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(54) Title: SUBSTITUTED TRICYCLIC COMPOUNDS WITH ACTIVITY TOWARDS EP1 RECEPTORS

(57) Abstract: The present invention belongs to the field of EP1 receptor ligands. More specifically it refers to compounds of general formula (I) having great affinity and selectivity for the EP1 receptor. The invention also refers to the process for their preparation, to their use as medicament for the treatment and/or prophylaxis of diseases or disorders mediated by the EP1 receptor as well as to pharmaceutical compositions comprising them.

SUBSTITUTED TRICYCLIC COMPOUNDS WITH ACTIVITY TOWARDS EP1 RECEPTORS

FIELD OF THE INVENTION

The present invention belongs to the field of EP1 receptor ligands. More specifically it refers to compounds of general formula (I) having great affinity and selectivity for the EP1 receptor. The invention also refers to the process for their preparation, to their use as medicament for the treatment and/or prophylaxis of diseases or disorders mediated by the EP1 receptor as well as to pharmaceutical compositions comprising them.

BACKGROUND OF THE INVENTION

Prostanoids are a family of eicosanoids that comprise prostaglandins (PGs), prostacyclins (PGIs), and thromboxanes (Txs). Their receptors belong to the G-protein coupled receptor (GPCR) superfamily of receptors and may be grouped into five classes, namely, prostaglandin D (DP), prostaglandin E (EP), prostaglandin F (FP), prostaglandin I (IP), and Thromboxane A (TP) based on their sensitivity to five naturally occurring prostanoids, PGD2, PGE2, PGF2[alpha], PGI2, and TxA2, respectively (Coleman, R. A., 2000).

Prostaglandins contribute to the sensitization of peripheral and central nociceptive neurons during peripheral inflammation (Dirig and Yaksh, 1999) and play an important role in the pathogenesis of neuropathic pain following nerve injury (Syriatowicz et al 1999; Kawahara et al, 2001; Samad et al, 2002; Ma and Eisenach, 2003; Durrenberger et al., 2006).

Prostaglandin E2 (PGE2) is considered to be the dominant pro-nociceptive prostanoid. Guay and colleagues, analyzing the concentrations of different prostaglandins in the cerebrospinal fluid, found that PGE2 was the most prevalent prostanoid and exhibited the highest increase after peripheral carrageenan-induced inflammation (Guay et al., 2004). PGE2 is generated in most cells in response to mechanical, thermal or chemical injury and inflammatory insult, resulting in sensitization or direct activation of nearby sensory nerve endings. Its production requires the activity of at least one of the

two cyclooxygenase isoforms, COX-1 constitutively expressed or COX-2 which is inducible and particularly relevant for inflammation-induced PGE2 formation. Therefore, non-selective inhibitors of COX-1 and COX-2, and selective COX-2 inhibitors provide good pain relief. However, the long-term use is associated with gastrointestinal or cardiovascular side effects, respectively.

Downstream components of the inflammatory cascade could be an alternative approach for the treatment of the PGE2 associated pain. PGE2 binds to four different G-protein coupled receptors named EP1, EP2, EP3 and EP4 (Narumiya et al., 1999).

Studies employing antagonists suggest that blocking EP1, EP2, EP3 or EP4 receptors may reduce certain types of pain (Oka et al. 1997; Omote et al., 2002; Lin et al, 2006) and agonists increase nociceptive responses (Minami et al., 1994). Among these PGE2 receptor subtypes, most of drug discovery studies have focused on the EP1 receptors (Hall et al., 2007).

EP1 receptor stimulation mediates increases in intracellular calcium ions, facilitating neurotransmitter release (Asbóth et al., 1996). EP1 receptor is preferentially expressed in primary sensory neurons, including their spinal cord terminals (Oidda et al., 1995) although it is also distributed in other tissues (Breyer et al., 2000; Schlötzer-Schrehardt et al., 2002). In the brain, marked differences in the level of EP1 expression among the cerebral regions were found. The strongest levels of EP1 mRNA were found in parietal cortex and cerebellum, followed in descending order by frontal cortex and striatum. The hypothalamus, hippocampus and brain stem displayed a low-level EP1 mRNA signal (Candelario-Jalil et al., 2005). In the spinal cord, several studies have reported the effects of PGE2 on neuronal excitability or synaptic transmission (Baba et al., 2001) and pain transmission (Nakayama et al., 2004). Therefore, EP1 receptor antagonists, blocking the positive feedback cascade mediated by PGE_2, may result in analgesic efficacy. In this regard, using EP receptor deficient mice, a prominent contribution of EP1 receptors has been described (Minami et al., 2001). EP1 -/- knockout mice demonstrated a role of this receptor in mediating peripheral heat sensitization after subcutaneous PGE2 injection (Moriyama et al. 2005; Johansson et al. 2011), and EP1 receptor antagonism has

been reported to reduce mechanical hyperalgesia in nerve injured rats (Kawahara et al., 2001), in the carrageenan model (Nakayama et al. 2002), or in the incisional model of postoperative pain (Omote et al 2002). Moreover, EP1 antagonists demonstrated analgesic activity in a complete Freund's adjuvant model of knee joint arthritis (Giblin et al, 2007; Hall et al, 2009). It has also been reported that the contribution of PGE2 in human visceral pain hypersensitivity is mediated through the EP1 receptor (Sarkar et al., 2003).

In addition to being useful for modulating pain, EP1 antagonists may also be useful for the treatment or prevention of other EP1 receptor-mediated diseases such as motility-related disorders including gastrointestinal disorders, urinary incontinence and other urinary tract diseases; dysmenorrhea; preterm labour; diabetic retinopathy; tumour angiogenesis; cancer; metastatic tumour growth; neurodegenerative diseases including senile dementia, Alzheimer's disease, Pick's disease, Huntington's chorea, Parkinson's disease, Creutzfeldt-Jakob disease, or amyotrophic lateral sclerosis; neuroprotection/stroke; glaucoma; osteoporosis; bone fractures; Paget's disease; hyperthermia including different types of fever as rheumatic fever; symptoms associated with influenza or other viral infections; gastrointestinal disorders related with chemotherapy or irritable bowel syndrome; gastrointestinal bleeding; coagulation disorders including anaemia, hypoprothrombinemia, haemophilia or other bleeding problems; kidney diseases including nephritis, particularly mesangial proliferative glomerulonephritis and nephritic syndrome; thrombosis and occlusive vascular diseases.

In turn, EP1 receptor agonists also may have a number of utilities. These include, but are not limited to treatment of influenza, bone fracture healing, bone disease, glaucoma, ocular hypertension, dysmenorrhoea, pre-term labour, immune disorders, osteoporosis, asthma, allergy, fertility, male sexual dysfunction, female sexual dysfunction, periodontal disease, gastric ulcer, and renal disease. EP receptor agonists may also be useful for expansion of hematopoietic stem cell populations.

Based on the above mentioned results coming from animal and human studies, EP1 receptor has been identified as a selective target for the development of new

potential therapies for the treatment of those disorders where PGE2 action is involved. In view of the potential therapeutic applications of agonists and antagonists of the EP1 receptor, a great effort is being directed to find selective ligands. Despite intense research efforts in this area, very few compounds with selective EP1 activity have been reported.

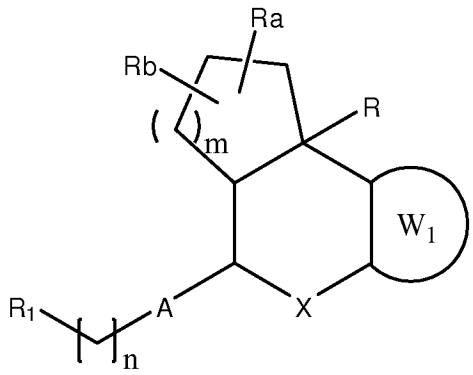
There is thus still a need to find compounds having pharmacological activity towards the EP1 receptor, being both effective and selective, and having good "drugability" properties, i.e. good pharmaceutical properties related to administration, distribution, metabolism and excretion.

The present invention hereby provide some novel compounds complying with the above mentioned properties.

OBJECT OF THE INVENTION

The present invention discloses novel compounds with great affinity to EP1 receptors which might be used for the treatment of EP1-related disorders or diseases.

Specifically, it is an object of the invention a compound of general formula I:



(I)

wherein:

W1 is a benzene ring optionally substituted by one or more R_2 and optionally fused to a carbocyclic ring; or a 5 or 6-membered heterocyclic ring containing 1 or 2 heteroatoms selected from N, O or S, optionally substituted by one or more R_2;

R is a hydrogen; or C_{1-6}-alkyl;

Ra and **Rb** are independently selected from hydrogen; =O; -OH; CH_2OH; -CO-C_{1-6}-alkyl; -SO_2-C_{1-6}-alkyl; C_{1-6}-alkyl; –O–C_{1-6}-alkyl or –O–C_{1-6}-haloalkyl;

$\mathbf{R_1}$ is a –COOH; a tetrazol; a –SO_2-NH-C(=O)-R_3; a –C(=O)NH-SO_2-R_4; a –SO_2-OH or a –CN;

$\mathbf{R_2}$ is independently selected from hydrogen; halogen; C_{1-6} alkyl; C_{1-6}-haloalkyl; –O–C_{1-6}-alkyl; –O–C_{1-6}-haloalkyl, C_{3-6}cycloalkyl; –O–C_{3-6}cycloalkyl; -$NR_5SO_2R_6$; phenyl; -$CONH_2$ or –CN;

$\mathbf{R_3}$, $\mathbf{R_4}$ are independently selected from a hydrogen; C_{1-6}-alkyl; an optionally substituted phenyl; or –$N(CH_3)_2$;

$\mathbf{R_5}$ and $\mathbf{R_6}$ are independently selected from a hydrogen; or C_{1-6}-alkyl;

$\mathbf{R_7}$ is selected from a hydrogen; C_{1-6}-alkyl; or a –COR_8

$\mathbf{R_8}$ is a C_{1-6}-alkyl;

X is selected from NR_7 or O;

A is a phenyl optionally substituted by one or more substituents selected from C_{1-6}-alkyl, halogen, C_{1-6}-haloalkyl, –O–C_{1-6}-alkyl, –O–C_{1-6}-haloalkyl, -NH-CO-CH_3, a –CN or a C_{3-6}cycloalkyl optionally substituted by a C_{1-6}-alkyl; or an heteroaromatic ring or ring system optionally substituted by one or more substituents selected from C_{1-6}-alkyl, halogen, C_{1-6}-haloalkyl, –O–C_{1-6}-alkyl, –O–C_{1-6}-haloalkyl -NH-CO-CH_3, a –CN or a C_{3-6}cycloalkyl optionally substituted by a C_{1-6}-alkyl ;

n is 0, 1 or 2,

m is 1, 2, or 3;

and the salts, solvates and prodrugs thereof.

It is also an object of the invention the process for the preparation of compounds of general formula (I).

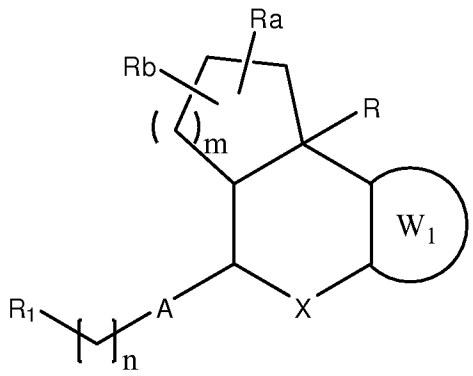
In another aspect, the invention relates to a compound of general formula (I) for use as a medicament.

Yet another object of the invention is a compound of general formula (I) for use in the treatment and/or prophylaxis of diseases or disorders mediated by the EP1 receptor. This includes but is not limited to diseases such as inflammatory related pain including low back and neck pain, skeletal pain, post-partum pain, toothache, sprains and straits, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases, gout and ankylosing spondylitis, bursitis, burns including radiation and corrosive chemical injuries and sunburns; postoperative pain; neuropathic pain; visceral pain; tension headache; cluster headaches; migraine; motility-related disorders including gastrointestinal disorders, urinary incontinence and other urinary tract diseases; dysmenorrhea; preterm labour; diabetic retinopathy; tumour angiogenesis; cancer; metastatic tumour growth; neurodegenerative diseases including senile dementia, Alzheimer's disease, Pick's disease, Huntington's chorea, Parkinson's disease, Creutzfeldt-Jakob disease, or amyotrophic lateral sclerosis; neuroprotection/stroke; glaucoma; osteoporosis; bone fractures; Paget's disease; hyperthermia including different types of fever as rheumatic fever; symptoms associated with influenza or other viral infections; gastrointestinal disorders related with chemotherapy or irritable bowel syndrome; gastrointestinal bleeding; coagulation disorders including anaemia, hypoprothrombinemia, haemophilia or other bleeding problems; kidney diseases including nephritis, particularly mesangial proliferative glomerulonephritis and nephritic syndrome; thrombosis and occlusive vascular diseases.

It is another object of the invention a pharmaceutical composition comprising at least one compound of general formula (I) and at least one pharmaceutically acceptable carrier, additive, adjuvant or vehicle.

DETAILED DESCRIPTION OF THE INVENTION

In a first aspect the invention relates to compounds of general formula (I):



(I)

wherein:

W1 is a benzene ring optionally substituted by one or more R_2 and optionally fused to a carbocyclic ring; or a 5 or 6-membered heterocyclic ring containing 1 or 2 heteroatoms selected from N, O or S, optionally substituted by one or more R_2;

R is a hydrogen; or C_{1-6}-alkyl;

Ra and **Rb** are independently selected from hydrogen; =O; -OH; CH_2OH; -CO-C_{1-6}-alkyl; -SO_2-C_{1-6}-alkyl; C_{1-6}-alkyl; –O–C_{1-6}-alkyl or –O–C_{1-6}-haloalkyl;

$\mathbf{R_1}$ is a –COOH; a tetrazol; a –SO_2-NH-C(=O)-R_3; a –C(=O)NH-SO_2-R_4; a –SO_2-OH or a –CN;

$\mathbf{R_2}$ is independently selected from hydrogen; halogen; C_{1-6} alkyl; C_{1-6}-haloalkyl; –O–C_{1-6}-alkyl; –O–C_{1-6}-haloalkyl; C_{3-6}cycloalkyl; –O–C_{3-6}cycloalkyl; -$NR_5SO_2R_6$; phenyl; -$CONH_2$ or –CN;

$\mathbf{R_3}$ and $\mathbf{R_4}$ are independently selected from a hydrogen; C_{1-6}-alkyl; an optionally substituted phenyl; or –$N(CH_3)_2$

$\mathbf{R_5}$ and $\mathbf{R_6}$ are independently selected from a hydrogen; or C_{1-6}-alkyl

$\mathbf{R_7}$ is selected from a hydrogen; C_{1-6}-alkyl; or a –COR_8

$\mathbf{R_8}$ is a C_{1-6}-alkyl;

X is selected from NR_7 or O;

A is a phenyl optionally substituted by one or more substituents selected from C_{1-6}-alkyl, halogen, C_{1-6}-haloalkyl, –O–C_{1-6}-alkyl, –O–C_{1-6}-haloalkyl, –O–C_{1-6}-haloalkyl, -NH-CO-CH_3, a –CN or a C_{3-6}cycloalkyl optionally substituted by a C_{1-6}-alkyl; or an heteroaromatic ring or ring system optionally substituted by one or

more substituents selected from C_{1-6}-alkyl, halogen, C_{1-6}-haloalkyl, –O–C_{1-6}-alkyl, –O–C_{1-6}-haloalkyl, –O–C_{1-6}-haloalkyl, -NH-CO-CH_3, a –CN or a C_{3-6}cycloalkyl optionally substituted by a C_{1-6}-alkyl;

n is 0, 1 or 2,

m is 1, 2 or 3

and the salts, solvates and prodrugs thereof.

Also included within the scope of the invention are the isomers, polymorphs, isotopes, salts, solvates and prodrugs of the compounds of formula (I). Any reference to a compound of formula (I) throughout the present specification includes a reference to any isomer, polymorph, isotope, salt, solvate or prodrug of such compound of formula I.

The compounds of formula I may exist in different physical forms, i.e. amorphous and crystalline forms. Moreover, the compounds of the invention may have the ability to crystallize in more than one form, a characteristic which is known as polymorphism. Polymorphs can be distinguished by various physical properties well known in the art such as X-ray diffraction pattern, melting point or solubility. All physical forms of the compounds of formula I, including all polymorphic forms ("polymorphs") thereof, are included within the scope of the invention.

Some of the compounds of the present invention may exist as several optical isomers and/or several diastereoisomers. Diastereoisomers can be separated by conventional techniques such as chromatography or fractional crystallization. Optical isomers can be resolved by conventional techniques of optical resolution to give optically pure isomers. This resolution can be carried out on any chiral synthetic intermediate or on the products of formula I. Optically pure isomers can also be individually obtained using enantiospecific synthesis. The present invention covers all individual isomers as well as mixtures thereof (for example racemic mixtures or mixtures of diastereomers), whether obtained by synthesis or by physically mixing them.

In addition, any formula given herein is intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{36}S, ^{18}F , ^{36}Cl, and ^{125}I, respectively, Such isotopically labelled compounds are useful in metabolic studies (preferably with 14C), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques [such as positron emission tomography (PET) or single- photon emission computed tomography (SPECT)] including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or ^{11}C labeled compound may be particularly preferred for PET or SPECT studies. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements. In addition to the unlabeled form, all isotopically labeled forms of the compounds of formula I are included within the scope of the invention.

“Halogen” or “halo” as referred in the present invention represent fluorine, chlorine, bromine or iodine.

The term "alkyl," alone or in combination, means an acyclic radical, linear or branched, preferably containing from 1 to about 6 carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, heptyl, octyl, and the like. Where no specific substitution is specified, alkyl radicals may be optionally substituted with groups consisting of hydroxy, sulfhydryl, methoxy, ethoxy, amino, cyano, chloro, and fluoro. The carbon atom content of various hydrocarbon-containing moieties is indicated by suffix designating a lower and upper number of carbon atoms in the moiety. Thus, for example, 'C_{1-6}-alkyl' refers to alkyl of 1 to 6 carbon atoms, inclusive.

An “alkylene” linking group preferably contains 1-4 carbon atoms and represents for example methylene, ethylene, propylene, butylene. The carbon atom content of various hydrocarbon-containing moieties is indicated by suffix designating a lower and upper number of carbon atoms in the moiety. Thus, for example, 'C_{1-4}-alkylene' refers to an alkylene of 1 to 4 carbon atoms, inclusive.

An “alkenylene” linking group preferably contains 2 to 4 carbon atoms and represents for example ethenylene, 1,3-propenylene, 1,4-but-1-enylene, 1,4-but-2-ethylene. The carbon atom content of various hydrocarbon-containing moieties is indicated by suffix designating a lower and upper number of carbon atoms in the moiety. Thus, for example, 'C_{2-4}-alkenylene' refers to alkenylene of 2 to 4 carbon atoms, inclusive.

"Cycloalkyl" is preferably a monocyclic cycloalkyl containing from three to six carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. The carbon atom content of various hydrocarbon-containing moieties is indicated by suffix designating a lower and upper number of carbon atoms in the moiety. Thus, for example, 'C_{3-6}-cycloalkyl' refers to cycloalkyl of 3 to 6 carbon atoms, inclusive.

The term “carbocyclic”, “carbocyclic ring” and “carbocyclyl” refer to a saturated, unsaturated or aromatic mono- or multi-ring cycloalkyl only formed from carbon atoms.

The terms "heterocycle", "heterocyclic ring" and "heterocyclyl" refer to a saturated, unsaturated or aromatic mono- or multi-ring cycloalkyl wherein one or more carbon atoms is replaced by N, S, or O. The terms "heterocycle", "heterocyclic ring system," and "heterocyclyl" include fully saturated ring structures such as piperazinyl, dioxanyl, tetrahydrofuranyl, oxiranyl, aziridinyl, morpholinyl, pyrrolidinyl, piperidinyl, thiazolidinyl, and others. The terms "heterocycle", "heterocyclic ring system," and "heterocyclyl" also include partially unsaturated ring structures such as dihydrofuranyl, dihydropyrrolyl, pyrazolinyl, imidazolinyl, pyrrolinyl, chromanyl, dihydrothienyl, and others. The term "heterocycle", "heterocyclic ring system," and "heterocyclyl" also include aromatic structures such as pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, thienyl, furanyl,

pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, and tetrazolyl, optionally substituted.

The term “heteroaromatic ring” refers to an aromatic heterocyclic ring. Examples of "heteroaromatic ring" include pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, thionyl, furanyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, and tetrazolyl, optionally substituted.

The term “ring” or “ring system” according to the present invention refers to ring systems comprising saturated, unsaturated or aromatic carbocyclic ring systems which contain optionally at least one heteroatom as ring member and which are optionally at least mono-substituted. Said ring systems may be condensed to other carbocyclic ring systems.

The term “monocyclic ring” refers to a ring system composed of a single ring.

The term “polycyclic ring” refers to a ring system composed of at least two rings.

The term “salt” must be understood as any form of an active compound used in accordance with this invention in which the said compound is in ionic form or is charged and coupled to a counter-ion (a cation or anion) or is in solution. This definition also includes quaternary ammonium salts and complexes of the active molecule with other molecules and ions, particularly complexes formed via ionic interactions. The definition particularly includes physiologically acceptable salts. This term must be understood as equivalent to “pharmaceutically acceptable salts”.

The term “pharmaceutically acceptable salts” in the context of this invention means any salt that is tolerated physiologically (normally meaning that it is not toxic, particularly as a result of the counter-ion) when used in an appropriate manner for a treatment, particularly applied or used in humans and/or mammals. These pharmaceutically acceptable salts may be formed with cations or bases and, in the context of this invention, are understood to be salts formed by at least one compound used in accordance with the invention – normally an acid (deprotonated) – such as an anion and at least one physiologically tolerated

cation, preferably inorganic, particularly when used on humans and/or mammals. Salts with alkali and alkali earth metals are particularly preferred, as well as those formed with ammonium cations (NH_4^+). Preferred salts are those formed with (mono) or (di)sodium, (mono) or (di)potassium, magnesium or calcium. These physiologically acceptable salts may also be formed with anions or acids and, in the context of this invention, are understood as being salts formed by at least one compound used in accordance with the invention –normally protonated, for example in nitrogen– such as a cation and at least one physiologically tolerated anion, particularly when used on humans and/or mammals. This definition specifically includes in the context of this invention a salt formed by a physiologically tolerated acid, i.e. salts of a specific active compound with physiologically tolerated organic or inorganic acids –particularly when used on humans and/or mammals. Examples of this type of salts are those formed with: hydrochloric acid, hydrobromic acid, sulphuric acid, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, malic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid or citric acid.

The term “solvate” in accordance with this invention should be understood as meaning any form of the active compound in accordance with the invention in which said compound is bonded by a non-covalent bond to another molecule (normally a polar solvent), especially including hydrates and alcoholates, for example methanolate.

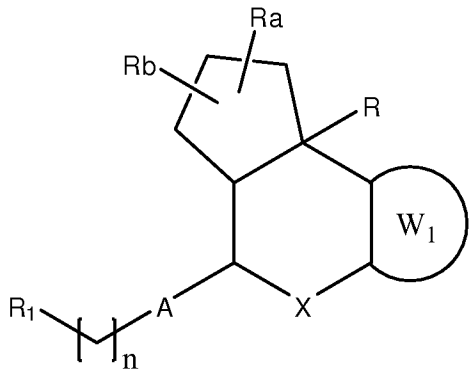
The term "prodrug" is used in its broadest sense and encompasses those derivatives that are converted in vivo to the compounds of the invention. Examples of prodrugs include, but are not limited to, derivatives and metabolites of the compounds of formula (I) that include biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Preferably, prodrugs of compounds with carboxyl functional groups are the lower alkyl esters of the carboxylic acid. The carboxylate esters are conveniently formed by esterifying any of the carboxylic acid moieties present on the molecule. Prodrugs can typically be prepared using well-known methods, such as those described by Burger "Medicinal Chemistry and Drug Discovery 6th ed. (Donald J. Abraham ed., 2001 , Wiley) and "Design

and Applications of Prodrugs" (H. Bundgaard ed., 1985, Harwood Academic Publishers).

The terms "prevention", "preventing", "preventive" "prevent" and “prophylaxis” refer to the capacity of a therapeutic to avoid, minimize or difficult the onset or development of a disease or condition before its onset.

The terms "treating" or "treatment" is meant at least a suppression or an amelioration of the symptoms associated with the condition afflicting the subject, where suppression and amelioration are used in a broad sense to refer to at least a reduction in the magnitude of a parameter, e.g., symptom associated with the condition being treated, such as pain. As such, the method of the present invention also includes situations where the condition is completely inhibited, terminated, such that the subject no longer experiences the condition.

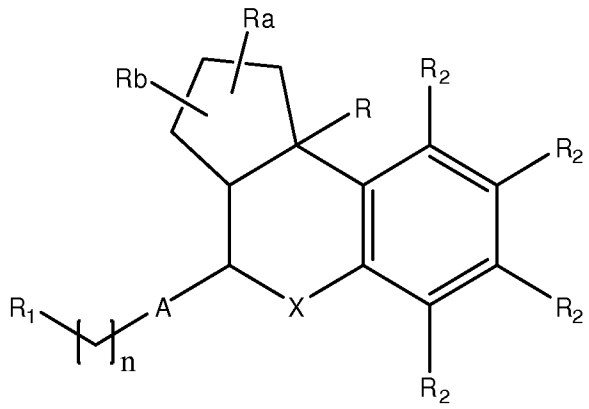
A particular embodiment of the invention compounds of formula (I) are represented by general formula (Ia):



(Ia)

where **W1**, **R**, **Ra**, **Rb**, R_1, **A**, **X** and **n** have the same meaning as for compounds of general formula (I);

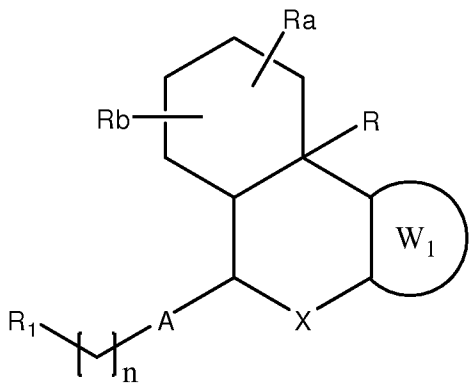
In another particular and preferred embodiment of the invention the compounds of formula (I) and more particularly those with formula (Ia) are represented by the more particular general formula (Ia'):



(Ia')

where **R**, **Ra**, **Rb**, R_1, R_2, **A**, **X** and **n** have the same meanings as for compounds of formula (Ia);

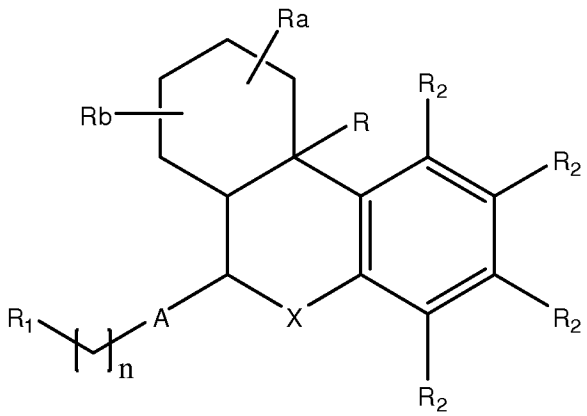
In another particular embodiment of the invention compounds of general formula (I) are represented by compounds of general formula (Ib):



(Ib)

where **W1**, **R**, **Ra**, **Rb**, R_1, **A**, **X** and **n** have the same meaning as for general formula (I).

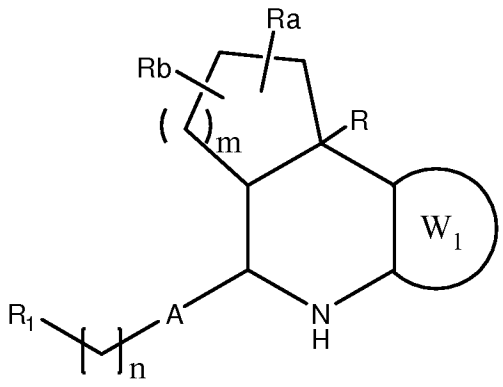
In another particular and preferred embodiment of the invention the compounds of formula (I) and more particularly those with formula (Ib) are represented by the more particular general formula (Ib'):



(Ib')

Where **R**, **Ra**, **Rb**, R_1, R_2, **A**, **X** and **n** have the same meanings as in general formula (I).

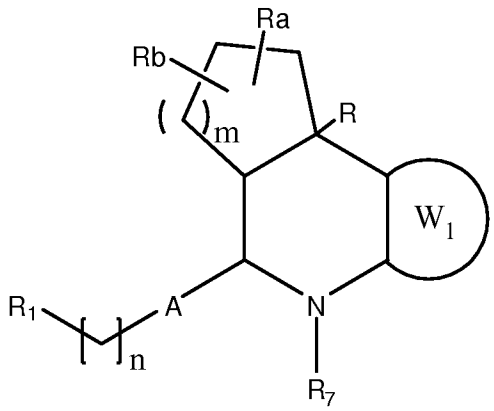
In another particular and preferred embodiment of the invention the compounds of formula (I) are represented by compounds of general formual (Ic):



(Ic)

where **R**, **Ra**, **Rb**, R_1, **A**, **W1**, **m** and **n** have the same meanings as in general formula (I).

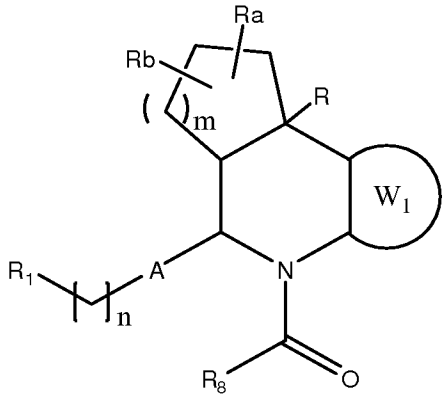
In another particular and preferred embodiment of the invention the compounds of formula (I) are represented by compounds of general formual (Id):



(Id)

where **R**, **Ra**, **Rb**, R_1, R_7, **A**, **W1**, **m** and **n** have the same meanings as in general formula (I).

In another particular and preferred embodiment of the invention the compounds of formula (I) are represented by compounds of general formual (Ie):



(Ie)

where **R**, **Ra**, **Rb**, R_1, R_8, **A**, **W1**, **m** and **n** have the same meanings as in general formula (I).

In a preferred embodiment of the invention R_1 is a –COOH group, a tetrazole or a –C(=O)NH-SO_2-R_4 in the compounds of general formula (I), (Ia), (Ia'), (Ib), (Ib'), (Ic), (Id) and (Ie).In another preferred embodiment of the invention **A** is a phenyl group optionally substituted by one or more substituents selected from C_{1-6}-alkyl, halogen, C_{1-6}-haloalkyl, –O–C_{1-6}-alkyl, –O–C_{1-6}-haloalkyl, –O–C_{1-6}-haloalkyl, -NH-CO-CH_3, a –CN or a C_{3-6}cycloalkyl optionally substituted by a C_{1-6}-alkyl; a pyridinyl group optionally substituted by one or more substituents selected from C_{1-6}-alkyl, halogen, C_{1-6}-haloalkyl, –O–C_{1-6}-alky, –O–C_{1-6}-haloalkyl, –O–C_{1-6}-haloalkyl, -NH-CO-CH_3, a –CN or a C_{3-6}cycloalkyl optionally substituted by a C_{1-6}-alkyl I; a pyrazolyl group optionally substituted by one or more substituents selected from C_{1-6}-alkyl, halogen, C_{1-6}-haloalkyl, –O–C_{1-6}-alkyl, –O–C_{1-6}-haloalkyl, –O–C_{1-6}-haloalkyl, -NH-CO-CH_3, a –CN or a C_{3-6}cycloalkyl optionally substituted by a C_{1-6}-alkyl; an imidazolyl group optionally substituted by one or more substituents selected from C_{1-6}-alkyl, halogen, C_{1-6}-haloalkyl, –O–C_{1-6}-alkyl, –O–C_{1-6}-haloalkyl, –O–C_{1-6}-haloalkyl, -NH-CO-CH_3, a –CN or a C_{3-6}cycloalkyl optionally substituted by a C_{1-6}-alkyl; a thiazolyl group optionally substituted by one or more substituents selected from C_{1-6}-alkyl, halogen, C_{1-6}-haloalkyl, –O–C_{1-6}-alkyl, –O–C_{1-6}-haloalkyl, –O–C_{1-6}-haloalkyl, -NH-CO-CH_3, a –CN or a C_{3-6}cycloalkyl optionally substituted by a C_{1-6}-alkyl; an indolyl group optionally substituted by one or more substituents selected from C_{1-6}-alkyl, halogen, C_{1-6}-haloalkyl, –O–C_{1-6}-alkyl, –O–C_{1-6}-haloalkyl, –O–C_{1-6}-haloalkyl, -NH-CO-CH_3, a –CN or a C_{3-6}cycloalkyl optionally substituted by a C_{1-6}-alky; or a benzimidazole group optionally substituted by one or more substituents selected from C_{1-6}-alkyl, halogen, C_{1-6}-haloalkyl, –O–C_{1-6}-alkyl, –O–C_{1-6}-haloalkyl, –O–C_{1-6}-haloalkyl, -NH-CO-CH_3, a –CN or a C_{3-6}cycloalkyl optionally substituted by a C_{1-6}-alky.

In another preferred embodiment in the compounds of the invention **X** is NR_7 where R_7 is a hydrogen .

In another preferred embodiment **n** is 0.

Another preferred embodiment is represented by compounds of formula (I) where **W1** is a benzene ring optionally substituted by one or more R_2 where R_2 has the same meaning as for general formula (I).

Among all the compounds encompassed by the general formula (I), (Ia), (Ia'), (Ib) (Ib'), (Ic), (Id) and/or (Ie) the following compounds are particularly preferred:

- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-8-bromo-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-8-(trifluoromethyl)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (enantiomer 1);
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (enantiomer 2);
- 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (enantiomer 1);
- 4-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (enantiomer 2);
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (enantiomer 1);
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (enantiomer 2);
- 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS, 4R, 9bR)-6-cyclopropyl-2, 3, 3a, 4, 5, 9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;

- 4-((3aS, 4S, 9bR)-8-cyclopropyl-2, 3, 3a, 4, 5, 9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS, 4R, 9bR)-8-cyclopropyl-2, 3, 3a, 4, 5, 9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- (+)-4-((3a*S*, 4*R*, 9b*R*)-8-cyclopropyl-2, 3, 3a, 4, 5, 9b-hexahydro-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid;
- (-)-4-((3a*S*, 4*R*, 9b*R*)-8-cyclopropyl-2, 3, 3a, 4, 5, 9b-hexahydro-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid;
- 4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-propyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS, 4R, 9bR)-8-fluoro-2, 3, 3a, 4, 5, 9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-phenyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS, 4R, 9bR)-8-tert-butyl-2, 3, 3a, 4, 5, 9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- (+)-4-((3a*S*,4*R*,9*bR*)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- (-)-4-((3a*S*,4*R*,9*bR*)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-8-carbamoyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-isopropyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-8-cyano-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-8-[(N-methylsulfonyl)amino]-)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-8-[(N-methyl-N-methylsulfonyl)amino]-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;

- 3-((3aS,4R,9bR)-8-bromo-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-7,8-dimethoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-7-(trifluoromethyl)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-9-(trifluoromethyl)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-7-methoxy-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-6,8-dimethyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-9-chloro-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-7-chloro-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-5,8-dimethyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-5-acetyl-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((6R, 6aS, 9aR)-6, 6a, 7, 8, 9, 9a-hexahydro-2-methyl-5H-cyclopenta[c][1,5]naphthyridin-6-yl)benzoic acid;
- 4-((6R,6aS,9aR)-6,6a,7,8,9,9a-hexahydro-2-methyl-5H-cyclopenta[c][1,8]naphthyridin-6-yl)benzoic acid;
- 2-(4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)phenyl)acetic acid;
- 3-(4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)phenyl)propanoic acid;
- 4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-2-methylbenzoic acid;
- 4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;

- (+)-4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- (-)-4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 4-((3aS, 4S, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 4-((3aS, 4R, 9bR)-8-chloro-2, 3, 3a, 4, 5, 9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 4-((3aS, 4R, 9bR)-8-fluoro-2, 3, 3a, 4, 5, 9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methoxy-5-methyl-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 4-((3aS, 4R, 9bR)-8-cyclopropyl-2, 3, 3a, 4, 5, 9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 4-((3aS, 4R, 9bR)-8-(cyclopropylmethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-isopropoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-isopropoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 3-chloro-4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methoxybenzoic acid;
- 4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-3-methoxybenzoic acid;
- 3-bromo-4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 3-bromo-4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;

- 3-ethyl-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzonitrile;
- 3-ethyl-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 3-ethyl-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 3-ethyl-4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-3,5-dimethylbenzoic acid;
- 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-3,5-dimethylbenzoic acid;
- 5-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)pyridine-2-carboxylic acid;
- 6-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)pyridine-3-carboxylic acid;
- 5-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-6-methylpyridine-2-carbonitrile;
- 5-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-6-methylpyridine-2-carboxylic acid;
- 5-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-1-methyl-1H-pyrazole-3-carboxylic acid;
- 5-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-1-methyl-1H-pyrazole-3-carboxylic acid;
- 3-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-1-methyl-1H-pyrazole-5-carboxylic acid;
- 3-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-1-methyl-1H-pyrazole-5-carboxylic acid;
- 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8,9b-dimethyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8,9b-dimethyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;

- 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4S,9bR)-8-cyclopropyl-2,3,3a,4,5,9b-hexahydro-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-8-cyclopropyl-2,3,3a,4,5,9b-hexahydro-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4S,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS, 4S, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8, 9b-dimethyl-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8, 9b-dimethyl-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-isobutoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-isobutoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 4-((3aS, 4S, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methoxy-5,9b-dimethyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS, 4R, 9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-5,9b-dimethyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- (+/-)-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-(trifluoromethoxy)-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- (+/-)4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-(trifluoromethoxy)-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- (+/-)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- (+/-)-3-fluoro-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;

- (+/-)-3-fluoro-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- (+/-)-4-((3aS,4R,9bR)-8-cyclopropyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid;
- (+/-)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid;
- (+/-)-4-((3aS,4R,9bR)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid;
- 3-(trifluoromethyl)-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 3-(trifluoromethyl)-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4S,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-dimethylbenzoic acid;
- (+/-)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluoro-5-methylbenzoic acid;
- (+/-)-4-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid;
- (+/-)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid;
- (+/-)-4-((3aS,4R,9bR)-8-cyclopropyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid;
- 3,5-dichloro-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 5-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-6-methylpyridine-2-carboxylic acid;
- 6-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-5-methylpyridine-3-carboxylic acid;
- 2-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-1-methyl-1H-imidazole-4-carboxylic acid;
- 7-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methyl-3H-benzo[d]imidazole-4-carboxylic acid;
- 7-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-1H-indole-4-carbonitrile;
- 2-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-

yl)thiazole-5-carboxylic acid;

- 2-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)thiazole-5-carboxylic acid;
- 4-chloro-5-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)thiazole-2-carboxylic acid;
- 4-chloro-5-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)thiazole-2-carboxylic acid;
- (3aS,4R,9bR)-4-(4-(1H-tetrazol-5-yl)phenyl)-8-methoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinoline;
- 3,5-difluoro-4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- (+/-)-4-((3aS,4R,9bR)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid;
- 3,5-difluoro-4-((3aS,4R,9bR)-8-methoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((6R,6aS,10aR)-2-chloro-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-3-methylbenzoic acid;
- (+/-)-4-((6S,6aS,10aR)-2-chloro-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-3-methylbenzoic acid;
- 4-((6R,6aS,10aR)-2-chloro-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoic acid;
- 4-((6S,6aS,10aR)-2-chloro-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoic acid;
- 4-((6S,6aS,10aR)-2-methyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoic acid;
- (+/-)-4-((6S,6aS,10aR)-2-(difluoromethoxy)-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoic acid;
- 3,5-dichloro-4-((6S,6aS,10aR)-2-methyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoic acid;
- 4-((6R,6aS,11aR)-2-methyl-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[c]quinolin-6-yl)benzoic acid;
- 2-fluoro-4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-

yl)-2-fluorobenzoic acid;

- 4-((3aS,4R,9bR)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-2-fluorobenzoic acid;
- 4-((6R,6aS,11aR)-2-chloro-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[c]quinolin-6-yl)benzoic acid;
- 4-((6S,6aS,11aR)-2-chloro-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[c]quinolin-6-yl)benzoic acid;
- 2,6-difluoro-4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((6R,6aS,10aR)-2-ethyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-2-fluorobenzoic acid;
- 4-((6S,6aS,10aR)-2-ethyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-2-fluorobenzoic acid;
- 3-fluoro-4-((3aS,4R,9bR)-8-(trifluoromethyl)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid;
- 3-fluoro-4-((6R,6aS,10aR)-2-methyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoic acid;
- 3-fluoro-4-((6S,6aS,10aR)-2-methyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoic acid;
- 4-((6R,6aS,10aR)-2-ethyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-3-fluorobenzoic acid;
- 4-((6S,6aS,10aR)-2-ethyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-3-fluorobenzoic acid;
- 4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-N-(methylsulfonyl)benzamide;
- 4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-N-(o-tolylsulfonyl)benzamide;
- N-(N,N-dimethylsulfamoyl)-4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzamide;
- 3-ethoxy-4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 3-chloro-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-

cyclopenta[c]quinolin-4-yl)benzoic acid;

- 3-chloro-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-5-fluorobenzoic acid;
- 2,3-difluoro-4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 2,5-difluoro-4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 2-isobutoxy-4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- methyl 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoate;
- ethyl 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoate;
- ethyl 3-(4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)phenyl)propanoate;
- ethyl 3-(4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)phenyl)propanoate.

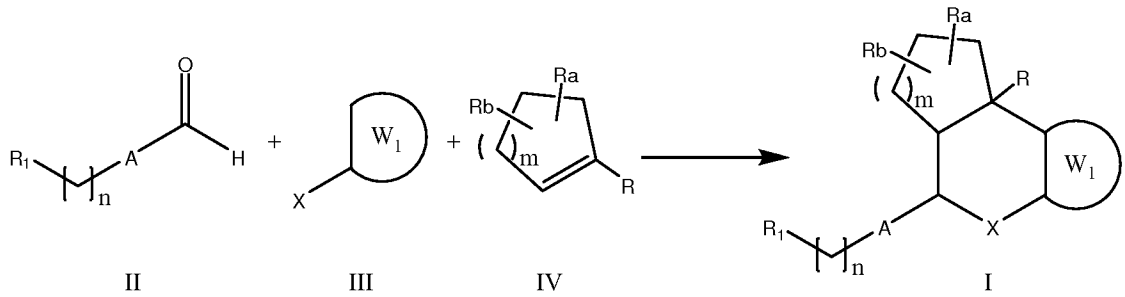
In another embodiment, the sodium salt of the previous compounds is preferred.

In another aspect the invention refers to a process for preparing the compounds of the invention.

The compounds of the invention may be made by a variety of methods, including standard chemistry. Any previously defined variable will continue to have the previously defined meaning unless otherwise indicated. Illustrative general synthetic methods are set out below and then the preparation of specific compounds of the invention is described in more detail in the Experimental Section.

Compounds of general formula (I) may be obtained following the synthetic scheme depicted in scheme 1.

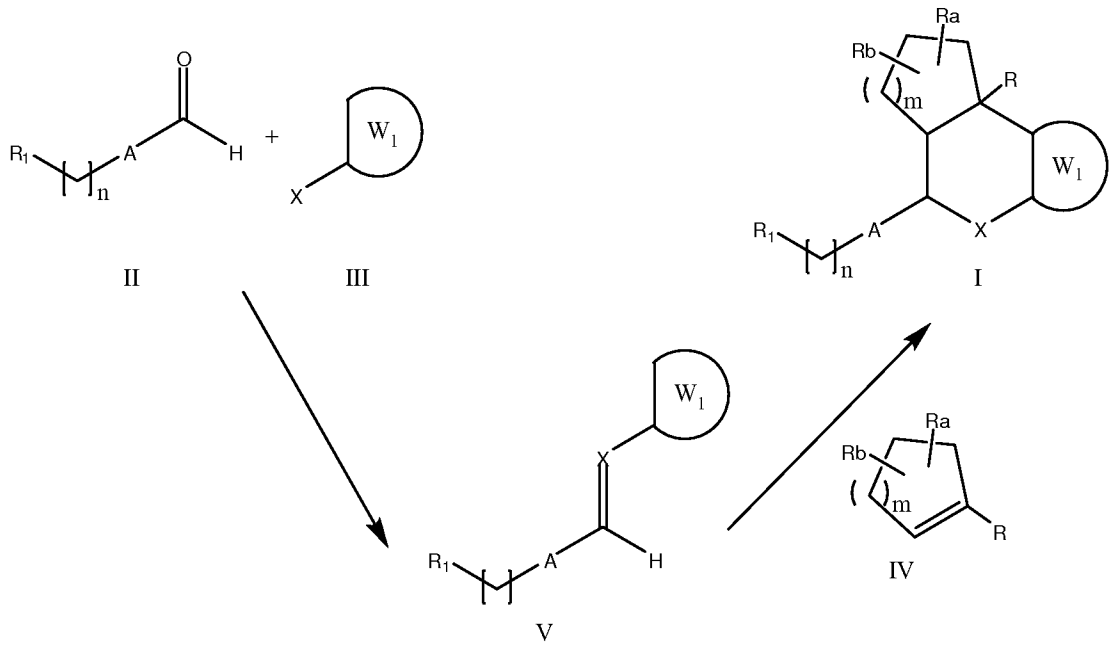
Scheme 1



II III IV I

The reaction of an aldehyde of general formula II with an amine of general formula III in the presence of an alkene of general formula IV under acidic catalysis yield compounds of general formula I. Several Lewis acids such as scandium triflate ytterbium triflate, dysprosium triflate, copper (II) triflate, tin triflate, zinc triflate, zirconium triflate, borontrifluoroetherate, indium chloride, iron (III) chloride, ytterbium chloride, aluminium chloride, lanthanum (III) chloride, gadolinium (III) chloride, Samarium (III) chloride, titanium (II) chloride, titanium (IV) chloride, or organic acids such as trifluoroacetic acid trifluoromethane sulphonic acid, octane sulphonic acid, mixture of acetic acid with sulphuric acid can be used to induce this Povarov reaction. The reaction is carried out preferably in the presence of an organic solvent such as acetonitrile, dichloromethane, 1,2-dichloroethane, toluene, chloroform, hexane, tetrahydrofurane, diethyl ether at a temperature between room temperature and the solvent boiling point.

Alternatively, the reaction can be performed in two steps as shown below in scheme 2.



In an initial step, reaction of aldehydes of formula II with amines of formula III in the presence of a dehydrating agent such as molecular sieves trimethyl orthoformate, acetic acid, titanium (IV) chloride, anhydrous magnesium sulphate or dehydration by Dean Stark system using p-toluenesulfonic acid in a solvent such as chloroform dichloromethane, toluene, methanol at a temperature between 20 and 150ºC to yield the corresponding imines V that upon isolation are allowed to further react with the corresponding alkenes of general formula IV in the presence of the same acids, solvents and conditions depicted above.

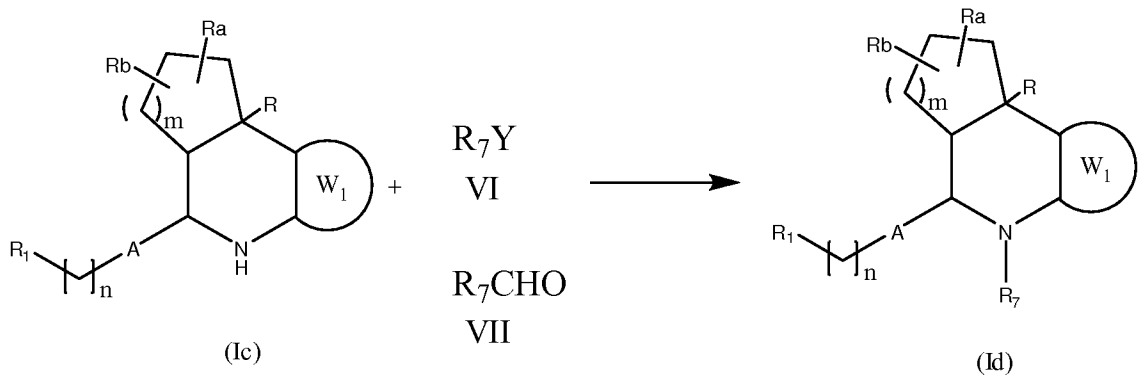
The reactions of scheme 1 and 2 are only applicable to the preparation of compounds of general formula I where X is NR_7.

Compounds of general formula II, III and IV are either commercially available or are synthesized according to methods known in the art.

In the particular case in which X is NR_7 with R_7 being C_{1-6}-alkyl, compounds of general formula (Id) can be obtained from compounds of general formula (Ic) by reaction with an alkylating agent such as VI wherein Y is an halogen atom such as chlorine, bromine or iodide or a sulphonate ester such as mesilate, tosilate or trifluoromethanesulphonate in basic media such as sodium hydride and in a solvent such as THF or DMF at a temperature from 0 to 150ºC (see scheme 3). Alternativelly, compounds of general formula (Id) can be obtained by reductive

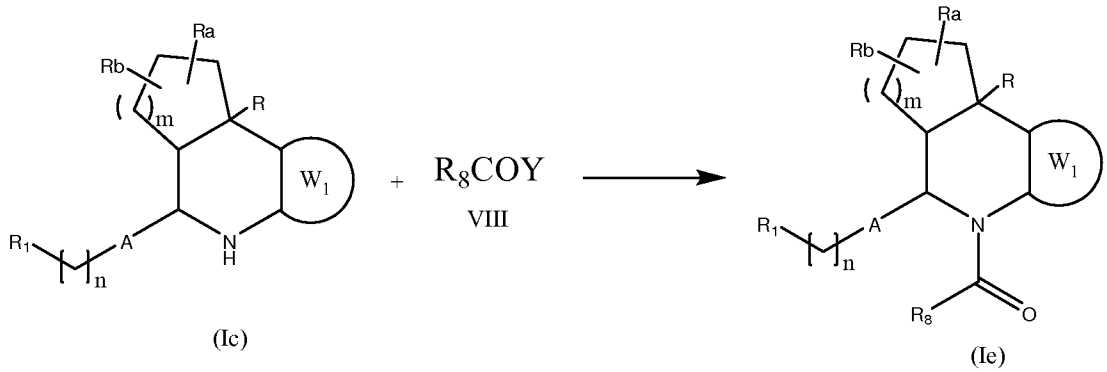
amination of aldehydes of general formual VII with amines of general formula (Ic) in acidic media such as acetic acid and in a protic solvent such as methanol or ethanol and with a reductive agent such as sodium borohydride, sodium triacetoxyborohydride or sodium cyanoborohydride at a temperature from 0ºC to the boiling point of the solvent. As an alternative to the acidic media a Lewis acid such as zinc chloride can be used.

Scheme 3



In the particular case in which X is NR_7 with R_7 being a $-COR_8$, compounds of general formual (Ie) (see scheme 4 below), can be obtained from compounds of general formula (Ic) by reaction of an acylating agent such as VIII in which R8 is a C_{1-6}-alkyl and Y is an halogen. The reaction takes place in basic media such as triethylamine, pyridine or diisopropylethylamine with a solvent such as dichloromethane, DMF, THF or pyridine at a temperature between 20 and 150ºC and in a standard reactor or in a microwave apparatus.

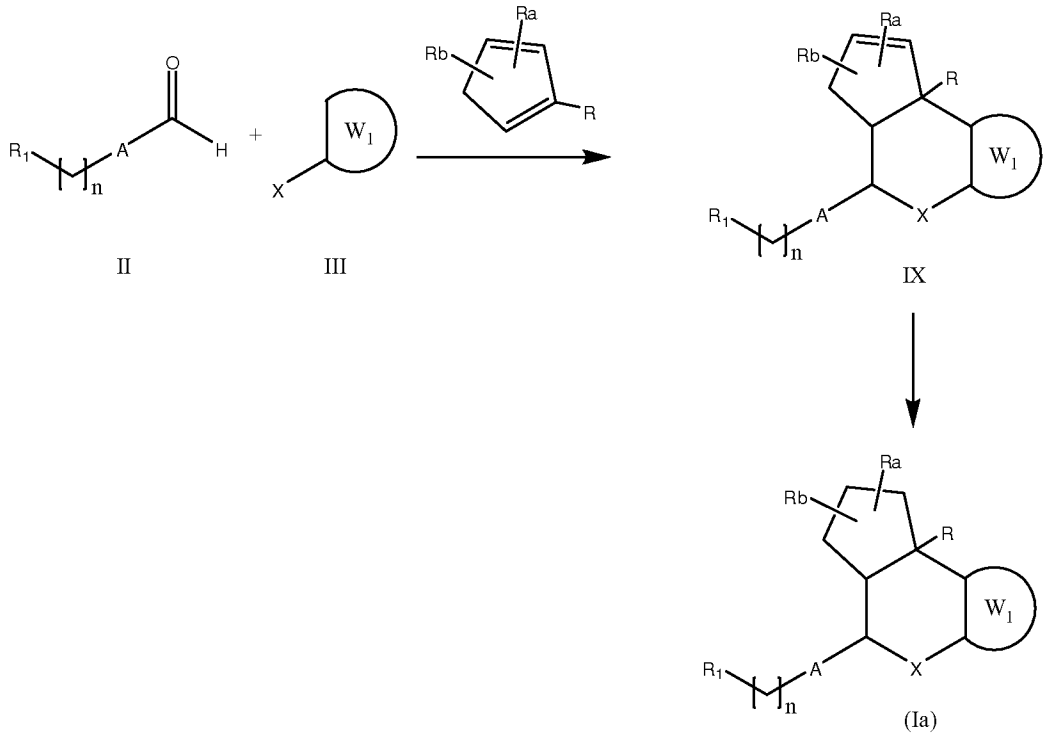
Scheme 4



In the particular case in which m is 1, compounds of general formula (Ia) can be obtained as depicted in scheme 5. Aldehydes of general formula II react with

amines of general formula III in the presence of cyclopentadiene under the conditions described above to yield compounds of general formula IX. Reaction of compounds of general formula IX under hydrogen using a catalyst such as Pd/C, Pd(OH)2/C, PtO2 in solvents such as methanol, ethanol, tetrahydrofurane, at atmospheric pressure or under hydrogen pressure at rt or higher yield the compounds of general formula (Ia).

Scheme 5



When the defined groups R_1 to R_8 are susceptible to chemical reaction under the conditions of the hereinbefore described processes or are incompatible with said processes, conventional protecting groups may be used in accordance with standard practice, for example see T.W. Greene and P.G.M. Wuts in "protective Groups in Organic Chemistry", 3rd Edition, John Wiley&Sons (1999). It may be that deprotection will form the last step in the synthesis of compounds of formula (I).

An additional aspect of the invention relates to the therapeutic use of the compounds of general formula (I). As mentioned above, compounds of general

formula (I) show a strong affinity to EP1 receptors. For this reason, they are suitable for the treatment and/or the prophylaxis of disorders and diseases mediated by EP1 receptors.

Compounds of the invention are particularly useful for modulating pain. The compounds of the present invention can treat or prevent the pain associated with several pathological conditions comprising, among others, inflammatory related pain (Hall et al. 2007) including low back and neck pain, skeletal pain, post-partum pain, toothache, sprains and straits, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns including radiation and corrosive chemical injuries and sunburns; postoperative pain (Omote et al. 2001) including dental procedures; neuropathic pain (Kawahara et al. 2001); visceral pain (Sarkar et al. 2003); tension headache; cluster headaches; migraine and the like.

Moreover, by inhibition of prostanoid-induced smooth muscle contraction by antagonizing contractile prostanoids or mimicking relaxing prostanoids, EP1 modulators may be used in the treatment of motility–related disorders (with or without pain) such as gastroinstestinal disorders (Sarkar et al. 2003; Mizuguchi et al 2010) and urinary incontinence and other urinary tract diseases (Teramura et al. 2000; Lee et al. 2007; Okada et al., 2010; Wilbraham et al 2010; Miki et al 2010), dysmenorrhea and preterm labour.

The compounds of the invention can also be useful in prostaglandin-mediated proliferation disorders such as in diabetic retinopathy and tumour angiogenesis, cancer (Watanabe et al. 1999; Niho et al. 2005), the inhibition of cellular neoplasic transformations and metastatic tumour growth.

They can further be used in the treatment of neurodegenerative diseases (including senile dementia, Alzheimer's disease, Pick's disease, Huntington's chorea, Parkinson's disease, Creutzfeldt-Jakob disease, or Amyotrophic Lateral Sclerosis) (Li et al. 2011), neuroprotection/stroke (Abe et al 2009), glaucoma (Woodward et al 1997), bone loss (osteoporosis) and the proportion of bone

formation (treatment of fractures) (Zhang et al 2011; Lee et al. 2007) and other bone diseases such as Paget's disease.

As PGE2-induced hyperthermia in the rat is mediated predominantly through the EP1 receptor (Hönemann et al. 2001; Oka et al. 2003) different kinds of fever as rheumatic fever, symptoms associated with influenza or other viral infections as well as common cold can be also target diseases for EP1 modulators.

The compounds of the invention can also have a cytoprotective activity in patients under different gastrointestinal disorders as related with chemotherapy, or irritable bowel disease. Other diseases that can be treated or prevented with the compounds of the invention include gastrointestinal bleeding, coagulation disorders including anaemia such as hypoprothrombinemia, haemophilia or other bleeding problems; kidney diseases (nephritis (Rahal et al. 2006), particularly mesangial proliferative glomerulonephritis and nephritic syndrome); thrombosis, and occlusive vascular diseases.

In this sense, compounds of formula (I) are suitable to treat or to prevent diseases or disorders comprising inflammatory related pain including low back and neck pain, skeletal pain, post-partum pain, toothache, sprains and straits, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (such as osteoarthritis), gout and ankylosing spondylitis, bursitis, burns including radiation and corrosive chemical injuries and sunburns; postoperative pain; neuropathic pain; visceral pain; tension headache; cluster headaches; migraine; motility-related disorders including gastrointestinal disorders, urinary incontinence and other urinary tract diseases; dysmenorrhea; preterm labour; diabetic retinopathy; tumour angiogenesis; cancer; metastatic tumour growth; neurodegenerative diseases including senile dementia, Alzheimer's disease, Pick's disease, Huntington's chorea, Parkinson's disease, Creutzfeldt-Jakob disease, or amyotrophic lateral sclerosis; neuroprotection/stroke; glaucoma; osteoporosis; bone fractures; Paget's disease; hyperthermia including different types of fever as rheumatic fever; symptoms associated with influenza or other viral infections; common cold, gastrointestinal disorders related with chemotherapy or irritable bowel syndrome; gastrointestinal bleeding; coagulation disorders including anaemia, hypoprothrombinemia,

haemophilia or other bleeding problems; kidney diseases including nephritis, particularly mesangial proliferative glomerulonephritis and nephritic syndrome; thrombosis and occlusive vascular diseases.

The invention thus relates to a compound of formula (I) for use in the treatment and/or prophylaxis of an EP1-mediated disease or disorder. In one embodiment, the EP1-mediated disease or disorder is selected from the group consisting of pain, motility-related disorders, gastrointestinal disorders, urinary tract diseases, cancer, neurodegenerative diseases, stroke, glaucoma, bone diseases, fever, coagulation disorders and occlusive vascular diseases. In a preferred embodiment, the EP1-mediated disease or disorder is pain. In another embodiment, the EP1-mediated disease or disorder is selected from the group consisting of inflammatory related pain including low back and neck pain, skeletal pain, post-partum pain, toothache, sprains and straits, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (such as osteoarthritis), gout and ankylosing spondylitis, bursitis, burns including radiation and corrosive chemical injuries and sunburns; postoperative pain; neuropathic pain; visceral pain; tension headache; cluster headaches; migraine; motility-related disorders including gastrointestinal disorders, urinary incontinence and other urinary tract diseases; dysmenorrhea; preterm labour; diabetic retinopathy; tumour angiogenesis; cancer; metastatic tumour growth; neurodegenerative diseases including senile dementia, Alzheimer's disease, Pick's disease, Huntington's chorea, Parkinson's disease, Creutzfeldt-Jakob disease, or amyotrophic lateral sclerosis; neuroprotection/stroke; glaucoma; osteoporosis; bone fractures; Paget's disease; hyperthermia including different types of fever as rheumatic fever; symptoms associated with influenza or other viral infections; common cold, gastrointestinal disorders related with chemotherapy or irritable bowel syndrome; gastrointestinal bleeding; coagulation disorders including anaemia, hypoprothrombinemia, haemophilia or other bleeding problems; kidney diseases including nephritis, particularly mesangial proliferative glomerulonephritis and nephritic syndrome; thrombosis and occlusive vascular diseases. In a preferred embodiment, the EP1-mediated disease or disorder is pain comprising inflammatory related pain, including low back and neck pain, skeletal pain, post-partum pain, toothache, sprains and straits, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis,

degenerative joint diseases (such as osteoarthritis), gout and ankylosing spondylitis, bursitis, burns including radiation and corrosive chemical injuries and sunburns; postoperative pain; neuropathic pain; visceral pain; tension headache; cluster headaches; migraine.

A related aspect refers to the use of at least one compound of general formula (I) for the manufacture of a medicament for the treatment and/or prophylaxis diseases or disorders mediated by EP1 receptors or in which EP1 receptors are involved.

In one embodiment, the EP1-mediated disease or disorder is selected from the group consisting of pain, motility-related disorders, gastrointestinal disorders, urinary tract diseases, cancer, neurodegenerative diseases, stroke, glaucoma, bone diseases, fever, coagulation disorders and occlusive vascular diseases. In a preferred embodiment, the EP1-mediated disease or disorder is pain. In another embodiment, the EP1-mediated disease or disorder is selected from the group consisting of inflammatory related pain including low back and neck pain, skeletal pain, post-partum pain, toothache, sprains and straits, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (such as osteoarthritis), gout and ankylosing spondylitis, bursitis, burns including radiation and corrosive chemical injuries and sunburns; postoperative pain; neuropathic pain; visceral pain; tension headache; cluster headaches; migraine; motility-related disorders including gastrointestinal disorders, urinary incontinence and other urinary tract diseases; dysmenorrhea; preterm labour; diabetic retinopathy; tumour angiogenesis; cancer; metastatic tumour growth; neurodegenerative diseases including senile dementia, Alzheimer's disease, Pick's disease, Huntington's chorea, Parkinson's disease, Creutzfeldt-Jakob disease, or amyotrophic lateral sclerosis; neuroprotection/stroke; glaucoma; osteoporosis; bone fractures; Paget's disease; hypertermia including different types of fever as rheumatic fever; symptoms associated with influenza or other viral infections; common cold, gastrointestinal disorders related with chemotherapy or irritable bowel syndrome; gastrointestinal bleeding; coagulation disorders including anaemia, hypoprothrombinemia, haemophilia or other bleeding problems; kidney diseases including nephritis, particularly mesangial proliferative glomerulonephritis and nephritic syndrome; thrombosis and

occlusive vascular diseases. In another embodiment, the EP1-mediated disease or disorder is selected from the group consisting of inflammatory related pain (including low back and neck pain, skeletal pain, post-partum pain, toothache, sprains and straits, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (such as osteoarthritis), gout and ankylosing spondylitis, bursitis, burns including radiation and corrosive chemical injuries and sunburns); postoperative pain; neuropathic pain; visceral pain; tension headache; cluster headaches; and migraine.

