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(71) **Applicant** *(for all designated States except US)*: **DARA BIOSCIENCES, INC.** [US/US]; 8601 Six Forks Road, Suite 160, Raleigh, North Carolina 27615 (US).

(72) **Inventor; and**
(75) **Inventor/Applicant** *(for US only)*: **DELMEDICO, Mary Katherine** [US/US]; 7625 Valley Run Drive, Raleigh, North Carolina 27615 (US).

(74) **Agent**: **MYERS BIGEL SIBLEY & SAJOVEC, P.A.**; P.O. Box 37428, Raleigh, North Carolina 27627 (US).

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(54) **Title**: METHODS OF TREATING OR PREVENTING PSORIASIS, AND/OR ALZHEIMER'S DISEASE USING INDANE ACETIC ACID DERIVATIVES

(57) **Abstract**: The present invention provides indane acetic acid and their derivatives and methods for the treating and/or preventing psoriasis and/or Alzheimer's diseases.

METHODS OF TREATING OR PREVENTING PSORIASIS, AND/OR ALZHEIMER'S DISEASE USING INDANE ACETIC ACID DERIVATIVES

Mary Katherine Delmedico

Field of the Invention

The present invention generally relates to the use of indane acetic acids and their derivatives to treat psoriasis and/or Alzheimer's disease.

Background of the Invention

Psoriasis is a chronic, genetically-influenced, remitting skin disorder. It is estimated that psoriasis affects 1 to 3 percent of the world's population. The skin lesions of psoriasis are variably pruritic. There are several types of psoriasis, including plaque, pustular, guttate and arthritic variants. The disease may appear at two different age ranges. Premature disease presentation (type 1), with a peak between 15 and 35 years of age, is the most frequent and is normally associated with family history. Late disease presentation (type 2) is presented with a peak between 55 and 60 years of age.

Currently, the available treatments for plaque psoriasis incorporate the use of emollients, keratolytic agents, coal tar, anthralin, corticosteroids of medium to strong potency, and calpotriene. All of these treatments have variable efficacy. However, none of these treatments can prevent frequent relapses of the disease, and they all exhibit different degrees of side effects. In some cases, systemic treatment has been used in patients with physically, socially, or economically disabling psoriasis who have not responded to topical treatment. The choices to date have been limited to phototherapy or systemic drug therapy. Generally, systemic treatment has employed phototherapy with Ultraviolet B irradiation, photo chemotherapy which combines the photosensitizing drug methoxsalen with Ultraviolet A phototherapy (PUVA), methotrexate, etretinate, systemic corticosteroids, and cyclosporine. However, each of these systemic treatments has variable efficacy and undesired side effects.

Alzheimer's disease ("AD") is a major cause of dementia among the elderly throughout the world. Beginning at age 65, the incidence of the disease rises steadily until age 85. An estimated 26.6 million people worldwide suffered from Alzheimer's in 2006.

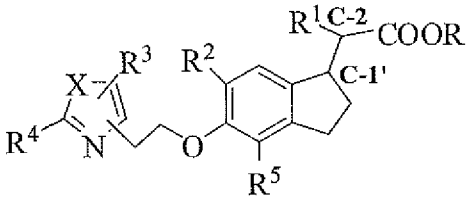
Alzheimer's disease has been identified as a protein misfolding disease caused by accumulation of abnormally folded A-β and tau proteins in the brain. Plaques are made up of small peptides, 39–43 amino acids in length, called beta-amyloid (also written as A-beta or Aβ). β-amyloid is a fragment from a larger protein called amyloid precursor protein (APP), a transmembrane protein that penetrates through the neuron's membrane. APP is involved in to neuronal growth, survival and post-injury repair. In Alzheimer's disease, APP is divided into smaller fragments by enzymes through proteolysis. One of these fragments gives rise to fibrils of beta-amyloid, which form clumps that deposit outside neurons in dense formations known as senile plaques. The disease typically results in an inexorable decline in cognitive functions often coupled with gross behavioral changes, leading to the patient's inability to care for his or herself in the

community resulting in the need for increased assistance for care givers and home care and nursing home providers. To date, there is no universally satisfactory treatment for Alzheimer's disease.

Accordingly, there is an ongoing need for an effective treatment for these diseases.

Summary of the Invention

The present invention provides methods of treating and/or preventing psoriasis and/or Alzheimer's disease. The methods include administering to a subject in need thereof an effective amount of a compound of Formula I:



Formula I

wherein in Formula I

R is H or C_1-C_6 alkyl;

R^1 is H, COOR, C_3-C_8 cycloalkyl, or

C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_1-C_6 alkoxy, each of which may be unsubstituted or substituted with fluoro, methylenedioxyphenyl, or phenyl which may be unsubstituted or substituted with R^6;

R^2 is H, halo, or C_1-C_6 alkyl which may be unsubstituted or substituted with C_1-C_6 alkoxy, oxo, fluoro, or

R^2 is phenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrrolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, or morpholinyl, each of which may be unsubstituted or substituted with R^6;

R^3 is H, C_1-C_6 alkyl, or phenyl, which may be unsubstituted or substituted with R^6;

X is O or S;

R^4 is C_1-C_6 alkyl or C_3-C_8 cycloalkyl, either of which may be unsubstituted or substituted with fluoro, oxo, or C_1-C_6 alkoxy which may be unsubstituted or substituted with C_1-C_6 alkoxy, or phenyl optionally substituted with R^6, or

each of which may be substituted with phenyl, naphthyl, furyl, thienyl, pyrrolyl, tetrahydrofuryl, pyrrolidinyl, pyrrolinyl, tetrahydrothienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperazinyl, morpholinyl, benzofuryl, dihydrobenzofuryl, benzothienyl, dihydrobenzothienyl, indolyl, indolinyl, indazolyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzisoxazolyl,

benzisothiazolyl, benzodioxolyl, quinolyl, isoquinolyl, quinazolinyl, quinoxazolinyl, dihydrobenzopyranyl, dihydrobenzothiopyranyl, or 1,4-benzodioxanyl,

each of which may be unsubstituted or further substituted with R^6, or

C_1-C_6 alkyl may also be substituted with C_3-C_8 cycloalkyl or with phenoxy which may be unsubstituted or substituted with R^6 or with phenyl, naphthyl, furyl, thienyl, pyrrolyl, tetrahydrofuryl, pyrrolidinyl, pyrrolinyl, tetrahydrothienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperazinyl, morpholinyl, benzofuryl, dihydrobenzofuryl, benzothienyl, dihydrobenzothienyl, indolyl, indolinyl, indazolyl, benzoxazolyl, benxothiazolyl, benzimidazolyl, benzisoxazolyl,benzisothiazolyl, benzodioxolyl, quinolyl, isoquinolyl, quinazolinyl, quinoxazolinyl, dihydrobenzopyranyl, dihydrobenzothiopyranyl, or 1,4-benzodioxanyl,

each of which may be unsubstituted or substituted with R^6, or

R^4 is phenyl, naphthyl, furyl, thienyl, pyrrolyl, tetrahydrofuryl, pyrrolidinyl, pyrrolinyl, tetrahydrothienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperazinyl, morpholinyl, benzofuryl, dihydrobenzofuryl, benzothienyl, dihydrobenzothienyl, indolyl, indolinyl, indazolyl, benzoxazolyl, benxothiazolyl, benzimidazolyl, benzisoxazolyl, benzisothiazolyl, benzodioxolyl, quinolyl, isoquinolyl, quinazolinyl, quinoxazolinyl, dihydrobenzopyranyl, dihydrobenzothiopyranyl, or 1,4-benzodioxanyl,

each of which may be unsubstituted or substituted with R^6, or with phenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrrolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, morpholinyl, benzodioxolyl, dihydrobenzofuranyl, indolyl, pyrimidinyl or phenoxy,

each of which may be unsubstituted or substituted with R^6;

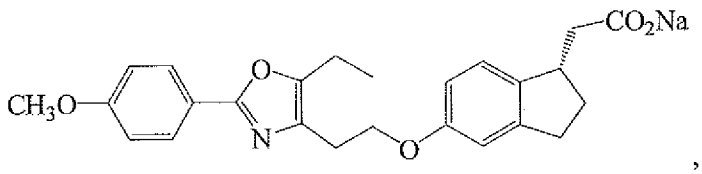
R^5 is H, halo or C_1-C_6 alkyl optionally substituted with oxo; and

R^6 is halo, CF_3, C_1-C_6 alkyl optionally substituted with oxo or hydroxy, or

C_1-C_6 alkoxy optionally substituted with fluoro;

or a pharmaceutically acceptable salt, ester, prodrug, stereoisomer, diastereomer, enantiomer, racemate or a combination thereof.

In one embodiment, the compound of Formula I is a meglumine, potassium or sodium salt thereof. In some embodiments, the compound of Formula I has the following structure:



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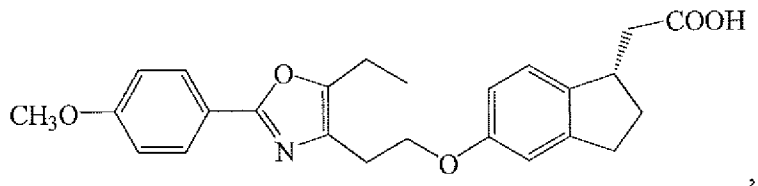

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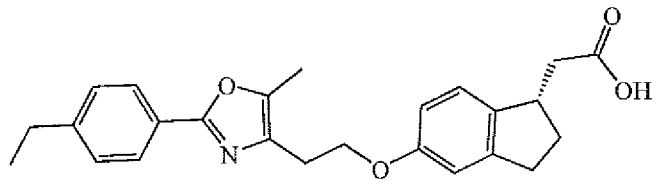

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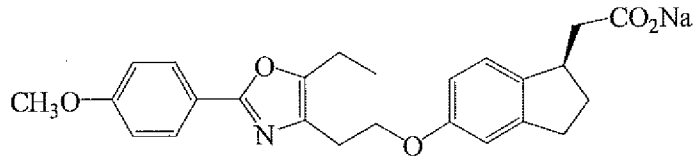

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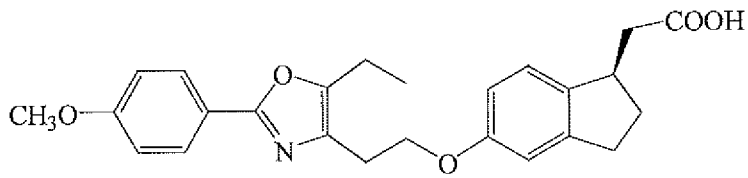

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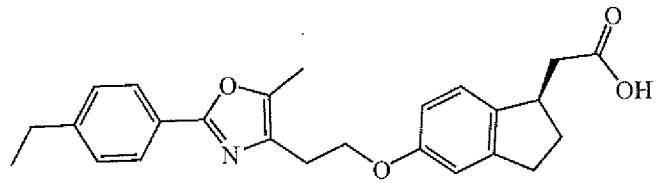

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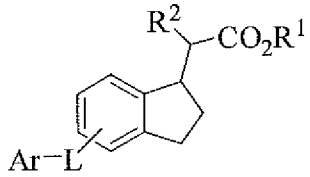
Another aspect of the present invention provides different methods of treating and/or preventing psoriasis and/or Alzheimer's disease. The methods include administering to a subject in need thereof an effective amount of a compound of Formula VI:

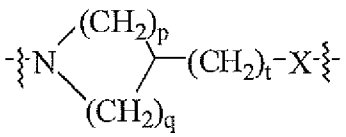


Formula VI

wherein

R^1 and R^2 are independently H, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

L is a linker and selected from the group consisting of $-(CH_2)_m-X-$, $-Y-(CH_2)_n-X-$, and



,

wherein

X is selected from the group O, S, S(=O), and $S(=O)_2$,

Y is selected from the group O, NR^5, S, S(=O), and $S(=O)_2$,

m is 1, 2, or 3,

n is 2, 3, or 4,

t is 0 or 1,

p is 0,1, 2, or 3,

q is 1, 2, 3, or 4,

wherein the sum of p and q is 1, 2, 3, or 4;

Ar is phenyl or a 6-membered heteroaryl containing up to three N atoms,

wherein said Ar is optionally substituted at any available position by 1 to 5 independently selected R^3 groups, and

optionally fused to a 5- or 6-membered saturated carbocyclic ring,

a 5- or 6-membered unsaturated carbocyclic ring, or

a 5- or 6-membered heterocyclic ring containing up to 3 additional heteroatoms selected from N, O, and S,

wherein said fused ring may be optionally substituted at any available position by 1 to 4 independently selected R^4 groups;

R^3 is selected from the group consisting of hydroxy, SH, halo, CN, NO_2, C(=O)OH, C(=O)-OC_1-C_6 alkyl, C(=O)-OC_3-C_6 cycloalkyl, NR^6R^7, $C(=O)NR^6R^7$, $C(=S)NR^6R^7$, C_1-C_6 alkyl optionally substituted with halo, OH, NR^6R^7, or C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 thioalkyl, C_2-C_6 alkenyl, C_1-C_6 haloalkoxy, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, phenoxy optionally substituted on the phenyl ring with halo, C_1-C_6 alkyl, or C_1-C_6 alkoxy, and

a mono or bicyclic ring radical selected from the group consisting of

a) phenyl optionally fused to

a 5- or 6-membered saturated or partially unsaturated carbocylic ring, or

a 5- or 6-membered saturated or partially unsaturated heterocyclic ring containing from 1-3 heteroatoms selected from N, O, and S,

b) a 5- or 6-membered heterocyclic ring radical containing up to 4 heteroatoms selected from N, O, or S, optionally fused to

a 5- or 6-membered saturated or partially unsaturated carbocylic ring, or

a 5- or 6-membered saturated or partially unsaturated heterocyclic ring containing from 1-3 heteroatoms selected from N, O, and S,

said mono or bicyclic ring radical being optionally substituted with up to 5 groups independently selected from the group consisting of halo, hydroxy, oxo, CN, C_1-C_6 alkyl optionally substituted with halo, OH, NR^6R^7, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 thioalkyl, C_1-C_6 haloalkoxy, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_6 acyl, C(=O)OH, $CH_2C(=O)OH$, NR^6R^7, $C(=O)NR^6R^7$, $C(=O)OC_1$-C_6 alkyl, and $C(=O)OC_3$-C_6 cycloalkyl;

R^4 is selected from the group consisting of oxo, hydroxy, halo, CN, NR^6R^7, C_1-C_6 alkyl optionally substituted with OH, NR^6R^7, or C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 thioalkyl, C_1-C_6 haloalkoxy, C_3-C_8 cycloalkyl, and C_3-C_8 cycloalkoxy;

R^5 is selected from the group consisting of H, C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl, C_1-C_6 acyl, benzyl optionally substituted with halo, C_1-C_6 alkoxy, (C_1-C_6)alkyl, CN, NH_2, N[(C_1-C_3)alkyl]$_2$, NO_2, or CF_3, C_3-C_6 cycloalkyl, and C(=O)OC_1-C_6 alkyl;

R^6 and R^7 are independently selected from the group consisting of H, C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl, C_1-C_6 acyl, benzyl optionally substituted with halo, C_1-C_6 alkoxy, (C_1-C_6)alkyl, CN, NH_2, N[(C_1-C_3)alkyl]$_2$, NO_2, or CF_3, C_3-C_6 cycloalkyl, and phenyl optionally substituted with halo, C_1-C_6 alkoxy, (C_1-C_6)alkyl, CN, N[(C_1-C_3)alkyl]$_2$, NO_2, or CF_3, or

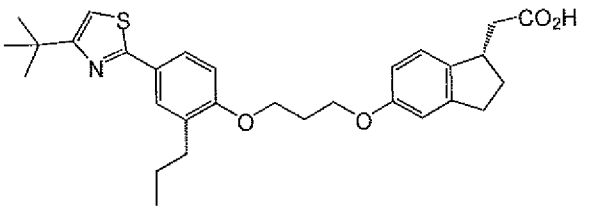
R^6 and R^7 may be taken together with the nitrogen atom to which they are attached to form a 5- or 6-membered heterocyclic ring optionally interrupted by NR^5 or O;

or a pharmaceutically acceptable salt, ester prodrug, stereoisomer, diastereomer, enantiomer, racemate or a combination thereof.

In some embodiments, the compound of formula (VI) is alkali metal salt, or a basic nitrogen containing group.

In some embodiments, the compound of formula (VI) is a meglumine, caclsium, magnesium, ammonium salts, potassium or sodium salt thereof.

In one embodiment, the compound of formula (VI) has the structure:



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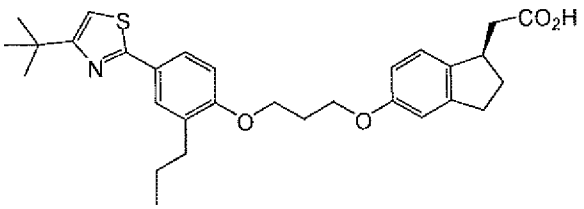


or a pharmaceutically acceptable salt thereof.

In another embodiment, the methods described herein may further include administration of one or more additional therapeutic agent.

Objects of the present invention will be appreciated by those of ordinary skill in the art from a reading of the Examples and the detailed description of the embodiments, which follow, such description being merely illustrative of the present invention.

Detailed Description

The foregoing and other aspects of the present invention will now be described in more detail with respect to the description and methodologies provided herein. It should be appreciated that the invention can be embodied in different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art.

The terminology used in the description of the invention herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention. As used in the description of the embodiments of the invention and the appended claims, the singular forms "a", "an" and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise. Also, the absence of articles "a", "an" are intended to include both the singular forms and plural forms. Also, as used herein, "and/or" refers to and encompasses any and all possible combinations of one or more of the associated listed items. Furthermore, the term "about," as used herein when referring to a measurable value such as an amount of a compound, dose, time, temperature, and the like, is meant to encompass variations of 20%, 10%, 5%, 1%, 0.5%, or even 0.1% of the specified amount. It will be further understood that the terms "comprises" and/or "comprising," when used in this specification, specify the presence of stated features, integers, steps, operations, elements, and/or components, but do not preclude the presence or addition of one or more other features, integers, steps, operations, elements, components, and/or groups thereof. Unless otherwise defined, all terms, including technical and scientific terms used in the description, have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. In the event that there is a plurality of definitions for a term used herein, those in this section prevail unless stated otherwise.

All patents, patent applications and publications referred to herein are incorporated by reference in their entirety. In case of a conflict in terminology, the present specification is controlling.

A. Definitions

The term "halo" means F, Cl, Br, or I.

The term "C_1-C_6 alkyl" means a straight or branched saturated hydrocarbon carbon chain of from 1 to about 6 carbon atoms, respectively. Examples of such groups include methyl, ethyl, isopropyl, sec-butyl, 2-methylpentyl, n-hexyl, and the like.

The term "C_2-C_6 alkenyl" means a straight or branched unsaturated hydrocarbon carbon chain of from 2 to about 6 carbon atoms. Examples of such groups include vinyl, allyl, isopropenyl, 2-butenyl, 3-ethyl-2-butenyl, 4-hexenyl, and the like.

The term "C_1-C_6 haloalkyl" means a C_1-C_6 alkyl group substituted by 1 to 3 halogen atoms or fluorine up to the perfluoro level. Examples of such groups include trifluoromethyl, tetrafluoroethyl, 1,2-dichloropropyl, 5-bromopentyl, 6-iodohexyl, and the like.

The terms "C_3-C_6 cycloalkyl" and "C_3-C_8 cycloalkyl" mean a saturated carbocyclic ring system of from 3 to about 6 carbon atoms or from 3 to about 8 carbon atoms, respectively. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

The term "C_1-C_6 acyl" means a C_1-C_6 alkyl group attached at the carbonyl carbon atom. The radical is attached to the rest of the molecule at the carbonyl bearing carbon atom. Examples of such groups include acetyl, propionyl, n- butanoyl, 2-methylpentantoyl, and the like.

The term "C_1-C_6 alkoxy" means a linear or branched saturated carbon group having from 1 to about 6 C atoms, said carbon group being attached to an O atom. The O atom is the point of attachment of the alkoxy substituent to the rest of the molecule. Such groups include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, and the like.

The term "C_1-C_6 thioalkyl" means a linear or branched saturated carbon group having from 1 to about 6 C atoms, said carbon group being attached to an S atom. The S atom is the point of attachment of the thioalkyl substituent to the rest of the molecule. Such groups include, for example, methylthio, propylthio, hexylthio, and the like.

The term "C_1-C_6 haloalkoxy" means a C_1-C_6 alkoxy group further substituted on C with 1 to 3 halogen atoms or fluorine up to the perfluoro level.

The term "C_3-C_8 cycloalkoxy" means a C_3-C_8 cycloalkyl group attached to an O atom. The O atom is the point of attachment of the cycloalkoxy group with the rest of the molecule.

The term "phenoxy" means a phenyl group attached to an O atom. The O atom is the point of attachment of the phenoxy group to the rest of the molecule.

The term "6-membered heteroaryl ring" means a 6-membered monocyclic heteroaromatic ring radical containing 1-5 carbon atoms and up to the indicated number of N atoms. Examples of 6-membered heteroaryl rings are pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, triazinyl, and the like.

The term "5- or 6-membered heterocyclic ring" means a 5 or 6-membered ring containing 1-5 C atoms and up to the indicated number of N, O, and S atoms, and may be aromatic, partially saturated, or fully saturated.

The term "optionally substituted" means that, unless indicated otherwise, the moiety so modified may have from one to up to the number of the substituents indicated, provided the resulting substitution is chemically feasible as recognized in the art. Each substituent may replace any H atom on the moiety so modified as long as the replacement is chemically possible and chemically stable. For example, a chemically unstable compound would be one where each of two substituents is bonded to a single C atom through each substituents heteroatom. Another example of a chemically unstable compound would be one where an alkoxy group is bonded to the unsaturated carbon of an alkene to form an enol ether. When there

are two or more substituents on any moiety, each substituent is chosen independently of the other substituent so that, accordingly, the substituents can be the same or different.

When the 5-or 6-membered heterocyclic ring is attached to the rest of the molecule as a substituent, it becomes a radical. Examples of 5- or 6-membered heteroaryl ring radicals are furyl, pyrrolyl, thienyl, pyrazolyl, isoxazolyl, imidazolyl, oxazolyl, thiazolyl, isothiazolyl, triazolyl, thiadiazolyl, oxadiazolyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, triazinyl, and the like. Examples of partially unsaturated 5- or 6-membered heterocyclic ring radicals include dihydropyrano, pyrrolinyl, pyrazolinyl, imidazolinyl, dihydrofuryl, and the like. Examples of saturated 5- or 6-membered heterocyclic ring radicals include pyrrolidinyl, tetrahydropyridyl, piperidinyl, morpholinyl, tetrahydrofuryl, tetrahydrothienyl, piperazinyl, and the like. The point of attachment of the radical may be from any available C or N atom of the ring to the rest of the molecule. When the 5- or 6-membered heterocyclic ring is fused to another ring contained in the rest of the molecule, it forms a bicyclic ring. Examples of such 5-and 6-heterocyclic fused rings include pyrrolo, furo, pyrido, piperido, thieno, and the like. The point of fusion is at any available face of the heterocyclic ring and parent molecule.

As used herein, "subject", as used herein, means a mammalian subject (e.g., dog, cat, horse, cow, sheep, goat, monkey, etc.), and particularly human subjects (including both male and female subjects, and including neonatal, infant, juvenile, adolescent, adult and geriatric subjects, and further including various races and ethnicities including, but not limited to, white, black, Asian, American Indian and Hispanic).

As used herein, "treatment", "treat", and "treating" refer to reversing, alleviating, mitigating or slowing the progression of or inhibiting the progress of a disorder or disease as described herein.

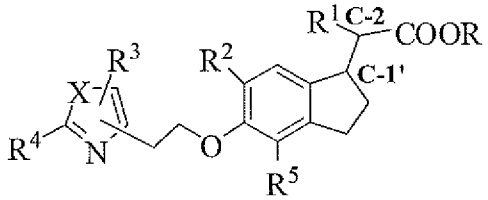
As used herein, "prevention", "prevent", and "preventing" refer to eliminating or reducing the incidence or onset of a disorder or disease as described herein, as compared to that which would occur in the absence of the measures taken.

As used herein, "an effective amount" refers to an amount that causes relief of symptoms of a disorder or disease as noted through clinical testing and evaluation, patient observation, and/or the like. An "effective amount" can further designate a dose that causes a detectable change in biological or chemical activity. The detectable changes may be detected and/or further quantified by one skilled in the art for the relevant mechanism or process. Moreover, an "effective amount" can designate an amount that maintains a desired physiological state, i.e., reduces or prevents significant decline and/or promotes improvement in the condition of interest. An "effective amount" can further refer to a therapeutically effective amount.

B. Compounds

(1). Formula I

The present invention encompasses the compounds of Formula I,



Formula I

wherein in Formula I

R is H or C_1 - C_6 alkyl;

R^1 is H, COOR, C_3-C_8 cycloalkyl, or C_1 - C_6 alkyl, C_2-C_6 alkenyl, or C_1-C_6 alkoxy each of which may be unsubstituted or substituted with fluoro, methylenedioxyphenyl, or phenyl which may be unsubstituted or substituted with R^6;

R^2 is H, halo, or C_1-C_6 alkyl which may be unsubstituted or substituted with C_1-C_6 alkoxy, oxo, fluoro, or

R^2 is phenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl,isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrrolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, or morpholinyl,

each of which may be unsubstituted or substituted with R^6;

R^3 is H, C_1-C_6 alkyl, or phenyl, which may be unsubstituted or substituted with R^6;

X is O or S;

R^4 is C_1-C_6 alkyl or C_3-C_8 cycloalkyl, either of which may be unsubstituted or substituted with fluoro, oxo, or C_1-C_6 alkoxy which may be unsubstituted or substituted with C_1-C_6 alkoxy, or phenyl optionally substituted with R^6,

each of which may be substituted with phenyl, naphthyl, furyl, thienyl, pyrrolyl, tetrahydrofuryl, pyrrolidinyl, pyrrolinyl, tetrahydrothienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperazinyl, morpholinyl, benzofuryl, dihydrobenzofuryl, benzothienyl, dihydrobenzothienyl, indolyl, indolinyl, indazolyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzisoxazolyl, benzisothiazolyl, benzodioxolyl, quinolyl, isoquinolyl, quinazolinyl, quinoxazolinyl, dihydrobenzopyranyl, dihydrobenzothiopyranyl, or 1,4-benzodioxanyl,

each of which may be unsubstituted or further substituted with R^6, or

C_1-C_6 alkyl may also be substituted with C_3-C_8 cycloalkyl or with phenoxy which may be unsubstituted or substituted with R^6 or with phenyl, naphthyl, furyl, thienyl, pyrrolyl, tetrahydrofuryl, pyrrolidinyl, pyrrolinyl, tetrahydrothienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperazinyl, morpholinyl, benzofuryl, dihydrobenzofuryl, benzothienyl, dihydrobenzothienyl, indolyl, indolinyl, indazolyl, benzoxazolyl, benxothiazolyl, benzimidazolyl,

benzisoxazolyl,benzisothiazolyl, benzodioxolyl, quinolyl, isoquinolyl, quinazolinyl, quinoxazolinyl, dihydrobenzopyranyl, dihydrobenzothiopyranyl, or 1,4-benzodioxanyl,

each of which may be unsubstituted or substituted with R^6, or

R^4 is phenyl, naphthyl, furyl, thienyl, pyrrolyl, tetrahydrofuryl, pyrrolidinyl, pyrrolinyl, tetrahydrothienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperazinyl, morpholinyl, benzofuryl, dihydrobenzofuryl, benzothienyl, dihydrobenzothienyl, indolyl, indolinyl, indazolyl, benzoxazolyl, benxothiazolyl, benzimidazolyl, benzisoxazolyl, benzisothiazolyl, benzodioxolyl, quinolyl, isoquinolyl, quinazolinyl, quinoxazolinyl, dihydrobenzopyranyl, dihydrobenzothiopyranyl, or 1,4-benzodioxanyl,

each of which may be unsubstituted or substituted with R^6, or with phenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrrolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, morpholinyl, benzodioxolyl, dihydrobenzofuranyl, indolyl, pyrimidinyl or phenoxy,

each of which may be unsubstituted or substituted with R^6;

R^5 is H, halo or C_1-C_6 alkyl optionally substituted with oxo; and

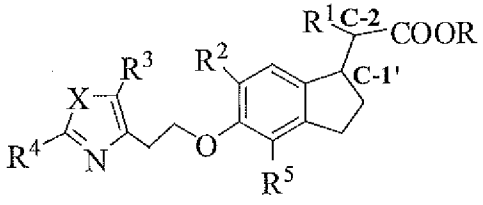
R^6 is halo, CF_3, C_1-C_6 alkyl optionally substituted with oxo or hydroxy, or

C_1-C_6 alkoxy optionally substituted with fluoro;

or a pharmaceutically acceptable salt, ester prodrug, stereoisomer, diastereomer, enantiomer, racemate or a combination thereof.

R^3 may be attached to the heterocyclic moiety of the compound of Formula I at either the 4 or 5 position (i.e., at either available carbon atom) and, accordingly, the remaining portion of the molecule will be attached at the remaining available carbon atom.

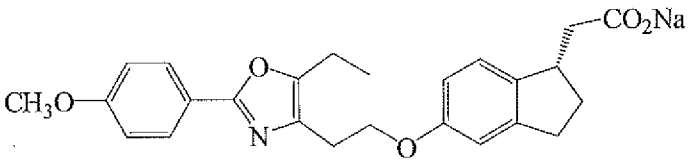
In some embodiments, the compound of Formula I has the following structure:



In some embodiments, the compound of Formula I is a meglumine, potassium or sodium salt thereof.

In other embodiments, for the compound of Formula I, R is H, R^1 is H, R^2 is H, R^3 is C_1-C_6 alkyl, X is O, and R^4 is a phenyl substituted with R^6, wherein R^6 is C_1-C_6 alkoxyl or C_1-C_6 alkyl, or a pharmaceutically acceptable salt thereof.

In one embodiment, the compound has the following structure:



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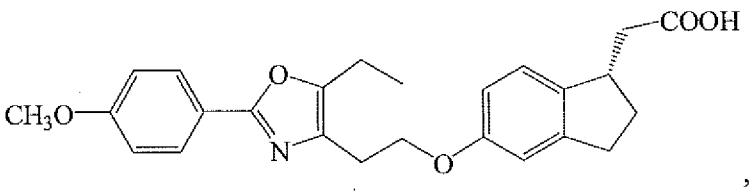

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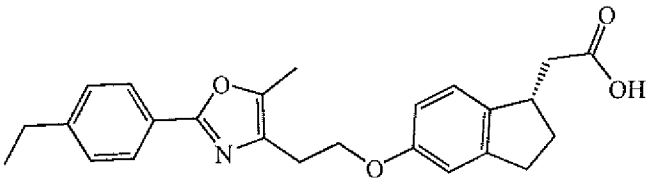

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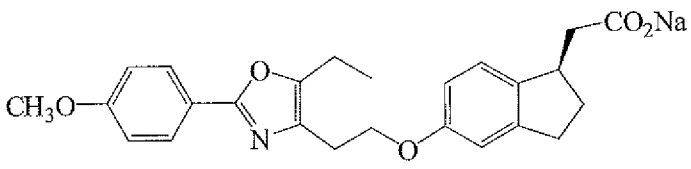

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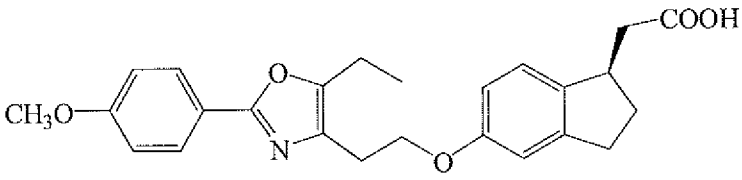
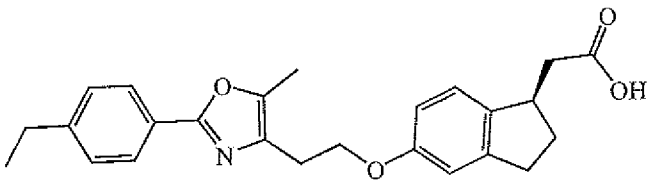
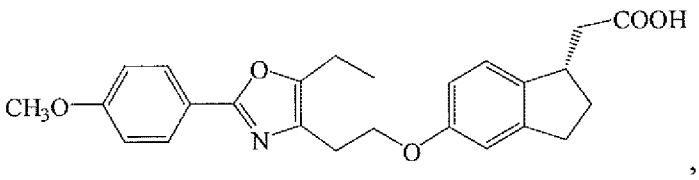


or



.

In other embodiment, the compound of Formula I is a meglumine, potassium or sodium salt of the structure



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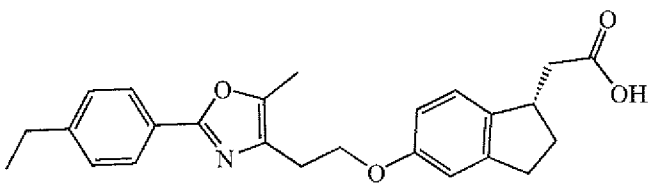

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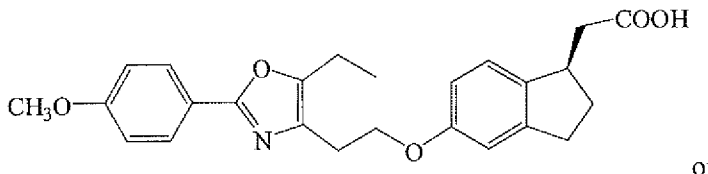
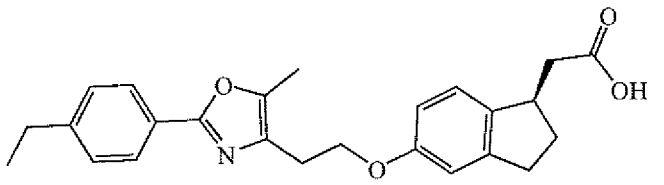
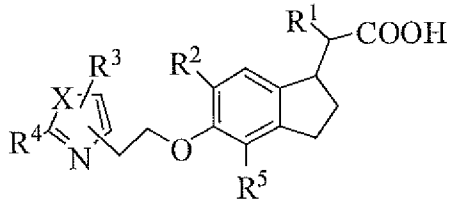


or

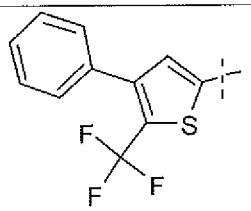


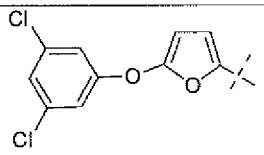
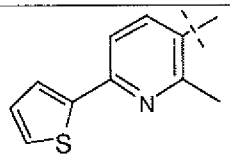
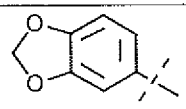
Exemplary compounds of Formula I are listed in Table 1.

