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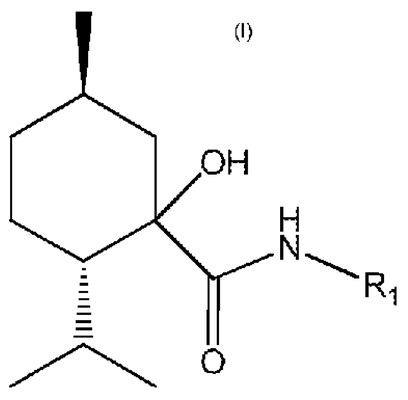
(54) **Title:** SUBSTITUTED CYCLOHEXANECARBOXAMIDES, THEIR PREPARATION AND THEIR THERAPEUTIC APPLICATION



(57) **Abstract:** Compounds of formula (1) wherein R_1 represents a $-C(R_2)(R_3)-[C(R_4)(R_5)]_m-L-R_6$ group or $-R_7$; and the preparation and the therapeutic uses of the compounds of formula (1) as agonists of TRPM8 receptors, useful especially in the treatment of oropharyngeal dysphagia.

SUBSTITUTED CYCLOHEXANECARBOXAMIDES, THEIR PREPARATION AND THEIR THERAPEUTIC APPLICATION

Provided herein are substituted cyclohexanecarboxamide compounds, processes for their preparation, pharmaceutical compositions containing the compounds, as well as therapeutic uses thereof.

Oropharyngeal dysphagia (OD) is a prevalent medical condition where patients have difficulty swallowing food or liquids, likely due to either a lack of nerve sensitivity or muscle weakness. Although dysphagia is commonly associated with aging, neurological injuries after stroke or trauma, neurological disorders (for example, multiple sclerosis, Parkinson disease, Alzheimer disease), and cancer treatments (for example, radiation/surgery sequalae), dysphagia can arise in many patient populations, including children with acquired brain injury or other neuromuscular disorders, craniofacial or airway malformations, as well as those with respiratory, cardiac, or gastrointestinal disease. Dysphagia may also present in all critically ill patients and large-scale clinical data show that post-extubation dysphagia (PED) is commonly observed in intensive care unit (ICU) patients. Dysphagia is a serious condition as it impairs quality of life and causes nutritional and respiratory complications associated with poor prognosis and high mortality rates. This disabling condition impacts an estimated over 50 million patients worldwide (Nat Rev Gastroenterol Hepatol. 2015, 12(5): 259-270).

There are currently no approved pharmacological therapies for OD. The current standard of care is mostly limited to food modification (e.g., thickeners) and physical rehabilitation (e.g., postural adjustments and behavioral exercises to both strengthen the muscles involved in swallowing and improve swallowing ability).

Transient receptor potential cation channel subfamily M member 8 (TRPM8), also called the cold and menthol receptor 1 (CMR1), is the primary molecular transducer of cold somatosensation in humans and is activated at cool and cold temperatures (Nature. 2002, 416(6876): 52-58). TRPM8 is also activated by a variety of chemical compounds such as icilin or menthol (J Pharm Pharm Sci. 2010, 13(2): 242-253). This activation provokes the intracellular entry of calcium and sodium, leading to the depolarization of the membrane and triggering action potential and activating multiple signaling pathways. TRPM8 is notably expressed in ganglia and

peripheral nerve fibers that innervate the skin (BMC Neurol. 2007, 7:11) and also in tongue, pharyngeal and laryngeal tissues (Neurogastroenterol Motil. 2018, (11): e13398), which are associated with swallowing functions. This expression of the channel provides the possibility for therapeutic activation of TRPM8 in various pathologies, such as, for example, chronic cough, dry and pruritic skin, dry eye syndrome, and oropharyngeal dysphagia.

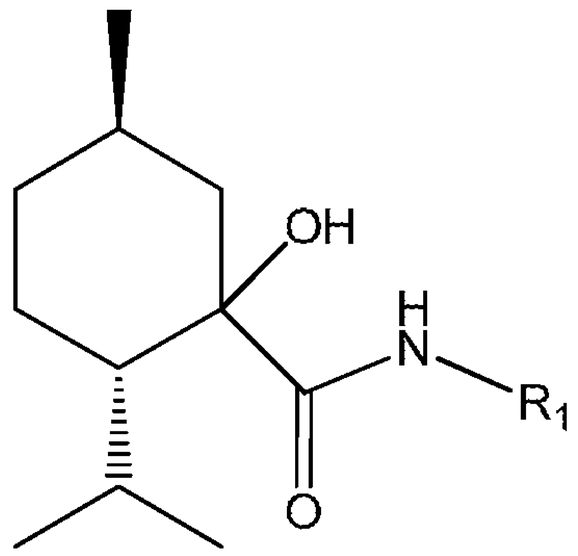
Activation of TRPM8 receptors in sensory nerves in the oral cavity and pharynx can activate swallowing reflexes in dysphagic patients (Journal of GHR. 2014, 3(5): 1066-1072). In particular, cold temperature (ice massage) and local application of menthol can reduce the abnormal delay in initiating the swallow reflex in dysphagic patients through TRPM8 activation (J Stroke Cerebrovasc Dis. 2013, 22(4): 378-382); Br J Clin Pharmacol. 2006, 62 (3): 369–371).

However, both approaches have limitations as therapeutic solutions: ice massage being impractical for daily living, and menthol presenting several disadvantages such as its low potency on TRPM8, poor selectivity (likely responsible for irritations), and its strong smell and taste.

Thus, there continues to be a need for activators of TRPM8 that can be used in the treatment of patients with a disease or condition affected by the activation of TRPM8 receptors.

Provided herein are novel compounds able to activate TRPM8, which may be useful in treating a disease, syndrome, or condition in a subject in which the disease, syndrome, or condition is affected by the activation of TRPM8 receptors, such as oropharyngeal dysphagia, chronic cough, pharyngeal irritation, dry and pruritic skin, and/or dry eye syndrome.

Provided herein is a compound of the formula (I):



(I)

wherein:

R_1 is $-C(R_2)(R_3)-[C(R_4)(R_5)]_m-L-R_6$ or $-R_7$;

m represents 0, 1, 2 or 3;

R_2 and R_3 independently represent a hydrogen atom, a deuterium atom, a –(C_1-C_6)-alkyl, a (C_1-C_6)-alkyl-OH group, a -C(=O)NH_2 group, a -(C_1-C_6)-alkoxyl group, or a -C(=O)O(C_1-C_6)-alkyl group;

R_4 and R_5 independently represent a hydrogen atom, a deuterium atom, a fluorine atom, a -NH_2 group, a -OH group, a -(C_1-C_6)-alkyl group, a -CF_3 group, a carboxyl group, or a -R_8-(C_1-C_6)-alkyl-R_9 group;

R_8 represents a bond, an -O-, a -OC(=O)- group, a -N(H)C(=O)- group, a -C(=O)O- group, or a -C(=O)N(H)- group;

R_9 represents a hydrogen atom, a -C(=O)-OH group, a -C(=O)O(C_1-C_3)-alkyl group, a -OH group, a -O(C_1-C_3)-alkyl group, or a -NH_2 group;

or R_4 and R_5 can form, together with the carbon atom to which they are attached, a heterocycloalkyl group comprising 3 to 5 carbon atoms and comprising from 1 or 2 heteroatoms selected from oxygen and nitrogen;

L represents a bond, a -(C_1-C_6)-alkylene- group, an -O-(C_1-C_6)-alkylene- group, an -O-, a -OC(=O)- group, a -N(H)- group, a -C(=O)- group, a -C(=O)O- group, a -C(=O)-O-(C_1-C_3)-alkyl- group, a -C(=O)-N(H)- or a -CONH(C_1-C_6)-alkyl- group;

R_6 is selected from the group consisting of a -OH group; a –(C_1-C_6)-alkyl group; a phenyl group; a monocyclic heteroaryl group comprising 3 to 5 carbon atoms and comprising from 1 to 2 heteroatoms independently selected from oxygen, nitrogen and sulfur; an ortho-fused bicyclic heteroaryl group comprising 7 to 10 carbon atoms and comprising from 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur; an ortho-fused bicyclic cycloalkyl group comprising 8 to 11 carbon atoms; and an ortho-fused bicyclic heterocycloalkyl group comprising 8 to 9 carbon atoms and comprising 1 or 2 heteroatoms independently selected from oxygen and nitrogen; said phenyl, monocyclic heteroaryl, ortho-fused bicyclic heteroaryl, ortho-fused bicyclic cycloalkyl, ortho-fused bicyclic heterocycloalkyl groups represented by R_6 are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of:

a halogen atom, a -OH group, an oxo group, an -O-(C_1-C_6)-alkyl group, a -(C_1-C_6)-alkyl group, a -NO_2 group, a -CN group, a -C(=O)H group, a -SO_2NH_2 group,

a -C(=O)NH_2 group, a -OCH_2C(=O)NH_2 group, a -C(=O)O(C_1-C_6)-alkyl group, or a -C(=O)N(C_1-C_3)-alkyl group, a -$(OCH_2CH_2)_n$-R_{10} group, and a -R_{11}-(C_1-C_6)-alkyl-R_{12} group which is unsubstituted or substituted on the (C_1-C_6)-alkyl with 1 to 3 substituents independently selected from a -OH group, a -NH_2 group and -OCH_3 group; wherein n represents 1, 2 or 3; R_{10} represents a -O(C_1-C_4)-alkyl group, a -N^+-$(CH_3)_3$ group, or -N^+H-$(CH_3)_2$ group; R_{11} represents a bond, an -O-, or a -C(=O)O- group; R_{12} represents a -OH group, a -C(=O)OH group, a -C(=O)O(C_1-C_3)-alkyl group, a -C(=O)N(C_1-C_3)-alkyl group, a -NH_2 group, a -NHC(=O)(C_1-C_3)-alkyl group, a -C(=O)H group, a heterocyclic group or an -O-heterocyclic group, said heterocyclic group and -O-heterocyclic group comprising 3 to 9 carbon atoms and comprising from 1 to 3 heteroatoms independently selected from oxygen, nitrogen and sulfur being unsubstituted or substituted with 1 to 3 substituents independently selected from an oxo group and a –(C_1-C_3)-alkyl group.

R_7 represents a phenyl group; a monocyclic cycloalkyl group comprising 4 to 7 carbon atoms; a monocyclic heterocycloalkyl group comprising 3 to 6 carbon atoms and comprising from 1 to 2 heteroatoms independently selected from oxygen and nitrogen; or an ortho-fused bicyclic heterocycloalkyl group comprising 8 to 9 carbon atoms and comprising 1 or 2 heteroatoms independently selected from oxygen and nitrogen; wherein said phenyl group is unsubstituted or substituted with 1 to 3 substituents independently selected from a halogen atom, a -(C_1-C_3)-alkyl group, an -O-(C_1-C_3)-alkyl group and a morpholine group; said monocyclic cycloalkyl, monocyclic heterocycloalkyl, an ortho-fused bicyclic heterocycloalkyl groups being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of: a halogen atom, an oxo group, a -(C_1-C_6)-alkyl group, a phenyl group, an -O-, a benzyl group, a -OH group, and an -O-(C_1-C_6)-alkyl group;

or a pharmaceutically acceptable salt thereof.

The compounds of formula (I) contain more than one asymmetric carbon atoms, more particularly one asymmetric carbon atom on the cyclohexyl group. They may therefore exist in the form of enantiomers. The compounds of formula (I) include enantiomers, racemates, and mixtures thereof. In particular, the carbon of the cyclohexyl group linked to the hydroxyl group of

the formula (I) may be in the absolute configuration (R) or (S). The carbon of the cyclohexyl group linked to the hydroxyl group is advantageously in the absolute configuration (S).

The compounds of formula (I) also include tautomer forms thereof.

The compounds of formula (I) may exist in the form of bases, acids, or zwitterions.

The compounds of formula (I) can be in the form of addition salts with acids or bases, for example: hydrochloride acid and citric acid. Hence, provided herein inter alia, are compounds of formula (I) or pharmaceutically acceptable salts thereof.

As used herein, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

As used herein, the term “alkyl” means a straight or branched aliphatic hydrocarbon group having 1 to about 12 carbon atoms in the chain. In one aspect, an alkyl has 1 to 6 carbon atoms in the chain. Another aspect, an alkyl has 1 to 3 carbon atoms in the chain. “Lower alkyl” means an alkyl group having 1 to about 4 carbon atoms in an alkyl chain that may be straight or branched. Branched means that one or more lower alkyl groups, such as methyl, ethyl or propyl, are attached to a linear alkyl chain. Additionally, the term “(C_1-C_6)-alkyl” denotes a straight or branched alkyl group having one to six carbon atoms. The term “(C_1-C_4)-alkyl” denotes a straight or branched alkyl group having one to four carbon atoms. The term “(C_1-C_3)-alkyl” denotes a straight or branched alkyl group having one to three carbon atoms. Exemplary alkyl includes methyl, ethyl, *i*-propyl, *t*-butyl, and the like.

As used herein, the term “alkoxy” means an alkyl-O- group wherein the alkyl group is as herein described. Exemplary alkoxy groups include methoxy, ethoxy, *n*-propoxy, *i*-propoxy, *n*-butoxy, *t*-butoxy, heptoxy, and the like.

As used herein, the term “alkylene” means a straight or branched bivalent hydrocarbon chain having from 1 to about 12 carbon atoms. In one aspect, an alkylene has 1 to about 10 carbon atoms in the chain. Another aspect, an alkylene has 1 to about 6 carbon atoms in the chain. A “lower alkylene” is an alkylene having from 1 to about 4 carbon atoms. Exemplary alkylene includes methylene, ethylene, propylene, and butylene.

As used herein, the term “aromatic” means a moiety wherein the constituent atoms make up an unsaturated ring system, all atoms in the ring system are sp2 hybridized and the total number of pi electrons is equal to 4n+2. An aromatic ring may be such that the ring atoms are only carbon atoms or may include carbon and non-carbon atoms (see Heteroaryl).

As used herein, the term “aryl” means an aromatic monocyclic or bicyclic ring system of about 5 to about 10 carbon atoms. Exemplary aryl include phenyl and naphthyl.

As used herein, the term “benzyl” means phenyl-CH_2- group.

As used herein, the term “carboxyl” means a substituent of the formula - C(=O)OH.

As used herein, the term “cycloalkyl” means a ring system comprising, unless otherwise mentioned, from 3 to 10 carbon atoms, that is saturated or partially unsaturated and unsubstituted or substituted. Said cycloalkyl group may be monocyclic or bicyclic. The term “monocyclic cycloalkyl” means an unsubstituted or substituted ring system comprising 3 to 7 carbon atoms; a “bicyclic cycloalkyl group” means a two-ring system comprising 8 to 11 carbon atoms. By way of examples, mention may be made of, but not limited to: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, spiro[2.2]pentyl, spiro[3.4]octyl, [5.5]undecyl, [4.5]decyl groups, and the like.

As used herein, the term “ortho-fused cycloalkyl group” means an unsubstituted or substituted 8-10 membered bicyclic ring group. Included within the scope of the definition of ortho-fused cycloalkyl group are bicyclic ring systems wherein one of the rings is saturated or partially unsaturated cycloalkyl ring and the other ring is an aromatic ring. By way of examples, mention may be made of, but not limited to: 1,2,3,4-tetrahydronaphthalen-1-yl, indan-1-yl, hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl, 1-hydroxy-2,3-dihydro-1H-inden-1-yl, 5-methoxyindan-1-yl, and 4-chloro-1-hydroxy-indan-1-yl.

As used herein, the terms “halo” or “halogen” mean fluoro, chloro, bromo, or iodo. Particular halogens are fluoro and chloro.

As used herein, the term “heteroaryl” whether used alone or with other terms, such as “heteroaryl group”, means a cyclic aromatic group containing 3 to 10 carbon atoms and containing between 1 and 4 heteroatoms, such as nitrogen, oxygen or sulfur. Said heteroaryl group may be monocyclic or bicyclic. As used herein, the term “monocyclic heteroaryl” means a cyclic aromatic group containing 3 to 5 carbon atoms and containing between 1 and 2 heteroatoms, such as

nitrogen, oxygen or sulfur. By way of examples of monocyclic heteroaryl groups, mention may be made of, but not limited to: benzimidazole, benzothiazole, benzothiadiazole, benzofuran, benzotriazole, benzoxazole, furanyl, furazanyl, indole, imidazolyl, isoxazole, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyridine, pyridyl, pyridinyl, pyrimidine, pyrimidinyl, pyrrolo[2,3-b]pyridine, pyrazinyl, pyrazolyl, pyridazinyl, pyrrolyl, thienyl, 1,2-oxazolyl, 1,2,4-thiadiazolyl, 1,2,4-triazinyl, 1,3,4-thiadiazolyl, thiazolyl, thienyl, triazolyl, thiophenyl and the like.

As used herein, the term “ortho-fused” means a ring system where the two adjacent rings have two adjacent atoms in common. The term “ortho-fused heteroaryl” means a bicyclic ring system comprising 7 to 10 carbon atoms and comprising from 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur. Included within the scope of the definition of ortho-fused heteroaryl group is a bicyclic ring system wherein one of the rings is heteroaryl and the other ring is aryl ring or both rings are heteroaryl. Examples include indolyl and benzimidazolyl.

The terms “heterocycle” and derivatives thereof such as “heterocyclyl” and “heterocyclic” mean an aromatic, a partially unsaturated or a saturated ring containing one or more carbon atoms and one or more heteroatoms such as nitrogen, oxygen and sulfur, but may be more specifically defined where appropriate in the specification, for example with respect to degree of saturation, number of members (i.e. atoms) in the ring and/or the type and quantity of heteroatoms in the ring. The point of attachment in a compound structure may be via any carbon or nitrogen in the heterocyclic ring which results in the creation of a stable structure, unless specified otherwise. The heterocyclic ring may be substituted on any available carbon or nitrogen in the ring which results in the creation of a stable structure, unless specified otherwise. Exemplary heterocyclyl groups include piperidinyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

As used herein, heterocycloalkyl means a cyclic alkyl group comprising, unless otherwise mentioned, from 3 to 9 carbon atoms and containing 1 or 2 heteroatoms such as oxygen, nitrogen or sulfur. Such heterocycloalkyl group may be saturated or partially saturated and unsubstituted or substituted and may be monocyclic or bicyclic. As used herein, the term “monocyclic heterocycloalkyl” means monocyclic heterocycloalkyl group comprising 3 to 6 carbon atoms and comprising from 1 or 2 heteroatoms selected from oxygen and nitrogen. By way of examples of monocyclic heterocycloalkyl groups, mention may be made of, but not limited to:

tetrahydropyridinyl, dihydropyridinyl, dihydropyranyl, 2-oxotetrahydrofuran-3-yl, tetrahydropyranyl groups, and the like.

As used herein, the term “ortho-fused” means a ring system where the two adjacent rings have two adjacent atoms in common. The term “ortho-fused bicyclic heterocycloalkyl” means a bicyclic ring system comprising 8 to 9 carbon atoms and comprising 1 or 2 heteroatoms independently selected from oxygen and nitrogen. Included within the scope of the definition of ortho-fused heterocycloalkyl group are bicyclic ring systems wherein only one of the rings is heterocycloalkyl, the other ring is aryl ring or heteroaryl ring. By way of examples of ortho-fused heterocycloalkyl group, mention may be made of, but not limited to: 2,3-dihydrobenzofuran-3-yl, 6-methoxy-2,3-dihydrobenzofuran-3-yl, chroman-4-yl, isochroman-1-yl, 4-hydroxychroman-4-yl, 3-oxo-1,3-dihydroisobenzofuran-1-yl.

As used herein, the term “patient” includes mammals, especially humans, who use the instant active agents for the prevention or treatment of a medical condition. Administering of the compound of formula (I) to the patient includes both self-administration and administration to the patient by another person. The patient may be in need of treatment for an existing disease or medical condition, or may desire prophylactic treatment to prevent or reduce the risk of medical condition.

As used herein, “treating,” unless otherwise indicated, means to partially or totally alleviate symptoms on a temporary or permanent basis, or to slow the worsening of symptoms of the named disorder or condition. The term “treatment” as used herein, unless otherwise indicated, refers to the act of treating.

As used herein, the phrase “a method of treating” or its equivalent, when applied to, for example, oropharyngeal dysphagia, refers to a procedure or course of action that is designed to reduce, eliminate, or inhibit the progression of medical condition in a patient; and/or to alleviate the symptoms of oropharyngeal dysphagia.

As used herein, the term “therapeutically effective amount” or “effective amount” means the amount of the subject compound, composition or combination that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

“Pharmaceutically acceptable salts,” as used herein, refers to the relatively non-toxic, inorganic and organic acid addition salts, and base addition salts, of compounds of Formula (I).

These salts can be prepared *in situ* during the final isolation and purification of the compounds. Some of the compounds of the invention are basic, and such compounds are useful in the form of the free base, or in the form of a pharmaceutically acceptable acid addition salt thereof.

Acid addition salts are a convenient form for use; and in practice, use of the salt form in essence amounts to use of the free base form. The acids which can be used to prepare the acid addition salts include preferably those which produce, when combined with the free base, pharmaceutically acceptable salts, that is, salts whose anions are non-toxic to the patient in pharmaceutical doses of the salts, so that the beneficial activation effects inherent in the free base are not vitiated by side effects ascribable to the anions. Although pharmaceutically acceptable salts of said basic compounds are preferred, all acid addition salts are useful as sources of the free base form even if the particular salt, *per se*, is desired only as an intermediate product as, for example, when the salt is formed only for purposes of purification, and identification, or when it is used as intermediate in preparing a pharmaceutically acceptable salt by ion exchange procedures. In particular, acid addition salts can be prepared by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Pharmaceutically acceptable salts within the scope of the invention include those derived from mineral acids and organic acids. See, for example S.M. Berge, et al., "Pharmaceutical Salts," *J. Pharm. Sci.*, (66), 1-19 (1977).

Where the compound disclosed is substituted with an acidic moiety, base addition salts may be formed and are simply a convenient form for use; and in practice, use of the salt form in essence amounts to use of the free acid form. The bases which can be used to prepare the base addition salts include preferably those which produce, when combined with the free acid, pharmaceutically acceptable salts, that is, salts whose cations are non-toxic to the patient in pharmaceutical doses of the salts, so that the beneficial activation effects inherent in the free base are not vitiated by side effects ascribable to the cations.

As well as being useful in themselves as active compounds, salts of compounds of the invention are useful for the purposes of purification of the compounds, for example by exploitation of the solubility differences between the salts and the parent compounds, side products and/or starting materials by techniques well known to those skilled in the art.

The compounds disclosed may contain more than one asymmetric center. These asymmetric centers may independently be in either the R or S configuration. It will be apparent to those skilled in the art that certain compounds of formula (I) may also exhibit geometrical

isomerism. It is to be understood that the present disclosure includes individual geometrical isomers and stereoisomers and mixtures thereof, including racemic mixtures, of compounds of formula (I) hereinabove. Such isomers can be separated from their mixtures, by the application or adaptation of known methods. Chiral chromatography techniques represent one means for separating isomers from mixtures thereof. Some compounds may be separated by chiral recrystallization techniques as an alternative means for separating isomers from mixtures thereof. Individual isomeric compounds can also be prepared by employing, where applicable, chiral precursors.

One embodiment is a compound of formula (I), wherein R_1 represents $-C(R_2)(R_3)-[C(R_4)(R_5)]_m-L-R_6$.

Another embodiment is a compound of formula (I), wherein R_1 represents $-R_7$.

Another embodiment is a compound of formula (I), wherein one of R_2 and R_3 independently represents a hydrogen atom.

Another embodiment is a compound of formula (I), wherein both R_2 and R_3 represent a hydrogen atom.

Another embodiment is a compound of formula (I), wherein one of R_2 and R_3 independently represents a deuterium atom.

Another embodiment is a compound of formula (I), wherein one of R_2 and R_3 independently represents a–$(C_1$-$C_6)$-alkyl group.

Another embodiment is a compound of formula (I), wherein one of R_2 and R_3 independently represents a–$(C_1$-$C_3)$-alkyl group.

Another embodiment is a compound of formula (I), wherein one of R_2 and R_3 independently represents a $(C_1$-$C_6)$-alkyl-OH group.

Another embodiment is a compound of formula (I), wherein one of R_2 and R_3 independently represents a $(C_1$-$C_3)$-alkyl-OH group.

Another embodiment is a compound of formula (I), wherein one of R_2 and R_3 independently represents a $-C(=O)NH_2$ group.

Another embodiment is a compound of formula (I), wherein one of R_2 and R_3 independently represents a -(C_1-C_6)-alkoxyl group.

Another embodiment is a compound of formula (I), wherein one of R_2 and R_3 independently represents a -(C_1-C_3)-alkoxyl group.

Another embodiment is a compound of formula (I), wherein one of R_2 and R_3 independently represents a -C(=O)O(C_1-C_6)-alkyl group.

Another embodiment is a compound of formula (I), wherein one of R_2 and R_3 independently represents a -C(=O)O(C_1-C_3)-alkyl group.

Another embodiment is a compound of formula (I), wherein m represents 0.

Another embodiment is a compound of formula (I), wherein m represents 1.

Another embodiment is a compound of formula (I), wherein m represents 2.

Another embodiment is a compound of formula (I), wherein m represents 3.

Another embodiment is a compound of formula (I), wherein one R_4 and R_5 independently represents a hydrogen atom.

Another embodiment is a compound of formula (I), wherein both R_4 and R_5 represent a hydrogen atom.

Another embodiment is a compound of formula (I), wherein one of R_4 and R_5 independently represents a deuterium atom.

Another embodiment is a compound of formula (I), wherein one of R_4 and R_5 independently represents a fluorine atom.

Another embodiment is a compound of formula (I), wherein both R_4 and R_5 represent a fluorine atom.

Another embodiment is a compound of formula (I), wherein one of R_4 and R_5 independently represents a -NH_2 group.

Another embodiment is a compound of formula (I), wherein one of R_4 and R_5 independently represents a -OH group.

Another embodiment is a compound of formula (I), wherein one of R_4 and R_5 independently represents a -(C_1-C_6)-alkyl group.

Another embodiment is a compound of formula (I), wherein one of R_4 and R_5 independently represents a -(C_1-C_3)-alkyl group.

Another embodiment is a compound of formula (I), wherein one of R_4 and R_5 independently represents a $-CF_3$ group.

Another embodiment is a compound of formula (I), wherein one of R_4 and R_5 independently represents a carboxyl group.

Another embodiment is a compound of formula (I), wherein one of R_4 and R_5 independently represents a -R_8-(C_1-C_6)-alkyl-R_9 group.

Another embodiment is a compound of formula (I), wherein one of R_4 and R_5 independently represents a -R_8-(C_1-C_3)-alkyl-R_9 group.

Another embodiment is a compound of formula (I), wherein R_4 and R_5 can form, together with the carbon atom to which they are attached, a heterocycloalkyl group comprising 3 to 5 carbon atoms and comprising from 1 or 2 heteroatoms selected from oxygen and nitrogen.

Another embodiment is a compound of formula (I), wherein L represents a bond.

Another embodiment is a compound of formula (I), wherein L represents a -(C_1-C_6)-alkylene- group.

Another embodiment is a compound of formula (I), wherein L represents a -(C_1-C_3)-alkylene- group.

Another embodiment is a compound of formula (I), wherein L represents an -O-.

Another embodiment is a compound of formula (I), wherein L represents a -OC(=O)- group.

Another embodiment is a compound of formula (I), wherein L represents a -N(H)- group.

Another embodiment is a compound of formula (I), wherein L represents a -C(=O)- group.

Another embodiment is a compound of formula (I), wherein L represents a -C(=O)O- group.

Another embodiment is a compound of formula (I), wherein L represents a -C(=O)-O-(C_1-C_3)-alkyl- group.

Another embodiment is a compound of formula (I), wherein L represents a -C(=O)-N(H)- group.

Another embodiment is a compound of formula (I), wherein L represents a -CONH(C_1-C_6)-alkyl- group.

Another embodiment is a compound of formula (I), wherein L represents a -CONH(C_1-C_3)-alkyl- group.

Another embodiment is a compound of formula (I), wherein R_6 represents a -OH group.

Another embodiment is a compound of formula (I), wherein R_6 represents a –(C_1-C_6)-alkyl- group.

Another embodiment is a compound of formula (I), wherein R_6 represents a –(C_1-C_3)-alkyl- group.

Another embodiment is a compound of formula (I), wherein R_6 represents a phenyl group; a monocyclic heteroaryl group comprising 3 to 5 carbon atoms and comprising from 1 to 2 heteroatoms independently selected from oxygen, nitrogen and sulfur; an ortho-fused bicyclic heteroaryl group comprising 7 to 10 carbon atoms and comprising from 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur; an ortho-fused bicyclic cycloalkyl group

comprising 8 to 11 carbon atoms; and an ortho-fused bicyclic heterocycloalkyl group comprising 8 to 9 carbon atoms and comprising 1 or 2 heteroatoms independently selected from oxygen and nitrogen; said phenyl, monocyclic heterocycloalkyl, monocyclic heteroaryl, ortho-fused bicyclic heteroaryl, ortho-fused bicyclic cycloalkyl, ortho-fused bicyclic heterocycloalkyl groups being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of:

a halogen atom, an oxo group, a -OH group, an -O-(C_1-C_6)-alkyl group, a -(C_1-C_6)-alkyl group, a -NO_2 group, a -CN group, a -C(=O)H group, a -SO_2NH_2 group, a -$C(=O)NH_2$ group, a -$OCH_2C(=O)NH_2$ group, a -C(=O)O(C_1-C_6)-alkyl group, a -C(=O)N(C_1-C_3)-alkyl group, a -$(OCH_2CH_2)_n$-R_{10} group, and a -R_{11}-(C_1-C_6)-alkyl-R_{12} group which is unsubstituted or substituted on the (C_1-C_6)-alkyl with 1 to 3 substituents independently selected from a -OH group, a -NH_2 group and -OCH_3 group; wherein n represents 1, 2 or 3; R_{10} represents a -O(C_1-C_4)-alkyl group, a -N^+-$(CH_3)_3$ group, or -N^+H-$(CH_3)_2$ group; R_{11} represents a bond, an -O-, or a -C(=O)O group; R_{12} represents a -OH group, a -C(=O)OH group, a -C(=O)O(C_1-C_3)-alkyl group, a -C(=O)N(C_1-C_3)-alkyl group, a -NH_2 group, a -NHC(=O)(C_1-C_3)-alkyl group, a -C(=O)H group, a heterocyclic group or an -O-heterocyclic group; said heterocyclic group and said -O-heterocyclic group comprising 3 to 9 carbon atoms and comprising from 1 to 3 heteroatoms independently selected from oxygen, nitrogen and sulfur being unsubstituted or substituted with 1 to 3 substituents independently selected from an oxo group and a –(C_1-C_3)-alkyl group.

Another embodiment is a compound of formula (I), R_6 represents a phenyl group; a monocyclic heteroaryl group comprising 3 to 5 carbon atoms and comprising from 1 to 2 heteroatoms independently selected from oxygen, nitrogen and sulfur; an ortho-fused bicyclic heteroaryl group comprising 7 to 10 carbon atoms and comprising from 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur; an ortho-fused bicyclic cycloalkyl group comprising 8 to 11 carbon atoms; and an ortho-fused bicyclic heterocycloalkyl group comprising 8 to 9 carbon atoms and comprising 1 or 2 heteroatoms independently selected from oxygen and nitrogen; said phenyl, monocyclic heterocycloalkyl, monocyclic heteroaryl, ortho-fused bicyclic heteroaryl, ortho-fused bicyclic cycloalkyl, and ortho-fused bicyclic heterocycloalkyl groups are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of:

a halogen atom, an oxo group, a -OH group, an -O-(C_1-C_3)-alkyl group, a -(C_1-C_3)-alkyl group, a -NO_2 group, a -CN group, a -C(=O)H group, a -SO_2NH_2 group, a -$C(=O)NH_2$ group, a -$OCH_2C(=O)NH_2$ group, a -C(=O)O(C_1-C_3)-alkyl group, or a -C(=O)N(C_1-C_3)-alkyl group, a -

$(OCH_2CH_2)_n$-R_{10} group, and a -R_{11}-(C_1-C_3)-alkyl-R_{12} group which is unsubstituted or substituted on the (C_1-C_6)-alkyl with 1 to 3 substituents independently selected from a -OH group, a -NH_2 group and -OCH_3 group; wherein n represents 1, 2 or 3; R_{10} represents a -O(C_1-C_4)-alkyl group, a -N^+-$(CH_3)_3$ group, or a-N^+H-$(CH_3)_2$ group; R_{11} represents a bond, an -O- or a -C(=O)O group; R_{12} represents a -OH group, a -C(=O)OH group, a -C(=O)O(C_1-C_3)-alkyl group, a -C(=O)N(C_1-C_3)-alkyl group, a -NH_2 group, a -NHC(=O)(C_1-C_3)-alkyl group, a -C(=O)H group, a heterocyclic group or an -O-heterocyclic group, said heterocyclic group and said -O-heterocyclic group comprising 3 to 9 carbon atoms and comprising from 1 to 3 heteroatoms independently selected from oxygen, nitrogen and sulfur being unsubstituted or substituted with 1 to 3 substituents independently selected from an oxo group and a –(C_1-C_3)-alkyl group.

Another embodiment is a compound of formula (I), wherein R_6 represents a phenyl group, said phenyl being unsubstituted.

Another embodiment is a compound of formula (I), wherein R_6 represents a phenyl group, said phenyl being substituted with 1 to 3 substituents independently selected from the group consisting of: a halogen atom, a -OH group, an -O-(C_1-C_6)-alkyl group, a -(C_1-C_6)-alkyl group, a -NO_2 group, a -CN group, a -C(=O)H group, a -SO_2NH_2 group, a -$C(=O)NH_2$ group, a -$OCH_2C(=O)NH_2$ group, a -C(=O)O(C_1-C_6)-alkyl group, and a -C(=O)N(C_1-C_3)-alkyl group.

Another embodiment is a compound of formula (I), wherein R_6 represents a phenyl group, said phenyl being substituted with 1 to 2 substituents independently selected from the group consisting of: a halogen atom, a -OH group, an -O-(C_1-C_3)-alkyl group, a -(C_1-C_3)-alkyl group, a -NO_2 group, a -CN group, a -C(=O)H group, a -SO_2NH_2 group, a -$C(=O)NH_2$ group, a -$OCH_2C(=O)NH_2$ group, a -C(=O)O(C_1-C_3)-alkyl group, and a -C(=O)N(C_1-C_3)-alkyl group.

Another embodiment is a compound of formula (I), wherein R_6 represents a phenyl group, said phenyl being substituted with 1 to 2 -$(OCH_2CH_2)_n$-R_{10} groups, wherein n independently represents 1, 2 or 3; and R_{10} independently represents an -O-(C_1-C_4)-alkyl group, a -N^+-$(CH_3)_3$ group, or a -N^+H-$(CH_3)_2$ group.

Another embodiment is a compound of formula (I), wherein R_6 represents a phenyl group, wherein said phenyl is substituted with 1 to 3 -R_{11}-(C_1-C_6)-alkyl-R_{12} group which is unsubstituted or substituted on the (C_1-C_6)-alkyl with 1 to 3 substituents independently selected from a -OH

group, a $-NH_2$ group and $-OCH_3$ group; R_{11} represents a bond, an -O-, or a -C(=O)O group; R_{12} represents a -OH group, a -C(=O)OH group, a $-C(=O)O(C_1-C_3)$-alkyl group, a $-C(=O)N(C_1-C_3)$-alkyl group, a $-NH_2$ group, a $-NHC(=O)(C_1-C_3)$-alkyl group, a -C(=O)H group, a heterocyclic group or an -O-heterocyclic group, said heterocyclic group and said -O-heterocyclic group comprising 3 to 9 carbon atoms and comprising from 1 to 3 heteroatoms independently selected from oxygen, nitrogen and sulfur being unsubstituted or substituted with 1 to 3 substituents independently selected from an oxo group and a $–(C_1-C_3)$-alkyl group.

Another embodiment is a compound of formula (I), wherein R_6 represents a phenyl group, wherein said phenyl is substituted with 1 to 2 $-R_{11}-(C_1-C_3)$-alkyl-R_{12} group which is unsubstituted or substituted on the (C_1-C_6)-alkyl with 1 to 3 substituents independently selected from a -OH group, a $-NH_2$ group and $-OCH_3$ group; R_{11} represents a bond, an -O-, or a -C(=O)O group; R_{12} represents a -OH group, a -C(=O)OH group, a $-C(=O)O(C_1-C_3)$-alkyl group, a $-C(=O)N(C_1-C_3)$-alkyl group, a $-NH_2$ group, a $-NHC(=O)(C_1-C_3)$-alkyl group, a -C(=O)H group, a heterocyclic group or an -O-heterocyclic group, said heterocyclic group and said -O-heterocyclic group comprising 3 to 9 carbon atoms and comprising from 1 to 3 heteroatoms independently selected from oxygen, nitrogen and sulfur being unsubstituted or substituted with 1 to 3 substituents independently selected from an oxo group and a $–(C_1-C_3)$-alkyl group.

Another embodiment is a compound of formula (I), wherein R_6 represents a monocyclic heteroaryl group comprising 3 to 5 carbon atoms and comprising from 1 to 2 heteroatoms independently selected from oxygen, nitrogen and sulfur, said monocyclic heteroaryl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of: a halogen atom, a -OH group, an $-O-(C_1-C_6)$-alkyl group, a $-(C_1-C_6)$-alkyl group, a $-NO_2$ group, a -CN group, a -C(=O)H group, a $-SO_2NH_2$ group, a $-C(=O)NH_2$ group, a $-OCH_2C(=O)NH_2$ group, a $-C(=O)O(C_1-C_6)$-alkyl group, and a $-C(=O)N(C_1-C_3)$-alkyl group.

Another embodiment is a compound of formula (I), wherein R_6 represents a monocyclic heteroaryl group comprising 3 to 5 carbon atoms and comprising from 1 to 2 heteroatoms independently selected from oxygen, nitrogen and sulfur,, said monocyclic heteroaryl group being unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of: a halogen atom, a -OH group, an $-O-(C_1-C_3)$-alkyl group, a $-(C_1-C_3)$-alkyl group, a $-NO_2$ group, a -CN group, a -C(=O)H group, a $-SO_2NH_2$ group, a $-C(=O)NH_2$ group, a $-OCH_2C(=O)NH_2$ group, a $-C(=O)O(C_1-C_3)$-alkyl group, and a $-C(=O)N(C_1-C_3)$-alkyl group.

Another embodiment is a compound of formula (I), wherein R_6 represents a monocyclic heteroaryl group comprising 3 to 5 carbon atoms and comprising from 1 to 2 heteroatoms independently selected from oxygen, nitrogen and sulfur, said monocyclic heteroaryl group being substituted with 1 to 3 $-(OCH_2CH_2)_n-R_{10}$ groups, wherein n independently represents 1, 2 or 3; R_{10} independently represents a $-O(C_1-C_4)$-alkyl group, a $-N^+-(CH_3)_3$ group, or a $-N^+H-(CH_3)_2$ group.

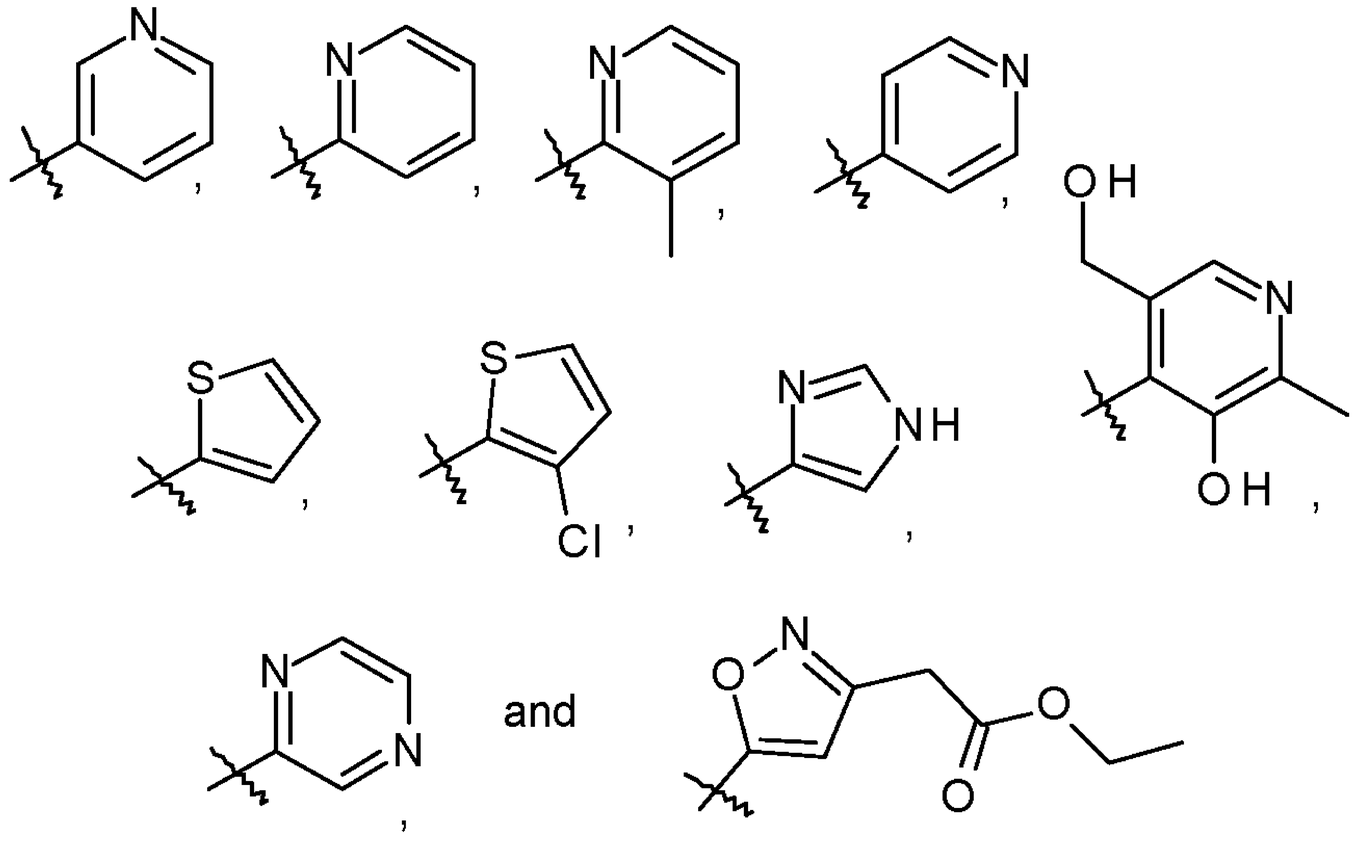
Another embodiment is a compound of formula (I), wherein R_6 represents a monocyclic heteroaryl group comprising 3 to 5 carbon atoms and comprising from 1 to 2 heteroatoms independently selected from oxygen, nitrogen and sulfur, said monocyclic heteroaryl group being substituted with 1 to 3 $-R_{11}-(C_1-C_6)$-alkyl-R_{12} group which is unsubstituted or substituted on the (C_1-C_6)-alkyl with 1 to 3 substituents independently selected from a -OH group, a $-NH_2$ group and $-OCH_3$ group; R_{11} represents a bond, an -O-, or a -C(=O)O group; R_{12} represents a -OH group, a -C(=O)OH group, a $-C(=O)O(C_1-C_3)$-alkyl group, a $-C(=O)N(C_1-C_3)$-alkyl group, a $-NH_2$ group, a $-NHC(=O)(C_1-C_3)$-alkyl group, a -C(=O)H group, or a heterocyclic group comprising 3 to 9 carbon atoms and comprising from 1 to 3 heteroatoms independently selected from oxygen, nitrogen and sulfur being unsubstituted or substituted with 1 to 3 substituents independently selected from an oxo group and a $-(C_1-C_3)$-alkyl group.

Another embodiment is a compound of formula (I), wherein R_6 represents a monocyclic heteroaryl group comprising 3 to 5 carbon atoms and comprising from 1 to 2 heteroatoms independently selected from oxygen, nitrogen and sulfur, said monocyclic heteroaryl group being substituted with 1 to 2 $-R_{11}-(C_1-C_3)$-alkyl-R_{12} group which is unsubstituted or substituted on the (C_1-C_6)-alkyl with 1 to 3 substituents independently selected from a -OH group, a $-NH_2$ group and $-OCH_3$ group, R_{11} represents a bond, an -O-, or a -C(=O)O group; R_{12} represents a -OH group, a -C(=O)OH group, a $-C(=O)O(C_1-C_3)$-alkyl group, a $-C(=O)N(C_1-C_3)$-alkyl group, a $-NH_2$ group, a $-NHC(=O)(C_1-C_3)$-alkyl group, a -C(=O)H group, or a heterocyclic group comprising 3 to 9 carbon atoms and comprising from 1 to 3 heteroatoms independently selected from oxygen, nitrogen and sulfur being unsubstituted or substituted with 1 to 2 substituents independently selected from an oxo group and a $-(C_1-C_3)$-alkyl group.

Another embodiment is a compound of formula (I), wherein R_6 is selected from a monocyclic heteroaryl group comprising 3 to 5 carbon atoms and comprising from 1 to 2 heteroatoms independently selected from oxygen, nitrogen and sulfur, said monocyclic heteroaryl

group being unsubstituted or substituted with 1 to 2 substituents independently selected from: a halogen atom, a -OH group, an -O-(C_1-C_3)-alkyl group, and a -(C_1-C_4)-alkyl-OH group.

Another embodiment is a compound of formula (I), wherein R_6 represents a monocyclic heteroaryl group selected from the following list:



Another embodiment is a compound of formula (I), wherein R_6 represents an ortho-fused bicyclic heteroaryl group comprising 7 to 10 carbon atoms and comprising from 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur, said ortho-fused bicyclic heteroaryl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of: a halogen atom, an oxo group, a -OH group, an -O-(C_1-C_6)-alkyl group, a -(C_1-C_6)-alkyl group, a -NO_2 group, a -CN group, a -C(=O)H group, a -SO_2NH_2 group, a -$C(=O)NH_2$ group, a -$OCH_2C(=O)NH_2$ group, a -C(=O)O(C_1-C_6)-alkyl group, and a -C(=O)N(C_1-C_3)-alkyl group.

Another embodiment is a compound of formula (I), wherein R_6 represents an ortho-fused bicyclic heteroaryl group comprising 7 to 10 carbon atoms and comprising from 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur, said ortho-fused bicyclic heteroaryl group being unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of: a halogen atom, a -OH group, an -O-(C_1-C_3)-alkyl group, a -(C_1-C_3)-alkyl group, a -NO_2 group, a -CN group, a -C(=O)H group, a -SO_2NH_2 group, a -$C(=O)NH_2$ group, a -$OCH_2C(=O)NH_2$ group, a -C(=O)O(C_1-C_3)-alkyl group, and a -C(=O)N(C_1-C_3)-alkyl group.

Another embodiment is a compound of formula (I), wherein R_6 represents an ortho-fused bicyclic heteroaryl group comprising 7 to 10 carbon atoms and comprising from 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur, said ortho-fused bicyclic heteroaryl group being substituted with a $-(OCH_2CH_2)_n-R_{10}$ group, wherein n represents 1, 2 or 3; R_{10} represents a $-O(C_1-C_4)$-alkyl group, a $-N^+-(CH_3)_3$ group, or a $-N^+H-(CH_3)_2$ group.

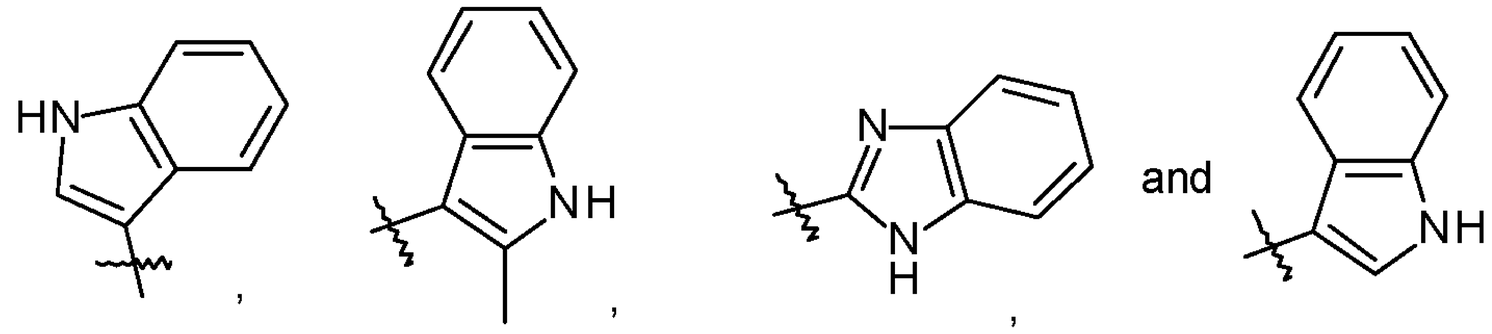
Another embodiment is a compound of formula (I), wherein R_6 represents an ortho-fused bicyclic heteroaryl group comprising 7 to 10 carbon atoms and comprising from 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur, said ortho-fused bicyclic heteroaryl group being substituted with 1 to 3 $-R_{11}-(C_1-C_6)$-alkyl-R_{12} group which is unsubstituted or substituted on the (C_1-C_6)-alkyl with 1 to 3 substituents independently selected from a -OH group, a $-NH_2$ group and $-OCH_3$ group; R_{11} represents a bond, an -O-, or a -C(=O)O group; R_{12} represents a -OH group, a -C(=O)OH group, a $-C(=O)O(C_1-C_3)$-alkyl group, a $-C(=O)N(C_1-C_3)$-alkyl group, a $-NH_2$ group, a $-NHC(=O)(C_1-C_3)$-alkyl group, a -C(=O)H group, or a heterocyclic group comprising 3 to 9 carbon atoms and comprising from 1 to 3 heteroatoms independently selected from oxygen, nitrogen and sulfur being unsubstituted or substituted with 1 to 3 substituents independently selected from an oxo group and a $–(C_1-C_3)$-alkyl group.

Another embodiment is a compound of formula (I), wherein R_6 represents an ortho-fused bicyclic heteroaryl group comprising 7 to 10 carbon atoms and comprising from 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur, said ortho-fused bicyclic heteroaryl group being substituted with 1 to 2 $-R_{11}-(C_1-C_3)$-alkyl-R_{12} group which is unsubstituted or substituted on the (C_1-C_6)-alkyl with 1 to 3 substituents independently selected from a -OH group, a $-NH_2$ group and $-OCH_3$ group; R_{11} represents a bond, an -O-, or a -C(=O)O group; R_{12} represents a -OH group, a -C(=O)OH group, a $-C(=O)O(C_1-C_3)$-alkyl group, a $-C(=O)N(C_1-C_3)$-alkyl group, a $-NH_2$ group, a $-NHC(=O)(C_1-C_3)$-alkyl group, a -C(=O)H group, or a heterocyclic group comprising 3 to 9 carbon atoms and comprising from 1 to 3 heteroatoms independently selected from oxygen, nitrogen and sulfur being unsubstituted or substituted with 1 to 2 substituents independently selected from an oxo group and a $–(C_1-C_3)$-alkyl group.

Another embodiment is a compound of formula (I), wherein R_6 is selected from a bicyclic heteroaryl group comprising 7 to 10 carbon atoms and comprising from 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur, said bicyclic heteroaryl group being unsubstituted or substituted with 1 to 2 substituents independently selected from: a halogen atom,

an oxo group, a -OH group, an -O-(C_1-C_3)-alkyl group, a -(C_1-C_3)-alkyl group and a -(C_1-C_4)-alkyl-OH group.

Another embodiment is a compound of formula (I), wherein R_6 represents a bicyclic heteroaryl group selected from the following list:



Another embodiment is a compound of formula (I), wherein R_6 represents an ortho-fused bicyclic cycloalkyl group comprising 8 to 11 carbon atoms, or an ortho-fused bicyclic heterocycloalkyl group comprising 8 to 9 carbon atoms and comprising 1 or 2 heteroatoms independently selected from oxygen and nitrogen; said ortho-fused bicyclic cycloalkyl group or ortho-fused bicyclic heterocycloalkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of: a halogen atom, an oxo group, a -OH group, an -O-(C_1-C_6)-alkyl group, a -(C_1-C_6)-alkyl group, a -NO_2 group, a -CN group, a -C(=O)H group, a -SO_2NH_2 group, a -$C(=O)NH_2$ group, a -$OCH_2C(=O)NH_2$ group, a -C(=O)O(C_1-C_6)-alkyl group, and a -C(=O)N(C_1-C_3)-alkyl group.

Another embodiment is a compound of formula (I), wherein R_6 represents an ortho-fused bicyclic cycloalkyl group comprising 8 to 11 carbon atoms, or an ortho-fused bicyclic heterocycloalkyl group comprising 8 to 9 carbon atoms and comprising 1 or 2 heteroatoms independently selected from oxygen and nitrogen; said ortho-fused bicyclic cycloalkyl group or ortho-fused bicyclic heterocycloalkyl group being unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of: a halogen atom, an oxo group, a -OH group, an -O-(C_1-C_3)-alkyl group, a -(C_1-C_3)-alkyl group, a -NO_2 group, a -CN group, a -C(=O)H group, a -SO_2NH_2 group, a -$C(=O)NH_2$ group, a -$OCH_2C(=O)NH_2$ group, a -C(=O)O(C_1-C_3)-alkyl group, and a -C(=O)N(C_1-C_3)-alkyl group.

Another embodiment is a compound of formula (I), wherein R_6 represents an ortho-fused bicyclic cycloalkyl group comprising 8 to 11 carbon atoms, or an ortho-fused bicyclic heterocycloalkyl group comprising 8 to 9 carbon atoms and comprising 1 or 2 heteroatoms independently selected from oxygen and nitrogen; said ortho-fused bicyclic cycloalkyl group or

ortho-fused bicyclic heterocycloalkyl group being substituted with a $-(OCH_2CH_2)_n-R_{10}$ group wherein n represents 1, 2 or 3; R_{10} represents a $-O(C_1-C_4)$-alkyl group, a $-N^+-(CH_3)_3$ group, or a $-N^+H-(CH_3)_2$ group.

Another embodiment is a compound of formula (I), wherein R_6 represents an ortho-fused bicyclic cycloalkyl group comprising 8 to 11 carbon atoms, or an ortho-fused bicyclic heterocycloalkyl group comprising 8 to 9 carbon atoms and comprising 1 or 2 heteroatoms independently selected from oxygen and nitrogen; said ortho-fused bicyclic cycloalkyl group or ortho-fused bicyclic heterocycloalkyl group being substituted with 1 to 3 $-R_{11}-(C_1-C_6)$-alkyl-R_{12} group which is unsubstituted or substituted on the (C_1-C_6)-alkyl with 1 to 3 substituents independently selected from a -OH group, a $-NH_2$ group and $-OCH_3$ group; R_{11} represents a bond, an -O-, or a -C(=O)O group; R_{12} represents a -OH group, a -C(=O)OH group, a $-C(=O)O(C_1-C_3)$-alkyl group, a $-C(=O)N(C_1-C_3)$-alkyl group, a $-NH_2$ group, a $-NHC(=O)(C_1-C_3)$-alkyl group, a -C(=O)H group, or a heterocyclic group comprising 3 to 9 carbon atoms and comprising from 1 to 3 heteroatoms independently selected from oxygen, nitrogen and sulfur that is unsubstituted or substituted with 1 to 3 substituents independently selected from an oxo group and a $-(C_1-C_3)$-alkyl group.

Another embodiment is a compound of formula (I), wherein R_6 is selected from an ortho-fused bicyclic cycloalkyl group comprising 8 to 11 carbon atoms, said ortho-fused bicyclic cycloalkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from: a halogen atom; a methyl group; a hydroxy group, an -O-methyl group, and an oxo group.

Another embodiment is a compound of formula (I), wherein R_6 is selected from a bicyclic cycloalkyl group selected from the following list:



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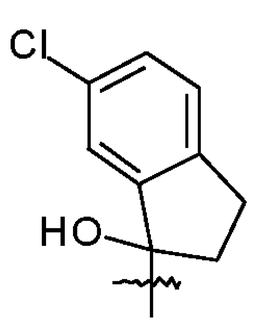

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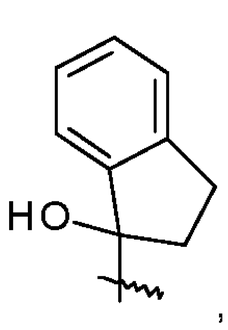

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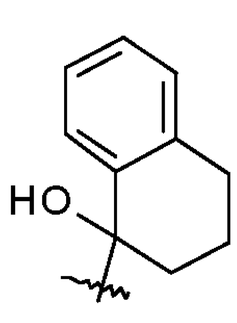

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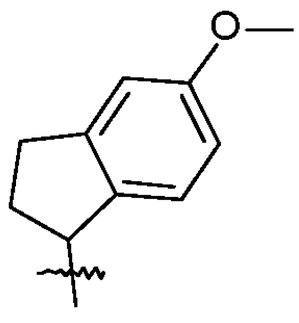
and


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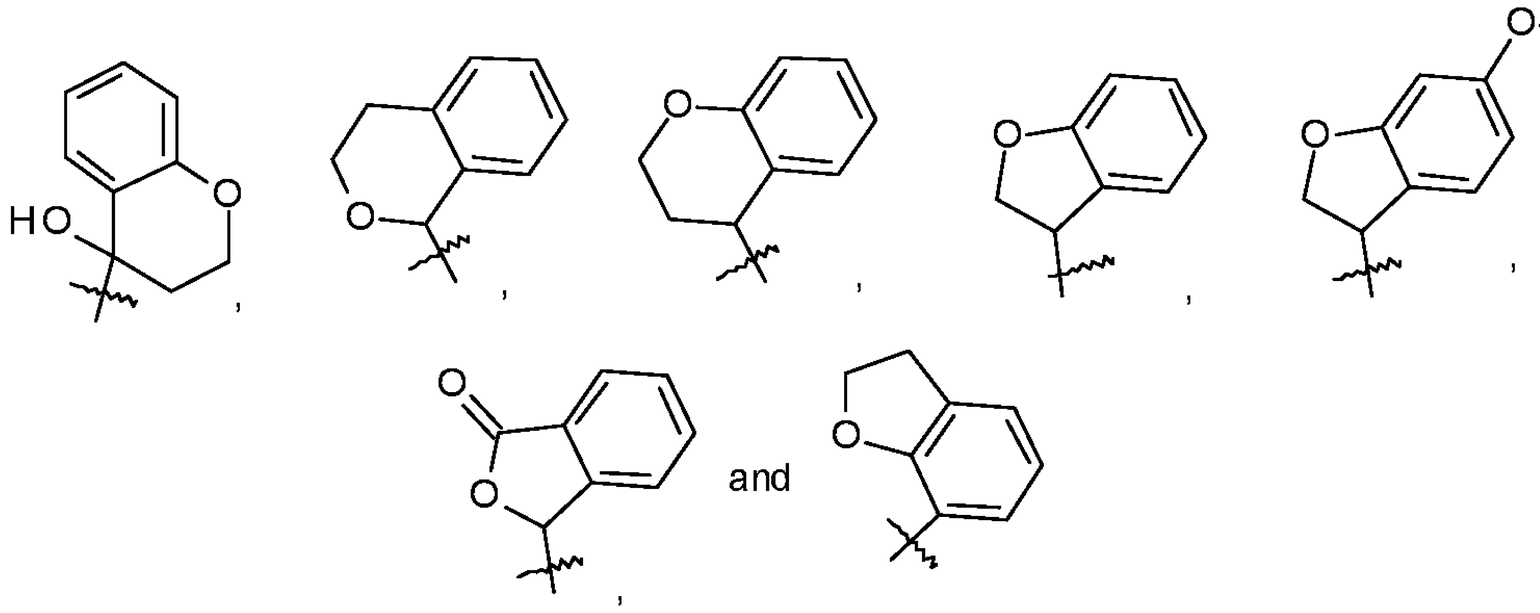
Another embodiment is a compound of formula (I), wherein R_6 is selected from a ortho-fused bicyclic heterocycloalkyl group comprising 8 to 9 carbon atoms and comprising 1 or 2 heteroatoms independently selected from oxygen and nitrogen, said bicyclic heterocycloalkyl

group being unsubstituted or substituted with 1 to 3 substituents independently selected from: a halogen atom, a methyl group, an -O-methyl group, and an oxo group.

Another embodiment is a compound of formula (I), wherein R_6 is selected from a bicyclic heterocycloalkyl group selected from the following list:



Another embodiment is a compound of formula (I), wherein R_7 represents a phenyl group, said phenyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a -(C_1-C_3)-alkyl group, an -O-(C_1-C_3)-alkyl group and a morpholine group.

Another embodiment is a compound of formula (I), wherein R_7 represents a monocyclic cycloalkyl group comprising 4 to 7 carbon atoms, or a monocyclic heterocycloalkyl group comprising 3 to 6 carbon atoms and comprising from 1 to 2 heteroatoms independently selected from oxygen and nitrogen, said cycloalkyl and heterocycloalkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of: a halogen atom, an oxo group, a -(C_1-C_6)-alkyl group, a phenyl group, an -O-, a benzyl group, a -OH group, and an -O-(C_1-C_6)-alkyl group.

Another embodiment is a compound of formula (I), wherein R_7 represents a monocyclic heterocycloalkyl group comprising 3 to 6 carbon atoms and comprising from 1 to 2 heteroatoms independently selected from oxygen and nitrogen and being unsubstituted or substituted with 1 or 2 substituents independently selected from an -O- group, a phenyl group and a benzyl group.

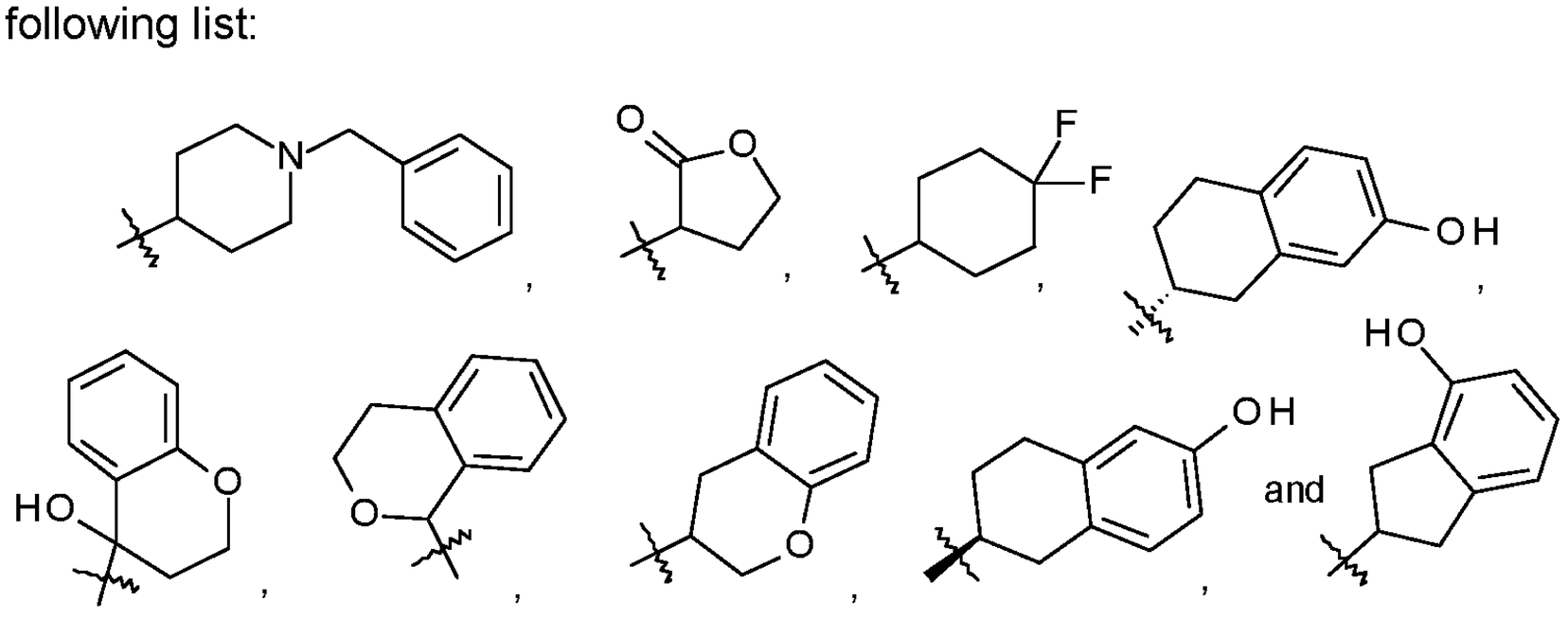
Another embodiment is a compound of formula (I), wherein R_7 represents an ortho-fused bicyclic heterocycloalkyl group comprising 8 to 9 carbon atoms and comprising 1 or 2 heteroatoms independently selected from oxygen and nitrogen; wherein said ortho-fused bicyclic

heterocycloalkyl groups being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of: a halogen atom, an oxo group, a -(C_1-C_6)-alkyl group, a phenyl group, an -O- group, a benzyl group, a -OH group, and an -O-(C_1-C_6)-alkyl group.

Another embodiment is a compound of formula (I), wherein R_7 represents an ortho-fused bicyclic cycloalkyl group comprising 8 to 11 carbon atoms, said bicyclic cycloalkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of: a halogen atom; a methyl group; a -OH group, an -O-(C_1-C_3)alkyl group, and an oxo group.

Another embodiment is a compound of formula (I), wherein R_7 is selected from an ortho-fused bicyclic heterocycloalkyl group comprising 8 to 9 carbon atoms and comprising 1 or 2 heteroatoms independently selected from oxygen and nitrogen, said bicyclic heterocycloalkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from: a halogen atom; a methyl group; a -OH group, an -O-(C_1-C_3)alkyl group, and an oxo group.

Another embodiment is a compound of formula (I), wherein R_7 represents a group selected from the following list:



Another embodiment is a compound of formula (I), wherein R_8 represents a bond.

Another embodiment is a compound of formula (I), wherein R_8 represents an -O-.

Another embodiment is a compound of formula (I), wherein R_8 represents a -OC(=O)- group.

Another embodiment is a compound of formula (I), wherein R_8 represents a -N(H)C(=O)- group.

Another embodiment is a compound of formula (I), wherein R_8 represents a -C(=O)O- group.

Another embodiment is a compound of formula (I), wherein R_8 represents a -C(=O)N(H)- group.

Another embodiment is a compound of formula (I), wherein R_9 represents a hydrogen atom.

Another embodiment is a compound of formula (I), wherein R_9 represents a -C(=O)-OH group.

Another embodiment is a compound of formula (I), wherein R_9 represents a -C(=O)O(C_1-C_3)-alkyl group.

Another embodiment is a compound of formula (I), wherein R_9 represents a -OH group.

Another embodiment is a compound of formula (I), wherein R_9 represents a -O(C_1-C_3)-alkyl group.

Another embodiment is a compound of formula (I), wherein R_9 represents a $-NH_2$ group.

Another embodiment is a compound of formula (I), wherein R_{10} represents an -O-(C_1-C_4)-alkyl group.

Another embodiment is a compound of formula (I), wherein R_{10} represents a $-N^+$-$(CH_3)_3$ group.

Another embodiment is a compound of formula (I), wherein R_{10} represents a $-N^+H$-$(CH_3)_2$ group.

Another embodiment is a compound of formula (I), wherein R_{11} represents a bond.

Another embodiment is a compound of formula (I), wherein R_{11} represents an -O-.

Another embodiment is a compound of formula (I), wherein R_{11} represents a -C(=O)O- group.

Another embodiment is a compound of formula (I), whereinR$_{12}$ represents a -OH group.

Another embodiment is a compound of formula (I), wherein R_{12} represents a -C(=O)OH group.

Another embodiment is a compound of formula (I), wherein R_{12} represents a -C(=O)O(C_1-C_3)-alkyl group.

Another embodiment is a compound of formula (I), wherein R_{12} represents a -C(=O)N(C_1-C_3)-alkyl group.

Another embodiment is a compound of formula (I), wherein R_{12} represents a $-NH_2$ group.

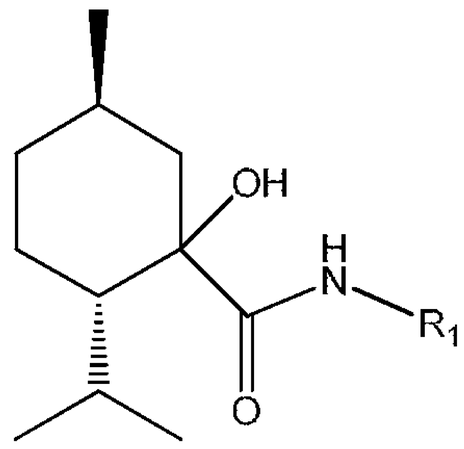
Another embodiment is a compound of formula (I), wherein R_{12} represents a -NHC(=O)(C_1-C_3)-alkyl group.

Another embodiment is a compound of formula (I), wherein R_{12} represents a -C(=O)H group.

Another embodiment is a compound of formula (I), wherein R_{12} represents or a heterocyclic group comprising 3 to 9 carbon atoms and comprising from 1 to 3 heteroatoms independently selected from oxygen, nitrogen and sulfur that is unsubstituted or substituted with 1 to 3 oxo group or –(C_1-C_3)-alkyl group.

Another embodiment is a compound of formula (I), wherein R_{12} represents or an -O-heterocyclic group comprising 3 to 9 carbon atoms and comprising from 1 to 3 heteroatoms independently selected from oxygen, nitrogen and sulfur being unsubstituted or substituted with 1 to 3 oxo group or –(C_1-C_3)-alkyl group.

One embodiment is a compound of formula (I):



(I)

wherein:

R_1 is $-C(R_2)(R_3)-[C(R_4)(R_5)]_m-L-R_6$ or $-R_7$

m represents 0, 1, 2 or 3;

R_2 and R_3 independently represent a hydrogen atom, a deuterium atom, a $-(C_1-C_6)$-alkyl group, a (C_1-C_6)-alkyl-OH group, a $-C(=O)NH_2$ group, a $-(C_1-C_6)$-alkoxyl group, or a $-C(=O)O(C_1-C_6)$-alkyl group;

R_4 and R_5 independently represent a hydrogen atom, a deuterium atom, a fluorine atom, a $-NH_2$ group, a -OH group, a $-(C_1-C_6)$-alkyl group, a $-CF_3$ group, a carboxyl group, or a $-R_8-(C_1-C_6)$-alkyl-R_9 group wherein:

R_8 represents a bond, an -O-, a -OC(=O)- group, a -N(H)C(=O)- group, a -C(=O)O- group, or a -C(=O)N(H)- group;

R_9 represents a hydrogen atom, a -C(=O)-OH group, a $-C(=O)O(C_1-C_3)$-alkyl group, a -OH group, an $-O-(C_1-C_3)$-alkyl group, or a $-NH_2$ group;

or R_4 and R_5 can form, together with the carbon atom to which they are attached, a heterocycloalkyl group comprising 3 to 5 carbon atoms and comprising from 1 or 2 heteroatoms selected from oxygen and nitrogen;

L represents a bond, a $-(C_1-C_6)$-alkylene- group, an $-O-(C_1-C_6)$-alkylene- group, an -O-, a -OC(=O)- group, a -N(H)- group, a -C(=O)- group, a -C(=O)O- group, a -C(=O)-O-(C_1-C_3)-alkyl- group, a -C(=O)-N(H)- or a $-CONH(C_1-C_6)$-alkyl- group;

R_6 is selected from the group consisting of a -OH group; a $-(C_1-C_6)$-alkyl group; a phenyl group, a monocyclic heteroaryl group comprising 3 to 5 carbon atoms and comprising from 1 to 2 heteroatoms independently selected from oxygen, nitrogen and sulfur, an ortho-fused bicyclic heteroaryl group comprising 7 to 10 carbon atoms and comprising from 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur, an ortho-fused bicyclic cycloalkyl group comprising 8 to 11 carbon atoms, and an ortho-fused bicyclic heterocycloalkyl group comprising 8 to 9 carbon atoms and comprising 1 or 2 heteroatoms independently selected from oxygen and nitrogen; said phenyl, monocyclic heteroaryl, ortho-fused bicyclic heteroaryl, ortho-fused bicyclic cycloalkyl, ortho-fused bicyclic heterocycloalkyl groups being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of:

a halogen atom, a -OH group, an oxo group, an $-O-(C_1-C_6)$-alkyl group, a $-(C_1-C_6)$-alkyl group, a $-NO_2$ group, a -CN group, a -C(=O)H group, a $-SO_2NH_2$ group, a $-C(=O)NH_2$ group, a $-OCH_2C(=O)NH_2$ group, a $-C(=O)O(C_1-C_6)$-alkyl group, a -

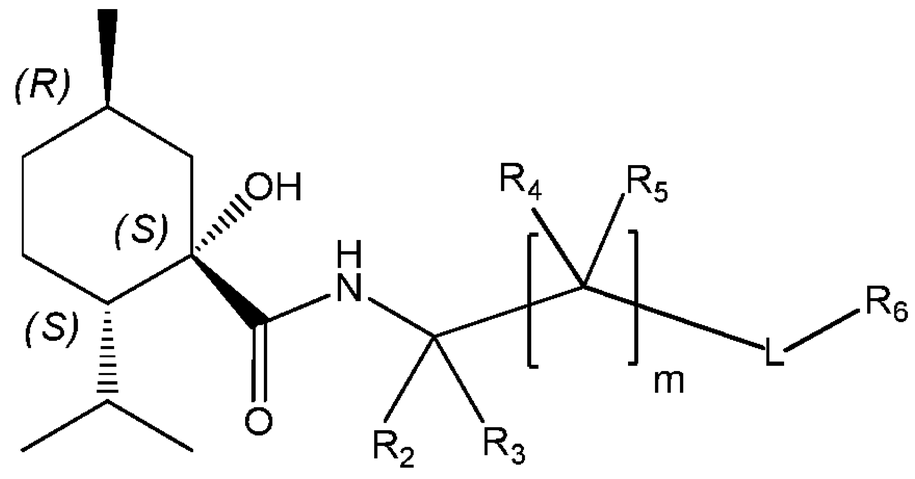
C(=O)N(C_1-C_3)-alkyl group, a -$(OCH_2CH_2)_n$-R_{10} group, and a -R_{11}-(C_1-C_6)-alkyl-R_{12} group which is unsubstituted or substituted on the (C_1-C_6)-alkyl with 1 to 3 substituents independently selected from a -OH group, a -NH_2 group and -OCH_3 group; wherein n represents 1, 2 or 3; R_{10} represents an -O-(C_1-C_4)-alkyl group, a -N^+-$(CH_3)_3$ group, or -N^+H-$(CH_3)_2$ group; R_{11} represents a bond, an -O-, or a -C(=O)O group; R_{12} represents a -OH group, a -C(=O)OH group, a -C(=O)O(C_1-C_3)-alkyl group, a -C(=O)N(C_1-C_3)-alkyl group, a -NH_2 group, a -NH-C(=O)(C_1-C_3)-alkyl group, a -C(=O)H group, a heterocyclic group or an -O-heterocyclic group, said heterocyclic group and said -O-heterocyclic group comprising 3 to 9 carbon atoms and comprising from 1 to 3 heteroatoms independently selected from oxygen, nitrogen and sulfur being unsubstituted or substituted with 1 to 3 substituents independently selected from an oxo group and a –(C_1-C_3)-alkyl group.

R_7 represents a phenyl group, a monocyclic cycloalkyl group comprising 4 to 7 carbon atoms, a monocyclic heterocycloalkyl group comprising 3 to 6 carbon atoms and comprising from 1 to 2 heteroatoms independently selected from oxygen and nitrogen, an ortho-fused bicyclic cycloalkyl group comprising 8 to 11 carbon atoms, or an ortho-fused bicyclic heterocycloalkyl group comprising 8 to 9 carbon atoms and comprising 1 or 2 heteroatoms independently selected from oxygen and nitrogen; wherein said phenyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from a halogen atom, a -(C_1-C_3)-alkyl group, an -O-(C_1-C_3)-alkyl group and a morpholine group; said monocyclic cycloalkyl, monocyclic heterocycloalkyl, an ortho-fused bicyclic heterocycloalkyl groups being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of: a halogen atom, an oxo group, a -(C_1-C_6)-alkyl group, a phenyl group, an -O- group, a benzyl group, a -OH group, and an -O-(C_1-C_6)-alkyl group;

or a pharmaceutically acceptable salt thereof.

Another embodiment is a compound of formula (I), wherein R_1 represents a -$C(R_2)(R_3)$-$[C(R_4)(R_5)]_m$-L-R_6 group; m represents 0 or 1; or a pharmaceutically acceptable salt thereof.