An aspect of the invention related to the therapeutic use of the compounds of general formula (I) is a method of treatment and/or prophylaxis of disorders and diseases mediated by EP1 receptors which comprises administering to a patient in need thereof a therapeutically effective amount of at least one compound of general formula (I). In one embodiment, the EP1-mediated disease or disorder is selected from the group consisting of pain, motility-related disorders, gastrointestinal disorders, urinary tract diseases, cancer, neurodegenerative diseases, stroke, glaucoma, bone diseases, fever, coagulation disorders and occlusive vascular diseases. In a preferred embodiment, the EP1-mediated disease or disorder is pain. In another embodiment, the EP1-mediated disease or disorder is selected from the group consisting of inflammatory related pain including low back and neck pain, skeletal pain, post-partum pain, toothache, sprains and straits, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (such as osteoarthritis), gout and ankylosing spondylitis, bursitis, burns including radiation and corrosive chemical injuries and sunburns; postoperative pain; neuropathic pain; visceral pain; tension headache; cluster headaches; migraine; motility-related disorders including gastrointestinal disorders, urinary incontinence and other urinary tract diseases; dysmenorrhea; preterm labour; diabetic retinopathy; tumour angiogenesis; cancer; metastatic tumour growth; neurodegenerative diseases including senile dementia, Alzheimer's disease, Pick's disease, Huntington's chorea, Parkinson's disease, Creutzfeldt-Jakob disease, or amyotrophic lateral sclerosis; neuroprotection/stroke; glaucoma; osteoporosis; bone fractures; Paget's disease; hyperthermia including different types of fever as rheumatic fever; symptoms associated with influenza or other viral infections; common cold, gastrointestinal disorders related with chemotherapy or irritable bowel syndrome; gastrointestinal

bleeding; coagulation disorders including anaemia, hypoprothrombinemia, haemophilia or other bleeding problems; kidney diseases including nephritis, particularly mesangial proliferative glomerulonephritis and nephritic syndrome; thrombosis and occlusive vascular diseases. In another embodiment, the EP1-mediated disease or disorder is selected from the group consisting of inflammatory related pain (including low back and neck pain, skeletal pain, post-partum pain, toothache, sprains and straits, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (such as osteoarthritis), gout and ankylosing spondylitis, bursitis, burns including radiation and corrosive chemical injuries and sunburns); postoperative pain; neuropathic pain; visceral pain; tension headache; cluster headaches; and migraine.

The amount of active ingredient that must be administered to the patient depends on the patient's weight, the type of application, the condition and severity of the disease. Normally, in human beings 1 to 1500 mg of the active compound is administered daily in one or several doses.

A further aspect of the invention regards a pharmaceutical composition which comprises a compound of general formula (I), and at least a pharmaceutically acceptable carrier, additive, adjuvant or vehicle.

The auxiliary materials or additives can be selected among carriers, excipients, support materials, lubricants, fillers, solvents, diluents, colorants, flavour conditioners such as sugars, antioxidants and/or agglutinants. In the case of suppositories, this may imply waxes or fatty acid esters or preservatives, emulsifiers and/or carriers for parenteral application. The selection of these auxiliary materials and/or additives and the amounts to be used will depend on the form of application of the pharmaceutical composition.

The pharmaceutical composition in accordance with the invention can be adapted to any form of administration, be it orally or parenterally, for example pulmonarily, nasally, rectally and/or intravenously. Therefore, the formulation in accordance with the invention may be adapted for topical or systemic application, particularly for dermal, subcutaneous, intramuscular, intra-articular, intraperitoneal,

pulmonary, buccal, sublingual, nasal, percutaneous, vaginal, oral or parenteral application.

Suitable preparations for oral applications are tablets, pills, chewing gums, capsules, granules, drops or syrups. Suitable preparations for parenteral applications are solutions, suspensions, reconstitutable dry preparations or sprays.

The compounds of the invention are formulated as deposits in dissolved form or in patches, for percutaneous application.

Skin applications include ointments, gels, creams, lotions, suspensions or emulsions.

The preferred form of rectal application is by means of suppositories.

EXPERIMENTAL SECTION

The following abbreviations are used along the experimental section:

DMF: dimethylformamide

BuLi: butyl lithium

EtAcO: ethyl acetate

EtOH: ethanol

DCM: dichloromethane

NMR: nuclear magnetic resonance

MeOH: methanol

NBS: *N*-bromosuccinimide

THF: tetrahydrofurane

Et_2O: diethyl ether

r.t.: room temperature

ACN: acetonitrile

TFA: trifluoroacetic acid

^tBuONa: sodium tert-butoxide

AIBN: 2,2'-azobis (2-methylpropionitrile)

HCl: hydrochloride acid

NaOH: sodium hydroxide

LiOH: lithium hydroxide

NH_4Cl: ammonium chloride

$NaHCO_3$: sodium bicarbonate

Na_2CO_3: sodium carbonate

Et_3N: triethylamine

$MgSO_4$: magnesium sulphate

$AgNO_3$: silver nitrate

AgBr: silver bromide

$NaIO_4$: sodium periodate

OsO_4: osmium tetraoxide

IPA: Isopropanol

$^{i}PrMgCl$: isopropylmagnesium chloride

$^{i}PrMgCl.LiCl$: isopropylmagnesium chloride lithium chloride

t_R: retention time (min)

$POCl_3$: phosphorus oxychloride

$BF_3.OEt_2$: boron trifluoride diethyletherate

$Pd_2(dba)_3$: tris(dibenzylidineacetone)dipalladium

(+)-BINAP: (R)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

$NiCl_2.6H_2O$: nickel (II) chloride hexahydrated.

HNO_3: nitric acid

$SnCl_2.2H_2O$: stannous chloride dihydrate

$NaBH_4$: sodium borohydride

$NaCNBH_3$: sodium cyanoborohydride

Pt_2O: platinum (iv) oxide

brs: broad signal

s: singlet

d: doublet

t: triplet

q: quartet

qn: quintet

m: multiplet

dd: doublet of doublets

dt: doublet of triplets

ddd: doublet of doublet of doublets

dm: doublet of multiplet

dq: doublet of quartet

The following HPLC methods for LC-MS spectra have been used:

Method 1: X-Bridge C18, 3.5 µm 4.6 x 50 mm column; temperature: 25ºC; rate 2.0 mL/min; eluent: A = HCOOH 1 mM, B = ACN:MeOH:HCOOH (1:1:0.0005); gradient: 100% to 5% A in 12 min, 5% A 1 min, 5 to 100% A 1 min.

Method 2: X-Bridge C18, 3.5 µm 4.6 x 50 mm column; temperature: 25ºC; rate 2.0 mL/min; eluent: A = HCOOH 1 mM, B = ACN:MeOH:HCOOH (1:1:0.0005); gradient: 95 to 0% A in 5.5 min, 0% A 3 min, 0 to 95% A 0.5 min.

Method 3: X-Bridge C18, 3.5 µm 4.6 x 50 mm column; temperature: 25ºC; rate 2.0 mL/min; eluent: A = HCOOH 1 mM, B = ACN:MeOH:HCOOH (1:1:0.0005); gradient: 95 to 0% A in 4.5 min, 0% A 1.5 min, 0 to 95% A 0.5 min.

Method 4: X-Bridge C18, 3.5 µm 4.6 x 50 mm column; temperature: 25ºC; rate 2.0 mL/min; eluent: A = NH4CO3 10 mM, B = ACN; gradient: 95 to 0% A in 7 min.

Method 5: X-Bridge C18 XP, 2.5 µm 4.6 x 30 mm column; temperature: 40ºC; rate 2.0 mL/min; eluent: A = NH4CO3 10 mM, B = ACN; gradient: 0.5 min. hold at 95% A, 95 to 0% A in 6.5 min., 1 min hold at 0% A.

Method 6: Waters Acquity UPLC BEH C18, 1.7 µm 2.1x50 mm; temperature 40 ºC; rate 0.5 mL/min; eluent A= ACN, B=NH4HCO3; gradient: 0 min 10 %A to 3.75 min 90 %A.

Separation of enantiomers was carried out in a Preparative Waters HPLC (pump Waters 600; Manual injector Waters 2700; Detector Waters 2487; Software: MassLynx 3.5). Using preparative packed column with Chiralpak IA (20 µm) using a self-packing system (195 mm x 50 mm). Flux 55 mL/min and fraction collection λ = 254 nm.

Optical purity of the separated enantiomers were determinated by HPLC (Chiralpak IA 250 x 4.6 mm, 5 µm, 10 µL, 1 mL/min). Using the same eluents of the preparative chiral chromatography.

Optical rotation of the separated enantiomers were determined in a polarimeter JASCO P-2000 with a cell of 1 mL.

Intermediate compounds

Intermediate compound 1: 1-cyclopropyl-4-nitrobenzene

Method 1: To a solution of 1-cyclopropylbenzene (8.46 mmol, 1g) dissolved in anhydride acetic acid (5 mL) and cooled to 0ºC was added HNO_3 (0.63 mL) and the resulting solution was stirred at room temperature 4 h. The reaction mixture was carefully poured in ice and the resulting solution extracted with diethyl ether. The combined extracts were evaporated. The crude product was purified by flash chromatography on silica gel using an elution of 8% dichloromethane in hexanes to afford a mixture of 1-cyclopropyl-2-nitrobenzene and 1-cyclopropyl-4-nitrobenzene (ratio 3:1).(430 mg. Yield:31%).

LC-MS: t_R = 3.10 $[M+H]^+$ = 164 (method 3)

Method 2: To a solution of 1-bromo-4-nitrobenzene (4.95 mmol, 1 g), cyclopropylboronic acid (6.43 mmol, 553 mg), palladium acetate (0.198 mmol, 45 mg), tricyclohexyl phosphine (0.445 mmol, 125 mg) and potassium carbonate (16.4 mmol, 3.5 g) was dissolved in Toluene (20mL) and H_2O (2 mL) under Argon. The resulting solution was heated for 1h at 80ºC. After the reaction mixture was cooled and concentrated *in vacuum*. The crude product was purified by flash chromatography on silica gel using an elution of 7% ethylacetate in hexanes to afford 1-cyclopropyl-4-nitrobenzene (800 mg. Yield: 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.1 (2H, dd, *J* = 2 & 6.8 Hz), 7.15 (2H, dd, *J* = 2 & 6.8 Hz), 1.99 (1H, m), 1.14-1.11 (2H, m), 0.83-080 (2H, m)

Intermediate compound 2: 2-cyclopropylbenzenamine

A mixture of 1-cyclopropyl-2-nitrobenzene and 4-cyclopropylbenzenamine (**intermediate compound 1**, method 1) (2.63 mmol, 430 mg) in dry MeOH was hydrogenated over Pd/C (2.5% w/w).The resulting solution was stirred 16 h at room temperature. The catalyst was removed by filtration and the solvent was evaporated. The crude product was purified by flash chromatography on silica gel using an elution of dichloromethane in hexanes to afford only 2-cyclopropylbenzamine (250 mg. Yield: 71%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07-7.03 (2H, m), 6.73-6.67 (2H, m), 1.72-1.65 (1H, m), 0.93-0.88 (2H, m), 0.63-0.6 (2H, m)

LC-MS: t_R = 1.28 $[M+H]^+$ = 134 (method 3)

Intermediate compound 3: 4-cyclopropylbenzenamine

Method 1: A solution of 1-cyclopropyl-4-nitrobenzene (**intermediate compound 1**, method 2) (1.32 mmol, 215 mg) in dry MeOH was hydrogenated over Pd/C (2.5% w/w).The resulting solution was stirred 16 h at room temperature. The catalyst was removed by filtration and the solvent was evaporated to give a mixture of 4-cyclopropylbenzenamine and 4-propylbenzenamine (8:2) (Yield: 90%).

LC-MS: t_R = 1.78 $[M+H]^+$ = 134 (method 3)

2.47 $[M+H]^+$ = 136 (method 3)

Method 2: A solution of 1-cyclopropyl-4-nitrobenzene (**intermediate compound 1**, method 2) (1.06 mmol, 176 mg) in EtOH (6 ml) and THF (6 mL) was hydrogenated over Pt_2O (5% mol).The resulting solution was stirred 16h at room temperature. The catalyst was removed by filtration and the solvent was evaporated to give the compound 4-cyclopropylbenzenamine (127 mg. Yield: 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (2H, dd, *J* = 2.0 & 6.4Hz), 6.61 (2H, dd, *J* = 2.0 & 6.4Hz), 1.81-1.79 (1H, m), 0.85-0.83 (2H, m), 0.58-0.56 (2H, m).

LC-MS: t_R = 1.78 $[M+H]^+$ = 134 (method 3)

Intermediate compound 4: 1-isopropoxy-4-nitrobenzene

4-Nitrophenol (1.79 mmol, 250 mg), propan-2-ol (2.67 mmol, 0.20 mL), triphenylphosphine (2.67 mmol, 702 mg) were combined in tetrahydrofuran (7.2 mL) and cooled to 0º C. Diisopropyl azodicarboxylate (2.67 mmol, 0.53 mL) was added dropwise. Once the addition was complete, the reaction was warmed to room temperature and stirred for 16 h. Reaction was concentrated and purified on silica gel, eluting with a gradient from 10% to 50% ethyl acetate in hexane to give 1-isopropoxy-4-nitrobenzene as an oil (320 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (2H, d, *J* = 9.2 Hz), 6.91 (1H, d, *J* = 9.2 Hz), 4.69-4.64 (1H, m), 1.39 (6H, d, *J* = 6.4 Hz)

LC-MS: t_R =3.20 $[M+H]^+$= 338 (method 3)

Intermediate compound 5: 4-isopropoxybenzenamine

To a solution of the **intermediate compound 4** (1.76 mmol, 320 mg) in absolute EtOH (8 mL), stannous chloride dehydrate (7.92 mmol, 1.78 g) was added and the reaction mixture was heated to reflux for 18 h. Reaction mixture was diluted with aqueous 1 N NaOH solution and ethyl acetate. The aqueous layer was extracted with EtAcO. The combined extracts were washed with brine, dried over anhydrous magnesium sulfate and concentrated in *vacuum* to give intermediate 5 (239 mg, 90%) with no further purification.

LC-MS: t_R =1.12 $[M+H]^+$= 152 (method 3)

Intermediate compound 6: 1-(cyclopropylmethoxy)-4-nitrobenzene

4-nitrophenol (9.3 mmol, 1.3g) was dissolved in DMF (20 mL). Potassium carbonate (3 eq., 28mmol, 3.8 g) and bromomethyl cyclopropane (1.1 eq., 10.23 mmol, 1mL) were added and the resulting mixture was stirred at room temperature for 60h. Then bromomethyl cyclopropane (1.1.eq.) and potassium carbonate (1eq.) were added and left at room temperature for 16h. The mixture was diluted with ethyl acetate and the organic layer washed by saturated sodium carbonate solution, brine, dried over anhydrous sodium sulfate, filtered and evaporated to afford a residue which was purified by chromatography over silica using hexane/ethyl acetate as eluents to give 1.67 g of the title compound (70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21-8.17 (2H, m), 6.96-6.93 (2H, m), 3.90 (2H, d, *J* = 7.2 Hz), 1.31-1.28 (1H, m), 0.71-0.67 (2H, m), 0.40-0.36 (2H, m).

LC-MS: t_R = 3.70 $[M+H]^+$= not ion (method 3)

Intermediate compound 7: 4-(cyclopropylmethoxy)benzenamine

1-(cyclopropylmethoxy)-4-nitrobenzene **intermediate compound 6** (8.6 mmol, 1.67g) was dissolved in ethanol (40 mL), and tin (II) chloride dihydrate (4.5 eq, 40.68 mmol, 9.18g) was added and the resulting mixture was refluxed for 16h. After cooling, the mixture was concentrated in vacuum. The residue was dissolved in ethyl acetate and 1N NaOH. This mixture was filtered through Celite®. The aqueous phase was extracted with ethyl acetate and the combine organic extracts were washed by brine, dried over anhydrous sodium sulphate, filtered and concentrated in vacuum to afford 1.18g as an oil which was used in the next step without further purification. (80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76-6.72 (2H, m), 6.65-6.62 (2H, m), 3.72 (2H, d, *J* = 6.8 Hz), 3.40 (2H, brs), 1.36-1.23 (1H, m), 0.63-0.58 (2H, m), 0.33-0.30 (2H, m).

LC-MS: t_R = 1.15 & 1.68 $[M+H]^+$= 164 (method 3).

Intermediate compound 8: N-(4-nitrophenyl)-methanesulfonamide

To a solution of 4-nitroaniline (7.24 mmol, 1 g) in DCM (10 mL) at 0ºC in an ice-bath, triethylamine (23.7 mmol, 3.3 mL) has been added under stirring. To this mixture a solution of methanesulphonyl chloride (23.7 mmol, 1.8 mL) has been added dropwise. The mixture was left to stir at room temperature 16 h. The reaction mixture was neutralized with saturated aqueous solution of NH_4Cl. The organic phase was separated, and, after evaporation of the solvent, the residue was washed with ethanol and filtered to give an bissulphonamide intermediate which was dissolved in a mixture ethanol:water (2:1, 36 mL). LiOH (39.1 mmol, 0.93 mg) was added to the solution and the reaction mixture was refluxed for two hours. After cooling at room temperature, the reaction mixture was neutralized with aqueous solution of NH_4Cl and the aqueous phase was extracted with DCM. The organic phase was separated and dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to give the title compound which was used in the next step without further purification. (1.3 g. Yield= 83%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (2H, d, *J* = 9.2 Hz), 7.31 (2H, d, *J* = 8.8 Hz), 3.15 (3H, s).

LC-MS: t_R =2.28 $[M+H]^+$= 215 (method 3)

Intermediate compound 9: N-(4-aminophenyl)-methanesulfonamide

To a solution of **intermediate compound 8** (3.23 mmol, 0.70 g) in MeOH (7 mL) Pd/C 10 % (10% w/w, 70 mg) was added and the mixture was hydrogenated at room temperature for 16 hours. After that, the reaction mixture was filtered through a pad of Celite© washing with THF. The solvent was evaporated under vacuum to give the title compound which was used at the next step without further purification. (0.4 g. Yield= 67%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.95 (1H, brs), 6.94 (2H, d, *J* = 8.8 Hz), 6.56 (2H, d, *J* = 8.8 Hz), 5.06 (1H, brs), 2.85 (3H, s).

LC-MS: t_R =0.36 $[M+H]^+$= 187 (method 3)

Intermediate compound 10: N-methyl-N-(4-nitrophenyl)-methanesulfonamide

To a solution of **intermediate compound 8** (2.31 mmol, 0.50 g) in anhydrous ACN (15 mL), anhydrous potassium carbonate (5.78 mmol, 0.79 g) and iodomethane (7.39 mmol, 0.46 mL) were added sequentially and the reaction mixture was stirred at room temperature for 18 h. The solvent was concentrated under vacuum and the crude residue was treated with water and EtAOc. The organic phase was separated and washed with saturated aqueous sodium carbonate solution and brine, dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum to give the title compound which was used in the next step without further purification. (0.50 g. Yield=95%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (2H, d, *J* = 9.2 Hz), 7.56 (2H, d, *J* = 9.2 Hz), 3.42 (3H, s), 2.92 (3H, s).

LC-MS: t_R =2.43 $[M+H]^+$= 231 (method 3)

Intermediate compound 11: N-(4-aminophenyl)-N-methyl-methanesulfonamide

$SnCl_2.2H_2O$ (10.8 mmol, 2.4 g) was added to a solution of **intermediate compound 10** (1.08 mmol, 0.25 g) in THF (15 ml). The mixture was kept under stirring at 70ºC for 16 h. After cooling, the solvent was evaporated under vacuum and the residue was treated with water and DCM. The mixture was neutralized with saturated $NaHCO_3$ and filtered through a pad of Celite© washing with DCM and water. The organic phase was separated in a funnel, washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum to give the title compound which was used in the next step without further purification. (0.19 g. Yield=87%)

LC-MS: t_R =0.93 $[M+H]^+$= 201 (method 3)

Intermediate compound 12: 3-(4-(hydroxymethyl)phenyl)propanoic acid

To a solution of 3-(4-formylphenyl)acrylic acid (5.68 mmol,1g) in EtOH (20mL), was added DIPEA (6.1 mmol, 1mL) and was hydrogenated over Pd/C (12.5% w/w).The resulting solution was stirred 2 h at room temperature. The catalyst was removed by filtration and the solvent was evaporated to give 3-(4-(hydroxymethyl)phenyl)propanoic acid (1 g. Yield:100%).

LC-MS: t_R = 2.12 $[M-H]^-$ = 179 (method 3).

Intermediate compound 13: 3-(4-formylphenyl)propanoic acid

To a solution of 3-(4-(hydroxymethyl)phenyl)propanoic acid (**intermediate compound 12**) (3.88 mmol, 700 mg) in dry chloroform (20 mL) was added Manganese (IV) oxide activated (19.4 mmol, 1.68 g). The reaction mixture was heated 48 h at 80ºC. The reaction mixture was cooled, filtered and concentrated *in vacuum*. The crude product was purified by flash chromatography on silica gel using an elution of methanol in dichloromethane to afford 3-(4-formylphenyl)propanoic acid (74mg. Yield:10%)

LC-MS: t_R = 2.37 $[M-H]^-$ = 177 (method 3).

Intermediate compound 14: methyl 2-(4-(hydroxymethyl)phenyl)acetate

To a solution of 2-(4-(hydroxymethyl)phenyl)acetic acid (1.2 mmol, 200mg) in dry MeOH (7 mL) was added acetyl chloride (2.4 mmol, 0.171 mL). The reaction mixture was stirred overnight at room temperature. The crude product was

concentrated *in vacuum* to give the compound methyl 2-(4-(hydroxymethyl)phenyl)acetate. (216 mg. Yield: 100%)

LC-MS: t_R = 2.28 $[M+H]^+$ = 181 (method 3).

Intermediate compound 15: methyl 2-(4-formylphenyl)acetate

A solution of 2-(4-(hydroxymethyl)phenyl)acetate (**intermediate compound 14**) (1.2 mmol, 216 mg) was dissolved in DCM (4 mL) and treated with manganese (IV) oxide (10.8 mmol, 938 mg) stirred 16h at room temperature. Total conversion was not achieved, then the reaction mixture was heated at 55ºC for 6 h. The crude product was filtered and concentrated *in vacuum* to give the compound methyl 2-(4-formylphenyl)acetate (150mg. Yield: 70%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.99 (1H, s), 7.87 (2H, d, *J*=6Hz), 7.50 (2H, d, *J*=5.6Hz), 3.83 (2H, s), 3.63 (3H, s).

LC-MS: t_R = 2.47 $[M+H]^+$ = 179 (method 3).

Intermediate compound 16: 4-formyl-2-methylbenzoic acid

A solution of 4-bromo-2-methylbenzoic acid (2.32 mmol, 500 mg) in dry THF (12 mL) was purged with argon. The solution was cooled at -78ºC, BuLi (2.5 M in hexane, 7.5 mmol, 3 ml), and DMF (5.16 mmol, 0.4 mL) was added and the reaction was stirred for 1h at -78ºC and then warmed to 25ºC and allowed to react for an additional hour. The reaction was quenched with aqueous 1N HCl and extracted with EtAcO. The organic layer was extracted with aqueous 1N NaOH and the aqueous layer was separated and the pH adjusted with aqueous 1N HCl. The aqueous was extracted with EtAcO, then washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The resulting crude was purified by flash chromatography on silica gel using an elution of methanol in dichloromethane. (112 mg. Yield: 29%)

LC-MS: t_R = 2.37 $[M-H]^-$ = 163 (method 3).

Intermediate compound 17: 3-chloro-4-formylbenzoic acid

To a solution of 4-bromo-3-chlorobenzoic acid (2.12 mmol, 500 mg) in anhydrous THF (6 mL) was added *i*-PrMgCl·LiCl (1.3 M in THF, 6.36 mmol, 4.9 mL) and was cooled at -78ºC under a N_2 atmosphere. After 10 minutes, the temperature was

raised to 0ºC and the reaction was stirred for a 1 h at 0ºC. DMF (10.6 mmol, 0.825 ml) was added. The reaction was warmed to room temperature, stirred for 1.5 h and quenched by saturated NH_4Cl. The layers were separated and the aqueous layer was extracted twice with EtAcO. The aqueous layer was separated and the pH adjusted with aqueous 1N HCl. The aqueous layer was extracted with EtAcO then washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to obtain the compound 3-chloro-4-formylbenzoic acid (300 mg. Yield:77%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.7 (1H, s), 10.37 (1H, s), 8.03-8.01 (2H, m), 7.97 (1H, d, *J*= 8Hz).

LC-MS: t_R = 2.47 $[M-H]^-$ = 183 (method 3).

Intermediate compound 18: 4-formyl-3-methylbenzoic acid

A solution of 4-bromo-3-methylbenzoic acid (2.32 mmol, 500 mg) in dry THF (12 mL) was purged with argon. The solution was cooled at -78ºC, BuLi (2.5M in hexane, 7.5 mmol, 3 mL), and DMF (5.16 mmol, 0.4 mL) was added and the reaction was stirred for 1h at -78ºC and then warmed to 25ºC and allowed to react for an additional hour. The reaction was quenched with aqueous 1N HCl and extracted with EtAcO. The organic layer was extracted with aqueous 1N NaOH and the aqueous layer was separated and the pH adjusted with aqueous 1N HCl. The aqueous was extracted with EtAcO then washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The resulting crude was purified by precipitation with hexane (90 mg. Yield: 23%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.25 (1H,s), 10.32 (1H, s), 7.92 (2H, m), 7.89 (1H, s), 2.67 (3H, s).

LC-MS: t_R = 2.53 $[M-H]^-$ = 163 (method 3).

Intermediate compound 19: methyl 4-formyl-3-methylbenzoate

A solution of methyl 4-iodo-3-methylbenzoate (21.7 mmol, 6 g) in dry THF (120 mL) was purged with argon. The solution was cooled to -15ºC, *i*-PrMgCl (2M in THF, 108.5 mmol, 54.25 mL), and DMF (130.2 mmol, 10 mL) were added and the reaction was stirred for 2 h at -15ºC and then warmed to 25ºC and allowed to react for an additional hour. The reaction was quenched with aqueous 1N HCl

and extracted with EtAcO. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The resulting crude was purified by flash chromatography on silica gel using an elution of 6% ethylacetate in hexanes to give methyl 4-formyl-3-methylbenzoate (3.08g .Yield: 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (1H, s), 8.00 (1H, d, *J*=8Hz), 7.99 (1H, s), 7.86 (1H, d, *J*=8Hz), 3.95 (3H, s), 2.72 (3H, s)

LC-MS: t_R = 2.85 $[M+H]^+$ = not ion (method 3).

Intermediate compound 20: methyl 4-formyl-3-methoxybenzoate

To a solution of methyl 4-(bromomethyl)-3-methoxybenzoate (1.93 mmol, 500 mg) in anhydrous DMSO (2.7 mL) was added $NaHCO_3$ (2.32 mmol, 195 mg). The reaction mixture was stirred for 3 h at 50ºC. Water was added to the reaction mixture, and the mixture was extracted with EtAcO. The organic layer was dried over anhydrous $MgSO_4$, the solvent was filtered and evaporated. The crude product was purified by flash chromatography on silica gel using an elution of 8% ethylacetate in hexanes to give methyl 4-formyl-3-methoxybenzoate (140 mg. Yield: 37%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.51 (1H, s), 7.87 (1H, d, J=8.Hz), 7.69-7.67 (2H, m), 4.00 (3H, s), 3.95 (3H, s).

LC-MS: t_R = 2.75 $[M+H]^+$ = 195 (method 3).

Intermediate compound 21 and 22: methyl 3-bromo-4-(dibromomethyl)benzoate and methyl 3-bromo-4-(bromomethyl)benzoate

Method 1: To a solution of methyl 3-bromo-4-methylbenzoate (2.18 mmol, 500 mg) in CCl_4 (3 mL), NBS (2.18 mmol, 389 mg), and benzoyl peroxide (0.111 mmol, 27 mg) were added. The reaction mixture was stirred 16 h at 82 ºC. The resulting solution extracted with dichloromethane and H_2O. The organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography on silica gel using an elution of 6% ethylacetate in hexanes afforded methyl 3-bromo-4-(bromomethyl)benzoate **22** (250 mg. Yield: 37%) and methyl 3-bromo-4-

(dibromomethyl)benzoate **21** which was again purified by flash chromatography on silica gel using an elution of 25% dichloromethane in hexane (110 mg. Yield: 17%).

Method 2: To a solution of methyl 3-bromo-4-methylbenzoate (2.18 mmol, 500 mg) in CCl_4 (3 mL), NBS (2.62 mmol, 466 mg), and AIBN (0.218 mmol, 36 mg) were added. The reaction mixture was stirred 16h at 90ºC. The resulting solution extracted with dichloromethane and H_2O. The organic layers were washed with saturated solution of $NaHCO_3$, dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography on silica gel using an elution of 4% ethylacetate in hexanes afforded methyl 3-bromo-4-(bromomethyl)benzoate **22** (250 mg. Yield: 37%) and methyl 3-bromo-4-(dibromomethyl)benzoate **21** which was again purified by flash chromatography on silica gel using an elution of 25% dichloromethane in hexane (110 mg. Yield: 17%)

Method 3: To a solution of methyl 3-bromo-4-methylbenzoate (2.18 mmol, 500 mg) in CCl_4 (5 mL), NBS (6.54mmol, 1170 mg), and benzoyl peroxide (0.218 mmol, 53 mg) were added. The reaction mixture was stirred 16h at 90 ºC. The reaction was cooled and the precipitate of succinimide and unreacted NBS was removed by filtration and washed with ethylacetate. The crude product was purified by flash chromatography on silica gel using an elution of 37% dichloromethane in hexanes afforded methyl 3-bromo-4-(dibromomethyl)benzoate **21**. (840 mg. Yield: 100%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (1H, d, *J*=1.6Hz), 8.09 (1H, d, *J*=8.8Hz), 8.04 (1H, dd, *J*= 1.6 & 8.4Hz), 7.07 (1H, s) 3.94 (3H, s).

LC-MS: t_R = 4.20 $[M+H]^+$ = not ion (method 3).

Methyl 3-bromo-4-(bromomethyl)benzoate **22**

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (1H, s), 7.95 (1H, d, *J*=8Hz), 7.53 (1H, d, *J*=8Hz), 4.61 (2H, s), 3.93 (3H, s).

LC-MS: t_R = 3.82 $[M+H]^+$ = not ion (method 3).

Intermediate compound 23: **methyl 3-bromo-4-formylbenzoate**

Method 1: To a solution of methyl 3-bromo-4-(dibromomethyl)benzoate (**intermediate compound 21**) (056 mmol, 220 mg) in acetonitrile (1mL) was added a solution of $AgNO_3$ (1.68 mmol, 285 mg) in water (0.5 mL), and the mixture was heated for 20 min under reflux. After the solution was allowed to cool, AgBr was filtered off and washed with DCM, the combined filtrate was washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by flash chromatography on silica gel using an elution of 4% ethylacetate in hexanes afforded methyl 3-bromo-4-formylbenzoate **23** (59 mg. Yield: 43%).

Method 2: To a solution of methyl 3-bromo-4-(bromomethyl)benzoate (**intermediate compound 22**) (1.43 mmol, 442 mg) in dichloromethane at 0ºC was added a DMSO solution (3.2 mL) of trimethylamine oxide (5.72 mmol, 430 mg). The reaction mixture was warmed at 28ºC for 8 h. To this mixture was added Na_2CO_3 solution, and the organic layer was extracted with DCM, and washed with brine, dried over $MgSO_4$ and concentrated to give methyl 3-bromo-4-formylbenzoate **23** (173 mg. Yield:49%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.41 (1H, s), 8.32 (1H, s), 8.07 (1H, d, *J* = 8Hz), 7.96 (1H, d, *J* = 8Hz), 3.97 (3H, s).

LC-MS: t_R = 3.25 $[M+H]^+$ = not ion (method 3).

Intermediate compound 24: 4-bromo-2-ethylbenzaldehyde

Method 1: To a solution of 4-bromo-2-ethyliodobenzene (1.61 mmol, 0.5 g) dissolved in anhydride THF (6 mL) at –78ºC was added 2.5 M *n*-butyllithium solution in hexane (1.9 mmol, 0.77 mL) dropwise. The mixture was stirred 30 min at -78 ºC before *N*-formylmorpholine (3.69 mmol, 0.37 mL) was added and the reaction stirred at this temperature for 1 h. The reaction was quenched with aqueous 1N HCl and extracted with EtAcO. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. Purification of the crude material by flash chromatography on silica gel using an elution of 3% ethylacetate in hexanes afforded the title compound (211 mg, 62%).

Method 2: The following compound was prepared using the same methodology as intermediate compound 19 using 4-bromo-2-ethyliodobenzene (6.4 mmol, 2g).

Purification of the crude material by flash chromatography on silica gel using an elution of 3% ethylacetate in hexanes afforded the title compound (1.18 g, 86%).

^{1}H (400 MHz, $CDCl_3$) δ 10.24 (1H, s), 7.69 (1H, d, *J* = 8.4 Hz), 7.51 (1H, dd, *J* = 8.4 & 2 Hz), 7.48 (1H, d, *J* = 2 Hz), 3.05 (2H, q, *J* = 7.6 Hz), 1.28 (3H, t, *J* = 7.6 Hz).

LC-MS: t_R = 3.67 $[M+H]^+$= 213/215 (method 3)

Intermediate compound 25: 3-ethyl-4-formylbenzonitrile

Method 1: the aldehyde **intermediate compound 24** (0.70 mmol, 150 mg), zinc cyanide (0.52 mmol, 61 mg) and tetrakis(triphenylphosphine)palladium (0) (0.02 mmol, 24 mg) were dissolved in anhydrous DMF (1.5 mL). The mixture was degassed with Argon for 5 min. The reaction was heated in a microwave at 220 ºC for 5 min. After that the reaction was diluted with water and extracted with toluene. The organic phase was separated and washed with brine, dried over and sodium sulfate, filtered and concentrated. Purification of the crude material by flash chromatography on silica gel using an elution of 3% ethylacetate in hexanes afforded the pure title compound (49 mg, 43%).

Method 2: the aldehyde **intermediate compound 24** (0.70 mmol, 150 mg) and copper (I) cyanide (0.91 mmol, 82 mg) were mixed in *N*-methyl-2-pyrrolidinone (2 mL). The mixture was heated in a microwave at 200 ºC for 15 min. The reaction was diluted with DCM and filtered through a pad of Celite® and concentrated to dryness. The crude material was purified by flash chromatography on silica gel using an elution of 3% ethylacetate in hexanes to afford the pure title compound (87 mg, 77%).

^{1}H (400 MHz, $CDCl_3$) δ 10.00 (1H, s), 7.93 (1H, d, *J* = 8 Hz), 7.66 (1H, dd, *J* = 8 & 1.2 Hz), 7.62 (1H, s), 3.11 (2H, q, *J* = 7.6 Hz), 1.31 (3H, t, *J* = 7.6 Hz).

LC-MS: t_R = 2.88 $[M+H]^+$ not ion (method 3).

Intermediate compound 26: 3-ethyl-4-formylbenzoic acid

A mixture of the 3-ethyl-4-formylbenzonitrile **intermediate compound 25** (1.38 mmol, 220 mg) and concentrated hydrochloric acid (2 mL) was boiled under reflux for 16 h. The mixture was cooled and diluted with water. The reaction mixture was extracted with Et_2O, the combined organic extracts were washed

with brine, dried over anhydrous magnesium sulfate and concentrated to dryness to afford the title compound which was used in the next step without further purification. (219 mg, 89%)

^{1}H (400 MHz, $CDCl_3$) δ 10.40 (1H, s), 8.09 (1H, dd, *J* = 8 & 1.2 Hz), 8.06 (1H, s), 7.94 (1H, d, *J* = 8.4 Hz), 3.15 (2H, q, *J* = 7.6 Hz), 1.33 (3H, t, *J* = 7.6 Hz).

LC-MS: t_R = 2.63 $[M+H]^-$ = 177 (method 3)

Intermediate compound 27: 4-bromo-2,6-dimethylbenzaldehyde

The following compound was prepared using the same methodology as in intermediate compound 19 using the 5-bromo-2-iodo-m-xylene (6.4 mmol, 2g). Purification of the crude material by flash chromatography on silica gel using an elution of 3% ethylacetate in hexanes afforded the title compound (1.27 g, 92%).

^{1}H (400 MHz, $CDCl_3$) δ 10.56 (1H, s), 7.28 (2H, brs), 2.59 (6H, s).

LC-MS: t_R = 3.73 $[M+H]^+$ not ion (method 3).

Intermediate compound 28: 4-formyl-3,5-dimethylbenzonitrile

The following compound was prepared using the same methodology as in intermediate compound 25 (method 2) using the aldehyde **intermediate compound 27** (0.70 mmol, 250 mg). The reaction was diluted with DCM and fltered through a pad of Celite® and concentrated to dryness. The crude material was purified by flash chromatography on silica gel using an elution of 15% ethylacetate in hexanes afforded the pure title compound (138 mg, 74%).

^{1}H (400 MHz, $CDCl_3$) δ 10.63 (1H, s), 7.40 (2H, brs), 2.63 (6H, s).

LC-MS: t_R = 2.88 $[M+H]^+$ not ion (method 3).

Intermediate compound 29: 4-formyl-3,5-dimethylbenzoic acid

The following compound was prepared using the same methodology as in intermediate compound 26 using the aldehyde **intermediate compound 28** (0.94 mmol, 150 mg). The mixture was cooled and diluted with water. The reaction mixture was extracted with Et_2O. The combined organic extracts were washed with brine, dried over magnesium sulfate and concentrated to dryness to afford the title compound which was used in the next step without further purification. (165 mg, 98%)

^{1}H (400 MHz, $CDCl_3$) δ 10.68 (1H, s), 7.83 (2H, s), 2.66 (6H, s).

LC-MS: t_R = 2.60 $[M+H]^-$ = 177 (method 3)

Intermediate compound 30: methyl 4-formyl-3,5-dimethylbenzoate

4-formyl-3,5-dimethylbenzoic acid **intermediate compound 29** (0.81 mmol, 145 mg) was dissolved in dry methanol (8 mL) and stirred for 10 min at 0ºC. Thionyl chloride (7.27 mmol, 0.53 mL) was added dropwise, the reaction mixture was slowly brought to room temperature and then stirred for 4 h. The methanol was evaporated and the resulting residue was extracted into DCM, washed with saturated sodium chloride, dried over anhydrous magnesium sulfate, filtered and evaporated to afford the title compound as a solid (141 mg, 91%).

^{1}H (400 MHz, $CDCl_3$) δ 10.66 (1H, s), 7.76 (2H, s), 3.94 (3H, s), 2.65 (6H, s).

LC-MS: t_R = 3.22 $[M+H]^+$ not ion (method 3).

Intermediate compound 31: 5-formylpyridine-2-carboxylic acid

To a solution of 6-bromopyridine-3-carbaldehyde (2.69 mmol, 500mg), was dissolved in a mixture of MeOH (2.7 mL) and DMF (2.7 mL) and Et_3N (5.38 mmol, 0.75 ml) was added. To this solution palladium (II) acetate (0.07 mmol, 15 mg), and 1,1-bis(diphenylphosphino)ferrocene (0.14 mmol, 75 mg) were added. The mixture was degassed and was bubbled carbon monoxide gas. The resulting solution was heated at 55ºC for 48 h. Total conversion was not achieved, then Et_3N (2.69 mmol, 0.38 mL), palladium(II)acetate (0.03mmol, 8 mg), and 1,1-bis(diphenylphosphino)ferrocene (0.07 mmol, 38 mg) were added again. The mixture was degassed and was again bubbled carbon monoxide gas. The resulting solution was heated at 55ºC for 24 hours. The crude product was poured into water and extracted with EtAcO. The aqueous layer was concentrated *in vacuum*, then was dissolved in EtAcO and washed with Na_2CO_3 saturated. The organic layer was dried with anhydrous sodium sulfate, filtered and concentrated *in vacuum* to give the compound methyl 5-formylpyridine-2-carboxylate (30 mg. Yield: 7%). The aqueous layer was concentrated and the crude was purified using reverse C_{18} chromatography using water (0.1% formic

acid) and acetonitrile (0.1% formic acid) as eluents to give the title compound 5-formylpyridine-2-carboxylic acid (84 mg. Yield: 19%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.6 (1H, s), 10.19 (1H, s), 9.17 (1H, s), 8.42 (1H, d, *J*=8Hz), 8.21 (1H, d, *J*=8Hz)

LC-MS: t_R = 1.8 $[M+H]^+$ = 166 (method 3).

Intermediate compound 32: 3-bromo-6-iodo-2-methylpyridine

Sodium iodide (2 eq., 16 mmol, 2.40 g) and 2,5-dibromo-6-methylpyridine (2.0 g, 8.0 mmol) were combined in propionitrile (20 mL) and the resulting slurry was stirred under nitrogen for 5 min. Iodotrimethylsilane (0.2 eq., 1.6 mmol, 0.23 mL) was added and the reaction mixture was heated at 95ºC with stirring under nitrogen for 16 h. The slurry was cooled to room temperature, diluted with a 1:1 mixture of ethylacetate and water. The mixture was stirred for 15 min and the aqueous and organic phases were then separated. The organic layer was washed sequentially with equal volume of saturated aqueous sodium bicarbonate solution, sodium thiosulfate (5% aqueous solution) and brine. The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduce pressure to afford the desired product which was purified by flash chromatography on silica gel using an elution of 4% ethylacetate in hexanes afforded the title compound as an oil (1.72 g, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (2H, s), 2.63 (3H, s).

LC-MS: t_R = 3.53 $[M+H]^+$= 298/300 (method 3)

Intermediate compound 33: 5-bromo-6-methylpyridine-2-carbonitrile

Under an inert atmosphere, 3- bromo-6-iodo-2-methylpyridine (**intermediate compound 32**) (1.25 g, 4.19 mmol) and acetonitrile (15 mL) were combined and stirred for 30 min with copper cyanide (0.5 eq., 2.0 mmol, 185 mg), sodium cyanide (0.8 eq., 3.35 mmol, 165 mg). The reaction mixture was heated at 80ºC with stirring under nitrogen for 16 h. The slurry was cooled to room temperature, diluted with a 0.5 M aqueous solution of ammonia and stirred for 15 min, filtered through Celite® and washed with ethylacetate. Organic layer was then separated. The organic layer was washed sequentially with 0.5 M aqueous solution of ammonia and brine. The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduce pressure. Purification by

flash chromatography on silica gel using an elution of 7% ethylacetate in hexanes afforded the title compound as an oil (650 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (1H, d, *J* = 8.4 Hz), 7.40 (1H, d, *J* = 8.4 Hz), 2.17 (3H, s).

LC-MS: t_R = 2.75 $[M+H]^+$= 197/199 (method 3)

Intermediate compound 34: 6-methyl-5-vinylpyridine-2-carbonitrile

An argon degassed solution of 5-bromo-6-methylpyridine-2-carbonitrile (**intermediate compound 33**) (650 mg, 3.3 mmol), 4,4,5,5,-tetramehyl-2-vinyl-1,3,2-dioxaborolane (3.3 mmol, 0.56 mL), tetrakis(triphenylphosphine)palladium (5 mol %, 0.16 mmol, 190 mg) and 2N aqueous sodium carbonate solution (3.4 eq., 11.22 mmol, 5.60 mL) in toluene/ethanol (2:1, 45 mL) was stirred at 95 ºC under argon for 16 h. The slurry was cooled to room temperature, diluted with ethylacetate and water. The organic layer was washed with brine and dried over anhydrous sodium sulphate, filtered and concentrated under reduce pressure to afford the desired product which was purified by flash chromatography on silica gel using an elution of 20% ethylacetate in hexanes afforded the title compound as an oil (246 mg, 52%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (1H, d, *J* = 8.0 Hz), 7.52 (1H, d, *J* = 8.0 Hz), 6.89 (1H, dd, *J* = 17.6 & 10.8 Hz), 5.79 (1H, d, *J* = 17.2 Hz), 5.58 (1H, d, *J* = 10.8 Hz), 2.62 (3H, s).

LC-MS: t_R = 2.58 $[M+H]^+$= 145 (method 3)

Intermediate compound 35: 5-formyl-6-methylpyridine-2-carbonitrile

6-Methyl-5-vinylpyridine-2-carbonitrile (**intermediate compound 34**) (245 mg, 1.7 mmol), was dissolved in acetone/water (6:1, 21 mL) and then OsO_4 (0.74 eq., 1.3 mmol, 330 mg) and $NaIO_4$ (3eq, 5.1 mmol, 1.09 g) were added thereto. The resulting mixture was kept at room temperature for 3 h. Filtration of the reaction mixture was carried out. Filtrate was diluted with ethylacetate. The organic layer was then separated and washed with a saturated aqueous sodium carbonate solution and brine, then dried over anhydrous sodium sulphate, filtered and concentrated under reduce pressure to afford the desired product which was purified by flash chromatography on silica gel using an elution of 40% ethylacetate in hexanes afforded the title compound as an solid (178 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.38 (1H, s), 8.23 (1H, d, *J* = 8.4 Hz), 7.73 (1H, d, *J* = 8.0 Hz), 2.94 (3H, s).

LC-MS: t_R = 1.68 & 1.77 $[M+H]^+$= not ion (method 3)

Intermediate compound 36: (E)-ethyl 2,4-dioxo-6-phenylhex-5-enoate

Sodium pellets (1eq, 0.1 mol, 2.3 g) were slowly added in absolute ethyl alcohol (100 mL). After the sodium had reacted, the solvent was removed under reduced pressure and anhydrous ether (130 mL) was added. The reaction mixture was cooled to -5ºC, and a solution of 4-phenyl-3-buten-2-one (14.6 g, 0.1 mol) and diethyl oxalate (1.2 eq., 0.12 mol, 16 mL) in anhydrous ether (25 mL) was added over 30 min. After stirring 16h at room temperature the yellow solid was filtered and washed with ether, after 1h of drying at room temperature the solid was partitioned between dichloromethane (600 mL) and 1N sulfuric acid (200 mL). The organic layer was then separated and dried over anhydrous sodium sulphate, filtered and concentrated under reduce pressure to afford the desired product (22.05 g, 89%) as a yellowish solid, which was used in the next step without further purification.

LC-MS: t_R = 3.80 $[M+H]^+$= 247 (method 3)

Intermediate compound 37 and 38: 1-methyl-5-styryl-1H-pyrazole-3-carboxylic acid ethyl ester and 2-methyl-5-styryl-2H-pyrazole-3-carboxylic acid ethyl ester

A solution of (*E*)-ethyl 2,4-dioxo-6-phenylhex-5-enoate (**intermediate compound 36**) (2.5 g, 0.01 mol) and methylhydrazine (1.2 eq., 0.012 mol, 0.65 mL) in ethanol was heated at reflux for 16h. The solvent was removed in vacuum and the residue was purified by flash chromatography on silica gel using hexane and ethylacetate as eluents. At 20% of ethylacetate in hexanes the isomer 2-methyl-5-styryl-2*H*-pyrazole-3-carboxylic acid ethyl ester **38** elutes firstly (710 mg), later at 40% of ethylacetate in hexanes the title isomer elutes to afford 1.64 g of 1-methyl-5-styryl-1*H*-pyrazole-3-carboxylic acid ethyl ester **37** (overall yield=92%).

1-methyl-5-styryl-1H-pyrazole-3-carboxylic acid ethyl ester **37**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (2H, dd, *J* = 8.8 & 1.6 Hz), 7.35 (2H, t, *J* = 7.2 Hz), 7.28-7.24 (1H, m), 7.14 & 7.11 (1H, 2s), 7.07 & 7.03 (1H, 2s), 7.01 (1H, s), 4.36 (2H, q, *J* = 6.8 Hz), 4.18 (3H, s), 1.40 (3H, t, *J* = 6.8 Hz).

LC-MS: t_R = 3.58 $[M+H]^+$= 257 (method 2)

2-methyl-5-styryl-2H-pyrazole-3-carboxylic acid ethyl ester **38**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.48 (2H, m), 7.41-7.36 (2H, m), 7.34-7.28 (1H, m), 7.10 & 7.06 (1H, 2s), 7.02 (1H, s), 6.92 & 6.87 (1H, 2s), 4.41 (2H, q, *J* = 7.2 Hz), 4.00 (3H, s), 1.41 (3H, t, *J* = 7.2 Hz).

LC-MS: t_R = 3.98 $[M+H]^+$= 257 (method 3)

Intermediate compound 39: 5-formyl-1-methyl-1H-pyrazole-3-carboxylic acid ethyl ester

The following compound was prepared using the same methodology as in Intermediate compound 35 using 1-methyl-5-styryl-1*H*-pyrazole-3-carboxylic acid ethyl ester (**intermediate compound 37**) (256 mg, 1.0 mmol) for 2h. Purification of the crude material using flash chromatography on silica gel using an elution of 25% ethylacetate in hexanes afforded the title compound as a solid (255 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (1H, s), 7.41 (1H, s), 4.43 (2H, q, *J* = 6.8 Hz), 4.25 (3H, s), 1.41 (3H, t, *J* = 7.6 Hz).

LC-MS: t_R = 1.78 & 2.05 $[M+H]^+$= not ion (method 3)

Intermediate compound 40: 3-formyl-1-methyl-1H-pyrazole-5-carboxylic acid ethyl ester

The following compound was prepared using the same methodology as in Intermediate compound 35 using 2-methyl-5-styryl-2*H*-pyrazole-3-carboxylic acid ethyl ester (**intermediate compound 38**) (700 mg, 2.73 mmol) for 1.30 h. Purification of the crude material using flash chromatography on silica gel using an elution of 26% ethylacetate in hexanes afforded the title compound as a solid (340 mg, 68%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (1H, s), 7.33 (1H, s), 4.36 (2H, q, *J* = 6.8 Hz), 4.28 (3H, s), 1.39 (3H, t, *J* = 7.6 Hz).

LC-MS: t_R = 1.78 & 2.05 $[M+H]^+$= not ion (method 3)

Intermediate compound 41: 4-((3aS,4R,9bR)-8-bromo-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

A catalytic amount of scandium trifluoromethanesulfonate (0.1 eq., 0.1 mmol, 49 mg) in anhydrous acetonitrile (5 mL) was added to a mixture of 4-formylbenzoic acid (1 mmol, 150 mg), 4-aminobromobenzene (1 mmol, 172 mg), and fresh distilled ciclopentadiene (5 eq, 5 mmol, 0.40 mL). The reaction mixture was stirred at room temperature for 16 h. Solvent was evaporated and purification of the crude material (1:23 mixture of regioisomers exo/endo) by flash chromatography on silica gel using an elution of 40% ethylacetate in hexanes afforded the title endo-isomer as a white solid (64 mg, 17%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (2H, d, *J* = 8 Hz), 7.54 (2H, d, *J* = 8.4 Hz), 7.16 (1H, s), 7.02 (1H, dd, *J* = 8.4 & 1.6 Hz), 6.69 (1H, d, *J* = 8.4 Hz), 5.92 (1H, brs), 5.86 (1H, brs), 5.57 (1H, d, *J* = 4 Hz), 4.58 (1H, s), 4.02 (1H, d, *J* = 6.8 Hz), 2.90-2.96 (1H, m), 2.39-2.32 (1H, m), 1.57 (1H, dd, *J* = 15.6 & 8.4 Hz).

LC-MS: t_R = 3.57 $[M+H]^+$= 370/372 (method 2)

Intermediate compound 42: 4-((3aS,4R,9bR)-8-(trifluoromethyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-trifluoromethylaniline (1 mmol). Solvent was evaporated and purification of the crude material (1:30 mixture of exo/endo regioisomers) by flash chromatography on silica gel using an elution of 40% ethylacetate in hexanes afforded the endo-compound as a solid. (318 mg. Yield: 88%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.90 (1H, brs), 7.94 (2H, d, *J* = 8.4 Hz), 7.55 (2H, d, *J* = 8.4 Hz), 7.30 (1H, s), 7.19 (1H, dd, *J* = 8.4 & 1.6 Hz), 6.85 (1H, d, *J* = 8.4 Hz), 6.41 (1H, s), 5.94-5.92 (1H, m), 5.58 (1H, d, *J* = 4.8 Hz), 4.70 (1H, d, *J* = 2.8 Hz), 4.08 (1H, d, *J* = 8.8 Hz), 2.97-2.92 (1H, m), 2.38-2.30 (1H, m), 1.59 (1H, dd, *J* = 14.8 & 8.4 Hz).

LC-MS: t_R = 7.90 $[M+H]^+$= 360 (method 1)

Intermediate compound 43: 4-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-methylaniline (1 mmol). Solvent was evaporated and purification of the crude material (1:20 mixture of exo/endo regioisomers) by flash chromatography on silica gel using an elution of 50% ethylacetate in hexanes afforded the endo-compound as a white solid which was precipitated in acetonitrile, filtered and dried in vacuum to give the title compound (121 mg. Yield: 39%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (2H, d, *J* = 8.4 Hz), 7.55 (2H, d, *J* = 8.4 Hz), 6.79 (1H, s), 6.68 (1H, dd, *J* = 8.0 & 1.6 Hz), 6.62 (1H, d, *J* = 8.4 Hz), 5.83-5.81 (1H, m), 5.53 (1H, d, *J* = 4.8 Hz), 5.47 (1H, brs), 4.52 (1H, d, *J* = 2.8 Hz), 3.98 (1H, d, *J* = 8.4 Hz), 2.91 (1H, dq, *J* = 9,2 & 4.5 Hz), 2.41-2.34 (1H, m), 2.13 (3H, s), 1.56 (1H, dd, *J* = 15.2 & 8.8 Hz).

LC-MS: t_R = 7.47 $[M+H]^+$= 306 (method 1)

Intermediate compound 44: 4-((3aS,4R,9bR)-8-chloro-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-chloroaniline (1mmol). Solvent was evaporated and purification of the crude material (1:20 mixture of exo/endo regioisomers) by flash chromatography on silica gel using an elution of 40% ethylacetate in hexanes afforded the endo-compound as a white solid which was precipitated in acetonitrile, filtered and dried in vacuum to give the title compound (250 mg. Yield: 77%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (2H, d, *J* = 8.4 Hz), 7.54 (2H, d, *J* = 8.4 Hz), 7.04 (1H, d, *J* = 2 Hz), 6.90 (1H, dd, *J* = 8.8 & 2.4 Hz), 6.73 (1H, d, *J* = 8.4 Hz), 5.90 (1H, s), 5.87-5.86 (1H, m), 5.56 (1H, d, *J* = 4.8 Hz), 4.58 (1H, d, *J* = 3.2 Hz), 4.03-4.00 (1H, m), 2.94-2.90 (1H, m), 2.40-2.32 (1H, m), 1.57 (1H, dd, *J* = 15.6 & 9.2 Hz).

LC-MS: t_R = 7.77 $[M+H]^+$= 326/328 (method 1)

Intermediate compound 45: *4-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-methoxy-3H-cyclopenta[c] quinolin-4-yl)benzoic acid*

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-formylbenzoic acid (3.33 mmol, 500 mg) and *p*-anisidine (3.33 mmol, 411.5 mg). Solvent was evaporated and purification of the crude material (1:8 mixture of exo/endo regioisomers) by flash chromatography on silica gel using an elution of 40% ethylacetate in hexanes afforded the endo-isomer. (550 mg.Yield:51%)

Endo-isomer: *4-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-methoxy-3H-cyclopenta[c] quinolin-4-yl)benzoic acid*

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (2H, d, *J*=8.4Hz), 7.57 (2H, d, *J*=8.4Hz), 6.69 (1H, d, *J*=8.8Hz), 6.63 (1H, d, *J*=2.8Hz), 6.54 (1H, dd, *J*=2.8 & 8.8Hz), 5.87-5.86 (1H,m), 5.57 (1H, da, *J*=4.4Hz), 5.36 (1H, s), 4.51(1H, d, *J*=2.8Hz), 4.04-4.01 (1H, m), 3.65 (3H, s), 2.95-2.92 (1H, m), 2.44-2.37 (1H, m), 1.62-1.56 (1H, m).

LC-MS: t_R = 4.40 $[M+H]^+$ = 322 (method 2)

Intermediate compound 46: 4-(6-cyclopropyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-formylbenzoic acid (1.88 mmol, 282 mg) and 2-cyclopropylbenzamine (**intermediate compound 2**) (1.88 mmol, 250 mg). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 30% ethylacetate in hexanes afforded the endo-isomer. (460 mg.Yield:73%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (2H, d, *J*=8.4Hz), 7.63 (2H, d, *J*= 8Hz), 6.9 (1H, d, *J*=7.6Hz), 6.75 (1H, d, *J*=7.2Hz), 6.59 (1H, t, *J*=4.6Hz), 5.58 (1H, m), 5.56 (1H,m), 4.77 (1H, s), 4.68 (1H,m), 4.08 (1H, d, *J*= 8.4Hz), 3.01-2.99 (1H, m), 2.44-2.38 (1H, m), 1.79-1.77 (1H, m), 1.65-1.59 (1H, m), 0.86-0.83 (2H, m), 0.59-0.57 (1H, m), 0.42-0.40 (1H, m).

LC-MS: t_R = 3.72 $[M+H]^+$ = 332 (method 3)

Intermediate compound 47 and 48: 4-(8-cyclopropyl-3a, 4, 5, 9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)benzoic acid and 4-(3a, 4, 5, 9b-tetrahydro-8-propyl-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-formylbenzoic acid (1.2 mmol, 181 mg) and 4-cyclopropylbenzenamine (**intermediate compound 3**, method 1) (1.2 mmol, 159 mg). Solvent was evaporated and purification of the crude material (1:9 mixture of exo/endo regioisomers of **47**) by flash chromatography on silica gel using an elution of 29% ethylacetate in hexanes afforded a mixture of endo-exo isomer cyclopropyl compound **47** (80%) and propyl compound **48** (17%). (220 mg.Yield:55%).

4-(8-cyclopropyl-3a, 4, 5, 9b-tetrahydro-3*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid (**47**)

LC-MS: $t_R = 5.17$ $[M+H]^+ = 332$ (method 2)

4-(3a, 4, 5, 9b-tetrahydro-8-propyl-3*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid (**48**)

C-MS: $t_R = 5.33$ $[M+H]^+ = 334$ (method 2)

Intermediate compound 49: 4-(8-fluoro-3a, 4, 5, 9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-formylbenzoic acid (1.35 mmol, 203 mg) and 4-fluoroaniline (1.35 mmol, 150 mg). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 50% ethylacetate in hexanes afforded the title compound. (339 mg.Yield:81%).

LC-MS: $t_R = 4.80$ $[M+H]^+ = 310$ (method 2)

Intermediate compound 50: 4-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-phenyl-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-phenylaniline (1 mmol). Solvent was

evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 80% ethylacetate in hexanes afforded the endo-isomer as a white solid which was precipitated in dichloromethane, filtered and dried in vacuum to give the title compound (113 mg, 30%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.88 (1H, brs), 7.94 (2H, d, *J* = 8.4 Hz), 7.59-7.54 (4H, m), 7.37 (2H, t, *J* = 7.6 Hz), 7.31 (1H, d, *J* = 2.0 Hz), 7.24-7.20 (2H, m), 6.82 (1H, d, *J* = 8.0 Hz), 5.97-5.96 (1H, m), 5.87 (1H, brs), 5.56 (1H, d, *J* = 4.8 Hz), 4.64 (1H, d, *J* = 2.8 Hz), 4.11 (1H, d, *J* = 8.4 Hz), 2.97 (1H, q, *J* = 8.8 Hz), 2.44-2.37 (1H, m), 1.60 (1H, dd, *J* = 16 & 9.6 Hz).

LC-MS: t_R = 10.92 $[M+H]^+$= 368 (method 1)

Intermediate compound 51: 4-(8-tert-butyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-formylbenzoic acid (1 mmol, 150 mg) and 4-tert-butylaniline (1 mmol, 150 mg). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 50% ethylacetate in hexanes afforded the title compound. (325 mg. Yield: 93%).

LC-MS: t_R = 5.37 $[M+H]^+$ = 348 (method 2)

Intermediate compound 52: 4-((3aS,4R,9bR)-8-ethyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-ethylaniline (1 mmol). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 40% ethylacetate in hexanes afforded the endo-isomer as a white solid which was precipitated in dichloromethane, filtered and dried in vacuum to give the title compound (230 mg, 53%).

LC-MS: t_R = 4.18 $[M+H]^+$= 320 (method 2)

Intermediate compound 53: 4-((3aS,4R,9bR)-8-carbamoyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-aminobenzamide (1 mmol). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 10% methanol in ethylacetate afforded the endo-isomer as a white solid (210 mg, 90%).

LC-MS: t_R = 2.33 $[M+H]^+$= 320 (method 2)

Intermediate compound 54: 4-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-isopropyl-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-isopropylaniline (1 mmol). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 40% ethylacetate in hexanes afforded the endo-isomer as a white solid (236 mg, 70%).

LC-MS: t_R = 4.40 $[M+H]^+$= 334 (method 2)

Intermediate compound 55: 4-((3aS,4R,9bR)-8-cyano-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-cyanoaniline (1 mmol). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 60% ethylacetate in hexanes afforded the endo-isomer as a white solid (180 mg, 57%).

LC-MS: t_R = 3.33 $[M+H]^+$= 317 (method 2)

Intermediate compound 56: 4-((3aS,4R,9bR)-8-[(N-methylsulfonyl)amino]-3a,4,5,9b-tetrahydro -3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-formylbenzoic acid (2.1 mmol, 0.32 g) and **intermediate compound 9** (2.1 mmol, 0.4 g). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an

elution of 40% ethylacetate in hexanes afforded the title compound as a solid slightly impurified, which was purified again by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give 297 mg of the pure title endo-isomer. (Yield= 43%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 (1H, brs), 7.94 (2H, d, *J* = 8.4 Hz), 7.56 (2H, d, *J* = 8.4 Hz), 6.87 (1H, d, *J* = 2.4 Hz), 6.79 (1H, dd, *J* = 2.4 & 8.8 Hz), 6.71 (1H, d, *J* = 8.8 Hz), 5.81-5.77 (1H, m), 5.73 (1H, brs), 5.59 (1H, d, *J* = 4.8 Hz), 4.59 (1H, d, J = 3.2 Hz), 4.03 (1H, d, *J* = 8.4 Hz), 3.00-2.91 (1H, m), 2.85 (3H, s), 2.43-2.63 (1H, m), 1.59 (1H, dd, *J* = 15.6 & 6.4 Hz).

LC-MS: t_R =7.22 $[M+H]^+$= 385 (method 1)

Intermediate compound 57: 4-((3aS,4R,9bR)-8-[(N-methyl-N-methylsulfonyl)amino]-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4yl) benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-formylbenzoic acid (1.1 mmol, 0.17 g) and **intermediate compound 11** (1.1 mmol, 0.23 g). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 9% methanol in dichloromethane afforded the pure title endo-isomer as a solid (327 mg. Yield=71%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (2H, d, *J* = 8 Hz), 7.57 (2H, d, *J* = 8 Hz), 7.05 (1H, d, *J* = 2.4 Hz), 6.93 (1H, dd, *J* = 2.4 & 8.4 Hz), 6.74 (1H, d, *J* = 8.4 Hz), 5.91(1H, s), 5.89-5.86 (1H, m), 5.58 (1H, d, *J* = 4.4 Hz), 4.63 (1H, d, *J* = 2.8 Hz), 4.04 (1H, d, *J* = 8.4 Hz), 3.14 (3H, s), 3.00-2.91 (1H, m), 2.88 (3H, s), 2.42-2.32 (1H, m), 1.63-1.56 (1H, m).