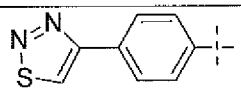
Table 1. Illustrative Examples of Compounds of Formula I

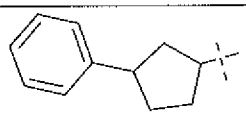
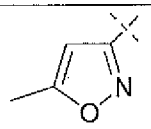
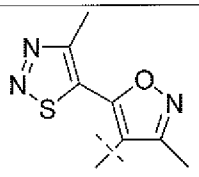
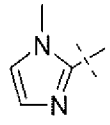
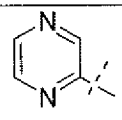


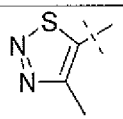
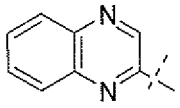
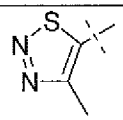
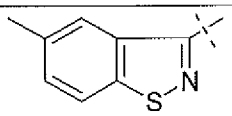
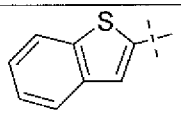
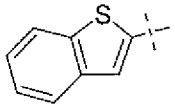
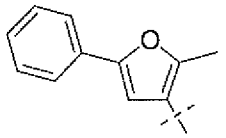
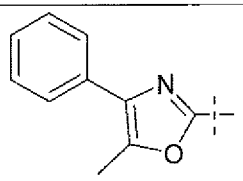
Formula I

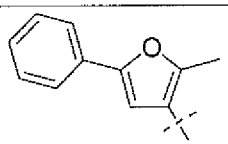
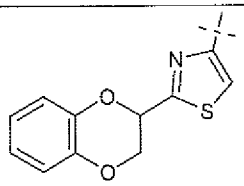
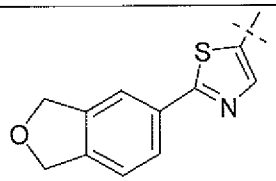
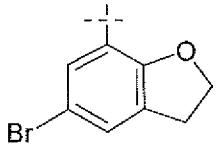
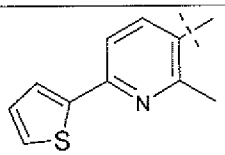
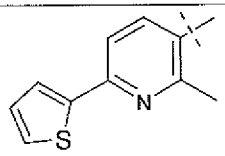
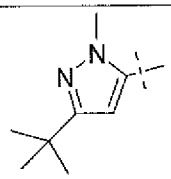
Entry No.	R^1	R^2	R^3	R^4	R^5	X
1	H	H	H	CH_3	H	O
2	H	H	H	n-butyl	H	O
3	H	H	H	cyclopropyl	H	O
4	H	H	H	cyclopentyl	H	O
5	H	H	H	cyclooctyl	H	O
6	H	H	H	Ph	H	O
7	H	H	H	Ph	H	S
8	H	H	H	2-Cl Ph	H	O
9	H	H	H	2,3-d-F Ph	H	O
10	H	H	H	2,4-di-CH_3 Ph	H	O
11	H	H	H	2-thienyl	H	O
12	H	H	H		H	O
13	H	H	H	2-furyl	H	O
14	H	H	H	2-furyl	H	S

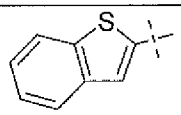
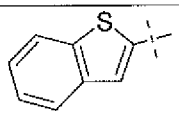
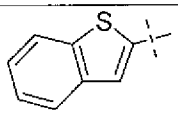
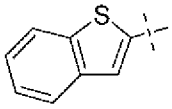
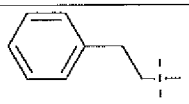
Entry No.	R^1	R^2	R^3	R^4	R^5	X
15	H	H	H	2-(4-CH_3)furyl	H	O
16	H	H	H		H	O
17	H	H	H	4-F Ph	H	O
18	H	H	H	4-F Ph	H	S
19	H	H	CH_3	4-F Ph	H	O
20	H	H	Et	4-F Ph	H	O
21	H	H	Et	4-F Ph	H	S
22	H	H	Et	3-pyridyl	H	O
23	H	H	Et		H	O
24	H	H	isopropyl	4-F Ph	H	O
25	H	H	isopropyl	2,4-di-F Ph	H	O
26	H	H	n-butyl	2,4-di-F Ph	H	O
27	H	H	n-hexyl	2,4-di-F Ph	H	O
28	H	H	Ph	2,4-di-F Ph	H	O
29	H	H	4-F Ph	2,4-di-F Ph	H	O
30	H	CH_3	Et	Ph	H	O
31	H	CH_3	Et	Ph	H	S
32	H	CH_3	Et	3-CH_3O Ph	H	O
33	H	H	Et	3-CH_3O Ph	H	O
34	H	H	Et	3-CH_3O Ph	H	S
35	H	H	Et	4-CH_3O Ph	H	O
36	H	H	Et	4-CH_3O Ph	H	S
37	H	H	Et	4-EtO Ph	H	S
38	H	H	Et	4-EtO Ph	H	O
39	H	H	Me		H	O
40	H	H	Me	$PhCH_2$	H	O
41	H	H	Me	3-Cl-4-F-Ph	H	O
42	H	H	Me	3-F-4-Me-Ph	H	O

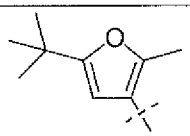
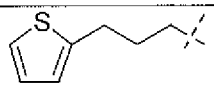
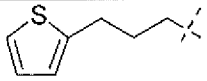
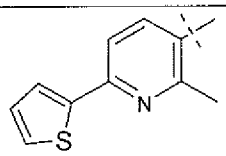
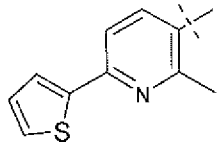
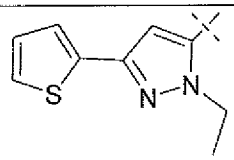
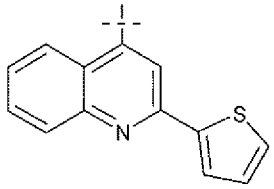
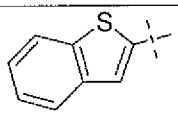
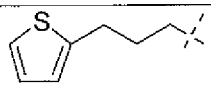
Entry No.	R^1	R^2	R^3	R^4	R^5	X
43	H	H	Me	3-Me-4-F-Ph	H	O
44	H	H	Me	3-NH_2-4-Me-Ph	H	O
45	H	H	Et	4-Et-Ph	H	O
46	H	H	Me	4-Et-Ph	H	O
47	H	H	Et	4-CN-Ph	H	O
48	H	H	Et	4-$(Et)_2N$-Ph	H	O
49	H	H	Me	4-i-Pr-Ph	H	O
50	H	H	Me	4-t-Bu-Ph	H	O
51	H	H	Me	4-Et-Ph	H	O
52	H	H	Me	4-n-Bu-Ph	H	O
53	H	H	Et	4-n-Pr-Ph	H	O
54	H	CH_3	Et	4-CH_3O Ph	H	O
55	H	CH_3	Et	4-CH_3O Ph	H	S
56	H	CH_3	Et	4-CH_3O Ph	CH_3	O
57	H	CH_3	Et	3,4-di-CH_3O Ph	CH_3	O
58	H	CH_3	Et	4-Ph Ph	CH_3	O
59	H	CH_3	Et	4-Ph Ph	CH_3	S
60	H	CH_3	Et		CH_3	O
61	H	CH_3	Ph	cyclopropyl	H	O
62	H	CH_3	Ph	cyclohexyl	H	O
63	H	CH_3	Ph	cyclohexyl	H	S
64	H	CH_3	p-F Ph	cyclohexyl	H	O
65	H	Cl	i-Pr	Ph	H	O
66	H	Cl	i-Pr	Ph	H	S
67	H	Cl	i-Pr	Ph	Cl	O
68	H	Cl	i-Pr	4-CH_3 Ph	Cl	O
69	H	Br	CH_3	Ph	Br	O
70	H	Br	CH_3	3-F Ph	Br	O
71	H	Br	CH_3	3-F Ph	Br	S
72	H	CH_3CO	CH_3	n-propyl	CH_3CO	O
73	H	CH_2OCH_3	Et	2-thienyl	H	O
74	H	Ph	H	2,4-di-Cl Ph	H	O
75	H	Ph	H	2,4-di-Cl Ph	H	S

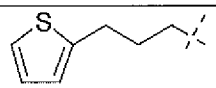
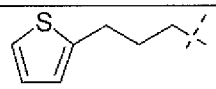
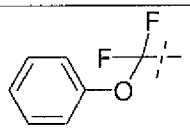
Entry No.	R^1	R^2	R^3	R^4	R^5	X
76	H	Ph	CH_3	2,4-di-Cl Ph	H	O
77	H	Ph	Et	2,4-di-Cl Ph	H	O
78	H	Ph	Ph	2,4-di-Cl Ph	H	O
79	H	Ph	Ph	2,4-di-Cl Ph	H	S
80	H	Ph	4-CH_3O-Ph	2,4-di-Cl Ph	H	O
81	H	4-F Ph	CH_3	4-F Ph	H	O
82	H	4-F Ph	CH_3	2,4-di-Cl Ph	H	O
83	H	3-pyridyl	CH_3	2,4-di-Cl Ph	H	O
84	H	3-pyridyl	CH_3	2,4-di-Cl Ph	H	S
85	H	2-thienyl	CH_3	Ph	H	O
86	H	2-thienyl	CH_3	2,4-di-Cl Ph	H	O
87	H	2-thienyl	CH_3	2,4-di-Cl Ph	H	S
88	H	2-thienyl	CH_3	3-pyridyl	H	O
89	H	2-thienyl	CH_3	cyclopentyl	H	O
90	H	2-thienyl	CH_3		H	O
91	H	2-thienyl	CH_3	Ph	2-thienyl	O
92	CH_3	H	H	Ph	H	O
93	CH_3	H	H	Ph	H	S
94	CH_3	H	H	2-thienyl	H	O
95	CH_3	H	H	2-thienyl	H	S
96	CH_3	H	H		H	O
97	CH_3	H	H		H	O
98	CH_3	H	H		H	O
99	CH_3	H	H	2-pyridyl	H	O
100	CH_3	H	H		H	O

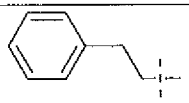
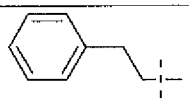
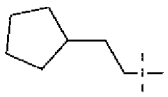
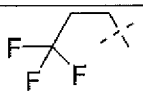
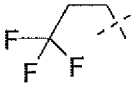
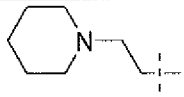
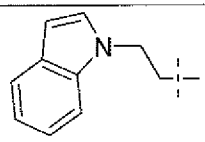
Entry No.	R^1	R^2	R^3	R^4	R^5	X
101	CH_3	H	CH_3	cyclobutyl	H	O
102	CH_3	H	CH_3	cyclohexyl	H	O
103	CH_3	H	CH_3	cyclohexyl	H	S
104	CH_3	H	CH_3	3,4-di-F Ph	H	O
105	CH_3	H	CH_3	3,4-di-F Ph	H	S
106	CH_3	H	CH_3	2-pyridyl	H	O
107	CH_3	H	CH_3		H	O
108	CH_3	H	CH_3		H	O
109	CH_3	H	Et	Ph	H	O
110	CH_3	H	Et	Ph	H	S
111	CH_3	H	Et	4-CF_3 Ph	H	O
112	CH_3	H	Et		H	O
113	CH_3	H	Et	2-napthyl	H	O
114	CH_3	H	Et		H	O
115	CH_3	H	Et		H	O
116	CH_3	H	Et		H	S
117	CH_3	H	Et		H	O
118	CH_3	H	Et		H	O
119	CH_3	H	i-Pr	Ph	H	O
120	CH_3	H	i-Pr	Ph	H	S

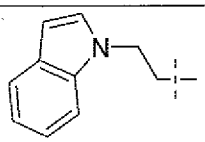
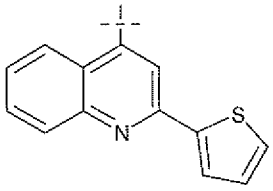
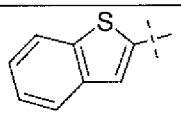
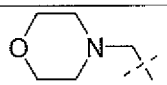
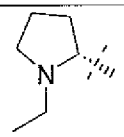
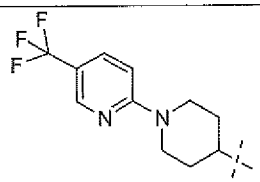
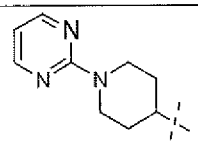
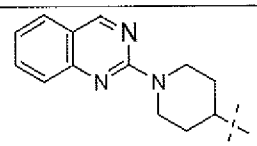
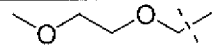
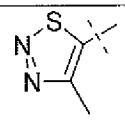
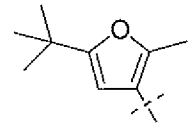
Entry No.	R^1	R^2	R^3	R^4	R^5	X
121	CH_3	H	i-Pr	3,4-di-F Ph	H	O
122	CH_3	H	i-Pr	3,4-di-Cl Ph	H	O
123	CH_3	H	i-Pr	4-Ph Ph	H	O
124	CH_3	H	i-Pr	4-Ph Ph	H	S
125	CH_3	H	i-Pr	4-(4-ClPh)Ph	H	O
126	CH_3	H	i-Pr	4-(4-ClPh)Ph	H	S
127	CH_3	H	i-Pr		H	O
128	CH_3	H	i-Pr		H	O
129	CH_3	H	i-Pr		H	O
130	CH_3	H	i-Pr		H	O
131	CH_3	H	i-Pr	3-(5- CH_3) pyridyl	H	O
132	CH_3	H	i-Pr		H	O
133	CH_3	H	i-Pr		H	S
134	CH_3	H	i-Pr		H	O
135	CH_3	CH_3	i-Pr	3,4-di-Cl Ph	CH_3	O
136	CH_3	n-propyl	i-Pr	3,4-di-Cl Ph	n-propyl	O
137	CH_3	Cl	i-Pr	4-Cl Ph	H	O

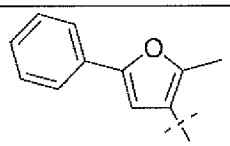
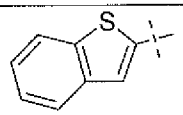
Entry No.	R^1	R^2	R^3	R^4	R^5	X
138	CH_3	Cl	i-Pr	4-Cl Ph	H	S
139	CH_3	Cl	i-Pr	3-CH_3O Ph	H	O
140	CH_3	Cl	i-Pr	3-CH_3O Ph	Cl	O
141	CH_3	Cl	i-Pr	3-CH_3O Ph	Cl	S
142	CH_3	Cl	i-Pr		Cl	O
143	CH_3	Br	i-Pr	Ph	H	O
144	CH_3	Br	i-Pr	3-Cl Ph	H	O
145	CH_3	Br	i-Pr	Ph	Br	O
146	CH_3	Br	i-Pr	Ph	Br	S
147	CH_3	CH_3	i-Pr	Ph	H	O
148	CH_3	CH_3	i-Pr	Ph	H	S
149	CH_3	CH_3	i-Pr	2-Cl Ph	H	O
150	CH_3	CH_3	i-Pr		H	O
151	CH_3	CH_3CO	i-Pr	3-F Ph	H	O
152	CH_3	CH_3CO	i-Pr	3-F Ph	H	S
153	CH_3	n-PrCO	i-Pr	3-F Ph	H	O
154	CH_3	n-BuCO	i-Pr	3-F Ph	H	O
155	CH_3	H	n-Bu	Ph	H	O
156	CH_3	H	n-Bu		H	O
157	CH_3	H	n-Bu		H	S
158	CH_3	H	n-Bu	2-Cl Ph	H	O
159	CH_3	H	n-Bu	2,4 di-F Ph	H	O
160	CH_3	H	n-Bu	3,4 di- CH_3O Ph	H	O
161	CH_3	H	n-Bu		H	O
162	CH_3	H	n-Bu	2-furyl	H	O

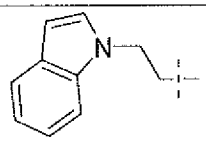
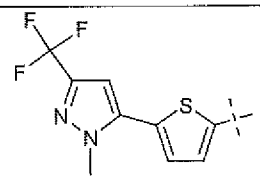
Entry No.	R^1	R^2	R^3	R^4	R^5	X
163	CH_3	H	n-Bu		H	O
164	CH_3	H	n-Bu		H	O
165	CH_3	H	n-Bu		H	S
166	CH_3	H	n-Bu		H	O
167	CH_3	H	n-Bu		H	S
168	CH_3	H	n-Bu		H	O
169	CH_3	H	n-Bu		H	O
170	CH_3	Br	n-Bu	2,4 di-F Ph	Br	O
171	CH_3	Cl	n-Bu	2,4 di-F Ph	H	O
172	CH_3	H	n-pentyl	Ph	H	O
173	CH_3	H	n-pentyl	2,4 di-F Ph	H	O
174	CH_3	H	n-pentyl	2,4 di-F Ph	H	S
175	CH_3	H	n-pentyl	4-pyridyl	H	O
176	CH_3	H	n-pentyl		H	O
177	CH_3	Cl	n-pentyl	Ph	H	O
178	CH_3	Cl	n-pentyl	Ph	H	S
179	CH_3	H	Ph		H	O

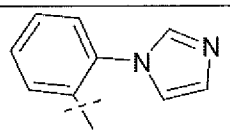
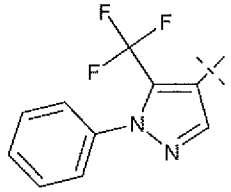
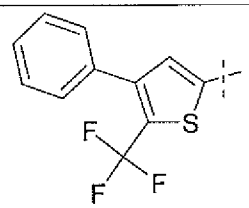
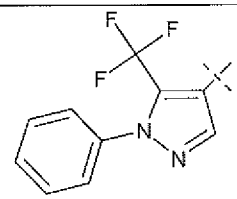
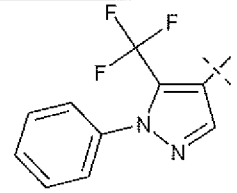
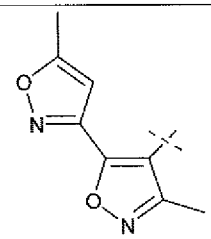
Entry No.	R^1	R^2	R^3	R^4	R^5	X
180	CH_3	H	2-Cl Ph		H	O
181	CH_3	H	2-Cl Ph		H	S
182	CH_3	H	H	$PhOCH_2$	H	O
183	CH_3	H	H	$(4\text{-}CH_3Ph)OCH_2$	H	O
184	CH_3	H	H		H	O
185	CH_3	H	CH_3	Et	H	O
186	CH_3	H	CH_3	Et	H	S
187	CH_3	H	CH_3	CF_3CF_2	H	O
188	CH_3	H	CH_3	t-butyl	H	O
189	CH_3	H	Et	3-(5- CH_3) pyridyl	H	O
190	CH_3	H	Et	4-pyridyl	H	O
191	CH_3	H	Et	4-pyridyl	H	S
192	CH_3	Et	CH_3	$PhOCH_2$	H	O
193	CH_3	Et	CH_3	$PhOCH_2$	H	S
194	CH_3	Et	CH_3	$PhCH_2OCH_2$	H	O
195	CH_3	n-propyl	CH_3	$PhOCH_2$	H	O
196	CH_3	n-propyl	CH_3	$PhOCH_2$	n-propyl	O
197	CH_3	n-butyl	CH_3	$PhOCH_2$	H	O
198	CH_3	n-hexyl	CH_3	$PhOCH_2$	H	O
199	CH_3	n-hexyl	CH_3	$PhOCH_2$	H	S
200	CH_3	n-hexyl	isopropyl	3-Cl Ph	H	O
201	CH_3	n-hexyl	Ph	3-Cl Ph	H	O
202	CH_3	CH_3OCH_2	CH_3	$PhOCH_2$	H	O
203	CH_3	Ph	n-butyl	3,4-di-F Ph	H	O
204	CH_3	3-F Ph	CH_3	1-napthyl	H	O
205	CH_3	4-pyridyl	H	4-CF_3 Ph	H	O
206	CH_3	4-pyridyl	H	4-CF_3 Ph	H	S
207	CH_3	Cl	CH_3	3,5-di-F-Ph	H	O
208	CH_3	Br	CH_3	CF_3CF_2	H	O
209	CH_3	Br	n-butyl	CF_3CF_2	H	O

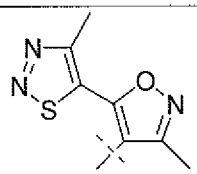
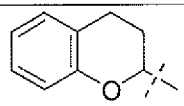
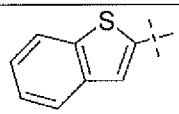
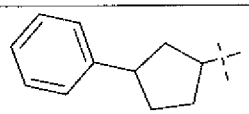
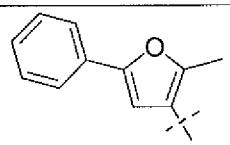
Entry No.	R^1	R^2	R^3	R^4	R^5	X
210	CH_3	Br	n-butyl	CF_3CF_2	Br	O
211	CH_3	Br	Ph	CF_3CF_2	Br	O
212	CH_3	2-furyl	CH_3	isobutyl	H	O
213	CH_3	2-furyl	CH_3	isobutyl	H	S
214	CH_3	2-furyl	CH_3	2-F-4-CF_3 Ph	H	O
215	CH_3	2-furyl	CH_3	2-napthyl	H	O
216	CH_3	2-furyl	i-Pr	isobutyl	H	O
217	CH_3	EtCO	n-propyl	3-CH_3O Ph	EtCO	O
218	Et	H	H	cyclopropyl	H	O
219	Et	H	H	4-F Ph	H	O
220	Et	H	H	3,5-di-F-Ph	H	O
221	Et	H	H	4-Cl $PhCH_2$	H	O
222	Et	H	H	2-quinolinyl	H	O
223	Et	H	CH_3	$PhCH_2$	H	O
224	Et	H	CH_3	4-F $PhCH_2$	H	O
225	Et	H	CH_3	3,4-di-F-$PhOCH_2$	H	O
226	Et	H	CH_3		H	O
227	Et	H	CH_3		H	S
228	Et	H	CH_3		H	O
229	Et	H	CH_3		H	O
230	Et	H	CH_3		H	S
231	Et	H	CH_3		H	O
232	Et	H	CH_3		H	O

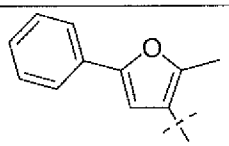
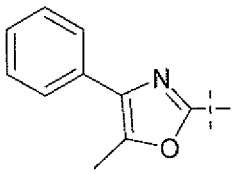
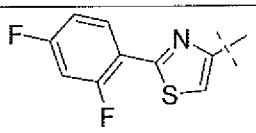
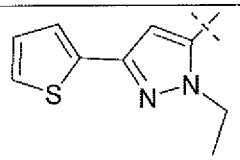
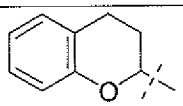
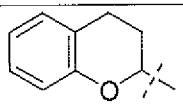
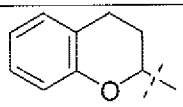
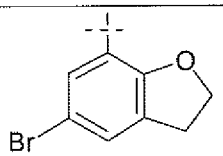
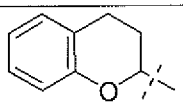
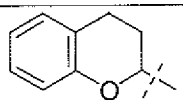
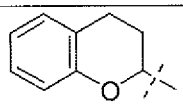
Entry No.	R^1	R^2	R^3	R^4	R^5	X
233	Et	H	CH_3		H	S
234	Et	H	CH_3	2-quinolinyl	H	O
235	Et	H	CH_3		H	O
236	Et	H	CH_3		H	O
237	Et	H	CH_3		H	O
238	Et	H	CH_3		H	O
239	Et	H	CH_3		H	O
240	Et	H	CH_3		H	O
241	Et	H	CH_3		H	O
242	Et	H	CH_3		H	O
243	Et	H	CH_3	(4-CH_3O) $PhCH_2CH_2$	H	O
244	Et	H	CH_3		H	O
245	Et	Cl	CH_3		H	O

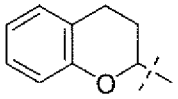
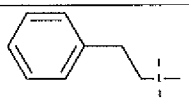
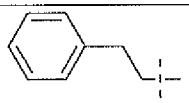
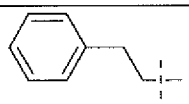
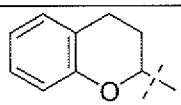
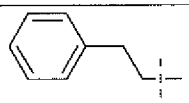
Entry No.	R^1	R^2	R^3	R^4	R^5	X
246	Et	Br	CH_3		H	O
247	Et	H	Et	4-Ph Ph	H	O
248	Et	H	Et	4-Ph Ph	H	S
249	Et	H	Et	4-(4-CH_3Ph)Ph	H	O
250	Et	CH_3	CH_3	2-F Ph	H	O
251	Et	CH_3	CH_3	2-F Ph	CH_3	O
252	Et	CH_3	CH_3	2-F Ph	CH_3	O
253	Et	CH_3	CH_3	2-F Ph	CH_3	S
254	Et	3-Cl Ph	Et	4-Ph Ph	H	O
255	Et	3-Cl Ph	Et	4-Ph Ph	H	S
256	Et	CH_3CO	H	4-F Ph	H	O
257	Et	CH_3CO	isopropyl	4-F Ph	H	O
258	Et	CH_3CO	Ph	4-F Ph	H	O
259	Et	CH_3CO	CH_3	cyclohexyl	CH_3CO	O
260	Et	CH_3CO	CH_3	4-F Ph	CH_3CO	O
261	Et	CH_3CO	Ph	4-F Ph	CH_3CO	O
262	Et	CH_3CO	Ph	4-F Ph	CH_3CO	S
263	Et	Cl	Et	4-(4-CH_3Ph)Ph	H	O
264	Et	Cl	Et	4-(4-CH_3Ph)Ph	Cl	O
265	Et	Cl	Et		Cl	O
266	Et	Br	Ph	2-OCH_3 Ph	Br	O
267	CF_3CH_2	H	H	n-butyl	H	O
268	CF_3CH_2	H	H	Ph	H	O
269	CF_3CH_2	H	H	3-pyridyl	H	O
270	CF_3CH_2	H	CH_3	cyclopentyl	H	O
271	CF_3CH_2	H	CH_3	4-(CF_3O)Ph	H	O
272	CF_3CH_2	H	CH_3	4-(CF_3O)Ph	H	S
273	CF_3CH_2	H	CH_3	4-(CHF_2O)Ph	H	O

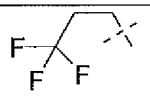
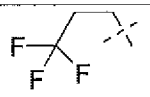
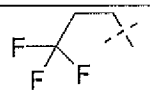
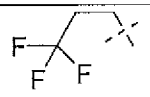
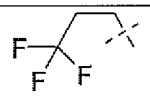
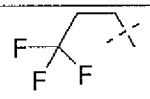
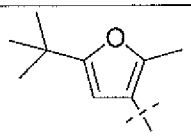
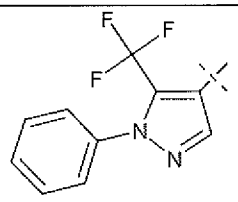
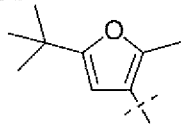
Entry No.	R^1	R^2	R^3	R^4	R^5	X
274	CF_3CH_2	H	CH_3		H	O
275	CF_3CH_2	H	n-butyl	(4-F Ph)OCH_2	H	O
276	CF_3CH_2	H	Ph	Ph	H	O
277	CF_3CH_2	H	Ph	Ph	H	S
278	CF_3CH_2	H	Ph	2-(5-CF_3) furyl	H	O
279	CF_3CH_2	H	Ph	2-thienyl	H	O
280	CF_3CH_2	H	4-F Ph	Ph	H	O
281	CF_3CH_2	CH_3	H	2-F Ph	H	O
282	CF_3CH_2	CH_3	H	2-F Ph	H	S
283	CF_3CH_2	CH_3	H	2-F Ph	CH_3	O
284	CF_3CH_2	CH_3	Et	3-CF_3 Ph	H	O
285	CF_3CH_2	CH_3	n-butyl	(4-F Ph)OCH_2	H	O
286	CF_3CH_2	CH_3	n-butyl	(4-F Ph)OCH_2	H	S
287	CF_3CH_2	CH_3	Ph	2-thienyl	H	O
288	n-propyl	H	H	CH_3	H	O
289	n-propyl	H	H	CH_3	H	S
290	n-propyl	H	H	n-propyl	H	O
291	n-propyl	H	H	cyclobutyl	H	O
292	n-propyl	H	H	cycloheptyl	H	O
293	n-propyl	H	H	3,4-di-CH_3 Ph	H	O
294	n-propyl	H	H	2-thienyl	H	O
295	n-propyl	H	H	2-thienyl	H	S
296	n-propyl	H	H		H	O
297	n-propyl	H	CH_3	CH_3	H	O
298	n-propyl	H	CH_3	CH_3	H	S
299	n-propyl	H	CH_3	3-CF_3 Ph	H	O
300	n-propyl	H	CH_3	2-thienyl	H	O
301	n-propyl	H	CH_3	3-(4-(OCH_3)thienyl)	H	O
302	n-propyl	H	CH_3	2-(5-(CH_3)thienyl)	H	O

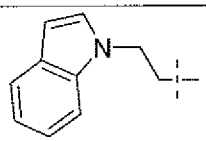
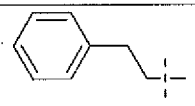
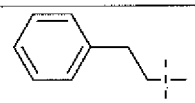
Entry No.	R^1	R^2	R^3	R^4	R^5	X
303	n-propyl	H	CH_3		H	O
304	n-propyl	H	CH_3		H	O
305	n-propyl	CH_3	CH_3	3-Br Ph	H	O
306	n-propyl	CH_3	CH_3	3-Br Ph	H	S
307	n-propyl	CH_3	CH_3	3-Br Ph	CH_3	O
308	n-propyl	CH_3	CH_3		H	O
309	n-propyl	CH_3	CH_3		H	O
310	n-propyl	n-propyl	CH_3	3-Cl Ph	H	O
311	n-propyl	n-propyl	CH_3	3-Cl Ph	H	S
312	n-propyl	CH_3OCH_2	CH_3	3-Cl Ph	H	O
313	n-propyl	CH_3CO	CH_3	3-Cl Ph	H	O
314	n-propyl	PrCO	CH_3	3-Cl Ph	H	O
315	n-propyl	PrCO	CH_3	3-Cl Ph	PrCO	O
316	n-propyl	Cl	CH_3		H	O
317	n-propyl	Cl	CH_3		H	O

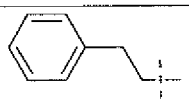
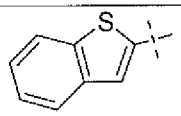
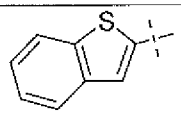
Entry No.	R^1	R^2	R^3	R^4	R^5	X
318	n-propyl	Cl	CH_3		H	O
319	n-propyl	Cl	H	Ph	Cl	O
320	n-propyl	Cl	CH_3	Ph	Cl	O
321	n-propyl	Cl	CH_3	Ph	Cl	S
322	n-propyl	Cl	n-propyl	3-CH_3O Ph	Cl	O
323	n-propyl	Cl	n-propyl	3-pyridyl	Cl	O
324	isopropyl	H	H	Ph	H	O
325	isopropyl	H	H	2-quinolinyl	H	O
326	isopropyl	H	H		H	O
327	isopropyl	H	CH_3	CH_3	H	O
328	isopropyl	H	CH_3	t-butyl	H	O
329	isopropyl	H	CH_3	n-heptyl	H	O
330	isopropyl	H	CH_3	n-heptyl	H	S
331	isopropyl	H	CH_3	2,4-di-F Ph	H	O
332	isopropyl	H	CH_3	2,4-di-F Ph	H	S
333	isopropyl	H	CH_3	2-F-4-CF_3 Ph	H	O
334	isopropyl	H	n-propyl	2-F-4-CF_3 Ph	H	O
335	isopropyl	H	n-propyl	3, 5-di-Cl Ph	H	O
336	isopropyl	H	Ph	2,4-di-CF_3 Ph	H	O
337	isopropyl	H	4-F Ph	2-F-4-CF_3 Ph	H	O
338	isopropyl	CH_3	Et		H	O
339	isopropyl	CH_3	Et		H	O
340	isopropyl	CH_3	Et		H	O

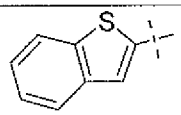
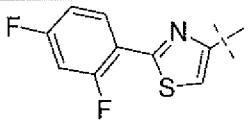
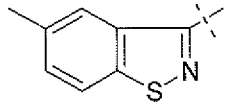
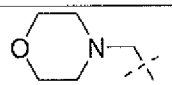
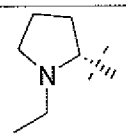
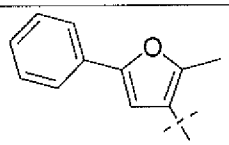
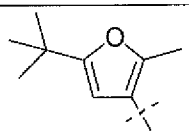
Entry No.	R^1	R^2	R^3	R^4	R^5	X
341	isopropyl	CH_3	Et		H	S
342	isopropyl	CH_3	Et		H	O
343	isopropyl	CH_3	Et		H	O
344	isopropyl	CH_3	Et		H	O
345	isopropyl	Et	CH_3	3-CF_3 Ph	H	O
346	isopropyl	Et	CH_3	3-Et Ph	H	O
347	isopropyl	n-propyl	H	$PhOCH_2$	H	O
348	isopropyl	n-propyl	H	$PhOCH_2$	n-propyl	O
349	isopropyl	n-propyl	H		H	O
350	isopropyl	n-propyl	H		n-propyl	O
351	isopropyl	n-propyl	H		H	S
352	isopropyl	n-propyl	H		H	O
353	isopropyl	n-propyl	n-butyl		H	O
354	isopropyl	n-propyl	Ph		H	O
355	isopropyl	n-butyl	H		H	O

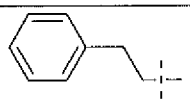
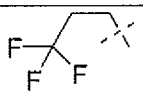
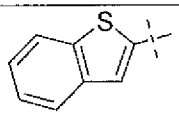
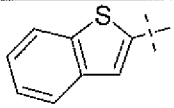
Entry No.	R^1	R^2	R^3	R^4	R^5	X
356	isopropyl	n-hexyl	H		H	O
357	isopropyl	Ph	H	CH_3	H	O
358	isopropyl	Ph	H	n-propyl	H	O
359	isopropyl	Ph	H	n-propyl	H	S
360	isopropyl	Ph	H		H	O
361	isopropyl	Ph	H		H	S
362	isopropyl	Ph	CH_3		H	O
363	isopropyl	Ph	CH_3		H	O
364	isopropyl	Cl	Et	Ph	H	O
365	isopropyl	Cl	Et	Ph	H	S
366	isopropyl	Cl	Et	2-CH_3 Ph	Cl	O
367	isopropyl	Cl	n-propyl	3-F Ph	H	O
368	isopropyl	Cl	isopropyl	3-F Ph	H	O
369	isopropyl	Cl	4-F Ph	3-F Ph	H	O
370	isopropyl	Br	Et	2-CH_3 Ph	Br	O
371	isopropyl	Br	Et	2-CH_3 Ph	Br	S
372	n-butyl	H	H	Cyclohexyl	H	O
373	n-butyl	H	H	Ph	H	O
374	n-butyl	H	H	4-F Ph	H	O
375	n-butyl	H	H	3, 5-di-Cl Ph	H	O
376	n-butyl	H	H	3, 5-di-Cl Ph	H	S
377	n-butyl	H	CH_3	3,4-di-CH_3OPh	H	O
378	n-butyl	H	CH_3	4-F PhOCH_2	H	O
379	n-butyl	H	CH_3		H	O
380	n-butyl	H	CH_3	(4-CH_3O) PhCH_2CH_2	H	O

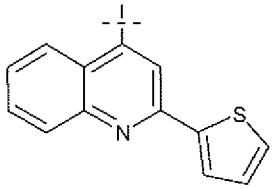
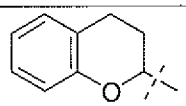
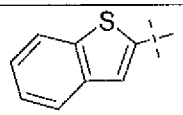
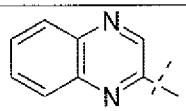
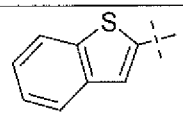
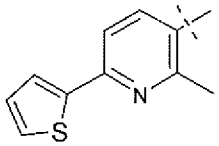
Entry No.	R^1	R^2	R^3	R^4	R^5	X
381	n-butyl	H	CH_3		H	O
382	n-butyl	H	CH_3		H	S
383	n-butyl	H	Et		H	O
384	n-butyl	H	n-propyl	cyclobutyl	H	O
385	n-butyl	H	n-propyl		H	O
386	n-butyl	H	isopropyl		H	O
387	n-butyl	H	Ph	n-propyl	H	O
388	n-butyl	H	Ph		H	O
389	n-butyl	H	Ph	Ph	H	O
390	n-butyl	H	Ph	Ph	H	S
391	n-butyl	CH_3	CH_3	4-CH_3 Ph	H	O
392	n-butyl	CH_3	CH_3	4-CH_3 Ph	CH_3	O
393	n-butyl	CH_3	Et	4-CH_3 Ph	H	O
394	n-butyl	CH_3	Ph	4-CH_3 Ph	H	O
395	n-butyl	CH_3OCH_2	CH_3	2,4-di-CH_3 Ph	H	O
396	n-butyl	Cl	CH_3		H	O
397	n-butyl	Cl	CH_3		H	O
398	n-butyl	Cl	Ph		H	O
399	n-pentyl	H	H	CH_3	H	O
400	n-pentyl	H	H	CH_3	H	S

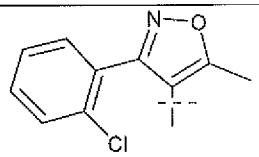
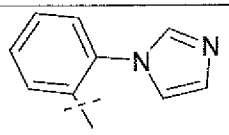
Entry No.	R^1	R^2	R^3	R^4	R^5	X
401	n-pentyl	H	H	Et	H	O
402	n-pentyl	H	H	cyclopentyl	H	O
403	n-pentyl	H	H	cyclopentyl	H	S
404	n-pentyl	H	H	cycloheptyl	H	O
405	n-pentyl	H	H	Ph	H	O
406	n-pentyl	H	H	Ph	H	S
407	n-pentyl	H	H	2-furyl	H	O
408	n-pentyl	H	H	2-(5-CF_3) furyl	H	O
409	n-pentyl	H	H	2-thienyl	H	O
410	n-pentyl	H	H	3,4-di-Cl Ph	H	O
411	n-pentyl	H	CH_3	n-butyl	H	O
412	n-pentyl	H	CH_3	n-butyl	H	S
413	n-pentyl	H	CH_3		H	O
414	n-pentyl	H	CH_3	$PhOCH_2$	H	O
415	n-pentyl	H	CH_3	$PhCH_2OCH_2$	H	O
416	n-pentyl	H	Et	2-F Ph	H	O
417	n-pentyl	H	Et	2-F Ph	H	S
418	n-pentyl	H	4-CH_3 Ph	2-F Ph	H	O
419	n-pentyl	CH_3	Et	4-CH_3 Ph	H	O
420	n-pentyl	Cl	CH_3	n-butyl	H	O
421	n-pentyl	Cl	CH_3	Ph	H	O
422	n-pentyl	Cl	CH_3	Ph	H	S
423	n-pentyl	Cl	CH_3	4-Ph Ph	H	O
424	n-pentyl	Cl	CH_3		H	O
425	n-pentyl	Cl	CH_3		Cl	O
426	n-pentyl	PrCO	CH_3	4-CH_3 Ph	PrCO	O
427	n-pentyl	Ph	CH_3	3-Br Ph	H	O
428	n-pentyl	2-thienyl	CH_3	3-Br Ph	2-thienyl	O
429	n-hexyl	H	H	2-F Ph	H	O

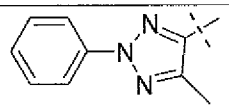
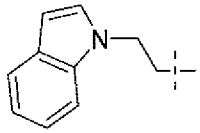
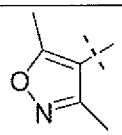
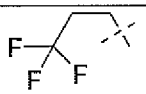
Entry No.	R^1	R^2	R^3	R^4	R^5	X
430	n-hexyl	H	CH_3	cyclopentyl	H	O
431	n-hexyl	H	CH_3	cycloheptyl	H	O
432	n-hexyl	H	CH_3	2-F Ph	H	O
433	n-hexyl	H	CH_3	2-F Ph	H	S
434	n-hexyl	H	Et	2-F Ph	H	O
435	n-hexyl	H	n-propyl	2-F Ph	H	O
436	n-hexyl	H	isopropyl	2-F Ph	H	O
437	n-hexyl	H	Ph	2-F Ph	H	O
438	n-hexyl	CH_3CO	CH_3	2,4-di-CH_3 Ph	H	O
439	n-hexyl	CH_3OCH_2	CH_3	2,4-di-CH_3 Ph	H	O
440	n-hexyl	Ph	Et	Ph	H	O
441	n-hexyl	Ph	Et	Ph	H	S
442	n-hexyl	Ph	Et	4-pyridyl	H	O
443	n-hexyl	Br	Et	Ph	Br	O
444	n-hexyl	Br	Et	2-F Ph	Br	O
445	cyclopropyl	H	H	cyclopentyl	H	O
446	cyclopropyl	H	H	2, 4-di-Cl Ph	H	O
447	cyclopropyl	H	H		H	O
448	cyclopropyl	H	CH_3	3-F Ph	H	O
449	cyclopropyl	H	CH_3	3-F Ph	H	S
450	cyclopropyl	H	CH_3		H	O
451	cyclopropyl	H	Et		H	O
452	cyclopropyl	H	n-propyl	4-CF_3 Ph	H	O
453	cyclopropyl	H	isopropyl	Ph	H	O
454	cyclopropyl	H	isopropyl	3-pyridyl	H	O
455	cyclopropyl	H	n-butyl	4-CF_3 Ph	H	O
456	cyclopropyl	H	n-hexyl	Ph	H	O
457	cyclopropyl	H	n-hexyl	4-CF_3 Ph	H	O
458	cyclopropyl	H	Ph	Ph	H	O
459	cyclobutyl	H	CH_3	4-CH_3 Ph	H	O

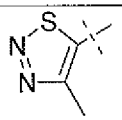
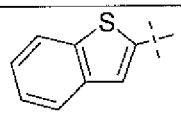
Entry No.	R^1	R^2	R^3	R^4	R^5	X
460	cyclobutyl	H	Et		H	O
461	cyclobutyl	H	Et		H	O
462	cyclobutyl	H	Et		H	O
463	cyclobutyl	H	Et		H	O
464	cyclobutyl	H	Et		H	O
465	cyclobutyl	H	4-F Ph		H	O
466	cyclobutyl	Cl	CH_3	3-Cl Ph	Cl	O
467	cyclobutyl	Cl	CH_3	3-Cl Ph	Cl	S
468	cyclopentyl	H	H	3-CF_3 Ph	H	O
469	cyclopentyl	H	CH_3	2,4-di-CF_3 Ph	H	O
470	cyclopentyl	H	CH_3	2,4-di-CF_3 Ph	H	S
471	cyclopentyl	H	n-butyl		H	O
472	cyclopentyl	H	3-F Ph	4-CH_3 Ph	H	O
473	cyclopentyl	CH_3	CH_3	Ph	H	O
474	cyclopentyl	CH_3	CH_3	3, 5-di-Cl Ph	H	O
475	cyclopentyl	CH_3	CH_3	Ph	H	S
476	cyclopentyl	Et	CH_3	Ph	H	O
477	cyclopentyl	Cl	CH_3	Ph	Cl	O
478	cyclopentyl	Cl	CH_3	Ph	Cl	S
479	cyclohexyl	H	H	3-F Ph	H	O
480	cyclohexyl	H	H	2, 4-di-CH_3 Ph	H	O