In one embodiment, the compound of formula (I) has the absolute configuration corresponding to a compound of formula (Ia):



(Ia)

wherein:

m represents 0, 1, 2 or 3;

R_2 and R_3 independently represent a hydrogen atom, a deuterium atom, a –(C_1-C_3)-alkyl group, a (C_1-C_3)-alkyl-OH group, a -C(=O)NH_2 group, a -(C_1-C_3)-alkoxyl group, or a -C(=O)O(C_1-C_3)-alkyl group;

R_4 and R_5 independently represent a hydrogen atom, a deuterium atom, a fluorine atom, a -NH_2 group, a -OH group, a -(C_1-C_6)-alkyl group, a -CF_3 group, a carboxyl group, or a -R_8-(C_1-C_6)-alkyl-R_9 group wherein:

R_8 represents a bond, an -O-, a -OC(=O)- group, a -N(H)C(=O)- group, a -C(=O)O- group, or a -C(=O)N(H)- group;

R_9 represents a hydrogen atom, a -C(=O)-OH group, a -C(=O)O(C_1-C_3)-alkyl group, a -OH group, an -O-(C_1-C_3)-alkyl group, or a -NH_2 group;

or R_4 and R_5 can form, together with the carbon atom to which they are attached, a heterocycloalkyl group comprising 3 to 5 carbon atoms and comprising from 1 or 2 heteroatoms selected from oxygen and nitrogen;

L represents a bond, a -(C_1-C_3)-alkylene- group, an -O-(C_1-C_3)-alkylene- group, an -O-, a -OC(=O)- group, a -N(H)- group, a -C(=O)- group, a -C(=O)O- group, a -C(=O)-O-(C_1-C_3)-alkyl- group, a -C(=O)-N(H)- or a -CONH(C_1-C_3)-alkyl- group;

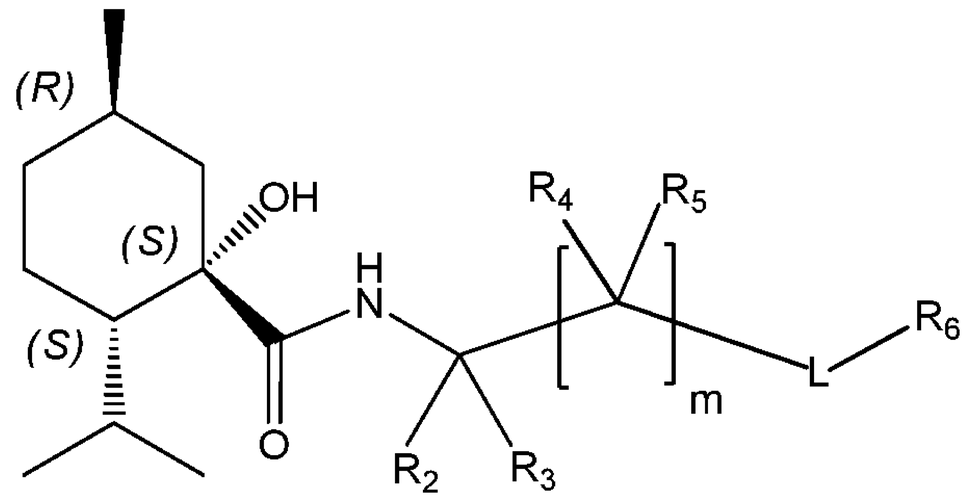
R_6 is selected from the group consisting of a -OH group; a –(C_1-C_3)-alkyl group; a phenyl group, a monocyclic heteroaryl group comprising 3 to 5 carbon atoms and comprising from 1 to 2 heteroatoms independently selected from oxygen, nitrogen and sulfur, an ortho-fused bicyclic heteroaryl group comprising 7 to 10 carbon atoms and comprising from 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur, an ortho-fused bicyclic cycloalkyl group comprising 8 to 11 carbon atoms, and an

ortho-fused bicyclic heterocycloalkyl group comprising 8 to 9 carbon atoms and comprising 1 or 2 heteroatoms independently selected from oxygen and nitrogen; said phenyl, monocyclic heteroaryl, ortho-fused bicyclic heteroaryl, ortho-fused bicyclic cycloalkyl, ortho-fused bicyclic heterocycloalkyl groups being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of:

a halogen atom, a -OH group, an oxo group, an -O-(C_1-C_3)-alkyl group, a -(C_1-C_3)-alkyl group, a -NO_2 group, a -CN group, a -C(=O)H group, a -SO_2NH_2 group, a -$C(=O)NH_2$ group, a -$OCH_2C(=O)NH_2$ group, a -C(=O)O(C_1-C_3)-alkyl group, a -C(=O)N(C_1-C_3)-alkyl group, a -$(OCH_2CH_2)_n$-R_{10} group, and a -R_{11}-(C_1-C_3)-alkyl-R_{12} group which is unsubstituted or substituted on the (C_1-C_6)-alkyl with 1 to 3 substituents independently selected from a -OH group, a -NH_2 group and -OCH_3 group; wherein n represents 1, 2 or 3; R_{10} represents an -O-(C_1-C_3)-alkyl group, a -N^+-$(CH_3)_3$ group, or -N^+H-$(CH_3)_2$ group; R_{11} represents a bond, an -O-, or a -C(=O)O group; R_{12} represents a -OH group, a -C(=O)OH group, a -C(=O)O(C_1-C_3)-alkyl group, a -C(=O)N(C_1-C_3)-alkyl group, a -NH_2 group, a -NH-C(=O)(C_1-C_3)-alkyl group, a -C(=O)H group, a heterocyclic group or an -O-heterocyclic group, said heterocyclic group and said -O-heterocyclic group comprising 3 to 9 carbon atoms and comprising from 1 to 3 heteroatoms independently selected from oxygen, nitrogen and sulfur being unsubstituted or substituted with 1 to 3 substituents independently selected from an oxo group and a –(C_1-C_3)-alkyl group;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the compound of formula (I) has the absolute configuration corresponding to a compound of formula (Ia):



(Ia)

wherein:

m represents 0, or 1;

R_2 and R_3 independently represent a hydrogen atom, a deuterium atom, a –(C_1-C_3)-alkyl group, a (C_1-C_3)-alkyl-OH group, a -C(=O)NH_2 group, a -(C_1-C_3)-alkoxyl group, or a -C(=O)O(C_1-C_3)-alkyl group;

R_4 and R_5 independently represent a hydrogen atom, a deuterium atom, a fluorine atom, a -NH_2 group, a -OH group, a -(C_1-C_3)-alkyl group, a -CF_3 group, a carboxyl group, or a -R_8-(C_1-C_4)-alkyl-R_9 group wherein:

R_8 represents a bond, an -O-, a -OC(=O)- group, a -N(H)C(=O)- group, a -C(=O)O- group, or a -C(=O)N(H)- group;

R_9 represents a hydrogen atom, a -C(=O)-OH group, a -C(=O)O(C_1-C_3)-alkyl group, a -OH group, an -O-(C_1-C_3)-alkyl group, or a -NH_2 group;

or R_4 and R_5 can form, together with the carbon atom to which they are attached, a heterocycloalkyl group comprising 3 to 5 carbon atoms and comprising from 1 or 2 heteroatoms selected from oxygen and nitrogen;

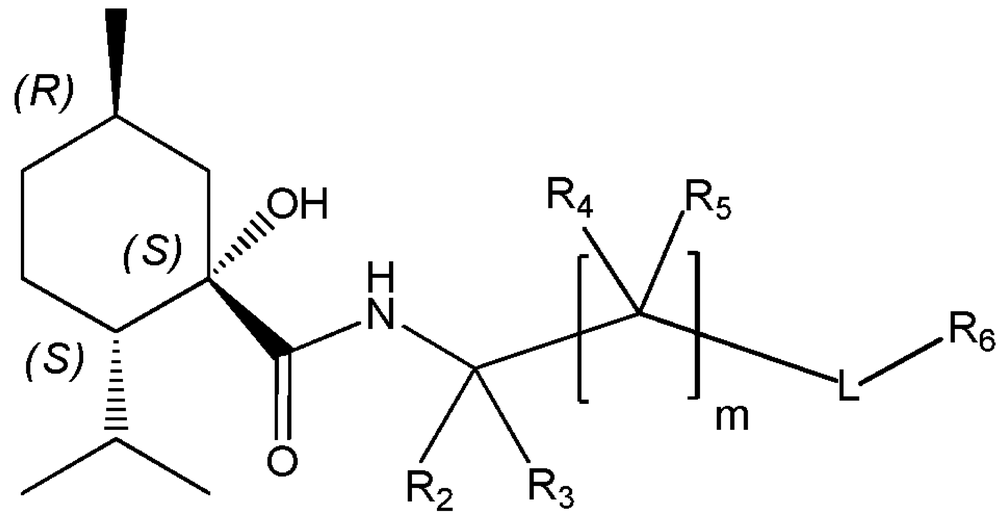
L represents a bond, a -(C_1-C_3)-alkylene- group, an -O-(C_1-C_3)-alkylene- group, an -O-, a -OC(=O)- group, a -N(H)- group, a -C(=O)- group, a -C(=O)O- group, a -C(=O)-O-(C_1-C_3)-alkyl- group, a -C(=O)-N(H)- or a -CONH(C_1-C_3)-alkyl- group;

R_6 represents a phenyl group, wherein said phenyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of:

a halogen atom, a -OH group, an -O-(C_1-C_3)-alkyl group, a -(C_1-C_3)-alkyl group, a -NO_2 group, a -CN group, a -C(=O)H group, a -SO_2NH_2 group, a -C(=O)NH_2 group, a -OCH_2C(=O)NH_2 group, a -C(=O)O(C_1-C_3)-alkyl group, a -C(=O)N(C_1-C_3)-alkyl group, a -(OCH_2CH_2)$_n$-R_{10} group, and a -R_{11}-(C_1-C_3)-alkyl-R_{12} group which is unsubstituted or substituted on the (C_1-C_6)-alkyl with 1 to 3 substituents independently selected from a -OH group, a -NH_2 group and -OCH_3 group; wherein n represents 1, 2 or 3; R_{10} represents an -O-(C_1-C_3)-alkyl group, a -N^+-(CH_3)$_3$ group, or -N^+H-(CH_3)$_2$ group; R_{11} represents a bond, an -O-, or a -C(=O)O group; R_{12} represents a -OH group, a -C(=O)OH group, a -C(=O)O(C_1-C_3)-alkyl group, a -C(=O)N(C_1-C_3)-alkyl group, a -NH_2 group, a -NH-C(=O)(C_1-C_3)-alkyl group, a -C(=O)H group, a heterocyclic group or an -O-heterocyclic group, said heterocyclic group and said -O-heterocyclic group comprising 3 to 9 carbon atoms and comprising from 1 to 3 heteroatoms independently selected from oxygen, nitrogen and sulfur being unsubstituted or substituted with 1 to 3 substituents independently selected from an oxo group and a –(C_1-C_3)-alkyl group;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the compound of formula (I) has the absolute configuration corresponding to a compound of formula (Ia):



(Ia)

wherein:

m represents 1;

R_2 and R_3 independently represent a hydrogen atom, a –(C_1-C_3)-alkyl group, a -(C_1-C_3)-alkyl-OH group

R_4 and R_5 independently represent a hydrogen atom, a deuterium atom, a fluorine atom, a -NH_2 group, a -OH group, a -(C_1-C_3)-alkyl group, a -CF_3 group,

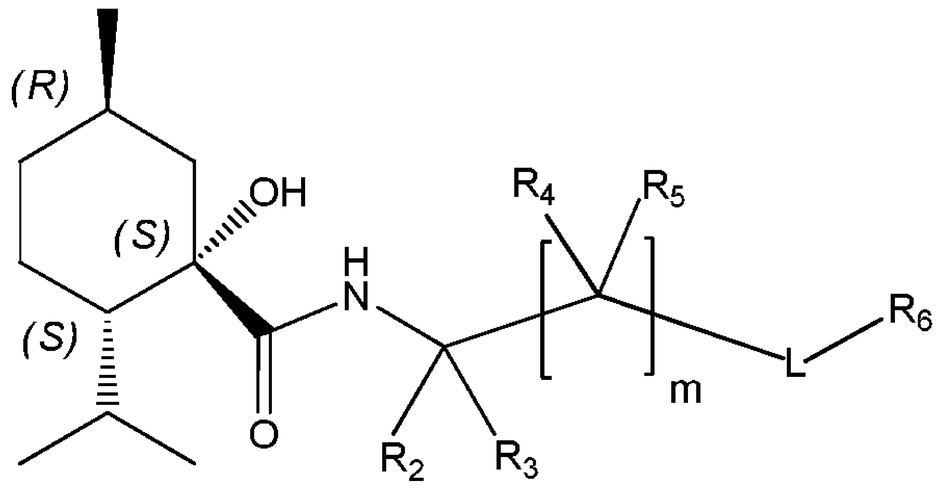
L represents a bond or a -C(=O)- group;

R_6 represents a phenyl group, wherein said phenyl group being unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of:

a halogen atom, a -OH group, an -O-(C_1-C_3)-alkyl group, a -(C_1-C_3)-alkyl group, a -NO_2 group, a -CN group, a -C(=O)H group, a -SO_2NH_2 group, a -C(=O)NH_2 group, a -$OCH_2C(=O)NH_2$ group, a -C(=O)O(C_1-C_3)-alkyl group, a -C(=O)N(C_1-C_3)-alkyl group, a -$(OCH_2CH_2)_n$-R_{10} group, and a -R_{11}-(C_1-C_3)-alkyl-R_{12} group which is unsubstituted or substituted on the (C_1-C_6)-alkyl with a -OH group or a -NH_2 group; wherein n represents 1, 2 or 3; R_{10} represents an -O-(C_1-C_3)-alkyl group, or a -N^+-$(CH_3)_3$ group; R_{11} represents a bond, an -O-, or a -C(=O)O group; R_{12} represents a -OH group, a -C(=O)OH group, a -C(=O)O(C_1-C_3)-alkyl group, a -C(=O)N(C_1-C_3)-alkyl group, a -NH_2 group, a -NH-C(=O)(C_1-C_3)-alkyl group, a -C(=O)H group;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the compound of formula (I) has the absolute configuration corresponding to a compound of formula (Ia):



(Ia)

wherein:

m represents 0, or 1;

R_2 and R_3 independently represent a hydrogen atom, a –(C_1-C_3)-alkyl group, a -(C_1-C_3)-alkyl-OH group, a -(C_1-C_3)-alkoxyl group

R_4 and R_5 independently represent a hydrogen atom, a deuterium atom, a fluorine atom, a -NH_2 group, a -OH group, a -(C_1-C_3)-alkyl group, a -CF_3 group, or a -R_8-(C_1-C_4)-alkyl-R_9 group wherein:

R_8 represents a bond, an -O-, a -OC(=O)- group, a -N(H)C(=O)- group, a -C(=O)O- group, or a -C(=O)N(H)- group;

R_9 represents a hydrogen atom, a -C(=O)-OH group, a -C(=O)O(C_1-C_3)-alkyl group, a -OH group, an -O-(C_1-C_3)-alkyl group, or a -NH_2 group;

L represents a bond or a -C(=O)- group;

R_6 represents a phenyl group, wherein said phenyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of:

a halogen atom, a -OH group, an -O-(C_1-C_3)-alkyl group, a -(C_1-C_3)-alkyl group, a -NO_2 group, a -CN group, a -C(=O)H group, a -SO_2NH_2 group, a -C(=O)NH_2 group, a -OCH_2C(=O)NH_2 group, a -C(=O)O(C_1-C_3)-alkyl group, a -C(=O)N(C_1-C_3)-alkyl group, a -(OCH_2CH_2)$_n$-R_{10} group, and a -R_{11}-(C_1-C_3)-alkyl-R_{12} group which is unsubstituted or substituted on the (C_1-C_6)-alkyl with 1 to 3 substituents independently selected from a -OH group, a -NH_2 group and -OCH_3

group; wherein n represents 1, 2 or 3; R_{10} represents an -O-(C_1-C_3)-alkyl group, a -N^+-(CH_3)$_3$ group, or -N^+H-(CH_3)$_2$ group; R_{11} represents a bond, an -O-, or a -C(=O)O group; R_{12} represents a -OH group, a -C(=O)OH group, a -C(=O)O(C_1-C_3)-alkyl group, a -C(=O)N(C_1-C_3)-alkyl group, a -NH_2 group, a -NH-C(=O)(C_1-C_3)-alkyl group, a -C(=O)H group;

or a pharmaceutically acceptable salt thereof.

Another embodiment is a compound of formula (I), wherein R_1 represents -R_7.

In one embodiment, the compound of formula (I) is (1S,2S,5R)-1-hydroxy-N-(3-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide; or a pharmaceutically acceptable salt thereof.

In one embodiment, the compound of formula (I) is 2-hydroxyethyl 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzoate; or a pharmaceutically acceptable salt thereof.

In one embodiment, the compound of formula (I) is (1S,2S,5R)-1-hydroxy-N-(2-(2-hydroxyethyl)phenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide; or a pharmaceutically acceptable salt thereof.

In one embodiment, the compound of formula (I) is methyl-3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate; or a pharmaceutically acceptable salt thereof.

In one embodiment, the compound of formula (I) is (1S,2S,5R)-N-(2-(2-amino-2-oxoethoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide; or a pharmaceutically acceptable salt thereof.

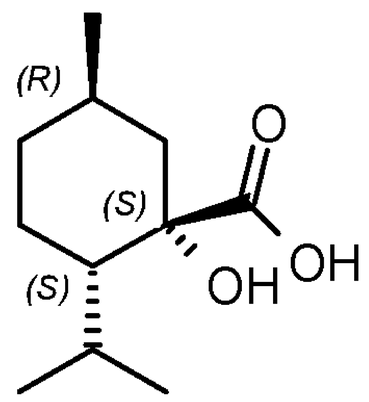
In one embodiment, the compound of formula (I) is (1S,2S,5R)-1-hydroxy-N-((S)-2-hydroxy-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide; or a pharmaceutically acceptable salt thereof.

In one embodiment, the compound of formula (I) is (1S,2S,5R)-1-hydroxy-N-((S)-2-hydroxy-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide; or a pharmaceutically acceptable salt thereof.

In one embodiment, the compound of formula (I) is 2-hydroxyethyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzoate; or a pharmaceutically acceptable salt thereof.

In one embodiment, the compound of formula (I) is (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-((3-phenyloxetan-3-yl)methyl)cyclohexane-1-carboxamide; or a pharmaceutically acceptable salt thereof.

Another embodiment is a process for preparing a compound of formula (I), comprising submitting a compound (intermediate 4):



to a coupling reaction with a compound of formula (Ic) or a compound of formula (Id)

$HN_2C(R_2)(R_3)[C(R_4)(R_5)]_mLR_6$ $H_2N\text{-}R_7$

Ic Id

wherein m, R_2, R_3, R_4, R_5, R_6, L, R_7 are as defined for a compound of formula (I).

In one embodiment, the compound of formula (I) is selected from the group consisting of:

(1S,2S,5R)-1-hydroxy-N-((S)-2-hydroxy-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

2-hydroxyethyl 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzoate;
(1S,2S,5R)-1-hydroxy-N-(3-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;
2-hydroxyethyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzoate;
(1S,2S,5R)-1-hydroxy-N-(2-(2-hydroxyethyl)phenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;
Methyl-3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate;
(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-((3-phenyloxetan-3-yl)methyl)cyclohexane-1-carboxamide;
(1S,2S,5R)-N-(2-(2-amino-2-oxoethoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;
or a pharmaceutically acceptable salt thereof.

The compounds of formula (I) include the compounds having any combination of the above-defined embodiments for R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, m, n, and L with each other.

In one embodiment, the compound of formula (I) is selected from the group consisting of:

(1S,2S,5R)-1-hydroxy-N-((S)-2-hydroxy-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(2-oxo-2-phenylethyl)cyclohexane-1-carboxamide;

(S)-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethyl acetate;

(1S,2S,5R)-N-(2,2-difluoro-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-N-(2-fluoro-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-N-(2-(2-aminoethoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-N-(2-(2-hydroxyethoxy)phenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-N-(2-(1H-benzo[d]imidazol-2-yl)ethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide 2-hydroxypropane-1,2,3-tricarboxylate;

(1S,2S,5R)-N-(2-(2,3-dihydroxypropoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-N-(3-(2,3-dihydroxypropoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

2-(2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenoxy)-N,N,N-trimethylethan-1-aminium iodide;

(1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-(m-tolyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

2-aminoethyl 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzoate hydrochloride;

(1S,2S,5R)-1-hydroxy-N-(2-(hydroxymethyl)phenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-N-(3-(hydroxymethyl)phenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

2-aminoethyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzoate hydrochloride;

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-((1RS)-(3-oxo-1,3-dihydroisobenzofuran-1-yl)methyl) cyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-((1RS)-(3-oxo-1,3-dihydroisobenzofuran-1-yl)methyl) cyclohexane-1-carboxamide;

methyl (S)-2-amino-3-(2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido) ethyl)phenyl)propanoate;

methyl (S)-2-amino-3-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1carboxamido) ethyl)phenyl)propanoate;

2-hydroxyethyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzoate;

2-hydroxyethyl 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzoate;

(1S,2S,5R)-1-hydroxy-N-((1-hydroxy-2,3-dihydro-1H-inden-1-yl)methyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-N-(2-((R)-2,3-dihydroxypropoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-N-(2-((S)-2,3-dihydroxypropoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

methyl O-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenyl)-D-serinate;

methyl O-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenyl)-L-serinate;

ethyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate;

(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate;

(1S,2S,5R)-N-(2-(benzylamino)-2-oxoethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-((3-phenyloxetan-3-yl)methyl)cyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-(3-hydroxyphenyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

methyl 2-(3-(1-hydroxy-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenoxy)acetate;

methyl 3-(1-hydroxy-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate;

(1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-(2-hydroxyphenyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

methyl 2-(2-(1-hydroxy-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenoxy)acetate;

(1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-(3-(hydroxymethyl)phenyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-N-(2-(2-hydroxyphenyl)-2-oxoethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-N-(2-(3-hydroxyphenyl)-2-oxoethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-N-(3-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-N-((2R)-hydroxy-2-(3-hydroxyphenyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-N-((2S)-hydroxy-2-(3-hydroxyphenyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-N-((2R)-hydroxy-2-(3-(hydroxymethyl)phenyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-N-((2S)-hydroxy-2-(3-(hydroxymethyl)phenyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-N-((2R)-hydroxy-2-(m-tolyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-N-((2S)-hydroxy-2-(m-tolyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-N-((2R)-1-hydroxy-3-phenylpropan-2-yl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-N-(3-cyanophenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzamide;

(1S,2S,5R)-N-((2S)-amino-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-phenethylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-N-(2-(2-hydroxyethyl)phenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-N-(2-(2-aminoethyl)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

isopropyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate;

2-((S)-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethoxy)acetic acid;

(1S,2S,5R)-1-hydroxy-N-((S)-2-(2-hydroxyethoxy)-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

methyl 2-((S)-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethoxy)acetate;

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(3-methylphenethyl)cyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(2-methylphenethyl)cyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(4-methylphenethyl)cyclohexane-1-carboxamide;

methyl 2-(2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenoxy)acetate;

(1S,2S,5R)-N-((S)-2-((R)-2-aminopropanamido)-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-N-((S)-2-((S)-2-aminopropanamido)-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

methyl 2-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenoxy)acetate;

methyl 4-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-3-phenyl butanoate;

(1S,2S,5R)-1-hydroxy-N-(4-hydroxy-2-phenylbutyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

phenyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate;

4-formyl-2-methoxyphenyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate;

methyl 4-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-3-phenyl butanoate;

(1S,2S,5R)-1-hydroxy-N-(3-hydroxy-2-phenylpropyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

2-aminoethyl 3-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-2-phenylpropanoate hydrochloride;

(1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-phenylethyl-2-d)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

2-amino-2-methylpropyl 3-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-2-phenylpropanoate hydrochloride;

methyl 2-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenyl)acetate;

methyl 3-(2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenoxy)propanoate;

3,5-dihydroxyphenyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate;

methyl 2-(2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenyl)acetate;

2-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenyl)acetic acid;

4-(hydroxymethyl)-2-methoxyphenyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate;

(1S,2S,5R)-1-hydroxy-N-(2-(3-hydroxypropoxy)phenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-N-(2-(2-amino-2-oxoethoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methyl cyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-((3RS)-3,3,3-trifluoro-2-hydroxy-2-phenylpropyl) cyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-((3RS)-3,3,3-trifluoro-2-hydroxy-2-phenylpropyl) cyclohexane-1-carboxamide;

(1S,2S,5R)-N-(2-(2-acetamidoethoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-N-(2-(2-fluorophenyl)-2-oxoethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-N-((R)-3-hydroxy-1-phenylpropyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

3-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) phenyl)propanoic acid;

(1S,2S,5R)-1-hydroxy-N-(2-((4-hydroxyphenyl)amino)-2-oxoethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-N-((2RS)-3-hydroxy-2-phenylpropyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-N-((2RS)-3-hydroxy-2-phenylpropyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-N-((2RS)-2-hydroxy-2-phenylethyl-2-d)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-N-((2RS)-2-hydroxy-2-phenylethyl-2-d)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

methyl 3-(2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido) ethyl)phenyl)propanoate;

(1S,2S,5R)-N-((3S)-chroman-3-yl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-N-((3R)-chroman-3-yl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-N-((4-hydroxychroman-4-yl)methyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-N-((1RS)-isochroman-1-ylmethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-N-((1RS)-isochroman-1-ylmethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-N-(2-(2,4-dimethoxyphenyl)-2-oxoethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-N-(2-(3,4-dihydroxyphenyl)-2-oxoethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-((3-(3-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)oxetan-3-yl)methyl)cyclohexane-1-carboxamide;

(1S,2S,5R)-N-(2-(2,4-dihydroxyphenyl)-2-oxoethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-N-(chroman-4-ylmethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-N-(2-(2,3-dihydroxyphenyl)-2-oxoethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(S)-2-hydroxypropyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate;

methyl 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate;

methyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate;

methyl 4-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido) ethyl)benzoate;

(1S,2S,5R)-1-hydroxy-N-(4-(hydroxymethyl)phenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-N-(2-hydroxyethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl benzoate;

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(2-oxotetrahydrofuran-3-yl)cyclohexane-1-carboxamide;

(1S,2S,5R)-N-[2-(3,4-dimethoxyphenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-N-[2-(4-hydroxy-3-methoxy-phenyl)ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-N-[2-(2,3-dimethoxyphenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-N-[2-(2-hydroxyphenyl)ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-N-[2-(4-hydroxyphenyl)ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-[2-(4-sulfamoylphenyl)ethyl]cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-[2-(4-pyridyl)ethyl]cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(2-phenoxyethyl)cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-2-isopropyl-N-[2-(4-methoxyphenyl)-2-oxo-ethyl]-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-N-[(1S,2S)-2-hydroxy-1-(methoxymethyl)-2-phenyl-ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-N-[2-(3,5-dimethoxyphenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-[2-(3-pyridyl)ethyl]cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-[2-(2-pyridyl)ethyl]cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-N-[2-(3-hydroxy-4-methoxy-phenyl)ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-[2-(3-methyl-2-pyridyl)ethyl]cyclohexanecarboxamide;

(1S,2S,5R)-N-[2-(2,5-dimethoxyphenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-N-(2-anilino-2-oxo-ethyl)-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-N-[2-(4-hydroxy-3,5-dimethoxy-phenyl)ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(2-pyrazin-2-ylethyl)cyclohexanecarboxamide;

benzyl 2-[[(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarbonyl]amino]acetate;

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-[2-(3-sulfamoylphenyl)ethyl]cyclohexanecarboxamide;

(1S,2S,5R)-N-[2-(4-chlorophenyl)-2-oxo-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-N-[2-(4-fluorophenyl)-2-oxo-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-N-[2-(3,4-difluorophenyl)-2-oxo-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-N-[2-(2,4-dichlorophenyl)-2-oxo-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-N-[2-(3,5-difluorophenyl)-2-oxo-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-N-[2-(2,5-difluorophenyl)-2-oxo-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-N-[2-(2-chlorophenyl)-2-oxo-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-[2-(m-tolyl)-2-oxo-ethyl]cyclohexanecarboxamide;

(1S,2S,5R)-N-[2-(2,3-difluorophenyl)-2-oxo-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-N-[2-(4-hydroxyphenyl)-2-oxo-ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-N-[(4-chloro-1-hydroxy-indan-1-yl)methyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-N-[(6-chloro-1-hydroxy-indan-1-yl)methyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-N-[(1S)-1-benzyl-2-hydroxy-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-N-(4,4-difluorocyclohexyl)-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-N-[2-(3-chloro-2-thienyl)-2-oxo-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-[2-oxo-2-(2-thienyl)ethyl]cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-N-[2-(1H-indol-3-yl)-2-oxo-ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-N-[(1R)-3-hydroxy-1-(2-thienylmethyl)propyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-2-isopropyl-N-[(5-methoxyindan-1-yl)methyl]-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-[2-(2-methyl-1H-indol-3-yl)ethyl]cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-2-isopropyl-N-[(6-methoxy-2,3-dihydrobenzofuran-3-yl)methyl]-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-2-isopropyl-N-[2-(2-methoxyphenyl)ethyl]-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(2-phenylpropyl)cyclohexanecarboxamide;

(1S,2S,5R)-N-[2-(2-fluorophenyl)-2-hydroxy-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-N-[2-(4-fluorophenyl)-2-hydroxy-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-N-[2-(2,3-dihydrobenzofuran-7-yl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-N-[2-(2-chlorophenyl)-2-hydroxy-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-N-[[3-(hydroxymethyl)phenyl]methyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-N-(2,3-dihydrobenzofuran-3-ylmethyl)-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-N-[3-hydroxy-1-(3-hydroxyphenyl)propyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-phenyl-propyl)-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-N-[(3-hydroxyphenyl)methyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-N-[2-(4-hydroxy-3-nitro-phenyl)ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-N-[3-(4-hydroxyphenyl)propyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-N-[(1S)-3-(4-hydroxyphenyl)-1-methyl-propyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-N-[2-(5-hydroxy-1H-indol-3-yl)ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-N-[(1R)-1-(hydroxymethyl)-2-(4-hydroxyphenyl)ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-N-[(2R)-7-hydroxytetralin-2-yl]-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-N-[2-(2-bromo-5-hydroxy-phenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-N-[2-(2,4-dihydroxyphenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-1-hydroxy-N-(((1RS)-hydroxy-2,3-dihydro-1H-inden-1-yl)methyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-N-(((1RS)-hydroxy-2,3-dihydro-1H-inden-1-yl)methyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-N-(((1RS)-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-N-((2R)-2-hydroxy-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1- carboxamide;

(1S,2S,5R)-N-((2R)-2-fluoro-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-N-((2S)-2-fluoro-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-N-((2RS)-2-((S)-2-aminopropanamido)-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-N-((2RS)-2-((S)-2-aminopropanamido)-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-N-((2RS)-(2-aminoacetamido)-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-N-((2RS)-2-((S)-2-aminopropanamido)-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;

(1S,2S,5R)-1-hydroxy-2-isopropyl-N-[2-[3-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]phenyl]ethyl]-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-N-[2,2-difluoro-2-(2-methoxyphenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-N-[2,2-difluoro-2-(3-methylphenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide;

(1S,2S,5R)-N-[2,2-difluoro-2-(3-methoxyphenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide; and

(1S,2S,5R)-1-hydroxy-N-(4-methoxyphenyl)-5-methyl-2-propan-2-ylcyclohexane-1-carboxamide;

or a pharmaceutically acceptable salt thereof.

Another embodiment is a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in therapy, especially as an agonist of TRPM8 receptors or an activator of TRPM8 receptors.

Another embodiment is a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as medicament.

Another embodiment is a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of oropharyngeal dysphagia.

Another embodiment is a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of pediatric dysphagia.

Another embodiment is a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of post-extubation dysphagia.

Another embodiment is a method of treating oropharyngeal dysphagia, comprising administering to a subject in need thereof, in particular a human, a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

Another embodiment is a method of treating pediatric dysphagia, comprising administering to a subject in need thereof, in particular a human, a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

Another embodiment is a method of treating post-extubation dysphagia, comprising administering to a subject in need thereof, in particular a human, a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

Another embodiment is a pharmaceutical composition comprising as active principle an effective dose of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

One embodiment is a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt and at least one pharmaceutically acceptable excipient.

One embodiment is a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient, wherein the compound of formula (I) is (1S,2S,5R)-1-hydroxy-N-((S)-2-hydroxy-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide; or a pharmaceutically acceptable salt thereof.

One embodiment is a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient, wherein the compound of formula (I) is 2-hydroxyethyl 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzoate; or a pharmaceutically acceptable salt thereof.

One embodiment is a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient, wherein the compound of formula (I) is (1S,2S,5R)-1-hydroxy-N-(3-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide; or a pharmaceutically acceptable salt thereof.

One embodiment is a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient, wherein the compound of formula (I) is 2-hydroxyethyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzoate; or a pharmaceutically acceptable salt thereof.

One embodiment is a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient, wherein the compound of formula (I) is (1S,2S,5R)-1-hydroxy-N-(2-(2-hydroxyethyl)phenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide; or a pharmaceutically acceptable salt thereof.

One embodiment is a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient, wherein the compound of formula (I) is Methyl-3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate; or a pharmaceutically acceptable salt thereof.

One embodiment is a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient, wherein the compound of formula (I) is (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-((3-phenyloxetan-3-yl)methyl)cyclohexane-1-carboxamide; or a pharmaceutically acceptable salt thereof.

One embodiment is a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient, wherein the compound of formula (I) is (1S,2S,5R)-N-(2-(2-amino-2-oxoethoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide; or a pharmaceutically acceptable salt thereof.

One embodiment is a method of treating a disease involving activation of TRPM8 receptors, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

One embodiment is a method of treating oropharyngeal dysphagia, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

The compounds of the formula (I) can be prepared by the following processes.

The compounds of the formula (I) are synthesized using techniques and materials described below or otherwise known by the skilled person in the art. In addition, solvents, temperatures and other reaction conditions presented below may vary as deemed appropriate to the skilled person in the art.

General below methods for the preparation of compounds of formula (I) are optionally modified by the use of appropriate reagents and conditions for the introduction of the various moieties found in the compound of formula (I) as described below.

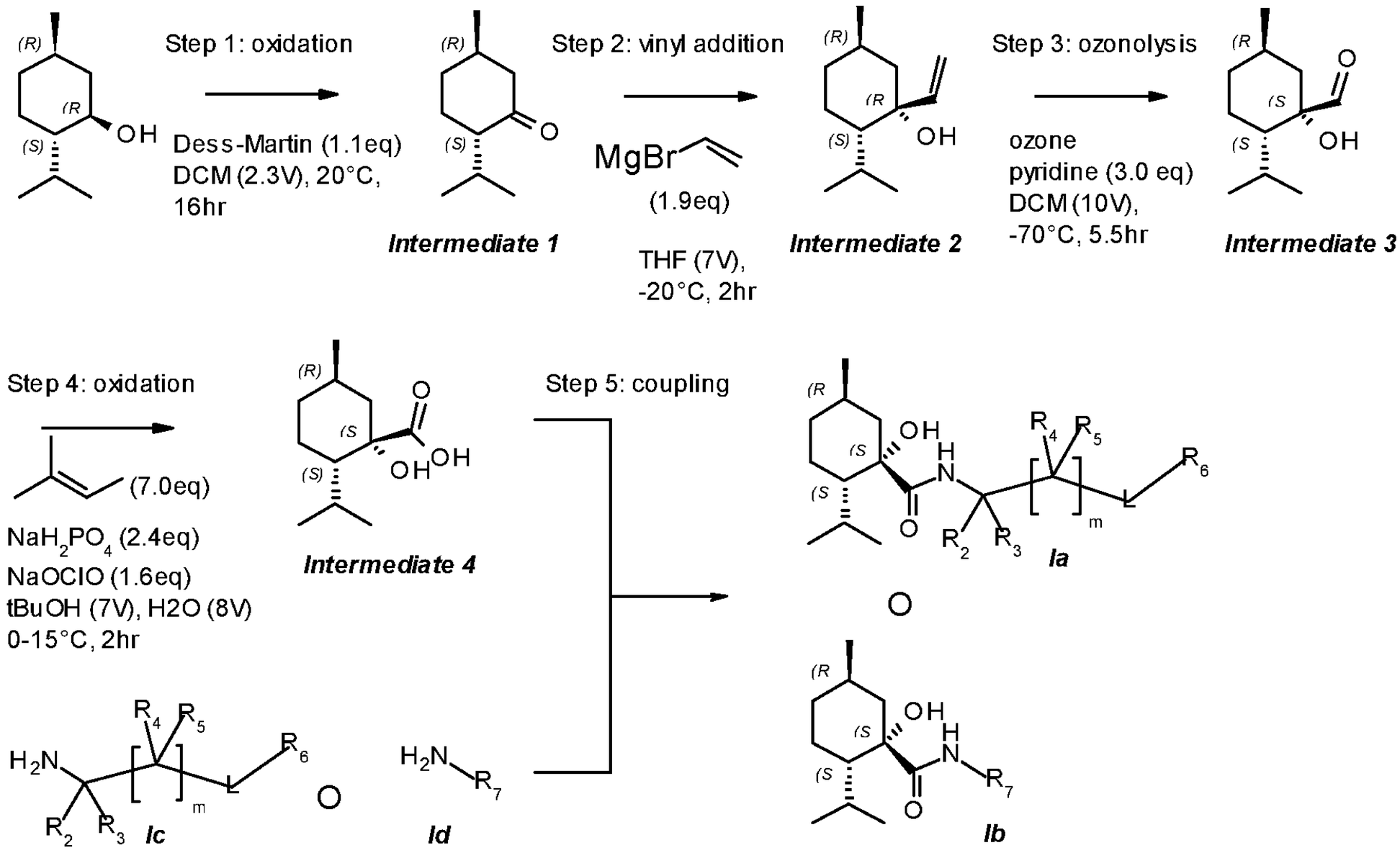
As used above, and throughout the description of the invention, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:

BBr_3	boron bromide
BH_3-THF	borane tetrahydrofuran
BOC-BETA-IODO-ALA-OME	N-(tert-butoxycarbonyl)-3-iodo-L-alanine methyl ester
BOC-D-SER-OME	N-(tert-butoxycarbonyl)-L-serine methyl ester,
BOC-D-ALA-OH	N-(tert-butoxycarbonyl)--D-alanine
BOC-L-ALA-OH	N-(tert-butoxycarbonyl)--L-alanine
BOC-GLY-OH	N-(tert-butoxycarbonyl)glycine
$CaCl_2$	calcium chloride
CDI	1,1′-carbonyldiimidazole
CH_3CN	methyl cyanide
CHO	Chinese hamster ovary
CO_2	carbon dioxide
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
Dess-Martin periodinane	1, 1, 1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(I*H*)-one
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DM	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
MeOH	methanol
EDAC	N-ethyl-N’-(3-dimethylaminopropyl)carbodiimide hydrochloride
EGTA	ethylene glycol-bis(2-aminoethylether)-N,N,N’,N’-tetraacetic acid
Eq	equivalent
Et2O	diethyl ether
EtOAc	ethyl acetate
ES+:	electrospray positive ionization
FA	formic acid
FCS	fetal calf serum
FLIP	FLIP assay results on human cell lines
FLIPR	FLIP assay results on pig cell lines
Gr	grams
HCl	hydrogen chloride
H_2	hydrogen

HBSS	Hank's balanced salt solution
HCOOH	formic acid
HEPES	4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid
HNMR	Proton NMR spectrum
HOBT	1-hydroxybenzotriazole hydrate
HPLC	High Performance Liquid Chromatography
hr	hour
K_2CO_3	potassium carbonate
KCl	potassium chloride
KF	potassium fluoride
KOH	potassium hydroxide
LCMS	liquid chromatography mass spectrometry
LDA	lithium diisopropylamide
$LiBH_4$	lithium borohydride
M	molar
MeCN	methyl cyanide
MeOH	methanol
MTBE	methyl tert-butyl ether
Mg	magnesium
$MgCl_2$	magnesium chloride
ml or mL	milliliter
N	normal
N-Boc	N-tert-butoxycarbonyl
NaCl	sodium chloride
NaN_3	sodium azide
NaH_2PO_4	sodium dihydrogen phosphate
NaOClO	sodium chlorite
NaOH	sodium hydroxide
Na_2SO_3	sodium sulfite
$Na_2S_2O_3$	sodium thiosulfate
Na_2SO_4	sodium sulfate
NH_4Cl	ammonium chloride
N_2	nitrogen
$Pd(Ph_3)_4$	tetrakis(triphenylphosphine)palladium(0)

PPh_3	triphenylphosphine
PPTS	pyridinium p-toluenesulfonate
PtO_2	platinum oxide
Pd	palladium
RP-HPLC	reversed-phase high performance liquid chromatography
rt	room temperature
RT	retention time
TBAF	tetra-n-butylammonium fluoride
t-BuOH	tert-butyl hydroxide
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
UPLC	ultra performance liquid chromatography
V	volume
XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
XPhos Pd	chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1 '-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II)

SCHEME 1: Preparation of compounds of the formula (Ia or Ib)

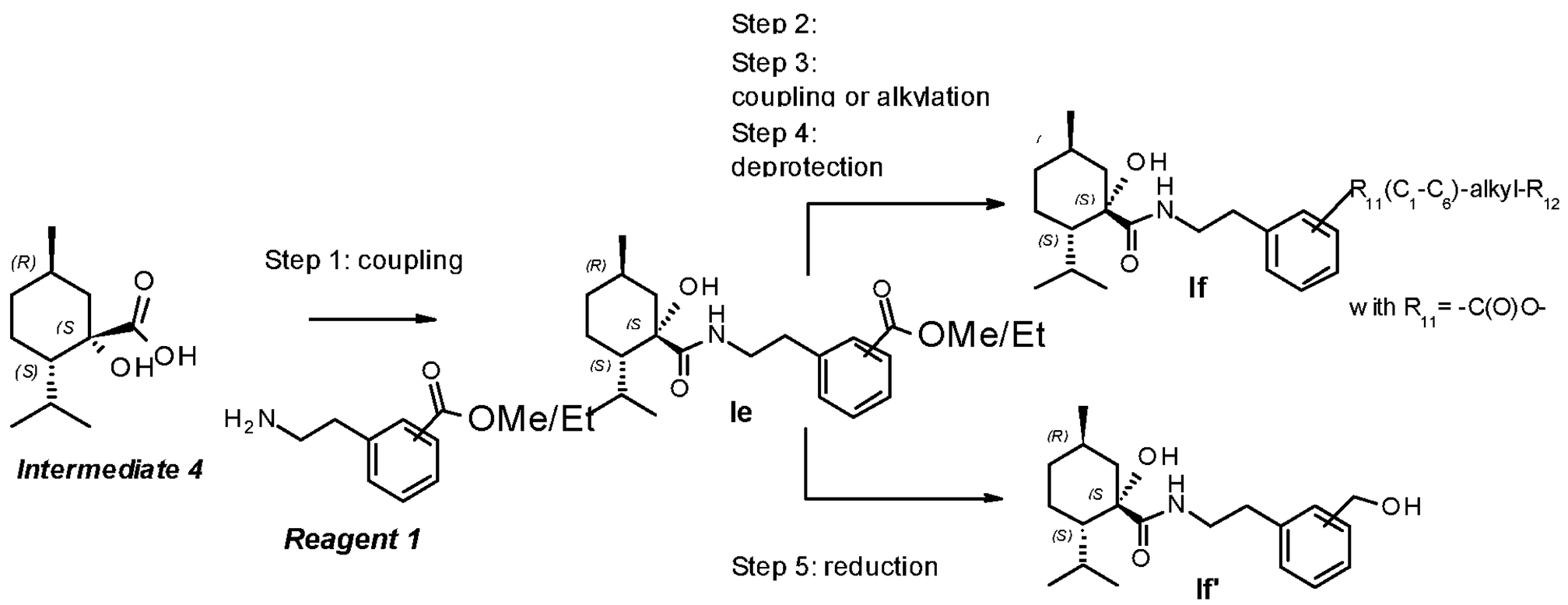


According to **SCHEME 1**, in which R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are defined as described above, L-Menthol is oxidized in Step 1 into corresponding ketone L-menthone (*intermediate 1*) for instance by treatment with Dess-Martin reagent in a solvent such as dichloromethane (DCM). This intermediate 1 is subjected in Step 2 to a vinyl addition by treatment for example with bromomagnesium vinyl in a solvent such as tetrahydrofuran (THF) to give *intermediate 2*.

The *intermediate 2* is then oxidized in Step 3 to give the aldehyde *intermediate 3*, for instance with ozone in a solvent such as dichloromethane (DCM) in the presence of a base, like pyridine. The *intermediate 3* is oxidized in Step 4 to generate the acid *intermediate 4* such as by treatment with sodium chlorite and sodium dihydrogen phosphate in the presence of 2-methyl-2-butene at room temperature.

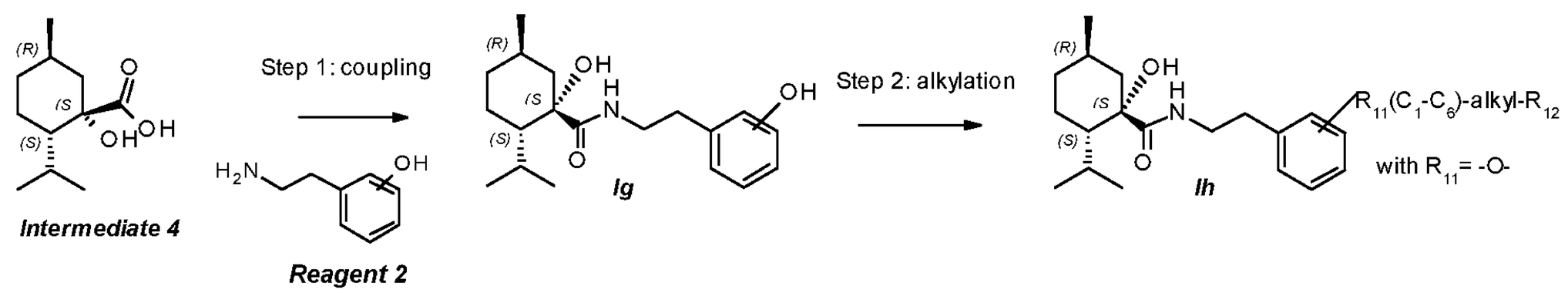
The *intermediate 4* is then subjected in Step 5 to a coupling reaction with an amino compound H_2N-$C(R_2)(R_3)$-$[C(R_4)(R_5)]_m$-L-R_6 (1c)or H_2N-R_7 (1d), wherein R_2, R_3, R_4, R_5, m, L, R_6 and R_7 are as above defined, using for example CDI in EtOAc, at room temperature or by heating up to reflux, to provide amide (Ia or Ib).

SCHEME 2



According to **SCHEME 2**, the *intermediate 4* can be coupled with an amine compound (*Reagent 1*) in Step 1 under condition B as described below in REACTION 1 to give an amid derivative (Ie). The amid derivative (Ie) can be transformed into compound of formula (If or If') by subjecting the amid derivative (Ie) to further reactions such as alkylation under condition D,E& F as described below in REACTION 3, coupling under condition C as described below in REACTION 1, saponification under conditions as described below in REACTION 5, or reduction under conditions A-C as described below in REACTION 6.

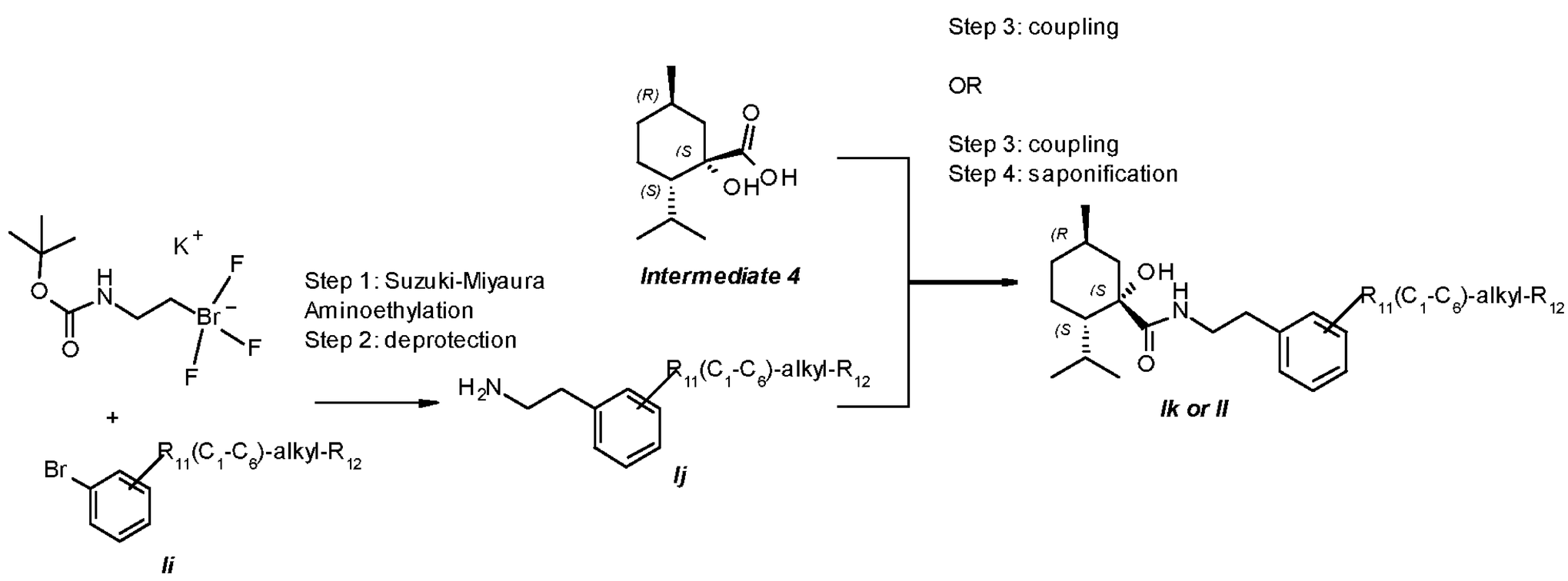
SCHEME 3



According to **SCHEME 3**, the *intermediate 4* is coupled with an amine compound (*Reagent 2*) in Step 1 under condition A or B as described below in REACTION 1 to give an amide derivative (Ig). The amide derivative (Ig) is transformed into compound of formula (Ih) in Step 2 by subjecting the amide derivative (Ig) to alkylation reaction under condition A, B or C as described below in REACTION 3.

According to **SCHEME 4**, potassium tert-butyl N-[2-(trifluoroboranuidyl)ethyl]carbamate and a bromo compound of formula (1i) is subjected to a Suzuki-miyaura aminoethylation reaction as shown in Step 1 with a suitable palladium reagent, for example 1,1'bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex, in a mixture of toluene and water and in the presence of a base, for example cesium carbonate. The intermediate obtained is then subjected to a deprotection reaction as shown in Step 2 of SCHEME 4 in the presence of a suitable acid for example HCl to give an amine compound of formula (Ij). The amine compound obtained (Ij) is then subjected in Step 3 to a coupling reaction or a coupling reaction under condition B as described below in REACTION 1 and a saponification under condition as described below in REACTION 5 to give compound of formula (Ik or Il).

SCHEME 4



An ester or amide can be obtained through a coupling reaction (step 5 in SCHEME 1; step 1 in SCHEME 2, step 1 in SCHEME 3, step 3 in SCHEME 4) of an acid (Intermediate 4) with an alcohol or an amine compound under conditions A & B described in **REACTION 1** as shown below:

REACTION 1: Coupling reactions: conversion of acid into an ester or amide

Coupling conditions A

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid is dissolved in EtOAc (0.1M) under inert atmosphere, and CDI (1eq) is added portionwise to the resulting solution. The reaction mixture is then stirred at rt for 2hrs, and the amine corresponding to the desired

amide (1.11 eq) is added portionwise. The reaction mixture is then heated at 60-70°C for 16hrs (The reaction temperature and time may vary depending on the amine and specific temperature and time is noted in example if it is different from 60-70°C for 16hrs). Water (0.5V) is then poured into the reaction mixture as well as an 1N aqueous solution of hydrochloric acid and the resulting mixture was stirred. The organic phase is separated and washed with an 1N aqueous solution of sodium hydroxide (1V), then with brine (1V). The organic phase is then dried over Na_2SO_4, filtrated and concentrated under vacuum yielding a residue which is purified by flash chromatography. Reprecipitation is carried out using DCM (0.12V) and n-pentane (0.12V) and leads to the pure desired amide.

Coupling conditions B

In a round bottom flask, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid is dissolved in acetonitrile (0.3M) under inert atmosphere and CDI (0.94eq) is added portionwise to the resulting solution. The reaction mixture is then stirred at rt for 50min and the amine corresponding to the desired amide (1.05 eq) is added portionwise followed by addition of pyridine (1.1eq). The reaction mixture is then stirred at rt for16hrs (The reaction temperature and time may vary depending on the amine and specific temperature and time is noted in example if it is different from rt for 16hrs). After concentration under vacuum of the reaction mixture, the resulting residue is dissolved in EtOAc (4V), and water (4V) was added. The aqueous solution is then acidified to pH 1-2 by addition of an 1N aqueous solution of hydrochloric acid, and, after extraction, the organic phase is recovered. The aqueous phase is brought to pH 11-12 by addition of drops of 35% aqueous solution of sodium hydroxide. The combined organic phases are then dried over Na_2SO_4, filtrated and concentrated under vacuum yielding a residue which is purified by flash chromatography. Reprecipitation is carried out using DCM (0.12V) and n-pentane (0.12V) and leads to the pure desired amide

Coupling conditions C

An acid (such as for example 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoic acid, 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoic acid or ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycine) is dissolved in THF (0.2M) under inert atmosphere and the alcohol (such as for example tert-butyl N-(2-hydroxyethyl)carbamate or phenol) (1.29eq) is then added. DCC (1.33eq) and DMAP (0.21eq) are added to the resulting solution. The reaction mixture is then stirred at rt during 50min and the amine corresponding to the desired amide (1.05

eq) is added portionwise followed by addition of pyridine (1.1eq). The reaction mixture is then stirred at rt over 16hrs. After concentration under vacuum of the reaction mixture, the resulting residue is dissolved in EtOAc (2V) and water (2V) is added. The aqueous solution is then acidified to pH 1-2 by addition of an 1N aqueous solution of hydrochloric acid. The organic phases are dried over Na_2SO_4, filtrated and concentrated under vacuum yielding the pure desired amide with or without flash chromatography.

Coupling conditions D

The acid (such as for example ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycine OR 3-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-2-phenylpropanoic acid) is dissolved in DCM (0.2M) under inert atmosphere and an alcohol/amine compound (such as for example vanillin, tert-butyl N-(2-hydroxyethyl)carbamate or N-Boc-2-amino-2-methyl-1-propanol) (1.1eq) is then added. DCC (1.1eq) and DMAP (0.1eq) are added to the resulting solution. The reaction mixture is then stirred at rt during 20hrs. After filtration of the reaction mixture, the resulting organic solution is washed with an 1N aqueous solution of sodium hydroxide (10V), an 1N aqueous solution of hydrochloric acid (10V), brine (10V), dried over Na_2SO_4, filtrated and concentrated under vacuum to provide the desired ester/amide with or without flash chromatography.

Coupling conditions E

An acid (such as for example 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoic acid or ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycine) and an alcohol/amine (such as for example ethanol, phloroglucinol, vanillin, 4-aminophenol or (S)-2-((tert-butyldimethylsilyl)oxy) propan-1-ol) (3.0eq) are dissolved in DMF (0.17M) and the resulting solution is cooled down to 0°C. EDAC(1.0eq) as well as DMAP (0.2eq) are added and once at room temperature, the reaction mixture is stirred for 4hr30. Water (5V) is added and the resulting solution is extracted with EtOAc (5V x 2). The combined organic phases are washed with brine (5V), dried over Na_2SO_4, filtrated and concentrated under vacuum. The residue is purified by flash chromatography to provide the desired ester/amide.

Coupling conditions F

(1S,2S,5R)-N-((S)-2-amino-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide is dissolved in THF (0.16M) under inert atmosphere and an alcohol/amine (such

as for example BOC-D-ALA-OH, BOC-L-ALA-OH, BOC-ALA-OH or BOC-GLY-OH) (1.1eq) is then added. EDAC (1.1eq), HOBT (1.1eq) and triethylamine (1.2eq) are added to the resulting solution. The reaction mixture is then stirred at rt during 16hrs. After addition of EtOAc (2V), the resulting organic solution is washed with an 1N aqueous solution of sodium hydroxide (5V), an 1N aqueous solution of hydrochloric acid (5V), brine (5V), dried over Na_2SO_4, filtrated and concentrated under vacuum yielding the pure desired amide with or without flash chromatography.

An alcohol or amine compound can be converted into a corresponding ester or amide by reacting the alcohol or amine compound with acetic anhydride are described in **REACTION 2** below.

REACTION 2: Acetylation reaction: conversion of an alcohol or an amine into corresponding ester or amide

Acetylation conditions

(1S,2S,5R)-1-hydroxy-N-((S)-2-hydroxy-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide is dissolved in pyridine (0.18M) and acetic anhydride (2.8eq) is added. The resulting solution is stirred at rt. EtOAc (10V) and water (10V) are added to the reaction mixture and this biphasic solution is acidified to pH 1-2 by addition of an 1N aqueous solution of hydrochloric acid. After separation, the organic phase is then extracted with water (10V) after pH of the aqueous phase is basified to pH 11-12 by addition of drops of 35% aqueous solution of sodium hydroxide. The resulting organic phase is then dried over Na_2SO_4, filtrated and concentrated under vacuum yielding the pure desired acylated product.

A phenol, an alcohol or an acid compound can be converted into a corresponding alkylated compound by reacting the phenol, the alcohol, or the acid compound with an alkylating agent (such as for example step 3 in SCHEME 2, step2 in SCHEME 3) under condition A-F ad described in **REACTION 3** as shown below:

REACTION 3: Alkylation reaction: conversion of an alcohol into corresponding alkylated compound.

Alkylation conditions A

In a microwave tube, an phenol/alcohol (such as for example (1S,2S,5R)-1-hydroxy-N-(2-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide) is dissolved in acetonitrile (0.04M) and cesium carbonate (3.94eq) is then added followed by a bromo alkylating agent (such

as for example tert-butyl N-(2-bromoethyl)carbamate, 2-(2-bromoethoxy)tetrahydro-2H-pyran, 2-bromoethyldimethylamine or tert-butyl N-(2-bromoethyl)carbamate) (1.64eq). The resulting reaction mixture is irradiated for 1hr at 100°C. After concentration under vacuum of the reaction mixture, the resulting residue is dissolved in EtOAc (2V) and water (2V) is added. The aqueous solution is brought to pH 11-12 by addition of drops of 35% aqueous solution of sodium hydroxide and washed once with EtOAc (2V). The combined organic phases are dried over Na_2SO_4, filtrated and concentrated under vacuum. The residue is purified by flash chromatography to yield the desired alkylated product (such as for example, compound of formula (If), compound of formula (Ih)).

Alkylation conditions B

(1S,2S,5R)-1-hydroxy-N-(2-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide was dissolved in ethanol (0.06M) and an alkylating agent (such as for example glycidol, (*R*)-glycidol or (*S*)-glycidol) (3.8eq) is then added followed by triethylamine (1.7eq). The resulting reaction mixture is heated at reflux over 5 days. After concentration under vacuum of the reaction mixture, the resulting residue is purified by flash chromatography to yield compound of formula (Ih).

Alkylation conditions C

An alcohol (such as for example (1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-(3-hydroxyphenyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide, (1S,2S,5R)-1-hydroxy-N-(3-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide or (1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-(2-hydroxyphenyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide) is dissolved in acetone (0.2M), and K_2CO_3 (2.5eq) was added followed by addition of an alkylating agent (such as for example methyl bromoacetate, 3-bromo-1-propanol, 2-bromoacetamide or 1-bromo-2-[2-(2-methoxyethoxy)ethoxy]ethane) (1.1eq). The reaction is then heated at reflux during 20min. The reaction mixture is filtrated and concentrated under vacuum. The resulting residue is dissolved in diethyl ether and the resulting organic solution is washed with water (10V), an 1N aqueous solution of sodium hydroxide (10V), with brine (10V), dried over Na_2SO_4, filtrated and concentrated under vacuum. The residue is purified by flash chromatography to yield the desired alkylated product.

Alkylation conditions D

An acid (such as for example 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoic acid or 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoic acid) is dissolved in acetonitrile (0.09M) and DBU (1.06eq) is then added as well as the alkylating agent (1.1eq). The reaction mixture is heated at 80°C during 7hr and then stirred at room temperature during 16hrs. After concentration under vacuum of the reaction mixture, the resulting residue is dissolved in EtOAc (2V) and water (2V) is added. The aqueous solution is brought to pH 11-12 by addition of drops of 35% aqueous solution of sodium hydroxide and washed another time with EtOAc (2V). The combined organic phases are washed with brine, dried over Na_2SO_4, filtrated and concentrated under vacuum. The residue is purified by flash chromatography to yield the desired alkylated product.

Alkylation conditions E

(1S,2S,5R)-1-((tert-butyldimethylsilyl)oxy)-N-((S)-2-hydroxy-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide is dissolved in DMF (0.4M) and the resulting solution is cooled down to 0°C. Sodium hydride (6.0eq) is added, and the reaction mixture is warmed up to room temperature. After cooling down to 0°C, an alkylating agent (methyl bromoacetate or 2-(2-bromoethoxy)tetrahydro-2H-pyran) (6.0eq) is added and is warmed up to room temperature. The reaction mixture is stirred during 24hrs and is then quenched with water (6V). The resulting mixture is extracted with diethyl ether (6V x 2). The organic phase is washed with brine, dried over Na_2SO_4, filtrated and concentrated under vacuum. The residue is purified by flash chromatography with cyclohexane and EtOAc to provide the desired alkylated product.

Alkylation conditions F

3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoic acid is dissolved in acetonitrile (0.07M) and K_2CO_3 (3.00eq) is then added as well as an alkylating agent (such as for example 4-chloromethyl-5-methyl-1,3-dioxol-2-one)(1.19eq). The reaction mixture is heated at 40°C for 1hr30mins, and then sodium iodide (0.11eq) is added. The reaction mixture is heated at 50°C for 16hr. After concentration under vacuum of the reaction mixture, the resulting residue is dissolved in EtOAc (4V) and water (4V) is added. The aqueous phase is again washed with EtOAc (4V). The combined organic phases are washed with brine, dried over Na_2SO_4, filtrated and concentrated under vacuum. The residue is purified by flash chromatography to yield the desired alkylated product

The reaction of removing the protecting group (step 2 in SCHEME 4), for instance a carbamate compound, can be performed in accordance with method A or method B as described in **REACTION 4** as shown below:

REACTION 4: Deprotection reaction

Deprotection conditions A

The carbamate/silylated alcohol was dissolved in DCM (0.08M) and HCl (15.4eq, 4N in dioxane) was added. The reaction mixture was stirred at room temperature over 3hr30. After concentration under vacuum, the residue was dissolved in MeOH and concentrated under vacuum to yield the pure desired amine.

Deprotection conditions B

The carbamate was dissolved in DCM (0.08M) and TFA (16.2eq) was added. The reaction mixture was stirred at room temperature over 21hr. Water (1V) was added followed by portionwise addition of sodium carbonate until pH is 9. DCM (1V) and water (1V) were added. The resulting mixture was filtered on hydrophobic Radley cartridge and the organic phase was concentrated under vacuum. The residue was purified by flash chromatography to yield the desired amine.

The saponification reaction (step 2 in SCHEME 2, step 4 in SCHEME 4) of an ester can be performed in an appropriate solvent in the presence of a base as described in **REACTION 5**.

REACTION 5: Saponification: conversion of an ester compound into corresponding acid compound.

Saponification conditions

An ester (such as for example methyl 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate, methyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate, methyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate or methyl 4-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-3-phenyl butanoate) is dissolved in methanol/THF mixture (50/50, 0.06M), and sodium hydroxide (1.0eq) is then added. The resulting reaction mixture is stirred at room temperature over 18hrs. After concentration under vacuum of the reaction mixture, the resulting residue is dissolved in EtOAc (2V), washed with water, and

acidified until obtention of biphasic mixture. The organic phase is dried over Na_2SO_4, filtrated and concentrated under vacuum to yield the desired acid.

The reduction reaction of an ester or ketone (step 5 in SCHEME 2) can be performed in accordance with condition A, B, or C in an appropriate solvent in the presence of a reducing reagent such as a borohydride agent as described in **REACTION 6**.

REACTION 6: Reduction: conversion of an ester or ketone compound into corresponding alcohol compound.

Reduction conditions A

methyl 3-(1-hydroxy-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate is dissolved in 1,4-dioxane/water mixture (50/50, 0.07M) and sodium borohydride (39-49eq) is then added. The resulting reaction mixture is stirred at room temperature over 20hrs. Hydrolysis of the reaction is carried out by addition of saturated solution of ammonium chloride at 0°C and the resulting mixture is concentrated under vacuum. The resulting residue is dissolved in EtOAc (2V) and water (2V). The organic phase is dried over Na_2SO_4, filtrated and concentrated under vacuum to yield the desired acid after flash chromatography or preparative HPLC.

Reduction conditions B

methyl 4-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-3-phenylbutanoate is dissolved in THF (0.15M) and LiBH4 (11eq) is added, followed by addition of dried MeOH (11eq). The reaction mixture is stirred at room temperature over 72hrs. An 1N aqueous solution of sodium hydroxide (3V) is then added and the resulting mixture is stirred at 50°C during 30min. MeOH (1.5V) is added and the resulting solution is stirred at 50°C during 22hrs. After being concentrated under vacuum, the remaining aqueous phase is extracted with EtOAc (3V x 2). The combined organic phase is washed with brine (3V), dried over Na_2SO_4, filtrated and concentrated under vacuum. The residue is purified by flash chromatography with cyclohexane and EtOAc to yield the desired alcohol.

Reduction conditions C

An ester/ketone (such as for example (1S,2S,5R)-1-hydroxy-N-(2-(2-hydroxyphenyl)-2-oxoethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide, (1S,2S,5R)-1-hydroxy-2-isopropyl-

5-methyl-N-(2-oxo-2-phenylethyl)cyclohexane-1-carboxamide or 4-formyl-2-methoxyphenyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate) is dissolved in MeOH (0.2M), and sodium borohydride (1eq) is then added portionwise. The resulting reaction mixture is stirred at room temperature over 45 minutes. Water (1V) and EtOAc (1V) are added to the reaction mixture at 0°C as well as Et_2O (2V), and an 1N aqueous solution of hydrochloric acid. The organic phase is washed with brine (2V), dried over Na_2SO_4, filtrated and concentrated under vacuum. The residue is purified by flash chromatography.

Experimental Procedures

The starting materials and intermediates may be prepared by the methods described in the present application or are available commercially or are described in the literature, or else may be prepared by methods which are described therein or which are known to a person skilled in the art. By appropriate selection of suitable starting materials, compounds of the formula (I) may be prepared according to the procedures described in the foregoing examples.

The 1H NMR data were performed at 400, 500 and 600 MHz with the chemical shifts (δ in ppm) in the solvent dimethyl sulfoxide-d6 (d6-DMSO) referenced at 2.5 ppm at a temperature of 303 K. Coupling constants (J) are given in Hertz.

The examples which follow describe the preparation of certain compounds in accordance with the disclosure. These examples are not limitative, and merely illustrate the present disclosure. Compounds of formula (I) are identified, for example, by the following analytical methods.

High Pressure Liquid Chromatography - Mass Spectrometry (LCMS) experiments to determine retention times (R_T) and associated mass ions are performed using one of the following analytical methods.

Method A: Acquity UPLC CSH C18 1.6 µm, dimension 2.1x50 mm, mobile phase H_2O + 0.1% Formic acid / Acetonitrile + 0.1% AF. Gradient (3 min) : 2 to 100 % of B in 2.0min ; 2.6min : 100 % of B; 2.70 min : 2% of B; 3.0min: 2% B.

Method B: Acquity UPLC CSH C18 1.6 µm, dimension 2.1x50 mm, mobile phase H_2O + 0.1% Formic acid / Acetonitrile + 0.1% Formic acid. Gradient (10 min) : 2 to100 % of B in 7.5min ; 9.2min : 100 % of B; 9.3 min : 2% of B; 10.0min: 2%B.

Method C: Waters ACQUITY UPLC BEH C18 1.7um 2.1x50mm; [H_2O+0.05% Formic acid]: [Acetonitrile+0.035% Formic acid] 98:2(0min) to 98:2(0.2min) to 2:98(3.8min) to 2:98(4.3min) to 98:2(4.5min), 1 ml/min 55°C ; Ionization method: ES+ ; MS-Type: UPLCesi ; MS-Method: Waters SQD2 Single Quadrupol, 0.25s scantime for mass 100-2000 ; UV detection wavelength: 220Nm.

Method D: ACQUITY CSH C18 - 1,7 µm - 2,1 x 50 mm; Solvants : A : H_2O (0.1 % formic acid) B : CH_3CN (0.1 % formic acid); Gradient (2.5 min) : 3 to100 % of B in 2.1min ; 2.45 min : 100 % of B; 2.50 min : 3 % of B; 1 ml/min 60°C ; UPLC-SQD2 Water apparatus; Ionization method: ES+.

Method E: Acquity UPLC CSH C18 (2.1x50mm), mobile phase A = H_2O + 0.02%HCOOH & B = CH_3CN + 0.02%HCOOH, 1 mL/min, 55°C. Gradient : t0 2% B, t4 min98% B, t4.5 min 98% B, t4.6 min 2% B , t5.0 min 2% B.

Method F: Acquity UPLC CSH C18 (2.1x50mm), mobile phase A = H_2O + 0.05%TFA Eluent B = CH_3CN + 0.035%TFA, 1 mL/min, 55°C. Gradient : t0 2% B, t4 min98% B, t4.5 min 98% B, t4.6 min2% B , t5.0 min 2% B.

The following Reverse phase preparative chromatography (RP-HPLC) parameters were used for purification:

Method G: Reverse phase preparative chromatography: Waters Sunfire Prep C_{18} OBD 5 µm 50 x 50 mm; Solvent A: H_2O + 0.1 % trifluoroacetic acid; Solvent B: Acetonitrile, Flow rate: 120 mL/min. Gradient (5 minutes) A : B = 90 : 10 or 70 : 30 at t = 0 min; A : B = 5 : 95 at t = 3.7min and A : B = 90 : 10 or 70 : 30 at t = 4.9min.

Method H: Waters Sunfire Prep C18 OBD 5 µm 50 x 50 mm; Solvent A: H_2O + 0.1 % trifluoroacetic acid; Solvent B: Acetonitrile, Flow rate: 120 mL/min. Gradient (7 minutes): A : B = 75 : 25 at t = 0min, A : B = 10 : 90 or 5 : 95 at t = 5.7 min and A : B = 25 : 75 or 95 : 5 at t = 6.9 min.

The following intermediates describe the procedures used for the preparation of various starting materials employed in the preparation of the compounds of formula (I).

INTERMEDIATES

Intermediate 1: L-menthone

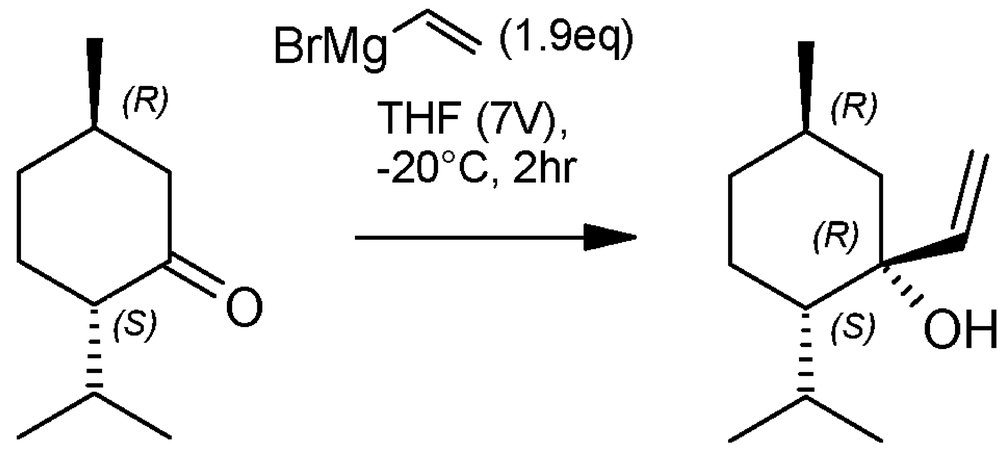


Three batches of the same reaction were carried out in parallel.

To a solution of (R)-menthol (300g) in DCM (2.7M) was added Dess-martin reagent (1.10eq) at 20°C under N_2. The reaction was stirred at 20°C for 16 hrs. The three reactions were combined for workup. The resulting mixture was poured into water (4.3V). The aqueous phase was extracted with DCM (1.4V x 3). The combined organic phases were washed with a saturated aqueous solution of Na_2SO_3 (1.4V x 2). The organic phase was checked by potassium iodide-starch test paper: the test paper did not change to blue. The organic phase was washed with brine (1.4V x 2), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash chromatography with petroleum ether & ethyl acetate to give L-menthone (836g) as colorless oil.

^{1}H NMR: 400 MHz DMSO-d_6 (δ ppm): 1.98-2.18 (m, 5H), 1.72-1.86 (m, 2H), 1.24-1.40 (m, 2H), 0.95 (d, J = 6.4 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.8 Hz, 3H).

Intermediate 2: *(1R,2S,5R)-2-isopropyl-5-methyl-1-vinylcyclohexan-1-ol*

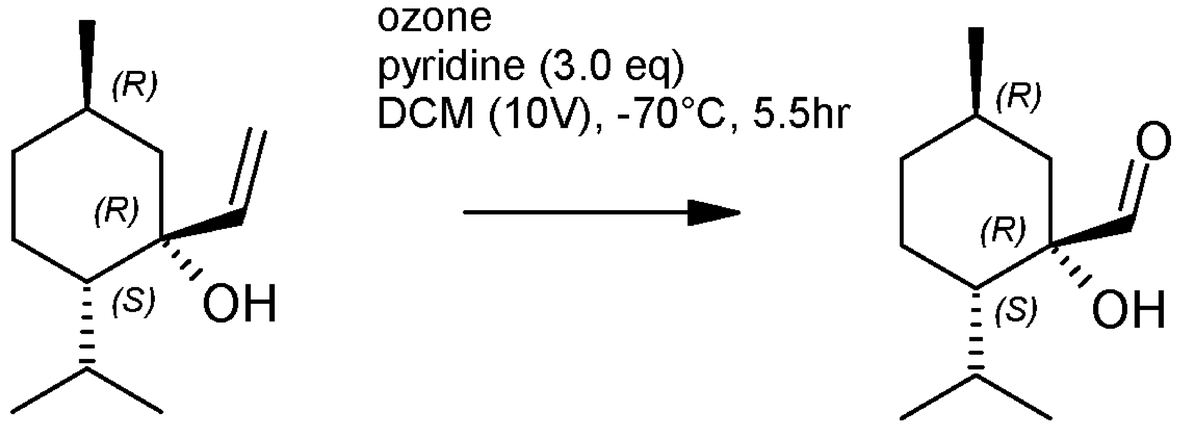


Six batches of the same reaction were carried out in parallel.

To a solution of L-menthone (148 g) in dry THF (0.93M) at -20°C was added dropwise bromomagnesium vinyl (1.90 eq) in THF under N_2. The reaction mixture was allowed to slowly warm to 15°C and stirred for 2 hrs. The six reactions were combined for workup. The resulting mixture was poured into a saturated aqueous solution of NH_4Cl (3V) slowly at 10°C and stirred for 30 mins. The aqueous phase was extracted with MTBE (4V x 2). The combined organic phases were washed with brine (2V x 2), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash chromatography with petroleum ether and ethyl acetate to yield (1R,2S,5R)-2-isopropyl-5-methyl-1-vinylcyclohexan-1-ol (910 g) as colorless oil.

^{1}H NMR: 400 MHz DMSO-d_6 (δ ppm): 5.75-5.83 (m, 1H), 5.20 (dd, J = 17.2 Hz, 2.0 Hz, 1H), 4.97 (dd, J = 10.8 Hz, 2.0 Hz, 1H), 3.99 (s, 1H), 1.67-1.92 (m, 3H), 1.36-1.52 (m, 3H), 1.00-1.10 (m, 2H), 0.78-0.88 (m, 10H).

Intermediate 3: (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbaldehyde

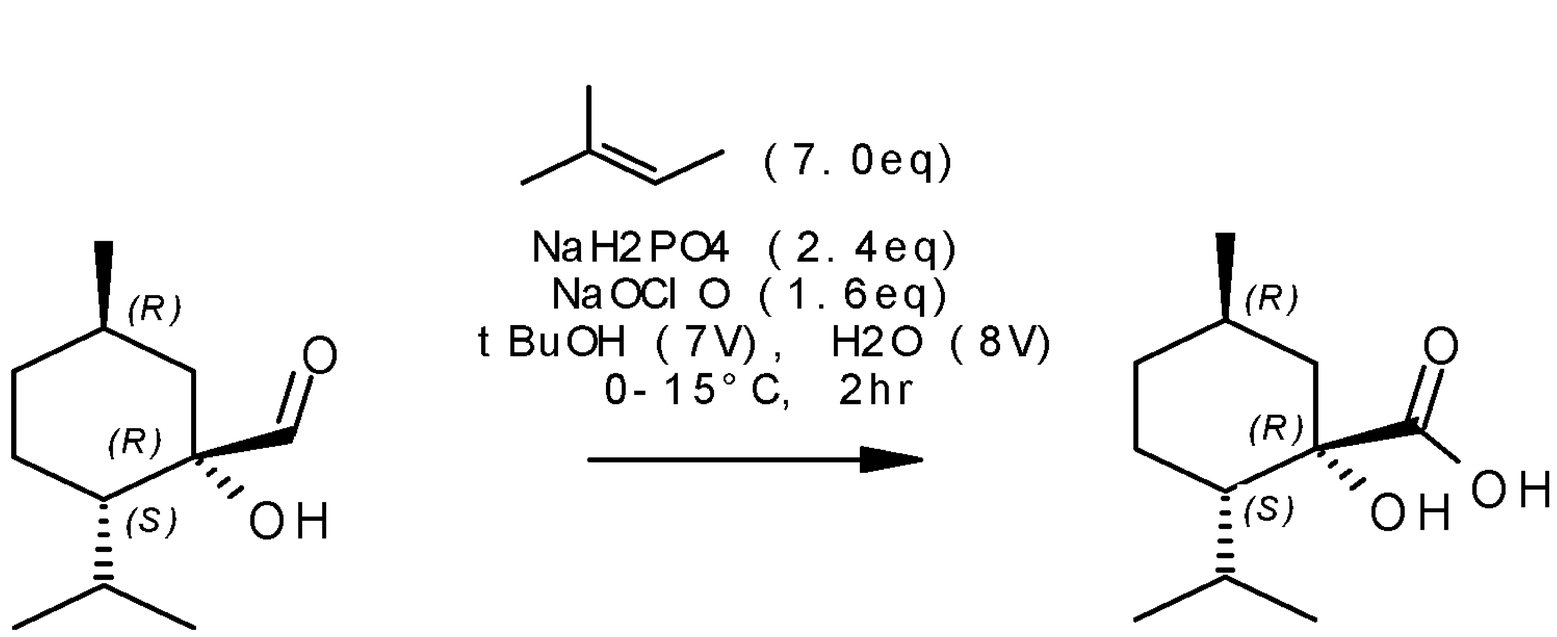


Two batches of same reactions were carried out in parallel.