LC-MS: t_R =3.47 $[M+H]^+$= 399 (method 3)

Intermediate compound 58: 3-((3aS,4R,9bR)-8-bromo-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 3-formylbenzoic (1mmol) acid and 4-bromoaniline (1 mmol). Solvent was evaporated and purification of the crude

material (1:17 mixture of exo/endo regioisomers) by flash chromatography on silica gel using an elution of 40% ethylacetate in hexanes afforded the endo-isomer as a solid which was precipitated in acetonitrile/hexane, filtered and dried in vacuum to give the title compound (110 mg. Yield: 30%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.95 (1H, brs), 8.02 (1H, s), 7.84 (1H, d, *J* = 7.6 Hz), 7.66 (1H, d, *J* = 7.6 Hz), 7.48 (1H, t, *J* = 7.6 Hz), 7.15 (1H, d, *J* = 2 Hz), 7.01 (1H, dd, *J* = 8.8 & 2.4 Hz), 6.69 (1H, d, *J* = 8.8 Hz), 5.93 (1H, s), 5.89-5.85 (1H, m), 5.57 (1H, d, *J* = 4.8 Hz), 4.58 (1H, d, *J* = 2.8 Hz), 4.03-4.00 (1H, m), 2.94-2.88 (1H, m), 2.39-2.34 (1H, m), 1.57 (1H, dd, *J* = 15.6 & 8.8 Hz).

LC-MS: t_R = 7.88 $[M+H]^+$= 370/372 (method 1)

Intermediate compound 59: 4-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-7,8-dimethoxy-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-formylbenzoic acid (1.6 mmol, 250 mg) and 3,4-dimethoxyaniline (1.6 mmol). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 70% EtAcO in hexanes afforded the endo-isomer as a white solid (243 mg, 43%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.93 (2H, d, *J* = 8.4 Hz), 7.54 (2H, d, *J* = 8.4 Hz), 6.62 (1H, s), 6.44 (1H, s), 5.88 (1H, m), 5.54 (1H, d, *J* = 4.8 Hz), 5.34 (1H, s), 4.51 (1H, d, *J* = 2.4 Hz), 3.95 (1H, d, *J* = 8.8 Hz), 3.65 (6H, s), 2.95-2.89 (1H, m), 2.41-2.32 (1H, m), 1.57 (1H, dd, *J*= 15.5 & 6.4 Hz).

LC-MS: t_R = 3.68 $[M+H]^+$= 352 (method 3)

Intermediate compound 60 and 61: 4-(7-(trifluoromethyl)-3a,4,5,9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)benzoic acid (60) & 4-(9-(trifluoromethyl)-3a,4,5,9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)benzoic acid (61)

The following compounds were prepared using the same methodology as in intermediate compound 41 using 4-formylbenzoic acid (1.42 mmol, 214 mg) and 5-amino-2-methylbenzotrifluoride (1.42 mmol, 250mg). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using

an elution with a gradient from 30% to 100% of ethylacetate in hexanes afforded 475 mg of a 1:1 mixture of 8,9-disustituted (**61**) & 7,8-disustituted (**60**) regioisomers as a solid. (89%)

LC-MS: t_R = 4.50 $[M+H]^+$= 374 (method 3) (Both regiosiomers)

Intermediate compound 62: 4-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-7-methoxy-8-methyl-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-formylbenzoic acid (1.45 mmol, 220 mg) and 2-methoxy-4-aminotoluene (1.45 mmol, 200 mg). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 35% ethylacetate in hexanes afforded the title compound as the major product of a 1:8 mixture of endo-8,9-disustituted & endo-7,8-disustituted regioisomers as a solid (162 mg, 33%)

4-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-7-methoxy-8-methyl-3H-cyclopenta[c]quinolin-4-yl)benzoic acid (7,8-disustituted regioisomer)

LC-MS: t_R = 4.32 $[M+H]^+$= 336 (method 3)

4-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-9-methoxy-8-methyl-3H-cyclopenta[c]quinolin-4-yl)benzoic acid (8,9-disutituted regioisomer)

LC-MS: t_R = 4.17 $[M+H]^+$= 336 (method 3)

Intermediate compound 63: 4-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-6,8-dimethyl-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-formylbenzoic acid (2.06 mmol, 310 mg) and 2,4-dimethylaniline (2.06 mmol, 250 mg). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 40% ethylacetate in hexanes afforded the title endo-isomer as a solid (467 mg, 71%).

^{1}H NMR (400 MHz, DMSO-d_6) : δ 7.95 (2H, d, *J* = 8 Hz), 7.60 (2H, d, *J* = 8.4 Hz), 6.69 (1H, s), 6.63 (1H, s), 5.85-5.83 (1H, m), 5.53 (1H, d, *J* = 5.2 Hz), 4.57 (1H, d, *J* = 2.8 Hz), 4.47 (1H, s), 4.04-4.01 (1H, m), 2.96-2.88 (1H, m), 2.41-2.34 (1H, m), 2.13 (3H, s), 2.10 (3H, s), 1.60-1.54 (1H, m).

LC-MS: t_R = 4.55 $[M+H]^+$= 320 (method 3)

Intermediate compound 64 and 65: 4-((3aS,4R,9bR)-9-chloro-3a,4,5,9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)benzoic acid (64) and 4-((3aS,4R,9bR)-7-chloro-3a,4,5,9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)benzoic acid (65)

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-formylbenzoic acid (1.41 mmol, 212 mg) and 3-chloro-4-methylaniline (1.41 mmol, 200 mg). Solvent was evaporated and the crude material (1:1,8 mixture of endo-8,9-disustituted & endo-7,8-disustituted regioisomers) was purified by flash chromatography on silica gel using an elution with a gradient from 35% to 60% of ethylacetate in hexanes. Only high purity fractions of each regioisomer were collected giving two enriched fractions with each regioisomer, which were purified again by precipitation in acetonitrile/drops of water to give 58 mg of pure 4-((3aS,4R,9bR)-9-chloro-3a,4,5,9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)benzoic acid (**64**) and 88 mg of pure 4-((3aS,4R,9bR)-7-chloro-3a,4,5,9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)benzoic acid (**65**). (Overall yield=30%).

4-((3aS,4R,9bR)-9-chloro-3a,4,5,9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)benzoic acid (8,9-disustituted isomer **64**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (2H, d, *J* = 8 Hz), 7.51 (2H, d, *J* = 8.4 Hz), 6.90 (1H, d, *J* = 8 Hz), 6.70 (1H, d, *J* = 8 Hz), 5.97 (1H, d, *J* = 3.6 Hz), 5.77 (1H, s), 5.62 (1H, d, *J* = 3.6 Hz), 4.47 (1H, d, *J* = 2.8 Hz), 4.23 (1H, d, *J* = 8.4 Hz), 3.17-3.10 (1H, m), 2.50 (1H, m), 2.19 (3H, s), 1.69-1.63 (1H, m).

LC-MS: t_R = 5.37 $[M+H]^+$= 340 (method 2)

4-((3aS,4R,9bR)-7-chloro-3a,4,5,9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)benzoic acid (7,8-disustituted isomer **65**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (2H, d, *J* = 8.4 Hz) , 7.49 (2H, d, *J* = 8.4 Hz,), 6.95 (1H, s), 6.79 (1H, s), 5.86-5.84 (1H, m), 5.80 (1H, s), 5.57 (1H, d, *J* = 4.8 Hz), 4.55 (1H, d, *J* = 2.8 Hz), 3.98 (1H, d, *J* = 9.2 Hz), 2.96-2.89 (1H, m), 2.41-2.32 (1H, m), 2.16 (3H, s), 1.62-1.56 (m, 1H).

LC-MS: t_R = 5.32 $[M+H]^+$= 340 (method 2)

Intermediate compound 66: methyl 4-(3a,4,5,9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)benzoate

The following compound was prepared using the same methodology as in intermediate compound 41 using methyl 4-formylbenzoate (5 mmol) and 4-methylaniline (5 mmol). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 33% ethylacetate in hexanes afforded a mixture of exo/endo regioisomers (1:17) of the title compound (1.09 mg, 68%).

Endo-Isomer: Methyl 4-((3a*S*,4*R*,9b*R*)-3a,4,5,9b-tetrahydro-8-methyl-3*H*-cyclopenta[c]quinolin-4-yl)benzoate

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (2H, d, *J* = 8.4 Hz), 7.55 (2H, d, *J* = 8.0 Hz), 6.79 (1H, s), 6.68 (1H, dd, *J* = 8.0 & 1.6 Hz), 6.62 (1H, d, *J* = 8.4 Hz), 5.83-5.81 (1H, m), 5.53 (1H, d, *J* = 4.8 Hz), 5.49 (1H, brs), 4.54 (1H, d, *J* = 2.8 Hz), 4.00 (1H, d, *J* = 8.4 Hz), 3.84 (3H, s), 2.90 (1H, m), 2.41-2.33 (1H, m), 2.13 (3H, s), 1.56 (1H, dd, *J* = 15.2 & 8.8 Hz).

LC-MS: t_R = 4.40 $[M+H]^+$= 320 (method 2)

Intermediate compound 67: methyl 4-(2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoate

The **intermediate compound 66** (1.09 g, 3.41 mmol) was dissolved in EtOH and THF (1:1, 50 mL) and platinum dioxide (5% w/w, 50 mg) was added. The solution was hydrogenated at r.t., for 1 h. HPLC analysis showed total conversion. Reaction mixture was filtered and filter washed with THF. Solvent was evaporated and purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give 662 mg a mixture of exo/endo regioisomers (1:17) of the title compound (68%).

Exo-Isomer LC-MS: t_R = 5.27 $[M+H]^+$= 322 (method 2)

Endo-Isomer LC-MS: t_R = 5.45 $[M+H]^+$= 322 (method 2)

Intermediate compound 68: methyl 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-5,8-dimethyl-1H-cyclopenta[c]quinolin-4-yl)benzoate

To a solution of **intermediate compound 67** (0.311 mmol, 100 mg) dissolved in DMF (5 mL) and cooled at 0ºC was added 95% NaH (0.33 mmol, 8.2 mg) and the resulting solution was stirred for 1 h at room temperature. Iodomethane (0.33 mmol, 0.022 mL) was added and the mixture was stirred 16 h at room temperature. Total conversion was not achieved, then 95% NaH (0.31 mmol, 8 mg) and iodomethane (0.622 mmol, 0.039 mL) were added and the mixture was stirred 24 h at room temperature. 95% NaH (0.46 mmol, 12 mg) and iodomethane (1.2 mmol, 0.078 mL) were added again and the mixture was stirred 5 days at room temperature. Then, 95% NaH (0.46 mmol, 12 mg) and iodomethane (1.2 mmol, 0.078 mL) were added and the mixture was stirred 24 h at room temperature. Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 3% ethylacetate in hexanes afforded the title compound (50 mg. Yield:50%).

LC-MS: t_R = 5.78 $[M+H]^+$= 336 (method 2)

Intermediate compound 69: methyl 4-((3aS,4R,9bR)-5-acetyl-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoate

The **intermediate compound 67** (0.31 mmol, 100 mg) was dissolved in anhydrous tetrahydrofurane (2 mL), pyridine (3.6 eq., 1.11 mmol, 0.09 mL), acetyl chloride (3 eq, 0.93 mmol, 0.07 mL) and acetyl anhydride (2eq., 0.65 mmol, 0.07 mL) were added at room temperature and the resulting solution was stirred at r.t. for 5h. Solvent was evaporated and the crude residue was dissolved in ethyl acetate and saturated aqueous sodium carbonate solution. The organic layer was extracted and washed with saturated aqueous sodium carbonate solution, 1N HCl and brine. Then it was dried over anhydrous sodium sulphate, filtered and solvent evaporated to give 110 mg (98%) of the endo-isomer, which was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (2H, d, *J* = 8.4 Hz), 7.14 (1H, s), 7.03-6.99 (4H, m), 6.14 (1H, brs), 3.85 (3H, s), 3.15-3.03 (2H, m), 2.38 (3H, s), 2.18 (3H, s), 2.19-2.12 (1H, m), 1.90-1.86 (1H, m), 1.60 (1H, brs), 1.52-1.40 (2H, m), 0.92-0.86 (1H, m).

LC-MS: t_R = 5.00 $[M+H]^+$= 364 (method 2)

Intermediate compound 70: 4-((6-methylpyridin-3-ylimino)methyl)benzoic acid

A solution of 4-formylbenzoic acid (1.39 mmol, 209 mg) and 6-methylpyridin-3-amine (1.39 mmol, 150 mg) in dry chloroform (15 mL) with molecular sieves was stirred at room temperature 48 h. The resulting solution was filtered and concentrated in vacuum to give the compound 4-((6-methylpyridin-3-ylimino)methyl)benzoic acid. The product is unstable and was used without further purification in the next step.

LC-MS: t_R = 2.20 $[M+H]^+$ = not ion (method 2)

Intermediate compound 71: 4-(6, 6a, 7, 9a-tetrahydro-2-methyl-5H-cyclopenta[c][1,5]naphthyridin-6-yl)benzoic acid

To a solution of cyclopenta-1, 3-diene (6.9 mmol, 563 mL) and $BF_3{\cdot}Et_2O$ (2.76 mmol, 350mL) were added to a solution of 4-((6-methylpyridin-3-ylimino)methyl)benzoic acid (**intermediate compound 70**) (1.38 mmol, 334 mg) in dry ACN (15 mL). The mixture was stirred 48 h at room temperature. The resulting solution was evaporated and the crude product was purified using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give the title compound. (42 mg. Yield:10%)

Endo-isomer **71**:

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (2H, d, *J*=8.4Hz), 7.58 (2H, d, *J*=8Hz), 6.98 (1H, d, *J*=8.4Hz), 6.78 (1H, d, *J*= 8.4Hz), 5.86-5.85 (1H, m), 5.71 (1H, s), 5.61-5.59 (1H, m), 4.62 (1H, d, *J*=2.8Hz), 4.04 (1H, d, *J*=7.6Hz), 3.06-2.99 (1H, m), 2.44-2.37 (1H, m), 2.29 (3H, s), 1.67-1.61 (1H, m).

LC-MS: t_R = 2.60 $[M+H]^+$ = 307 (method 2)

Intermediate compound 72: 4-(6,6a,7,9a-tetrahydro-2-methyl-5H-cyclopenta[c][1,8]naphthyridin-6-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 2-amino-5-methylpyridine (1.8 mmol, 0.20 g). Total conversion was not achieved, additional scandium

trifluoromethanesulfonate (0.5 eq, 0.92 mmol, 0.45 g) was added and the mixture reaction was left to stir at 65ºC 16 h. HPLC analysis showed total conversion. Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 10% methanol in dichloromethane afforded the pure title compound. (323 mg. Yield= 57%)

LC-MS: t_R =2.20 $[M+H]^+$= 307 (method 3)

Intermediate compound 73: methyl 2-(4-(3a, 4, 5, 9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)phenyl)acetate

The following compound was prepared using the same methodology as in intermediate compound 41 using methyl 2-(4-formylphenyl)acetate (**intermediate compound 15**) (0.84 mmol, 150 mg) and *p*-toluidine (0.84 mmol, 91 mg). Solvent was evaporated and purification of the crude material (2:8 mixture of exo/endo regioisomers) by flash chromatography on silica gel using an elution of 20% ethylacetate in hexanes afforded the title compound. (115 mg. Yield: 41%).

LC-MS: t_R = 5.07 $[M+H]^+$ = 334 (method 2)

Intermediate compound 74: methyl 2-(4-(2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)phenyl)acetate

The following compound was prepared using the same methodology as in intermediate compound 67 using **intermediate compound 73** (0.345 mmol, 115mg) for 1 h. Purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded methyl 2-(4-(2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1*H*-cyclopenta[*c*]quinolin-4-yl)phenyl)acetate (74 mg. Yield: 64%).

LC-MS: t_R = 5.25 $[M+H]^+$ = 336 (method 2)

Intermediate compound 75: 3-(4-(3a, 4, 5, 9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)phenyl)propanoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 3-(4-formylphenyl)propanoic acid (**intermediate compound 13**) (0.415 mmol, 74 mg) and *p*-toluidine (0.145 mmol, 45 mg). Solvent was evaporated and purification of the crude material (1:6 mixture of

exo/endo regioisomers) by flash chromatography on silica gel using an elution of 50% ethylacetate in hexanes afforded the title compound. (42 mg. Yield: 30%).

LC-MS: t_R = 4.98 $[M+H]^+$ = 334 (method 2)

Intermediate compound 76: 4-(3a, 4, 5, 9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)-2-methylbenzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-formyl-2-methylbenzoic acid (**intermediate compound 16**) (0.4 mmol, 65 mg) and *p*-toluidine (0.4 mmol, 43 mg). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 50% ethylacetate in hexanes afforded the title compound. (61 mg. Yield: 47%).

LC-MS: t_R = 5.12 $[M+H]^+$ = 320 (method 2)

Intermediate compound 77: 4-(3a, 4, 5, 9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-formyl-3-methylbenzoic acid (**intermediate compound 18**) (0.55 mmol, 90 mg) and *p*-toluidine (0.55 mmol, 59 mg). Solvent was evaporated and purification of the crude material (2:8 mixture of exo/endo regioisomers) by flash chromatography on silica gel using an elution of 20% ethylacetate in hexanes afforded the title compound. (115 mg. Yield: 65%).

LC-MS: t_R = 5.15 $[M+H]^+$ = 320 (method 2)

Intermediate compound 78: methyl 4-(3a, 4, 5, 9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoate

The following compound was prepared using the same methodology as in intermediate compound 41 using methyl 4-formyl-3-methylbenzoate (**intermediate compound 19**) (3.53 mmol, 630 mg) and *p*-toluidine (3.53 mmol, 379 mg). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 8% ethylacetate in hexanes afforded the title compound. (1 g. Yield: 85%).

LC-MS: t_R = 4.85 $[M+H]^+$ = 320 (method 2)

Intermediate compound 79: methyl 4-(2,3,3a, 4, 5, 9b-hexahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoate

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 78** for 1h. Solvent was evaporated and purification of the crude material by precipitation with DMSO/ACN, filtration of the white solid which was washed with ACN, dried under vacuum to give 1:9 exo/endo regioisomers mixture. (746 mg: Yield: 74%).

LC-MS: t_R = 5.15 $[M+H]^+$ = 320 (method 2)

Intermediate compound 80: 4-(8-chloro-3a, 4, 5, 9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-formyl-3-methylbenzoic acid (**intermediate compound 18**) (0.46 mmol, 75 mg) and 4-chloroaniline (0.46 mmol, 59 mg). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 30% ethylacetate in hexanes afforded the title compound. (64 mg. Yield: 41%).

LC-MS: t_R = 5.23 $[M+H]^+$ = 340 (method 2)

Intermediate compound 81: 4-(8-fluoro-3a, 4, 5, 9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-formyl-3-methylbenzoic acid (**intermediate compound 18**) (0.46 mmol, 75 mg) and 4-fluoroaniline (0.46 mmol, 52 mg). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 40% ethylacetate in hexanes afforded the title compound. (58 mg. Yield: 33%).

LC-MS: t_R = 4.97 $[M+H]^+$ = 324 (method 2)

Intermediate compound 82: 4-(3a, 4, 5, 9b-tetrahydro-8-methoxy-3H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-formyl-3-methylbenzoic acid (**intermediate**

compound 18) (0.91 mmol, 150 mg) and p-anisidine (0.91 mmol, 113 mg). Total conversion was not achieved after 16 h, then $Sc(OTf)_3$ (0.091 mmol, 45 mg) and cyclopentadiene (4.55 mmol 0.37 mL) were added again and the reaction mixture was stirred 24 h at room temperature. Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 38% ethylacetate in hexanes afforded the title compound. (129 mg. Yield: 42%).

LC-MS: t_R = 4.67 $[M+H]^+$ = 336 (method 2)

Intermediate compound 83: 4-(8-cyclopropyl-3a, 4, 5, 9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-formyl-3-methylbenzoic acid (**intermediate compound 18**) (0.68 mmol, 112 mg) and 4-cyclopropylbenzenamine (**intermediate compound 3**, method 2) (0.68 mmol, 91 mg). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 35% ethylacetate in hexanes afforded the title compound. (90 mg. Yield: 38%).

LC-MS: t_R = 5.30 $[M+H]^+$ = 346 (method 2)

Intermediate compound 84: methyl 4-(8-(cyclopropylmethoxy)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoate

The following compound was prepared using the same methodology as in intermediate compound 41 using methyl-4-formyl-3-methyl benzoate (**intermediate compound 19**) (1 eq.) and 4-(cyclopropylmethoxy)benzenamine (1 eq) (**intermediate compound 7**) (1 eq). The reaction mixture was stirred at room temperature for 16h. Then, scandium trifluoromethanesulfonate (0.4 eq) was added and left stirring at room temperature for 60 h. Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using hexane and ethylacetate as eluents to afford 128 mg of a mixture of isomers exo/endo (1:4) of the impure title-compound.

LC-MS: t_R = 4.78 & 4.92 $[M+H]^+$ = 390 (method 2).

Intermediate compound 85: methyl 4-((3aS, 4R, 9bR)-8-(cyclopropylmethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoate

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 84** (128 mg, 0.32 mmol) for 16 h. Solvent was evaporated and purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give 34 mg of the endo-isomer (25%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (1H, dd, *J* = 8.0 & 1.6 Hz), 7.83 (1H, s), 7.73 (1H, d, *J* = 8.0 Hz), 6.73 (1H, d, *J* = 2.8 Hz), 6.63 (1H, dd, *J* = 8.4 & 2.8 Hz), 6.54 (1H, d, *J* = 8.8 Hz), 4.69 (1H, d, *J* = 3.2 Hz), 3.91 (3H, s), 3.74 (2H, d, *J* = 6.8 Hz), 3.47-3.42 (1H, m), 2.52-2.46 (1H, m), 2.39 (3H, s), 2.17-2.14 (1H, m) 1.79-1.70 (2H, m), 1.44-1.38 (1H, m), 1.28-1.23 (1H, m), 1.14-1.12 (1H, m), 0.64-0.60 (2H, m), 0.35-0.31 (2H, m).

LC-MS: t_R = 5.03 $[M+H]^+$= 392 (method 2)

Intermediate compound 86: methyl 4-(3a,4,5,9b-tetrahydro-8-isopropoxy-3H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoate

The following compound was prepared using the same methodology as in intermediate compound 41 using **intermediate compound 19** (1.32 mmol, 236 mg) and **intermediate compound 5** (1.32 mmol, 200 mg). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 15% ethylacetate in hexanes afforded the title compound as a 1:9 mixture of exo/endo isomers. (322 mg. Yield:64%).

LC-MS: t_R =4.13 $[M+H]^+$= 152 (method 3) (Both isomers)

Intermediate compound 87 & 88: methyl 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-isopropoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoate (87) & methyl 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-isopropoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoate (88)

The following compounds were prepared using the same methodology as in intermediate compound 67 from **intermediate compound 86** (0.85 mmol, 322 mg) for 1 h. Purification of the crude material (1:6.5 mixture of exo/endo isomers)

by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give 132 mg of the pure endo-isomer methyl 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-isopropoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoate (**87**) and 16.9 mg of the pure exo-isomer methyl 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-isopropoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoate (**88**) (Overall yield= 46%).

Methyl-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-isopropoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoate (endo-isomer **87**) :

LC-MS: t_R =5.05 $[M+H]^+$= 152 (method 2)

Methyl-4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-isopropoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoate (exo-isomer **88**):

LC-MS: t_R =4.82 $[M+H]^+$= 152 (method 2)

Intermediate compound 89: 3-chloro-4-(3a, 4, 5, 9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 3-chloro-4-formylbenzoic acid (**intermediate compound 17**) (1.62 mmol, 300 mg) and *p*-toluidine (1.62 mmol, 173 mg). Solvent was evaporated and purification of the crude material (1:9 mixture of exo/endo regioisomers) by flash chromatography on silica gel using an elution of 35% ethylacetate in hexanes afforded the exo-endo isomer. (305 mg. Yield: 55%).

LC-MS: t_R = 5.40 $[M+H]^+$ = 340 (method 2)

Intermediate compound 90: methyl 4-(3a, 4, 5, 9b-tetrahydro-8-methoxy-3H-cyclopenta[c]quinolin-4-yl)-3-methoxybenzoate

The following compound was prepared using the same methodology as in intermediate compound 41 using methyl 4-formyl-3-methoxybenzoate (**intermediate compound 20**) (0.72 mmol, 140 mg) and *p*-anisidine (0.72 mmol, 89 mg). Solvent was evaporated and purification of the crude material (1:4.5 mixture of exo/endo regioisomers) by flash chromatography on silica gel using an

elution of 2% ethylacetate in hexanes afforded the mixture exo-endo isomer. (193 mg. Yield: 73%).

LC-MS: t_R = 4.73 $[M+H]^+$ = 366 (method 2)

Intermediate compound 91: methyl 4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methoxybenzoate

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 90** (0.53 mmol, 193 mg). Solvent was evaporated and purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give endo-isomer methyl 4-((3a*S*, 4*R*, 9b*R*)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methoxy-1*H*-cyclopenta[*c*]quinolin-4-yl)-3-methoxybenzoate (80 mg. Yield: 41%).

LC-MS: t_R = 4.80 $[M+H]^+$ = 368 (method 2)

Intermediate compound 92: methyl 4-(3a, 4, 5, 9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)-3-methoxybenzoate

The following compound was prepared using the same methodology as in intermediate compound 41 using methyl 4-formyl-3-methoxybenzoate (**intermediate compound 20**) (0.72 mmol, 140 mg) and *p*-toluidine (0.72 mmol, 78 mg). Solvent was evaporated and purification of the crude material (1:3.6 mixture of exo/endo regioisomers) by flash chromatography on silica gel using an elution of 8% ethylacetate in hexanes afforded the mixture regioisomer compound. (154 mg. Yield: 61%).

LC-MS: t_R = 5.18 $[M+H]^+$ = 350 (method 2)

Intermediate compound 93: methyl 4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-3-methoxybenzoate

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 92** (0.44 mmol, 154 mg) The crude material endo-isomer methyl 4-((3a*S*, 4*R*, 9b*R*)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1*H*-cyclopenta[*c*]quinolin-4-yl)-3-methoxybenzoate was used in the next step without purification (135 mg. Yield: 87%).

LC-MS: t_R = 5.40 $[M+H]^+$ = 352 (method 2)

Intermediate compound 94: methyl 3-bromo-4-(3a,4,5,9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)benzoate

The following compound was prepared using the same methodology as in intermediate compound 41 using methyl 3-bromo-4-formylbenzoate (**intermediate compound 23**) (0.243 mmol, 59 mg) and *p*-toluidine (0.243 mmol, 26 mg). Solvent was evaporated and purification of the crude material (1:10 mixture of exo/endo regioisomers) by flash chromatography on silica gel using an elution of 29% ethylacetate in hexanes afforded the exo-endo isomer. (75 mg. Yield: 40%).

Endo-Isomer **94**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.3 (1H, d, *J*=8Hz), 8.24 (1H, d, *J*= 1.6Hz), 7.74 (1H, d, *J*=8Hz), 6.91 (1H, s), 6.82 (1H, d, *J*=8Hz), 6.57 (1H, d, *J*=8Hz), 5.86 (1H, m), 5.65 (1H, m), 4.97 (1H, d, *J*=3.2Hz), 4.13-4.10 (1H, m), 3.93 (3H, s), 3.27-3.24 (1H, m), 2.65-2.55 (1H, m), 2.25 (3H, s), 1.72-1.66 (1H, m).

LC-MS: t_R = 5.53 $[M+H]^+$ = 398-400 (method 2)

Intermediate compound 95: methyl 3-bromo-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoate

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 94** (0.188 mmol, 75 mg) but using platinum dioxide (2.5% w/w, 2 mg). Purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give endo-isomer methyl 3-bromo-4-((3a*S*,4*R*,9b*R*)-2,3,3a,4,5,9b-hexahydro-8-methyl-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoate (54 mg. Yield:71%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (1H, d, *J*=1.6Hz), 7.99 (1H, dd, *J*=1.6 & 7.6Hz), 7.81 (1H, d, *J*=8Hz), 6.86 (1H, s), 6.73 (1H, d, *J*=7.6Hz), 6.58 (1H, d, *J*=8.4Hz), 5.60 (1H, s), 4.68 (1H, d, *J*=2.8Hz), 3.87 (3H, s), 3.38-3.35 (1H, m), 2.61-2.54 (1H, m), 2.17 (3H, s), 2.11-2.06 (1H, m), 1.71-1.69 (1H, m), 1.56-1.53 (1H, m), 1.41-1.37 (2H, m), 0.96-0.94 (1H, m).

LC-MS: t_R = 5.72 $[M+H]^+$ = 400-402 (method 2)

Intermediate compound 96: methyl 3-bromo-4-(3a, 4, 5, 9b-tetrahydro-8-methoxy-3H-cyclopenta[c]quinolin-4-yl)benzoate

The following compound was prepared using the same methodology as in intermediate compound 41 using methyl 3-bromo-4-formylbenzoate (**intermediate compound 23**) (0.71 mmol, 173 mg) and *p*-anisidine (0.71 mmol, 88 mg). The crude product was purified by precipitation with acetonitrile to give a white solid methyl 3-bromo-4-(3a, 4, 5, 9b-tetrahydro-8-methoxy-3*H*-cyclopenta[*c*]quinolin-4-yl)benzoate (1:6 exo:endo isomer) (161 mg. Yield:54%)

Endo-Isomer **96**:

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (1H, d, *J*=2Hz), 8.01 (1H, dd, *J*= 1.6 & 8.4Hz), 7.81 (1H, d, *J*=8Hz), 6.68-6.65 (2H, m), 6.56 (1H, dd, *J*=2.8 & 8.8Hz), 5.88 (1H, m),5.58 (1H, d, *J*=5.2Hz), 5.40 (1H, s), 4.69(1H, d, *J*=2.8Hz), 4.04-4.02 (1H, d, *J*=9.2Hz), 3.88 (3H, s), 3.65 (3H, s), 3.11-3.08 (1H, m), 2.46-2.41 (1H, m), 1.58-1.54 (1H, m)

LC-MS: t_R = 5.22 $[M+H]^+$ = 414-416 (method 2)

Intermediate compound 97: methyl 3-bromo-4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoate

The following compound was prepared using the same methodology as in intermediate compound 95 from **intermediate compound 96** (0.39 mmol, 161 mg) Purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give endo-isomer methyl 3-bromo-4-((3a*S*,4*R*,9b*R*)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoate (129 mg. Yield: 79%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (1H, d, *J*=1.6Hz), 7.80 (1H, dd, *J*=1.6 & 7.6Hz), 7.82 (1H, d, *J*=8Hz), 6.65-6.63 (2H, m), 6.57 (1H, dd, *J*=2.4 & 8.4Hz), 5.46 (1H, s), 4.63 (1H, d, *J*=3.2Hz), 3.87 (3H, s), 3.66 (3H, s), 3.41-3.37 (1H, m), 2.63-2.60 (1H, m), 2.12-2.07 (1H, m), 1.70-1.66 (1H, m), 1.60-1.54 (1H, m), 1.41-1.38 (2H, m), 0.97-0.94 (1H, m).

LC-MS: t_R = 5.43 $[M+H]^+$ = 416-418 (method 2)

Intermediate compound 98: 3-ethyl-4-((3aS,9bR)-3a,4,5,9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)benzonitrile

The following compound was prepared using the same methodology as in intermediate compound 41 using the **intermediate compound 25** (0.30 mmol, 48 mg) and p-toluidine (0.30 mmol, 32 mg). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 40% ethylacetate in hexanes afforded the title compound as a 7:1 mixture of endo/exo-isomers as a white solid (71 mg. Yield: 75%).

Endo isomer **98**:

^{1}H (400 MHz, $CDCl_3$) δ 7.79 (1H, d, *J* = 8 Hz), 7.54 (1H, dd, *J* = 8 & 1.6 Hz), 7.51 (1H, d, *J* = 1.6 Hz), 6.91 (1H, s), 6.84 (1H, dd, *J* = 8 & 1.6 Hz), 6.57 (1H, d, *J* = 8 Hz), 5.87 (1H, m), 5.70 (1H, m), 4.87 (1H, d, *J* = 2.8 Hz), 4.11 (1H, m), 3.01-2.94 (1H, m), 2.86-2.78 (1H, m), 2.74-2.62 (2H, m), 2.26 (3H, s), 1.76-1.69 (1H, m), 1.29-1.25 (3H, m).

LC-MS: t_R = 5.23 $[M+H]^+$= 315 (method 2)

Intermediate compound 99: 3-ethyl-4-((3aS,9bR)-3a,4,5,9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using the **intermediate compound 26** (0.46 mmol, 82 mg) and using p-toluidine (0.46 mmol, 49 mg). Purification of the crude material by flash chromatography on silica gel using an elution of 40% ethylacetate in hexanes afforded the title compound as a 5.4:1 mixture of endo/exo- isomers as a white solid (104 mg. Yiled: 68%).

Endo isomer **99**:

^{1}H (400 MHz, $CDCl_3$) δ 7.79 (2H, s), 7.69 (1H, d, J = 8.8 Hz), 6.81 (1H, s), 6.69 (1H, dd, J = 8 & 1.6 Hz), 6.62 (1H, d, J = 8 Hz), 5.85 (1H, m), 5.57 (1H, d, J = 4.8 Hz), 5.32 (1H, s), 4.71 (1H, d, J = 2.8 Hz), 4.02 (1H, d, J = 8.8 Hz), 2.92-2.78 (2H, m), 2.74-2.64 (2H, m), 2.15 (3H, s), 1.59-1.53 (1H, m), 1.22-1.18 (3H, m).

LC-MS: t_R = 5.05 $[M+H]^+$= 334 (method 2)

Intermediate compound 100: 3-ethyl-4-((3aS,9bR)-3a,4,5,9b-tetrahydro-8-methoxy-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using the **intermediate compound 26** (0.67 mmol, 120 mg) and *p*-anisidine (0.67 mmol, 83 mg). Purification of the crude material by flash chromatography on silica gel using an elution of 40% ethylacetate in hexanes afforded the title compound as a 2:1 mixture of endo/exo-isomers as a solid (79 mg. Yield: 34%).

LC-MS (endo-isomer): t_R = 4.53 $[M+H]^+$= 350 (method 2)

LC-MS (exo-isomer): t_R = 4.40 $[M+H]^+$= 350 (method 2)

Intermediate compound 101: methyl 4-((3aS,4S,9bR)-3a,4,5,9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)-3,5-dimethylbenzoate

A catalytic amount of scandium trifluoromethanesulfonate (0.5 eq., 0.31 mmol, 153 mg) in anhydrous acetonitrile (10 mL) was added to a mixture of **intermediate compound 30** (0.62 mmol, 120 mg), *p*-toluidine (0.62 mmol, 67 mg) and fresh distilled ciclopentadiene (5 eq., 3.12 mmol, 0.25 mL). The reaction mixture was stirred at 50ºC for 16h. Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 10% ethylacetate in hexanes afforded the pure title exo-compound. (144 mg. Yield: 66%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 (2H, brs), 7.10 (1H, s), 6.86 (1H, dd, *J* = 8 & 1.6 Hz), 6.53 (1H, d, *J* = 7.6 Hz), 5.99-5.96 (1H, m), 5.74-5.70 (1H, m), 4.36 (1H, d, *J* = 11.2 Hz), 4.02-3.98 (1H, m), 3.92 (3H, s), 3.22-3.14 (1H, m), 2.74-2.68 (3H, brs), 2.50-2.38 (2H, m), 2.34-2.23 (3H, brs), 2.29 (3H, s).

LC-MS: t_R = 5.45 $[M+H]^+$= 348 (method 2)

Intermediate compound 102: methyl 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-3,5-dimethylbenzoate

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 101** (0.41 mmol, 144

mg). Purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave 83 mg of the pure exo-compound methyl 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-3,5-dimethylbenzoate (Yield: 57%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62 (2H, s), 6.69 (1H, dd, *J* = 8 & 2 Hz), 6.52 (1H, d, *J* = 7.6 Hz), 5.69 (1H, s), 4.20 (1H, d, *J* = 11.2 Hz), 3.83 (3H, s), 2.98-2.91 (1H, m), 2.68-2.60 (1H, m), 2.60-2.52 (3H, brs), 2.45-2.37 (3H, brs), 2.26-2.20 (1H, m), 2.15 (3H, s), 1.74-1.50 (4H, m), 1.14-1.08 (1H, m).

LC-MS: t_R = 5.57 $[M+H]^+$= 350 (method 2)

Intermediate compound 103: methyl 4-((3aS,4S,9bR)-3a,4,5,9b-tetrahydro-8-methoxy-3H-cyclopenta[c]quinolin-4-yl)-3,5-dimethylbenzoate

The following compound was prepared using the same methodology as in intermediate compound 100 using *p-anisidine* (0.75 mmol, 93 mg). Purification of the crude material by flash chromatography on silica gel using an elution of 10% ethylacetate in hexanes afforded the exo-isomer as a solid. (152 mg. Yield: 55%)

LC-MS: t_R = 5.13 $[M+H]^-$ = 364 (method 3)

Intermediate compound 104: methyl 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-3,5-dimethylbenzoate

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 103** (0.42 mmol, 152 mg). Purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave 59 mg of the pure exo-isomer methyl 4-((3*aS*,4*S*,9*bR*)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-3,5-dimethylbenzoate as a solid (Yield: 39%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62 (2H, s), 6.68 (1H, d, *J* = 2.4 Hz), 6.58-6.53 (2H, m), 5.53 (1H, s), 4.16 (1H, d, *J* = 11.2 Hz), 3.83 (3H, s), 3.65 (3H, s), 2.99-2.93 (1H, m), 2.72-2.52 (4H, m), 2.45-2.38 (3H, brs), 2.30-2.22 (1H, m), 1.72-1.50 (4H, m), 1.14-1.06 (1H, m).

LC-MS: t_R = 5.25 $[M+H]^+$= 366 (method 2)

Intermediate compound 105: 5-((3aS, 4R, 9bR)-3a, 4, 5, 9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)pyridine-2-carboxylic acid

To a solution of 5-formylpyridine-2-carboxylic acid **intermediate compound 31** (60 mg, 0.4 mmol) in anhydrous ACN (15 ml) was added *p*-toluidine (43 mg, 0.4 mmol), cyclopenta-1, 3-diene (163 mLl, 2 mmol) and $BF_3 \cdot Et_2O$ (101 mL, 0.8 mmol). The reaction mixture was stirred 16h at room temperature. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and methanol (0.1% formic acid) as eluents to give 17 mg of the endo-isomer 5-((3a*S*, 4*R*, 9b*R*)-3a, 4, 5, 9b-tetrahydro-8-methyl-3*H*-cyclopenta[*c*]quinolin-4-yl)pyridine-2-carboxylic acid (Yield: 13%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (1H, s), 8.06-8.00 (2H, m), 6.83 (1H, s), 6.72 (1H, d, *J*=8Hz), 6.23 (1H, d, *J*=8Hz), 5.85 (1H, m), 5.61 (1H, s), 5.56 (1H, m), 4.63 (1H, d, *J*=2.8Hz), 4.01 (1H, d, *J*=8.8Hz), 3.00-2.97 (1H, m), 2.42-2.36 (1H, m), 2.16 (3H, s), 1.66-1.60 (1H, m).

LC-MS: t_R = 8.07 $[M+H]^+$ = 307 (method 1)

Intermediate compound 106: methyl 6-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)pyridine-3-carboxylate

The following compound was prepared using the same methodology as in intermediate compound 41 using methyl-6-formylnicotinate (1 mmol) and 4-methylaniline (1 mmol). The reaction mixture was stirred at room temperature for 16h. Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using hexane and ethylacetate as eluents to afford 249 mg of the impure title endo-isomer (Yield=78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (1H, dd, *J* = 2.4 & 1.6 Hz), 8.31 (1H, dd, *J* = 8.0 & 2.0 Hz), 7.54 (1H, d, *J* = 8.0 Hz), 6.89 (1H, s), 6.73 (1H, dd, *J* = 8.0 & 2.0 Hz), 6.64 (1H, d, *J* = 8.0 Hz), 5.84-5.81 (1H, m), 5.62-5.61(1H, m), 4.75 (1H, d, *J* = 3.2 Hz), 4.13-4.16 (1H, m), 3.97 (3H, s), 3.33 (1H, dq, *J* = 8.8 & 3.2 Hz), 2.46-2.39 (1H, m), 2.25 (3H, s), 1.86-1.79 (1H, m).

LC-MS: t_R = 4.77 min $[M+H]^+$ = 321 (method 2)

Intermediate compound 107: 6-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)pyridine-3-carboxylic acid

To a solution of **intermediate compound 106** (0.20 mmol, 65 mg) in THF (1.5 mL) was added 1M LiOH (0.30 mL, 0.30 mmol). The reaction mixture was stirred 16 h at room temperature. The solvent was evaporated and the crude was purified by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents, to give 49 mg of the title endo-isomer. (Yield: 80%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 (1H, d, *J* = 1.6 Hz), 8.27 (1H, dd, *J* = 8.0 & 2.0 Hz), 7.64 (1H, d, *J* = 8.4 Hz), 6.80 (1H, s), 6.70 (1H, dd, *J* = 8.4 & 1.6 Hz), 6.64 (1H, d, *J* = 8.4 Hz), 5.82-5.80 (1H, m), 5.60 (1H, brs), 5.51 (1H, d, *J* = 5.2 Hz), 4.56 (1H, d, *J* = 3.2 Hz), 4.01 (1H, d, *J* = 8.8 Hz), 3.20-3.12 (1H, m), 2.26-2.22 (1H, m), 2.13 (3H, s), 1.62-1.56 (1H, m).

LC-MS: t_R = 8.73 $[M+H]^+$= 307 (method 1)

Intermediate compound 108: methyl 6-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)pyridine-3-carboxylate

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 106** (180 mg, 0.56 mmol) for 2 h. After filtration, solvents were evaporated to obtain 170 mg of the pure endo-isomer, which was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (1H, d, *J* = 1.2 Hz), 8.30 (1H, dd, *J* = 8.4 & 2.4 Hz), 7.54 (1H, d, *J* = 8.0 Hz), 6.95 (1H, s), 6.83 (1H, dd, *J* = 8.4 & 1.6 Hz), 6.60 (1H, d, *J* = 8.0 Hz), 4.69 (1H, d, *J* = 3.2 Hz), 4.35 (1H, brs), 3.96 (3H, s), 3.49 (1H, dt, *J* = 7.6 & 2.8 Hz), 2.80 (1H, dq, *J* = 8.8 & 3.2 Hz), 2.25 (3H, s), 2.15-2.09 (1H, m), 1.83-1.80 (1H, m), 1.60-1.43 (3H, m), 1.25-1.15 (1H, m).

LC-MS: t_R = 4.95 $[M+H]^+$= 323 (method 2)

Intermediate compound 109: 5-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)-6-methylpyridine-2-carbonitrile

The following compound was prepared using the same methodology as in intermediate compound 41 using 5-formyl-6-methylpyridine-2-carbonitrile (**intermediate compound 35**) (1 mmol) and 4-methylaniline (1 mmol). Purification of the crude material by flash chromatography on silica gel using

hexane and ethylacetate as eluents to afford 281 mg of the title endo-isomer (Yield=93%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (1H, d, *J* = 8.0 Hz), 7.89 (1H, d, *J* = 8.0 Hz), 6.82 (1H, s), 6.69 (1H, dd, *J* = 8.0 & 1.6 Hz), 6.58 (1H, d, *J* = 7.6 Hz), 5.86-5.83 (1H, m), 5.54(1H, d, *J* = 4.8 Hz), 5.40 (1H, s), 4.67 (1H, d, *J* = 2.8 Hz), 4.03-4.00 (1H, m), 3.29 (3H, s), 3.00-2.95 (1H, m), 2.40-2.33 (1H, m), 2.13 (3H, s), 1.57-1.51 (1H, m).

LC-MS: t_R = 4.72 $[M+H]^+$= 302 (method 2)

Intermediate compound 110: ethyl 5-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)-1-methyl-1H-pyrazole-3-carboxylate

The following compound was prepared using the same methodology as in intermediate compound 41 using 5-formyl-1-methyl-1*H*-pyrazole-3-carboxylic acid ethyl ester (**intermediate compound 39**) (1 mmol.) and 4-methylaniline (1mmol). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using hexane and ethylacetate as eluents to afford 229 mg of the title endo-isomer (Yield=91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (2H, m), 6.82 (1H, dd, *J* = 8.4 & 2 Hz), 6.54 (1H, d, *J* = 7.6 Hz), 5.82-5.80 (1H, m), 5.67-5.66 (1H, m), 4.65 (1H, d, *J* = 3.2 Hz), 4.45-4.34 (2H, m), 4.12-4.07 (1H, m), 3.96 (3H, s), 3.60 (1H, s), 3.05-2.98 (1H, m), 2.73-2.66 (1H, m), 2.24 (3H, s), 2.00-1.92 (1H, m), 1.40 (3H, t, *J* = 7.6 Hz).

LC-MS: t_R = 4.48 $[M+H]^+$= 338 (method 2)

Intermediate compound 111: ethyl 5-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-1-methyl-1H-pyrazole-3-carboxylate

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 110** (225 mg, 0.67 mmol). Solvent was evaporated to give 209 mg of the title endo-isomer, which was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (1H, s), 6.88 (1H, s), 6.82 (1H, dd, *J* = 7.6 & 1.2 Hz), 6.51 (1H, d, *J* = 8.0 Hz), 4.57 (1H, d, *J* = 3.2 Hz), 4.41-4.34 (2H, m), 3.93

(3H, s), 3.63 (1H, s), 3.44-3.39 (1H, m), 2.57-2.48 (1H, m), 2.25 (3H, s), 2.18-2.09 (1H, m), 1.84-1.74 (2H, m), 1.52-1.39 (2H, m), 1.40 (3H, t, *J* = 7.6 Hz).

LC-MS: t_R = 4.78 $[M+H]^+$= 340 (method 2)

Intermediate compound 112: ethyl 5-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-methoxy-3H-cyclopenta[c]quinolin-4-yl)-1-methyl-1H-pyrazole-3-carboxylate

The following compound was prepared using the same methodology as in intermediate compound 41 using 5-formyl-1-methyl-1*H*-pyrazole-3-carboxylic acid ethyl ester (**intermediate compound 39**) (1 mmol) and 4-methoxyaniline (1mmol). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using hexane and ethylacetate as eluents to afford 190 mg of the title endo-isomer (Yield=91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (1H, s), 6.65-6.57 (3H, m), 5.82-5.78 (1H, m), 5.69-5.66 (1H, m), 4.62 (1H, d, *J* = 2.8 Hz), 4.45-4.36 (2H, m), 4.13-4.01 (1H, m), 3.96 (3H, s), 3.75 (3H, s), 3.52 (1H, s), 3.03-3.00 (1H, m), 2.73-2.66 (1H, m), 2.04-1.94 (1H, m), 1.40 (3H, t, *J* = 7.2 Hz).

LC-MS: t_R = 4.02 $[M+H]^+$= 354 (method 2)

Intermediate compound 113: ethyl 5-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-1-methyl-1H-pyrazole-3-carboxylate

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 112** (190 mg, 0.54 mmol). Solvent was evaporated to give 174 mg of the title endo-isomer, which was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (1H, s), 6.88 (1H, s), 6.70 (1H, d, *J* = 2.4 Hz), 6.63 (1H, dd, *J* = 8.4 & 2.8 Hz), 6.55 (1H, d, *J* = 8.4 Hz), 4.54 (1H, d, *J* = 2.8 Hz), 4.44-4.38 (2H, m), 3.93 (3H, s), 3.76 (3H, s), 3.53 (1H, s), 3.45-3.41 (1H, m), 2.54-2.49 (1H, m), 2.17-2.12 (1H, m), 1.81-1.71 (2H, m), 1.53-1.33 (2H, m), 1.40 (3H, t, *J* = 7.6 Hz).

LC-MS: t_R = 4.30 $[M+H]^+$= 356 (method 2)

Intermediate compound 114: ethyl 3-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)-1-methyl-1H-pyrazole-5-carboxylate

The following compound was prepared using the same methodology as in intermediate compound 41 using 3-formyl-1-methyl-1*H*-pyrazole-5-carboxylic acid ethyl ester (**intermediate compound 40**) (1 mmol) and 4-methylaniline (1 mmol). Purification of the crude material by flash chromatography on silica gel using hexane and ethylacetate as eluents to afford 128 mg of the title endo-isomer (Yield: 46%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (1H, s), 6.82 (1H, s), 6.80 (1H, dd, *J* = 8.0 & 2.0 Hz), 6.60 (1H, d, *J* = 8.4 Hz), 5.83-5.79 (1H, m), 5.67-5.65 (1H, m), 4.63 (1H, d, *J* = 3.2 Hz), 4.37 (2H, q, *J* = 7.6 Hz), 4.16 (3H, s), 4.07 (1H, d, *J* = 7.6 Hz), 3.20-3.12 (1H, m), 2.64-2.56 (1H, m), 2.23 (3H, s), 2.14-2.07 (1H, m), 1.39 (3H, t, *J* = 7.6 Hz).

LC-MS: t_R = 4.93 $[M+H]^+$= 338 (method 2)

Intermediate compound 115: ethyl 3-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-1-methyl-1H-pyrazole-5-carboxylate

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 114** (120 mg, 0.36 mmol). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using hexane and ethylacetate as eluents to afford 104 mg of the title endo-isomer (Yield: 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (1H, s), 6.82 (1H, s), 6.80 (1H, dd, *J* = 7.6 & 1.6 Hz), 6.53 (1H, d, *J* = 8.4 Hz), 4.56 (1H, d, *J* = 3.2 Hz), 4.34 (2H, q, *J* = 7.2 Hz), 4.16 (3H, s), 3.44-3.39 (1H, m), 2.66-2.60 (1H, m), 2.24 (3H, s), 2.12-2.07 (1H, m), 1.80-1.71 (1H, m), 1.70-1.65 (1H, m), 1.54-1.45 (2H, m), 1.40 (3H, t, *J* = 7.6 Hz).

LC-MS: t_R = 5.12 $[M+H]^+$= 339 (method 2)

Intermediate compound 116: ethyl 3-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-methoxy-3H-cyclopenta[c]quinolin-4-yl)-1-methyl-1H-pyrazole-5-carboxylate

The following compound was prepared using the same methodology as in intermediate compound 41 using 3-formyl-1-methyl-1H-pyrazole-5-carboxylic acid ethyl ester (**intermediate compound 40**) (1 mmol) and 4-methoxyaniline (1

mmol). Purification of the crude material by flash chromatography on silica gel using hexane and ethylacetate as eluents to afford 94 mg of the title endo-isomer (Yield: 34%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (1H, s), 6.64-6.58 (3H, m), 5.82-5.78 (1H, m), 5.68-5.65 (1H, m), 4.59 (1H, d, *J* = 3.6 Hz), 4.37 (2H, q, *J* = 7.6 Hz), 4.16 (3H, s), 4.07 (1H, d, *J* = 7.6 Hz), 3.75 (3H, s), 3.20-3.12 (1H, m), 2.62-2.54 (1H, m), 2.15-2.08 (1H, m), 1.37 (3H, t, *J* = 7.6 Hz).

LC-MS: t_R = 4.42 $[M+H]^+$= 354 (method 2)

Intermediate compound 117: ethyl 3-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-1-methyl-1H-pyrazole-5-carboxylate

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 116** (90 mg, 0.36 mmol). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using hexane and ethylacetate as eluents to afford 69 mg of the title endo-isomer (Yield: 76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (1H, s), 6.69 (1H, d, *J* = 2.8 Hz), 6.63-6-51 (3H, m), 4.52 (1H, d, *J* = 2.8 Hz), 4.41-4.31 (3H, m), 4.16 (3H, s), 3.75 (3H, s), 3.45-3.40 (1H, m), 2.67-2.64 (1H, m), 2.13-2.08 (1H, m), 1.79-1.75 (1H, m), 1.70-1.64 (1H, m), 1.51-1.44 (2H, m), 1.40 (3H, t, *J* = 7.6 Hz).

LC-MS: t_R = 4.48 $[M+H]^+$= 356 (method 2)

Intermediate compound 118: 1-isobutoxy-4-nitrobenzene

The following compound was prepared using the same methodology as in intermediate compound 4 from 2-methylpropan-1-ol (2.67 mmol, 0.25 mL). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel, eluting with a gradient from 10% to 50% ethyl acetate in hexane gave 1-isobutoxy-4-nitrobenzene as an oil (350 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (2H, d, *J* = 9.2 Hz), 6.95 (2H, d, *J* = 9.2 Hz), 3.82 (2H, d, *J*= 6.8 Hz), 2.2-2.1 (1H, m), 1.05 (2H, d, *J*= 6.4 Hz)

LC-MS: t_R =3.58 $[M+H]^+$= 196 (method 3).

Intermediate compound 119: 4-isobutoxybenzenamine

The following compound was prepared using the same methodology as in intermediate compound 5 from **intermediate compound 118** (1.79 mmol, 350 mg). Reaction mixture was diluted with aqueous 1 N NaOH solution and ethyl acetate. The aqueous layer was extracted with EtAcO. The combined extracts were washed with brine, dried over anhydrous magnesium sulfate and concentrated in *vacuum* to give intermediate 119 (205 mg, 69%) with no further purification.

LC-MS: t_R =1.62 $[M+H]^+$= 166 (method 3)

Intermediate compound 120: methyl 4-(3a,4,5,9b-tetrahydro-8-isobutoxy-3H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoate

The following compound was prepared using the same methodology as in intermediate compound 41 using **intermediate compound 19** (1.21 mmol, 215 mg) and **intermediate compound 119** (1.21 mmol, 200 mg). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 15% ethylacetate in hexanes afforded the title compound as a 1:12 mixture of exo/endo isomers. (323 mg. Yield: 68%).

LC-MS: t_R =5.17 $[M+H]^+$= 392 (method 2) (Both isomers)

Intermediate compound 121 & 122: methyl 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-isobutoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoate (121) and methyl 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-isobutoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoate (122)

The following compounds were prepared using the same methodology as in intermediate compound 67 from **intermediate compound 120** (0.82 mmol, 323 mg) for 1 h. Purification of the crude material (1:6.5 mixture of exo/endo isomers) by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave 187 mg of the pure endo-isomer methyl 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-isobutoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoate (**121**) and 13.2 mg of the pure exo-isomer methyl 4-

((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-isobutoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoate (**122**) (Overall yield= 61%).

Methyl-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-isobutoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoate (endo-isomer **121**) :

LC-MS: t_R =5.43 $[M+H]^+$= 394 (method 2)

Methyl-4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-isobutoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoate (exo-isomer **122**):

LC-MS: t_R =5.27 $[M+H]^+$= 394 (method 2)

Intermediate compound 123: 4-(dibromomethyl)-3-fluorobenzoic acid

To a solution of 3-fluoro-4-methylbenzoic acid (6.49 mmol, 1 g) in CCl_4 (15 mL), NBS (19.47 mmol, 3.46 g), and benzoyl peroxide (0.649 mmol, 158 mg) were added. The reaction mixture was stirred 16h at 90ºC. The reaction was cooled and the precipitate of succinimide and unreacted NBS was removed by filtration and washed with ethyl acetate. Solvent was evaporated and the crude product was purified by flash chromatography on silica gel using an elution of 8% ethyl acetate in hexanes to afford 4-(dibromomethyl)-3-fluorobenzoic acid (1.85 g, Yield:92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (2H, m), 7.76 (1H, d, *J* = 11.2 Hz), 6.94 (1H, s)

LC-MS: t_R = 3.40 $[M+H]^+$ = not ion (method 3)

Intermediate compound 124: 3-fluoro-4-formylbenzoic acid

To a solution of 4-(dibromomethyl)-3-fluorobenzoic acid **intermediate compound 123** (35.6 mmol, 11.1 g) in acetonitrile (60 mL) and water (30 mL) $AgNO_3$ (106.8 mmol, 18 g) was added, and the mixture was heated for 30 min under reflux. Then, the solution was allowed to cool down, AgBr was filtered off and washed with ethyl acetate. The combined filtrate was washed with brine and dried over anhydrous magnesium sulfate and concentrated to dryness to afford

the title compound which was used in the next step without further purification (4.2 g, Yield: 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (1H, s), 7.93-7.88 (2H, m), 7.83 (1H, d, *J* = 10.4Hz)

LC-MS: t_R = 2.10 $[M+H]^+$ = not ion (method 3)

Intermediate compound 125: 4-bromo-2-(trifluoromethyl)benzaldehyde

A solution of 4-bromo-2-(trifluoromethyl)-1-iodobenzene (2.85 mml, 1 g) in dry THF (18 mL) was degassed with Argon. The solution was cooled to -15ºC, i-PrMgCl (2M in THF, 11.4 mmol, 5.7 mL) was added and the reaction was stirred for 2 h at -15ºC. Then, dry DMF (14.24 mmol, 1.1 mL) was added and the reaction was allowed to warm over 1 h. The reaction was quenched with aqueous 1M HCl and extracted with EtAcO. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The resulting crude was purified by flash chromatography on silica gel using an elution of 10% ethylacetate in hexanes to give 4-bromo-2-(trifluoromethyl)benzaldehyde (488 mg. Yield: 68%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35-10.33 (1H, m), 8.00 (1H, d, *J* = 8 Hz), 7.94 (1H, d, *J* = 1.6 Hz), 7.86 (1H, dd, *J* = 8.8 & 1.6 Hz).

LC-MS: t_R = 3.68 $[M+H]^+$ not ion (method 3).

Intermediate compound 126: 3-(trifluoromethyl)-4-formylbenzonitrile

The following compound was prepared using the same methodology as in intermediate compound 25 (method 2) using the aldehyde **intermediate compound 125** (0.59 mmol, 150 mg). The reaction was diluted with DCM, filtered through a pad of Celite® and concentrated to dryness. The crude material was purified by flash chromatography on silica gel using an elution of 7% ethylacetate in hexanes to afford the pure title compound (86 mg, Yield:73%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44-10.42 (1H, m), 8.26 (1H, d, *J* = 8 Hz), 8.09 (1H, s), 7.86 (1H, d, *J* = 8.4 Hz).

LC-MS: t_R = 2.93 $[M+H]^+$ not ion (method 3).

Intermediate compound 127: 3-(trifluoromethyl)-4-formylbenzoic acid

The following compound was prepared using the same methodology as in intermediate compound 26 using the aldehyde **intermediate compound 126** (1.18 mmol, 235 mg). The mixture was cooled and diluted with water. The reaction mixture was extracted with Et_2O. The combined organic extracts were washed with brine, dried over magnesium sulfate and concentrated to dryness to afford the title compound which was used in the next step without further purification. (215 mg, Yield: 83%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.49-10.47 (1H, m), 8.54 (1H, s), 8.43 (1H, d, *J* = 8 Hz), 8.25 (1H, d, *J* = 8 Hz).

LC-MS: t_R = 2.88 $[M+H]^-$ = 217 (method 3)

Intermediate compound 128: methyl 3, 5-dichloro-4-methylbenzoate

Method 1: To a solution of 3,5-dichloro-4-methylbenzoic acid (4.88 mmol, 1 g) dissolved in dry MeOH (13.5 mL) at 0ºC concentrated sulfuric acid (2 mL) was added dropwise. The mixture was heated at 75ºC for 48h. Solvent was evaporated and the crude was dissolved with ethyl acetate. The solution was washed with saturated aqueous sodium bicarbonate solution, brine, dried over anhydrous sodium sulfate, filtered and concentrated to dryness to afford the title compound which was used in the next step without further purification (857 mg, Yield: 85%).