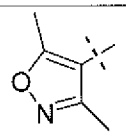
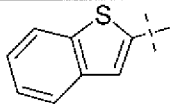
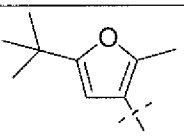
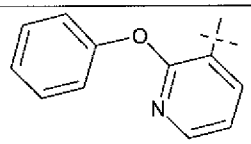
Entry No.	R^1	R^2	R^3	R^4	R^5	X
481	cyclohexyl	H	H		H	O
482	cyclohexyl	H	CH_3	n-propyl	H	O
483	cyclohexyl	H	CH_3	n-propyl	H	S
484	cyclohexyl	H	CH_3		H	O
485	cyclohexyl	H	CH_3	3-Cl Ph	H	O
486	cyclohexyl	H	CH_3	3-Cl Ph	H	S
487	cyclohexyl	H	CH_3		H	O
488	cyclohexyl	H	Et		H	O
489	cyclohexyl	H	n-propyl	4-CF_3 Ph	H	O
490	cyclohexyl	H	n-propyl	3-pyridyl	H	O
491	cyclohexyl	H	isopropyl	Ph	H	O
492	cyclohexyl	H	isopropyl	3-pyridyl	H	O
493	cyclohexyl	H	n-butyl	3-Cl Ph	H	O
494	cyclohexyl	H	n-pentyl	3-Cl Ph	H	O
495	cyclohexyl	H	n-hexyl	4-CF_3 Ph	H	O
496	cyclohexyl	H	4-F Ph	Ph	H	O
497	cyclohexyl	CH_3	CH_3	3-CH_3 Ph	H	O
498	cyclohexyl	CH_3	CH_3	3-CH_3 Ph	H	S
499	cyclohexyl	CH_3	Et	3-pyridyl	CH_3	O
500	cyclohexyl	Et	CH_3	2-F-4-CF_3 Ph	Et	O
501	cyclohexyl	2-thienyl	i-Pr	3-pyridyl	H	O
502	cyclohexyl	Cl	CH_3	2,3-di-CH_3 Ph	H	O
503	cyclohexyl	Cl	CH_3	2,3-di-CH_3 Ph	H	S
504	2-propenyl	H	H	CH_3	H	O
505	2-propenyl	H	H	isopentyl	H	O
506	2-propenyl	H	H	cyclopentyl	H	O
507	2-propenyl	H	H	Ph	H	O
508	2-propenyl	H	H	Ph	H	S

Entry No.	R^1	R^2	R^3	R^4	R^5	X
509	2-propenyl	H	H	2-quinolinyl	H	O
510	2-propenyl	H	H		H	O
511	2-propenyl	H	CH_3		H	O
512	2-propenyl	H	CH_3	2,4-di-F Ph	H	O
513	2-propenyl	H	CH_3	2,4-di-F Ph	H	S
514	2-propenyl	H	CH_3	2-F-4-CF_3 Ph	H	O
515	2-propenyl	H	Et	2-napthyl	H	O
516	2-propenyl	H	Et	2-napthyl	H	S
517	2-propenyl	H	Et		H	O
518	2-propenyl	H	Et		H	O
519	2-propenyl	H	n-propyl	2-F-4-CF_3 Ph	H	O
520	2-propenyl	H	Ph	2,4-di-CF_3 Ph	H	O
521	2-propenyl	H	4-F Ph	2-F-4-CF_3 Ph	H	O
522	2-propenyl	CH_3	Et		H	O
523	2-propenyl	Cl	CH_3	3-CF_3 Ph	Cl	O
524	2-propenyl	Cl	CH_3	3-CF_3 Ph	Cl	S
525	2-propenyl	Br	Et	3-CF_3 Ph	Br	O
526	2-isobutenyl	H	H	3-pyridyl	H	O
527	2-isobutenyl	H	H		H	O
528	2-isobutenyl	H	CH_3	4-(CF_3O)Ph	H	O
529	2-isobutenyl	H	CH_3	4-(CF_3O)Ph	H	O
530	2-isobutenyl	H	CH_3	4-(CF_3O)Ph	H	S

Entry No.	R^1	R^2	R^3	R^4	R^5	X
531	2-isobutenyl	H	n-butyl	4-(CH_3O)Ph	H	O
532	2-isobutenyl	H	n-butyl	(4-F Ph)OCH_2	H	O
533	2-isobutenyl	H	n-butyl	(4-CH_3O) $PhCH_2CH_2$	H	O
534	2-isobutenyl	H	Ph	2-thienyl	H	O
535	2-isobutenyl	H	4-F Ph	Ph	H	O
536	2-isobutenyl	CH_3CO	Ph	cyclohexyl	H	O
537	2-isobutenyl	CH_3CO	Ph	3-F Ph	H	O
538	4-pentenyl	H	CH_3	Ph	H	O
539	4-pentenyl	H	CH_3	Ph	H	S
540	5-hexenyl	H	H	Ph	H	O
541	5-hexenyl	H	CH_3	2-F Ph	H	O
542	5-hexenyl	H	CH_3	2-F Ph	H	S
543	5-hexenyl	H	CH_3		H	O
544	5-hexenyl	H	isopropyl	4-(CF_3O)Ph	H	O
545	5-hexenyl	H	Ph	4-(CF_3O)Ph	H	O
546	5-hexenyl	CH_3CO	CH_3	2-CH_3 Ph	CH_3CO	O
547	CH_3O	H	H	cyclobutyl	H	O
548	CH_3O	H	H	2,4-di-F Ph	H	O
549	CH_3O	H	H	(4-CH_3) $PhCH_2$	H	O
550	CH_3O	H	H	2-quinolinyl	H	O
551	CH_3O	H	CH_3	CH_3	H	O
552	CH_3O	H	CH_3	CH_3	H	S
553	CH_3O	H	CH_3	3-CF_3 Ph	H	O
554	CH_3O	H	CH_3	2-furyl	H	O
555	CH_3O	H	CH_3	2-furyl	H	S
556	CH_3O	H	CH_3	2- thienyl	H	O
557	CH_3O	H	CH_3	3-(4-(OCH_3)thienyl)	H	O
558	CH_3O	H	CH_3		H	O
559	CH_3O	H	n-propyl	4-(CF_3O)Ph	H	O

Entry No.	R^1	R^2	R^3	R^4	R^5	X
560	CH_3O	H	4-F Ph	4-(CF_3O)Ph	H	O
561	CH_3O	Br	isobutyl	3-CF_3 Ph	Br	O
562	CH_3O	H	CH_3		H	O
563	EtO	3-F Ph	Et	cyclopentyl	H	O
564	EtO	H	H	CH_3	H	O
565	EtO	H	H	CH_3	H	S
566	EtO	H	H	3,4-di-CH_3 Ph	H	O
567	EtO	H	CH_3	n-propyl	H	O
568	EtO	H	CH_3	cyclobutyl	H	O
569	EtO	H	CH_3	cycloheptyl	H	O
570	EtO	H	CH_3	cycloheptyl	H	S
571	EtO	H	CH_3		H	O
572	EtO	H	CH_3	3,4-di-F Ph	H	O
573	EtO	H	CH_3		H	O
574	EtO	H	n-butyl	2-thienyl	H	O
575	EtO	H	Ph	2-thienyl	H	O
576	EtO	CH_3	CH_3	4-Br Ph	H	O
577	EtO	Cl	CH_3	n-hexyl	H	O
578	EtO	Cl	CH_3	2-Cl Ph	H	O
579	EtO	Cl	CH_3	2-Cl Ph	H	S
580	EtO	Cl	n-butyl	Ph	Cl	O
581	(i-Pr)O	H	H	CH_3	H	O
582	(i-Pr)O	H	H	CH_3	H	S
583	(i-Pr)O	H	H	3, 5-di-Cl Ph	H	O
584	(i-Pr)O	H	CH_3		H	O
585	(i-Pr)O	H	CH_3	3-Cl-5-F Ph	H	O
586	(i-Pr)O	H	CH_3	3-Cl-5-F Ph	H	S

Entry No.	R^1	R^2	R^3	R^4	R^5	X
587	(i-Pr)O	H	CH_3		H	O
588	(i-Pr)O	H	isopropyl	4-Br Ph	H	O
589	(i-Pr)O	H	4-F Ph	3,4-di-F Ph	H	O
590	(i-Pr)O	CH_3	Et	2-thienyl	H	O
591	(i-Pr)O	CH_3CO	Et	2-thienyl	CH_3CO	O
592	(i-Pr)O	Cl	3-F Ph	2,4-di-F Ph	Cl	O
593	n-BuO	H	H	cyclpentyl	H	O
594	n-BuO	H	H	cyclooctyl	H	O
595	n-BuO	H	H	cyclooctyl	H	S
596	n-BuO	H	Et	cyclooctyl	H	O
597	n-BuO	H	Et	Ph	H	O
598	n-BuO	H	Et	2,4-di-F Ph	H	O
599	n-BuO	H	Et	$PhOCH_2$	H	O
600	n-BuO	H	isopropyl	cyclooctyl	H	O
601	n-BuO	H	n-hexyl	cyclooctyl	H	O
602	n-BuO	CH_3	CH_3	3,5-di-F Ph	H	O
603	n-BuO	PrCO	Et	3,5-di-CH_3 Ph	H	O
604	n-BuO	Br	Ph	cyclooctyl	Br	O
605	(n-pentyl)O	H	CH_3	3-Br Ph	H	O
606	(n-pentyl)O	H	CH_3	3-Br Ph	H	S
607	(n-pentyl)O	H	CH_3	2-napthyl	H	O
608	(n-pentyl)O	H	CH_3		H	O
609	(n-hexyl)O	H	CH_3	cyclopropyl	H	O
610	(n-hexyl)O	H	CH_3	n-pentyl	H	O
611	(n-hexyl)O	H	CH_3	3-Br Ph	H	O
612	(n-hexyl)O	H	CH_3	2-napthyl	H	O
613	(i-hexyl)O	CH_3OCH_2	Et	Ph	H	O
614	(i-hexyl)O	CH_3OCH_2	Et	Ph	H	S
615	CO_2H	H	H	3, 5-di-Cl Ph	H	O
616	CO_2H	H	CH_3	3, 5-di-Cl Ph	H	O
617	CO_2H	H	propyl	Ph	H	O

Entry No.	R^1	R^2	R^3	R^4	R^5	X
618	CO_2H	H	propyl		H	O
619	CO_2H	H	CH_3	Ph	H	O
620	CO_2H	H	CH_3		H	O
621	CO_2H	H	CH_3		H	O
622	CO_2H	CH_3	CH_3	3, 5-di-Cl Ph	H	O
623	CO_2H	CH_3	isopropyl	3-Br Ph	H	O
624	CO_2H	CH_3	isopropyl	3-Br Ph	CH_3	O
625	CO_2H	CH_3	4-F Ph	propyl	H	O
626	CO_2H	Et	H	4-F Ph	H	O
627	CO_2H	Et	H	4-F Ph	Et	O
628	CO_2H	Et	CH_3	4-F Ph	Et	O
629	CO_2H	Et	propyl	Ph	H	O
630	CO_2H	Et	propyl	Ph	H	S
631	CO_2H	Ph	CH_3	2-furyl	H	O
632	CO_2H	Ph	CH_3	2-furyl	H	S
633	CO_2H	3-Br Ph	Ph	2-thienyl	H	O
634	CO_2H	n-PrCO	H	3-Cl Ph	H	O
635	CO_2H	n-PrCO	H	3-pyridyl	H	O
636	CO_2H	n-PrCO	H		H	O
637	CO_2H	n-PrCO	CH_3	3-Cl Ph	H	O
638	CO_2H	n-PrCO	CH_3	3-Cl Ph	n-PrCO	O
639	CO_2H	n-pentylCO	Ph	3-Cl Ph	H	O

The particular process to be utilized in the preparation of the compounds of this invention depends upon the specific compound desired. Such factors as the selection of the specific X moiety, and the specific substituents possible at various locations on the molecule, all play a role in the path to be followed in the

preparation of the specific compounds of this invention. Those factors are readily recognized by one of ordinary skill in the art.

In general, the compounds of this invention may be prepared by standard techniques known in the art and by known processes analogous thereto. For example, the compounds may be prepared according to methods described in U.S. Patent No. 6,828,335, which is incorporated by reference in its entirety.

For example, the compounds of Formula I may generally be synthesized according to Reaction Schemes 1, 2, and 3. Reaction Schemes 1 and 2 demonstrate how to make intermediates that are coupled in Reaction Scheme 3 to provide the compounds of Formula I.

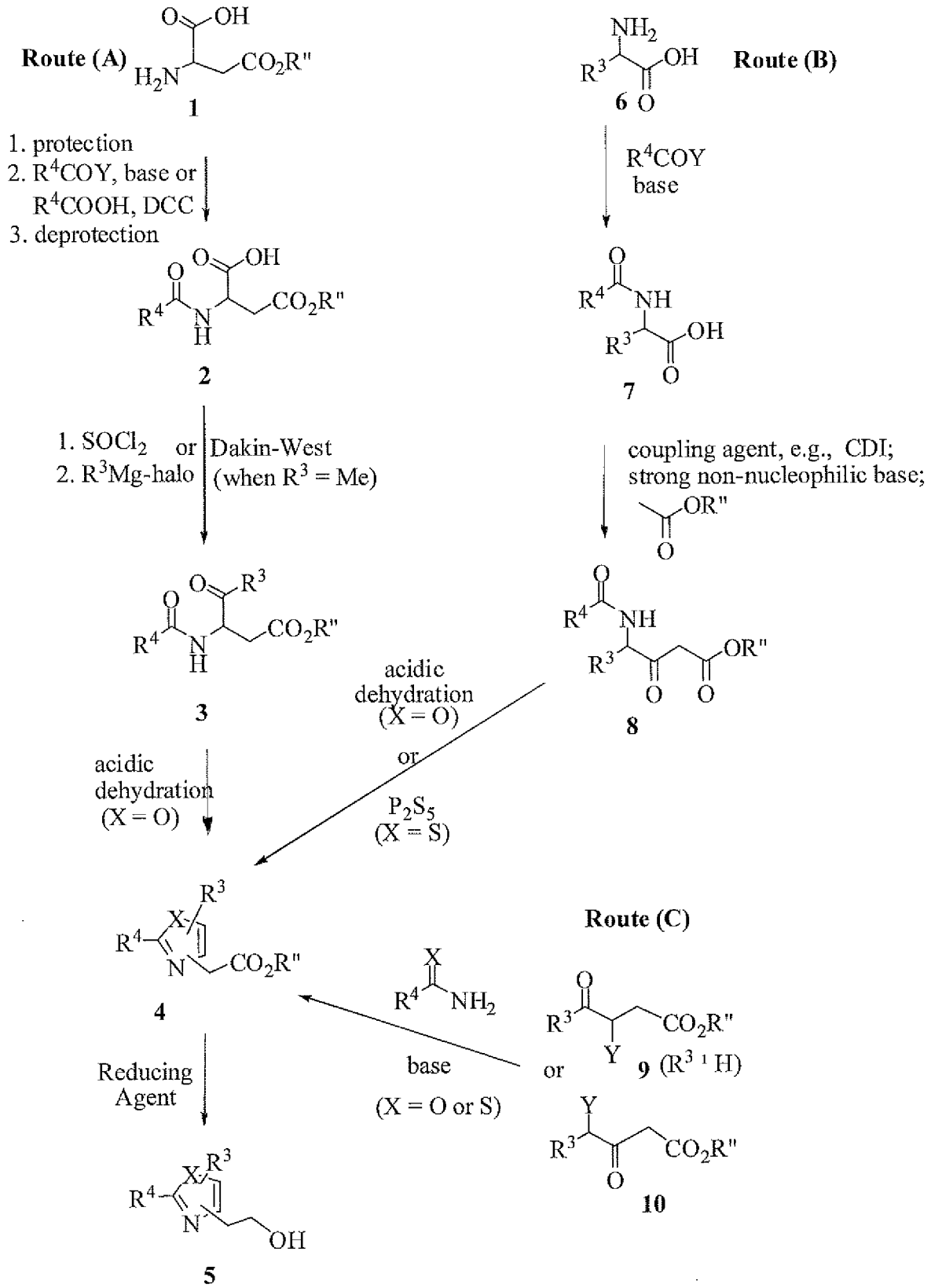
Route (A) of Reaction Scheme 1 provides a method to prepare compounds 4 and 5 where R'' is C_1-C_6 lower alkyl or benzyl, R^3 is not hydrogen, and X is O. The first step shows protection of the acid group of a commercially available aspartate derivative compound 1 by means well known in the art such as, for example, by forming a silyl ester, followed by N-acylation with the appropriate R^4-acid derivative, R^4COY, where Y is a leaving group such as halo. Finally, the compound is deprotected by means well known in the art such as, for example, in the case of a silyl ester, an aqueous work up, to give compound 2. Alternatively, condensation of the protected form of compound 1 with a free carboxylic acid such as R^4COOH in the presence of a dehydrating reagent, such as DCC or EDCI, also provides compound 2. Compound 2 may then be converted to compound 3, where R^3 is as defined for Formula I compounds by several methods. For example, one such method, when R^3 = Me, is the well known Dakin-West reaction which is typically performed using acetic anhydride and pyridine. When R^3 is other than hydrogen, compound 2 may be converted to an acid chloride with a reagent such as thionyl chloride and reacted with a Grignard reagent such as R^3Mg-halo, to provide compound 3. Other methods for the formation of ketones of compound 3 from acids and acid derivatives may also be employed, for example, by using Weinreb amides, which are known to those skilled in the art. Compound 3 is then cyclized under acid dehydrative conditions using, for example, phosphorus oxychloride, or a mixture of sulfuric acid and acetic anhydride, generally with heating, to provide compound 4 where X is O and the R^3 group is attached at the 5 position.

It will be recognized by those skilled in the art that compound 4 and thus, compound 5, may exist in two regioisomeric forms with respect to the attachment point of the R^3, CH_2CO_2R'', and CH_2CH_2OH groups. Using Route (B), one can prepare compound 4 in which the R^3 is attached at the 4-position and carboxymethyl side chain is attached at the 5-position, that is, the groups are reversed from that of Route (A). In Route (B), a commercially available amino acid, compound 6, may be acylated under basic conditions, for example, with aqueous sodium hydroxide, with an appropriate R^4-acid derivative, (e.g., R^4COY), where Y is a leaving group such as chloro, to provide the N-acylated product 7. Compound 7 may be then coupled with an acetic acid ester in the presence of a strong non-nucleophilic base to make the keto ester 8, where R'' is C_1-C_6 alkyl or benzyl. Cyclization of compound 8 using a dehydrating reagent such as $POCl_3$ provides compound 4 where X = O and R^3 is attached at the 4 position. Reaction of compound 8 with a nucleophilic S reagent such as P_2S_5 in solvents such as pyridine or acetonitrile/triethylamine, with heating as necessary, gives compound 4 where X = S and R^3 is attached at the 4 position.

Route (C) of Reaction Scheme 1 depicts the preparation of compound 4 from ketoesters 9 or 10, where Y is a leaving group such as halo and R'' is C_1-C_6 alkyl or benzyl. Either compound 9 or 10 may be chosen as the starting material depending on whether the R^3 group in the desired end product is hydrogen or is attached at the 4 or 5 position. Accordingly, compound 9 or 10 may be reacted with an amide or thioamide where X is either O or S to yield compound 4. Ketoesters 9 or 10 are commercially available, or may be prepared by methods well known in the art such as by bromination of commercially available ketoesters 9 and 10 where Y is hydrogen. Amides ($R^4C(=X)NH_2$) where X is O may be commercially available carboxylic amides, or may be prepared from the corresponding available acids or acid chlorides by well known methods. Thioamides ($R^4C(=X)NH_2$) where X is S may be commercially available thioamides, or may be prepared from the corresponding available amides by known methods such as through the use of Lawesson's reagent. Reaction of ketoester 9 with an amide or thioamide in the presence of a base provides compound 4 as an oxazole or a thiazole, respectively, where R^3 is other than hydrogen and located at the 4-position. Reaction of ketoester 10 with an amide or thioamide in the presence of base provides compound 4 as an oxazole or thiazole, where R^3 is located at the 5-position.

Routes (A), (B), and (C) each provide compound 4 where R^3 and R^4 are each as described for a compound of Formula I and where R" is a lower alkyl or benzyl. Compound 4 may then be reduced to compound 5 using reducing agents such as lithium aluminum hydride, lithium borohydride, or other suitable hydride donors under conditions well known in the art.

Reaction Scheme 1



Reaction Scheme 2 depicts the conversion of commercially available hydroxy ketone 11 to a protected derivative 12, by reaction with R^7-Y in the presence of a base, where R^7 is C_1-C_6 alkyl optionally substituted with phenyl or oxo, C_1-C_6 trialkylsilyl, arylalkylsilyl, or COR^8; and R^8 is C_1-C_6 alkyl or phenyl

optionally substituted with C_1-C_6 alkyl, halo, or nitro; and Y is a leaving group. "C_1-C_6 trialkylsilyl" means three independently selected straight or branched chain alkyl groups having from one to about six carbon atoms, each of which are bound to silicon and includes such groups as trimethylsilyl, *tert*-butyldimethyl silyl, and the like. "Arylalkylsilyl" means at least one phenyl or substituted phenyl group bound to silicon, with an appropriate number of independently selected straight or branched chain alkyl groups having from one to about six carbon atoms, each of which are also bound to silicon, and includes such groups as t-butyldiphenylsilyl methyldiphenylsilyl, dimethylpentafluorophenylsilyl, and the like. "Leaving group" includes halides such as I, Br, and Cl; carboxylates such as acetates, and trifluoroacetates; and aryl and alkyl sulfonates such as methanesulfonates (mesylates) and p-toluene sulfonates (tosylates), and the like.

Compound 12 is substituted with R^2 (as described in Formula I) by means of, for example, reaction with a source of electrophilic halogen, or a Friedel-Crafts reaction in the presence of a Lewis acid and R^2-Y where Y is as described above, to form a substituted ketone 13. Alternatively, a halogenated compound formed in this manner (for example, substituted with bromine or iodine) may be reacted with a range of coupling partners under metal catalysis, using complexes and compounds of elements such as palladium and nickel well known to those skilled in the art, to form further substituted ketone 13. Exemplary catalysts include, but are not limited to, tetrakis(triphenylphosphine)palladium(0), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), and similar nickel(0) and nickel(II) compounds; and examples of coupling partners include boronic acids and esters (the well known Suzuki coupling, carried out in solvents such as toluene in the presence of a base such as potassium carbonate), and organometallics such as Grignard reagents, organozincs (Negishi coupling), and organotin derivatives (Stille coupling), reaction conditions for which are widely known. Furthermore, such halogenated compounds may be coupled with secondary amines such as piperidine using similar palladium or nickel catalysts (Hartwig or Buchwald coupling) to provide further substituted ketones 13.

Further reaction of compound 13 with a halogen source or R^5-Y, (where R^5 is as described in Formula I), under similar conditions gives disubstituted compound 14. A Wittig reaction, or the Horner-Emmons–Wadsworth variation, each well known in the art, may be used to convert 14 to compound 15. For example, reaction of compound 14 with a trialkylphosphonoacetate, where R'' is lower alkyl and R is as described in Formula I, in the presence of a strong base such as sodium hydride, provides compound 15. In like manner, compound 13 may be converted to compound 15 where R^5 is H.

Regardless of the isomeric mixture of isomers of 15 produced in the reaction, either isomer (*E* or *Z*) or a mixture of both, may be converted to the corresponding compound 17 by catalytic hydrogenation or reduction with a hydride reagent capable of 1,4 (conjugate) addition, which are known to those skilled in the art. This route is particularly advantageous for preparing compound 17 where R^1 is hydrogen.

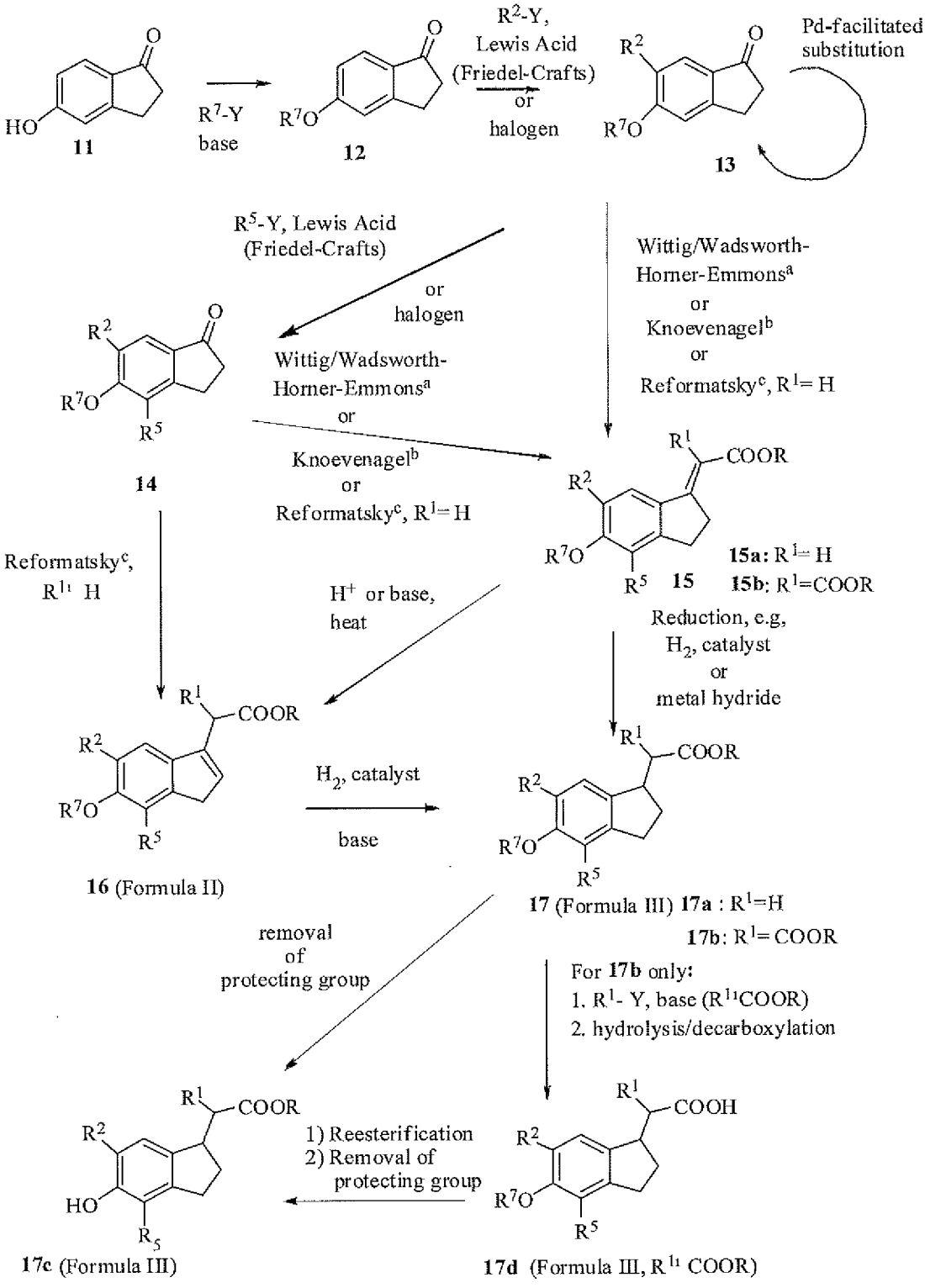
Compound 17 where R^1 is COOR, may be prepared through standard condensation reactions, for example, the well known Knoevenagel reaction. In such cases, the ketone 13 or 14 may be reacted with a suitable active-hydrogen coupling partner, under the influence of acidic reagents such as titanium tetrachloride, or basic reagents such as piperidine, in appropriate solvents. The product 15b (compound 15

where R^1 is COOR), may be reduced to 17b (compound 17 where R^1 is COOR), which may be further alkylated with another R^1 group in the presence of base, hydrolyzed and decarboxylated to give 17d (compound 17 where R^1 is other than COOH and R is H). Reesterification of 17d and removal of the protecting group R^7 would afford 17c. Reesterification may be performed using standard conditions using the well-known Fischer esterification by treatment with an acid and an alcohol or by reaction with diazoalkyl reagents or with an electrophilic species such as, for example, methyl iodide or dimethyl sulfate. Compound 17 where R^1 is alkoxy may be prepared by a similar condensation reaction of ketone 13 or 14 with a silylated enol ester of Formula $R^1CH=C(OR")O$-alkylsilyl, where R^1 is alkoxy, under the influence of acidic reagents such as titanium tetrachloride, and reducing the intermediate compound 15, where R^1 is alkoxy, in the presence of hydrogen and a catalyst as described above.

A general coupling reaction of compound 13 or 14 via the Reformatsky reaction produces compound 16 (Formula II), when R^1 is alkyl, or compound 15a when R^1 is H. The ketone is condensed with an appropriate organozinc reagent prepared in situ from Zn and R^1CHYCO_2R, where Y is halo. The alpha-halo ester compounds of formula R^1CHYCO_2R, are either commercial reagents or are prepared by halogenation of commercially available $R^1CH_2CO_2R$ compounds by methods well known to those skilled in the art.

The conversion of 16 to 17 may be accomplished by standard hydrogenation conditions, for example, Pd/C and hydrogen; and deprotection of compound 17, where R^7 is a protecting group, to compound 17c, where R^7 is hydrogen, may be accomplished by standard means. For example, when the R^7 group is alkyl (e.g., methyl), the compound 17a may be generated by nucleophilic cleavage with a reagent such as an alkali metal thiolate. Alternatively, compound 17 when R^7 is methyl, may be converted to compound 17c by reaction with a Lewis acid such as a bromoborane. When R^7 is benzyl, the compound 17 may be converted to 17c under hydrogenation conditions, typically carried out using a catalyst such as palladium. Other conditions for the removal of the protecting group R^7 from compound 17, where R^7 is other than hydrogen which produces the hydroxy compound 17c, are dependent on the specific protecting group chosen from among those which are well known by those skilled in the art.

Reaction Scheme 2



Notes:

a. $(R"O)_2P(=O)CHR^1COOR$, where R^1 = H, strong base

b. R^1CH_2COOR, where R^1 = COOR, acid or base catalyst

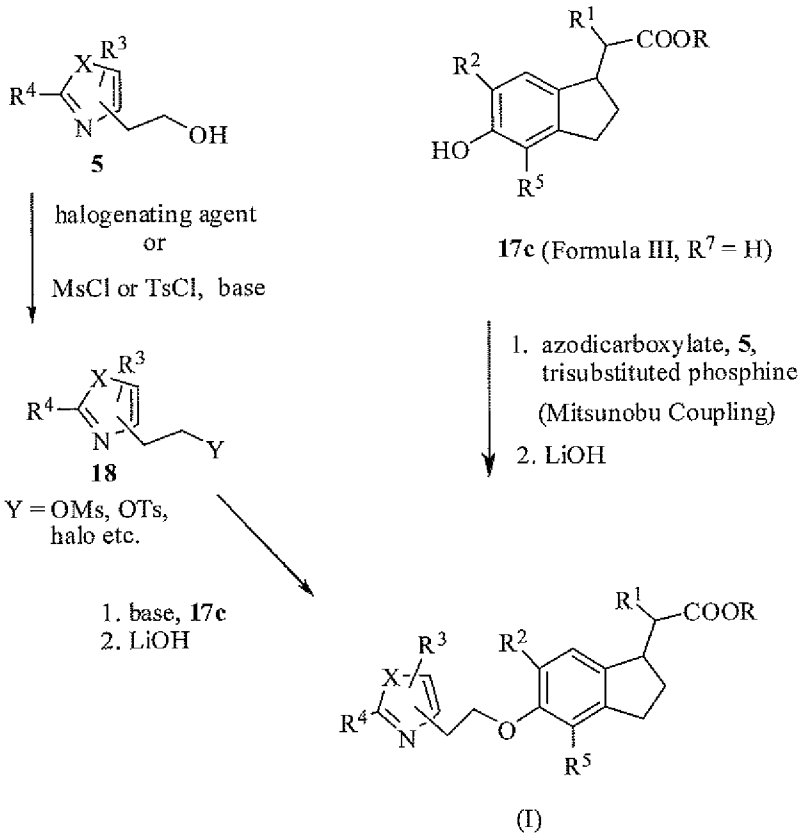
c. $R^1CHBrCO_2R$, Zn

The final step in the preparation of Formula I compounds is shown in Reaction Scheme 3. The alcohol 5 (from Reaction Scheme 1) is coupled with the hydroxy indane 17c (from Reaction Scheme 2) via a

Mitsunobu coupling, facilitated by an azodicarboxylate reagent such as DEAD, and a phosphine such as triphenylphosphine to make the compounds of Formula I. Alternatively, the hydroxy group of alcohol 5 is converted to a leaving group such as halo, tosylate (OTs), or mesylate (OMs), by reaction with a halogenating agent such as thionyl chloride or CCl_4/triphenylphosphine; or by reaction with a Y-halo compound, where Y is tosyl (Ts) or mesyl (Ms), in the presence of a base, providing compound 18. Compound 18 may be reacted with compound 17c in the presence of a base, providing the compounds of Formula I.

Compounds of Formula I in which R is alkyl, may be converted to compounds of Formula I in which R is H by treatment with a base (e.g., KOH) in a suitable solvent (e.g., methanol, THF, or water, or mixtures thereof) with heating. Alternatively, this conversion may be accomplished by reaction with a nucleophile such as iodide or cyanide, in a suitable solvent, such as pyridine. In addition, when R is benzyl, the cleavage to compounds of Formula I in which R is H may be affected through hydrogenolysis by means well known in the art.

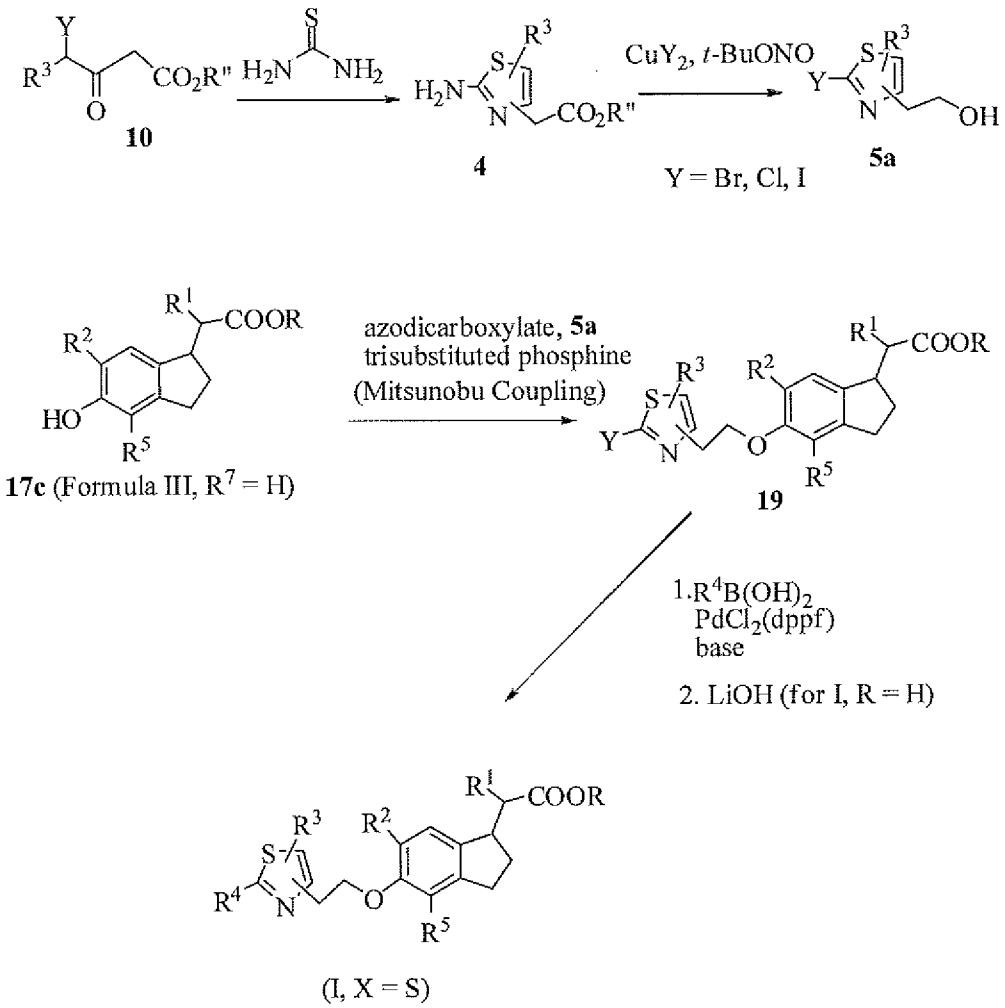
Reaction Scheme 3



(I)

An alternative route to Formula I compounds, useful when X = S and the R^4 group contains one or more R^6 substituents labile to the reaction conditions of Scheme 1 or 2, is shown in Reaction Scheme 3a.

Reaction Scheme 3a



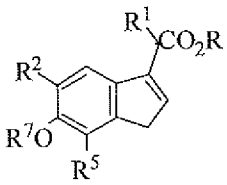
In Scheme 3a, a 2-aminothiazole **4** may be prepared using thiourea (similar to Route C, Reaction Scheme 1) and converted to a 2-halo thiazole **5a** as shown above (Erlenmeyer et al., Helv. Chim. Acta 28:362-363, 1945). Mitsunobu coupling of 5a by a method analogous to Reaction Scheme 3 is then accomplished, and product 19 is further elaborated by a Palladium-catalyzed cross-coupling reaction to introduce the R^4 substituent. Hydrolysis as described in Reaction Scheme 3 gives Formula I compounds where R = H.

The foregoing reaction schemes are further illustrated by the specific Examples described herein.

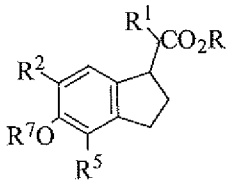
The salts and esters of this invention may be readily prepared by conventional chemical processes as described previously herein.

The invention is further directed to novel Formula II compounds (compound 16) and Formula III (compounds 17, including compounds 17a-d) compounds shown in Reaction Scheme 2. These compounds are useful in the preparation of the compounds of Formula I, and are further described as follows.

The present invention encompasses the compounds of Formula II and Formula III,



(II)

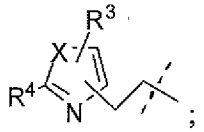


(III)

wherein

R, R^1, R^2, R^3, R^4, R^5, R^6, and X are as defined for Formula I above; and

R^7 is H, C_1-C_6 alkyl optionally substituted with phenyl or oxo, C_1-C_6 trialkylsilyl, arylalkylsilyl, COR^8, $COOR^8$, or



;

R^8 is C_1-C_6 alkyl, or phenyl optionally substituted with C_1-C_6 alkyl, halo, or nitro; and

the salts thereof.

C_1-C_6 trialkylsilyl means three independently selected straight or branched chain alkyl groups having from one to about six carbon atoms, each of which are bound to silicon and includes such groups as trimethylsilyl, *tert*-butyldimethyl silyl, and the like.

Arylalkylsilyl means at least one phenyl or substituted phenyl group bound to silicon, with an appropriate number of independently selected straight or branched chain alkyl groups having from one to about six carbon atoms, each of which are also bound to silicon, and includes such groups as t-butyldiphenylsilyl methyldiphenylsilyl, dimethylpentafluorophenylsilyl, and the like.

The salts of this invention may be readily prepared by conventional chemical processes as described previously herein.

The compounds of Formula II and Formula III may each contain one or more asymmetric centers, depending upon the location and nature of the various substituents desired. Asymmetric carbon atoms may be present in the (*R*) or (*S*) configuration. Preferred isomers are those with the absolute configuration, which produces the compound of Formula II or Formula III that will be useful in producing the compounds of Formula I having a more desirable biological activity. In certain instances, asymmetry may also be present due to restricted rotation about a given bond, for example, the central bond adjoining two aromatic rings of the specified compounds.

