/z = 519 [M+H]+, Rt = 2.5 min (Method A21)

Example Procedure o:

benzyl (7S)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate

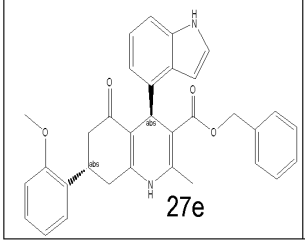


In an RBF, at 0 °C, 27i (2.00 g, 3.63 mmol) was dissolved in DCM-Anhydrous (23.7 mL) and 4,5-dichloro-3,6-dioxo-cyclohexa-1,4-diene-1,2-dicarbonitrile (0.823 g, 3.63 mmol) was added. The reaction was then stirred at 0° C for 1 h. The reaction mixture was filtered, the solid was washed with DCM and the filtrate was concentrated under reduced pressure. The crude material was purified by Flash chromatography on silica gel using a gradient of Acetone in toluene from 0% to 20%. Fractions were combined and evaporated to afford the title compound.

1H NMR (400 MHz, DMSO-d6) δ 11.14 (d, J = 8.0 Hz, 1H), 7.38 (dd, J = 8.2, 2.7 Hz, 1H), 7.30 – 7.12 (m, 7H), 7.11 – 7.01 (m, 2H), 7.00 – 6.90 (m, 1H), 6.80 – 6.68 (m, 3H), 5.92 (ddt, J = 24.5, 2.9, 1.2 Hz, 1H), 4.91 – 4.59 (m, 2H), 3.81 (d, J = 3.0 Hz, 4H), 3.56 – 3.33 (m, 1H), 3.07 (dd, J = 15.2, 11.9 Hz, 1H), 2.74 – 2.52 (m, 1H), 2.49 (s, 3H)

Example Procedure p: 27e

In a vial, benzyl (7*S*)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-7,8-dihydro-6H-quinoline-3-carboxylate (1.90 g, 3.64 mmol) was dissolved in DCM-anhydrous (18.3 mL). Then, diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (95%, 1.94 g, 7.28 mmol) and *R*-TRIP (112 mg, 0.15 mmol) were added. The reaction mixture was stirred at 40 °C overnight. Then diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (971 mg, 3.64 mmol) and *R*-TRIP (50.0 mg, 0.065 mmol) were added and the reaction was stirred at 40 °C overnight again. The reaction mixture was concentrated to afford a crude. The crude was purified by Flash chromatography on silica gel using a gradient of acetone in toluene from 0% to 25%. Fractions were combined and evaporated to afford the title compound.

Structure Cpd. No.	NMR	MS
 27e	1H NMR (DMSO-d6, 600 MHz): δ 10.86-10.98 (m, 1H), 9.28 (s, 1H), 7.27 (dd, J = 7.8, 1.8 Hz, 1H), 7.19-7.25 (m, 5H), 7.16-7.19 (m, 1H), 7.05-7.09 (m, 2H), 6.95 (dd, J = 8.3, 1.0 Hz, 1H), 6.89-6.94 (m, 2H), 6.80 (dd, J = 7.4, 0.8 Hz, 1H), 6.59 (ddd, J = 3.1, 2.1, 0.9 Hz, 1H), 5.35 (s, 1H), 4.88-4.98 (m, 2H), 3.72 (s, 3H), 3.34 (br s, 1H), 2.82 (dd, J = 17.0, 12.0 Hz, 1H), 2.60 (ddd, J = 17.0, 4.1, 1.5 Hz, 1H), 2.45 (dd, J = 16.3, 13.1 Hz, 1H), 2.30 (s, 3H), 2.19 (ddd, J = 16.3, 3.8, 1.5 Hz, 1H)	M/z = 519 [M+H]+, Rt = 2.5 min (Method A21)

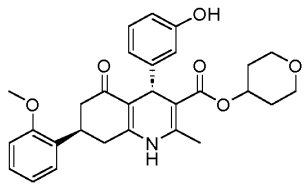
EXAMPLE 8

Screening assay for assessing the relative potency of compounds with coronin 1 promoter inhibitory activity.

Towards identifying compounds that suppress coronin 1 promoter, the present inventors developed a coronin 1 promotor-based screening assay (the principle of the assay is shown in Fig. 1). In brief, the essential coronin 1 promoter element comprising the 1500 bp upstream of the Transcription Start Site (TSS, Table 7) was fused to a promoterless plasmid coding the sequence of a destabilized Green Fluorescent Proteins (dsGFP, Clonetech, pZsGreen1-DR). This allows for the identification of small molecules that rapidly suppress coronin 1 promoter activity. As an internal control for non-specific inhibition as well as toxicity, we cloned the early CMV promoter upstream of a promoterless plasmid

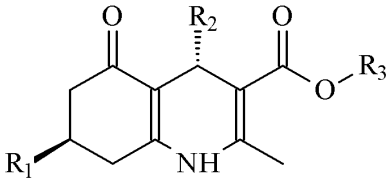
driving destabilized RFP (dsRFP, Clonetech, pZsRed-Express-DR). The plasmids were separately transfected into an immune lineage cell line (RBL, Rat Basophil Leukemia cell line) and the transfected cells were enriched, expanded and showed robust expression of both GFP and RFP proteins whose fluorescence could be assayed using flow cytometry or other fluorescence read-out methodologies. Compound induced down regulation of GFP expression was assessed in a flow cytometry-based assay using aforementioned RBL cell lines. In individual 96 well plates linear six-point serial dilutions ranging from 2000 nM to 2 nM compound concentration were prepared in RPMI 1640 medium starting from 60 mM dimethyl sulfoxide (DMSO) stock solutions leading to a final concentration of DMSO below 0.1 %. Compounds and vehicle (DMSO) treated controls were assessed in duplicates. The dsGFP and dsRFP expressing cells were mixed in equal numbers and 10'000 cells/well were added to the prediluted compounds. After incubation for ~62 hours at 37 °C the cells in 5% CO2, they were harvested and stained with live-dead marker at 4 °C. Subsequently, the samples were acquired on a Attune Flow Cytometer (Thermo Fisher Scientific Inc.) followed by assessment of the cell viability, the median fluorescence intensities (MFI) for GFP and RFP fluorescence using FlowJo software (Tree Star). In addition to the GFP MFI, the cell viability (% live) as well as the RFP MFI were analyzed to rule out non-specific promoter inhibition and cytotoxicity (Table 4).

To standardize the calculation of the EC_{50} values for compound induced GFP inhibition, the measured GFP MFI were normalized to a set value of 10'000 using the average MFI of the DMSO treated wells as a scaling factor for the plate. The EC_{50} values were calculated from the normalized GFP MFI by a symmetrical sigmoidal curve fit in GraphPad Prim (GraphPad Software, LLC) using the normalized value of the DMSO as upper boundary and zero as the lower boundary. To minimize the inter-assay variability of the EC_{50} values (inherently linked to cell-based screening assays) led to the use of a relative potency scale wherein the compound **Ref13a** in PCT-Patent Application PCT/EP2023/077188 was set as the reference compound with a relative potency value of 1.00 (relative potency calculated as [EC_{50} GFP inhibition **Ref13a**] / [EC_{50} GFP inhibition compound of interest]) (Table 2-6). Said compound **Ref13a** is a compound of formula:

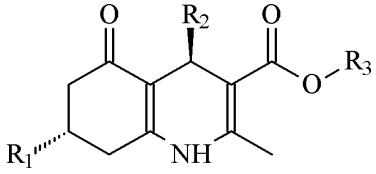


which has been provided in PCT-Patent Application PCT/EP2023/077188.

Based on the analysis of the inhibition of coronin 1 promoter driven GFP fluorescence the compound of formula (I) is preferably in a configuration R_1 and R_2 substituents are present on the opposite faces of the ring system. Thus, preferably, the compound of formula (I) is a compound of formula:



or a compound of formula:



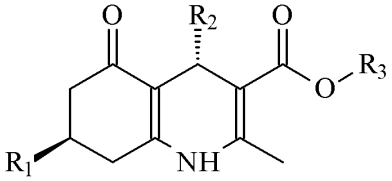
This preference is showcased in Table 2 comparing the activities of the relative configuration of exemplary compounds. The (4*S*,7*R*)-configurated compounds (indicated with the letter **a** after their number) show increased potency over the (4*R*,7*R*)-configurated compounds (indicated with the letter **g** after their number).