Method 2: To a solution of 3,5-dichloro-4-methylbenzoic acid (4.88 mmol, 1 g) dissolved in dry MeOH (13.5 mL) at 0ºC thionyl chloride (43.9 mmol, 3.2 mL) was added dropwise. The mixture was stirred at room temperature for 16h. Solvent was evaporated and the crude was dissolved with ethyl acetate. The solution was washed with saturated aqueous sodium bicarbonate solution, brine, dried over

anhydrous magnesium sulfate and concentrated to dryness to afford the title compound which was used in the next step without further purification (975 mg, Yield : 100%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (2H, s), 3.87 (3H, s), 2.48 (3H, s)

LC-MS: t_R = 4.28 $[M+H]^+$ = not ion (method 3)

Intermediate compound 129: methyl 4-(bromomethyl)-3, 5-dichlorobenzoate

To a solution of methyl 3,5-dichloro-4-methylbenzoate **intermediate compound 128** (4.45 mmol, 975 mg) in CCl_4 (30 mL), NBS (13.35 mmol, 2.38 g) and benzoyl peroxide (0.445 mmol, 108 mg) were added. The reaction mixture was stirred 16h at 90ºC. The reaction was cooled down and the precipitate of succinimide and unreacted NBS was removed by filtration and washed with DCM. Solvent was evaporated. The crude product was purified by flash chromatography on silica gel using an elution of 10% ethyl acetate in hexanes to afford methyl 4-(bromomethyl)-3,5-dichlorobenzoate (1.3 g, Yield:100%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (2H, s), 4.74 (2H, s), 3.92 (3H, s)

LC-MS: t_R = 4.15 $[M+H]^+$ = not ion (method 3)

Intermediate compound 130: methyl 3,5-dichloro-4-formylbenzoate

To a solution of methyl 4-(bromomethyl)-3,5-dichlorobenzoate **intermediate compound 129** (4.36 mmol, 1.3 g) in dichloromethane (30 mL) at 0ºC, trimethylamine oxide (17.44 mmol, 1.3 g) in DMSO (10 mL) was added. The reaction was warmed at 28ºC for 7 h. To this reaction mixture water was added, and the organic layer was extracted with Et_2O, dried over $MgSO_4$ and concentrated to afford the title compound which was used in the next step without further purification (532 mg, Yield: 52%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (1H, s), 8.01 (2H, s), 3.91 (3H, s)

LC-MS: t_R = 3.45 $[M+H]^+$ = not ion (method 3)

Intermediate compound 131: 4-bromo-2-fluoro-6-methylbenzenamine

A solution of 2-fluoro-6-methylbenzenamine (32 mmol, 4 g) in DMF (40 mL) was cooled in an ice bath, place under a nitrogen atmosphere, treated with NBS (32 mmol, 5.7 g). The reaction mixture was stirred 30 min at room temperature. The mixture was diluted with ethyl acetate and the organic layer washed by water, brine, dried over anhydrous sodium sulfate, filtered and concentrated to afford the title compound which was used in the next step without further purification (6 g, Yield:91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (1H, dd, *J* = 9.6 & 2 Hz), 6.98 (1H, brs), 2.17 (3H, s)

LC-MS: t_R = 3.28 $[M+H]^+$ = 204/206 (method 3)

Intermediate compound 132: 4-amino-3-fluoro-5-methylbenzonitrile

To a solution of 4-bromo-2-fluoro-6-methylbenzenamine **intermediate compound 131** (7.35 mmol, 1.5 g) in *N*-methyl-2-pyrrolidinone (10 mL) copper (I) cyanide (9.55 mmol, 856 mg) was added. The mixture was heated at 200 ºC for 16 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and water. Organic layer was then separated, washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduce pressure to afford the desired product which was purified by flash chromatography on silica gel using an elution of 20% ethyl acetate in hexanes to afford 4-amino-3-fluoro-5-methylbenzonitrile (917 mg, Yield: 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15-7.12 (2H, m), 4.21 (2H, s), 2.18 (3H, s)

LC-MS: t_R = 2.35 $[M+H]^+$ = not ion (method 3)

Intermediate compound 133: 3-fluoro-4-iodo-5-methylbenzonitrile

4-amino-3-fluoro-5-methylbenzonitrile **intermediate compound 132** (24.4 mmol, 3.67 g) was gradually added to concentrated sulphuric acid (50 mL). The mixture

was then stirred at room temperature for 20 min and then cooled to 0ºC. To this mixture was then added gradually sodium nitrite (26.8 mmol, 1.86 g) and stirred at 5ºC over 2.5 h. The mixture thus obtained was then added to ice-water (65 g) and potassium iodide (29.3 mmol, 4.87 g), stirred at 5ºC for 15 min and then at room temperature for 1 h. The reaction mixture was extracted with diethyl ether. The organic layer was washed with an aqueous solution of sodium thiosulfate, dried over magnesium sulphate, filtered and concentrated. The reaction crude was purified by flash chromatography on silica gel using an elution of 8% ethyl acetate in hexanes to afford 3-fluoro-4-iodo-5-methylbenzonitrile (2.4 g, Yield: 40%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68-7.66 (2H, m), 2.47 (3H, s)

LC-MS: t_R =3.55 $[M+H]^+$ = not ion (method 3)

Intermediate compound 134: 3-fluoro-5-methyl-4-vinylbenzonitrile

A solution of 3-fluoro-4-iodo-5-methylbenzonitrile **intermediate compound 133** (9.08 mmol, 2.37 g), 2-vinyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (18.16 mmol, 2.8 g), tetrakis(triphenylphosphine)palladium (5 % w/w, 118.5 mg) and 2N aqueous sodium carbonate solution (30.9 mmol, 15.5 mL) in toluene/ethanol (2:1, 30 mL) was degassed by argon and stirred at 90 ºC for 16 h. Total conversion was not achieved, then 2-vinyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (9.08 mmol, 1.4 g), tetrakis(triphenylphosphine)palladium (2.5 % w/w, 60 mg) and 2N aqueous sodium carbonate solution (15.5 mmol, 7 mL) were added again and stirred at 90ºC for additional 16h. The reaction mixture was cooled to room temperature and concentrated. The reaction crude was purified by flash chromatography on silica gel using an elution of 6% ethyl acetate in hexanes to afford 3-fluoro-5-methyl-4-vinylbenzonitrile (1.07 g, Yield:73%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (1H, d, *J* = 10.8 Hz), 6.63 (1H, dd, *J* = 18 & 12 Hz), 5.87 (1H, d, *J* = 18 Hz), 5.73 (1H, d, *J* = 11.6 Hz), 2.39 (3H, s)

LC-MS: t_R = 3.52 $[M+H]^+$ =not ion (method 3)

Intermediate compound 135: 3-fluoro-4-formyl-5-methylbenzonitrile

3-Fluoro-5-methyl-4-vinylbenzonitrile **intermediate compound 134** (6.64 mmol, 1.07 g), was dissolved in acetone/water (6:1, 46 mL), OsO_4 (4.91 mmol, 1.25 g) and $NaIO_4$ (19.9 mmol, 4.26 g) were added. The resulting mixture was kept at room temperature for 1.5 h, then filtrated, the solid was washed with ethyl acetate and the filtrate was concentrated under reduce pressure to afford the desired product which was purified by flash chromatography on silica gel using an elution of 7% ethyl acetate in hexanes to afford the title compound as a solid (926 mg, Yield: 85%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.39 (1H, s), 7.90 (1H, d, *J* = 11.2 Hz), 7.73 (1H, s), 2.58 (3H, s)

LC-MS: t_R = 2.67 $[M+H]^+$ = not ion (method 3)

Intermediate compound 136: 3-fluoro-4-formyl-5-methylbenzoic acid

To a solution of 3-fluoro-4-formyl-5-methylbenzonitrile **intermediate compound 135** (5.64 mmol, 920 mg) was dissolved in concentrated HCl (26 mL). The reaction mixture was stirred at 90ºC for 16h and cooled to room temperature. The crude product was filtered and the solid washed with water to afford the title compound which was used in the next step without further purification (839 mg, Yield: 81%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.41 (1H, s), 7.69 (1H, s), 7.61 (1H, d, *J* = 11.6 Hz), 2.59 (3H, s)

LC-MS: t_R = 2.50 $[M+H]^-$ = 181 (method 3)

Intermediate compound 137: 3,5-difluoro-4-formylbenzoic acid

To a solution of 3,5-difluorobenzoic acid (20 g, 126.5 mmol) in 2-methyltetrahydrofuran (225 mL) N,N,N',N'-tetramethylethylenediamine (TMEDA), (2.2 eq., 278.3 mmol, 43 mL) was added at room temperature. The resulting solution was cooled to -78ºC. Afterward, ^{n}Butyllithium (^{n}BuLi 2.5 M in hexane) (2.5 eq., 316.2 mmol, 126.5 mL) was added dropwise, during which the

temperature of the mixture remained at less than -65ºC. The mixture was then stirred at -78ºC for 1.5 h. Anhydrous methyl formate (2.1 eq., 265.6 mmol, 16.4 mL) was added dropwise at a rate that allowed the temperature to be maintained at less than -65ºC. The resulting solution was allowed to stir at -78ºC for 45 min, then the bath was removed and the reaction mixture was allowed to warm to room temperature while being stirred for 18h. The mixture was then cooled to 0-5ºC and excess base was quenched with 6 M aqueous HCl (7 eq., 885.5 mmol, 140 mL). The phases were then separated, and the aqueous layer was extracted 3 times with ethyl acetate. The combined organic phases were washed with 1N HCl solution, saturated brine, dried over anhydrous sodium sulphate, filtered and concentrated under vacuum. The residue was triturated in the minimum amount of ethyl acetate. A white solid precipitated which was collected by filtration, rinsed with hexanes and dried under vacuum to form the title compound (8.48g, Yield: 36%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.41 (1H, s), 7.72 (2H, d, *J* = 8.4 Hz).

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.95 (1H, s), 10.22 (1H, s), 7.65 (2H, d, *J* = 9.2 Hz).

Intermediate compound 138: 5-bromo-2-iodo-3-methylpyridine

The following compound was prepared using the same methodology as in intermediate compound 32 from 2,5-dibromo-3-methylpyridine (7.97 mmol, 2 g). Solvent was evaporated and purification of the crude product by flash chromatography on silica gel using an elution of 13% ethyl acetate in hexanes afforded the title compound as an oil (2.03 g, Yield: 86%).

LC-MS: t_R = 3.53 $[M+H]^+$=298/300 (method 3)

Intermediate compound 139: 5-bromo-3-methylpyridine-2-carbaldehyde

The following compound was prepared using the same methodology as in intermediate compound 125 using the 5-bromo-2-iodo-3-methylpyridine **intermediate compound 138** (6.71 mmol, 2 g). Purification of the crude material

by flash chromatography on silica gel using an elution of 10% ethyl acetate in hexanes afforded the 5-bromo-3-methylpyridine-2-carbaldehyde (673 mg, Yield: 52%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.14 (1H, s), 8.71-8.70 (1H, m), 7.82-7.80 (1H, m), 2.66 (3H, s).

LC-MS: t_R = 2.75 $[M+H]^+$=200/202 (method 3)

Intermediate compound 140: methyl 2-bromo-1-methyl-1H-imidazole-4-carboxylate

To a solution of methyl 1-methyl-1H-imidazole-4-carboxylate (14.3 mmol, 2 g) in CCl_4 (40 mL), NBS (15.3 mmol, 2.72 g) and AIBN (0.715 mmol, 117 mg) were added. The reaction mixture was stirred 4h at 60ºC and then cooled to room temperature. The solvent was evaporated. The reaction crude was purified by flash chromatography on silica gel using an elution of 8% methanol in ethyl acetate to afford methyl 2-bromo-1-methyl-1H-imidazole-4-carboxylate (529 mg, Yield:17%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (1H, s), 3.91 (3H, s), 3.67 (3H, s)

LC-MS: t_R = 1.60 $[M+H]^+$ = 219/221 (method 3)

Intermediate compound 141: methyl 1-methyl-2-styryl-1H-imidazole-4-carboxylate

A solution of methyl 2-bromo-1-methyl-1H-imidazole-4-carboxylate **intermediate compound 140** (529 mg, 2.41 mmol), 2-phenylvinylboronic acid (2.41 mmol, 357 mg), tetrakis(triphenylphosphine)palladium (5 % w/w, 27 mg) and 2N aqueous sodium carbonate solution (8.21 mmol, 4 mL) in toluene/ethanol (2:1, 18 mL) was degassed by argon and stirred at 90 ºC for 16 h, then cooled to room temperature and concentrated. The reaction crude was purified using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give methyl 1-methyl-2-styryl-1H-imidazole-4-carboxylate (337 mg, Yield: 57%).

LC-MS: t_R = 2.75 $[M+H]^+$ = 243 (method 3)

Intermediate compound 142: methyl 2-formyl-1-methyl-1H-imidazole-4-carboxylate

Methyl 1-methyl-2-styryl-1H-imidazole-4-carboxylate **intermediate compound 141** (337 mg, 1.4 mmol), was dissolved in acetone/water (6:1, 10.5 mL) OsO_4 (1.04 mmol, 264 mg) and $NaIO_4$ (4.2 mmol, 899 mg) were added. The resulting mixture was kept at room temperature for 1.5 h and then filtrated. The solid was washed with ethyl acetate and the filtrate was concentrated under reduce pressure to afford the desired product which was purified by flash chromatography on silica gel using an elution of 100% ethyl acetate in hexanes to afford the title compound as a solid (102 mg, Yield: 43%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.31 (1H, s), 8.06 (1H, s), 3.87 (3H, s), 3.86 (3H, s)

LC-MS: t_R = 1.38 $[M+H]^+$ = 169 (method 3)

Intermediate compound 143: methyl 3-formamido-4-methylbenzoate

A solution of methyl 3-amino-4-methylbenzoate (30.27 mmol, 5 g) in formic acid (1.12 mmol, 42 mL) was heated at 110ºC for 4h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and water. Organic layer was then separated and washed by water (x3), dried over anhydrous sodium sulphate, filtered and concentrated under reduce pressure to afford the desired product (4 g, Yield: 68%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (1H, s), 8.44 (1H, d, *J* = 2 Hz), 8.34 (1H, s), 7.64 (1H, dd, *J* = 1.6 & 8 Hz), 7.36 (1H, d, *J* = 7.6 Hz), 3.83 (3H, s), 2.31 (3H, s).

LC-MS: t_R = 2.20 $[M+H]^+$ = 194 (method 3)

Intermediate compound 144: methyl 3-formamido-4-methyl2-nitrobenzoate

Fuming nitric acid (15 mL) was cooled at 0ºC and methyl 3-formamido-4-methylbenzoate **intermediate compound 143** (22.1 mmol, 4.27 g) was added in small portions over 45 min. The reaction mixture was stirred at 0ºC for an additional 1h, and then ice water (50 g) was added and stirred for 1.5h at room temperature. The precipitated solid was filtered, washed with water and dried to afford the title compound which was used in the next step without further purification (2.4 g, Yield: 46%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (1H, s), 8.25 (1H, s), 8.34 (1H, s), 7.88 (1H, d, J = 8 Hz), 7.68 (1H, d, J = 8 Hz), 3.83 (3H, s), 2.28 (3H, s).

LC-MS: t_R = 2.02 $[M+H]^+$= not ion (method 3)

Intermediate compound 145: methyl 7-methyl-3H-benzo[d]imidazole-4-carboxylate

To a solution of methyl 3-formamido-4-methyl2-nitrobenzoate **intermediate compound 144** (2.1 mmol, 500 mg) in methanol (5 mL) iron powder (10.5 mmol, 587 mg) and acetic acid (2.3 mL) were added. The reaction mixture was heated at 70ºC for 3h and then cooled at room temperature, filtered and the filter was washed with ethyl acetate. The solvent was evaporated. The crude was dissolved with ethyl acetate and saturated aqueous sodium bicarbonate solution. The organic layer was separated, washed with water and brine, dried over magnesium sulphate and concentrated to afford the title compound which was used in the next step without further purification (300 mg, Yield: 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.5 (1H, brs), 8.12 (1H, s), 7.85 (1H, d, J = 7.6 Hz), 7.14 (1H, d, J = 7.6 Hz), 3.99 (3H, s), 2.75 (3H, s).

LC-MS: t_R = 1.48 $[M+H]^+$= 191 (method 3)

Intermediate compound 146: methyl 3,7-dimethyl-3H-benzo[d]imidazole-4-carboxylate

To a solution of methyl 7-methyl-3H-benzo[d]imidazole-4-carboxylate **intermediate compound 145** (0.34 mmol, 64 mg) in DMF (2 mL) iodomethane

(0.51 mmol, 0.032 mL) and potassium carbonate (1.7 mmol, 235 mg) were added. The reaction mixture was heated at 50ºC for 1.5h and then partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic layer was separated, washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, filtered and concentrated to afford the title compound which was used in the next step without further purification (42 mg, Yield: 60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (1H, s), 7.79 (1H, d, *J* = 7.6 Hz), 7.08 (1H, d, *J* = 8 Hz), 4.05 (3H, s), 3.95 (3H, s), 2.71 (3H, s).

LC-MS: t_R = 1.85 $[M+H]^+$ = 205 (method 3)

Intermediate compound 147: methyl 7-(dibromomethyl)-3-methyl-3H-benzo[d]imidazole-4-carboxylate

To a solution of methyl 3,7-dimethyl-3H-benzo[d]imidazole-4-carboxylate **intermediate compound 146** (1.2 mmol, 246mg) in CCl_4 (12 mL), NBS (3.6 mmol, 641 mg) and benzoyl peroxide (0.12 mmol, 29 mg) were added. The reaction mixture was stirred 16h at 90ºC and then cooled at room temperature. The solvent was evaporated and the reaction crude was purified by flash chromatography on silica gel using an elution of 63% DCM in hexanes to afford methyl 7-(dibromomethyl)-3-methyl-3H-benzo[d]imidazole-4-carboxylate (210 mg ,Yield: 48%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (2H, m), 7.78 (1H, d, *J* = 8 Hz), 7.58 (1H, s), 4.06 (3H, s), 3.98 (3H, s).

LC-MS: t_R = 3.43 $[M+H]^+$ = 361/363 (method 3)

Intermediate compound 148: methyl 7-formyl-3-methyl-3H-benzo[d]imidazole-4-carboxylate

To a solution of methyl 7-(dibromomethyl)-3-methyl-3H-benzo[d]imidazole-4-carboxylate **intermediate compound 147** (0.7 mmol, 255 mg) in acetonitrile (10 mL) and water (5 mL) $AgNO_3$ (2.1 mmol, 359 mg) was added, the mixture was heated for 30 min under reflux. The reaction mixture was cooled down, AgBr was

filtered off and washed with ethyl acetate. The combined filtrate was washed with brine, dried over anhydrous magnesium sulfate and concentrated to dryness to afford the title compound which was used in the next step without further purification (130 mg, Yield: 85%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.82 (1H, s), 8.55 (1H, s), 7.82 (1H, d, *J* = 7.6 Hz), 7.75 (1H, d, *J* = 8 Hz), 3.98 (3H, s), 3.96 (3H, s).

LC-MS: t_R = 1.80 $[M+H]^+$ = 219 (method 3)

Intermediate compound 149: 4-((3aS,9bR)-3a,4,5,9b-tetrahydro-8-(trifluoromethoxy)-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-trifluoromethoxyaniline (1 mmol). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 45% ethylacetate in hexanes afforded the title compound as a white solid (1:16 mixture of exo/endo regioisomer) (283 mg, Yield: 75%).

Endo-isomer: 4-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-(trifluoromethoxy)-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (2H, d, *J* = 8.0 Hz), 7.55 (2H, d, *J* = 8.4 Hz), 6.92 (1H, s), 6.87 (1H, dd, *J* = 8.4 & 2 Hz), 6.63 (1H, d, *J* = 8.4 Hz), 5.83-5.81 (1H, m), 5.68-5.67 (1H, m), 4.72 (1H, d, *J* = 3.2 Hz), 4.12 (1H, d, *J* = 7.6 Hz), 3.04 (1H, dq, *J* = 8.8 & 3.6 Hz), 2.62-2.55 (1H, m), 1.82-1.75 (1H, m).

LC-MS: t_R = 4.92 $[M+H]^+$ = 376 (method 2)

Intermediate compound 150: 4-((3aS,9bR)-8-(difluoromethoxy)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-difluoromethoxyaniline (1 mmol). Solvent was evaporated and purification of the crude material by flash chromatography on

silica gel using an elution of 58% ethylacetate in hexanes afforded the title compound. (149 mg, Yield: 40%).

LC-MS: t_R = 4.47 $[M+H]^+$= 358 (method 2)

Intermediate compound 151: methyl 4-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-(trifluoromethoxy)-3H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoate

The following compound was prepared using the same methodology as in intermediate compound 41 using methyl 4-formyl-3-methylbenzoate (**intermediate compound 19**) (1 mmol, 178 mg) and 4-trifluoromethoxyaniline (1 mmol, 177 mg). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 28% ethylacetate in hexanes afforded the endo-compound as a white solid (80 mg, Yield: 20%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (1H, d, *J* = 8.4 Hz), 7.87 (1H, m), 7.66 (1H, d, *J* = 8.0 Hz), 6.93 (1H, m), 6.86 (1H, d, *J* = 9.2 Hz), 6.61 (1H, d, *J* = 8.8 Hz), 5.82-5.80 (1H, m), 5.70-5.67 (1H, m), 4.84 (1H, d, *J* = 2.8 Hz), 4.11 (1H, d, *J* = 8.8 Hz), 3.92 (3H, s), 3.70 (1H, brs), 3.05 (1H, dq, *J* = 9.2 & 3.2 Hz), 2.69-2.60 (1H, m), 2.43 (3H, s), 1.77-1.70 (1H, m).

LC-MS: t_R = 5.35 $[M+H]^+$= 404 (method 2)

Intermediate compound 152: methyl 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-(trifluoromethoxy)-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoate

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 151** (75 mg, 0.18 mmol) for 1h. HPLC analysis showed total conversion. Reaction mixture was filtered and filter washed with THF. Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using hexane and ethylacetate as eluents to afford 52 mg of the title endo-isomer (Yield: 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (1H, dd, *J* = 7.6 & 2.0 Hz), 7.86-7.84 (1H, m), 7.69 (1H, d, *J* = 8.4 Hz), 6.98-6.97 (1H, m), 6.88-6.85 (1H, m), 6.57 (1H, d, *J* = 8.8 Hz), 4.78 (1H, d, *J* = 3.2 Hz), 3.92 (3H, s), 3.74 (1H, brs), 3.47 (1H, dt, *J* = 8.4

& 3.6 Hz), 2.51-2.43 (1H, m), 2.40 (3H, s), 2.21-2.16 (1H, m), 1.78-1.67 (1H, m), 1.60-1.53 (1H, m), 1.48-1.43 (1H, m), 1.16-1.13 (1H, m).

LC-MS: t_R = 5.53 $[M+H]^+$= 406 (method 2)

Intermediate compound 153: methyl 4-((3aS,4R,9bR)-8-(difluoromethoxy)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoate

The following compound was prepared using the same methodology as in intermediate compound 41 using methyl 4-formyl-3-methylbenzoate **intermediate compound 19** (1 mmol, 178 mg) and 4-difluoromethoxyaniline (1 mmol, 177 mg). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 13% ethylacetate in hexanes afforded the endo-compound as a white solid (248 mg, Yield: 64%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (1H, d, *J* = 8.4 Hz), 7.86 (1H, m), 7.67 (1H, d, *J* = 8.0 Hz), 6.86 (1H, m), 6.79 (1H, dd, *J* = 8.4 & 2.8 Hz), 6.60 (1H, d, *J* = 8.8 Hz), 6.39 (1H, t, *J* = 74.5 Hz), 5.82-5.80 (1H, m), 5.70-5.67 (1H, m), 4.82 (1H, d, *J* = 3.2 Hz), 4.10 (1H, d, *J* = 10 Hz), 3.92 (3H, s), 3.64 (1H, brs), 3.04 (1H, dq, *J* = 9.2 & 2.8 Hz), 2.69-2.60 (1H, m), 2.43 (3H, s), 1.77-1.70 (1H, m).

LC-MS: t_R = 5.02 $[M+H]^+$= 386 (method 2)

Intermediate compound 154: (+/-)-methyl 4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoate. (-)-methyl 4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoate (154a) & (+)-methyl 4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoate (154b)

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 153** (248 mg, 0.64 mmol) for 30min. HPLC analysis showed total conversion. Reaction mixture was filtered and filter washed with THF. Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using hexane and

ethylacetate as eluents to afford 244 mg of the title racemic endo-isomer (Yield: 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (1H, dd, *J* = 8.46 & 2.0 Hz), 7.86-7.84 (1H, m), 7.70 (1H, d, *J* = 8.4 Hz), 6.91 (1H, d, *J* = 2.8 Hz), 6.80 (1H, dd, *J* = 8.4 & 2.8 Hz), 6.56 (1H, d, *J* = 8.8 Hz), 6.40 (1H, 7, *J* = 74.8 Hz), 4.75 (1H, d, *J* = 2.8 Hz), 3.91 (3H, s), 3.68 (1H, brs), 3.46 (1H, dt, *J* = 8.0 & 3.6 Hz), 2.54-2.43 (1H, m), 2.39 (3H, s), 2.21-2.14 (1H, m), 1.78-1.68 (2H, m), 1.60-1.53 (1H, m), 1.47-1.42 (1H, m), 1.17-1.12 (1H, m).

LC-MS: t_R = 5.20 $[M+H]^+$= 388 (method 2)

Separation of 1.24 g of (+/-)-methyl 4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoate (**154**) by preparative chiral chromatography was carried out using heptane/EtOH (98:2) as eluents to yield:

427 mg of the enantiomer (-)-methyl 4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoate (**154a**)

Preparative HPLC: t_R = 21.3

Optical Purity: 99.9% ee

226 mg of the enantiomer (+)-methyl 4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoate (**154b**)

Preparative HPLC: t_R =57.4

Optical Purity: 99.9% ee

Intermediate compound 155: 3-fluoro-4-(3a,4,5,9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in Intermediate compound 41 using 3-fluoro-4-formylbenzoic acid **intermediate compound 124** (0.63 mmol, 105 mg) and *p*-toluidine (0.63 mmol, 67.5 mg). Solvent was evaporated and purification of the crude material by flash

chromatography on silica gel using an elution of 35% ethyl acetate in hexanes afforded the endo:exo isomer (7:1) (78 mg, Yield:38%).

Endo-isomer: 3-fluoro-4-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (1H, dd, *J* = 1.6 & 8 Hz), 7.75 (1H, d, *J* = 7.6 Hz), 7.65 (1H, d, *J* = 11.2 Hz), 6.82 (1H, s), 6.72 (1H, d, *J* = 8.8 Hz), 6.63 (1H, d, *J* = 8.4 Hz), 5.84 (1H, brs), 5.56 (1H, brs), 5.47 (1H, s), 4.75 (1H, s), 4.01 (1H, d, *J* = 8.4 Hz), 3.02-2.96 (1H, m), 2.45-2.38 (1H, m), 2.15 (3H, s), 1.66-1.60 (1H, m).

LC-MS: t_R = 4.23 $[M+H]^+$ = 324 (method 3)

Intermediate compound 156: 3-fluoro-4-(3a,4,5,9b-tetrahydro-8-methoxy-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in Intermediate compound 41 using 3-fluoro-4-formylbenzoic acid **intermediate compound 124** (0.81 mmol, 136 mg) and *p*-anisidine (0.81 mmol, 100 mg). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 35% ethyl acetate in hexanes afforded the endo:exo isomer (17:1) (132 mg, Yield: 48%).

Endo-isomer: 3-fluoro-4-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-methoxy-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (1H, dd, *J* = 1.2 & 7.6 Hz), 7.75 (1H, m), 7.65 (1H, d, *J* = 10.8 Hz), 6.68 (1H, d, *J* = 8.8 Hz), 6.64 (1H, d, *J* = 2.4 Hz), 6.55 (1H, dd, *J* = 3.2 & 8.8 Hz), 5.86 (1H, brs), 5.57 (1H, brs), 5.33 (1H, s), 4.71 (1H, s), 4.03 (1H, d, *J* = 8.4 Hz), 3.65 (3H, s), 3.02-2.96 (1H, m), 2.49-2.41 (1H, m), 1.66-1.61 (1H, m).

LC-MS: t_R = 3.83 $[M+H]^+$ = 340 (method 3)

Intermediate compound 157: 4-(8-cyclopropyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid

The following compound was prepared using the same methodology as in Intermediate compound 41 using 3-fluoro-4-formylbenzoic acid **intermediate compound 124** (4.46 mmol, 750 mg) and 4-cyclopropylbenzenamine **intermediate compound 3** (4.46 mmol, 595 mg). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 35% ethyl acetate in hexanes afforded a slightly impure solid. The solid was precipitated in ACN, filtered and washed to afford 4-(8-cyclopropyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid (870 mg, Yield:55%).

LC-MS: t_R = 5.07 $[M+H]^+$ = 350 (method 2)

Intermediate compound 158: 4-(8-(difluoromethoxy)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid

The following compound was prepared using the same methodology as in Intermediate compound 41 using 3-fluoro-4-formylbenzoic acid **intermediate compound 124** (5.95 mmol, 1000 mg) and 4-(difluoromethoxy)benzenamine (5.95 mmol, 0.738 mL). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 34% ethyl acetate in hexanes afforded the title compound as a solid (1300 mg, Yield:58%).

Endo-isomer: 4-((3aS,4R,9bR)-8-(difluoromethoxy)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (1H, dd, *J* = 1.6 & 8.4 Hz), 7.74 (1H, m), 7.65 (1H, dd, *J* = 1.6 & 10.8 Hz), 6.98 (1H, t, *J* = 74.8 Hz), 6.88 (1H, s), 6.72 (2H, m), 5.86 (1H, brs), 5.76 (1H, s), 5.59 (1H, brs), 4.78 (1H, d, *J* = 2.8 Hz), 4.06 (1H, d, *J* = 8.4 Hz), 3.01-2.98 (1H, m), 2.49-2.37 (1H, m), 1.68-1.64 (1H, m).

LC-MS: t_R = 4.63 $[M+H]^+$ = 376 (method 2)

Intermediate compound 159: 4-(8-ethyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid

The following compound was prepared using the same methodology as in Intermediate compound 41 using 3-fluoro-4-formylbenzoic acid **intermediate compound 124** (5.95 mmol, 1000 mg) and 4-ethylbenzenamine (5.95 mmol, 0.740 mL). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 25% ethyl acetate in hexanes afforded the title compound as a solid (1200 mg, Yield:60%).

Endo-isomer: 4-((3aS,4R,9bR)-8-ethyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (1H, dd, *J* = 1.6 & 8 Hz), 7.75 (1H, m), 7.65 (1H, dd, *J* = 1.6 & 10.8 Hz), 6.84 (1H, s), 6.75 (1H, dd, *J* = 1.6 & 8.4 Hz), 6.65 (1H, d, *J* = 8 Hz), 5.86-5.84 (1H, brs), 5.56 (1H, brs), 5.48 (1H, s), 4.76 (1H, d, *J* = 2.8 Hz), 4.02 (1H, d, *J* = 8.4 Hz), 3.01-2.95 (1H, m), 2.48-2.38 (3H, m), 1.66-1.640 (1H, m), 1.12 (3H, t, *J* = 7.6 Hz)

LC-MS: t_R = 5.12 $[M+H]^+$ = 338 (method 2)

Intermediate compound 160: 3-(trifluoromethyl)-4-(3a,4,5,9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 101 using the aldehyde **intermediate compound 127** (0.41 mmol, 90 mg). Solvent was evaporated and purification of the crude material (1:2.5 mixture of exo/endo isomers) by flash chromatography on silica gel using an elution of 60% ethylacetate in hexanes afforded the title compound as a 1:4 mixture of exo/endo-isomers as a white solid (89 mg. Yield: 57%).

Endo-isomer: 3-(trifluoromethyl)-4-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26-8.20 (2H, m), 8.11 (1H, d, *J* = 8 Hz), 6.83 (1H, s), 6.74-6.70 (1H, m), 6.59 (1H, d, *J* = 8 Hz), 5.91-5.88 (1H, m), 5.63 (1H, s),

5.64-5.60 (1H, m), 4.78 (1H, s), 3.98 (1H, d, *J* = 8.4 Hz), 2.87-2.78 (1H, m), 2.67-2.60 (1H, m), 2.15 (3H, s), 1.68-1.60 (1H, m).

LC-MS: t_R = 5.17 $[M+H]^+$=374 (method 2)

Intermediate compound 161: 3-(trifluoromethyl)-4-(3a,4,5,9b-tetrahydro-8-methoxy-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 101 using the aldehyde **intermediate compound 127** (0.41 mmol, 90 mg) and *p*-anisidine (0.41 mmol, 51 mg). Solvent was evaporated and purification of the crude material (1:1.6 mixture of exo/endo isomers) by flash chromatography on silica gel using an elution of 60% ethyl acetate in hexanes afforded the title compound as a 1:6 mixture of exo/endo-isomers as a white solid (97 mg. Yield: 60%).

Endo-isomer: 3-(trifluoromethyl)-4-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-methoxy-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27-8.2 (2H, m), 8.13 (1H, d, *J* = 8.4 Hz), 6.66-6.62 (2H, m), 6.55 (1H, dd, *J* = 8.8 & 2.4 Hz), 5.94-5.92 (1H, m), 5.64-5.61 (1H, m), 5.49 (1H, s), 4.75 (1H, s), 4.02-3.98 (1H, m), 3.65 (3H, s), 2.86-2.80 (1H, m), 2.70-2.61 (1H, m), 1.68-1.62 (1H, m).

LC-MS: t_R = 4.78 $[M+H]^+$=388 (method 2)

Intermediate compound 162: methyl 4-((3aS,4S,9bR)-8-chloro-3a,4,5,9b-tetrahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-dimethylbenzoate

The following compound was prepared using the same methodology as in intermediate compound 101 using 4-chloroaniline (0.702 mmol, 89 mg). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 7% ethyl acetate in hexanes afforded the pure title exo-compound (177 mg, Yield: 68%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (2H, m), 7.24 (1H, dd, *J* = 2.4 & 0.8 Hz), 6.98 (1H, dd, *J* = 8.8 & 2 Hz), 6.51 (1H, d, *J* = 8.4 Hz), 5.95-5.92 (1H, m), 5.76-5.72 (1H, m), 4.34 (1H, d, *J* = 11.2 Hz),4.02-3.98 (1H, m), 3.92 (3H, s), 3.18-3.10 (1H, m), 2.67 (3H, brs), 2.49-2.40 (1H, m), 2.32 (3H, brs), 1.86-1.82 (1H, m).

LC-MS: t_R = 5.52 $[M+H]^+$=368 (method 2)

Intermediate compound 163: methyl 4-((3aS,4S,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-dimethylbenzoate

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 162** for 1h. Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 6% ethyl acetate in hexanes afforded the exo-isomer methyl 4-((3aS,4S,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-dimethylbenzoate (137 mg, Yield: 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (2H, s), 7.14 (1H, d, *J* = 2 Hz), 6.97 (1H, dd, *J* = 8.4 & 2 Hz), 6.54-6.51 (1H, m), 4.35 (1H, d, *J* = 11.6 Hz), 3.92 (3H, s), 3.10-3.04 (1H, m), 2.88-2.80 (1H, m), 2.64-2.40 (6H, m), 2.36-2.28 (1H, m), 1.80-1.62 (4H, m), 1.30-1.23 (1H, m).

LC-MS: t_R = 4.75 $[M+H]^+$=370 (method 3)

Intermediate compound 164: (+/-)-4-((3aS,4R,9bR)- 8-(difluoromethoxy)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-3-fluoro-5-methylbenzoic acid (164). (+)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-3-fluoro-5-methylbenzoic acid (164a) & (-)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-3-fluoro-5-methylbenzoic acid (164b)

The following compound was prepared using the same methodology as in Intermediate compound 41 using 3-fluoro-4-formyl-5-methylbenzoic acid **intermediate compound 136** (2.52 mmol, 460 mg) and 4-

(difluoromethoxy)benzenamine (2.52 mmol, 0.313 mL). Solvent was evaporated and the reaction crude was purified by two reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to afford the (+/-) endo-isomer compound (540 mg, Yield: 55%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62 (1H, s), 7.46 (1H, dd, *J* = 1.6 & 10.8 Hz), 6.95 (1H, t, *J* = 75.6 Hz), 6.86 (1H, d, *J* = 2.4 Hz), 6.73 (1H, dd, *J* = 2 & 8.4 Hz), 6.65 (1H, d, *J* = 8.4 Hz), 5.86 (2H, m), 5.65 (1H, d, *J* = 5.2 Hz), 4.83 (1H, s), 4.07-4.05 (1H, m), 2.98-2.91 (1H, m), 2.77-2.66 (1H, m) 1.93-1.87 (1H, m).

LC-MS: t_R = 4.68 $[M+H]^+$ = 390 (method 2)

Enantiomeric separation of 617 mg of (+/-)-4-((3aS,4R,9bR)- 8-(difluoromethoxy)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-3-fluoro-5-methylbenzoic acid (**164**) by preparative chiral chromatography was carried out using Heptane/EtOH (95:5) as eluents to yield:

124 mg of the enantiomer (+)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-3-fluoro-5-methylbenzoic acid (**164a**)

Preparative HPLC: t_R = 24.9

Optical Purity: 99.9 % ee

186 mg of the enantiomer (-)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-3-fluoro-5-methylbenzoic acid (**164b**)

Preparative HPLC: t_R = 41.2

Optical Purity: 89.8 % ee

Intermediate compound 165: 4-((3aS,9bR)-8-chloro-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 3,5-difluoro-4-formylbenzoic acid **intermediate compound 137** (6.0 mmol, 1.12 g) and 4-chloroaniline (6.0 mmol, 765 mg). The

suspension reaction was filtered and solid washed by the minimum amount of cold acetonitrile to afford the title compound as a white solid (1:6 mixture of exo/endo regioisomers) (1.58 g, Yield: 73%).

Endo-isomer: *4-((3aS,4R,9bR)*-8-chloro-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54 (2H, d, *J* = 9.2 Hz), 7.04 (1H, d, *J* = 2.4 Hz), 6.90 (1H, dd, *J* = 8.4 & 2.4 Hz), 6.62 (1H, d, *J* = 8.4 Hz), 6.06 (1H, s), 5.86-5.84 (1H, m), 5.62-5.60 (1H, m), 4.88 (1H, d, *J* = 3.2 Hz), 4.04-4.01 (1H, m), 3.60-3.55 (1H, m), 2.95-2.88 (1H, m), 2.69-2.62 (1H, m), 1.99-1.93 (1H, m)

LC-MS: t_R = 4.97 $[M+H]^+$= 362/364 (method 2)

Intermediate compound 166: 4-((3aS,9bR)-8-(difluoromethoxy)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 3,5-difluoro-4-formylbenzoic acid **intermediate compound 137** (3.17 mmol, 590 mg) and 4-difluoromethoxyaniline (3.17 mmol, 0.39 mL). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using hexane and ethylacetate as eluents afforded 668 mg of the title compound (1:20 mixture of exo/endo regioisomers) (Yield: 61%).

Endo-isomer: 4-((3aS,4R,9bR)-8-(difluoromethoxy)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54 (2H, d, *J* = 9.6 Hz), 6.95 (1H, t, *J* = 74.8 Hz), 6.85 (1H, d, *J* = 2.4 Hz), 6.73 (1H, dd, *J* = 8.0 & 2.8 Hz), 6.63 (1H, d, *J* = 8.4 Hz), 5.94 (1H, s), 5.85-5.82 (1H, m), 5.62-5.60 (1H, m), 4.87 (1H, d, *J* = 2.4 Hz), 4.06-3.98 (1H, m), 2.95-2.89 (1H, m), 2.71-2.65 (1H, m), 1.99-1.93 (1H, m).

LC-MS: t_R = 4.97 $[M+H]^+$= 362/364 (method 2)

Intermediate compound 167: 4-((3aS,9bR)-8-cyclopropyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using 3,5-difluoro-4-formylbenzoic acid **intermediate compound 137** (9.56 mmol, 1.78 g) and 4-cyclopropylbenzenamine **intermediate compound 3** (9.56 mmol, 1.30 mg). Reaction mixture was filtered and solid washed by minimum amount of acetonitrile, then with hexane and dried to obtain 850 mg of the title compound as a mixture of regioisomers 1:10 exo/endo. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave 800 mg of the pure title endo-isomer (Yield: 45%).

Endo-isomer: 4-((3aS,4R,9bR)-8-cyclopropyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53 (2H, d, *J* = 10.0 Hz), 6.72 (1H, d, *J* = 2.0 Hz), 6.59 (1H, dd, *J* = 8.0 & 2.0 Hz), 6.50 (1H, d, *J* = 8.0 Hz), 5.83-5.80 (1H, m), 5.64 (1H, s), 5.58 (1H, d, *J* = 5.20 Hz), 4.82 (1H, d, *J* = 3.2 Hz), 4.00 (1H, t, *J* = 7.2 Hz), 2.88 (1H, dq, *J* = 8.4 & 1.6 Hz), 2.72-2.64 (1H, m), 1.97-1.89 (1H, m), 1.77-1.70 (1H, m), 0.82-0.76 (2H, m), 0.54-0.46 (2H, m).

LC-MS: t_R = 5.03 $[M+H]^+$= 368 (method 2)

Intermediate compound 168: methyl 3,5-dichloro-4-(3a,4,5,9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)benzoate

The following compound was prepared using the same methodology as in Intermediate compound 101 using methyl 3,5-dichloro-4-formylbenzoate **intermediate compound 130** (0.64 mmol, 150 mg) and *p*-toluidine (0.64 mmol, 69 mg). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 8 % ethyl acetate in hexanes afforded the title compound as a 6:4 mixture of exo/endo-isomers as a white solid (182 mg, Yield:73%).

LC-MS: t_R = 5.58 $[M+H]^+$ = 388/390 (method 2)

Intermediate compound 169 & 170: methyl 3,5-dichloro-4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoate (169) & methyl 3,5-dichloro-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoate (170)

The following compound was prepared using the same methodology as in Intermediate compound 67 from **intermediate compound 168** (0.47 mmol, 182 mg) for 1h. Purification of the crude material (4:3 mixture of isomers exo-endo) by flash chromatography on silica gel using an elution of 6 % ethyl acetate in hexanes afforded the exo-isomer (**169**) methyl 3,5-dichloro-4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoate (60 mg, Yield: 32%) and the endo-isomer (**170**) methyl 3,5-dichloro-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoate (40 mg, Yield: 22%).

Exo-isomer: methyl 3,5-dichloro-4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoate (**169**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (2H, m), 6.86 (1H, s), 6.71 (1H, dd, *J* = 1.6 & 8.4 Hz), 6.47 (1H, d, *J* = 8.4 Hz), 5.90 (1H, s), 4.65 (1H, d, *J* = 10.4 Hz), 3.89 (3H, s), 2.97-2.94 (2H, m), 2.24-2.22 (1H, m), 2.15 (3H, s), 1.77-1.46 (4H, m), 1.24-1.20 (1H, m).

LC-MS: t_R = 5.68 $[M+H]^+$= 390/392 (method 2)

Endo-isomer: methyl 3,5-dichloro-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoate (**170**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (2H, m), 6.83 (1H, s), 6.71 (1H, d, *J* = 8 Hz), 6.49 (1H, d, *J* = 7.6 Hz), 5.66 (1H, s), 5.15 (1H, d, *J* = 2.8 Hz), 3.38-3.35 (1H, m), 3.33 (3H, s), 2.55-2.51 (1H, m), 2.15 (3H, s), 2.12-2.07 (1H, m) 1.96-1.91 (1H, m), 1.71-1.66 (1H, m), 1.57-1.55 (1H, m), 1.43-1.40 (1H, m), 1.30-1.23 (1H, m).

LC-MS: t_R = 5.80 $[M+H]^+$= 390/392 (method 2)

Intermediate compound 171: 5-((3aS,4R,9bR)-8-chloro-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-6-methylpyridine-2-carbonitrile

The following compound was prepared using the same methodology as in intermediate compound 41 using 5-formyl-6-methylpyridine-2-carbonitrile **intermediate compound 35** (0.31 mmol, 46 mg) and 4-chloroaniline (0.31 mmol, 39 mg). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 30% ethyl acetate in hexanes afforded the endo-compound as a white solid (77 mg, Yield: 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (1H, d, *J* = 7.6 Hz), 7.60 (1H, d, *J* = 8.0 Hz), 7.05 (1H, d, *J* = 2.4 Hz), 6.97 (1H, dd, *J* = 8.8 & 2.8 Hz), 6.58 (1H, d, *J* = 8.4 Hz), 5.86-5.84 (1H, m), 5.69-5.67 (1H, m), 4.82 (1H, d, *J* = 3.2 Hz), 4.10 (1H, d, *J* = 8.0 Hz), 3.56 (1H, brs), 3.04 (1H, dq, *J* = 8.8 & 2.8 Hz), 2.66 (3H, s), 2.58-2.50 (1H, m), 1.75-1.69 (1H, m)

LC-MS: t_R = 4.77 $[M+H]^+$= 322/324 (method 2)

Intermediate compound 172: 5-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-6-methylpyridine-2-carbonitrile

The **intermediate compound 171** (75 mg, 0.23 mmol) was dissolved in EtOH and THF (1:1, 3 mL) and platinum dioxide (2% w/w, 1.5 mg) was added. The solution was hydrogenated at room temperature for 30min. HPLC analysis showed total conversion. Reaction mixture was filtered and the filter washed by THF. Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 24% ethyl acetate in hexanes afforded the endo-compound as a white solid (66 mg, Yield: 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (1H, d, *J* = 8.0 Hz), 7.58 (1H, d, *J* = 7.6 Hz), 7.11 (1H, d, *J* = 1.6 Hz), 6.97 (1H, dd, *J* = 8.8 & 2.4 Hz), 6.54 (1H, d, *J* = 8.4 Hz), 4.75 (1H, d, *J* = 2.8 Hz), 3.60 (1H, brs), 3.46 (1H, dt, *J* = 8.0 & 3.2 Hz), 2.63 (3H, s), 2.60-2.47 (1H, m), 2.24-2.14 (1H, m), 1.84-1.76 (1H, m),1.70-1.55 (2H, m), 1.50-1.43 (1H, m), 1.15-1.08 (1H, m),

LC-MS: t_R = 5.05 $[M+H]^+$= 324/326 (method 2)

Intermediate compound 173: (3aS,4R,9bR)-4-(5-bromo-3-methylpyridin-2-yl)-8-chloro-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline

The following compound was prepared using the same methodology as in intermediate compound 41 using the aldehyde **intermediate compound 139** (1.17 mmol, 235 mg) and 4-chloroaniline (1.17 mmol, 150 mg). The reaction mixture was stirred at room temperature for 16h. Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 9% ethylacetate in hexanes afforded 370 mg of the pure endo-isomer (Yield= 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (1H, d, *J* = 2.4 Hz), 7.67 (1H, d, *J* = 2.4 Hz), 7.06 (1H, d, *J* = 2.4 Hz), 6.98 (1H, dd, *J* = 8.8 & 2.4 Hz), 6.75 (1H, d, *J* = 8.4 Hz), 5.79-5.75 (1H, m), 5.66-5.63 (1H, m), 4.83 (1H, d, *J* = 3.2 Hz), 4.14-4.10 (1H, m), 3.26-3.18 (1H, m), 2.60-2.50 (1H, m), 2.41 (3H, s), 1.76-1.68 (1H, m).

LC-MS: t_R = 5.15 $[M+H]^+$=375/377 (method 2)

Intermediate compound 174: (3aS,4R,9bR)-4-(5-bromo-3-methylpyridin-2-yl)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinoline

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 173** (0.49 mmol, 185 mg) using platinum dioxide (2.5% w/w, 4 mg) for 30 min. Reaction mixture was filtered and the filter washed with THF. Solvent was evaporated and purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave endo-isomer (3aS,4R,9bR)-4-(5-bromo-3-methylpyridin-2-yl)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinoline (94 mg, Yield: 51%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (1H, d, *J* = 1.6 Hz), 7.67 (1H, d, *J* = 1.6 Hz), 7.13 (1H, d, *J* = 1.6 Hz), 7.01 (1H, dd, *J* = 8.4 & 2 Hz), 6.77 (1H, d, *J* = 8.8 Hz), 4.78 (1H, d, *J* = 2.8 Hz), 3.49-3.44 (1H, m), 2.72-2.64 (1H, m), 2.39 (3H, s), 2.16-2.07 (1H, m), 1.86-1.78 (1H, m), 1.65-1.42 (3H, m), 1.12-1.04 (1H, m).

LC-MS: t_R = 5.40 $[M+H]^+$=377/379 (method 2)

Intermediate compound 175: 6-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-5-methylpyridine-3-carbonitrile

The following compound was prepared using the same methodology as in intermediate compound 25 method 2 from **intermediate compound 174** (0.243 mmol, 92 mg). Purification of the crude material by flash chromatography on silica gel using an elution of 8% ethylacetate in hexanes afforded the pure title compound (52 mg, Yield: 66%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 (1H, d, *J* = 1.6 Hz), 8.14 (1H, d, *J* = 1.2 Hz), 7.05 (1H, d, *J* = 2 Hz), 6.90 (1H, dd, *J* = 8.4 & 2.4 Hz), 6.74 (1H, d, *J* = 8.4 Hz), 5.79 (1H, s), 4.83 (1H, d, *J* = 2 Hz), 3.45-3.40 (1H, m), 2.70-2.62 (1H, m), 2.42 (3H, s), 2.06-1.96 (1H, m), 1.72-1.65 (1H, m), 1.57-1.47 (1H, m), 1.40-1.30 (2H, m), 0.98-0.90 (1H, m).

LC-MS: t_R = 4.95 $[M+H]^+$=324 (method 2)

Intermediate compound 176: methyl 2-(8-chloro-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-1-methyl-1H-imidazole-4-carboxylate

The following compound was prepared using the same methodology as in Intermediate compound 41 using methyl 2-formyl-1-methyl-1H-imidazole-4-carboxylate **intermediate compound 142** (0.48 mmol, 80 mg), 4-chlorobenzenamine (0.48 mmol, 62 mg) and scandium trifluoromethanesulfonate (1 eq., 0.48 mmol, 237 mg). Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the title compound as a white solid (80 mg, Yield: 48%).

Endo-isomer: methyl 2-((3aS,4R,9bR)-8-chloro-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-1-methyl-1H-imidazole-4-carboxylate

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (1H, s), 7.45 (1H, s), 7.04 (1H, d, *J* = 2.4 Hz), 6.96 (1H, dd, *J* = 2.4 & 8.8 Hz), 6.60 (1H, d, *J* = 8.4 Hz), 5.89 (1H, brs), 5.72 (1H,

brs), 5.62 (1H, d, *J* = 3.6 Hz), 4.10-4.08 (1H, m), 3.96 (3H, s), 3.89 (3H, s), 3.13-3.10 (1H, m), 2.68-2.61 (1H, m), 2.07-2.02 (1H, m).

LC-MS: t_R = 4.13 $[M+H]^+$ = 344 (method 2)

Intermediate compound 177: methyl 2-(8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-1-methyl-1H-imidazole-4-carboxylate

The following compound was prepared using the same methodology as in Intermediate compound 67 from **intermediate compound 176** (0.23 mmol, 80 mg) for 1h. Purification of the crude material (1:7 mixture of isomers exo-endo) by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded methyl 2-(8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-1-methyl-1H-imidazole-4-carboxylate (48 mg, Yield: 59%).

LC-MS: t_R = 4.43 $[M+H]^+$= 346 (method 2)

Intermediate compound 178: methyl 7-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-methoxy-3H-cyclopenta[c]quinolin-4-yl)-3-methyl-3H-benzo[d]imidazole-4-carboxylate

The following compound was prepared using the same methodology as in example 66 and 67 using methyl 7-formyl-3-methyl-3H-benzo[d]imidazole-4-carboxylate **intermediate compound 148** (0.12 mmol, 25 mg) and *p*-anisidine (0.12 mmol, 0.15 mg) in DCM (2 mL). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 100 % ethyl acetate in hexanes afforded the title compound as a white solid (23 mg, Yield: 49%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (1H, d, *J* = 7.6 Hz), 7.87 (1H, s), 7.50 (1H, d, *J* = 8 Hz), 6.74 (1H, s), 6.65-6.61 (2H, m), 5.82 (1H, brs), 5.62 (1H, brs), 5.40 (1H, d, *J* = 2.8 Hz), 4.22 (1H, brs), 4.05 (3H, s), 3.98 (3H, s), 3.76 (3H, s), 2.65-2.55 (1H, m), 1.73-1.69 (1H, m), 1.17-1.13 (1H, m).

LC-MS: t_R = 4.05 $[M+H]^+$ = 390 (method 2)

Intermediate compound 179: methyl 7-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methyl-3H-benzo[d]imidazole-4-carboxylate

The following compound was prepared using the same methodology as in Intermediate compound 67 from **intermediate compound 178** (0.118 mmol, 47 mg) for 1h. Total conversion was not achieved, PtO_2 (2.5% w/w) was added and stirred for 15 min at room temperature. The crude reaction was filtered and washed with EtOH. The solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the endo-isomer methyl 7-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methyl-3H-benzo[d]imidazole-4-carboxylate (11 mg, Yield: 24%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (1H, s), 8.02 (1H, s), 7.91 (1H, d, *J* = 8 Hz), 7.56 (1H, d, *J* = 7.6 Hz), 6.74 (1H, s), 6.65-6.60 (2H, m), 5.29 (1H, d, *J* = 2.8 Hz), 4.08 (3H, s), 3.98 (3H, s), 3.77 (3H, s), 3.60-3.56 (1H, m), 2.86-2.83 (1H, m), 2.16-2.11 (1H, m), 1.81-1.74 (1H, m), 1.73-1.67 (1H, m), 1.53-1.48 (1H, m), 1.44-1.39 (1H, m), 1.08-1.05 (1H, m).

LC-MS: t_R = 4.37 $[M+H]^+$ = 392 (method 2)

Intermediate compound 180: 4-bromo-7-methyl-1H-indole

A solution of 4-bromo-1-methyl-2-nitrobenzene (11.57 mmol, 2.5 g) in THF (116 mL) under nitrogen atmosphere was cooled to -40 ºC and vinylmagnesium bromide (46.28 mmol, 46 mL) was added. The reaction mixture was stirred for 40 min and quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with ethyl acetate twice and the combined organic layers were dry with Na_2SO_4, filtered and concentrated. The crude product thus obtained was dissolved in THF (35 mL) and cooled to 0 ºC. 0.5 N HCl (4.4 mL) was added and the reaction mixture stirred at 0ºC for 1 h, when it was quenched with $NaHCO_3$ (44 mL). The aqueous layer was extracted with ethyl acetate twice and the combined organic extracts were dried with Na_2SO_4, filtered and concentrated.

Purification of the crude material by flash chromatography on silica gel using an elution of 11% ethyl acetate in hexanes afforded the pure title compound (1.05 g. Yield: 43%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (1H, brs), 7.28-7.26 (1H, m), 7.21 (1H, d, *J* = 7.2 Hz), 6.87 (1H, d, *J* = 6.8 Hz), 6.63-6.61 (1H, m), 2.47 (3H, s).

LC-MS: t_R = 3.58 $[M+H]^+$=not ion (method 3)

Intermediate compound 181: 7-methyl-1H-indole-4-carbonitrile

The following compound was prepared using the same methodology as in intermediate compound 25 method 2 from **intermediate compound 180** (4.76 mmol, 1 g). Purification of the crude material by flash chromatography on silica gel using an elution of 21% ethyl acetate in hexanes afforded the pure title compound (550 mg, Yield: 73%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (1H, brs), 7.42 (1H, d, *J* = 7.2 Hz), 7.40-7.38 (1H, m), 7.05 (1H, d, *J* = 8 Hz), 6.79-6.78 (1H, m), 2.58 (3H, s).

LC-MS: t_R = 2.83 $[M+H]^+$=not ion (method 3)

Intermediate compound 182: ethyl 4-cyano-7-methyl-1H-indole-1-carboxylate

To a solution of 7-methyl-1H-indole-4-carbonitrile **intermediate compound 181** (4.48 mmol, 700 mg) in benzene (8.5 mL), 50% NaOH solution (3.5 mL) and a catalytic amount of tetrabutylammonium hydrogen sulphate were added and stirred vigorously for 15 min. Ethyl chloroformate (8.96 mmol, 0.857 mL) was slowly added (15 min). The two-phase system was stirred at room temperature for 10 min and diluted with water (15 mL). The organic layer was separated, and the aqueous layer was extracted with benzene. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated to dryness to afford the title compound which was used in the next step without further purification (944 mg, Yield: 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (1H, d, *J* = 3.6 Hz), 7.49 (1H, d, *J* = 7.2 Hz), 7.17 (1H, d, *J* = 8 Hz), 6.82 (1H, d, *J* = 4 Hz), 4.48 (2H, q, *J* = 7.2 Hz), 2.72 (3H, s), 1.47 (3H, t, *J* = 7.2 Hz).

LC-MS: t_R = 3.73 $[M+H]^+$ = 229 (method 3).

Intermediate compound 183: ethyl 7-(bromomethyl)-4-cyano-1H-indole-1-carboxylate

The following compound was prepared using the same methodology as in intermediate compound 129 using **intermediate compound 182** (5.26 mmol, 1.2 g). The crude product was purified by flash chromatography on silica gel using an elution of 6% ethyl acetate in hexanes to afford the ethyl 7-(bromomethyl)-4-cyano-1H-indole-1-carboxylate (1.2 g, Yield: 74%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (1H, d, *J* = 4 Hz), 7.56 (1H, d, *J* = 7.6 Hz), 7.37 (1H, d, *J* = 7.6 Hz), 6.88 (1H, d, *J* = 4 Hz), 5.19 (2H, s), 4.55 (2H, q, *J* = 7.2 Hz), 1.51 (3H, t, *J* = 7.2 Hz).

LC-MS: t_R = 3.83 $[M+H]^+$ =not ion (method 3).

Intermediate compound 184: 7-formyl-1H-indole-4-carbonitrile

The following compound was prepared using the same methodology as in intermediate compound 130 using the **intermediate compound 183** (1.18 mmol, 235 mg) for 4 h. To this reaction mixture water was added, and the organic layer was extracted with Et_2O, dried over Na_2SO_4 and concentrated under reduce pressure. The crude product was purified by flash chromatography on silica gel using an elution of 30% ethyl acetate in hexanes to give the desired product slightly impure which was triturated in hexane, filtered and washed by hexane to give 7-formyl-1H-indole-4-carbonitrile (214 mg, Yield: 32%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.16 (1H, brs), 10.28 (1H, s), 7.91 (1H, d, *J* = 7.2 Hz), 7.78 (1H, d, *J* = 7.6 Hz), 7.70 (1H, d, *J* = 2.4 Hz), 6.74 (1H, d, *J* = 2.8 Hz).

LC-MS: t_R = 2.60 $[M+H]^-$ = 169 (method 3)

Intermediate compound 185: 7-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-methoxy-3H-cyclopenta[c]quinolin-4-yl)-1H-indole-4-carbonitrile

The following compound was prepared using the same methodology as in intermediate compound 101 using **intermediate compound 184** (0.82 mmol, 140 mg) and *p*-anisidine (0.82 mmol, 101 mg). Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 20% ethylacetate in hexanes afforded the pure title endo-isomer (97 mg. Yield: 35%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (1H, brs), 7.48 (1H, d, *J* = 7.6 Hz), 7.41 (1H, m), 7.20 (1H, d, *J* = 7.6 Hz), 6.80 (1H, m), 6.71-6.68 (3H, m), 5.92-5.88 (1H, m), 5.68-5.64 (1H, m), 4.92 (1H, d, *J* = 3.6 Hz), 4.16-4.14 (1H, m), 3.90 (1H, brs), 3.79 (3H, s), 3.14-3.06 (1H, m), 2.68-2.60 (1H, m), 1.86-1.79 (1H, m).

LC-MS: t_R = 4.48 $[M+H]^+$= 342 (method 2)

Intermediate compound 186: 2-(1,3-dioxolan-2-yl)thiazole

A mixture of thiazole-2-carbaldehyde (22.1 mmol, 2.5 g), 4-methylbenzenesulfonic acid hydrate (6.6 mmol, 1.26 g) and ethane-1,2-diol (66.3 mmol, 3.7 mL) in toluene (25 mL) was heated at reflux temperature overnight using a Dean-Stark trap. The mixture was diluted with Et_2O (50 mL) and washed with $NaHCO_3$ saturated aqueous solution (50 mL) and brine (50 mL). The separated organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure to give 2.25 g of the title compound (Yield: 64%).

LC-MS: t_R = 1.73 $[M+H]^+$= 158 (method 4)

Intermediate compound 187: ethyl 2-(1,3-dioxolan-2-yl)thiazole-5-carboxylate

n-Butyllithium (15.8 mmol, 6.3 mL, 2.5 M in hexane) was added dropwise to a mixture of **intermediate compound 186** (14.3 mmol, 2.2 g) in dry THF (31.5 ml) at -78 ºC (dry ice/acetone bath). The mixture was stirred at -78 ºC for 2 h before addition of ethyl chloroformate (21.5 mmol, 2 mL). The mixture was then warmed to room temperature and stirred overnight. The crude reaction was partitioned between CH_2Cl_2 and water. The separated aqueous layer was extracted with CH_2Cl_2 (3 times), dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash chromatography on silica gel using cyclohexane/ethyl acetate as eluents gave 1.97 g of the title compound (Yield: 60%).

LC-MS: t_R = 3.17 $[M+H]^+$= 230 (method 4)

Intermediate compound 188: ethyl 2-formylthiazole-5-carboxylate

A mixture of **intermediate compound 187** (8.98 mmol, 2.06 g) and 3N aqueous HCl (269 mmol, 90 mL) in acetone (103 mL) was stirred at reflux temperature for 6 h. Then Et_2O was added and the layers were separated. The organic layer was extracted several times with Et_2O, dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude obtained was purified by flash chromatography on silica gel using cyclohexane/ethyl acetate as eluents to give 0.89 g of the title compound (Yield: 53%).

LC-MS: t_R = 2.08 $[M+H]^+$= 186 (method 4)

Intermediate compound 189: ethyl 2-((3aS,4R,9bR)-8-methyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)thiazole-5-carboxylate

The following compound was prepared using the same methodology as in intermediate compound 41 using ethyl 2-formylthiazole-5-carboxylate **intermediate compound 188** (2.4 mmol, 0.45 g) and *p*-toluidine (2.4 mmol, 0.26 g). Solvent was evaporated and the crude was purified by flash chromatography

on silica gel using cyclohexane/ethyl acetate as eluents to afford 0.76 g of the title compound (Yield: 93%).

LC-MS: t_R = 5.52 $[M+H]^+$= 341 (method 4)

Intermediate compound 190: ethyl 2-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)thiazole-5-carboxylate

The following compound was prepared using the same methodology as in intermediate compound 67 using **intermediate compound 189** (2.2 mmol, 761 mg). The solution was hydrogenated for 3 h at r.t. Reaction mixture was filtered and washed with CH_2Cl_2/MeOH. Solvent was evaporated and purification of the crude material using flash chromatography on silica gel and cyclohexane/EtOAc as eluents gave 121 mg of the title compound (Yield: 16%).

LC-MS: t_R = 5.92 $[M+H]^+$= 343 (method 4)

Intermediate compound 191: ethyl 2-((3aS,4R,9bR)-8-chloro-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)thiazole-5-carboxylate

The following compound was prepared using the same methodology as in intermediate compound 41 using ethyl 2-formylthiazole-5-carboxylate **intermediate compound 188** (2.4 mmol, 0.45 g) and 4-chloroaniline (2.4 mmol, 0.31 g). Solvent was evaporated and the crude was purified by flash chromatography on silica gel using cyclohexane/ethyl acetate as eluents to afford 0.89 g of the title compound (Yield: quantitative).

LC-MS: t_R = 5.63 $[M+H]^+$= 361 (method 4)

Intermediate compound 192: ethyl 2-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)thiazole-5-carboxylate

The following compound was prepared using the same methodology as in intermediate compound 67 using **intermediate compound 191** (2.4 mmol, 0.89 g). The solution was hydrogenated for 3 h at r.t. Reaction mixture was filtered and

washed with CH_2Cl_2/MeOH. Solvent was evaporated and purification of the crude material using flash chromatography on silica gel and cyclohexane/EtOAc as eluents gave 309 mg of the title compound (Yield: 35%).

LC-MS: t_R = 6.01 $[M+H]^+$= 363 (method 4)

Intermediate compound 193: 2,4-dichloro-5-(1,3-dioxolan-2-yl)thiazole

To a solution of 2,4-dichlorothiazole-5-carbaldehyde (27.3 mmol, 5.0 g) in toluene (60 mL), ethyleneglycol (82.0 mmol, 4.6 mL) and *p*-toluenesulfonic acid (1.3 mmol, 260 mg) were added. The resulting mixture was heated at 120ºC with a Dean-Stark trap. After 6 h, the reaction mixture was washed with 20% Na_2CO_3 solution (2 x 40 mL) and water (40 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure. After purification by column chromatography (SiO_2, Chx / EtOAc), the title compound was isolated (5.2 g. Yield: 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (1H, s), 4.12 (2H, m), 4.02 (2H, m).

Intermediate compound 194: lithium 4-chloro-5-(1,3-dioxolan-2-yl)thiazole-2-carboxylate

To a solution of previously obtained **intermediate compound 193** (23.0 mmol, 5.2 g), under Ar atmosphere and at -78ºC, nBuLi 2.5 N in hexane (24.1 mmol, 9.6 mL) was dropwise added. After 20 min, solid CO_2 was added and reaction mixture was gradually warmed to room temperature. After 18 h, solvent was removed under reduced pressure. The resulting crude was dispersed in EtOAc (10 mL, 5 min) and the resulting red solid was filtered, washed with cold EtOAc (2 mL) and dried. The title compound was obtained pure enough and not further purification was carried out (4.5 g. Yield: 82%).

^{1}H NMR (400 MHz, MeOD) δ 6.07 (1H, s), 4.12 (2H, m), 4.02 (2H, m).

LC-MS: t_R = 1.27 $[M-Li]^+$= 238 (method 4)

Intermediate compound 195: ethyl 4-chloro-5-(1,3-dioxolan-2-yl)thiazole-2-carboxylate

To a mixture of the previously obtained **intermediate compound 194** (3.9 mmol, 933 mg,), 1-hydroxybenzotriazole (3.9 mmol, 522 mg) and EDCI (5.0 mmol, 958 mg), in anhydrous DMF (8 mL) under Ar atmosphere, EtOH (0.8 mL) was added. After 18 h, solvent was removed under reduced pressure. The resulting crude was partitioned between Et_2O (5 mL) and 1N HCl (10 mL). The aqueous layer was extracted with EtOAc (3x 5 mL). The combined organic extracts were washed with $NaHCO_3$ sat (2 x 10 mL), H_2O (2 x 10 mL), dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure to afford the title compound as a solid (705 mg. Yield: 70 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (1H, s), 4.47 (2H, q, *J* = 6.8 Hz), 4.14 (2H, m), 4.05 (2H, m), 1.43 (3H, t, *J* = 7.2 Hz).

Intermediate compound 196: ethyl 4-chloro-5-formylthiazole-2-carboxylate

Intermediate compound 195 (6.8 mmol, 1.8 g) was stirred in a mixture of Et_2O (65 mL) and HCl 6 N (4 mL) overnight. Once starting material was consumed (TLC control), pH of the mixture was adjusted to 7-8 with sat. $NaHCO_3$ and organic layer was separated. Aqueous layer was extracted with Et_2O (2 x 20 mL), the combined organic extracts dried over anhydrous $MgSO_4$, filtered and the solvent removed under reduced pressure. After purification by flash chromatography (SiO_2, Chx/EtOAc), the title compound was obtained as orange oil (1.2 g. Yield: 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (1H, s), 4.53 (2H, q, *J* = 6.8 Hz), 1.45 (3H, t, *J* = 7.2 Hz).