Substituents on a ring may also be present in either cis or trans form, and a substituent on a double bond may be present in either *Z* or *E* form.

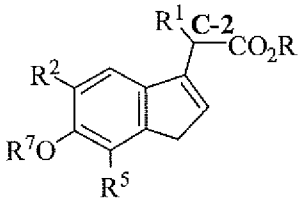
It is intended that all isomers (including enantiomers and diastereomers), either by nature of asymmetric centers or by restricted rotation as described above, as separated, pure or partially purified isomers or racemic mixtures thereof, be included within the scope of the present invention. The purification

of said isomers and the separation of said isomeric mixtures may be accomplished by standard techniques known in the art, as well as by the novel means described herein.

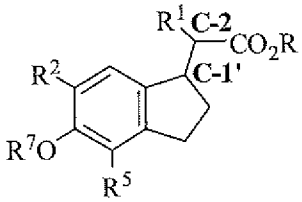
For example, Formula II compounds may contain an asymmetric center (labeled **C-2**) and Formula III compounds may contain two asymmetric centers (labeled **C-2** and **C-1'**) which give rise to enantiomers and diastereomers. Examples of these and other compounds of Formula II and Formula III, which are illustrative of the present invention, are shown in Table 2.

Table 2

Illustrative Examples of Compounds II and III



(II)



(III)

Entry No.	Formula	absolute configuration		R^1	R^2	R^5	R^7
		C-2	C-1'				
1	II	R	---	H	H	H	CH_3
2	III	R	R	H	H	H	CH_3
3	II	R	---	Cl	H	H	t-Bu$(CH_3)_2$Si
4	III	R	S	Cl	H	H	t-Bu$(CH_3)_2$Si
5	II	S	---	H	H	H	CH_3
6	III	S	S	H	H	H	CH_3
7	II	R	---	CH_3	H	H	CH_3
8	III	R	R	CH_3	H	H	CH_3
9	II	S	---	CH_3	H	H	CH_3
10	III	S	R	CH_3	H	H	CH_3
11	II	R	---	CH_3	H	H	$PhCH_2$
12	III	R	S	CH_3	H	H	$PhCH_2$
13	II	S	---	CH_3	H	H	$PhCH_2$
14	III	S	S	CH_3	H	H	$PhCH_2$
15	II	R	---	CH_3	H	H	t-Bu$(CH_3)_2$Si
16	III	R	R	CH_3	H	H	t-Bu$(CH_3)_2$Si
17	II	S	---	CH_3	H	H	t-Bu$(CH_3)_2$Si
18	II	R	---	CH_3	H	H	t-BuCO
19	III	R	S	CH_3	H	H	t-BuCO

Entry No.	Formula	absolute configuration		R^1	R^2	R^5	R^7
		C-2	C-1'				
20	II	S	---	CH_3	H	H	t-BuCO
21	III	S	S	CH_3	H	H	t-BuCO
22	II	R	---	CH_3	CH_3	H	$PhCH_2$
23	II	R	---	CH_3	CH_3CO	H	$PhCH_2$
24	II	S	---	CH_3	2-thienyl	H	t-Bu$(CH_3)_2$Si
25	III	S	R	CH_3	2-thienyl	H	t-Bu$(CH_3)_2$Si
26	II	S	---	CH_3	Ph	H	CH_3
27	II	R	---	CH_3	Cl	H	CH_3
28	II	S	---	CH_3	Cl	H	CH_3
29	III	S	S	CH_3	Cl	H	CH_3
30	II	R	---	CH_3	Br	H	Ph$(CH_3)_2$Si
31	III	R	R	CH_3	Br	H	Ph$(CH_3)_2$Si
32	II	S	---	CH_3	Br	H	Ph$(CH_3)_2$Si
33	III	S	R	CH_3	Br	H	Ph$(CH_3)_2$Si
34	II	S	---	CH_3	Cl	Cl	CH_3
35	II	R	---	Et	H	H	CH_3
36	III	R	R	Et	H	H	CH_3
37	II	S	---	Et	H	H	$PhCH_2$
38	III	S	S	Et	H	H	$PhCH_2$
39	II	R	---	Et	H	H	t-Bu
40	II	S	---	Et	H	H	t-Bu
41	II	S	---	Et	CH_3	H	Ph$(CH_3)_2$Si
42	III	S	S	Et	CH_3	H	Ph$(CH_3)_2$Si
43	II	R	---	Et	n-propyl	H	CH_3
44	II	S	---	Et	Ph	H	CH_3
45	II	S	---	Et	3-Cl Ph	H	t-Bu$(CH_3)_2$Si
46	III	S	R	Et	3-Cl Ph	H	t-Bu$(CH_3)_2$Si
47	II	S	---	Et	4-pyridyl	H	t-Bu$(CH_3)_2$Si
48	III	S	S	Et	4-pyridyl	H	t-Bu$(CH_3)_2$Si
49	II	S	---	Et	CH_3	H	Ph$(CH_3)_2$Si
50	II	R	---	Et	n-propyl	Cl	CH_3
51	II	R	---	Et	Br	Br	t-Bu$(CH_3)_2$Si
52	III	R	R	Et	Br	Br	t-Bu$(CH_3)_2$Si

Entry No.	Formula	absolute configuration		R^1	R^2	R^5	R^7
		C-2	C-1'				
53	II	S	---	CF_3CH_2	H	H	CH_3
54	II	S	---	CF_3CH_2	CH_3	CH_3	$(4\text{-}CH_3O)PhCH_2$
55	III	S	S	CF_3CH_2	CH_3	CH_3	$(4\text{-}CH_3O)PhCH_2$
56	II	S	---	n-propyl	H	H	$(i\text{-}Pr)_3Si$
57	II	R	---	n-propyl	PrCO	PrCO	t-Bu
58	II	R	---	n-propyl	Cl	Cl	$(i\text{-}Pr)_3Si$
59	III	R	R	n-propyl	Cl	Cl	$(i\text{-}Pr)_3Si$
60	II	S	---	isopropyl	CH_3	H	CH_3
61	III	S	R	isopropyl	CH_3	H	CH_3
62	II	R	---	isopropyl	n-hexyl	H	$(4\text{-}CH_3O)PhCH_2$
63	III	R	S	isopropyl	n-hexyl	H	$(4\text{-}CH_3O)PhCH_2$
64	II	S	---	n-butyl	H	H	$PhCH_2$
65	II	S	---	n-butyl	CH_3OCH_2	H	$t\text{-}Bu(CH_3)_2Si$
66	III	S	S	n-butyl	CH_3OCH_2	H	$t\text{-}Bu(CH_3)_2Si$
67	II	R	---	n-butyl	Cl	H	CH_3
68	II	R	---	n-pentyl	Cl	Cl	$(4\text{-}CH_3O)PhCH_2$
69	II	S	---	n-pentyl	2-thienyl	2-thienyl	CH_3
70	III	S	S	n-pentyl	2-thienyl	2-thienyl	CH_3
71	II	R	---	n-hexyl	CH_3CO	H	$t\text{-}Bu(CH_3)_2Si$
72	III	R	S	n-hexyl	CH_3CO	H	$t\text{-}Bu(CH_3)_2Si$
73	II	R	---	n-hexyl	Ph	H	$Ph(CH_3)_2Si$
74	III	R	R	n-hexyl	Ph	H	$Ph(CH_3)_2Si$
75	II	R	---	cyclopropyl	H	H	t-BuCO
76	II	S	---	cyclopropyl	CH_3	H	$(i\text{-}Pr)_3Si$
77	II	S	---	cyclobutyl	H	H	CH_3
78	III	S	S	cyclobutyl	H	H	CH_3
79	II	S	---	cyclobutyl	Cl	Cl	$(4\text{-}CH_3O)PhCH_2$
80	II	R	---	cyclopentyl	CH_3	H	$t\text{-}Bu(CH_3)_2Si$
81	III	R	S	cyclopentyl	CH_3	H	$t\text{-}Bu(CH_3)_2Si$
82	II	S	---	cyclohexyl	Et	Et	CH_3
83	II	R	---	cyclohexyl	2-thienyl	H	CH_3CO
84	II	R	---	cyclohexyl	Cl	H	CH_3
85	III	R	R	cyclohexyl	Cl	H	CH_3

Entry No.	Formula	absolute configuration		R^1	R^2	R^5	R^7
		C-2	C-1'				
86	II	S	---	2-propenyl	H	H	t-Bu$(CH_3)_2$Si
87	II	R	---	2-propenyl	CH_3	H	CH_3CO
88	II	S	---	2-isobutenyl	CH_3CO	H	CH_3
89	II	S	---	5-hexenyl	CH_3CO	CH_3CO	CH_3
90	II	S	---	CH_3O	H	H	$PhCH_2$
91	III	S	R	CH_3O	H	H	$PhCH_2$
92	II	R	---	CH_3O	3-F Ph	H	(4-CH_3O)$PhCH_2$
93	II	S	---	EtO	Cl	Cl	$PhCH_2$
94	III	S	R	EtO	Cl	Cl	$PhCH_2$
95	II	R	---	(i-Pr)O	H	H	$PhCH_2$
96	III	R	R	(i-Pr)O	H	H	$PhCH_2$
97	II	S	---	(n-pentyl)O	CH_3	H	t-Bu$(CH_3)_2$Si
98	III	S	S	(n-pentyl)O	CH_3	H	t-Bu$(CH_3)_2$Si
99	II	S	---	CO_2H	H	H	(4-CH_3O)$PhCH_2$

Another embodiment of the present invention is an improved process for the preparation of compounds having a specific isomeric configuration when that specific configuration is desired for the ultimate desired end product of Formula I. The improved process yields these intermediate compounds in significantly greater diastereomeric excess than was heretofore possible.

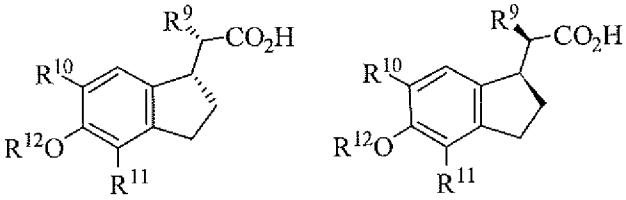
Previously, for example, in the absence of stereocontrol during the hydrogenation step of Reaction Scheme 2, hydrogenation of a Formula II compound, where R^1 is alkyl may produce an unequal mixture of diastereomeric products of Formula III, in which one pair of enantiomers is favored because of the asymmetric nature of the starting material. Separation of such compounds may be accomplished by stepwise separation of the enantiomeric pairs, then by resolution of each enantiomer by crystallization or by chiral HPLC. Prior resolution of the starting material into a single enantiomer produces mixtures with enrichment of a single enantiomer that may likewise be separated.

However, when a compound of a specific relative configuration, namely a syn form (defined below) is desired, the yield is low when R^1 is alkyl, because the conditions of the hydrogenation step described in the art may favor the other (i.e., anti) diastereomers.

The desired isomeric configurations realized from this improved process are in the syn form where, for example, in compounds of Formula Va and Vb (depicted in Reaction Schemes 4 and 5), the R^9 group and the 2' methylene carbon of the cyclopentane ring are both below the plane or are both above the plane. Anti diastereomers are those compounds where, for example, R^9 is above the plane and 2' methylene is below the plane. This is further exemplified in Figures 1 and 2 below, in which solid wedge bonds are used to indicate

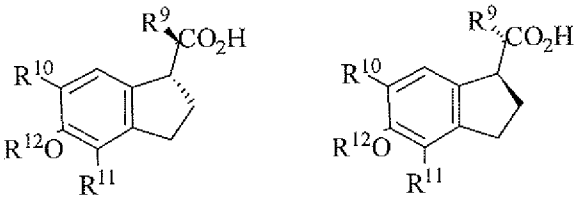
projection of the bond above the plane and dashed wedge bonds are used to indicate projection of the bond below the plane.

Figure 1. syn diastereomers of Formula V



(Va) (Vb)

Figure 2. anti diastereomers of Formula V

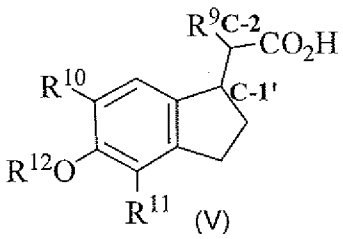


(Ve) (Vf)

The improved process of this invention yields compounds in the syn form (Formulas Va and Vb, as drawn in Figure 1 and Reaction Schemes 4 and 5) in significantly higher diastereomeric excess than was generally possible.

The intermediate compounds used as starting materials for this process (compound IV of Reaction Schemes 4 and 5) are related to the compounds of Formula II (compound 16) in Reaction Scheme 2, and may be prepared by the same or analogous methods. These intermediates may be reacted under certain conditions to yield Formula V compounds that are related to compounds of Formula III (compounds 17 and 17a of Reaction Scheme 2), or to directly yield compounds of Formula I. However, due to the constraints of the improved process, only certain substituents are appropriate for completing this process.

Accordingly, the present invention relates to an improved process for the preparation of a substantially enriched syn form of a compound of Formula V,



(V)

wherein

R^9 is methoxy optionally substituted by fluoro, C_2-C_6 alkoxy, C_1-C_6 alkyl, or C_4-C_8 cycloalkyl each optionally substituted by fluoro, methylenedioxyphenyl or phenyl optionally substituted with R^{13};

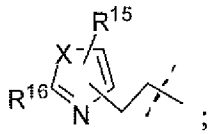
R^{10} is hydrogen, fluoro, methyl optionally substituted with fluoro, oxo, or C_2-C_6 alkyl which may be unsubstituted or substituted with C_1-C_6 alkoxy, oxo, fluoro, or with phenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrrolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, or morpholinyl,

each of which may be unsubstituted or substituted with R^{13}, or

R^{10} is phenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrrolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, or morpholinyl, each of which may be unsubstituted or substituted with R^{13};

R^{11} is halo or C_1-C_6 alkyl optionally substituted with oxo;

R^{12} is hydrogen, methyl optionally substituted with fluoro or oxo, C_2-C_6 alkyl optionally substituted with phenyl, fluoro, or oxo, C_1-C_6 trialkylsilyl, arylalkylsilyl, COR^{14}, $COOR^{14}$, or



;

R^{13} is fluoro, CF_3, C_1-C_6 alkyl optionally substituted with oxo, or C_1-C_6 alkoxy optionally substituted with fluoro;

R^{14} is C_1-C_6 alkyl, or phenyl optionally substituted with C_1-C_6 alkyl or fluoro;

R^{15} is hydrogen, C_1-C_6 alkyl or phenyl substituted with R^{13};

R^{16} is methyl optionally substituted with fluoro, oxo or with phenyl, naphthyl, furyl, thienyl, pyrrolyl, tetrahydrofuryl, pyrrolidinyl, pyrrolinyl, tetrahydrothienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperazinyl, morpholinyl, benzofuryl, dihydrobenzofuryl, benzothienyl, dihydrobenzothienyl, indolyl, indolinyl, indazolyl, benzoxazolyl, benxothiazolyl, benzimidazolyl, benzisoxazolyl, benzisothiazolyl, benzodioxolyl, quinolyl, isoquinolyl, quinazolinyl, quinoxazolinyl, dihydrobenzopyranyl, dihydrobenzothiopyranyl, or 1,4-benzodioxanyl,

each of which may be unsubstituted or substituted with R^{13}, or C_4-C_8 cycloalkyl or C_2-C_6 alkyl, either of which may be unsubstituted or substituted with fluoro, methoxy, C_2-C_6 alkoxy optionally substituted with phenyl or C_1-C_6 alkoxy, oxo or with, phenyl, naphthyl, furyl, thienyl, pyrrolyl, tetrahydrofuryl, pyrrolidinyl, pyrrolinyl, tetrahydrothienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperazinyl, morpholinyl, benzofuryl, dihydrobenzofuryl, benzothienyl, dihydrobenzothienyl, indolyl, indolinyl, indazolyl, benzoxazolyl, benxothiazolyl, benzimidazolyl, benzisoxazolyl, benzisothiazolyl, benzodioxolyl, quinolyl, isoquinolyl, quinazolinyl, quinoxazolinyl, dihydrobenzopyranyl, dihydrobenzothiopyranyl, or 1,4-benzodioxanyl,

each of which may be unsubstituted or substituted with R^{13}, or C_2-C_6 alkyl which may also be substituted with C_4-C_8 cycloalkyl or with phenoxy which may be unsubstituted or substituted with R^6 or with phenyl, naphthyl, furyl, thienyl, pyrrolyl, tetrahydrofuryl, pyrrolidinyl, pyrrolinyl, tetrahydrothienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperazinyl, morpholinyl, benzofuryl, dihydrobenzofuryl, benzothienyl, dihydrobenzothienyl, indolyl, indolinyl, indazolyl, benzoxazolyl, benxothiazolyl, benzimidazolyl, benzisoxazolyl, benzisothiazolyl, benzodioxolyl, quinolyl, isoquinolyl, quinazolinyl, quinoxazolinyl, dihydrobenzopyranyl, dihydrobenzothiopyranyl, or 1,4-benzodioxanyl,
each of which may be unsubstituted or substituted with R^{13},

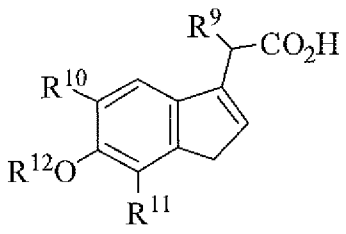
or

R^{16} is phenyl, naphthyl, furyl, thienyl, pyrrolyl, tetrahydrofuryl, pyrrolidinyl, pyrrolinyl, tetrahydrothienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperazinyl, morpholinyl, benzofuryl, dihydrobenzofuryl, benzothienyl, dihydrobenzothienyl, indolyl, indolinyl, indazolyl, benzoxazolyl, benxothiazolyl, benzimidazolyl, benzisoxazolyl, benzisothiazolyl, benzodioxolyl, quinolyl, isoquinolyl, quinazolinyl, quinoxazolinyl, dihydrobenzopyranyl, dihydrobenzothiopyranyl, or 1,4-benzodioxanyl,

each of which may be unsubstituted or substituted with R^{13}, or with phenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrrolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, morpholinyl, pyrimidinyl or phenoxy each of which may be unsubstituted or substituted with R^{13}, and

X is O or S;

comprising hydrogenation of a racemic mixture or isolated optical isomer of a compound of Formula IV,



(IV)

wherein the substituents are as defined above, in the presence of hydrogen source, a catalyst, optionally in the presence of a base.

Substantially enriched syn form means at least about seventy percent (70%) or greater of one or both of the compounds of the configuration of Va or Vb. This is equivalent to at least about 40% de

(diastereomeric excess) of the syn diastereomer. Diastereomeric excess of the syn diastereomer is calculated from the following formula:

$$\%\ \text{de (syn)} = \frac{[\text{syn}] - [\text{anti}]}{[\text{syn}] + [\text{anti}]} \times 100 = \%\ \text{syn diastereomer} - \%\ \text{anti diastereomer}$$

in which

% de (syn) represents the diastereomeric excess of the syn diastereomer

[syn] represents the concentration of the syn diastereomer

[anti] represents the concentration of the anti diastereomer,

and where

% syn + % anti = 100%.

Thus, a 40% de of the syn diastereomer is calculated from a mixture of 70% syn diastereomer and 30% anti diastereomer:

40% de (syn) = 70 % syn diastereomer - 30% anti diastereomer

Catalyst means any of the transition metal catalysts well known in the art to effect hydrogenation reactions (P.A. Chaloner, *Handbook of Co-ordination Catalysis in Organic Chemistry*, Butterworth, 1986), and includes homogeneous hydrogenation catalysts. A homogeneous catalyst is a catalyst which is at least partially soluble in the reaction medium and which effects the reduction of a double bond in the presence of hydrogen. Such catalysts include, for example, $ClRh[P(Ph)_3]_3$ (Wilkinson's catalyst), (1,5-cyclooctadiene)tricyclohexylphosphinepyridinoiridium(I)hexafluorophosphate, (1,5-cyclooctadiene)bis(methyldiphenylphosphine)iridium(I) hexafluorophosphate (Crabtree's catalysts), and the like.

Base means a substance with a pK_b sufficient to form a salt in situ with a carboxylic acid (*see, e.g.*, *Advanced Organic Chemistry*, 3rd Ed., Jerry March, pp 220-222). The base which is used in this reaction may be any inorganic or organic base, and may be soluble in the reaction medium. Such bases include, for example, mono, di, and tri(C_1-C_6 alkyl)amines such as isopropyl amine, diisopropyl amine, triethylamine, and the like; additional primary amines such as, for example, cyclohexane methylamine and ethanolamine; additional secondary amines such as, for example, morpholine and piperidine; and additional tertiary amines such as, for example, 1,8-diazaobicyclo[5.4.0]undec-7-ene and 1,5-diazabicyclo[4.3.0]non-5-ene as well as inorganic bases such as alkali metal and alkaline earth hydroxides, carbonates, bicarbonates, and optically active bases such as quinine, cinchonine or (+)- or (-)-alpha-methylbenzylamine.

Such bases also include, for example, the chiral bases named below that are useful for resolution. Hydrogen source refers to any means of delivering hydrogen to the reaction medium and includes the use of hydrogen gas. Hydrogenation may by performed under a broad range of hydrogen pressures, that is, from about atmospheric pressure to about 1000 psi, preferably from about 20 to about 100 psi. Suitable hydrogenation solvents include, but are not limited to, protic solvents such as ethanol, methanol, water, 2-proponal, *tert*-butanol, methyl cellosolve and the like, and mixtures thereof, or optionally mixtures thereof

with a miscible aprotic solvent such as THF, such that the hydrogenation catalyst, the base, and the starting material are each at least partially soluble.

The resolution of the starting indene acetic acid derivatives of Formula IV or of the indane acetic acid derivatives of Formula V may be accomplished by means well known in the art, for example, by using optically active bases as resolving agents such as, for example, a readily available base such as quinine, cinchonine or (+)- or (-)-alpha-methylbenzylamine. Choice of the base will depend on the solubility properties of the salt formed, so that resolution by differential recrystallization may be readily accomplished. By selecting bases with opposite absolute configuration, separation of the salt of each enantiomer may be accomplished. For example, for the embodiment illustrated in Reaction Scheme 4, the desired enantiomer IVc or IVd may be separated, and the undesired isomer may be recycled by racemization under basic conditions to the starting material of Formula IV.

Suitable crystallization solvents refer to those solvents in which one diastereomeric salt of a mixture is more soluble than the other, enabling them to be separated by recrystallization. Such solvents include, for example, acetonitrile, acetone, *t*-butanol, 2-propanol, ethanol, methanol, and the like, and mixtures thereof.

Aqueous mineral acids include, for example, the commonly used inorganic acids such as hydrochloric or sulfuric acid, and the like.

The process may be carried out starting with a racemate of Formula IV (see Reaction Scheme 4), or with a Formula V compound with the configuration at one asymmetric carbon which corresponds to that of the desired end product (see Reaction Scheme 5). Starting with the generally pure configuration is preferred, although either process will yield the desired configuration of the end product (V) in substantially enriched syn form.

One embodiment of this process is shown in the example of Reaction Scheme 4 and includes the steps of

(1) formation of diastereomeric salts of IVc and IVd by treatment of IV with a suitable basic resolving agent,

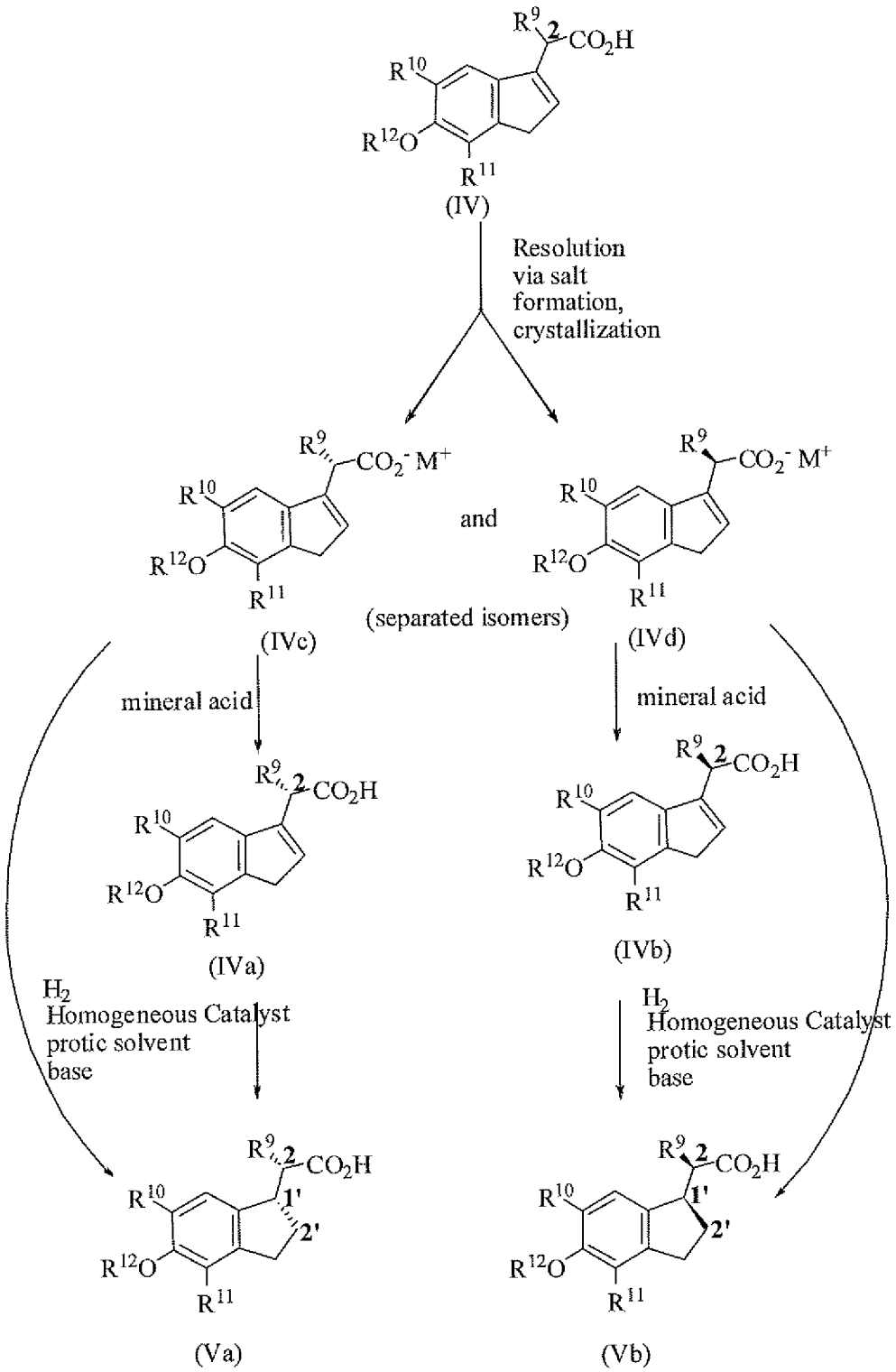
(2) separation of the diastereomeric salts IVc and IVd by crystallization in a suitable crystallization solvent,

(3) optionally liberating the individual antipodes IVa and IVb from the separated salts by treatment with aqueous mineral acid, and

(4) reduction of either the separated diastereomeric salts IVc and Vd or the individual antipodes IVa and IVb by hydrogenation in the presence of a homogeneous hydrogenation catalyst, a suitable solvent and a base, wherein M+ is a cation selected from an alkali metal, alkaline earth metal, ammonium, and mono-, di-, tri- or quaternary alkylammonium or aralkylammonium, and R^9-R^{12} are as defined above.

The enantiomeric purity of the product Va and Vb will correspond to the enantiomeric purity of the isomer IVa or IVb used, respectively, but will not include any substantial amount of the other (anti) diastereoisomer.

Reaction Scheme 4



A second embodiment of this process is shown in Reaction Scheme 5 and includes the steps of

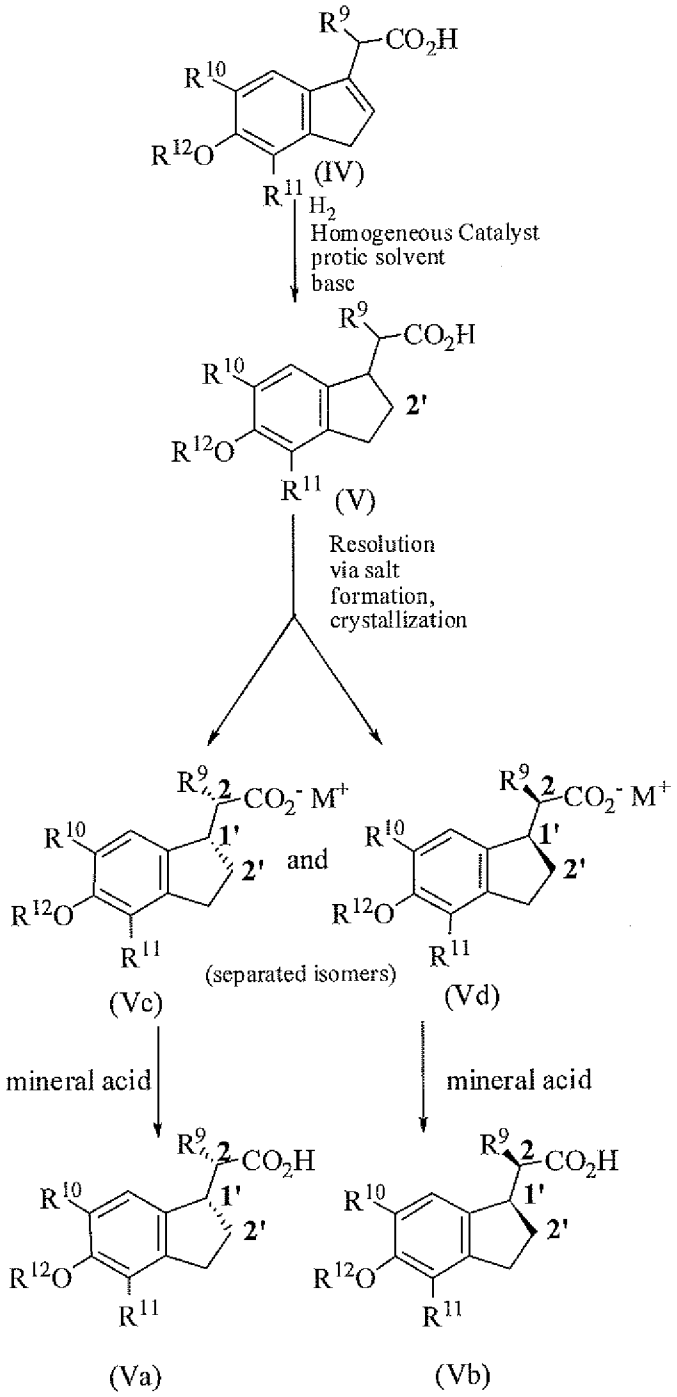
(1) reduction of the indene carboxylic acid of Formula IV by hydrogenation in the presence of a homogeneous hydrogenation catalyst, a suitable solvent, and a base,

(2) formation of diastereomeric salts of Vc and Vd by treatment of V with a suitable basic resolving agent,

(3) separation of the diastereomeric salts Vc and Vd by crystallization in a suitable crystallization solvent, and

(4) liberating the individual antipodes Va and Vb from the separated salts by treatment with aqueous mineral acid.

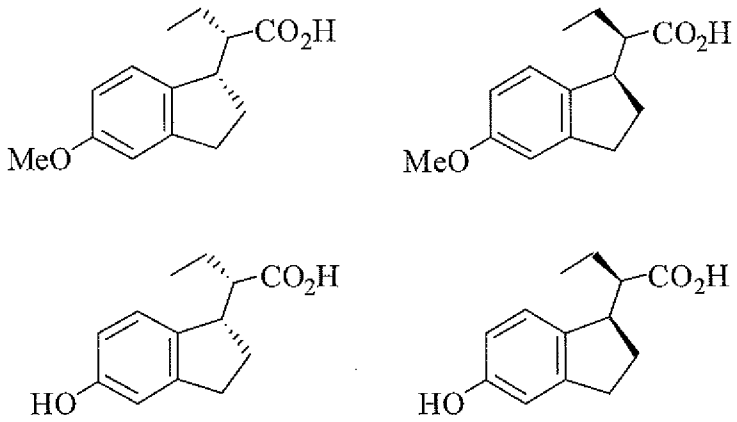
Reaction Scheme 5



The resolution of the racemate of either Formula IV or Formula V compounds may be accomplished by means well known in the art, such as by chiral HPLC, crystallization of chiral salt derivatives, chiral ester derivatives, and the like.

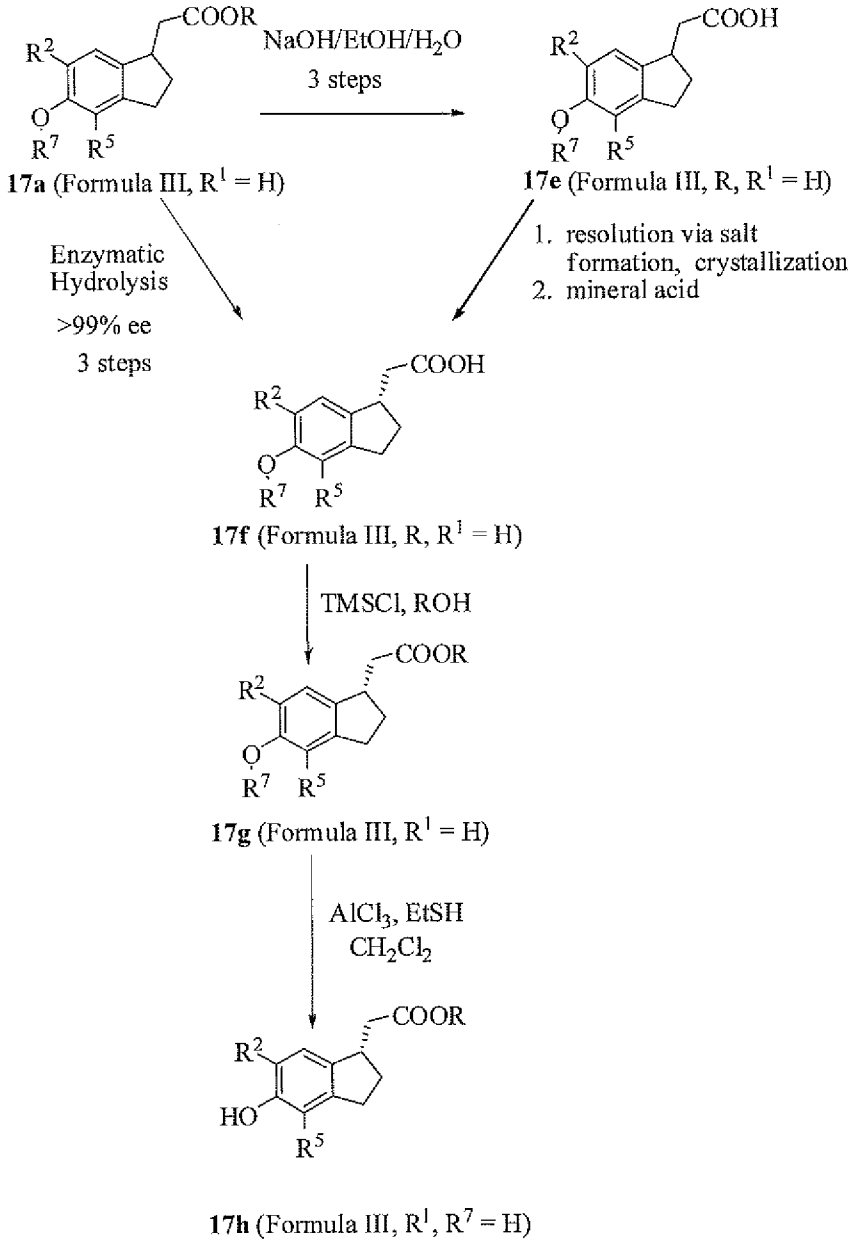
The determination of absolute chirality of IVa, IVb, IVc, IVd, Va, and Vb may be accomplished by several means known to those skilled in the art. X-ray crystallographic methods may provide such information under certain well-established conditions. For example, the presence in the crystallographic unit cell of another component of known chirality, such as a chiral resolving agent or auxiliary in the form of a salt, complex, or covalently attached group, may allow such determination. Another method known in the art, heavy atom scattering technique may be utilized when the compound to be assayed contains an atom of sufficient mass (for example, bromine or iodine). Other methods involving optical properties and the use of plane-polarized light may also be employed. For example, one skilled in the art would recognize that such techniques as circular dichroism may be applicable to a given structure or structural class.

Specific examples of the intermediates that may be made with the process of the present invention are shown below by way of example, and not by way of limitation, and may be used for the preparation of compounds of Formula I of the same absolute configuration.



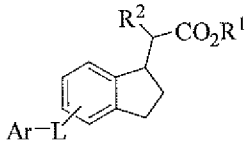
Compounds of Formula III in which R^1 = H may also be prepared in an optically active fashion by the methods summarized in Reaction Scheme 6. Resolution of racemic ester **17a** (Formula III, where R^1 is H) may be accomplished by selective enzymatic hydrolysis using Amano Lipase PS to yield **17f**. Alternatively, **17e**, which may be prepared by hydrolysis of **17a**, may be resolved by crystallization of the diastereomeric salts formed with an optically active amine, for example, *(S)*-(-)-α-methyl-benzylamine, followed by regeneration of the carboxylic acid by treating the salt with mineral acid. Further conversion of **17f** to the intermediates **17g** and **17h** may be accomplished by means analogous to that described for the preparation of **17c** in Reaction Scheme 2: reesterification and removal of the R^7 protecting group.