Table 2: Relative potency (RP) values for coronin 1 promoter inhibition

Cpd. No.	RP* GFP Inhibition
12a	0.13
12g	<0.06
13a	0.24
13g	<0.06
14a	0.46
14g	<0.06
19a	4.42
19g	<0.07
20a	0.47
20g	<0.07
70a	0.89
70g	<0.10

*RP (relative potency) calculated as [EC_{50} GFP inhibition **Ref13a**] / [EC_{50} GFP inhibition compound of interest] compound **Ref13a** from PCT-Patent Application PCT/EP2023/077188.

More preferably, the compound of formula (I) has an absolute configuration of its stereogenic centers as shown in the formula:



This preference is showcased in Table 3 comparing the activities of the stereoisomers of compound **27**. The mixture of isomers **27h** contains the active isomer of compound **27,** whilst **27i** being inactive. Examining the individual stereoisomers of **27h** reveals the (4*S*,7*R*)-configurated **27a** as eutomer.

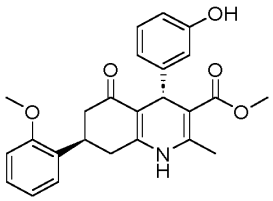
Table 3: Relative potency (RP) values for coronin 1 promoter inhibition

Cpd. No.	Configuration of isomers	RP* GFP Inhibition
27h	mixture of (4*S*,7*R*) and (4*R*,7*R*)	0.43
27i	mixture of (4*R*,7*S*) and (4*S*,7*S*)	<0.10
27a	(4*S*,7*R*)	0.95
27e	(4*R*,7*S*)	<0.10

*RP (relative potency) calculated as [EC_{50} GFP inhibition **Ref13a**] / [EC_{50} GFP inhibition compound of interest] compound **Ref13a** from PCT-Patent Application PCT/EP2023/077188.

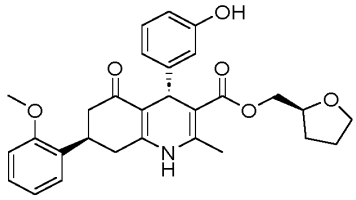
Combining the above mentioned observations indicate that for compounds of formula (I) containing two stereocenters the eutomers shown are (4*S*,7*R*)-configurated and for compounds of formula (I) with more than two stereocenters the most active core configuration shown is as well (4*S*,7*R*).

Additionally, this is exemplified for compounds sharing the same core scaffold containing two stereocenters by eutomers **Ref13a** and **Ref11c**. Said compound **Ref11c** is a compound of formula:



which has been provided in PCT-Patent Application PCT/EP2023/077188.

For compounds with more than two stereocenters the most active core configuration is as well (4*S*,7*R*) shown for compound **Ref12e**. Said compound **Ref12e** is a compound of formula:



which has been provided in PCT-Patent Application PCT/EP2023/077188.

Table 4: Relative potency (RP) values and EC_{50} for coronin 1 promoter inhibition.

Cpd. No.	Configuration of 4 and 7 stereocenters	RP* GFP Inhibition	EC_{50} GFP inhibition
Ref11a	mixture of (4*S*,7*R*) and (4*R*,7*S*)		0.5 µM
Ref11b	mixture of (4*S*,7*S*) and (4*R*,7*R*)		> 36.0 µM
Ref11c	(4*S*,7*R*)		0.175 µM
Ref11d	(4R,7S)		2.0 µM
Ref12a	mixture of (4*S*,7*R*) and (4*R*,7*S*)		0.2 µM
Ref12b	mixture of (4*S*,7*S*) and (4*R*,7*R*)		> 30.0 µM
Ref12e	(4*S*,7*R*)		0.07 µM
Ref12f	(4R,7S)		2.5 µM
Ref13a	(4*S*,7*R*)	1.00	
Ref13d	(4R,7S)	0.09	
Ref13e	(4*S*,7*S*)	<0.01	
Ref13f	(4*R*,7*R*)	<0.01	

*RP (relative potency) calculated as [EC_{50} GFP inhibition **Ref13a**] / [EC_{50} GFP inhibition compound of interest] compound **Ref13a** from PCT-Patent Application PCT/EP2023/077188. The structures of the most active isomers are shown hereinabove, and other stereoisomers of the compounds are indicated by different letters after their respective numbers.

Table 5: Percent changes in GFP/RFP fluorescence upon compound treatment at 2 µM after 62 h. Particularly desirable is selective reduction of GFP values, with minimal alterations of RFP values.

Cpd. No.	GFP Values (%)	RFP Values (%)
DMSO	**100**	**100**
1h	79*	97*

2h	48	90
3h	78	102
4a	58	86
11h	68	88
17j	53	87
60a	52	87
72b	51	74
78h	72	97
81h	54	74
87k	79	88
87l	ns	ns
88a	68	78
91a	74	88
93	61	77
101j	71	77

*used at 1 µM. ns (not significant). The core structure configurations are indicated by letters after their respective numbers: a = (4*S*,7*R*)-configurated compounds, h = mixture of (4*S*,7*R*) and (4*R*,7*R*) -configurated compounds, j = mixture of (4*S*,7*S*) and (4*S*,7*R*)-configurated compounds, k = mixture of (4*S*,7*R*) and (4*R*,7*S*)-configurated compounds and l = mixture of (4*S*,7*S*) and (4*R*,7*R*)-configurated compounds.

Table 6: Relative potency (RP) values for coronin 1 promoter inhibition

Cpd. No.	**RP* GFP Inhibition**
5h	0.07
6h	0.10
7h	0.10
8h	0.09
9h	0.13
10h	0.09
15h	0.09
16h	0.14
18h	0.15
19h	1.22

21a	1.4
22h	0.14
23j	0.34
24j	0.34
25a	3.13
26a	0.65
28h	0.30
29h	0.60
30a	1.05
31a	2.48
32a	2.48
33a	4.82
34b	0.56
34a	3.7
35a	0.49
36a	1.62
37a	1.26
38a	0.79
39a	1.05
40a	0.57
41a	1.16
42a	3.98
43a	4.02
44a	5.27
45a	0.53
46a	5.88
47a	2.15
48a	5.64
49a	2.55
50a	3.82
51b	3.72
51a	3.48
52a	4.22

53a	3.85
54a	2.17
55a	3.46
56a	2.7
57a	1.08
58a	2.31
58b	1.45
59a	0.71
61a	4.54
62a	6.86
63a	5.85
64a	4.27
65b	1.54
65a	1.39
66a	1.14
66b	1.47
67a	1.31
68b	0.87
68a	1.73
69a	1.53
69b	2.65
71b	1.15
71a	1.16
73a	3.01
74a	0.77
75a	0.64
76a	1.4
77a	0.23
79b	1.19
80b	0.57
82b	3.33
83a	1.38
84a	1.32

85a	0.88
86a	0.11
89h	0.47
90a	0.25
92h	0.21
94a	2.21
95a	6.07
97a/97b/98 (45/45/10)	0.18
99a	1.72

*RP (relative potency) calculated as [EC_{50} GFP inhibition **Ref13a**] / [EC_{50} GFP inhibition compound of interest] compound **Ref13a** from PCT-Patent Application PCT/EP2023/077188. The core structure configurations are indicated by letters after their respective numbers: a-b = (4*S*,7*R*)-configurated compounds, h = mixture of (4*S*,7*R*) and (4*R*,7*R*)-configurated compounds and j = mixture of (4*S*,7*S*) and (4*S*,7*R*)-configurated compounds.

The characterization of the screening assay identified compounds together with the validation studies done in *in vitro* and *in vivo* biological assays shown in PCT-Patent Application PCT/EP2023/077188 reveals that the screening assay identified compounds are immunosuppressive in nature and are capable of inhibiting coronin 1 promoter activity.