To a solution of (1R,2S,5R)-2-isopropyl-5-methyl-1-vinylcyclohexan-1-ol (100 g) in DCM (0.55M) and pyridine (3.00 eq) cooled at -70°C was bubbled ozone until the reaction turned yellow (~ 5hrs). The flow of ozone was stopped, and the solution was degassed using N_2 for 0.5 hr. The two reactions were combined for work up. The combined reaction mixture was poured into water (2V). The aqueous phase was extracted with DCM (1V x 3). The combined organic phase was washed with saturated aqueous Na_2SO_3 (1V x 2) and the organic phase was checked by potassium iodide-starch test paper: the test paper did not change to blue. The combined organic phase was washed saturated citric acid solution (0.50V x 2). The combined organic phase was washed with brine (0.50 V), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum to (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbaldehyde (180 g) as colorless oil was used into the next step without further purification.

^{1}H NMR: 400 MHz DMSO-d_6 (δ ppm): 9.63 (s, 1H), 1.98-2.16 (m, 2H), 1.30-1.57 (m, 7H), 0.82-0.86 (m, 9H).

Intermediate 4: *(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid*



Two batches of the same reaction were carried out in parallel.

To a suspension of (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbaldehyde (90.0 g) in t-BuOH (0.8M) was added 2-methyl-2-butene (7.0 eq) and a solution of NaH_2PO_4 (2.40 eq) in H_2O (1.2V). The reaction was cooled to 0°C and NaOClO (1.60 eq) was added portion wise. The reaction was stirred for 2 hrs at 15°C. The two reactions were worked up separately. Each reaction mixture was poured into an 1M aqueous solution of NaOH (1V) and MTBE (0.5V) and the resulting mixture was stirred for 10 min. The organic layer was extracted with an 1M

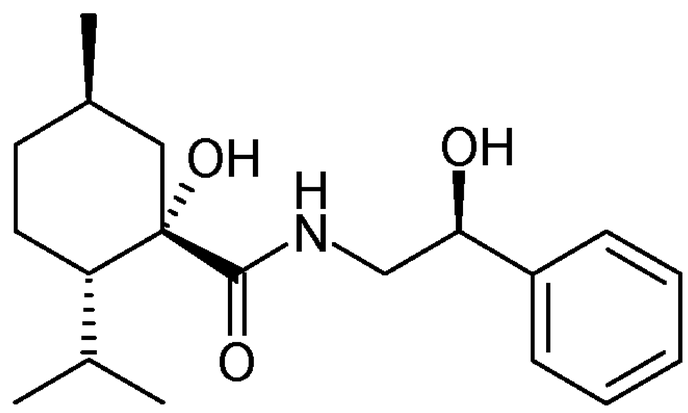
aqueous solution of NaOH (0.5V x 5). All aqueous phases were combined and MTBE (0.5V) was added. The pH value of the mixture was adjusted to ~2 with 12N HCl. The resulting solution was extracted with MTBE (0.5V x 3). The combined organic phase was washed with saturated aqueous Na_2SO_3 (0.5V) and checked by potassium iodide-starch test paper: the test paper did not change to blue. An aqueous solution of Na_2SO_3 was added and stirring until the test paper did not changed to blue. The organic layer was washed with brine (0.50V), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The other reaction was worked up as described above. The product from two reactions were combined for analysis to yield (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (55.0 g).

^{1}H NMR: 400 MHz DMSO-d_6 (δ ppm)12.5 (br.s, 1H), 4.38 (br.s, 1H), 1.67-1.70 (m, 2H), 1.25-1.58 (m, 6H), 0.80-0.90 (m, 10H). **LCMS** : RT = 2.344 min, M-17 = 183.1.

EXAMPLES

Example 1

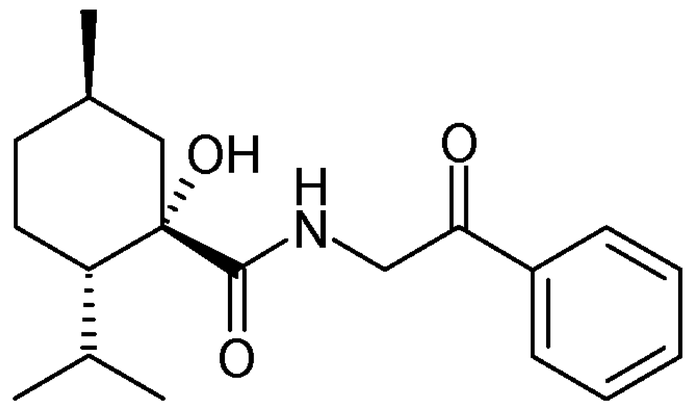
(1S,2S,5R)-1-hydroxy-N-((S)-2-hydroxy-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (2gr) and (S)-2-amino-1-phenylethanol (1.11eq) led to (1S,2S,5R)-1-hydroxy-N-((S)-2-hydroxy-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (1.62gr) as white powder after flash chromatography with a gradient between DCM & MeOH and reprecipitation.

Example 2

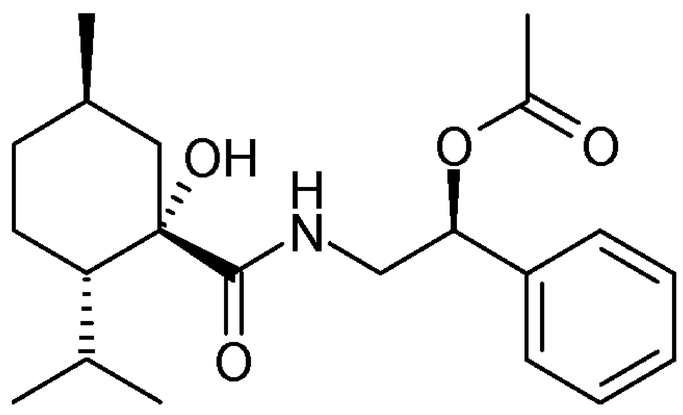
(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(2-oxo-2-phenylethyl)cyclohexane-1-carboxamide



Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (400mg) and 2-aminoacetophenone hydrochloride (1.05eq) led to (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(2-oxo-2-phenylethyl)cyclohexane-1-carboxamide (320mg) as white powder after flash chromatography with a gradient between DCM & MeOH and reprecipitation.

Example 3

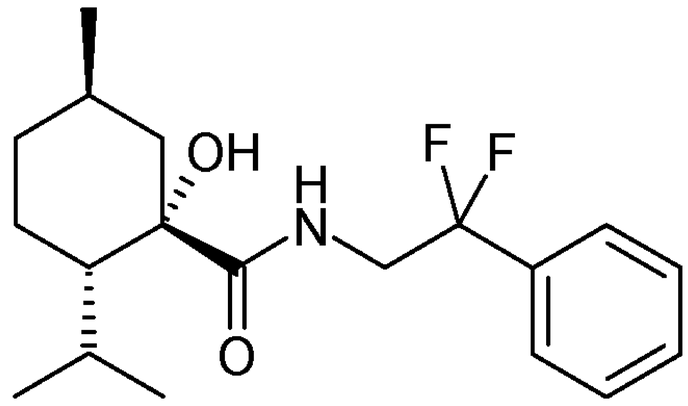
(S)-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethyl acetate



Acetylation conditions A with (1S,2S,5R)-1-hydroxy-N-((S)-2-hydroxy-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (115mg) led to (S)-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethyl acetate (91mg).

Example 4

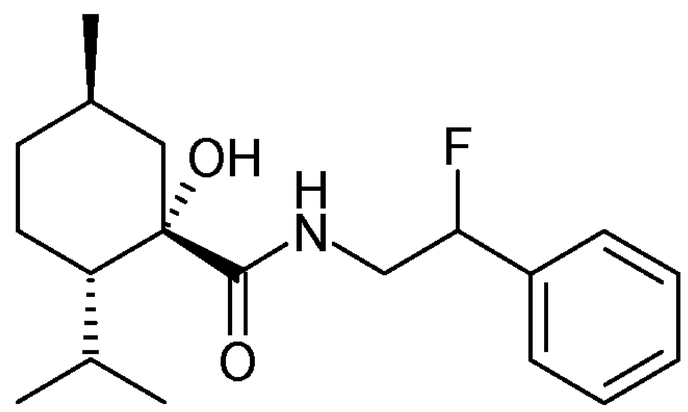
(1S,2S,5R)-N-(2,2-difluoro-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (200mg) and 2,2-difluoro-2-phenylethan-1-amine hydrochloride (1.06eq) led to (1S,2S,5R)-N-(2,2-difluoro-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (160mg) as white powder without flash chromatography and reprecipitation.

Example 5

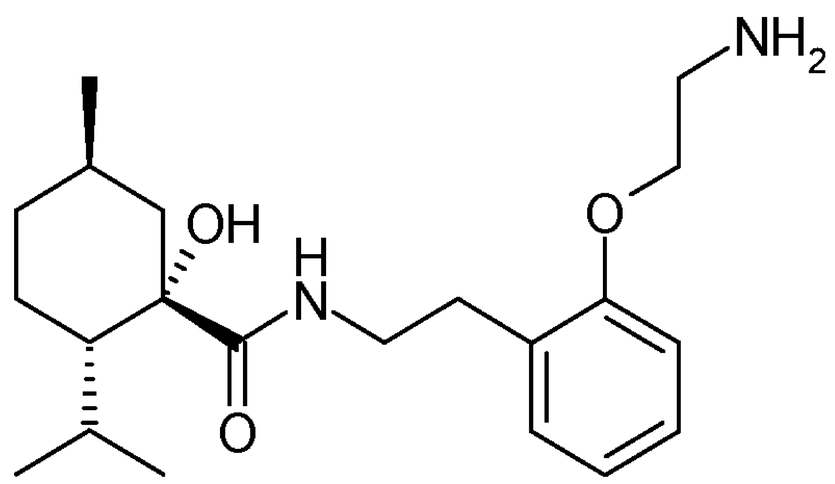
(1S,2S,5R)-N-(2-fluoro-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (200mg) and 2-fluoro-2-phenylethan-1-amine (1.1eq) [after amine addition, the reaction was heated at 55°C during 16hrs] led to (1S,2S,5R)-N-(2-fluoro-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (175mg) as white powder after flash chromatography with cyclohexane/EtOAc and without reprecipitation.

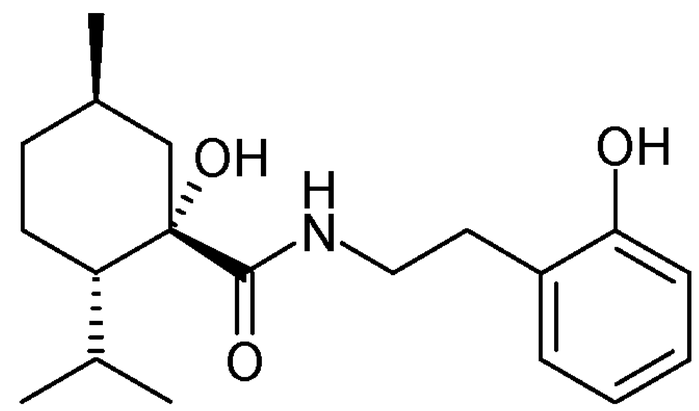
Example 6

(1S,2S,5R)-N-(2-(2-aminoethoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (750mg) and 2-(2-aminoethyl)phenol (1.05eq) [after amine addition, the reaction was heated at 50°C during 16hrs] led to (1S,2S,5R)-1-hydroxy-N-(2-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (702mg) as yellow powder after flash chromatography with cyclohexane/EtOAc and without reprecipitation.

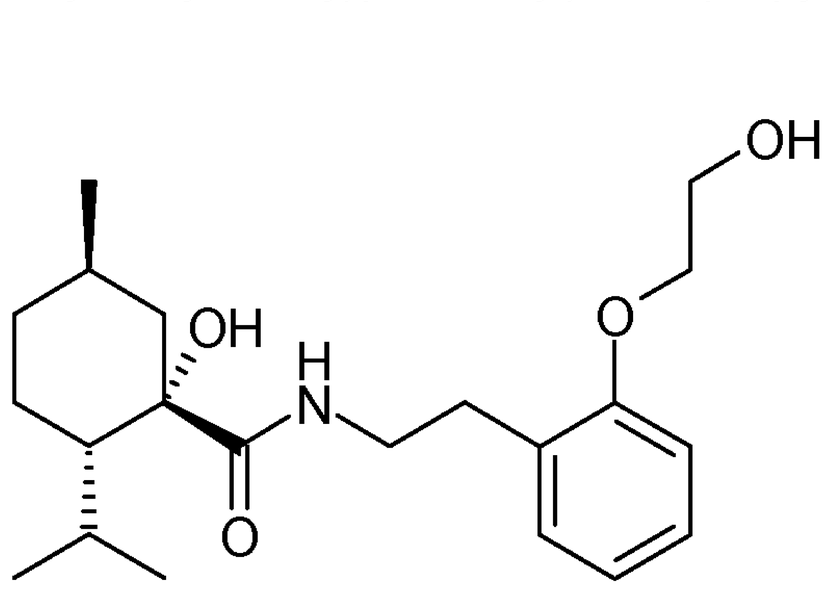
(1S,2S,5R)-1-hydroxy-N-(2-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under alkylation conditions A, (1S,2S,5R)-1-hydroxy-N-(2-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (150mg) in the presence of tert-butyl N-(2-bromoethyl)carbamate (1.24eq) and followed by treatment with TFA (180µL) in DCM (6ml) over 14hrs led to (1S,2S,5R)-N-(2-(2-aminoethoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (40mg) as a yellow wax.

Example 7

(1S,2S,5R)-1-hydroxy-N-(2-(2-hydroxyethoxy)phenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide



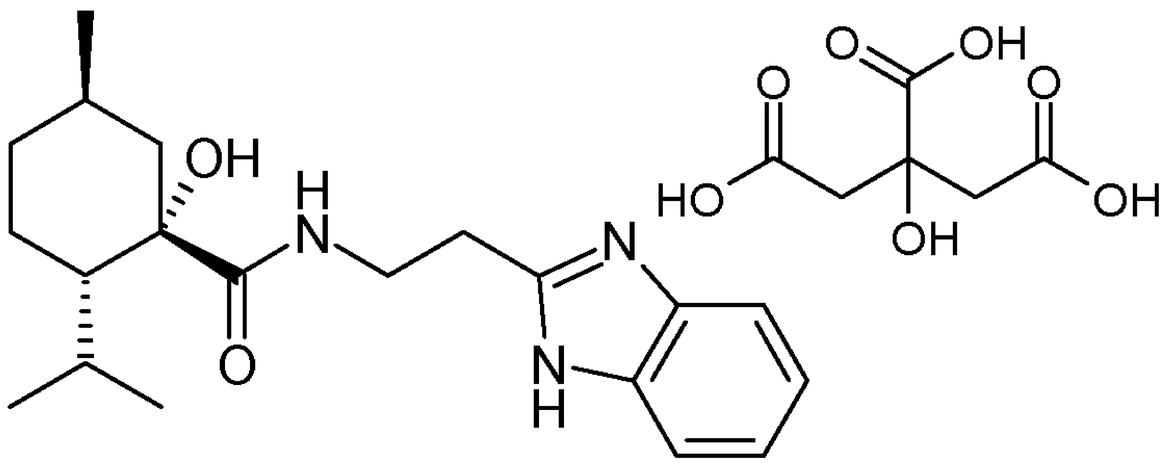
Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (750mg) and (S)-2-amino-1-phenylethanol (1.05eq) [after amine addition, the reaction was heated at 50°C during 16hrs] led to (1S,2S,5R)-1-hydroxy-N-(2-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (702mg) as yellow powder after flash chromatography with a gradient between cyclohexane and EtOAc and without reprecipitation.

Under alkylation conditions A, (1S,2S,5R)-1-hydroxy-N-(2-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (150mg) in the presence of 2-(2-bromoethoxy)tetrahydro-2H-pyran (1.62eq) and followed by treatment with HCl (4N in dioxane, 5eq) in dioxane (2V) over

14hrs led to (1S,2S,5R)-1-hydroxy-N-(2-(2-hydroxyethoxy)phenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (40mg) as a yellow wax.

Example 8

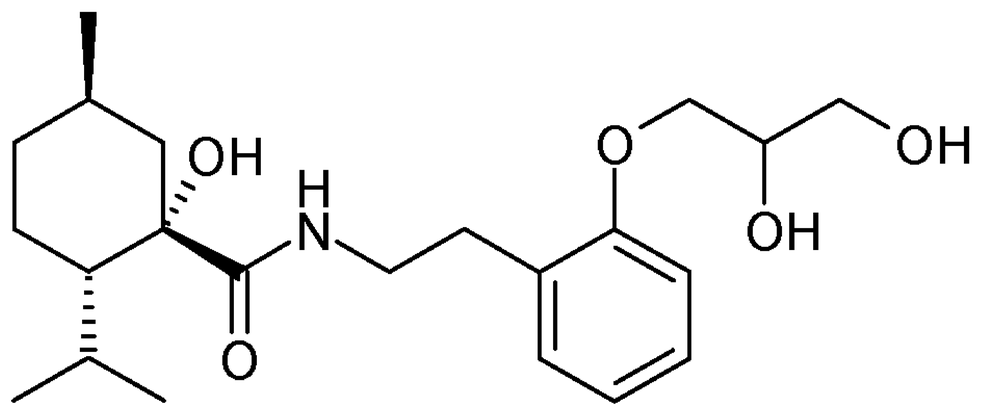
(1S,2S,5R)-N-(2-(1H-benzo[d]imidazol-2-yl)ethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide 2-hydroxypropane-1,2,3-tricarboxylate



Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (500mg) and 2-(1H-benzo[D]imidazol-2-yl)ethanamine (1.12eq) [after amine addition, the reaction was heated at 85°C during 16hrs] led to (1S,2S,5R)-N-(2-(1H-benzo[d]imidazol-2-yl)ethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide 2-hydroxypropane-1,2,3-tricarboxylate (210mg) as white powder and as a citric acid salt due to a wash with a 10% aqueous solution of citric acid after usual sodium hydroxide wash. No flash chromatography & reprecipitation were needed.

Example 9

(1S,2S,5R)-N-(2-(2,3-dihydroxypropoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide

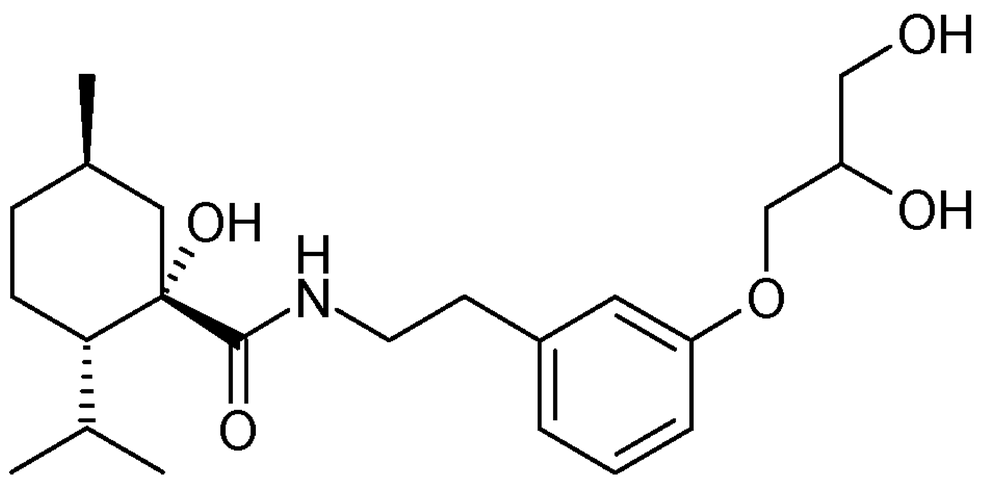


Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (750mg) and (S)-2-amino-1-phenylethanol (1.05eq) [after amine addition, the reaction was heated at 75°C during 16hrs] led to (1S,2S,5R)-1-hydroxy-N-(2-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (770mg) as yellow powder after flash chromatography with a gradient between cyclohexane and EtOAc and without reprecipitation.

Under alkylation conditions B, (1S,2S,5R)-1-hydroxy-N-(2-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (100mg) in the presence of glycidol (0.95eq) led to (1S,2S,5R)-N-(2-(2,3-dihydroxypropoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (36mg) as yellow wax after flash chromatography with DCM & MeOH.

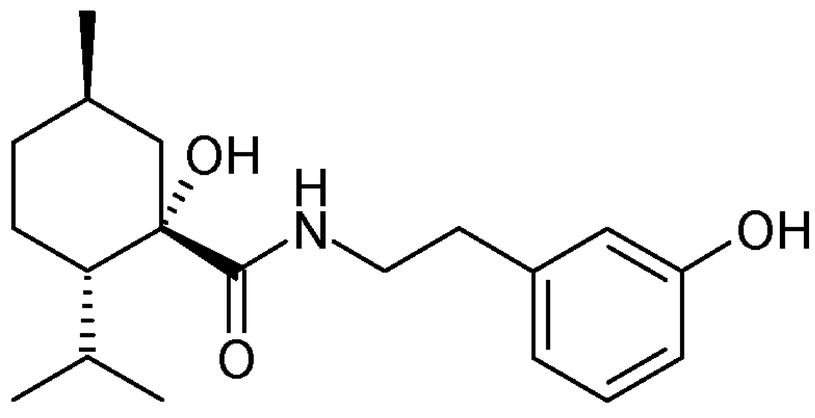
Example 10

(1S,2S,5R)-N-(3-(2,3-dihydroxypropoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (750mg) and 3-hydroxyphenethylamine hydrochloride (0.67eq) [after amine addition, the reaction was heated at 55°C during 16hrs] led to (1S,2S,5R)-3-hydroxy-N-(3-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (450mg) as yellow powder after flash chromatography with between cyclohexane and EtOAc and without reprecipitation.

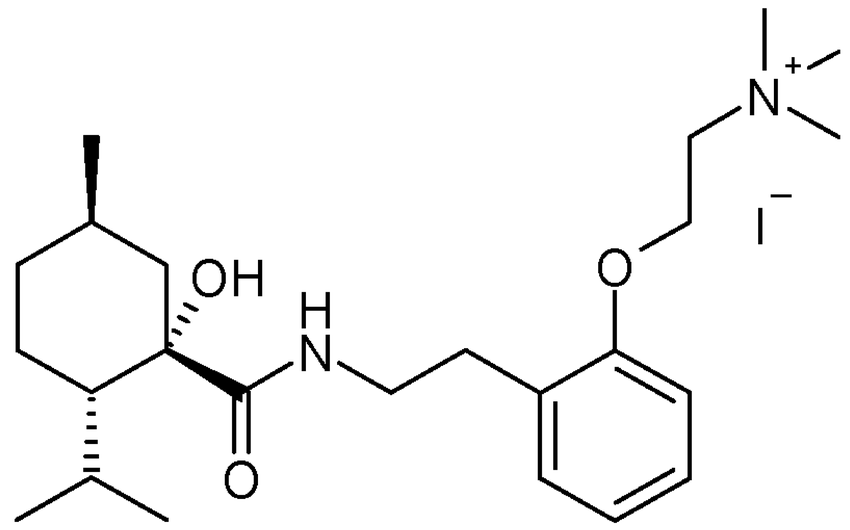
(1S,2S,5R)-3-hydroxy-N-(3-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under alkylation conditions B, (1S,2S,5R)-1-hydroxy-N-(3-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (100mg) in the presence of glycidol (1.82eq) led to (1S,2S,5R)-N-(3-(2,3-dihydroxypropoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (48mg) as white solid after flash chromatography with DCM & MeOH.

Example 11

2-(2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenoxy)-N,N,N-trimethylethan-1-aminium iodide



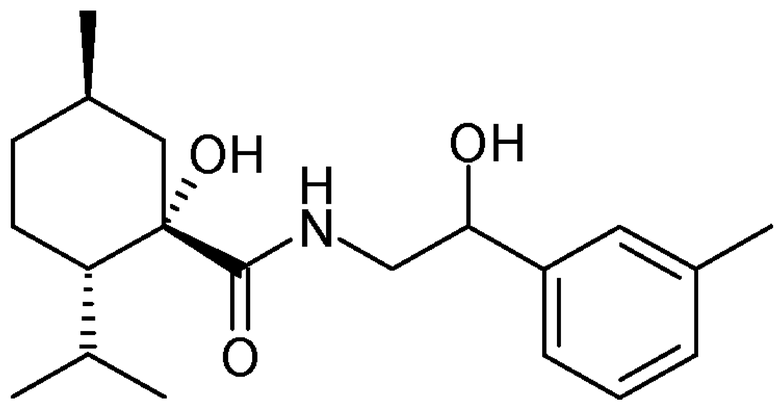
Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (750mg) and (S)-2-amino-1-phenylethanol (1.05eq) [after amine addition, the reaction was heated at 50°C during 16hrs] led to (1S,2S,5R)-1-hydroxy-N-(2-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (702mg) as yellow powder after flash chromatography with a gradient between cyclohexane and EtOAc and without reprecipitation.

Under alkylation conditions A, (1S,2S,5R)-1-hydroxy-N-(2-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (100mg) in the presence of 2-bromoethyldimethylamine (1.5eq) led to (1S,2S,5R)-N-(2-(2-(dimethylamino)ethoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (31mg) as yellow wax.

(1S,2S,5R)-N-(2-(2-(Dimethylamino)ethoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (30 mg) was dissolved in THF (0.04M) and iodomethane (4.16eq) was added. The reaction mixture was stirred at room temperature over 72hrs. After concentration under vacuum, the residue was dissolved in EtOAc (5V) and water (5V) was then added. The organic phase was dried over Na_2SO_4, filtrated and concentrated under vacuum to yield an orange wax which was dissolved with MeOH and concentrated under vacuum to provide 2-(2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenoxy)-N,N,N-trimethylethan-1-aminium iodide (34mg) as an orange powder.

Example 12

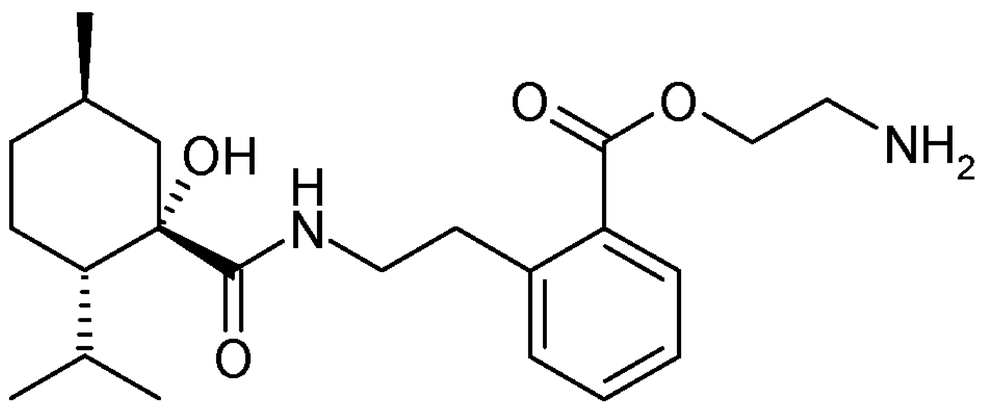
(1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-(m-tolyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (100mg) and 2-amino-1-(3-methylphenyl)ethan-1-ol (1.07eq) [after amine addition, the reaction was heated at 50°C during 22hrs] led to (1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-(m-tolyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (99mg) as white powder without flash chromatography and reprecipitation.

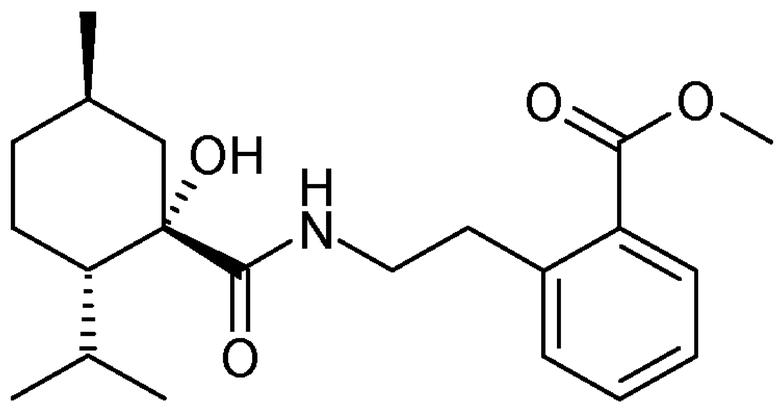
Example 13

2-aminoethyl 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzoate hydrochloride



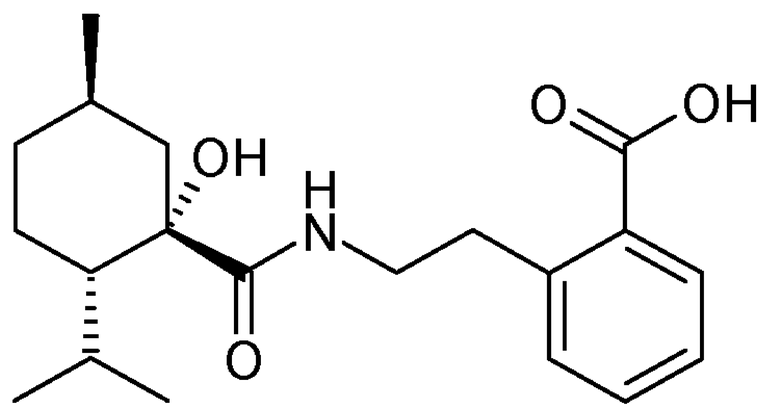
Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (654mg) and methyl 2-(2-aminoethyl)benzoate hydrochloride (1.0eq) [after amine addition, the reaction was heated at 50°C during 22hrs] led to methyl 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (699mg) as white powder after flash chromatography with cyclohexane and EtOAc.

methyl 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzoate



Under saponification conditions, methyl 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (250mg) in the presence of NaOH (1.0eq) led to 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoic acid (247mg).

2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoic acid

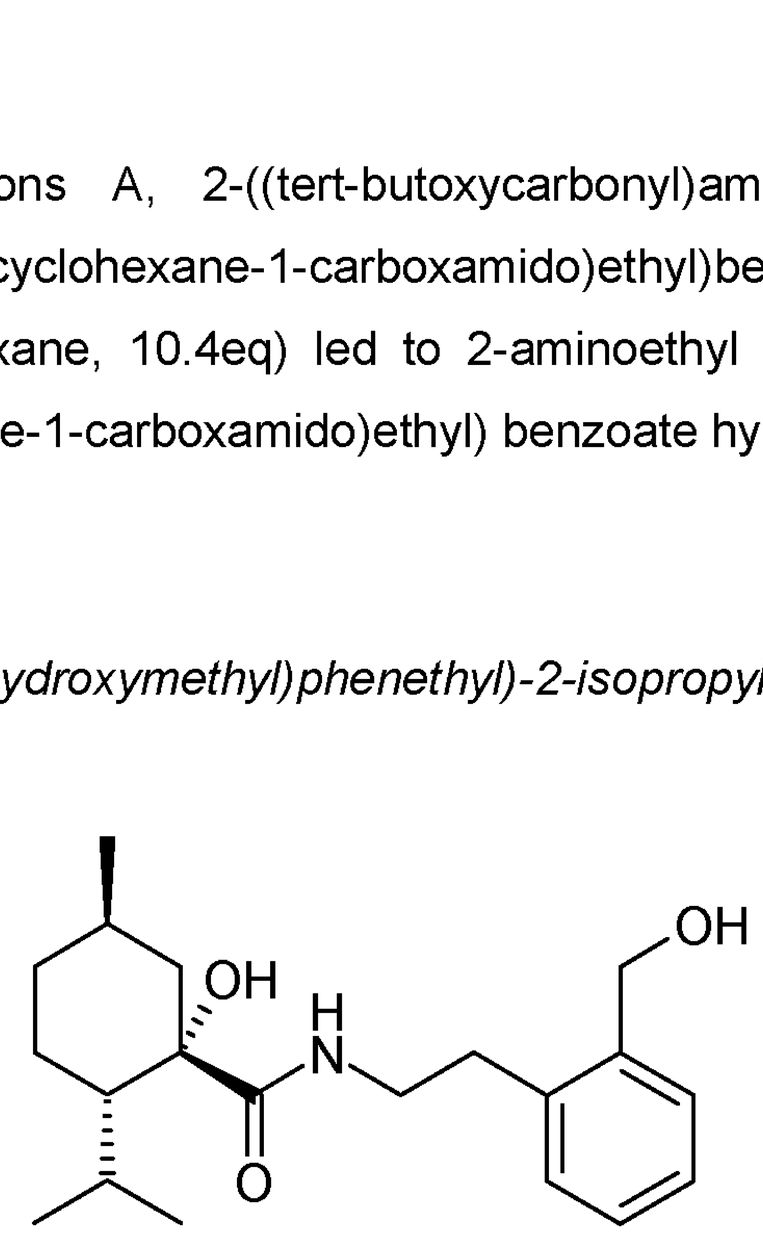


Under coupling conditions C, with 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoic acid (247 mg) and tert-butyl N-(2-hydroxyethyl)carbamate (1.29eq) led to 2-((tert-butoxycarbonyl)amino)ethyl 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (118mg) after flash chromatography with cyclohexane/EtOAc.

Under deprotection conditions A, 2-((tert-butoxycarbonyl)amino)ethyl 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (113 mg) in the presence of HCl (4N in dioxane, 10.4eq) led to 2-aminoethyl 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzoate hydrochloride (96mg).

Example 14

(1S,2S,5R)-1-hydroxy-N-(2-(hydroxymethyl)phenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide

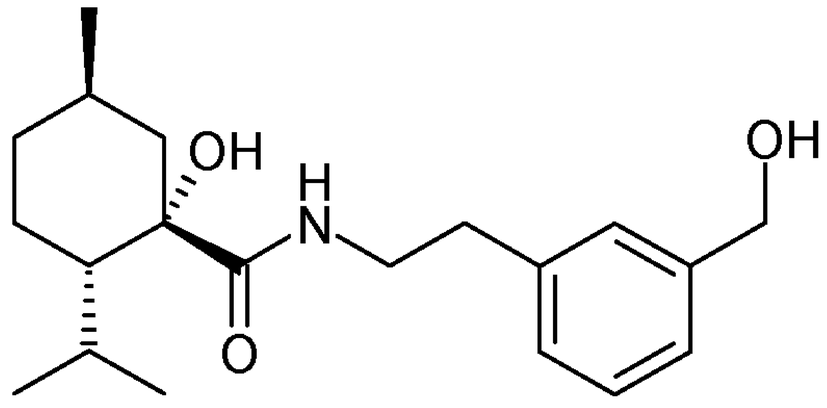


Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (654mg) and methyl 2-(2-aminoethyl)benzoate hydrochloride (1.0eq) [after amine addition, the reaction was heated at 50°C during 22hrs] led to methyl 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (699mg) as white powder after flash chromatography with cyclohexane and EtOAc.

Under reduction condition A, methyl 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (345mg) in the presence of NaBH4 (39.5eq) led to (1S,2S,5R)-1-hydroxy-N-(2-(hydroxymethyl)phenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (170mg) after preparative HPLC using Xselect CSH Prep C18 5µm OBD 50x250mm column with water+0.1%formic acid and acetonitrile (with this last eluent from 30% to 100%).

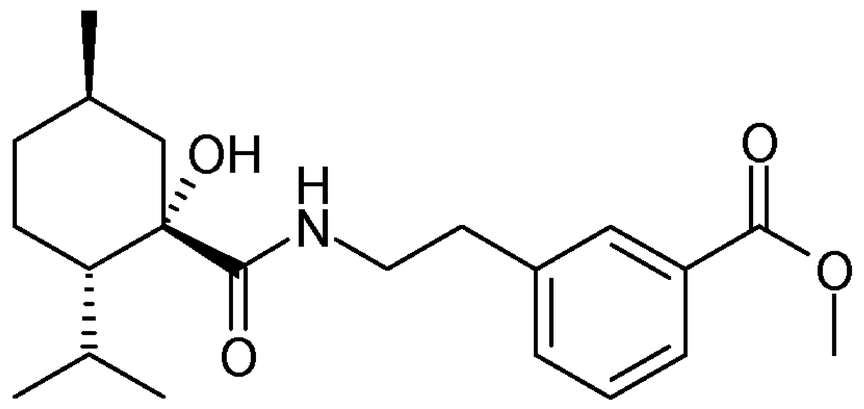
Example 15

(1S,2S,5R)-1-hydroxy-N-(3-(hydroxymethyl)phenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (808mg) and methyl 2-(2-aminoethyl)benzoate hydrochloride (1.05eq) [after amine addition, the reaction was heated at 50°C during 1hr20] led to methyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (916mg) as white powder after flash chromatography with cyclohexane and EtOAc.

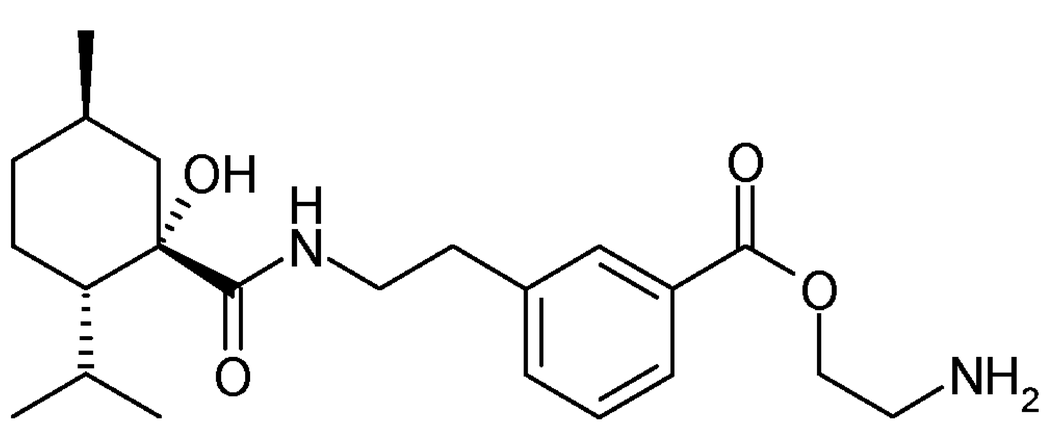
methyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzoate



Under reduction condition A, methyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (645mg) in the presence of NaBH4 (38.8eq) led to (1S,2S,5R)-1-hydroxy-N-(3-(hydroxymethyl)phenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (175mg) after preparative HPLC using Xselect CSH Prep C18 5µm OBD 50x250mm column with water+0.1%formic acid and acetonitrile (with this last eluent from 29% to 100%).

Example 16

2-aminoethyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzoate hydrochloride



Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (808mg) and methyl 2-(2-aminoethyl)benzoate hydrochloride (1.05eq) [after amine addition, the reaction was heated at 50°C during 1hr20] led to methyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (916mg) as white powder after flash chromatography with cyclohexane and EtOAc.

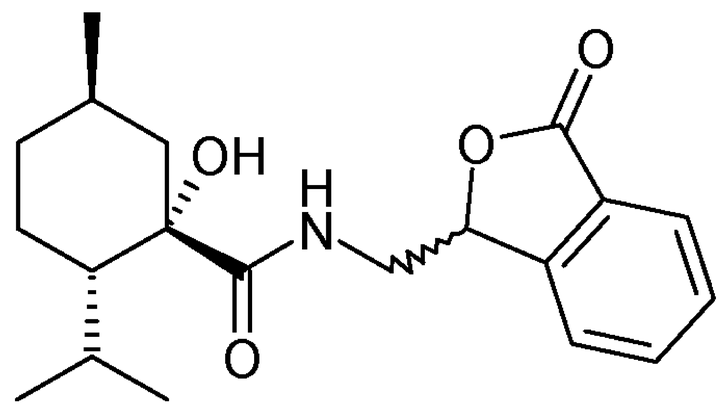
Under saponification conditions, methyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (259.2mg) in the presence of sodium hydroxide (4N in dioxane, 1.0eq) led to 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoic acid (260mg).

Under coupling conditions C, with 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoic acid (260mg) and tert-butyl N-(2-hydroxyethyl)carbamate (1.3eq) led to 2-((tert-butoxycarbonyl)amino)ethyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (221mg) as white powder after flash chromatography with cyclohexane/EtOAc.

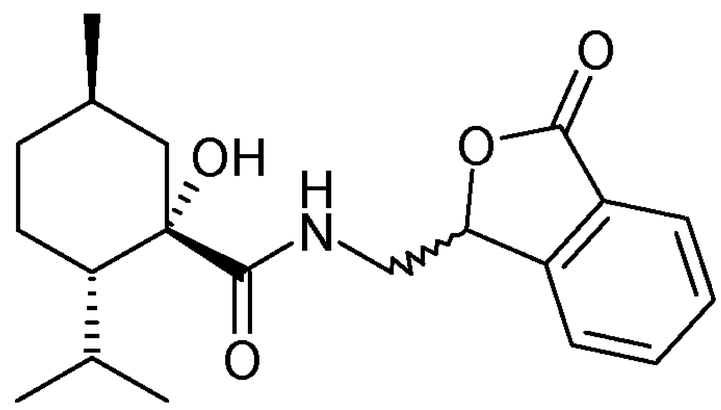
Under deprotection conditions A, 2-((tert-butoxycarbonyl)amino)ethyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (220 mg) in the presence of HCl (4N in dioxane, 15.2eq) led to 2-aminoethyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzoate hydrochloride (105mg) after preparative HPLC using Xselect CSH Prep C18 5µm OBD 50x250mm column with water+0.1%formic acid and acetonitrile (with this last eluent from 9% to 100%).

Examples 17 & 18

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(((1RS)-3-oxo-1,3-dihydroisobenzofuran-1-yl)methyl) cyclohexane-1-carboxamide (**17**)



(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(((1RS)-3-oxo-1,3-dihydroisobenzofuran-1-yl)methyl) cyclohexane-1-carboxamide (**18**)

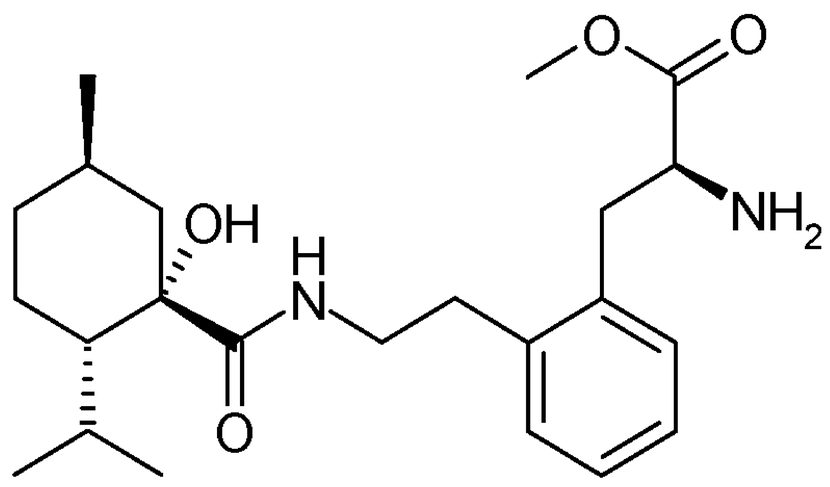


Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (75mg) and 3-(aminomethyl)isobenzofuran-1(3H)-one hydrochloride (1.11eq) [after amine addition, the reaction was heated at 55°C during 1hr20] led to (1S,2S,5R)-1-hydroxy-

2-isopropyl-5-methyl-N-(((1RS)-3-oxo-1,3-dihydroisobenzofuran-1-yl)methyl) cyclohexane-1-carboxamide (***example 17***, 22mg) as white powder after flash chromatography with cyclohexane and EtOAc. After flash chromatography, a mixture of both diastereomers was also isolated and purification of this mixture by preparative HPLC using Xselect CSH C18 OBD 5µm 250x50 mm column with water+0.1%formic acid and acetonitrile (with this last eluent from 29% to 100%) led to (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(((1RS)-3-oxo-1,3-dihydroisobenzofuran-1-yl)methyl) cyclohexane-1-carboxamide (***example 18***, 11mg).

Example 19

methyl (S)-2-amino-3-(2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido) ethyl)phenyl)propanoate



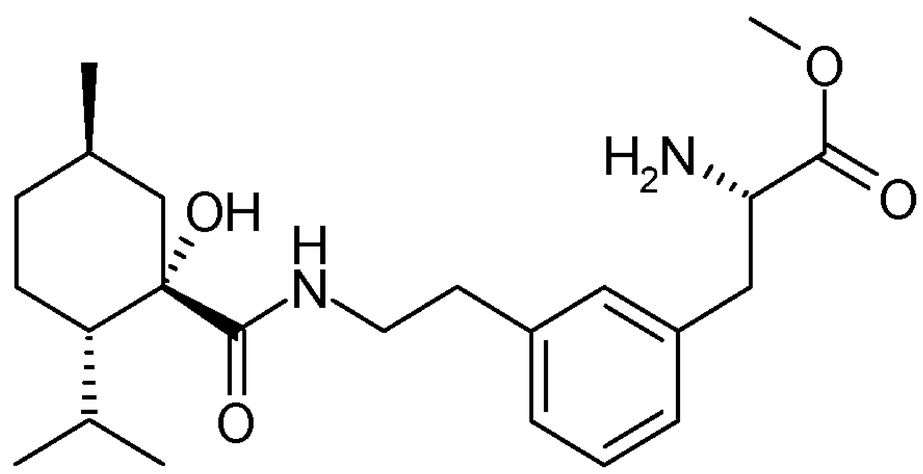
Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (1.55g) and methyl 2-bromophenethylamine (1.06eq) [here no pyridine was added and after amine addition, the reaction was heated at 55°C during 16hr] led to (1S,2S,5R)-N-(2-bromophenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (1.05g) as white powder after flash chromatography with cyclohexane and EtOAc.

Zinc (3.19eq) was added to dried DMF (0.67M). Iodine (0.12eq) was then added followed by addition of BOC-BETA-IODO-ALA-OME (230mg). Iodine (0.12eq) was again added and after stirring at room temperature during 5 minutes, tris(dibenzylideneacetone)dipalladium(0) (16mg) and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (0.03eq) were added to the reaction mixture followed by (1S,2S,5R)-N-(2-bromophenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (1.36eq). The resulting was heated at 50°C during 4hrs and then at room temperature over 16hrs. Water (2V) was added as well as EtOAc (2V). The organic phase was dried over Na_2SO_4, filtrated and concentrated under vacuum to yield the N-Boc amine as orange residue.

This residue was dissolved in DCM (5V) and TFA (350µl) was added to this solution. The resulting reaction mixture was stirred at room temperature over 5hrs. DCM (5V) and a saturated solution of sodium bicarbonate (5V). The resulting biphasic solution was filtrated over a hydrophobic Radely cartridge. The organic phase was concentrated under vacuum to provide an orange residue. This residue was purified by preparative HPLC using Xselect CSH C18 OBD 5µm 250x50 mm column with water+0.1%formic acid and acetonitrile (with this last eluent from 29% to 100%) to provide methyl (S)-2-amino-3-(2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenyl)propanoate (42mg).

Example 20

methyl (S)-2-amino-3-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenyl)propanoate



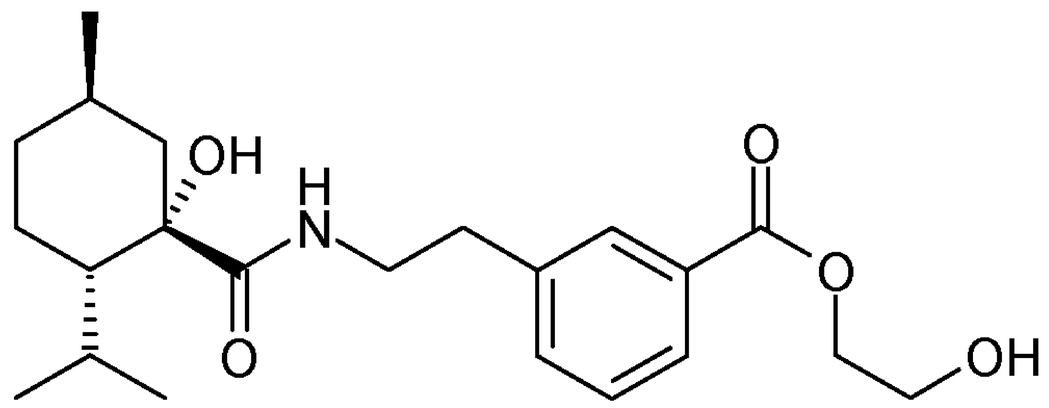
Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (1.55g) and methyl 3-bromophenethylamine (1.06eq) [here no pyridine was added and after amine addition, the reaction was heated at 55°C during 16hr] led to (1S,2S,5R)-N-(3-bromophenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (1.77g) as white powder after flash chromatography with cyclohexane and EtOAc.

Zinc (3.19eq) was added to dried DMF (0.67M) and iodine (0.12eq) was added followed by addition of BOC-BETA-IODO-ALA-OME (230mg). Iodine (0.12eq) was again added and after stirring at room temperature during 5 minutes, tris(dibenzylideneacetone)dipalladium(0) (0.03eq) and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (0.05eq) were added to the reaction mixture followed by (1S,2S,5R)-N-(3-bromophenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (350mg). The resulting was heated at 50°C during 4hrs and then at room temperature over 16hrs. Water (2V) was added as well as EtOAc (2V). The organic phase was dried over Na2SO4, filtrated and concentrated under vacuum to yield the N-Boc amine as orange residue.

This residue was dissolved in DCM (5V) and TFA (350µl) was added to this solution. The resulting reaction mixture was stirred at room temperature over 5hrs. DCM (5V) and a saturated solution of sodium bicarbonate (5V). The resulting biphasic solution was filtrated over a hydrophobic Radely cartridge. The organic phase was concentrated under vacuum to provide an orange residue. This residue was purified by preparative HPLC using Xselect CSH C18 OBD 5µm 250x50 mm column with water+0.1%formic acid and acetonitrile (with this last eluent from 29% to 100%) to give methyl (S)-2-amino-3-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenyl)propanoate (98mg) as a white solid.

Example 21

2-hydroxyethyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzoate



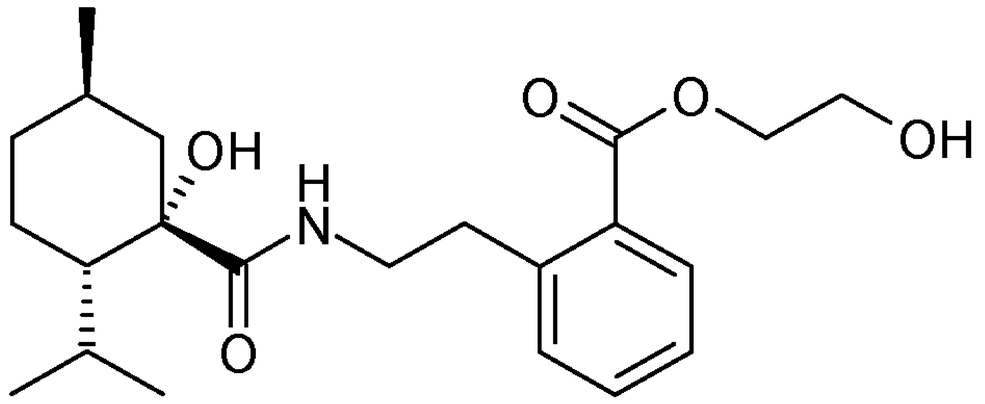
Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (1.5g) and methyl 3-(2-aminoethyl)benzoate hydrochloride (1.0eq) [after amine addition, the reaction was heated at 55°C during 16hr] led to methyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (1.86g) as beige powder after reprecipitation in DCM/n-pentane.

Under saponification conditions, methyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (1.0g) in the presence of sodium hydroxide (1N in water, 3.6eq) led to 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoic acid (920mg).

Under alkylation conditions D, 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoic acid (150 mg), in the presence of 2-bromoethanol (1.11eq) led to 2-hydroxyethyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzoate (31mg) as yellow wax after flash chromatography with DCM/MeOH.

Example 22

2-hydroxyethyl 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzoate



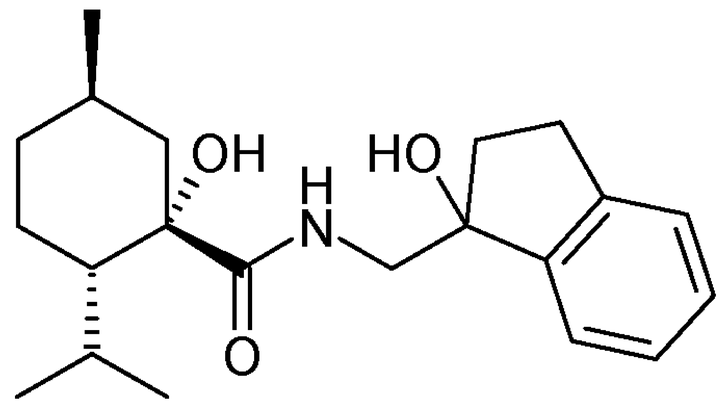
Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (1.5g) and methyl 2-(2-aminoethyl)benzoate hydrochloride (1.06eq) [after amine addition, the reaction was heated at 55°C during 16hr] led to methyl 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (1.49g) as colorless wax after flash chromatography with cyclohexane/EtOAc.

Under saponification conditions, methyl 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (1.05g) in the presence of sodium hydroxide (1N in water, 3.4eq) led to 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoic acid (785mg).

Under alkylation conditions D, 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoic acid (150 mg), in the presence of 2-bromoethanol (1.1eq) led to 2-hydroxyethyl 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzoate (101mg) as yellow wax after flash chromatography with DCM/MeOH.

Example 23

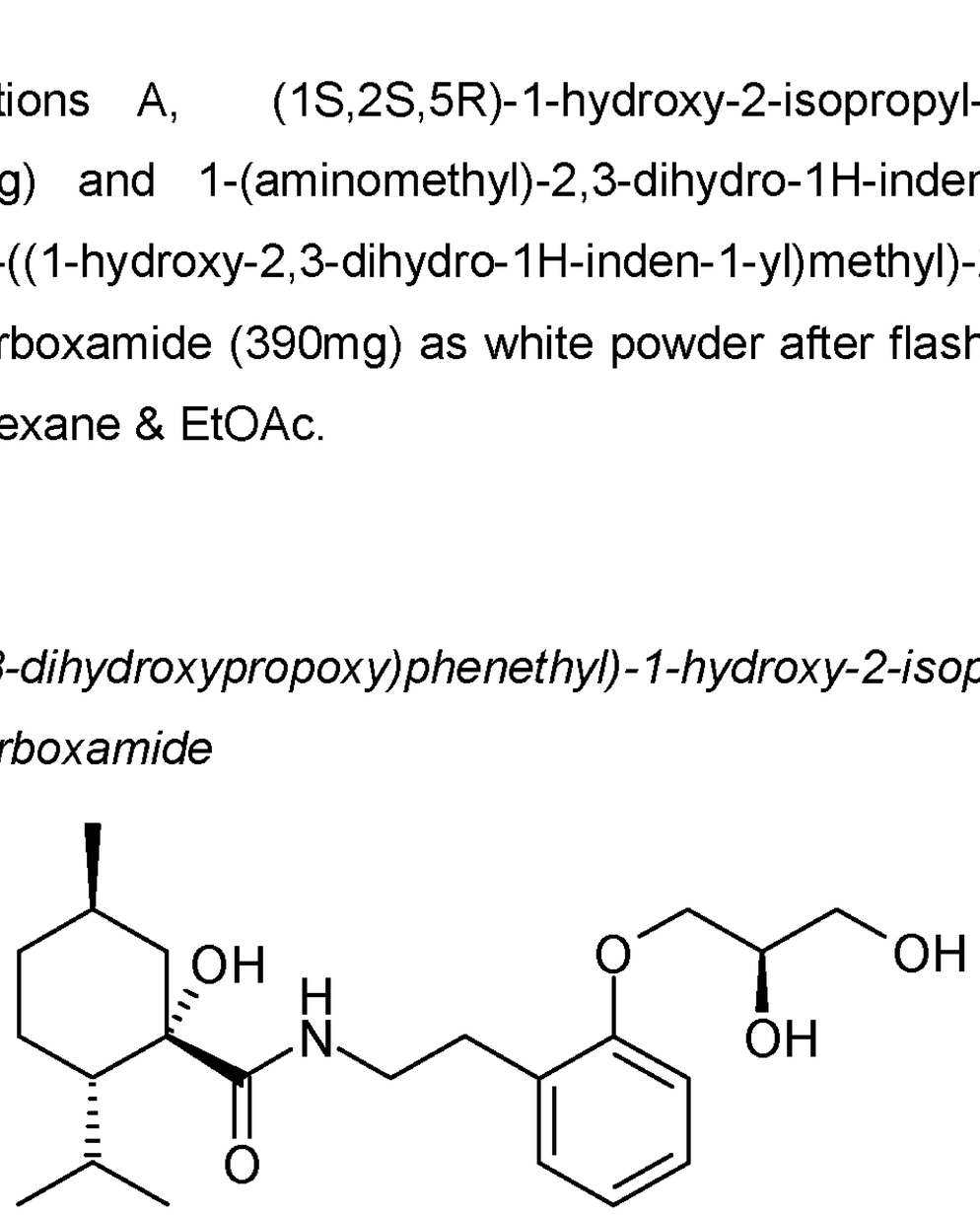
(1S,2S,5R)-1-hydroxy-N-((1-hydroxy-2,3-dihydro-1H-inden-1-yl)methyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (500mg) and 1-(aminomethyl)-2,3-dihydro-1H-inden-1-ol (1.05eq) led to (1S,2S,5R)-1-hydroxy-N-((1-hydroxy-2,3-dihydro-1H-inden-1-yl)methyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (390mg) as white powder after flash chromatography with a gradient between cyclohexane & EtOAc.

Example 24

(1S,2S,5R)-N-(2-((R)-2,3-dihydroxypropoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide

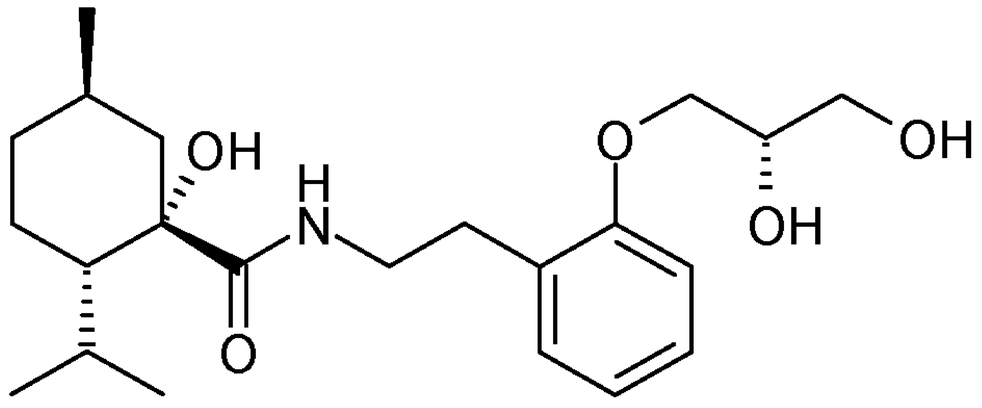


Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (3gr) and 2-(2-aminoethyl)phenol (1.06eq) [the reaction mixture was heated at 80°C during 16hr] led to (1S,2S,5R)-1-hydroxy-N-(2-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (3.01g) as orange powder after flash chromatography with cyclohexane & EtOAc.

Under alkylation conditions B, (1S,2S,5R)-1-hydroxy-N-(2-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (600mg) in the presence of (*R*)-glycidol (0.98eq) [the reaction mixture was heated at 80°C during 40hr] led to (1S,2S,5R)-N-(2-((R)-2,3-dihydroxypropoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (492mg) as white powder after flash chromatography with DCM & MeOH.

Example 25

(1S,2S,5R)-N-(2-((S)-2,3-dihydroxypropoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide

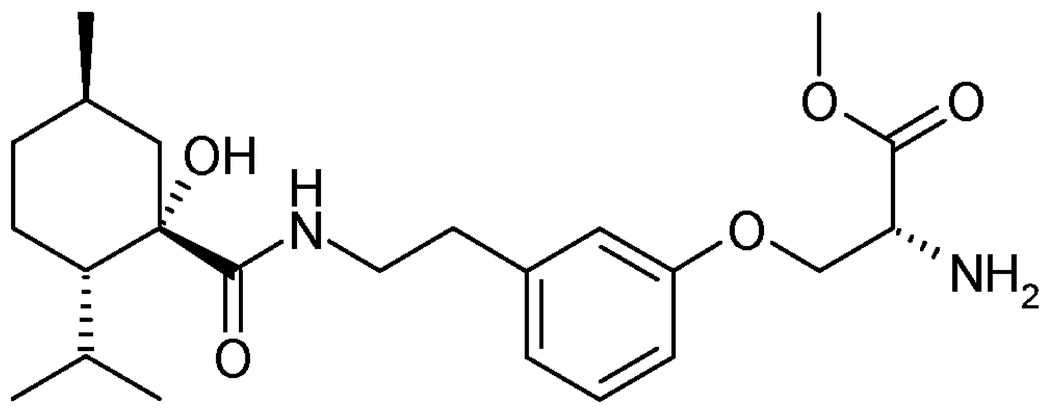


Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (3gr) and 2-(2-aminoethyl)phenol (1.06eq) [the reaction mixture was heated at 80°C during 16hr] led to (1S,2S,5R)-1-hydroxy-N-(2-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (3.01g) as orange powder after flash chromatography with cyclohexane & EtOAc.

Under alkylation conditions B, (1S,2S,5R)-1-hydroxy-N-(2-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (600mg) in the presence of (*S*)-glycidol (1.0eq) [the reaction mixture was heated at 80°C during 40hr] led to (1S,2S,5R)-N-(2-((S)-2,3-dihydroxypropoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (563mg) as white powder after flash chromatography with DCM & MeOH.

Example 26

methyl O-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenyl)-D-serinate



Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (1.55gr) and 3-bromophenethylamine (1.06eq) led to (1S,2S,5R)-N-(3-

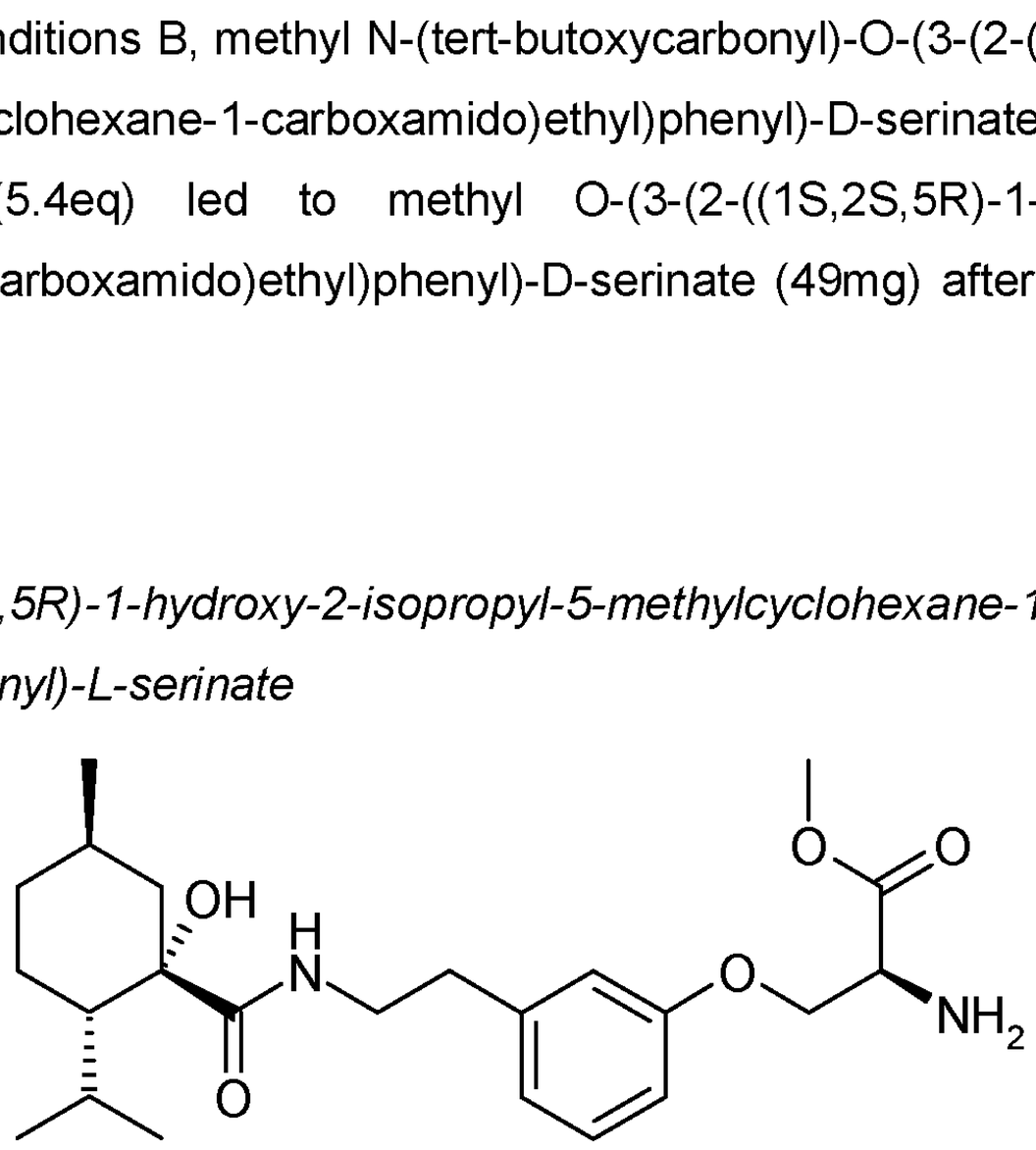
bromophenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (1.77gr) as white powder after flash chromatography with cyclohexane & EtOAc.

In photochemistry vial, (1S,2S,5R)-N-(3-bromophenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (380mg) was dissolved in dried acetonitrile (0.5M) and quinuclidine (0.11eq) was added as well as potassium carbonate (0.99eq) and (IR[DF(CF3)PPY]2(DTBPY))PF6 complex (0.01eq). A solution of nickel(II) chloride ethylene glycol dimethyl ether complex (0.05eq) and 4,4'-di-tert-butyl-2,2'-bipyridine (0.05eq) in acetonitrile (1V) was added dropwise. Under argon atmosphere, a solution of BOC-D-SER-OME (1.47eq) in acetonitrile (0.5V) was added to the reaction mixture. The resulting was stirred under irradiation over 12hr. After concentration under vacuum, the residue was dissolved in EtOAc (10V) and water (10V) was added. The aqueous phase was washed with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, filtrated and concentrated under vacuum. The residue was purified by flash chromatography first with cyclohexane and EtOAc, and secondly with DCM and methanol to yield methyl N-(tert-butoxycarbonyl)-O-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenyl)-D-serinate (93mg).

Under deprotection conditions B, methyl N-(tert-butoxycarbonyl)-O-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenyl)-D-serinate (90mg) in the presence of TFA (5.4eq) led to methyl O-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenyl)-D-serinate (49mg) after flash chromatography with DCM/MeOH.

Example 27

methyl O-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenyl)-L-serinate



Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (3gr) and 3-bromophenethylamine (1.1eq) led to (1S,2S,5R)-N-(3-

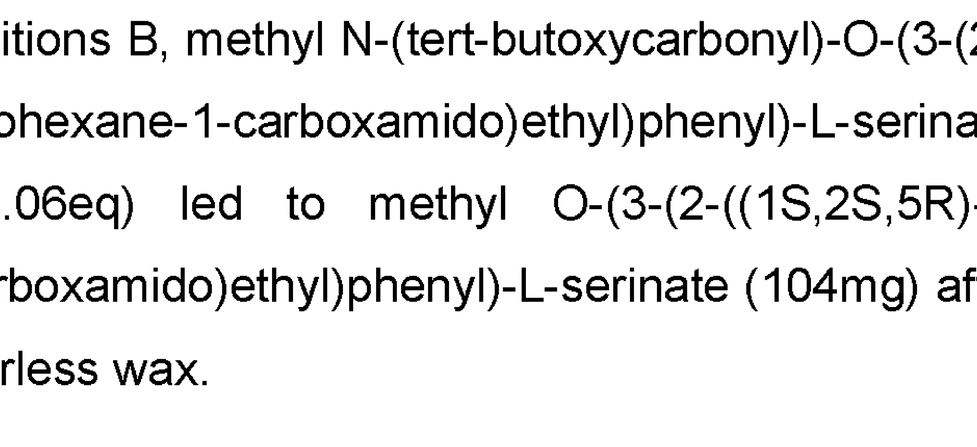
bromophenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (3.75gr) as white powder after flash chromatography with cyclohexane & EtOAc.

In photochemistry vial, (1S,2S,5R)-N-(3-bromophenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (380mg) was dissolved in dried acetonitrile (0.5M) and quinuclidine (0.11eq) was added as well as potassium carbonate (0.99eq) and (IR[DF(CF3)PPY]2(DTBPY))PF6 complex (0.01eq). A solution of nickel(II) chloride ethylene glycol dimethyl ether complex (0.05eq) and 4,4'-di-tert-butyl-2,2'-bipyridine (0.05eq) in acetonitrile (1V) was added dropwise. Under argon atmosphere, a solution of BOC-L-SER-OME (1.5eq) in acetonitrile (0.5V) was added to the reaction mixture. The resulting was stirred under irradiation over 12hr. After concentration under vacuum, the residue was dissolved in EtOAc (10V) and water (10V) was added. The aqueous phase was washed with EtOAc. The combined organic phase was washed with brine, dried over Na_2SO_4, filtrated and concentrated under vacuum. The residue was purified by flash chromatography first with cyclohexane and EtOAc, and secondly with DCM and methanol to yield methyl N-(tert-butoxycarbonyl)-O-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenyl)-L-serinate (176mg) as white powder.

Under deprotection conditions B, methyl N-(tert-butoxycarbonyl)-O-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenyl)-L-serinate (173mg) in the presence of TFA (20.06eq) led to methyl O-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenyl)-L-serinate (104mg) after flash chromatography with DCM/MeOH as colorless wax.

Example 28

ethyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate



Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (1.5g) and methyl 3-(2-aminoethyl)benzoate hydrochloride (1.0eq) [after amine

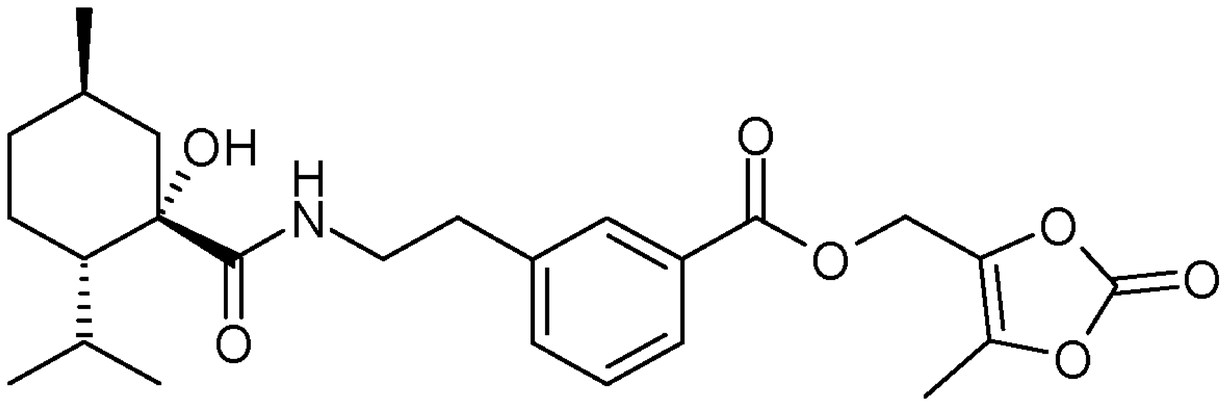
addition, the reaction was heated at 55°C during 16hr] led to methyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (1.86g) as beige powder after reprecipitation in DCM/n-pentane.

Under saponification conditions, methyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (1.0g) in the presence of sodium hydroxide (1N in water, 3.6eq) led to 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoic acid (920mg).

Under coupling conditions E, with 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoic acid (150mg) and ethanol (2.70eq) led to ethyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzoate (69mg) after flash chromatography with cyclohexane/EtOAc.

Example 29

(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate



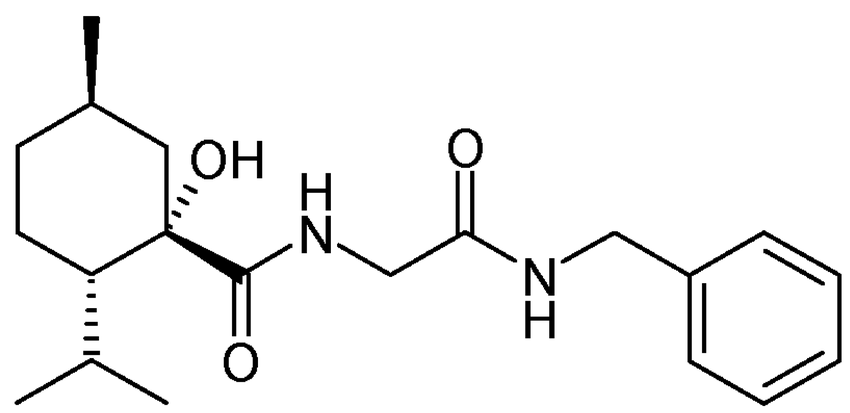
Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (1.5g) and methyl 3-(2-aminoethyl)benzoate hydrochloride (1.0eq) [after amine addition, the reaction was heated at 55°C during 16hr] led to methyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (1.86g) as beige powder after reprecipitation in DCM/n-pentane.

Under saponification conditions, methyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (1.0g) in the presence of sodium hydroxide (1N in water, 3.6eq) led to 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoic acid (920mg).

Under alkylation conditions F, 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoic acid (150 mg) in the presence of 4-chloromethyl-5-methyl-1,3-dioxol-2-one (1.19eq) led to (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (140mg).

Example 30

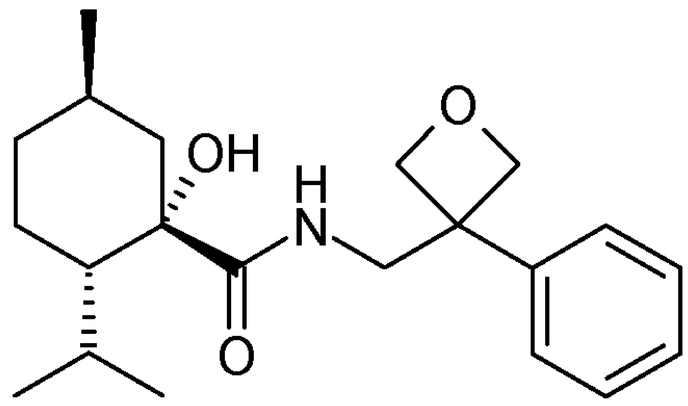
(1S,2S,5R)-N-(2-(benzylamino)-2-oxoethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (80mg) and 2-amino-N-benzylacetamide (1.05eq) [after amine addition, the reaction was heated at 75°C during 16hr] led to (1S,2S,5R)-N-(2-(benzylamino)-2-oxoethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (65mg) as white powder.

Example 31

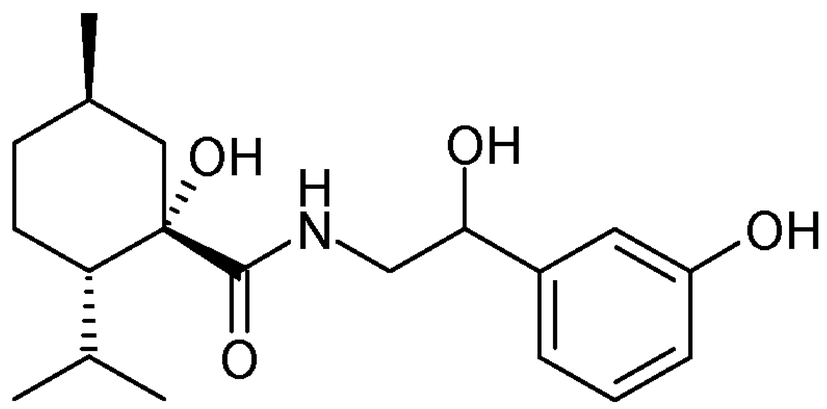
(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-((3-phenyloxetan-3-yl)methyl)cyclohexane-1-carboxamide



Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (100mg) and (3-phenyloxetan-3-yl)methanamine (1.3eq) [after amine addition, the reaction was heated at 70°C during 3hr] led to (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-((3-phenyloxetan-3-yl)methyl)cyclohexane-1-carboxamide (86mg) as white powder.