Reaction Scheme 6



(2) Formula VI

The present invention also encompasses compounds of Formula VI:

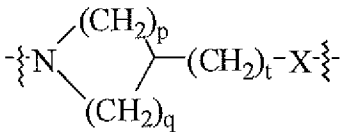


Formula VI

wherein

R^1 and R^2 are independently H, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

L is a linker and selected from the group consisting of $-(CH_2)_m-X-$, $-Y-(CH_2)_n-X-$, and



,

wherein

X is selected from the group O, S, S(=O), and $S(=O)_2$,

Y is selected from the group O, NR^5, S, S(=O), and $S(=O)_2$,

m is 1, 2, or 3,

n is 2, 3, or 4,

t is 0 or 1,

p is 0,1, 2, or 3,

q is 1, 2, 3, or 4,

wherein the sum of p and q is 1, 2, 3, or 4;

Ar is phenyl or a 6-membered heteroaryl containing up to three N atoms,

wherein said Ar is optionally substituted at any available position by 1 to 5 independently selected R^3 groups, and

optionally fused to a 5- or 6-membered saturated carbocyclic ring,

a 5- or 6-membered unsaturated carbocyclic ring, or

a 5- or 6-membered heterocyclic ring containing up to 3 additional heteroatoms selected from N, O, and S,

wherein said fused ring may be optionally substituted at any available position by 1 to 4 independently selected R^4 groups;

R^3 is selected from the group consisting of hydroxy, SH, halo, CN, NO_2, C(=O)OH, $C(=O)\text{-}OC_1\text{-}C_6$ alkyl, $C(=O)\text{-}OC_3\text{-}C_6$ cycloalkyl, NR^6R^7, $C(=O)NR^6R^7$, $C(=S)NR^6R^7$, $C_1\text{-}C_6$ alkyl optionally substituted with halo, OH, NR^6R^7, or $C_1\text{-}C_6$ alkoxy, $C_1\text{-}C_6$ haloalkyl, $C_1\text{-}C_6$ alkoxy, $C_1\text{-}C_6$ thioalkyl, $C_2\text{-}C_6$ alkenyl, $C_1\text{-}C_6$ haloalkoxy, $C_3\text{-}C_8$ cycloalkyl, $C_3\text{-}C_8$ cycloalkoxy, phenoxy optionally substituted on the phenyl ring with halo, $C_1\text{-}C_6$ alkyl, or $C_1\text{-}C_6$ alkoxy, and

a mono or bicyclic ring radical selected from the group consisting of

c) phenyl optionally fused to

a 5- or 6-membered saturated or partially unsaturated carbocylic ring, or

a 5- or 6-membered saturated or partially unsaturated heterocyclic ring containing from 1-3 heteroatoms selected from N, O, and S,

d) a 5- or 6-membered heterocyclic ring radical containing up to 4 heteroatoms selected from N, O, or S, optionally fused to

a 5- or 6-membered saturated or partially unsaturated carbocylic ring, or

a 5- or 6-membered saturated or partially unsaturated heterocyclic ring containing from 1-3 heteroatoms selected from N, O, and S,

said mono or bicyclic ring radical being optionally substituted with up to 5 groups independently selected from the group consisting of halo, hydroxy, oxo, CN, C_1-C_6 alkyl optionally substituted with halo, OH, NR^6R^7, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 thioalkyl, C_1-C_6 haloalkoxy, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_6 acyl, C(=O)OH, $CH_2C(=O)OH$, NR^6R^7, $C(=O)NR^6R^7$, $C(=O)OC_1$-C_6 alkyl, and $C(=O)OC_3$-C_6 cycloalkyl;

R^4 is selected from the group consisting of oxo, hydroxy, halo, CN, NR^6R^7, C_1-C_6 alkyl optionally substituted with OH, NR^6R^7, or C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 thioalkyl, C_1-C_6 haloalkoxy, C_3-C_8 cycloalkyl, and C_3-C_8 cycloalkoxy;

R^5 is selected from the group consisting of H, C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl, C_1-C_6 acyl, benzyl optionally substituted with halo, C_1-C_6 alkoxy, $(C_1$-$C_6)$alkyl, CN, NH_2, $N[(C_1$-$C_3)alkyl]_2$, NO_2, or CF_3, C_3-C_6 cycloalkyl, and $C(=O)OC_1$-C_6 alkyl;

R^6 and R^7 are independently selected from the group consisting of H, C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl, C_1-C_6 acyl, benzyl optionally substituted with halo, C_1-C_6 alkoxy, $(C_1$-$C_6)$alkyl, CN, NH_2, $N[(C_1$-$C_3)alkyl]_2$, NO_2, or CF_3, C_3-C_6 cycloalkyl, and phenyl optionally substituted with halo, C_1-C_6 alkoxy, $(C_1$-$C_6)$alkyl, CN, $N[(C_1$-$C_3)alkyl]_2$, NO_2, or CF_3, or

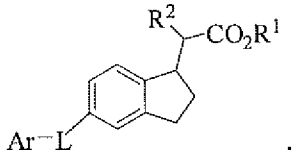
R^6 and R^7 may be taken together with the nitrogen atom to which they are attached to form a 5- or 6-membered heterocyclic ring optionally interrupted by NR^5 or O;

or a pharmaceutically acceptable salt, ester prodrug, stereoisomer, diastereomer, enantiomer, racemate or a combination thereof.

In some embodiments, the compound of Formula VI is a meglumine, potassium or sodium salt thereof.

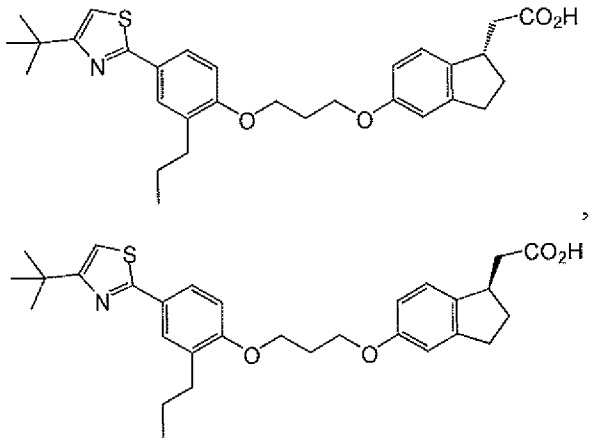
In one embodiment, the compound of Formula VI, R^1 and R^2 are H, L is $-O-(CH_2)_n-O$, wherein n is 2, 3 or 4, Ar is a phenyl substituted with one to five R^3, wherein each occurrence of R^3 is independently C_1-C_6 alkyl or a 5- or 6-member heterocyclic ring containing up to 4 hetero atoms selected from the group consisting of N, O and S, wherein the heterocyclic ring is substituted with C_1-C_6 alkyl.

In some embodiments, the compound of Formula VI has a structure of



.

In another embodiment, the compound of Formula VI has the structure:

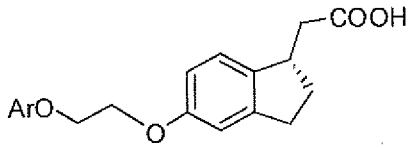


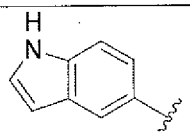
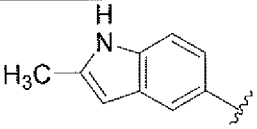
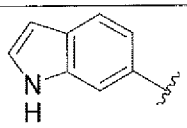
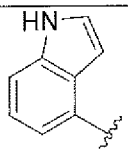
or a pharmaceutically acceptable salt thereof. In one embodiment, the pharmaceutically acceptable salt is a meglumine, potassium or sodium salt of the above two structures.

In some embodiments, the linker L is substituted at either the 4- or 5- carbon atom (as shown above) of the indane ring in Formula (VI), replacing H atom.

Exemplary compounds of Formula (VI), wherein R^2 and R^1 are H, L is -Y-$(CH_2)_n$-X-, X and Y are O, and n is 2, are shown in Table 3a below.

Table 3a



Ex. No	**Ar**	**HPLC RT (min)**	LC-MS $[M+H]^+$
1		2.87	352.2
2		3.00	366.2
3		2.95	352.1
4		2.91	352.1

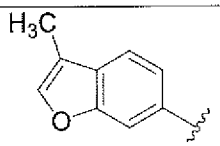
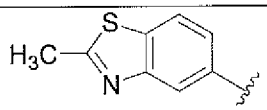
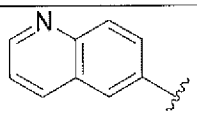
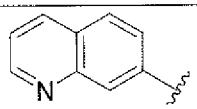
Ex. No	Ar	HPLC RT (min)	LC-MS $[M+H]^+$
5		3.33	367.5
6		2.93	384.3
7		2.02	364.2
8		2.08	364.3

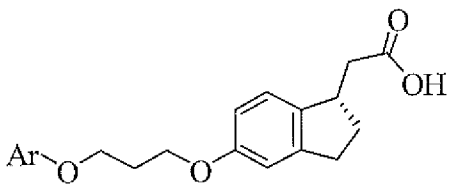
Table 3b

IUPAC Names for Compounds in Table 3a

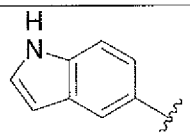
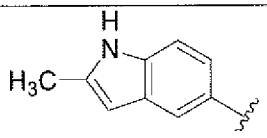
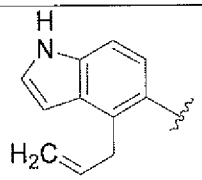
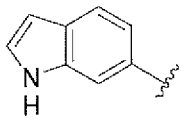
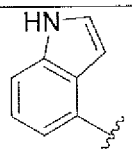
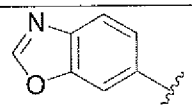
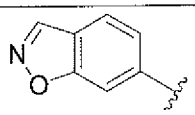
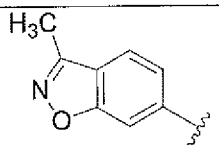
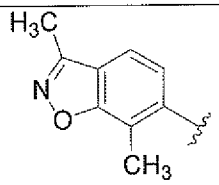
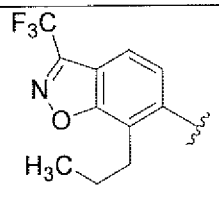
Ex. No.	IUPAC Name
37	2-[(1S)-5-(2-indol-5-yloxyethoxy)indanyl]acetic acid
38	2-{(1S)-5-[2-(2-methylindol-5-yloxy)ethoxy]indanyl}acetic acid
39	2-[(1S)-5-(2-indol-6-yloxyethoxy)indanyl]acetic acid
40	2-[(1S)-5-(2-indol-4-yloxyethoxy)indanyl]acetic acid
41	2-{(1S)-5-[2-(3-methylbenzo[3,4-b]furan-6-yloxy)ethoxy]indanyl}acetic acid
42	2-{(1S)-5-[2-(2-methylbenzothiazol-5-yloxy)ethoxy]indanyl}acetic acid
43	2-[(1S)-5-(2-(6-quinolyloxy)ethoxy)indanyl]acetic acid
44	2-[(1S)-5-(2-(7-quinolyloxy)ethoxy)indanyl]acetic acid

Examples of compounds of Formula (Imm) [Formula (II), where R^2 and R^1 are H, L is -Y-$(CH_2)_n$-X-, X and Y are O, and n is 3], as shown in Table 4a below.

Table 4a



Formula Imm

Ex. No	Ar	HPLC RT (min)	LC-MS $[M+H]^+$ or NMR data
9		3.13	366.0
10		3.16	380.2
11		3.40	406.0
12		3.19	366.2
13		3.07	366.2
14		3.28	368.1
15		2.76	367.9
16		2.97	382.1
17		3.84	396.3
18		4.18	477.9

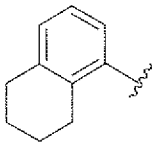
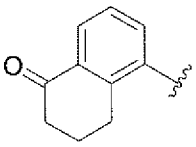
Ex. No	Ar	HPLC RT (min)	LC-MS $[M+H]^+$ or NMR data
19		4.51	[a]
20		3.90	[b]

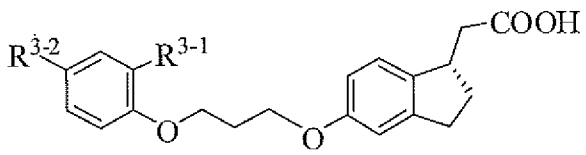
Table 4b

IUPAC Names for Compounds in Table 4a

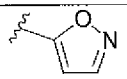
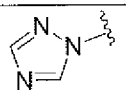
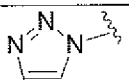
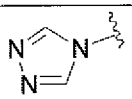
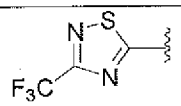
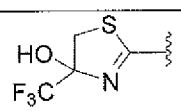
Ex. No.	IUPAC Name
74	2-[(1S)-5-(3-indol-5-yloxypropoxy)indanyl]acetic acid
75	2-{(1S)-5-[3-(2-methylindol-5-yloxy)propoxy]indanyl}acetic acid
76	2-{(1S)-5-[3-(4-prop-2-enylindol-5-yloxy)propoxy]indanyl}acetic acid
77	2-[(1S)-5-(3-indol-6-yloxypropoxy)indanyl]acetic acid
78	2-[(1S)-5-(3-indol-4-yloxypropoxy)indanyl]acetic acid
79	2-[(1S)-5-(3-benzoxazol-6-yloxypropoxy)indanyl]acetic acid
80	2-[(1S)-5-(3-benzo[d]isoxazol-6-yloxypropoxy)indanyl]acetic acid
81	2-{(1S)-5-[3-(3-methylbenzo[d]isoxazol-6-yloxy)propoxy]indanyl}acetic acid
82	2-{(1S)-5-[3-(3,7-dimethylbenzo[d]isoxazol-6-yloxy)propoxy]indanyl}acetic acid
83	((1S)-5-{3-[(3-methyl-7-propyl-1,2-benzisoxazol-6-yl)oxy]propoxy}-2,3-dihydro-1H-inden-1-yl)acetic acid
84	2-[(1S)-5-(3-(5,6,7,8-tetrahydronaphthyloxy)propoxy)indanyl]acetic acid
85	2-{(1S)-5-[3-(5-oxo(6,7,8-trihydronaphthyloxy))propoxy]indanyl}acetic acid

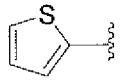
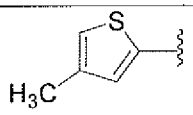
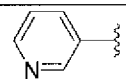
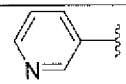
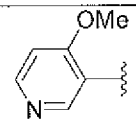
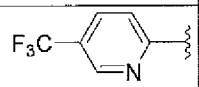
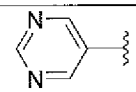
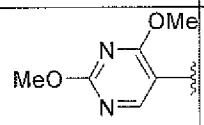
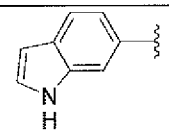
The compounds of Formula (Inn) [Formula (II) where R^1 and R^2 are H, L is $-Y-(CH_2)_n-X-$, X and Y are O, Ar is substituted phenyl, and n is 3] are shown below in Table 5a.

Table 5a



Formula Inn

Ex. No	R^{3-1}	R^{3-2}	HPLC RT (min)	LC-MS $[M+H]^+$
21	H	H	3.98	*
22	n-Pr	H	4.44	*
23	H	Me	4.14	*
24	Me	Me	3.80	*
25	OMe	Me	3.25	371.0
26	OEt	Me	3.42	385.0
27	Br	Me	4.29	*
28	-NH(C(=O)C_3H_7)	Me	3.35	426.2
29		Me	3.22	407.8
30	H	Et	4.26	355.0
31	OMe	Et	3.47	384.9
32	H	i-Pr	3.96	369.2
33	H	CF_3	3.67	*
34	H	CN	3.31	351.8
35	n-Pr	CN	3.70	393.8
36	OMe	CN	3.06	381.8
37	H	OMe	3.18	*
38	n-Pr	OPh	4.21	*
39	H	OEt	3.47	370.9
40	H	OCF_3	3.75	*
41	OMe	Br	5.00	435.2 (M-H)-
42	H		3.51	394.3
43	-NH(C(=O)CH_3		3.25	451.2
44	Cl		2.73	428.1
45	Me		4.16	492.9 **
46	H		3.34	496.0

Ex. No	R^{3-1}	R^{3-2}	HPLC RT (min)	LC-MS $[M+H]^+$
47	H		3.55	393.0
48	OMe		5.49	437.2 (M-H)-
49	OMe		3.75	453.0
50	H	Ph	3.84	*
51	OMe	4-MeO-Ph-	5.44	461.3 (M-H)-
52	OMe	4-F-Ph-	5.57	449.3 (M-H)-
53	H		2.42	404.2
54	OMe		2.36	434.0
55	H		3.47	434.2
56	H		3.82	472.1
57	H		2.95	405.1
58	H		3.31	465.2
59	H		3.57	492.0

* These compounds did not ionize under ESI-MS conditions.

Table 5b

IUPAC Names for Compounds in Table 5a

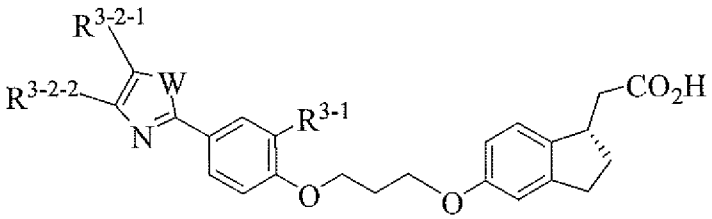
Ex. No.	IUPAC Name
104	2-[(1S)-5-(3-phenoxypropoxy)indanyl]acetic acid

105	2-{(1S)-5-[3-(2-propylphenoxy)propoxy]indanyl}acetic acid
106	2-{(1S)-5-[3-(4-methylphenoxy)propoxy]indanyl}acetic acid
107	2-{(1S)-5-[3-(2,4-dimethylphenoxy)propoxy]indanyl}acetic acid
108	2-{(1S)-5-[3-(2-methoxy-4-methylphenoxy)propoxy]indanyl}acetic acid
109	2-{(1S)-5-[3-(2-ethoxy-4-methylphenoxy)propoxy]indanyl}acetic acid
110	2-{(1S)-5-[3-(2-bromo-4-methylphenoxy)propoxy]indanyl}acetic acid
111	2-((1S)-5-{3-[2-(butanoylamino)-4-methylphenoxy]propoxy}indanyl)acetic acid
112	2-{(1S)-5-[3-(2-isoxazol-5-yl-4-methylphenoxy)propoxy]indanyl}acetic acid
113	2-{(1S)-5-[3-(4-ethylphenoxy)propoxy]indanyl}acetic acid
114	2-{(1S)-5-[3-(4-ethyl-2-methoxyphenoxy)propoxy]indanyl}acetic acid
115	2-((1S)-5-{3-[4-(methylethyl)phenoxy]propoxy}indanyl)acetic acid
116	2-((1S)-5-{3-[4-(trifluoromethyl)phenoxy]propoxy}indanyl)acetic acid
117	2-{(1S)-5-[3-(4-cyanophenoxy)propoxy]indanyl}acetic acid
118	2-{(1S)-5-[3-(4-cyano-2-propylphenoxy)propoxy]indanyl}acetic acid
119	2-{(1S)-5-[3-(4-cyano-2-methoxyphenoxy)propoxy]indanyl}acetic acid
120	2-{(1S)-5-[3-(4-methoxyphenoxy)propoxy]indanyl}acetic acid
121	2-{(1S)-5-[3-(4-phenoxy-2-propylphenoxy)propoxy]indanyl}acetic acid
122	2-{(1S)-5-[3-(4-ethoxyphenoxy)propoxy]indanyl}acetic acid
123	2-((1S)-5-{3-[4-(trifluoromethoxy)phenoxy]propoxy}indanyl)acetic acid
124	2-{(1S)-5-[3-(4-bromo-2-methoxyphenoxy)propoxy]indanyl}acetic acid
125	2-{(1S)-5-[3-(4-(1,2,4-triazolyl)phenoxy)propoxy]indanyl}acetic acid
126	2-((1S)-5-{3-[2-(acetylamino)-4-(1,2,3-triazolyl)phenoxy]propoxy}indanyl) acetic acid
127	2-{(1S)-5-[3-(2-chloro-4-(1,2,4-triazol-4-yl)phenoxy)propoxy]indanyl}acetic acid
128	2-[(1S)-5-(3-{2-methyl-4-[3-(trifluoromethyl)(1,2,4-thiadiazol-5-yl)]phenoxy}propoxy)indanyl]acetic acid
129	2-[(1S)-5-(3-{4-[4-hydroxy-4-(trifluoromethyl)(1,3-thiazolin-2-yl)]phenoxy} propoxy)indanyl]acetic acid
130	2-{(1S)-5-[3-(4-(3-furyl)phenoxy)propoxy]indanyl}acetic acid
131	2-{(1S)-5-[3-(2-methoxy-4-(2-thienyl)phenoxy)propoxy]indanyl}acetic acid
132	2-((1S)-5-{3-[2-methoxy-4-(4-methyl(2-thienyl))phenoxy]propoxy}indanyl) acetic acid
133	{(1S)-5-[3-(1,1'-biphenyl-4-yloxy)propoxy]-2,3-dihydro-1H-inden-1-yl}acetic acid
134	2-((1S)-5-{3-[2-methoxy-4-(4-methoxyphenyl)phenoxy]propoxy}indanyl) acetic acid

135	2-((1S)-5-{3-[4-(4-fluorophenyl)-2-methoxyphenoxy]propoxy}indanyl)acetic acid
136	2-{(1S)-5-[3-(4-(3-pyridyl)phenoxy)propoxy]indanyl}acetic acid
137	2-{(1S)-5-[3-(2-methoxy-4-(3-pyridyl)phenoxy)propoxy]indanyl}acetic acid
138	2-((1S)-5-{3-[4-(4-methoxy-(3-pyridyl))phenoxy]propoxy}indanyl)acetic acid
139	2-[(1S)-5-(3-{4-[5-(trifluoromethyl)(2-pyridyl)]phenoxy}propoxy)indanyl]acetic acid
140	2-{(1S)-5-[3-(4-pyrimidin-5-ylphenoxy)propoxy]indanyl}acetic acid
141	2-((1S)-5-{3-[4-(2,4-dimethoxypyrimidin-5-yl)phenoxy]propoxy}indanyl)acetic acid
142	2-{(1S)-5-[3-(4-indol-6-ylphenoxy)propoxy]indanyl}acetic acid

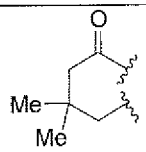
Compounds of Formula (Ioo)) [Formula (II), where R^1 and R^2 are H, L is -Y-$(CH_2)_n$-X-, X and Y are O, Ar is heterocyclyl substituted phenyl, and n is 3], and (Ipp) [Formula (II), where R^1 and R^2 are H, L is -Y-$(CH_2)_n$-X-, X and Y are O, Ar is substituted phenyl, and n is 3], are listed in Table 6a and Table 7a, respectively, below.

Table 6a



Formula Ioo

Ex. No	W	R^{3-2-1}	R^{3-2-2}	R^{3-1}	HPLC RT (min)	LC-MS $[M+H]^+$
60	S	H	H	n-Pr	3.73	452.1
61	S	H	Me	OMe	3.18	454.3
62	S	H	Et	H	3.56	438.3
63	O	H	Et	H	3.35	422.3
64	O	H	Et	n-Pr	3.82	464.2
65	S	H	t-Bu	n-Pr	4.64	508.3
66	O	H	t-Bu	H	3.77	450.2
67	O	H	t-Bu	OMe	3.69	480.2
68	S	H	CF_3	n-Pr	4.18	520.2
69	S	H	CF_3	OMe	3.63	507.9
70	O	H	CF_3	H	3.58	462.1

Ex. No	W	R^{3-2-1}	R^{3-2-2}	R^{3-1}	HPLC RT (min)	LC-MS $[M+H]^+$
71	O	H	CF_3	OMe	3.52	491.9
72	S	Me	Me	H	3.31	438.3
73	S	Me	Me	OMe	3.19	468.3
74	S			H	3.66	450.3
75	S			n-Pr	4.12	492.4
76	S			OMe	3.51	480.4
77	S			H	3.61	464.4
78	S			OMe	3.49	494.2
79	O			H	3.47	448.4
80	O			n-Pr	3.98	490.3
81	S			OEt	3.59	508.3
82	S			O-Pr	3.80	522.3
83	O			OMe	3.39	478.2
84	S			OMe	3.41	496.4
85	S			n-Pr	4.12	548.3
86	S	H	OMe	H	3.41	440.2
87	S	H	OMe	OMe	3.27	470.3
88	S	H	OEt	H	3.60	454.2
89	S	H	OEt	n-Pr	4.10	496.2
90	S	H	OEt	OMe	3.46	484.3
91	S	H	O-i-Pr	n-Pr	4.24	510.1
92	S	Me	OEt	n-Pr	4.51	510.2
93	S	Me	OEt	OMe	3.90	498.2
94	S	Et	OEt	OMe	4.07	512.1
95	S	$C(=O)CH_3$	Me	H	3.50	466.1
96	S	$C(=O)CH_3$	Me	n-Pr	3.99	508.2
97	S	$C(=O)CH_3$	Me	OMe	3.30	496.3
98	O	$C(=O)CH_3$	Me	H	3.21	450.3
99	O	$C(=O)CH_3$	Me	n-Pr	3.74	492.1
100	O	$C(=O)CH_3$	Me	OMe	3.08	480.3

Ex. No	W	R^{3-2-1}	R^{3-2-2}	R^{3-1}	HPLC RT (min)	LC-MS $[M+H]^+$
101	S	C(=O)NMe$_2$	Me	n-Pr	3.42	537.5
102	S	C(=O)NMe$_2$	Me	OMe	2.96	525.1
103	S	C(=O)OH	Me	H	3.13	468.3
104	S	C(=O)OH	Me	n-Pr	3.58	510.2

Table 6b

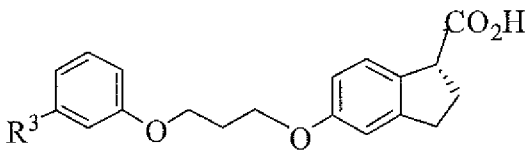
IUPAC Names for Compounds in Table 6a

Ex. No.	IUPAC Name
175	2-{(1S)-5-[3-(2-propyl-4-(1,3-thiazol-2-yl)phenoxy)propoxy]indanyl}acetic acid
176	2-((1S)-5-{3-[2-methoxy-4-(4-methyl(1,3-thiazol-2-yl))phenoxy]propoxy}indanyl) acetic acid
177	2-((1S)-5-{3-[4-(4-ethyl(1,3-thiazol-2-yl))phenoxy]propoxy}indanyl)acetic acid
178	2-((1S)-5-{3-[4-(4-ethyl(1,3-oxazol-2-yl))phenoxy]propoxy}indanyl)acetic acid
179	2-((1S)-5-{3-[4-(4-ethyl(1,3-oxazol-2-yl))-2-propylphenoxy]propoxy}indanyl) acetic acid
180	2-[(1S)-5-(3-{4-[4-(tert-butyl)(1,3-thiazol-2-yl)]-2-propylphenoxy}propoxy) indanyl]acetic acid
181	2-[(1S)-5-(3-{4-[4-(tert-butyl)(1,3-oxazol-2-yl)]phenoxy}propoxy)indanyl]acetic acid
182	2-[(1S)-5-(3-{4-[4-(tert-butyl)(1,3-oxazol-2-yl)]-2-methoxyphenoxy}propoxy) indanyl]acetic acid
183	2-[(1S)-5-(3-{2-propyl-4-[4-(trifluoromethyl)(1,3-thiazol-2-yl)]phenoxy}propoxy) indanyl]acetic acid
184	2-[(1S)-5-(3-{2-methoxy-4-[4-(trifluoromethyl)(1,3-thiazol-2-yl)]phenoxy} propoxy)indanyl]acetic acid
185	2-[(1S)-5-(3-{4-[4-(trifluoromethyl)(1,3-oxazol-2-yl)]phenoxy}propoxy) indanyl]acetic acid
186	2-[(1S)-5-(3-{2-methoxy-4-[4-(trifluoromethyl)(1,3-oxazol-2-yl)]phenoxy} propoxy)indanyl]acetic acid
187	2-((1S)-5-{3-[4-(4,5-dimethyl(1,3-thiazol-2-yl))phenoxy]propoxy}indanyl)acetic acid
188	2-((1S)-5-{3-[4-(4,5-dimethyl(1,3-thiazol-2-yl))-2-methoxyphenoxy]propoxy} indanyl)acetic acid
189	2-{(1S)-5-[3-(4-(4,5,6-trihydrocyclopenta[1,2-d]1,3-thiazol-2-yl)phenoxy)

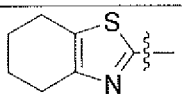
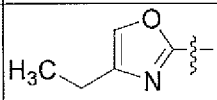
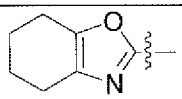
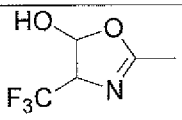
Ex. No.	IUPAC Name
	propoxy]indanyl}acetic acid
190	2-{(1S)-5-[3-(2-propyl-4-(4,5,6-trihydrocyclopenta[1,2-d]1,3-thiazol-2-yl) phenoxy)propoxy]indanyl}acetic acid
191	2-{(1S)-5-[3-(2-methoxy-4-(4,5,6-trihydrocyclopenta[1,2-d]1,3-thiazol-2-yl)phenoxy)propoxy]indanyl}acetic acid
192	2-{(1S)-5-[3-(4-(4,5,6,7-tetrahydrobenzothiazol-2-yl)phenoxy)propoxy] indanyl}acetic acid
193	2-{(1S)-5-[3-(2-methoxy-4-(4,5,6,7-tetrahydrobenzothiazol-2-yl)phenoxy) propoxy]indanyl}acetic acid
194	2-{(1S)-5-[3-(4-(4,5,6,7-tetrahydrobenzoxazol-2-yl)phenoxy)propoxy]indanyl} acetic acid
195	2-{(1S)-5-[3-(2-propyl-4-(4,5,6,7-tetrahydrobenzoxazol-2-yl)phenoxy)propoxy] indanyl}acetic acid
196	2-{(1S)-5-[3-(2-ethoxy-4-(4,5,6,7-tetrahydrobenzothiazol-2-yl)phenoxy) propoxy]indanyl}acetic acid
197	2-{(1S)-5-[3-(2-propoxy-4-(4,5,6,7-tetrahydrobenzothiazol-2-yl)phenoxy) propoxy]indanyl}acetic acid
198	2-{(1S)-5-[3-(2-methoxy-4-(4,5,6,7-tetrahydrobenzoxazol-2-yl)phenoxy) propoxy]indanyl}acetic acid
199	2-{(1S)-5-[3-(2-methoxy-4-(5,6,7-trihydro-2H-pyrano[2,3-d]1,3-thiazol-2-yl)phenoxy)propoxy]indanyl}acetic acid
200	2-((1S)-5-{3-[4-(5,5-dimethyl-7-oxo(4,5,6-trihydrobenzothiazol-2-yl))-2-propylphenoxy]propoxy}indanyl)acetic acid
201	2-((1S)-5-{3-[4-(4-methoxy(1,3-thiazol-2-yl))phenoxy]propoxy}indanyl)acetic acid
202	2-((1S)-5-{3-[2-methoxy-4-(4-methoxy(1,3-thiazol-2-yl))phenoxy]propoxy} indanyl)acetic acid
203	2-((1S)-5-{3-[4-(4-ethoxy(1,3-thiazol-2-yl))phenoxy]propoxy}indanyl)acetic acid
204	2-((1S)-5-{3-[4-(4-ethoxy(1,3-thiazol-2-yl))-2-propylphenoxy]propoxy}indanyl) acetic acid
205	2-((1S)-5-{3-[4-(4-ethoxy(1,3-thiazol-2-yl))-2-methoxyphenoxy]propoxy} indanyl)acetic acid
206	2-[(1S)-5-(3-{4-[4-(methylethoxy)(1,3-thiazol-2-yl)]-2-propylphenoxy}propoxy) indanyl]acetic acid
207	2-((1S)-5-{3-[4-(4-ethoxy-5-methyl(1,3-thiazol-2-yl))-2-propylphenoxy]propoxy} indanyl)acetic acid

Ex. No.	IUPAC Name
208	2-((1S)-5-{3-[4-(4-ethoxy-5-methyl(1,3-thiazol-2-yl))-2-methoxyphenoxy] propoxy}indanyl)acetic acid
209	2-((1S)-5-{3-[4-(4-ethoxy-5-ethyl(1,3-thiazol-2-yl))-2-methoxyphenoxy] propoxy}indanyl)acetic acid
210	2-((1S)-5-{3-[4-(5-acetyl-4-methyl(1,3-thiazol-2-yl))phenoxy]propoxy}indanyl) acetic acid
211	2-((1S)-5-{3-[4-(5-acetyl-4-methyl(1,3-thiazol-2-yl))-2-propylphenoxy]propoxy} indanyl)acetic acid
212	2-((1S)-5-{3-[4-(5-acetyl-4-methyl(1,3-thiazol-2-yl))-2-methoxyphenoxy] propoxy}indanyl)acetic acid
213	2-((1S)-5-{3-[4-(5-acetyl-4-methyl(1,3-oxazol-2-yl))phenoxy]propoxy}indanyl) acetic acid
214	2-((1S)-5-{3-[4-(5-acetyl-4-methyl(1,3-oxazol-2-yl))-2-propylphenoxy]propoxy} indanyl)acetic acid
215	2-((1S)-5-{3-[4-(5-acetyl-4-methyl(1,3-oxazol-2-yl))-2-methoxyphenoxy] propoxy}indanyl)acetic acid
216	2-[(1S)-5-(3-{4-[5-(N,N-dimethylcarbamoyl)-4-methyl(1,3-thiazol-2-yl)]-2-propylphenoxy}propoxy)indanyl]acetic acid
217	2-[(1S)-5-(3-{4-[5-(N,N-dimethylcarbamoyl)-4-methyl(1,3-thiazol-2-yl)]-2-methoxyphenoxy}propoxy)indanyl]acetic acid
218	2-(4-{3-[(1S)-1-(carboxymethyl)indan-5-yloxy]propoxy}phenyl)-4-methyl-1,3-thiazole-5-carboxylic acid
219	2-(4-{3-[(1S)-1-(carboxymethyl)indan-5-yloxy]propoxy}-3-propylphenyl)-4-methyl-1,3-thiazole-5-carboxylic acid

Table 7a



Formula Ipp

Ex. No	R^3	HPLC RT (min)	LC-MS $[M+H]^+$
105		3.79	464.3
106		3.49	422.2
107		3.64	448.3
108		3.17	480.1 *

* Elimination of water did not occur in this case.

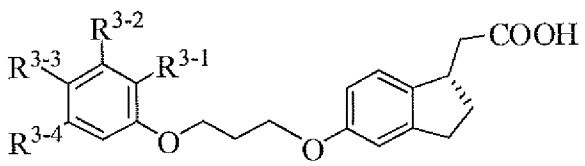
Table 7b

IUPAC Names for Compounds in Table 7a

Ex. No.	IUPAC Name
220	((1S)-5-{3-[3-(4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)phenoxy] propoxy}-2,3-dihydro-1H-inden-1-yl)acetic acid
221	((1S)-5-{3-[3-(4-ethyl-1,3-oxazol-2-yl)phenoxy]propoxy}-2,3-dihydro-1H-inden-1-yl)acetic acid
222	((1S)-5-{3-[3-(4,5,6,7-tetrahydro-1,3-benzoxazol-2-yl)phenoxy] propoxy}-2,3-dihydro-1H-inden-1-yl)acetic acid
223	((1S)-5-{3-[3-(4-hydroxy-5-methyl-4,5-dihydro-1,3-oxazol-2-yl)phenoxy]propoxy}-2,3-dihydro-1H-inden-1-yl)acetic acid

Compounds of Formula (Iqq) [Formula (II), where R^1 and R^2 are H, L is $-Y-(CH_2)_n-X-$, X and Y are O, Ar is substituted phenyl, and n is 3], appear in Table 8a below.

Table 8a



Formula Iqq

Ex. No	R^{3-1}	R^{3-2}	R^{3-3}	R^{3-4}	HPLC RT (min)	LC-MS $[M+H]^+$
109	H	Me	H	H	3.45	*
110	H	OMe	H	H	3.23	357.0
111	H	Ph	H	H	3.53	*
112	OMe	OMe	H	H	3.07	387.0
113	H	H	$NHC(=O)CH_3$	OMe	3.38	414.1
114	H	H	Me	Me	4.24	*
115	H	OMe	OMe	OMe	3.73	417.2

*These compounds did not ionize under ESI-MS conditions.

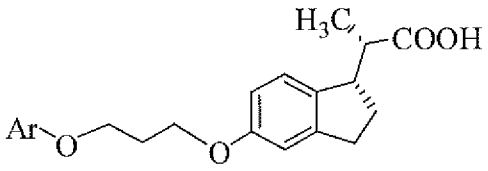
Table 8b

IUPAC Names for Compounds in Table 8a

Ex. No.	IUPAC Name
227	2-{(1S)-5-[3-(3-methylphenoxy)propoxy]indanyl}acetic acid
228	2-{(1S)-5-[3-(3-methoxyphenoxy)propoxy]indanyl}acetic acid
229	2-{(1S)-5-[3-(3-phenylphenoxy)propoxy]indanyl}acetic acid
230	2-{(1S)-5-[3-(2,3-dimethoxyphenoxy)propoxy]indanyl}acetic acid
231	2-((1S)-5-{3-[4-(acetylamino)-3-methoxyphenoxy]propoxy} indanyl)acetic acid
232	2-{(1S)-5-[3-(3,4-dimethylphenoxy)propoxy]indanyl}acetic acid
233	2-{(1S)-5-[3-(3,4,5-trimethoxyphenoxy)propoxy]indanyl}acetic acid

Exemplary compounds of Formula (Irr)) [Formula (II), where R^1 is H, R^2 is methyl, L is -Y-$(CH_2)_n$-X-, X and Y are O, and n is 3] is shown in Table 9a below.