Table 7: Sequences

SEQ ID NO:	Nucleic acid sequence
3	**Murine P1.5:** AAATAAATCCTGGTTCTCTGCAAGAACAGTGAGCGCTCTTCACCACTGAGCTGTCTCT CTAGCCCGGCACCTAGCTTATGTGATGCTGGAGGCCATGCCTTTATGCATGCTATGAG GTGTTCTGCCAGCTGAACTCCATTCTCAGCCCCATTACTGTTATCACTTTAGCTGGAGA CTCTAGAGTCGCTGGCTACAGTCACAGAGCCTCAGGCACTATCCAACCCTGTACTGA GTAACTGCAGAACACTTCAGACTACACCTTACGCACCGCACCGTTAGCTGTGAGGTG GGCAGGACTTCTTGTTTCTCTCCTACAGAAACTGAGGTTCAGGGAGGTGGGGCCTCTT GGCCAAGATCACACGGCTAATCAGTACAACTGGAGCCCCTTCTGTTCTTTCGAACTAC TTCTACCTTAAAGAAGAGTTTCTTCTGACTGGGTCTTGCTATGTAGCCCAGGCTGGCC TCCTGCCTCAGCTTCCTGACTACAGATGACTGTCAGCACACCTGTGTCCTTGAGCTTT GCTGACACTGCGCCTCAGCCCCCTACCCTTCTCCAGAGCCACTTGTGGTGTTTCCTCT TCCTCCCAGGATAGCCCAAAGCTTTGGTAAATGGCAATAATGAAAAGAACCAACATCT TTTGGGTTTTTGAAACAGGGTCTCACTATGTAGCCTTGGTCTGGAGCTTACATGTGGA CCAGGCTGGCCTTGGTTTCACTGACCCTTCTGCCTCTGCCTCCGTAGTAATGGATTTA CAGGTGTGGGCCACCATATCTGACTGTAAGACCCCAACACTAATTAATACCTGCCACT CTGTAGATGCAAATCCAGCTATCCTTGGAGTGACCATCTCCATACGAAGGCAGGTAAG ACTGTTATAGACAGGAAACTGGGGCTGAGATTAAATTAACCTGCCCAAGGTCACTCAA ATGAGTGACAGCCAGGAGTCACAACAATGGTTCCAGCAAAGGCCTTTCTTCCTCTGCC CTTGCTACCGTGACAACCCACTCCCCTCAAGGGACAGGAATGGACCACAGCCCAGCT GTGTGTGATATCAGACTTCTGTGTGTACTCAGTGGCTTTTAAACTGTGTCAGACGGAC TCCCGACTCCCTCTTCTCATGGCCCGAGAGCTCTCTAGAGGGGGAGCACTACTCATTT GCCTCCATAGCCCCAGCACAGAACAGGTGCTCCATAATGCCCAGTTATTTTACTTCTT CCGGGCCTCAATGCCACGAAGCAGAGGACAAGGGTGTCCCCGCTGAAGCCCTAAATC CCTAGAAAGGAGAAATGACCCCCCCAAGGCCTCCCAGAAATCCATTTGGGGTAACGA CAGGAGAGGTCCCTCCTGTAGCAGAGAAGGCTCTCAAGCTGGTTGAAGCCGTTCTAA AGCTTTCTCCGGTGCCAGGGAAAGGACCTCGAGGAGGCAGCGGGCGGCTGGGGGA GGGATGAAGGAACGGGATATTTTTGCGTTCTGACATTAAAAGAAGAGTTGATTCGCGT CAGCATCTGTTCGGGGGTTGGAGCTGACAGCATGGGGAGCGGTCCCAGTCTTGCAG CCCTGGAGCGAAGGGCCGGGCCTC**CATGAGCTCCGCCCAAAGGGGCGCTACCACC** **CGGAGGAGGCCGGCGCACGGCCGCTGCTCATTCATTGTCTTGACAGAGCA**

Coronin-1 Promoter Inhibitors

Throughout the present experimental description, a reference to C1PI (coronin-1 promoter inhibitors) is made. According to this indication, if an experiment was done with a compound referred to as C1PI, it means the experiment has been performed with a compound selected from the following compounds:

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (19a);
methyl-d3 (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (36a);
2-hydroxyethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (57a);
methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (21a);
2-hydroxy-2-methylpropyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (83a);
(1-hydroxycyclopropyl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (84a);
2-hydroxyethyl-1,1,2,2-d4 (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (85a);
(S)-4,4-difluoro-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (68a); and
(1-methyl-1H-pyrazol-4-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (52a).

EXAMPLE 9

To identify the target of the coronin 1 modulatory compounds, Protein Integral Solubility Analysis (PISA), a methodology based on the property of proteins to alter their thermal stability upon interactions with small molecules (Gaetani M et al., *J Proteome Res* (2019) 18, 4027-37), was employed. To that end, Rat Basophil Leukemia (RBL) or human acute monocytic leukemia (THP-1) cells were incubated with C1PI or controls followed by gradient thermal denaturation (47.9 to 59.1 degree C) and mass spectrometric assessment of proteins that get either stabilized or destabilized upon interacting with the compound performed. This procedure led to the identification of Bromodomain-containing 3 (BRD3) protein as the top hit to be stabilized by the C1PI (Figure 2). Interestingly, this was the only member to get stabilized amongst the *b*romodomain and *e*xtra-*t*erminal (BET) family of proteins. Currently there exists no compound that selectively targets BRD3, nor is an effect of selective BRD3 inhibition or BRD3 depletion through gene knock-out *in vivo* in animal models known.

The BET family consists of four members (BDR2, BRD3, BRD4 and BRDT) that are characterized by the presence of two bromodomains, namely Bromodomain 1 (BD1) and Bromodomain (BD2), that recognize acetylated N-terminal tails of histones thereby acting as readers of lysine acetylation state of chromatin. Moreover, by interacting with components of the transcriptional machinery and chromatin remodeling enzymes (Taniguchi, Y., Int J Mol Sci, 2016. **17**(11)), they regulate diverse transcriptional processes involving cell cycle, organogenesis, oncogenic and inflammatory pathways. The bromodomains of the four BET family members are highly conserved, about ~110 amino acids in length that fold in to bromodomain modules comprising of a left-handed bundle of four alpha helices (aZ, aA, aB, aC), linked by loop regions (ZA and BC loop) that contribute to substrate specificity (Fujisawa, T. and P. Filippakopoulos, Nat Rev Mol Cell Biol, 2017. **18**(4): p. 246-262.). While BRD2 and BRD4 are involved in cell cycle regulation, learning and memory and inflammation (Korb, E., et al., Nat Neurosci, 2015. **18**(10): p. 1464-73, Belkina, A.C., et.al, J Immunol, 2013. **190**(7): p. 3670-8, LeRoy, et. Al, Mol Cell, 2008. **30**(1): p. 51-60), a function for BRD3 is less clear and has been suggested to be redundant with BRD2 (Stonestrom, A.J., et al., Blood, 2015. **125**(18): p. 2825-34).

"BET inhibitors" are compounds that interact with these bromodomains BD1 and BD2 to inhibit their function. Compounds that interact with these bromodomains non-selectively by binding to both BD1 and BD2 have been identified with the small molecule JQ1 being the predecessor (Filippakopoulos, P., et al., Nature, 2010. **468**(7327): p. 1067-73). However, such compounds have toxicities due to non-selectivity and inhibition of all the BET family members (Shorstova, T., et. Al. Br J Cancer, 2021. **124**(9): p. 1478-1490, Qi, J. and Y. Shi, Cancer Cell, 2020. **37**(6): p. 764-766). To minimize these issues, compounds that selectively bind with either BD1 of all the BET family or BD2 of the BET family have been recently developed and characterized (Gilan, O., et al., Science, 2020. **368**(6489): p. 387-394, Faivre, E.J., et al., Nature, 2020. **578**(7794): p. 306-310). However, no compound that selectively targets BRD3 is reported in the literature to the best of our knowledge. Interestingly, with our C1PI compounds, BRD3 was the only member to get stabilized in a statistically significant manner amongst the BET family of proteins. The profiles for BRD2 and BRD4 revealed insignificant changes. A similar observation was made with **Ref12e** from PCT-Patent Application PCT/EP2023/077188 in a related method called Thermal Proteome Profiling. These observations, strikingly contrast with the reported thermal stability data for other BET inhibitory compounds (JQ1, IBET-BD1, IBET-BD2, RVX-208, IBET-151, ABBV-744) that trigger thermal stabilization of BRD2, BRD3 and BRD4 proteins by binding to their bromodomains BD1 and/or BD2. Currently, there exists no compound that selectively targets BRD3, nor is an effect of selective BRD3 inhibition or BRD3 depletion through gene knock-out *in vivo* in animal models well characterized. BRD3 depletion in cellular systems and mice seems to be better tolerated in comparison to BRD2 or BRD4

depletion, but further characterization is needed (see www.mousephenotype.org – insofar BRD2/3/4 is concerned – assessed on April 2, 2025; Shang E et al. Dev Dynamics (2009), 238, 908-917; Houzelstein D et al. Mol Cell Biol (2002), 22, 3794-3802; Stonestrom AJ et al. Blood (2015), 125, 2825-2834).