Example 32

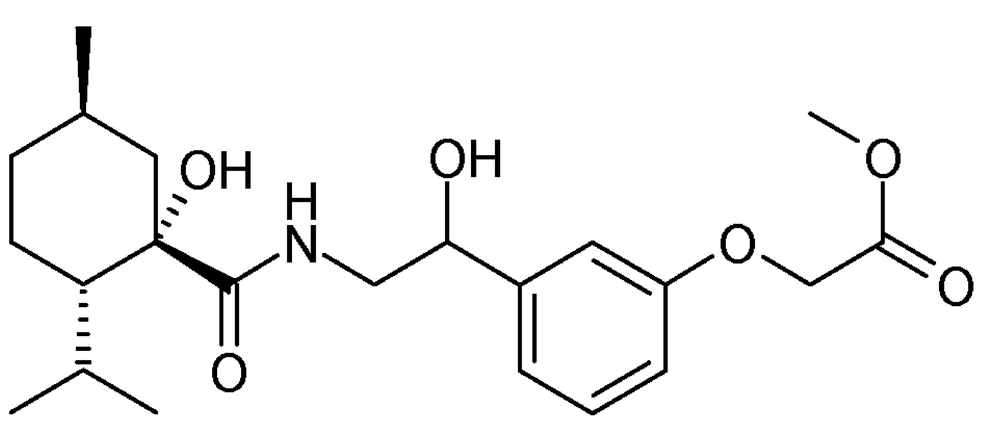
(1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-(3-hydroxyphenyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (507mg) and norfenefrine (1.05eq) [after amine addition, the reaction was heated at 70°C during 3hr] led to (1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-(3-hydroxyphenyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (455mg) as white solid.

Example 33

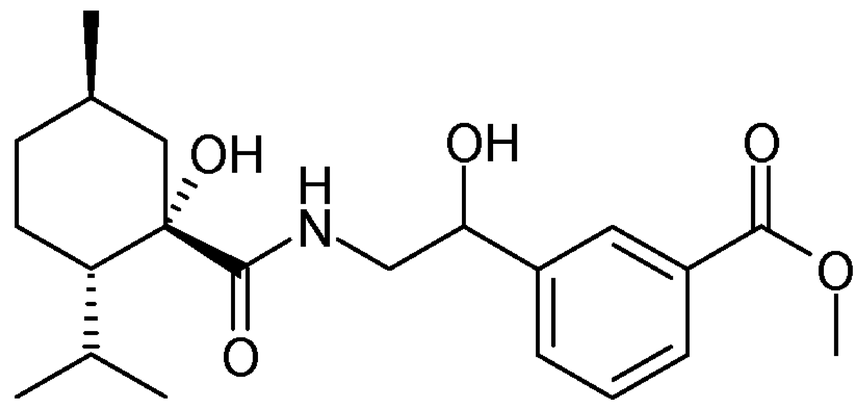
methyl 2-(3-(1-hydroxy-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenoxy)acetate



Under alkylation conditions C, (1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-(3-hydroxyphenyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (302mg) in the presence of methyl bromoacetate (1.1eq) led to methyl 2-(3-(1-hydroxy-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenoxy)acetate (256mg) as a colorless wax.

Example 34

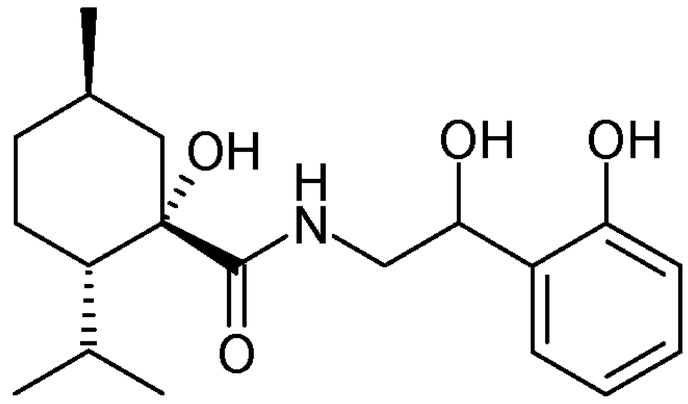
methyl 3-(1-hydroxy-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate



Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (400mg) and methyl 3-(2-amino-1-hydroxyethyl)benzoate (1.05eq) [after amine addition, the reaction was heated at 75°C during 3hr] led to methyl 3-(1-hydroxy-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (205mg) as white solid after preparative HPLC using CSH 250X50 MM - 5 µM column with water and acetonitrile containing 0.1% formic acid.

Example 35

(1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-(2-hydroxyphenyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide

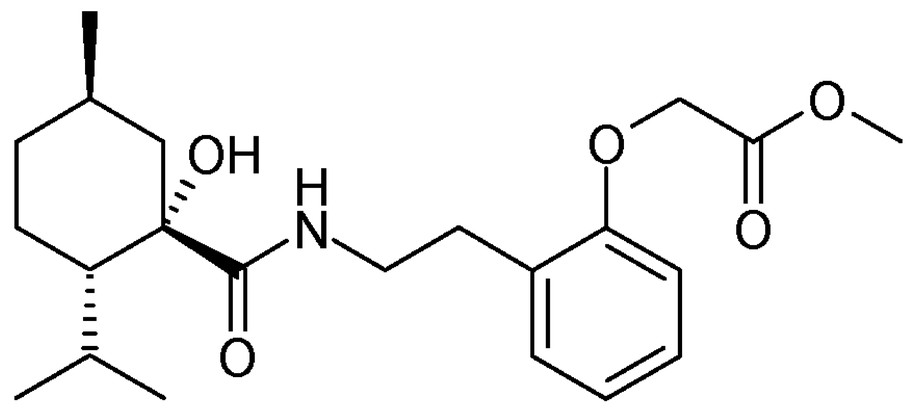


Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (300mg) and 2-amino-1-(2-hydroxyphenyl)ethan-1-one hydrobromide (1.05eq) [after amine addition, the reaction was heated at 50°C during 2hr] led to (1S,2S,5R)-1-hydroxy-N-(2-(2-hydroxyphenyl)-2-oxoethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (376mg) as orange solid after flash chromatography with cyclohexane and EtOAc.

Under reduction conditions C, (1S,2S,5R)-1-hydroxy-N-(2-(2-hydroxyphenyl)-2-oxoethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (374mg) in the presence of NaBH4 (1.05eq) led to (1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-(2-hydroxyphenyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (46mg) after flash chromatography with cyclohexane & EtOAc followed by trituration DCM/pentane.

Example 36

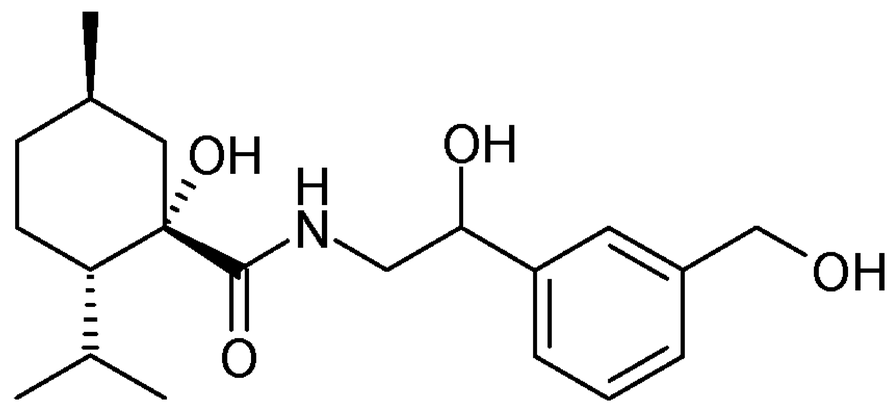
methyl 2-(2-(1-hydroxy-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenoxy)acetate



Under alkylation conditions C, (1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-(2-hydroxyphenyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (135mg) in the presence of methyl bromoacetate (1.1eq) led to methyl 2-(2-(1-hydroxy-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenoxy)acetate (116mg) as a white wax after flash chromatography with cyclohexane and EtOAc.

Example 37

(1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-(3-(hydroxymethyl)phenyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide



Methyl 3-formylbenzoate (1.64g) was dissolved in THF (1.0M) and the resulting solution was cooled down to 0°C. Nitromethane (10.0eq) was added followed by slow addition of DBU (0.1eq). The reaction mixture was stirred at room temperature during 2hr30. Diethyl ether (1.5V) was added and the resulting solution was washed with a 0.1N aqueous solution of hydrochloric acid (1.5V), brine (1.5V) dried over Na_2SO_4, filtrated and concentrated under vacuum. The residue was purified by flash chromatography with cyclohexane and EtOAc to provide methyl 3-(1-hydroxy-2-nitroethyl)benzoate (2.11g) as orange oil.

Methyl 3-(1-hydroxy-2-nitroethyl)benzoate (2.11g) was dissolved in ethanol (0.31M) and PtO_2 (0.05eq) was added. The reaction mixture was put under hydrogen atmosphere (H_2 1 bar) and

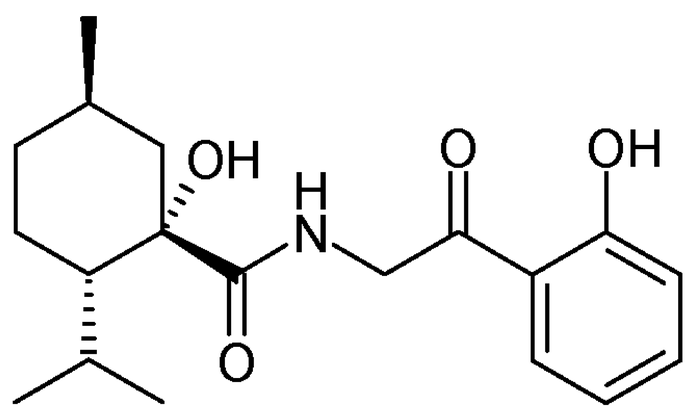
stirred at room temperature under H_2 during 4hr. The reaction mixture was filtrated on GF/F Whatman filter paper and the column was washed with ethanol (2V). The combined solutions were concentrated under vacuum to give methyl 3-(2-amino-1-hydroxyethyl)benzoate (1.46g) as yellow oil.

Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (400mg) and methyl 3-(2-amino-1-hydroxyethyl)benzoate (1.05eq) [after amine addition, the reaction was heated at 50°C during 2hr] led to methyl 3-(1-hydroxy-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (316mg) as orange solid after flash chromatography with cyclohexane and EtOAc.

Under reduction conditions A, methyl 3-(1-hydroxy-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (316mg) in the presence of $NaBH_4$ (5.0eq) led to (1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-(3-(hydroxymethyl)phenyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (155mg) as colorless oil after flash chromatography with cyclohexane & EtOAc.

Example 38

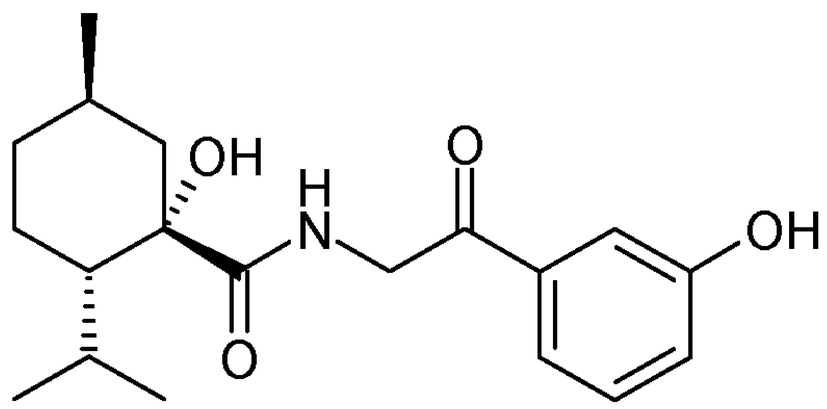
(1S,2S,5R)-1-hydroxy-N-(2-(2-hydroxyphenyl)-2-oxoethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (400mg) and 2-amino-1-(2-hydroxyphenyl)ethan-1-one hydrobromide (1.05eq) [after CDI addition, pyridine (1.1eq) was added and after amine addition, the reaction was heated at 50°C during 2hr] led to (1S,2S,5R)-1-hydroxy-N-(2-(2-hydroxyphenyl)-2-oxoethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (417mg) as yellow solid after flash chromatography with cyclohexane and EtOAc and trituration with n-pentane.

Example 39

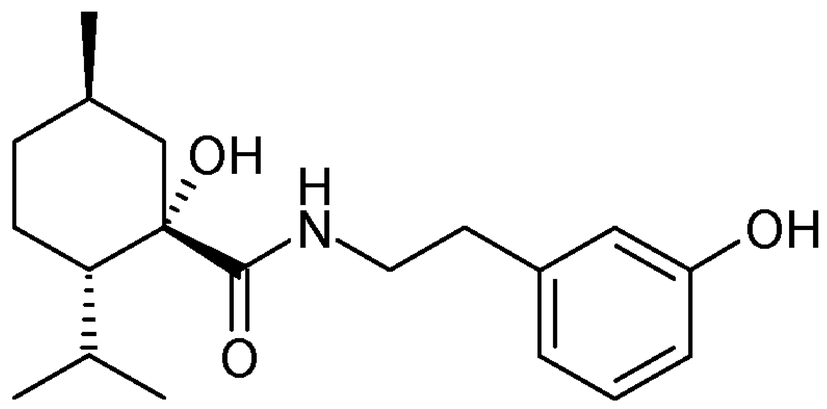
(1S,2S,5R)-1-hydroxy-N-(2-(3-hydroxyphenyl)-2-oxoethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (300mg) and 2-amino-1-(3-hydroxyphenyl)ethan-1-one hydrochloride (1.05eq) [after CDI addition, pyridine (1.1eq) was added and after amine addition, the reaction was heated at 50°C during 2hr] led to (1S,2S,5R)-1-hydroxy-N-(2-(3-hydroxyphenyl)-2-oxoethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (62mg) as white solid after flash chromatography with cyclohexane and EtOAc followed by preparative HPLC using CSH 250X50 MM - 5 µM column with water and acetonitrile containing 0.1% formic acid.

Example 40

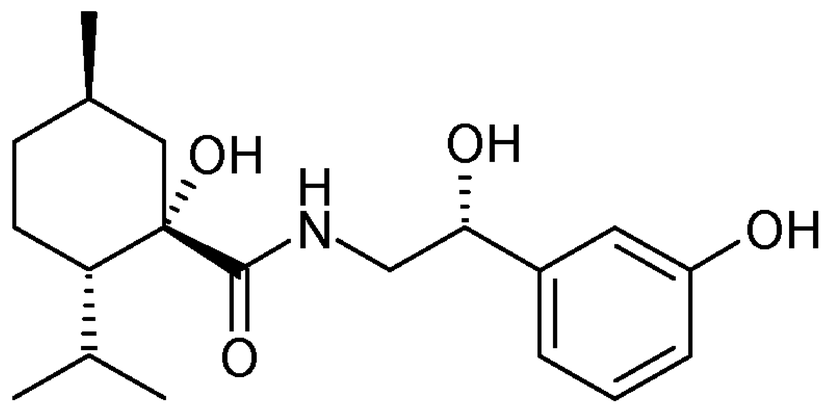
(1S,2S,5R)-1-hydroxy-N-(3-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide



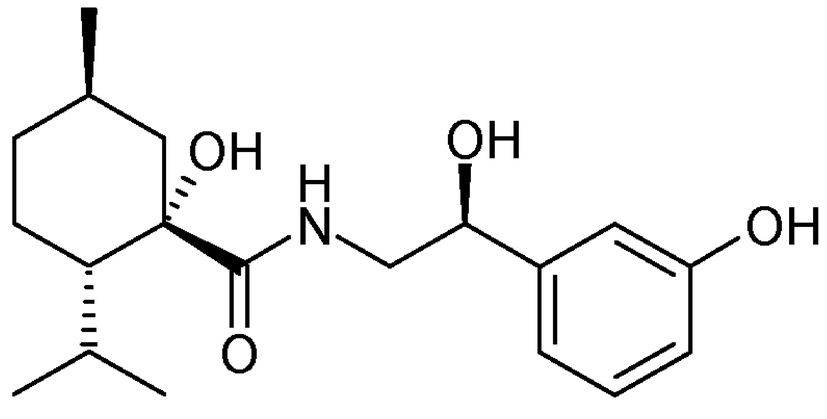
Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (1.5g) and 3-(2-aminoethyl)phenol hydrobromide (1.05eq) [after amine addition, the reaction was heated at 50°C during 4hr and at room temperature during 16hr] led to (1S,2S,5R)-1-hydroxy-N-(3-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (1.4g, 93% purity) as yellow solid after flash chromatography with cyclohexane and EtOAc. A small portion of this amide (260mg) is further purified by preparative HPLC using CSH 250X50 MM - 5 µM column with water and acetonitrile containing 0.1% formic acid to give (1S,2S,5R)-1-hydroxy-N-(3-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (180mg) as white solid.

Examples 41 & 42

(1S,2S,5R)-1-hydroxy-N-((2R)-hydroxy-2-(3-hydroxyphenyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide **(41)**



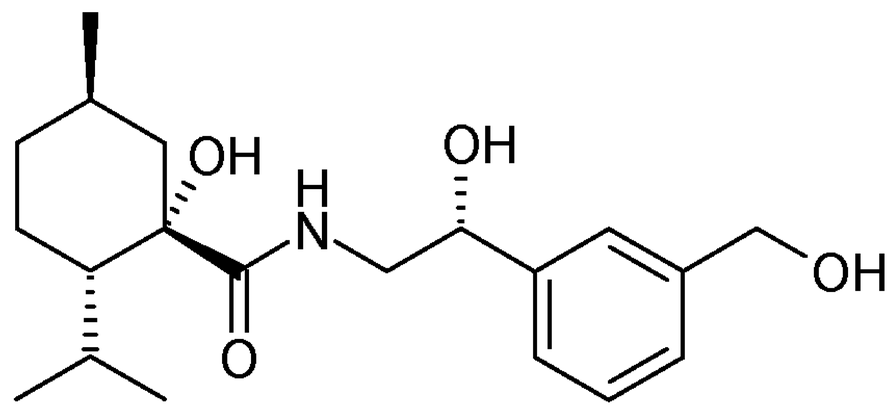
(1S,2S,5R)-1-hydroxy-N-((2S)-hydroxy-2-(3-hydroxyphenyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide **(42)**



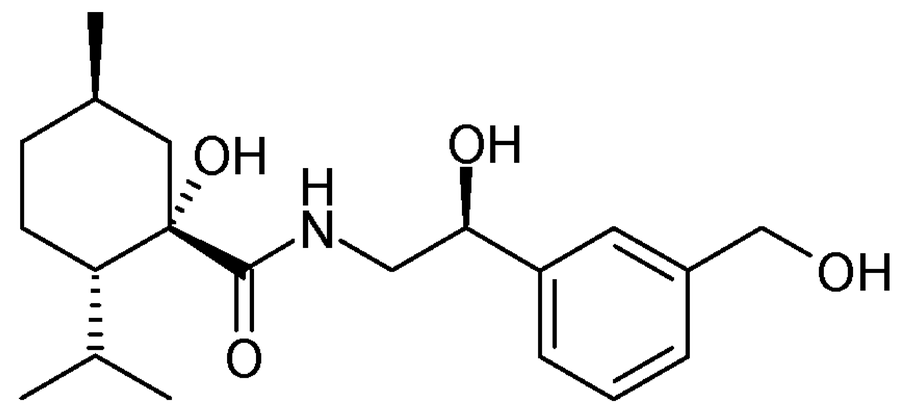
Chiral separation of (1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-(3-hydroxyphenyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (142.8mg) carried out by liquid chromatography using CHIRALPAK IA with heptane and ethanol led to (1S,2S,5R)-1-hydroxy-N-((2R)-hydroxy-2-(3-hydroxyphenyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (***example 41***, 83mg) and (1S,2S,5R)-1-hydroxy-N-((2S)-hydroxy-2-(3-hydroxyphenyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (***example 42,*** 64mg).

Examples 43 & 44

(1S,2S,5R)-1-hydroxy-N-((2R)-hydroxy-2-(3-(hydroxymethyl)phenyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide **(43)**



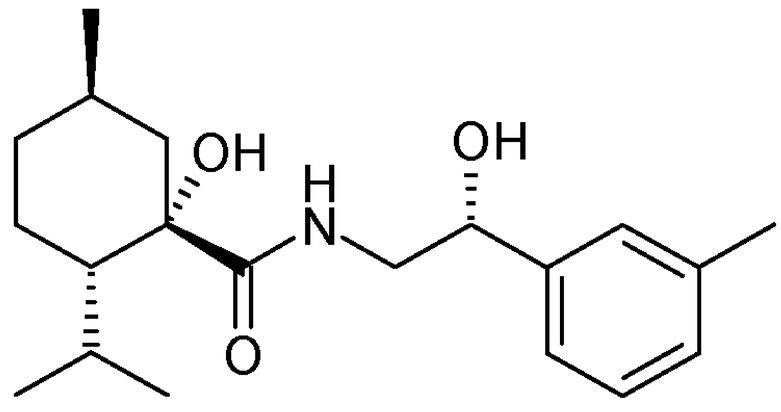
(1S,2S,5R)-1-hydroxy-N-((2S)-hydroxy-2-(3-(hydroxymethyl)phenyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide **(44)**



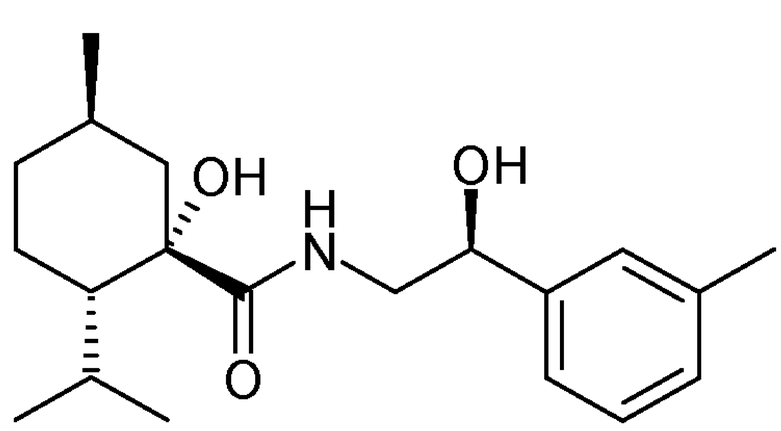
Chiral separation of (1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-(3-(hydroxymethyl)phenyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (142.3mg) carried out by liquid chromatography using CHIRALPAK IA with heptane and ethanol led to (1S,2S,5R)-1-hydroxy-N-((2R)-hydroxy-2-(3-(hydroxymethyl)phenyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (***example 43***, 67mg) and (1S,2S,5R)-1-hydroxy-N-((2S)-hydroxy-2-(3-(hydroxymethyl)phenyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (***example 44,*** 65mg).

Examples 45 and 46

(1S,2S,5R)-1-hydroxy-N-((2R)-hydroxy-2-(m-tolyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide **(45)**



(1S,2S,5R)-1-hydroxy-N-((2S)-hydroxy-2-(m-tolyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide **(46)**

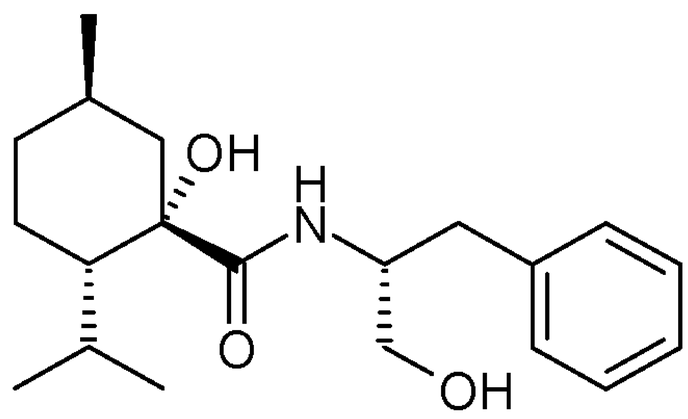


Chiral separation of (1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-(m-tolyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (85.8mg) carried out by liquid chromatography using

CHIRALPAK IA with heptane and ethanol to (1S,2S,5R)-1-hydroxy-N-((2R)-hydroxy-2-(m-tolyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (***example 45,*** 45mg) and (1S,2S,5R)-1-hydroxy-N-((2S)-hydroxy-2-(m-tolyl)ethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (***example 46,*** 49mg).

Example 47

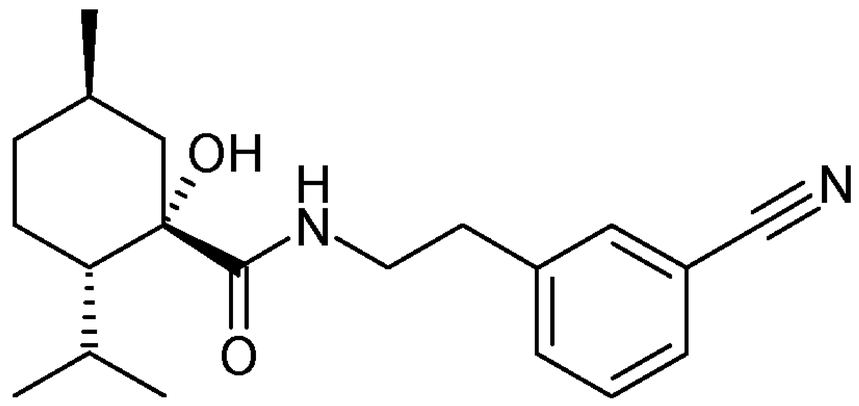
(1S,2S,5R)-1-hydroxy-N-((2R)-1-hydroxy-3-phenylpropan-2-yl)-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (300mg) and D-phenylalaninol (1.1eq) [after amine addition, the reaction was heated at 50°C during 3hr] led to (1S,2S,5R)-1-hydroxy-N-((2R)-1-hydroxy-3-phenylpropan-2-yl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (172mg) as white solid after flash chromatography with cyclohexane and EtOAc followed by trituration with DCM and n-pentane.

Example 48

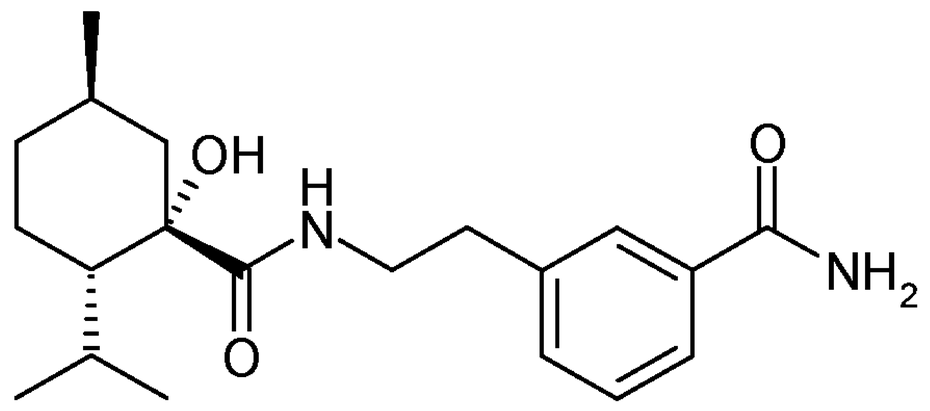
(1S,2S,5R)-N-(3-cyanophenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (300mg) and 3-(2-aminoethyl)benzonitrile hydrochloride (1.05eq) [after amine addition, the reaction was heated at 50°C during 6hr and at room temperature during 16hrs] led to (1S,2S,5R)-N-(3-cyanophenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (226mg) as white solid after flash chromatography with cyclohexane and EtOAc followed by trituration with DCM and n-pentane.

Example 49

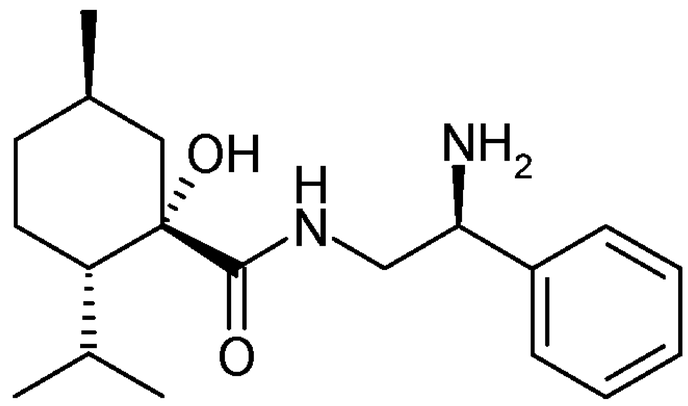
3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzamide



(1S,2S,5R)-N-(3-Cyanophenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (115mg) was dissolved in DMSO (2M) and cooled down to 5-10°C. K_2CO_3 (0.5eq) was added followed by dropwise addition of hydrogen peroxide (4eq). The reaction was then vigorously stirred over 15 minutes. EtOAc (15V) was added and after first extraction, the aqueous phase was washed again with EtOAc (5V). The combined organic phases were washed with brine, dried over Na_2SO_4, filtrated and concentrated under vacuum to provide 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzamide (50mg) as white solid.

Example 50

(1S,2S,5R)-N-((2S)-amino-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide

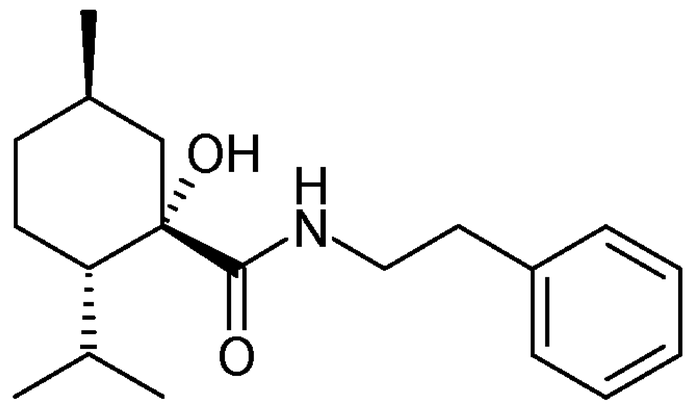


Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (500mg) and (S)-tert-butyl (2-amino-1-phenylethyl)carbamate (1.2eq) [after amine addition, the reaction was stirred at room temperature during 16hr] led to tert-butyl ((S)-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethyl)carbamate (482mg) as white solid after flash chromatography with cyclohexane and acetone.

Under deprotection conditions B, tert-butyl ((S)-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethyl)carbamate (440mg) in the presence of TFA (810µl) led to (1S,2S,5R)-N-((2S)-amino-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (304mg) as white solid.

Example 51

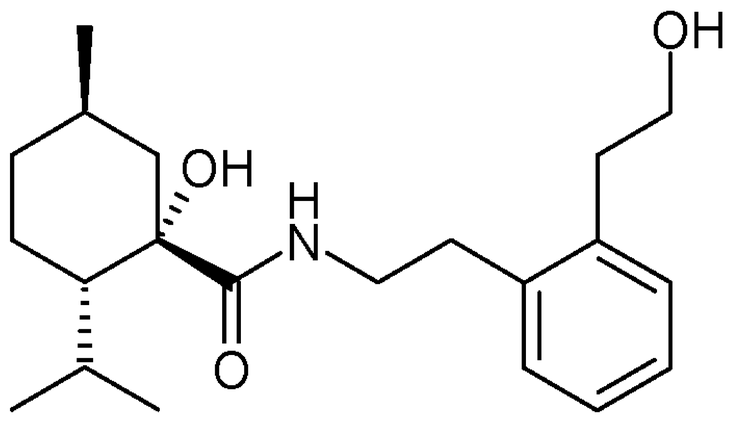
(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-phenethylcyclohexane-1-carboxamide



Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (75mg) and phenethylamine (2.1eq) [after amine addition, the reaction was heated at 70°C during 2hr] led to (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-phenethylcyclohexane-1-carboxamide (83mg) as white solid after flash chromatography with cyclohexane and EtOAc.

Example 52

(1S,2S,5R)-1-hydroxy-N-(2-(2-hydroxyethyl)phenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide



2-Bromophenethylamine (1.438gr) was dissolved in THF (0.2M) under argon and K_2CO_3 (1.3eq) was added followed by addition of benzyl chloroformate (1.1eq). The reaction mixture was stirred at room temperature during 22hr and was then filtrated. The resulting organic phase was washed with water (1V), an 1N aqueous solution of HCl (1V), brine (1V), dried over Na_2SO_4, filtrated and concentrated under vacuum. The residue was purified by flash chromatography with cyclohexane and EtOAc to provide benzyl (2-bromophenethyl)carbamate (719mg) as white solid.

Benzyl (2-bromophenethyl)carbamate (719mg) was dissolved in DME (0.13M) and the solution was degassed with argon. $Pd(Ph_3)_4$ (0.04eq) was added and the resulting mixture was stirred at room temperature during 20 minutes. K_2CO_3 (1.23eq) and water (0.33V) were added followed by addition of 2,4,6-trivinylboroxine pyridine complex (1.2eq). The reaction mixture was heated at reflux over 16hr. After concentration under vacuum, the residue was dissolved in Et_2O (1V) and water (1V). The organic phase was washed with brine (1V), dried over Na_2SO_4, filtrated and concentrated under vacuum. The residue was purified by flash chromatography with cyclohexane and EtOAc to yield benzyl (2-vinylphenethyl)carbamate (513mg) as yellow oil.

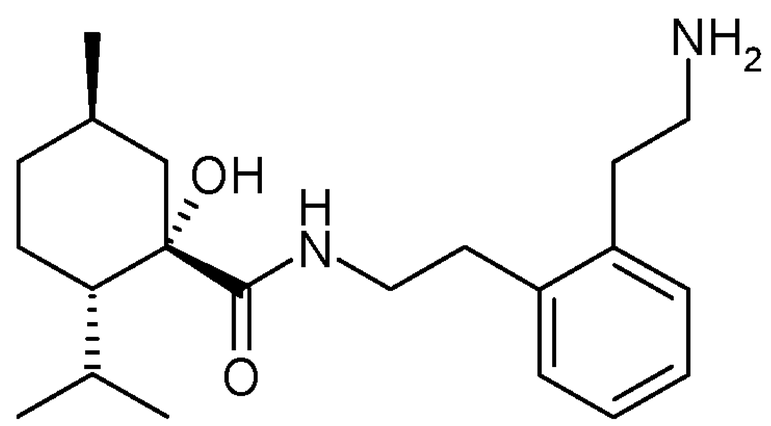
Benzyl (2-vinylphenethyl)carbamate (512mg) was dissolved in THF (1M) and the resulting solution was cooled down to 0°C before dropwise addition of BH_3-THF complex (1.21eq, 1M). Once at room temperature, the reaction mixture was stirred during 2hr. An 1N aqueous solution of sodium hydroxide (1.0eq) was added dropwise at 0°C followed by addition of 30% H_2O_2 (5eq) and the resulting solution was then warmed up to room temperature. Water (5V) and Et_2O (10V) were added and the organic phase was then washed with brine (5V), dried over Na_2SO_4, filtrated and concentrated under vacuum. The residue was purified by flash chromatography with cyclohexane/EtOAc to yield benzyl 2-(2-hydroxyethyl)phenethyl)carbamate (294mg) as colorless oil.

Benzyl 2-(2-hydroxyethyl)phenethyl)carbamate (333mg) was dissolved in MeOH (0.08M) and the resulting solution was degassed with argon. 10% Palladium on charcoal (0.1eq) was added and the reaction mixture was stirred under 3 bars of hydrogen during 5hr. The solution was filtrated on GF/F Whatman filter paper and concentrated under vacuum to provide 2-(2-(2-aminoethyl)phenylethan-1-ol (179mg) as white solid.

Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (217mg) and 2-(2-(2-aminoethyl)phenylethan-1-ol (1.0eq) [after amine addition, the reaction was heated at 70°C during 2hr and stirred at room temperature during 1-hr] led to (1S,2S,5R)-1-hydroxy-N-(2-(2-hydroxyethyl)phenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (151mg) as colorless wax after flash chromatography with cyclohexane and acetone.

Example 53

(1S,2S,5R)-N-(2-(2-aminoethyl)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide



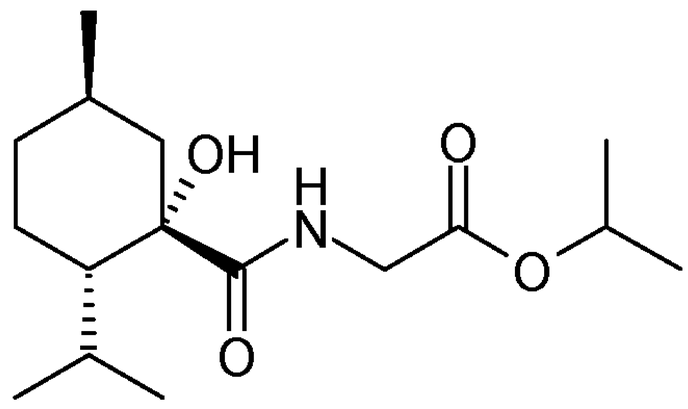
(1S,2S,5R)-1-Hydroxy-N-(2-(2-hydroxyethyl)phenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (98mg) was dissolved in DCM (0.11M) and cooled down to 0°C under argon. Mesyl chloride (1.1eq) and triethylamine (1.53eq) were then added. Once at room temperature, the reaction mixture was stirred over 5hr and water (1V) was added as well as DCM (1V). The organic phase was dried over Na_2SO_4, filtrated and concentrated under vacuum to yield the desired mesylate (127mg).

2-(2-((1S,2S,5R)-1-Hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenethyl methanesulfonate (119mg) was dissolved in DMF and NaN_3 (1.5eq) was added. The reaction mixture was heated at 60°C during 3hr. Once at room temperature, water (20V) and EtOAc (20V) were added. The organic phase was washed with brine (10V), dried over Na_2SO_4, filtrated and concentrated under vacuum.

The residue was then dissolved in THF (2V) and water (6.0eq) was added as well as PPh_3 (1.5eq). The reaction mixture was then stirred at room temperature over 16hr. After addition of EtOAc (2V), the solution was washed with an 1N aqueous solution of NaOH (4V) and brine (4V). The organic phase was dried over Na_2SO_4, filtrated and concentrated under vacuum. The residue was purified by preparative HPLC using CSH 250X50MM - 5 µM column with water and acetonitrile containing 0.1% formic acid to give (1S,2S,5R)-N-(2-(2-aminoethyl)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (59mg).

Example 54

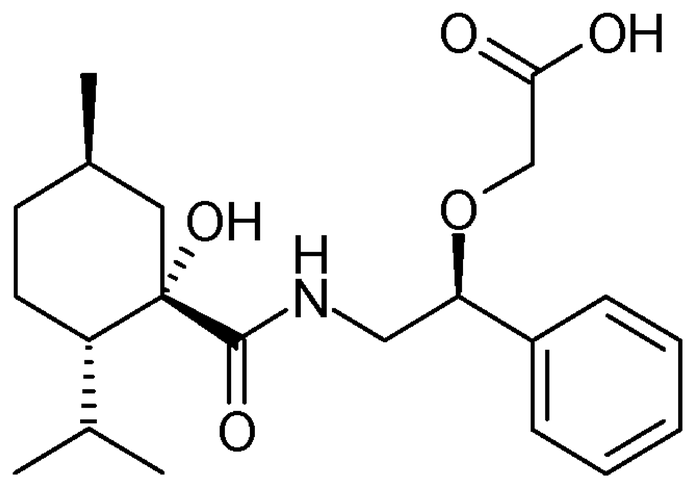
isopropyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate



Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (300mg) and isopropyl 2-aminoacetate hydrochloride (1.1eq) [after amine addition, the reaction was heated at 50-55°C during 16hr] led to isopropyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate (155mg) as white solid after flash chromatography with cyclohexane and EtOAc followed by trituration with DCM and n-pentane.

Example 55

2-((S)-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethoxy)acetic acid



Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (700mg) and (S)-2-amino-1-phenylethanol (1.05eq) [after amine addition, the reaction was heated at 60°C during 6hr and stirred at room temperature during 72hr] led to (1S,2S,5R)-1-hydroxy-N-((S)-2-hydroxy-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (754mg) as ecru solid after flash chromatography with cyclohexane and acetone.

Under Acetylation conditions A, (1S,2S,5R)-1-hydroxy-N-((S)-2-hydroxy-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (724mg) in the presence of acetic anhydride (1.6eq) led to (S)-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethyl acetate (825mg) as pale yellow wax.

(S)-2-((1S,2S,5R)-1-Hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethyl acetate (778mg) was dissolved in DCM (0.61M) and the resulting solution was cooled down to

0°C. Triethylamine (4.0eq) was added followed by addition of tert-butyldimethylsilyl trilfuoromethanesulfonate (4.0eq). The reaction mixture was stirred at room temperature during 16hrs.After addition of DCM (1V), the organic phase was washed with an 1N aqueous solution of HCl (2V), with brine (2V), dried over Na_2SO_4, filtrated and concentrated under vacuum. The residue was purified by flash chromatography with cyclohexane and EtOAc to provide (S)-2-((1S,2S,5R)-1-((tert-butyldimethylsilyl)oxy)-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethyl acetate (694mg) as colorless oil.

(S)-2-((1S,2S,5R)-1-((tert-Butyldimethylsilyl)oxy)-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethyl acetate (693mg) was dissolved in methanol (0.2M) and K_2CO_3 (2.0eq) was added. The reaction mixture was stirred at room temperature during 16hrs. after filtration and concentration under vacuum, the residue was dissolved in diethyl ether, washed with water (1.4V), with brine (1.4V), dried over Na_2SO_4, filtrated and concentrated under vacuum to yield (1S,2S,5R)-1-((tert-butyldimethylsilyl)oxy)-N-((S)-2-hydroxy-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (595mg) as colorless wax.

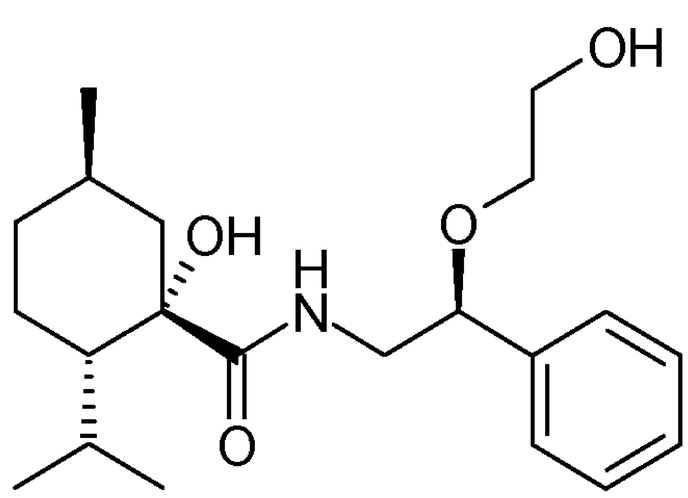
Under alkylation conditions E, (1S,2S,5R)-1-((tert-butyldimethylsilyl)oxy)-N-((S)-2-hydroxy-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (295mg) in the presence of methyl bromoacetate (6eq) led to methyl 2-((S)-2-((1S,2S,5R)-1-((tert-butyldimethylsilyl)oxy)-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethoxy)acetate (107mg) as colorless oil after flash chromatography with cyclohexane and EtOAc.

Methyl 2-((S)-2-((1S,2S,5R)-1-((tert-butyldimethylsilyl)oxy)-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethoxy)acetate (106mg) was dissolved in THF (0.5M) and cooled down to 0°C. TBAF (15.5eq) was added dropwise at 0°C and the reaction mixture was warmed up to room temperature. The reaction mixture was stirred during 46hrs at this temperature. After concentration under vacuum, the residue was dissolved in Et2O (10V) and the organic phase was washed with a saturated aqueous solution of ammonium chloride. The aqueous phase was acidified with HCl 1N up to pH 1 and was extracted with diethyl ether (10v x 3). The combined organic phase was dried over Na_2SO_4, filtrated and concentrated under vacuum.
The residue was dissolved in DCM (0.5M) and HCl (1N, 3.82eq) was added. The reaction mixture was stirred at room temperature during 5hrs. After concentration under vacuum, the residue was dissolved in Et_2O (10V), was washed with water (10V) and brine (10V). The organic phase was dried over Na_2SO_4, filtrated and concentrated under vacuum. The residue was purified by flash

chromatography with DCM and methanol to yield 2-((S)-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethoxy)acetic acid (25mg) as white solid.

Example 56

(1S,2S,5R)-1-hydroxy-N-((S)-2-(2-hydroxyethoxy)-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (700mg) and (S)-2-amino-1-phenylethanol (1.05eq) [after amine addition, the reaction was heated at 60°C during 6hr and stirred at room temperature during 72hr] led to (1S,2S,5R)-1-hydroxy-N-((S)-2-hydroxy-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (754mg) as ecru solid after flash chromatography with cyclohexane and acetone.

Under Acetylation conditions A, (1S,2S,5R)-1-hydroxy-N-((S)-2-hydroxy-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (724mg) in the presence of acetic anhydride (1.6eq) led to (S)-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethyl acetate (825mg) as pale yellow wax.

(S)-2-((1S,2S,5R)-1-Hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethyl acetate (778mg) was dissolved in DCM (0.61M) and the resulting solution was cooled down to 0°C. Triethylamine (4.0eq) was added followed by addition of tert-butyldimethylsilyl trilfuoromethanesulfonate (4.0eq). The reaction mixture was stirred at room temperature during 16hrs.After addition of DCM (1V), the organic phase was washed with an 1N aqueous solution of HCl (2V), with brine (2V), dried over Na_2SO_4, filtrated and concentrated under vacuum. The residue was purified by flash chromatography with cyclohexane and EtOAc to provide (S)-2-((1S,2S,5R)-1-((tert-butyldimethylsilyl)oxy)-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethyl acetate (694mg) as colorless oil.

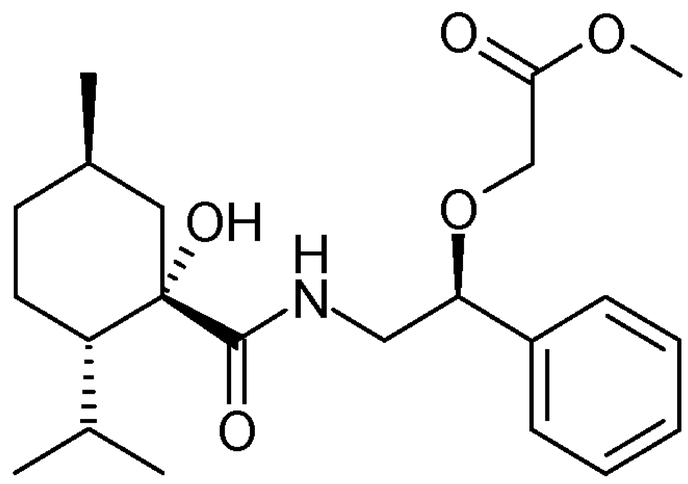
(S)-2-((1S,2S,5R)-1-((tert-Butyldimethylsilyl)oxy)-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethyl acetate (693mg) was dissolved in methanol (0.2M) and K_2CO_3 (2.0eq) was added. The reaction mixture was stirred at room temperature during 16hrs. after filtration and concentration under vacuum, the residue was dissolved in diethyl ether, washed with water (1.4V), with brine (1.4V), dried over Na_2SO_4, filtrated and concentrated under vacuum to yield (1S,2S,5R)-1-((tert-butyldimethylsilyl)oxy)-N-((S)-2-hydroxy-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (595mg) as colorless wax.

Under alkylation conditions E, (1S,2S,5R)-1-((tert-butyldimethylsilyl)oxy)-N-((S)-2-hydroxy-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (291mg) in the presence of 2-(2-bromoethoxy)tetrahydro-2H-pyran (3eq) [3eq 60% NaH was used] led to (1S,2S,5R)-1-((tert-butyldimethylsilyl)oxy)-2-isopropyl-5-methyl-N-((2S)-2-phenyl-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)ethyl)cyclohexane-1-carboxamide (287mg) as colorless oil after flash chromatography with cyclohexane and EtOAc.

Under deprotection conditions A, (1S,2S,5R)-1-((tert-butyldimethylsilyl)oxy)-2-isopropyl-5-methyl-N-((2S)-2-phenyl-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)ethyl)cyclohexane-1-carboxamide (271mg) in the presence of HCl (49.8eq) led to (1S,2S,5R)-1-hydroxy-N-((S)-2-(2-hydroxyethoxy)-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (85mg) as white solid after flash chromatography with cyclohexane and EtOAc.

Example 57

methyl 2-((S)-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethoxy)acetate

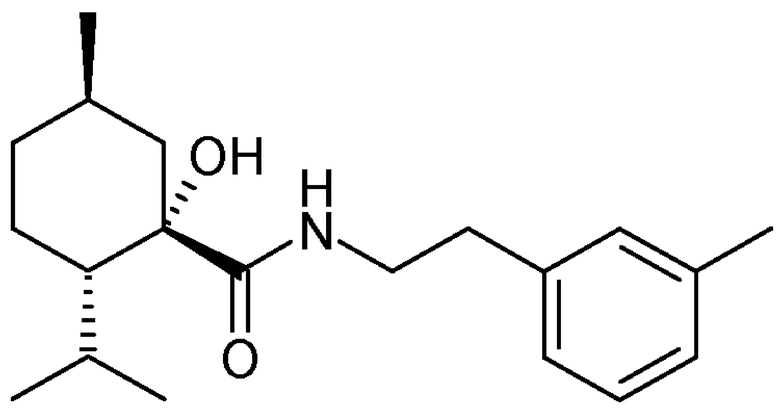


Isopropyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate (79mg) was dissolved in DCM/methanol (2/1, 0.1M) and the resulting solution was cooled down to 0°C. A 2M trimethylsilyl-diazomethane solution in hexane (1.6eq) was added and after warming up to

room temperature, the reaction mixture was stirred during 3hr30. The reaction was quenched by dropwise addition of acetic acid (1.0eq) and the reaction mixture was then concentrated under vacuum. The residue was dissolved in diethyl ether (10V), washed with an 1N aqueous solution of sodium hydroxide (10V), with brine (10V), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography with cyclohexane and EtOAc to provide methyl 2-((S)-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethoxy)acetate (46.9mg) as colorless oil.

Example 58

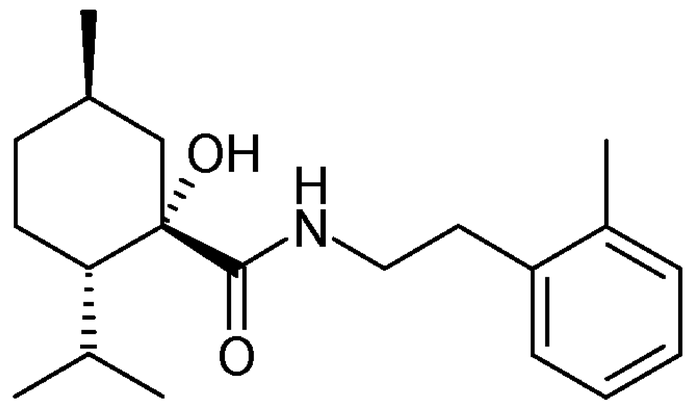
(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(3-methylphenethyl)cyclohexane-1-carboxamide



Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (130mg) and 3-methylphenethylamine (1.05eq) [after amine addition, the reaction was heated at 50-55°C during 16hr] led to (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(3-methylphenethyl)cyclohexane-1-carboxamide (149mg) as white solid after flash chromatography with cyclohexane and EtOAc.

Example 59

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(2-methylphenethyl)cyclohexane-1-carboxamide

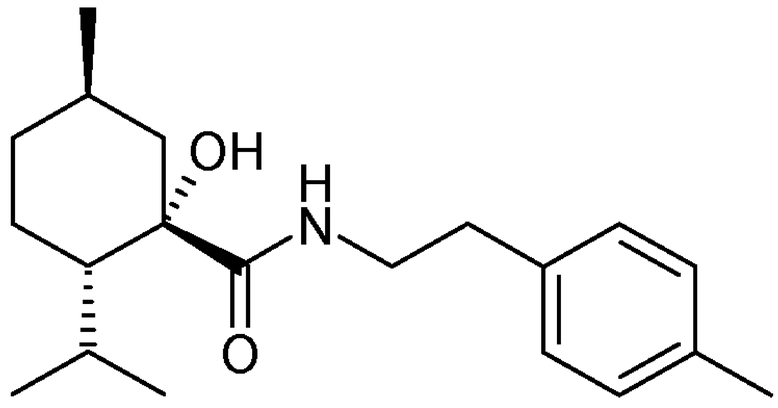


Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (110mg) and 2-methylphenethylamine (1.05eq) [after amine addition, the reaction was heated at 50-55°C during 16hr] led to (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(2-

methylphenethyl)cyclohexane-1-carboxamide (61mg) as white solid after flash chromatography with cyclohexane and EtOAc.

Example 60

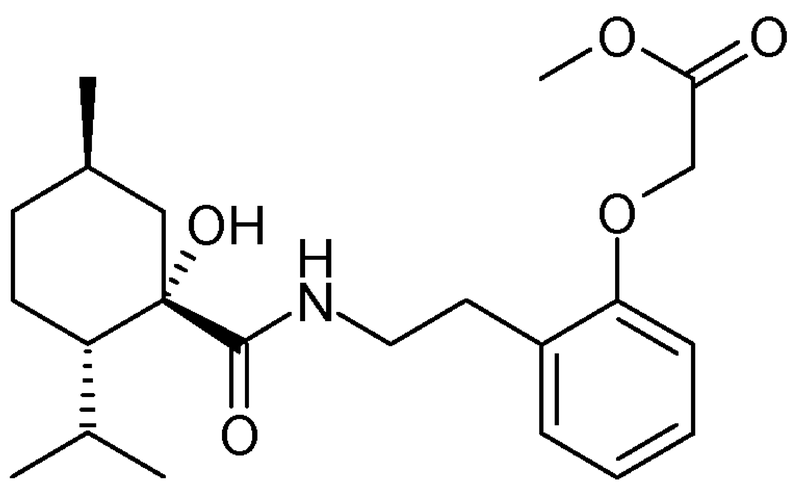
(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(4-methylphenethyl)cyclohexane-1-carboxamide



Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (110mg) and 4-methylphenethylamine (1.05eq) [after amine addition, the reaction was heated at 50-55°C during 16hr] led to (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(4-methylphenethyl)cyclohexane-1-carboxamide (95mg) as white solid after flash chromatography wih cyclohexane and EtOAc.

Example 61

methyl 2-(2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenoxy)acetate



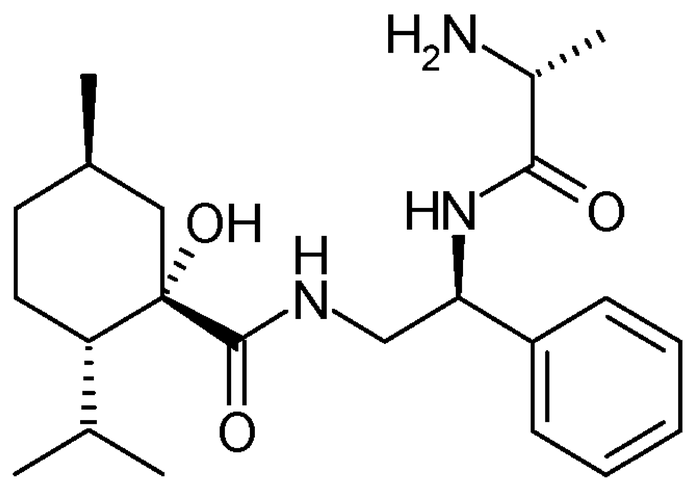
Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (750mg) and (S)-2-amino-1-phenylethanol (570mg) [after amine addition, the reaction was heated at 50°C during 16hrs] led to (1S,2S,5R)-1-hydroxy-N-(2-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (702mg) as yellow powder after flash chromatography with cyclohexane and EtOAc, and without reprecipitation.

Under alkylation conditions C, (1S,2S,5R)-1-hydroxy-N-(2-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (90mg) in the presence of methyl bromoacetate (1.5eq) [NB

the reaction mixture was irradiated at 100°C in a microwave] led to methyl 2-(2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenoxy)acetate (92mg) as white solid after flash chromatography with cyclohexane/EtOAc.

Example 62

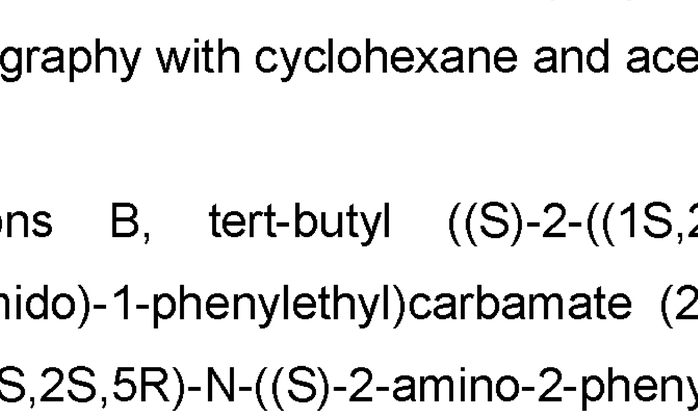
(1S,2S,5R)-N-((S)-2-((R)-2-aminopropanamido)-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (1.7 g) and (S)-tert-butyl (2-amino-1-phenylethyl)carbamate (1.05eq) [after amine addition, the reaction was stirred at 50-55°C during 16hr] led to tert-butyl ((S)-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethyl)carbamate (2.26g) as white solid after flash chromatography with cyclohexane and acetone.

Under deprotection conditions B, tert-butyl ((S)-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethyl)carbamate (2.26g) in the presence of TFA (10eq) led to (1S,2S,5R)-N-((S)-2-amino-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (1.11g) as ecru solid.

(1S,2S,5R)-N-((S)-2-amino-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide

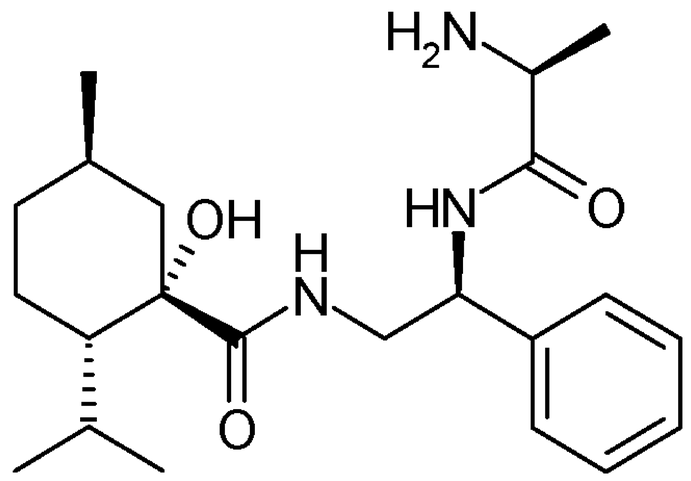


Under coupling conditions F, with (1S,2S,5R)-N-((S)-2-amino-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (100mg) and BOC-D-ALA-OH (1.1eq) led to tert-butyl ((R)-1-(((S)-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethyl)amino)-1-oxopropan-2-yl)carbamate (143mg) [no purification by flash chromatography was needed] as white foam.

Under deprotection conditions B, tert-butyl ((R)-1-(((S)-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethyl)amino)-1-oxopropan-2-yl)carbamate (140mg) in the presence of TFA (8.2eq) led to (1S,2S,5R)-N-((S)-2-((R)-2-aminopropanamido)-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (95mg) after flash chromatography with DCM and methanol.

Example 63

(1S,2S,5R)-N-((S)-2-((S)-2-aminopropanamido)-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (1.7 g) and (S)-tert-butyl (2-amino-1-phenylethyl)carbamate (1.05eq) [after amine addition, the reaction was stirred at 50-55°C during 16hr] led to tert-butyl ((S)-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethyl)carbamate (2.26g) as white solid after flash chromatography with cyclohexane and acetone.

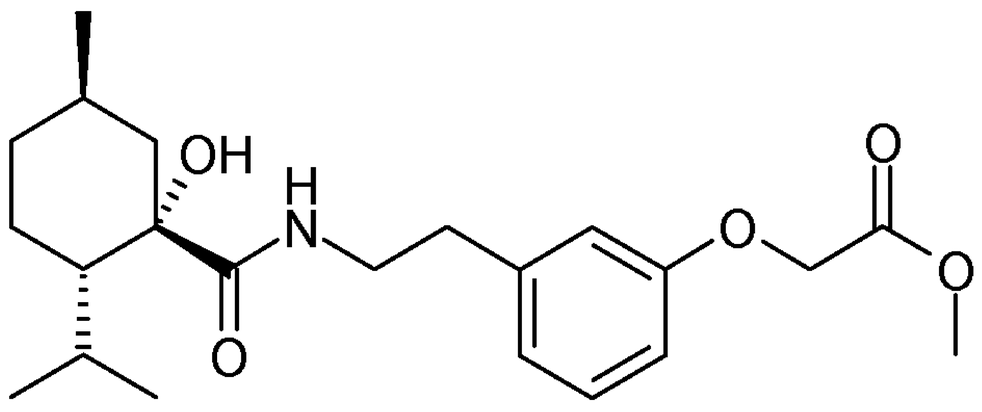
Under deprotection conditions B, tert-butyl ((S)-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethyl)carbamate (2.26g) in the presence of TFA (10eq) led to (1S,2S,5R)-N-((S)-2-amino-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (1.11g) as ecru solid.

Under coupling conditions F, with (1S,2S,5R)-N-((S)-2-amino-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (100mg) and BOC-L-ALA-OH (1.1eq) led to tert-butyl ((S)-1-(((S)-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethyl)amino)-1-oxopropan-2-yl)carbamate (156mg) as ecru solid [no purification by flash chromatography was needed].

Under deprotection conditions B, tert-butyl ((S)-1-(((S)-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethyl)amino)-1-oxopropan-2-yl)carbamate (155mg) in the presence of TFA (10.2eq) led to (1S,2S,5R)-N-((S)-2-((S)-2-aminopropanamido)-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (103mg) as white solid.

Example 64

methyl 2-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenoxy)acetate

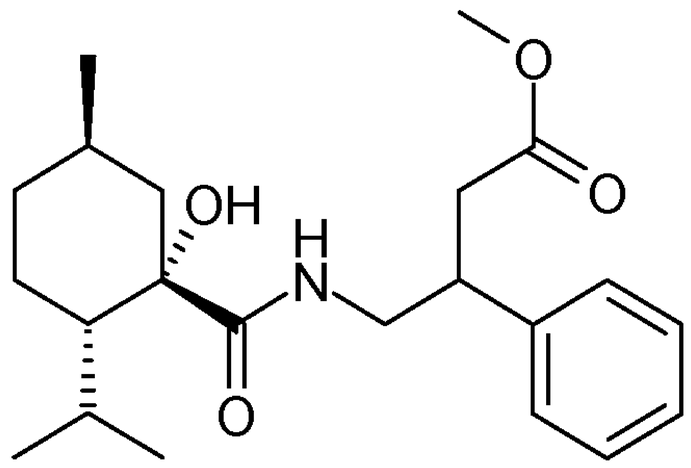


Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (750mg) and 3-hydroxyphenythylamine (0.67eq) [CDI (0.58eq) & pyridine (0.71eq) were added and after amine addition, the reaction mixture was stirred at 50-55°C during 4hr] led to (1S,2S,5R)-1-hydroxy-N-(3-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (450mg) as white solid after flash chromatography with cyclohexane and EtOAc.

Under alkylation conditions C, (1S,2S,5R)-1-hydroxy-N-(3-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (90mg) in the presence of methyl bromoacetate (1.5eq) [NB the reaction mixture was irradiated at 100°C in a microwave] led to methyl 2-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenoxy)acetate (99mg) as white solid after flash chromatography with cyclohexane/EtOAc.

Example 65

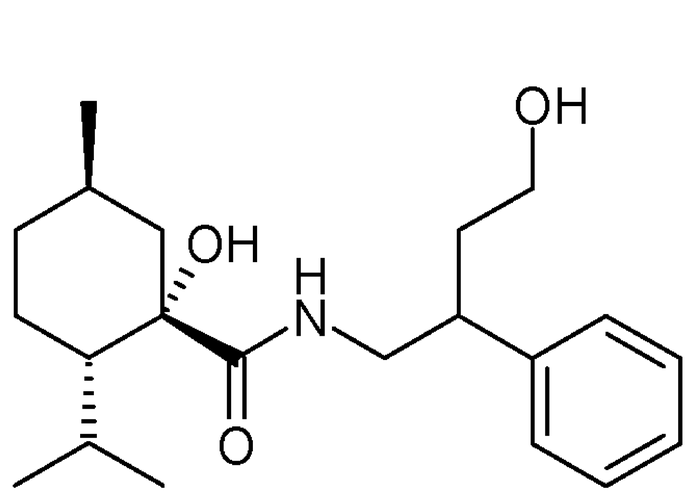
methyl 4-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-3-phenyl butanoate



Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (1.02g) and methyl 4-amino-3-phenylbutanoate hydrochloride (1.05eq) [after amine addition, the reaction was heated at 50-55°C during 16hr] led to methyl 4-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-3-phenyl butanoate (1.445g) as white solid after flash chromatography with cyclohexane and EtOAc.

Example 66

(1S,2S,5R)-1-hydroxy-N-(4-hydroxy-2-phenylbutyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide

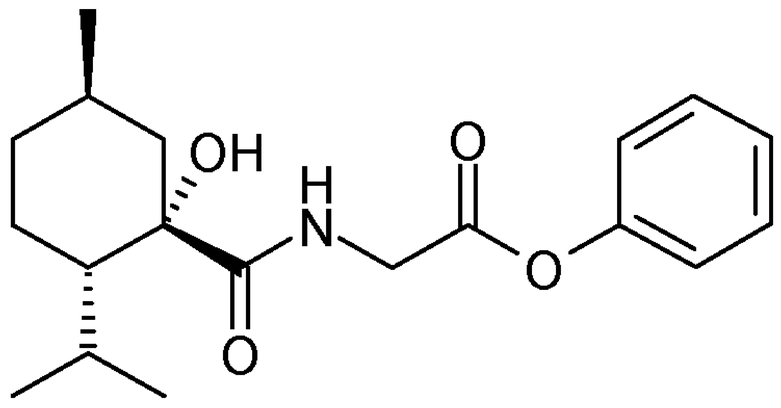


Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (1.02g) and methyl 4-amino-3-phenylbutanoate hydrochloride (1.03eq) *[* after amine addition, the reaction was stirred at 50-55°C during 5hr] led to methyl 4-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-3-phenylbutanoate (1.445g) as white solid after flash chromatography with cyclohexane and EtOAc.

Under reduction conditions B, methyl 4-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-3-phenylbutanoate (200mg) in the presence of $LiBH_4$ (11eq) led to (1S,2S,5R)-1-hydroxy-N-(4-hydroxy-2-phenylbutyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (143mg) as white solid after flash chromatography with cyclohexane/EtOAc.

Example 67

phenyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate



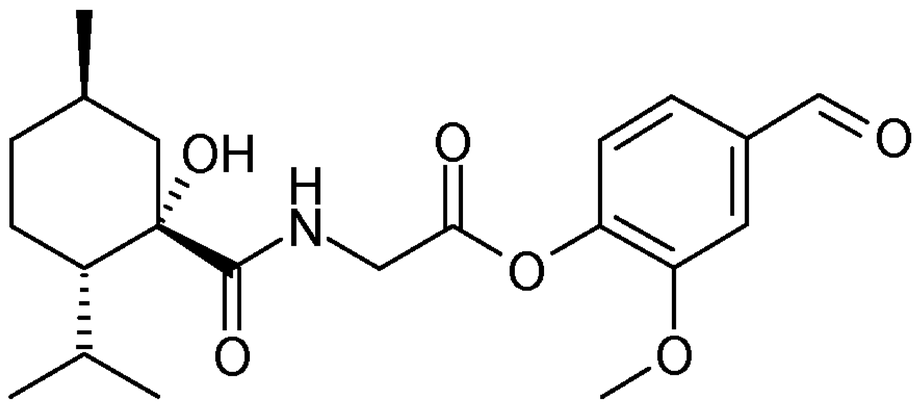
Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (1.0g) and glycine methyl ester hydrochloride (1.02eq) [after amine addition, the reaction was heated at 50-55°C during 3hr] led to methyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate (1.15g) as white solid.

Under saponification conditions, methyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate (1.15g) in the presence of sodium hydroxide (1M, 5eq) led to ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycine (862mg).

Under coupling conditions C, with ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycine (100mg) and phenol as well as DCC (1.05eq) and pyridine (1.8eq) [no addition of DMAP for this reaction] led to phenyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate (86mg) as white solid after flash chromatography with cyclohexane and EtOAc.

Example 68

4-formyl-2-methoxyphenyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate



Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (1.0g) and glycine methyl ester hydrochloride (1.02eq) [after amine addition, the

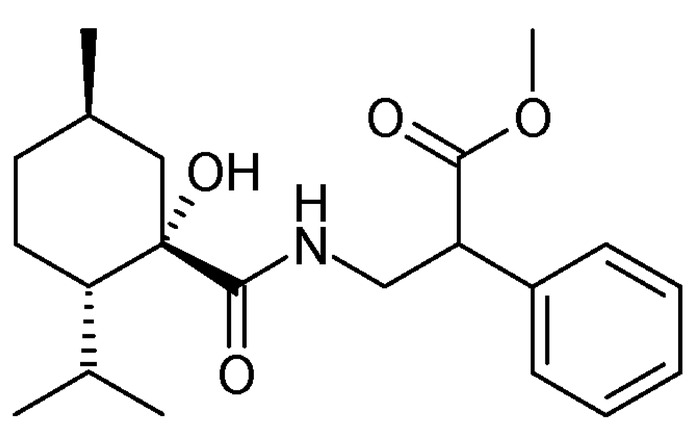
reaction was heated at 50-55°C during 3hr] led to methyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate (1.15g) as white solid.

Under saponification conditions, methyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate (1.15g) in the presence of sodium hydroxide (1M, 5eq) led to ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycine (862mg).

Under coupling conditions D, with ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycine (90mg) and vanillin (1.0eq) led to 4-formyl-2-methoxyphenyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate (45mg) as white foam after flash chromatography with cyclohexane and EtOAc.

Example 69

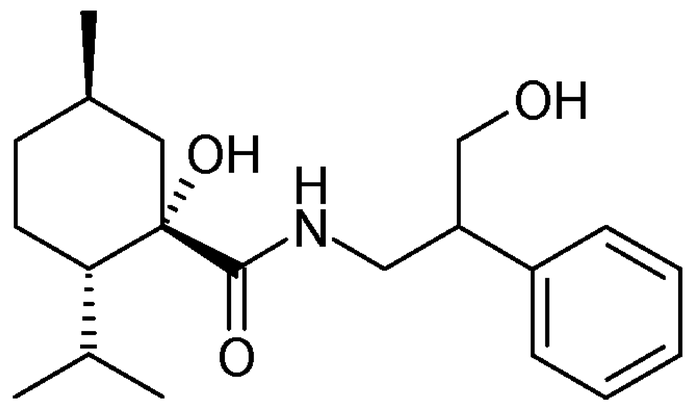
methyl 4-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-3-phenyl butanoate



Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (0.86g) and methyl 3-amino-2-phenylpropanoate hydrochloride (1.05eq) [after amine addition, the reaction was heated at 50-55°C during 16hr] led to methyl 4-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-3-phenyl butanoate (1.107g) as white solid after flash chromatography with cyclohexane and EtOAc followed by trituration in DCM and n-pentane.

Example 70

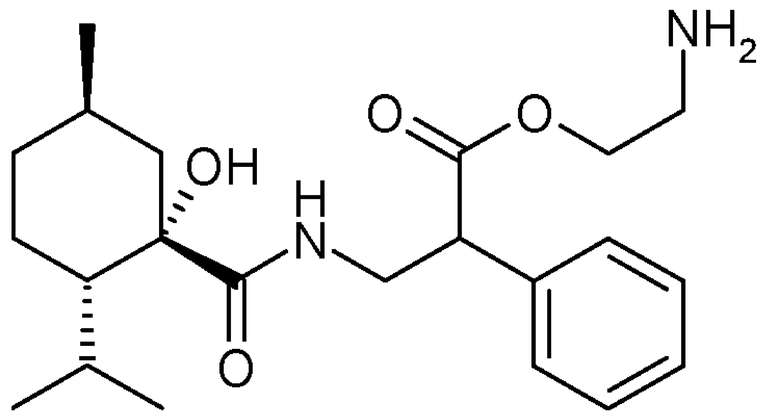
(1S,2S,5R)-1-hydroxy-N-(3-hydroxy-2-phenylpropyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under reduction conditions B, methyl 4-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-3-phenyl butanoate (190mg) in the presence of $LiBH_4$ (7eq) led to (1S,2S,5R)-1-hydroxy-N-(3-hydroxy-2-phenylpropyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (113mg) as white solid after flash chromatography with cyclohexane/EtOAc followed by preparative HPLC using Xselect CSH Prep C18 5ìm OBD 50x250m column with water and acetonitrile containing 0.1% formic acid.

Example 71

2-aminoethyl 3-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-2-phenylpropanoate hydrochloride



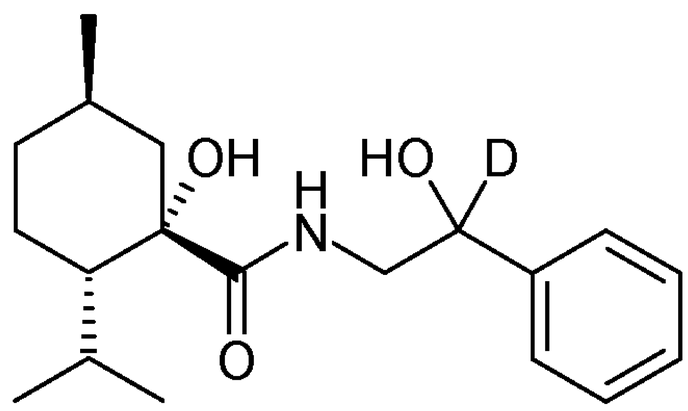
Under saponification conditions, methyl 4-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-3-phenyl butanoate (650mg) in the presence of sodium hydroxide (12M, 5eq) led to 3-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-2-phenylpropanoic acid (615mg).

Under coupling conditions D, with 3-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-2-phenylpropanoic acid (150mg) and tert-butyl N-(2-hydroxyethyl)carbamate (1.2eq) led to 2-((tert-butoxycarbonyl)amino)ethyl 3-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-2-phenylpropanoate (180mg) as colorless wax after flash chromatography with cyclohexane and EtOAc.

Under deprotection conditions A, 2-((tert-butoxycarbonyl)amino)ethyl 3-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-2-phenylpropanoate (177mg) in the presence of HCl (2M, 10eq) led to 2-aminoethyl 3-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-2-phenylpropanoate hydrochloride (145mg).

Example 72

(1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-phenylethyl-2-d)-2-isopropyl-5-methylcyclohexane-1-carboxamide

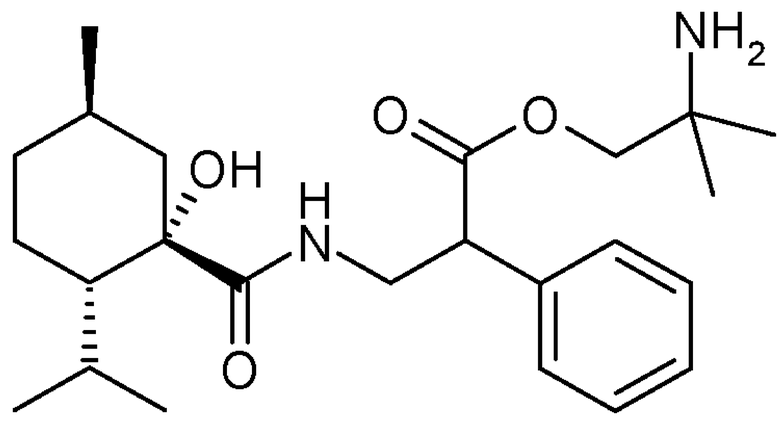


Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (2.0g) and 2-aminoacetophenone hydrochloride (1.0eq) [after amine addition, the reaction mixture was heated at 55°C during 16hr] led to (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(2-oxo-2-phenylethyl)cyclohexane-1-carboxamide (1.81g) as pale yellow solid.

Under reduction conditions C, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(2-oxo-2-phenylethyl)cyclohexane-1-carboxamide (1.80g) in the presence of NaBD4 (1.25eq) led to (1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-phenylethyl-2-d)-2-isopropyl-5-methylcyclohexane-1-carboxamide (1.593g) as ecru solid.

Example 73

2-amino-2-methylpropyl 3-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-2-phenylpropanoate hydrochloride



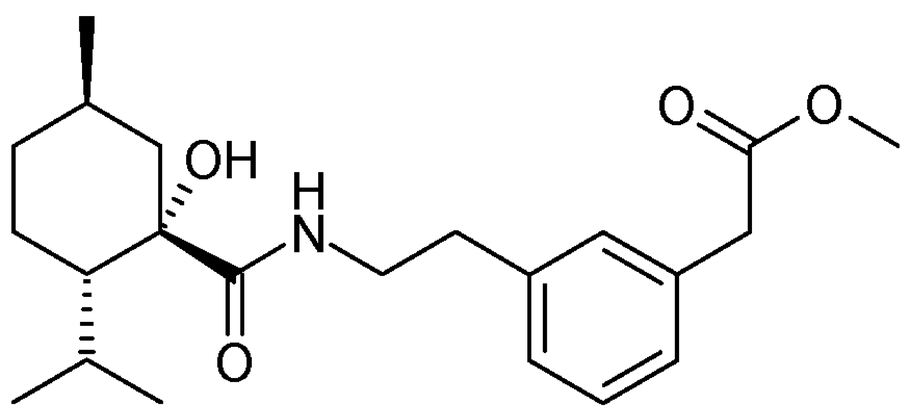
Under saponification conditions, methyl 4-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-3-phenyl butanoate (650mg) in the presence of sodium hydroxide (12M, 5eq) led to 3-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-2-phenylpropanoic acid (615mg).