Intermediate compound 197: ethyl 4-chloro-5-((3aS,4R,9bR)-8-methyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)thiazole-2-carboxylate

The following compound was prepared using the same methodology as in intermediate compound 41 using ethyl 4-chloro-5-formylthiazole-2-carboxylate

intermediate compound 196 (5.3 mmol, 1.2 g) and *p*-toluidine (5.3 mmol, 0.6 g). Solvent was evaporated and the crude was purified by flash chromatography on silica gel using cyclohexane/ethyl acetate as eluents to afford 1.8 g of the title compound (Yield: 86%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 6.89 (1H, d, *J* = 0.8 Hz), 6.83 (2H, dd, *J* = 8 and 1.8 Hz), 6.55 (1H, d, *J* = 8 Hz), 5.89 (1H, m), 5.66 (1H, m), 4.90 (1H, d, *J* = 2.8 Hz), 4.47 (2H, dq, *J* = 6.8 & 2 Hz), 4.08 (1H, d, *J* = 9.2 Hz), 3.76 (1H, brs), 3.15 (1H, dq, *J* = 8.8 & 3.6 Hz), 2.66 (1H, m), 2.25 (3H, s), 2.02 (1H, m), 1.44 (3H, t, *J* = 7 Hz).

LC-MS: t_R = 5.962 $[M+H]^+$= 375 (method 4)

Intermediate compound 198: ethyl 4-chloro-5-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)thiazole-2-carboxylate

The following compound was prepared using the same methodology as in intermediate compound 67 using **intermediate compound 197** (4.8 mmol, 1.79 g). The solution was hydrogenated for 1.5 h at r.t. Reaction mixture was filtered and washed with CH_2Cl_2/MeOH. Solvent was evaporated and the crude obtained was stirred in acetonitrile at room temperature until a solid was precipitated off. The solvent was removed by filtration. The solid was washed with cold acetonitrile and dried at room temperature under vacuum to give 693 mg of the title compound (Yield: 38%).

LC-MS: t_R = 6.41 $[M+H]^+$= 377 (method 4)

Intermediate compound 199: ethyl 4-chloro-5-((3aS,4R,9bR)-8-chloro-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)thiazole-2-carboxylate

The following compound was prepared using the same methodology as in intermediate compound 41 using ethyl 4-chloro-5-formylthiazole-2-carboxylate **intermediate compound 196** (4.5 mmol, 0.98 g) and 4-chloroaniline (4.5 mmol, 570 mg). Solvent was evaporated and the crude was purified by flash

chromatography on silica gel using cyclohexane/ethyl acetate as eluents to afford 1.4 g of the title compound (Yield: 77%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.05 (1H, d, *J* = 2 Hz), 6.97 (1H, dd, *J* = 8 & 2.4 Hz), 6.57 (1H, d, *J* = 8.4 Hz), 5.87 (1H, m), 5.69 (1H, m), 5.01 (1H, d, *J* = 3.6 Hz), 4.48 (2H, dq, *J* = 6.8 & 2 Hz), 4.09 (1H, d, *J* = 8.4 Hz), 3.87 (1H, brs), 3.15 (1H, dq, *J* = 9.2 & 3.6 Hz), 2.62 (1H, m), 2.05 (1H, m), 1.44 (3H, t, *J* = 6.8 Hz).

LC-MS: t_R = 6.04 $[M+H]^+$= 395 (method 4)

Intermediate compound 200: ethyl 4-chloro-5-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)thiazole-2-carboxylate

The following compound was prepared using the same methodology as in intermediate compound 67 using **intermediate compound 199** (3.4 mmol, 1.4 g). The solution was hydrogenated for 1 h at r.t. Reaction mixture was filtered and washed with CH_2Cl_2/MeOH. Solvent was evaporated and the crude obtained was stirred in acetonitrile at room temperature until a solid precipitated off. The solvent was removed by filtration. The solid was washed with cold acetonitrile and dried at room temperature under vacuum to give 835 mg of the title compound (Yield: 62%).

LC-MS: t_R = 6.44 $[M+H]^+$= 397/399 (method 4)

Intermediate compound 201: 4-(1H-tetrazol-5-yl)benzaldehyde

A mixture of 4-formylbenzonitrile (15.3 mmol, 2 g), sodium azide (22.9 mmol, 1.5 g) and iodine (0.9 mmol, 230 mg) in dry DMF (38 mL) was heated at 120 ºC overnight. The mixture was then partitioned between EtOAc (240 mL) and 4 M HCl solution (160 mL). The aqueous layer was extracted twice with EtOAc (80 mL each). The combined organic extracts were washed twice with saturated Na_2SO_3 aqueous solution (80 mL each) and twice with water (80 mL each). The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure to give 2.3 g of the title compound (Yield: 85%).

LC-MS: t_R = 1.39 $[M+H]^+$= 175 (method 4)

Intermediate compound 202: (3aS,4R,9bR)-4-(4-(1H-tetrazol-5-yl)phenyl)-8-methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline

The following compound was prepared using the same methodology as in intermediate compound 41 using 4-(1H-tetrazol-5-yl)benzaldehyde **intermediate compound 201** (5.7 mmol, 1 g) and 4-methoxyaniline (5.7 mmol, 710 mg). Solvent was evaporated and the crude was purified by flash chromatography on silica gel using cyclohexane/ethyl acetate as eluents. The solid obtained (407 mg) was stirred in acetonitrile at room temperature, the solvent was removed by filtration. The solid was washed with cold acetonitrile and dried under vacuum at room temperature to afford 307 mg of the title compound (Yield: 16%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (2H, d, *J* = 8.8 Hz), 7.66 (2H, d, *J* = 8 Hz), 6.68 (1H, d, *J* = 8.8 Hz), 6.62 (1H, d, *J* = 2.8 Hz), 6.53 (1H, dd, *J* = 8.8 & 2.8 Hz), 5.85 (1H, dd, *J* = 2.8 &1.6 Hz), 5.56 (1H, d, *J* = 4.8 Hz), 5.37 (1H, s), 4.52 (1H, d, *J* = 2.8 Hz), 4.01 (1H, m), 3.63 (3 H, s), 2.94 (1H, m), 2.45 (1H, m), 1.61 (1H, m).

LC-MS: t_R = 7.47 $[M+H]^+$= 348 (method 1)

Intermediate compound 203: 3,5-difluoro-4-((3aS,4R,9bR)-8-methyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using **intermediate compound 137** (4.3 mmol, 0.8 g) and *p*-toluidine (4.3 mmol, 460 mg). The suspension was filtered. The solid was washed with cold acetonitrile and dried under vacuum at room temperature to give 435 mg of title compound. Additional product was recovered from mother liquors which were purified by flash chromatography on silica gel using cyclohexane/ethyl acetate as eluents (1.4 g, Global yield: 92%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53 (2H, d, *J* = 10 Hz), 6.79 (1H, s), 6.68 (1H, dd, *J* = 8.4 & 2 Hz), 6.51 (1H, d, *J* = 8 Hz), 5.8 (1H, m), 5.64 (1H, s), 5.59 (1H, d,

J = 4.8 Hz), 4.83 (1H, d, *J* = 2.4 Hz), 4.0 (1H, m), 2.9 (1H, m), 2.69 (1H, m), 2.13 (3H, s), 1.92 (1H, m).

LC-MS: t_R = 3.51 $[M+H]^+$= 342 (method 5)

Intermediate compound 204: 4-((3aS,4R,9bR)-8-ethyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using **intermediate compound 137** (9.7 mmol, 1.8 g) and 4-ethylaniline (9.7 mmol, 1.2 mL). Solvent was removed under reduced pressure. The residue was stirred at room temperature with acetonitrile. The solid was separated by filtration, washed with cold acetonitrile and dried under vacuum at room temperature to yield 1.9 g of the title compound (Yield: 56%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63 (2H, d, *J* = 8.8 Hz), 6.91 (1H, s), 6.85 (1H, dd, *J* = 8 & 1.6 Hz), 6.6 (1H, d, *J* = 8 Hz), 5.82 (1H, m), 5.58 (1H, s), 5.08 (1H, d, *J* = 2.8 Hz), 4.14 (1H, d, *J* = 9.2 Hz), 3.11 (1H, ddd, *J* = 18, 8.8 & 2.8 Hz), 2.87 (1H, m), 2.55 (2H, q, *J* = 7.2 Hz), 2.06 (1H, m), 1.2 (3H, t, *J* = 7.6 Hz).

LC-MS: t_R = 3.79 $[M+H]^+$= 356 (method 5)

Intermediate compound 205: 3,5-difluoro-4-((3aS,4R,9bR)-8-methoxy-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 41 using **intermediate compound 137** (10.7 mmol, 2.0 g) and 4-methoxyaniline (10.7 mmol, 1.3 g). After 18 h, solvent was removed under reduced pressure. The residue was stirred at 0ºC with acetonitrile (5 mL). The solid was separated by filtration and washed with cold acetonitrile. The solid was dried under vacuum at room temperature to yield 1.2 g of the title compound (Yield: 32%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53 (2 H, d, *J* = 10.4 Hz), 6.6-6.5 (3 H, m), 5.81 (1 H, m), 5.55 (1 H, m), 5.37 (1 H, m), 4.47 (1 H, m), 3.99 (1 H, s), 3.64 (3 H, s), 2.85 (1H, m), 1.92 (1H, m).

LC-MS: t_R = 3.10 $[M+H]^+$= 358 (method 5)

Intermediate compound 206 & 207: methyl 4-((6S,6aS,10aR)-2-chloro-5,6,6a,7,8,10a-hexahydrophenanthridin-6-yl)-3-methylbenzoate (206) & methyl 4-((6R,6aS,10aR)-2-chloro-5,6,6a,7,8,10a-hexahydrophenanthridin-6-yl)-3-methylbenzoate (207)

To a stirred solution of methyl 4-formyl-3-methylbenzoate **intermediate compound 19**, 5.6 mmol, 1.0 g), 4-chloroaniline (5.6 mmol, 0.7 g) and 1,3-cyclohexadiene (22.4 mmol, 2.1 mL) in anhydrous acetonitrile (60 mL), $BF_3.Et_2O$ (5.6 mmol, 0.7 mL) was added. After 18 h solvent was removed under reduced pressure and the residue was partitioned between CH_2Cl_2 and aqueous saturated $NaHCO_3$ solution. Organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. Combined organic extracts were washed over anhydrous $MgSO_4$, filtered and solvent removed under reduced pressure. After purification by flash chromatography (SiO_2, Chx/EtOAc), regiosiomer *exo* (360 mg. Yield: 17%) and *endo* (513 mg. Yield: 25%) were obtained as pale yellow solids.

Exo-isomer: methyl 4-((6S,6aS,10aR)-2-chloro-5,6,6a,7,8,10a-hexahydrophenanthridin-6-yl)-3-methylbenzoate (**206**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.8-7.9 (2H, m), 7.37 (1H, d, *J* = 8.0 Hz), 7.10 (1H, m), 6.94 (1H, m), 6.46 (1H, d, *J* = 8.4 Hz), 6.19 (1H, m), 5.92 (1H, m), 5.6-5.7 (2H, m), 4.53 (1H, d, *J* = 6.4 Hz), 4.0 (1H, m), 3.90 (3H, s), 3.32 (1H, m), 2.44 (3H, s), 1.4-1.5 (2H, m).

LC-MS: t_R = 6.42 $[M+H]^+$= 368 (method 4)

Endo-isomer: methyl 4-((6R,6aS,10aR)-2-chloro-5,6,6a,7,8,10a-hexahydrophenanthridin-6-yl)-3-methylbenzoate (**207**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.8-7.9 (2H, m), 7.65 (1H, d, *J* = 8.0 Hz), 7.17 (1H, m), 6.96 (1H, m), 6.52 (1H, d, *J* = 8.8 Hz), 6.19 (1H, m), 5.82 (1H, m), 5.6-5.5 (2H, m), 4.87 (1H, d, *J* = 2.0 Hz), 3.92 (3H, s), 3.78 (1H, m), 3.73 (1H, m), 2.39 (3H, s), 1.9-2.1 (2H, m).

LC-MS: t_R = 6.42 $[M+H]^+$= 368 (method 4)

Intermediate compound 208: methyl 4-((6S,6aS,10aR)-2-chloro-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-3-methylbenzoate

A mixture of **intermediate compound 206** (1.0 mmol, 360 mg) and $PtO_2.H_2O$ (5% w/w, 18 mg) in THF/EtOH (1:1, 7.2 mL) was hydrogenated for 2 h (1 bar). After that, reaction mixture was filtered and solvent removed under reduced pressure to obtain the title compound (346 mg. Yield: 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (1H, s), 7.79 (1 H, d, *J* = 12.4 Hz), 7.32 (1 H, d, *J* = 8.4 Hz), 7.07 (1 H, d, *J* = 2.4 Hz), 6.97 (1 H, dd, *J* = 8.8 & 2.4 Hz), 6.45 (1 H, d, *J* = 8.4 Hz), 4.63 (1 H, d, *J* = 5.2 Hz), 4.07(1 H, brs), 3.89 (3 H, s), 2.72 (1 H, m), 2.43 (3H, s), 2.0 (2H, m), 1.51-1.62 (4H, m), 1.3-1.4 (2H m).

LC-MS: t_R = 6.65 $[M+H]^+$= 370 (method 5)

Intermediate compound 209: methyl 4-((6R,6aS,10aR)-2-chloro-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-3-methylbenzoate

A mixture of **intermediate compound 207** (1.4 mmol, 510 mg) and $PtO_2.H_2O$ (5% w/w, 26 mg) in THF/EtOH (1:1, 10 mL) was hydrogenated for 2 h (1 bar). After that, reaction mixture was filtered and solvent removed under reduced pressure to obtain the title compound (458 mg. Yield: 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.86 (2H, m), 7.61 (1 H, d, *J* = 8.0 Hz), 7.17 (1 H, m), 6.98 (1 H, m), 6.51 (1 H, d, *J* = 8.4 Hz), 4.84 (1 H, d, *J* = 2.8 Hz), 3.91 (3 H, s), 3.82 (1 H, m), 3.37 (1H, m), 2.40 (1H, brs), 2.34 (3H, s), 1.96-1.91 (1H, m), 1.72-1.60 (2H m), 1.41-1.48 (1H, m), 1.34-1.20 (2H, m), 1.18-1.07 (1H, m).

LC-MS: t_R = 6.82 $[M+H]^+$= 370 (method 5)

Intermediate compound 210 & 211: methyl 4-((6R,6aS,10aR)-2-chloro-5,6,6a,7,8,10a-hexahydrophenanthridin-6-yl)benzoate (210) & methyl 4-((6S,6aS,10aR)-2-chloro-5,6,6a,7,8,10a-hexahydrophenanthridin-6-yl)benzoate (211)

The same methodology as in intermediate compound 206 but starting from methyl 4-formylbenzoate (6.1 mmol, 1.0 g) was used. The title compounds were isolated after purification of the crude by column chromatography (SiO_2, Chx/EtOAc) as yellow solids (exo-isomer 325 mg. Yield: 16%; endo-isomer, 194 mg. Yield: 9%).

Endo-isomer: methyl 4-((6R,6aS,10aR)-2-chloro-5,6,6a,7,8,10a-hexahydrophenanthridin-6-yl)benzoate (**210**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (2H, d, *J* = 8.4 Hz), 7.49 (2H, d, *J* = 8.0 Hz), 7.16 (1H, d, *J* = 1.2 Hz), 6.96 (1H, dd, *J* = 8.0 & 1.2 Hz), 6.53 (1H, d, *J* = 8.4 Hz), 6.18 (1H, m), 5.85 (1H, m), 4.73 (1H, d, *J* = 2.8 Hz), 3.93 (3H, s), 3.73 (1H, brs), 2.1 (1H, m), 1.99 (1H, m), 1.85 (1H, m), 1.42 (1H, m), 1.35 (1H, m).

LC-MS: t_R = 6.26 $[M+H]^+$= 354 (method 4)

Exo-isomer: methyl 4-((6S,6aS,10aR)-2-chloro-5,6,6a,7,8,10a-hexahydrophenanthridin-6-yl)benzoate (**211**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (2H, d, *J* = 8.4 Hz), 7.45 (2H, d, *J* = 8.4 Hz), 7.09 (1H, m), 6.96 (1H, m), 6.47 (1H, d, *J* = 8.8 Hz), 5.78 (1H, m), 5.72 (1H, m), 4.29 (1H, d, *J* = 8.4 Hz), 3.93 (3H, s), 3.40 (1H, brs), 2.28 (1H, m), 2.04-2.02 (2H, m), 1.67 (1H, m), 1.40 (1H, m).

LC-MS: t_R = 6.27 $[M+H]^+$= 354 (method 4)

Intermediate compound 212: methyl 4-((6S,6aS,10aR)-2-chloro-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoate

Following the same methodology as in intermediate compound 208 but starting from **intermediate compound 211** (0.92 mmol, 325 mg), the title compound was obtained after purification by column chromatography (SiO_2, Chx/EtOAc) as a white solid (97 mg. Yield: 30%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (2H, d, *J* = 8.4 Hz), 7.38 (2H, d, *J* = 8.0 Hz), 7.02 (1H, d, *J* = 2.4 Hz), 6.95 (1H, dd, *J* = 8.4 & 2.4 Hz), 6.45 (1H, d, *J* = 8.0 Hz), 4.52 (1H, d, *J* = 8.0 Hz), 4.09 (1H, brs), 3.91 (3H, s), 2.70 (1H, m), 2.08 (1H, m), 1.88 (1H, m), 1.65 (1H, m), 1.53-1.46 (1H, m), 1.53-1.46 (4H, m), 1.33 (1H, m).

LC-MS: t_R = 6.49 $[M+H]^+$= 356 (method 4)

Intermediate compound 213: methyl 4-((6R,6aS,10aR)-2-chloro-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoate

Following the same methodology as in intermediate compound 208 but starting from **intermediate compound 210** (0.55 mmol, 194 mg), the title compound was obtained after purification by column chromatography (SiO_2, Chx/EtOAc) as a white solid (99 mg. Yield: 50%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (2H, d, *J* = 8.8 Hz), 7.45 (2H, d, *J* = 8.0 Hz), 7.17 (1H, m), 6.98 (1H, dd, *J* = 8.4 & 2.4 Hz), 6.52 (1H, d, *J* = 8.8 Hz), 4.70 (1H, d, *J* = 2.8 Hz), 3.92 (3H, s), 3.38 (1H, brs), 2.4 (1H, m), 1.95 (1H, m), 1.67 (1H, m), 1.59 (1H, m), 1.42 (1H, m), 1.24 (2H, m), 1.09 (2H, m).

LC-MS: t_R = 6.49 $[M+H]^+$= 356 (method 4)

Intermediate compound 214: methyl 4-((6S,6aS,10aR)-2-chloro-5,6,6a,7,8,10a-hexahydrophenanthridin-6-yl)benzoate

The same methodology as in intermediate compound 206 but starting from methyl 4-formylbenzoate (6.1 mmol, 1.0 g) and 4-toluidine (6.1 mmol, 652 mg) was used. The title compound was isolated after purification of the crude by column chromatography (SiO_2, Chx/EtOAc) as a yellow solid (186 mg. Yield: 9%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (2H, dd, *J* = 6.8 & 1.6 Hz), 7.46 (2H, dd, *J* = 6.4 & 1.2 Hz), 6.95 (1 H, s), 6.83 (1 H, dd, *J* = 8.4 & 2.0 Hz), 6.46 (1H, d, *J* = 7.6 Hz), 5.81 (1H, m), 5.68 (1H, m), 4.27 (1H, d, *J* = 8.4 Hz), 3.91 (3H, s), 3.41 (1H, m), 2.31 (1H, m), 2.25 (3H, s), 2.1-1.9 (2H, m), 1.65 (1H m), 1.38 (1H, m).

LC-MS: t_R = 6.23 $[M+H]^+$= 334 (method 5)

Intermediate compound 215: methyl 4-((6S,6aS,10aR)-2-methyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoate

Following the same methodology as in intermediate compound 208 but starting from **intermediate compound 214** (0.16 mmol, 55 mg) the title compound was obtained as a white solid (52 mg. Yield: 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (2H, dd, *J* = 6.8 Hz & 1.6 Hz), 7.41 (1H, d, *J* = 8.8 Hz), 6.85 (1 H, s), 6.82 (1 H, d, *J* = 8.4 Hz), 6.45 (1 H, d, *J* = 8.0 Hz), 4.53 (1 H, d, *J* = 8.4 Hz), 3.93 (1H, brs), 3.91 (3H, s), 2.70 (1 H, m), 2.23 (3 H, s), 2.10 (1H, m), 1.86 (1H, m), 1.70 (1H, m), 1.60-1.30 (5H, m).

LC-MS: t_R = 6.47 $[M+H]^+$= 336 (method 5)

Intermediate compound 216 & 217: methyl 4-((6R,6aS,10aR)-2-(difluoromethoxy)-5,6,6a,7,8,10a-hexahydrophenanthridin-6-yl)benzoate (216) & methyl 4-((6S,6aS,10aR)-2-(difluoromethoxy)-5,6,6a,7,8,10a-hexahydrophenanthridin-6-yl)benzoate (217)

The same methodology as in intermediate compound 206 but starting from methyl 4-formylbenzoate (6.1 mmol, 1.0 g) and 4-(difluoromethoxy)aniline (6.1 mmol, 0.8 mL) was used. The title compounds were isolated after purification of the crude by column chromatography (SiO_2, Chx/EtOAc) as a non-separable mixture of regioisomers (ratio endo/exo 1:1) (692 mg. Yield: 29%)

Endo-isomer: methyl 4-((6R,6aS,10aR)-2-(difluoromethoxy)-5,6,6a,7,8,10a-hexahydrophenanthridin-6-yl)benzoate (**216**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (2H, d, *J* = 8.4 Hz), 7.50 (2H, d, *J* = 8.0 Hz), 6.98 (1H, d, *J* = 3.2 Hz), 6.83 (1H, m), 6.56 (1H, d, *J* = 8.8 Hz), 6.39 (1H, t , *J* = 74.8 Hz), 6.17 (1H, m), 5.82 (1H, m), 4.73 (1H, d, *J* = 2.8 Hz), 3.93 (3H, s), 3.75 (1H, brs), 2.15 (1H, m), 1.85 (1H, m), 1.43 (2H, m), 1.30 (1H, m).

LC-MS: t_R = 5.84 $[M+H]^+$= 386 (method 4)

Exo-isomer: methyl 4-((6S,6aS,10aR)-2-(difluoromethoxy)-5,6,6a,7,8,10a-hexahydrophenanthridin-6-yl)benzoate (**217**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (2H, d, *J* = 8.4 Hz), 7.46 (2H, d, *J* = 8.4 Hz), 6.93 (1H, d, *J* = 2.4 Hz), 6.81 (1H, m), 6.50 (1H, d, *J* = 8.8 Hz), 6.38 (1H, t , *J* = 74.8 Hz), 5.76 (1H, m), 5.73 (1H, m), 4.29 (1H, d, *J* = 8.8 Hz), 3.92 (3H, s), 3.43 (1H, brs), 2.41 (1H, m), 2.04 (3H, s), 2.02 (2H, m), 1.70 (1H, m), 1.35 (1H, m).

LC-MS: t_R = 5.83 $[M+H]^+$= 386 (method 4)

Intermediate compound 218 & 219: methyl 4-((6R,6aS,10aR)-2-(difluoromethoxy)-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoate (218) & methyl 4-((6S,6aS,10aR)-2-(difluoromethoxy)-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoate (219)

Following the same methodology as in intermediate compound 208 but starting from a mixture of **intermediate compound 216 & 217** (2.22 mmol, 856 mg), the title compound was obtained as a yellow foam (868 mg, Yield: quantitative, endo/exo 1:1 mixture).

Endo-isomer: methyl 4-((6R,6aS,10aR)-2-(difluoromethoxy)-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoate (**218**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (2H, d, *J* = 8.4 Hz), 7.46 (2H, d, *J* = 8.4 Hz), 7.00 (1H, brs), 6.82 (1H, m), 6.55 (1H, d, *J* = 8.8 Hz), 6.40 (1H, t , *J* = 75.2 Hz), 4.70 (1H, d, *J* = 2.8 Hz), 3.92 (3H, s), 3.39 (1H, m), 2.41 (1H, m), 1.91 (1H, m), 1.86-1.83 (1H, m), 1.70-1.51 (4H, m), 1.18-1.08 (2H, m).

LC-MS: t_R = 6.12 $[M+H]^+$= 388 (method 4)

Exo-isomer: methyl 4-((6S,6aS,10aR)-2-(difluoromethoxy)-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoate (**219**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (2H, d, *J* = 8.4 Hz), 7.40 (2H, d, *J* = 8.0 Hz), 6.86 (1H, m), 6.85 (1H, m), 6.47 (1H, d, *J* = 8.4 Hz), 6.38 (1H, t , *J* = 75.2 Hz), 4.53 (1H, d, *J* = 8.4 Hz), 3.91 (3H, s), 2.70 (1H, m), 2.10 (1H, m), 1.95-1.90 (1H, m), 1.45 – 1.41 (4H, m), 1.18 – 1.22 (2H, m), 0.96 (1H, m).

LC-MS: t_R = 6.02 $[M+H]^+$= 388 (method 4)

Intermediate compound 220: methyl 3,5-dichloro-4-((6S,6aS,10aR)-2-methyl-5,6,6a,7,8,10a-hexahydrophenanthridin-6-yl)benzoate

The same methodology as in intermediate compound 206 but starting from **intermediate compound 130** (3.5 mmol, 823 mg) and 4-toluidine (3.5 mmol, 378 mg) was used. The title compound was isolated after purification of the crude by column chromatography (SiO_2, Chx/EtOAc) (1.0 g. Yield: 96%)

LC-MS: t_R = 6.28 $[M+H]^+$= 402 (method 4)

Intermediate compound 221: methyl 3,5-dichloro-4-((6S,6aS,10aR)-2-methyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoate

Following the same methodology as in intermediate compound 208 but starting from **intermediate compound 220** (2.5 mmol, 1.0 g) the title compound was obtained as a yellow solid (745 mg. Yield: 74%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (2 H, s), 6.83 (2 H, m), 6.41 (1 H, d, *J* = 7.6 Hz), 5.52 (1 H, d, *J* = 10.8 Hz), 3.93 (3H, s), 3.69 (1H, brs), 2.98 (1 H, m), 2.75 (1 H, m), 2.24 (3H, s), 1.80 (2H, m), 1.67 (2H, m), 1.45 (1H, m), 1.28 (2H, m).

LC-MS: t_R = 6.49 $[M+H]^+$= 404 (method 5)

Intermediate compound 222 & 223: methyl 4-((6R,6aS,11aR)-2-methyl-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[c]quinolin-6-yl)benzoate (222) & methyl 4-((6S,6aS,11aR)-2-methyl-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[c]quinolin-6-yl)benzoate (223).

The following mixture of compounds was prepared using the same methodology as in intermediate compound 105 using methyl 4-formylbenzoate (2.44 mmol, 400 mg) and cycloheptene (12.18 mmol, 1.42 ml). The mixture was refluxed for 3h. Solvent was evaporated. The crude material was treated with 0.2 N $NaHCO_3$ aqueous solution and it was washed twice with DCM. The combined organic

layers were dried over anhydrous Na_2SO_4, filtered and evaporated. It was purified by flash chromatography on silica gel using hexane / ethyl acetate 1:1 as eluents to obtain a non separable mixture of isomers (320 mg, yield: 37.6%, mixture endo-exo-isomer).

LC-MS: t_R = 3.40 $[M+H]^+$ = 351 (method 6)

LC-MS: t_R = 3.43 $[M+H]^+$ = 351 (method 6)

Intermediate compound 224: 2-fluoro-4-((3aS,4R,9bR)-8-methyl-3a,4,5,9b-tetrahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid.

The following compound was prepared using the same methodology as in intermediate compound 41 from 2-fluoro-4-formylbenzoic acid (0.89 mmol, 150 mg), p-toluidine (0.89 mmol, 96 mg) and indium(III) trifluoromethanesulfonate (0.09 mmol, 50.1 mg) instead of scandium trifluoromethanesulfonate. Solvent was evaporated. The crude material was treated with water and it was washed twice with EtAcO. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated (289 mg, yield: 100%, endo-isomer).

LC-MS: t_R = 1.78 $[M+H]^+$ = 324 (method 6)

Intermediate compound 225: 4-((3aS,4R,9bR)-8-chloro-3a,4,5,9b-tetrahydro-1H-cyclopenta[c]quinolin-4-yl)-2-fluorobenzoic acid.

The following compound was prepared using the same methodology as in intermediate compound 41 using 2-fluoro-4-formylbenzoic acid (0.89 mmol, 150 mg) and 4-chloroaniline (0.89 mmol, 114 mg). Solvent was evaporated and the crude material was treated with water and it was washed twice with EtAcO. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated (307 mg, yield: 100%, endo-isomer).

LC-MS: t_R = 1.83 $[M+H]^+$ = 344 (method 6)

Intermediate compound 226: 4-((3aS,4R,9bR)-8-ethyl-3a,4,5,9b-tetrahydro-1H-cyclopenta[c]quinolin-4-yl)-2-fluorobenzoic acid.

The following compound was prepared using the same methodology as in intermediate compound 41 using 2-fluoro-4-formylbenzoic acid (0.89 mmol, 150 mg) and 4-ethylaniline (0.89 mmol, 108 mg). Solvent was evaporated and the crude material was treated with water and it was washed twice with EtAcO. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated (301 mg, yield: 100%, endo-isomer).

LC-MS: t_R = 1.89 $[M+H]^+$ = 338 (method 6)

Intermediate compound 227 & 228: methyl 4-((6R,6aS,11aR)-2-chloro-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[c]quinolin-6-yl)benzoate(227) & methyl 4-((6S,6aS,11aR)-2-chloro-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[c]quinolin-6-yl)benzoate (228).

The following mixture of compounds was prepared using the same methodology as in intermediate compound 105 using methyl 4-formylbenzoate (2.44 mmol, 400 mg), 4-chloroaniline (2.44 mmol, 311 mg) and cycloheptene (12.18 mmol, 1.42 ml). The mixture was stirred at r.t. for 16h. Afterthat, It was refluxed for 5h and solvents were evaporated. The crude material was treated with 0.2 N $NaHCO_3$ aqueous solution and it was washed twice with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated. It was purified by flash chromatography on silica gel, using hexane / ethyl acetate 10% as eluents. To obtain a non separable mixture of isomers (140 mg, yield: 15.5%, mixture endo-exo-isomer).

LC-MS: t_R = 3.42 $[M+H]^+$ = 370 (method 6)

LC-MS: t_R = 3.42 $[M+H]^+$ = 370 (method 6)

Intermediate compound 229: 2,6-difluoro-4-((3aS,4R,9bR)-8-methyl-3a,4,5,9b-tetrahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid.

The following compound was prepared using the same methodology as in intermediate compound 41 using 2,6-difluoro-4-formylbenzoic acid (1.34 mmol, 250 mg) and p-toluidine (1.34 mmol, 144 mg). Solvent was evaporated and the crude material was treated with 0.1 N HCl aqueous solution and it was washed twice with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated (444 mg, yield: 97%, endo-isomer).

LC-MS: t_R = 1.74 $[M+H]^+$ = 342 (method 6)

Intermediate compound 230 & 231: 4-((6R,6aS,10aR)-2-ethyl-5,6,6a,7,8,10a-hexahydrophenanthridin-6-yl)-2-fluorobenzoic acid (230) & 4-((6S,6aS,10aR)-2-ethyl-5,6,6a,7,8,10a-hexahydrophenanthridin-6-yl)-2-fluorobenzoic acid (231).

The following mixture of compounds was prepared using the same methodology as in intermediate compound 105 using 2-fluoro-4-formylbenzoic acid (1.49 mmol, 250 mg), 4-ethylaniline (1.49 mmol, 180 mg) and cyclohexa-1,3-diene (7.44 mmol, 596 mg). The mixture was refluxed for 16h. After that, solvent was evaporated. The crude material was treated with 0.1 N HCl aqueous solution and it was washed twice with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to obtain a non separable mixture of isomers (523 mg, yield: 100%, mixture endo-exo-isomer).

LC-MS: t_R = 1.78 $[M+H]^+$ = 352 (method 6)

LC-MS: t_R = 1.78 $[M+H]^+$ = 352 (method 6)

Intermediate compound 232: methyl 3-fluoro-4-formylbenzoate.

The following compound was prepared using the same methodology as in intermediate compound 19 using methyl 4-bromo-3-fluorobenzoate (8.58 mmol, 2000 mg). The reaction mixture was stirred at -15ºC for 2h and at r.t. for 16h. The reaction mixture was quenched with 0.1 N HCl aqueous solution and extracted

with EtAcO. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered and evaporated. It was purified by flash chromatography on silica gel, using hexane / ethyl acetate 3% as eluents. (949 mg, yield: 60.7%).

^1H NMR (300 MHz, DMSO-d_6) δ 10.42 (1H, s), 7.98-7.91 (2H, m), 7.85 (1H, d, *J*=10.2Hz), 3.97 (3H, s).

Intermediate compound 233: methyl 4-((3aS,4R,9bR)-8-ethyl-3a,4,5,9b-tetrahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoate.

The following compound was prepared using the same methodology as in intermediate compound 41 using **intermediate compound 232** (0.82 mmol, 150 mg) and 4-ethylaniline (0.82mmol, 100 mg). The reaction mixture was stirred at r.t. for 16h. Solvent was evaporated. The crude material was treated with 0.2 N $NaHCO_3$ aqueous solution and it was washed twice with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated. It was purified by flash chromatography on silica gel. (158 mg, yield: 54.6%, endo-isomer).

LC-MS: t_R = 3.34 $[M+H]^+$ = 353 (method 6)

Intermediate compound 234: methyl 4-((3aS,4R,9bR)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoate.

The following compound was prepared using the same methodology as in intermediate compound 67 using **intermediate compound 233** (0.45 mmol, 158 mg) .The reaction mixture was stirred at r.t. for 1h. It was filtered over celite® and solvents were evaporated. (153 mg, yield: 96%, endo-isomer).

LC-MS: t_R = 3.55 $[M+H]^+$ = 354 (method 6)

Intermediate compound 235: methyl 3-fluoro-4-((3aS,4R,9bR)-8-(trifluoromethyl)-3a,4,5,9b-tetrahydro-1H-cyclopenta[c]quinolin-4-yl)benzoate.

The following compound was prepared using the same methodology as in intermediate compound 41 using **intermediate compound 232** (0.82 mmol, 150 mg) and 4-(trifluoromethyl)aniline (0.82 mmol, 133 mg).The reaction mixture was stirred at r.t. for 16h. Solvent was evaporated. The crude material was treated with 0.2 N $NaHCO_3$ aqueous solution and it was washed twice with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated. It was purified by flash chromatography on silica gel (190 mg, yield: 59%, endo-isomer).

LC-MS: t_R = 3.22 $[M+H]^+$ = 392 (method 6)

Intermediate compound 236: methyl 3-fluoro-4-((3aS,4R,9bR)-8-(trifluoromethyl)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoate.

The following compound was prepared using the same methodology as in intermediate compound 67 using **intermediate compound 235** (0.48 mmol, 190 mg) .The reaction mixture was stirred at r.t. for 1h. It was filtered over celite® and the solvent was evaporated. (189 mg, yield: 99%, endo-isomer).

LC-MS: t_R = 3.38 $[M+H]^-$ = 392 (method 6)

Intermediate compound 237: methyl 4-((3aS,4R,9bR)-8-chloro-3a,4,5,9b-tetrahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoate.

The following compound was prepared using the same methodology as in intermediate compound 41 using **intermediate compound 232** (0.82 mmol, 150 mg) and 4-chloroaniline (0.82 mmol, 105 mg). The reaction mixture was stirred at r.t. for 16h. Solvent was evaporated. The crude material was treated with 0.2 N $NaHCO_3$ aqueous solution and it was washed twice with DCM. The combined

organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated. It was purified by flash chromatography on silica gel (199 mg, yield: 67.5%, endo-isomer).

LC-MS: t_R = 3.24 $[M+H]^+$ = 358 (method 6)

Intermediate compound 238: methyl 4-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoate.

The following compound was prepared using the same methodology as in intermediate compound 67 using **intermediate compound 237** (0.56 mmol, 199 mg) .The reaction mixture was stirred at r.t. for 1h. It was filtered over celite® and the solvent was evaporated. (192 mg, yield: 96%, endo-isomer).

LC-MS: t_R = 3.42 $[M+H]^+$ = 360 (method 6)

Intermediate compound 239 & 240: methyl 3-fluoro-4-((6R,6aS,10aR)-2-methyl-5,6,6a,7,8,10a-hexahydrophenanthridin-6-yl)benzoate (239) & methyl 3-fluoro-4-((6S,6aS,10aR)-2-methyl-5,6,6a,7,8,10a-hexahydrophenanthridin-6-yl)benzoate (240).

The following mixture of compounds was prepared using the same methodology as in intermediate compound 105 using **intermediate compound 232** (1.10 mmol, 200 mg) and cyclohexa-1,3-diene (5.49 mmol, 440 mg). The reaction mixture was refluxed for 16h. The solvent was evaporated. The crude material was treated with 0.2 N $NaHCO_3$ aqueous solution and it was washed twice with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to obtain a non separable mixture of isomers (386 mg, yield: 100%, mixture endo-exo-isomer).

LC-MS: t_R = 3.30 $[M+H]^+$ = 352 (method 6)

LC-MS: t_R = 3.34 $[M+H]^+$ = 352 (method 6)

Intermediate compound 241 & 242: methyl 3-fluoro-4-((6R,6aS,10aR)-2-methyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoate (241) & methyl 3-fluoro-4-((6S,6aS,10aR)-2-methyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoate (242).

The following mixture of compounds was prepared using the same methodology as in intermediate compound 67 using the mixture of **intermediate compounds 239 and 240** (1.10 mmol, 386 mg). The reaction mixture was stirred at r.t. for 16h. It was filtered over celite® and the solvent was evaporated. It was purified by flash chromatography on silica gel using hexane / EtAcO 15% as eluents to obtain a non separable mixture of isomers (104 mg, yield: 26.8%, mixture endo-exo-isomer).

LC-MS: t_R = 3.42 $[M+H]^+$ = 354 (method 6)

LC-MS: t_R = 3.52 $[M+H]^+$ = 354 (method 6)

Intermediate compound 243 & 244: methyl 4-((6R,6aS,10aR)-2-ethyl-5,6,6a,7,8,10a-hexahydrophenanthridin-6-yl)-3-fluorobenzoate (243) & methyl 4-((6S,6aS,10aR)-2-ethyl-5,6,6a,7,8,10a-hexahydrophenanthridin-6-yl)-3-fluorobenzoate (244).

The following mixture of compounds was prepared using the same methodology as in intermediate compound 105 using **intermediate compound 232** (0.6 mmol, 110 mg), cyclohexa-1,3-diene (3.02 mmol, 242 mg) and 4-ethylaniline (0.6 mmol, 73.2 mg). The mixture was refluxed for 4h. The solvent was evaporated. The crude material was treated with 0.2 N $NaHCO_3$ aqueous solution and it was washed twice with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated. It was purified by flash chromatography on silica gel using hexane / EtAcO 20% as eluents to obtain a non separable mixture of isomers (200 mg, yield: 91%, mixture endo-exo-isomer).

LC-MS: t_R = 3.32 $[M+H]^+$ = 366 (method 6)

LC-MS: t_R = 3.32 $[M+H]^+$ = 366 (method 6)

Intermediate compound 245 & 246: methyl 4-((6R,6aS,10aR)-2-ethyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-3-fluorobenzoate (245) & methyl 4-((6S,6aS,10aR)-2-ethyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-3-fluorobenzoate (246).

The following mixture of compounds was prepared using the same methodology as in intermediate compound 67 using the reaction mixture of **intermediate compounds 243 and 244** (0.55 mmol, 200 mg). The mixture was stirred at r.t. for 7h. It was filtered over celite® and the solvent was evaporated to obtain a non separable mixture of isomers (185 mg, yield: 92%, mixture endo-exo-isomer).

LC-MS: t_R = 3.43 $[M+H]^+$ = 369 (method 6)

LC-MS: t_R = 3.52 $[M+H]^+$ = 369 (method 6)

Intermediate compound 247: ethyl 2-hydroxy-4-methylbenzoate.

To a solution of 2-hydroxy-4-methylbenzoic acid (65.7 mmol, 10000 mg) in EtOH (178 ml), sulfuric acid (89.0 mmol, 8700 mg) was added. The mixture was refluxed for 16h. Solvent was evaporated. It was washed twice with EtAcO /satured $NaHCO_3$ aqueous solution. The combined organic layers were dried over Na_2SO_4, filtered and evaporated. (7702 mg, yield: 65%).

LC-MS: t_R = 2.51 $[M+H]^+$ = 181 (method 6)

Intermediate compound 248: dimethylaminosulfonylamine.

Dimethylsulfamoyl chloride (6.96 mmol, 0.748 ml) was treated with 7N ammonia methanol solution (104 mmol , 14.92 ml) in a sealed High-Pressure flask at 60ºC for 16 h. The reaction mixture was evaporated. The solid obtained was suspended in DCM, filtered, washed with DCM and dried under reduced pressure affording the title compound which was used in the next step without further purification (850 mg. Yield: 98%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.40 (2H, s), 2.38 (6H, s).

Intermediate compound 249: ethyl 3-ethoxy-4-formylbenzoate.

To a solution of 4-formyl-3-hydroxybenzoic acid (3.01 mmol, 500 mg) in ACN (3ml), iodoethane (9.03 mmol, 1408 mg) and cesium carbonate (9.03 mmol, 2942 mg) were added. The reaction mixture was refluxed for 4h. Solvents were evaporated. It was washed twice with EtAcO / water. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated (121 mg, yield: 18%).

LC-MS: t_R = 2.33 $[M+H]^+$ = 223 (method 6)

Intermediate compound 250: ethyl 3-ethoxy-4-((3aS,4R,9bR)-8-methyl-3a,4,5,9b-tetrahydro-1H-cyclopenta[c]quinolin-4-yl)benzoate.

The following compound was prepared using the same methodology as in intermediate compound 41 using **intermediate compound 249** (0.54 mmol, 121 mg) and p-toluidine (0.54mmol, 58.3 mg). The reaction mixture was stirred at r.t. for 16h. Solvent was evaporated. The crude material was treated with 0.2 N $NaHCO_3$ aqueous solution and it was washed twice with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated. It was purified by flash chromatography on silica gel (109 mg, yield: 53%, endo-isomer).

LC-MS: t_R = 3.36 $[M+H]^+$ = 379 (method 6)

Intermediate compound 251: ethyl 3-ethoxy-4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoate.

The following compound was prepared using the same methodology as in intermediate compound 67 using **intermediate compound 250** (0.29 mol, 109 mg) .The reaction mixture was stirred at r.t. for 1h. It was filtered over celite® and the solvent was evaporated. It was purified by flash chromatography on silica gel (80 mg, yield: 73%, endo-isomer).

LC-MS: t_R = 3.48 $[M+H]^+$ = 381 (method 6)

Intermediate compound 252: 3-chloro-5-fluoro-4-formylbenzoic acid.

To a solution of 3-chloro-5-fluorobenzoic acid (28.6 mmol, 5000 mg) in 2-methyltetrahydrofuran (100 mL) N1,N1,N2,N2-tetramethylethane-1,2-diamine (63.0 mmol, 9.51 ml), was added at room temperature. The resulting solution was cooled at -78ºC. Afterward, butyllithium (68.7 mmol, 27.5 ml) was added drop-wise, during which the temperature of the mixture remained at less than -65ºC. The mixture was then stirred at -78ºC for 1.5 h. Anhydrous methyl formate (60.2 mmol, 3.71 ml) was added dropwise at a rate that allowed the temperature to be maintained at less than -65ºC. The resulting solution was allowed to warm at room temperature and then maintained at room temperature while being stirred for 18 h.

The reaction was then cooled to 0ºC, and excess base was quenched with 1M HCl aqueous solution (40 mL). The phases were then separated, and the aqueous layer was extracted 3 times with EtAcO. The combined organic phases were washed with brine, dried over anhydrous MgSO4, filtered, and concentrated under vacuum. The residue was dissolved in EtAcO (8 mL) at reflux, and cooled to room temperature. Hexanes (10 mL) were then added, and the resulting mixture was further cooled to 0ºC. The solid was collected by filtration, rinsed with hexanes, and dried under vacuum. (2970 mg, yield: 51.2%).

LC-MS: t_R = 0.63 $[M+H]^-$ = 201 (method 6)

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.32 (1H, s) 8.47 (1H, brs), 7.96-769 (2H, m).

Intermediate compound 253: 3-chloro-4-((3aS,4R,9bR)-8-(difluoromethoxy)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)-5-fluorobenzoic acid.

The following compound was prepared using the same methodology as in intermediate compound 41 using **intermediate compound 252** (1.88 mmol, 382 mg) and 4-(difluoromethoxy)aniline (1.88mmol, 300 mg). The reaction mixture was stirred at r.t. for 16h. Solvent was evaporated. It was purified by flash chromatography on silica gel using hexane /EtAcO (0-100%) as eluents (242 mg, yield: 31,3%, endo-isomer).

LC-MS: t_R = 1.89 $[M+H]^-$ = 408 (method 6)

Intermediate compound 254: ethyl 2,3-difluoro-4-methylbenzoate.

To a solution of 2,3-difluoro-4-methylbenzoic acid (17.43mmol, 3000 mg) in EtOH (20 ml) thionyl chloride (31.4 mmol, 2.29 ml) was added. The mixture was stirred at 60ºC for 16h. Solvent was evaporated. It was washed twice with EtAcO/water. The combined organic layers were dried over Na_2SO_4, filtered and evapotared. (3330 mg, yield: 95%).

LC-MS: t_R = 2.52 $[M+H]^+$ = 201 (method 6)

Intermediate compound 255: ethyl 4-(dibromomethyl)-2,3-difluorobenzoate.

To a solution of **intermediate compound 254** (7.99 mmol, 1600 mg) in carbon tetrachloride (20 ml) NBS (19.98 mmol, 3560 mg) and benzoyl peroxide (0.21 mmol, 50 mg) were added. The mixture was refluxed for 5h. Solvent was evaporated. It was washed twice with EtAcO/water. The combined organic layers were dried over Na_2SO_4, filtered and evaporated. It was purified by flash chromatography on silica gel using Hexane /EtAcO (0-25%) as eluents (2188 mg, yield: 76%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.79-7.73 (1H, m), 7.70-7.60 (1H, m), 7.51 (1H, s), 4.41-4.28 (2H, q, *J*=6.9Hz), 1.32 (3H, t, *J*=6.9Hz).

Intermediate compound 256: ethyl 2,3-difluoro-4-formylbenzoate.

To a solution of **intermediate compound 255** (4.69 mmol1680 mg) in DCM (28 ml), at 0ºC trimethylamine oxide (18.77 mmol, 1410 mg) and DMSO (5 ml) were added. The mixture was stirred at r.t. for 16h. Satured Na_2CO_3 aqueous solution was added. And it was washed thrice with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated. It was purified by flash chromatography on silica gel using hexane /EtAcO (0-25%) as eluents (208 mg, yield: 20.7%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.22 (1H, s), 7.86-7.68 (2H, m), 4.44-4.29 (2H, m), 1.33 (3H, t, *J*=4.5Hz).

Intermediate compound 257: ethyl 2,3-difluoro-4-((3aS,4R,9bR)-8-methyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)benzoate

The following compound was prepared using the same methodology as in intermediate compound 41 using **intermediate compound 256** (0.70 mmol, 150 mg) and p-toluidine (0.70 mmol, 75 mg). The reaction mixture was stirred at r.t. for 16h. Solvent was evaporated. It was purified by flash chromatography on silica gel using Hexane /EtAcO (0-50%) as eluents (223 mg, yield: 86%, endo-isomer).

LC-MS: t_R = 3.18 $[M+H]^+$ = 371 (method 6)

Intermediate compound 258: 2,3-difluoro-4-((3aS,4R,9bR)-8-methyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)benzoic acid.

To a solution of **intermediate compound 257** (0.60 mmol, 223 mg) in MeOH (4ml) 1 N NaOH aqueous solution (6.04mmol, 6.04 ml) was added. The reaction mixture was refluxed for 2 h. The solvent was removed in vacuum. The crude reaction was dissolved in water. The pH of the solution was adjusted to 1-2 by adding 1 N HCl aqueous solution. The resulting solid was filtered (127 mg, yield: 61.6%, endo-isomer).

LC-MS: t_R = 1.79 $[M+H]^+$ = 342 (method 6)

Intermediate compound 259: ethyl 2,5-difluoro-4-methylbenzoate.

The following compound was prepared using the same methodology as in intermediate compound 254 using 2,5-difluoro-4-methylbenzoic acid (5.81 mmol, 1000 mg). The reaction mixture was stirred at 60ºC for 16h. Solvent was evaporated. It was washed twice with EtAcO / water. The combined organic layers were dried over Na_2SO_4, filtered and evapotared. (1142 mg, yield: 98%).

LC-MS: t_R = 2.52 $[M+H]^+$ = 201 (method 6)

Intermediate compound 260: ethyl 4-(dibromomethyl)-2,5-difluorobenzoate.

The following compound was prepared using the same methodology as in intermediate compound 255 using **intermediate compound 259** (5.69 mmol, 1142 mg). The reaction mixture was refluxed for 5h. Solvent was evaporated. It was washed twice with EtAcO/water. The combined organic layers were dried over Na_2SO_4, filtered and evaporated. It was purified by flash chromatography on silica gel using hexane /EtAcO (0-25%) as eluents (1407 mg, yield: 69%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.81-7.61 (2H, m), 4.70 (1H, s), 4.41-4.29 (2H, m), 1.31 (3H, t, *J*=6.6Hz).

Intermediate compound 261: ethyl 2,5-difluoro-4-formylbenzoate.

The following compound was prepared using the same methodology as in intermediate compound 256 using **intermediate compound 260** (3.93 mmol, 1407 mg). The reaction mixture was stirred at r.t. for 16h. It was quenched with satured Na_2CO_3 aqueous solution and extrated twice with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated. It was purified by flash chromatography on silica gel using Hexane /EtAcO (0-25%) as eluents (790 mg, yield: 93.8%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.2 (1H, s), 7.85-7.65 (2H, m), 4.42-4.29 (2H, m), 1.31 (3H, t, *J*=6.6Hz).

Intermediate compound 262: ethyl 2,5-difluoro-4-((3aS,4R,9bR)-8-methyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)benzoate.

The following compound was prepared using the same methodology as in intermediate compound 41 using **intermediate compound 261** (0.70 mmol, 150 mg) and p-toluidine (0.70 mmol, 75 mg). The reaction mixture was stirred at r.t. for 16h. Solvent was evaporated. It was purified by flash chromatography on silica gel using Hexane /EtAcO (0-50%) as eluents (218 mg, yield: 84%, endo-isomer).

LC-MS: t_R = 3.20 $[M+H]^+$ = 371 (method 6)

Intermediate compound 263: 2,5-difluoro-4-((3aS,4R,9bR)-8-methyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)benzoic acid.

To a solution of **intermediate compound 262** (0.59 mmol, 218 mg) in MeOH (4 ml), 1 N NaOH aqueous solution (5.90 mmol, 5.90 ml) was added. The reaction mixture was refluxed for 2 h. The solvent was removed in vacuum. The crude reaction was dissolved in water. The pH of the solution was adjusted to 1-2 by adding 1 N HCl aqueous solution. The resulting solid was filtered (142 mg, yield: 70.5%, endo-isomer).

LC-MS: t_R = 1.81 $[M+H]^+$ = 342 (method 6)

Intermediate compound 264: ethyl 2-isobutoxy-4-methylbenzoate.

To a solution of **intermediate compound 247** (8.32 mmol, 1500 mg) in ACN (83 ml), cesium carbonate (24.97 mmol, 8136 mg) and 1-iodo-2-methylpropane (24.97 mmol, 4595 mg) were added. The mixture was refluxed for 16h. Solvent was evaporated. It was washed twice with EtAcO / water. The combined organic layers were dried over Na_2SO_4, filtered and evaporated. It was purified by flash chromatography on silica gel using hexane /EtAcO (0-3%) as eluents (1280 mg, yield: 65.1%).

LC-MS: t_R = 2.81 $[M+H]^+$ = 238 (method 6)

Intermediate compound 265: ethyl 4-(bromomethyl)-2-isobutoxybenzoate.

To a solution of **intermediate compound 264** (5.42 mmol, 1280 mg) in carbon tetrachloride (14 ml), NBS (5.75 mmol, 1022 mg) and benzoyl peroxide (0.03 mmol, 6,75 mg) were added. The mixture was refluxed for 16h. Solvent was evaporated. It was washed twice with EtAcO / satured $NaHCO_3$ aqueous solution. The combined organic layers were dried over Na_2SO_4, filtered and evaporated. (1668 mg, yield: 98%).

LC-MS: t_R = 2.84 $[M+H]^+$ = 317 (method 6)

Intermediate compound 266: ethyl 4-formyl-2-isobutoxybenzoate.

To a solution of **intermediate compound 265** (5.29 mmol, 1668 mg) in DMSO (16 ml) sodium hydrogencarbonate (26.5 mmol, 2223 mg) was added. The reaction mixture was refluxed for 1h. It was washed twice with Et_2O/brine. The combined organic layers were dried over Na_2SO_4, filtered and evaporated. It was purified by flash chromatography on silica gel using hexane /EtAcO (0-10%) as eluents (100 mg, yield: 7.55%).

LC-MS: t_R = 2.52 $[M+H]^+$ = 251 (method 6)

Intermediate compound 267: ethyl 2-isobutoxy-4-((3aS,4R,9bR)-8-methyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)benzoate.

The following compound was prepared using the same methodology as in intermediate compound 41 using **intermediate compound 266** (0.40 mmol, 100 mg) and p-toluidine (0.40mmol, 42.8 mg). The reaction mixture was stirred at r.t. for 16h. Solvent was evaporated. It was washed twice with EtAcO / water. The combined organic layers were dried over Na_2SO_4, filtered and evaporated. It was purified by flash chromatography on silica gel using Hexane /EtAcO (0-25%) as eluents (90 mg, yield: 55.5%, endo-isomer).

LC-MS: t_R = 3.40 $[M+H]^+$ = 407 (method 6)

Intermediate compound 268: ethyl 2-isobutoxy-4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoate.

The following compound was prepared using the same methodology as in intermediate compound 67 using **intermediate compound 267** (0.22 mmol, 90 mg) and PtO_2 (5% w/w, 3.53 mg). The reaction mixture was stirred at r.t. for 2h. It was filtered over celite® and the solvent was evaporated. (90 mg, yield: 100%, endo-isomer).

LC-MS: t_R = 3.54 $[M+H]^+$ = 408 (method 6)

Intermediate compound 269: ethyl 3-(4-formylphenyl)propanoate

A solution of 4-bromobenzaldehyde (1.35 mmol, 250 mg), acrolein diethyl acetal (4.05 mmol, 0.62 mL), tributylamine (2.7 mmol, 0.64 mL), tetrabutylammonium chloride (1.35 mmol, 376 mg) and palladium(II) acetate (0.047 mmol, 11 mg) in DMF (5 mL) was degassed by argon and stirred at 90 ºC for 16 h. The reaction mixture was cooled to room temperature and diluted with ethylacetate and saturated aqueous sodium carbonate solution. Organic layer was then separated, washed with aqueous sodium carbonate solution (x2), brine (x2) and dried over anhydrous sodium sulphate, filtered and concentrated under reduce pressure to afford the desired product which was purified by flash chromatography on silica gel using an elution of 30% ethylacetate in hexanes to afford ethyl 3-(4-formylphenyl)propanoate (207 mg, Yield: 74%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (1 H, s), 7.80 (2 H, dd, *J* = 6.4 & 1.6 Hz), 7.37 (2 H, d, *J* = 8 Hz), 4.12 (2 H, q, *J* = 7.2 Hz), 3.03 (2H, t, *J* = 7.6 Hz), 2.66 (2H, t, *J* = 7.6 Hz), 2.39 (3 H, t, *J* = 7.2 Hz).

LC-MS: t_R = 3.15 $[M+H]^+$= 207 (method 3)

Intermediate compound 270: ethyl 3-(4-((3aS,9bR)-3a,4,5,9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)phenyl)propanoate

The following compound was prepared using the same methodology as in intermediate compound 41 using ethyl 3-(4-formylphenyl)propanoate (**intermediate compound 269**) (4 mmol, 900 mg) and *p*-toluidine (4 mmol, 428 mg) for 36h. Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 18% ethylacetate in hexanes afforded a mixture (1:7) of exo/endo regioisomers (250 mg. Yield: 35%).

Endo-isomer: ethyl 3-(4-((3aS,4R,9bR)-3a,4,5,9b-tetrahydro-8-methyl-3H-cyclopenta[c]quinolin-4-yl)phenyl)propanoate

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (2H, d, *J* = 8.0 Hz), 7.19 (2H, d, *J* = 8 Hz), 6.88 (1H, s), 6.80 (1H, dd, *J* = 8 & 2 Hz), 6.54 (1H, d, *J* = 8Hz), 5.85-5.82 (1H, m), 5.66-5.64 (1H, m), 4.56 (1H, d, *J* = 3.2 Hz), 4.12 (2H, q, *J* = 7.2 Hz), 4.06 (1H, d, *J* = 8 Hz), 3.00-2.94 (1H, m), 2.96 (2H, t, *J* = 7.6 Hz), 2.67-2.61 (1H, m), 2.62 (2H, t, *J* = 7.6 Hz), 2.23 (3H, s), 1.84-1.77 (1H, m), 1.24 (3H, t, *J* = 6.8 Hz).

LC-MS: t_R = 5.30 $[M+H]^+$= 362 (method 3)

The following examples illustrate the scope of the invention.

Examples of compounds of general formula

Example 1: 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta [c]quinolin-4-yl)benzoic acid

The **Intermediate compound 41** (60 mg, 0.16 mmol,) was dissolved in ethanol and tetrahydrofurane (1:1, 2 mL) and platinum dioxide (10%w/w, 6 mg) was added. The solution was hydrogenated at r.t., for 6h. HPLC analysis showed total conversion. Reaction mixture was filtered and washed with THF. Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 30% ethylacetate in hexanes afforded the title compound as a 3:1 mixture of compounds as a white solid (32 mg, 53%), which

was purified using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give 5 mg of 4-((3a*S*,4*R*,9b*R*)-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid **1** and 18 mg 4-((3a*S*,4*R*,9b*R*)-8-bromo-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid **2.**

4-((3a*S*,4*R*,9b*R*)-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic **1**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (2H, d, *J* = 8.4 Hz), 7.55 (2H, d, *J* = 8.0 Hz), 7.13 (1H, d, *J* = 7.6 Hz), 7.01 (1H, dt, *J* = 7,2 & 0.8 Hz), 6.78 (1H, dt, *J* = 7,6 & 1.2 Hz), 6.62 (1H, dd, *J* = 7.6 & 0.8 Hz), 4.65 (1H, d, *J* = 2.8 Hz), 3.52-3.47 (1H, m), 2.54-2.47 (1H, m), 2.21-2.11 (1H, m), 1.85-1.80 (1H, m), 1.78-1.69 (1H, m), 1.62-1.52 (1H, m), 1.50-1.40 (1H, m), 1.22-1.14 (1H, m).

LC-MS: t_R = 7.73 $[M+H]^+$= 294 (method 1)

Example 2: 4-((3aS,4R,9bR)-8-bromo-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 using **Intermediate compound 41** (370 mg, 1 mmol,). The solution was hydrogenated at r.t., for 2 h. HPLC analysis showed total conversion. Reaction mixture was filtered and washed with THF. Solvent was evaporated and purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded 154 mg (41%) of 4-((3a*S*,4*R*,9b*R*)-8-bromo-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid as a white solid.

4-((3a*S*,4*R*,9b*R*)-8-bromo-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[*c*]quinolin-4-yl) benzoic acid **2**:

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (2H, d, *J* = 8.4 Hz), 7.52 (2H, d, *J* = 8.0 Hz), 7.14 (1H, d, *J* = 1.6 Hz), 7.01 (1H, dd, *J* = 8.4 & 2 Hz), 6.65 (1H, d, *J* = 8.4 Hz), 6.03 (1H, s), 4.53 (1H, d, *J* = 3.2 Hz), 3.38 (1H, dt, *J* = 7.2 & 1.6 Hz), 2.48-2.40 (1H, m), 2.08-2.01 (1H, m), 1.72-1.64 (1H, m), 1.52-1.44 (1H, m), 1.40-1.34 (1H, m), 1.03-0.98 (1H, m).

LC-MS: t_R = 8.67 $[M+H]^+$= 372/374 (method 1)

Example 3: 4-((3aS,4R,9bR)-8-(trifluoromethyl)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 42** (270 mg, 0.75 mmol) for 1.30 h. Purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give 140 mg of the title compound which was precipitated in hexane, filtered and dried in vacuum to obtain 128 mg (47%) of the pure endo-isomer.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (2H, d, *J* = 8.4 Hz), 7.54 (2H, d, *J* = 8.4 Hz), 7.37 (1H, s), 7.24 (H, dd, *J* = 10 & 2 Hz), 6.64 (1H, d, *J* = 8.4 Hz), 4.72 (1H, d, *J* = 2.8 Hz), 3.52-3.48 (1H, m), 2.54-2.50 (1H, m), 2.22-2.16 (1H, m), 1.89-1.85 (1H, m), 1.69-1.47 (3H, m), 1.25-1.18 (1H, m).

LC-MS: t_R = 8.52 $[M+H]^+$= 362 (method 1)

Example 4: 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 43** (70 mg, 0.23 mmol) for 16 h. Purification of the crude material by precipitation in dichloromethane, filtration, solid washed by ether and dried to give 25 mg of the title compound (Yield: 35%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (2H, d, *J* = 8.4 Hz), 7.55 (2H, d, *J* = 8.0 Hz), 6.95 (1H, s), 6.83 (1H, d, *J* = 8.0 Hz), 6.54 (1H, d, *J* = 8.0 Hz), 4.60 (1H, d, *J* = 3.2 Hz), 3.46 (1H, dt, *J* = 8.0 & 3.2 Hz), 2.49 (1H, dq, *J* = 10.4 & 2.8 Hz), 2.26 (3H, s), 1.82-1.76 (1H, m), 1.74-1.67 (1H, m), 1.57-1.53 (1H, m), 1.46-1.39 (3H, m), 1.21-1.12 (1H, m).