To assess the role of BRD3 in regulating coronin 1 expression, RBL cells expressing GFP under the control of the coronin 1 promoter were treated with siRNA or CRISPR/Cas9 targeting brd3 that resulted in significant downregulation of coronin 1 promoter driven GFP and coronin 1 levels significantly (Fig. 3). Together these data suggest that the compounds bind to BRD3 thereby repressing coronin 1 transcription.

Protein Integral Solubility Analysis (PISA):

PISA was performed as described (Gaetani M et al., *J Proteome Res* (2019) 18, 4027-37). In brief, THP-1 or RBL cells were incubated with the vehicle DMSO, C1PI or ABBV-744 at 6 μM concentration for a period of 1 h at the end of which, the cells were washed in ice cold PBS, counted and subjected to thermal denaturation (47.9 to 59.1 °C) for 3 minutes, lysed by freeze thawing in liquid nitrogen, pooled and supernatant containing the soluble proteins were pooled and separated by centrifugation at 100'000 g for 30 minutes. Equal volumes of the supernatant were taken, subjected to tryptic digestion and the peptides analyzed and quantitated using mass spectrometry.

BRD3 siRNA analysis:

Accel siRNAs against brd3 (target specific siRNA) and a control siRNA (non-targeting siRNA) were purchased from Dharmacon Horizon Discovery and 100 mM stocks prepared in the supplied siRNA buffer. In parallel, 5000 cells (WT RBL or GFP RBL cells) were seeded per well with 200 mL of Accell media in a 48 well plate. siRNA was added from the prepared stock into appropriately labelled wells at a final concentration of 1 μM. The plate was incubated at 37°C for 72h with 5% CO2 and at the end, washed with FACS buffer (PBS with 2% Fetal calf serum and 10 mM EDTA) and further incubated for 20 minutes on ice with Live-dead marker (Thermofisher) in FACS buffer. The cells were washed once again in FACS buffer and acquired using a flow cytometer (BD Fortessa) and the GFP fluorescence analyzed using the program FlowJo (TreeStar) and the suppression of coronin 1 promoter activity assessed as a measure of GFP reduction (Fig. 3A).

BRD3 gene knock out RBL cells using CRISPR/Cas9 approach:

The plasmid containing two gRNA targeting rat Brd3 gene for generating brd3 knockouts in RBL cells was generated at VectorBuilder (Neu-Isenburg, Germany) using as gRNA#1

(TGGGATGCCAAGCCTTCCCG) (SEQ ID NO.: 1) and gRNA#6771 (AGGGCTTCGCTGCCGATATC) (SEQ ID NO.: 2) followed by a protospacer adjacent motif (PAM) from *Streptococcus pyogenes* targeting exon 2 and exon 7, respectively. RBL cells ($2.5x10^5$) were transfected with 0.5 µg of plasmid by electroporation at 1200V, 20 ms and 2 pulses in 10 µL Neon™ Transfection System pipette using the Neon™ Transfection System (Invitrogen) according to the manufacturer guidelines.

Transfected puromycin resistant cells were selected and single cells clones expanded in 96-well tissue culture plate and screened for BRD3 and coronin 1 expression by flow cytometric analysis of the median fluorescence intensity (MFI) from intracellularly-stained cells (Fig. 3B).

BRD3 Bromoscan analysis:

T7 phage strains displaying bromodomains were grown in 24-well blocks in an *E. coli* host derived from the BL21 strain. *E. coli* were grown to log-phase and infected with T7 phage from a frozen stock (multiplicity of infection = 0.4) and incubated with shaking at 32°C until lysis (90-150 minutes). The lysates were centrifuged (5,000 x g) and filtered (0.2µm) to remove cell debris. Streptavidin-coated magnetic beads were treated with biotinylated small molecule or acetylated peptide ligands for 30 minutes at room temperature to generate affinity resins for bromodomain assays. The liganded beads were blocked with excess biotin and washed with blocking buffer (SeaBlock (Pierce), 1 % BSA, 0.05 % Tween 20, 1 mM DTT) to remove unbound ligand and to reduce non-specific phage binding. Binding reactions were assembled by combining bromodomains, liganded affinity beads, and test compounds in 1x binding buffer (17% SeaBlock, 0.33x PBS, 0.04% Tween 20, 0.02% BSA, 0.004% Sodium azide, 7.4 mM DTT). Test compounds were prepared as 1000X stocks in 100% DMSO. Kds were determined using an 11-point 3-fold compound dilution series with one DMSO control point. All compounds for Kd measurements are distributed by acoustic transfer (non-contact dispensing) in 100% DMSO. The compounds were then diluted directly into the assays such that the final concentration of DMSO was 0.09%. All reactions performed in polypropylene 384-well plates. Each was a final volume of 0.02 ml. The assay plates were incubated at room temperature with shaking for 1 hour and the affinity beads were washed with wash buffer (1x PBS, 0.05% Tween 20). The beads were then resuspended in elution buffer (1x PBS, 0.05% Tween 20, 2 µM non-biotinylated affinity ligand) and incubated at room temperature with shaking for 30 minutes. The bromodomain concentration in the eluates was measured by qPCR. The bromoscan analysis results are shown in Table 8.

Table 8 Bromoscan method based assessment of binding affinity of the indicated compounds against the Bromodomain 1 (BD1) and Bromodomain 2 (BD2) of BRD3.

	BRD3(BD1)	**BRD3(BD2)**

Compound Name	Kd (nM)	Kd (nM)
13a	340	8.6
20a	68	1.7
35a	25	0.26
36a	80	0.62
45a	46	0.51
52a	23	0.82
57a	41	0.53
62a	30	0.77
65a	15	0.35
83a	44	0.60

EXAMPLE 10

Imiquimod-induced psoriasis and qPCR analysis of inflammatory cytokines from inflamed ears:

The experiments were performed with wild type mice (BALB/c strain, 8 weeks), males, their dorsal skin was shaved with a trimmer on an area of ~ 2 cm2 and subjected to topical application of 5% imiquimod cream (Aldara) on the dorsal site as well the right ears starting from day 1 and continued for up to 7 days in the morning. For compound administration, the indicated compounds were applied through per-oral route (perorally), twice a day at the indicated dose starting day 1 and throughout the duration of the experiment up to day 7 (however, as apparent to the skilled person, the experiment could also be performed using another route of administration, such as intraperitoneal administration route or subcutaneous administration route). Administered was a compound referred to as C1PI compound. Mice were scored every day to arrive at the PASI score of the inflammatory lesion as follows:

Grade	Erythema	Scales	Skin thickening
0	No	No	Normal skin
1	Mild	Thin flakes	Mild
2	Moderate	Moderate flakes	Moderate
3	Severe (< 1 cm2)	Thick flakes (<1 cm2)	Rough and hard
4	Severe (>1 cm2)	Thick flakes (>1 cm2)	Un-foldable

On day 7, the mice were sacrificed and the right ears, processed in Trizol to extract the RNA followed by means of qPCR for various inflammatory markers (coronin 1 and interleukin-17) and using SYBR green reaction mix on a StepOnePlus Real-Time PCR System using StepOne v2.2 software (both from Applied Biosystems). Results were analyzed using the comparative CT method based on standard method recommended by the kit manufacturer. The data is presented in Fig. 4A/B. According to the present inventors, the error bars are in part due to strong inter animal differences. The PASI score was checked for significance using unpaired T-test against the vehicle treated group, p value < 0.0001 = ****. The fold change in qPCR was checked for significance using unpaired T-test against the vehicle treated group, p < 0.05 = *, p < 0.001 = *** and p < 0.0001 = ****.