Under coupling conditions D, with 3-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-2-phenylpropanoic acid (150mg) and N-Boc-2-amino-2-methyl-1-propanol (1.2eq) led to 2-((tert-butoxycarbonyl)amino)-2-methylpropyl 3-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-2-phenylpropanoate (87mg) as colorless wax after flash chromatography with cyclohexane and EtOAc followed by preparative HPLC using Xselect CSH Prep C18 5ìm OBD 50x250m column with water and acetonitrile containing 0.1% formic acid.

Under deprotection conditions A, 2-((tert-butoxycarbonyl)amino)-2-methylpropyl 3-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexan-1-carboxamido)-2-phenylpropanoate (86mg) in the presence of HCl (2M, 12eq) led to 2-amino-2-methylpropyl 3-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-2-phenylpropanoate hydrochloride (77mg) as white solid.

Example 74

methyl 2-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenyl)acetate



Methyl 2-(3-bromophenyl)acetate (1.04g) and potassium tert-butyl N-[2-(trifluoroboranuidyl)ethyl]carbamate (1.1eq) as well as cesium carbonate (3.0eq) were dissolved in a 3/1 mixture of toluene and water (0.27M). The resulting solution was degassed using argon and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (0.04eq) was added. The reaction mixture was then heated at 80°C during 16hrs. Once at room temperature, EtOAc (1V) was added and the resulting mixture was washed with water (1V x 2). The organic phase was washed with an 1N aqueous solution of HCl (1V), with brine (1V), dried over Na2SO4, filtrated and concentrated under vacuum. The residue was purified by flash

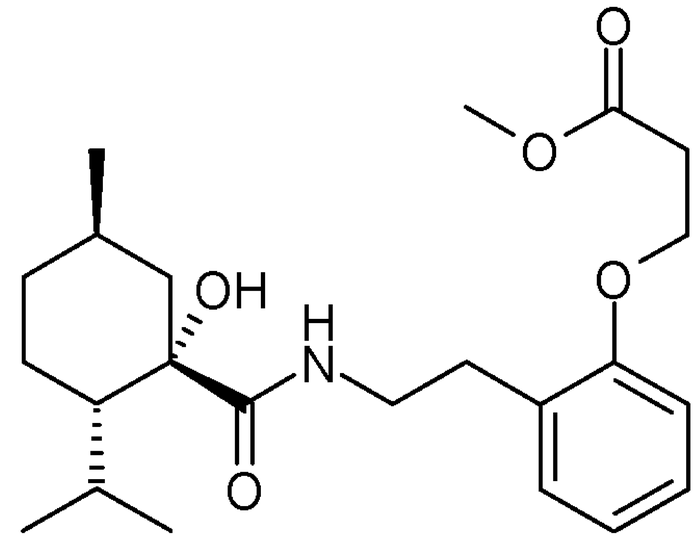
chromatography with cyclohexane and EtOAc to provide methyl 2-(3-(2-((tert-butoxycarbonyl)amino)ethyl)phenyl)acetate (998mg) as colorless oil.

Under deprotection conditions A, methyl 2-(3-(2-((tert-butoxycarbonyl)amino)ethyl)phenyl)acetate (996mg) in the presence of HCl (2M, 5.9eq) led to methyl 2-(3-(2-aminoethyl)phenyl)acetate hydrochloride (760mg) as white solid.

Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (0.64g) and methyl 2-(3-(2-aminoethyl)phenyl)acetate hydrochloride (1.05eq) [after amine addition, the reaction was heated at 50-55°C during 16hr] led to methyl 2-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) phenyl)acetate (564mg) as colorless wax after flash chromatography with cyclohexane and EtOAc.

Example 75

methyl 3-(2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenoxy)propanoate



Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (0.64g) and 2-(2-aminoethyl)phenol (1.03eq) [after amine addition, the reaction was heated at 55°C during 16hr] led to (1S,2S,5R)-1-hydroxy-N-(2-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (965mg) as white solid after flash chromatography with cyclohexane and EtOAc.

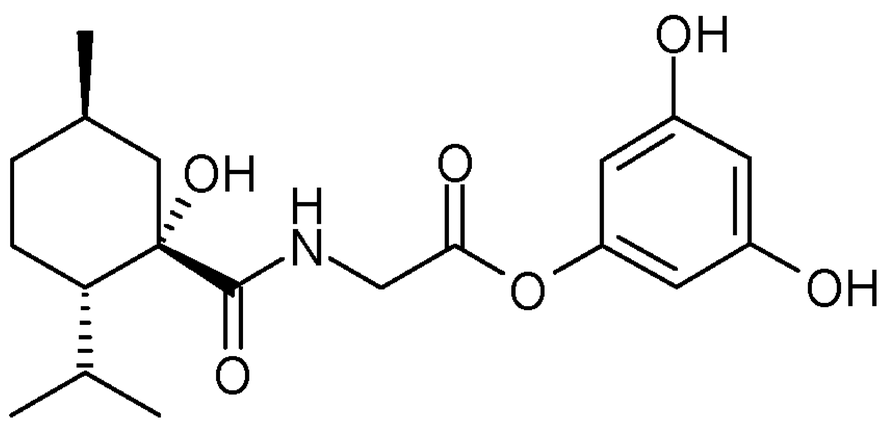
Under alkylation conditions C, (1S,2S,5R)-1-hydroxy-N-(2-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (400mg) in the presence of 3-bromo-1-propanol (1.1eq) led to (1S,2S,5R)-1-hydroxy-N-(2-(3-hydroxypropoxy)phenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (371mg) as colorless wax after flash chromatography with cyclohexane and EtOAc.

(1S,2S,5R)-1-Hydroxy-N-(2-(3-hydroxypropoxy)phenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (369mg) was dissolved in acetone (0.15M) and the resulting solution was cooled down to 0°C. Chromium trioxide (3.6eq) was added dropwise during 20min and the reaction mixture was stirred at 0°C during 2hr. Sodium metabisulfite was added and the resulting mixture was stirred at room temperature until the solution turned green. Water (10V) was added and the resulting solution was extracted with diethyl ether (10v x 2). The combined organic phase was washed with an 1N aqueous solution of sodium hydroxide (5V). The combined sodium hydroxide phases were acidified with an 5N aqueous solution of hydrochloric acid and were extracted with diethyl ether (10V x 2). All combined diethyl ether phases were washed with brine (10V), dried over Na2SO4, filtrated and concentrated under vacuum to provide 3-(2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenoxy)propanoic acid (211mg) as white foam.

3-(2-(2-((1S,2S,5R)-1-Hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenoxy)propanoic acid (199mg) was dissolved in DCM/methanol (2/1, 0.1M) and the resulting solution was cooled down to 0°C. A 2M trimethylsilyl-diazomethane solution in hexane (2.2eq) was added and after warming up to room temperature, the reaction mixture was stirred during 26hr. The reaction was quenched by dropwise addition of acetic acid (2.0eq) and the reaction mixture was then concentrated under vacuum. The residue was dissolved in DCM (5V), washed with a saturated aqueous solution of sodium bicarbonate (5V), with brine (5V), dried over Na2SO4 and concentrated under vacuum. The residue was purified by flash chromatography with cyclohexane and EtOAc to provide methyl 3-(2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenoxy) propanoate (165mg).

Example 76

3,5-dihydroxyphenyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate



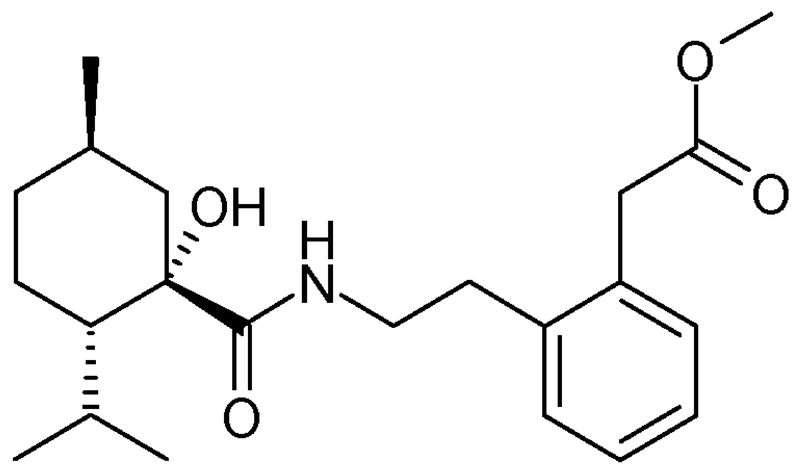
Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (1.0g) and glycine methyl ester hydrochloride (1.02eq) [after amine addition, the reaction was heated at 50-55°C during 3hr] led to methyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate (1.15g) as white solid.

Under saponification conditions, methyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate (1.15g) in the presence of sodium hydroxide (1M, 5eq) led to ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycine (862mg).

Under coupling conditions E, with ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycine (130mg) and phloroglucinol (3.0eq) led to 3,5-dihydroxyphenyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate (51mg) as white solid after flash chromatography with cyclohexane and EtOAc followed by preparative HPLC using Xselect CSH Prep C18 5ìm OBD 50x250m column with water and acetonitrile containing 0.1% formic acid.

Example 77

methyl 2-(2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenyl)acetate



Methyl 2-(2-bromophenyl)acetate (1.008g) and potassium tert-butyl N-[2-(trifluoroboranuidyl)ethyl]carbamate (1.1eq) as well as cesium carbonate (3.0eq) were dissolved in a 3/1 mixture of toluene and water (0.27M). the resulting solution was degassed using argon and 1,1'bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.04eq) was added. The reaction mixture was then heated at 80°C during 16hrs. Once at room temperature, EtOAc (1V) was added and the resulting mixture was washed with water (1V x 2). The organic phase was washed with an 1N aqueous solution of HCl (1V), with brine (1V), dried over Na2SO4, filtrated and concentrated under vacuum. The residue was purified by flash

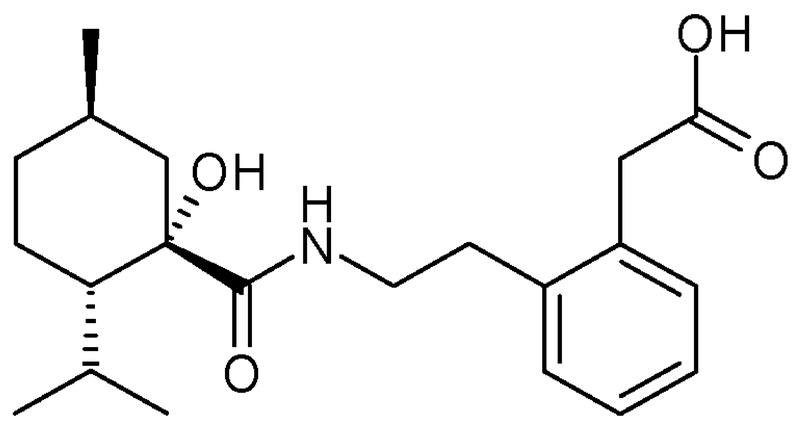
chromatography with cyclohexane and EtOAc to provide methyl 2-(2-(2-((tert-butoxycarbonyl)amino)ethyl)phenyl)acetate (1.039g).

Under deprotection conditions A, methyl 2-(2-(2-((tert-butoxycarbonyl)amino)ethyl)phenyl)acetate (1.036g) in the presence of HCl (2M, 5.0eq) led to methyl 2-(2-(2-aminoethyl)phenyl)acetate hydrochloride (760mg)

Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (150mg) and methyl 2-(2-(2-aminoethyl)phenyl)acetate hydrochloride (1.02eq) [after amine addition, the reaction was heated at 55°C during 4hr30 and at room temperature during 72hrs] led to methyl 2-(2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenyl)acetate (360mg) as colorless wax after flash chromatography with cyclohexane and EtOAc followed by preparative HPLC using Xselect CSH Prep C18 5ìm OBD 50x250m column with water and acetonitrile containing 0.1% formic acid.

Example 78

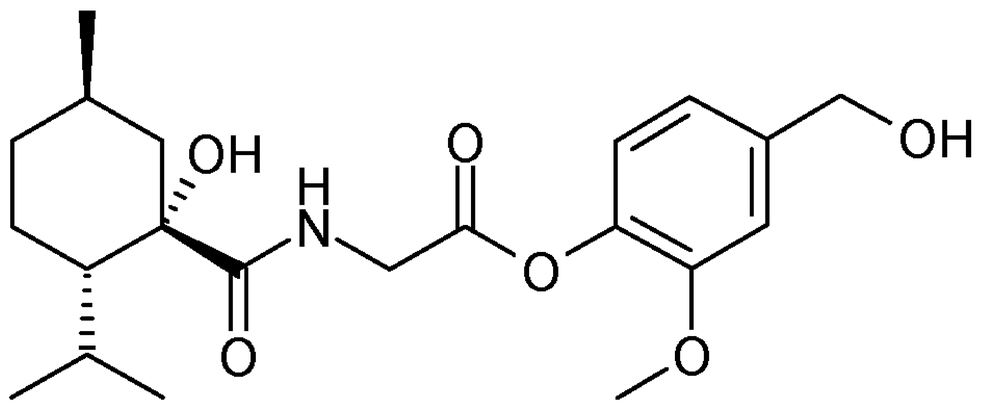
2-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) phenyl)acetic acid



Under saponification condition, methyl 2-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) phenyl)acetate (460mg) in the presence of sodium hydroxide (1M, 4.08eq) led to 2-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) phenyl)acetic acid (436mg) as a white solid.

Example 79

4-(hydroxymethyl)-2-methoxyphenyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate



Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (1.0g) and glycine methyl ester hydrochloride (1.02eq) [after amine addition, the reaction was heated at 50-55°C during 3hr] led to methyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate (1.15g) as white solid.

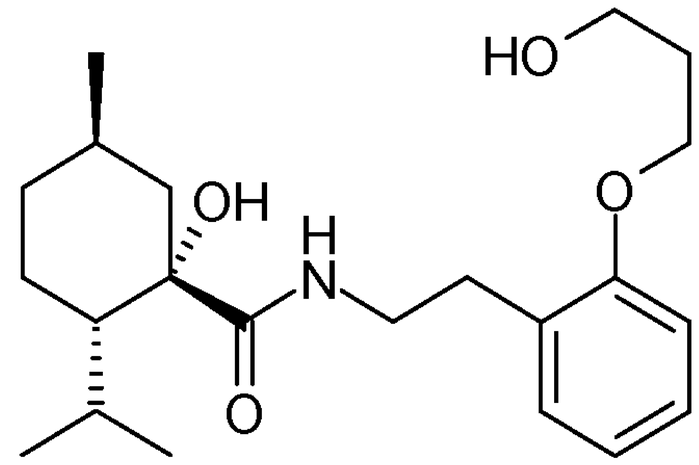
Under saponification conditions, methyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate (1.15g) in the presence of sodium hydroxide (1M, 5eq) led to ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycine (862mg).

Under coupling conditions E, with ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycine (90mg) and vanillin (12eq) led to 4-formyl-2-methoxyphenyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate (110mg) as yellow wax after flash chromatography with cyclohexane and EtOAc.

Under reduction conditions C, 4-formyl-2-methoxyphenyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate (108mg) in the presence of $NaBH_4$ (1.1eq) led to 4-(hydroxymethyl)-2-methoxyphenyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate (29mg) after preparative HPLC using Xselect CSH Prep C18 5µm OBD 50x250m column with water and acetonitrile containing 0.1% formic acid.

Example 80

(1S,2S,5R)-1-hydroxy-N-(2-(3-hydroxypropoxy)phenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide

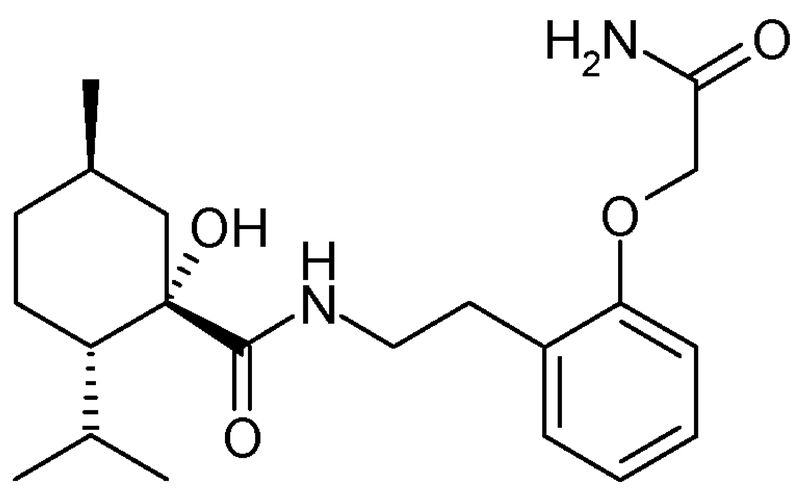


Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (1.4g) and 2-(2-aminoethyl)phenol (1.03eq) [after amine addition, the reaction was heated at 65°C during 4hr] led to (1S,2S,5R)-1-hydroxy-N-(2-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (1.296g) as brown solid after flash chromatography with cyclohexane and EtOAc.

Under alkylation conditions C, (1S,2S,5R)-1-hydroxy-N-(2-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (100mg) in the presence of 3-bromo-1-propanol (1.1eq) led to (1S,2S,5R)-1-hydroxy-N-(2-(3-hydroxypropoxy)phenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (77.6mg) as colorless wax after flash chromatography with cyclohexane and EtOAc.

Example 81

(1S,2S,5R)-N-(2-(2-amino-2-oxoethoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methyl cyclohexane-1-carboxamide

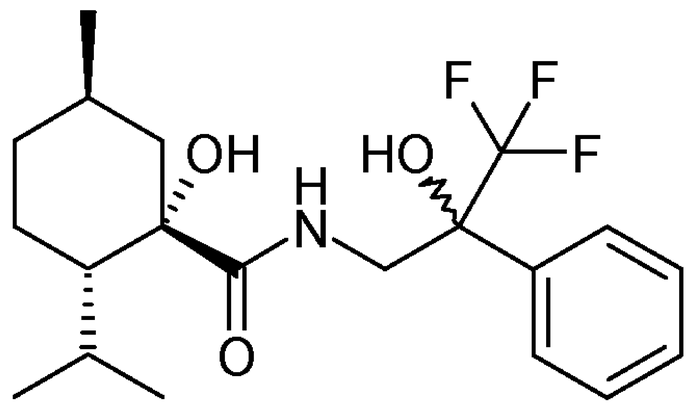


Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (1.4g) and 2-(2-aminoethyl)phenol (1.03eq) [after amine addition, the reaction was heated at 65°C during 4hr] led to (1S,2S,5R)-1-hydroxy-N-(2-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (1.296g) as brown solid after flash chromatography with cyclohexane and EtOAc.

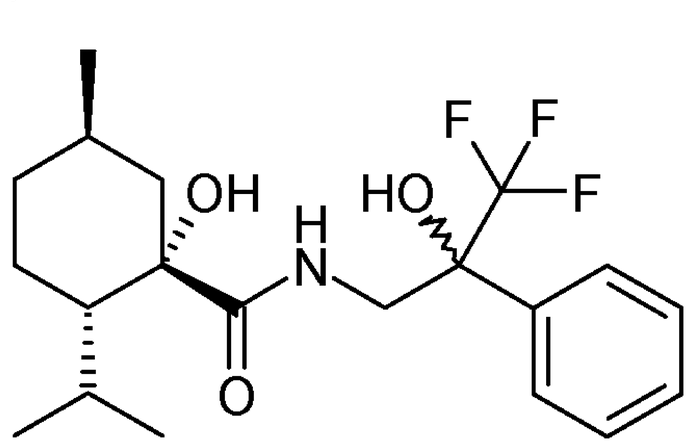
Under alkylation conditions C, (1S,2S,5R)-1-hydroxy-N-(2-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (100mg) in the presence of 2-bromoacetamide (1.2eq) led to (1S,2S,5R)-N-(2-(2-amino-2-oxoethoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (85.2mg) as white foam after flash chromatography with cyclohexane and EtOAc.

Examples 82 & 83

*(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-((3RS)-3,3,3-trifluoro-2-hydroxy-2-phenylpropyl) cyclohexane-1-carboxamide (**82**)*



*(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-((3RS)-3,3,3-trifluoro-2-hydroxy-2-phenylpropyl) cyclohexane-1-carboxamide (**83**)*



Trifluoroacetophenone (400µl) and potassium carbonate (0.97eq) were dissolved in nitromethane (8.93eq) at room temperature. The reaction mixture was stirred during 1hr. Water (10V) and EtOAc (10V) were added. The aqueous phase was extracted with EtOAc (10V). The combined organic phases were washed with an 1N aqueous solution of HCl (10V), with brine (10V), dried over Na_2SO_4, filtrated and concentrated under vacuum to give 1,1,1-Trifluoro-3-nitro-2-phenylpropan-2-ol (648mg) as colorless oil.

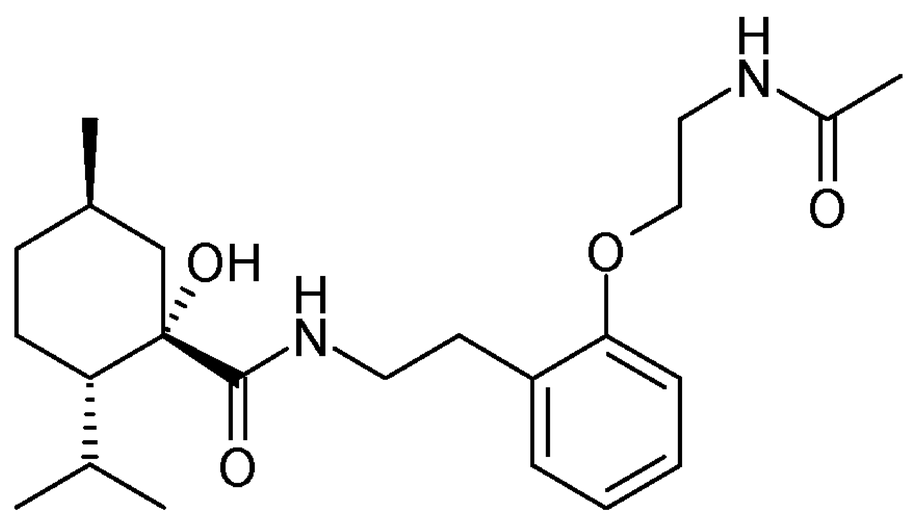
1,1,1-Trifluoro-3-nitro-2-phenylpropan-2-ol (646mg) was dissolved in methanol (0.27M) and Pd on charcoal (0.08eq) was added. The resulting solution was then put under hydrogen atmosphere and the reaction mixture was stirred at room temperature under hydrogen atmosphere during

8hrs. The solution was filtrated on GF/F Whatman filter paper and the filter paper was rinsed with methanol: the filtrate was concentrated under vacuum. The residue was dissolved in diethyl ether (1V) and an 1N aqueous solution of HCl (1V) was added. The organic phase was then washed again with 1N aqueous solution of HCl (1V), The combined HCl phases were then brought to pH 12 by addition of a concentrated solution of sodium hydroxide. The resulting aqueous was then extracted with diethyl ether (1V x 4). The combined organic phases were dried over Na_2SO_4, filtrated and concentrated under vacuum. The residue was purified by flash chromatography with DCM and methanol to yield 3-amino-1,1,1-trifluoro-
2-phenylpropan-2-ol (318mg) as white solid.

Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (1.4g) and the previously isolated amine (1.02eq) [after amine addition, the reaction was heated at 65°C during 21hr] led to (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-((3RS)-3,3,3-trifluoro-2-hydroxy-2-phenylpropyl) cyclohexane-1-carboxamide (***example 82***, 77mg) and (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-((3RS)-3,3,3-trifluoro-2-hydroxy-2-phenylpropyl) cyclohexane-1-carboxamide (***example 83***, 74mg) as white solid for both after preparative HPLC using Xselect CSH Prep C18 5µm OBD 50x250m column with water and acetonitrile containing 0.1% formic acid.

Example 84

(1S,2S,5R)-N-(2-(2-acetamidoethoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide



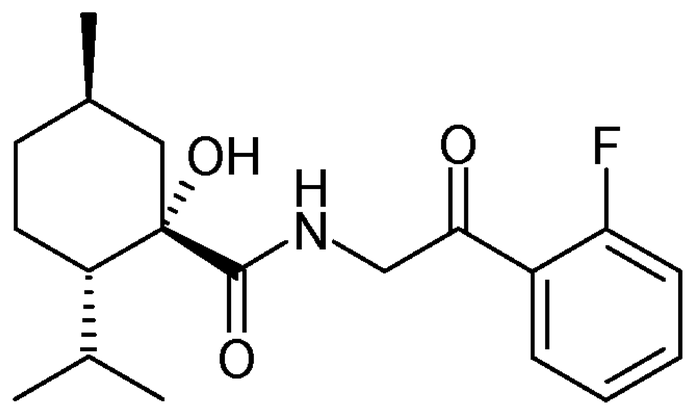
Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (1.4g) and 2-(2-aminoethyl)phenol (1.03eq) [after amine addition, the reaction was heated at 65°C during 4hr] led to the desired amide (1.296g) as brown solid after flash chromatography with cyclohexane and EtOAc.

Under alkylation conditions A, the previously amide (150mg) in the presence of tert-butyl N-(2-bromoethyl)carbamate (1.5eq) led to tert-butyl (2-(2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenoxy)ethyl)carbamate (196mg) after flash chromatography with cyclohexane/EtOAc.

Under deprotection conditions B, tert-butyl (2-(2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenoxy)ethyl)carbamate in the presence of TFA(3.06eq) led to (1S,2S,5R)-N-(2-(2-aminoethoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (118mg). (1S,2S,5R)-N-(2-(2-Aminoethoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (118mg) was then dissolved in DCM (0.1M) followed by addition of triethylamine (1.15eq). The resulting solution was cooled down to 0°C and acetic anhydride (0.76eq) was added. The reaction was stirred at room temperature during 16hrs. After addition of DCM (10V), the resulting solution was washed with water (10V), an 1N aqueous solution of HCl (10V), brine (10V), dried over Na_2SO_4, filtrated and concentrated under vacuum. The residue was purified by flash chromatography with cyclohexane and EtOAc to yield (1S,2S,5R)-N-(2-(2-acetamidoethoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (113mg).

Example 85

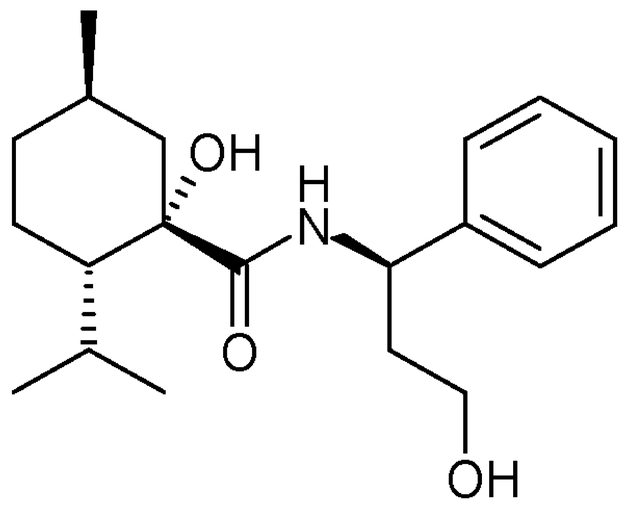
(1S,2S,5R)-N-(2-(2-fluorophenyl)-2-oxoethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (150mg) and 2-amino-1-(2-fluorophenyl)ethanone hydrochloride (1.02eq) [after amine addition, the reaction was heated at 65°C during 16hr] led to (1S,2S,5R)-N-(2-(2-fluorophenyl)-2-oxoethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (139mg) as colorless wax after flash chromatography with cyclohexane and EtOAc.

Example 86

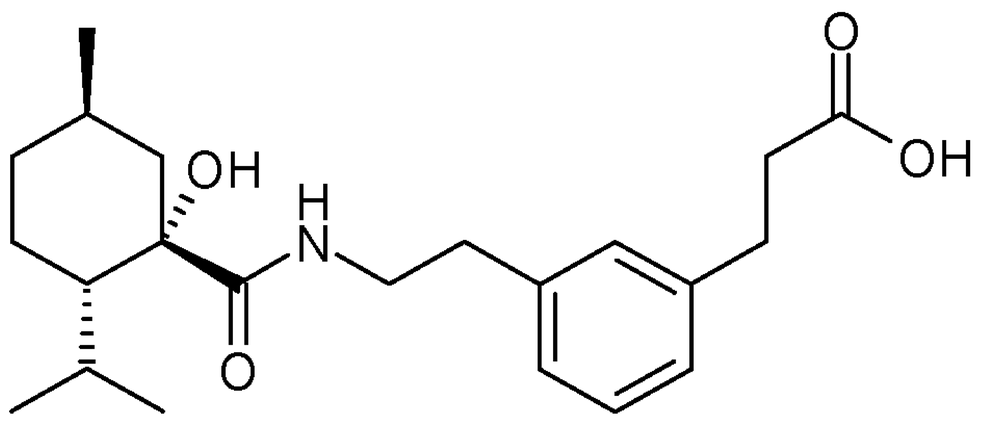
(1S,2S,5R)-1-hydroxy-N-((R)-3-hydroxy-1-phenylpropyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (120mg) and (1R)-1-phenyl-3-propanolamine (1.02eq) [after amine addition, the reaction was heated at 65°C during 16hr] led to (1S,2S,5R)-1-hydroxy-N-((R)-3-hydroxy-1-phenylpropyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (49mg) as white solid after flash chromatography with cyclohexane and EtOAc.

Example 87

3-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) phenyl)propanoic acid



Methyl 2-(3-bromophenyl)acetate (977mg) and potassium tert-butyl N-[2-(trifluoroboranuidyl)ethyl]carbamate (1.1eq) as well as cesium carbonate (3.0eq) were dissolved in a 3/1 mixture of toluene and water (0.27M). The resulting solution was degassed using argon and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (0.04eq) was added. The reaction mixture was then heated at 80°C during 16hrs. Once at room temperature, EtOAc (1V) was added and the resulting mixture was washed with water (1V x 2). The organic phase was washed with an 1N aqueous solution of HCl (1V), with brine (1V), dried

over Na_2SO_4, filtrated and concentrated under vacuum. The residue was purified by flash chromatography with cyclohexane and EtOAc to provide methyl 3-(3-(2-((tert-butoxycarbonyl)amino)ethyl)phenyl)propanoate (872mg) as colorless oil.

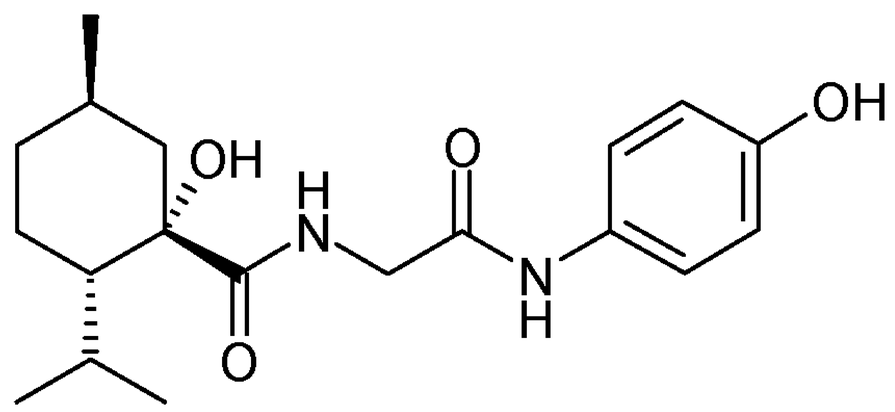
Under deprotection conditions A, methyl 3-(3-(2-((tert-butoxycarbonyl)amino)ethyl)phenyl)propanoate (870mg) in the presence of HCl (1M, 4.95eq) led to methyl 3-(3-(2-aminoethyl)phenyl)propanoate hydrochloride (387mg).

Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (200mg) and methyl 3-(3-(2-aminoethyl)phenyl)propanoate hydrochloride (1.03eq) [after amine addition, the reaction was heated at 55°C during 16hr] led to methyl 3-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenyl)propanoate (250mg) as colorless wax after flash chromatography with cyclohexane and EtOAc.

Under saponification conditions, methyl 3-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)phenyl)propanoate (170mg) in the presence of sodium hydroxide (4.6eq) led to 3-(3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) phenyl)propanoic acid (149mg).

Example 88

(1S,2S,5R)-1-hydroxy-N-(2-((4-hydroxyphenyl)amino)-2-oxoethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide



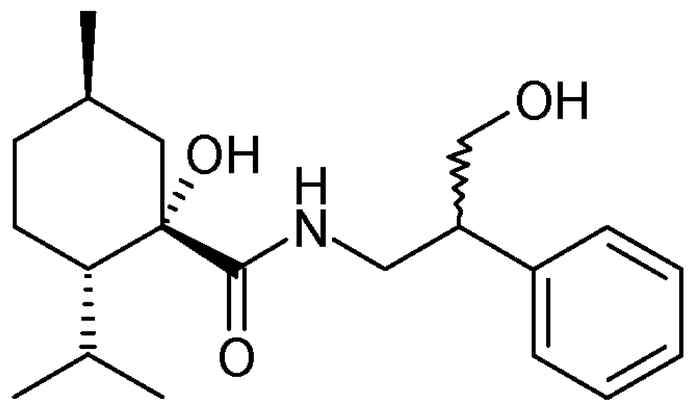
Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (0.5g) and glycine methyl ester hydrochloride (1.02eq) [after amine addition, the reaction was heated at 65°C during 16hr30] led to methyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate (577mg) as white solid.

Under saponification conditions, methyl ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycinate (577mg) in the presence of sodium hydroxide (12M, 4.8eq) led to ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycine (470mg).

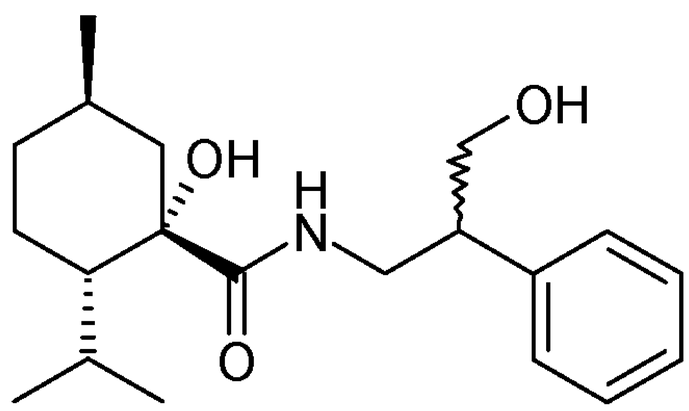
Under coupling conditions E, with ((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carbonyl)glycine (90mg) and 4-aminophenol (1.3eq) led to (1S,2S,5R)-1-hydroxy-N-(2-((4-hydroxyphenyl)amino)-2-oxoethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (158mg) as white solid.

Examples 89 & 90

*(1S,2S,5R)-1-hydroxy-N-((2RS)- 3-hydroxy-2-phenylpropyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (**89**)*



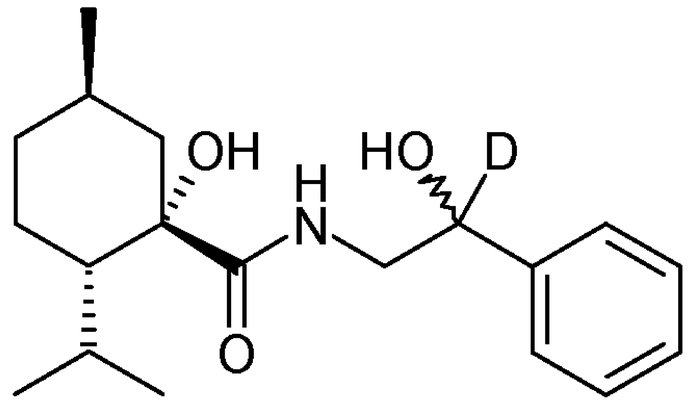
*(1S,2S,5R)-1-hydroxy-N-((2RS)- 3-hydroxy-2-phenylpropyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (**90**)*



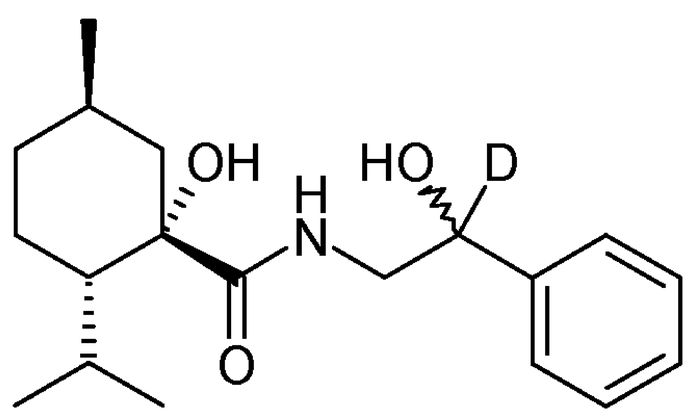
Chiral separation of (1S,2S,5R)-1-hydroxy-N-(3-hydroxy-2-phenylpropyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (103.7mg) carried out by liquid chromatography using CHIRALPAK IA with heptane and ethanol led to (1S,2S,5R)-1-hydroxy-N-(3-hydroxy-2-phenylpropyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (***example 89***, 43mg) and (1S,2S,5R)-1-hydroxy-N-(3-hydroxy-2-phenylpropyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (***example 90,*** 45mg).

Examples 91 & 92

*(1S,2S,5R)-1-hydroxy-N-((2RS)-2-hydroxy-2-phenylethyl-2-d)-2-isopropyl-5-methylcyclohexane-1-carboxamide (**91**)*



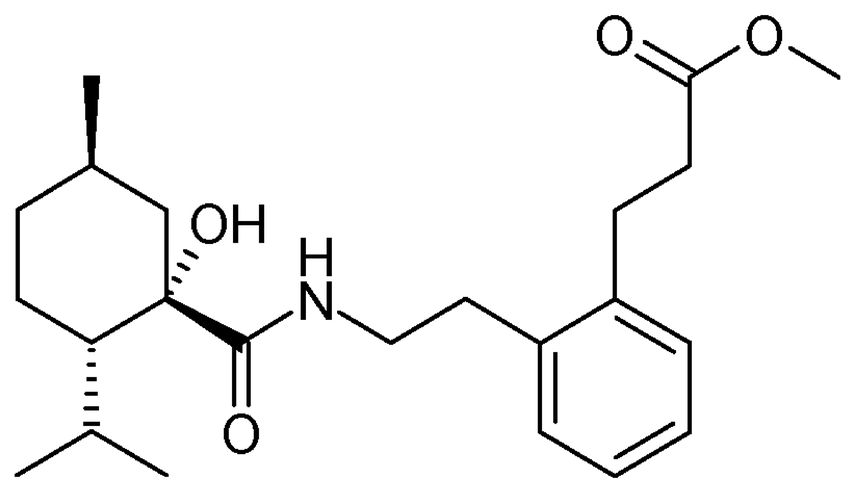
*(1S,2S,5R)-1-hydroxy-N-((2RS)-2-hydroxy-2-phenylethyl-2-d)-2-isopropyl-5-methylcyclohexane-1-carboxamide (**92**)*



Chiral separation of (1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-phenylethyl-2-d)-2-isopropyl-5-methylcyclohexane-1-carboxamide (245.1mg) carried out by liquid chromatography using CHIRALPAK IA with heptane and ethanol led to (1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-phenylethyl-2-d)-2-isopropyl-5-methylcyclohexane-1-carboxamide (***example 91***, 134mg) and (1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-phenylethyl-2-d)-2-isopropyl-5-methylcyclohexane-1-carboxamide (***example 92,*** 117mg).

Example 93

methyl 3-(2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido) ethyl)phenyl)propanoate



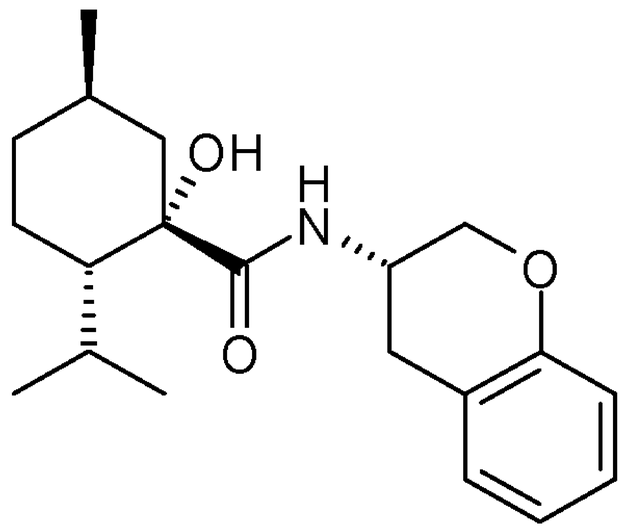
Methyl 2-(3-bromophenyl)acetate (1.01g) and potassium tert-butyl N-[2-(trifluoroboranuidyl)ethyl]carbamate (1.1eq) as well as cesium carbonate (3.0eq) were dissolved in a 3/1 mixture of toluene and water (0.35M). The resulting solution was degassed using argon and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (0.04eq) was added. The reaction mixture was then heated at 80°C during 16hrs. Once at room temperature, EtOAc (1V) was added and the resulting mixture was washed with water (1V x 2). The organic phase was washed with an 1N aqueous solution of HCl (1V), with brine (1V), dried over Na2SO4, filtrated and concentrated under vacuum. The residue was purified by flash chromatography with cyclohexane and EtOAc to provide methyl 3-(2-(2-((tert-butoxycarbonyl)amino)ethyl)phenyl)propanoate (961mg) as colorless oil.

Under deprotection conditions A, the tert-butyl N-carbamate (870mg) in the presence of HCl (1M, 5.0eq) led to methyl 3-(2-(2-aminoethyl)phenyl)propanoate hydrochloride (640mg).

Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (170mg) and methyl 3-(2-(2-aminoethyl)phenyl)propanoate hydrochloride (1.04eq) [after amine addition, the reaction was heated at 65°C during 16hr] led to methyl 3-(2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido) ethyl)phenyl)propanoate (170mg) as white solid after flash chromatography with cyclohexane and EtOAc.

Example 94

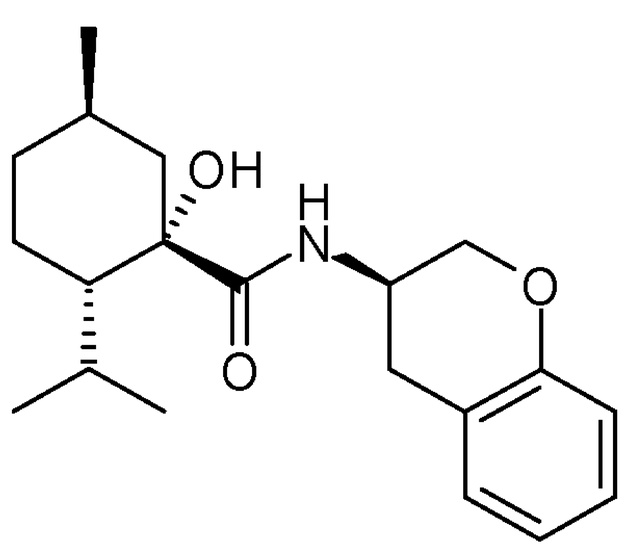
(1S,2S,5R)-N-((3S)-chroman-3-yl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (120mg) and (3S)-chroman-3-amine hydrochloride (1.03eq) [after amine addition, the reaction was heated at 65°C during 16hr] led to (1S,2S,5R)-N-((3S)-chroman-3-yl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (65mg) as white solid after flash chromatography with cyclohexane and EtOAc.

Example 95

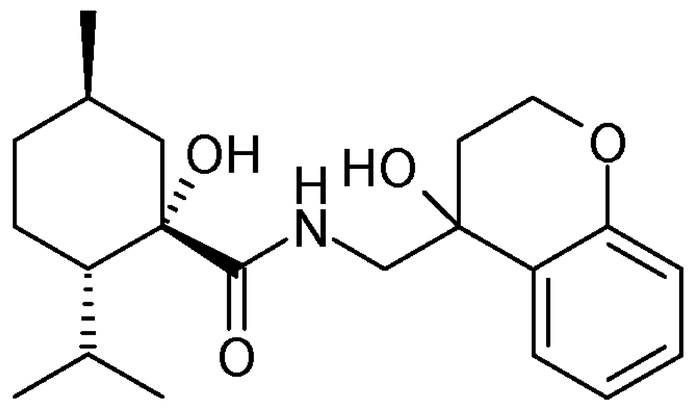
(1S,2S,5R)-N-((3R)-chroman-3-yl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (120mg) and (3R)-chroman-3-amine hydrochloride (1.03eq) [after amine addition, the reaction was heated at 65°C during 16hr] led to (1S,2S,5R)-N-((3R)-chroman-3-yl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (46mg) as white solid after flash chromatography with cyclohexane and EtOAc.

Example 96

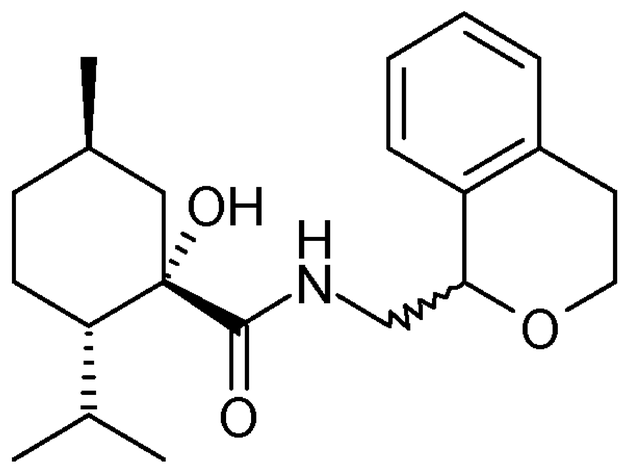
(1S,2S,5R)-1-hydroxy-N-((4-hydroxychroman-4-yl)methyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide



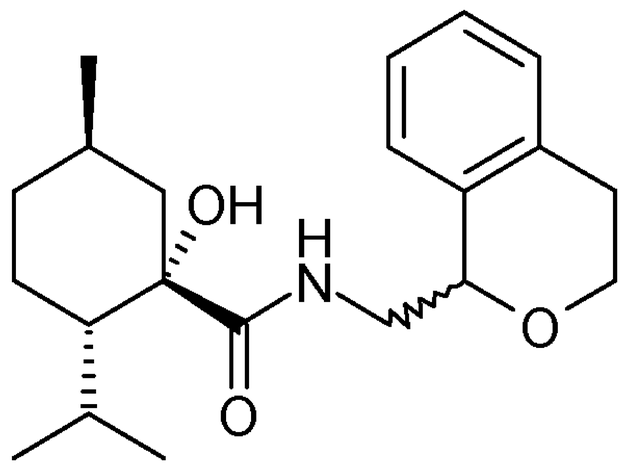
Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (150mg) and (3R)-chroman-3-amine hydrochloride (1.04eq) [after amine addition, the reaction was heated at 60°C during 16hr] led to (1S,2S,5R)-1-hydroxy-N-((4-hydroxychroman-4-yl)methyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (210mg) as white solid after flash chromatography with cyclohexane and EtOAc.

Examples 97 and 98

*(1S,2S,5R)-1-hydroxy-N-((1RS)-isochroman-1-ylmethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (**97**)*



*(1S,2S,5R)-1-hydroxy-N-((1RS)-isochroman-1-ylmethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (**98**)*

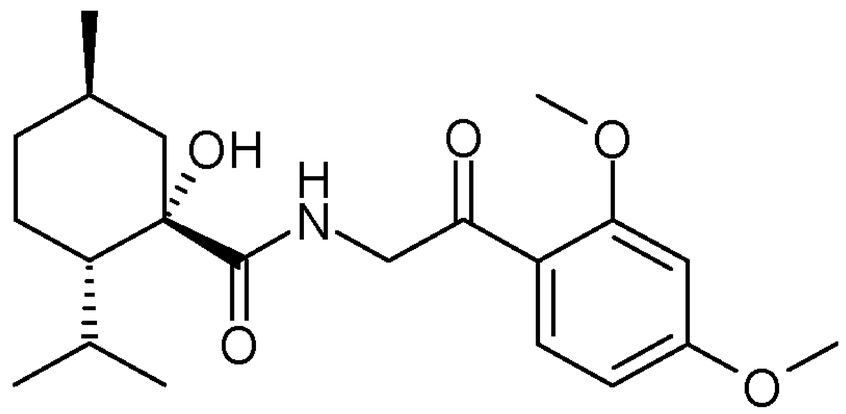


Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (150mg) and (3,4-dihydro-1H-isochromen-1-ylmethyl)amine hydrochloride (1.04eq) [after amine addition, the reaction was heated at 60°C during 16hr] led to (1S,2S,5R)-1-hydroxy-N-((1RS)-isochroman-1-ylmethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide

(***example 97***, 84mg) and (1S,2S,5R)-1-hydroxy-N-((1RS)-isochroman-1-ylmethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (***example 98***, 110mg)as white solid after flash chromatography with cyclohexane and EtOAc.

Example 99

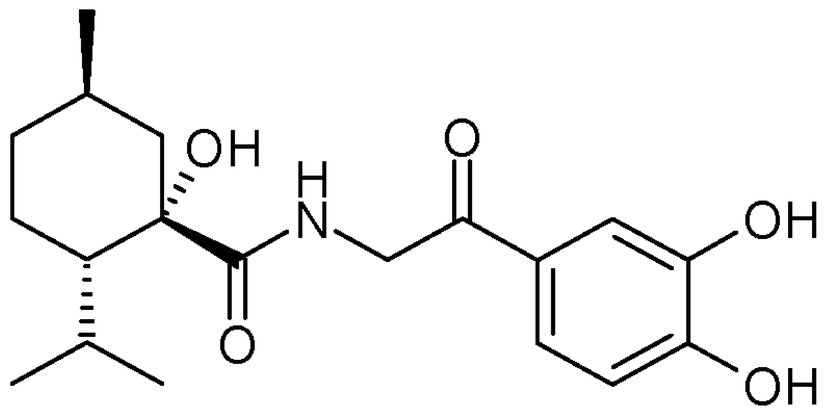
(1S,2S,5R)-N-(2-(2,4-dimethoxyphenyl)-2-oxoethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (350mg) and 2-(2,4-dimethoxyphenyl)-2-oxoethan-1-aminium chloride (1.04eq) [after amine addition, the reaction was heated at 60°C during 16hr] led to (1S,2S,5R)-N-(2-(2,4-dimethoxyphenyl)-2-oxoethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (549mg) as white solid after flash chromatography with cyclohexane and EtOAc.

Example 100

(1S,2S,5R)-N-(2-(3,4-dihydroxyphenyl)-2-oxoethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide

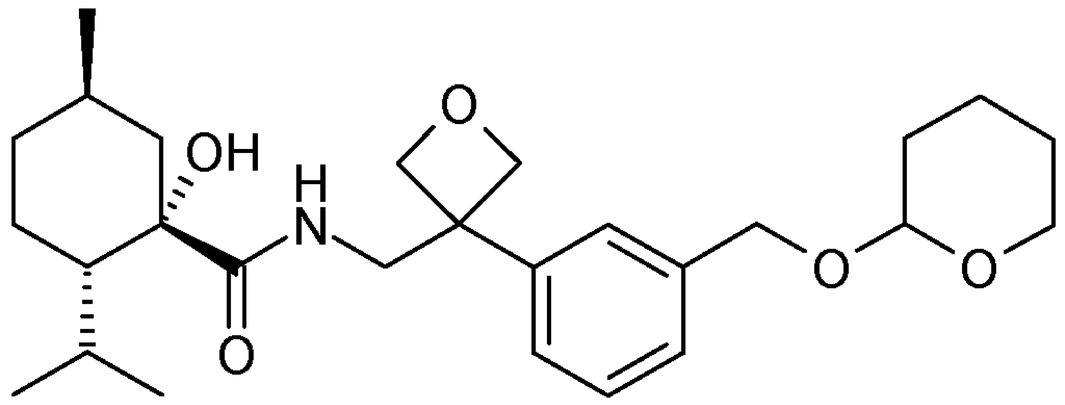


Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (450mg) and 2-(3,4-dimethoxyphenyl)-2-oxoethan-1-aminium chloride (1.04eq) [after amine addition, the reaction was heated at 65°C during 16hr] led to (1S,2S,5R)-N-(2-(3,4-dimethoxyphenyl)-2-oxoethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (605mg) as white solid after flash chromatography with cyclohexane and EtOAc.

(1S,2S,5R)-N-(2-(3,4-Dimethoxyphenyl)-2-oxoethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (445mg) was dissolved in DCM under argon and cooled down to 0°C. BBr3 (3.31eq) was then added dropwise and the reaction was kept under stirring during 10min. Once at room temperature, the reaction mixture was stirred during 6hrs. Before addition of methanol (3ml), the reaction mixture was cooled to 0°C. The resulting solution was concentrated under vacuum and the residue was dissolved in EtOAc (2V). Water (2V) was added and the aqueous phase was extracted with EtOAc (2V x2). The combined organic phases were washed with brine, dried over Na_2SO_4, filtrated and concentrated under vacuum. The residue was purified by preparative HPLC using Xselect CSH Prep C18 5µm OBD 50x250m column with water and acetonitrile containing 0.1% formic acid to give (1S,2S,5R)-N-(2-(3,4-dihydroxyphenyl)-2-oxoethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (194mg) as pink-orange solid.

Example 101

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-((3-(3-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)oxetan-3-yl)methyl)cyclohexane-1-carboxamide



To chloro(1,5-cyclooctadiene)rhodium(I) dimer suspension (0.05eq) in 1,4-dioxane (21ml) was added potassium hydroxide (1.5M, 1.3eq) at room temperature. Ethyl 2-(oxetan-3-ylidene)acetate (1.0g) was added dropwise followed by portionwise addition of 3-(hydroxymethyl)phenylboronic acid (1.6eq). The reaction mixture was stirred at room temperature during 4hrs. EtOAc (1V) was added and the resulting organic solution was washed with water (1V x 2), brine (1V), dried over Na2SO4, filtrated and concentrated under vacuum. The residue was purified by flash chromatography with cyclohexane and EtOAc to isolate ethyl 2-(3-(3-(hydroxymethyl)phenyl)oxetan-3-yl)acetate (1.356g) as pale-yellow oil.

Ethyl 2-(3-(3-(hydroxymethyl)phenyl)oxetan-3-yl)acetate (1.355g) was dissolved in DCM and 3,4-dihydro-2H-pyran (3.14eq) was added as well as PPTS (0.20eq). The reaction mixture was

sonicated and stirred at room temperature during 16hr30. DCM (1V) was added and the organic phase was washed with water (1V), brine (1V), dried over Na_2SO_4, filtrated and concentrated under vacuum to yield ethyl 2-(3-(3-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)oxetan-3-yl)acetate (1.82g) as pale yellow oil.

Ethyl 2-(3-(3-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)oxetan-3-yl)acetate (1.81g) was dissolved in THF/Ethanol (0.15M) and NaOH (12N, 4.44eq) was added. The reaction mixture was stirred at room temperature during 17hrs. Solvents were removed and water (5V) was added to the remaining solution: this mixture was extracted with diethyl ether (5V). The aqueous phase was acidified up to pH 1 with HCl 1N and was extracted with diethyl ether (5V x 2). The combined organic phases were dried over Na_2SO_4, filtrated and concentrated under vacuum to give 2-(3-(3-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)oxetan-3-yl)acetic acid (1.57g) as yellow wax.

2-(3-(3-(((Tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)oxetan-3-yl)acetic acid (1.455g) was dissolved in toluene and under argon, triethylamine (1.1eq) was added followed by addition of diphenylphosphoryl azide (1.05eq). The reaction mixture was then stirred at 80°C during 25min. Once at room temperature, 2-(trimethylsilyl)ethanol was added and after this addition the reaction was stirred at 80°C during 4hr45. Once at room temperature, EtOAc (5V) was added and the resulting mixture was washed with an 1N aqueous solution of citric acid (5V), a saturated aqueous solution of sodium bicarbonate (5V), brine (5V), dried over Na_2SO_4, filtrated and concentrated under vacuum. The residue was purified by flash chromatography with cyclohexane and EtOAc to yield 2-(trimethylsilyl)ethyl ((3-(3-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)oxetan-3-yl)methyl)carbamate (1.337g) as colorless oil.

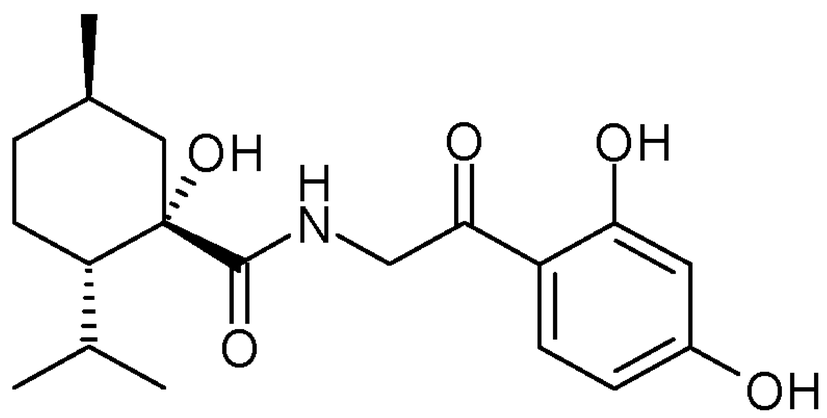
2-(Trimethylsilyl)ethyl ((3-(3-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)oxetan-3-yl)methyl)carbamate (404mg) was dissolved in DMF (0.2M) and CsF (2.89eq) was added. The reaction mixture was stirred at 60°C during 20hrs. An 1N aqueous solution of sodium hydroxide (5V) was added and the resulting mixture was extracted with EtOAc (5V x 2). The combined organic phases were washed with an 1N aqueous solution of sodium hydroxide (5V), brine (5V), dried over Na_2SO_4, filtrated and concentrated under vacuum to provide (3-(3-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)oxetan-3-yl)methanamine (265mg) as yellow oil.

Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (170mg) and (3-(3-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)oxetan-3-

yl)methanamine (1.12eq) [after amine addition, the reaction was heated at 60°C during 16hr] led to (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-((3-(3-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)oxetan-3-yl)methyl)cyclohexane-1-carboxamide (289mg) as white solid after flash chromatography with cyclohexane and EtOAc.

Example 102

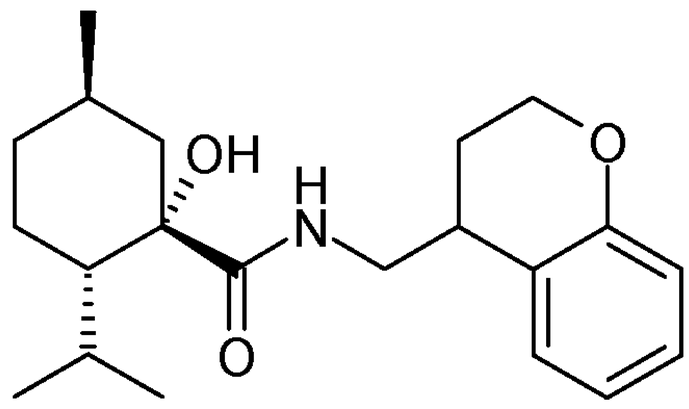
(1S,2S,5R)-N-(2-(2,4-dihydroxyphenyl)-2-oxoethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide



(1S,2S,5R)-N-(2-(2,4-dimethoxyphenyl)-2-oxoethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (470mg) was dissolved in DCM (0.1M) under argon and cooled down to 0°C. BBr_3 (6.6eq) was then added dropwise and the reaction was kept under stirring during 10min. Once at room temperature, the reaction mixture was stirred during 24hrs. The reaction was then stirred during 16hrs at reflux. Before addition of methanol (5ml), the reaction mixture was cooled to 0°C. The resulting solution was concentrated under vacuum and the residue was dissolved in EtOAc (2V). Water (2V) was added and the aqueous phase was extracted with EtOAc (2V x2). The combined organic phases were washed with brine, dried over Na_2SO_4, filtrated and concentrated under vacuum. The residue was purified by preparative HPLC using Xselect CSH Prep C18 5µm OBD 50x250m column with water and acetonitrile containing 0.1% formic acid to give (1S,2S,5R)-N-(2-(2,4-dihydroxyphenyl)-2-oxoethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (7.5mg) as ecru solid.

Example 103

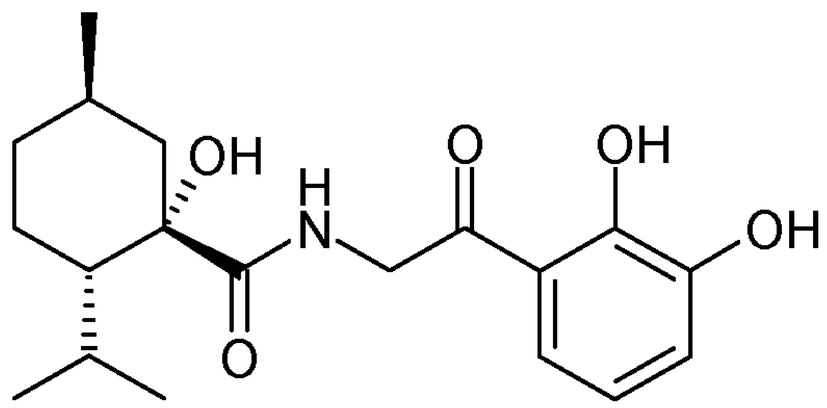
(1S,2S,5R)-N-(chroman-4-ylmethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (134mg) and 3,4-dihydro-2H-1-benzopyran-4-ylmethanamine (1.04eq) [after amine addition, the reaction was heated at 60°C during 16hr] led to (1S,2S,5R)-N-(chroman-4-ylmethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (148mg) as white solid after flash chromatography with cyclohexane and EtOAc.

Example 104

(1S,2S,5R)-N-(2-(2,3-dihydroxyphenyl)-2-oxoethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (1.49eq) and 2-amino-1-(2,3-dimethoxyphenyl)ethane-1-ol (322mg) [after amine addition, the reaction was heated at 60°C during 21hr] led to (1S,2S,5R)-N-(2-(2,3-dimethoxyphenyl)-2-hydroxyethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (122mg) as white solid after flash chromatography with cyclohexane and EtOAc.

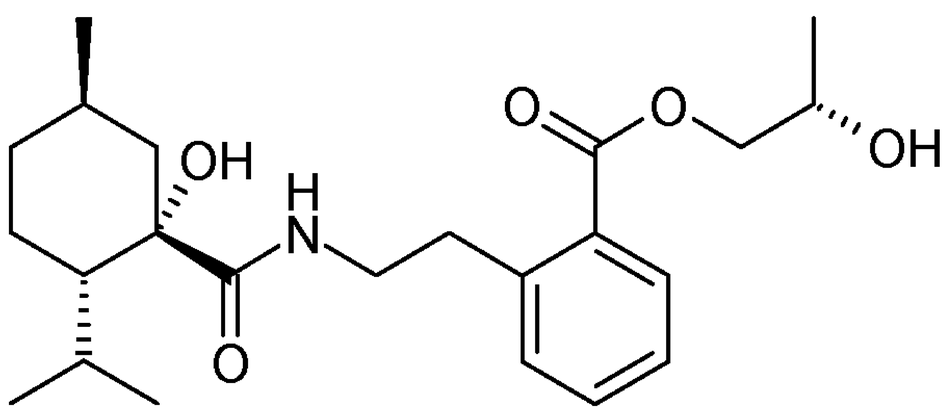
(1S,2S,5R)-N-(2-(2,3-Dimethoxyphenyl)-2-hydroxyethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (121mg) was dissolved in DCM (0.15M) and once cooled down to 0°C, the Dess-Martin reagent (1.7eq) was added portionwise. The reaction mixture was stirred at room temperature during 17hrs. DCM (10V) was added and the resulting organic solution was washed with an 20% aqueous of $Na_2S_2O_3$ (10V), an 1N aqueous solution of sodium hydroxide (10V), brine (10V), dried over Na_2SO_4, filtrated and concentrated under vacuum. The residue was purified by preparative HPLC using Xselect CSH Prep C18 5µm OBD 50x250m

column with water and acetonitrile containing 0.1% formic acid to give (1S,2S,5R)-N-(2-(2,3-dimethoxyphenyl)-2-oxoethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (111mg) as white solid.

(1S,2S,5R)-N-(2-(2,3-Dimethoxyphenyl)-2-oxoethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (110mg) was dissolved in DCM (0.1M) under argon and cooled down to 0°C. BBr3 (3.3eq) was then added dropwise and the reaction was kept under stirring during 10min. Once at room temperature, the reaction mixture was stirred during 4hrs. Before addition of methanol (2ml), the reaction mixture was cooled to 0°C. The resulting solution was concentrated under vacuum and the residue was dissolved in EtOAc (2V). Water (2V) was added and the aqueous phase was extracted with EtOAc (2V x2). The combined organic phases were washed with brine, dried over Na_2SO_4, filtrated and concentrated under vacuum. The residue was purified by preparative HPLC using Xselect CSH Prep C18 5µm OBD 50x250m column with water and acetonitrile containing 0.1% formic acid to give (1S,2S,5R)-N-(2-(2,3-dihydroxyphenyl)-2-oxoethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (49mg) as white solid.

Example 105

(S)-2-hydroxypropyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate



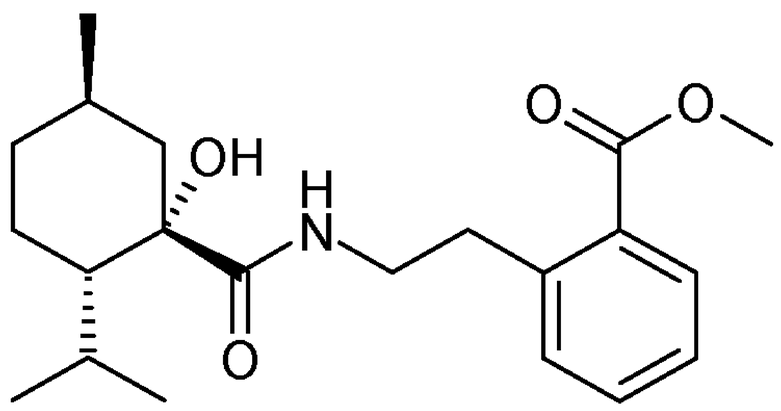
Under coupling conditions E, with 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoic acid (150mg) and (S)-2-((tert-butyldimethylsilyl)oxy) propan-1-ol (1.2eq) led to (S)-2-((tert-butyldimethylsilyl)oxy)propyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (177mg) as colorless wax after flash chromatography with cyclohexane and EtOAc.

(S)-2-((tert-Butyldimethylsilyl)oxy)propyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (166mg) was dissolved in methanol (0.1M)

and HCl (1N, 10.33eq) was added followed by addition of THF (0.6V). The reaction mixture was stirred at room temperature during 3hr. Once the solvent was removed, the remaining aqueous solution was extracted with EtOAc (5V x 2). The combined organic phases were washed with brine (5V), dried over Na_2SO_4, filtrated and concentrated under vacuum. The residue was purified by flash chromatography with cyclohexane and EtOAc to yield (S)-2-hydroxypropyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (94mg) as white solid.

Example 106

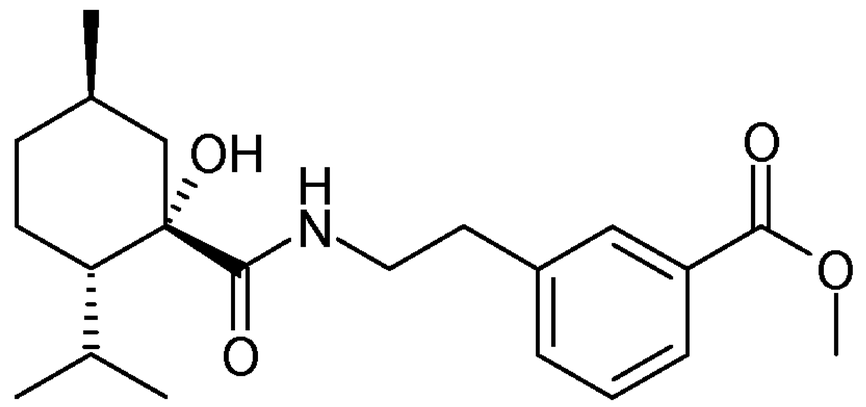
methyl 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate



Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (507mg) and methyl 2-(2-aminoethyl)benzoate hydrochloride (478mg) [after amine addition, the reaction was heated at 50°C during 16hr] led to methyl 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (358mg) as white powder after flash chromatography with cyclohexane and EtOAc.

Example 107

methyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate

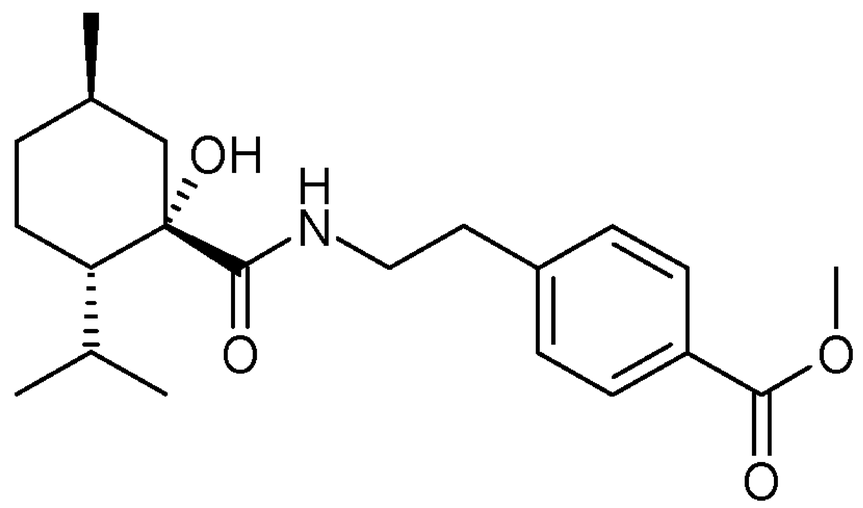


Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (404mg) and methyl 3-(2-aminoethyl)benzoate hydrochloride (478mg) [after

amine addition, the reaction was heated at 50°C during 16hr] led to methyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate (399mg) as white powder after flash chromatography with cyclohexane and EtOAc.

Example 108

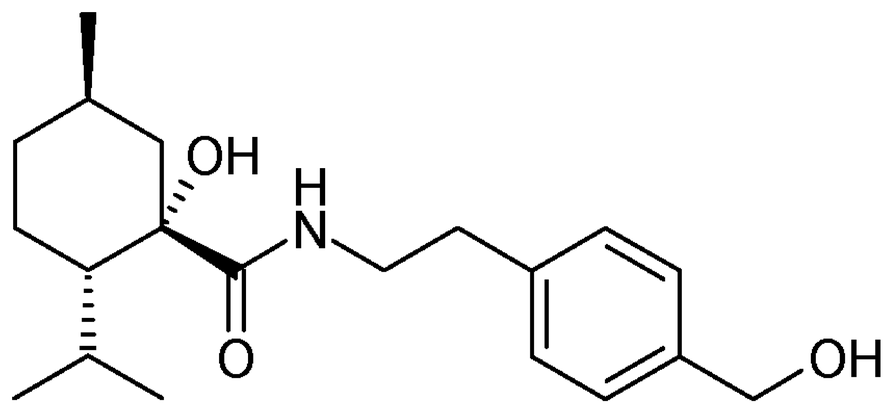
methyl 4-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido) ethyl)benzoate



Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (408mg) and methyl 4-(2-aminoethyl)benzoate hydrochloride (1.04eq) [after amine addition, the reaction was heated at 50°C during 6hr followed by 72hrs at room temperature] led to methyl 4-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido) ethyl)benzoate (389mg) as white solid after flash chromatography with cyclohexane and EtOAc.

Example 109

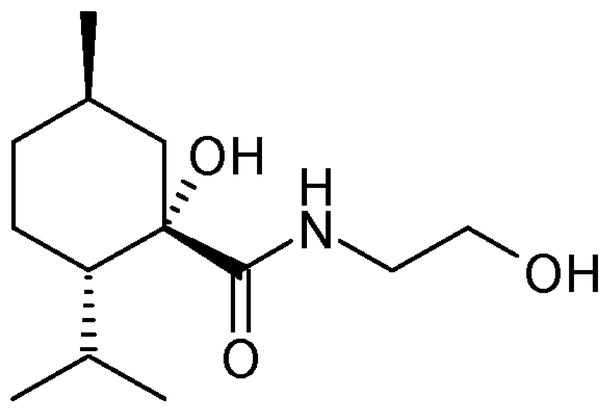
(1S,2S,5R)-1-hydroxy-N-(4-(hydroxymethyl)phenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under reduction condition A, methyl 4-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido) ethyl)benzoate (173mg) in the presence of NaBH4 (41.0eq) led to (1S,2S,5R)-1-hydroxy-N-(4-(hydroxymethyl)phenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (108mg) after flash chromatography with cyclohexane and EtOAc.

Example 110

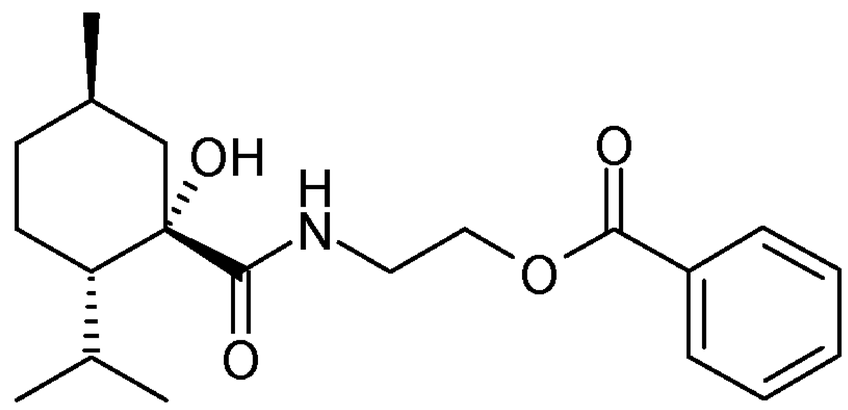
(1S,2S,5R)-1-hydroxy-N-(2-hydroxyethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide



Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (125mg) and ethanolamine (1.05eq) [after amine addition, the reaction was heated at 60°C during 5hr] led to (1S,2S,5R)-1-hydroxy-N-(2-hydroxyethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (87mg) as white solid after flash chromatography with cyclohexane and EtOAc.

Example 111

2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl benzoate



Under coupling conditions B, benzoic acid (700mg) and tert-butyl N-(2-hydroxyethyl)carbamate (1.1eq) [acetonitrile was replaced by DCM & after amine addition, the reaction was heated at 60°C during 2hr] led to 2-((tert-butoxycarbonyl)amino)ethyl benzoate (1.073g) as white solid.

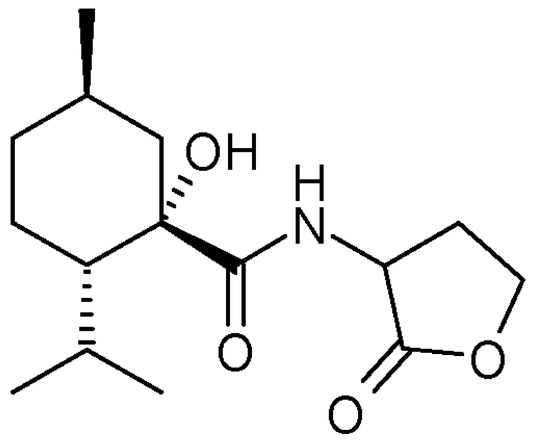
Under deprotection conditions A, 2-((tert-butoxycarbonyl)amino)ethyl benzoate (1.073g) in the presence of HCl (2M, 10eq) led to 2-aminoethyl benzoate hydrochloride (771mg).

Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (125mg) and 2-aminoethyl benzoate hydrochloride (1.1eq) [after amine addition, the reaction mixture was heated at 55°C during 66hr] led to 2-((1S,2S,5R)-1-hydroxy-2-isopropyl-

5-methylcyclohexane-1-carboxamido)ethyl benzoate (93mg) as white solid after flash chromatography with cyclohexane and EtOAc.

Example 112

(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(2-oxotetrahydrofuran-3-yl)cyclohexane-1-carboxamide



Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (100mg) and alpha-amino-gamma-butyrolactone hydrobromide (1.1eq) [after amine addition, the reaction was heated at 55°C during 16hr] led to (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(2-oxotetrahydrofuran-3-yl)cyclohexane-1-carboxamide (54mg) as white solid after flash chromatography with cyclohexane and EtOAc.

Examples 1 to 112 were characterized by 1H NMR and LC-MS analysis as shown below in Table 1.