LC-MS: t_R = 8.13 $[M+H]^+$= 308 (method 1)

Separation of 100 mg of (+/-) endo-isomer 4-((3a*S*,4*R*,9b*R*)-2,3,3*a*,4,5,9*b*-hexahydro-8-methyl-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid (**4**) by chiral

preparative chromatography was carried out using Heptane/IPA/TFA (80:20:0.1) as eluents to yield:

34 mg of the enantiomer 1 (**4a**):

Preparative HPLC: t_R = 13.65

28 mg of the enantiomer 2 (**4b**):

Preparative HPLC: t_R = 23.72

Example 5: 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compounds were prepared using the same methodology as in intermediate compound 67 from **a mixture endo/exo of intermediate compound 43** from (663 mg, 2.07 mmol) for 3 h. Purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give 32 mg of the 4-((3a*S*,4*S*,9b*R*)-2,3,3*a*,4,5,9*b*-hexahydro-8-methyl-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid (exo-isomer **5**) and 455 mg of 4-((3a*S*,4*R*,9b*R*)-2,3,3*a*,4,5,9*b*-hexahydro-8-methyl-1H-cyclopenta[*c*]quinolin-4-yl)benzoic acid (endo-isomer **4**). (yield 77%)

4-((3a*S*,4*S*,9b*R*)-2,3,3*a*,4,5,9*b*-hexahydro-8-methyl-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid (exo-isomer **5**):

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (2H, d, *J* = 8.4 Hz), 7.45 (2H, d, *J* = 8.0 Hz), 6.84 (1H, m), 6.68 (1H, dd, *J* = 8.0 & 1.6 Hz), 6.54 (1H, t, *J* = 8 Hz), 5.72 (1H, s), 3.67 (1H, d, *J* = 10 Hz), 2.87 (1H, q, *J* = 7.6 Hz), 2.45-2.39 (2H, m), 2.20-2.17 (1H, m), 2.14 (3H, s), 1.67-1.47 (3H, m), 1.31-1.26 (1H, m).

LC-MS: t_R = 9.47 $[M+H]^+$= 308 (method 1)

Example 6: 4-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 44** (228 mg, 0.7 mmol) for 4 h. Purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give 96

mg of the title compound which was precipitated in ether, filtered and dried in vacuum to obtain 75 mg (33%) of the pure endo-isomer.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (2H, d, *J* = 8 Hz), 7.52 (2H, d, *J* = 8.4 Hz), 7.02 (1H, s), 6.90 (1H, dd, *J* = 8.8 & 2.2 Hz), 6.69 (1H, d, *J* = 8.4 Hz), 6.00 (1H, s), 4.53 (1H, s), 3.39-3.34 (1H, m), 2.49-2.41 (1H, m), 2.07-2.00 (1H, m), 1.70-1.67 (1H, m), 1.49-1.40 (1H, m), 1.38-1.34 (1H, m), 1.05-0.98 (1H, m).

LC-MS: t_R = 8.43 min $[M+H]^+$= 328/330 (method 1)

Separation of 200 mg of (+/-)-4-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (**6**) by preparative chiral chromatography was carried out using Heptane/IPA/HCOOH (95:5:0.1) as eluents to yield:

94 mg of the enantiomer 1 (**6a**):

Preparative HPLC: t_R = 31

85 mg of the enantiomer 2 (**6b**):

Preparative HPLC: t_R = 54

Example 7: 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 45** (1.15g, 3.58 mmol) for 1 h. Purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give 700 mg of the title compound.(Yield: 60%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (2H, d, *J* = 8.4 Hz), 7.53 (2H, d, *J* = 8.4 Hz), 6.63 (1H, d, *J* = 8.4 Hz), 6.60 (1H, d, *J* = 2.4 Hz), 6.53 (1H, d, *J* = 8.8 & 2.8 Hz), 6.40 (1H, s), 4.43 (1H, d, *J* = 2.8 Hz), 3.63 (3H, s), 3.38-3.34 (1H, m), 2.45-2.41 (1H, m), 2.07-2.01 (1H, m), 1.70-1.67 (1H, m), 1.55-1.48 (1H, m), 1.38-1.32 (2H, m), 1.02-0.96 (1H, m).

LC-MS: t_R = 6.68 $[M+H]^+$= 324 (method 1)

Separation of 213 mg of (+/-)-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (**7**) by preparative chiral chromatography was carried out using Heptane/IPA (90:10) as eluents to yield:

45 mg of the enantiomer 1 (**7a**):

Preparative HPLC: t_R = 18

83 mg of the enantiomer 2 (**7b**):

Preparative HPLC: t_R = 39

Example 8: 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 45** for 1h. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give exo-isomer 4-((3a*S*,4*S*,9b*R*)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1-*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid (23 mg. Yield: 4%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.9 (2H, d, *J*=8.4Hz), 7.5 (2H, d, *J*=8.4Hz), 6.66 (1H, d, *J*=2.4Hz), 6.59 (1H, d, *J*=8.8Hz), 6.53 (1H, dd, *J*=2.8 & 8.8Hz), 5.57 (1H, s), 3.66 (1H, d, *J*=10Hz), 3.63 (3H, s), 2.92-2.88 (1H, m), 2.23-2.19 (2H, m), 1.67-1.63 (1H, m), 1.58-1.47 (2H, m), 1.30-1.27 (1H, m).

LC-MS: t_R = 8.17 $[M+H]^+$ = 324 (method 1)

Example 9: 4-((3aS, 4R, 9bR)-6-cyclopropyl-2, 3, 3a, 4, 5, 9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 46** for 1h. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give the endo-isomer 4-((3a*S*, 4*R*, 9b*R*)-6-cyclopropyl-2, 3, 3a, 4, 5, 9b-hexahydro-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid (89 mg. Yield:43%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (2H, d, *J*=8.4Hz), 7.61 (2H, d, *J*=8Hz), 6.94 (1H, d, *J*=7.2Hz), 6.76 (1H, d, *J*=7.2Hz), 6.59 (1H, t, *J*=7.6Hz), 4.88 (1H, s), 4.65 (1H, d, *J*=2.8Hz), 3.46-3.42 (1H, m), 2.09-2.04 (1H, m), 1.78-1.73 (2H, m), 1.53-1.50 (1H, m), 1.38-1.35 (2H, m), 1.04-1.03 (1H, m), 0.87-0.83 (2H, m), 0.60-0.57 (1H, m), 0.43-0.40 (1H, m).

LC-MS: t_R = 11.28 $[M+H]^+$ = 334 (method 1)

Example 10, 11 and 12: 4-((3aS, 4S, 9bR)-8-cyclopropyl-2, 3, 3a, 4, 5, 9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (10); (+)-4-((3aS, 4R, 9bR)-8-cyclopropyl-2, 3, 3a, 4, 5, 9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (11a); (-)-4-((3aS, 4R, 9bR)-8-cyclopropyl-2, 3, 3a, 4, 5, 9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (11b) and 4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-propyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (12)

The following compounds were prepared using the same methodology as in intermediate compound 67 from **intermediate compound 47 & 48** for 1h. Solvent were evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give the exo-isomer 4-((3a*S*, 4*S*, 9b*R*)-8-cyclopropyl-2, 3, 3a, 4, 5, 9b-hexahydro-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid (4 mg) (**10**), the endo isomer 4-((3a*S*, 4*R*, 9b*R*)-8-cyclopropyl-2, 3, 3a, 4, 5, 9b-hexahydro-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid (**11**) (81 mg) and 4-((3a*S*, 4*R*, 9b*R*)-2, 3, 3a, 4, 5, 9b-hexahydro-8-propyl-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid (**12**) (13 mg) (Overall Yield: 47%).

Exo-isomer **10**: 4-((3a*S*, 4*S*, 9b*R*)-8-cyclopropyl-2, 3, 3a, 4, 5, 9b-hexahydro-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91(2H, d, *J*=8Hz), 7.48 (2H, d, *J*=8Hz), 6.80 (1H, s), 6.60 (1H, dd, *J*=1.6 & 8Hz), 6.55 (1H, d, *J*=8Hz), 5.75 (1H, s), 3.69 (1H, d, *J*=10Hz), 2.90-2.88 (1H, m), 2.19-2.17 (2H, m), 1.77-1.73 (1H, m), 1.67-1.65 (1H, m), 1.59-1.49 (3H, m), 1.32-1.30 (1H, m), 0.81-0.77 (2H, m), 0.52-0.49 (2H, m).

LC-MS: t_R = 10.35 $[M+H]^+$ = 334 (method 1)

Endo-isomer **11**: 4-((3a*S*, 4*R*, 9b*R*)-8-cyclopropyl-2, 3, 3a, 4, 5, 9b-hexahydro-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92(2H, d, *J*=8Hz), 7.53 (2H, d, *J*=8Hz), 6.77 (1H, s), 6.60 (2H, m), 5.57 (1H, s), 4.48 (1H, d, *J*=2Hz), 3.37-3.34 (1H, m), 2.44-2.41 (1H, m), 2.05-2.02 (1H, m), 1.77-1.70 (2H, m), 1.53-1.50 (1H, m), 1.38-1.34 (2H, m), 1.02-0.99 (1H, m), 0.81-0.79 (2H, m), 0.53-0.49 (2H, m).

LC-MS: t_R = 10.75 $[M+H]^+$ = 334 (method 1)

Separation of 592 mg of (+/-)-4-((3a*S*, 4*R*, 9b*R*)-8-cyclopropyl-2, 3, 3a, 4, 5, 9b-hexahydro-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid (**11**) by preparative chiral chromatography was carried out using Heptane/IPA (90:10) as eluents to yield:

195 mg of the enantiomer 1: (+)-4-((3a*S*, 4*R*, 9b*R*)-8-cyclopropyl-2, 3, 3a, 4, 5, 9b-hexahydro-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid (**11a**)

Preparative HPLC: t_R = 15

Optical Purity: 99.9% ee

$[\alpha]^{Na}_D$= + 34.8 (0.5, $CHCl_3$)

146 mg of the enantiomer 2: (-)-4-((3a*S*, 4*R*, 9b*R*)-8-cyclopropyl-2, 3, 3a, 4, 5, 9b-hexahydro-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid (**11b**)

Preparative HPLC: t_R =49

Optical Purity: 99.9% ee

$[\alpha]^{Na}_D$= - 38.6 (0.5, $CHCl_3$)

Endo-isomer propyl **12**: 4-((3a*S*, 4*R*, 9b*R*)-2, 3, 3a, 4, 5, 9b-hexahydro-8-propyl-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (2H, d, *J*=8Hz), 7.54 (2H, d, *J*=8Hz), 6.83 (1H, s), 6.71 (1H, d, *J*=8Hz), 6.61 (1H, d, *J*= 8Hz), 5.58 (1H, s), 4.50 (1H, d, *J*=2Hz), 3.39-3.36 (1H, m), 2.44-2.38 (3H, m), 2.08-2.03 (1H, m), 1.71-1.68 (1H, m), 1.55-1.48 (3H, m), 1.40-1.35 (2H, m), 1.03-0.98 (1H, m), 0.89-0.85 (3H, m).

LC-MS: t_R = 11.17 $[M+H]^+$ = 336 (method 1)

Example 13: 4-((3aS, 4R, 9bR)-8-fluoro-2, 3, 3a, 4, 5, 9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 49** for 1h. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the endo-isomer 4-((3a*S*, 4*R*, 9b*R*)-8-fluoro-2, 3, 3a, 4, 5, 9b-hexahydro-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid (121 mg. Yield:35%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (2H, d, *J*= 8.4Hz), 7.54 (2H, d, *J*=8Hz), 6.85 (1H, dd, *J*=2.4 & 10Hz), 6.75-6.68 (2H, m), 5.77 (1H, s), 4.55 (1H, d, *J*= 2.8Hz), 3.41-3.38 (1H, m), 2.47-2.45 (1H, m), 2.09-2.04 (1H, m), 1.70-1.67 (1H, m), 1.52-1.49 (1H, m), 1.41-1.36 (2H, m), 1.03-1.01 (1H, m).

LC-MS: t_R = 10.07 $[M+H]^+$ = 312 (method 1)

Example 14: 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-phenyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 50** (70 mg, 0.19 mmol) for 4 h. Purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give 45 mg of the title compound which was purified again by silica chromatography using dichloromethane and methanol (6%) to obtain 21 mg (30%) of the pure endo-isomer.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (2H, d, *J* = 8.4 Hz), 7.58-7.52 (4H, m), 7.38-7.32 (3H, m), 7.22 (2H, dd, *J* = 8 & 0.8 Hz), 6.77 (1H, d, *J* = 8.4 Hz), 5.97 (1H, s), 4.59 (1H, d, *J* = 2.4 Hz), 3.46 (1H, t, *J* = 7.2 Hz), 2.12-2.05 (1H, m), 1.85-1.78 (1H, m), 1.58-1.48 (1H, m), 1.50-1.44 (1H, m), 1.42-1.35 (2H, m), 1.07-1.00 (1H, m).

LC-MS: t_R = 11.25 $[M+H]^+$ = 370 (method 1)

Example 15: 4-((3aS, 4R, 9bR)-8-tert-butyl-2, 3, 3a, 4, 5, 9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 51** for 1h. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the endo-isomer 4-((3a*S*, 4*R*, 9b*R*)-8-*tert*-butyl-2, 3, 3a, 4, 5, 9b-hexahydro-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid (140 mg. Yield: 42%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (2H, d, *J*=8Hz), 7.54 (2H, d, *J*=8Hz), 7.01 (1H, d, *J*=2Hz), 6.93 (1H, dd, *J*=2.4 & 8.4Hz), 6.62 (1H, d, *J*= 8.4Hz), 5.58 (1H, s), 4.50 (1H, d, *J*= 2.8Hz), 3.41-3.38 (1H, m), 2.51-2.43 (1H, m), 2.11-2.06 (1H, m), 1.73-1.69 (1H, m), 1.55-1.50 (1H, m), 1.42-1.36 (2H, m), 1.23 (9H, s), 1.04-1.00 (1H, m).

LC-MS: t_R = 11.25 $[M+H]^+$ = 350 (method 1)

Example 16: (+)-4-((3aS,4R,9bR)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (16a) acid & (-)-4-((3aS,4R,9bR)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (16b)

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 52** (230 mg, 0.72 mmol) for 1 h. Purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give 90 mg (52%) of the racemic title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (2H, d, *J* = 8.4 Hz), 7.52 (2H, d, *J* = 8.4 Hz), 6,83 (1H, s), 6.72 (1H, dd, *J* = 8.0 & 1.6 Hz), 6.60 (1H, d, *J* = 8.4 Hz), 5.56 (1H, s), 4.48 (1H, d, *J* = 2.8 Hz), 3.37-3.30 (1H, m), 2.47-2.40 (2H, q, *J* = 7.6 Hz), 2.07-2.01 (1H, m), 1.70-1.66 (1H, m), 1.53-1.48 (1H, m), 1.38-1.33 (2H, m), 1.10 (1H, t, *J* = 8.0 Hz), 1.02-0.98 (1H, m).

LC-MS: t_R = 8.67 $[M+H]^+$= 322 (method 1)

Separation of 900 mg of (+/-)-4-((3a*S*,4*R*,9*bR*)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (**16**) by preparative chiral chromatography was carried out using Heptane/IPA (90:10) as eluents to yield:

369 mg of the enantiomer 1: (+)-4-((3a*S*,4*R*,9*bR*)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (**16a**)

Preparative HPLC: t_R = 12

Optical Purity: 99.9% ee

$[\alpha]^{Na}_D$= + 51.0 (0.5, $CHCl_3$)

339 mg of the enantiomer 2: (-)-4-((3a*S*,4*R*,9*bR*)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (**16b**)

Preparative HPLC: t_R =27

Optical Purity: 99.9% ee

$[\alpha]^{Na}_D$= - 49.9 (0.5, $CHCl_3$)

Example 17: 4-((3aS,4R,9bR)-8-carbamoyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 53** (300 mg, 0.72 mmol) for 1 h. Purification of the crude material using precipitation in acetonitrile, filtration and dryness gave 200 mg (67%) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (2H, d, *J* = 8.0 Hz), 7.61 (1H, s), 7.53 (2H, d, *J* = 8.8 Hz), 7.44 (1H, dd, *J* = 8.4 & 1.6 Hz), 6.85 (1H, s), 6.66 (1H, d, *J* = 8.4 Hz), 6,34 (1H, s), 4.64 (1H, d, *J* = 3.2 Hz), 3.39 (1H, t, *J* = 6.8 Hz), 2.44-2.41 (1H, m), 2.09-1.98 (1H, m), 1.89-1.84 (1H, m), 1.51-1.32 (3H, m), 1.06-0.99 (1H, m).

LC-MS: t_R = 4.58 $[M+H]^+$= 337 (method 1)

Example 18: 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-isopropyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 54** (236 mg, 0.70 mmol) for 1 h. Purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded 130 mg (55%) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (2H, d, *J* = 8.4 Hz), 7.53 (2H, d, *J* = 8.4 Hz), 6.85 (1H, d, *J* = 1.6 Hz), 6.76 (1H, dd, *J* = 8.0 & 2 Hz), 6.60 (1H, d, *J* = 8.4 Hz), 5.56 (1H, s), 4.48 (1H, d, *J* = 3.2 Hz), 3.40-3.30 (1H, m), 2.74-2.67 (1H, m), 2.44-1.37 (1H, m), 2.08-2.01 (1H, m), 1.72-1.65 (1H, m), 1.53-1.45 (1H, m), 1.40-1.31 (2H, m), 1.13 (6H, dd, *J* = 6.8 & 2 Hz).

LC-MS: t_R = 9.07 $[M+H]^+$= 336 (method 1)

Example 19: 4-((3aS,4R,9bR)-8-cyano-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 55** (180 mg, 0.57 mmol) for 1 h. Purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give 104 mg (58%) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (2H, d, *J* = 8.0 Hz), 7.51 (2H, d, *J* = 8.0 Hz), 7.42 (1H, s), 7.27 (1H, dd, *J* = 8.8 & 2.0 Hz), 6,88 (1H, s), 6.76 (1H, d, *J* = 8.8 Hz), 4.71 (1H, d, *J* = 3.2 Hz), 3.36 (1H, t, *J* = 6.8 Hz), 2.44-2.41 (1H, m), 2.05-1.99 (1H, m), 1.87-1.83 (1H, m), 1.42-1.34 (2H, m), 1.05-1.00 (1H, m).

LC-MS: t_R = 6.80 $[M+H]^+$= 319 (method 1)

Example 20: 4-((3aS,4R,9bR)-8-[(N-methylsulfonyl)amino]-)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 56** (239 mg, 0.62 mmol) for 1 h. Purification of the crude material by reverse C18 chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the title-compound slightly impure, which was purified again using reverse C_{18} chromatography eluting with water (0.1% HCOOH) and acetonitrile (0.1% HCOOH) to give 99 mg of the pure title endo-isomer.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (2H, d, *J* = 8.4 Hz), 7.53 (2H, d, *J* = 8.4 Hz), 6.91 (1H, d, *J* = 2 Hz), 6.80 (1H, dd, *J* = 2.4 & 8.4 Hz), 6.67 (1H, d, *J* = 8.8 Hz), 5.82 (1H, brs), 4.54 (1H, d, *J* = 2.8 Hz), 3.41-3.36 (1H, m), 2.84 (3H, s), 2.50-2.41 (1H, m), 2.12-2.02 (1H, m), 1.71-1.64 (1H, m), 1.56-1.46 (1H, m), 1.42-1.34 (2H, m), 1.06-0.98 (1H, m).

LC-MS: t_R =7.55 $[M+H]^+$= 387 (method 1)

Example 21: 4-((3aS,4R,9bR)-8-[(N-methyl-N-methylsulfonyl)amino]-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 57** (250 mg, 0.62 mmol) for 1 h. Purification of the crude material by reverse C18 chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave 162 mg of the title compound, which was triturated in acetonitrile-drops of water, filtered and dried to obtain 83 mg the pure title endo-isomer as a solid (Yield: 33%)

1H NMR (400 MHz, CD_3OD) δ 8.01 (2H, d, *J* = 8 Hz), 7.56 (2H, d, *J* = 8.4 Hz), 7.12 (1H, d, *J* = 1.6 Hz), 6.99 (1H, dd, *J* = 2.4 & 8.4 Hz), 6.70 (1H, d, *J* = 8.4 Hz), 4.62 (1H, d, *J* = 3.2 Hz), 3.50-3.45 (1H, m), 3.24 (3H, s), 2.87 (3H, s), 2.57-2.50 (1H, m), 2.22-2.12 (1H, m), 1.85-1.77 (1H, m), 1.71-1.61 (1H, m), 1.57-1.40 (2H, m), 1.19-1.10 (1H, m).

LC-MS: t_R =8.38 $[M+H]^+$= 401 (method 1)

Example 22: 3-((3aS,4R,9bR)-8-bromo-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 58** (110 mg, 0.29 mmol) for 1 h. Purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave 48 mg of the title compound which was precipitated in hexane, filtered and dried in vacuum to obtain 39 mg (35%) of the pure endo-isomer.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.95 (1H, brs), 8.07 (1H,s), 7.83 (1H, d, *J* = 7.6 Hz), 7.63 (1H, d, *J* = 7.6 Hz), 7.47 (1H, t, *J* = 7.2 Hz), 7.14 (1H, d, *J* = 1.6 Hz), 7.02 (1H, d, *J* = 8.4 & 2.0 Hz), 6.65 (1H, d, *J* = 8.4 Hz), 6.03 (1H, s), 4.53 (1H, d, *J* = 2.8 Hz), 3.39-3.34 (1H, m), 2.45-2.39 (1H, m), 2.08-2.01 (1H, m), 1.70-1.66 (1H, m), 1.50-1.44 (1H, m), 1.41-1.36 (2H, m), 1.01-0.97 (1H, m).

LC-MS: t_R = 8.52 $[M+H]^+$= 372/374 (method 1)

Example 23: 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-7,8-dimethoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 59** (0.69 mmol, 243 mg) for 1 h. Purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give 63 mg (26%) of the title pure endo-isomer.

^{1}H NMR (400 MHz, DMSO-d_6) : δ 7.92 (2H, d, *J* = 8.4 Hz), 7.54 (2H, d, *J* = 8 Hz), 6.60 (1H, s), 6.38 (1H, s), 5.47 (1H, s), 4.47 (1H, d, *J* = 2.4 Hz), 3.66 (3H, s), 3.65 (3H, s), 3.35-3.30 (1H, m), 2.50-2.41 (1H, m), 2.05-1.95 (1H, m), 1.74-1.68 (1H, m), 1.55-1.48 (1H, m), 1.39-1.32 (1H, m), 1.04-0.97 (1H, m)

LC-MS: t_R = 8.72 $[M+H]^+$= 354 (method 1)

Example 24 and 25: 4-((3aS,4R,9bR)-7-(trifluoromethyl)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (24) and 4-((3aS,4R,9bR)-9-(trifluoromethyl)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (25)

The following compounds were prepared using the same methodology as in intermediate compound 67 from the **intermediate mixture of compounds 60 and 61** (1.27 mmol, 475 mg) for 1h. Solvent was evaporated and the crude material (a mixture of endo-8,9-disustituted and endo-7,8-disustituted regioisomers) was purified by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents. Only high purity fractions of each regioisomer were collected giving two enriched fractions with each regioisomer, which were purified again by precipitation in hexane to give 30.7 mg of 4-((3aS,4R,9bR)-7-(trifluoromethyl)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (**24**) and 55.6 mg of 4-((3aS,4R,9bR)-9-(trifluoromethyl)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (**25**).(Overall yield=18%).

4-((3aS,4R,9bR)-7-(trifluoromethyl)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (endo-7,8-disustituted regioisomer **24**)

^{1}H NMR (400 MHz, DMSO-d_6) : δ 7.93 (2H, d, *J* = 8.4 Hz), 7.53 (2H, d, *J* = 8.4 Hz), 6.96 (2H, s), 5.91 (1H, s), 4.30 (1H, d, *J* = 3.6 Hz), 3.83-3.77 (1H, m), 2.67-

2.63 (1H, m), 2.31(3H, d, J = 3.2 Hz), 2.21-2.15 (1H, m), 1.58-1.42 (2H, m), 1.33-1.15 (2H, m), 1.04-0.98 (1H, m).

LC-MS: t_R = 11.03 $[M+H]^+$= 376 (method 1)

4-((3aS,4R,9bR)-9-(trifluoromethyl)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (endo-8,9-disustituted regioisomer **25**)

^{1}H NMR (400 MHz, DMSO-d_6) : δ 7.94 (2H, d, *J* = 8.4 Hz), 7.54 (2H, d, *J* = 8 Hz), 7.05 (2H, d, *J* = 9.2 Hz), 6.09 (1H, s), 4.56 (1H, d, *J* = 3.2 Hz), 3.42-3.39 (1H, m), 2.27 (3H, d, *J* = 1.2 Hz), 2.14-2.04 (1H, m), 1.79-1.72 (1H, m), 1.53-1.34 (3H, m), 1.07-0.99 (1H, m).

LC-MS: t_R = 11.12 $[M+H]^+$= 376 (method 1)

Example 26: 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-7-methoxy-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 62** (0.48 mmol, 162 mg) for 1h. Purification of the crude material (1:6 mixture of endo-8,9-disustituted & endo-7,8-disustituted regioisomers) by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents only allowed to obtain 62 mg of the major title endo-7,8-disustituted regioisomer (**26**) (Yield: 38%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (2H, d, *J* = 8.4 Hz), 7.54 (2H, d, *J* = 8.4 Hz,), 6.75 (1H, s), 6.32 (1H, s) , 5.59 (1H, s), 4.51 (1H, d, *J* = 2.4 Hz), 3.67 (3H, s), 2.50-2.37 (m, 2H), 2.01 (3H, s), 1.99-1.93 (1H, m), 1.73-1.67 (1H, m), 1.57-1.45 (1H, m), 1.39-1.31 (2H, m), 1.03-0.95 (1H, m).

LC-MS: t_R = 10.52 $[M+H]^+$= 338 (method 1)

Example 27: 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-6,8-dimethyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 63** (1.44 mmol, 460 mg) for 1h. Purification of the crude material using reverse C_{18} chromatography

using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give 280 mg of the title compound which was precipitated in acetonitrile/drops of water, filtered and dried in vacuum to obtain 193 mg (42%) of the pure endo-isomer.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.93 (2H, d, *J* = 8 Hz), 7.59 (2H, d, *J* = 8.4 Hz), 6.73 (1H, s), 6.64 (1H, s), 4.59 (1H, s), 4.53 (1H, d, *J* = 2.4 Hz), 3.41-3.33 (1H, m), 2.48-2.40 (1H, m), 2.14 (3H, s), 2.11 (3H, s), 2.07-1.99 (1H, m), 1.76-1.69 (1H, m), 1.56-1.46 (1H, m), 1.38-1.30 (2H, m), 1.04-0.96 (1H, m).

LC-MS: t_R = 11.15 $[M+H]^+$= 322 (method 1)

Example 28: 4-((3aS,4R,9bR)-9-chloro-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 64** (0.26 mmol, 88 mg) for 1h. Purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave 28 mg of the pure endo-isomer (Yield: 31%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.93 (2H, d, *J* = 8 Hz), 7.53 (2H, d, *J* = 8.4 Hz), 6.89 (1H, d, *J* = 8.4 Hz), 6.69 (1H, d, *J* = 8.4 Hz), 5.76 (1H, s), 4.31 (1H, d, *J* = 3.6 Hz), 3.57-3.51 (1H, m), 2.65-2.57 (1H, m), 2.47-2.39 (1H, m), 2.21 (3H, s), 1.60-1.44 (2H, m), 1.34-1.18 (2H, m), 1.06-1.00 (m, 1H).

LC-MS: t_R = 11.15 min $[M+H]^+$= 342 (method 1)

Example 29: 4-((3aS,4R,9bR)-7-chloro-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 65** (0.17 mmol, 58 mg) for 1h. Purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded 28 mg of the pure endo-isomer (Yield: 47%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.93 (2H, d, *J* = 8.4 Hz), 7.53 (2H, d, *J* = 8.4 Hz), 6.98 (1H, s), 6.75 (1H, s), 5.92 (1H, s), 4.53 (1H, d, *J* = 3.2 Hz), 3.32 (1H,

m), 2.48-2.40 (1H, m), 2.17 (3H, s), 2.08-1.99 (1H, m), 1.76-1.69 (1H, m), 1.53-1.44 (1H, m), 1.41-1.33 (2H, m), 1.05-0.97 (1H, m).

LC-MS: t_R = 11.12 $[M+H]^+$= 342 (method 1)

Example 30 : ***4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-5,8-dimethyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid***

To a solution of methyl 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-5,8-dimethyl-1H-cyclopenta[c]quinolin-4-yl)benzoate (**intermediate compound 68**) (50 mg, 0.15 mmol) in THF (5 mL) was added 1M LiOH (0.30 mL, 0.30 mmol). The reaction mixture was stirred 16 h at room temperature. Total conversion was not achieved, then 1N LiOH (0.3 mmol) was added and was stirred for 48 h at room temperature. Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using an elution of 8% MeOH in DCM afforded the title compound (32 mg. Yield: 66%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (2H, d, *J*= 8Hz), 7.37 (2H, d, *J*= 8Hz), 6.91 (1H, s), 6.87 (1H, d, *J*= 8Hz), 6.69 (1H, d, *J*= 8.4Hz), 4.42 (1H, d, *J*= 4.4Hz), 3.26-3.24 (1H, m), 2.63 (3H, s), 2.46-2.38 (1H, m), 2.19 (3H, s), 2.01-1.96 (1H, m), 1.79-1.74 (1H, m), 1.60-1.55 (1H, m), 1.38-1.35 (1H, m), 1.29-1.21 (1H, m), 1.19-1.16 (1H, m).

LC-MS: t_R = 11.20 $[M+H]^+$= 322 (method 1)

Example 31: 4-((3aS,4R,9bR)-5-acetyl-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 69** (110 mg, 0.30 mmol) using 1N LiOH (3 eq.) for 16h. Solvent was evaporated and the crude residue was dissolved in ethyl acetate and water. Aqueous layer was separated and acidified using 1N HCl until pH 2. Ethyl acetate was added and the organic layer was extracted, washed with brine and dried over anhydrous sodium sulphate, filtered and concentrated to obtain 113 mg of the title compound, which was triturated

using hexane. The white solid was filtered and washed with hexane, dried over vacuum to afford 70 mg of the pure endo-isomer (67%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.4 Hz), 7.15 (1H, s), 7.05-7.02 (4H, m), 6.16 (1H, brs), 3.16-3.03 (2H, m), 2.39 (3H, s), 2.20 (3H, s), 2.18-2.10 (1H, m), 1.94-1.88 (1H, m), 1.52-1.37 (3H, m), 0.88-0.81 (1H, m).

LC-MS: t_R = 9.37 min $[M+H]^+$= 350 (method 1)

Example 32: 4-((6R, 6aS, 9aR)-6, 6a, 7, 8, 9, 9a-hexahydro-2-methyl-5H-cyclopenta[c][1,5]naphthyridin-6-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 71** for 1h. Solvent was evaporated. Due to the insolubility of the crude material in all solvents it was purified by precipitation and filtration to give the endo-isomer 4-((6*R*, 6a*S*, 9a*R*)-6,6a,7,8,9,9a-hexahydro-2-methyl-5*H*-cyclopenta[*c*][1,5]naphthyridin-6-yl)benzoic acid (15 mg. Yield: 37%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (2H, d, *J*=8.4Hz), 7.56 (2H, d, *J*=8.4Hz), 6.93 (1H, d, *J*=8Hz), 6.78 (1H, d, *J*=8.4Hz), 5.81 (1H, s), 4.60 (1H, d, *J*=2.8Hz), 3.39-3.31 (1H, m), 2.49(1H, m), 2.30 (3H, s), 2.08-1.97 (2H, m), 1.51-1.44 (1H, m), 1.40-1.35 (2H, m), 1.08-1.00 (1H, m).

LC-MS: t_R = 5.13 $[M+H]^+$ = 309 (method 1)

Example 33: 4-((6R,6aS,9aR)-6,6a,7,8,9,9a-hexahydro-2-methyl-5H-cyclopenta[c][1,8]naphthyridin-6-yl)benzoic acid

To a solution of **intermediate compound 72** (3.23 mmol, 0.70 g) in EtOH : THF (1:1, 18 mL), 10 % Pd/C (10% w/w, 10 mg) was added and the mixture was hydrogenated at room temperature for 4 h. HPLC analysis showed total conversion. Reaction mixture was filtered and filter washed by THF. Solvent was evaporated and purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave 11.7 mg of the title compound as a solid. (Yield= 6%)

1H NMR (400 MHz, DMSO-d_6) δ 7.99 (1H, brs), 7.89 (2H, d, *J* = 8.4 Hz), 7.72 (1H, dd, *J* = 1.6 & 9.2 Hz), 7.39 (1H, d, *J* = 8 Hz), 7.20 (1H, d, *J* = 8.8 Hz), 5.03 (1H, d, *J* = 3.6 Hz), 4.86-4.82 (1H, m), 2.91-2.82 (1H, m), 2.34-2.25 (1H, m), 2.20 (3H, s), 2.21-2.12 (1H, m), 1.57-1.31 (3H, m), 1.31-1.22 (1H, m).

LC-MS: t_R =4.68 $[M+H]^+$= 309 (method 1)

Example 34: 2-(4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)phenyl)acetic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 74** (74 mg, 0.22 mmol) using 1M LiOH (0.33 mL, 0.33 mmol) for 16 h. Purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the endo-isomer 2-(4-((3a*S*, 4*R*, 9b*R*)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1*H*-cyclopenta[*c*]quinolin-4-yl)phenyl)acetic acid (32 mg. Yield: 45%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35 (2H, d, *J*= 8Hz), 7.22 (2H, d, *J*=8.4Hz), 6.82 (1H, s), 6.68 (1H, d, *J*=8Hz), 6.57 (1H, d, *J*=8Hz), 5.43 (1H, s), 4.39 (1H, d, *J*=2.4Hz), 3.53 (2H, s), 2.41-2.38 (1H, m), 2.15 (3H, s), 2.06-20.1 (1H, m), 1.71-1.67 (1H, m), 1.59-1.53 (1H, m), 1.40-1.35 (2H, m), 1.09-1.04 (1H, m).

LC-MS: t_R = 9.85 $[M+H]^+$ = 322 (method 1)

Example 35: 3-(4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)phenyl)propanoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 75** for 1h. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the endo-isomer 3-(4-((3a*S*, 4*R*, 9b*R*)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1*H*-cyclopenta[*c*]quinolin-4-yl)phenyl)propanoic acid (10 mg. Yield: 25%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.32 (2H, d, *J*= 8Hz), 7.19 (2H, d, *J*=8Hz), 6.81 (1H, s), 6.68 (1H, d, *J*= 8Hz), 6.57 (1H, d, *J*=8Hz), 5.42 (1H, s), 4.37 (1H, d, *J*=2.4Hz), 2.81 (2H, t, *J*=7.6Hz), 2.38-2.33 (1H, m), 2.15 (3H, s), 2.06-2.01 (1H, m), 1.70-1.66 (1H, m), 1.58-1.53 (1H, m), 1.40-1.34 (2H, m), 1.08-1.05 (1H, m).

LC-MS: t_R = 10.07 $[M+H]^+$ = 336 (method 1)

Example 36: 4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-2-methylbenzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 76** for 1h. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give the endo-isomer 4-((3a*S*, 4*R*, 9b*R*)-2,3,3a,4,5,9b-hexahydro-8-methyl-1*H*-cyclopenta[*c*]quinolin-4-yl)-2-methylbenzoic acid (10 mg. Yield: 24%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (1H, d, *J*=7.6Hz), 7.34-7.32 (2H, m), 6.83 (1H, s), 6.70 (1H, d, *J*=8Hz), 6.60 (1H, d, *J*=8.4Hz), 5.51 (1H, s), 4.42 (1H, d, *J*=2.4Hz), 3.37-3.33 (1H, m), 2.53 (3H, s), 2.45-2.42 (1H, m), 2.15 (3H, s), 2.07-2.05 (1H, m), 1.71-1.67 (1H, m), 1.56-1.50 (1H, m), 1.40-1.35 (2H, m), 1.06-1.02 (1H, m).

LC-MS: t_R = 10.63 $[M+H]^+$ = 322 (method 1)

Example 37: (+/-)-4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 77** for 1h. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents (52% ACN) to give the endo-isomer (+/-)-4-((3a*S*, 4*R*, 9b*R*)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1*H*-cyclopenta[*c*]quinolin-4-yl)-3-methylbenzoic acid (62 mg. Yield: 53%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (1H, d, *J*=8Hz), 7.75 (1H, s), 7.68 (1H, d, *J*=8.4Hz), 5.38 (1H, s), 4.61 (1H, d, *J*=2.8Hz), 3.39-3.35 (1H, m), 2.46-2.43 (1H,

m), 2.37 (3H, s), 2.16 (3H, s), 2.10-2.05 (1H, m), 1.69-1.58 (2H, m), 1.41-1.36 (2H, m), 0.10-0.96 (1H, m).

LC-MS: t_R = 10.72 $[M+H]^+$ = 322 (method 1)

Separation of 400 mg of (+/-)-4-((3a*S*, 4*R*, 9b*R*)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1*H*-cyclopenta[*c*]quinolin-4-yl)-3-methylbenzoic acid (**37**) by preparative chiral chromatography was carried out using Heptane/IPA/TFA (95:5:0.1) as eluents to yield:

155 mg of the enantiomer 1: (+)-4-((3a*S*, 4*R*, 9b*R*)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1*H*-cyclopenta[*c*]quinolin-4-yl)-3-methylbenzoic acid (**37a**)

Preparative HPLC: t_R = 16

Optical Purity: 99.9% ee

$[\alpha]^{Na}_D$= + 23.4 (0.6, $CHCl_3$)

167 mg of the enantiomer 2 (**37b**): (-)-4-((3a*S*, 4*R*, 9b*R*)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1*H*-cyclopenta[*c*]quinolin-4-yl)-3-methylbenzoic acid (**37b**)

Preparative HPLC: t_R =27

Optical Purity: 99.9% ee

Example 38: 4-((3aS, 4S, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 79** (2.22 mmol, 746 mg). It was necessary 72 h to complete the reaction. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave endo-isomer (513 mg) and exo-isomer title compound (10 mg) (Overall yield: 76%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (2H, m), 7.46 (1H, d, *J* = 8.8Hz), 6.87 (1H, s), 6.69 (1H, dd, *J* = 8.4 & 1.6 Hz), 5.63 (1H, s), 3.98 (1H, d, *J* = 9.6 Hz), 2.92-2.90 (1H, m), 2.38 (3H, s), 2.33-2.31 (1H, m), 2.29-2.18 (1H, m), 2.15 (3H, s), 1.66-1.54 (4H, m), 1.20-1.18 (1H, m).

LC-MS: t_R = 8.05 $[M+H]^+$ = 322 (method 1)

Example 39: 4-((3aS, 4R, 9bR)-8-chloro-2, 3, 3a, 4, 5, 9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 80** for 1h. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the endo-isomer 4-((3a*S*, 4*R*, 9b*R*)-8-chloro-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[*c*]quinolin-4-yl)-3-methylbenzoic acid (21 mg. Yield: 33%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (1H, d, *J*=8.4Hz), 7.75 (1H, s), 7.65 (1H, d, *J*=8Hz), 7.04 (1H, d, *J*=2Hz), 6.91 (1H, dd, *J*=2.4Hz & 8.8Hz), 6.70 (1H, d, *J*=8.4Hz), 5.84 (1H,s), 4.67 (1H, d, *J*=2.8Hz), 3.43-3.40 (1H, m), 2.49-2.45 (1H, m), 2.38 (3H, s), 2.12-2.06 (1H, m), 1.70-1.67 (1H, m), 1.59-1.54 (1H, m), 1.42-1.38 (2H, m), 1.00-0.98 (1H, m).

LC-MS: t_R = 10.93 $[M+H]^+$ = 342 (method 1).

Example 40: 4-((3aS, 4R, 9bR)-8-fluoro-2, 3, 3a, 4, 5, 9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 81** for 1h. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the endo-isomer 4-((3a*S*,4*R*,9b*R*)-8-fluoro-2, 3, 3a, 4, 5, 9b-hexahydro-1*H*-cyclopenta[*c*]quinolin-4-yl)-3-methylbenzoic acid (4.7 mg. Yield: 8%)

^{1}H NMR (400 MHz, CD_3OD) δ 7.85 (1H, d, *J*=8Hz), 7.82 (1H, s), 7.73 (1H, d, *J*=8Hz), 6.80 (1H, dd, J= 2.8Hz & 10Hz), 6.68-6.65 (2H, m), 4.70 (1H, d, *J*=2.4Hz), 3.45-3.43 (1H, m), 2.58-2.55 (1H, m), 2.42 (3H, s), 2.20-2.15 (1H, m), 1.78-1.69 (2H, m), 1.57-1.45 (2H, m), 1.13-1.10 (1H, m).

LC-MS: t_R = 10.38 $[M+H]^+$ = 326 (method 1)

Example 41: 4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 82** for 1h. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the endo-isomer 4-((3a*S*, 4*R*, 9b*R*)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methoxy-1*H*-cyclopenta[*c*]quinolin-4-yl)-3-methylbenzoic acid (71 mg. Yield: 55%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (1H, d, *J*=8Hz), 7.74 (1H, s), 7.69 (1H, d, *J*=8Hz), 6.65-6.62 (2H, m), 6.54 (1H, dd, *J*=2.8Hz & 8.4Hz), 5.23 (1H, s), 4.57 (1H, d, *J*=2.8Hz), 3.65 (3H, s), 3.41-3.39 (1H, m), 2.50-2.49 (1H, m), 2.37 (3H, s), 2.11-2.06 (1H, m), 1.68-1.59 (2H, m), 1.41-1.35 (2H, m), 0.99-0.96 (1H, m).

LC-MS: t_R = 9.35 $[M+H]^+$ = 338 (method 1)

Example 42: 4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methoxy-5-methyl-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid

To a solution of 4-((3a*S*, 4*R*, 9b*R*)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methoxy-1*H*-cyclopenta[*c*]quinolin-4-yl)-3-methylbenzoic acid **Example 41** (32 mg, 0.098 mmol) in dry methanol (2 mL) anhydrous THF (0.5 mL) was added formaldehyde (0.04 mL, 0.49 mmol, 37 % in water).The reaction mixture was stirred overnight at room temperature. Then, $NaBH_3CN$ (28 mg, 0.44 mmol) was added and the reaction was stirred for 3 h at room temperature. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the endo-isomer 4-((3a*S*, 4*R*, 9b*R*)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methoxy-5-methyl-1*H*-cyclopenta[*c*]quinolin-4-yl)-3-methylbenzoic acid (23 mg. Yield: 67%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76-7.74 (2H, m), 7.45 (1H, d, *J*= 8.4Hz), 6.79 (1H, d, *J*=9.2Hz), 6.69-6.67 (2H, m), 4.55 (1H, d, *J*=3.2Hz), 3.68 (3H, s), 2.57 (3H, s), 2.39 (3H, s), 2.36-2.32 (1H, m), 2.00-1.94 (2H, m), 1.53-1.50 (1H, m), 1.38-1.34 (2H, m), 1.07-1.05 (1H, m).

LC-MS: t_R = 10.62 $[M+H]^+$ = 352 (method 1)

Example 43: 4-((3aS, 4R, 9bR)-8-cyclopropyl-2, 3, 3a, 4, 5, 9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 83** for 1h. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the endo isomer 4-((3a*S*, 4*R*, 9b*R*)-8-cyclopropyl-2, 3, 3a, 4, 5, 9b-hexahydro-1*H*-cyclopenta[*c*]quinolin-4-yl)-3-methylbenzoic acid (28 mg: Yield: 31%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (1H, d, *J*=7.2Hz), 7.74 (1H, s), 7.66 (1H, d, *J*=8.4Hz), 6.77 (1H, s), 6.59 (2H, m), 5.38 (1H, s), 4.61 (1H, s), 2.37 (3H, s), 2.10-2.05 (1H, m), 1.80-1.75 (1H, m), 1.67-1.58 (2H, m), 1.41-1.37 (2H, m), 1.00-0.97 (1H, m), 0.81-0.79 (2H, m), 0.51 (2H, m).

LC-MS: t_R = 11.07 $[M+H]^+$ = 348 (method 1)

Example 44: 4-((3aS, 4R, 9bR)-8-(cyclopropylmethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 85** (0.08 mmol, 30 mg). Solvent was evaporated and the residue was purified by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents, to give 29 mg of the title compound, which was triturated in hexane, filtered and dried to obtain 18 mg the pure title compound as a solid (Yield: 60%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (1H, d, *J* = 8.0), 7.83 (1H, s), 7.73 (1H, s), 7.67 (1H, d, *J* = 8.0 Hz), 6.62-6.59 (2H, m), 6.52 (1H, dd, *J* = 8.8 & 2.4Hz), 5.21 (1H, s), 4.55 (1H, d, *J* = 2.4 Hz), 3.67 (2H, d, *J* = 6.8 Hz), 2.49-2.43 (1H, m), 2.36 (3H, s), 2.09-2.04 (1H, m), 1.66-1.57 (2H, m) 1.40-1.34 (2H, m), 1.17-1.13 (1H, m), 0.98-0.95 (1H, m), 0.54-0.50 (2H, m), 0.28-0.26 (2H, m).

LC-MS: t_R = 8.18 $[M+H]^+$= 378 (method 1)

Example 45: 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-isopropoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 87** (0.34 mmol, 132 mg). The mixture

was stirred at r.t. until HPLC showed no starting material left. It was necessary 48 h and an additional 1.1 mL of 1M LiOH to complete the reaction. After that, the solvent was removed in vacuum and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave 84.6 mg of the pure title endo-isomer (Yield: 66%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (1H, d, *J* = 8 Hz), 7.74 (1H, s), 7.67 (1H, d, *J* = 8.4 Hz), 6.62-6.59 (2H, m), 6.52 (1H, dd, *J* = 8.8 & 2.8 Hz), 5.22 (1H, s), 4.57 (1H, d, *J* = 2.8 Hz), 4.34-4.39 (1H, m), 3.40-3.36 (1H, m), 2.50-2.42 (1H, m), 2.37 (3H, s), 2.13-2.04 (1H, m), 1.67-1.57 (2H, m), 1.44-1.32 (2H, m),1.21 (3H, d, *J* = 1.2 Hz), 1.19 (3H, d, *J* = 1.6 Hz), 1.02-0.94 (1H, m).

LC-MS: t_R = 8.15 $[M+H]^+$= 366 (method 1)

Example 46: 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-isopropoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 88** (0.04 mmol, 17 mg,). It was necessary 40 h and an additional 0.13 mL of 1M LiOH to complete the reaction. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave 9.9 mg of the pure title exo-isomer (Yield: 61%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77-7.75 (1H, m), 7.51-7.49 (1H, m), 6.66 (1H, d, *J* = 2 Hz), 6.57-6.50 (2H, m), 5.46 (1H, s), 4.39-4.33 (1H, m), 3.94 (1H, d, *J* = 10 Hz), 2.96-2.90 (1H, m), 2.40 (3H, s), 2.35-2.28 (1H, m), 2.24-2.20 (1H, m), 1.66-1.52 (4H, m), 1.20 (6H, d, *J* = 6 Hz), 1.2-1.14 (1H, m).

LC-MS: t_R = 7.58 $[M+H]^+$= 366 (method 1)

Example 47: 3-chloro-4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 89** for 1 h but using Pt_2O (2.5 mmol%, 4 mg). Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the endo-isomer 3-chloro-4-

((3a*S*, 4*R*, 9b*R*)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid (225mg. Yield: 75%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (1H, d, *J*=8Hz), 7.91 (1H, s), 7.81 (1H, d, *J*=8Hz), 6.85 (1H, s), 6.72 (1H, d, *J*=8.4Hz), 6.59 (1H, d, *J*=8Hz), 5.55 (1H, s), 4.74 (1H, d, *J*= 2.8Hz), 3.37-3.32 (1H, m), 2.60-2.57 (1H, m), 2.16 (3H, s), 2.10-2.05 (1H, m), 1.71-1.68 (1H, m), 1.58-1.53 (1H, m), 1.43-1.37 (2H, m), 0.99-0.95 (1H, m).

LC-MS: t_R = 11.32 $[M+H]^+$ = 342 (method 1)

Example 48: 4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methoxybenzoic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 91** (80 mg, 0.22 mmol). Total conversion was not achieved, 1 N LiOH (0.88 mmol) was added and was stirred for 48 h at room temperature. Solvent was evaporated and purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the endo-isomer 4-((3a*S*, 4*R*, 9b*R*)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methoxy-1*H*-cyclopenta[*c*]quinolin-4-yl)-3-methoxybenzoic acid (66 mg. Yield: 84%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (1H, d, *J*=8Hz), 7.56 (1H, d, *J*=8Hz), 7.47 (1H, s), 6.63-6.59 (2H, m), 6.52 (1H, dd, *J*=2.8 & 8.8Hz), 5.14 (1H, s), 4.61 (1H, d, *J*=2.8Hz), 3.84 (3H, s), 3.63 (3H, s), 3.33-3.29 (1H, m), 2.55-2.53 (1H, m), 2.06-2.01 (1H, m), 1.65-1.61 (1H, m), 1.55-1.49 (1H, m), 1.36-1.34 (2H, m), 0.98-0.94 (1H, m).

LC-MS: t_R = 8.32 $[M+H]^+$ = 354 (method 1)

Example 49: 4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-3-methoxybenzoic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 93** (135 mg, 0.39 mmol). The reaction mixture was stirred for 48 hours at room temperature. Solvent was evaporated and purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded

the endo-isomer 4-((3a*S*, 4*R*, 9b*R*)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1*H*-cyclopenta[*c*]quinolin-4-yl)-3-methoxybenzoic acid (82 mg. Yield: 62%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63 (1H, d, *J*=8Hz), 7.59 (1H, d, *J*=8.8Hz), 7.49 (1H, s), 6.82 (1H, s), 6.69 (1H, d, *J*=7.6Hz), 6.59 (1H, d, *J*=8Hz), 5.32 (1H, s), 4.68 (1H, d, *J*=2.8Hz), 3.86 (3H, s), 3.32-3.29 (1H, m), 2.56-2.53 (1H, m), 2.15 (3H, s), 2.06-2.01 (1H, m), 1.69-1.65 (1H, m), 1.53-1.50 (1H, m), 1.39-1.34 (2H, m), 0.97-0.95 (1H, m).

LC-MS: t_R = 10.00 $[M+H]^+$ = 338 (method 1)

Example 50: 3-bromo-4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 95** (54 mg, 0.135 mmol). Total conversion was not achieved, 1N LiOH (0.405 mmol) was added and was stirred for 6 hours at room temperature. Solvent was evaporated and purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the endo-isomer 3-bromo-4-((3a*S*, 4*R*, 9b*R*)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid (18 mg. Yield: 34%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (1H, s), 7.95 (1H, d, *J*=7.2Hz), 7.75 (1H, d, *J*=7.6Hz), 6.85 (1H, s), 6.72 (1H, d, *J*=7.6Hz), 6.58 (1H, d, *J*=8.4Hz), 5.57 (1H, s), 4.67 (1H, s), 3.39 (1H, m), 2.61-2.56 (1H, m), 2.16 (3H, s), 2.11-2.06 (1H, m), 1.71-1.69 (1H, m), 1.57-1.54 (1H, m), 1.41-1.37 (2H, m), 0.98-0.96 (1H, m).

LC-MS: t_R = 10.87 $[M+H]^+$ = 386-388 (method 1)

Example 51: 3-bromo-4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 97** (129 mg, 0.31 mmol). Total conversion was not achieved, 1N LiOH (0.3mmol) was added and it was stirred for 48 hours at room temperature. Solvent was evaporated and purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the endo-isomer 3-bromo-

4-((3a*S*, 4*R*, 9b*R*)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid (93 mg. Yield:75%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (1H, s), 7.97 (1H, dd, *J*= 2 & 8.4Hz), 7.79 (1H, d, *J*=8Hz), 6.65-6.62 (2H, m), 6.57 (1H, dd, *J*=2.8 & 8.4Hz), 5.44 (1H, s), 4.63 (1H, d, *J*=3.2Hz), 3.66 (3H, s), 3.41-3.36 (1H, m), 2.61-2.52 (1H, m), 2.12-2.09 (1H, m), 1.70-1.66 (1H, m), 1.60-1.55 (1H, m), 1.44-1.38 (2H, m), 0.99-0.95 (1H, m).

LC-MS: t_R = 9.87 $[M+H]^+$ = 402-404 (method 1).

Example 52: 3-ethyl-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzonitrile

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 98** (0.22 mmol, 71 mg). Purification of the crude material by flash chromatography on silica gel using an elution of 40% ethylacetate in hexanes afforded a mixture of exo/endo isomers (1:5.3) as a solid (45 mg, 65%), which was purified again by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave 20.4 mg of the title pure endo-isomer (Yield: 29%).

1H NMR (400 MHz, DMSO-d6) δ 7.77 (1H, d, J = 8.8 Hz), 7.68 (2H, m), 6.83 (1H, s), 6.71 (1H, dd, J = 8 & 2 Hz), 6.57 (1H, d, J = 7.6 Hz), 5.44 (1H, s), 4.66 (1H, d, J = 2.8 Hz),3.32-3.30 (1H, m), 2.83-2.73 (1H, m), 2.70-2.60 (1H, m), 2.41-2.32 (1H, m), 2.16 (3H, s), 2.11-2.02 (1H, m), 1.72-1.53 (2H, m), 1.45-1.33 (2H, m), 1.18 (3H, t, J = 7.6 Hz), 1.01-0.93 (1H, m).

LC-MS: t_R = 10.98 $[M+H]^+$= 317 (method 1)

Example 53: 3-ethyl-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 99** (0.31 mmol, 104 mg). Purification of the crude material (1:6 mixture of regioisomers exo/endo) by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave 55.5 mg of the pure endo-compound. (Yield: 55%)

1H NMR (400 MHz, DMSO-d6) δ 7.78 (2H, m), 7.70 (1H, d, J = 8.4 Hz), 6.83 (1H, s), 6.70 (1H, dd, J = 8 & 1.6 Hz), 6.58 (1H, d, J = 8 Hz), 5.39 (1H, s), 4.66 (1H, d, J = 2.4 Hz), 3.32-3.30 (1H, m), 2.83-2.73 (1H, m), 2.70-2.60 (1H, m), 2.42-2.35 (1H, m), 2.19 (3H, s), 2.11-2.02 (1H, m), 1.72-1.57 (2H, m), 1.44-1.32 (2H, m), 1.19 (3H, t, J = 7.6 Hz), 1.04-0.96 (1H, m).

LC-MS: t_R = 10.53 [M+H]+= 336 (method 1)

Example 54 and 55: 3-ethyl-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (54) and 3-ethyl-4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (55)

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate mixture compound 100** (0.22 mmol, 79 mg). Purification of the crude material (1:3 mixture of exo/endo isomers) by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded 6.3 mg of the exo-isomer 3-ethyl-4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (**55**) and 22.3 mg of the pure endo-isomer 3-ethyl-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (**54**).(Overall yield=36%).

3-Ethyl-4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (exo-isomer **55**):

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.78 (2H, m), 7.53 (1H, d, *J* = 7.6 Hz), 6.69 (1H, d, *J* = 2.4 Hz), 6.60 (1H, d, *J* = 8.8 Hz), 6.54 (1H, dd, *J* = 8.8 & 2.4 Hz), 5.47 (1H, s), 3.95 (1H, d, *J* = 9.6 Hz), 3.65 (3H, s), 3.00-2.93 (1H, m), 2.83-2.66 (2H, m), 2.38-2.32 (1H, m), 2.28-2.22 (1H, m), 1.66-1.52 (4H, m), 1.224-1.14 (4H, m).

LC-MS: t_R = 8.67 $[M+H]^+$= 352 (method 1)

3-Ethyl-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (endo-isomer **54**):

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.78 (2H, m), 7.71 (1H, d, *J* = 8.8 Hz), 6.63 (2H, d, *J* = 8.8 Hz), 6.54 (1H, dd, *J* = 8.8 & 2.4 Hz), 5.25 (1H, s), 4.61 (1H, d, *J* = 2 Hz), 3.65 (3H, s), 3.43-3.31 (1H, m), 2.83-2.74 (1H, m), 2.70-2.61 (1H, m), 2.46-2.36 (1H, m), 2.13-2.04 (1H, m), 1.68-1.58 (2H, m), 1.45-1.33 (2H, m), 1.23-1.17 (3H, m), 1.05-0.96 (1H, m).

LC-MS: t_R = 9.22 $[M+H]^+$= 352 (method 1)

Example 56: 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-3,5-dimethylbenzoic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 102** (0.24 mmol, 83 mg). It was necessary 22 h and an additional 0.75 mL of 1M LiOH to complete the reaction. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave 53.4 mg of the pure title exo-compound (Yield: 67%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (2H, m), 7.01 (1H, d, *J* = 2 Hz), 6.85 (1H, dd, *J* = 8.4 & 1.6 Hz), 6.52 (1H, d, *J* = 8 Hz), 4.36 (1H, d, *J* = 10.8 Hz), 3.11-3.05 (1H, m), 2.92-2.84 (1H, m), 2.72-2.61 (3H, brs), 2.50-2.40 (3H, brs), 2.36-2.30 (1H, m), 2.28 (3H, s), 1.81-1.61 (4H, m), 1.28-1.21 (1H, m).

LC-MS: t_R = 10.52 $[M+H]^+$= 336 (method 1)

Example 57: 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-3,5-dimethylbenzoic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 104** (0.16 mmol, 59 mg). It was necessary 18 h and an additional 0.32 mL of 1M LiOH to complete the reaction. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave 36 mg of the pure title exo-compound (Yield: 63%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (2H, m), 7.79 (1H, d, *J* = 2.4 Hz), 6.67 (1H, dd, *J* = 8.4 & 2.8 Hz), 6.55 (1H, d, *J* = 8.8 Hz), 4.34 (1H, d, *J* = 11.6 Hz), 3.78

(3H, s), 3.13-3.06 (1H, m), 2.94-2.86 (1H, m), 2.73-2.60 (3H, brs), 2.50-2.40 (3H, brs), 2.37-2.31 (1H, m), 1.79-1.60 (4H, m), 1.28-1.21 (1H, m).

LC-MS: t_R = 9.43 $[M+H]^+$= 352 (method 1)

Example 58: 5-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)pyridine-2-carboxylic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 105** (0.17 mmol, 54 mg) but using Pt_2O (15 % w/w, 8 mg) for 18 h. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave the endo-isomer 5-((3a*S*, 4*R*, 9b*R*)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1*H*-cyclopenta[*c*]quinolin-4-yl)pyridine-2-carboxylic acid (5 mg. Yield: 10%).

^{1}H NMR (400 MHz, CD_3OD) δ 8.74 (1H, s), 8.17-8.09 (2H, m), 6.90 (1H, s), 6.76 (1H, d, *J*=8.4Hz), 6.59 (1H, d, *J*=8Hz), 4.62 (1H, s), 3.46-3.44 (1H, m), 2.56-2.54 (1H, m), 2.21 (3H, s), 2.17-2.12 (1H, m), 1.78-1.76 (1H, m), 1.68-1.65 (1H, m), 1.51-1.44 (2H, m), 1.14-1.12 (1H, m).

LC-MS: t_R = 8.65 $[M+H]^+$ = 309 (method 1)

Example 59: 6-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)pyridine-3-carboxylic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 108** (0.53 mmol). The crude residue was purified by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents, to give 119 mg of the title endo-isomer. (Yield: 73%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (1H, d, *J* = 1.6 Hz), 8.27 (1H, dd, *J* = 8.4 & 2.4 Hz), 7.64 (1H, d, *J* = 8.4 Hz), 6.83 (1H, s), 6.70 (1H, d, *J* = 8.0 Hz), 6.61 (1H, d, *J* = 8.0 Hz), 5.69 (1H, s), 4.51 (1H, d, *J* = 3.2 Hz), 3.54-3.50 (1H, m), 2.71-2.64 (1H, m), 2.14 (3H, s), 2.07-1.97 (1H, m), 1.73-1.67 (1H, m), 1.45-1.29 (3H, m), 1.00-1.94 (1H, m).

LC-MS: t_R = 9.05 $[M+H]^+$= 309 (method 1)

Example 60: 5-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-6-methylpyridine-2-carbonitrile

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 109** (275 mg, 0.91 mmol). Purification of the crude material using flash chromatography on silica gel using an elution of 23% ethylacetate in hexanes afforded the title endo-isomer as a solid (245 mg. Yield: 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (1H, d, *J* = 8.4 Hz), 7.58 (1H, d, *J* = 8.0 Hz), 6.96 (1H, s), 6.84 (1H, dd, *J* = 7.6 & 1.6 Hz), 6.53 (1H, d, *J* = 8.4 Hz), 4.73 (1H, d, *J* = 3.2 Hz), 3.49-3.44 (2H,m), 2.62 (3H, s), 2.61-2.47 (1H, m), 2.26 (3H, s), 2.23-2.14 (1H, m), 1.83-1.76 (1H, m), 1.70-1.59 (1H, m), 1.57-1.41 (1H, m), 1.12-1.07 (1H,s).

LC-MS: t_R = 9.85 $[M+H]^+$= 304 (method 1)

Example 61: 5-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-6-methylpyridine-2-carboxylic acid

The pyridine-2-carbonitrile **Example 60** (30 mg, 0.1 mmol) was suspended in a mixture of acetic acid: water: concentrated hydrochloric acid (1:1:2, 1 mL) and the mixture was heated at 110ºC for 5h. Reaction mixture was cooled down and left at r.t. for 16 h, when the solvent was evaporated. Purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded 13.4 mg of the title endo-isomer. (Yield: 34%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (1H, d, *J* = 8.0 Hz), 7.89 (1H, d, *J* = 8.0 Hz), 6.83 (1H, s), 6.70 (1H, d, *J* = 7.6 Hz), 6.56 (1H, d, *J* = 8.4 Hz), 5.44 (1H, s), 4.61 (1H, d, *J* = 2.8 Hz), 3.39-3.31 (1H, m), 2.56 (3H, s), 2.15 (3H, s), 2.11-2.02 (1H, m), 1.71-1.64 (1H, m), 1.56-1.48 (1H, m), 1.41-1.35 (2H, m), 0.98-0.92 (1H, m).

LC-MS: t_R = 7.58 $[M+H]^+$= 323 (method 1)

Example 62: 5-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-1-methyl-1H-pyrazole-3-carboxylic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 111** (225 mg, 0.66 mmol) using 1M LiOH (4 eq.) for 16 h. Purification of the crude material was carried out by precipitation at pH 6 using 1M HCl. The white solid was filtered, washed by water and dried under vacuum at 40ºC to give 84 mg of the title endo-isomer. (Yield: 41%)

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.5 (1H, brs), 6.82 (1H, s), 6.68 (1H, d, *J* = 8.0 Hz), 6.61 (1H, s), 6.55 (1H, d, *J* = 8.0 Hz), 5.46 (1H, s), 4.53 (1H, s), 3.86 (3H, s), 2.52-2.49 (1H, m), 2.13 (3H, s), 2.04-1.98 (1H, m), 1.67 (1H, m), 1.60-1.53 (1H, m), 1.39-1.36 (2H, m), 1.22-1.20 (1H, m).

LC-MS: t_R = 8.08 $[M+H]^+$= 312 (method 1)

Example 63: 5-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-1-methyl-1H-pyrazole-3-carboxylic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 113** (190 mg, 0.54 mmol) using 1M LiOH (4 eq.) for 16 h. After neutralising the reaction mixture with 1M HCl until pH 6 and evaporation of the solvents, purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave the title compound which was precipitated in acetonitrile, filtered and dried to give 74 mg of the pure title endo-carboxylic acid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.5 (1H, brs), 6.61-6.60 (3H, m), 6.53 (1H, dd, *J* = 8.8 & 2.8 Hz), 5.32 (1H, s), 4.49 (1H, d, *J* = 2.8 Hz), 3.86 (3H, s), 3.63 (3H, s), 3.38-3.36 (1H, m), 2.55-2.49 (1H, m), 2.08-1.96 (1H, m), 1.69-1.54 (2H, m), 1.46-1.32 (1H, m), 1.26-1.13 (1H, m).