The primers used are as follows

B2MForward: 5'-ACC GTC TAC TGG GAT CGA GA-3' (SEQ ID NO: 4)

B2MReverse: 5'-TGC TAT TTC TTT CTG CGT GCA T-3' (SEQ ID NO: 5)

Cor1Forward: 5'-TGG CTC TGA TCT GTG AGG C-3' (SEQ ID NO: 6)

Cor1Reverse: 5'-TCT TGT CTA CTC GTC CAG TCT-3' (SEQ ID NO: 7)

IL-17aForward: 5'-CCT GGA CTC TCC ACC GCA A-3' (SEQ ID NO: 8)

IL-17aReverse: 5'-TTC CCT CCG CAT TGA CAC AG-3' (SEQ ID NO: 9)

TNFαForward: 5'-GTC CCC AAA GGG ATG AGA AGT-3' (SEQ ID NO: 10)

TNFαReverse: 5'-TTT GCTACG ACG TGG GCTAC-3' (SEQ ID NO: 11)

EXAMPLE 11

OT-II T cell responses against ova-peptide presented in infectious context and auto-antigenic context:

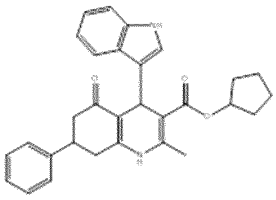
OT-II T cells (as responders) that recognize the 323-339 chicken ovalbumin peptide, were isolated from the spleens of OT-II mice (C57BL/6) using the StemCell total T cell isolation kit (#19851) and seeded in U-bottom 96 well plates at a cell density of 200'000 cells/well. To mimic infectious context, splenocytes (as stimulators) from OT-II mice were co-cultured with heat-killed OVA-expressing Salmonella typhimurium at OD_{600} 0.1 for 6 hours at 37 °C/5% CO_2 and subjected to mitomycin (25 µg/ml for 1 h, 37 degrees/5% CO_2). Likewise, to mimic a "self" immune context, splenocytes (as stimulators) isolated from Act-mOVA mice (C57BL/6) that express chicken ovalbumin was as well subjected to mitomycin treatment as above. In defined wells, these stimulator cells were seeded at 300'000 cells/well in the presence and absence of the indicated compounds (3 µM). After 4 days of incubation, tritiated thymidine (0.25 µCi) was added. Cells were further incubated for 20-24 h followed by freeze-thawing and harvesting on a GF/C filter and measuring the DNA-incorporated counts using a Packard instrument as a measure of T cell responses. The data is presented in Figure 5.

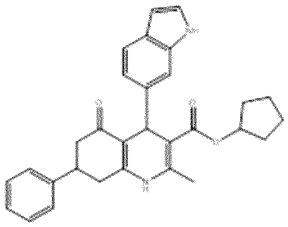
EXAMPLE 12

Cpd. No.	Structure	Compound name
200		cyclopentyl 4-(1H-indol-3-yl)-2-methyl-5-oxo-7-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (Ref20)
201		cyclopentyl 4-(1H-indol-6-yl)-2-methyl-5-oxo-7-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (Ref21)

Example Procedure q: 200

In a microwave vial, 1H-indole-3-carbaldehyde (10.0 mg, 0.07 mmol), cyclopentyl 3-oxobutanoate (12.0 mg,0.07 mmol), 3-butyl-1-methyl-1H-imidazol-3-ium tetrafluoroborate (1.5 uL, 8.02 umol), 5-phenylcyclohexane-1,3-dione (12.8 mg, 0.07 mmol), acetic acid;ammonia (7.9 mg, 0.10 mmol) was added. The reaction mixture was stirred at 90 °C for 25 min. The crude material was purified by Flash chromatography on silica gel using a gradient of heptane in ethyl acetate from 0% to 50%. Fractions were combined and evaporated to afford the title compound.

Structure Cpd. No.	NMR Mixture of 2 diastereomers	MS
 **200**	(65/35) 1H NMR (500 MHz, DMSO-d6) δ 10.66 (d, J = 2.3 Hz, 0.65H), 10.62 (d, J = 2.5 Hz,0.35H), 9.20 (s, 0.65H), 9.11 (s, 0.35H), 7.68 – 7.57 (m, 1H), 7.35 – 7.21 (m, 5H), 7.19 – 7.13 (m, 1H), 7.02 – 6.97 (m, 1H),6.94 – 6.80 (m, 2H), 5.18 (s, 1H), 5.14 (s, 0.65H), 5.01 – 4.97 (m, 0.35H), 3.44 – 3.37 (m, 0.35H), 3.12 – 3.06 (m, 0.65H),2.81 – 2.63 (m, 2H), 2.58 – 2.52 (m, 1H), 2.49 – 2.39 (m, 1H), 2.31 – 2.26 (m, 3H), 1.80 – 1.70 (m, 1H), 1.68 – 1.55 (m, 3H),1.53 – 1.41 (m, 3H), 1.37 – 1.30 (m, 1H)	M/z = 465 [M–H]-, Rt = 3.18 and 3.20 min (Method A21)

 **201**	(65/35) 1H NMR (500 MHz, DMSO-d6) δ 10.91 – 10.81 (m, 1H), 9.13 (s, 0.65H), 9.03 (s, 0.35H), 7.36 – 7.28 (m, 4H), 7.25 – 7.15 (m, 4H), 6.95 – 6.81 (m, 1H), 6.31 – 6.29 (m, 1H), 5.02 – 4.92 (m, 2H), 3.44 – 3.39 (m, 0.35H),3.17 – 3.10 (m, 0.65H), 2.82 – 2.71 (m, 1H), 2.69 – 2.53 (m, 2H), 2.49 – 2.41 (m, 1H), 2.36 – 2.28 (m, 4H), 1.78 – 1.72 (m,1H), 1.68 – 1.45 (m, 5H), 1.41 – 1.33 (m, 1H)	M/z = 467 [M+H]+, Rt = 8.40 and 8.55 min (Method A20)

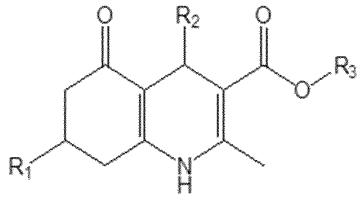
Activity data

Table 9: Percent changes in GFP/RFP fluorescence upon compound treatment at 2 µM after 62 h. Particularly desirable is selective reduction of GFP values, with minimal alterations of RFP values.

Cpd. No.	GFP Values (%)	RFP Values (%)
201	81	92

CLAIMS

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt, stereoisomer, diastereoisomer, enantiomer, polymorph, racemic mixture, or solvate thereof, wherein:

R_1 is selected from phenyl, a monocyclic heteroaryl containing at least one N atom (such as pyridyl) and thienyl, wherein said phenyl and said pyridyl are each optionally substituted with one or more optional substituents independently selected from -OH, -NO_2, -NH_2, -CN, halogen, -C_1-C_6-alkyl, –O-C_1-C_6-alkyl, and –O-C_1-C_6-haloalkyl;

R_2 is a bicyclic heteroaryl, optionally substituted with one or more groups selected from R_S, a monocyclic heteroaryl containing at least one N atom, optionally substituted with one or more groups selected from R_S, or naphtalenyl optionally substituted with one or more groups selected from R_S;