Table 1:

Example	LCMS Method	$[M+H]^+$	1H NMR spectrum (δ ppm , DMSO-d_6)
1	A	320	(400 MHz, DMSO- d_6) 0.67 - 0.93 (m, 10 H), 1.32 - 1.43 (m, 4 H), 1.47 - 1.52 (m, 2 H), 1.67 (br d, J=13 Hz, 2 H), 3.14 - 3.20 (m, 1 H), 3.34 - 3.47 (m, 1 H), 4.63 (br s, 1 H), 4.85 (s, 1 H), 5.50 (br d, J=3 Hz, 1 H), 7.22 - 7.36 (m, 5 H), 7.61 (br t, J=6 Hz, 1 H)
2	A	318	(400 MHz, DMSO- d_6) 0.74 - 0.93 (m, 10 H), 1.35 - 1.48 (m, 3 H), 1.48 - 1.58 (m, 2 H), 1.63 - 1.80 (m, 3 H), 4.63 (d, J=5 Hz, 2 H), 4.98 (s, 1 H), 7.54 (t, J=7 Hz, 2 H), 7.66 (t, J=6 Hz, 1 H), 7.99 (d, J=7 Hz, 2 H), 8.06 (br t, J=5 Hz, 1 H)

Example	LCMS Method	$[M+H]^+$	1H NMR spectrum (δ ppm , DMSO-d_6)
3	A	362	(400 MHz, DMSO- d_6) 0.71 - 0.89 (m, 10 H), 1.31 - 1.53 (m, 6 H), 1.62 - 1.76 (m, 2 H), 2.04 (s, 3 H), 3.33 - 3.47 (m, 1 H), 3.55 (br dd, J=6, 5 Hz, 1 H), 4.83 (s, 1 H), 5.82 (dd, J=8, 4 Hz, 1 H), 7.29 - 7.41 (m, 5 H), 7.76 (br t, J=6 Hz, 1 H)
4	A	340	(400 MHz, DMSO- d_6) 0.60 - 0.95 (m, 10 H), 1.21 - 1.52 (m, 6 H), 1.61 - 1.79 (m, 2 H), 3.79 - 4.04 (m, 2 H), 4.92 (s, 1 H), 7.48 - 7.55 (m, 5 H), 7.75 (br t, J=6 Hz, 1 H)
5	A	322	(400 MHz, DMSO- d_6) 0.71 - 0.90 (m, 10 H), 1.31 - 1.54 (m, 6 H), 1.64 - 1.75 (m, 2 H), 3.33 - 3.68 (m, 2 H), 4.86 (s, 1 H), 5.53 - 5.69 (m, 1 H) ,7.35 - 7.43 (m, 5 H), 7.85 (br t, J=6 Hz, 1 H)
6	A	363	(400 MHz, DMSO- d_6) 0.72 - 0.91 (m, 10 H), 1.31 - 1.52 (m, 6 H), 1.63 - 1.73 (m, 2 H), 2.66 - 2.81 (m, 2 H), 2.92 (t, J=5 Hz, 2 H), 3.34 - 3.41 (m, 2 H), 3.93 (t, J=5 Hz, 2 H), 4.75 - 4.86 (m, 1 H), 6.84 (td, J=7, 1 Hz, 1 H), 6.92 (d, J=8 Hz, 1 H), 7.11 (dd, J=7, 2 Hz, 1 H), 7.16 (t, J=7 Hz, 1 H), 7.70 (br t, J=6 Hz, 1 H)
7	A	364	(400 MHz, DMSO- d_6) 0.71 - 0.91 (m, 10 H), 1.32 - 1.54 (m, 6 H), 1.68 (br d, J=12 Hz, 2 H), 2.68 - 2.81 (m, 2 H), 3.32 - 3.43 (m, 2 H), 3.76 (q, J=5 Hz, 2 H), 4.00 (t, J=5 Hz, 2 H), 4.75 (s, 1 H), 4.89 (t, J=6 Hz, 1 H), 6.85 (t, J=7 Hz, 1 H), 6.94 (d, J=8 Hz, 1 H), 7.11 (dd, J=7, 1 Hz, 1 H), 7.17 (t, J=8 Hz, 1 H), 7.69 (br t, J=6 Hz, 1 H)
8	A	344	(400 MHz, DMSO- d_6) 0.66 (t, J=7 Hz, 6 H), 0.74 - 0.92 (m, 4 H), 1.23 - 1.49 (m, 6 H), 1.65 (br d, J=10 Hz, 2 H), 3.01 (t, J=7 Hz, 2 H), 3.46 - 3.67 (m, 3 H), 4.78 (s, 1 H), 7.12 - 7.16 (m, 2 H), 7.46 - 7.51 (m, 2 H), 7.96 (t, J=6 Hz, 1 H)
9	A	394	(500 MHz, DMSO- d_6) 0.74 - 0.91 (m, 10 H), 1.33 - 1.54 (m, 6 H), 1.64 - 1.74 (m, 2 H), 2.67 - 2.81 (m, 2 H), 3.32 - 3.45 (m, 2 H), 3.47 - 3.56 (m, 2 H), 3.79 - 3.94 (m, 2 H), 3.95 - 4.07 (m, 1 H), 4.63 (t, J=5 Hz, 1 H), 4.75 (s, 1 H), 4.96 (t, J=5 Hz, 1 H), 6.85 (td, J=7, 1 Hz, 1 H), 6.93 (d, J=8 Hz, 1 H), 7.11 (dd, J=7, 2 Hz, 1 H), 7.17 (t, J=8 Hz, 1 H), 7.65 - 7.75 (m, 1 H)

Example	LCMS Method	$[M+H]^+$	1H NMR spectrum (δ ppm , DMSO-d_6)
10	A	394	(500 MHz, DMSO- d_6) 0.74 - 0.91 (m, 10 H), 1.33 - 1.54 (m, 6 H), 1.62 - 1.75 (m, 2 H), 2.66 - 2.76 (m, 2 H), 3.31 - 3.51 (m, 4 H), 3.76 - 3.87 (m, 2 H), 3.97 (dd, J=10, 4 Hz, 1 H), 4.62 (t, J=6 Hz, 1 H), 4.74 (s, 1 H), 4.89 (d, J=5 Hz, 1 H), 6.75 - 6.80 (m, 3 H), 7.18 (t, J=8 Hz, 1 H), 7.67 (br t, J=6 Hz, 1 H)
11	A	406	(400 MHz, DMSO- d_6) 0.70 - 0.89 (m, 10 H), 1.30 - 1.55 (m, 6 H), 1.68 (br d, J=10 Hz, 2 H), 2.60 - 2.78 (m, 2 H), 3.22 (s, 11 H), 3.86 (br s, 2 H), 4.46 (br s, 2 H), 4.81 (br s, 1 H), 6.92 (t, J=7 Hz, 1 H), 7.01 (d, J=8 Hz, 1 H), 7.12 - 7.27 (m, 2 H), 7.79 (br t, J=6 Hz, 1 H)
12	A	334	(400 MHz, DMSO- d_6) 0.69 - 0.88 (m, 10 H), 1.29 - 1.54 (m, 6 H), 1.67 (br d, J=12 Hz, 2 H), 2.29 (s, 3 H), 3.08 - 3.20 (m, 1 H), 3.33 - 3.47 (m, 1 H), 4.59 (br s, 1 H), 4.85 (br s, 1 H), 5.47 (br d, J=10 Hz, 1 H), 7.05 (d, J=7 Hz, 1 H), 7.10 - 7.22 (m, 3 H), 7.51 - 7.63 (m, 1 H)
13	B	391	(400 MHz, DMSO- d_6) 0.69 - 0.87 (m, 10 H), 1.23 - 1.53 (m, 6 H), 1.67 (br d, J=10 Hz, 2 H), 2.98 - 3.19 (m, 2 H), 3.20 - 3.29 (m, 1 H), 3.35 - 3.54 (m, 2 H), 3.63 - 3.77 (m, 1 H), 4.46 (t, J=5 Hz, 2 H), 4.74 (br s, 1 H), 7.32 - 7.38 (m, 2 H), 7.47 - 7.55 (m, 1 H), 7.77 (br t, J=6 Hz, 1 H), 8.00 (d, J=8 Hz, 1 H), 8.11 (br s, 3 H)
14	A	334	(400 MHz, DMSO- d_6) 0.73 - 0.92 (m, 10 H), 1.31 - 1.54 (m, 6 H), 1.67 (br d, J=10 Hz, 2 H), 2.66 - 2.81 (m, 2 H), 3.27 - 3.31 (m, 2 H), 4.56 (d, J=4 Hz, 2 H), 4.73 (s, 1 H), 5.08 (br s, 1 H), 7.13 - 7.21 (m, 3 H), 7.34 - 7.39 (m, 1 H), 7.79 (br t, J=6 Hz, 1 H)
15	A	334	(400 MHz, DMSO- d_6) 0.72 - 0.91 (m, 10 H), 1.32 - 1.54 (m, 6 H), 1.63 - 1.74 (m, 2 H), 2.67 - 2.76 (m, 2 H), 3.33 - 3.42 (m, 2 H), 4.45 - 4.49 (m, 2 H), 4.73 (br s, 1 H), 5.11 (br s, 1 H), 7.06 (d, J=7 Hz, 1 H), 7.13 - 7.17 (m, 2 H), 7.19 - 7.26 (m, 1 H), 7.70 (br t, J=6 Hz, 1 H)
16	A	391	(400 MHz, DMSO- d_6) 0.69 - 0.89 (m, 10 H), 1.28 - 1.51 (m, 6 H), 1.66 (br d, J=10 Hz, 2 H), 2.80 - 2.90 (m, 2 H), 3.20 - 3.29 (m, 2 H), 3.33 - 3.39 (m, 2 H), 4.42 - 4.46 (m, 2 H), 7.43 - 7.48 (m, 1 H), 7.53 (d, J=7 Hz, 1 H), 7.76 (t, J=6 Hz, 1 H), 7.92 - 7.95 (m, 2 H), 8.16 (br s, 3 H)

Example	LCMS Method	$[M+H]^+$	1H NMR spectrum (δ ppm , DMSO-d_6)
17	A	346	(400 MHz, DMSO- d_6) 0.53 (d, J=7 Hz, 3 H), 0.58 (br d, J=7 Hz, 3 H), 0.68 - 0.87 (m, 5 H), 1.21 - 1.41 (m, 5 H), 1.63 (br d, J=12 Hz, 2 H), 3.65 (dt, J=14, 4 Hz, 1 H), 3.87 - 3.96 (m, 1 H), 4.82 (s, 1 H), 5.74 (t, J=4 Hz, 1 H), 7.56 - 7.83 (m, 5 H)
18	A	346	(500 MHz, DMSO- d_6) 0.68 - 0.85 (m, 10 H), 1.09 - 1.21 (m, 2 H), 1.26 - 1.51 (m, 4 H), 1.63 (br d, J=10 Hz, 2 H), 3.69 - 3.79 (m, 2 H), 4.77 (s, 1 H), 5.73 (t, J=4 Hz, 1 H), 7.60 (t, J=8 Hz, 1 H), 7.63 - 7.85 (m, 4 H)
19	A	405	(400 MHz, DMSO- d_6) 0.71 - 0.88 (m, 10 H), 1.29 - 1.55 (m, 6 H), 1.68 (br d, J=12 Hz, 2 H), 2.67 - 2.83 (m, 2 H), 3.08 - 3.17 (m, 1 H), 3.19 - 3.35 (m, 3 H), 3.61 (s, 3 H), 4.20 (br s, 1 H), 7.14 - 7.24 (m, 4 H), 7.81 (t, J=6 Hz, 1 H), 8.62 (br s, 3 H)
20	B	405	(400 MHz, DMSO- d_6) 0.72 - 0.88 (m, 10 H), 1.28 - 1.54 (m, 6 H), 1.67 (br d, J=10 Hz, 2 H), 2.60 - 2.77 (m, 2 H), 3.04 - 3.27 (m, 2 H), 3.36 - 3.48 (m, 2 H), 3.70 (s, 3 H), 4.29 (br s, 1 H), 4.62 - 4.93 (m, 1 H), 7.03 - 7.15 (m, 3 H), 7.25 (t, J=8 Hz, 1 H), 7.78 (br t, J=6 Hz, 1 H), 8.49 (br s, 3 H)
21	A	391	(400 MHz, DMSO- d_6) 0.68 - 0.90 (m, 10 H), 1.27 - 1.51 (m, 6 H), 1.67 (br d, J=13 Hz, 2 H), 2.78 - 2.90 (m, 2 H), 3.32 - 3.51 (m, 2 H), 3.68 - 3.74 (m, 2 H), 4.25 - 4.30 (m, 2 H), 4.71 (s, 1 H), 4.91 (t, J=6 Hz, 1 H), 7.42 - 7.53 (m, 2 H), 7.73 (br t, J=6 Hz, 1 H), 7.82 - 7.86 (m, 2 H)
22	A	392	(400 MHz, DMSO- d_6) 0.69 - 0.91 (m, 10 H), 1.27 - 1.51 (m, 6 H), 1.67 (br d, J=12 Hz, 2 H), 3.00 - 3.16 (m, 2 H), 3.31 - 3.48 (m, 2 H), 3.70 - 3.75 (m, 2 H), 4.26 - 4.32 (m, 2 H), 4.71 (s, 1 H), 4.92 (t, J=6 Hz, 1 H), 7.30 - 7.38 (m, 2 H), 7.50 (t, J=8 Hz, 1 H), 7.73 (br t, J=6 Hz, 1 H), 7.85 (d, J=7 Hz, 1 H)
23	B	344	(400 MHz, DMSO- d_6) 0.71 - 0.88 (m, 10 H), 1.32 - 1.56 (m, 6 H), 1.69 (br d, J=12 Hz, 2 H), 1.91 - 2.00 (m, 1 H), 2.16 (td, J=9, 4 Hz, 1 H), 2.70 - 2.79 (m, 1 H), 2.87 (br d, J=9 Hz, 1 H), 3.31 - 3.43 (m, 2 H), 5.00 (d, J=3 Hz, 1 H), 5.46 (d, J=14 Hz, 1 H), 7.16 - 7.24 (m, 3 H), 7.30 - 7.37 (m, 1 H), 7.60 (br t, J=6 Hz, 1 H)

Example	LCMS Method	$[M+H]^+$	1H NMR spectrum (δ ppm , DMSO-d_6)
24	A	394	(400 MHz, DMSO- d_6) 0.63 - 0.97 (m, 10 H), 1.22 - 1.58 (m, 6 H), 1.67 (br d, J=12 Hz, 2 H), 2.68 - 2.79 (m, 2 H), 3.23 - 3.28 (m, 1 H), 3.36 - 3.43 (m, 1 H), 3.50 (br t, J=5 Hz, 2 H), 3.82 - 3.89 (m, 2 H), 3.99 - 4.02 (m, 1 H), 4.63 (t, J=6 Hz, 1 H), 4.74 (s, 1 H), 4.94 - 5.02 (m, 1 H), 6.84 (t, J=7 Hz, 1 H), 6.92 (d, J=8 Hz, 1 H), 7.10 (dd, J=7, 2 Hz, 1 H), 7.14 - 7.19 (m, 1 H), 7.68 (br t, J=6 Hz, 1 H)
25	A	394	(400 MHz, DMSO- d_6) 0.73 - 0.91 (m, 10 H), 1.34 - 1.53 (m, 6 H), 1.64 - 1.72 (m, 2 H), 2.66 - 2.78 (m, 2 H), 3.32 - 3.41 (m, 2 H), 3.50 (br t, J=4 Hz, 2 H), 3.82 - 3.90 (m, 2 H), 3.98 - 4.02 (m, 1 H), 4.62 (br t, J=6 Hz, 1 H), 4.74 (s, 1 H), 4.93 - 4.97 (m, 1 H), 6.84 (t, J=7 Hz, 1 H), 6.92 (d, J=8 Hz, 1 H), 7.10 (dd, J=7, 2 Hz, 1 H), 7.16 (t, J=8 Hz, 1 H), 7.68 (br t, J=6 Hz, 1 H)
26	A	421	(400 MHz, DMSO- d_6) 0.70 - 0.88 (m, 10 H), 1.29 - 1.53 (m, 6 H), 1.67 (br d, J=12 Hz, 2 H), 1.94 (br s, 2 H), 2.64 - 2.76 (m, 2 H), 3.33 - 3.44 (m, 2 H), 3.65 (s, 3 H), 3.72 (br s, 1 H), 4.02 - 4.12 (m, 2 H), 4.73 (s, 1 H), 6.72 - 6.80 (m, 3 H), 7.18 (t, J=8 Hz, 1 H), 7.66 (br t, J=6 Hz, 1 H)
27	A	421	(500 MHz, DMSO- d_6) 0.69 - 0.88 (m, 10 H), 1.32 - 1.44 (m, 4 H), 1.44 - 1.53 (m, 2 H), 1.58 - 1.79 (m, 2 H), 2.08 (s, 2 H), 2.64 - 2.80 (m, 2 H), 3.27 - 3.34 (m, 1 H), 3.35 - 3.51 (m, 1 H), 3.66 (s, 3 H), 3.75 (t, J=5 Hz, 1 H), 4.03 - 4.16 (m, 2 H), 4.73 (s, 1 H), 6.74 - 6.83 (m, 3 H), 7.19 (t, J=8 Hz, 1 H), 7.64 - 7.75 (m, 1 H)
28	A	376	(400 MHz, DMSO- d_6) 0.67 - 0.90 (m, 10 H), 1.24 - 1.49 (m, 9 H), 1.67 (br d, J=13 Hz, 2 H), 2.78 - 2.89 (m, 2 H), 3.31 - 3.50 (m, 2 H), 4.31 (q, J=7 Hz, 2 H), 4.70 (s, 1 H), 7.41 - 7.53 (m, 2 H), 7.70 (br t, J=6 Hz, 1 H), 7.80 (dt, J=4, 2 Hz, 2 H)
29	A	460	(400 MHz, DMSO- d_6) 0.65 - 0.90 (m, 10 H), 1.26 - 1.49 (m, 6 H), 1.66 (br d, J=11 Hz, 2 H), 2.23 (s, 3 H), 2.79 - 2.90 (m, 2 H), 3.31 - 3.37 (m, 1 H), 3.43 - 3.52 (m, 1 H), 4.69 (s, 1 H), 5.22 (s, 2 H), 7.45 (t, J=8 Hz, 1 H), 7.54 (d, J=8 Hz, 1 H), 7.70 (t, J=6 Hz, 1 H), 7.80 - 7.86 (m, 2 H)

Example	LCMS Method	$[M+H]^+$	1H NMR spectrum (δ ppm , DMSO-d_6)
30	A	347	(400 MHz, DMSO- d_6) 0.72 - 0.90 (m, 10 H), 1.33 - 1.62 (m, 6 H), 1.68 (br d, J=11 Hz, 2 H), 3.72 - 3.84 (m, 2 H), 4.31 (d, J=6 Hz, 2 H), 4.91 (br s, 1 H), 7.20 - 7.35 (m, 5 H), 7.95 (br t, J=5 Hz, 1 H), 8.25 (br t, J=6 Hz, 1 H)
31	A	346	(400 MHz, DMSO- d_6) 0.71 - 0.91 (m, 10 H), 1.30 - 1.55 (m, 6 H), 1.67 (br d, J=11 Hz, 2 H), 3.56 (dd, J=13, 6 Hz, 1 H), 3.69 (dd, J=13, 7 Hz, 1 H), 4.66 - 4.79 (m, 4 H), 4.85 (s, 1 H), 7.14 (d, J=8 Hz, 2 H), 7.24 - 7.30 (m, 1 H), 7.33 - 7.40 (m, 2 H), 7.59 (br t, J=6 Hz, 1 H)
32	B	336	(400 MHz, DMSO- d_6) 0.69 - 0.88 (m, 10 H), 1.30 - 1.56 (m, 6 H), 1.67 (br d, J=11 Hz, 2 H), 3.03 - 3.48 (m, 2 H), 4.49 - 4.56 (m, 1 H), 4.89 (s, 1 H), 5.47 (dd, J=10, 4 Hz, 1 H), 6.63 (dd, J=8, 2 Hz, 1 H), 6.72 - 6.79 (m, 2 H), 7.10 (td, J=8, 2 Hz, 1 H), 7.52 - 7.65 (m, 1 H), 9.29 (s, 1 H)
33	B	408	(400 MHz, DMSO- d_6) 0.69 - 0.88 (m, 10 H), 1.26 - 1.55 (m, 6 H), 1.67 (br d, J=10 Hz, 2 H), 3.09 - 3.21 (m, 1 H), 3.37 - 3.51 (m, 1 H), 3.71 (s, 3 H), 4.58 - 4.64 (m, 1 H), 4.77 (d, J=2 Hz, 2 H), 4.86 (s, 1 H), 5.54 (dd, J=12, 4 Hz, 1 H), 6.80 (dd, J=8, 2 Hz, 1 H), 6.89 - 7.01 (m, 2 H), 7.24 (t, J=8 Hz, 1 H), 7.57 (s, 1 H)
34	A	378	(400 MHz, DMSO- d_6) 0.62 - 0.85 (m, 10 H), 1.20 - 1.49 (m, 6 H), 1.65 (br d, J=11 Hz, 2 H), 3.18 - 3.28 (m, 1 H), 3.44 (br dd, J=13, 7 Hz, 1 H), 3.85 (s, 3 H), 4.73 - 4.82 (m, 2 H), 5.63 - 5.72 (m, 1 H), 7.46 (t, J=8 Hz, 1 H), 7.55 - 7.67 (m, 2 H), 7.84 (d, J=7 Hz, 1 H), 7.95 (d, J=2 Hz, 1 H)
35	A	336	(400 MHz, DMSO- d_6) 0.62 - 0.96 (m, 10 H), 1.29 - 1.59 (m, 6 H), 1.67 (br d, J=11 Hz, 2 H), 3.00 - 3.24 (m, 1 H), 3.35 - 3.54 (m, 1 H), 4.86 - 4.94 (m, 2 H), 5.13 - 5.60 (m, 1 H), 6.74 - 6.79 (m, 2 H), 7.04 (t, J=8 Hz, 1 H), 7.29 - 7.34 (m, 1 H), 7.58 (q, J=5 Hz, 1 H), 9.13 - 9.56 (m, 1 H)

Example	LCMS Method	$[M+H]^+$	1H NMR spectrum (δ ppm , DMSO-d_6)
36	A	408	(500 MHz, DMSO- d_6) 0.59 - 0.91 (m, 10 H), 1.27 - 1.56 (m, 6 H), 1.63 - 1.73 (m, 2 H), 3.13 - 3.28 (m, 1 H), 3.42 - 3.56 (m, 1 H), 3.71 (d, J=1 Hz, 3 H), 4.83 (d, J=6 Hz, 2 H), 4.88 (d, J=11 Hz, 1 H), 4.96 - 5.14 (m, 1 H), 5.38 - 5.47 (m, 1 H), 6.87 (d, J=8 Hz, 1 H), 6.97 (t, J=7 Hz, 1 H), 7.20 (t, J=8 Hz, 1 H), 7.45 (ddd, J=7, 6, 1 Hz, 1 H), 7.50 - 7.58 (m, 1 H)
37	A	350	(400 MHz, DMSO- d_6) 0.71 - 0.89 (m, 10 H), 1.27 - 1.58 (m, 6 H), 1.68 (br d, J=10 Hz, 2 H), 3.08 - 3.54 (m, 2 H), 4.50 (d, J=6 Hz, 2 H), 4.62 (br d, J=5 Hz, 1 H), 4.86 (s, 1 H), 5.14 (t, J=6 Hz, 1 H), 5.50 (dd, J=8, 4 Hz, 1 H), 7.18 - 7.32 (m, 4 H), 7.51 - 7.74 (m, 1 H)
38	A	334	(400 MHz, DMSO- d_6) 0.75 - 0.93 (m, 10 H), 1.35 - 1.48 (m, 3 H), 1.48 - 1.58 (m, 2 H), 1.62 - 1.80 (m, 3 H), 4.62 (d, J=6 Hz, 2 H), 4.99 (s, 1 H), 6.95 (t, J=8 Hz, 1 H), 7.00 (dd, J=8, 1 Hz, 1 H), 7.51 (ddd, J=8, 7, 2 Hz, 1 H), 7.87 (dd, J=8, 2 Hz, 1 H), 8.06 (t, J=5 Hz, 1 H), 11.42 (s, 1 H)
39	A	334	(400 MHz, DMSO- d_6) 0.74 - 0.93 (m, 10 H), 1.35 - 1.48 (m, 3 H), 1.48 - 1.58 (m, 2 H), 1.62 - 1.80 (m, 3 H), 4.57 (d, J=5 Hz, 2 H), 4.98 (s, 1 H), 7.04 (dd, J=8, 2 Hz, 1 H), 7.28 - 7.37 (m, 2 H), 7.44 (d, J=8 Hz, 1 H), 8.02 (t, J=5 Hz, 1 H), 9.78 (s, 1 H)
40	A	320	(400 MHz, DMSO- d_6) 0.72 - 0.91 (m, 10 H), 1.30 - 1.54 (m, 6 H), 1.63 - 1.75 (m, 2 H), 2.58 - 2.69 (m, 2 H), 3.21 - 3.29 (m, 1 H), 3.32 - 3.39 (m, 1 H), 4.73 (s, 1 H), 6.57 - 6.63 (m, 3 H), 7.06 (t, J=8 Hz, 1 H), 7.66 (br t, J=6 Hz, 1 H), 9.21 (s, 1 H)
41	A	336	(400 MHz, DMSO- d_6) 0.67 - 0.95 (m, 10 H), 1.21 - 1.54 (m, 6 H), 1.61 - 1.74 (m, 2 H), 3.19 - 3.28 (m, 2 H), 4.53 (br s, 1 H), 4.87 (s, 1 H), 5.41 - 5.49 (m, 1 H), 6.62 (dd, J=8, 2 Hz, 1 H), 6.69 - 6.85 (m, 2 H), 7.09 (t, J=8 Hz, 1 H), 7.55 (br t, J=5 Hz, 1 H), 9.28 (br s, 1 H)
42	A	336	(400 MHz, DMSO- d_6) 0.71 - 0.90 (m, 10 H), 1.28 - 1.59 (m, 6 H), 1.67 (br d, J=12 Hz, 2 H), 3.05 - 3.15 (m, 1 H), 3.36 - 3.42 (m, 1 H), 4.49 - 4.55 (m, 1 H), 4.85 (s, 1 H), 5.42 (d, J=4 Hz, 1 H), 6.62 (dd, J=8, 2 Hz, 1 H), 6.71 - 6.80 (m, 2 H), 7.09 (t, J=8 Hz, 1 H), 7.60 (t, J=6 Hz, 1 H), 9.25 (s, 1 H)

Example	LCMS Method	$[M+H]^+$	1H NMR spectrum (δ ppm , DMSO-d_6)
43	A	350	(400 MHz, DMSO- d_6) 0.70 - 0.90 (m, 10 H), 1.31 - 1.52 (m, 6 H), 1.62 - 1.74 (m, 2 H), 3.21 - 3.38 (m, 2 H), 4.49 (d, J=6 Hz, 2 H), 4.59 - 4.64 (m, 1 H), 4.86 (s, 1 H), 5.14 (t, J=6 Hz, 1 H), 5.52 (d, J=4 Hz, 1 H), 7.18 - 7.30 (m, 4 H), 7.58 (t, J=6 Hz, 1 H)
44	A	350	(400 MHz, DMSO- d_6) 0.71 - 0.90 (m, 10 H), 1.29 - 1.59 (m, 6 H), 1.63 - 1.74 (m, 2 H), 3.09 - 3.25 (m, 1 H), 3.42 - 3.48 (m, 1 H), 4.49 (d, J=6 Hz, 2 H), 4.58 - 4.65 (m, 1 H), 4.86 (s, 1 H), 5.14 (t, J=6 Hz, 1 H), 5.49 (d, J=4 Hz, 1 H), 7.17 - 7.31 (m, 4 H), 7.63 (br t, J=6 Hz, 1 H)
45	A	334	(400 MHz, DMSO- d_6) 0.69 - 0.87 (m, 10 H), 1.28 - 1.52 (m, 6 H), 1.59 - 1.74 (m, 2 H), 2.29 (s, 3 H), 3.30 - 3.33 (m, 2 H), 4.56 - 4.61 (m, 1 H), 4.85 (s, 1 H), 5.49 (d, J=4 Hz, 1 H), 7.05 (d, J=8 Hz, 1 H), 7.11 - 7.22 (m, 3 H), 7.54 (br t, J=6 Hz, 1 H)
46	A	334	(400 MHz, DMSO- d_6) 0.71 - 0.88 (m, 10 H), 1.27 - 1.56 (m, 6 H), 1.60 - 1.74 (m, 2 H), 2.29 (s, 3 H), 3.11 - 3.25 (m, 1 H), 3.39 - 3.48 (m, 1 H), 4.57 - 4.62 (m, 1 H), 4.86 (s, 1 H), 5.45 (d, J=4 Hz, 1 H), 7.05 (d, J=7 Hz, 1 H), 7.11 - 7.22 (m, 3 H), 7.60 (br t, J=6 Hz, 1 H)
47	A	334	(400 MHz, DMSO- d_6) 0.67 - 0.95 (m, 10 H), 1.18 - 1.54 (m, 6 H), 1.63 - 1.70 (m, 2 H), 2.70 - 2.74 (m, 1 H), 2.86 (dd, J=14, 6 Hz, 1 H), 3.34 - 3.40 (m, 1 H), 3.95 (br d, J=5 Hz, 1 H), 4.78 (s, 1 H), 4.85 (br s, 1 H), 7.15 - 7.27 (m, 6 H), 7.48 (d, J=9 Hz, 1 H)
48	A	329	(400 MHz, DMSO- d_6) 0.67 - 0.89 (m, 10 H), 1.26 - 1.48 (m, 6 H), 1.62 - 1.73 (m, 2 H), 2.79 - 2.87 (m, 2 H), 3.32 - 3.51 (m, 2 H), 4.71 (s, 1 H), 7.46 - 7.51 (m, 1 H), 7.57 (d, J=7 Hz, 1 H), 7.63 - 7.73 (m, 3 H)
49	A	347	(400 MHz, DMSO- d_6) 0.68 - 0.90 (m, 10 H), 1.30 - 1.52 (m, 6 H), 1.67 (br d, J=12 Hz, 2 H), 2.80 (br t, J=7 Hz, 2 H), 3.36 - 3.49 (m, 2 H), 4.73 (br s, 1 H), 7.26 - 7.40 (m, 3 H), 7.67 - 7.77 (m, 3 H), 7.90 (br s, 1 H)

Example	LCMS Method	$[M+H]^+$	1H NMR spectrum (δ ppm , DMSO-d_6)
50	A	319	(500 MHz, DMSO- d_6) 0.71 - 0.89 (m, 10 H), 1.29 - 1.51 (m, 6 H), 1.63 - 1.73 (m, 2 H), 1.88 (br s, 2 H), 3.14 (ddd, J=13, 8, 5 Hz, 1 H), 3.31 - 3.39 (m, 1 H), 3.92 (dd, J=7, 6 Hz, 1 H), 4.78 (s, 1 H), 7.19 - 7.23 (m, 1 H), 7.27 - 7.38 (m, 4 H), 7.63 (br t, J=6 Hz, 1 H)
51	A	304	(500 MHz, DMSO- d_6) 0.71 - 0.90 (m, 10 H), 1.30 - 1.52 (m, 6 H), 1.64 - 1.73 (m, 2 H), 2.69 - 2.78 (m, 2 H), 3.31 - 3.43 (m, 2 H), 4.73 (s, 1 H), 7.17 - 7.22 (m, 3 H), 7.24 - 7.32 (m, 2 H), 7.67 (br t, J=6 Hz, 1 H)
52	A	348	(400 MHz, DMSO- d_6) 0.74 - 0.93 (m, 10 H), 1.33 - 1.56 (m, 6 H), 1.64 - 1.77 (m, 2 H), 2.73 - 2.84 (m, 4 H), 3.23 - 3.39 (m, 2 H), 3.49 - 3.69 (m, 2 H), 4.64 (br t, J=5 Hz, 1 H), 4.75 (s, 1 H), 7.10 - 7.19 (m, 4 H), 7.80 (br t, J=6 Hz, 1 H)
53	A	347	(400 MHz, DMSO- d_6) 0.74 - 0.91 (m, 10 H), 1.33 - 1.54 (m, 6 H), 1.64 - 1.75 (m, 2 H), 2.67 - 2.79 (m, 6 H), 3.27 - 3.37 (m, 2 H), 4.77 (br s, 1 H), 7.09 - 7.17 (m, 4 H), 7.80 (br t, J=6 Hz, 1 H)
54	A	300	(400 MHz, DMSO- d_6) 0.74 - 0.92 (m, 10 H), 1.18 (dd, J=6, 1 Hz, 6 H), 1.30 - 1.57 (m, 5 H), 1.63 - 1.78 (m, 3 H), 3.72 - 3.86 (m, 2 H), 4.86 - 4.94 (m, 2 H), 8.04 (t, J=6 Hz, 1 H)
55	A	378	(400 MHz, DMSO- d_6) 0.72 - 0.90 (m, 10 H), 1.24 - 1.52 (m, 6 H), 1.63 - 1.74 (m, 2 H), 3.27 - 3.33 (m, 1 H), 3.44 - 3.52 (m, 1 H), 3.58 (s, 1 H), 3.79 (d, J=16 Hz, 1 H), 3.95 (d, J=16 Hz, 1 H), 4.57 (dd, J=7, 5 Hz, 1 H), 4.80 (s, 1 H), 7.30 - 7.39 (m, 5 H), 7.82 (br s, 1 H)
56	A	364	(400 MHz, DMSO- d_6) 0.73 - 0.90 (m, 10 H), 1.32 - 1.56 (m, 6 H), 1.67 (br d, J=12 Hz, 2 H), 3.15 - 3.29 (m, 3 H), 3.40 - 3.55 (m, 3 H), 4.42 (dd, J=8, 5 Hz, 1 H), 4.54 (t, J=5 Hz, 1 H), 4.84 (s, 1 H), 7.27 - 7.38 (m, 5 H), 7.57 - 7.65 (m, 1 H)

Example	LCMS Method	$[M+H]^+$	1H NMR spectrum (δ ppm , DMSO-d_6)
57	A	392	(400 MHz, DMSO- d_6) 0.64 - 0.90 (m, 10 H), 1.28 - 1.52 (m, 6 H), 1.66 (br d, J=10 Hz, 2 H), 3.29 - 3.36 (m, 1 H), 3.43 - 3.57 (m, 1 H), 3.63 (s, 3 H), 3.91 (d, J=16 Hz, 1 H), 4.06 (d, J=16 Hz, 1 H), 4.57 (dd, J=7, 5 Hz, 1 H), 4.84 (s, 1 H), 7.28 - 7.40 (m, 5 H), 7.69 (br d, J=5 Hz, 1 H)
58	A	318	(400 MHz, DMSO- d_6) 0.69 - 0.92 (m, 10 H), 1.29 - 1.54 (m, 6 H), 1.63 - 1.74 (m, 2 H), 2.27 (s, 3 H), 2.69 (td, J=7, 4 Hz, 2 H), 3.22 - 3.46 (m, 2 H), 4.73 (s, 1 H), 6.97 - 7.02 (m, 3 H), 7.16 (t, J=7 Hz, 1 H), 7.66 (br t, J=6 Hz, 1 H)
59	A	318	(400 MHz, DMSO- d_6) 0.73 - 0.89 (m, 10 H), 1.29 - 1.57 (m, 6 H), 1.63 - 1.76 (m, 2 H), 2.30 (s, 3 H), 2.68 - 2.77 (m, 2 H), 3.25 - 3.36 (m, 2 H), 4.74 (s, 1 H), 7.07 - 7.15 (m, 4 H), 7.77 (br t, J=6 Hz, 1 H)
60	A	318	(400 MHz, DMSO- d_6) 0.71 - 0.88 (m, 10 H), 1.29 - 1.54 (m, 4 H), 1.62 - 1.74 (m, 2 H), 2.26 (s, 3 H), 2.68 (td, J=7, 3 Hz, 2 H), 3.22 - 3.28 (m, 1 H), 3.33 - 3.42 (m, 1 H), 4.73 (s, 1 H), 7.08 (s, 4 H), 7.64 (t, J=6 Hz, 1 H)
61	A	392	(400 MHz, DMSO- d_6) 0.70 - 0.88 (m, 10 H), 1.29 - 1.56 (m, 6 H), 1.67 (br d, J=10 Hz, 2 H), 2.78 (dt, J=11, 7 Hz, 2 H), 3.33 - 3.43 (m, 2 H), 3.70 (s, 3 H), 4.72 (br s, 1 H), 4.82 (s, 2 H), 6.85 - 6.92 (m, 2 H), 7.12 - 7.18 (m, 2 H), 7.61 (br t, J=6 Hz, 1 H)
62	A	390	(400 MHz, DMSO- d_6) 0.68 - 0.89 (m, 10 H), 1.14 (d, J=7 Hz, 3 H), 1.24 - 1.53 (m, 6 H), 1.62 - 1.75 (m, 2 H), 1.81 (br s, 2 H), 3.17 - 3.30 (m, 2 H), 3.38 - 3.50 (m, 1 H), 4.82 (s, 1 H), 4.90 (br d, J=5 Hz, 1 H), 7.21 - 7.34 (m, 5 H), 7.83 (t, J=6 Hz, 1 H), 8.22 (br d, J=7 Hz, 1 H)
63	A	390	(400 MHz, DMSO- d_6) 0.68 - 0.88 (m, 10 H), 1.11 (d, J=7 Hz, 3 H), 1.27 - 1.53 (m, 6 H), 1.62 - 1.71 (m, 2 H), 1.74 (br s, 2 H), 3.22 - 3.28 (m, 1 H), 3.32 - 3.37 (m, 1 H), 3.38 - 3.50 (m, 1 H), 4.80 (s, 1 H), 4.86 - 4.94 (m, 1 H), 7.21 - 7.34 (m, 5 H), 7.81 (t, J=6 Hz, 1 H), 8.18 (br d, J=8 Hz, 1 H)

Example	LCMS Method	$[M+H]^+$	1H NMR spectrum (δ ppm , DMSO-d_6)
64	A	392	(400 MHz, DMSO- d_6) 0.71 - 0.88 (m, 10 H), 1.29 - 1.53 (m, 6 H), 1.63 - 1.74 (m, 2 H), 2.65 - 2.76 (m, 2 H), 3.33 - 3.43 (m, 2 H), 3.70 (s, 3 H), 4.76 (s, 3 H), 6.73 - 6.83 (m, 3 H), 7.19 (t, J=8 Hz, 1 H), 7.68 (br t, J=6 Hz, 1 H)
65	A	376	(400 MHz, DMSO- d_6) 0.62 - 0.94 (m, 10 H), 1.22 - 1.55 (m, 6 H), 1.66 (br d, J=11 Hz, 2 H), 2.51 - 2.61 (m, 2 H), 2.64 - 2.78 (m, 1 H), 3.28 - 3,32 (m, 2 H), 3.47 (s, 3 H), 4.72 (br d, J=8 Hz, 1 H), 7.15 - 7.36 (m, 5 H), 7.53 - 7.67 (m, 1 H)
66	A	348	(400 MHz, DMSO- d_6) 0.63 - 0.87 (m, 10 H), 1.22 - 1.51 (m, 6 H), 1.58 - 1.70 (m, 3 H), 1.74 - 1.85 (m, 1 H), 2.87 - 2.96 (m, 1 H), 3.16 - 3.28 (m, 3 H), 3.32 - 3.45 (m, 1 H), 4.34 - 4.38 (m, 1 H), 4.69 (d, J=5 Hz, 1 H), 7.16 - 7.22 (m, 3 H), 7.25 - 7.43 (m, 3 H)
67	A	334	(400 MHz, DMSO- d_6) 0.72 - 0.93 (m, 10 H), 1.34 - 1.58 (m, 5 H), 1.65 - 1.79 (m, 3 H), 4.05 - 4.17 (m, 2 H), 4.95 (s, 1 H), 7.10 (d, J=8 Hz, 2 H), 7.23 - 7.31 (m, 1 H), 7.43 (t, J=7 Hz, 2 H), 8.26 (t, J=6 Hz, 1 H)
68	A	392	(400 MHz, DMSO- d_6) 0.70 - 0.90 (m, 10 H), 1.34 - 1.59 (m, 5 H), 1.63 - 1.78 (m, 3 H), 3.87 (s, 3 H), 4.16 (dd, J=6, 3 Hz, 2 H), 4.94 (s, 1 H), 7.32 (d, J=8 Hz, 1 H), 7.57 - 7.64 (m, 2 H), 8.28 (t, J=6 Hz, 1 H), 9.98 (s, 1 H)
69	A	362	(400 MHz, DMSO- d_6) 0.66 - 0.86 (m, 10 H), 1.24 - 1.49 (m, 6 H), 1.61 - 1.72 (m, 2 H), 3.41 - 3.76 (m, 5 H), 3.95 - 4.02 (m, 1 H), 4.76 (br d, J=13 Hz, 1 H), 7.25 - 7.36 (m, 5 H), 7.72 (br s, 1 H)
70	A	334	(400 MHz, DMSO- d_6) 0.65 - 0.88 (m, 10 H), 1.23 - 1.50 (m, 6 H), 1.65 (br d, J=11 Hz, 2 H), 2.87 - 2.95 (m, 1 H), 3.30 (s, 1 H), 3.38 - 3.47 (m, 1 H), 3.52 - 3.61 (m, 2 H), 4.69 - 4.75 (m, 2 H), 7.17 - 7.30 (m, 5 H), 7.53 (dt, J=12, 6 Hz, 1 H)

Example	LCMS Method	$[M+H]^+$	1H NMR spectrum (δ ppm , DMSO-d_6)
71	A	391	(400 MHz, DMSO- d_6) 0.66 - 0.88 (m, 10 H), 1.20 - 1.52 (m, 6 H), 1.58 - 1.70 (m, 2 H), 3.07 (br s, 2 H), 3.36 - 3.60 (m, 2 H), 3.69 - 3.90 (m, 1 H), 4.03 (q, J=7 Hz, 1 H), 4.11 - 4.29 (m, 2 H), 4.78 (br s, 1 H), 7.26 - 7.37 (m, 5 H), 7.78 (dt, J=18, 6 Hz, 1 H), 8.04 (br s, 3 H)
72	A	321	(400 MHz, DMSO- d_6) 0.68 - 0.89 (m, 10 H), 1.28 - 1.53 (m, 6 H), 1.66 (br d, J=10 Hz, 2 H), 3.10 - 3.52 (m, 2 H), 4.85 (s, 1 H), 5.48 (br d, J=11 Hz, 1 H), 7.22 - 7.37 (m, 5 H), 7.51 - 7.65 (m, 1 H)
73	A	419	(400 MHz, DMSO- d_6) 0.65 - 0.88 (m, 10 H), 1.16 - 1.49 (m, 12 H), 1.65 (br d, J=10 Hz, 2 H), 3.51 - 3.65 (m, 1 H), 3.71 - 3.84 (m, 1 H), 3.96 - 4.13 (m, 3 H), 4.78 (br d, J=5 Hz, 1 H), 7.27 - 7.37 (m, 5 H), 7.75 (dt, J=18, 6 Hz, 1 H), 8.15 (br s, 3 H)
74	A	376	(400 MHz, DMSO- d_6) 0.71 - 0.89 (m, 10 H), 1.30 - 1.54 (m, 6 H), 1.67 (br d, J=13 Hz, 2 H), 2.60 - 2.77 (m, 2 H), 3.34 - 3.43 (m, 2 H), 3.58 - 3.66 (m, 5 H), 4.73 (br s, 1 H), 7.07 - 7.13 (m, 3 H), 7.23 (t, J=7 Hz, 1 H), 7.71 (br t, J=6 Hz, 1 H)
75	A	406	(400 MHz, DMSO- d_6) 0.68 - 0.88 (m, 10 H), 1.24 - 1.53 (m, 6 H), 1.67 (br d, J=11 Hz, 2 H), 2.60 - 2.74 (m, 2 H), 2.83 (t, J=6 Hz, 2 H), 3.18 - 3.44 (m, 2 H), 3.64 (s, 3 H), 4.21 (t, J=6 Hz, 2 H), 4.73 (br s, 1 H), 6.83 - 6.90 (m, 1 H), 6.96 (d, J=8 Hz, 1 H), 7.11 (br d, J=7 Hz, 1 H), 7.17 (t, J=7 Hz, 1 H), 7.56 (br t, J=5 Hz, 1 H)
76	A	366	(400 MHz, DMSO- d_6) 0.72 - 0.91 (m, 10 H), 1.33 - 1.57 (m, 5 H), 1.65 - 1.78 (m, 3 H), 3.97 - 4.10 (m, 2 H), 4.92 (s, 1 H), 5.94 (d, J=2 Hz, 2 H), 6.09 (t, J=2 Hz, 1 H), 8.21 (t, J=6 Hz, 1 H), 9.48 (s, 2 H)
77	A	376	(400 MHz, DMSO- d_6) 0.74 - 0.89 (m, 10 H), 1.31 - 1.56 (m, 6 H), 1.68 (br d, J=11 Hz, 2 H), 2.67 - 2.76 (m, 2 H), 3.19 - 3.28 (m, 2 H), 3.61 (s, 3 H), 3.77 (d, J=3 Hz, 2 H), 4.75 (s, 1 H), 7.14 - 7.21 (m, 4 H), 7.81 (t, J=6 Hz, 1 H)

Example	LCMS Method	$[M+H]^+$	1H NMR spectrum (δ ppm , DMSO-d_6)
78	A	362	(400 MHz, DMSO- d_6) 0.73 - 0.88 (m, 10 H), 1.32 - 1.54 (m, 6 H), 1.63 - 1.74 (m, 2 H), 2.66 - 2.76 (m, 2 H), 3.34 - 3.41 (m, 2 H), 3.52 (s, 2 H), 4.73 (s, 1 H), 7.07 - 7.11 (m, 3 H), 7.20 - 7.25 (m, 1 H), 7.71 (t, J=6 Hz, 1 H), 12.00 - 12.64 (br s, 1H)
79	A	394	(400 MHz, DMSO- d_6) 0.72 - 0.90 (m, 10 H), 1.33 - 1.58 (m, 5 H), 1.65 - 1.78 (m, 3 H), 3.76 (s, 3 H), 4.11 (dd, J=6, 3 Hz, 2 H), 4.48 (br d, J=4 Hz, 2 H), 4.92 (s, 1 H), 5.21 (br s, 1 H), 6.89 (d, J=8 Hz, 1 H), 6.98 (d, J=8 Hz, 1 H), 7.08 (s, 1 H), 8.22 (br t, J=6 Hz, 1 H)
80	A	378	(400 MHz, DMSO- d_6) 0.70 - 0.90 (m, 10 H), 1.30 - 1.52 (m, 6 H), 1.67 (br d, J=11 Hz, 2 H), 1.89 (quin, J=6 Hz, 2 H), 2.65 - 2.79 (m, 2 H), 3.33 - 3.43 (m, 2 H), 3.57 - 3.63 (m, 2 H), 4.04 (t, J=6 Hz, 2 H), 4.46 - 4.56 (m, 1 H), 4.71 (br s, 1 H), 6.83 (t, J=7 Hz, 1 H), 6.93 (d, J=7 Hz, 1 H), 7.10 (dd, J=7, 2 Hz, 1 H), 7.16 (t, J=8 Hz, 1 H), 7.61 (br t, J=6 Hz, 1 H)
81	A	377	(400 MHz, DMSO- d_6) 0.68 - 0.97 (m, 10 H), 1.28 - 1.57 (m, 6 H), 1.61 - 1.78 (m, 2 H), 2.72 - 2.88 (m, 2 H), 3.22 - 3.48 (m, 2 H), 4.32 - 4.52 (m, 2 H), 4.75 (s, 1 H), 6.79 - 6.94 (m, 2 H), 7.10 - 7.25 (m, 2 H), 7.39 - 7.62 (m, 2 H), 7.82 (t, J=6 Hz, 1 H)
82	A	388	(400 MHz, DMSO- d_6) 0.49 (br dd, J=10, 7 Hz, 7 H), 0.76 (br d, J=6 Hz, 5 H), 1.30 (br s, 4 H), 1.62 (br d, J=11 Hz, 2 H), 3.50 - 3.58 (m, 1 H), 4.25 (br dd, J=14, 8 Hz, 1 H), 4.90 (br s, 1 H), 7.12 (br s, 1 H), 7.35 (br d, J=6 Hz, 3 H), 7.51 - 7.64 (m, 3 H)
83	A	388	(400 MHz, DMSO- d_6) 0.52 - 0.90 (m, 10 H), 1.04 - 1.42 (m, 6 H), 1.60 (br d, J=10 Hz, 2 H), 3.67 (dd, J=14, 4 Hz, 1 H), 4.14 (dd, J=14, 8 Hz, 1 H), 4.91 (br s, 1 H), 7.27 - 7.41 (m, 4 H), 7.56 (br d, J=7 Hz, 2 H), 7.81 (br dd, J=7, 4 Hz, 1 H)

Example	LCMS Method	$[M+H]^+$	1H NMR spectrum (δ ppm , DMSO-d_6)
84	A	405	(400 MHz, DMSO- d_6) 0.72 - 0.89 (m, 10 H), 1.34 - 1.44 (m, 4 H), 1.44 - 1.55 (m, 2 H), 1.68 (br d, J=10 Hz, 2 H), 1.83 (s, 3 H), 2.66 - 2.78 (m, 2 H), 3.32 - 3.40 (m, 2 H), 3.42 - 3.51 (m, 2 H), 3.97 (t, J=5 Hz, 2 H), 4.79 (s, 1 H), 6.85 (t, J=7 Hz, 1 H), 6.92 (d, J=8 Hz, 1 H), 7.11 (dd, J=7, 2 Hz, 1 H), 7.16 (t, J=8 Hz, 1 H), 7.83 (br t, J=6 Hz, 1 H), 8.23 (br t, J=6 Hz, 1 H)
85	A	336	(400 MHz, DMSO- d_6) 0.71 - 0.93 (m, 10 H), 1.29 - 1.83 (m, 8 H), 4.48 (dd, J=5, 3 Hz, 2 H), 4.98 (s, 1 H), 7.33 - 7.42 (m, 2 H), 7.65 - 7.75 (m, 1 H), 7.87 (td, J=8, 2 Hz, 1 H), 8.11 (t, J=5 Hz, 1 H)
86	A	334	(400 MHz, DMSO- d_6) 0.61 - 0.95 (m, 10 H), 1.31 - 1.54 (m, 6 H), 1.64 - 1.79 (m, 2 H), 1.80 - 1.97 (m, 2 H), 3.32 - 3.43 (m, 2 H), 4.51 (t, J=5 Hz, 1 H), 4.77 (s, 1 H), 4.95 (td, J=8, 6 Hz, 1 H), 7.15 - 7.37 (m, 5 H), 8.06 (d, J=9 Hz, 1 H)
87	A	376	(400 MHz, DMSO- d_6) 0.73 - 0.91 (m, 10 H), 1.31 - 1.54 (m, 6 H), 1.63 - 1.74 (m, 2 H), 2.49 - 2.56 (m, 2 H), 2.64 - 2.90 (m, 4 H), 3.34 - 3.42 (m, 2 H), 4.58 - 4.92 (m, 1 H), 7.01 - 7.07 (m, 3 H), 7.16 - 7.21 (m, 1 H), 7.68 (t, J=6 Hz, 1 H), 11.73 - 12.65 (br s, 1H)
88	A	349	(400 MHz, DMSO- d_6) 0.74 - 0.93 (m, 10 H), 1.27 - 1.81 (m, 8 H), 3.87 (d, J=6 Hz, 2 H), 4.96 (s, 1 H), 6.66 - 6.73 (m, 2 H), 7.33 (m, J=9 Hz, 2 H), 7.94 (t, J=5 Hz, 1 H), 9.16 (br s, 1 H), 9.66 (s, 1 H)
89	B	334	(400 MHz, DMSO- d_6) 0.68 - 0.90 (m, 10 H), 1.25 - 1.51 (m, 6 H), 1.66 (br d, J=10 Hz, 2 H), 2.86 - 2.99 (m, 1 H), 3.26 - 3.36 (m, 1 H), 3.53 - 3.62 (m, 3 H), 4.71 - 4.78 (m, 2 H), 7.18 - 7.32 (m, 5 H), 7.54 (br t, J=6 Hz, 1 H)
90	B	334	(400 MHz, DMSO- d_6) 0.65 - 0.91 (m, 10 H), 1.24 - 1.48 (m, 6 H), 1.57 - 1.72 (m, 2 H), 2.92 (quin, J=7 Hz, 1 H), 3.38 - 3.49 (m, 2 H), 3.53 - 3.62 (m, 2 H), 4.70 - 4.78 (m, 2 H), 7.18 - 7.30 (m, 5 H), 7.56 (br t, J=6 Hz, 1 H)

Example	LCMS Method	$[M+H]^+$	1H NMR spectrum (δ ppm , DMSO-d_6)
91	B	321	(400 MHz, DMSO- d_6) 0.68 - 0.90 (m, 10 H), 1.28 - 1.52 (m, 6 H), 1.62 - 1.75 (m, 2 H), 3.32 - 3.48 (m, 2 H), 4.86 (s, 1 H), 5.51 (s, 1 H), 7.22 - 7.36 (m, 5 H), 7.57 (br t, J=6 Hz, 1 H)
92	B	321	(400 MHz, DMSO- d_6) 0.73 - 0.84 (m, 10 H), 1.30 - 1.53 (m, 6 H), 1.67 (br d, J=13 Hz, 2 H), 3.13 - 3.22 (m, 1 H), 3.44 (dd, J=13, 7 Hz, 1 H), 4.86 (s, 1 H), 5.48 (s, 1 H), 7.19 - 7.40 (m, 5 H), 7.62 (br t, J=6 Hz, 1 H)
93	A	390	(400 MHz, DMSO- d_6) 0.72 - 0.89 (m, 10 H), 1.29 - 1.56 (m, 6 H), 1.68 (br d, J=10 Hz, 2 H), 2.59 (t, J=8 Hz, 2 H), 2.67 - 2.80 (m, 2 H), 2.87 - 2.94 (m, 2 H), 3.20 - 3.39 (m, 2 H), 3.59 (s, 3 H), 4.73 (s, 1 H), 7.11 - 7.18 (m, 4 H), 7.82 (br t, J=6 Hz, 1 H)
94	A	332	(400 MHz, DMSO- d_6) 0.56 - 0.95 (m, 10 H), 1.28 - 1.54 (m, 6 H), 1.66 (br d, J=12 Hz, 2 H), 2.82 (br dd, J=16, 6 Hz, 1 H), 2.95 (br dd, J=16, 5 Hz, 1 H), 3.98 (dd, J=10, 7 Hz, 1 H), 4.08 (br d, J=10 Hz, 1 H), 4.18 (br s, 1 H), 4.90 (br s, 1 H), 6.78 (d, J=8 Hz, 1 H), 6.85 (t, J=7 Hz, 1 H), 7.02 - 7.12 (m, 2 H), 7.60 (br d, J=7.91 Hz, 1 H)
95	A	332	(400 MHz, DMSO- d_6) 0.73 - 0.93 (m, 10 H), 1.29 - 1.61 (m, 6 H), 1.63 - 1.73 (m, 2 H), 2.80 (dd, J=16, 7 Hz, 1 H), 2.96 (dd, J=16, 5 Hz, 1 H), 3.93 (dd, J=10, 7 Hz, 1 H), 4.05 (dd, J=10, 2 Hz, 1 H), 4.14 - 4.23 (m, 1 H), 4.89 (s, 1 H), 6.79 (d, J=8 Hz, 1 H), 6.85 (td, J=7, 1 Hz, 1 H), 7.06 - 7.11 (m, 2 H), 7.61 (br d, J=8 Hz, 1 H)
96	A		(400 MHz, DMSO- d_6) 0.73 - 0.90 (m, 10 H), 1.32 - 1.55 (m, 6 H), 1.64 - 1.74 (m, 2 H), 1.82 - 1.97 (m, 2 H), 3.31 - 3.35 (m, 1 H), 3.60 (dd, J=14, 7 Hz, 1 H), 4.15 - 4.20 (m, 2 H), 4.99 (d, J=8 Hz, 1 H), 5.52 (d, J=11 Hz, 1 H), 6.74 (d, J=8 Hz, 1 H), 6.88 (t, J=7 Hz, 1 H), 7.14 (t, J=8 Hz, 1 H), 7.46 (ddd, J=8, 4, 2 Hz, 1 H), 7.57 - 7.62 (m, 1 H)
97	A	346	(400 MHz, DMSO- d_6) 0.72 - 0.90 (m, 10 H), 1.24 - 1.46 (m, 4 H), 1.50 - 1.72 (m, 4 H), 2.66 - 2.73 (m, 1 H), 2.81 - 2.90 (m, 1 H), 3.44 (ddd, J=14, 8, 6 Hz, 1 H), 3.62 - 3.73 (m, 2 H), 4.06 (dt, J=11, 5 Hz, 1 H), 4.77 (dd, J=8, 3 Hz, 1 H), 4.86 (s, 1 H), 7.12 - 7.19 (m, 4 H), 7.56 (br t, J=6 Hz, 1 H)

Example	LCMS Method	$[M+H]^+$	1H NMR spectrum (δ ppm , DMSO-d_6)
98	A	346	(400 MHz, DMSO- d_6) 0.60 (t, J=7 Hz, 6 H), 0.80 (d, J=6 Hz, 4 H), 0.96 - 1.09 (m, 1 H), 1.24 - 1.48 (m, 5 H), 1.66 (br d, J=11 Hz, 2 H), 2.65 - 2.72 (m, 1 H), 2.82 - 2.91 (m, 1 H), 3.39 - 3.50 (m, 1 H), 3.66 - 3.77 (m, 2 H), 4.06 - 4.13 (m, 1 H), 4.81 - 4.90 (m, 2 H), 7.11 - 7.19 (m, 4 H), 7.47 - 7.54 (m, 1 H)
99	A	378	(400 MHz, DMSO- d_6) 0.73 - 0.90 (m, 10 H), 1.30 - 1.82 (m, 8 H), 3.86 (s, 3 H), 3.94 (s, 3 H), 4.42 (s, 2 H), 4.96 (s, 1 H), 6.61 - 6.72 (m, 2 H), 7.76 (d, J=9 Hz, 1 H), 7.99 (t, J=5 Hz, 1 H)
100	A	350	(400 MHz, DMSO- d_6) 0.73 - 0.94 (m, 10 H), 1.35 - 1.57 (m, 6 H), 1.62 - 1.79 (m, 2 H), 4.51 (d, J=5 Hz, 2 H), 4.98 (br s, 1 H), 6.82 (d, J=8 Hz, 1 H), 7.35 (d, J=2 Hz, 1 H), 7.40 (dd, J=8, 2 Hz, 1 H), 7.96 (t, J=5 Hz, 1 H), 9.34 (br s, 1 H), 9.89 (s, 1 H)
101	A	460	(400 MHz, DMSO- d_6) 0.69 - 0.88 (m, 10 H), 1.30 - 1.56 (m, 10 H), 1.58 - 1.80 (m, 4 H), 3.44 - 3.60 (m, 2 H), 3.64 - 3.73 (m, 1 H), 3.75 - 3.86 (m, 1 H), 4.45 (d, J=12 Hz, 1 H), 4.65 - 4.76 (m, 6 H), 4.83 (s, 1 H), 7.06 (d, J=8 Hz, 1 H), 7.09 (s, 1 H), 7.25 (d, J=8 Hz, 1 H), 7.35 (t, J=8 Hz, 1 H), 7.63 (br t, J=6 Hz, 1 H)
102	A	350	(400 MHz, DMSO- d_6) 0.72 - 0.94 (m, 10 H), 1.32 - 1.61 (m, 5 H), 1.64 - 1.80 (m, 3 H), 4.55 (d, J=6 Hz, 2 H), 4.99 (s, 1 H), 6.31 (d, J=2 Hz, 1 H), 6.38 (dd, J=9, 2 Hz, 1 H), 7.80 (d, J=9 Hz, 1 H), 8.03 (t, J=5 Hz, 1 H), 10.57 (s, 1 H), 11.85 (s, 1 H)
103	A	346	(400 MHz, DMSO- d_6) 0.75 - 0.93 (m, 10 H), 1.32 - 1.63 (m, 6 H), 1.66 - 1.92 (m, 4 H), 2.95 (dq, J=9, 4 Hz, 1 H), 3.27 - 3.48 (m, 2 H), 4.07 - 4.17 (m, 2 H), 4.82 (d, J=9 Hz, 1 H), 6.74 (d, J=8 Hz, 1 H), 6.84 (t, J=7 Hz, 1 H), 7.08 (t, J=8 Hz, 1 H), 7.19 (d, J=8 Hz, 1 H), 7.95 (q, J=6 Hz, 1 H)
104	A	350	(400 MHz, DMSO- d_6) 0.77 - 0.94 (m, 10 H), 1.36 - 1.48 (m, 3 H), 1.50 - 1.58 (m, 2 H), 1.64 - 1.80 (m, 3 H), 4.62 (d, J=6 Hz, 2 H), 4.98 (br s, 1 H), 6.76 (t, J=8 Hz, 1 H), 7.04 (dd, J=8, 1 Hz, 1 H), 7.34 (dd, J=8, 1 Hz, 1 H), 8.06 (t, J=5 Hz, 1 H)

Example	LCMS Method	$[M+H]^+$	1H NMR spectrum (δ ppm , DMSO-d_6)
105	A	406	(400 MHz, DMSO- d_6) 0.62 - 0.92 (m, 10 H), 1.14 (d, J=6 Hz, 3 H), 1.21 - 1.55 (m, 6 H), 1.59 - 1.77 (m, 2 H), 2.76 - 2.93 (m, 2 H), 3.32 - 3.51 (m, 2 H), 3.89 - 4.00 (m, 1 H), 4.04 - 4.21 (m, 2 H), 4.70 (s, 1 H), 4.93 (d, J=5 Hz, 1 H), 7.37 - 7.56 (m, 2 H), 7.71 (t, J=6 Hz, 1 H), 7.80 - 7.88 (m, 2 H)
106	A	362	(400 MHz, DMSO- d_6) 0.70 - 0.96 (m, 10 H), 1.27 - 1.51 (m, 6 H), 1.62 - 1.74 (m, 2 H), 2.99 - 3.16 (m, 2 H), 3.32 - 3.47 (m, 2 H), 3.85 (s, 3 H), 4.71 (s, 1 H), 7.30 - 7.38 (m, 2 H), 7.46 - 7.54 (m, 1 H), 7.71 (br t, J=5.65 Hz, 1 H), 7.80 (d, J=8.17 Hz, 1 H)
107	A	362	(400 MHz, DMSO- d_6) 0.68 - 0.87 (m, 10 H), 1.27 - 1.42 (m, 5 H), 1.43 - 1.50 (m, 1 H), 1.63 - 1.73 (m, 2 H), 2.78 - 2.89 (m, 2 H), 3.32 - 3.39 (m, 1 H), 3.41 - 3.50 (m, 1 H), 3.85 (s, 3 H), 4.70 (s, 1 H), 7.42 - 7.53 (m, 2 H), 7.70 (br t, J=6 Hz, 1 H), 7.78 - 7.83 (m, 2 H) d_6
108	A	362	(400 MHz, DMSO- d_6) 0.65 - 0.88 (m, 10 H), 1.24 - 1.53 (m, 6 H), 1.60 - 1.75 (m, 2 H), 2.84 (br t, J=6.96 Hz, 2 H), 3.32 - 3.40 (m, 1 H), 3.41 - 3.50 (m, 1 H), 3.84 (s, 3 H), 4.72 (s, 1 H), 7.37 (m, J=8.28 Hz, 2 H), 7.71 (br t, J=5.77 Hz, 1 H), 7.88 (m, J=8.28 Hz, 2 H)
109	A	334	(400 MHz, DMSO- d_6) 0.71 - 0.92 (m, 10 H), 1.32 - 1.55 (m, 6 H), 1.62 - 1.76 (m, 2 H), 2.66 - 2.77 (m, 2 H), 3.22 - 3.47 (m, 2 H), 4.46 (d, J=6 Hz, 2 H), 4.75 (s, 1 H), 5.08 (t, J=6 Hz, 1 H), 7.16 (m, J=8 Hz, 2 H), 7.23 (m, J=8 Hz, 2 H), 7.67 (br t, J=6 Hz, 1 H)
110	A	244	(400 MHz, DMSO- d_6) 0.68 - 0.97 (m, 10 H), 1.30 - 1.60 (m, 6 H), 1.63 - 1.80 (m, 2 H), 3.16 (qd, J=6, 2 Hz, 2 H), 3.37 - 3.45 (m, 2 H), 4.68 (t, J=5 Hz, 1 H), 4.81 (s, 1 H), 7.66 (br t, J=6 Hz, 1 H)
111	A	348	(400 MHz, DMSO- d_6) 0.59 - 0.95 (m, 10 H), 1.29 - 1.80 (m, 8 H), 3.31 (s, 2 H), 3.53 - 3.61 (m, 1 H), 4.31 (t, J=5 Hz, 2 H), 4.77 (s, 1 H), 7.45 - 7.55 (m, 2 H), 7.59 - 7.74 (m, 1 H), 7.87 - 8.09 (m, 2 H)
112	A	284	(400 MHz, DMSO- d_6) 0.70 - 1.00 (m, 10 H), 1.29 - 1.58 (m, 6 H), 1.61 - 1.81 (m, 2 H), 2.19 - 2.39 (m, 2 H), 4.20 (ddd, J=10, 9, 7 Hz, 1 H), 4.33 (td, J=9, 2 Hz, 1 H), 4.49 - 4.67 (m, 1 H), 4.88 (s, 1 H), 8.26 (d, J=8 Hz, 1 H)

Examples 113 to 174 were synthesized by parallel synthesis by set of 20 to 40 amines from a solution A and purified by RP-HPLC chromatography as described above in **Experiment procedures**.

(1S,2S,5R)-1-Hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxylic acid (1.24g) was dissolved in EtOAc (0.1M) and CDI (1.05eq) was added. The resulting solution (solution A) was allowed to stir at room temperature for one hour and said solution ("solution A"), was used for coupling reactions with 31 amines.

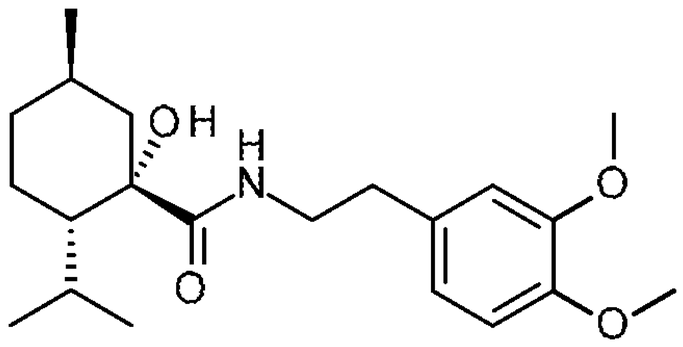
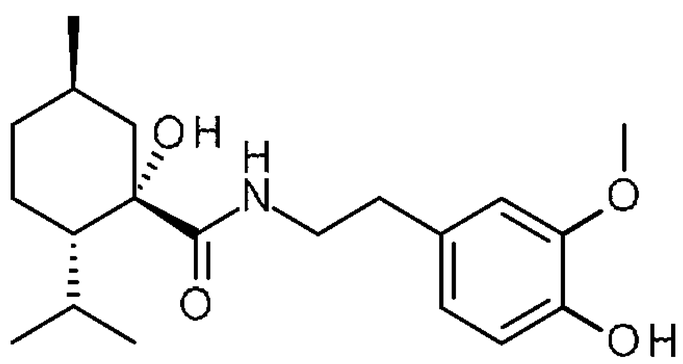
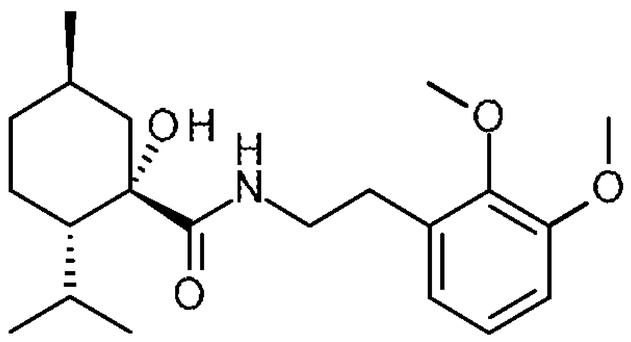
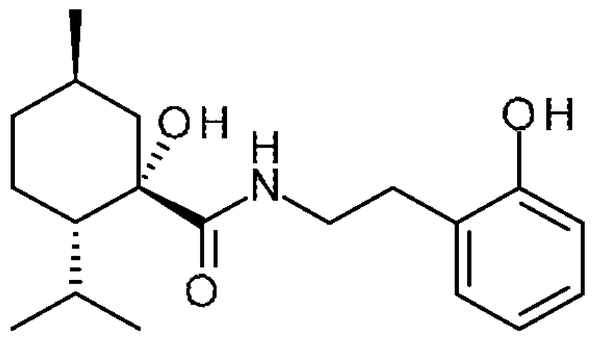
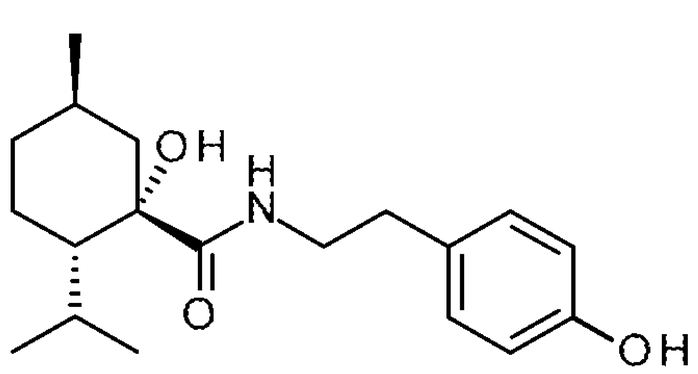
Example 113: *(1S,2S,5R)-N-[2-(3,4-dimethoxyphenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide*

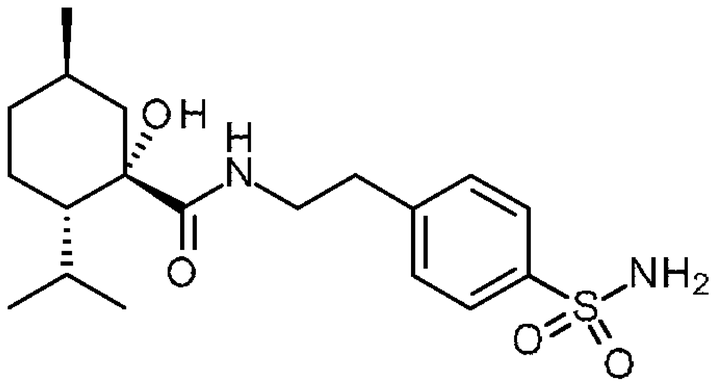
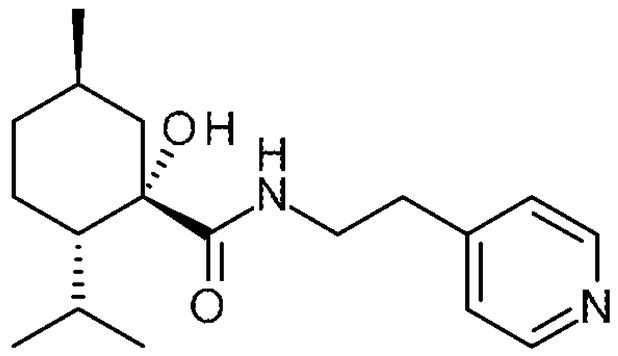
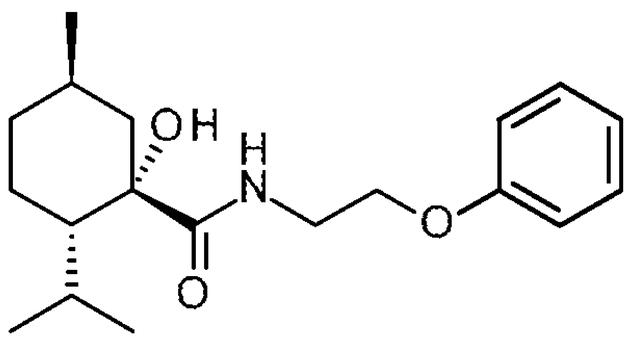
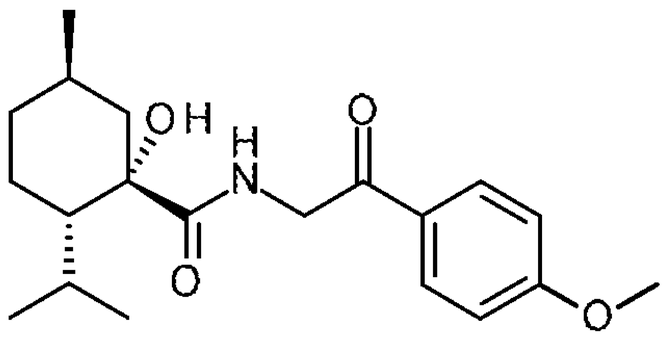
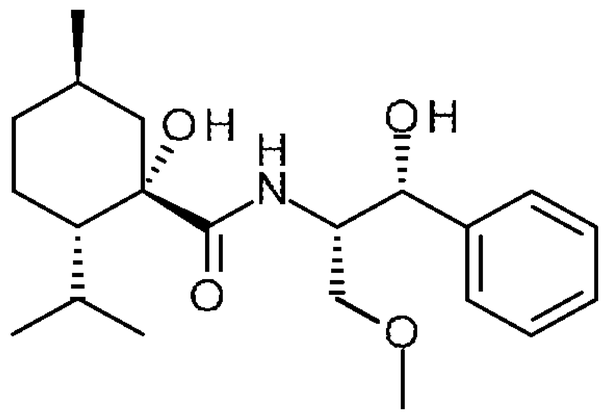
The solution A (2ml, 0.2mmol) was added to 2-(3,4-dimethoxyphenyl)ethanamine (0.2mmol, 1.0eq) at room temperature and the resulting reaction mixture was then heated at 80°C btw 150 and 210min. The solvent was removed in vacuo and the residue was dissolved in 2 ml of a 9:1 DMF/TFA mixture (9/1, 2ml). The resulting crude solution was purified by RP-HPLC chromatography under conditions E below to yield (1S,2S,5R)-N-[2-(3,4-dimethoxyphenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide.

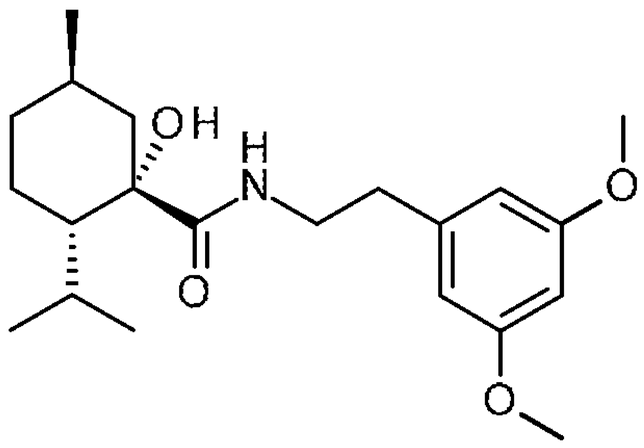
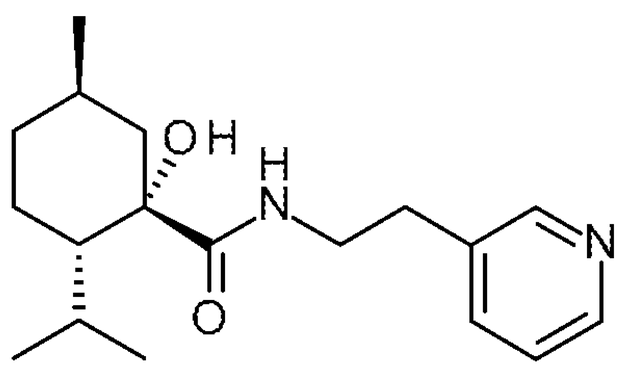
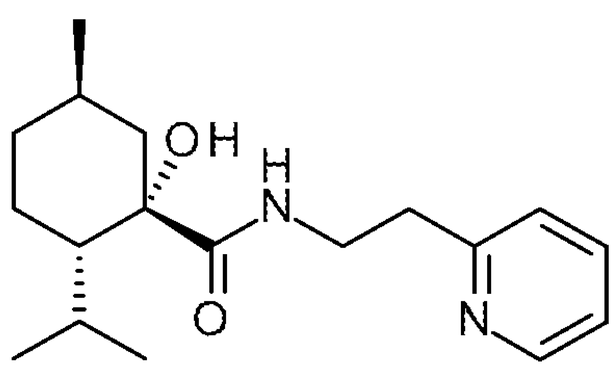
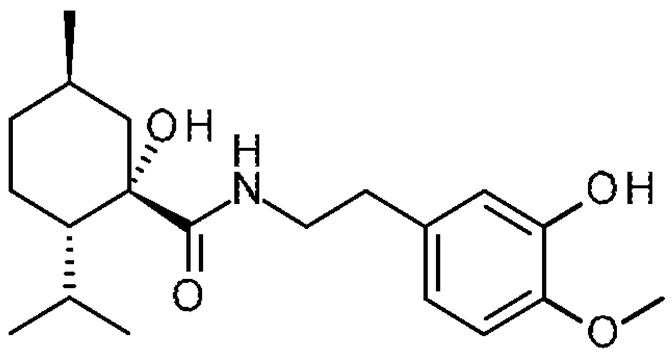
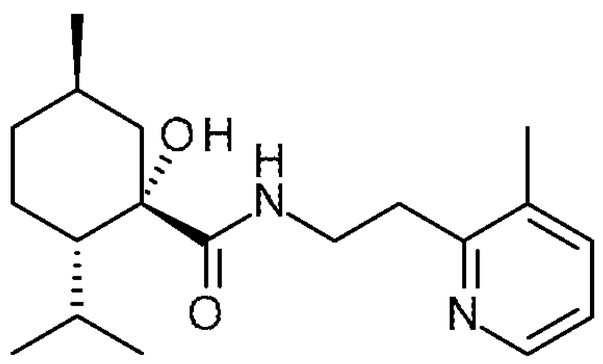
Examples 114 to 152 and examples 156 to 174 were synthesized under same experimental conditions as for **example 113** and purified by RP-HPLC chromatography **Method G** as described above.