LC-MS: t_R = 6.73 $[M+H]^+$= 328 (method 1)

Example 64: 3-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-1-methyl-1H-pyrazole-5-carboxylic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 115** (100 mg, 0.29 mmol) using 1M LiOH (3 eq.) for 16 h. Purification of the crude material using reverse C_{18}

chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded 74 mg of the pure title endo-carboxylic acid (Yield: 70%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 6.78 (1H, d, *J* = 8.4 Hz), 6.77 (1H, s), 6.67 (1H, dd, *J* = 8.0 & 2.0 Hz), 6.56 (1H, d, *J* = 8.4 Hz), 5.36 (1H, s), 4.36 (1H, d, *J* = 2.8 Hz), 4.09 (3H, s), 3.30-3.27 (1H, m), 2.55-2.49 (1H, m), 2.13 (3H, s), 2.02-1.97 (1H, m), 1.68-1.63 (1H, m), 1.55-1.50 (1H, m), 1.41-1.29 (2H, m).

LC-MS: t_R = 8.13 $[M+H]^+$= 312 (method 1)

Example 65: 3-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-1-methyl-1H-pyrazole-5-carboxylic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 117** (65 mg, 0.18 mmol) using 1M LiOH (3 eq.) for 16 h. After neutralising the reaction mixture with 1M HCl until pH 6 and evaporation of the solvents, purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave the title compound which was precipitated in acetonitrile, filtered and dried under vacuum to give 31 mg of the pure title endo-carboxylic acid (Yield: 52%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 6.77 (1H, s), 6.62-6.49 (3H, m), 5.23 (1H, s), 4.32 (1H, d, *J* = 2.8 Hz), 4.03 (3H, s), 3.62 (3H, s), 3.32-3.26 (1H, m), 2.58-2.51 (1H, m), 2.03-1.96 (1H, m), 1.68-1.61 (1H, m), 1.56-1.49 (1H, m), 1.43-1.27 (2H, m).

LC-MS: t_R = 6.12 $[M+H]^+$= 328 (method 1)

Example 66 and 67: 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8,9b-dimethyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (66) and 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8,9b-dimethyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (67)

Boron trifluoride diethyletherate (2 eq., 2 mmol, 0.25 mL) in anhydrous acetonitrile (4 mL) was added to a mixture of 4-formylbenzoic acid (150 mg, 1 mmol), 4-methylaniline (1 mmol, 107 mg), and 1-methyl-1-cyclopentene (5 eq., 5 mmol, 0.53 mL). The reaction mixture was stirred at 50ºC for 24 h. Reaction mixture was diluted with saturated aqueous sodium bicarbonate solution and

ethyl acetate. The aqueous layer was extracted with ethylacetate, then acidified to pH 3 with 1N HCl solution and extracted with ethylacetate. The last combined organic layers was washed with brine, dried over anhydrous MgSO4, filtered, the solvent evaporated under vacuum and purification of the crude material (1:1.3 mixture of regioisomers) by flash chromatography on silica gel using an elution of 13% methanol in dichloromethane afforded 2 fractions of each regioisomer. These fractions were purified again using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give 18 mg of 4-((3*aS*,4*S*,9*bR*)-2,3,3*a*,4,5,9*b*-hexahydro-8,9*b*-dimethyl-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid and 45 mg (30%) of the pure endo-compound (Overall yield= 19%).

4-((3*aS*,4*S*,9*bR*)-2,3,3*a*,4,5,9*b*-hexahydro-8,9*b*-dimethyl-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid (exo-isomer **66**):

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (2H, d, *J* = 8.0 Hz), 7.51 (2H, d, *J* = 8.0 Hz), 6.94 (1H, m), 6.70 (1H, dd, *J* = 8.0 & 1.6 Hz), 6.58 (1H, t, *J* = 8 Hz), 5.67 (1H, s), 3.73 (1H, d, *J* = 9.6 Hz), 2.16 (3H, s), 1.98-1.94 (1H, m), 1.90-1.86 (1H, m), 1.81-1.78 (1H, m), 1.71-1.67 (1H, m), 1.62-1.56 (2H, m), 1.36-1.32 (1H, m), 1.10 (3H, s).

LC-MS: t_R = 9.88 $[M+H]^+$= 322 (method 1)

4-((3*aS*,4*R*,9*bR*)-2,3,3*a*,4,5,9*b*-hexahydro-8,9*b*-dimethyl-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid (endo-isomer **67**):

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (2H, d, *J* = 8.4 Hz), 7.52 (2H, d, *J* = 8.0 Hz), 6.92 (1H, m), 6.68 (1H, dd, *J* = 8.0 & 1.6 Hz), 6.57 (1H, t, *J* = 8.4 Hz), 5.75 (1H, s), 4.45 (1H, d, *J* = 2.46 Hz), 2.14 (3H, s), 2.09-2.03 (1H, m), 1.93-1.88 (1H, ta, *J* = 8.4 Hz), 1.60-1.68 (1H, m), 1.52-1.57 (1H, m), 1.40 (3H, s), 1.39-1.31 (1H, m), 1.17-1.12 (1H, m), 1.08-1.00 (1H, m).

LC-MS: t_R = 10.70 $[M+H]^+$= 322 (method 1)

Example 68 and 69 : 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (68) and 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (69)

The following compounds were prepared using the same methodology as in example 66 and 67 using *p*-anisidine (1 mmol, 107 mg). Solvent was evaporated and the crude material (1:1.4 mixture of endo/exo isomers) was purified by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid). Only high purity fractions of each isomer were collected giving two enriched fractions with each regioisomer 51 mg of the fraction enriched in the exo-isomer was precipitated in acetonitrile/drops of water to give 29 mg of 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (**68**). The fraction enriched in the endo-isomer was purified again by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give 24 mg of the pure endo-compound 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-9b-methyl-1Hcyclopenta[c]quinolin-4-yl)benzoic acid (**69**) (overall yield= 16%).

4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (exo-isomer **68**):

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (2H, d, *J* = 8 Hz), 7.52 (2H, d, *J* = 8 Hz), 6.73 (1H, d, *J* = 2.4 Hz), 6.63 (1H, d, *J* = 8.4 Hz), 6.54 (1H, dd, *J* = 2.8 & 8.8 Hz), 5.52 (1H, s), 3.68 (1H, d, *J* = 10 Hz), 3.65 (3H, s), 1.99-1.89 (2H, m), 1.84-1.76 (1H, m), 1.73-1.57 (3H, m), 1.37-1.29 (1H, m), 1.14 (3H, m).

LC-MS: t_R = 8.40 $[M+H]^+$= 338 (method 1).

4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (endo-isomer **69**):

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.93 (2H, d, *J* = 8.4 Hz), 7.55 (2H, d, *J* = 8.4 Hz), 6.71 (1H, d, *J* = 2.4 Hz), 6.63 (1H, d, *J* = 8.4 Hz), 6.56 (1H, dd, *J* = 2.8 & 8.4 Hz), 5.62 (1H, s), 4.44 (1H, d, *J* = 1.6 Hz), 3.65 (3H, s), 2.09-2.05 (1H, m), 1.97-1.90 (1H, m), 1.71-1.53 (2H, m), 1.44 (3H, s), 1.40-1.34 (1H, m), 1.21-1.12 (1H, m), 1.09-1.00 (1H, m).

LC-MS: t_R = 9.70 $[M+H]^+$= 338 (method 1).

Example 70 and 71: 4-((3aS,4S,9bR)-8-cyclopropyl-2,3,3a,4,5,9b-hexahydro-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (70) and 4-((3aS,4R,9bR)-8-cyclopropyl-2,3,3a,4,5,9b-hexahydro-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (71)

The following compounds were prepared using the same methodology as in example 66 and 67 using **the intermediate compound 3 (method 2)** (1.2 mmol, 160 mg). Solvent was evaporated and purification of the crude material (1:1,1 mixture of exo/endo isomers) by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) afforded 38.5 mg of 4-((3aS,4S,9bR)-8-cyclopropyl-2,3,3a,4,5,9b-hexahydro-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic (**70**) acid and 53.30 mg of 4-((3aS,4R,9bR)-8-cyclopropyl-2,3,3a,4,5,9b-hexahydro-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (**71**) both as a white solids. (Overall yield: 22%).

4-((3aS,4S,9bR)-8-cyclopropyl-2,3,3a,4,5,9b-hexahydro-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (exo-isomer **70**):

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.91 (2H, d, *J* = 8.4 Hz), 7.51 (2H, d, *J* = 8 Hz), 6.90 (1H, s), 6.57 (2H, d, *J* =0.8 Hz), 5.69 (1H, s), 3.74 (1H, d, *J* = 9.6 Hz), 1.99-1.87 (2H, m), 1.83-1.66 (3H, m), 1.62-1.55 (2H, m), 1.38-1.29 (1H, m), 1.11 (3H, s), 0.83-0.78 (2H, m), 0.53-0.49 (2H, m).

LC-MS: t_R = 10.47 $[M+H]^+$= 348 (method 1)

4-((3aS,4R,9bR)-8-cyclopropyl-2,3,3a,4,5,9b-hexahydro-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (endo-isomer **71**):

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (2H, d, *J* = 8.4 Hz), 7.54 (2H, d, *J* = 8.4 Hz), 6.89 (1H, s), 6.58 (2H, s), 5.78 (1H, s), 4.47 (1H, d, *J* = 2.4 Hz), 2.12-2.07 (1H, m), 1.95-1.90 (1H, m), 1.79-1.72 (1H, m), 1.70-1.50 (2H, m), 1.42 (3H, s), 1.41-1.32 (1H, m), 1.21-0.99 (2H, m), 0.83-0.78 (2H, m), 0.53-0.49 (m, 2H).

LC-MS: t_R = 11.10 $[M+H]^+$= 348 (method 1)

Example 72 and 73: 4-((3aS,4S,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (72) and 4-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (73)

The following compounds were prepared using the same methodology as in example 66 and 67 using 4-chloroaniline (1 mmol, 127 mg). Solvent was evaporated and purification of the crude material (1:1,3 mixture of exo/endo regioisomers) by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) afforded two fractions of each regioisomer. These fractions were purified again by precipitation in hexane/acetonitrile, filtered and dried in vacuum to give 76.5 mg of 4-((3aS,4S,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic (**72**) acid and 37 mg of the pure endo-compound 4-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (**73**) (Overall yield: 33%).

4-((3aS,4S,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (exo-isomer **72**):

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (2H, d, *J* = 8 Hz), 7.52 (2H, d, *J* = 8.4 Hz), 7.15 (1H, d, *J* = 2 Hz), 6.91 (1H, dd, *J* = 2.4 & 8.8 Hz), 6.69 (1H, d, *J* = 8.8 Hz), 6.15 (1H, s), 3.80 (1H, d, *J* = 9.2 Hz), 2.00-1.87 (2H, m), 1.84-1.68 (2H, m), 1.63-1.55 (2H, m), 1.39.1.30 (1H, m), 1.15 (3H, m).

LC-MS: t_R = 10.65 $[M+H]^+$= 342 (method 1)

4-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (endo-isomer **73**):

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.94 (2H d, *J* = 8 Hz), 7.54 (2H, d, *J* = 8.4 Hz), 7.15 (1H, d, *J* = 2.4 Hz), 6.92 (1H, dd, *J* = 2.4 & 8.4 Hz), 6.70 (1H, d, *J* = 8.4 Hz), 6.23 (1H, s), 4.52 (1H, d, *J* = 2.8 Hz), 2.11-2.05 (1H, m), 1.97-1.92 (1H, m), 1.71-1.63 (1H, m), 1.56-1.46 (1H, m), 1.42 (3H, s), 1.42-1.35 (1H, m), 1.23-1.01 (2H, m)

LC-MS: t_R = 10.90 $[M+H]^+$= 342 ((method 1)

Example 74 and 75: 4-((3aS, 4S, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8, 9b-dimethyl-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid (74) and 4-

((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8, 9b-dimethyl-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid (75)

The following compound was prepared using the same methodology as in example 66 and 67 from **intermediate compound 18** (120 mg, 0.73 mmol) and *p*-toluidine (79 mg, 0.73 mmol). Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and methanol (0.1% formic acid) as eluents afforded two products, the exo-isomer 4-((3a*S*, 4*S*, 9b*R*)-2, 3, 3a, 4, 5, 9b-hexahydro-8, 9b-dimethyl-1*H*-cyclopenta[*c*]quinolin-4-yl)-3-methylbenzoic acid (**74**) (14.7 mg. Yield: 6%) and the endo-isomer 4-((3a*S*, 4*R*, 9b*R*)-2, 3, 3a, 4, 5, 9b-hexahydro-8, 9b-dimethyl-1*H*-cyclopenta[*c*]quinolin-4-yl)-3-methylbenzoic acid (**75**) (33.6 mg. Yield: 14%).

4-((3a*S*, 4*S*, 9b*R*)-2, 3, 3a, 4, 5, 9b-hexahydro-8,9b-dimethyl-1*H*-cyclopenta[*c*]quinolin-4-yl)-3-methylbenzoic acid (exo-isomer **74)**

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (2H, m), 7.53 (1H, m), 6.96 (1H, s), 6.69 (1H, d, *J*=8Hz), 6.55 (1H, d, *J*=8Hz), 5.56 (1H, s), 3.99 (1H, d, *J*=9.2Hz), 2.39 (3h, s), 2.17 (3H, s), 2.06-2.04 (1H, m), 1.90-1.87 (2H, m), 1.79-1.73 (1H, m), 1.61-1.59 (2H, m), 1.23 (1H, m), 1.14 (3H, m).

LC-MS: t_R = 10.22 $[M+H]^+$ = 336 (method 1)

4-((3a*S*, 4*R*, 9b*R*)-2, 3, 3a, 4, 5, 9b-hexahydro-8, 9b-dimethyl-1*H*-cyclopenta[*c*]quinolin-4-yl)-3-methylbenzoic acid (endo-isomer **75**)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (1H, d, J=8.4Hz), 7.75 (1H, s), 7.68 (1H, d, J=8Hz), 6.95 (1H, s), 6.70 (1H, dd, *J*= 1.2 & 8Hz), 6.57 (1H, d, *J*=8Hz), 5.59 (1H, s), 4.62 (1H, d, *J*=2Hz), 2.38 (3H, s), 2.16 (3H, s), 2.09-2.04 (1H, m), 1.95-1.92 (1H, m), 1.69-1.64 (2H, m), 1.43 (3H, s), 1.38-1.37 (1H, m), 1.23-1.17 (1H, m), 1.03-1.01 (1H, m).

LC-MS: t_R = 11.02 $[M+H]^+$ = 336 (method 1)

Example 76: 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-isobutoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 121** (0.47 mmol, 187 mg). The

mixture was stirred at r.t. until HPLC showed no starting material left. It was necessary 48 h and an addicional 1.5 mL of 1M LiOH to complete the reaction. After that, the solvent was removed in vacuum and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave 135 mg of the pure title endo-isomer (Yield: 75%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (1H, d, *J* = 8 Hz), 7.74 (1H, s), 7.69 (1H, d, *J* = 8 Hz), 6.63-6.61 (2H, m), 6.53 (1H, dd, *J* = 8.4 & 2.8 Hz), 5.22 (1H, s), 4.57 (1H, d, *J* = 2.4 Hz), 3.62 (2H, d, *J* = 6.8 Hz), 3.41-3.36 (1H, m), 2.50-2.42 (1H, m), 2.37 (3H, s), 2.13-2.04 (1H, m), 2.00-1.90 (2H, m), 1.69-1.56 (2H, m),1.44-1.32 (2H, m), 1.02-0.94 (1H, m), 0.96 (6 H, d, *J* = 6.8 Hz)

LC-MS: t_R = 9.18 $[M+H]^+$= 380 (method 1)

Example 77: 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-isobutoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 122** (0.03 mmol, 13 mg). It was necessary 40 h and an addicional 0.07 mL of 1M LiOH to complete the reaction. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave 6 mg of the pure title exo-isomer (Yield: 47%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77-7.75 (2H, m), 7.52-7.50 (1H, m), 6.67 (1H, d, *J* = 2.4 Hz), 6.58-6.52 (2H, m), 5.46 (1H, s), 3.95 (1H, d, *J* = 10 Hz), 3.61 (2H, d, *J* = 6.8 Hz), 2.97-2.90 (1H, m), 2.40 (3H, s), 2.36-2.28 (1H, m), 2.27-2.20 (1H, m), 1.99-1.90 (2H, m),1.68-1.50 (4H, m), 1.23-1.12 (1H, m), 0.96 (6 H, d, *J* = 6.8 Hz).

LC-MS: t_R = 8.62 $[M+H]^+$= 380 (method 1)

Example 78: 4-((3aS, 4S, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methoxy-5,9b-dimethyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in example 42 using **example 68** 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (0.1 mmol, 33 mg). The crude material was purified by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give the pure title exo-isomer (15 mg. Yield: 43%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (2H, d, *J*= 8.4 Hz), 7.23 (2H, d, *J*= 8 Hz), 6.75 (1H, d, *J*=2.8 Hz), 6.70 (1H, dd, *J*= 2.8 & 8.8 Hz), 6.64 (1H, d, *J*= 8.8 Hz), 4.51 (1H, d, *J*= 4.8 Hz), 3.67 (3H, s), 2.75 (3H, s), 2.30-2.24 (1H, m), 1.99-1.87 (2H,m), 1.79-1.71 (1H, m), 1.56-1.46 (2H, m), 1.38-1.30 (1H, m).

LC-MS: t_R = 10.27 $[M+H]^+$ = 352 (method 1)

Example 79: 4-((3aS, 4R, 9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-5,9b-dimethyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in example 42 using **example 69** 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (0.37 mmol, 126 mg). The crude material was purified by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give the pure title endo-isomer (46 mg. Yield: 35%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (2H, d, *J*= 8.4 Hz), 7.45 (2H, d, *J*= 8.4 Hz), 6.80 (1H, d, *J*= 9.2 Hz), 6.77 (1H, d, *J*= 2.8 Hz), 6.69 (1H, dd, *J*= 2.8 & 8.8 Hz), 4.30 (1H, d, *J*= 3.6 Hz), 3.68 (3H, s), 2.65 (3H, s), 2.25-2.19 (1H, m), 1.89-1.84 (1H,m), 1.65-1.52 (2H, m), 1.38-1.30 (1H, m), 1.19-1.04 (2H, m)

LC-MS: t_R = 10.63 $[M+H]^+$ = 352 (method 1)

Example 80: (+/-)-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-(trifluoromethoxy)-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (80). (+)-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-(trifluoromethoxy)-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (80a) & (-)-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-(trifluoromethoxy)-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (80b).

The following compound was prepared using the same methodology as in intermediate compound 67 using **Intermediate compound 149** (275 mg, 0.73 mmol). The solution was hydrogenated at r.t. for 1 h. HPLC analysis showed total conversion. Reaction mixture was filtered and the filter washed with THF. Solvent was evaporated and purification of the crude material by flash chromatography on silica gel using hexane and ethylacetate as eluents afforded 106 mg of the racemic endo-isomer (Yield: 38%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.8 (1H,brs), 7.92 (2H, d, *J* = 8.4 Hz), 7.52 (2H, d, *J* = 8.4 Hz), 6.97 (1H,m), 6.88 (1H, d, *J* = 8.4 Hz), 6.74 (1H, d, *J* = 9.2 Hz), 6.08 (1H, s), 4.56 (1H, d, *J* = 2.8 Hz), 3.40 (1H, t, *J* = 6.8 Hz), 2.44-2.40 (1H, m), 2.09-2.03 (1H, m), 1.72-1.64 (1H, m), 1.50-1.44 (1H, m), 1.42-1.32 (1H, m), 1.05-0.98 (1H, m).

LC-MS: t_R = 10.35 $[M+H]^+$= 378 (method 1)

Enantiomeric separation of 733 mg of (+/-)-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-(trifluoromethoxy)-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (**80**) by preparative chiral chromatography was carried out using heptane/2-propanol (90:10) as eluents to yield:

236 mg of the enantiomer (+)-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-(trifluoromethoxy)-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (**80 a**)

Preparative HPLC: t_R = 16.8

Optical Purity: 99.9% ee

$[\alpha]^{Na}_D$= + 60.7 (0.5, $CHCl_3$)

226 mg of the enantiomer (-)-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-(trifluoromethoxy)-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (**80 b**)

Preparative HPLC: t_R = 45.7

Optical Purity: 94.4% ee

$[\alpha]^{Na}_D$= - 61.6 (0.5, $CHCl_3$)

Example 81: (+/-)4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (81). (+)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (81a) & (-)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (81b)

The following compound was prepared using the same methodology as in intermediate compound 67 using **Intermediate compound 150** (168 mg, 0.47 mmol). The solution was hydrogenated at r.t. for 30 min. HPLC analysis showed total conversion. Reaction mixture was filtered and the filter washed with THF. Solvent was evaporated and purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents. Only high purity fractions were collected to give 116 mg (69%) of the pure racemic endo-isomer.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.85 (1H,brs), 7.92 (2H, d, *J* = 8.0 Hz), 7.53 (2H, d, *J* = 8.4 Hz), 6.96 (1H, t, *J* = 75.0 Hz), 6.84 (1H, m), 6.75-6.68 (2H, m), 5.87 (1H, s), 4.52 (1H, d, *J* = 2.8 Hz), 3.38 (1H, dt, *J* = 7.6 & 2.0 Hz), 2.44-2.40 (1H, m), 2.10-2.01 (1H, m), 1.72-1.64 (1H, m), 1.53-1.43 (1H, m), 1.40-1.32 (1H, m), 1.05-0.97 (1H, m).

LC-MS: t_R = 9.33 $[M+H]^+$= 360 (method 1)

Enantiomeric separation of 1.6 g of (+/-)4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (**81**) by preparative chiral chromatography was carried out using heptane/2-propanol (90:10) as eluents to yield:

222 mg of the enantiomer (+)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (**81 a**)

Preparative HPLC: t_R = 21.8

Optical Purity: 99.9% ee

$[\alpha]^{Na}_D$= + 48.3 (0.5, $CHCl_3$)

282 mg of the enantiomer (-)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (**81 b**)

Preparative HPLC: t_R =63.3

Optical Purity: 99.9% ee

$[\alpha]^{Na}_D$= - 53.8 (0.5, $CHCl_3$)

Example 82: 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-(trifluoromethoxy)-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 152** (0.12 mmol, 50 mg,). It was necessary 40 h and an additional 1.5 eq of 1M LiOH to complete the reaction. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave 36 mg of the pure endo-isomer (Yield: 78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (1H, dd, *J* = 8.0 & 1.6 Hz), 7.92 (1H, m), 7.74 (1H, d, *J* = 8.0 Hz), 6.99-6.98 (1H, m), 6.89-6.85 (1H, m), 6.58 (1H, d, *J* = 8.4 Hz), 4.80 (1H, d, *J* = 3.2 Hz), 3.47 (1H, dt, *J* = 7.6 & 2.8 Hz), 2.55-2.46 (1H, m), 2.42 (3H, s), 2.24-2.15 (1H, m), 1.79-1.68 (2H, m), 1.64-1.48 (1H, m), 1.47-1.41 (1H, m), 1.20-1.15 (1H, m).

LC-MS: t_R = 10.62 $[M+H]^+$= 392 (method 1)

Example 83: (+/-)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid (83). (-)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid (83a) & (+)-4-

((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid (83b)

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 154** (0.12 mmol, 50 mg). It was necessary 36 h and an additional 2 eq of 1M LiOH to complete the reaction. Reaction mixture was acidified with 2 N HCl until pH 3. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave 60 mg of the pure racemic endo-isomer (Yield: 26%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (1H, dd, *J* = 8.0 & 1.6 Hz), 7.73 (1H, m), 7.65 (1H, d, *J* = 8.0 Hz), 6.95 (1H, d, *J* = 75.2 Hz), 6.84 (1H, m), 6.74-6.67 (2H, m), 5.69 (1H, m), 4.64 (1H, d, *J* = 2.8 Hz), 3.47 (1H, dt, *J* = 7.2 & 2.4 Hz), 2.52-2.46 (1H, m), 2.36 (3H, s), 2.11-2.06 (1H, m), 1.69-1.63 (1H, m), 1.60-1.54 (1H, m), 1.44-1.36 (1H, m), 0.99-0.95 (1H, m).

LC-MS: t_R = 9.62 $[M+H]^+$= 374 (method 1)

The separated enantiomerically pure intermediate compounds **154a** and **154b** were saponified to yield the corresponding carboxylic acids:

(-)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid (**83 a**).

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 154a** (1.10 mmol, 427 mg). Additional 1 M LiOH solution (6.6 mmol, 6.6 mL) and additional 18 h were needed to complete the reaction. Solvent was evaporated and water was added. The mixture was cooled to 0-5 ºC and 2N aqueous HCl solution was added until a solid was formed (pH 2). The suspension was stirred for 30 minutes at this temperature before it was filtered under vacuum. The crude material was purified by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give 122 mg of the pure title compound (Yield: 30%).

$[\alpha]^{Na}_{D}$= - 88.6 (0.5, $CHCl_3$)

(+)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid (**83 b**).

The following compound was prepared using the same methodology as in example 83a from **intermediate compound 154b** (1.09 mmol, 424 mg) to give 348 mg of the title compound (Yield: 86%).

$[\alpha]^{Na}_{D}$= + 64.6 (0.5, $CHCl_3$)

Example 84: (+/-)-3-fluoro-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (84). (+)-3-fluoro-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (84a) & (-)-3-fluoro-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (84b).

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 155** for 1h. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the racemic endo-isomer 3-fluoro-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (40 mg, Yield: 51%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (1H, dd, *J* = 1.2 & 8 Hz), 7.75 (1H, d, *J* = 7.2 Hz), 7.62 (1H, dd, *J* = 1.6 & 11.2 Hz), 6.84 (1H, s), 6.72 (1H, d, *J* = 8 Hz), 6.60 (1H, d, *J* = 8.4 Hz), 5.52 (1H, s), 4.69 (1H, d, *J* = 2 Hz), 3.38-3.34 (1H, m), 2.55-2.50 (1H, m), 2.16 (3H, s), 2.08-2.03 (1H, m), 1.72-1.67 (1H, m), 1.57-1.51 (1H, m), 1.42-1.34 (2H, m), 1.06-1.01 (1H, m).

LC-MS: t_R = 10.27 $[M+H]^+$ = 326 (method 1)

Enantiomeric separation of 487 mg of (+/-)-3-fluoro-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (**84**) by preparative chiral chromatography was carried out using heptane/EtOH (95:5) as eluents to yield:

167 mg of the enantiomer (+)-3-fluoro-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (**84a**)

Preparative HPLC: t_R = 14.9

Optical Purity: 99.9% ee

$[\alpha^{Na}_D$= + 57.2 (0.5, THF)

197 mg of the enantiomer (-)-3-fluoro-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (**84b**)

Preparative HPLC: t_R =21.2

Optical Purity: 97.4% ee

$[\alpha]^{Na}_D$= - 58.6 (0.5, THF)

Example 85: (+/-)-3-fluoro-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (85). (+)-3-fluoro-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (85a) & (-)-3-fluoro-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (85b).

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 156** for 1h. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the racemic endo-isomer 3-fluoro-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (80 mg, Yield: 60 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (1H, d, *J* = 8.4 Hz), 7.75 (1H, m), 7.62 (1H, d, *J* = 10 Hz), 6.66-6.62 (1H, m), 6.56 (1H, dd, *J* = 2.8 Hz & 8.4 Hz), 5.38 (1H, s), 4.65 (1H, d, *J* = 2.4 Hz), 3.65 (3H, s), 3.41-3.36 (1H, m), 2.54-2.50 (1H, m), 2.10-2.05 (1H, m), 1.71-1.66 (1H, m), 1.58-1.52 (1H, m), 1.42-1.36 (2H, m), 1.06-1.02 (1H, m).

LC-MS: t_R = 9.13 $[M+H]^+$ = 342 (method 1)

Enantiomeric separation of 413 mg of (+/-)-3-fluoro-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (**85**) by preparative chiral chromatography was carried out using heptane/2-propanol (90:10) as eluents to yield:

135 mg of the enantiomer (+)-3-fluoro-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (**85a**)

Preparative HPLC: t_R = 12.5

Optical Purity: 99.9% ee

$[\alpha]^{Na}_D$= + 69.7 (0.5, THF)

197 mg of the enantiomer (-)-3-fluoro-4-((3aS,4R,9bR)-8-methoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (**85b**)

Preparative HPLC: t_R = 32.1

Optical Purity: 99.9% ee

$[\alpha]^{Na}_D$= - 65.6 (0.5, THF)

Example 86: (+/-)-4-((3aS,4R,9bR)-8-cyclopropyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid (86). (+)-4-((3aS,4R,9bR)-8-cyclopropyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid (86a) & (-)-4-((3aS,4R,9bR)-8-cyclopropyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid (86b)

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 157** for 1h. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the racemic endo-isomer 4-((3aS,4R,9bR)-8-cyclopropyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid (545 mg, Yield: 70 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (1H, d, *J* = 8.4 Hz), 7.71 (1H, m), 7.61 (1H, d, *J* = 10.8 Hz), 6.77 (1H, s), 6.61 (2H, m), 5.52 (1H, s), 4.69 (1H, d, *J* = 2.4 Hz), 3.37-3.34 (1H, m), 2.54-2.50 (1H, m), 2.09-2.02 (1H, m), 1.79-1.66 (2H, m), 1.57-1.49 (1H, m), 1.41-1.34 (2H, m), 1.07-1.01 (1H, m), 0.83-0.78 (2H, m), 0.53-0.49 (2H, m).

LC-MS: t_R = 10.63 $[M+H]^+$ = 352 (method 1)

Enantiomeric separation of 545 mg of (+/-)-4-((3aS,4R,9bR)-8-cyclopropyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid (**86**) by preparative chiral chromatography was carried out using Heptane/EtOH (90:10) as eluents to yield:

209 mg of the enantiomer (+)-4-((3aS,4R,9bR)-8-cyclopropyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid (**86a**)

Preparative HPLC: t_R = 10.8

Optical Purity: 99.9% ee

$[\alpha]^{Na}_D$= + 49.4 (0.5, THF)

240 mg of the enantiomer (-)-4-((3aS,4R,9bR)-8-cyclopropyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid (**86b**)

Preparative HPLC: t_R = 24.2

Optical Purity: 99.9% ee

$[\alpha]^{Na}_D$= - 39.5 (0.5, THF)

Example 87: (+/-)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid (87). (+)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid (87a) & (-)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid (87b)

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 158** for 1h. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the racemic endo-isomer 4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid (570 mg, Yield: 43 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (1H, dd, *J* = 1.6 & 8 Hz), 7.75 (1H, m), 7.64 (1H, dd, *J* = 1.2 & 10.8 Hz), 6.98 (1H, t, *J* = 75.2 Hz), 6.87 (1H, d, *J* = 2 Hz),6.77 (1H, dd, *J* = 2.8 & 9.2 Hz), 6.71 (1H, d, *J* = 9.2 Hz), 5.85 (1H, s), 4.74 (1H, d, *J* = 2.8 Hz), 3.42-3.39 (1H, m), 2.54-2.50 (1H, m), 2.11-2.06 (1H, m), 1.73-1.67 (1H, m), 1.54-1.47 (1H, m), 1.43-1.36 (2H, m), 1.06-1.02 (1H, m).

LC-MS: t_R = 9.68 $[M+H]^+$ = 378 (method 1)

Enantiomeric separation of 677 mg of (+/-)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid (**87**) by preparative chiral chromatography was carried out using Heptane/EtOH (95:5) as eluents to yield:

260 mg of the enantiomer (+)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid (**87a**)

Preparative HPLC: t_R = 27.9

Optical Purity: 99.9% ee

$[\alpha]^{Na}_D$= + 65.6 (0.5, THF)

298 mg of the enantiomer (-)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid (**87b**)

Preparative HPLC: t_R = 54.7

Optical Purity: 98.4% ee

$[\alpha]^{Na}_D$= - 64.9 (0.5, THF)

Example 88: (+/-)-4-((3aS,4R,9bR)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid (88). (+)-4-((3aS,4R,9bR)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid (88a) & (-)-4-((3aS,4R,9bR)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid (88b)

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 159** for 1h. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the endo-isomer (+/-)-4-((3aS,4R,9bR)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid (700 mg, Yield: 58 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (1H, dd, *J* = 1.6 & 8 Hz), 7.76 (1H, m), 7.63 (1H, dd, *J* = 1.6 & 11.6 Hz), 6.86 (1H, s), 6.75 (1H, dd, *J* = 1.6 & 8.4 Hz),6.62 (1H, d, *J* = 8 Hz), 5.54 (1H, s), 4.71 (1H, d, *J* = 2.8 Hz), 3.41-3.38 (1H, m), 2.49-2.43 (2H, q, *J* = 7.6 Hz), 2.10-2.04 (1H, m), 1.73-1.67 (1H, m), 1.57-1.49 (1H, m), 1.42-1.35 (2H, m), 1.12 (3H, t, *J* = 7.2 Hz), 1.05-1.01 (1H, m).

LC-MS: t_R = 10.68 $[M+H]^+$ = 340 (method 1)

Enantiomeric separation of 677 mg of (+/-)-4-((3aS,4R,9bR)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid (**88**) by preparative chiral chromatography was carried out using Heptane/IPA (98:2) as eluents to yield:

267 mg of the enantiomer (+)-4-((3aS,4R,9bR)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid (**88a**)

Preparative HPLC: t_R = 20.7

Optical Purity: 99.9% ee

$[\alpha]^{Na}_D$= + 53.1 (0.5, THF)

246 mg of the enantiomer (-)-4-((3aS,4R,9bR)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid (**88b**)

Preparative HPLC: t_R = 55.2

Optical Purity: 99.9% ee

$[\alpha]^{Na}_{D}$= - 50.8 (0.5, THF)

Example 89: 3-(trifluoromethyl)-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 160** for 1h. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the endo-isomer 3-(trifluoromethyl)-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (22.2 mg, Yield: 25%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (1H, d, *J* = 8.8 Hz), 8.20 (1H, s), 8.13 (1H, d, *J* = 8.4 Hz), 6.85 (1H, s), 6.72 (1H, d, *J* = 7.6 Hz), 6.56 (1H, d, *J* = 8 Hz), 5.70 (1H, s), 4.74 (1H, s), 3.38-3.32 (1H, m), 2.36-2.30 (1H, m), 2.16 (3H, s), 2.15-2.06 (1H, m), 1.77-1.67 (2H, m), 1.50-1.36 (2H, m), 1.14-1.08 (1H, m).

LC-MS: t_R = 10.85 $[M+H]^+$=376 (method 1)

Example 90: 3-(trifluoromethyl)-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 161** for 1h. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the endo-isomer 3-(trifluoromethyl)-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (24.2 mg, Yield: 25%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (1H, dd, *J* = 8 & 1.6 Hz), 8.20 (1H, d, *J* = 1.6 Hz), 8.14 (1H, d, *J* = 8 Hz), 6.63-6.55 (3H, m), 5.56 (1H, s), 4.69 (1H, s), 3.65

(3H, s), 3.41-3.35 (1H, m), 2.36-2.32 (1H, m), 2.16-2.07 (1H, m), 1.79-1.65 (2H, m), 1.52-1.36 (2H, m), 1.13-1.06 (1H, m).

LC-MS: t_R = 10.85 $[M+H]^+$=376 (method 1)

Example 91: 4-((3aS,4S,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-dimethylbenzoic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 163** (0.36 mmol, 135 mg). It was necessary 40 h and an additional 0.750 mL of 1M LiOH to complete the reaction. After that, the solvent was removed in vacuum and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave 81.4 mg of the pure title exo-isomer (Yield: 63%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (2H, s), 7.15 (1H, d, *J* = 2.8 Hz), 6.98 (1H, dd, *J* = 8.8 & 2.4 Hz), 6.53 (1H, d, *J* = 8.4 Hz), 4.37 (1H, d, *J* = 11.2 Hz), 3.12-3.04 (1H, m), 2.89-2.81 (1H, m), 2.69-2.40 (6H, m), 2.36-2.30 (1H, m), 1.82-1.63 (4H, m), 1.31-1.24 (1H, m).

LC-MS: t_R = 10.65 $[M+H]^+$=356/358 (method 1)

Example 92: (+/-)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluoro-5-methylbenzoic acid (92). (+)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluoro-5-methylbenzoic acid (92a) & (-)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluoro-5-methylbenzoic acid (92b)

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 164** (0.308 mmol, 120 mg) for 1h. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the endo-isomer (+/-)-4-((3aS,4R,9bR)-8-

(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluoro-5-methylbenzoic acid (40 mg, Yield: 33 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 (1H, s), 7.46 (1H, d, *J* = 11.6 Hz), 6.96 (1H, t, *J* = 75.2 Hz), 6.84 (1H, d, *J* = 2.8 Hz), 6.73 (1H, dd, *J* = 8.8 & 2.4 Hz), 6.60 (1H, d, *J* = 8.4 Hz), 5.92 (1H, s), 4.82 (1H, d, *J* = 2 Hz), 3.42-3.40 (1H, m), 2.5-2.49 (3H, brs), 2.5-2.43 (1H, m), 2.19-2.11 (1H, m), 1.82-1.76 (1H, m), 1.67-1.54 (2H, m), 1.46-1.38 (1H, m), 1.29-1.24 (1H, m).

LC-MS: t_R = 9.60 $[M+H]^+$ = 392 (method 1)

(+)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluoro-5-methylbenzoic acid **(92a)** was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 164a** (0.318 mmol, 124 mg) for 1h. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the endo-isomer (+)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluoro-5-methylbenzoic acid (75 mg, Yield: 60 %).

$[\alpha]^{Na}_D$= + 39.1 (0.5, THF)

(-)4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluoro-5-methylbenzoic acid **(92b)** was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 164b** (0.478 mmol, 186 mg) for 1h. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the endo-isomer (-)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluoro-5-methylbenzoic acid (117 mg, Yield: 63 %).

$[\alpha]^{Na}_D$= - 40.9 (0.5, THF)

Example 93: (+/-)-4-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid (93). (+)-4-

((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid (93a) & (-)-4-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid (93b)

The **intermediate compound 165** (1.58 g, 4.37 mmol) was dissolved in EtOH and THF (1:1, 40 mL) and platinum dioxide (1% w/w, 16 mg) was added. The solution was hydrogenated at r.t. for 30min. HPLC analysis showed total conversion. Reaction mixture was filtered and the filter washed by THF. Solvent was evaporated and the crude material was purified by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents. Only high purity fractions were collected. Residue was triturated in the minimum amount of dichloromethane, the solid was filtered and washed with hexane to give 597 mg (37%) of the pure racemic endo-isomer.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54 (2H, d, *J* = 9.6 Hz), 7.01 (1H, d, *J* = 2.0 Hz), 6.89 (1H, dd, *J* = 8.8 & 2.4 Hz), 6.58 (1H, d, *J* = 8.4 Hz), 6.13 (1H, s), 4.85 (1H, d, *J* = 3.2 Hz), 3.39-3.30 (1H, m), 3.39-3.30 (1H, m), 2.47-2.40 (1H, m), 2.11-2.05 (1H, m), 1.75-1.73 (1H, m), 1.65-1.63 (1H, m), 1.61-1.42 (2H, m), 1,33-1,28 (1H, m),

LC-MS: t_R = 10.40 $[M+H]^+$= 362/364 (method 1)

Enantiomeric separation of 595 mg of (+/-)-4-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid (**93**) by preparative chiral chromatography was carried out using Heptane/EtOH (95:5) as eluents to yield:

116 mg of the enantiomer (+)-4-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid (**93 a**)

Preparative HPLC: t_R = 21.1

Optical Purity: 99.9% ee

$[\alpha]^{Na}_D$= + 17.1 (0.5, THF)

224 mg of the enantiomer (-)-4-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid (**93 b**)

Preparative HPLC: t_R = 30.8

Optical Purity: 94.4% ee

$[\alpha]^{Na}_D$= - 12.1 (0.5, THF)

Example 94: (+/-)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid (94). (+)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid (94a) & (-)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid (94b)

The following compound was prepared using the same methodology as in intermediate compound 172 using **Intermediate compound 166** (750 mg, 1.90 mmol). The solution was hydrogenated at r.t. for 1 h. HPLC analysis showed total conversion. Reaction mixture was filtered and the filter washed with THF. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave 555 mg of the title endo-isomer together with 5% of the exo-isomer. This solid was triturated in hexane, filtered and washed by hexane to give 320 mg of the racemic endo-isomer (contaminated with 5% exo-isomer) (Yield: 42%.)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53 (2H, d, *J* = 9.6 Hz), 6.95 (1H, t, *J* = 75.2 Hz), 6.83 (1H, d, *J* = 2.0 Hz), 6.72 (1H, dd, *J* = 8.8 & 2.8 Hz), 6.58 (1H, d, *J* = 8.4 Hz), 5.99 (1H, s), 4.83 (1H, d, *J* = 2.8 Hz), 3.39-3.30 (1H, m), 2.48-2.41 (1H, m), 2.38-2.24 (1H, m), 2.15-2.06 (1H, m), 1.79-1.71 (1H, m), 1.65-1.57 (1H, m), 1.50-1.32 (2H, m).

LC-MS: t_R = 9.62 $[M+H]^+$= 396 (method 1)

Enantiomeric separation of 450 mg of (+/-)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid (**94**) by preparative chiral chromatography was carried out using Heptane/EtOH-0.2%TFA (90:10) as eluents to yield:

94 mg of the enantiomer (+)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid (**94 a**)

Preparative HPLC: t_R = 19.1

Optical Purity: 99.9% ee

$[\alpha]^{Na}_D$= + 37.1 (0.5, THF)

142 mg of the enantiomer (-)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid (**94 b**)

Preparative HPLC: t_R = 33.8

Optical Purity: 98.6% ee

$[\alpha]^{Na}_D$= - 33.2 (0.5, THF)

Example 95: (+/-)-4-((3aS,4R,9bR)-8-cyclopropyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid (95) & (+)-4-((3aS,4R,9bR)-8-cyclopropyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid (95a)

The following compound was prepared using the same methodology as in intermediate compound 172 using **Intermediate compound 167** (1.3 g, 3.54 mmol). The solution was hydrogenated at r.t. for 2 h. HPLC analysis showed total conversion. Reaction mixture was filtered and the filter washed with THF. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave 635 mg of the racemic endo-isomer contaminated with 7% of the exo-isomer.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.51 (2H, d, *J* = 9.2 Hz), 6.73 (1H, d, *J* = 1.6 Hz), 6.57 (1H, dd, *J* = 8.0 & 2.0 Hz), 6.47 (1H, d, *J* = 8.4 Hz), 5.68 (1H, s), 4.78 (1H, d, *J* = 3.2 Hz), 3.35-3.28 (1H, m), 2.50-2.47 (1H, m), 2.44-2.36 (1H, m), 2.11-2.04 (1H, m), 1.82-1.70 (1H, m), 1.64-1.55 (1H, m), 1.50-1.28 (3H, m), 0.81-0.76 (2H, m), 0.50-0.47 (2H, m).

LC-MS: t_R = 5.28 $[M+H]^+$= 370 (method 2)

Enantiomeric separation of 800 mg of (+/-)-4-((3aS,4R,9bR)-8-cyclopropyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid (**95**) by preparative chiral chromatography was carried out using using heptane/EtOH (98:2) as eluents to yield only the first enantiomer:

62 mg of the enantiomer 1: (+)-4-((3aS,4R,9bR)-8-cyclopropyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid (**95a**)

Preparative HPLC: t_R = 22.9

Optical Purity: 99.9% ee

$[\alpha]^{Na}_{D}$= + 7.99 (0.5, THF)

The enantiomer (-)-4-((3aS,4R,9bR)-8-cyclopropyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid could not be pure isolated.

Example 96: 3,5-dichloro-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 170** (0.14 mmol, 48 mg). The mixture was stirred at room temperature until HPLC showed not starting material left. It was necessary 16 h. The solvent was removed in vacuum and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the title compound as a white solid (30 mg, Yield: 75 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (2H, m), 6.82 (1H, s), 6.70 (1H, d, *J* = 7.6 Hz), 6.48 (1H, d, *J* = 7.6 Hz), 5.64 (1H, s), 5.14 (1H, d, *J* = 3.2 Hz), 3.35-3.32 (1H, m), 2.55-2.52 (1H, m), 2.15 (3H, s), 2.14-2.07 (1H, m) 1.97-1.92 (1H, m), 1.70-1.66 (1H, m), 1.58-1.53 (1H, m), 1.43-1.39 (1H, m), 1.29-1.25 (1H, m).

LC-MS: t_R = 11.08 $[M+H]^+$ = 376/378 (method 1)

Example 97: 5-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-6-methylpyridine-2-carboxylic acid

The following compound was prepared using the same methodology as in example 61 from **intermediate compound 172** (0.09 mmol, 60 mg). After 4 h of reaction more reactants were added (1 mL) and left 2h at 110ºC. Solvent was evaporated and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave 23 mg of the pure title endo-isomer (Yield: 76%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (1H, d, *J* = 8.0 Hz), 7.90 (1H, d, *J* = 8.4 Hz), 7.05 (1H, d, *J* = 2.4 Hz), 6.92 (1H, dd, *J* = 8.0 & 2.4 Hz), 6.68 (1H, d, *J* = 8.4 Hz), 5.89 (1H, s), 4.68 (1H, d, *J* = 2.8 Hz), 3.41 (1H, dt, *J* = 7.6 & 2.4 Hz), 2.57 (3H, s), 2.53-2.47 (1H, m), 2.12-2.03 (1H, m), 1.72-1.65 (1H, m),1.54-1.44 (1H, m), 1.42-1.34 (1H, m), 1.00-0.94 (1H, m),

LC-MS: t_R = 7.98 $[M+H]^+$= 343/345 (method 1)

Example 98: 6-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-5-methylpyridine-3-carboxylic acid

The following compound was prepared using the same methodology as in example 61 from **intermediate compound 175** (0.161 mmol, 52 mg). Total conversion was not achieved, an addicional 0.5 mL of mixture of acetic acid: water: concentrated hydrochloric acid (1:1:2) was added and left 2 h to complete the reaction. Reaction mixture was cooled down, the solvent was evaporated and the crude material was purified by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to afford 8.6 mg of the title endo-isomer (Yield: 16%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (1H, d, *J* = 2 Hz), 8.06 (1H, d, *J* = 1.6 Hz), 7.05 (1H, d, *J* = 2 Hz), 6.90 (1H, dd, *J* = 8.4 & 2.4 Hz), 6.75 (1H, d, *J* = 8.8 Hz), 5.81 (1H, s), 4.82 (1H, d, *J* = 2.4 Hz), 3.45-3.40 (1H, m), 2.71-2.64 (1H, m), 2.42 (3H, s), 2.61-1.96 (1H, m), 1.72-1.66 (1H, m), 1.58-1.48 (1H, m), 1.41-1.31 (2H, m), 0.98-0.89 (1H, m).

LC-MS: t_R = 8.22 $[M+H]^+$=343 (method 1)

Example 99: 2-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-1-methyl-1H-imidazole-4-carboxylic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 177** (0.14 mmol, 48 mg). It was necessary 60 h and an addicional 1.4 mL of 1M LiOH (10 eq) to complete the reaction. After that, the solvent was removed in vacuum and purification of the crude material by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents afforded the title compound as a white solid (32 mg, Yield: 68 %).

^{1}H NMR (400 MHz, CD_3CN) δ 8.38 (1H, s), 7.65 (1H, s), 7.10 (1H, s), 6.93 (1H, d, *J* = 8.4 Hz), 6.64 (1H, d, *J* = 8.8 Hz),5.14 (1H, s), 3.79 (3H, s), 3.40-3.39 (1H, m), 2.5-2.44 (1H, m), 2.15-2.11 (1H, m), 1.86-1.80 (1H, m), 1.62-1.57 (1H, m), 1.48-1.44 (2H, m), 1.27-1.23 (1H, m).

LC-MS: t_R = 6.47 $[M+H]^+$ = 332 (method 1)

Example 100: 7-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methyl-3H-benzo[d]imidazole-4-carboxylic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 179** (0.028 mmol, 11 mg). It was necessary 60 h and 0.22 mL of 1M LiOH (8 eq). The solvent was removed in vacuum, added water, cooled with an ice/water bath and acidified by 1M HCl until a white solid appeared. The solid was filtered, washed with cold water and dried under vacuum at 40ºC to give the endo-isomer compound 7-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methyl-3H-benzo[d]imidazole-4-carboxylic acid (7 mg, Yield: 64%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (1H, s), 7.75 (1H, d, *J* = 6.4 Hz), 7.45 (1H, brs), 6.65 (2H, m), 6.57 (1H, s), 5.39 (1H, s), 5.11 (1H, s), 3.98 (3H, s), 3.66 (3H, s), 3.35-3.32 (1H, m), 2.87-2.80 (1H, m), 2.14-2.07 (1H, m), 1.71-1.55 (2H, m), 1.36-1.23 (2H, m), 1.96 (1H, m).

LC-MS: t_R = 6.45 $[M+H]^+$ = 378 (method 1)

Example 101: 7-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-1H-indole-4-carbonitrile

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 185** (0.28 mmol, 97 mg) using platinum dioxide (2 % w/w, 2 mg) for 30 min. Reaction mixture was filtered and the filter washed with THF. Solvent was evaporated and purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave endo-isomer 7-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-1H-indole-4-carbonitrile (49 mg, Yield: 51%).

^{1}H NMR (400 MHz, $CDCl_3$) 9.81 (1H, brs), 7.46 (1H, d, *J* = 7.2 Hz), 7.40 (1H, dd, *J* = 2.8 Hz), 7.15 (1H, d, *J* = 8 Hz), 6.80-6.78 (1H, m), 6.74 (1H, d, *J* = 2 Hz), 6.66 (1H, d, *J* = 2.8 Hz), 6.65 (1H, s), 4.83 (1H, d, *J* = 3.2 Hz), 3.79 (3H,s), 3.55-3.50 (1H, m), 2.60-2.52 (1H, m), 2.30-2.21 (1H, m), 1.82-1.71 (2H, m), 1.65-1.60 (1H, m), 1.48-1.38 (1H, m), 1.23-1.16 (1H, m).

LC-MS: t_R = 9.22 $[M+H]^+$=344 (method 1)

Example 102: 2-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)thiazole-5-carboxylic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 190** (0.35 mmol, 121 mg). Solvent was evaporated and water was added. The mixture was cooled to 0-5 ºC and 2N aqueous HCl solution was added until a solid was formed (pH 2). The suspension was stirred for 30 minutes at this temperature before it was filtered under vacuum. The crude material was purified by reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents to give 17 mg of the pure title endo-isomer (Yield: 15%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.4 (1H, brs), 8.26 (1H, s), 6.85 (1H, brs), 6.38 (1H, d, *J* = 7.6 Hz), 6.59 (1H, d, *J* = 8.0 Hz), 6.03 (1H, s), 4.74 (1H, d, *J* = 2.4 Hz), 3.30 (1H, m), 2.60 (1H, m), 2.15 (3H, s), 2.02 (1H, m), 1.75 (1H, m), 1.52 (1H, m), 1.38 (2H, m), 1.15 (1H, m).

LC-MS: t_R = 7.34 $[M+H]^+$= 315 (method 1)

Example 103: 2-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)thiazole-5-carboxylic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 192** (0.85 mmol, 309 mg). Solvent was evaporated and water was added. The mixture was cooled to 0-5 ºC and 2N aqueous HCl solution was added until a solid was formed (pH 2). The suspension was stirred for 30 minutes at this temperature before it was filtered under vacuum and washed with cold water. The solid obtained was dried at room temperature under reduced pressure to give 270 mg of the pure title compound (Yield: 95%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.5 (1H, brs), 8.27 (1H, s), 7.07 (1H, d, *J* = 2.4 Hz), 6.96 (1H, dd, *J* = 8.4 and 2.4 Hz), 6.72 (1H, d, *J* = 8.4 Hz), 6.42 (1H, s), 4.81 (1H, d, *J* = 3.2Hz), 3.37 (1H, m), 2.59 (1H, m), 2.04 (1H, m), 1.74 (1H, m), 1.47 (1H, m), 1.36 (2H, m), 1.18 (1H, m).

LC-MS: t_R = 7.58 $[M+H]^+$= 335 (method 1)

Example 104: 4-chloro-5-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)thiazole-2-carboxylic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 198** (1.8 mmol, 692 mg). Solvent was evaporated and water was added. The mixture was cooled to 0-5 ºC and 2N aqueous HCl solution was added until a solid was formed (pH 2). The suspension was stirred for 30 minutes at this temperature before it was filtered under vacuum and washed with cold water. Then the solid was stirred with acetonitrile at room temperature. The solvent was removed by filtration and the solid obtained was

dried at 40 ºC under reduced pressure to give 403 mg of the pure title compound (Yield: 64%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 6.84 (1H, s), 6.71 (1H, d, *J* = 8 Hz), 6.51 (1H, d, *J* = 8 Hz), 4.68 (1H, d, *J* = 2.8 Hz), 3.31 (1H, m), 2.50 (1H, m), 2.13 (3H, s), 2.02 (1H, m), 1.72 (1H, m), 1.55 (1H, m), 1.41 (2H, m), 1.27 (1H, m).

LC-MS: t_R = 7.89 $[M+H]^+$= 349 (method 1)

Example 105: 4-chloro-5-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)thiazole-2-carboxylic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 200** (2.1 mmol, 835 mg). Solvent was evaporated and water was added. The mixture was cooled to 0-5 ºC and 2N aqueous HCl solution was added until a solid was formed (pH 2). The suspension was stirred for 30 minutes at this temperature before it was filtered under vacuum and washed with cold water. Then the solid was stirred with acetonitrile at room temperature. The solvent was removed by filtration and the solid obtained was dried at 40 ºC under reduced pressure to give 701 mg of the pure title compound (Yield: 90%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.05 (1H, s), 6.94 (1H, d, *J* = 8.8 Hz), 6.64 (1H, d, *J* = 8.4 Hz), 4.74 (1H, d, *J* = 2.8 Hz), 3.36 (1H, m), 2.48 (1H, m), 2.05 (1H, m), 1.73 (1H, m), 1.52 (1H, m), 1.43 (2H, m), 1.30 (1H, m).

LC-MS: t_R = 8.05 $[M+H]^+$= 370 (method 1)

Example 106: (3aS,4R,9bR)-4-(4-(1H-tetrazol-5-yl)phenyl)-8-methoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinoline

The following compound was prepared using the same methodology as in intermediate compound 67 using **intermediate compound 202** (0.89 mmol, 307 mg). The solution was hydrogenated for 1 h at r.t. Reaction mixture was filtered and washed with CH_2Cl_2. Solvent was evaporated and the solid obtained was stirred with acetonitrile at room temperature. The solvent was removed by

filtration and the solid was washed with cold acetonitrile. The solid obtained was then stirred with MeOH in the same manner as before to give 217 mg of the title compound (Yield: 70%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (2H, d, *J* = 8 Hz), 7.64 (2H, d, *J* = 8.4 Hz), 6.64 (1H, d, *J* = 8.8 Hz), 6.61 (1H, d, *J* = 2.8 Hz), 6.54 (1H, dd, *J* = 8.4 and 2.8 Hz), 5.43 (1H, s), 4.45 (1H, d, *J* = 2.8 Hz), 3.64 (3H, s), 3.4 (1H, m), 2.5 (1H, m), 2.08 (1H, m), 1.68 (1H, m), 1.55 (1H, m), 1.36 (2H, m), 1.03 (1H, m).

LC-MS: t_R = 7.73 $[M+H]^+$= 348 (method 1)

Example 107: 3,5-difluoro-4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 using **intermediate compound 203** (3.95 mmol, 1.35 g). The solution was hydrogenated for 1 h at r.t. Reaction mixture was filtered and washed with CH_2Cl_2/MeOH. The solvent was removed by filtration and the solid was purified by flash chromatography on silica gel using cyclohexane/ethyl acetate as eluents to give impure title compound. It was then purified by reverse C_{18} chromatography using water (NH_4CO_3, pH 8) and acetonitrile as eluents to give 80 mg of the title compound (Yield: 6%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.38 (2H, d, *J* = 10 Hz), 6.79 (1H, s,), 6.67 (1H, dd, *J* = 8 and 1.6 Hz), 6.48 (1H, d, *J* = 8 Hz), 5.6 (1H, s), 4.74 (1H, d, *J* = 2.8 Hz), 3.3 (1H, m), 2.4 (1H, m), 2.25 (3H, s), 2.1 (1H, m), 1.8 (1H, m), 1.61 (1H, m), 1.49 (1H, m), 1.42 (1H, m), 1.31 (1H, m).

LC-MS: t_R = 10.1 $[M+H]^+$= 344 (method 1)

Example 108: (+/-)-4-((3aS,4R,9bR)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid (108). (+)-4-((3aS,4R,9bR)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid (108a) & (-)-4-((3aS,4R,9bR)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid (108b)

The following compound was prepared using the same methodology as in intermediate compound 67 using **intermediate compound 204** (5.4 mmol, 1.92 g). The solution was hydrogenated for 2 h at r.t. Reaction mixture was filtered and washed with EtOAc. The solvent was removed by filtration and the solid was purified by reverse C_{18} chromatography using water (NH_4CO_3, pH 8) and acetonitrile as eluents to give 672 mg of the title compound (Yield: 35%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (2H, d, *J* = 10 Hz), 6.81 (1H, d, *J* = 1.2 Hz), 6.7 (1H, dd, *J* = 8 and 1.6 Hz), 6.5 (1H, d, *J* = 7.6 Hz), 5.65 (1H, s), 4.74 (1H, d, *J* = 2.8 Hz), 3.46 (1H, m), 2.44 (2H, q, *J* = 7.6 Hz), 2.07 (1H, m), 1.81 (1H,m,), 1.61 (1H, m), 1.47 (1H, m), 1.39 (1H, m), 1.33 (1H, m), 1.1 (3H, t, *J* = 7.2 Hz).

LC-MS: t_R = 10.6 $[M+H]^+$= 358 (method 1)

The racemic mixture (672 mg) was separated by preparative chiral HPLC using heptane/EtOH-0.2% TFA (98:2) as eluents to yield:

138 mg of the enantiomer (+)-4-((3aS,4R,9bR)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid (**108a**)

Preparative HPLC: t_R = 21.0

Optical Purity: 99.9% ee

$[\alpha]^{Na}_D$= + 26.3 (0.5, THF)

254 mg of the enantiomer (-)-4-((3aS,4R,9bR)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid (**108b**) (which needed to be again purified by reverse C_{18} chromatography using water (NH_4CO_3, pH 8) and acetonitrile as eluents to yield 35 mg of pure title compound)

Preparative HPLC: t_R = 46.7

Optical Purity: 99.9% ee

$[\alpha]^{Na}_{D}$= - 18.5 (0.5, THF)

Example 109: 3,5-difluoro-4-((3aS,4R,9bR)-8-methoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid

The following compound was prepared using the same methodology as in intermediate compound 67 using **intermediate compound 205** (2.9 mmol, 1.05 g). The solution was hydrogenated for 1.5 h at r.t. Reaction mixture was filtered, washed with EtOAc and the solvent was removed under reduced pressure to afford the title compound (883 mg. Yield: 84%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.51 (d, 2 H, *J* = 10.4 Hz), 6.66-6.51 (3 H, m), 5.35 (s, 1 H), 4.66 (1 H, s), 3.62 (3H + 1H, brs), 2.37 (m, 1H), 2.04 (m, 1H), 1.79 (m, 1 H), 1.54 (m, 1 H), 1.43 (m, 1 H), 1.28 (m, 1 H).

LC-MS: t_R = 3.24 $[M+H]^+$= 360 (method 4)

The racemic mixture (880 mg) could not be separated by preparative chiral HPLC using heptane/EtOH-0.2% TFA (95:5) as eluents because this product was unstable.

Example 110: 4-((6R,6aS,10aR)-2-chloro-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-3-methylbenzoic acid

The following compound was prepared using the same methodology as in example 30 from **intermediate compound 209** (1.2 mmol, 460 mg). Additional 1M LiOH solution was added to complete the reaction. Solvent was evaporated and EtOAC and water were added. The separated aqueous layer was cooled to 0-5 ºC and 2N aqueous HCl solution was added until a solid was formed (pH 2). The suspension was stirred for 30 minutes at this temperature before it was filtered under vacuum. The solid was washed with cold water and then with cold acetonitrile. Then it was dried at 40 ºC under vacuum to give 51 mg of the pure title compound (Yield: 12%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (1H, d, *J* = 8.8 Hz), 7.75 (1H, s), 7.54 (1H, d, *J* = 8 Hz), 7.07 (1H, s), 6.92 (1H, d, *J* = 8 Hz), 6.65 (1H, d, *J* = 8.8 Hz), 6.04 (1H, s), 4.77 (1H, s), 2.4 (1H, m), 2.3 (1H, m), 2.3 (3H, s), 1.89 (1H, m), 1.61 (1H, m), 1.52 (1H, m), 1.35 (1H, m), 1.07 (3H, m), 0.94 (1H, m).

LC-MS: t_R = 10.2 $[M+H]^+$= 356/358 (method 1)

Example 111: (+/-)-4-((6S,6aS,10aR)-2-chloro-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-3-methylbenzoic acid (111). (-)-4-((6S,6aS,10aR)-2-chloro-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-3-methylbenzoic acid (111a).

To a stirred solution of **intermediate compound 208** (0.9 mmol, 346 mg) in THF (4.1 mL), 1N LiOH (5.6 mmol, 5.6 mL) was added. After 66 h, THF was removed under reduced pressure. The aqueous extract was acidified to pH 3 with HCl 2 N. After stirring 30 min at 0ºC, the solid was filtered and washed with cold water (0ºC). The crude was dispersed in ACN (0ºC, 15 min) filtered and dried (40ºC) to afford the title compound as a white solid (164 mg. Yield: 50%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (1H, s), 7.68 (1H, d, *J* = 8.0 Hz), 7.21 (1H , d, *J* = 7.6 Hz), 6.98 (1H, m), 6.93 (1H, dd, *J* = 8.8 & 2.4 Hz), 6.55 (1H, d, *J* = 8.8 Hz), 6.34 (1H, brs), 4.51 (1H, brs), 2.59 (1H, brs), 2.38 (3H, s), 2.06 (1H, brs), 1.95 (1H, brs), 1.51 (3H, brs), 1.36 (3H, brs), 1.2 (1H, m).

LC-MS: t_R = 3.9 $[M+H]^+$= 356 (method 4)

The racemic mixture (689 mg) was separated by preparative chiral HPLC using heptane/EtOH-0.2% TFA (98:2) as eluents to yield only the (-)-enantiomer (the (+)- enantiomer could not be pure isolated):

21 mg of the enantiomer (-)-4-((6S,6aS,10aR)-2-chloro-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-3-methylbenzoic acid (**111a**)

Preparative HPLC: t_R = 47.9

Optical Purity: 99.9% ee

$[\alpha]^{Na}_D$= - 94.3 (0.5, $CHCl_3$)

Example 112: 4-((6R,6aS,10aR)-2-chloro-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoic acid

Following the same methodology as in Example 111, but starting from **intermediate compound 213** (0.26 mmol, 93 mg), the title compound was obtained (49 mg. Yield: 55%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.89 (1H, brs), 7.94 (2H, d, *J* = 8.8 Hz), 7.50 (2H, d, *J* = 8.4 Hz), 7.08 (1H, brs), 6.93 (1 H, dd, *J* = 8.0 & 1.6 Hz), 6.67 (1H, d, *J* = 8.8 Hz), 6.21 (1H, brs), 4.67 (1H, brs), 3.3 (1H, brs), 2.36 (1H, m), 1.90 (1H, m), 1.61 (1H, m), 1.51 (1H, m), 1.36 (1H, m), 1.06 (3H, m), 0.93 (1H, m).