R_3 is selected from –C_1-C_8-alkyl, –(C_1-C_6-alkylene)-S–C_1-C_6-alkyl, –(C_1-C_6-alkylene)-SO_2–C_1-C_6-alkyl, –(C_1-C_6-alkylene)-OH, –(C_1-C_6-alkylene)-O–C_1-C_6-alkyl, –(C_2-C_4-alkylene–O)$_m$–H wherein m is an integer from 1 to 10 (preferably from 1 to 5, more preferably from 2 to 3, even more preferably 2), –(C_2-C_4-alkylene–O)$_m$–(C_1-C_6-alkyl) wherein m is an integer from 1 to 10 (preferably from 1 to 5, more preferably from 2 to 3, even more preferably 2), –C_1-C_6-alkylene-cycloalkyl, cycloalkyl, –C_1-C_6-alkylene-(oxygen-containing saturated heterocyclyl), oxygen-containing saturated heterocyclyl, –C_1-C_6-alkylene-(sulfur-containing saturated heterocyclyl), sulfur-containing saturated heterocyclyl, –C_1-C_6-alkylene-(nitrogen-containing saturated heterocyclyl), nitrogen-containing saturated heterocyclyl, –C_1-C_6-alkylene-(5 or 6-membered heteroaryl), 5 or 6-membered heteroaryl, –C_1-C_6-alkylene-aryl and aryl;

wherein said –C_1-C_8-alkyl is optionally substituted with one or more groups selected from Hal and -OH;

wherein said cycloalkyl, the cycloalkyl in the –C_1-C_6-alkylene-cycloalkyl, the oxygen-containing saturated heterocyclyl moiety in said –C_1-C_6-alkylene-(oxygen-containing saturated heterocyclyl), said oxygen-containing saturated heterocyclyl, the nitrogen-containing saturated heterocyclyl moiety in said –C_1-C_6-

alkylene-(nitrogen-containing saturated heterocyclyl), said nitrogen-containing saturated heterocyclyl, the sulfur-containing saturated heterocyclyl moiety in said –C_1-C_6-alkylene-(sulfur-containing saturated heterocyclyl), said sulfur-containing saturated heterocyclyl, the 5 or 6-membered heteroaryl moiety in said –C_1-C_6-alkylene-(5 or 6-membered heteroaryl), said 5 or 6-membered heteroaryl, the aryl moiety in said –C_1-C_6-alkylene-aryl and said aryl are each optionally substituted with one or more groups selected from R_S; and

each R_S is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-OH, -(C_{0-3} alkylene)-O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-OH, -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-OH, -(C_{0-3} alkylene)-NH-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-O(C_{1-5} alkyl), -(C_{0-3} alkylene)-halo, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-O-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-NO_2, -(C_{0-3} alkylene)-CHO, -(C_{0-3} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-O-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-NH-(C_{1-5} alkyl), -(C_{0-3} alkylene)-O-CO-N(C_{1-5} alkyl)-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-NH_2, -(C_{0-3} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(O)(NH)(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(O)(N(C_{1-5} alkyl))(C_{1-5} alkyl), -(C_{0-3} alkylene)-N=S(O)(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-P(O)(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-P(O)(O(C_{1-5} alkyl))(O(C_{1-5} alkyl)), -(C_{0-3} alkylene)-P(O)(O(C_{1-5} alkyl))(C_{1-5} alkyl), -(C_{0-3} alkylene)-carbocyclyl, and -(C_{0-3} alkylene)-heterocyclyl, wherein the carbocyclyl moiety in said -(C_{0-3} alkylene)-carbocyclyl and the heterocyclyl moiety in said -(C_{0-3} alkylene)-heterocyclyl are each optionally substituted with one or more groups independently selected from C_{1-4} alkyl, halo, -CN, -NO_2, -OH, -O-(C_{1-4} alkyl), -SH, -S-(C_{1-4} alkyl), -NH_2, -NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)(C_{1-4} alkyl), -COOH, -COO(C_{1-4} alkyl), -$CONH_2$, -CONH(C_{1-4} alkyl), -CON(C_{1-4} alkyl)(C_{1-4} alkyl), -NHCO(C_{1-4} alkyl) and -N(C_{1-4} alkyl)-CO(C_{1-4} alkyl).

2. The compound of claim 1, wherein R_1 is selected from phenyl and pyridyl, wherein said phenyl and said pyridyl are each optionally substituted with one or more optional substituents independently selected from -OH, -NO_2, halogen, –O-C_1-C_6-alkyl and –O-C_1-C_6-haloalkyl.

3. The compound of claim 2, wherein R_1 is selected from phenyl, wherein said phenyl is optionally substituted with one or more –O-C_1-C_6-alkyl.

4. The compound of claim 3, wherein R_1 is phenyl optionally substituted with methoxy.

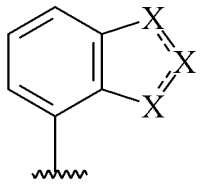
5. The compound of any one of claims 1 to 4, wherein R_1 is selected from 2-methoxyphenyl and phenyl.

6. The compound of claim 5, wherein R_1 is 2-methoxyphenyl.

7. The compound of any one of claims 1 to 6, wherein R_2 is a bicyclic heteroaryl containing at least one N atom optionally substituted with one or more groups selected from R_S.

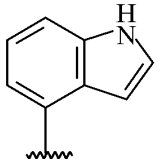
8. The compound of claim 7, wherein the bicyclic heteroaryl in R_2 includes a benzene ring fused to a 5 membered heteroaryl ring including at least one N atom, connected to the rest of the molecule through said benzene ring, wherein said phenyl ring and said 5-membered heteroaryl ring are each optionally substituted with one or more groups selected from R_S.

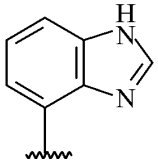
9. The compound of claim 7 or 8, wherein R_2 is of formula:

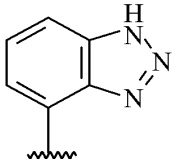


wherein each X is independently selected from CH, O, S, N and NH, provided that at least one X is N or NH, wherein the moiety is further optionally substituted with one or more groups selected from R_S, preferably with one or more groups selected from halogen, -CN, -OH, -O-(C_{1-5} alkyl) and C_{1-5} alkyl.

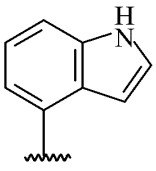
10. The compound of claim 9, wherein R_2 is selected from:

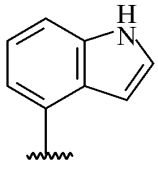


, 

, and 

, wherein each of depicted moieties is optionally substituted with one or more groups selected from R_S, preferably with or more groups selected from halogen, -CN, -OH, -O-(C_{1-5} alkyl) and C_{1-5} alkyl.

11. The compound of claim 10, wherein R_2 is  optionally substituted with one or more groups selected from R_S, preferably with or more groups selected from halogen, -CN, -OH, -O-(C_{1-5} alkyl) and C_{1-5} alkyl.

12. The compound of any one of claims 9 to 11, wherein R_2 is .

13. The compound of any one of claims 1 to 12, wherein R_3 is selected from –C_1-C_8-alkyl, –(C_1-C_6-alkylene)-S–C_1-C_6-alkyl, –(C_1-C_6-alkylene)-SO_2–C_1-C_6-alkyl, –(C_1-C_6-alkylene)-OH, –(C_1-C_6-alkylene)-O–C_1-C_6-alkyl, –(C_2-C_4-alkylene–O)$_m$–H wherein m is an integer from 1 to 10 (preferably from 1 to 5, more preferably from 2 to 3, even more preferably 2), –(C_2-C_4-alkylene–O)$_m$–(C_1-C_6-alkyl) wherein m is an integer from 1 to 10 (preferably from 1 to 5, more preferably from 2 to 3, even more preferably 2), –C_1-C_6-alkylene-cycloalkyl, cycloalkyl, –C_1-C_6-alkylene-(oxygen-containing saturated heterocyclyl), oxygen-containing saturated heterocyclyl, –C_1-C_6-alkylene-(nitrogen-containing saturated heterocyclyl), nitrogen-containing saturated heterocyclyl, –C_1-C_6-alkylene-(5 or 6-membered heteroaryl), 5 or 6-membered heteroaryl, –C_1-C_6-alkylene-aryl and aryl,

wherein said –C_1-C_8-alkyl is optionally substituted with one or more groups selected from Hal and -OH;

wherein said cycloalkyl, the cycloalkyl in the –C_1-C_6-alkylene-cycloalkyl, the oxygen-containing saturated heterocyclyl moiety in said –C_1-C_6-alkylene-(oxygen-containing saturated heterocyclyl), said oxygen-containing saturated heterocyclyl, the nitrogen-containing saturated heterocyclyl moiety in said –C_1-C_6-alkylene-(nitrogen-containing saturated heterocyclyl), said nitrogen-containing saturated heterocyclyl, the 5 or 6-membered heteroaryl moiety in said –C_1-C_6-alkylene-(5 or 6-membered heteroaryl), said 5 or 6-membered heteroaryl, the aryl moiety in said –C_1-C_6-alkylene-aryl and said aryl are each optionally substituted with one or more groups selected from R_S.