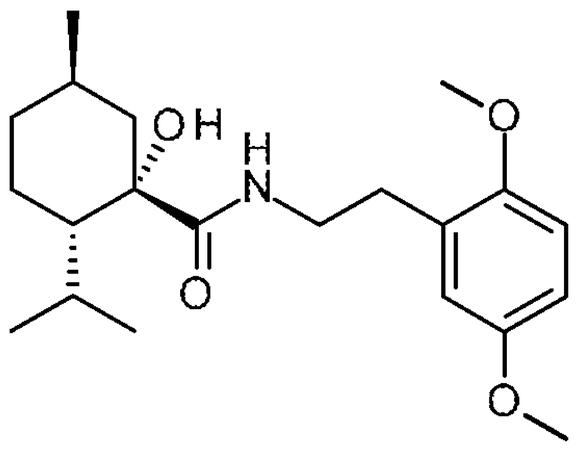
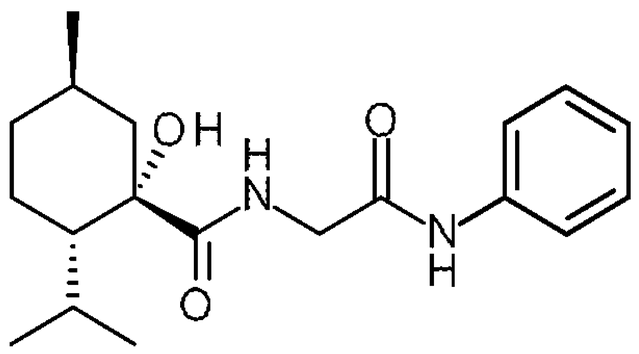
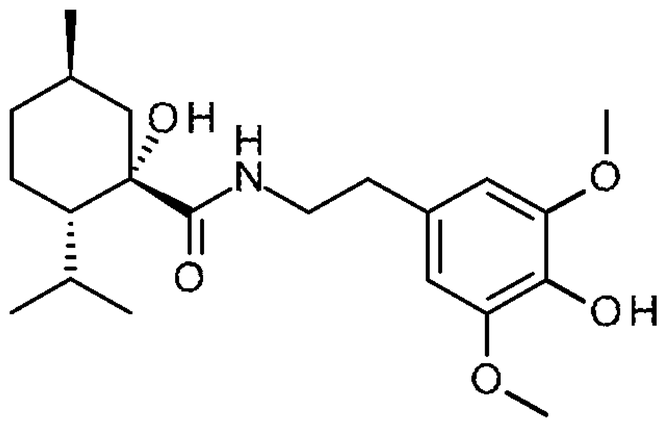
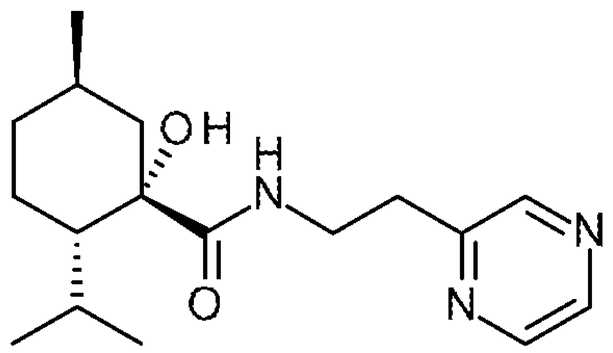
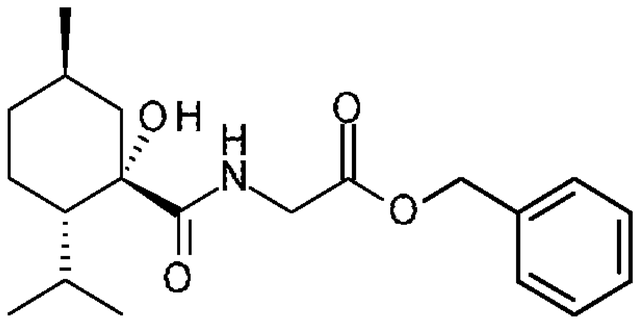
The compound structure and compound name for Examples, 113 to 152 and 156 to 174, the amine used for synthesis and the RP-HPLC purification method are shown in **Table 2**.

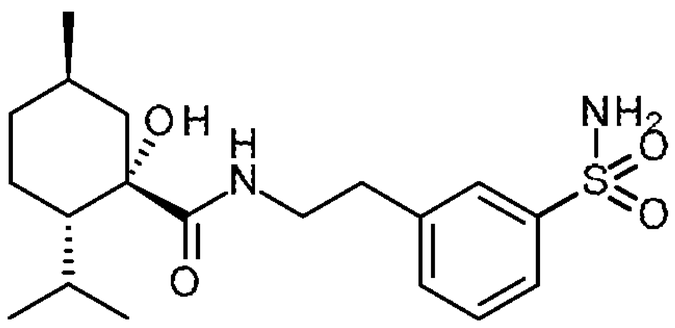
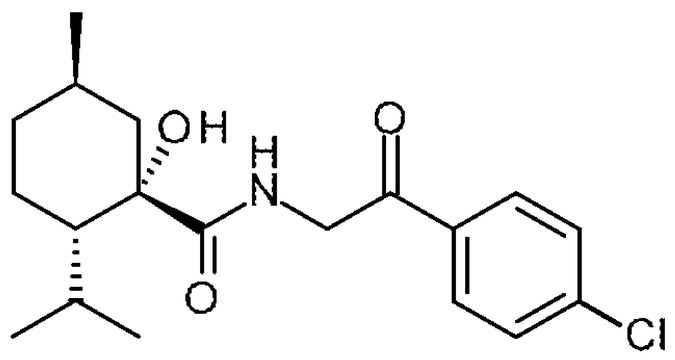
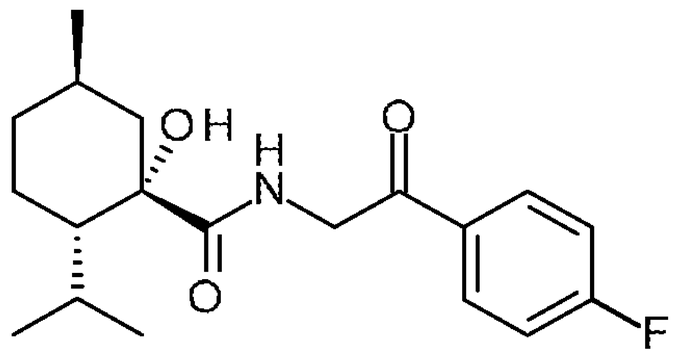
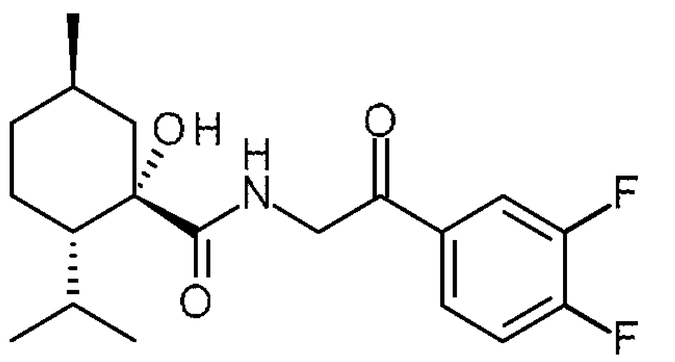
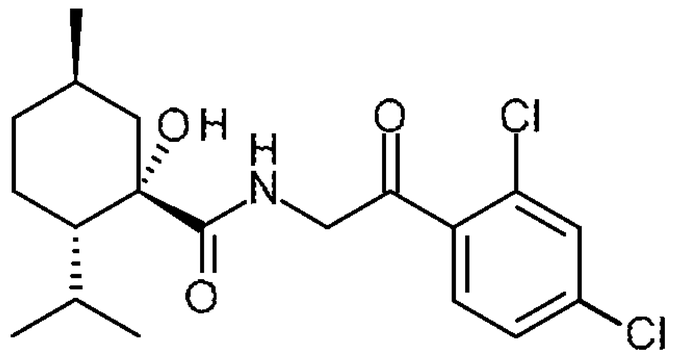
Table 2

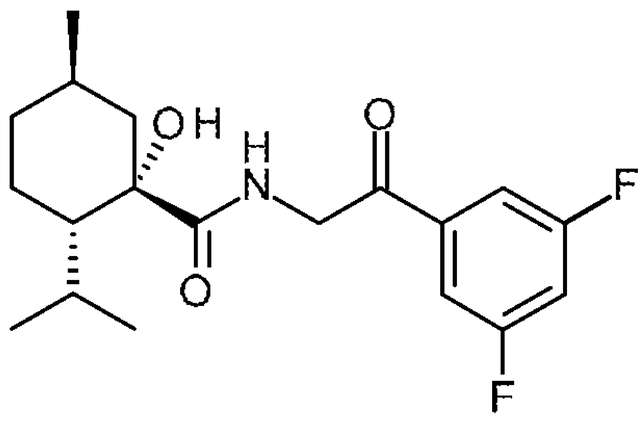
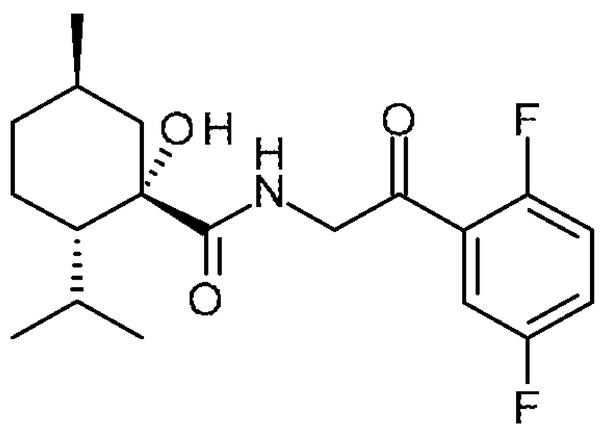
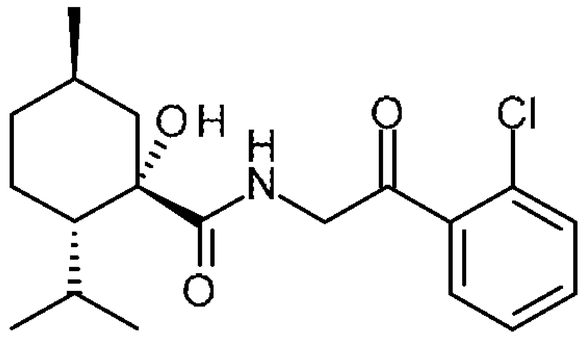
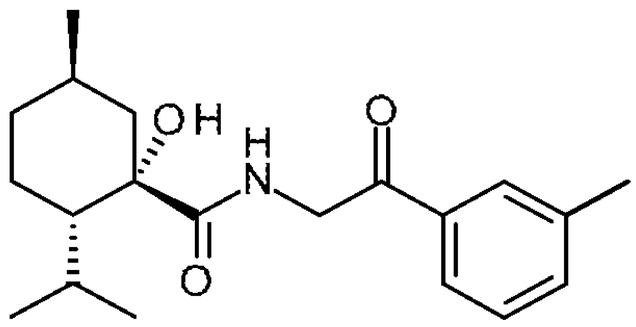
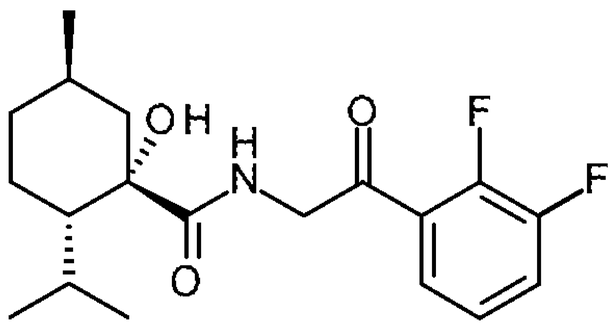
Example	Structure	Compound Name	Amine used	RP-HPLC Purification method
113		(1S,2S,5R)-N-[2-(3,4-dimethoxyphenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	2-(3,4-dimethoxyphenyl)ethanamine	G
114		(1S,2S,5R)-1-hydroxy-N-[2-(4-hydroxy-3-methoxy-phenyl)ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	4-(2-aminoethyl)-2-methoxy-phenol	G
115		(1S,2S,5R)-N-[2-(2,3-dimethoxyphenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	2-(2,3-dimethoxyphenyl)ethanamine	G
116		(1S,2S,5R)-1-hydroxy-N-[2-(2-hydroxyphenyl)ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	2-(2-aminoethyl) phenol	G
117		(1S,2S,5R)-1-hydroxy-N-[2-(4-hydroxyphenyl)ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	4-(2-aminoethyl) phenol	G

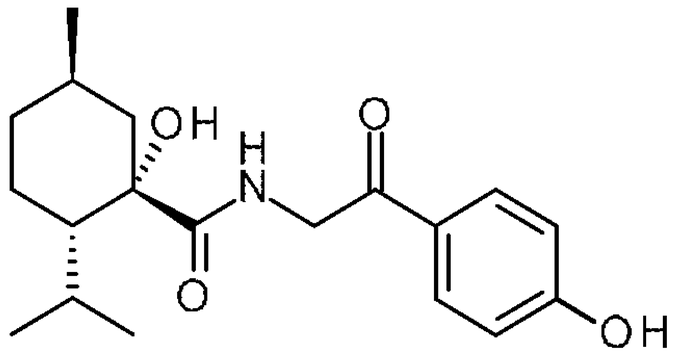
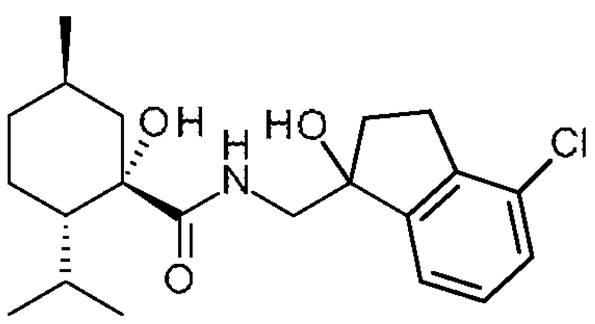
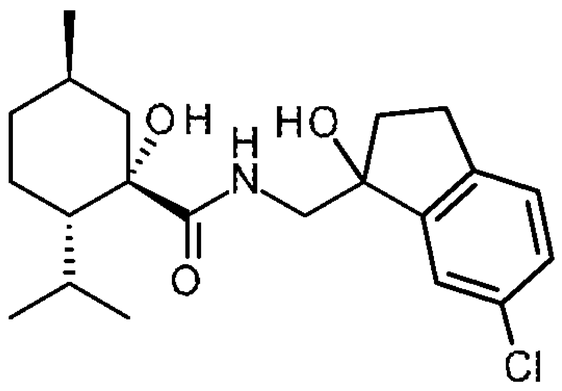
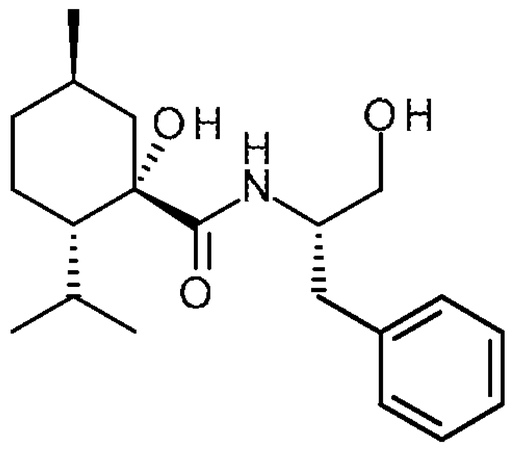
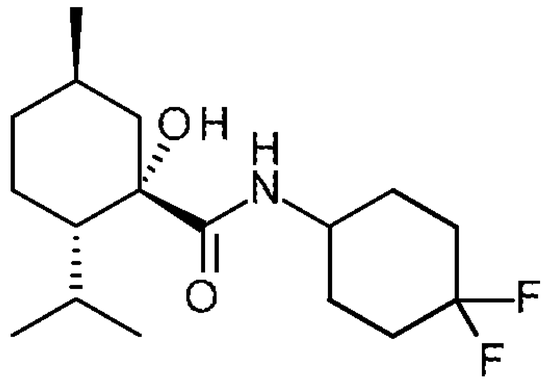
Example	Structure	Compound Name	Amine used	RP-HPLC Purification method
118		(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-[2-(4-sulfamoylphenyl)ethyl]cyclohexanecarboxamide	4-(2-aminoethyl) benzenesulfonamide	G
119		(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-[2-(4-pyridyl)ethyl]cyclohexanecarboxamide	2-(4-pyridyl)ethanamine	G
120		(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(2-phenoxyethyl)cyclohexanecarboxamide	2-phenoxyethanamine	G
121		(1S,2S,5R)-1-hydroxy-2-isopropyl-N-[2-(4-methoxyphenyl)-2-oxo-ethyl]-5-methyl-cyclohexanecarboxamide	2-amino-1-(4-methoxyphenyl)ethanone	G
122		(1S,2S,5R)-1-hydroxy-N-[(1S,2S)-2-hydroxy-1-(methoxymethyl)-2-phenyl-ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	(1S,2S)-2-amino-3-methoxy-1-phenyl-propan-1-ol	G

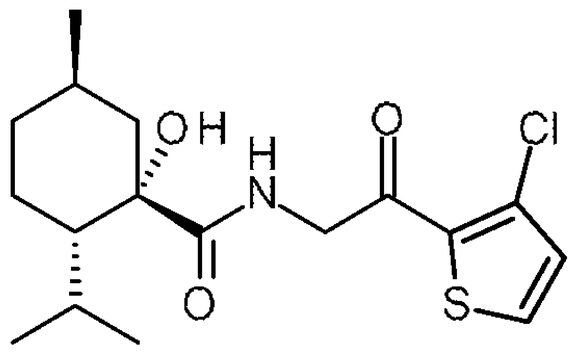
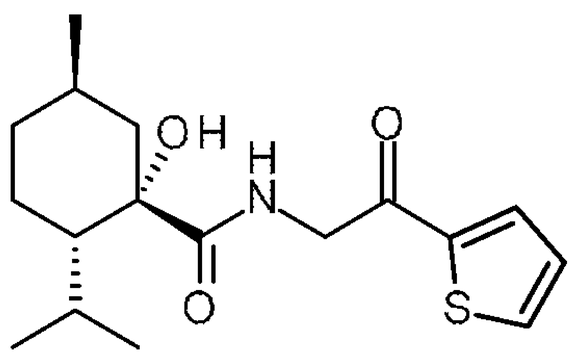
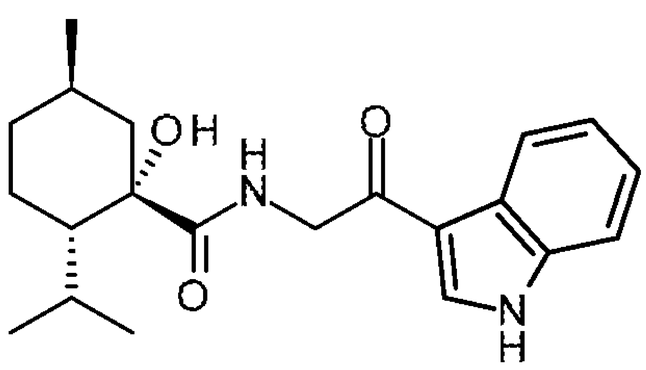
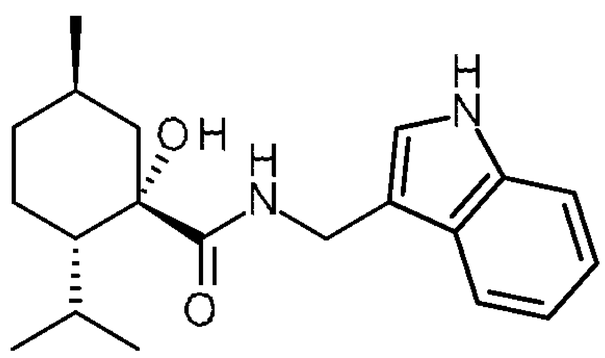
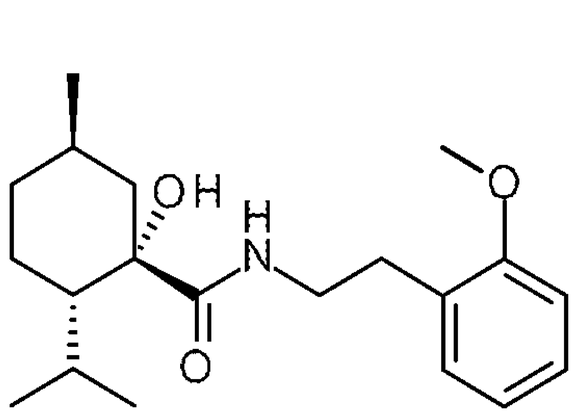
Example	Structure	Compound Name	Amine used	RP-HPLC Purification method
123		(1S,2S,5R)-N-[2-(3,5-dimethoxyphenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	2-(3,5-dimethoxyphenyl)ethanamine	G
124		(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-[2-(3-pyridyl)ethyl]cyclohexanecarboxamide	2-(3-pyridyl)ethanamine	G
125		(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-[2-(2-pyridyl)ethyl]cyclohexanecarboxamide	2-(2-pyridyl)ethanamine	G
126		(1S,2S,5R)-1-hydroxy-N-[2-(3-hydroxy-4-methoxy-phenyl)ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	5-(2-aminoethyl)-2-methoxy-phenol	G
127		(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-[2-(3-methyl-2-pyridyl)ethyl]cyclohexanecarboxamide	2-(3-methyl-2-pyridyl)ethanamine	G

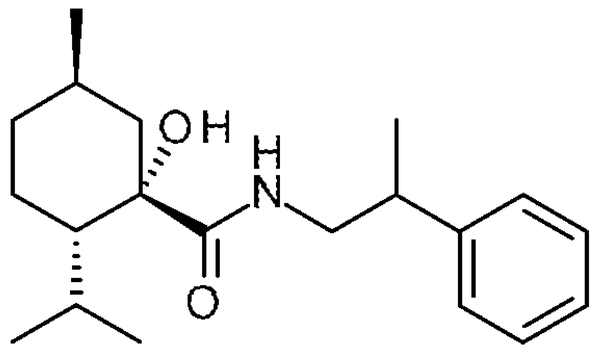
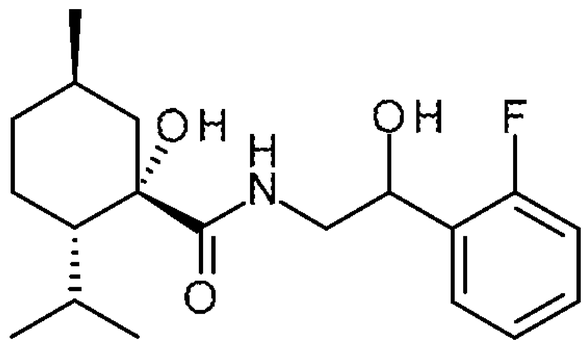
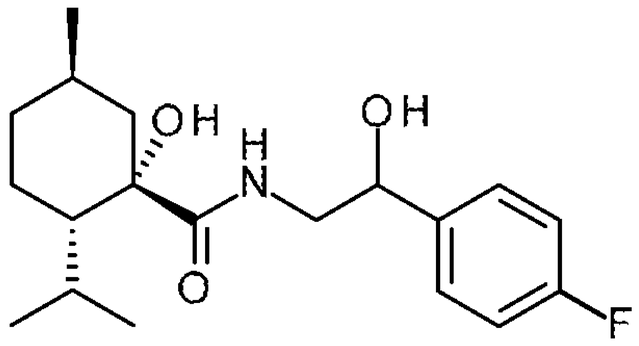
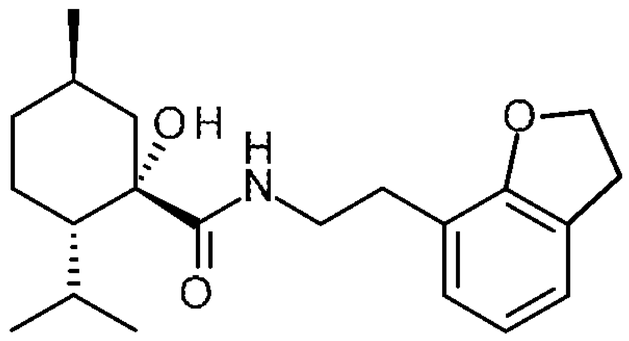
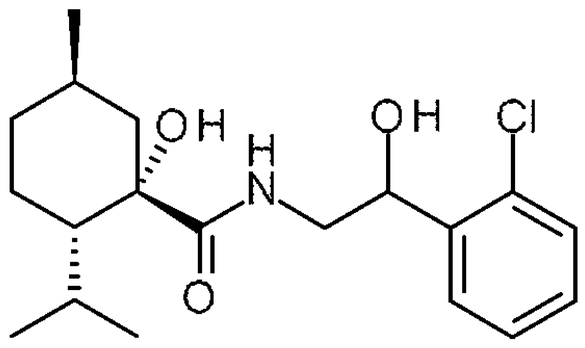
Example	Structure	Compound Name	Amine used	RP-HPLC Purification method
128		(1S,2S,5R)-N-[2-(2,5-dimethoxyphenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	2-(2,5-dimethoxyphenyl)ethanamine	G
129		(1S,2S,5R)-N-(2-anilino-2-oxo-ethyl)-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	2-amino-N-phenyl-acetamide	G
130		(1S,2S,5R)-1-hydroxy-N-[2-(4-hydroxy-3,5-dimethoxy-phenyl)ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	4-(2-aminoethyl)-2,6-dimethoxy-phenol	G
131		(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(2-pyrazin-2-ylethyl)cyclohexanecarboxamide	2-pyrazin-2-ylethanamine	G
132		benzyl 2-[[(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarbonyl]amino]acetate	benzyl 2-aminoacetate	G

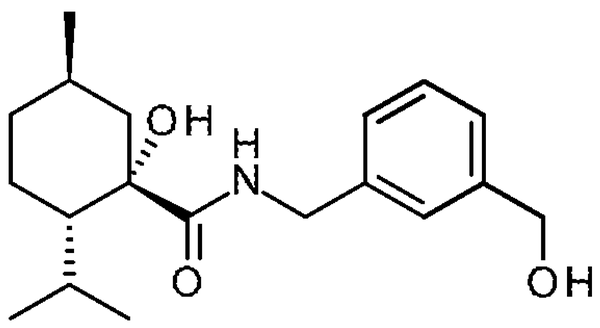
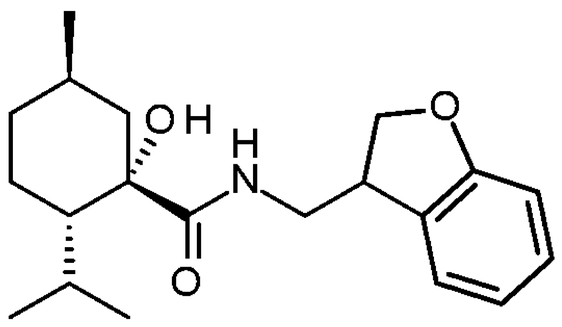
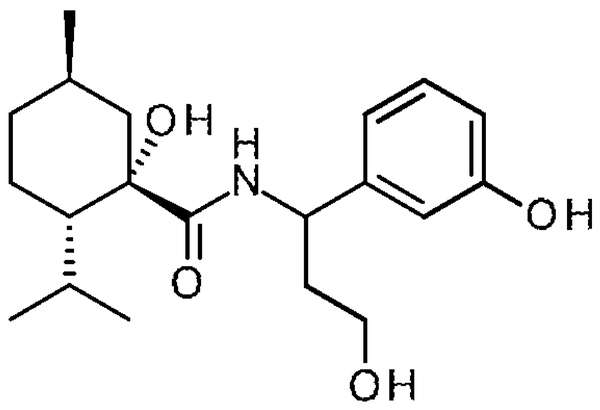
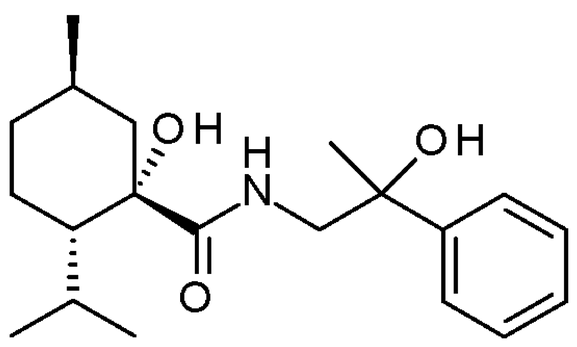
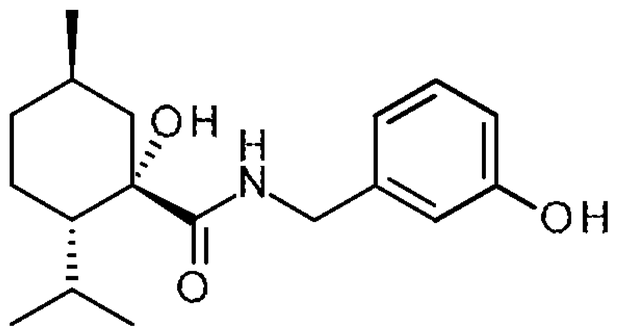
Example	Structure	Compound Name	Amine used	RP-HPLC Purification method
133		(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-[2-(3-sulfamoylphenyl)ethyl]cyclohexanecarboxamide	3-(2-aminoethyl) benzenesulfonamide	G
134		(1S,2S,5R)-N-[2-(4-chlorophenyl)-2-oxo-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	2-amino-1-(4-chlorophenyl)ethanone	G
135		(1S,2S,5R)-N-[2-(4-fluorophenyl)-2-oxo-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	2-amino-1-(4-fluorophenyl)ethanone	G
136		(1S,2S,5R)-N-[2-(3,4-difluorophenyl)-2-oxo-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	2-amino-1-(3,4-difluorophenyl)ethanone	G
137		(1S,2S,5R)-N-[2-(2,4-dichlorophenyl)-2-oxo-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	2-amino-1-(2,4-dichlorophenyl)ethanone	G

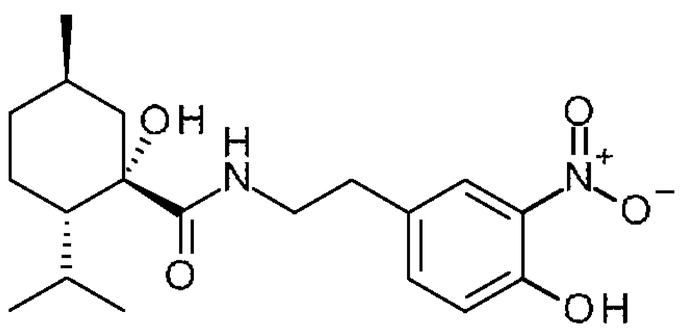
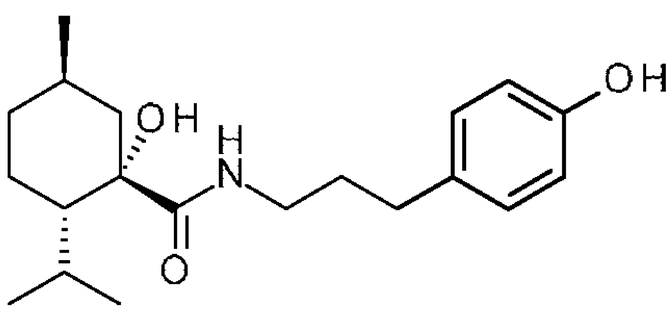
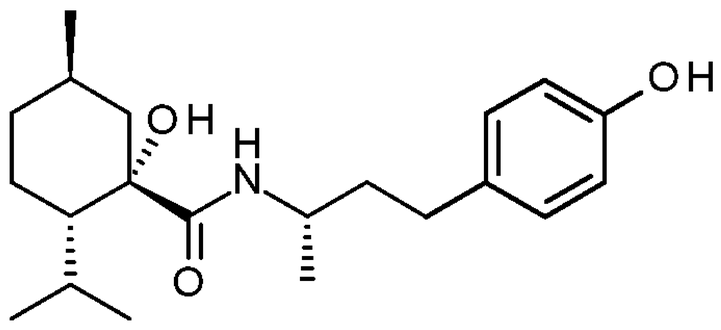
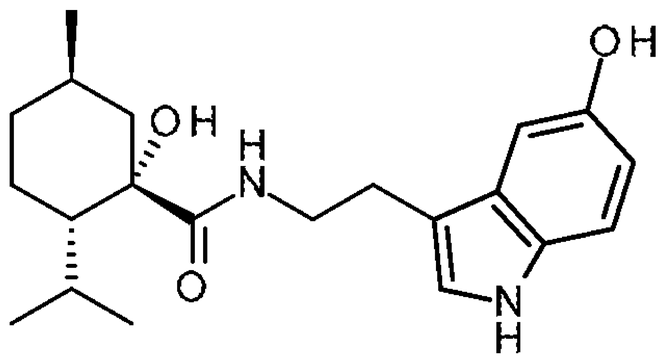
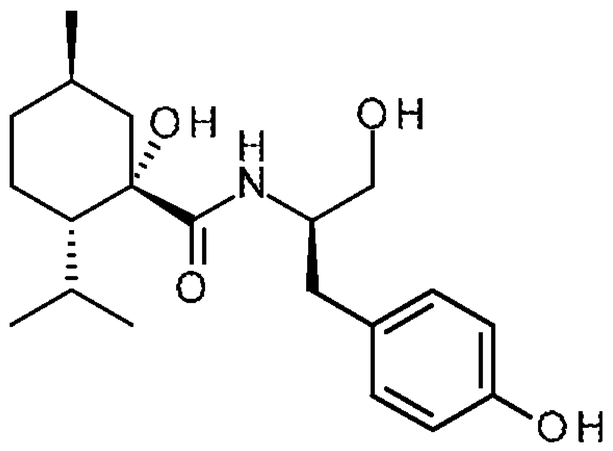
Example	Structure	Compound Name	Amine used	RP-HPLC Purification method
138		(1S,2S,5R)-N-[2-(3,5-difluorophenyl)-2-oxo-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	2-amino-1-(3,5-difluorophenyl)ethanone	G
139		(1S,2S,5R)-N-[2-(2,5-difluorophenyl)-2-oxo-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	2-amino-1-(2,5-difluorophenyl)ethanone	G
140		(1S,2S,5R)-N-[2-(2-chlorophenyl)-2-oxo-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	2-amino-1-(2-chlorophenyl)ethanone	G
141		(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-[2-(m-tolyl)-2-oxo-ethyl]cyclohexanecarboxamide	2-amino-1-(m-tolyl)ethanone	G
142		(1S,2S,5R)-N-[2-(2,3-difluorophenyl)-2-oxo-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	2-amino-1-(2,3-difluorophenyl)ethanone	G

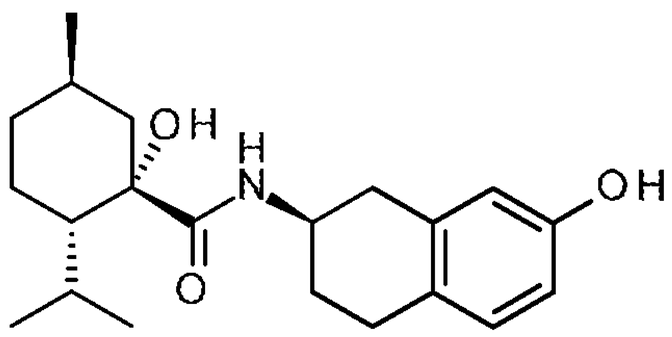
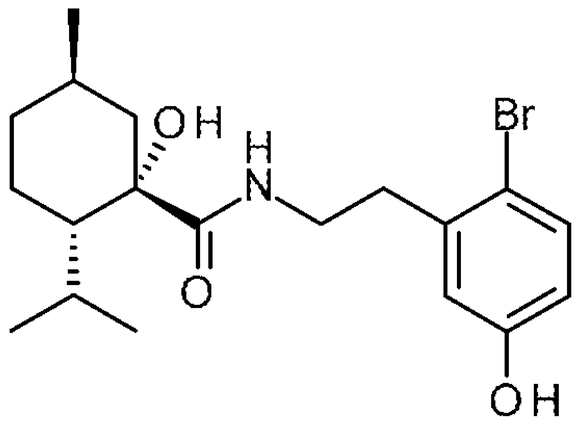
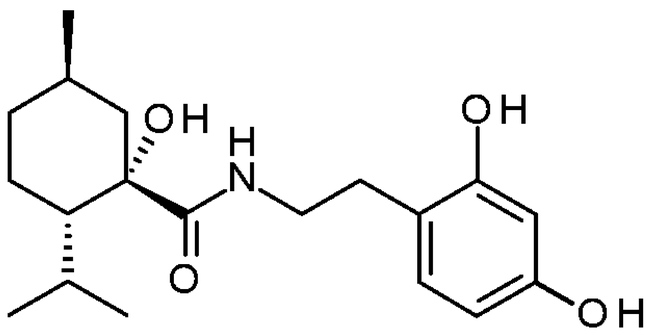
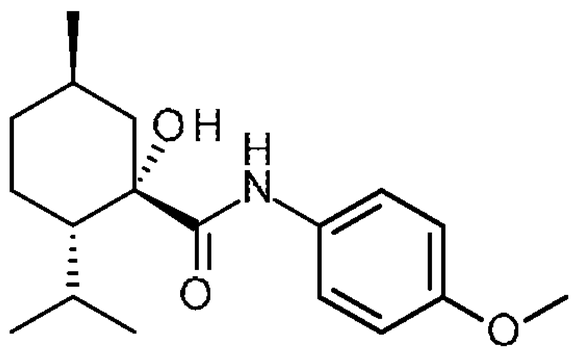
Example	Structure	Compound Name	Amine used	RP-HPLC Purification method
143		(1S,2S,5R)-1-hydroxy-N-[2-(4-hydroxyphenyl)-2-oxo-ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	2-amino-1-(4-hydroxyphenyl)ethanone	G
144		(1S,2S,5R)-N-[(4-chloro-1-hydroxy-indan-1-yl)methyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	1-(aminomethyl)-4-chloro-indan-1-ol	G
145		(1S,2S,5R)-N-[(6-chloro-1-hydroxy-indan-1-yl)methyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	1-(aminomethyl)-6-chloro-indan-1-ol	G
146		(1S,2S,5R)-N-[(1S)-1-benzyl-2-hydroxy-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	(2S)-2-amino-3-phenyl-propan-1-ol	G
147		(1S,2S,5R)-N-(4,4-difluorocyclohexyl)-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	4,4-difluorocyclohexanamine	G

Example	Structure	Compound Name	Amine used	RP-HPLC Purification method
148		(1S,2S,5R)-N-[2-(3-chloro-2-thienyl)-2-oxo-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	2-amino-1-(3-chloro-2-thienyl)ethanone	G
149		(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-[2-oxo-2-(2-thienyl)ethyl]cyclohexanecarboxamide	2-amino-1-(2-thienyl)ethanone	G
150		(1S,2S,5R)-1-hydroxy-N-[2-(1H-indol-3-yl)-2-oxo-ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	2-amino-1-(1H-indol-3-yl)ethanone	G
151		(1S,2S,5R)-1-hydroxy-N-[(1R)-3-hydroxy-1-(2-thienylmethyl)propyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	(3R)-3-amino-4-(2-thienyl)butan-1-ol	G
155		(1S,2S,5R)-1-hydroxy-2-isopropyl-N-[2-(2-methoxyphenyl)ethyl]-5-methyl-cyclohexanecarboxamide	2-(2-methoxyphenyl)ethanamine	G

Example	Structure	Compound Name	Amine used	RP-HPLC Purification method
156		(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(2-phenylpropyl)cyclohexanecarboxamide	2-phenylpropan-1-amine	G
157		(1S,2S,5R)-N-[2-(2-fluorophenyl)-2-hydroxy-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	2-amino-1-(2-fluorophenyl)ethanol	G
158		(1S,2S,5R)-N-[2-(4-fluorophenyl)-2-hydroxy-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	2-amino-1-(4-fluorophenyl)ethanol	G
159		(1S,2S,5R)-N-[2-(2,3-dihydrobenzofuran-7-yl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	2-(2,3-dihydrobenzofuran-7-yl)ethanamine	G
160		(1S,2S,5R)-N-[2-(2-chlorophenyl)-2-hydroxy-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	2-amino-1-(2-chlorophenyl)ethanol	G

Example	Structure	Compound Name	Amine used	RP-HPLC Purification method
161		(1S,2S,5R)-1-hydroxy-N-[[3-(hydroxymethyl)phenyl]methyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	[3-(aminomethyl)phenyl]methanol	G
162		(1S,2S,5R)-N-(2,3-dihydrobenzofuran-3-ylmethyl)-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	2,3-dihydrobenzofuran-3-ylmethanamine	G
163		(1S,2S,5R)-1-hydroxy-N-[3-hydroxy-1-(3-hydroxyphenyl)propyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	3-(1-amino-3-hydroxy-propyl)phenol	G
164		(1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-phenyl-propyl)-2-isopropyl-5-methyl-cyclohexanecarboxamide	1-amino-2-phenyl-propan-2-ol	G
165		(1S,2S,5R)-1-hydroxy-N-[(3-hydroxyphenyl)methyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	3-(aminomethyl)phenol	G

Example	Structure	Compound Name	Amine used	RP-HPLC Purification method
166		(1S,2S,5R)-1-hydroxy-N-[2-(4-hydroxy-3-nitro-phenyl)ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	4-(2-aminoethyl)-2-nitro-phenol	G
167		(1S,2S,5R)-1-hydroxy-N-[3-(4-hydroxyphenyl)propyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	4-(3-aminopropyl)phenol	G
168		(1S,2S,5R)-1-hydroxy-N-[(1S)-3-(4-hydroxyphenyl)-1-methyl-propyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	4-[(3S)-3-aminobutyl]phenol	G
169		(1S,2S,5R)-1-hydroxy-N-[2-(5-hydroxy-1H-indol-3-yl)ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	3-(2-aminoethyl)-1H-indol-5-ol	G
170		(1S,2S,5R)-1-hydroxy-N-[(1R)-1-(hydroxymethyl)-2-(4-hydroxyphenyl)ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	4-[(2R)-2-amino-3-hydroxy-propyl]phenol	G

Example	Structure	Compound Name	Amine used	RP-HPLC Purification method
171		(1S,2S,5R)-1-hydroxy-N-[(2R)-7-hydroxytetralin-2-yl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	(3R)-3-aminotetralin-6-ol	G
172		(1S,2S,5R)-N-[2-(2-bromo-5-hydroxy-phenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	3-(2-aminoethyl)-4-bromo-phenol	G
173		(1S,2S,5R)-N-[2-(2,4-dihydroxyphenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	4-(2-aminoethyl) benzene-1,3-diol	G
174		(1S,2S,5R)-1-hydroxy-N-(4-methoxyphenyl)-5-methyl-2-propan-2-ylcyclohexane-1-carboxamide	4-Methoxyphenylamine	G

Example 152

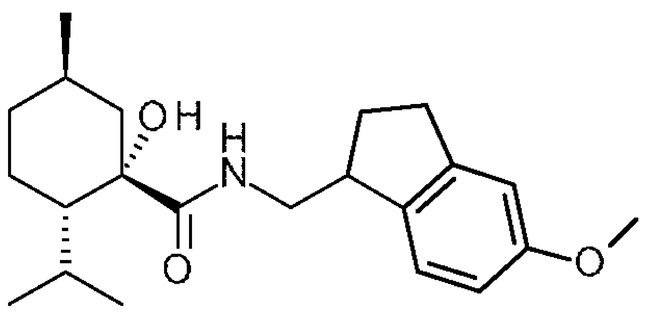
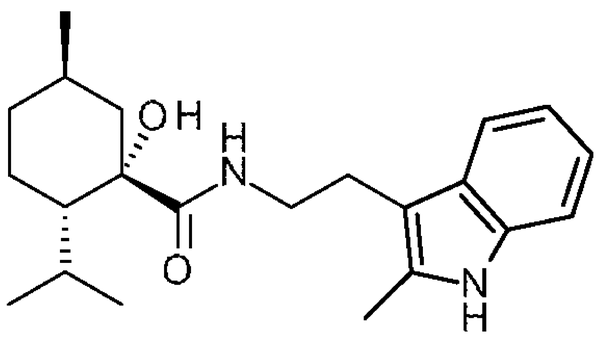
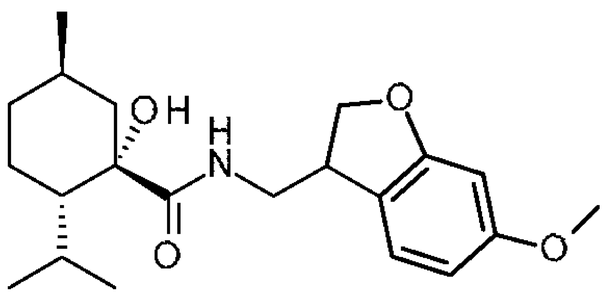
(1S,2S,5R)-1-hydroxy-2-isopropyl-N-[(5-methoxyindan-1-yl)methyl]-5-methyl-cyclohexanecarboxamide

Solution A (2ml, 0.2mmol) was added to (5-methoxyindan-1-yl)methanamine (0.2mmol, 1.0eq) at room temperature and the resulting reaction mixture was then heated at 80°C btw 150 and 210min. The solvent was removed in vacuo and the residue was dissolved in 2 ml of a 9:1 DMF/TFA

mixture (9/1, 2ml). The resulting crude solution was subjected to RP-HPLC chromatography under conditions F.

Examples, 153 and ***154,*** were synthesized and purified under same experimental conditions as for ***example 152*** as shown in Table 3.

Table 3

Example	Structure	Compound Name	Amine used	Purification Method
152		(1S,2S,5R)-1-hydroxy-2-isopropyl-N-[(5-methoxyindan-1-yl)methyl]-5-methyl-cyclohexanecarboxamide	(5-methoxyindan-1-yl)methanamine	H
153		(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-[2-(2-methyl-1H-indol-3-yl)ethyl]cyclohexanecarboxamide	2-(2-methyl-1H-indol-3-yl)ethanamine	H
154		(1S,2S,5R)-1-hydroxy-2-isopropyl-N-[(6-methoxy-2,3-dihydrobenzofuran-3-yl)methyl]-5-methyl-cyclohexanecarboxamide	(6-methoxy-2,3-dihydrobenzofuran-3-yl)methanamine	H

Examples 113 to **174**, were characterized by 1H NMR and LC-MS analysis as shown below in **Table 4**:

Table 4

Example	Compound Name	1H NMR spectrum (δ ppm, DMSO-d_6)	LCMS Method	[M+H]+
113	(1S,2S,5R)-N-[2-(3,4-dimethoxyphenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	(400.23 MHz, DMSO-d_6) 7.63 (br t, J=5.69, 5.69 Hz, 1 H), 6.84 (d, J=8.15 Hz, 1 H), 6.80 (d, J=1.86 Hz, 1 H), 6.71 (dd, J=8.19, 1.96 Hz, 1 H), 4.74 (br s), 3.68-3.77 (m, 6 H), 3.42 (br u), 3.39-3.33 (m), 3.33-3.22 (m), 2.73-2.60 (m, 2 H), 2.50 (u), 2.08 (u), 2.07 (u), 1.74-1.62 (m, 2 H), 1.54-1.30 (m, 6 H), 0.92-0.70 (m)	C	364
114	(1S,2S,5R)-1-hydroxy-N-[2-(4-hydroxy-3-methoxy-phenyl)ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	(400.23 MHz, DMSO-d_6) 8.67 (br s), 7.61 (br t, J=5.62, 5.62 Hz, 1 H), 6.75 (d, J=1.83 Hz, 1 H), 6.67 (d, J=7.95 Hz, 1 H), 6.58 (dd, J=7.95, 1.83 Hz, 1 H), 4.75 (br s), 3.75 (s, 3 H), 3.42 (br u), 3.38-3.31 (m), 3.31-3.20 (m), 2.67-2.57 (m, 2 H), 2.50 (u), 2.09 (u), 1.74-1.62 (m, 2 H), 1.54-1.32 (m, 6 H), 0.89-0.72 (m)	C	350
115	(1S,2S,5R)-N-[2-(2,3-dimethoxyphenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	(400.23 MHz, DMSO-d_6) 7.72 (br t, J=5.75, 5.75 Hz, 1 H), 6.99-6.94 (m, 1 H), 6.90 (dd, J=8.29, 1.55 Hz, 1 H), 6.76 (dd, J=7.52, 1.53 Hz, 1 H), 4.72 (br s), 3.80-3.70 (m, 6 H), 3.41 (br u), 3.37-3.21 (m), 2.78-2.65 (m, 2 H), 2.50 (u), 1.74-1.62 (m, 2 H), 1.53-1.30 (m, 6 H), 0.93-0.71 (m, 10 H)	C	364
116	(1S,2S,5R)-1-hydroxy-N-[2-(2-hydroxyphenyl)ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	(400.23 MHz, DMSO-d_6) 7.64-7.53 (m, 1 H), 7.36-7.20 (m, 5 H), 5.63-5.43 (br m), 4.86 (br s, 1 H), 4.67-4.60 (m, 1 H), 3.48-3.43 (m), 3.32 (u), 3.20-3.13 (m), 2.50 (u), 1.74-1.62 (m, 2 H), 1.55-1.27 (m), 0.91-0.67 (m)	C	320

Example	Compound Name	1H NMR spectrum (δ ppm, DMSO-d_6)	LCMS Method	[M+H]+
117	(1S,2S,5R)-1-hydroxy-N-[2-(4-hydroxyphenyl)ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	(400.23 MHz, DMSO-d_6) 9.13 (br s, 1 H), 7.62 (br t, J=5.93, 5.93 Hz, 1 H), 7.00-6.96 (m, 2 H), 6.68-6.64 (m, 2 H), 4.72 (br s, 1 H), 3.33 (br u), 3.30-3.17 (m), 2.64-2.56 (m), 2.50 (u), 2.09 (u), 1.74-1.63 (m, 2 H), 1.54-1.30 (m, 6 H), 0.91-0.72 (m)	C	320
118	(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-[2-(4-sulfamoylphenyl)ethyl]cyclohexanecarboxamide	(400.23 MHz, DMSO-d_6) 7.78-7.70 (m, 3 H), 7.60 (u), 7.42-7.36 (m, 2 H), 7.27 (s, 2 H), 4.74 (br s), 3.47-3.40 (m), 3.39 (br u) 3.36-3.28 (m), 2.87-2.76 (m, 2 H), 2.50 (u), 2.08 (u), 1.75-1.63 (m, 2 H), 1.53-1.30 (m, 6 H), 0.92-0.70 (m, 10 H)	C	383
119	(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-[2-(4-pyridyl)ethyl]cyclohexane carboxamide	(400.23 MHz, DMSO-d_6) 8.72-8.68 (m, 2 H), 7.85 (br t, J=5.81, 5.81 Hz, 1 H), 7.72-7.68 (m, 2 H), 4.75 (br s, 1 H), 3.57 (br u), 3.58-3.48 (m), 3.48-3.39 (m), 3.02-2.94 (m, 2 H), 2.50 (u), 1.73-1.62 (m, 2 H), 1.47-1.22 (m, 6 H), 0.89-0.76 (m, 4 H), 0.73 (d, J=6.74 Hz, 3 H), 0.67 (d, J=6.87 Hz, 3 H)	C	305
120	(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(2-phenoxyethyl)cyclohexanecarboxamide	(400.23 MHz, DMSO-d_6) 7.86 (br t, J=5.81, 5.81 Hz, 1 H), 7.32-7.24 (m, 2 H), 6.95-6.89 (m, 3 H), 4.85 (s, 1 H), 4.04-3.95 (m, 2 H), 3.55-3.40 (m), 3.31 (u), 2.50 (u), 1.76-1.33 (m, 8H), 0.93-0.69 (m, 10 H)	C	320
121	(1S,2S,5R)-1-hydroxy-2-isopropyl-N-[2-(4-methoxyphenyl)-2-oxo-ethyl]-5-methyl-cyclohexanecarboxamide	(400.23 MHz, DMSO-d_6) 8.05-7.95 (m, 3 H), 7.08-7.02 (m, 2 H), 4.99 (s, 1 H), 4.59 (d, J=5.38 Hz, 2 H), 3.85 (s, 3 H), 3.30 (u), 2.50 (u), 1.80-1.63 (m, 3 H), 1.58-1.35 (m, 5 H), 0.94-0.74 (m, 10 H)	C	348

Example	Compound Name	1H NMR spectrum (δ ppm, DMSO-d_6)	LCMS Method	[M+H]+
122	(1S,2S,5R)-1-hydroxy-N-[(1S,2S)-2-hydroxy-1-(methoxymethyl)-2-phenyl-ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	-	C	364
123	(1S,2S,5R)-N-[2-(3,5-dimethoxyphenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	(400.23 MHz, DMSO-d_6) 7.65 (br t, J=6.01, 6.01 Hz, 1 H), 6.40-6.30 (m, 3 H), 4.75 (br s), 3.71 (s, 6 H), 3.45-3.36 (m), 3.33 (br u), 3.30-3.23 (m), 2.73-2.61 (m, 2 H), 2.50 (u), 1.73-1.63 (m, 2 H), 1.53-1.29 (m, 6 H), 0.92-0.71 (m, 10 H)	C	364
124	(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-[2-(3-pyridyl)ethyl]cyclohexane carboxamide	(400.23 MHz, DMSO-d_6) 8.69-8.64 (m, 2 H), 8.18-8.13 (m, 1 H), 7.84 (br t, J=5.87, 5.87 Hz, 1 H), 7.74 (dd, J=7.82, 5.38 Hz, 1 H), 4.64 (br s), 3.64 (br u), 3.55-3.45 (m), 3.45-3.36 (m), 2.97-2.87 (m, 2H), 2.50 (u), 1.73-1.62 (m, 2 H), 1.46-1.21 (m, 6 H), 0.89-0.65 (m, 10 H)	C	305
125	(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-[2-(2-pyridyl)ethyl]cyclohexane carboxamide	(400.23 MHz, DMSO-d_6) 8.68-8.63 (m, 2 H), 8.17-8.12 (m, 1 H), 7.83 (br t, J=5.87, 5.87 Hz, 1 H), 7.74 (dd, J=7.95, 5.38 Hz, 1 H), 4.74 (br s), 3.65 (br u), 3.55-3.45 (m), 3.45-3.36 (m), 2.97-2.86 (m, 2H), 2.50 (u), 1.73-1.62 (m, 2 H), 1.46-1.21 (m, 6 H), 0.88-0.64 (m, 10 H)	C	305

Example	Compound Name	1H NMR spectrum (δ ppm, DMSO-d_6)	LCMS Method	[M+H]+
126	(1S,2S,5R)-1-hydroxy-N-[2-(3-hydroxy-4-methoxy-phenyl)ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	(400.23 MHz, DMSO-d_6) 8.77 (br s), 7.63 (br t, J=5.62, 5.62 Hz, 1 H), 6.80 (d, J=8.19 Hz, 1 H), 6.62 (d, J=1.96 Hz, 1 H), 6.56 (dd, J=8.07, 1.96 Hz, 1 H), 4.70 (br s), 3.72 (s, 3 H), 3.46 (br u), 3.37-3.27 (m), 3.27-3.16 (m), 2.62-2.53 (m), 2.50 (u), 1.75-1.61 (m, 2 H), 1.54-1.29 (m, 6 H), 0.92-0.70 (m)	C	350
127	(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-[2-(3-methyl-2-pyridyl)ethyl]cyclohexane carboxamide	(400.23 MHz, DMSO-d_6) 8.78 (br s), 7.63 (br t, J=5.78, 5.78 Hz, 1 H), 6.80 (d, J=8.13 Hz, 1 H), 6.62 (d, J=2.00 Hz, 1 H), 6.56 (dd, J=8.13, 2.00 Hz, 1 H), 4.71 (br s), 3.71 (s, 3 H), 3.45 (br u), 3.37-3.27 (m), 3.27-3.16 (m), 2.61-2.54 (m), 2.50 (u), 2.08 (u), 1.74-1.62 (m, 2 H), 1.54-1.30 (m, 6 H), 0.92-0.72 (m)	C	319
128	(1S,2S,5R)-N-[2-(2,5-dimethoxyphenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	(400.23 MHz, DMSO-d_6) 7.65 (br t, J=5.56, 5.56 Hz, 1 H), 6.88-6.84 (m, 1 H), 6.75-6.71 (m, 2 H), 4.70 (br s), 3.75-3.66 (m, 6 H), 3.40 (br u), 3.36-3.22 (m), 2.77-2.62 (m, 2 H), 2.50 (u), 1.73-1.62 (m, 2 H), 1.53-1.29 (m, 6 H), 0.91-0.69 (m, 10 H)	C	364
129	(1S,2S,5R)-N-(2-anilino-2-oxo-ethyl)-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	(400.23 MHz, DMSO-d_6) 9.94 (s, 1 H), 7.98 (t, J=5.56, 5.56 Hz, 1 H), 7.56 (d, J=7.58 Hz, 2 H), 7.34-7.27 (m, 2 H), 7.07-7.02 (m, 1 H), 4.98 (s, 1 H), 3.92 (d, J=5.62 Hz, 2 H), 3.31 (u), 2.50 (u), 1.79-1.34 (m, 8 H), 0.94-0.74 (m, 10 H)	C	333

Example	Compound Name	1H NMR spectrum (δ ppm, DMSO-d_6)	LCMS Method	[M+H]+
130	(1S,2S,5R)-1-hydroxy-N-[2-(4-hydroxy-3,5-dimethoxy-phenyl)ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	(400.23 MHz, DMSO-d_6) 8.05 (br s), 7.61 (br t, J=5.91, 5.91 Hz, 1 H), 6.45 (s, 2 H), 4.75 (br s), 3.73 (s, 6 H), 3.47 (br u), 3.43-3.34 (m), 3.32-3.22 (m), 2.69-2.56 (m, 2 H), 2.50 (u), 2.09 (u), 1.74-1.63 (m, 2 H), 1.54-1.31 (m, 6 H), 0.92-0.71 (m, 10 H)	C	380
131	(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(2-pyrazin-2-ylethyl)cyclohexanecarboxamide	(400.23 MHz, DMSO-d_6) 8.56-8.52 (m, 2 H), 8.47 (d, J=2.57 Hz, 1 H), 7.82 (br t, J=5.69, 5.69 Hz, 1 H), 4.73 (s, 1 H), 3.60-3.42 (m, 2 H), 3.31 (u), 2.96 (t, J=6.79, 6.79 Hz, 2 H), 2.50 (u), 1.72-1.62 (m, 2 H), 1.48-1.27 (m, 6 H), 0.90-0.67 (m, 10 H)	C	306
132	benzyl 2-[[(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarbonyl]amino]acetate	(400.23 MHz, DMSO-d_6) 8.13 (t, J=6.05, 6.05 Hz, 1 H), 7.40-7.30 (m, 5 H), 5.16-5.07 (m, 2 H), 4.89 (s, 1 H), 3.97-3.84 (m, 2 H), 3.31 (u), 2.50 (u), 2.09 (u), 1.76-1.63 (m, 3 H), 1.55-1.30 (m, 5 H), 0.92-0.71 (m, 10 H)	C	348
133	(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-[2-(3-sulfamoylphenyl)ethyl]cyclohexanecarboxamide	(400.23 MHz, DMSO-d_6) 7.81 (br t, J=5.93, 5.93 Hz, 1 H), 7.70-7.64 (m, 2 H), 7.50-7.41 (m, 2 H), 7.28 (s, 2 H), 4.74 (br s), 3.39 (br u), 3.35-3.30 (m), 2.86-2.76 (m, 2 H), 2.50 (u), 2.09 (u), 1.75-1.63 (m, 2 H), 1.54-1.31 (m, 6 H), 0.92-0.72 (m, 10 H)	C	383

Example	Compound Name	1H NMR spectrum (δ ppm, DMSO-d_6)	LCMS Method	[M+H]+
134	(1S,2S,5R)-N-[2-(4-chlorophenyl)-2-oxo-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	(600.05 MHz, DMSO-d_6) 8.09 (t, J=5.41, 5.41 Hz, 1 H), 8.01-7.98 (m, 2 H), 7.61-7.58 (m, 2 H), 4.98 (s, 1 H), 4.63-4.54 (m, 2 H), 3.31 (u), 2.50 (u), 1.77-1.65 (m, 2 H), 1.63-1.58 (m, 1 H), 1.54-1.47 (m, 2 H), 1.45-1.33 (m, 3 H), 0.92-0.79 (m, 7 H), 0.75 (d, J=6.79 Hz, 3 H)	C	352
135	(1S,2S,5R)-N-[2-(4-fluorophenyl)-2-oxo-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	(600.05 MHz, DMSO-d_6) 8.10-8.06 (m, 3 H), 7.38-7.33 (m, 2 H), 4.99 (s, 1 H), 4.64-4.56 (m, 2 H), 3.31 (u), 2.50 (u), 1.78-1.61 (m, 3 H), 1.55-1.48 (m, 2 H), 1.46-1.35 (m, 3 H), 0.93-0.79 (m, 7 H), 0.76 (d, J=6.79 Hz, 3 H)	C	336
136	(1S,2S,5R)-N-[2-(3,4-difluorophenyl)-2-oxo-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	(600.05 MHz, DMSO-d_6) 8.12 (t, J=5.41, 5.41 Hz, 1 H), 8.07-8.02 (m, 1 H), 7.90-7.86 (m, 1 H), 7.63-7.58 (m, 1 H), 4.98 (br s, 1 H), 4.62-4.53 (m, 2 H), 3.31 (u), 2.50 (u), 1.77-1.66 (m, 2 H), 1.62-1.56 (m, 1 H), 1.54-1.47 (m, 2 H), 1.45-1.33 (m, 3 H), 0.92-0.79 (m, 7 H), 0.74 (d, J=6.97 Hz, 3 H)	C	354
137	(1S,2S,5R)-N-[2-(2,4-dichlorophenyl)-2-oxo-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	(600.05 MHz, DMSO-d_6) 8.24 (t, J=5.59, 5.59 Hz, 1 H), 7.72-7.67 (m, 2 H), 7.53 (dd, J=8.44, 2.02 Hz, 1 H), 4.90 (s, 1 H), 4.36-4.27 (m, 2 H), 3.31 (u), 2.50 (u), 2.09 (u), 1.72-1.62 (m, 2 H), 1.46 (br s, 1 H), 1.47-1.42 (m, 1 H), 1.41-1.27 (m, 3 H), 1.25-1.19 (m, 2 H), 0.88-0.76 (m, 4 H), 0.74 (d, J=6.79 Hz, 3 H), 0.67 (d, J=6.97 Hz, 3 H)	C	386

Example	Compound Name	1H NMR spectrum (δ ppm, DMSO-d_6)	LCMS Method	[M+H]+
138	(1S,2S,5R)-N-[2-(3,5-difluorophenyl)-2-oxo-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	(600.05 MHz, DMSO-d_6) 8.16 (t, J=5.41, 5.41 Hz, 1 H), 7.70-7.65 (m, 2 H), 7.61-7.56 (m, 1 H), 4.97 (br s, 1 H), 4.61-4.51 (m, 2 H), 3.31 (u), 2.50 (u), 2.09 (u), 1.77-1.65 (m, 2 H), 1.59-1.46 (m, 3 H), 1.44-1.32 (m, 3 H), 0.91-0.78 (m, 7 H), 0.73 (d, J=6.79 Hz, 3 H)	C	354
139	(1S,2S,5R)-N-[2-(2,5-difluorophenyl)-2-oxo-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	(600.05 MHz, DMSO-d_6) 8.14 (br t, J=5.41, 5.41 Hz, 1 H), 7.63-7.58 (m, 1 H), 7.58-7.52 (m, 1 H), 7.48-7.42 (m, 1 H), 4.98 (br s, 1 H), 4.46-4.42 (m, 2 H), 3.29 (u), 2.50 (u), 2.09 (u), 1.76-1.65 (m, 2 H), 1.55-1.48 (m, 2 H), 1.48-1.30 (m, 4 H), 0.92-0.78 (m, 7 H), 0.73 (d, J=6.79 Hz, 3 H)	C	354
140	(1S,2S,5R)-N-[2-(2-chlorophenyl)-2-oxo-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	(600.05 MHz, DMSO-d_6) 8.18 (t, J=5.50, 5.50 Hz, 1 H), 7.70-7.67 (m, 1 H), 7.54-7.50 (m, 2 H), 7.46-7.42 (m, 1 H), 4.91 (br s, 1 H), 4.39-4.36 (m, 2 H), 3.40 (u), 2.50 (u), 2.08 (u), 1.74-1.64 (m, 2 H), 1.51-1.46 (m, 1 H), 1.45-1.32 (m, 4 H), 1.30-1.25 (m, 1 H), 0.89-0.74 (m, 7 H), 0.70 (d, J=6.79 Hz, 3 H)	C	352
141	(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-[2-(m-tolyl)-2-oxo-ethyl]cyclohexanecarboxamide	(600.05 MHz, DMSO-d_6) 8.06 (t, J=5.41, 5.41 Hz, 1 H), 7.81 (s, 1 H), 7.79 (d, J=7.70 Hz, 1 H), 7.47 (d, J=7.52 Hz, 1 H), 7.42 (t, J=7.61, 7.61 Hz, 1 H), 4.99 (br s, 1 H), 4.65-4.56 (m, 2 H), 3.31 (u), 2.50 (u), 2.41-2.35 (m, 3 H), 2.07 (u), 1.78-1.63 (m, 3 H), 1.56-1.49 (m, 2 H), 1.46-1.36 (m, 3H), 0.92-0.80 (m, 7 H), 0.76 (d, J=6.97 Hz, 3 H)	C	332

Example	Compound Name	1H NMR spectrum (δ ppm, DMSO-d_6)	LCMS Method	[M+H]+
142	(1S,2S,5R)-N-[2-(2,3-difluorophenyl)-2-oxo-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	(600.05 MHz, DMSO-d_6) 8.23 (br t, J=5.41, 5.41 Hz, 1 H), 7.63-7.57 (m, 1 H), 7.22-7.17 (m, 2 H), 4.88 (s, 1 H), 4.28-4.25 (m, 2 H), 3.31 (u), 2.50 (u), 1.73-1.63 (m, 2 H), 1.50-1.-45 (m, 1 H), 1.42-1.28 (m, 4 H), 1.25-1.19 (m, 1 H), 0.88-0.73 (m, 7 H), 0.70 (d, J=6.79 Hz, 3 H)	C	354
143	(1S,2S,5R)-1-hydroxy-N-[2-(4-hydroxyphenyl)-2-oxo-ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	(600.05 MHz, DMSO-d_6) 12.47 (u), 10.39 (s, 1 H), 8.00 (t, J=5.32, 5.32 Hz, 1 H), 7.89-7.85 (m, 2 H), 6.87-6.84 (m, 2 H), 4.99 (br s, 1 H), 4.55 (d, J=5.32 Hz, 2 H), 4.38 (u), 3.31 (u), 2.50 (u), 1.78-1.64 (m), 1.57-1.26 (m), 0.92-0.74 (m)	C	334
144	(1S,2S,5R)-N-[(4-chloro-1-hydroxy-indan-1-yl)methyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	(600.05 MHz, DMSO-d_6) 7.61-7.55 (m, 1 H), 7.32-7.26 (m, 2 H), 7.25-7.20 (m, 1 H), 5.63 (br s), 4.95 (br s), 3.45-3.41 (m), 3.37-3.35 (m), 3.34 (u), 3.32-3.28 (m), 2.94-2.87 (m, 1 H), 2.78-2.71 (m, 1 H), 2.50 (u), 2.26-2.21 (m, 1 H), 2.08 (u), 2.00-1.95 (m, 1 H), 1.73-1.64 (m, 2 H), 1.51-1.28 (m, 6 H), 0.88-0.75 (m, 7 H), 0.73-0.69 (m, 3 H)	C	378
145	(1S,2S,5R)-N-[(6-chloro-1-hydroxy-indan-1-yl)methyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	(600.05 MHz, DMSO-d_6) 7.62 (m, 1 H), 7.31 (m, 1 H), 7.24 (m, 2 H), 5.59 (br s), 5.00 (br s), 3.37 (u), 3.36-3.33 (m), 2.88-2.82 (m, 1 H), 2.76-2.68 (m, 1 H), 2.50 (u), 2.22-2.16 (m, 1 H), 2.08 (u), 2.00-1.92 (m, 1 H), 1.76-1.64 (m, 2 H), 1.55-1.26 (m, 6 H), 0.91-0.77 (m, 7 H), 0.72 (d, J=6.90 Hz, 3 H)	C	378

Example	Compound Name	1H NMR spectrum (δ ppm, DMSO-d_6)	LCMS Method	[M+H]+
146	(1S,2S,5R)-N-[(1S)-1-benzyl-2-hydroxy-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	(600.05 MHz, DMSO-d_6) 7.40-7.36 (m, 1 H), 7.26-7.22 (m, 2 H), 7.21-7.18 (m, 2 H), 7.18-7.14 (m, 1 H), 4.72 (br s), 4.04-3.96 (m, 1 H), 3.43 (u), 3.39-3.35 (m), 3.31-3.27 (m), 2.89-2.85 (m, 1 H), 2.72-2.67 (m, 1 H), 2.50 (u), 1.71-1.62 (m, 2 H), 1.48-1.16 (m), 0.89-0.80 (m), 0.78 (d, J= 6.45 Hz, 3 H), 0.69 (d, J= 6.77 Hz, 3 H), 0.61 (d, J= 6.94 Hz, 3 H)	C	334
147	(1S,2S,5R)-N-(4,4-difluorocyclohexyl)-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	(600.05 MHz, DMSO-d_6) 7.54 (br d, J=7.89 Hz, 1 H), 4.73 (br s, 1 H), 3.80-3.72 (m, 1 H), 3.33 (u), 2.50 (u), 2.04-1.84 (m, 4 H), 1.78-1.65 (m, 4 H), 1.63-1.49 (m, 4 H), 1.46-1.33 (m, 4 H), 0.92-0.76 (m, 10 H)	C	318
148	(1S,2S,5R)-N-[2-(3-chloro-2-thienyl)-2-oxo-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	(600.05 MHz, DMSO-d_6) 8.10 (d, J=5.32 Hz, 1 H), 8.06 (br t, J=5.50, 5.50 Hz, 1 H), 7.29 (d, J=5.14 Hz, 1 H), 5.01 (s, 1 H), 4.57-4.54 (m, 2 H), 3.30 (u), 2.50 (u), 2.07 (u), 1.78-1.66 (m, 3 H), 1.56-1.50 (m, 2 H), 1.47-1.35 (m, 3 H), 0.91-0.80 (m, 7 H), 0.78 (d, J=7.12 Hz, 3H)	C	358
149	(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-[2-oxo-2-(2-thienyl)ethyl]cyclohexane carboxamide	(600.05 MHz, DMSO-d_6) 8.11-8.01 (m, 3 H), 7.27-7.24 (m, 1 H), 4.97 (s, 1 H), 4.60-4.51 (m, 2 H), 3.30 (u), 2.50 (u), 2.07 (u), 1.78-1.65 (m, 3 H), 1.56-1.49 (m, 2 H), 1.46-1.34 (m, 3 H), 0.92-0.73 (m, 10 H)	C	324

Example	Compound Name	1H NMR spectrum (δ ppm, DMSO-d_6)	LCMS Method	[M+H]+
150	(1S,2S,5R)-1-hydroxy-N-[2-(1H-indol-3-yl)-2-oxo-ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	(600.05 MHz, DMSO-d_6) 12.01 (br s, 1 H), 8.45 (d, J=3.12 Hz, 1 H), 8.34 (u), 8.17-8.14 (m, 1 H), 8.05 (t, J=5.14, 5.14 Hz, 1 H), 7.49-7.46 (m, 1 H), 7.24-7.17 (m, 2 H), 5.02 (s, 1 H), 4.57-4.48 (m, 2 H), 3.30 (u), 2.50 (u), 1.79-1.63 (m, 3 H), 1.59-1.51 (m, 2 H), 1.47-1.28 (m, 3 H), 0.93-0.81 (m, 7 H), 0.78 (d, J=6.97 Hz, 3 H)	C	357
151	(1S,2S,5R)-1-hydroxy-N-[(1R)-3-hydroxy-1-(2-thienylmethyl)propyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	(600.05 MHz, DMSO-d_6) 10.88 (br s, 1 H), 7.71 (br t, J=5.50, 5.50 Hz, 1 H), 7.56-7.53 (m, 1 H), 7.35-7.33 (m, 1 H), 7.23 (d, J=2.20 Hz, 1 H), 7.09-7.05 (m, 1 H), 6.98-6.94 (m, 1 H), 4.79 (br s), 4.49-4.39 (m, 2 H), 3.33 (u), 2.50 (u), 2.07 (u), 1.72-1.64 (m, 2 H), 1.60-1.54 (m, 2 H), 1.46-1.33 (m), 0.92-0.73 (m)	C	329
152	(1S,2S,5R)-1-hydroxy-2-isopropyl-N-[(5-methoxyindan-1-yl)methyl]-5-methyl-cyclohexanecarboxamide	(600.05 MHz, DMSO-d_6) 7.69-6.65 (m, 1 H), 7.15-7.12 (m, 1 H), 6.80-6.77 (m, 1 H), 6.70-6.67 (m, 1 H), 4.80 (br s), 3.72-3.69 (m, 3 H), 3.40 (u), 3.37-3.33 (m), 3.27-.312 (m, 2 H), 2.88-2.80 (m, 1 H), 2.78-2.71 (m, 1 H), 2.50 (u), 2.15-2.08 (m, 1 H), 2.07 (u), 1.78-1.65 (m, 3 H), 1.55-1.47 (m, 2 H), 1.44-1.34 (m, 3 H), 0.93-0.74 (m, 10 H)	C	360

Example	Compound Name	1H NMR spectrum (δ ppm, DMSO-d_6)	LCMS Method	[M+H]+
153	(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-[2-(2-methyl-1H-indol-3-yl)ethyl]cyclohexanecarboxamide	(600.05 MHz, DMSO-d_6) 10.69 (s, 1 H), 7.70 (br t, J=5.78, 5.78 Hz, 1 H), 7.46 (d, J=7.70 Hz, 1 H), 7.21 (d, J=8.07 Hz, 1 H), 6.98-6.94 (m, 1 H), 6.93-6.89 (m, 1 H), 4.74 (br s, 1 H), 3.38 (u), 3.34-3.29 (m), 3.26-3.19 (m, 1 H), 2.82-2.70 (m, 2 H), 2.50 (u), 2.33 (s, 3 H), 1.72-1.65 (m, 2 H), 1.56-1.50 (m, 2 H), 1.45-1.33 (m, 4 H), 0.91-0.74 (m, 10 H)	C	357
154	(1S,2S,5R)-1-hydroxy-2-isopropyl-N-[(6-methoxy-2,3-dihydrobenzofuran-3-yl)methyl]-5-methyl-cyclohexanecarboxamide	-	C	362
155	(1S,2S,5R)-1-hydroxy-2-isopropyl-N-[2-(2-methoxyphenyl)ethyl]-5-methyl-cyclohexanecarboxamide	(400.23 MHz, DMSO-d_6) 7.66 (br t, J=5.50, 5.50 Hz, 1 H), 7.22-7.15 (m, 1 H), 7.13-7.09 (m, 1 H), 6.97-6.92 (m, 1 H), 6.88-6.82 (m, 1 H), 4.71 (br s, 1 H), 3.78 (s, 3 H), 3.38 (u), 3.35-3.22 (m), 2.78-2.65 (m, 2 H), 2.50 (u), 1.74-1.62 (m, 2 H), 1.55-1.26 (m, 6 H), 1.06 (u), 0.94-0.69 (m, 10 H)	C	334
156	(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-(2-phenylpropyl)cyclohexane carboxamide	(400.23 MHz, DMSO-d_6) 7.55-7.47 (m, 1 H), 7.32-7.25 (m, 2 H), 7.24-7.16 (m, 3 H), 4.72 (br s, 1 H), 3.38 (u), 3.34-3.28 (m), 3.27-3.18 (m, 1 H), 2.50 (u), 1.71-1.61 (m, 2 H), 1,53-1,28 (m, 6 H), 1.16 (dd, J=6.97, 1.22 Hz, 3 H), 0.89-0.66 (m, 10 H)	C	318

Example	Compound Name	1H NMR spectrum (δ ppm, DMSO-d_6)	LCMS Method	[M+H]+
157	(1S,2S,5R)-N-[2-(2-fluorophenyl)-2-hydroxy-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	(400.23 MHz, DMSO-d_6) 7.67-7.57 (m, 1 H), 7.53-7.46 (m, 1 H), 7.33-7.26 (m, 1 H), 7.21-7.08 (m, 2 H), 5.62 (br s), 4.97-4.90 (m, 1 H), 4.84 (br s, 1 H), 3.54-3.46 (m), 3.38 (u), 3.28-3.18 (m), 2.50 (u), 2.08 (u), 1.72-1.61 (m, 2 H), 1.52-1.22 (m, 6 H), 1.06 (u), 0.92-0.62 (m, 10 H)	C	338
158	(1S,2S,5R)-N-[2-(4-fluorophenyl)-2-hydroxy-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	(400.23 MHz, DMSO-d_6) 8.35 (u), 7.64-7.51 (m, 1 H), 7.42-7.32 (m, 2 H), 7.18-7.08 (m, 2 H), 5.57 (br s), 4.84 (br s, 1 H), 4.70-4.60 (m, 1 H), 3.46-3.38 (m), 3.33 (u), 3.22-3-14 (m, 1 H), 2.50 (u), 2.07 (u), 1.76-1.23 (m, 8 H), 1.05 (u), 0.89-0.64 (m, 10 H)	C	338
159	(1S,2S,5R)-N-[2-(2,3-dihydrobenzofuran-7-yl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	(400.23 MHz, DMSO-d_6) 7.69 (br t, J=5.26, 5.26 Hz, 1 H), 7.09-7.04 (m, 1 H), 6.94-6.89 (m, 1 H), 6.76-6.70 (m, 1 H), 4.69 (br s), 4.51 (t, J=8.74, 8.74 Hz, 2 H), 3.42 (u), 3.38-3.22 (m), 3.16 (t, J=8.64, 8.64 Hz, 2 H), 2.73-2.59 (m, 2 H), 2.50 (u), 1.74-1.62 (m, 2 H), 1.53-1.29 (m, 6 H), 0.92-0.70 (m, 10 H)	C	346
160	(1S,2S,5R)-N-[2-(2-chlorophenyl)-2-hydroxy-ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	(400.23 MHz, DMSO-d_6) 7.66-7.55 (m, 2 H), 7.40-7.24 (m, 3 H), 5.70 (br s), 5.03-4.98 (m, 1 H), 4.89 (br s, 1 H), 3.57-3.48 (m), 3.42 (u), 3.35-3.27 (m), 3.22-3.14 (m, 1 H), 2.50 (u), 2.08 (u), 1.74-1.61 (m, 2 H), 1.55-1.22 (m, 6 H), 1.06 (u), 0.94-0.59 (m, 10 H)	C	354