Table 9a



Formula Irr

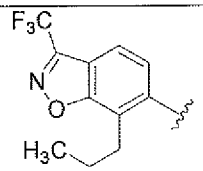
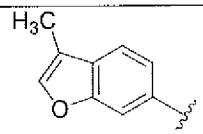
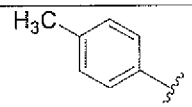
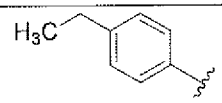
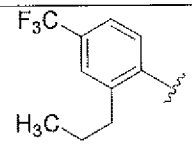
Ex. No	Ar	HPLC RT (min)	LC-MS $[M+H]^+$
116		4.21	*
117		3.79	395.0
118		3.70	*
119		3.87	369.1
120		4.06	*

Table 9b

IUPAC Names for Compounds in Table 9a

Ex. No.	IUPAC Name
237	(2S)-2-((1S)-5-{3-[7-propyl-3-(trifluoromethyl)benzo[d]isoxazol-6-yloxy] propoxy}indanyl)propanoic acid
238	(2S)-2-{(1S)-5-[3-(3-methylbenzo[3,4-b]furan-6-yloxy)propoxy]indanyl} propanoic acid
239	(2S)-2-{(1S)-5-[3-(4-methylphenoxy)propoxy]indanyl}propanoic acid
240	(2S)-2-{(1S)-5-[3-(4-ethylphenoxy)propoxy]indanyl}propanoic acid
241	(2S)-2-((1S)-5-{3-[2-propyl-4-(trifluoromethyl)phenoxy]propoxy}indanyl) propanoic acid

Table 10a

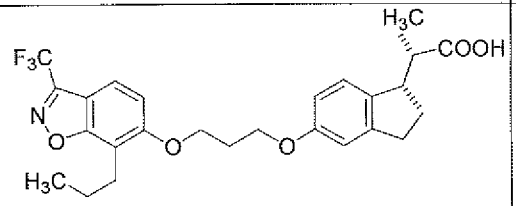
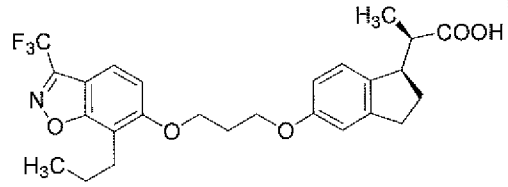
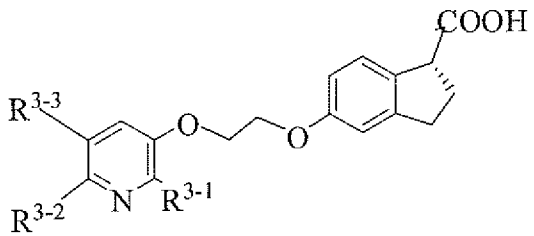
Ex. No	Structure	HPLC RT (min)	LC-MS $[M+H]^+$
121		4.21	*
122		4.20	*

Table 10b

IUPAC Names for Compounds in Table 10a

Ex. No.	IUPAC Name
244	(2S)-2-[(1S)-5-(3-{[7-propyl-3-(trifluoromethyl)-1,2-benzisoxazol-6-yl]oxy} propoxy)-2,3-dihydro-1H-inden-1-yl]propanoic acid
245	(2R)-2-[(1R)-5-(3-{[7-propyl-3-(trifluoromethyl)-1,2-benzisoxazol-6-yl]oxy} propoxy)-2,3-dihydro-1H-inden-1-yl]propanoic acid

Table 11a



Formula Iss

Ex. No.	R^{3-1}	R^{3-2}	R^{3-3}	LC-MS RT (min)	LC-MS $[M+H]^+$
123	H	H	H	1.66	314.3

Ex. No.	R^{3-1}	R^{3-2}	R^{3-3}	LC-MS RT (min)	LC-MS $[M+H]^+$
124	H	CH_3	H	1.73	328.2
125	CH_3	H	H	2.15	328.3
126	H	H	Cl	3.46	348.2
127	H	H	C(=O)OH	2.79	358.2

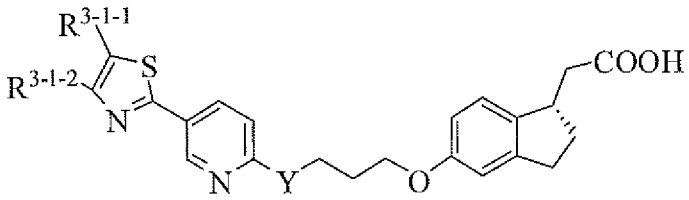
Table 11b

IUPAC Names for Compounds in Table 11a

Ex. No.	IUPAC Name
252	2-[(1S)-5-(2-(3-pyridyloxy)ethoxy)indanyl]acetic acid
253	2-{(1S)-5-[2-(6-methyl(3-pyridyloxy))ethoxy]indanyl}acetic acid
254	2-{(1S)-5-[2-(2-methyl(3-pyridyloxy))ethoxy]indanyl}acetic acid
255	2-{(1S)-5-[2-(5-chloro(3-pyridyloxy))ethoxy]indanyl}acetic acid
256	5-{2-[(1S)-1-(carboxymethyl)indan-5-yloxy]ethoxy}pyridine-3-carboxylic acid

5

Table 12a



Formula Itt

Ex. No.	R^{3-1-1}	R^{3-1-2}	Y	LC-MS RT (min)	LC-MS $[M+H]^+$
128	H	Et	O	3.55	439.1
129	$CH_3C(=O)$	CH_3	O	3.30	467.1
130	$-CH_2CH_2CH_2CH_2-$		O	3.67	465.1
131	H	EtO	O	3.40	455.1
132	H	Et	NH	2.31	438.2
133	$CH_3C(=O)$	CH_3	NH	2.35	466.2
134	CH_3	CH_3	NH	2.27	438.2

Ex. No.	R^{3-1-1}	R^{3-1-2}	Y	LC-MS RT (min)	LC-MS $[M+H]^+$
135	H	Et	NCH_3	2.40	452.4
136	$CH_3C(=O)$	CH_3	NCH_3	2.52	480.4
137	CH_3	CH_3	NCH_3	2.32	452.4
138	H	Et	N-n-Pr	2.84	480.2
139	$CH_3C(=O)$	CH_3	N-n-Pr	3.03	508.2

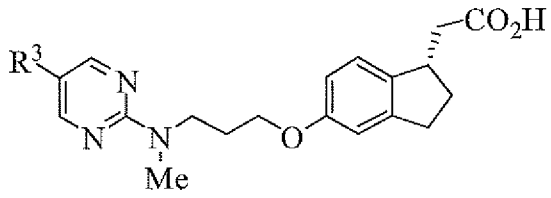
Table 12b

IUPAC Names for Compounds in Table 12a

Ex. No.	IUPAC Name
269	2-((1S)-5-{3-[5-(4-ethyl(1,3-thiazol-2-yl))(2-pyridyloxy)]propoxy}indanyl)acetic acid
270	2-((1S)-5-{3-[5-(5-acetyl-4-methyl(1,3-thiazol-2-yl))(2-pyridyloxy)]propoxy} indanyl)acetic acid
271	2-{(1S)-5-[3-(5-(4,5,6,7-tetrahydrobenzothiazol-2-yl)(2-pyridyloxy))propoxy] indanyl}acetic acid
272	2-((1S)-5-{3-[5-(4-ethoxy(1,3-thiazol-2-yl))(2-pyridyloxy)]propoxy}indanyl) acetic acid
273	2-[(1S)-5-(3-{[5-(4-ethyl(1,3-thiazol-2-yl))(2-pyridyl)]amino}propoxy)indanyl] acetic acid
274	2-[(1S)-5-(3-{[5-(5-acetyl-4-methyl(1,3-thiazol-2-yl))(2-pyridyl)]amino}propoxy) indanyl]acetic acid
275	2-[(1S)-5-(3-{[5-(4,5-dimethyl(1,3-thiazol-2-yl))(2-pyridyl)]amino}propoxy) indanyl]acetic acid
276	2-[(1S)-5-(3-{[5-(4-ethyl(1,3-thiazol-2-yl))(2-pyridyl)]methylamino}propoxy) indanyl]acetic acid
277	2-[(1S)-5-(3-{[5-(5-acetyl-4-methyl(1,3-thiazol-2-yl))(2-pyridyl)]methylamino} propoxy)indanyl]acetic acid
278	2-[(1S)-5-(3-{[5-(4,5-dimethyl(1,3-thiazol-2-yl))(2-pyridyl)]methylamino} propoxy)indanyl]acetic acid
279	2-[(1S)-5-(3-{[5-(4-ethyl(1,3-thiazol-2-yl))(2-pyridyl)]propylamino}propoxy) indanyl]acetic acid
280	2-[(1S)-5-(3-{[5-(5-acetyl-4-methyl(1,3-thiazol-2-yl))(2-pyridyl)]propylamino} propoxy)indanyl]acetic acid

5

Table 13a



Formula Iuu

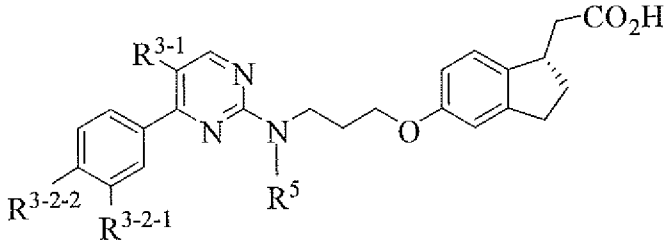
Example	R^3	LCMS (M+H)	RT (min)
140	3,4-dioxolane-Ph	462.2	3.02
141	4-F-Ph	436.2	3.18
142	4-MeO-Ph	448.3	3.01
143	4-t-Bu	474.2	3.70
144	3-thienyl	424.1	3.07
145	2-benzothienyl	474.2	3.72

Table 13b

IUPAC Names for Compounds in Table 13a

Ex. No.	IUPAC Name
284	((1S)-5-{3-[[5-(1,3-benzodioxol-5-yl)-2-pyrimidinyl](methyl)amino]propoxy}-2,3-dihydro-1H-inden-1-yl)acetic acid
285	2-[(1S)-5-(3-{[5-(4-fluorophenyl)pyrimidin-2yl]methylamino}propoxy)indanyl] acetic acid
286	2-[(1S)-5-(3-{[5-(4-methoxyphenyl)pyrimidin-2-yl]methylamino}propoxy)indanyl] acetic acid
287	2-{(1S)-5-[3-({5-[4-(tert-butyl)phenyl]pyrimidin-2-yl}methylamino)propoxy] indanyl}acetic acid
288	2-((1S)-5-{3-[methyl(5-(3-thienyl)pyrimidin-2-yl)amino]propoxy}indanyl)acetic acid
289	2-((1S)-5-{3-[(5-benzo[b]thiophen-2-ylpyrimidin-2-yl)methylamino]propoxy} indanyl)acetic acid

Table 14a



Formula Ivv

Ex. No.	R^{3-1}	R^5	R^{3-2-1}	R^{3-2-2}	LCMS (M+H)	RT (min)
146	H	Me	H	CF_3	3.28	486.4
147	H	n-Pr	H	CF_3	3.73	514.4
148	H	n-Pr	-O-CH_2-O-		2.94	490.2
149[1]	CF_3	Me	H	Et	4.04	514.3
150[1]	CF_3	Me	H	MeO	3.73	516.3
151[1]	CF_3	Me	H	Cl	3.96	520.3
152[1]	CF_3	Me	-O-CH_2-O-		3.68	530.3

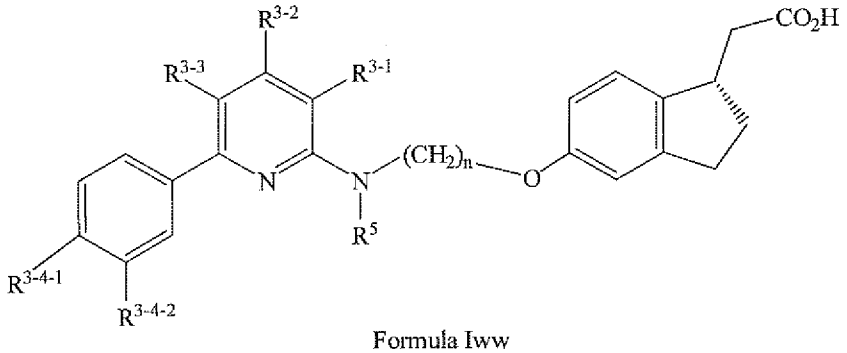
Table 14b

IUPAC Names for Compounds in Table 14a

Ex. No.	IUPAC Name
294	2-{(1S)-5-[3-(methyl{4-[4-(trifluoromethyl)phenyl]pyrimidin-2-yl}amino) propoxy]indanyl}acetic acid
295	2-{(1S)-5-[3-(propyl{4-[4-(trifluoromethyl)phenyl]pyrimidin-2-yl}amino) propoxy]indanyl}acetic acid
296	((1S)-5-{3-[[4-(1,3-benzodioxol-5-yl)-2-pyrimidinyl](propyl)amino]propoxy}-2,3-dihydro-1H-inden-1-yl)acetic acid
297	2-[(1S)-5-(3-{[4-(4-ethylphenyl)-5-(trifluoromethyl)pyrimidin-2-yl]methyl amino}propoxy)indanyl]acetic acid
298	2-[(1S)-5-(3-{[4-(4-methoxyphenyl)-5-(trifluoromethyl)pyrimidin-2-yl]methyl amino}propoxy)indanyl]acetic acid
299	2-[(1S)-5-(3-{[4-(4-chlorophenyl)-5-(trifluoromethyl)pyrimidin-2-yl]methyl amino}propoxy)indanyl]acetic acid
300	2-[(1S)-5-(3-{[4-(2H-benzo[3,4-d]1,3-dioxolan-5-yl)-5-(trifluoromethyl) pyrimidin-2-yl]methylamino}propoxy)indanyl]acetic acid

Table 15a

Exemplary Compounds of Formula (Iww)



Formula Iww

Ex. No.	R^{3-1}	R^{3-2}	R^{3-3}	R^{3-4-1}	R^{3-4-2}	R^5	n	LC-MS RT (min)	LC-MS $[M+H]^+$
153	CF_3	H	H	CH_3O	F	H	3	3.80	519.3
154	CF_3	H	H	CH_3O	CH_3O	H	3	3.61	531.3
155	CF_3	H	H	-OCH_2O-		H	3	3.76	515.3
156	CF_3	H	H	F	H	H	3	4.02	489.1
157	CF_3	H	H	CH_3	H	H	3	4.69	485.3
158	CF_3	H	H	H	H	H	3	4.00	471.1
159	CF_3	H	H	Et	H	H	2	4.04	485.3
160	CF_3	H	H	Et	H	CH_3	3	4.50	513.2
161	CF_3	H	H	Et	H	CH_3	2	4.44	499.1
162	H	H	CF_3	CH_3O	F	H	3	3.38	519.1
163	H	H	CF_3	CH_3O	CH_3O	H	3	3.02	531.1
164	H	H	CF_3	-OCH_2O-		H	3	3.23	515.1
165	H	H	CF_3	F	H	H	3	3.46	489.1
166	H	H	CF_3	CH_3	H	H	3	3.37	485.2
167	H	H	CF_3	H	H	H	3	3.31	471.2
168	F	H	CN	Et	H	CH_3	3	3.86	488.3
169	H	CH_3	CN	Et	H	CH_3	3	3.78	484.4
170	H	CH_3	CN	CH_3O	H	CH_3	3	3.54	486.4

Table 15b

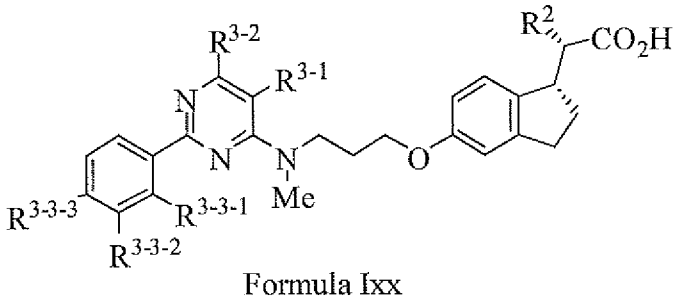
IUPAC Names for Compounds in Table 15a

Ex. No.	IUPAC Name
321	2-[(1S)-5-(3-{[6-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)(2-pyridyl)] amino}propoxy)indanyl]acetic acid
322	2-[(1S)-5-(3-{[6-(3,4-dimethoxyphenyl)-3-(trifluoromethyl)(2-pyridyl)]amino} propoxy)indanyl]acetic acid
323	2-[(1S)-5-(3-{[6-(2H-benzo[3,4-d]1,3-dioxolan-5-yl)-3-(trifluoromethyl)(2-pyridyl)]amino}propoxy)indanyl]acetic acid
324	2-[(1S)-5-(3-{[6-(4-fluorophenyl)-3-(trifluoromethyl)(2-pyridyl)]amino}propoxy) indanyl]acetic acid
325	2-[(1S)-5-(3-{[6-(4-methylphenyl)-3-(trifluoromethyl)(2-pyridyl)]amino}propoxy) indanyl]acetic acid
326	2-[(1S)-5-(3-{[6-phenyl-3-(trifluoromethyl)(2-pyridyl)]amino}propoxy)indanyl] acetic acid
327	2-[(1S)-5-(2-{[6-(4-ethylphenyl)-3-(trifluoromethyl)(2-pyridyl)]amino}ethoxy) indanyl]acetic acid
328	2-[(1S)-5-(3-{[6-(4-ethylphenyl)-3-(trifluoromethyl)(2-pyridyl)]methylamino} propoxy)indanyl]acetic acid
329	2-[(1S)-5-(2-{[6-(4-ethylphenyl)-3-(trifluoromethyl)(2-pyridyl)]methylamino} ethoxy)indanyl]acetic acid
330	2-[(1S)-5-(3-{[6-(3-fluoro-4-methoxyphenyl)-5-(trifluoromethyl)(2-pyridyl)] amino}propoxy)indanyl]acetic acid
331	2-[(1S)-5-(3-{[6-(3,4-dimethoxyphenyl)-5-(trifluoromethyl)(2-pyridyl)]amino} propoxy)indanyl]acetic acid
332	2-[(1S)-5-(3-{[6-(2H-benzo[3,4-d]1,3-dioxolan-5-yl)-5-(trifluoromethyl)(2-pyridyl)]amino}propoxy)indanyl]acetic acid
333	2-[(1S)-5-(3-{[6-(4-fluorophenyl)-5-(trifluoromethyl)(2-pyridyl)]amino}propoxy) indanyl]acetic acid
334	2-[(1S)-5-(3-{[6-(4-methylphenyl)-5-(trifluoromethyl)(2-pyridyl)]amino}propoxy) indanyl]acetic acid
335	2-[(1S)-5-(3-{[6-phenyl-5-(trifluoromethyl)(2-pyridyl)]amino}propoxy)indanyl] acetic acid
336	2-[(1S)-5-(3-{[5-cyano-6-(4-ethylphenyl)-3-fluoro(2-pyridyl)]methylamino}

	propoxy)indanyl]acetic acid
337	2-[(1S)-5-(3-{[5-cyano-6-(4-ethylphenyl)-4-methyl(2-pyridyl)]methylamino} propoxy)indanyl]acetic acid
338	2-[(1S)-5-(3-{[5-cyano-6-(4-methoxyphenyl)-4-methyl(2-pyridyl)]methyl amino}propoxy)indanyl]acetic acid

Exemplary compounds of Formula (Ixx) and (Iyy) were listed in Table 16a and Table 17a below.

Table 16a



Formula Ixx

Ex. No.	**R^2**	**R^{3-1}**	**R^{3-2}**	**R^{3-3-1}**	**R^{3-3-2}**	**R^{3-3-3}**	**LCMS (M+H)**	**RT (min)**
171	H	H	H	H	H	Me	432.2	2.41
172	H	H	H	H	H	Et	446.4	2.27
173	H	H	H	H	H	F	436.3	2.27
174	H	H	H	H	-O-CH_2-O-		462.3	2.25
175	H	H	H	H	H	EtO	462.3	2.50
176	H	H	H	H	H	MeO	448.4	2.30
177	H	H	H	H	MeO	MeO	478.4	2.20
178	H	H	H	H	H	Ac	460.3	2.31
179	H	Me	H	H	H	F	450.2	2.44
180	H	Me	H	H	-O-CH_2-O-		476.3	2.43
181	H	Me	H	H	H	MeO	462.3	2.44
182	H	Me	H	H	H	Me	446.4	2.38
183	H	Me	H	H	H	t-Bu	488.5	2.64
184	H	Me	H	H	F	Me	464.4	2.43
185	H	Me	H	H	EtO	H	476.4	2.41
186	H	Me	H	H	MeO	MeO	492.4	2.27
187	H	Me	H	H	Me	Me	460.3	2.46
188	H	Me	H	H	H	i-Pr	474.5	2.56
189	H	Me	H	H	H	EtO	476.4	2.43

Ex. No.	R^2	R^{3-1}	R^{3-2}	R^{3-3-1}	R^{3-3-2}	R^{3-3-3}	LCMS (M+H)	RT (min)
190	H	Me	H	H	H	Ac	474.3	2.25
191	H	Me	H	H	H	H	432.4	2.27
192	H	Me	H	H	Me	H	446.3	2.38
193	H	Me	H	H	Cl	H	466.4	3.18
194	H	Me	H	H	H	Cl	466.3	2.43
195	Me	Me	H	H	H	Et	474.5	2.59
196	Me	Me	H	H	H	MeO	476.5	2.44
197	Me	Me	H	H	H	Cl	480.4	2.55
198	Me	Me	H	H	-O-CH_2-O-		490.5	2.40
199	H	F	H	H	H	MeO	466.4	2.57
200	H	F	H	H	H	CF_3	504.4	3.58
201	H	F	H	H	H	i-Pr	478.4	3.01
202	H	F	H	H	H	Ac	478.4	3.00
203	H	F	H	H	H	Cl	470.3	3.28
204	H	F	H	H	H	H	436.2	2.88
205	H	F	H	H	H	CF_3O	520.2	3.64
206	H	F	H	H	H	EtO	480.3	2.83
207	H	F	H	H	H	Me	450.2	2.93
208	H	F	H	H	H	F	454.2	3.20
209	H	F	H	H	H	Et	464.3	3.06
210	H	F	H	H	-O-CH_2-O-		480.4	2.66
211	H	Et	H	H	H	F	464.3	2.49
212	H	Et	H	H	H	Et	474.5	2.61
213	H	Et	H	H	-O-CH_2-O-		490.4	2.43
214	H	H	Me	H	H	Et	460.3	2.56
215	H	H	Me	H	H	i-Pr	474.3	2.62
216	H	H	Me	H	H	EtO	476.3	2.53
217	H	H	Me	H	H	Cyclohexyl	514.4	2.97
218	H	H	Me	H	H	n-butyl	488.6	2.69
219	H	H	Me	H	H	Me	448.3	2.46
220	H	H	Me	H	H	t-Bu	448.3	2.30
221	H	H	Me	H	H	Ac	474.3	2.30
222	H	H	Me	H	-O-CH_2-O-		476.3	2.36
223	H	H	Me	H	H	F	450.4	2.29

Ex. No.	R^2	R^{3-1}	R^{3-2}	R^{3-3-1}	R^{3-3-2}	R^{3-3-3}	LCMS (M+H)	RT (min)
224	H	H	Me	F	H	H	450.4	2.22

Table 16b

IUPAC Names for Compounds in Table 16a

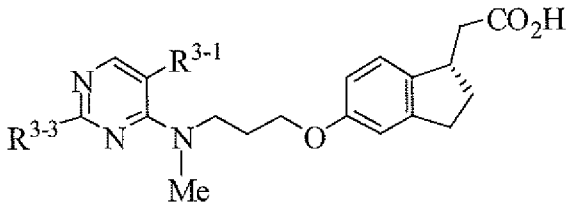
Ex. No.	IUPAC Name
347	2-[(1S)-5-(3-{[2-(4-methylphenyl)pyrimidin-4-yl]methylamino}propoxy) indanyl]acetic acid
348	2-[(1S)-5-(3-{[2-(4-ethylphenyl)pyrimidin-4-yl]methylamino}propoxy) indanyl]acetic acid
349	2-[(1S)-5-(3-{[2-(4-fluorophenyl)pyrimidin-4-yl]methylamino}propoxy) indanyl]acetic acid
350	2-((1S)-5-{3-[(2-(2H-benzo[3,4-d]1,3-dioxolan-5-yl)pyrimidin-4-yl)methyl amino]propoxy}indanyl)acetic acid
351	2-[(1S)-5-(3-{[2-(4-ethoxyphenyl)pyrimidin-4-yl]methylamino}propoxy) indanyl]acetic acid
352	2-[(1S)-5-(3-{[2-(4-methoxyphenyl)pyrimidin-4-yl]methylamino}propoxy) indanyl]acetic acid
353	2-[(1S)-5-(3-{[2-(3,4-dimethoxyphenyl)pyrimidin-4-yl]methylamino}propoxy) indanyl]acetic acid
354	2-[(1S)-5-(3-{[2-(4-acetylphenyl)pyrimidin-4-yl]methylamino}propoxy) indanyl]acetic acid
355	2-[(1S)-5-(3-{[2-(4-fluorophenyl)-5-methylpyrimidin-4-yl]methylamino}propoxy) indanyl]acetic acid
356	2-((1S)-5-{3-[(2-(2H-benzo[3,4-d]1,3-dioxolan-5-yl)-5-methylpyrimidin-4-yl) methylamino]propoxy}indanyl)acetic acid
357	2-[(1S)-5-(3-{[2-(4-methoxyphenyl)-5-methylpyrimidin-4-yl]methylamino} propoxy)indanyl]acetic acid
358	2-[(1S)-5-(3-{methyl[5-methyl-2-(4-methylphenyl)pyrimidin-4-yl]amino} propoxy)indanyl]acetic acid
359	2-{(1S)-5-[3-({2-[4-(tert-butyl)phenyl]-5-methylpyrimidin-4-yl}methylamino) propoxy]indanyl}acetic acid
360	2-[(1S)-5-(3-{[2-(3-fluoro-4-methylphenyl)-5-methylpyrimidin-4-yl]methylamino} propoxy)indanyl]acetic acid
361	2-[(1S)-5-(3-{[2-(3-ethoxyphenyl)-5-methylpyrimidin-4-yl]methylamino}

Ex. No.	IUPAC Name
	propoxy)indanyl]acetic acid
362	2-[(1S)-5-(3-{[2-(3,4-dimethoxyphenyl)-5-methylpyrimidin-4-yl]methylamino} propoxy)indanyl]acetic acid
363	2-[(1S)-5-(3-{[2-(3,4-dimethylphenyl)-5-methylpyrimidin-4-yl]methylamino} propoxy)indanyl]acetic acid
364	2-{(1S)-5-[3-(methyl{5-methyl-2-[4-(methylethyl)phenyl]pyrimidin-4-yl}amino) propoxy]indanyl}acetic acid
365	2-[(1S)-5-(3-{[2-(4-ethoxyphenyl)-5-methylpyrimidin-4-yl]methylamino} propoxy)indanyl]acetic acid
366	2-[(1S)-5-(3-{[2-(4-acetylphenyl)-5-methylpyrimidin-4-yl]methylamino} propoxy)indanyl]acetic acid
367	2-((1S)-5-{3-[methyl(5-methyl-2-phenylpyrimidin-4-yl)amino]propoxy}indanyl) acetic acid
368	2-[(1S)-5-(3-{methyl[5-methyl-2-(3-methylphenyl)pyrimidin-4-yl]amino} propoxy)indanyl]acetic acid
369	2-[(1S)-5-(3-{[2-(3-chlorophenyl)-5-methylpyrimidin-4-yl]methylamino} propoxy)indanyl]acetic acid
370	2-[(1S)-5-(3-{[2-(4-chlorophenyl)-5-methylpyrimidin-4-yl]methylamino} propoxy)indanyl]acetic acid
371	(2S)-2-[(1S)-5-(3-{[2-(4-ethylphenyl)-5-methylpyrimidin-4-yl]methylamino} propoxy)indanyl]propanoic acid
372	(2S)-2-[(1S)-5-(3-{[2-(4-methoxyphenyl)-5-methylpyrimidin-4-yl]methylamino} propoxy)indanyl]propanoic acid
373	(2S)-2-[(1S)-5-(3-{[2-(4-chlorophenyl)-5-methylpyrimidin-4-yl]methylamino} propoxy)indanyl]propanoic acid
374	(2S)-2-((1S)-5-{3-[(2-(2H-benzo[3,4-d]1,3-dioxolan-5-yl)-5-methylpyrimidin-4-yl)methylamino]propoxy}indanyl)propanoic acid
375	2-[(1S)-5-(3-{[5-fluoro-2-(4-methoxyphenyl)pyrimidin-4-yl]methylamino} propoxy)indanyl]acetic acid
376	2-{(1S)-5-[3-({5-fluoro-2-[4-(trifluoromethyl)phenyl]pyrimidin-4-yl}methyl amino)propoxy]indanyl}acetic acid
377	2-{(1S)-5-[3-({5-fluoro-2-[4-(methylethyl)phenyl]pyrimidin-4-yl}methylamino) propoxy]indanyl}acetic acid
378	2-[(1S)-5-(3-{[2-(4-acetylphenyl)-5-fluoropyrimidin-4-yl]methylamino}propoxy) indanyl]acetic acid

Ex. No.	IUPAC Name
379	2-[(1S)-5-(3-{[2-(4-chlorophenyl)-5-fluoropyrimidin-4-yl]methylamino} propoxy)indanyl]acetic acid
380	((1S)-5-{3-[(5-fluoro-2-phenyl-4-pyrimidinyl)(methyl)amino]propoxy}-2,3-dihydro-1H-inden-1-yl)acetic acid
381	2-{(1S)-5-[3-({5-fluoro-2-[4-(trifluoromethoxy)phenyl]pyrimidin-4-yl}methyl amino)propoxy]indanyl}acetic acid
382	2-[(1S)-5-(3-{[2-(4-ethoxyphenyl)-5-fluoropyrimidin-4-yl]methylamino} propoxy)indanyl]acetic acid
383	2-[(1S)-5-(3-{[5-fluoro-2-(4-methylphenyl)pyrimidin-4-yl]methylamino} propoxy)indanyl]acetic acid
384	2-[(1S)-5-(3-{[5-fluoro-2-(4-fluorophenyl)pyrimidin-4-yl]methylamino} propoxy)indanyl]acetic acid
385	2-[(1S)-5-(3-{[2-(4-ethylphenyl)-5-fluoropyrimidin-4-yl]methylamino} propoxy)indanyl]acetic acid
386	2-((1S)-5-{3-[(2-(2H-benzo[3,4-d]1,3-dioxolan-5-yl)-5-fluoropyrimidin-4-yl) methylamino]propoxy}indanyl)acetic acid
387	((1S)-5-{3-[[5-ethyl-2-(4-fluorophenyl)-4-pyrimidinyl](methyl)amino]propoxy}-2,3-dihydro-1H-inden-1-yl)acetic acid
388	2-[(1S)-5-(3-{[5-ethyl-2-(4-ethylphenyl)pyrimidin-4-yl]methylamino}propoxy) indanyl]acetic acid
389	2-((1S)-5-{3-[(2-(2H-benzo[3,4-d]1,3-dioxolan-5-yl)-5-ethylpyrimidin-4-yl) methylamino]propoxy}indanyl)acetic acid
390	((1S)-5-{3-[[2-(4-ethylphenyl)-6-methyl-4-pyrimidinyl](methyl)amino]propoxy}-2,3-dihydro-1H-inden-1-yl)acetic acid
391	2-{(1S)-5-[3-(methyl{6-methyl-2-[4-(methylethyl)phenyl]pyrimidin-4-yl}amino) propoxy]indanyl}acetic acid
392	2-[(1S)-5-(3-{[2-(4-ethoxyphenyl)-6-methylpyrimidin-4-yl]methylamino} propoxy)indanyl]acetic acid
393	2-[(1S)-5-(3-{[2-(4-cyclohexylphenyl)-6-methylpyrimidin-4-yl]methylamino} propoxy)indanyl]acetic acid
394	2-[(1S)-5-(3-{[2-(4-butylphenyl)-6-methylpyrimidin-4-yl]methylamino} propoxy)indanyl]acetic acid
395	2-[(1S)-5-(3-{methyl[6-methyl-2-(4-methylphenyl)pyrimidin-4-yl]amino} propoxy)indanyl]acetic acid
396	2-{(1S)-5-[3-({2-[4-(tert-butyl)phenyl]-6-methylpyrimidin-4-yl}methylamino)

Ex. No.	IUPAC Name
	propoxy]indanyl}acetic acid
397	2-[(1S)-5-(3-{[2-(4-acetylphenyl)-6-methylpyrimidin-4-yl]methylamino} propoxy)indanyl]acetic acid
398	2-((1S)-5-{3-[(2-(2H-benzo[3,4-d]1,3-dioxolan-5-yl)-6-methylpyrimidin-4-yl) methylamino]propoxy}indanyl)acetic acid
399	2-[(1S)-5-(3-{[2-(4-fluorophenyl)-6-methylpyrimidin-4-yl]methylamino} propoxy)indanyl]acetic acid
400	2-[(1S)-5-(3-{[2-(2-fluorophenyl)-6-methylpyrimidin-4-yl]methylamino}propoxy) indanyl]acetic acid

Table 17a



Formula Iyy

Ex. No.	R^{3-1}	R^{3-3}	LCMS (M+H)	RT (min)
225	H	Cl	390.3	3.46
226	Me	3-thienyl	438.3	2.25
227	Me	4-MeO-Ph-O	478.5	2.35
228	Me	4-F-Ph-O	466.4	2.41
229	Me	3-F-Ph-O	478.5	2.39
230	H	2-benzofuryl	458.3	2.45
231	F	2-benzofuryl	476.4	3.10

Table 17b

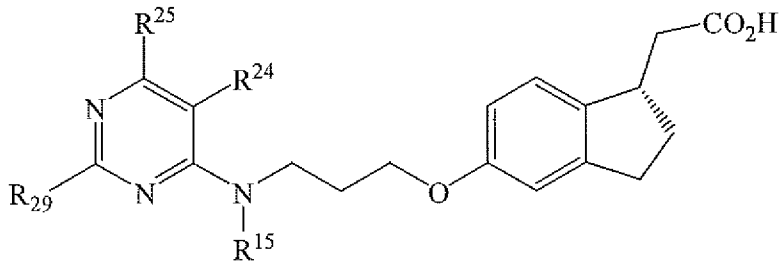
IUPAC Names for Compounds in Table 17a

Ex. No.	IUPAC Name
401	((1S)-5-{3-[(2-chloro-4-pyrimidinyl)(methyl)amino]propoxy}-2,3-dihydro-1H-inden-1-yl)acetic acid
402	2-((1S)-5-{3-[methyl(5-methyl-2-(3-thienyl)pyrimidin-4-yl)amino]propoxy} indanyl)acetic acid
403	((1S)-5-{3-[[2-(4-methoxyphenoxy)-5-methyl-4-pyrimidinyl](methyl)amino]

	propoxy}-2,3-dihydro-1H-inden-1-yl)acetic acid
404	((1S)-5-{3-[[2-(4-fluorophenoxy)-5-methyl-4-pyrimidinyl](methyl)amino] propoxy}-2,3-dihydro-1H-inden-1-yl)acetic acid
405	((1S)-5-{3-[[2-(3-methoxyphenoxy)-5-methyl-4-pyrimidinyl](methyl) amino]propoxy}-2,3-dihydro-1H-inden-1-yl)acetic acid
406	2-((1S)-5-{3-[(2-benzo[d]furan-2-ylpyrimidin-4-yl)methylamino]propoxy} indanyl)acetic acid
407	2-((1S)-5-{3-[(2-benzo[d]furan-2-yl-5-fluoropyrimidin-4-yl)methylamino] propoxy}indanyl)acetic acid

Exemplary compounds of Formula (Izz) is listed in Table 18a.

Table 18a



Formula Izzz

Ex. No.	**R^5**	**R^{3-1}**	**R^{3-2}**	**R^{3-3}**	**LCMS (M+H)**	**RT (min)**
232	H	H	Ph	H	404.3	2.11
233	H	H	H	4-MePh	418.4	3.02
234	H	Me	H	4-Et-Ph	446.3	2.46
235	H	Me	H	4-MePh	432.3	2.46
236	H	Me	H	4-MeOPh	448.4	2.30
237	H	Me	H	3,4-dioxolane-Ph	462.3	2.25
238	H	Me	H	3-thienyl	424.3	2.20
239	H	Me	H	4-F-Ph	436.3	2.28
240	H	Me	H	3-MePh	432.3	2.34
241	H	Me	H	3-MeO-Ph	448.3	2.29
242	H	Me	H	4-CF_3-Ph	486.3	2.48
243	n-Pr	Me	H	4-Me-Ph	474.4	3.29
244	n-Pr	Me	H	4-MeO-Ph	490.4	3.24
245	n-Pr	Me	H	3,4-dioxolane-Ph	504.4	3.20

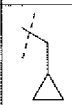
Ex. No.	R^5	R^{3-1}	R^{3-2}	R^{3-3}	LCMS (M+H)	RT (min)
246	n-Pr	Me	H	3-thienyl	466.3	3.17
247	n-Pr	Me	H	4-F-Ph	478.4	3.24
248	n-Pr	Me	H	3-Me-Ph	474.4	3.29
249	n-Pr	H	H	4-Me-Ph	460.3	2.65
250	n-Pr	H	H	4-Et-Ph	474.3	2.77
251	n-Pr	H	H	3,4-dioxolane-Ph	490.3	2.53
252	n-Pr	H	H	4-MeO-Ph	476.5	2.46
253		H	H	4-Et	500.5	2.74
254	Et	Me	H	4-Et-Ph	474.5	2.61
255	Et	Me	H	4-Me-Ph	460.4	2.52
256	Et	Me	H	3,4-dioxolane-Ph	490.4	2.42
257	Ac	Me	H	4-Et-Ph	488.1	3.35
258	Ac	Me	H	3,4-dioxolane-Ph	504.2	2.92

Table 18b

IUPAC Names for Compounds in Table 18a

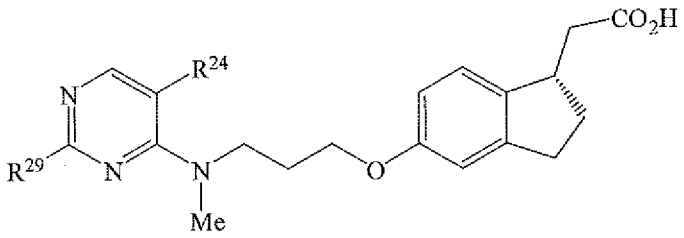
Ex. No.	IUPAC Name
411	((1S)-5-{3-[(6-phenyl-4-pyrimidinyl)amino]propoxy}-2,3-dihydro-1H-inden-1-yl)acetic acid
412	2-[(1S)-5-(3-{[2-(4-methylphenyl)pyrimidin-4-yl]amino}propoxy)indanyl]acetic acid
413	2-[(1S)-5-(3-{[2-(4-ethylphenyl)-5-methylpyrimidin-4-yl]amino}propoxy) indanyl]acetic acid
414	2-[(1S)-5-(3-{[5-methyl-2-(4-methylphenyl)pyrimidin-4-yl]amino}propoxy) indanyl]acetic acid
415	2-[(1S)-5-(3-{[2-(4-methoxyphenyl)-5-methylpyrimidin-4-yl]amino}propoxy) indanyl]acetic acid
416	2-((1S)-5-{3-[(2-(2H-benzo[3,4-d]1,3-dioxolan-5-yl)-5-methylpyrimidin-4-yl)amino]propoxy}indanyl)acetic acid
417	2-((1S)-5-{3-[(5-methyl-2-(3-thienyl)pyrimidin-4-yl)amino]propoxy}indanyl) acetic acid
418	2-[(1S)-5-(3-{[2-(4-fluorophenyl)-5-methylpyrimidin-4-yl]amino}propoxy) indanyl]acetic acid

Ex. No.	IUPAC Name
419	2-[(1S)-5-(3-{[5-methyl-2-(3-methylphenyl)pyrimidin-4-yl]amino}propoxy) indanyl]acetic acid
420	2-[(1S)-5-(3-{[2-(3-methoxyphenyl)-5-methylpyrimidin-4-yl]amino}propoxy) indanyl]acetic acid
421	2-{(1S)-5-[3-({5-methyl-2-[4-(trifluoromethyl)phenyl]pyrimidin-4-yl}amino) propoxy]indanyl}acetic acid
422	2-[(1S)-5-(3-{[5-methyl-2-(4-methylphenyl)pyrimidin-4-yl]propylamino} propoxy)indanyl]acetic acid
423	((1S)-5-{3-[[2-(4-methoxyphenyl)-5-methyl-4-pyrimidinyl](propyl)amino] propoxy}-2,3-dihydro-1H-inden-1-yl)acetic acid
424	2-((1S)-5-{3-[(2-(2H-benzo[3,4-d]1,3-dioxolan-5-yl)-5-methylpyrimidin-4-yl)propylamino]propoxy}indanyl)acetic acid
425	2-((1S)-5-{3-[(5-methyl-2-(3-thienyl)pyrimidin-4-yl)propylamino]propoxy} indanyl)acetic acid
426	2-[(1S)-5-(3-{[2-(4-fluorophenyl)-5-methylpyrimidin-4-yl]propylamino} propoxy)indanyl]acetic acid
427	2-[(1S)-5-(3-{[5-methyl-2-(3-methylphenyl)pyrimidin-4-yl]propylamino} propoxy)indanyl]acetic acid
428	2-[(1S)-5-(3-{[2-(4-methylphenyl)pyrimidin-4-yl]propylamino}propoxy) indanyl]acetic acid
429	2-[(1S)-5-(3-{[2-(4-ethylphenyl)pyrimidin-4-yl]propylamino}propoxy) indanyl]acetic acid
430	2-((1S)-5-{3-[(2-(2H-benzo[3,4-d]1,3-dioxolan-5-yl)pyrimidin-4-yl)propylamino] propoxy}indanyl)acetic acid
431	2-[(1S)-5-(3-{[2-(4-methoxyphenyl)pyrimidin-4-yl]propylamino}propoxy) indanyl]acetic acid
432	2-[(1S)-5-(3-{(cyclopropylmethyl)[2-(4-ethylphenyl)-5-methylpyrimidin-4-yl]amino}propoxy)indanyl]acetic acid
433	2-[(1S)-5-(3-{ethyl[2-(4-ethylphenyl)-5-methylpyrimidin-4-yl]amino}propoxy) indanyl]acetic acid
434	[(1S)-5-(3-{ethyl[5-methyl-2-(4-methylphenyl)-4-pyrimidinyl]amino}propoxy)-2,3-dihydro-1H-inden-1-yl]acetic acid
435	2-((1S)-5-{3-[(2-(2H-benzo[3,4-d]1,3-dioxolan-5-yl)-5-methylpyrimidin-4-yl)ethylamino]propoxy}indanyl)acetic acid
436	2-[(1S)-5-(3-{N-[2-(4-ethylphenyl)-5-methylpyrimidin-4-yl]acetylamino}

Ex. No.	IUPAC Name
	propoxy)indanyl]acetic acid
437	[(1S)-5-(3-{acetyl[2-(1,3-benzodioxol-5-yl)-5-methyl-4-pyrimidinyl]amino} propoxy)-2,3-dihydro-1H-inden-1-yl]acetic acid

Exemplary compounds of Formula (Iaaa) are listed in Table 19a below.