14. The compound of any one of claims 1 to 13, wherein R_3 is selected from –C_1-C_8-alkyl, –(C_1-C_6-alkylene)-S–C_1-C_6-alkyl, –(C_1-C_6-alkylene)-OH, –(C_2-C_4-alkylene–O)$_m$–H wherein m is an integer from 1 to 10 (preferably from 1 to 5, more preferably from 2 to 3, even more preferably 2), –(C_1-C_6-alkylene)-O–C_1-C_6-

alkyl, –(C_2-C_4-alkylene–O)$_m$–(C_1-C_6-alkyl) wherein m is an integer from 1 to 10 (preferably from 1 to 5, more preferably from 2 to 3, even more preferably 2), –C_1-C_6-alkylene-cycloalkyl, and cycloalkyl, wherein said cycloalkyl, and the cycloalkyl in the –C_1-C_6-alkylene-cycloalkyl are each optionally substituted with one or more groups selected from R_S.

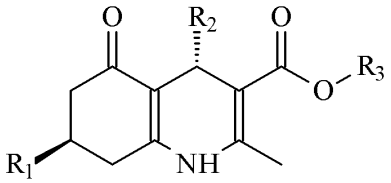
15. The compound of any one of claims 1 to 13, wherein R_3 is selected from –C_1-C_6-alkylene-(oxygen-containing saturated heterocyclyl), oxygen-containing saturated heterocyclyl, –C_1-C_6-alkylene-(sulfur-containing saturated heterocyclyl), and sulfur-containing saturated heterocyclyl, wherein the oxygen-containing saturated heterocyclyl moiety in said –C_1-C_6-alkylene-(oxygen-containing saturated heterocyclyl), said oxygen-containing saturated heterocyclyl, the sulfur-containing saturated heterocyclyl moiety in said –C_1-C_6-alkylene-(sulfur-containing saturated heterocyclyl), and said sulfur-containing saturated heterocyclyl are each optionally substituted with one or more groups selected from R_S.

16. The compound of claim 15, wherein R_3 is –C_1-C_6-alkylene-(oxygen-containing saturated heterocyclyl), or oxygen-containing saturated heterocyclyl, wherein the oxygen-containing saturated heterocyclyl moiety in said –C_1-C_6-alkylene-(oxygen-containing saturated heterocyclyl), and said oxygen-containing saturated heterocyclyl, are each optionally substituted with one or more groups selected from R_S.

17. The compound of any one of claims 1 to 13, wherein R_3 is –C_1-C_6-alkylene-(nitrogen-containing saturated heterocyclyl), or nitrogen-containing saturated heterocyclyl, wherein the nitrogen-containing saturated heterocyclyl moiety in said –C_1-C_6-alkylene-(nitrogen-containing saturated heterocyclyl), and said nitrogen-containing saturated heterocyclyl are each optionally substituted with one or more groups selected from R_S.

18. The compound of any one of claims 1 to 13, wherein R_3 is –C_1-C_6-alkylene-(5 or 6-membered heteroaryl), 5 or 6-membered heteroaryl, –C_1-C_6-alkylene-aryl or aryl, wherein the 5 or 6-membered heteroaryl moiety in said –C_1-C_6-alkylene-(5 or 6-membered heteroaryl), said 5 or 6-membered heteroaryl, the aryl moiety in said –C_1-C_6-alkylene-aryl and said aryl are each optionally substituted with one or more groups selected from R_S.

19. The compound of any one of claims 1 to 18, wherein the compound of formula (I) has an absolute configuration of its stereogenic centers as shown in the formula:



wherein R_1, R_2 and R_3 are as defined in any one of claims 1 to 18.

20. The compound of claim 1, selected from the group consisting of:

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(4-(dimethylamino)naphthalen-1-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (1a);

tetrahydro-2H-pyran-4-yl (4S,7R)-8'-fluoro-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-[4,4'-biquinoline]-3-carboxylate (2a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(3-acetamidopyridin-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (3a);

methyl (4S,7R)-4-(1H-indol-4-yl)-2-methyl-5-oxo-7-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(benzofuran-6-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(benzo[d]oxazol-5-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (6a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(benzo[d]thiazol-5-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (7a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(benzo[d]thiazol-6-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (8a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(1H-indol-5-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (9a);

tetrahydro-2H-pyran-4-yl (4S,7R)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-[4,4'-biquinoline]-3-carboxylate (10a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(isoquinolin-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (11a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(4-fluoronaphthalen-1-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (12a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(1H-indol-6-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (13a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(isoquinolin-5-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (14a);

tetrahydro-2H-pyran-4-yl (4S,7R)-7-(2-methoxyphenyl)-2-methyl-4-(1-methyl-1H-indol-3-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (15a);

tetrahydro-2H-pyran-4-yl (4S,7R)-7-(2-methoxyphenyl)-2-methyl-5-oxo-4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (16a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(1H-indazol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (17a);

tetrahydro-2H-pyran-4-yl (4S,7R)-7-(2-methoxyphenyl)-2-methyl-4-(7-methyl-1H-indol-4-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (18a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (19a);

tetrahydro-2H-pyran-4-yl (4S,7R)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydro-[4,5'-biquinoline]-3-carboxylate (20a);

methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (21a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(7-cyano-1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (22a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(1H-benzo[d][1,2,3]triazol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (23a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(1H-benzo[d]imidazol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (24a);

4-methyltetrahydro-2H-pyran-4-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (25a);

tert-butyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (26a);

benzyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (27a);

4-methoxybenzyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (28a);

2-nitrobenzyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (29a);

(1-methyl-1H-imidazol-5-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (30a);

oxazol-2-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (31a);

3-(methylsulfonyl)benzyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (32a);

thiazol-5-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (33a);

(1R,3s,5S)-8-oxabicyclo[3.2.1]octan-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (34a);

(1R,3r,5S)-8-oxabicyclo[3.2.1]octan-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (34b);

(S)-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (35a);

(R)-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (35b);

methyl-d3 (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (36a);

ethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (37a);

isopropyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (38a);

cyclopropyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (39a);

cyclopropylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (40a);

furan-3-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (41a);

oxazol-5-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (42a);

isoxazol-5-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (43a);

(1-methyl-1H-pyrazol-5-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (44a);

2-(methylsulfonyl)ethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (45a);

isoxazol-3-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (46a);

pyrimidin-2-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (47a);

pyrimidin-4-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (48a);

isothiazol-3-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (49a);

isothiazol-4-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (50a);

(S)-tetrahydrofuran-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (51a);

(R)-tetrahydrofuran-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (51b);

(1-methyl-1H-pyrazol-4-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (52a);

isothiazol-5-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (53a);

2-(2-methoxyethoxy)ethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (54a);

(1-methyl-1H-pyrazol-3-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (55a);

2-methoxyethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (56a);

2-hydroxyethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (57a);

((S)-tetrahydrofuran-2-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (58a);

((R)-tetrahydrofuran-2-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (58b);

2-(2-hydroxyethoxy)ethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (59a);

difluoromethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (60a);

pyridin-2-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (61a);

pyridin-3-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (62a);

isoxazol-4-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (63a);

pyridin-4-ylmethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (64a);

(S)-1-methylpiperidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (65a);

(R)-1-methylpiperidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (65b);

(S)-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (66a);

(R)-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (66b);

(S)-1-methyl-6-oxopiperidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (67a);

(R)-1-methyl-6-oxopiperidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (67b);

(S)-4,4-difluoro-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (68a);

(R)-4,4-difluoro-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (68b);

(S)-1-(2,2-difluoroethyl)pyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (69a);

(R)-1-(2,2-difluoroethyl)pyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (69b);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(7-fluoro-1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (70a);