Example	Compound Name	1H NMR spectrum (δ ppm, DMSO-d_6)	LCMS Method	[M+H]+
161	(1S,2S,5R)-1-hydroxy-N-[[3-(hydroxymethyl)phenyl]methyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	(400.23 MHz, DMSO-d_6) 8.21-8.14 (m, 1 H), 7.37-7.08 (m, 4 H), 5.39 (u), 4.94-4.65 (br m), 4.46 (s, 2 H), 4.36-4.22 (m, 2 H), 3.41 (u), 2.50 (u), 1.77-1.34 (m, 8 H), 0.97-0.71 (m, 10 H)	C	320
162	(1S,2S,5R)-N-(2,3-dihydrobenzofuran-3-ylmethyl)-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	(400.23 MHz, DMSO-d_6) 7.97-7.88 (m, 1 H), 7.28-7.23 (m, 1 H), 7.14-7.08 (m, 1 H), 7.86-7.73 (m, 2 H), 4.91-4.74 (m), 4.53-4.44 (m, 1 H), 4.35-4.29 (m, 1 H), 3.72-3.60 (m), 3.36 (u), 3.32-3.21 (m), 2.50 (u), 2.07 (u), 1.77-1.64 (m), 1.56-1.31 (m), 0.94-0.70 (m)	C	332
163	(1S,2S,5R)-1-hydroxy-N-[3-hydroxy-1-(3-hydroxyphenyl)propyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	(400.23 MHz, DMSO-d_6) 9.34-9.20 (m, 1 H), 8.01-7.91 (m, 1 H), 7.12-7.04 (m, 1 H), 6.76-6.67 (m, 2 H), 6.65-6.57 (m, 1 H), 4.90-4.81 (m, 1 H), 4.80-4.64 (m), 4.40-4.28 (m), 3.37 (u), 2.50 (u), 2.09 (u), 1.92-1.30 (m), 0.95-0.63 (m)	C	350
164	(1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-phenyl-propyl)-2-isopropyl-5-methyl-cyclohexanecarboxamide	(400.23 MHz, DMSO-d_6) 7.52-7.37 (m, 3 H), 7.33-7.25 (m, 2 H), 7.23-7.16 (m, 1 H), 5,59-5.24 (br m), 4.88 (br s), 3.56-3.49 (m), 3.46-3.40 (m), 3.36 (u), 3.33-3.23 (m), 2.50 (u), 2.08 (u), 1.71-1.20 (m), 1.05 (u), 0.92-0.70 (m), 0.65-0.54 (m)	C	332

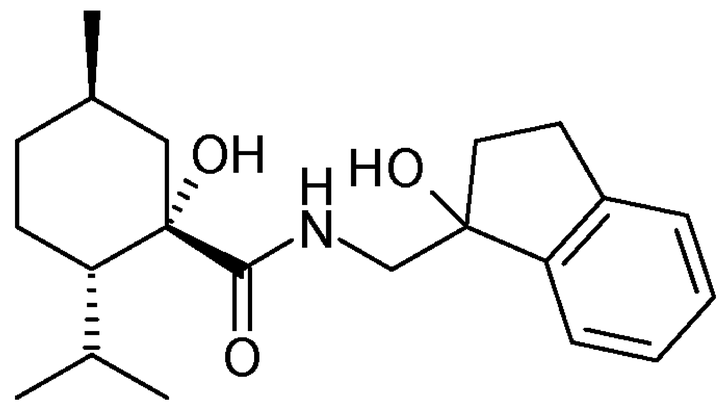
Example	Compound Name	1H NMR spectrum (δ ppm, DMSO-d_6)	LCMS Method	[M+H]+
165	(1S,2S,5R)-1-hydroxy-N-[(3-hydroxyphenyl)methyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	(600.05 MHz, DMSO-d_6) 9.27 (br s, 1 H), 8.11-8.07 (m, 1 H), 7.10-7.05 (m, 1 H), 6.68-6.64 (m, 2 H), 6.62-6.59 (m, 1 H), 4.80 (br s), 4.29-4.23 (m, 1 H), 4.18-4.13 (m, 1 H), 3.61 (u), 2.50 (u), 2.08 (u), 1.76-1.65 (m, 2 H), 1.61-1.35 (m), 1.08 (u), 0.95-0.70 (m)	C	306
166	(1S,2S,5R)-1-hydroxy-N-[2-(4-hydroxy-3-nitro-phenyl)ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	(600.05 MHz, DMSO-d_6) 10.69 (br s, 1 H), 7.73-7-62 (m, 2 H), 7.41-7.38 (m, 1 H), 7.05-7.02 (m, 1 H), 4.66 (br s), 3.85 (u), 3.45-3.38 (m, 1 H), 3.32-3.25 (m, 1 H), 2.78-2.69 (m, 2 H), 2.50 (u), 2.08 (u), 1.71-1.61 (m, 2 H), 1.51-1.22 (m, 6 H), 1.05 (u), 0.89-0.64 (m, 10 H)	C	365
167	(1S,2S,5R)-1-hydroxy-N-[3-(4-hydroxyphenyl)propyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	(600.05 MHz, DMSO-d_6) 9.09 (br s, 1 H), 7.70 (br t, J=5.78, 5.78 Hz, 1 H), 6.98-6.93 (m, 2 H), 6.67-6.63 (m, 2 H), 4.72 (br s), 3.68 (u), 3.11-3.05 (m, 2 H), 2.50 (u), 2.46-2.41 (m, 2 H), 2.08 (u), 1.74-1.61 (m, 4 H), 1.59-1.51 (m, 2 H), 1.46-1.34 (m, 4 H), 0.91-0.76 (m, 10 H)	C	334
168	(1S,2S,5R)-1-hydroxy-N-[(1S)-3-(4-hydroxyphenyl)-1-methyl-propyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	(600.05 MHz, DMSO-d_6) 9.08 (br s, 1 H), 7.40 (br d, J=8.62 Hz, 1 H), 6.98-6.91 (m, 2 H), 6.67-6.61 (m, 2 H), 4.74 (br s, 1 H), 3.80-3.73 (m, 1 H), 3.34 (u), 2.50 (u), 2.48-2.43 (m), 2.41-2.35 (m, 1 H), 1.75-1.53 (m, 6 H), 1.47-1.35 (m, 4 H), 1.10-1.01 (m, 3 H), 0.95-0.77 (m, 10 H)	C	348

Example	Compound Name	1H NMR spectrum (δ ppm, DMSO-d_6)	LCMS Method	[M+H]+
169	(1S,2S,5R)-1-hydroxy-N-[2-(5-hydroxy-1H-indol-3-yl)ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	(600.05 MHz, DMSO-d_6) 10.47 (s, 1 H), 8.72-8.39 (br m), 7.75-7.71 (m, 1 H), 7.12-7.09 (m, 1 H), 7.03-7.01 (m, 1 H), 6.86-6.85 (m, 1 H), 6.59-6.56 (m, 1 H), 4.85-4.48 (br m), 3.95 (u), 3.41-3.30 (m, 2 H), 2.78-2.68 (m, 2 H), 2.50 (u), 2.08 (u), 1.83 (u), 1.74-1.27 (m), 0.91-0.68 (m)	C	359
170	(1S,2S,5R)-1-hydroxy-N-[(1R)-1-(hydroxymethyl)-2-(4-hydroxyphenyl)ethyl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	(600.05 MHz, DMSO-d_6) 9.08 (br s, 1 H), 7.31 (d, J=8.80 Hz, 1 H), 6.98-6.95 (m, 2 H), 6.64-6.61 (m, 2 H), 4.73 (br s), 4.45-4.28 (br m), 3.93-3.87 (m, 1 H), 3.52 (u), 3.37-3.32 (m), 3.28-3.24 (m), 2.75-2.70 (m), 2.60-2.55 (m), 2.50 (u), 2.08 (u), 1.70-1.61 (m, 2 H), 1.44-1.22 (m, 6 H), 0.87-0.59 (m)	C	350
171	(1S,2S,5R)-1-hydroxy-N-[(2R)-7-hydroxytetralin-2-yl]-2-isopropyl-5-methyl-cyclohexanecarboxamide	(600.05 MHz, DMSO-d_6) 9.01 (br s, 1 H), 7.51 (br d, J=8.07 Hz, 1 H), 6.86 (d, J=8.44 Hz, 1 H), 6.52 (dd, J=8.16, 2.48 Hz, 1 H), 6.44 (d, J=2.38 Hz, 1 H), 4.79 (br s, 1 H), 3.96 (m, 1 H), 2.79 (dd, J=16.23, 4.86 Hz, 1 H), 2.69 (br t, J=6.51, 6.51 Hz, 2 H), 2.62 (br dd, J=16.32, 8.99 Hz, 1 H), 2.50 (u), 1.83 (br dd, J=11.92, 4.03 Hz, 1 H), 1.69 (m, 3 H), 1.56 (m, 2 H), 1.42 (m, 4 H), 0.89 (br dd, J=12.84, 3.48 Hz, 1 H), 0.80 (m, 9 H)	C	346

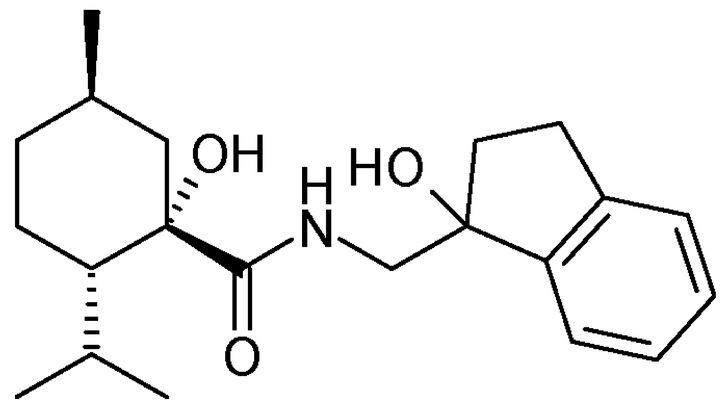
Example	Compound Name	1H NMR spectrum (δ ppm, DMSO-d_6)	LCMS Method	[M+H]+
172	(1S,2S,5R)-N-[2-(2-bromo-5-hydroxy-phenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	(600.05 MHz, DMSO-d_6) 9.56 (br s, 1 H), 7.76 (br t, J=5.78, 5.78 Hz, 1 H), 7.32 (d, J=8.62 Hz, 1 H), 6.72 (d, J=2.75 Hz, 1 H), 6.58 (dd, J=8.62, 2.93 Hz, 1 H), 4.71 (br s), 3.60 (u), 3.39-3.25 (m, 2 H), 2.80-2.69 (m, 2 H), 2.50 (u), 2.08 (u), 1.73-1.63 (m, 2 H), 1.52-1.45 (m, 2 H), 1.44-1.28 (m, 4 H), 1.07 (u), 0.91-0.71 10 H)	C	398
173	(1S,2S,5R)-N-[2-(2,4-dihydroxyphenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide	(600.05 MHz, DMSO-d6) 9.15 (br s, 1 H), 8.95 (br s, 1 H), 7.62-7.58 (br m, 1 H), 6.80-6.76 (m, 1 H), 6.27-6.25 (m, 1 H), 6.13-6.09 (m, 1 H), 4.70 (br s), 3.71 (u), 3.30-3.27 (m, 1 H), 3.22-3.15 (m, 1 H), 2.62-2.51 (m), 2.50 (u), 2.08 (u), 1.73-1.63 (m, 2 H), 1.55-1.47 (m, 2 H), 1.44-1.32 (m, 4 H), 0.91-0.72 (m, 10 H)	C	336
174	(1S,2S,5R)-1-hydroxy-N-(4-methoxyphenyl)-5-methyl-2-propan-2-ylcyclohexane-1-carboxamide	-	C	306

Examples 175 & 176

(1S,2S,5R)-1-hydroxy-N-(((1RS)-hydroxy-2,3-dihydro-1H-inden-1-yl)methyl)-2-isopropyl-5-meth
ylcyclohexane-1-carboxamide **(175)**



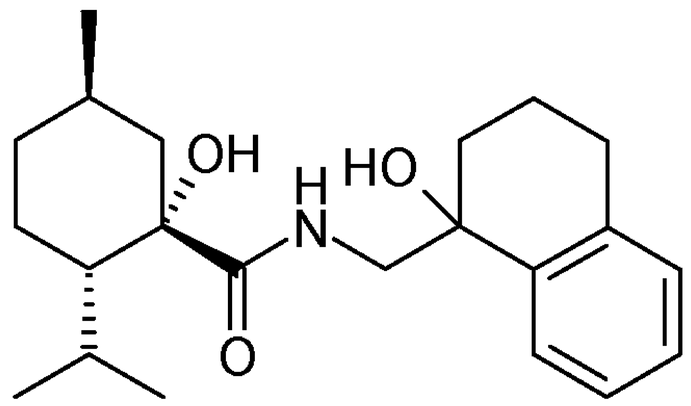
(1S,2S,5R)-1-hydroxy-N-(((1RS)-hydroxy-2,3-dihydro-1H-inden-1-yl)methyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide **(176)**



Chiral separation of (1S,2S,5R)-1-hydroxy-N-((1-hydroxy-2,3-dihydro-1H-inden-1-yl)methyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (230mg) carried out by liquid chromatography using Chiralcel OZ with heptane and ethanol led to (1S,2S,5R)-1-hydroxy-N-(((1RS)-hydroxy-2,3-dihydro-1H-inden-1-yl)methyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (***example 175***, 124mg) and (1S,2S,5R)-1-hydroxy-N-(((1RS)-hydroxy-2,3-dihydro-1H-inden-1-yl)methyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (***example 176,*** 103mg).

Example 177

(1S,2S,5R)-1-hydroxy-N-(((1RS)-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide **(177)**

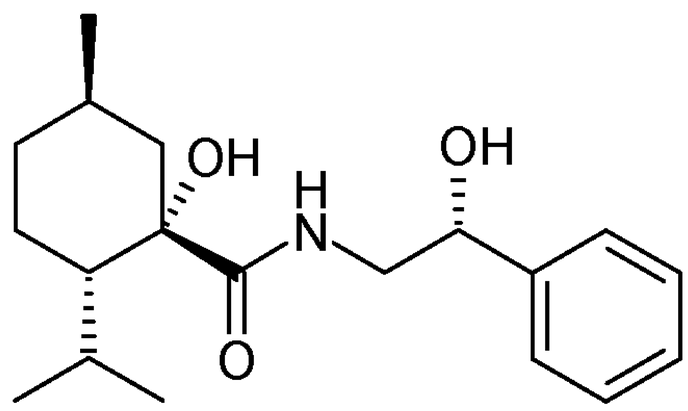


Chiral separation of (1S,2S,5R)-1-hydroxy-N-((1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (230mg) carried out by liquid

chromatography using Chiralcel OZ with heptane and ethanol led to (1S,2S,5R)-1-hydroxy-N-(((1RS)-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)methyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (***example 177***,126mg) and its diastereoisomer (121mg).

Example 178

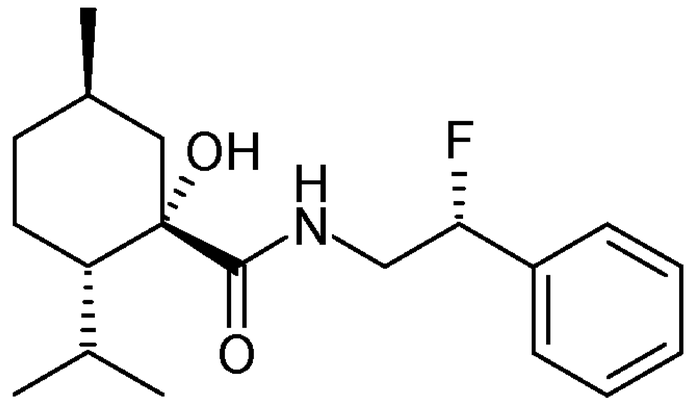
(1S,2S,5R)-1-hydroxy-N-((2R)-2-hydroxy-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide **(178)**



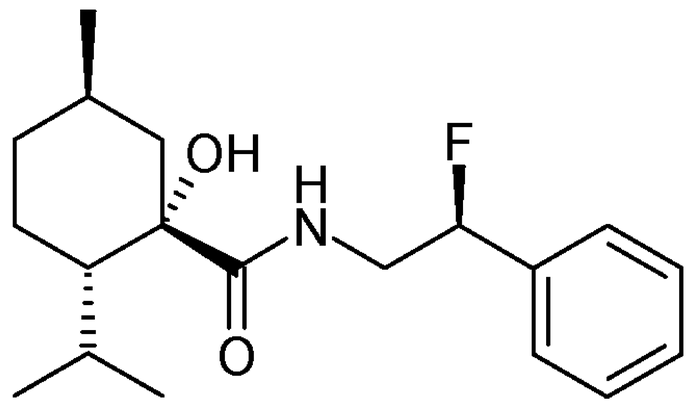
Chiral separation of (1S,2S,5R)-1-hydroxy-N-(2-hydroxy-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (262mg) carried out by liquid chromatography using Chirlapak AD with heptane and ethanol led to 1S,2S,5R)-1-hydroxy-N-((2R)-2-hydroxy-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (***example 178***, 23mg) and (1S,2S,5R)-1-hydroxy-N-((2S)-2-hydroxy-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (***example 1***, 173mg).

Examples 179 & 180

(1S,2S,5R)-N-((2R)-2-fluoro-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide **(179)**



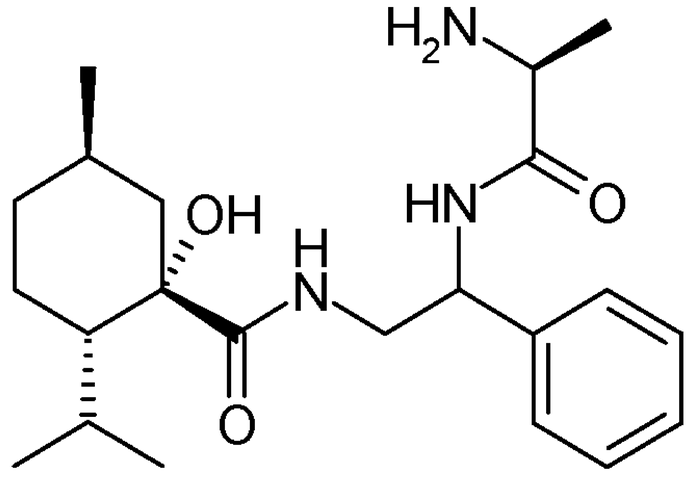
(1S,2S,5R)-N-((2S)-2-fluoro-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide **(180)**



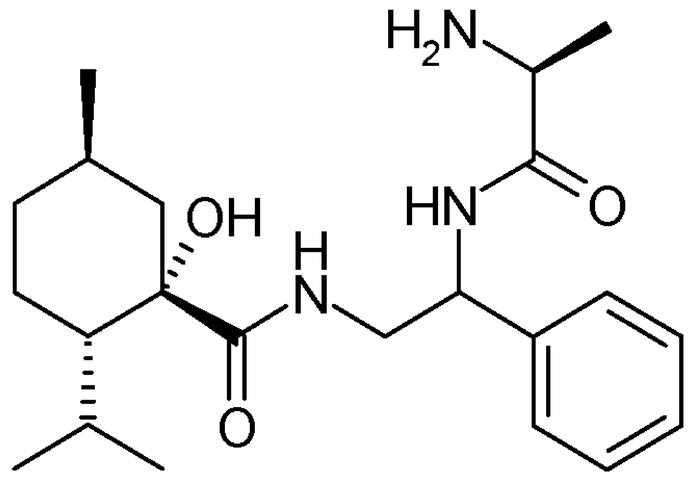
Chiral separation of (1S,2S,5R)-N-(2-fluoro-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (144mg) carried out by SFC using Cellulose with CO2 90% MeOH 0.1% TEA 10% led to (1S,2S,5R)-N-((2R)-2-fluoro-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (***example 179***, 66mg) and (1S,2S,5R)-N-((2S)-2-fluoro-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (***example 180,*** 57mg).

Examples 181 & 182

(1S,2S,5R)-N-((2RS)-2-((S)-2-aminopropanamido)-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide **(181)**



(1S,2S,5R)-N-((2RS)-2-((S)-2-aminopropanamido)-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide **(182)**



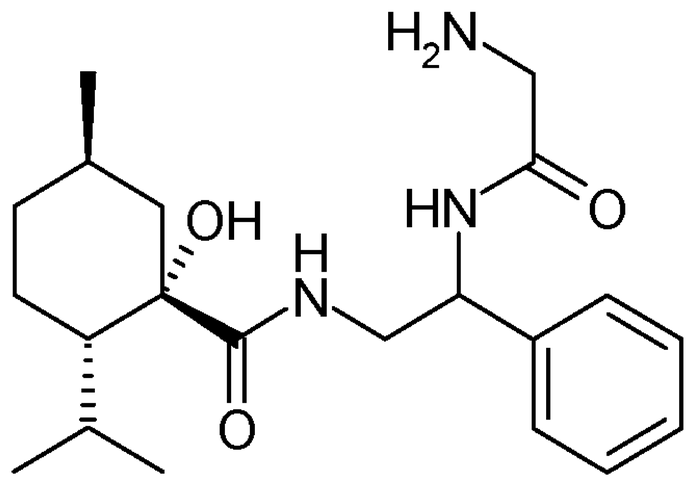
Under coupling conditions F, with (1S,2S,5R)-N-((2S)-amino-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (100mg) and BOC-ALA-OH (1.1eq) [NB THF was used as solvent instead of DMF] led to tert-butyl ((S)-1-(((S)-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethyl)amino)-1-oxopropan-2-yl)carbamate (127mg).

Under deprotection conditions B, to tert-butyl ((S)-1-(((S)-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethyl)amino)-1-oxopropan-2-yl)carbamate (124.4mg) in the presence of TFA (9.7eq) led to (1S,2S,5R)-N-((S)-2-((S)-2-aminopropanamido)-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (95.5mg) as white solid.

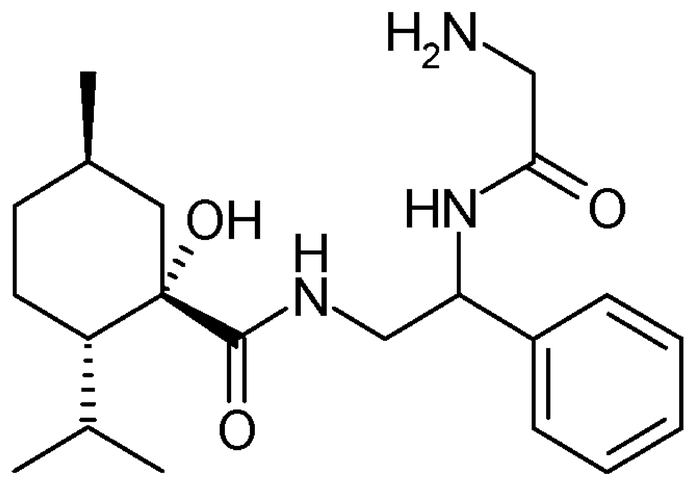
Chiral separation of (1S,2S,5R)-N-(2-((S)-2-aminopropanamido)-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (91mg) carried out by liquid chromatography using Chiralpak AD-H with heptane and ethanol led to (1S,2S,5R)-N-((2RS)-2-((S)-2-aminopropanamido)-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (***example 181***, 6.7mg) and (1S,2S,5R)-N-((2RS)-2-((S)-2-aminopropanamido)-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (***example 182,*** 47.1mg).

Examples 183 & 184

(1S,2S,5R)-N-((2RS)-(2-aminoacetamido)-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide **(183)**



(1S,2S,5R)-N-((2RS)-2-((S)-2-aminopropanamido)-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide **(184)**



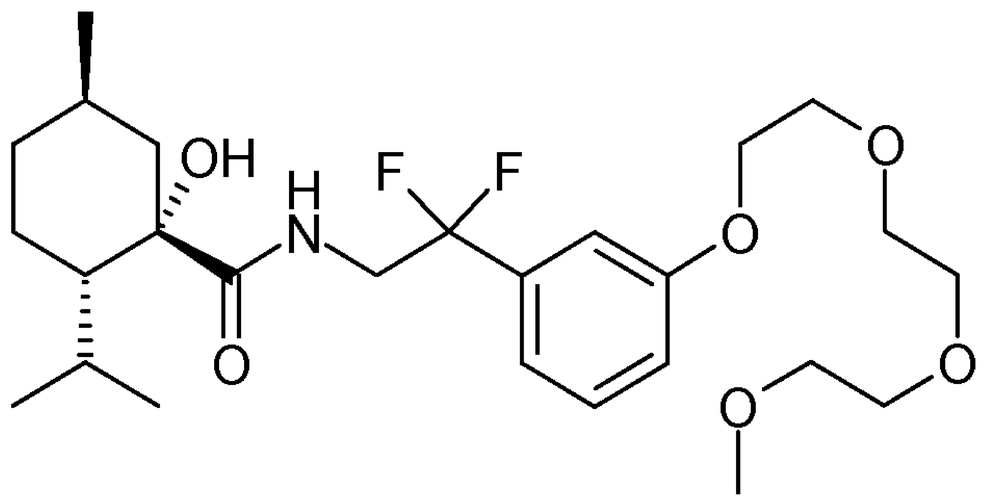
Under coupling conditions F, with (1S,2S,5R)-N-((2S)-amino-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (100mg) and BOC-GLY-OH (1.1eq) [NB THF was used as solvent instead of DMF] led to tert-butyl (2-(((S)-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethyl)amino)-2-oxoethyl)carbamate (142mg).

Under deprotection conditions B, tert-butyl (2-(((S)-2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)-1-phenylethyl)amino)-2-oxoethyl)carbamate (140mg) in the presence of TFA (9.7eq) led to (1S,2S,5R)-N-((S)-2-(2-aminoacetamido)-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (81.9mg) as white solid.

Chiral separation of (1S,2S,5R)-N-(2-(2-aminoacetamido)-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (32mg) carried out by SFC using Chiralpak AD-H with mobile phase CO2 85% MeOH 15% TEA 0.1% led to (1S,2S,5R)-N-((2RS)-(2-aminoacetamido)-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (***example 183***, 14.8mg) and (1S,2S,5R)-N-((2RS)-(2-aminoacetamido)-2-phenylethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide (***example 184,*** 2.3mg).

Example 185

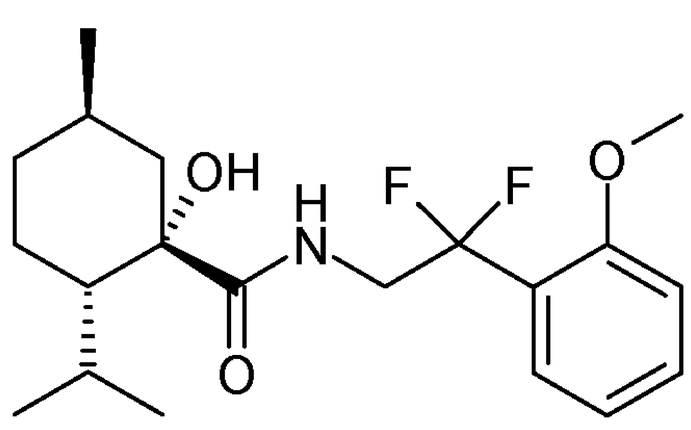
(1S,2S,5R)-1-hydroxy-2-isopropyl-N-[2-[3-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]phenyl]ethyl]-5-methyl-cyclohexanecarboxamide



Under alkylation conditions C, (1S,2S,5R)-1-hydroxy-N-(3-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide (50mg) in the presence of 1-bromo-2-[2-(2-methoxyethoxy)ethoxy]ethane (1.2eq) led to (1S,2S,5R)-1-hydroxy-2-isopropyl-N-[2-[3-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]phenyl]ethyl]-5-methyl-cyclohexanecarboxamide (32mg) after flash chromatography with heptane and EtOAc.

Example 186

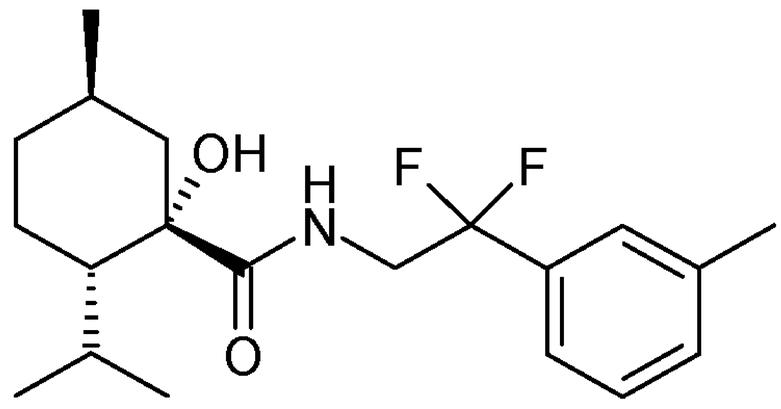
(1S,2S,5R)-N-[2,2-difluoro-2-(2-methoxyphenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide



Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (200mg) and 2,2-difluoro-2-(2-methoxyphenyl)ethan-1-amine hydrochloride (1.1eq) [after amine addition, the reaction was heated at 70°C during 17hr] led to (1S,2S,5R)-N-[2,2-difluoro-2-(2-methoxyphenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide (150.6mg) after flash chromatography with heptane and EtOAc.

Example 187

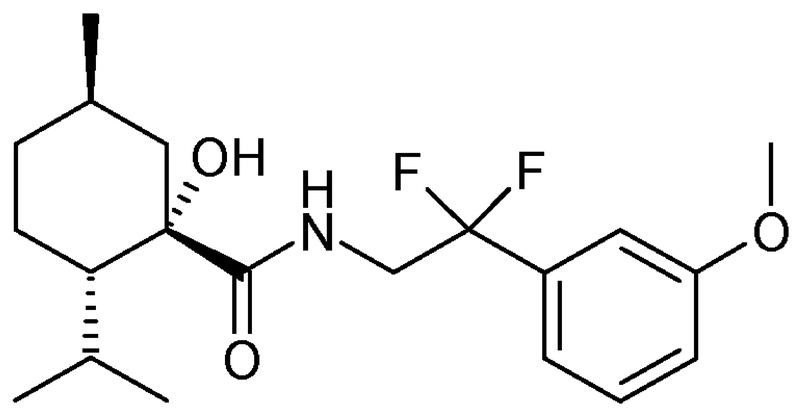
(1S,2S,5R)-N-[2,2-difluoro-2-(3-methylphenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide



Under coupling conditions B, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (90mg) and 2,2-difluoro-2-(3-methylphenyl)ethan-1-amine (1.1eq) [after amine addition, the reaction was heated at 70°C during 17hr] led to (1S,2S,5R)-N-[2,2-difluoro-2-(m-tolyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide (52.5mg) after flash chromatography with heptane and EtOAc.

Example 188

(1S,2S,5R)-N-[2,2-difluoro-2-(3-methoxyphenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide



Under coupling conditions A, (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxylic acid (90mg) and 2,2-difluoro-2-(3-methoxyphenyl)ethan-1-amine (1.1eq) [after amine addition, the reaction was heated at 70°C during 17hr] led to (1S,2S,5R)-N-[2,2-difluoro-2-(3-methoxyphenyl)ethyl]-1-hydroxy-2-isopropyl-5-methyl-cyclohexanecarboxamide (102.5mg) after flash chromatography with heptane and EtOAc.

Examples 175 to 188 were characterized by 1H NMR and LCMS analysis as shown below in Table 5:

Table 5

Example	LCMS Method	$[M+H]^+$	$[M-H]^-$	1H NMR spectrum (400 MHz, DMSO-d_6) δ ppm
175	D	-	344	0.72 (d, J=7 Hz, 3 H), 0.80 (d, J=7 Hz, 6 H), 0.86 (m, 1 H), 1.21 - 1.54 (m, 6 H), 1.62 - 1.78(m, 2 H), 1.94 (m, 1 H), 2.15 (m, 1 H), 2.75 (m, 1 H), 2.87 (m, 1 H), 3.31 (m , 2 H), 5.05 (m, 1 H), 5.49 (s, 1 H), 7.09 - 7.25 (m, 3 H), 7.31 (d, J=7 Hz, 1 H), 7.60 (t, J=6 Hz, 1 H)
176	D	-	344	0.75 (d, J=7 Hz, 3 H), 0.80 (d, J=7 Hz, 6 H), 0.87 (m, 1 H), 1.28 - 1.58 (m, 6 H), 1.61 - 1.79 (m, 2 H), 1.93 (dt, J=13, 8 Hz, 1 H), 2.15 (m, 1 H), 2.75 (m, 1 H), 2.87 (br dd, J=9, 4 Hz, 1 H), 3.27 (m, 1 H), 3.37 (m, 1 H), 5.01 (s, 1 H), 5.46 (s, 1 H), 7.14 - 7.23 (m, 3 H), 7.34 (d, J=7 Hz, 1 H), 7.60 (t, J=6 Hz, 1 H)
177	D	-	358	0.77 (d, J=7 Hz, 3 H), 0.81 (dd, J=7, 5 Hz, 6 H), 0.89 (m, 1 H), 1.29 - 1.48 (m, 4 H), 1.49 - 1.82 (m, 7 H), 1.89 (br dd, J=13, 5 Hz, 1 H), 2.7 (m, 2 H), 3.09 (dd, J=13, 4 Hz, 1 H), 3.55 (dd, J=13, 8 Hz, 1 H), 5.02 (s, 1 H), 5.32 (s, 1 H), 7.04 (m, 1 H), 7.10 - 7.20 (m, 2 H), 7.51 (m, 1 H), 7.58 (m, 1 H)
178	D	320	318	0.70 (d, J=7 Hz, 3 H), 0.74 (d, J=7 Hz, 3 H), 0.79 (d, J=6 Hz, 3 H), 0.86 (m, 1 H), 1.20 - 1.51 (m, 6 H), 1.59 - 1.76 (m, 2 H), 3.33 (m, 2 H), 4.64 (q, J=6 Hz, 1 H), 4.87 (s, 1 H), 5.54 (d, J=4 Hz, 1 H), 7.22 (m, 1 H), 7.27 - 7.40 (m, 4 H), 7.56 (t, J=6 Hz, 1 H)
179	D	322	320	0.73 (d, J=7 Hz, 3 H), 0.75 (d, J=7 Hz, 3 H), 0.80 (d, J=6 Hz, 3 H), 0.88 (m, 1 H), 1.30 - 1.54 (m, 6 H), 1.63 - 1.76 (m, 2 H), 3.38 - 3.70 (m, 2 H), 4.88 (s, 1 H), 5.61 (ddd, J=48, 8, 4 Hz, 1 H), 7.35 - 7.45 (m, 5 H), 7.86 (br t, J=6 Hz, 1 H)
180	D	322	-	-

Example	LCMS Method	$[M+H]^+$	$[M-H]^-$	1H NMR spectrum (400 MHz, DMSO-d_6) δ ppm
181	D	390	388	0.71 - 0.89 (m, 10 H), 1.12 (d, J=7 Hz, 3 H), 1.22 - 1.56 (m, 6 H), 1.59 - 1.75 (m, 2 H), 2.08 (br s, 2 H), 3.25 (m, 1 H), 3.34 - 3.47 (m, 2 H), 4.81 (s, 1 H), 4.91 (m, 1 H), 7.13 - 7.43 (m, 5 H), 7.79 (t, J=6 Hz, 1 H), 8.25 (br d, J=8 Hz, 1 H)
182	D	390	388	0.71 (d, J=7 Hz, 3 H), 0.75 (d, J=7 Hz, 3 H), 0.79 (d, J=6 Hz, 3 H), 0.85 (m, 1 H), 1.13 (d, J=7 Hz, 3 H), 1.29 - 1.55 (m, 6 H), 1.56 - 1.85 (m, 2 H), 3.25 - 3.30 (m, 2 H), 3.45 (m, 1 H), 4.83 (s, 1 H), 4.91 (m, 1 H), 7.23 (m, 1 H), 7.27 - 7.36 (m, 4 H), 7.83 (t, J=6 Hz, 1 H), 8.23 (br d, J=7 Hz, 1 H)
183	D	376	374	0.70 (d, J=7 Hz, 3 H), 0.75 (d, J=7 Hz, 3 H), 0.80 (d, J=6 Hz, 3 H), 0.87 (m, 1 H), 1.22 - 1.51 (m, 6 H), 1.60 - 1.74 (m, 2 H), 1.81 (br s, 2 H), 3.09 (s, 2 H), 3.28 (m, 1 H), 3.47 (m, 1 H), 4.82 (s, 1 H), 4.96 (m, 1 H), 7.24 (m, 1 H), 7.27 - 7.35 (m, 4 H), 7.83 (t, J=6 Hz, 1 H), 8.21 (br d, J=8 Hz, 1 H)
184	D	376	374	0.74 (d, J=4 Hz, 3 H), 0.75 (d, J=4 Hz, 3 H), 0.79 (d, J=6 Hz, 3 H), 0.87 (m, 1 H), 1.30 - 1.52 (m, 6 H), 1.61 - 1.72 (m, 2 H), 1.73 - 1.94 (m, 2 H), 3.09 (s, 2 H), 3.38 (m, 1 H), 3.46 (m, 1 H), 4.81 (s, 1 H), 4.92 - 5.02 (m, 1 H), 7.23 (m, 1 H), 7.28 - 7.35 (m, 4 H), 7.79 (t, J=6 Hz, 1 H), 8.24 (br d, J=8 Hz, 1 H)
185	E	-	466	-
186	F	-	370	-
187	F	-	354	-

Example	LCMS Method	$[M+H]^+$	$[M-H]^-$	1H NMR spectrum (400 MHz, DMSO-d_6) δ ppm
188	F	-	370	-

Some compounds of formula (I) were subjected to pharmacological tests for determining their activation effects on TRPM8 receptor.

In vitro pig and human TRPM8 fluorescence calcium flux assays

For functional expression of TRPM8, the full-length cDNA encoding human (NM_024080) and pig (XM_001927892.1) TRPM8 sequences were subcloned into p658 and pcDNA5/FRT/TO mammalian expression vectors, respectively. Engineered recombinant CHO cell lines expressing human or pig TRPM8 were generated. Culture media was Ham-F12 with 10% FCS for both lines, and for the pig cell line only 400 µg/ml hygromycin B and 30 µg/mL blasticidin were added as selection antibiotics (all reagents were obtained from Invitrogen, Fisher Scientific). Cells were grown in culture flasks up to 80% confluence where they were harvested using accutase (Sigma, MO, USA) to detach the cells by enzymatic dissociation and either seeded directly into assay plates or cryopreserved for future use.

For calcium flux assays, cells were plated into clear base poly-D-lysine coated 384-well plates (BD Biosciences, NJ USA) at a density of 15,000 cells per well in appropriate culture medium and grown overnight. The following day, all medium was removed then the cells were incubated with 2 µM of Fluo4-AM Dye (Molecular Probes) prepared in complete HBSS assay buffer containing 20 mM HEPES, 0.1% BSA, and 2.5 mM probenecid at room temperature for one hour. Following incubation, plates were inserted into a FDSS6000 instrument (Hamamatsu, Photonics, Japan) instrument, where cells were challenged with compounds of the formula (at varying concentrations) and intracellular calcium was measured kinetically for 3 min after addition.

This protocol allowed the determination of an EC50 value, from the sixteen-point dose response data, for each compound of the formula tested. Maximal fluorescence intensity achieved upon addition of 100 µM menthol (stock solution prepared in ethanol from solid, Sigma-Aldrich) was exported from the FDSS and further analyzed using IDBS XLFit 5. Data were normalized to the average 100 µM menthol response (maximum control wells) included in each plate. The dose

response curves from the average of wells for each data point were analyzed by using nonlinear regression of sigmoidal dose response (formula 205). Finally, the (menthol-related) EC50 values (Half maximal effective concentration) were calculated with the best-fit dose curve determined by IDBS XLFit 5 software.

In vitro pig and human TRPM8 automated patch-clamp assays

Automated whole-cell recordings of compound effects were performed on the SyncroPatch 384PE (Nanion Technologies, Munich, Germany) incorporated into a Biomek FX pipetting robot (Beckman Coulter, Jersey City, NJ, USA) using the same engineered CHO cell lines expressing human or pig TRPM8 channels. Data acquisition and analysis were performed with the proprietary software PatchControl 384 and DataControl 384, respectively (Nanion Technologies, Munich, Germany). All recordings were carried out using planar borosilicate glass patch clamp chips in a 384-microtiter plate format with patch hole resistances of 2–4 MΩ. For recordings, standard intracellular solution was used containing (in mM): 130 KF, 4 NaCl, 1 $MgCl_2$, 0.5 $CaCl_2$, 10 HEPES and 10 EGTA/KOH (pH 7.2) and standard extracellular solution contained in mM: 150 NaCl, 4 KCl, 0.5 $CaCl_2$, 1 $MgCl_2$ and 10 HEPES (pH 7.3).

Prior to the electrophysiological measurements, cells were harvested using Accutase (GIBCO, Fisher Scientific) and resuspended in warmed extracellular solution. The cell suspension was kept in the dedicated cell reservoir at 28°C at a 1 million/ml cell density and shaken at 500 rounds per min (rpm). Experiments were performed at 28°C throughout. Cells were distributed in high resistance 4-holes-per-well Nanion chips where they were caught on the patch holes by application of a −80 mbar pressure. The cell membrane was ruptured to obtain the whole-cell configuration with a pressure pulse of −250 mbar for 2 seconds. Voltage protocols were constructed using PatchControl 384. The cells were held at a holding potential of −60 mV and TRPM8 currents were recorded using a ramp protocol from -80 to +80 mV every 5 seconds before and after compound addition. Resulting currents were recorded at both -80 and + 80 mV and current kinetics were exported and analyzed. From each plate, control wells with 200 µM menthol were recorded to validate the assay. One concentration of compound was applied to each of the other wells. For each concentration, compound response was determined by subtracting the baseline current recorded before compound addition from the maximum peak elicited currents obtained after compound addition. Then, each compound response was normalized to control condition without compound and maximum current (Emax) obtained for each compound. Nanion

DataControl 384 software plotted current response for each compound concentration and was able to calculate an EC50 value for each active compound.

The Table 6 below indicates the in vitro results of pig and human TRPM8 fluorescence calcium flux assays and of pig TRPM8 automated patch-clamp assay for compounds of formula (I), and demonstrates that the compounds tested have an agonist activity regarding TRPM8 receptor

Table 6

Example	Pig TRPM8 Calcium Flux EC50 (nM)	Human TRPM8 Calcium Flux EC50 (nM)	Pig TRPM8 Automated Patch-Clamp EC50 (nM)	Human TRPM8 Automated Patch-Clamp EC50 (nM)
1	1.2	1.7	733	810
2	0.7	1.2	596	450
3	35.5	36.8	9912	1120
4	1.2	2.8	467	541
5	0.7	1.3	478	950
6	0.5	0.3	237	72
7	8.1	8.5	6193	2800
8	712.9	1514.9	-	-
9	6.3	8.8	4095	2400
10	9.7	21.4	4799	4130
11	298.5	148.0	4901	3700
12	2.0	3.0	-	-
13	2.0	1.0	782	150
14	6.7	10.3	3296	2720
15	2.1	3.0	1505	1430
16	13.0	16.0	2366	1290
17	191.0	410.0	-	-
18	242.1	757.3	-	-
19	19.9	7.1	1522	1700
20	6.6	3.2	1416	1400
21	56.3	65.1	5293	5500
22	34.5	25.2	3838	3600
23	6.0	7.0	1068	500
24	13.4	7.8	1700	2580

Example	Pig TRPM8 Calcium Flux EC50 (nM)	Human TRPM8 Calcium Flux EC50 (nM)	Pig TRPM8 Automated Patch-Clamp EC50 (nM)	Human TRPM8 Automated Patch-Clamp EC50 (nM)
25	32.8	14.5	3400	2150
26	5.5	3.7	1100	1800
27	10.3	3.1	4000	2400
28	311.3	249.7	5400	1440
29	221.3	210.7	-	-
30	766.2	3250.6	> 10000	-
31	9.3	10.4	3155	2078
32	3.0	3.0	507	1230
33	38.0	65.0	4309	4200
34	80.0	97.0	3207	4590
35	3.0	3.0	1328	1010
36	36.0	47.0	3808	1880
37	11.0	17.0	2357	3100
38	1.8	2.4	276	470
39	0.9	1.2	430	460
40	1.4	2.5	1755	1445
41	74.5	194.7	5114	1100
42	3.8	12.4	921	910
43	56.9	191.3	3967	4000
44	10.6	34.9	711	1800
45	18.2	48.5	-	-
46	4.6	11.9	-	-
47	585.7	640.7	-	-
48	5.0	13.5	4600	2630
49	24.2	67.0	1400	1940
50	0.4	0.4	71	140
51	4.5	7.8	823	3030
52	24.3	26.0	864	1300
53	2.6	2.4	326	200
54	91.1	225.6	8728	5650
55	54.3	102.3	3548	4470
56	11.2	19.6	6156	> 10000
57	219.5	253.8	> 10000	-
58	2.2	5.2	887	1030

Example	Pig TRPM8 Calcium Flux EC50 (nM)	Human TRPM8 Calcium Flux EC50 (nM)	Pig TRPM8 Automated Patch-Clamp EC50 (nM)	Human TRPM8 Automated Patch-Clamp EC50 (nM)
59	4.3	6.2	-	-
60	7.1	43.5	-	-
61	7.4	11.1	5045	2915
62	2.3	1.6	-	-
63	5.7	2.6	57	53
64	8.3	16.6	3866	5821
65	729.0	353.0	-	-
66	75.0	51.0	6058	3700
67	5.0	9.0	3360	2700
68	32.0	44.0	3641	2690
69	42.0	46.0	1579	1930
70	8.0	9.0	3742	3990
71	2.0	1.0	862	183
72	2.0	3.0	790	1390
73	8.0	4.0	1122	690
74	9.0	41.0	5186	2900
75	109.0	84.0	-	-
76	364.6	501.3	-	-
77	93.0	90.0	-	-
78	327.0	575.0	-	-
79	57.6	84.5	5159	5500
80	82.0	40.2	3966	1800
81	25.2	27.7	4246	1500
82	486.4	332.2	-	-
83	136.4	167.9	-	-
84	140.7	143.2	-	-
85	2.4	3.3	967	700
86	749.1	546.7	> 10000	-
87	258.6	982.3	-	-
88	20.0	56.7	1092	1500
89	47.6	90.3	3252	3300
90	14.4	41.8	2003	3000
91	5.2	19.0	-	-
92	2.3	4.1	-	-
93	67.8	49.3	2000	2800

Example	Pig TRPM8 Calcium Flux EC50 (nM)	Human TRPM8 Calcium Flux EC50 (nM)	Pig TRPM8 Automated Patch-Clamp EC50 (nM)	Human TRPM8 Automated Patch-Clamp EC50 (nM)
94	7.7	6.4	1500	1070
95	3.1	3.6	-	-
96	25.2	10.3	1100	630
97	29.2	11.1	-	-
98	64.7	52.8	-	-
99	99.1	110.3	-	-
100	2.9	2.2	-	-
101	173.8	376.3	-	-
102	69.0	42.0	-	-
103	14.9	18.8	-	-
104	0.6	1.1	-	-
105	28.4	30.8	-	-
106	23.2	29.3	> 10000	-
107	21.7	42.8	2439	3800
108	73.0	211.5	> 10000	-
109	11.9	22.4	1769	2200
110	639.2	1639.1	> 10000	-
111	25.1	72.7	5070	5100
112	892.4	1580.5	-	-
113	93.5	99.4	9635	1400
114	28.2	59.8	-	-
115	362.4	786.0	-	-
116	2.5	3.3	504	1300
117	4.5	17.8	2334	2500
118	264.1	557.4	-	-
119	6.3	37.4	7209	3200
120	13.9	31.1	5597	3600
121	4.9	18.7	-	-
122	748.6	7512.2	-	-
123	229.0	334.3	-	-
124	11.7	36.6	6757	6500
125	15.2	42.3	7740	5900
126	25.7	92.5	-	-
127	151.5	359.3	-	-
128	212.2	303.1	-	-

Example	Pig TRPM8 Calcium Flux EC50 (nM)	Human TRPM8 Calcium Flux EC50 (nM)	Pig TRPM8 Automated Patch-Clamp EC50 (nM)	Human TRPM8 Automated Patch-Clamp EC50 (nM)
129	2.6	6.9	1250	3000
130	185.4	433.4	-	-
131	266.8	602.7	-	-
132	79.1	303.5	-	-
133	72.2	140.3	-	-
134	1.3	3.4	-	-
135	1.1	2.1	-	-
136	1.3	2.7	510	610
137	41.6	125.1	-	-
138	1.7	3.8	-	-
139	1.7	5.3	-	-
140	3.3	9.4	-	-
141	1.2	2.7	-	-
142	4.0	12.0	3288	1410
143	7.3	5.6	985	1100
144	1.8	4.8	-	-
145	2.7	2.9	515	230
146	16.0	16.0	2386	1200
147	901.0	1160.0	-	-
148	4.0	4.0	-	-
149	2.0	6.0	1556	2300
150	4.0	4.0	-	-
151	126.0	188.0	-	-
152	47.0	310.0	-	-
153	76.0	130.0	-	-
154	46.0	85.0	-	-
155	17.4	23.8	3500	1200
156	21.5	42.4	1900	1800
157	4.7	8.4	-	-
158	3.0	7.0	940	1900
159	4.9	9.2	1030	1000
160	16.4	16.1	480	620
161	516.2	881.7	-	-
162	4.0	5.3	1400	-
163	939.7	658.3	-	-

Example	Pig TRPM8 Calcium Flux EC50 (nM)	Human TRPM8 Calcium Flux EC50 (nM)	Pig TRPM8 Automated Patch-Clamp EC50 (nM)	Human TRPM8 Automated Patch-Clamp EC50 (nM)
164	21.2	34.3	1040	2200
165	368.7	330.3	-	-
166	15.2	16.6	-	-
167	91.8	58.4	-	-
168	343.0	333.9	-	-
169	27.4	20.9	-	-
170	60.3	37.1	-	-
171	6.1	3.2	-	-
172	19.0	9.7	-	-
173	21.7	24.6	-	-
174	33.4	118.7	2167	-
175	534.6	43.0	-	-
176	1.3	1.1	-	-
177	3.4	3.6	-	-
178	357.6	1258.8	-	-
179	0.6	1.1	598	590
180	1.2	3.0	1007	1700
181	61.4	22.5	-	-
182	3.8	3.7	52	66
183	2.8	2.7	20	120
184	28.1	14.5	567	600
185	68.1	110.0	-	-
186	26.1	43.9	2100	1000
187	6.2	33.8	550	510
188	24.1	76.2	-	-

For testing the efficacy of TRPM8 agonists for enhancing swallowing, experiment using the pig model can be conducted according to assay described below. The efficacy can be compared to a vehicle control.

In vivo assay

Male castrated German Landrace pigs (weight range of 20 to 35 kg) were used. Anesthesia was induced by injecting 20 ml of a urethane solution (20 g/100 mL dissolved in saline) into an ear vein corresponding to a dose of around 16.8 mg/Kg. Anesthesia was maintained by continuous infusion of 15-20 mL per hour of the urethane solution, which was infused into an

epigastric vein, and additionally by infusion of Zoletil and Rompun (500mg Zoletil is disssovled in 10 ml of Rompun 2%, then diluted 1:10 with saline and 3-5mL per hour of this diluted solution. Bupivacain 0.5% JENAPHARM® was injected for additional infiltration anesthesia. Anesthesia was monitored via pulsoximetry (ear) and regular reflex testing for pain. Body temperature was monitored and maintained by an infrared lamp.

Preparation of pigs: Swallowing responses were assessed by manometry with a pressure probe placed into the mouth of the pig. The pressure probe consisted of a plastic tube (diameter 3.3mm) to which a small balloon was attached. The tube was advanced about 12-14cm into the mouth related to the snout. The balloon was then inflated with air to yield a pressure of 20-30mbar (vehicle). Ideally a swallowing response with 1ml of fluid raised this pressure by 20-50mbar which was then referred to as the swallowing pressure (the increment of this pre-set pressure in the inflated balloon after swallowing) to be further enhanced by an effective test drug.

The free end of the tube was connected to a differential pressure transducer MPX Type 399/2 (Hugo Sachs Elektronik – Harvard Apparatus) and a Hugo Sachs Plugsys-amplifier system. The biological signals were recorded by a Hugo Sachs Plugsys-amplifier system and continuously stored on a computer hard disk by an on line data acquisition and analysis system (Hem 4.2 Notocord Systems, Croissy-sur-Seine, France).

A second tube referred to as injection tube was placed dorsally to the manometer tube to enable the administration of the vehicle that induced the baseline swallowing activity, or of this same vehicle containing the test compound.

Induction and assessment of swallowing activity: 0.5h after anesthesia induction 1ml of a fluid or the vehicle for the test drug was injected into the injection tube placed into the oral cavity. The number of swallows was counted and the highest-pressure increment was registered. Challenges with vehicle were repeated at intervals of 30min until two consecutive vehicle challenges show an about equal swallowing response. The next challenge was the vehicle loaded with the test drug (otherwise same procedure). The efficacy of a compound to enhance swallowing as shown in Table 7 was expressed as the % increase in pressure and frequency of swallowing after administration of the compound compared to the pressure and frequency recorded for its vehicle administered just before.

Table 7

Efficacy of tested compound			
Example	dose per pig (mg)	% increase pressure vs vehicle	% increase frequence vs vehicle
1	10	274	231
50	10	63	100
51	10	186	250
52	10	202	172
4	10	221	417
40	10	393	62
54	10	64	75
108	10	169	114
14	10	73	62
31	10	253	119
63	10	186	191
13	10	53	100
80	10	86	91
21	10	181	171
22	10	182	500
81	10	315	247
49	10	133	300
25	10	168	173

It is therefore apparent that the compounds of formula (I), or a pharmaceutically acceptable salt thereof can activate TRPM8 receptors. The compounds of formula (I), or a

pharmaceutically acceptable salt thereof, can therefore be used for preparing medicaments, especially medicaments which are agonists or openers of TRPM8 receptor.

Accordingly, also provided herein is medicament which comprises a compound of the formula (I), or a pharmaceutically acceptable salt thereof.

In one embodiment, provided herein is a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, for use in therapy, especially as agonist of TRPM8 receptor.

In one embodiment, provided herein is a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, for use in the treatment of oropharyngeal dysphagia, chronic cough, pharyngeal irritation, chronic itch, dry and pruritic skin.

In one embodiment, provided herein is a compound of formula (I) defined above, or a pharmaceutically acceptable salt thereof, for use in the treatment of oropharyngeal dysphagia.

In one embodiment, provided is a method of treating the pathological conditions indicated above, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof. In an embodiment of this method of treatment, the subject is a human.

In one embodiment, provided is the use of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament useful in treating any of the pathological conditions indicated above, more particularly the use in treating oropharyngeal dysphagia.

In one embodiment, provided is a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and also at least one pharmaceutically acceptable excipient. The said excipients are selected, in accordance with the pharmaceutical form and method of administration desired, from the customary excipients, which are known to a person skilled in the art.

In one embodiment, provided is a pharmaceutical composition for oral administration including an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt

thereof and excipients in the form of orally disintegrating tablet, liquid, lozenge, film, oral solution, suspension, drop, droplet, dropper, spray, emulsion or syrup. Compositions intended for oral use are prepared according to any method known in the art for the manufacture of pharmaceutical compositions.

In one embodiment, provided is a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof being administered to a patient via topical, sublingual, buccal, pharynx, oropharyngeal, throat administration. In certain embodiment, pharmaceutical composition is administered directly to the oral cavity or the oropharyngeal surface of the patient (e.g., in the form of a spray or drops).

In one embodiment, provided is a delivery device for delivering a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof to a patient.

In one embodiment, the delivery device may be a spraying or atomising device, such as a pump-action spray or an aerosol spray.

In one embodiment, the delivery device may be spray containers, bottles, vials, or small portable devices such as pumps, atomizers.

In one embodiment, the delivery device is a standard dropper mounted into a cap for closing a bottle containing the pharmaceutical composition.

In one embodiment, the delivery device is a syringe.

In one embodiment, the delivery device is an oral catheter inserted in the oral cavity. The pharmaceutical composition is administered through this catheter reaching the back of the oral cavity or the oropharyngeal surface of a patient.

In one embodiment, provided is a kit, the kit comprising: i) a pharmaceutical composition comprising a compound of formula (I) and ii) a delivery device for delivering the pharmaceutical composition to a patient. The pharmaceutical composition may be separate from the delivery device.

One embodiment is a pharmaceutical composition comprising a compound of formula (I) in an amount of 0.3 mg/mL to 20 mg/mL in a form of a spray, drop, dropper, buccal spray, pharynx spray or throat spray.

In one embodiment, the composition further comprises a PEG 400, polyethylene glycol (15)-hydroxystearate, ethanol.

In one embodiment, provided is use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in a method of treatment.

In one embodiment, provided is a method of treatment of a condition, comprising: contacting a pharmaceutical composition comprising as active principle a compound of formula (I) or a pharmaceutically acceptable salt thereof and a excipient with, e.g., the oral cavity, or the oropharyngeal surface of the human, thereby delivering an amount of the compound therapeutically effective for treatment of (e.g., alleviation of) the condition.

In one embodiment, provided is a method of treatment of oropharyngeal dysphagia comprising: contacting a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable excipient with oral cavity, or the oropharyngeal surface of the human, thereby delivering an effective amount of the compound to the mucous membranes of a human.

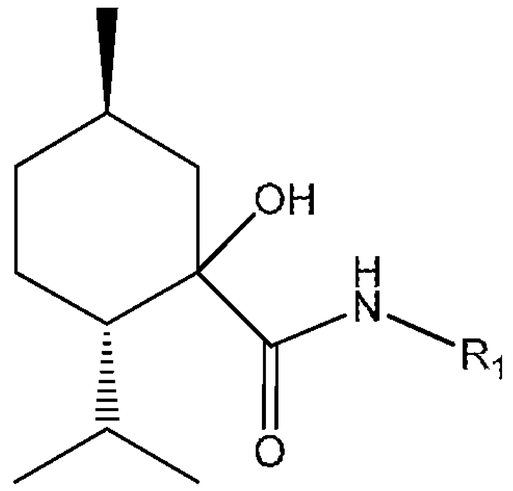
In one embodiment, provided is a method of treatment of (e.g., alleviation of) oropharyngeal dysphagia.

There may be particular cases in which higher or lower dosages are appropriate. According to usual practice, the dosage that is appropriate for each patient is determined by the doctor according to the mode of administration and the weight and response of the said patient.

Claims

What is claimed is:

1. A compound of formula (I):



(I)

wherein:

R_1 is $-C(R_2)(R_3)-[C(R_4)(R_5)]_m-L-R_6$ or $-R_7$

m represents 0, 1, 2 or 3;

R_2 and R_3 independently represent a hydrogen atom, a deuterium atom, a $-(C_1-C_6)$-alkyl group, a (C_1-C_6)-alkyl-OH group, a $-C(=O)NH_2$ group, a $-(C_1-C_6)$-alkoxyl group, or a $-C(=O)O(C_1-C_6)$-alkyl group;

R_4 and R_5 independently represent a hydrogen atom, a deuterium atom, a fluorine atom, a $-NH_2$ group, a -OH group, a $-(C_1-C_6)$-alkyl group, a $-CF_3$ group, a carboxyl group, or a $-R_8-(C_1-C_6)$-alkyl-R_9 group wherein:

R_8 represents a bond, an -O-, a -OC(=O)- group, a -N(H)C(=O)- group, a -C(=O)O- group, or a -C(=O)N(H)- group;

R_9 represents a hydrogen atom, a -C(=O)-OH group, a $-C(=O)O(C_1-C_3)$-alkyl group, a -OH group, an $-O-(C_1-C_3)$-alkyl group, or a $-NH_2$ group;

or R_4 and R_5 can form, together with the carbon atom to which they are attached, a heterocycloalkyl group comprising 3 to 5 carbon atoms and comprising from 1 or 2 heteroatoms selected from oxygen and nitrogen;

L represents a bond, a -(C_1-C_6)-alkylene- group, an -O-(C_1-C_6)-alkylene- group, an -O-, a -OC(=O)- group, a -N(H)- group, a -C(=O)- group, a -C(=O)O- group, a -C(=O)-O-(C_1-C_3)-alkyl- group, a -C(=O)-N(H)- or a -CONH(C_1-C_6)-alkyl- group;

R_6 is selected from the group consisting of a -OH group; a –(C_1-C_6)-alkyl group; a phenyl group, a monocyclic heteroaryl group comprising 3 to 5 carbon atoms and comprising from 1 to 2 heteroatoms independently selected from oxygen, nitrogen and sulfur, an ortho-fused bicyclic heteroaryl group comprising 7 to 10 carbon atoms and comprising from 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur, an ortho-fused bicyclic cycloalkyl group comprising 8 to 11 carbon atoms, and an ortho-fused bicyclic heterocycloalkyl group comprising 8 to 9 carbon atoms and comprising 1 or 2 heteroatoms independently selected from oxygen and nitrogen; said phenyl, monocyclic heteroaryl, ortho-fused bicyclic heteroaryl, ortho-fused bicyclic cycloalkyl, ortho-fused bicyclic heterocycloalkyl groups being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of:

a halogen atom, a -OH group, an oxo group, an -O-(C_1-C_6)-alkyl group, a -(C_1-C_6)-alkyl group, a -NO_2 group, a -CN group, a -C(=O)H group, a -SO_2NH_2 group, a -$C(=O)NH_2$ group, a -$OCH_2C(=O)NH_2$ group, a -C(=O)O(C_1-C_6)-alkyl group, a -C(=O)N(C_1-C_3)-alkyl group, a -$(OCH_2CH_2)_n$-R_{10} group, and a -R_{11}-(C_1-C_6)-alkyl-R_{12} group which is unsubstituted or substituted on the (C_1-C_6)-alkyl with 1 to 3 substituents independently selected from a -OH group, a -NH_2 group and -OCH_3 group; wherein n represents 1, 2 or 3; R_{10} represents an -O-(C_1-C_4)-alkyl group, a -N^+-(CH_3)$_3$ group, or -N^+H-(CH_3)$_2$ group; R_{11} represents a bond, an -O-, or a -C(=O)O group; R_{12} represents a -OH group, a -C(=O)OH group, a -C(=O)O(C_1-C_3)-alkyl group, a -C(=O)N(C_1-C_3)-alkyl group, a -NH_2 group, a -NH-C(=O)(C_1-C_3)-alkyl group, a -C(=O)H group, a heterocyclic group or an -O-heterocyclic group, said heterocyclic group and said -O-heterocyclic group comprising 3 to 9 carbon atoms and comprising from 1 to 3 heteroatoms independently selected from oxygen, nitrogen and sulfur being unsubstituted or substituted with 1 to 3 substituents independently selected from an oxo group and a –(C_1-C_3)-alkyl group;

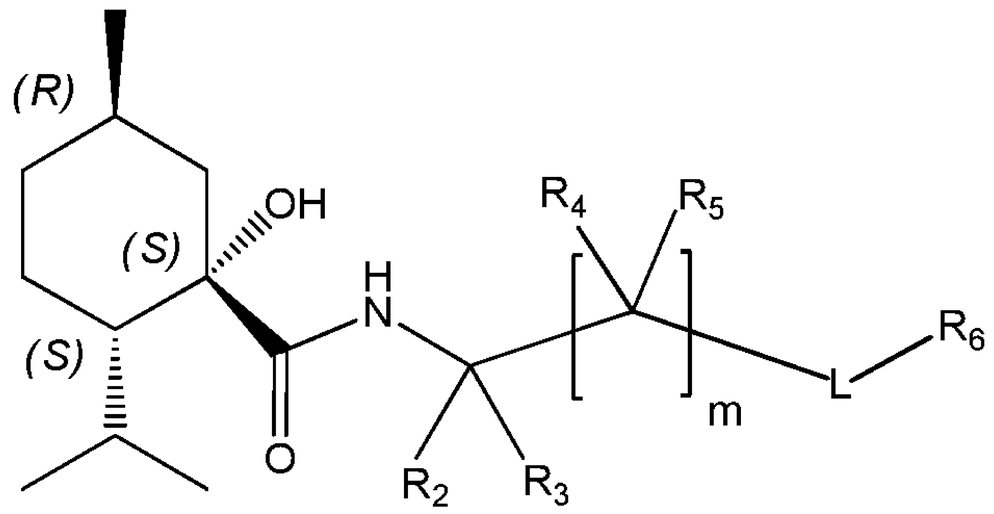
R_7 represents a phenyl group, a monocyclic cycloalkyl group comprising 4 to 7 carbon atoms, a monocyclic heterocycloalkyl group comprising 3 to 6 carbon atoms and comprising from 1 to 2 heteroatoms independently selected from oxygen and nitrogen, an

ortho-fused bicyclic cycloalkyl group comprising 8 to 11 carbon atoms, or an ortho-fused bicyclic heterocycloalkyl group comprising 8 to 9 carbon atoms and comprising 1 or 2 heteroatoms independently selected from oxygen and nitrogen; wherein said phenyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from a halogen atom, a -(C_1-C_3)-alkyl group, an -O-(C_1-C_3)-alkyl group and a morpholine group; said monocyclic cycloalkyl, monocyclic heterocycloalkyl, an ortho-fused bicyclic heterocycloalkyl groups being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of: a halogen atom, an oxo group, a -(C_1-C_6)-alkyl group, a phenyl group, an -O- group, a benzyl group, a -OH group, and an -O-(C_1-C_6)-alkyl group;

or a pharmaceutically acceptable salt thereof.

2. The compound of formula (I) according to claim 1, wherein R_1 represents a -$C(R_2)(R_3)$-$[C(R_4)(R_5)]_m$-L-R_6 group; m represents 0 or 1; or a pharmaceutically acceptable salt thereof.

3. The compound of formula (I) according to claim 1 having the absolute configuration corresponding to a compound of formula (Ia),



(Ia)

wherein:

m represents 0 or 1;

R_6 represents a phenyl group, wherein said phenyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of:

a halogen atom, a -OH group, an -O-(C_1-C_3)-alkyl group, a -(C_1-C_3)-alkyl group, a -NO_2 group, a -CN group, a -C(=O)H group, a -SO_2NH_2 group, a -$C(=O)NH_2$ group, a -$OCH_2C(=O)NH_2$ group, a -C(=O)O(C_1-C_3)-alkyl group, a -

$C(=O)N(C_1\text{-}C_3)$-alkyl group, a $-(OCH_2CH_2)_n\text{-}R_{10}$ group, and a $-R_{11}\text{-}(C_1\text{-}C_3)\text{-alkyl-}R_{12}$ group which is unsubstituted or substituted on the $(C_1\text{-}C_6)$-alkyl with 1 to 3 substituents independently selected from a -OH group, a $-NH_2$ group and $-OCH_3$ group; wherein n represents 1, 2 or 3; R_{10} represents an $-O\text{-}(C_1\text{-}C_3)$-alkyl group, a $-N^+\text{-}(CH_3)_3$ group, or $-N^+H\text{-}(CH_3)_2$ group; R_{11} represents a bond, an -O-, or a -C(=O)O group; R_{12} represents a -OH group, a -C(=O)OH group, a $-C(=O)O(C_1\text{-}C_3)$-alkyl group, a $-C(=O)N(C_1\text{-}C_3)$-alkyl group, a $-NH_2$ group, a $-NH\text{-}C(=O)(C_1\text{-}C_3)$-alkyl group, a -C(=O)H group, a heterocyclic group or an -O-heterocyclic group, said heterocyclic group and said -O-heterocyclic group comprising 3 to 9 carbon atoms and comprising from 1 to 3 heteroatoms independently selected from oxygen, nitrogen and sulfur being unsubstituted or substituted with 1 to 3 substituents independently selected from an oxo group and a $-(C_1\text{-}C_3)$-alkyl group;

or a pharmaceutically acceptable salt thereof.

4. The compound of formula (Ia) according to claim 3, wherein

R_2 and R_3 independently represent a hydrogen atom, a $-(C_1\text{-}C_3)$-alkyl group, a $(C_1\text{-}C_3)$-alkyl-OH group, a $-(C_1\text{-}C_3)$-alkoxyl group;

R_4 and R_5 independently represent a hydrogen atom, a deuterium atom, a fluorine atom, a $-NH_2$ group, a -OH group, a $-(C_1\text{-}C_3)$-alkyl group, a $-CF_3$ group, or a $-R_8\text{-}(C_1\text{-}C_4)\text{-alkyl-}R_9$ group wherein:

R_8 represents a bond, an -O-, a -OC(=O)- group, a -N(H)C(=O)- group, a -C(=O)O- group, or a -C(=O)N(H)- group;

R_9 represents a hydrogen atom, a -C(=O)-OH group, a $-C(=O)O(C_1\text{-}C_3)$-alkyl group, a -OH group, an $-O\text{-}(C_1\text{-}C_3)$-alkyl group, or a $-NH_2$ group;

L represents a bond, an -O-, a -OC(=O)- group, a -C(=O)- group, a -C(=O)O- group, a $-C(=O)\text{-}O\text{-}(C_1\text{-}C_3)\text{-alkyl-}$ group, or a -C(=O)-N(H)-;

R_6 represents a phenyl group, wherein said phenyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of: a halogen atom, a -OH group, an $-O\text{-}(C_1\text{-}C_3)$-alkyl group, a $-(C_1\text{-}C_3)$-alkyl group, a $-NO_2$ group, a -CN group, a -C(=O)H group, a $-SO_2NH_2$ group, a $-C(=O)NH_2$ group, a -

$OCH_2C(=O)NH_2$ group, a -C(=O)O(C_1-C_3)-alkyl group, a -C(=O)N(C_1-C_3)-alkyl group, a -$(OCH_2CH_2)_n$-R_{10} group, and a -R_{11}-(C_1-C_3)-alkyl-R_{12} group which is unsubstituted or substituted on the (C_1-C_6)-alkyl with 1 to 3 substituents independently selected from a -OH group, a -NH_2 group and -OCH_3 group; wherein n represents 1, 2 or 3; R_{10} represents an -O-(C_1-C_3)-alkyl group, or a -N^+-$(CH_3)_3$ group, or -N^+H-$(CH_3)_2$ group; R_{11} represents a bond, an -O-, or a -C(=O)O group; R_{12} represents a -OH group, a -C(=O)OH group, a -C(=O)O(C_1-C_3)-alkyl group, a -C(=O)N(C_1-C_3)-alkyl group, a -NH_2 group, a -NH-C(=O)(C_1-C_3)-alkyl group, a -C(=O)H group;

or a pharmaceutically acceptable salt thereof.

5. The compound of formula (Ia) according to claim 3, wherein:

m represents 1;

R_2 and R_3 independently represent a hydrogen atom, a –(C_1-C_3)-alkyl group, a -(C_1-C_3)-alkyl-OH group;

R_4 and R_5 independently represent a hydrogen atom, a deuterium atom, a fluorine atom, a -NH_2 group, a -OH group, a -(C_1-C_3)-alkyl group, or a -CF_3 group,

L represents a bond or a -C(=O)- group;

R_6 represents a phenyl group, wherein said phenyl group being unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of:

a halogen atom, a -OH group, an -O-(C_1-C_3)-alkyl group, a -(C_1-C_3)-alkyl group, a -NO_2 group, a -CN group, a -C(=O)H group, a -SO_2NH_2 group, a -$C(=O)NH_2$ group, a -$OCH_2C(=O)NH_2$ group, a -C(=O)O(C_1-C_3)-alkyl group, a -C(=O)N(C_1-C_3)-alkyl group, a -$(OCH_2CH_2)_n$-R_{10} group, and a -R_{11}-(C_1-C_3)-alkyl-R_{12} group which is unsubstituted or substituted on the (C_1-C_6)-alkyl with a -OH group or a -NH_2 group; wherein n represents 1, 2 or 3; R_{10} represents an -O-(C_1-C_3)-alkyl group or a -N^+-$(CH_3)_3$ group; R_{11} represents a bond, an -O-, or a -C(=O)O group; R_{12} represents a -OH group, a -C(=O)OH group, a -C(=O)O(C_1-C_3)-alkyl group, a -C(=O)N(C_1-C_3)-alkyl group, a -NH_2 group, a -NH-C(=O)(C_1-C_3)-alkyl group, or a -C(=O)H group;

or a pharmaceutically acceptable salt thereof.

6. The compound of formula (I) according to claim 1, which is (1S, 2S, 5R)-1-hydroxy-N-(3-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexanecarboxamide; or a pharmaceutically acceptable salt thereof.

7. The compound of formula (I) according to claim 1, which is 2-hydroxyethyl 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzoate; or a pharmaceutically acceptable salt thereof.

8. The compound of formula (I) according to claim 1, which is (1S,2S,5R)-1-hydroxy-N-(2-(2-hydroxyethyl)phenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide; or a pharmaceutically acceptable salt thereof.

9. The compound of formula (I) according to claim 1, which is Methyl-3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate; or a pharmaceutically acceptable salt thereof.

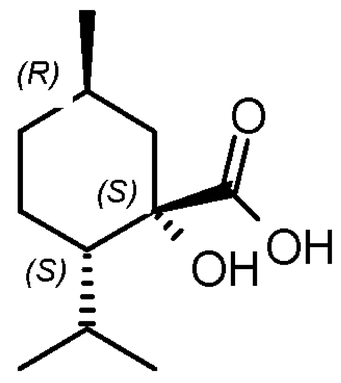
10. The compound of formula (I) according to claim 1, which is (1S,2S,5R)-N-(2-(2-amino-2-oxoethoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide; or a pharmaceutically acceptable salt thereof.

11. The compound of formula (I) according to claim 1, which is (1S,2S,5R)-1-hydroxy-N-((S)-2-hydroxy-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide; or a pharmaceutically acceptable salt thereof.

12. The compound of formula (I) according to claim 1, which is (2-hydroxyethyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzoate; or a pharmaceutically acceptable salt thereof.

13. The compound of formula (I) according to claim 1, which is (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-((3-phenyloxetan-3-yl)methyl)cyclohexane-1-carboxamide; or a pharmaceutically acceptable salt thereof.

14. A process for preparing a compound of formula (I) according to claim 1, comprising submitting a compound (intermediate 4)



(Intermediate 4)

to a coupling reaction with a compound of formula (Ic) or a compound of formula (Id)

$HN_2C(R_2)(R_3)[C(R_4)(R_5)]_mLR_6$ $H_2N\text{-}R_7$

(Ic) (Id)

wherein m, R_2, R_3, R_4, R_5, R_6, L, R_7 are as defined in claim 1.

15. A compound selected from the group consisting of:
(1S,2S,5R)-1-hydroxy-N-((S)-2-hydroxy-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;
2-hydroxyethyl 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzoate;
(1S,2S,5R)-1-hydroxy-N-(3-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;
2-hydroxyethyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzoate;
(1S,2S,5R)-1-hydroxy-N-(2-(2-hydroxyethyl)phenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide;
Methyl-3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate;
(1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-((3-phenyloxetan-3-yl)methyl)cyclohexane-1-carboxamide; and
(1S,2S,5R)-N-(2-(2-amino-2-oxoethoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide;
or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt and at least one pharmaceutically acceptable excipient.

17. The pharmaceutical composition according to claim 16, wherein the compound of formula (I) is (1S,2S,5R)-1-hydroxy-N-((S)-2-hydroxy-2-phenylethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide; or a pharmaceutically acceptable salt thereof.

18. The pharmaceutical composition according to claim 16, wherein the compound of formula (I) is 2-hydroxyethyl 2-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzoate; or a pharmaceutically acceptable salt thereof.

19. The pharmaceutical composition according to claim 16, wherein the compound of formula (I) is (1S,2S,5R)-1-hydroxy-N-(3-hydroxyphenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide; or a pharmaceutically acceptable salt thereof.

20. The pharmaceutical composition according to claim 16, wherein the compound of formula (I) is 2-hydroxyethyl 3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl) benzoate; or a pharmaceutically acceptable salt thereof.

21. The pharmaceutical composition according to claim 8, wherein the compound of formula (I) is (1S,2S,5R)-1-hydroxy-N-(2-(2-hydroxyethyl)phenethyl)-2-isopropyl-5-methylcyclohexane-1-carboxamide; or a pharmaceutically acceptable salt thereof.

22. The pharmaceutical composition according to claim 16, wherein the compound of formula (I) is Methyl-3-(2-((1S,2S,5R)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamido)ethyl)benzoate; or a pharmaceutically acceptable salt thereof.

23. The pharmaceutical composition according to claim 16, wherein the compound of formula (I) is (1S,2S,5R)-1-hydroxy-2-isopropyl-5-methyl-N-((3-phenyloxetan-3-yl)methyl)cyclohexane-1-carboxamide; or a pharmaceutically acceptable salt thereof.

24. The pharmaceutical composition according to claim 16, wherein the compound of formula (I) is (1S,2S,5R)-N-(2-(2-amino-2-oxoethoxy)phenethyl)-1-hydroxy-2-isopropyl-5-methylcyclohexane-1-carboxamide; or a pharmaceutically acceptable salt thereof.

25. A method of treating a disease involving activation of TRPM8 receptors, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof.

26. A method of treating oropharyngeal dysphagia, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof.

27. A medicament, characterized in that it comprises a compound of formula (I) according to any of claims 1 to 5, or a pharmaceutically acceptable salt thereof.

28. A compound of formula (I) according to any of claims 1 to 5, or a pharmaceutically acceptable salt thereof, for use in the treatment of oropharyngeal dysphagia.