Table 19a



Formula Iaaa

Ex. No.	R^{3-1}	R^{3-2}	LCMS (M+H)	RT (min)
259	4-Ac-Ph	4-Ac-Ph	578.2	2.75
260	4-CF_3-Ph	4-CF_3-Ph	630.5	3.61
261	4-F-Ph	4-F-Ph	530.3	2.78
262	4-Et-Ph	Cl	480.6	3.34
263	4-CF_3O-Ph	Cl	536.5	3.90
264	4-Ac-Ph	Cl	494.5	3.37
265	4-CF_3-Ph	Cl	520.5	3.96
266	3,4-dioxolane-Ph	Cl	496.3	3.06
267	4-F-Ph	Cl	470.5	3.41
268	4-Me-Ph	Cl	466.2	3.16
269	3,4-diF-Ph	Cl	488.2	3.81

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Table 19b

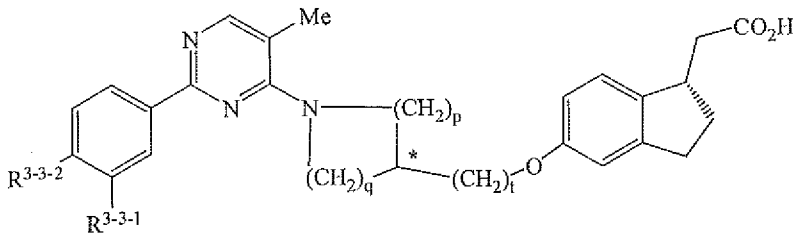
IUPAC Names for Compounds in Table 19a

Ex. No.	IUPAC Name
447	2-[(1S)-5-(3-{[2,5-bis(4-acetylphenyl)pyrimidin-4-yl]methylamino}propoxy) indanyl]acetic acid
448	2-{(1S)-5-[3-({2,5-bis[4-(trifluoromethyl)phenyl]pyrimidin-4-yl}methylamino) propoxy]indanyl}acetic acid
449	2-[(1S)-5-(3-{[2,5-bis(4-fluorophenyl)pyrimidin-4-yl]methylamino}propoxy) indanyl]acetic acid

450	2-[(1S)-5-(3-{[2-chloro-5-(4-ethylphenyl)pyrimidin-4-yl]methylamino} propoxy)indanyl]acetic acid
451	2-{(1S)-5-[3-({2-chloro-5-[4-(trifluoromethoxy)phenyl]pyrimidin-4-yl}methyl amino)propoxy]indanyl}acetic acid
452	2-[(1S)-5-(3-{[5-(4-acetylphenyl)-2-chloropyrimidin-4-yl]methylamino} propoxy)indanyl]acetic acid
453	2-{(1S)-5-[3-({2-chloro-5-[4-(trifluoromethyl)phenyl]pyrimidin-4-yl}methyl amino)propoxy]indanyl}acetic acid
454	2-((1S)-5-{3-[(5-(2H-benzo[3,4-d]1,3-dioxolan-5-yl)-2-chloropyrimidin-4-yl) methylamino]propoxy}indanyl)acetic acid
455	2-[(1S)-5-(3-{[2-chloro-5-(4-fluorophenyl)pyrimidin-4-yl]methylamino} propoxy)indanyl]acetic acid
456	((1S)-5-{3-[[2-chloro-5-(4-methylphenyl)-4-pyrimidinyl](methyl)amino] propoxy}-2,3-dihydro-1H-inden-1-yl)acetic acid
457	((1S)-5-{3-[[2-chloro-5-(3,4-difluorophenyl)-4-pyrimidinyl](methyl)amino] propoxy}-2,3-dihydro-1H-inden-1-yl)acetic acid

Exemplary compounds of Formula (Ibbb) are shown in Table 20a below.

Table 20a



Formula Ibbb

Ex. No.	R^{3-3-2}	R^{3-3-1}	p	q	t	LCMS (M+H)	RT (min)
270[1]	Et	H	0	3	1	472.5	2.57
271	F	H	2	2	0	462.3	2.52
272	i-Pr	H	2	2	0	486.4	2.76
273	MeO	H	2	2	0	474.3	2.47
274	Cl	H	2	2	0	478.3	2.70
275	$-O-CH_2-O-$		2	2	0	488.3	2.45

[1] The absolute configuration at carbon * is S.

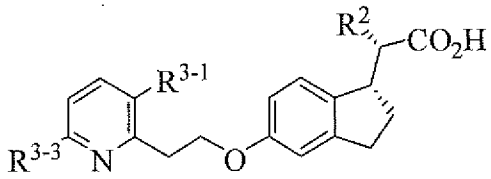
Table 20b

IUPAC Names for Compounds in Table 20a

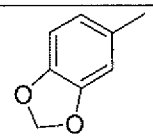
Ex. No.	IUPAC Name
461	[(1S)-5-({(2S)-1-[2-(4-ethylphenyl)-5-methyl-4-pyrimidinyl]-2-pyrrolidinyl}methoxy)-2,3-dihydro-1H-inden-1-yl]acetic acid
462	[(1S)-5-({1-[2-(4-fluorophenyl)-5-methyl-4-pyrimidinyl]-4-piperidinyl}oxy)-2,3-dihydro-1H-inden-1-yl]acetic acid
463	[(1S)-5-({1-[2-(4-i-propylphenyl)-5-methyl-4-pyrimidinyl]-4-piperidinyl}oxy)-2,3-dihydro-1H-inden-1-yl]acetic acid
464	[(1S)-5-({1-[2-(4-methoxyphenyl)-5-methyl-4-pyrimidinyl]-4-piperidinyl}oxy)-2,3-dihydro-1H-inden-1-yl]acetic acid
465	[(1S)-5-({1-[2-(4-chlorophenyl)-5-methyl-4-pyrimidinyl]-4-piperidinyl}oxy)-2,3-dihydro-1H-inden-1-yl]acetic acid
466	[(1S)-5-({1-[2-(1,3-benzodioxol-5-yl)-5-methyl-4-pyrimidinyl]-4-piperidinyl}oxy)-2,3-dihydro-1H-inden-1-yl]acetic acid

More exemplary compounds of Formula (Iccc), is listed in Table 21a below.

Table 21a



Formula Iccc

Ex. No.	R^2	R^{3-1}	R^{3-3}	LCMS (M+H)	RT (min)
276	H	Me	H	312.2	1.75
277	H	H	4-Me-Ph	388.2	2.64
278	H	H	4-Ac-Ph	416.2	2.94
279	H	H	4-MeO-Ph	404.1	2.55
280	H	H		418.1	2.67
281	H	H	4-Cl-Ph	408.1	3.24
282	H	H	4-F-Ph	392.1	2.93
283	H	H	H	374.2	2.69

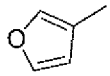
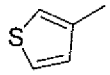
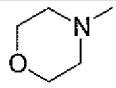
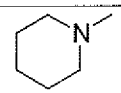
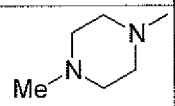
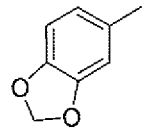
Ex. No.	R^2	R^{3-1}	R^{3-3}	LCMS (M+H)	RT (min)
284	H	H		364.1	2.43
285	H	H	4-CF_3-Ph	442.2	4.13
286	H	H		380.3	3.19
287	H	H		383.3	2.68
288	H	H		381.3	2.10
289	H	H		396.3	1.91
290	Et	H		446.3	3.74
291	Et	H	4-Et-Ph	430.4	3.74
292	Et	H	4-CF_3-Ph	470.4	4.35
293	H	Me	4-Et-Ph	416.2	2.85
294	H	Me	4-CF_3-Ph	456.2	3.57
295	Me	H	Et	340.2	2.07
296	H	H	Et	326.2	1.94

Table 21b

IUPAC Names for Compounds in Table 21a

Ex. No.	IUPAC Name
483	2-{(1S)-5-[2-(3-methyl(2-pyridyl))ethoxy]indanyl}acetic acid, trifluoromethanane acetic acid salt
484	2-(5-{2-[6-(4-methylphenyl)-2-pyridyl]ethoxy}indanyl)acetic acid
485	2-((1S)-5-{2-[6-(4-acetylphenyl)(2-pyridyl)]ethoxy}indanyl)acetic acid
486	2-((1S)-5-{2-[6-(4-methoxyphenyl)(2-pyridyl)]ethoxy}indanyl)acetic acid
487	2-{5-[2-(6-(2H-benzo[3,4-d]1,3-dioxolan-5-yl)(2-pyridyl))ethoxy] (1S)indanyl}acetic acid
488	2-((1S)-5-{2-[6-(4-chlorophenyl)(2-pyridyl)]ethoxy}indanyl)acetic acid
489	2-((1S)-5-{2-[6-(4-fluorophenyl)(2-pyridyl)]ethoxy}indanyl)acetic acid

490	2-{(1S)-5-[2-(6-phenyl(2-pyridyl))ethoxy]indanyl}acetic acid
491	2-{(1S)-5-[2-(6-(3-furyl)(2-pyridyl))ethoxy]indanyl}acetic acid
492	2-((1S)-5-{2-[6-(4-trifluoromethylphenyl)(2-pyridyl)]ethoxy}indanyl)acetic acid
493	2-{(1S)-5-[2-(6-(3-thienyl)(2-pyridyl))ethoxy]indanyl}acetic acid
494	2-{(1S)-5-[2-(6-morpholin-4-yl(2-pyridyl))ethoxy]indanyl}acetic acid
495	((1S)-5-{2-[6-(1-piperidinyl)-2-pyridinyl]ethoxy}-2,3-dihydro-1H-inden-1-yl) acetic acid
496	2-((1S)-5-{2-[6-(4-methylpiperazinyl)(2-pyridyl)]ethoxy}indanyl)acetic acid
497	2-{5-[2-(6-(2H-benzo[3,4-d]1,3-dioxolan-5-yl)(2-pyridyl))ethoxy] (1S)indanyl}(2S)butanoic acid
498	(2S)-2-((1S)-5-{2-[6-(4-ethylphenyl)(2-pyridyl)]ethoxy}indanyl)butanoic acid
499	(2S)-2-[(1S)-5-(2-{6-[4-(trifluoromethyl)phenyl](2-pyridyl)}ethoxy) indanyl]butanoic acid
500	2-((1S)-5-{2-[6-(4-ethylphenyl)-3-methyl(2-pyridyl)]ethoxy}indanyl)acetic acid, chloride
501	2-[(1S)-5-(2-{3-methyl-6-[4-(trifluoromethyl)phenyl](2-pyridyl)}ethoxy) indanyl]acetic acid
502	(2S)-2-{(1S)-5-[2-(5-ethyl(2-pyridyl))ethoxy]indanyl}propanoic acid
503	2-{(1S)-5-[2-(5-ethyl(2-pyridyl))ethoxy]indanyl}acetic acid

In general, the compounds of Formula VI of this invention may be prepared by standard techniques known in the art and by known processes analogous thereto. For example, the compounds may be prepared according to methods described in U.S. Patent Application Publication No. 2006/0084680, which is incorporated by reference in its entirety.

The present invention also encompasses indane acetic acid compounds and derivatives described in U.S. Patent No. 7,476,742 and U.S. Patent Application Publication No. 2006/0264486, which are incorporated by references in their entirety.

The compounds described in Tables 1-20 are intended to be representative examples of the invention, and it will be understood that the scope of the invention is not limited by the scope of the examples. Those skilled in the art will recognize that the invention may be practiced with variations on the disclosed structures, materials, compositions and methods, and such variations are regarded as within the ambit of the invention.

A salt of a compound described in the present invention may be prepared in situ during the final isolation and purification of a compound or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Likewise, when the compound described in the present invention contain a carboxylic acid moiety, (e.g., R = H), a salt of said

compound may be prepared by separately reacting it with a suitable inorganic or organic base and isolating the salt thus formed. The term "pharmaceutically acceptable salt" refers to a relatively non-toxic, inorganic or organic acid addition salt of a compound of the present invention (see, e.g., Berge et al., J. Pharm. Sci. 66:1-19, 1977).

Representative salts of the compounds described in the present invention include the conventional non-toxic salts and the quaternary ammonium salts, which are formed, for example, from inorganic or organic acids or bases by means well known in the art. For example, such acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cinnamate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, itaconate, lactate, maleate, mandelate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfonate, tartrate, thiocyanate, tosylate, undecanoate, and the like.

Base salts include, for example, alkali metal salts such as potassium and sodium salts, alkaline earth metal salts such as calcium and magnesium salts, and ammonium salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine. Additionally, basic nitrogen containing groups in the conjugate base may be quaternized with alkyl halides, e.g., C_{1-9} alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, and dibutyl sulfate; and diamyl sulfates, C_{10-40} alkyl halides such as decyl, lauryl, myristyl and strearyl chlorides, bromides and iodides; or aralkyl halides like benzyl and phenethyl bromides. In some embodiments, the salts are alkali salt such as sodium or potassium salt or an adduct with an acceptable nitrogen base such as meglumine (N-Methyl-d-glucamine) salt.

The esters of the compounds described in the present invention are non-toxic, pharmaceutically acceptable esters, for example, alkyl esters such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, or pentyl esters. Additional esters such as, for example, methyl ester or phenyl-C_1-C_5 alkyl may be used. The compound described in the present invention may be esterified by a variety of conventional procedures including reacting the appropriate anhydride, carboxylic acid, or acid chloride with the alcohol group of the compounds described in the present invention compound. The appropriate anhydride may be reacted with the alcohol in the presence of a base to facilitate acylation such as 1,8-bis[dimethylamino]naphthalene or N,N-dimethylaminopyridine. An appropriate carboxylic acid may be reacted with the alcohol in the presence of a dehydrating agent such as dicyclohexylcarbodiimide, 1-[3-dimethylaminopropyl]-3-ethylcarbodiimide, or other water soluble dehydrating agents which are used to drive the reaction by the removal of water, and optionally, an acylation catalyst. Esterification may also be effected using the appropriate carboxylic acid in the presence of trifluoroacetic anhydride and optionally, pyridine, or in the presence of N, N-carbonyldiimidazole with pyridine. Reaction of an acid chloride with the alcohol may be carried out with an acylation catalyst such as 4-DMAP or pyridine.

One skilled in the art would readily know how to successfully carry out these as well as other methods of esterification of alcohols.

Additionally, sensitive or reactive groups on the compound described in the present invention may need to be protected and deprotected during any of the above methods for forming esters. Protecting groups in general may be added and removed by conventional methods well known in the art (see, e.g., T. W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis; Wiley: New York, (1999)).

The compounds described in the present invention may contain one or more asymmetric centers, depending upon the location and nature of the various substituents desired. Asymmetric carbon atoms may be present in the (R) or (S) configuration. Preferred isomers are those with the absolute configuration, which produces the compound of described in the present invention with the more desirable biological activity. In certain instances, asymmetry may also be present due to restricted rotation about a given bond, for example, the central bond adjoining two aromatic rings of the specified compounds.

Substituents on a ring may also be present in either cis or trans form, and a substituent on a double bond may be present in either Z or E form.

It is intended that all isomers (including enantiomers and diastereomers), either by nature of asymmetric centers or by restricted rotation as described above, as separated, pure or partially purified isomers or racemic mixtures thereof, be included within the scope of the instant invention. The purification of said isomers and the separation of said isomeric mixtures may be accomplished by standard techniques known in the art.

As described herein, compounds of the invention may optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention. In general, the term "substituted" refers to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. Unless otherwise indicated, a substituted group may have a substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds.

C. Evaluation of biological activity of compounds

Some recent research indicates that agonists of the peroxisome proliferator-activated receptor (PPAR) may be used as potential treatment for psoriasis (*See* Romanowska, *PPARd Enhances Keratinocyte Proliferation in Psoriasis and Induces Heparin-Binding EGF-Like, Growth Factor,* J Investigative Dermatology,128, 110-124, (2008); Ellis, *Troglitazone Improves Psoriasis and Normalizes Models of Proliferative Skin Disease*, Arch Dermatology, 136, 609-616 (2000), and Bongartz, Rheumatology, V 44, 2004, p. 126). It is also indicated that PPAR agonists may be used to treat Alzheimer's disease. (*See* Escribano et al., *Rosiglitazone reverses memory decline and hippocampal glucocorticoid receptor down-*

regulation in an Alzheimer's disease mouse model, Biochemical and Biophysical Research Communications, 379, 406–410(2009)).

PPAR receptor agonist activity may be determined by conventional screening methods known to the skilled in the art. For example, methods described in U.S. Patent Application Publication No. 2007/0054907, 2008/0262047 and U.S. Patent No. 7,314,879, which are incorporated by reference in their entireties. Exemplary screening tests are described below:

(1) Binding Assay

Compounds may be tested for their ability to bind to hPPAR gamma, hPPAR alpha or hPPAR delta using a Scintillation Proximity Assay (SPA). The PPAR ligand binding domain (LBD) may be expressed in E. coli as polyHis tagged fusion proteins and purified. The LBD may then be labelled with biotin and immobilized on streptavidin-modified scintillation proximity beads. The beads may then be incubated with a constant amount of the appropriate radioligand (5-{4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-benzyl}-thiazolidine-2,4-dio-ne (J. Med. Chem. 1994, 37(23), 3977), for PPAR gamma), and labelled GW 2433 (see Brown, P. J et al. Chem. Biol. 1997 4: 909-918), for the structure and synthesis of this ligand) for PPAR alpha and PPAR delta) and variable concentrations of test compound, and after equilibration the radioactivity bound to the beads may be measured by a scintillation counter. The amount of nonspecific binding, as assessed by control wells containing 50 μM of the corresponding unlabeled ligand, is subtracted from each data point. For each compound tested, plots of ligand concentration vs. CPM of radioligand bound may be constructed and apparent Ki values are estimated from nonlinear least squares fit of the data assuming simple competitive binding. The details of this assay have been reported elsewhere (see, Blanchard, S. G. et. al. Anal. Biochem., 257 112-119 (1998)).

(2). Functional Assays

(a) Functional cell based assays are developed to discriminate agonists and antagonists.

Agonist Assay: HEK 293 cells stably expressing a human melanocortin receptor (see e.g., Yang, et al., Mol-Endocrinol., 11(3): 274-80, 1997) are dissociated from tissue culture flasks using a trypsin/EDTA solution (0.25%; Life Technologies, Rockville, Md.). Cells are collected by centrifugation and resuspended in DMEM (Life Technologies, Rockville, Md.) supplemented with 1% L-glutamine and 0.5% fetal bovine serum. Cells are counted and diluted to 4.5×10^5/ml.

A compound of the present invention is diluted in dimethylsulfoxide (DMSO) (3×10^{-5} to 3×10^{-10} M final concentrations) and 0.05 volume of compound solution is added to 0.95 volumes of cell suspension; the final DMSO concentration is 0.5%. After incubation at 37°C /5% CO_2 for 5 hours, cells are lysed by addition of luciferin solution (50 mM Tris, 1 mM $MgCl_2$, 0.2% Triton-X100, 5 mM DTT, 500 micromolar Coenzyme A, 150 micromolar ATP, and 440 micromolar luciferin) to quantify the activity of the reporter gene luciferase, an indirect measurement of intracellular cAMP production.

Luciferase activity is measured from the cell lysate using a Wallac Victor 2 luminometer. The amount of lumen production which results from a compound of present invention is compared to that amount of lumens produced in response to NDP-alpha-MSH, defined as a 100% agonist, to obtain the relative efficacy of a compound. The EC_{50} is defined as the compound concentration that results in half maximal stimulation, when compared to its own maximal level of stimulation.

(b) Melanocortin Receptor Whole Cell cAMP Accumulation Assay Compound preparation:

In the agonist assay, compounds are prepared as 10 mM and NDP-aMSH (control) as 33.3 μM stock solutions in 100% DMSO. These are serially diluted in 100% DMSO. The compound plate is further diluted 1:200 in compound dilution buffer (HBSS-092, 1 mM Ascorbic Acid, 1 mM IBMX, 0.6% DMSO, 0.1% BSA). The final concentration range being 10 μM-100 pM for compound and 33.33 nM-0.3 pM for control in 0.5% DMSO. Transfer 20 μl from this plate into four PET 96-well plates (all assays are performed in duplicate for each receptor).

(c) Cell Culture and Cell Stimulation:

HEK 293 cells stably transfected with the MC3R and MC4R are grown in DMEM containing 10% FBS and 1% Antibiotic/Antimycotic Solution. On the day of the assay the cells are dislodged with enzyme free cell dissociation solution and resuspended in cell buffer (HBSS-092, 0.1% BSA, 10 mM HEPES) at 1× e6 cells/ml. Add 40 μl of cells/well to the PET 96-well plates containing 20 ul diluted compound and control. Incubate @ 37 °C. in a water bath for 20 minutes. Stop the assay by adding 50 μl Quench Buffer (50 mM Na Acetate, 0.25% Triton X-100).

(3) Radioligand Binding Assays

Radioligand binding assays are run in SPA buffer (50 mM Sodium Acetate, 0.1% BSA). The beads, antibody and radioligand are diluted in SPA buffer to provide sufficient volume for each 96-well plate. To each quenched assay well is added 100 ul cocktail containing 33.33 μl of beads, 33.33 μl antibody and 33.33 μl ^{125} I-cAMP. This is based on a final concentration of 6.3 mg/ml beads, 0.65% anti-goat antibody and 61 pM of ^{125} I-cAMP (containing 25000-30000 CPM) in a final assay volume of 210 μl. The plates are counted in a Wallac MicroBeta counter after a 12-hour incubation.

The data is converted to pmoles cAMP using a standard curve assayed under the same conditions. The data is analyzed using Activity Base software to generate agonist potencies (EC_{50}) and percent relative efficacy data to NDP-aMSH.

(4) Transfection Assay

Compounds may be screened for functional potency in transient transfection assays in CV-1 cells for their ability to activate the PPAR subtypes (transactivation assay). A previously established chimeric receptor system may be utilized to allow comparison of the relative transcriptional activity of the receptor

subtypes on the same target gene and to prevent endogenous receptor activation from complicating the interpretation of results. See, for example, Lehmann, J. M et al J. Biol. Chem., 1995 270:12953-6. The ligand binding domains for murine and human PPAR alpha, PPAR gamma and PPAR delta are each fused to the yeast transcription factor GAL4 DNA binding domain. CV-1 cells are transiently transfected with expression vectors for the respective PPAR chimera along with a reporter construct containing five copies of the GAL4 DNA binding site driving expression of secreted placental alkaline phosphatase (SPAP) and beta-galactosidase. After 16 h, the medium are exchanged to DME medium supplemented with 10% delipidated fetal calf serum and the test compound at the appropriate concentration. After an additional 24 h, cell extracts are prepared and assayed for alkaline phosphatase and beta-galactosidase activity. Alkaline phosphatase activity is corrected for transfection efficiency using the beta-galactosidase activity as an internal standard (see, for example, Kliewer, S. A., et. al. Cell 1995 83: 813-819). Rosiglitazone (BRL 49653) may be used as a positive control in the hPPAR gamma assay. The positive control in the hPPAR alpha assays may be 2-4-[2-(3-[4-fluorophenyl]-1-heptylureido)ethyl]-phenoxy-(2-methyl propionic acid (WO 97/36579). The positive control for PPAR delta assays may be 2-{2-methyl-4-[({4-methyl-2-{trifluoromethyl)phenyl]-1,3-thiazol-5-yl}methyl)sulfanyl]phenoxy}acetic acid (WO 01/00603). An EC50 may be determined as the concentration at which a compound achieves 50% activation relative to the appropriate positive control.

An "agonist" will typically have a pKi of at least 6.0 preferably at least 7.0 to the relevant PPAR in the Binding Assay described above, and achieves at least 50% activation of the relevant PPAR relative to the appropriate indicated positive control in the Transfection Assay described above at concentrations of 10^{-5} M or less.

(5) Cross Curve PPAR Transactivation test

The activation of receptors with an agonist (activator) in HeLN cells leads to the expression of a reporter gene, luciferase, which, in the presence of a substrate, generates light. The modulation of the receptors is measured as quantity of luminescence produced after incubating the cells in the presence of a reference agonist. The ligands will displace the agonist from its site. The measurement of the activity is performed by quantification of the light produced. This measurement makes it possible to determine the modulatory activity of the compounds according to the invention by determining the constant, which is the affinity of the molecule for the receptor. Since this value can fluctuate according to the basal activity and the expression of the receptor, it is called apparent Kd (Kd app in nM).

To determine this constant, the cells are in contact with a concentration of the product to be tested and a concentration of the reference agonist, 2-(4-{2-[3-(2,4-difluorophenyl)-1-heptylureido]ethyl}phenylsulfanyl)-2-methylpropionic acid for PPARα, {2-methyl-4-[4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-ylmethylsulfanyl]phenoxy}acetic acid for PPARδ and 5-{4-[2-(methylpyridin-2-ylamino)ethoxy]benzyl}thiazolidine-2,4-dione for PPARγ. Measurements are also carried out for the controls total agonist with the same products.

The HeLN cell lines used are stable transfectants containing the plasmids ERE-βGlob-Luc-SV-Neo (reporter gene) and PPAR (α, δ, γ) Gal-hPPAR. These cells are inoculated into 96-well plates in an amount of 10 000 cells per well in 100 µl of DMEM medium free of phenol red and supplemented with 10% lipid-free calf serum. The plates are then incubated at 37 ° C, 7% CO_2 for 16 hours.

The various dilutions of the test products and of the reference ligand are added in an amount of 5 µl per well. The plates are then incubated for 18 hours at 37 °C., 7% CO_2. The culture medium is removed by turning over and 100 µl of a 1:1 PBS/Luciferin mixture are added to each well. After 5 minutes, the plates are read by the luminescence reader.

These cross curves make it possible to determine the AC_{50} values (concentrations at which 50% activation is observed) for the reference ligand at various concentrations of test product. These AC_{50} values are used to calculate the Schild regression by plotting a straight line corresponding to the Schild equation ("*Quantitation in Receptor Pharmacology*" Terry P. Kenakin, *Receptors and Channels,* 2001, 7, 371-385) which leads to Kd app values being obtained (in nM).

(6) Animal Model

(a) Alzheimer's disease

The compounds described in the present invention may be tested in any animal model known to those skilled in the art. Exemplary animal models include, but are not limited to, transgenic mouse models of Alzheimer's disease; aged rats; rats with induced damage to the entorhinal cortex; aged rhesus monkeys, and monkeys with entorhinal cortex damage.

For each model, the test result is compared with a control group that is not treated with the compounds described in the present invention. The treated animals are expected to demonstrate significant improvement in the performance of a variety of learning and memory tests. For example, it is expected to observe that the brains of the treated animals also exhibit enhanced cell size, improved cell signaling, and/or activation of function in neurons that would otherwise have degenerated, compared to untreated animals. These benefits may extend to the degenerating hippocampus where short-term memory is processed, one of the first regions of the brain to suffer damage in Alzheimer's disease.

(b) Psoriasis

Any animal model known to those skilled in the art may be used in the present invention. Exemplary animal model include, but are not limited to, human psoriatic skin-severe combined immunodeficient (SCID) mouse transplant model and AGR_{129} mice model. An exemplary SCID mouse model is described below.

Skin transplanted to SCID mice from normal human volunteers or from psoriatic lesional skin is allowed to heal for 3 to 5 weeks before application of compounds of the present invention. During this period, psoriatic skin, which is about 3- 4 fold thicker than the corresponding normal skin before transplantation, maintains its phenotype (ie, increased epidermal thickness, rete ridges with blunted ends, and intralesional presence of T lymphocytes). Transplanted normal human skin, however, undergoes a

hyperplastic response during this period, resulting in about 2-3 fold increase in epidermal thickness. After the healing period, animals transplanted with normal or psoriatic skin are treated for 14 days by an appropriate application of compounds described in the present invention such as topical application or injection. At the end of the treatment period, the mice are sacrificed and the tissue is evaluated morphometrically for changes in epidermal thickness and immunohistologically for the presence of T lymphocytes for psoriatic lesional skin and normal skin.

D. Pharmaceutical Compositions

According to another aspect of the present invention, pharmaceutical compositions of compounds described herein are provided. In some embodiments, the pharmaceutical compositions further include a pharmaceutically acceptable carrier.

In some embodiments, the pharmaceutical compositions described herein may further include one or more additional therapeutic agents.

In one embodiment, the additional therapeutic agents are used to treat or prevent Alzheimer's disease. Exemplary additional therapeutic agents include, but are not limited to, cholinesterase inhibitors (for example tacrine, galantamine, rivastigamine or donepezil) and NMDA inhibitors (for example memantine). The compounds described herein may be administered in combination with one or more further medicaments of use for the treatment or prevention of other dementias. Other further medicaments include non-steroidal anti-inflammatory drugs (NSAIDs) such as such as naproxen, ibuprofen, diclofenac, indomethacin, nabumetone, piroxicam, celecoxib and aspirin. Other medicaments that may be combined with compounds described herein include HMG-CoA reductase inhibitors such as statins (e.g., simvastatin (Zocor), atovastatin (Lipitor), rosuvastatin (Crestor), fluvastatin (Lescol)).

In some embodiments, the additional therapeutic agents are used to treat or prevent other diseases. Exemplary additional therapeutical agents include, but are not limited to, an antioxidant, an anti-inflammatory, a gamma secretase inhibitor, a neurotrophic agent, an acetyl cholinesterase inhibitor, a statin, an A beta peptide, and an anti-A beta peptide. Yet, in a different embodiment, exemplary additional therapeutic agents include, but are not limited to, corticoid; a vitamin D analog; methrotrexate; ciclosporin; a fumarate; adalimunag; alefecept; afalizumab; etanercept; infliximab; a steroid, a retinoid; an antimicrobial compound; an antioxidant; an anti-inflammatory compound; salicylic acid; an endothelin antagonist; an immunomodulating agent; an angiogenesis inhibitor; a inhibitor of FGF, VEGF, HGF or EGF; an inhibitor of an EGF, FGF, VEGF, or HGF receptor; a tyrosine kinase inhibitor; a protein kinase C inhibitor; and a combination thereof.

Based on well known assays used to determine the efficacy for treatment of conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the compounds of this invention can readily be determined for treatment of each desired indication. The amount of the active ingredient (e.g., compounds) to be

administered in the treatment of one of these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

The total amount of the active ingredient to be administered may generally range from about 0.0001 mg/kg to about 200 mg/kg, and preferably from about 0.01 mg/kg to about 200 mg/kg body weight per day. A unit dosage may contain from about 0.05 mg to about 1500 mg of active ingredient, and may be administered one or more times per day. The daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous, and parenteral injections, and use of infusion techniques may be from about 0.01 to about 200 mg/kg. The daily rectal dosage regimen may be from 0.01 to 200 mg/kg of total body weight. The transdermal concentration may be that required to maintain a daily dose of from 0.01 to 200 mg/kg.

Of course, the specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific compound employed, the age of the patient, the diet of the patient, time of administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of treatment and number of doses of a compound of the present invention may be ascertained by those skilled in the art using conventional treatment tests.

The compounds of this invention may be utilized to achieve the desired pharmacological effect by administration to a patient in need thereof in an appropriately formulated pharmaceutical composition. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for a particular condition or disease. Therefore, the present invention includes pharmaceutical compositions which include a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound. A pharmaceutically acceptable carrier is any carrier which is relatively non-toxic and innocuous to a patient at concentrations consistent with effective activity of the active ingredient so that any side effects ascribable to the carrier do not vitiate the beneficial effects of the active ingredient. A therapeutically effective amount of a compound is that amount which produces a result or exerts an influence on the particular condition being treated. The compounds described herein may be administered with a pharmaceutically-acceptable carrier using any effective conventional dosage unit forms, including, for example, immediate and timed release preparations, orally, parenterally, topically, or the like.

For oral administration, the compounds may be formulated into solid or liquid preparations such as, for example, capsules, pills, tablets, troches, lozenges, melts, powders, solutions, suspensions, or emulsions, and may be prepared according to methods known to the art for the manufacture of pharmaceutical compositions. The solid unit dosage forms may be a capsule which can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers such as lactose, sucrose, calcium phosphate, and corn starch.

In another embodiment, the compounds of this invention may be tableted with conventional tablet bases such as lactose, sucrose, and cornstarch in combination with binders such as acacia, cornstarch, or

gelatin; disintegrating agents intended to assist the break-up and dissolution of the tablet following administration such as potato starch, alginic acid, corn starch, and guar gum; lubricants intended to improve the flow of tablet granulation and to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, for example, talc, stearic acid, or magnesium, calcium or zinc stearate; dyes; coloring agents; and flavoring agents intended to enhance the aesthetic qualities of the tablets and make them more acceptable to the patient. Suitable excipients for use in oral liquid dosage forms include diluents such as water and alcohols, for example, ethanol, benzyl alcohol, and polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent, or emulsifying agent. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance tablets, pills or capsules may be coated with shellac, sugar or both.

Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, those sweetening, flavoring and coloring agents described above, may also be present.

The pharmaceutical compositions of this invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil such as liquid paraffin or a mixture of vegetable oils. Suitable emulsifying agents may be (1) naturally occurring gums such as gum acacia and gum tragacanth, (2) naturally occurring phosphatides such as soy bean and lecithin, (3) esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, and (4) condensation products of said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil such as, for example, arachis oil, olive oil, sesame oil, or coconut oil; or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as, for example, beeswax, hard paraffin, or cetyl alcohol. The suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate; one or more coloring agents; one or more flavoring agents; and one or more sweetening agents such as sucrose or saccharin.

Syrups and elixirs may be formulated with sweetening agents such as, for example, glycerol, propylene glycol, sorbitol, or sucrose. Such formulations may also contain a demulcent, and preservative, flavoring and coloring agents.

The compounds of this invention may also be administered parenterally, that is, subcutaneously, intravenously, intramuscularly, or interperitoneally, as injectable dosages of the compound in a physiologically acceptable diluent with a pharmaceutical carrier which may be a sterile liquid or mixture of liquids such as water, saline, aqueous dextrose and related sugar solutions; an alcohol such as ethanol, isopropanol, or hexadecyl alcohol; glycols such as propylene glycol or polyethylene glycol; glycerol ketals such as 2,2-dimethyl-1,1-dioxolane-4-methanol, ethers such as poly(ethyleneglycol) 400; an oil; a fatty acid;

a fatty acid ester or glyceride; or an acetylated fatty acid glyceride with or without the addition of a pharmaceutically acceptable surfactant such as a soap or a detergent, suspending agent such as pectin, carbomers, methycellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agent and other pharmaceutical adjuvants.

Illustrative of oils which can be used in the parenteral formulations of this invention are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, sesame oil, cottonseed oil, corn oil, olive oil, petrolatum, and mineral oil. Suitable fatty acids include oleic acid, stearic acid, and isostearic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl myristate. Suitable soaps include fatty alkali metal, ammonium, and triethanolamine salts and suitable detergents include cationic detergents, for example, dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates; anionic detergents, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates; nonionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylenepolypropylene copolymers; and amphoteric detergents, for example, alkyl-beta-aminopropionates, and 2-alkylimidazoline quarternary ammonium salts, as well as mixtures.

The parenteral compositions of this invention may typically contain from about 0.5% to about 25% by weight of the active ingredient in solution. Preservatives and buffers may also be used advantageously. In order to minimize or eliminate irritation at the site of injection, such compositions may contain a non-ionic surfactant having a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulation ranges from about 5% to about 15% by weight. The surfactant can be a single component having the above HLB or can be a mixture of two or more components having the desired HLB.

Illustrative of surfactants used in parenteral formulations are the class of polyethylene sorbitan fatty acid esters, for example, sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

The pharmaceutical compositions may be in the form of sterile injectable aqueous suspensions. Such suspensions may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents such as, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents which may be a naturally occurring phosphatide such as lecithin, a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate, a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadecaethyleneoxycetanol, a condensation product of ethylene oxide with a partial ester derived form a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or a condensation product of an ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Diluents and solvents that may be employed are, for example, water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile fixed oils are

conventionally employed as solvents or suspending media. For this purpose, any bland, fixed oil may be employed including synthetic mono or diglycerides. In addition, fatty acids such as oleic acid may be used in the preparation of injectables.

A composition of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions may be prepared by mixing the drug (e.g., compound) with a suitable non-irritation excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such material are, for example, cocoa butter and polyethylene glycol.

Another formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art (see, e.g., U.S. Patent No. 5,023,252, incorporated herein by reference). Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

It may be desirable or necessary to introduce the pharmaceutical composition to the patient via a mechanical delivery device. The construction and use of mechanical delivery devices for the delivery of pharmaceutical agents is well known in the art. For example, direct techniques for administering a drug directly to the brain usually involve placement of a drug delivery catheter into the patient's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of agents to specific anatomical regions of the body, is described in U.S. Patent No. 5,011,472, incorporated herein by reference.

The compositions of the invention may also contain other conventional pharmaceutically acceptable compounding ingredients, generally referred to as carriers or diluents, as necessary or desired. Any of the compositions of this invention may be preserved by the addition of an antioxidant such as ascorbic acid or by other suitable preservatives. Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized.

Commonly used pharmaceutical ingredients which may be used as appropriate to formulate the composition for its intended route of administration include: acidifying agents, for example, but are not limited to, acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid; and alkalinizing agents such as, but are not limited to, ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, trolamine.

Other pharmaceutical ingredients include, for example, but are not limited to, adsorbents (e.g., powdered cellulose and activated charcoal); aerosol propellants (e.g., carbon dioxide, CCl_2F_2, $F_2ClC\text{-}CClF_2$ and $CClF_3$); air displacement agents (e.g., nitrogen and argon); antifungal preservatives (e.g., benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate); antimicrobial preservatives (e.g., benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal); antioxidants (e.g.,

ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite); binding materials (e.g., block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones and styrene-butadiene copolymers); buffering agents (e.g., potassium metaphosphate, potassium phosphate monobasic, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate); carrying agents (e.g., acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup, syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection); chelating agents (e.g., edetate disodium and edetic acid); colorants (e.g., FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red); clarifying agents (e.g., bentonite); emulsifying agents (but are not limited to, acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyethylene 50 stearate); encapsulating agents (e.g., gelatin and cellulose acetate phthalate); flavorants (e.g., anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin); humectants (e.g., glycerin, propylene glycol and sorbitol); levigating agents (e.g., mineral oil and glycerin); oils (e.g., arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil); ointment bases (e.g., lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment); penetration enhancers (transdermal delivery) (e.g., monohydroxy or polyhydroxy alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas); plasticizers (e.g., diethyl phthalate and glycerin); solvents (e.g., alcohol, corn oil, cottonseed oil, glycerin, isopropyl alcohol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation); stiffening agents (e.g., cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax); suppository bases (e.g., cocoa butter and polyethylene glycols (mixtures)); surfactants (e.g., benzalkonium chloride, nonoxynol 10, oxtoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan monopalmitate); suspending agents (e.g., agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum); sweetening e.g., aspartame, dextrose, glycerin, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose); tablet anti-adherents (e.g., magnesium stearate and talc); tablet binders (e.g., acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, povidone and pregelatinized starch); tablet and capsule diluents (e.g., dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch); tablet coating agents (e.g., liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac); tablet direct compression excipients (e.g., dibasic calcium phosphate); tablet disintegrants (e.g., alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, sodium alginate, sodium

starch glycollate and starch); tablet glidants (e.g., colloidal silica, corn starch and talc); tablet lubricants (e.g., calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate); tablet/capsule opaquants (e.g., titanium dioxide); tablet polishing agents (e.g., carnuba wax and white wax); thickening agents (e.g., beeswax, cetyl alcohol and paraffin); tonicity agents (e.g., dextrose and sodium chloride); viscosity increasing agents (e.g., alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose, povidone, sodium alginate and tragacanth); and wetting agents (e.g., heptadecaethylene oxycetanol, lecithins, polyethylene sorbitol monooleate, polyoxyethylene sorbitol monooleate, and polyoxyethylene stearate).