(S)-1-methyl-5-oxopyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (71a);

(R)-1-methyl-5-oxopyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (71b);

(S)-5-oxopyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (72a);

(R)-5-oxopyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (72b);

4-(methylsulfonyl)benzyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (73a);

3-(methylsulfonyl)propyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (74a);

4-(methylsulfonyl)butyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (75a);

1,1-dioxidotetrahydro-2H-thiopyran-4-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (76a);

2,2,2-trifluoroethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (77a);

tetrahydro-2H-pyran-4-yl (4S,7R)-7-(2-methoxyphenyl)-2-methyl-4-(6-nitropyridin-2-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (78a);

(S)-5,5-difluoro-1-methylpiperidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (79a);

(R)-5,5-difluoro-1-methylpiperidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (79b);

(S)-1-(cyanomethyl)pyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (80a);

(R)-1-(cyanomethyl)pyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (80b);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(2-aminothiazol-5-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (81a);

(S)-1-(2-fluoroethyl)pyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (82a);

(R)-1-(2-fluoroethyl)pyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (82b);

2-hydroxy-2-methylpropyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (83a);

(1-hydroxycyclopropyl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (84a);

2-hydroxyethyl-1,1,2,2-d4 (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (85a);

methyl (4S,7R)-7-(2-bromophenyl)-4-(1H-indol-4-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (86a);

methyl (4S,7R)-4-(1H-indol-4-yl)-2-methyl-5-oxo-7-(pyridin-2-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (87a);

methyl (4S,7R)-7-(2-aminophenyl)-4-(1H-indol-4-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (88a);

methyl (4S,7R)-4-(6-fluoro-1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (89a);

methyl (4S,7R)-4-(1H-indol-4-yl)-2-methyl-5-oxo-7-(o-tolyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (90a);

methyl (4S,7R)-7-(2-hydroxyphenyl)-4-(1H-indol-4-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (91a);

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(6-aminopyridin-2-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (92a);

methyl (4S,7R)-4-(1H-indol-4-yl)-7-(3-methoxypyridin-4-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (93a);

2-(2,2,2-trifluoroethyl)-2-azaspiro[3.3]heptan-6-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (94a);

(6-cyanopyridin-2-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (95a);

(3S,5S)-5-(methoxycarbonyl)-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (96a);

(3R,5S)-5-(methoxycarbonyl)-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (96b);

(3S,5R)-5-(methoxycarbonyl)-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (96c);

(3R,5R)-5-(methoxycarbonyl)-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (96d);

(S)-2,3-dihydroxypropyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (97a);

(R)-2,3-dihydroxypropyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (97b);

1,3-dihydroxypropan-2-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (98a);

methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-(methoxy-d3)phenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (99a);

methyl-d3 (4S,7R)-4-(1H-indol-4-yl)-7-(2-(methoxy-d3)phenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (100a); and

methyl (4S,7R)-4-(1H-indol-4-yl)-2-methyl-5-oxo-7-(2-(trifluoromethoxy)phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (101a),

or a pharmaceutically acceptable salt thereof.

21. The compound of claim 1, selected from the group consisting of

tetrahydro-2H-pyran-4-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (19a);

methyl-d3 (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (36a);

2-hydroxyethyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (57a);

methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (21a);

2-hydroxy-2-methylpropyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (83a);

(1-hydroxycyclopropyl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (84a);

2-hydroxyethyl-1,1,2,2-d4 (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (85a);

(S)-4,4-difluoro-1-methylpyrrolidin-3-yl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (68a); and

(1-methyl-1H-pyrazol-4-yl)methyl (4S,7R)-4-(1H-indol-4-yl)-7-(2-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (52a);

or a pharmaceutically acceptable salt thereof.

22. A pharmaceutical composition comprising a compound of any one of claims 1 to 21 or a pharmaceutically acceptable salt, stereoisomer, diastereoisomer, enantiomer, polymorph, racemic mixture, or solvate thereof and a pharmaceutically acceptable carrier.

23. The compound of any one of claims 1 to 21 or a pharmaceutically acceptable salt, stereoisomer, diastereoisomer, enantiomer, polymorph, racemic mixture, or solvate thereof, or the pharmaceutical composition of claim 22 for use as a medicament.

24. The compound of any one of claims 1 to 21 or a pharmaceutically acceptable salt, stereoisomer, diastereoisomer, enantiomer, polymorph, racemic mixture, or solvate thereof, or the pharmaceutical composition of claim 22 for use in the induction of immunosuppression or in the treatment and/or prevention of a disease or disorder selected from the group consisting of transplant rejection, autoimmune diseases, inflammatory diseases, infectious diseases, and lymphoproliferative disorders.

25. The compound for use or the pharmaceutical composition for use of claim 24,
wherein said autoimmune disease is selected from the group consisting of psoriasis, vitiligo, primary sclerosing cholangitis, multiple sclerosis, systemic lupus erythematosus, Hashimoto's thyroiditis, rheumatoid arthritis, myasthenia gravis, diabetes type I or II, disorders secondary to diabetes type I or II, vasculitis, pernicious anaemia, Sjogren syndrome, uveitis, Graves' ophthalmopathy, alopecia areata, allergic asthma, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, myocarditis, hepatitis, and allergic contact dermatitis;
wherein said transplant rejection is selected from the group consisting of acute or chronic rejection of cells, tissue, organ, allografts and xenografts, poor graft functional states, graft versus host disease; rejection of cardiac transplant, skin transplant, renal transplant, liver transplant, islet transplant, pancreas transplant, lung transplant, bowel transplant, corneal transplant, vascular transplant, adrenal transplant, hair transplant, bone transplant, cartilage transplant and ligamental transplant;
wherein said inflammatory disease is selected from the group consisting of inflammatory bowel disease, Crohn's disease, ulcerative colitis, intrinsic asthma, inflammatory lung injury, inflammatory liver injury, inflammatory glomerular injury, atherosclerosis, osteoarthritis, myositis, polymyositis, prurigo nodularis, eosinophilic esophagitis, hidradenitis suppurativa, fibrotic disorders, cardio vasculopathy, allergic disorders, irritant contact dermatitis, eczematous dermatitis, seborrhoeic dermatitis, cutaneous manifestations of immunologically-mediated disorders, inflammatory eye diseases, keratoconjunctivitis, myocardial infarction, stroke, gut ischemia, renal failure, hemorrhage shock, traumatic shock, toxic shock, septic shock and adult respiratory distress syndrome;

wherein said lymphoproliferative disorder is T cell lymphoma or T cell leukaemia;
wherein said infectious disease is selected from the group consisting of tuberculosis, preferably caused by mycobacteria, Salmonella sp. infections, Helicobacter sp. infections, retroviral infections, preferably HIV or HTLV, cytomegalo viral infection, candida infection, Staphylococcus infections, lympho-choriomeningitis viral infections and viral hepatitis.

26. The compound for use or the pharmaceutical composition for use of claim 25, wherein the compound inhibits coronin 1 expression.

27. The compound for use or the pharmaceutical composition for use of claim 26, wherein the compound inhibits coronin 1 expression by targeting selectively the bromodomains of BRD3.

28. The compound of any one of claims 1 to 21 or a pharmaceutically acceptable salt, stereoisomer, diastereoisomer, enantiomer, polymorph, racemic mixture, solvate or isomers and mixtures thereof, or the pharmaceutical composition of claim 22 for use in the treatment and/or prevention of BRD3-driven malignancy.

29. The compound for use or the pharmaceutical for use of claim 28, wherein the BRD3-driven malignancy is selected from Testis (NUT) Midline Carcinoma (NMC), BRD3-driven Ovarian Clear Cell Carcinoma (OCCC), colorectal carcinoma, and rhabdomyosarcoma, or their metastasis.

30. The compound for use or the pharmaceutical composition for use of claim 29, wherein the compound inhibits coronin 1 expression.

31. The compound for use or the pharmaceutical composition for use of claim 29, wherein the compound inhibits coronin 1 expression by targeting selectively the bromodomains of BRD3.

32. The compound for use or the pharmaceutical composition for use of any one of claims 24 to 31, wherein the compound or the pharmaceutical composition is administered perorally.