LC-MS: t_R = 3.89 $[M+H]^+$= 342 (method 4)

Example 113: 4-((6S,6aS,10aR)-2-methyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoic acid

Following the same methodology as in example 111, but starting from **intermediate compound 212** (0.25 mmol, 89 mg), the title compound was obtained (37 mg. Yield: 43%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.86 (1H, brs), 7.91 (1H, d, *J* = 8.0 Hz), 7.42 (1H, d, *J* = 8.4 Hz), 6.97 (1H, d, *J* = 2.4 Hz), 6.90 (1 H, dd, *J* = 8.4 & 1.6 Hz), 6.67 (1H, d, *J* = 8.8 Hz), 6.21 (1H, brs), 4.67 (1H, brs), 3.3 (1H, brs), 2.36 (1H, m), 1.90 (1H, m), 1.61 (1H, m), 1.51 (1H, m), 1.36 (1H, m), 1.06 (3H, m), 0.93 (1H, m).

LC-MS: t_R = 3.87 $[M+H]^+$= 342 (method 4)

Example 114: 4-((6S,6aS,10aR)-2-methyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoic acid

Following the same methodology as in example 111 but starting from **intermediate compound 215** (0.25 mmol, 87 mg), the title compound was obtained (50 mg. Yield: 60%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.82 (1H, brs), 7.89 (2H, d, *J* = 8.0 Hz), 7.42 (2H, d, *J* = 8.0 Hz), 6.77 (1H, s), 6.70 (1 H, d, *J* = 8.0 Hz), 6.47 (1H, d, *J* = 8.0

Hz), 5.92 (1H, brs), 4.43 (1H, *J* = 7.2 Hz)), 2.50 (1H, s), 2.14 (3H, s), 1.90-1.79 (2H, m), 1.61-1.40 (4H, m), 1.40-1.30 (2H, m), 1.20 (1H, m).

LC-MS: t_R = 10.02 $[M+H]^+$= 322 (method 1)

Example 115: (+/-)-4-((6S,6aS,10aR)-2-(difluoromethoxy)-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoic acid (115) & (-)-4-((6S,6aS,10aR)-2-(difluoromethoxy)-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoic acid (115a).

A mixture of **intermediate compounds 218 & 219** (0.98 mmol, 379 mg) was stirred at 70 ºC in a mixture of 1M NaOH/THF (1:1, 20 mL) for 7 h. After that, THF was removed under reduced pressure. The aqueous extract was acidified to pH 3 with HCl 2 N. After stirring 30 min at 0ºC, the solid was filtered and washed with cold water (0ºC) and dried under vacuum (40ºC) to afford the title compound as a endo/exo (1:1 mixture, 233 mg). The crude mass was dispersed in ACN/MeOH (5:1, 1.2 mL, 5 min) and filtered. The resulting solid (53 mg) was a mixture 95:5 enriched in the desired exo regioisomer (as checked by NMR). An additional dispersion of the solid, afforded the pure exo isomer (35 mg. Yield: 9%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.86 (1H, brs), 7.90 (2H, d, *J* = 8.0 Hz), 7.42 (2H, d, *J* = 8.4 Hz), 6.94 (1H, t, *J* = 75.2 Hz), 6.82 (1H, d, *J* = 2.4 Hz), 6.75 (1H, dd, *J* = 8.00 & 2.80 Hz), 6.57 (1H, d, *J* = 8.8 Hz), 6.25 (1H, brs), 4.46 (1H, d, *J* = 6.8 Hz), 2.60 (1H, s), 1.96 (1H, m), 1.89 (1H, m), 1.60-1.45 (4H, m), 1.37 (2H, m), 1.17 (1H, m).

LC-MS: t_R = 4.78 $[M+H]^+$= 374 (method 4)

A second batch of the racemic mixture (542 mg) obtained as previously described, was separated by preparative chiral HPLC using heptane/EtOH-0.2% TFA (90:10) as eluents to yield only the (-)-enantiomer which was further stirred with acetonitrile (the (+)- enantiomer could not be pure isolated):

117 mg of the enantiomer (-)-4-((6S,6aS,10aR)-2-(difluoromethoxy)-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoic acid (**115a**)

Preparative HPLC: t_R = 32.1

Optical Purity: 91.4% ee

$[\alpha]^{Na}_{D}$= - 19.7 (0.5, THF)

Example 116: 3,5-dichloro-4-((6S,6aS,10aR)-2-methyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoic acid

Following the same methodology as in example 115, but starting from **intermediate compound 221** (1.8 mmol, 745 mg), the title compound was obtained (507 mg, Yield: 70%). An analytical sample (100 mg) was purified by column chromatography (C18, ACN/ aq $NaHCO_3$ pH 8) to afford 25 mg of chemically pure title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (2H, s), 6.71 (1H, s), 6.66 (1 H, d, *J* = 8.4 Hz), 6.35 (1H, d, *J* = 8.0 Hz), 5.71 (1H, brs), 5.30 (1H, d, *J* = 10.8 Hz), 2.74 (1H, m), 2.65 (1H, m), 2.10 (3H, s), 1.73-1.38 (7H, m), 1.28 (1H, m).

LC-MS: t_R = 11.15 $[M+H]^+$= 390 (method 1)

Example 117 & 118*: *4-((6R,6aS,11aR)-2-methyl-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[c]quinolin-6-yl)benzoic acid (117); 4-((6S,6aS,11aR)-2-methyl-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[c]quinolin-6-yl)benzoic acid (118)

The following compounds were prepared using the same methodology as in example 30 from **intermediate compound 222 and 223** (0.92 mmol, 320 mg). The reaction mixture was stirred at room temperature until HPLC showed not starting material left. It was stirred for 64 h. The solvent was removed in vacuum. The crude reaction was dissolved in water. The pH of the solution was adjusted to 1-2 by adding 1 N HCl aqueous solution. The resulting solid was filtered. The crude material was purified by preparative HPLC. Endo-isomer (117) 26.39 mg; Exo-isomer (118) 59.48 mg; (Overall yield: 28 %).

Endo-isomer (117) 4-((6R,6aS,11aR)-2-methyl-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[c]quinolin-6-yl)benzoic acid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.94 (2H, d, *J*=8.4Hz), 7.54 (2H, d, *J*=8.4Hz), 6.89 (1H, s), 6.73 (1H, d, *J*=8.4Hz), 6.59 (1H, d, *J*=8.1Hz), 5.65 (1H, s), 4.52 (1H, s), 2.42-2.27 (1H, m), 2.16 (3H, s), 2.16-2.07 (1H, m), 1.70-1.67 (3H, m), 1.59-1.42 (3H, m), 1.24-1.13 (2H, m), 0.98-0.83 (2H, m).

LC-MS: t_R = 2.28 $[M+H]^+$ = 336 (method 6)

Exo-isomer (118) 4-((6S,6aS,11aR)-2-methyl-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[c]quinolin-6-yl)benzoic acid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.85 (1H, s), 7.90 (2H, d, *J*=8.1Hz), 7.49 (2H, d, *J*=8.4Hz), 6.82 (1H, s), 6.69 (1H, d, *J*=8.1Hz), 6.46 (1H, d, *J*=8.1Hz), 5.85 (1H, s), 3.97 (1H, d, *J*=8.4Hz), 2.79-2.72 (1H, m), 2.15 (3H, s), 2.12-2.03 (1H, m), 1.79-1.67 (4H, m), 1.67-1.42 (2H, m), 1.42-1.31 (3H, m), 1.03-0.95 (1H, m).

LC-MS: t_R = 2.38 $[M+H]^+$ = 336 (method 6)

Example 119: 2-fluoro-4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid.

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 224** (0.89 mmol, 289 mg) and using platinum dioxide (7%w/w, 14.21 mg). It was stirred at r.t. for 2h. It was filtered over celite® and washed with MeOH. Solvent was evaporated and the crude material was purified by flash chromatography on silica gel (183.3 mg; yield: 63%, endo-isomer).

^{1}H NMR (300 MHz, DMSO-d_6) δ 13.15 (1H, s), 7.86 (1H, m), 7.35 (2H, m), 6.84 (1H, s), 6.72 (1H, d, *J*=8.1Hz), 6.60 (1H, d, *J*=8.1Hz), 5.63 (1H, s), 4.49 (1H, s), 3.40-3.33 (1H, m), 2.58-2.51 (1H, m), 2.16 (3H, s), 2.11.-1.99 (1H, m), 1.79-1.65 (1H, m), 1.52-1.34 (3H, m), 1.09-0.99 (1H, m).

LC-MS: t_R = 1.84 $[M+H]^+$ = 326 (method 6)

Example 120: 4-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-2-fluorobenzoic acid.

The following compound was prepared using the same methodology in intermediate compound 67 from **intermediate compound 225** (0.89 mmol, 289 mg). It was filtered over celite® and washed with MeOH. Solvent was evaporated and the crude material was purified by flash chromatography on silica gel (200.5 mg; yield: 65%, endo-isomer).

^{1}H NMR (300 MHz, DMSO-d_6) δ 13.19 (1H, s), 7.88 (1H, m), 7.35 (2H, m), 7.06 (1H, s), 6.97 (1H, dd, *J*=2.4&8.7Hz), 6.71 (1H, d, *J*=8.7Hz), 6.06 (1H, s), 4.55 (1H, d, *J*=2.7Hz), 3.43-3.40 (1H, m), 2.61-2.58 (1H, m), 2.09-2.03 (1H, m), 1.71-1.69 (1H, m), 1.52-1.39 (3H, m), 1.09-1.03 (1H, m).

LC-MS: t_R = 1.98 $[M+H]^-$ = 344 (method 6)

Example 121: 4-((3aS,4R,9bR)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-2-fluorobenzoic acid.

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 226** (0.89 mmol, 301 mg). It was filtered over celite® and washed with MeOH. Solvent was evaporated and the crude material was purified by flash chromatography on silica gel (46 mg; yield: 15.19%, endo-isomer).

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.86 (1H, m), 7.37-7.32 (2H, m), 6.85 (1H, s), 6.75 (1H, d, *J*=8.1Hz), 6.62 (1H, d, *J*=8.1Hz), 5.65 (1H, s), 4.50 (1H, s), 3.40-3.37 (1H, m), 2.58-2.51 (1H, m), 2.44 (2H, m), 2.09-2.00 (1H, m), 1.73-1.67 (1H, m), 1.55-1.30 (3H, m), 1.12 (3H, t, *J*=7.8Hz), 1.12-0.97 (1H, m).

LC-MS: t_R = 1.99 $[M+H]^-$ = 340 (method 6)

Example 122 & 123: 4-((6R,6aS,11aR)-2-chloro-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[c]quinolin-6-yl)benzoic acid (122); 4-((6S,6aS,11aR)-2-chloro-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[c]quinolin-6-yl)benzoic acid (123).

To a solution of **intermediate compounds 227 and 228** (0.38 mmol, 140 mg) in MeOH, 2N NaOH aqueous solution (3.80 mmol, 1.89 ml) was added. It was refluxed for 2h. The solvent was removed in vacuum. The crude reaction was dissolved in water. The pH of the solution was adjusted to 1-2 by adding 1 N HCl aqueous solution. The resulting solid was filtered. The solid was purified by preparative HPLC. Endo-isomer (122) 10.03 mg; Exo-isomer (123) 29.40 mg; (Overall yield: 29.28 %).

Endo-isomer (122) 4-((6R,6aS,11aR)-2-chloro-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[c]quinolin-6-yl)benzoic acid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.41 (1H, s), 7.91 (2H, d, *J*=8.1Hz), 7.47 (2H, d, *J*=8.1Hz), 7.10 (1H, s), 6.94 (1H, dd, *J*=2.1&6.3Hz), 6.71 (1H, d, *J*=8.7Hz), 6.09 (1H, s), 4.56 (1H, s), 2.40-2.36 (1H, m), 2.19-2.08 (1H, m), 1.65-1.52 (6H, m), 1.26-1.12 (2H, m), 0.94-0.87 (2H, m).

LC-MS: t_R = 2.04 $[M+H]^+$ = 356 (method 6)

Exo-isomer (123) 4-((6S,6aS,11aR)-2-chloro-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[c]quinolin-6-yl)benzoic acid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.95 (1H, m), 7.76 (2H, d, *J*=8.4Hz), 7.47 (2H, d, *J*=8.4Hz), 7.02 (1H, d, *J*=2.4Hz), 6.90 (1H, dd, *J*=2.4&6.0Hz), 6.57 (1H, d, *J*=8.4Hz), 6.31 (1H, s), 4.03 (1H, d, *J*=8.7Hz), 2.80-2.73 (1H, m), 2.09-2.03 (1H, m), 1.80-1.74 (4H, m), 1.64-1.46 (2H, m), 1.42-1.04 (3H, m), 1.01-0.92 (1H, m).

LC-MS: t_R = 2.06 $[M+H]^+$ = 356 (method 6)

Example 124: 2,6-difluoro-4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid.

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 229** (1.30 mmol, 444 mg). It was filtered over celite® and washed with MeOH. Solvent was evaporated and the crude material was purified by flash chromatography on silica gel. It was purified again by preparative HPLC (105.2 mg; yield: 23.55%, endo-isomer).

LC-MS: t_R = 1.68 $[M+H]^-$ = 344 (method 6)

Example 125 & 126: 4-((6R,6aS,10aR)-2-ethyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-2-fluorobenzoic acid (125); 4-((6S,6aS,10aR)-2-ethyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-2-fluorobenzoic acid (126).

The following compounds were prepared using the same methodology as in intermediate compound 67 using the **intermediate mixture of compounds 230 & 231** (1.49 mmol, 523 mg). It was filtered over celite® and washed with THF. The crude material was purified by preparative HPLC. Endo-isomer (125) 25.0 mg; Exo-isomer (126) 49.0 mg; (Overall yield: 14.1 %).

Endo-isomer (125) 4-((6R,6aS,10aR)-2-ethyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-2-fluorobenzoic acid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 13.14 (1H, s), 7.86 (1H, m), 7.34-7.28 (2H, m), 6.94 (1H, s), 6.77 (1H, m), 6.59 (1H, m), 5.82 (1H, s), 4.62 (1H, s), 2.60-2.52 (2H, m), 2.48-2.39 (2H, m), 2.01-1.92 (1H, m), 1.64-1.48 (2H, m), 1.42-1.33 (1H, m), 1.25 (1H, s), 1.12 (3H, t, *J*=7.8Hz), 1.12-1.04 (2H, m), 0.93-0.84 (1H, m).

LC-MS: t_R = 1.85 $[M+H]^+$ = 354 (method 6)

Exo-isomer (126) 4-((6S,6aS,10aR)-2-ethyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-2-fluorobenzoic acid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 13.16 (1H, s), 7.83 (1H, m), 7.26-7.19 (2H, m), 6.81 (1H, s), 6.76 (1H, d, *J*=8.1Hz), 6.50 (1H, d, *J*=8.1Hz), 6.01 (1H, s), 4.43 (1H, d, *J*=6.6Hz), 2.60-2.52 (2H, m), 2.49-2.40 (2H, m), 2.01-1.89 (2H, m), 1.64-1.31 (6H, m), 1.12 (3H, t, *J*=7.5Hz).

LC-MS: t_R = 1.83 $[M+H]^+$ = 354 (method 6)

Example 127: 4-((3aS,4R,9bR)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid. (idem as Example 88 but using another synthetic route)

The following compound was prepared using the same methodology as in example 122 from **intermediate compound 234** (0.44 mmol, 153 mg). Solvent was evaporated and the crude material was dissolved in water. The pH of the solution was adjusted to 1-2 by adding 1 N HCl aqueous solution and it was extracted with EtAcO. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated. It was purified by flash chromatography on silica gel. (16 mg; yield: 10.89%, endo-isomer).

^{1}H NMR (300 MHz, DMSO-d_6) δ 13.20 (1H, s), 7.84-7.73 (2H, m), 7.64 (1H, dd, *J*=1.2&9.9Hz), 6.86 (1H, s), 6.76 (1H, d, *J*=8.2Hz), 6.62 (1H, d, *J*=8.1Hz), 5.56 (1H, s), 4.71 (1H, d, *J*=2.7Hz), 4.12-4.09 (1H, m), 3.40-3.38 (1H, m), 3.17 (1H, m), 2.58-2.51 (2H, m), 2.11-2.04 (1H, m), 1.73-1.69 (1H, m), 1.58-1.51 (1H, m), 1.43-1.36 (2H, m), 1.13 (3H, t, *J*=7.5Hz).

LC-MS: t_R = 1.89 $[M+H]^+$ = 340 (method 6)

Example 128: 3-fluoro-4-((3aS,4R,9bR)-8-(trifluoromethyl)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid.

The following compound was prepared using the same methodology as in example 122 from **intermediate compound 236** (0.48 mmol, 189 mg). Solvent was evaporated and the crude material was dissolved in water. The pH of the solution was adjusted to 1-2 by adding 1 N HCl aqueous solution. And it was extracted with EtAcO. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated. It was purified by flash chromatography on silica gel. (80.04 mg; yield: 43.9%, endo-isomer).

^{1}H NMR (300 MHz, DMSO-d_6) δ 13.28 (1H, s), 7.85 (1H, m), 7.75-7.63 (2H, m), 7.33 (1H, s), 7.23 (1H, d, *J*=8.7Hz), 6.83 (1H, d, *J*=8.4Hz), 6.53 (1H, s), 4.90 (1H, s), 4.13-4.09 (1H, m), 3.49-3.43 (1H, m), 3.17 (1H, d, *J*=5.1Hz), 1.82-1.74 (1H, m), 1.52-1.34 (3H, m), 1.12-1.05 (1H, m).

LC-MS: t_R = 1.91 $[M+H]^-$ = 378 (method 6)

Example 129: 4-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid.

The following compound was prepared using the same methodology as in example 122 from **intermediate compound 238** (0.53 mmol, 192 mg). Solvent was evaporated and the crude material was dissolved in water. The pH of the solution was adjusted to 1-2 by adding 1 N HCl aqueous solution. And it was extracted with EtAcO. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated. It was purified by flash chromatography on silica gel. (91.79 mg; yield: 49.7%, endo-isomer).

^{1}H NMR (300 MHz, DMSO-d_6) δ 13.24 (1H, s), 7.83 (1H, m), 7.76-7.74 (1H, m), 7.65 (1H, dd, *J*=1.5&9.6Hz), 7.06 (1H, d, *J*=2.1Hz), 6.95 (1H, dd, *J*=2.4&6.3Hz), 6.72 (1H, d, *J*=8.4Hz), 5.99 (1H, s), 4.76 (1H, d, *J*=2.7Hz), 4.13-4.07 (1H, m), 3.16 (1H, d, *J*=5.1Hz), 2.12-2.03 (1H, m), 1.76-1.68 (1H, m), 1.55-1.36 (3H, m), 1.11-0.99 (1H, m).

LC-MS: t_R = 1.85 $[M+H]^-$ = 346 (method 6)

Example 130 & 131*: *3-fluoro-4-((6R,6aS,10aR)-2-methyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoic acid (130); 3-fluoro-4-((6S,6aS,10aR)-2-methyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoic acid (131).

The following compounds were prepared using the same methodology as in example 122 from the mixture of **intermediate compounds 241 and 242.** The crude material precipitated was filtered and purified by preparative HPLC. Endo-isomer (130) 10.8 mg; Exo-isomer (131) 10.3 mg; (Overall yield: 21.1 %).

Endo-isomer (130) 3-fluoro-4-((6R,6aS,10aR)-2-methyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoic acid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 13.25 (1H, s), 7.80 (1H, dd, *J*=1.2&6.6Hz), 7.70 (1H, dd, *J*=1.2&9.6Hz), 7.49 (1H, m), 6.87 (1H, s), 6.79 (1H, d, *J*=8.1Hz), 6.54 (1H, d, *J*=8.1Hz), 6.05 (1H, s), 4.74 (1H, s), 2.21 (3H, s), 2.08-1.93 (2H, m), 1.68-1.25 (8H, m).

LC-MS: t_R = 1.78 $[M+H]^+$ = 340 (method 6)

Exo-isomer (131) 3-fluoro-4-((6S,6aS,10aR)-2-methyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoic acid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 13.20 (1H, s), 7.81 (1H, dd, *J*=1.5&6.6Hz), 7.78-7.69 (1H, m), 7.64 (1H, dd, *J*=1.5&9.6Hz), 6.94 (1H, s), 6.75 (1H, d, *J*=8.4Hz), 6.57 (1H, d, *J*=8.1Hz), 5.74 (1H, s), 4.84 (1H, s), 4.13-4.08 (1H, m), 3.16 (1H, d, *J*=5.1Hz), 2.18 (3H, s), 2.01-1,91 (1H, m), 1.64-1.01 (7H, m).

LC-MS: t_R = 1.74 $[M+H]^+$ = 340 (method 6)

Example 132 & 133*: *4-((6R,6aS,10aR)-2-ethyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-3-fluorobenzoic acid (132); 4-((6S,6aS,10aR)-2-ethyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-3-fluorobenzoic acid (133).

The following compounds were prepared using the same methodology as in example 122 from the mixture of **intermediate compounds 245 and 246.** Solvent was evaporated and the crude material was dissolved in water. The pH of the solution was adjusted to 1-2 by adding 1 N HCl aqueous solution. And it was extracted with EtAcO. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated. It was purified by preparative HPLC. Endo-isomer (132) 17.38 mg; Exo-isomer (131) 37.59 mg; (Overall yield: 30.9 %).

Endo-isomer (132) 4-((6R,6aS,10aR)-2-ethyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-3-fluorobenzoic acid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.80 (1H, dd, *J*=1.2&6.9Hz), 7.69 (1H, dd, *J*=1.5&9.6Hz), 7.49 (1H, m), 6.96 (1H, s), 6.82 (1H, dd, *J*=1.5&6.6Hz), 6.56 (1H, d, *J*=8.1Hz), 6.04 (1H, s), 4.76-4.70 (1H, m), 2.54-2.46 (3H, m), 2.11-1.92 (2H, m), 1.70-1.29 (7H, m), 1.19 (3H, t, *J*=7.5Hz).

LC-MS: t_R = 2.07 $[M+H]^+$ = 354 (method 6)

Exo-isomer (133) 4-((6S,6aS,10aR)-2-ethyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-3-fluorobenzoic acid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 13.25 (1H, s), 7.81 (1H, m), 7.72-7.60 (2H, m), 6.96 (1H, s), 6.78 (1H, d, *J*=7.8Hz), 6.59 (1H, d, *J*=8.1Hz), 5.75 (1H, s), 4.85 (1H, s), 4.10 (1H, s),3.17 (1H, s), 2.48-2.39 (3H, m), 2.03-1.93 (1H, m), 1.68-1.50 (2H, m), 1.40-1.31 (1H, m), 1.13 (3H, t, *J*=7.5Hz), 1.11-1.04 (2H, m), 0.98-0.89 (1H, m).

LC-MS: t_R = 2.10 $[M+H]^+$ = 354 (method 6)

Example 134: 4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-N-(methylsulfonyl)benzamide

To a solution of the **example 4** (0.33 mmol, 100 mg), N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (0.39 mmol, 75 mg), N,N-dimethylpyridin-4-amine (0.07 mmol, 8 mg), N,N-diisopropylethylamine (0.39 mmol, 0.07 ml) in DCM, methanesulfonamide (0.49 mmol, 46 mg), was added. The reaction mixture was stirred at r.t. for 16h and then, it was diluted by adding DCM and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated. It was purified by flash chromatography on silica gel using hexane / EtAcO 50% as eluents (56.07 mg; yield: 44.8%, endo-isomer).

1H NMR (300 MHz, DMSO-d6) δ 12.1 (1H, s), 7.94 (2H, d, J = 8.4 Hz), 7.63 (2H, d, J = 8.4 Hz), 6.81 (1H, s), 6.70 (1H, d, J = 12 Hz), 6.66 (1H, d, J = 11.7 Hz), 5.61 (1H, s), 4.50 (1H, d, J = 2.4 Hz), 2.91 (3H, s), 2.0 (1H, m), 2.01-2.15 (2H, m), 2.16 (3H, s),1.48-1.52 (1H, m) 1.25-1.36 (3H, m), 1.01-1.10 (1H, m).

LC-MS: t_R = 1.97 $[M+H]^-$ = 385 (method 6)

Example 135: 4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-N-(o-tolylsulfonyl)benzamide.

The following compound was prepared using the same methodology as in example 134 from **example 4** (0.33 mmol, 100 mg) and 2-methylbenzenesulfonamide (0.49 mmol, 84 mg). The reaction mixture was diluted by adding DCM and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated. It was purified by flash

chromatography on silica gel using hexane / EtAcO 50% as eluents (52.65 mg; yield: 35.1%, endo-isomer).

1H NMR (300 MHz, DMSO-d6) δ 12.65 (1H, s), 7.99 (2H, m) 7.88 (2H, d, J = 8.4 Hz), 7.46 (2H, d, J = 8.4 Hz), 7.25-7.45 (3H, m), 6.82 (1H, s), 6.73 (1H, d, J = 12 Hz), 6.62 (1H, d, J = 11.7 Hz), 5.54 (1H, s), 4.44 (1H, d, J = 2.4 Hz), 2.57 (3H, s), 2.35-2.50 (1H, m) 2.15 (3H, s), 1.98-2.10 (1H, m), 1.62-1.78 (1H, m)1.48-1.60 (1H, m) 1.31-1.45 (3H, m), 0.95-1.05 (1H, m).

LC-MS: t_R = 2.25 $[M+H]^+$ = 461(method 6)

Example 136: N-(N,N-dimethylsulfamoyl)-4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzamide.

The following compound was prepared using the same methodology as in example 134 from **example 4** (0.65 mmol, 200 mg) and **intermediate compound 248** (0.98 mmol, 121 mg). The reaction mixture was diluted by adding DCM and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated. It was purified by flash chromatography on silica gel using hexane / EtAcO 100% as eluents (9.23 mg; yield: 3.43%, endo-isomer).

LC-MS: t_R = 2.07 $[M+H]^+$ = 414(method 6)

1H NMR (300 MHz, DMSO-d6) δ 11.78 (1H, s), 7.93 (2H, d, J = 7.5 Hz), 7.54 (2H, d, J = 7.5 Hz), 6.83 (1H, s), 6.71 (1H, d, J = 7.8 Hz), 6.60 (1H, d, J = 7.8 Hz), 5.59 (1H, s), 4.49 (1H, d, J = 2.4 Hz), 2.93 (6H, s), 2.01-2.15 (3H, m), 2.15 (3H, s),1.60-1.75 (1H, m) 1.20-1.55 (3H, m), 0.90-1.05 (1H, m).

Example 137: 3-ethoxy-4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid.

The following compound was prepared using the same methodology as in example 122 from **intermediate compound 251** (0.21 mmol, 80 mg). Solvent was evaporated and the crude material was dissolved in water. The pH of the

solution was adjusted to 1-2 by adding 1 N HCl aqueous solution. And it was extracted with EtAcO. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated. It was purified by flash chromatography on silica gel. (70.3 mg; yield: 95%, endo-isomer).

LC-MS: t_R = 2.01 $[M+H]^+$ = 352 (method 6)

1H NMR (300 MHz, DMSO-d6) δ 12.95 (1H, s), 7.60 (2H, m), 7.55 (1H, d, J = 3 Hz), 6.82 (1H, s), 6.70 (1H, d, J = 8.1 Hz), 6.58 (1H, d, J = 8.1 Hz), 5.31 (1H, s), 4.69 (1H, d, J = 2.7 Hz), 4.05-4.20 (2H, m), 2.16 (3H, s), 2.01-2.10 (2H, m), 1.55-1.80 (2H, m), 1.20-1.45 (6H, m), 0.98 (1H, m).

Example 138: 3-chloro-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-5-fluorobenzoic acid.

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 253** (0.59 mmol, 242 mg). It was filtered over celite® and washed with EtOH. Solvent was evaporated and the crude material was purified by flash chromatography on silica gel using hexane /EtAcO (0-100%) as eluents. It was purified again by preparative HPLC (13.24 mg; yield: 5.45%, endo-isomer).

LC-MS: t_R = 1.96 $[M+H]^-$ = 412 (method 6)

1H NMR (300 MHz, methanol-d4) δ 7.85 (1H, s), 7.51 (1H, dd, J = 11 Hz, J = 2.4 Hz), 6.78 (1H, m), 6.67 (1H, m), 6.55 (2H, m), 4.94 (2H, s), 3.25-3.40 (1H, m), 2.50-2.65 (1H, m), 2.01-2.22 (1H, m), 1.80-1.95 (1H, m), 1.45-1.65 (3H, m), 1.20-1.45 (1H, m), 1.10-1.21 (1H, m).

Example 139: 2,3-difluoro-4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid.

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 258** (0.37 mmol, 127 mg) and PtO_2 (7%w/w, 5,91 mg). It was stirred at r.t. for 2 h. It was filtered over

celite® and washed with MeOH. Solvent was evaporated. (80.21 mg; yield: 62.8%, endo-isomer).

LC-MS: t_R = 1.92 $[M+H]^+$ = 344 (method 6)

1H NMR (300 MHz, DMSO-d6) δ 7.64 (1H, m), 7.47 (1H, m), 6.84 (1H, s), 6.72 (1H, d, J = 8.4 Hz), 6.59 (1H, d, J = 8.4 Hz), 5.61 (1H, s), 4.70 (1H, d, J = 2 Hz), 3.30 (1H, s), 2.16 (3H, s), 1.98-2.10 (2H, m), 1.45-1.55 (1H, m), 1.60-1.75 (1H, m), 1.30-1.45 (3H, m), 1.05-1.15 (1H, m).

Example 140: 2,5-difluoro-4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid.

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 263** (0.42 mmol, 142 mg) and PtO_2 (7%w/w). It was stirred at r.t. for 2 h. It was filtered over celite® and washed with MeOH. Solvent was evaporated. (93.09 mg; yield: 65.2%, endo-isomer).

LC-MS: t_R = 1.93 $[M+H]^+$ = 344 (method 6)

1H NMR (300 MHz, DMSO-d6) δ 7.74 (1H, m), 7.50 (1H, m), 6.84 (1H, s), 6.76 (1H, d, J = 8.4 Hz), 6.60 (1H, d, J = 8.4 Hz), 5.57 (1H, s), 4.65 (1H, d, J = 2 Hz), 3.30 (1H, s), 2.15 (3H, s), 2.02-2.10 (2H, m), 1.60-1.75 (1H, m), 1.35-1.55 (4H, m), 1.05-1.15 (1H, m).

Example 141: 2-isobutoxy-4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid.

The following compound was prepared using the same methodology as in example 122 from **intermediate compound 268** (0.22 mmol, 90 mg). It was refluxed for 2h. The solvent was removed in vacuum and the crude material was dissolved in water. The pH of the solution was adjusted to 1-2 by adding 1 N HCl aqueous solution. The result solid was filtered. It was purified by flash chromatography on silica gel using hexane / EtAcO (0 – 30%) as eluents (31.51 mg; yield: 37.6%, endo-isomer).

LC-MS: t_R = 2.15 $[M+H]^+$ = 381 (method 6)

1H NMR (300 MHz, DMSO-d6) δ 12.45 (1H, s), 7.62 (1H, d, J = 8.1 Hz), 7.12 (1H, s), 7,03 (1H, d, J = 8.1 Hz), 6.83 (1H, s), 6.70 (1H, d, J = 8.1 Hz), 6.59 (1H, d, J = 8.1 Hz), 5.54 (1H, s), 4.43 (1H, d, J = 2.4 Hz), 3.82 (2H, d, J = 6 Hz), 2.16 (3H, s), 1.98-2.10 (3H, m), 1.65-1.75 (1H, m), 1.65-1.50 (1H, m), 1.35-1.45 (2H, m), 1.07 (6H, d, J = 6.6 Hz), 1.00-1.10 (2H, m).

Example 142: methyl 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoate

Intermediate compound 67 was purified from 130 mg of the exo/endo-mixture (1:17) by precipitation in cold acetonitrile. The solid was filtered, washed with acetonitrile, hexane and dried over vacuum to give 68 mg of the pure endo-compound (Yield: 52%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (2H, d, *J* = 8.0 Hz), 7.58 (2H, d, *J* = 8.0 Hz), 6.83 (1H, s), 6.71 (1H, dd, *J* = 8.0 & 1.6 Hz), 6.60 (1H, d, *J* = 8.0 Hz), 5.59 (1H, s), 4.50 (1H, d, *J* = 3.2 Hz), 3.85 (3H, s), 3.36 (1H, dt, *J* = 7.6 & 2.8 Hz), 2.50-2.40 (1H, m), 2.15 (3H, s), 2.09-2.00 (1H, m), 1.73-1.66 (1H, m), 1.56-1.46 (1H, m), 1.39-1.32 (2H, m), 1.03-0.95 (1H, m).

LC-MS: t_R = 10.70 $[M+H]^+$= 322 (method 1)

Example 143: ethyl 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoate

To a solution of **example 4** (0.70 mmol, 215 mg) dissolved in THF (15 mL) potassium carbonate (2.8 mmol, 387 mg) was added and the resulting solution was stirred for 1 h at room temperature. Iodoethane (4.9 mmol, 0.39 mL) was added and the mixture was stirred 16h at room temperature. Only 3% reaction conversion was achieved, then potassium carbonate (2.8 mmol, 387 mg) and iodoethane (4.9 mmol, 0.39 mL) were added and the mixture was heated at 50ºC for 5h. Total conversion was not achieved. Then, iodoethane (4.9 mmol, 0.39 mL) was added and left at 50ºC for 2.5 h and at room temperature for 36h. Solvent

was evaporated and the residue was dissolved in EtOAc and water. Organic layer was separated and washed by saturated aqueous Na_2CO_3 solution, brine, dried over Na_2SO_4, filtered and concentrated. Purification of the crude material by flash chromatography on silica gel using an elution of 11% ethyl acetate in hexanes afforded the racemic endo-isomer (**143**) (180 mg, Yield: 77%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (2H, d, *J* = 8.0 Hz), 7.55 (2H, d, *J* = 8.4 Hz), 6.81 (1H, s), 6.69 (1H, dd, *J* = 8.4 & 1.6 Hz), 6.58 (1H, d, *J* = 7.6 Hz), 5.56 (1H, s), 4.48 (1H, d, *J* = 2.8 Hz), 4.30 (2H, q, *J* = 7.2 Hz), 3.63-3.31 (1H, m), 2.50-2.40 (1H, m), 2.14 (3H, s), 2.05-2.00 (1H, m), 1.70-1.65 (1H, m), 1.52-1.44 (1H, m), 1.38-1.29 (2H, m), 1.31 (3H, t, *J* = 7.2 Hz), 0.99-0.95 (1H, m).

LC-MS: t_R = 11.10 $[M+H]^+$ = 336 (method 1)

Example 144 & 145: ethyl 3-(4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)phenyl)propanoate (144) & ethyl 3-(4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)phenyl)propanoate (145)

The following compound was prepared using the same methodology as in intermediate compound 67 from **intermediate compound 270** (0.69 mmol, 250 mg). Purification of the crude material using reverse C_{18} chromatography using water (0.1% formic acid) and acetonitrile (0.1% formic acid) as eluents gave 17 mg of exo-isomer (144) and 125 mg of endo-isomer (145). Overall yield: 56%

*Ethyl 3-(4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)phenyl)propanoate (*144*)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28 (2H, d, *J* = 8.4 Hz), 7.18 (2H, d, *J* = 8.4 Hz), 6.82 (1H, s), 6.66 (1H, dd, *J* = 8 & 2 Hz), 6.52 (1H, d, *J* = 8Hz), 5.59 (1H, s), 4.02 (2H, q, *J* = 7.2 Hz), 3.55 (1H, d, *J* = 10.4 Hz), 2.90-2.80 (1H, m), 2.83 (2H, t, *J* = 8 Hz), 2.59 (2H, t, *J* = 7.6 Hz), 2.18-2.13 (2H, m), 2.13 (3H, s), 1.65-1.40 (4H, m), 1.29-1.21 (1H, m), 1.14 (3H, t, *J* = 7.6 Hz).

LC-MS: t_R = 10.47 $[M+H]^+$ = 364 (method 1)

*Ethyl 3-(4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)phenyl)propanoate (*145*)*

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.30 (2H, d, *J* = 8.4 Hz), 7.17 (2H, d, *J* = 8 Hz), 6.79 (1H, s), 6.66 (1H, dd, *J* = 8 & 1.6 Hz), 6.55 (1H, d, *J* = 8Hz), 5.40 (1H, s), 4.36 (1H, d, *J* = 3.2 Hz), 4.02 (2H, q, *J* = 7.2 Hz), 3.33-3,29 (1H, m), 2.82 (2H, t, *J* = 7.2 Hz), 2.56 (2H, t, *J* = 7.2 Hz), 2.39-2.30 (1H, m), 2.13 (3H, s), 2.06-1.97 (1H, m), 1.70-1.62 (1H, m), 1.56-1.47 (1H, m), 1.38-1.29 (2H, m), 1.14 (3H, t, *J* = 6.8 Hz), 1.07-0.98 (1H, m).

LC-MS: t_R = 11.03 $[M+H]^+$ = 364 (method 1)

Examples of biological activity

In the following examples the biological activity of compounds of formula (I) towards EP1 receptors is shown.

Human EP1 receptor radioligand binding assay

To investigate binding properties of EP1 receptor ligands to human EP1 receptor, transfected HEK-293 cell membranes and [3H]-PGE2 (Perkin Elmer) were used. In 96-well plates the assay was carried out with a total reaction volume of 250 µl, containing 25 µl of membrane suspension (30 µg protein/well), 25 µl of [3H]-PGE2 (10 nM) in either absence or presence of 25 µl of either buffer or PGE2 (10 µM) for total and non-specific binding, respectively. Binding buffer contained 10 mM MES, 1 mM MgCl2 and 1 mM EDTA at pH 6.0. Plates were incubated at 25 ℃ for 60 minutes. After the incubation period, 200 µl of incubate were transferred to MultiScreen HTS, FB plates (Millipore), filtered and plates were washed 6 times with ice-cold 10 mM MES, 1 mM MgCl2 and 1 mM EDTA at pH 6.0. Filters were dried and counted in a MicroBeta scintillation counter (Perkin-Elmer) using EcoScint liquid scintillation cocktail.

Percentage inhibition was calculated relating compounds activity to the 0% inhibition of the wells incubated with 10 nM [3H]-PGE2 alone (total binding) and 100% inhibition of the wells incubated with 10 nM [3H]-PGE2 plus 10 µM PGE2 (non-specific binding). Competition binding curves were carried out by assaying 6

different concentrations with duplicated points. The inhibition constant (Ki) of each compound was calculated by the Cheng-Prusoff equation:

$K_i = IC_{50} / (1 + [L] / KD)$

where IC_{50} is the concentration of compound that displaces the binding of radioligand by 50%, [L] is the free concentration of radioligand and KD is the dissociation constant of each radioligand. IC_{50} values were obtained by fitting the data with non-linear regression using XlFit software (IDBS).

The results obtained in the biological assays disclosed above with representative compounds of formula (I) are shown in the Table below in which A means a Ki < 100nM, B means a Ki value between 100nM and 500nM and C means a Ki > 500 nM.

EXAMPLE	Ki Binding
EXAMPLE 02	B
EXAMPLE 04	B
EXAMPLE 06a	A
EXAMPLE 07	A
EXAMPLE 12	C
EXAMPLE 18	B
EXAMPLE 19	C
EXAMPLE 29	C
EXAMPLE 30	C
EXAMPLE 36	C
EXAMPLE 37a	A
EXAMPLE 43	B
EXAMPLE 47	B
EXAMPLE 55	B
EXAMPLE 56	A
EXAMPLE 57	A
EXAMPLE 62	C
EXAMPLE 69	B
EXAMPLE 75	B
EXAMPLE 83b	A
EXAMPLE 91	A
EXAMPLE 95a	A
EXAMPLE 96	A
EXAMPLE 97	C
EXAMPLE 98	C
EXAMPLE 99	C
EXAMPLE 100	C
EXAMPLE 101	C
EXAMPLE 105	B
EXAMPLE 106	A
EXAMPLE 109	A
EXAMPLE 111a	A
EXAMPLE 113	B
EXAMPLE 115a	A
EXAMPLE 116	A
EXAMPLE 117	C
EXAMPLE 122	C
EXAMPLE 124	C
EXAMPLE 131	A
EXAMPLE 132	B
EXAMPLE 134	C
EXAMPLE 135	B
EXAMPLE 138	A
EXAMPLE 139	B
EXAMPLE 142	C

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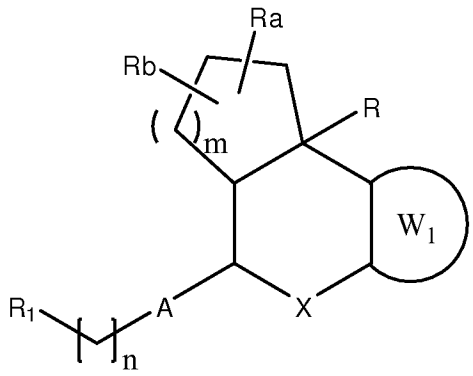
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CLAIMS

1- A compound of general formula **(I)**:



(I)

wherein:

W1 is a benzene ring optionally substituted by one or more R_2 and optionally fused to a carbocyclic ring; or a 5 or 6-membered heterocyclic ring containing 1 or 2 heteroatoms selected from N, O or S, optionally substituted by one or more R_2;

R is a hydrogen; or C_{1-6}-alkyl;

Ra and **Rb** are independently selected from hydrogen; -OH; -CH_2OH; C_{1-6}-alkyl; –O–C_{1-6}-alkyl or –O–C_{1-6}-haloalkyl;

$\mathbf{R_1}$ is a –COOH; a tetrazol; a –SO_2-NH-C(=O)-R_3; a –C(=O)NH-SO_2-R_4; a –SO_2-OH or a –CN;

$\mathbf{R_2}$ is independently selected from hydrogen; halogen; C_{1-6} alkyl; C_{1-6}-haloalkyl; –O–C_{1-6}-alkyl; –O–C_{1-6}-haloalkyl; C_{3-6}cycloalkyl; –O–C_{3-6}cycloalkyl; -$NR_5SO_2R_6$; phenyl; -$CONH_2$ or –CN;

$\mathbf{R_3}$ and $\mathbf{R_4}$ are independently selected from a hydrogen; C_{1-6}-alkyl; an optionally substituted phenyl; or –$N(CH_3)_2$;

$\mathbf{R_5}$ and $\mathbf{R_6}$ are independently selected from a hydrogen; or C_{1-6}-alkyl

R_7 is selected from a hydrogen; C_{1-6}-alkyl; or a $–COR_8$

R_8 is a C_{1-6}-alkyl;

X is selected from NR_7 or O;

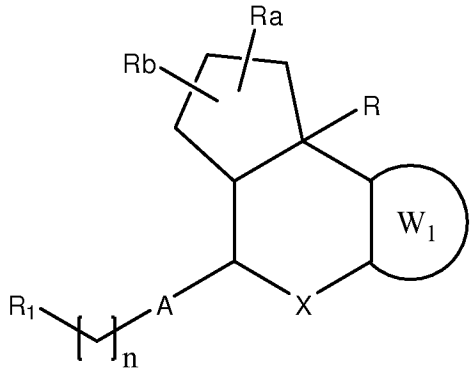
A is a phenyl optionally substituted by one or more substituents selected from C_{1-6}-alkyl, halogen, C_{1-6}-haloalkyl, $–O–C_{1-6}$-alkyl, $–O–C_{1-6}$-haloalkyl, -NH-CO-CH_3, a –CN or a C_{3-6}cycloalkyl optionally substituted by a C_{1-6}-alkyl; or an heteroaromatic ring or ring system optionally substituted by one or more substituents selected from C_{1-6}-alkyl, halogen, C_{1-6}-haloalkyl, $–O–C_{1-6}$-alkyl, $–O–C_{1-6}$-haloalkyl, -NH-CO-CH_3, a –CN or a C_{3-6}cycloalkyl optionally substituted by a C_{1-6}-alkyl ;

n is 0, 1 or 2;

m is 1, or 2 or 3;

and the salts, solvates and prodrugs thereof.

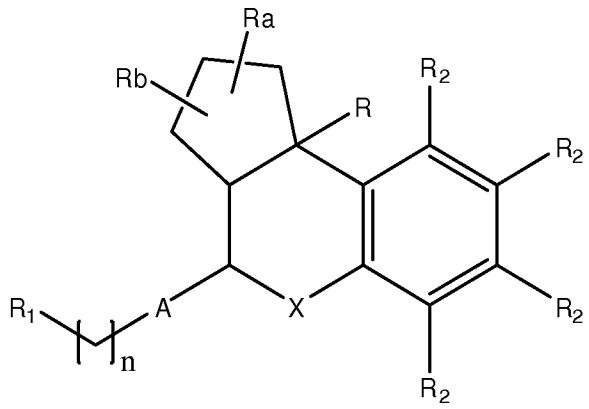
2- A compound according to claim 1 having general formula **(Ia)**:



(Ia)

where **W1**, **R**, **Ra**, **Rb**, R_1, **A**, **X** and **n** have the same meanings as in claim 1.

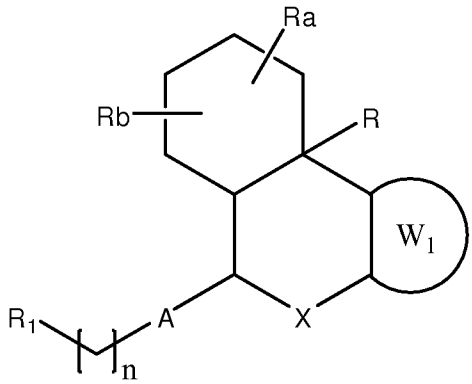
3- A compound according to any of claim 1 or 2 having general formula **(Ia')**:



(Ia')

where **R**, **Ra**, **Rb**, R_1, R_2, **A**, **X** and **n** have the same meanings as in claim 1.

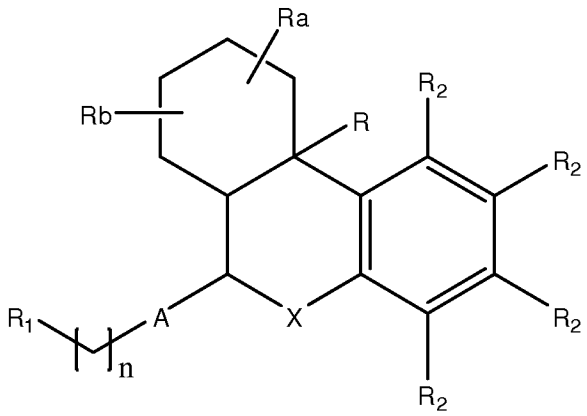
4- A compound according to claim 1 having general formula **(Ib)**:



(Ib)

where **W1**, **R**, **Ra**, **Rb**, R_1, **A**, **X** and **n** have the same meanings as in claim 1.

5- A compound according to any of claims 1 or 4 having general formula **(Ib')**:



(Ib')

where **R**, **Ra**, **Rb**, R_1, R_2, **A**, **X** and **n** have the same meanings as in claim 1.

6- A compound according to claim 1 where **W1** is a benzene ring optionally substituted by one or more R_2 where R_2 has the same meaning as in claim 1.

7- A compound according to any of claims 1 to 6 where R_1 is a –COOH, a tetrazole or a –C(=O)NH-SO_2-R_4.

8- A compound according to any of claims 1 to 7 where **A** is a phenyl group optionally substituted by one or more substituents selected from C_{1-6}-alkyl, halogen, C_{1-6}-haloalkyl, –O–C_{1-6}-alkyl, –O–C_{1-6}-haloalkyl, -NH-CO-CH_3, a –CN or a C_{3-6}cycloalkyl optionally substituted by a C_{1-6}-alkyl ; a pyridinyl group optionally substituted by one or more substituents selected from C_{1-6}-alkyl, halogen, C_{1-6}-haloalkyl, –O–C_{1-6}-alkyl, –O–C_{1-6}-haloalkyl, -NH-CO-CH_3, a –CN or a C_{3-6}cycloalkyl optionally substituted by a C_{1-6}-alkyl; a pyrazolyl group optionally substituted by one or more substituents selected from C_{1-6}-alkyl, halogen, C_{1-6}-haloalkyl, –O–C_{1-6}-alkyl, –O–C_{1-6}-haloalkyl, -NH-CO-CH_3, a –CN or a C_{3-6}cycloalkyl optionally substituted by a C_{1-6}-alkyl; an imidazolyl group optionally substituted by one or more substituents selected from C_{1-6}-alkyl, halogen, C_{1-6}-haloalkyl, –O–C_{1-6}-alkyl, –O–C_{1-6}-haloalkyl, -NH-CO-CH_3, a –CN or a C_{3-6}-

cycloalkyl optionally substituted by a C_{1-6}-alkyl; a thiazolyl group optionally substituted by one or more substituents selected from C_{1-6}-alkyl, halogen, C_{1-6}-haloalkyl, –O–C_{1-6}-alkyl, –O–C_{1-6}-haloalkyl, -NH-CO-CH_3, a –CN or a C_{3-6}cycloalkyl optionally substituted by a C_{1-6}-alkyl; an indolyl group optionally substituted by one or more substituents selected from C_{1-6}-alkyl, halogen, C_{1-6}-haloalkyl, –O–C_{1-6}-alkyl, –O–C_{1-6}-haloalkyl, –O–C_{1-6}-haloalkyl, -NH-CO-CH_3, a –CN or a C_{3-6}cycloalkyl optionally substituted by a C_{1-6}-alky; or a benzimidazole group optionally substituted by one or more substituents selected from C_{1-6}-alkyl, halogen, C_{1-6}-haloalkyl, –O–C_{1-6}-alkyl, –O–C_{1-6}-haloalkyl, –O–C_{1-6}-haloalkyl, -NH-CO-CH_3, a –CN or a C_{3-6}cycloalkyl optionally substituted by a C_{1-6}-alky.

9- A compound according to any of claims 1 to 8 where **X** is NR_7 where R_7 is a hydrogen .

10- A compound according to claim 1 to 9 where n=0.

11- A compound according to claim 1 where **W1** is a benzene ring optionally substituted by one or more $\mathbf{R_2}$;

$\mathbf{R_1}$ is a –COOH;

A is a phenyl group optionally substituted by one or more substituents selected from C_{1-6}-alkyl, halogen, C_{1-6}-haloalkyl, –O–C_{1-6}-alkyl, –O–C_{1-6}-haloalkyl, -NH-CO-CH_3, a –CN or a C_{3-6}cycloalkyl optionally substituted by a C_{1-6}-alkyl ; a pyridinyl group optionally substituted by one or more substituents selected from C_{1-6}-alkyl, halogen, C_{1-6}-haloalkyl, –O–C_{1-6}-alkyl, –O–C_{1-6}-haloalkyl, -NH-CO-CH_3, a –CN or a C_{3-6}cycloalkyl optionally substituted by a C_{1-6}-alkyl ; a pyrazolyl group optionally substituted by one or more substituents selected from C_{1-6}-alkyl, halogen, C_{1-6}-haloalkyl, –O–C_{1-6}-alkyl, –O–C_{1-6}-haloalkyl, -NH-CO-CH_3, a –CN or a C_{3-6}cycloalkyl optionally substituted by a C_{1-6}-alkyl ; an imidazolyl group optionally substituted by one or more substituents selected from C_{1-6}-alkyl, halogen, C_{1-6}-haloalkyl, –O–C_{1-6}-alkyl, –O–C_{1-6}-haloalkyl, -NH-CO-CH_3, a –CN or a C_{3-6}cycloalkyl optionally substituted by a C_{1-6}-alkyl ; or a thiazolyl group

optionally substituted by one or more substituents selected from C_{1-6}-alkyl, halogen, C_{1-6}-haloalkyl, –O–C_{1-6}-alkyl, –O–C_{1-6}-haloalkyl, -NH-CO-CH_3, a –CN or a C_{3-6}cycloalkyl optionally substituted by a C_{1-6}-alkyl;

X is NR_7 where R_7 is a hydrogen ; and

n is 0.

12- A compound according to claim 1 selected from :

- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-8-bromo-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-8-(trifluoromethyl)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (enantiomer 1);
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (enantiomer 2);
- 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (enantiomer 1);
- 4-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (enantiomer 2);
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (enantiomer 1);

- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid (enantiomer 2);
- 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS, 4R, 9bR)-6-cyclopropyl-2, 3, 3a, 4, 5, 9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS, 4S, 9bR)-8-cyclopropyl-2, 3, 3a, 4, 5, 9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS, 4R, 9bR)-8-cyclopropyl-2, 3, 3a, 4, 5, 9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- (+)-4-((3a*S*, 4*R*, 9b*R*)-8-cyclopropyl-2, 3, 3a, 4, 5, 9b-hexahydro-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid;
- (-)-4-((3a*S*, 4*R*, 9b*R*)-8-cyclopropyl-2, 3, 3a, 4, 5, 9b-hexahydro-1*H*-cyclopenta[*c*]quinolin-4-yl)benzoic acid;
- 4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-propyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS, 4R, 9bR)-8-fluoro-2, 3, 3a, 4, 5, 9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-phenyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS, 4R, 9bR)-8-tert-butyl-2, 3, 3a, 4, 5, 9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- (+)-4-((3a*S*,4*R*,9*bR*)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- (-)-4-((3a*S*,4*R*,9*bR*)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-8-carbamoyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-isopropyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;

- 4-((3aS,4R,9bR)-8-cyano-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-8-[(N-methylsulfonyl)amino]-)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-8-[(N-methyl-N-methylsulfonyl)amino]-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 3-((3aS,4R,9bR)-8-bromo-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-7,8-dimethoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-7-(trifluoromethyl)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-9-(trifluoromethyl)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-7-methoxy-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-6,8-dimethyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-9-chloro-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-7-chloro-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-5,8-dimethyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-5-acetyl-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((6R, 6aS, 9aR)-6, 6a, 7, 8, 9, 9a-hexahydro-2-methyl-5H-cyclopenta[c][1,5]naphthyridin-6-yl)benzoic acid;
- 4-((6R,6aS,9aR)-6,6a,7,8,9,9a-hexahydro-2-methyl-5H-cyclopenta[c][1,8]naphthyridin-6-yl)benzoic acid;
- 2-(4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)phenyl)acetic acid;

- 3-(4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)phenyl)propanoic acid;
- 4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-2-methylbenzoic acid;
- 4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- (+)-4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- (-)-4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 4-((3aS, 4S, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 4-((3aS, 4R, 9bR)-8-chloro-2, 3, 3a, 4, 5, 9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 4-((3aS, 4R, 9bR)-8-fluoro-2, 3, 3a, 4, 5, 9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methoxy-5-methyl-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 4-((3aS, 4R, 9bR)-8-cyclopropyl-2, 3, 3a, 4, 5, 9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 4-((3aS, 4R, 9bR)-8-(cyclopropylmethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-isopropoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-isopropoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 3-chloro-4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methoxybenzoic acid;

- 4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-3-methoxybenzoic acid;
- 3-bromo-4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 3-bromo-4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 3-ethyl-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzonitrile;
- 3-ethyl-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 3-ethyl-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 3-ethyl-4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-3,5-dimethylbenzoic acid;
- 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-3,5-dimethylbenzoic acid;
- 5-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)pyridine-2-carboxylic acid;
- 6-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)pyridine-3-carboxylic acid;
- 5-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-6-methylpyridine-2-carbonitrile;
- 5-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-6-methylpyridine-2-carboxylic acid;
- 5-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-1-methyl-1H-pyrazole-3-carboxylic acid;
- 5-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-1-methyl-1H-pyrazole-3-carboxylic acid;
- 3-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)-1-methyl-1H-pyrazole-5-carboxylic acid;

- 3-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-1-methyl-1H-pyrazole-5-carboxylic acid;
- 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8,9b-dimethyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8,9b-dimethyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4S,9bR)-8-cyclopropyl-2,3,3a,4,5,9b-hexahydro-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-8-cyclopropyl-2,3,3a,4,5,9b-hexahydro-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4S,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-9b-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS, 4S, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8, 9b-dimethyl-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 4-((3aS, 4R, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8, 9b-dimethyl-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-isobutoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-isobutoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- 4-((3aS, 4S, 9bR)-2, 3, 3a, 4, 5, 9b-hexahydro-8-methoxy-5,9b-dimethyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS, 4R, 9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-5,9b-dimethyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- (+/-)-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-(trifluoromethoxy)-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- (+/-)4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-

cyclopenta[c]quinolin-4-yl)benzoic acid;

- 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-(trifluoromethoxy)-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- (+/-)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-methylbenzoic acid;
- (+/-)-3-fluoro-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- (+/-)-3-fluoro-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- (+/-)-4-((3aS,4R,9bR)-8-cyclopropyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid;
- (+/-)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid;
- (+/-)-4-((3aS,4R,9bR)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid;
- 3-(trifluoromethyl)-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 3-(trifluoromethyl)-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4S,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-dimethylbenzoic acid;
- (+/-)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluoro-5-methylbenzoic acid;
- (+/-)-4-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid;
- (+/-)-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid;
- (+/-)-4-((3aS,4R,9bR)-8-cyclopropyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid;
- 3,5-dichloro-4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 5-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-6-methylpyridine-2-carboxylic acid;
- 6-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-5-methylpyridine-3-carboxylic acid;

- 2-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-1-methyl-1H-imidazole-4-carboxylic acid;
- 7-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-3-methyl-3H-benzo[d]imidazole-4-carboxylic acid;
- 7-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methoxy-1H-cyclopenta[c]quinolin-4-yl)-1H-indole-4-carbonitrile;
- 2-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)thiazole-5-carboxylic acid;
- 2-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)thiazole-5-carboxylic acid;
- 4-chloro-5-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)thiazole-2-carboxylic acid;
- 4-chloro-5-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)thiazole-2-carboxylic acid;
- (3aS,4R,9bR)-4-(4-(1H-tetrazol-5-yl)phenyl)-8-methoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinoline;
- 3,5-difluoro-4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- (+/-)-4-((3aS,4R,9bR)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3,5-difluorobenzoic acid;
- 3,5-difluoro-4-((3aS,4R,9bR)-8-methoxy-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((6R,6aS,10aR)-2-methyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-3-methylbenzoic acid;
- (+/-)-4-((6S,6aS,10aR)-2-chloro-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-3-methylbenzoic acid;
- 4-((6R,6aS,10aR)-2-chloro-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoic acid;
- 4-((6S,6aS,10aR)-2-chloro-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoic acid;
- 4-((6S,6aS,10aR)-2-methyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoic acid;
- (+/-)-4-((6S,6aS,10aR)-2-(difluoromethoxy)-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoic acid;

- 3,5-dichloro-4-((6S,6aS,10aR)-2-methyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoic acid;
- 4-((6R,6aS,11aR)-2-methyl-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[c]quinolin-6-yl)benzoic acid;
- 2-fluoro-4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-2-fluorobenzoic acid;
- 4-((3aS,4R,9bR)-8-ethyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-2-fluorobenzoic acid;
- 4-((6R,6aS,11aR)-2-chloro-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[c]quinolin-6-yl)benzoic acid;
- 4-((6S,6aS,11aR)-2-chloro-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[c]quinolin-6-yl)benzoic acid;
- 2,6-difluoro-4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((6R,6aS,10aR)-2-ethyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-2-fluorobenzoic acid;
- 4-((6S,6aS,10aR)-2-ethyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-2-fluorobenzoic acid;
- 3-fluoro-4-((3aS,4R,9bR)-8-(trifluoromethyl)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 4-((3aS,4R,9bR)-8-chloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-3-fluorobenzoic acid;
- 3-fluoro-4-((6R,6aS,10aR)-2-methyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoic acid;
- 3-fluoro-4-((6S,6aS,10aR)-2-methyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)benzoic acid;
- 4-((6R,6aS,10aR)-2-ethyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-3-fluorobenzoic acid;
- 4-((6S,6aS,10aR)-2-ethyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridin-6-yl)-3-fluorobenzoic acid;
- 4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-N-(methylsulfonyl)benzamide;

- 4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-N-(methylsulfonyl)benzamide;
- 4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-N-(o-tolylsulfonyl)benzamide;
- N-(N,N-dimethylsulfamoyl)-4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzamide;
- 3-ethoxy-4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 3-chloro-4-((3aS,4R,9bR)-8-(difluoromethoxy)-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)-5-fluorobenzoic acid;
- 2,3-difluoro-4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 2,5-difluoro-4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- 2-isobutoxy-4-((3aS,4R,9bR)-8-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinolin-4-yl)benzoic acid;
- methyl 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoate;
- ethyl 4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)benzoate;
- ethyl 3-(4-((3aS,4S,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)phenyl)propanoate;
- ethyl 3-(4-((3aS,4R,9bR)-2,3,3a,4,5,9b-hexahydro-8-methyl-1H-cyclopenta[c]quinolin-4-yl)phenyl)propanoate.

13- A compound according to any of the claims 1 to 12 for use as a medicament.

14- A compound according to any of claims 1 to 12 for use in the treatment and/or prophylaxis of diseases or disorders mediated by the EP1 receptor.

15- A compound for use according to claim 14 where the disease or disorders comprises inflammatory related pain including low back and neck pain, skeletal pain, post-partum pain, toothache, sprains and straits, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases, gout and ankylosing spondylitis, bursitis, burns including radiation and corrosive chemical injuries and sunburns; postoperative pain; neuropathic pain; visceral pain; tension headache; cluster headaches; migraine; motility-related disorders including gastrointestinal disorders, urinary incontinence and other urinary tract diseases; dysmenorrhea; preterm labour; diabetic retinopathy; tumour angiogenesis; cancer; metastatic tumour growth; neurodegenerative diseases including senile dementia, Alzheimer's disease, Pick's disease, Huntington's chorea, Parkinson's disease, Creutzfeldt-Jakob disease, or amyotrophic lateral sclerosis; neuroprotection/stroke; glaucoma; osteoporosis; bone fractures; Paget's disease; hyperthermia including different types of fever as rheumatic fever; symptoms associated with influenza or other viral infections; gastrointestinal disorders related with chemotherapy or irritable bowel syndrome; gastrointestinal bleeding; coagulation disorders including anaemia, hypoprothrombinemia, haemophilia or other bleeding problems; kidney diseases including nephritis, particularly mesangial proliferative glomerulonephritis and nephritic syndrome; thrombosis and occlusive vascular diseases.

16- A compound for use according to claim 14 where the disease or disorders comprises pain, inflammatory related pain including low back and neck pain, skeletal pain, post-partum pain, toothache, sprains and straits, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases, gout and ankylosing spondylitis, bursitis, burns including radiation and corrosive chemical injuries and sunburns; postoperative pain; neuropathic pain; visceral pain; tension headache; cluster headaches; migraine.

17- Pharmaceutical composition comprising at least one compound according to any of claims 1-12 and at least one pharmaceutically acceptable carrier, additive, adjuvant or vehicle.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/056886

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D221/26 C07D401/04 A61K31/473 C07D221/16
ADD. A61P1/00 A61P7/00 A61P13/00 A61P19/00 A61P25/00
A61P31/00 A61P35/00 A61P37/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/098600 A1 (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; BECKER CHRISTOPHER [US];) 18 November 2004 (2004-11-18) Formula (II); claims 1,2,3,5-8 -----	1-3, 6-11, 13-17
A	WO 2005/016255 A2 (LIGAND PHARM INC [US]; MICHELLYS PIERRE [US]; CHEN JYUN-HUNG [US]; MEY) 24 February 2005 (2005-02-24) claims 1-19 -----	1-3, 6-15,17
A	WO 2004/072046 A2 (CAREX S A [FR]; KOUTNIKOVA HANA [FR]; SIERRA MICHAEL [FR]; BRAUN-EGLES) 26 August 2004 (2004-08-26) abstract; page 99 - page 103; claims 1,3,5-8 -----	1-3,6, 8-10, 13-17

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

☒ See patent family annex.

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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 April 2013	07/05/2013

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2013/056886

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