The compounds described herein may be administered as the sole pharmaceutical agent or in combination with one or more other pharmaceutical agents where the combination causes no unacceptable adverse effects. For example, the compounds of this invention can be combined with known anti-obesity, or with known antidiabetic or other indication agents, and the like, as well as with admixtures and combinations thereof.

The compounds described herein may also be utilized, in free base form or in compositions, in research and diagnostics, or as analytical reference standards, and the like. Therefore, the present invention includes compositions which include an inert carrier and an effective amount of a compound identified by the methods described herein, or a salt or ester thereof. An inert carrier is any material which does not interact with the compound to be carried and which lends support, means of conveyance, bulk, traceable material, and the like to the compound to be carried. An effective amount of compound is that amount which produces a result or exerts an influence on the particular procedure being performed.

The compounds may be administered to subjects by any suitable route, including orally (inclusive of administration via the oral cavity), parenterally, by inhalation spray, topically, transdermally, rectally, nasally, sublingually, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. In some embodiments, the compositions are administered orally, parenterally, transdermally or by inhalation spray.

It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, gender, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present invention in the composition will also depend upon the particular compound in the composition.

The following examples are presented to illustrate the invention described herein, but should not be construed as limiting the scope of the invention in any way.

Capsule Formulation

A capsule formula is prepared from:

Compound of this invention	10 mg

Starch	109 mg
Magnesium stearate	1 mg

The components are blended, passed through an appropriate mesh sieve, and filled into hard gelatin capsules.

Tablet Formulation

A tablet is prepared from:

Compound of this invention	25 mg
Cellulose, microcrystalline	200 mg
Colloidal silicon dioxide	10 mg
Stearic acid	5.0 mg

The ingredients are mixed and compressed to form tablets. Appropriate aqueous and non-aqueous coatings may be applied to increase palatability, improve elegance and stability or delay absorption.

Sterile IV Solution

A mg/mL solution of the desired compound of this invention is made using sterile, injectable water, and the pH is adjusted if necessary. The solution is diluted for administration with sterile 5% dextrose and is administered as an IV infusion.

Intramuscular suspension

The following intramuscular suspension is prepared:

Compound of this invention	50 µg/mL
Sodium carboxymethylcellulose	5 mg/mL
TWEEN 80	4 mg/mL
Sodium chloride	9 mg/mL
Benzyl alcohol	9 mg/mL

The suspension is administered intramuscularly.

Hard Shell Capsules

A large number of unit capsules are prepared by filling standard two-piece hard galantine capsules each with powdered active ingredient, 150 mg of lactose, 50 mg of cellulose, and 6 mg of magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil, or olive oil is prepared and injected by means of a positive displacement pump into molten gelatin to form soft gelatin capsules containing the active ingredient. The capsules are washed and dried. The active ingredient can be

dissolved in a mixture of polyethylene glycol, glycerin and sorbitol to prepare a water miscible medicine mix.

Immediate Release Tablets/Capsules

These are solid oral dosage forms made by conventional and novel processes. These units are taken orally without water for immediate dissolution and delivery of the medication. The active ingredient is mixed in a liquid containing ingredient such as sugar, gelatin, pectin, and sweeteners. These liquids are solidified into solid tablets or caplets by freeze drying and solid state extraction techniques. The drug compounds may be compressed with viscoelastic and thermoelastic sugars and polymers or effervescent components to produce porous matrices intended for immediate release, without the need of water.

F. Methods of use

(1) Psoriasis

Another aspect of the present invention provides methods of preventing or treating psoriasis in a subject. The methods include administering to a subject in need thereof an effective amount of a compound of the present invention. In some embodiments, the compound of the present invention is administered topically. In another embodiment, the compound of the present invention is administered intracutaneously, subcutaneously, orally, buccally, transdermally, rectally, or otically.

In some embodiments, the compounds of the present invention may be administered in combination with one or more therapeutic agents. In one embodiment, the therapeutic agent is selected from the group consisting of a corticoid; a vitamin D analog; methrotrexate; ciclosporin; a fumarate; adalimunag; alefecept; afalizumab; etanercept; infliximab; a steroid, a retinoid; an antimicrobial compound; an antioxidant; an anti-inflammatory compound; salicylic acid; an endothelin antagonist; an immunomodulating agent; an angiogenesis inhibitor; a inhibitor of FGF, VEGF, HGF or EGF; an inhibitor of an EGF, FGF, VEGF, or HGF receptor; a tyrosine kinase inhibitor; a protein kinase C inhibitor; and a combination thereof.

In another embodiment, the compounds of the present invention may be administered in combination with one or more coadjuvant therapy selected from phototherapy and/or photochemotherapy.

(2) Alzheimer's disease

According to one aspect of the present invention, methods of preventing or treating Alzheimer's disease are provided. The methods include administering to a subject in need of such treatment an effective amount of a compound of the present invention. In some embodiments, the compound is administered intravenously, orally, buccally, transdermally, rectally, nasally or otically.

In another embodiment, the compounds of the present invention may be administered in combination with one or more additional therapeutic agent. Exemplary additional therapeutic agents include, but are not limited to, an antioxidant, an anti-inflammatory, a gamma secretase inhibitor, a neurotrophic agent, an acetyl cholinesterase inhibitor, a statin, an A beta peptide, and an anti-A beta peptide.

The compounds described herein may be administered in combination with one or more further medicaments of use for the treatment or prevention of Alzheimer's disease. Further medicaments for the treatment or prevention of Alzheimer's disease include cholinesterase inhibitors (for example tacrine, galantamine, rivastigamine or donepezil) and NMDA inhibitors (for example memantine). The compounds described herein may be administered in combination with one or more further medicaments of use for the treatment or prevention of other dementias. Other further medicaments include non-steroidal anti-inflammatory drugs (NSAIDs) such as such as naproxen, ibuprofen, diclofenac, indomethacin, nabumetone, piroxicam, celecoxib and aspirin. Other medicaments that may be combined with compounds described herein include HMG-CoA reductase inhibitors such as statins (eg simvastatin (Zocor), atovastatin (Lipitor), rosuvastatin (Crestor), fluvastatin (Lescol)).

Depending on the individual medicaments utilized in a combination therapy for simultaneous administration, they may be formulated in combination (where a stable formulation may be prepared and where desired dosage regimes are compatible) or the medicaments may be formulated separately (for concomitant or separate administration through the same or alternative routes).

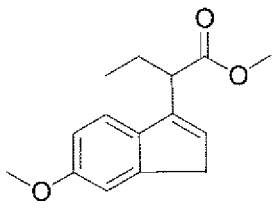
In some embodiments, the subject of the present invention possesses one or more risk factors for developing Alzheimer's disease selected from a family history of the disease; a genetic predisposition for the disease; elevated serum cholesterol; adult-onset diabetes mellitus; elevated baseline hippocampal volume; elevated cerebrospinal fluid levels of total tau; elevated cerebrospinal fluid levels of phospho-tau; and lowered cerebrospinal fluid levels of A β(1-42).

G. Examples

The present invention will now be described in more detail with reference to the following examples. However, these examples are given for the purpose of illustration and are not to be construed as limiting the scope of the invention

Example 1

Preparation of methyl 2-(6-methoxy-1*H*-inden-3-yl) butanoate

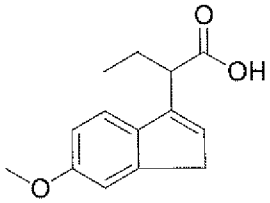


An oven dried 5-L four-necked round-bottomed flask was fitted with a thermometer, a condenser, an addition funnel, and a mechanical stirrer. Under Ar protection, a suspension of 5-methoxy-1-indanone (80.0 g, 494 mmol), Zn powder (Lancaster, 56.2 g, 865 mmol) in 2 L anhydrous THF was stirred at 60°C (internal temperature), while a solution of methyl bromobutyrate (134.1 g, 741 mmol) in 400 mL anhydrous THF was added slowly through an addition funnel. After completion of the addition, the reaction mixture was stirred at 60°C (internal temperature) for 1 hour. The reaction was followed by TLC analysis of aliquots following

1N aqueous HCl work-up. After the reaction was completed, it was cooled in an ice-water bath followed by slow addition of 3 L of 1N HCl solution. The pot temperature was kept below 20°C. The mixture was then extracted with 1 L EtOAc. The organic layer was washed with water until pH 6.0-7.0, then saturated NaCl solution, and dried over Na_2SO_4. The product (127 g, >99%), a yellow oil, was obtained after solvent removal and drying under vacuum. ^{1}H NMR (DMSO-d_6) δ 7.28(d, 1H), 7.05(d, 1H), 6.82(dd, 1H), 6.22(s, 1H), 3.72(s, 3H), 3.60(m, 1H), 3.58(s, 3H), 3.28(s, 2H), 1.95(m, 1H), 1.80(m, 1H), 0.88(t, 3H).

Example 2a

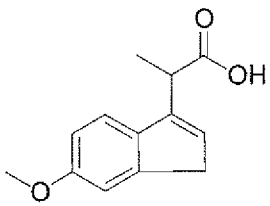
Preparation of 2-(6-methoxy-1*H*-inden-3-yl) butanoic acid



To a solution of the ester prepared in Example **1** (14.0 g, 58.9 mmol) in 140 mL MeOH, was added a solution of KOH (6.4 g, 113.8 mmol) in 5 mL water. The reaction mixture was stirred at 60°C (pot temperature) for 2 hours. TLC showed 70% conversion. A solution of KOH (3.0 g, 53.6 mmol) in 100 mL water was then slowly added to the pot. After 1 hour, the reaction was completed. After cooling to room temperature, the solvents were removed at a reduced pressure. The residue was dissolved in 500 mL water, and then washed with EtOAc. The aqueous layer was cooled in an ice-water bath, and then acidified with conc. HCl to pH<3.0. The product was extracted into 300 mL CH_2Cl_2, washed with water (2 x 100 mL), then dried over Na_2SO_4. After Na_2SO_4 was filtered off, the CH_2Cl_2 solution was stirred with 3.0 g of charcoal for 2 hours. The charcoal was removed by filtration through a pad of Celite®. The title product (12.5 g, 95%) was obtained as a light brown solid after solvent removal and vacuum drying. ^{1}H NMR (DMSO-d_6) δ 12.20(b, 1H), 7.30(d, 1H), 7.06(d, 1H), 6.82(dd, 1H), 6.22(s, 1H), 3.75(s, 3H), 3.45(t, 1H), 3.30(s, 2H), 1.90(m, 1H), 1.78(m, 1H), 0.90(t, 3H).

Example 2b

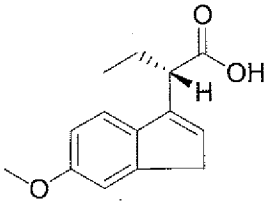
Preparation of 2-(6-methoxy-1H-inden-3-yl) propanoic acid



This substrate was prepared using the same procedures as described for Examples **1** and **2a,** starting with 5-methoxyl-1-indanone and methyl 2-bromopropionate. Yield: 68%. ^{1}H NMR (CD_2Cl_2) δ 7.34 (d, J= 9, 1H), 7.07 (d, J= 2, 1H), 6.85 (dd, J= 9, J= 2, 1H), 6.32 (m, 1H), 3.82 (m, 4H), 3.36 (m, 2H), 1.56 (d, J= 7, 3H).

Example 3

Preparation of (2*S*)-2-(6-methoxy-1*H*-inden-3-yl)butanoic acid



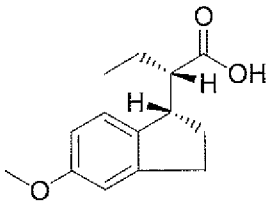
To a solution of the racemic indene acid prepared in Example **2a** (300 g, 1.29 mol) in 4.5 L CH_3CN, was added quinine (324 g, 1.0 mol) at rt. The mixture was stirred for 1 hour, and became a solution. A small amount of insoluble particles was removed by filtration through a microfiber filter under vacuum. The filtrate was then mechanically stirred under Ar over night. After 24 hours, a small sample of solid was taken and analyzed, showing 76.2% ee. The agitation was stopped after two more days. The suspension was filtered. The filter cake was washed with CH_3CN (3 x 200 mL), and then dried under vacuum at 40°C for 3 hours. This solid was stirred with 4.5 L CH_3CN at 70°C until all solids went into solution. The solution was allowed to cool down to rt slowly. The resulting suspension was stirred at rt for 24 hours. The suspension was filtered. The filter cake was washed with CH_3CN (3 x 250 mL), and then dried under vacuum at 40°C for 24 hours. This quinine salt was collected as a white solid (254.6 g, 35.4% yield, 96.8% ee).

The quinine salt (544.3 g, 0.98 mol) was dissolved in 4.0 L CH_2Cl_2 to obtain a clear solution. It was stirred vigorously with 4.0 L of 2N HCl solution in a 22-L round-bottomed flask with a bottom valve. After 30 minutes, the mixture was allowed to settle. The bottom layer was separated and top aqueous layer was extracted with 1 L CH_2Cl_2. The combined CH_2Cl_2 layers were washed with water (3 x 2.0 L) until pH 5.0-6.0, and then dried over Na_2SO_4. The product (230.8 g, 99%, 96.8% ee) was obtained as an off white solid after solvent removal and vacuum drying. ^1H NMR was identical to that of the racemic material described in Example **2a**.

Treatment of the mother liquor in similar fashion gave the (*R*) isomer. Alternatively, the mother liquor may be subjected to aqueous basic conditions in order to effect racemization and recovery of racemic starting material.

Example 4

Preparation of (2*S*)-2-[(1*S*)-5-methoxy-2,3-dihydro-1*H*-inden-1-yl]butanoic acid

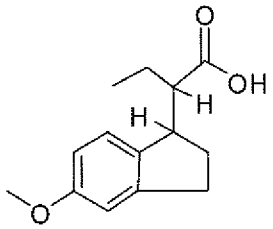


A solution of the product obtained in Example **3** (105 g, 453 mmol), $ClRh(PPh_3)_3$ (21.0 g, 5% eq.) and triethylamine (68.8 g, 679.5 mmol) in EtOH (945 mL) and THF (105 mL) was shaken in a 2-L pressure bottle under 60 psi H_2 for 16 hours. The solvents were removed at a reduced pressure. The resulting mixture was stirred in 1.5 L of 1N HCl solution and 1.5 L CH_2Cl_2. The aqueous layer was extracted with

CH_2Cl_2 (2 x 250 mL). The combined CH_2Cl_2 layers were washed with 1 L of 1N HCl solution and stirred with 1 L of 1N NaOH solution. The organic layer was extracted with 1N NaOH solution (2 x 0.5 L). The combined aqueous layer was washed with CH_2Cl_2 (2 x 250 mL), and acidified (pH 2.0-3.0) by a slow addition of conc. HCl solution at below 15°C. The acidic mixture was extracted with CH_2Cl_2 (2 x 1.5 L), and washed with water (2 x 0.5 L) until pH 5.0-6.0. After washing with brine and drying over anhydrous Na_2SO_4, solvent was evaporated under a reduced pressure. The product (101.0 g, 95% yield, 96.8% ee) was obtained as a light yellow oil. ^{1}H NMR (DMSO-d_6) δ 12.20(s, 1H), 7.04(d, 1H), 6.78(d, 1H), 6.66(dd, 1H), 3.70(s, 3H), 3.28(m, 1H), 2.72(m, 2H), 2.32(m, 1H), 2.06(m, 1H), 1.80(m, 1H), 1.50(m, 1H), 1.36(m, 1H), 0.82(t, 3H).

Example 5a

Preparation of *syn*-2-[5-methoxy-2,3-dihydro-1*H*-inden-1-yl]butanoic acid



A suspension of racemic indene acid (Example **2**, 980 mg, 4.2 mmol), $ClRh(PPh_3)_3$ (139 mg, 0.15 mmol), $NaHCO_3$ (378 mg, 4.5 mmol) in EtOH (20 mL), and H_2O (10 mL) was shaken in a 500 mL pressure bottle under 60 psi H_2 for 30 hours. Additional $ClRh(PPh_3)_3$ (300 mg, 0.33 mmol) was added to the reaction mixture and hydrogenation was continued for 3 more days. After this time, EtOH was removed at a reduced pressure and the residue was diluted with 200 mL water. The black solid was removed by filtration and the filtrate was washed with EtOAc (2 x 200 mL). The aqueous solution was then acidified with conc. HCl, and extracted with CH_2Cl_2 (2 x 100 mL). The combined CH_2Cl_2 layer was washed with brine and dried over Na_2SO_4. Removal of the solvent in vacuum afforded the indane acid as light yellow oil (600 mg, 60%). The product mixture resulted a diastereomeric mixture (87:13) in favor of the syn isomers as determined by NMR analysis, using the ratio of integration of NMR peaks δ 7.11 (d, 1H) for the anti, and δ 7.03 (d, 1H) for the syn isomers.

Resolution of the product into optical isomers may be accomplished as follows:

to a mechanically stirred solution of the *syn* indane acetic acid [*(2R,1R)* and *(2S,1S)*, 14.69 g, 62.7 mmol] in acetonitrile (290 mL) at rt, was added (*R*)-(+)-α-methylbenzylamine (8.49 mL, 65.9 mmol) in one portion. The resulting mixture was stirred overnight. Little solid formation was observed. The reaction mixture was concentrated to dryness and the residue was redissolved in acetonitrile (200 mL) with heating. Magnetic stirring was begun to initiate precipitation. The mixture was stirred overnight. The solids were collected by filtration, and washed three times with a small amount of cold acetonitrile. The solids were then dried under vacuum for 1.5 hours (8.1 g, 86% ee). The slightly wet solids were recrystallized in acetonitrile (120 mL) to give 6.03 g of the (2*S*)-2-[(1*S*)-5-methoxy-2,3-dihydro-1*H*-inden-1-yl]butanoic acid, (R)-α-methylbenzylamine salt (94.4% ee). A second crop was collected from various filtrates (0.89 g, 97.6% ee).

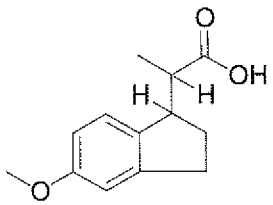
The overall yield of resolution was 31% (62% based on the maximum content of (2*S*,1*S*) acid in the racemate). The material was identical to that obtained in Example **4**.

Optical purity for this Example and that of Example **4** may also be analyzed by chiral HPLC; Column: Chiracel AD, 4.6 (I.D.) x 250 mm; Mobile Phase, A: 0.1% TFA (trifluoroacetic acid) in hexanes, B: 0.1% TFA in IPA (isopropyl alcohol); Method, Isocratic 95%A (5%B), 20 min.; Flow Rate, 1.5 mL/min.; Detector (UV), 284 nm. Retention times for the four possible diastereomers are 5.163 min. (2*S,1R*), 6.255 min. (2*R,1S*), 10.262 min. (2*R,1R*) and 14.399 min. (2*S,1S*). The first locator (*2S* or *2R*) denotes the absolute configuration of the carbon adjacent to the carboxyl group (the 2-positon); the second locator (*1S* or *1R*) denotes the absolute configuration of the indane ring carbon (its 1-position).

The stereochemical assignment for each peak was determined by chiral HPLC analysis of a non-equal (syn/anti) racemic diastereomeric mixture of compound **5**, which provided four baseline-resolved peaks. Peaks 3 and 4, and peaks 1 and 2 represented enantiomer pairs, based on UV integration. The absolute configuration of the compound of peak 4 was determined to be 2*S,1S* by X-ray structural analysis. Peak 3, the corresponding enantiomer, was then assigned a 2*R,1R* configuration with certainty. Peak 1 was assigned to the (2*S,1R*)-diastereomer (retention time: 5.363 min., ca. 0.97% area) by comparison to the minor product obtained from the reduction of the chiral acid (Example **3**) as described in Example **4**. The remaining peak 2, could then be assigned with certainty to the compound with 2*R,1S* configuration.

Example 5b

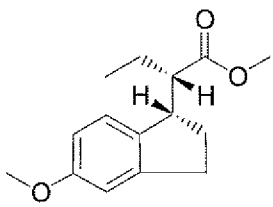
Preparation of syn-2-[5-methoxy-2,3-dihydro-1H-inden-1-yl]propanoic acid



The compound was prepared in 71% yield and >99% de using the same procedure as described for Example **4** starting with (racemic) Example **2b**: ^{1}H NMR (DMSO-d_6) δ 12.18 (s, 1H), 7.03 (d, J = 8, 1H), 6.75 (d, J = 2, 1H), 6.67 (dd, J_1 = 8, J_2 = 2, 1H), 3.68 (s, 3H), 3.37 (m, 1H), 2.72 (m, 3H), 2.03 (m, 1H), 1.75 (m, 1H), 0.89 (d, J = 7, 3H); ^{13}C NMR (CD_2Cl_2) δ 12.626, 28.228, 31.950, 43.300, 46.445, 55.607, 110.054, 112.510, 124.552, 136.702, 146.411, 159.464, 182.330.

Example 6

Preparation of methyl (2*S*)-2-[(1*S*)-5-methoxy-2,3-dihydro-1*H*-inden-1-yl]butanoate

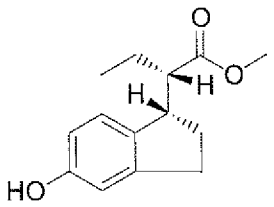


A suspension of acid prepared in Example **4** (220.0 g, 0.94 mol), $NaHCO_3$ (237.0 g, 2.82 mol), CH_3I (200 g, 1.41 mol) in 2.0 L DMF was stirred under Ar at rt for 18 hours. NMR analysis showed 95%

reaction. Adding CH_3I (100 g), and stirring for additional 24 hours at rt caused completion of the reaction. The reaction mixture was poured into 4.0 L water, and extracted with EtOAc (2 x 2 L). The organic layer was sequentially washed with water (2 x 1 L), 1 L of 1N NaOH solution, water (2 x 1 L), and 500 mL brine, and dried over Na_2SO_4. The product (233 g, 99%) was obtained as a light yellow oil after solvent removal and vacuum drying. ^{1}H NMR (DMSO-d_6) δ 6.90(d, 1H), 6.78(d, 1H), 6.66(dd, 1H), 3.70(s, 3H), 3.60(s, 3H), 3.20(m, 1H), 2.80(m, 2H), 2.40(m, 1H), 2.08(m, 1H), 1.80(m, 1H), 1.58(m, 1H), 1.40(m, 1H), 0.80(t, 3H).

Example 7

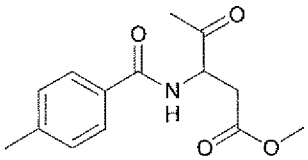
Preparation of methyl (2*S*)-2-[(1*S*)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl]butanoate



To a cold solution (ice water bath) of the compound prepared in Example **6** (233 g, 0.94 mol) in 2.5 L CH_2Cl_2, was added $AlCl_3$ (630 g, 4.7 mol) slowly under Ar. The pot temperature was kept below 20°C, and the color of the reaction turned purple. EtSH (345 mL, 4.7 mol) was added slowly via an addition funnel to the reaction mixture, and the inside temperature was kept below 15°C. After 2 hours of stirring at below 20°C, the reaction went to completion by NMR analysis. The pot mixture was slowly poured into 2.5 L ice water with a strong agitation. The organic layer was separated, and the aqueous layer was extracted with 1L CH_2Cl_2. The combined CH_2Cl_2 layers were washed with water (4 x 1 L) until pH 6.0-7.0, and then dried over Na_2SO_4. The product (216 g, 98%) was obtained as a white solid after solvent removal and vacuum drying. ^{1}H NMR (DMSO-d_6) δ 9.10(s, 1H), 6.78(d, 1H), 6.58(d, 1H), 6.50(dd, 1H), 3.60(s, 3H), 3.20(q, 1H), 2.70(m, 2H), 2.40(m, 1H), 2.08(m, 1H), 1.80(m, 1H), 1.50(m, 2H), 0.80(t, 3H).

Example 8

Preparation of methyl 3-[(4-methylbenzoyl)amino]-4-oxopentanoate

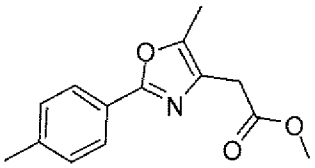


To a suspension of L-aspartic acid □-methyl ester hydrochloride (250 g, 1.36 mol) in chilled (<5°C) CH_2Cl_2 (4 L) was added Et_3N (440 g, 4.35 mol) in a steady flow followed by a slow addition of Me_3SiCl (324 g, 2.99 mol). The mixture was warmed to 25°C and stirred for one hour, cooled again (< 10°C), and *p*-toluoyl chloride (205 g, 1.36 mol) was added dropwise. The mixture was allowed to warm to ambient slowly with stirring for 16 hours. The reaction mixture was then diluted with CH_2Cl_2 (500 mL) and washed with 1N HCl (500 mL), brine (500 mL), and dried over Na_2SO_4. The resultant amide product (310 g, 91%), a white solid, was obtained after solvent removal and drying under vacuum. It was then dissolved in

pyridine (1.25 L) and DMAP (5 g) was added. Acetic anhydride (840 mL) was added slowly and then the reaction was heated at 90°C for 2 hours. The cooled solution was poured into 7 L ice water and extracted with 6 L EtOAc. The organic layer was washed with 2N HCl (3 x 1 L) and 1N NaOH (1 L), dried over $MgSO_4$ and concentrated to afford the title compound as a white solid (301 g, 93%).

Example 9

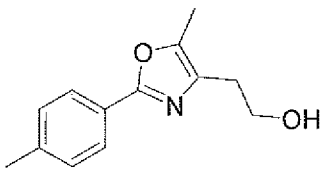
Preparation of methyl [5-methyl-2-(4-methylphenyl)-1,3-oxazol-4-yl]acetate



The intermediate prepared in Example **8** (280 g, 1.06 mol) was dissolved in acetic anhydride (650 mL) followed by slow addition of conc. H_2SO_4 (60 mL). The pot temperature reached 80°C. The reaction was then held at 85°C for 1 hour, cooled, and the acetic anhydride removed *in vacuo*. The residue was poured into ice water (2 L) and extracted with EtOAc (4 L total). The organic layer was then stirred with 1 N NaOH (500 mL) for 1 hour, separated, then dried with $MgSO_4$ and concentrated to afford the title ester as a clear oil (223 g, 87%), which slowly solidified to a white solid.

Example 10

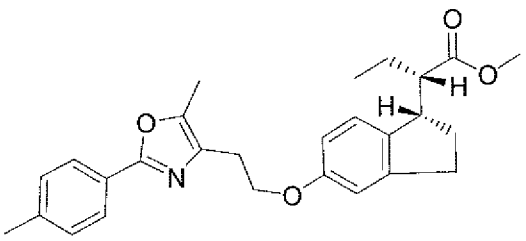
Preparation of 2-[5-methyl-2-(4-methylphenyl)-1,3-oxazol-4-yl]ethanol



The oxazole ester prepared in Example **9** (300 g, 1.22 mol) was dissolved in THF (2.7 L) and solid $LiBH_4$ (26.6 g, 1.22 mol) was added in 5-g portions while maintaining temperature below 45°C. Reaction was complete within an hour after addition. Solvent was reduced to half volume and then poured into ice water (3 L). The mixture was then acidified by slowly adding 1 N HCl (1 L). A white precipitate formed and was collected by filtration and oven dried over P_2O_5 to give the desired oxazole ester (214 g, 83%).

Example 11

Preparation of methyl (2*S*)-2-((1*S*)-5-{2-[5-methyl-2-(4-methylphenyl)-1,3-oxazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)butanoate

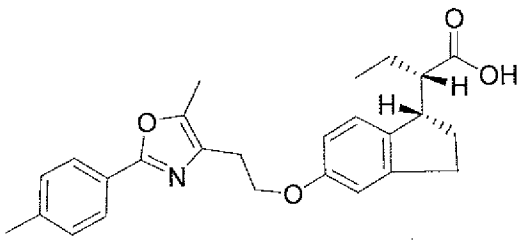


A suspension of the hydroxyindane carboxylate prepared in Example 7 (208 g, 889 mmol), oxazole alcohol prepared in Example **10** (212 g, 977 mmol), ADDP (335 g, 1.33 mol), Ph_3P (348 g, 1.33 mol) in 6.0 L anhydrous THF was stirred at rt under Ar. The reaction was followed by ^1H NMR. No further progress

was observed after 2 days. After solids were removed by filtration, THF was removed under reduced pressure. The remaining mixture was stirred in 3 L of 50/50 mixture EtOAc/hexane for 10 minutes, and more solids were formed and removed by filtration. The filtrate was concentrated and subjected to the same procedure with 25/75 mixture of EtOAc/hexane. After solvents were removed, the resulting oily mixture was purified on a silica gel (3.0 kg) column using CH_2Cl_2 (10.0 L) and 20% CH_3CN/ CH_2Cl_2 (10.0 L) as solvent. Fractions containing product were collected, and then concentrated. The crude mixture was dissolved in 4.0 L CH_2Cl_2, and the unreacted hydroxy compound was removed by washing with 1N NaOH (3 x 1 L). The CH_2Cl_2 layer was dried over Na_2SO_4. The product (358 g, 93%) was obtained as a light yellow oil after solvent removal and vacuum drying. ^{1}H NMR (DMSO-d_6) δ 7.78(d, 2H), 7.30(d, 2H), 6.90(d, 1H), 6.75(d, 1H), 6.65(dd, 1H), 4.15(t, 2H), 3.60(s, 3H), 3.25(q, 1H), 2.90(t, 2H), 2.75(m, 2H), 2.40(m, 1H), 2.35(s, 3H), 2.32(s, 3H), 2.05(m, 1H), 1.80(m, 1H), 1.50(m, 2H), 0.80(t, 3H).

Example 12

Preparation of (2*S*)-2-((1*S*)-5-{2-[5-methyl-2-(4-methylphenyl)-1,3-oxazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)butanoic acid

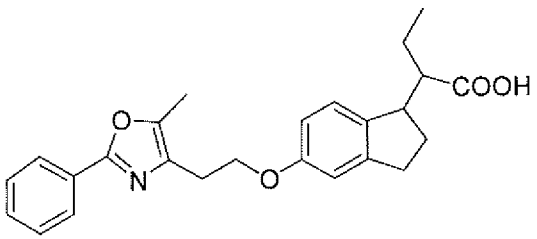


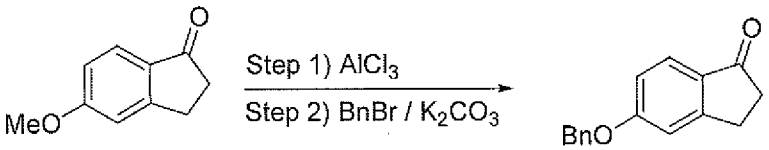
To a solution of LiOH (90.4 g, 3.76 mol) in 1.3 L water and 1.3 L MeOH, was added a solution of the ester prepared in Example **11** (325 g, 0.75 mol) in 3.9 L THF at rt. The solution turned cloudy. This mixture was heated at 60°C (pot temperature) for 4 hours, and TLC (50% EtOAc/hexane) analysis showed ca. 50% conversion. A solution of LiOH (30.1 g, 1.25 mol) in water (200 mL) was added to the reaction mixture. After 2 hours, TLC analysis showed ca. 85% reaction. Again, a solution of LiOH (30.1 g, 1.25 mol) in water (200 mL) was added to the reaction mixture. After 2 hours, TLC analysis showed very little starting ester left. After the reaction mixture was cooled to rt, THF and MeOH were removed at a reduced pressure. The residue was diluted with water until the solids dissolved (a total of 60 L of water used). Conc. HCl solution was slowly added to this aqueous solution until pH 2.0-3.0. The solid was collected by filtration, and dried under house vacuum overnight. This solid was stirred with 15 L EtOAc and 2 L of 1N HCl solution for 30 minutes. The EtOAc layer was separated and washed with 1N HCl solution (2 x 1 L). The organic phase was then washed with water (4 x 2 L) until pH = 5.0-6.0. Under Ar protection, the EtOAc solution was reduced to 2.5 L by normal pressure distillation, then cooled to rt without disturbance. White solid precipitated out. After further cooling in an ice water bath for 2 hours, the solid was filtrated and washed with 500 mL cold EtOAc. After drying under high vacuum at 35°C to a constant weight, the final product (266 g, 81%, 98% ee,) was collected as a white crystal. ^{1}H NMR ($CDCl_3$) δ 7.82(d, 2H), 7.20(d, 2H), 7.05(d, 1H), 6.75(d, 1H), 6.70(dd, 1H), 4.20(t, 2H), 3.42(q, 1H), 2.95(t, 2H), 2.80(m, 2H),

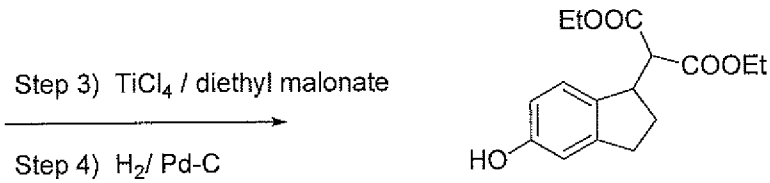
2.50(m, 1H), 2.35(s, 3H), 2.32(s, 3H), 2.20(m, 1H), 1.90(m, 1H), 1.65(m, 1H), 1.45(m, 1H), 0.90(t, 3H). Chiral purity, 99% ee, [□]$_D$=+16.11($CHCl_3$), mp 149.5-150.5°C.

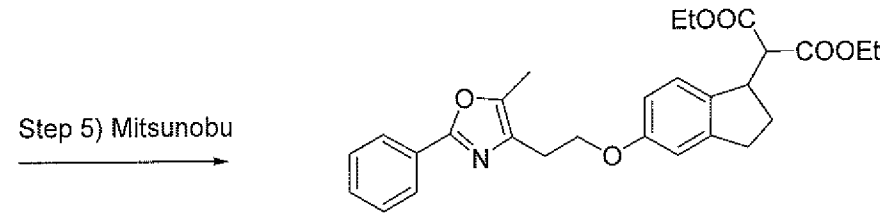
Example 13

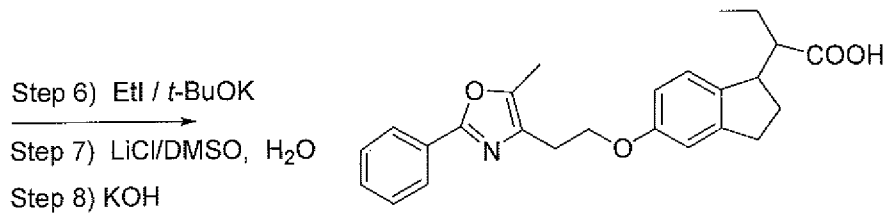
Preparation of 2-{5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}butanoic acid











Step 1. To a solution of 5-methoxy-indanone (10 g) dissolved in toluene (150 mL) was added $AlCl_3$ (15 g). The mixture was refluxed for 4 hours until a precipitate appeared. The resulting mixture was cooled and poured into ice water (150 mL). The precipitate was filtered and washed with water, then air-dried to give the desired product (8.5 g, 90%).

Step 2. Benzyl bromide (17 g), 5-hydroxyl-indanone (15 g), K_2CO_3 (20 g), and 200 mL acetone were mixed in a round-bottom flask (500 mL). The mixture was refluxed for 1 hour. The K_2CO_3 was

filtered off, and the filtrate was evaporated. The resulting residue was crystallized from EtOAc to give 18 g product (75%).

Step 3. A solution of 5-benzyloxyl-indanone (1.14 g, 4.79 mmol) and diethyl malonate (0.844 g, 5.29 mmol) in THF (20 mL) was cooled to 0°C under argon, and $TiCl_4$ (10 mL, 1M in CH_2Cl_2) was added dropwise. Pyridine (2 mL) was added finally. The resulting mixture was stirred overnight at rt. After filtration, EtOAc (30 mL) was added into the filtrate. The organic layer was washed with brine (20 mL x 3), dried with Na_2SO_4, and evaporated. The residue was separated by silica gel chromatography to give 800 mg product (50%).

Step 4. The product of step 3 (1.7 g) was dissolved in MeOH (25 mL), and Pd-C (300 mg) was added as a slurry in MeOH, and placed under 60 psi H_2 in a Parr shaker for 6 hours. After filtration and concentration, 1.2 g product was obtained (92%).

Step 5. $P(Ph)_3$ (420 mg) and ADDP (420 mg) were dissolved in THF (5 mL) at 0°C, and stirred for 10 minutes. A THF solution of oxazole (300 mg) and phenol (430 mg) was added to the flask. The resulting mixture was stirred for 24 hours, and filtered. The filtrate was evaporated and the resulting residue was separated by silica gel chromatography to give product (320 mg, 45%).

Step 6. The intermediate prepared in step 5 (160 mg) was dissolved in THF (5 mL), and iodoethane (0.5 mL) and *t*-BuOK (50 mg) were added to the solution and stirred overnight. After filtration, the product was separated by using TLC, providing 100 mg (65%).

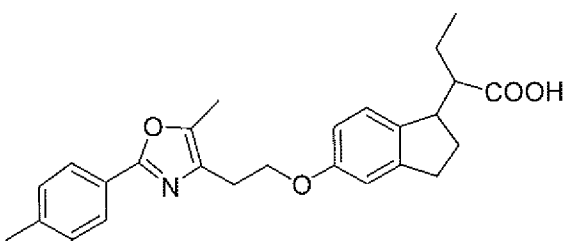
Step 7. The intermediate prepared in step 6 (30 mg) was dissolved in DMSO (1 mL). LiCl (160 mg) was added into the flask. The mixture was refluxed for 5 hours. From the resulting mixture, the product was separated by TLC, giving 13 mg (52%).

Step 8. The intermediate prepared in step 7 was subjected to hydrolysis in aqueous KOH as described for Example **2** to obtain the product: LC-MS, RT 3.57 min., M+1 406; ^{1}H NMR (CD_2Cl_2): δ 0.93 (t, 3H), 1.40-1.70 (m, 2H), 1.80-2.20 (m, 2H), 2.30 (s, 3H), 2.40 (m, 1H), 2.60-2.80 (m, 2H), 2.90 (t, 2H), 3.20-3.40 (m, 1H), 4.10 (t, 2H), 6.60 (dd, 1H), 6.70 (d, 1H), 7.00 (d, 1H), 7.30 (m, 3H), 7.90 (m, 2H).

By using the procedures from Examples **1-13** together in some cases with the chiral HPLC separation method described in the general section, and by using the appropriate starting materials, the following were prepared and characterized in a similar manner:

Example 14

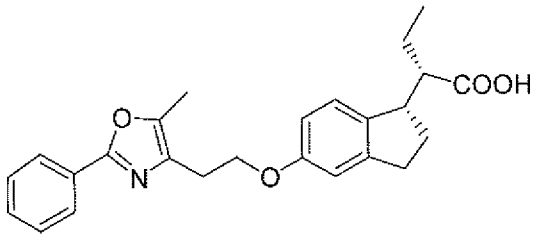
2-(5-{2-[5-methyl-2-(4-methylphenyl)-1,3-oxazol-4-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)butanoic acid



LC-MS, RT 3.70 min., M+1 420; ^{1}H NMR (CD_2Cl_2): δ 0.93 (t, 3H), 1.40-1.70 (m, 2H), 1.80-2.20 (m, 2H), 2.30 (s, 3H),2.35 (s, 3H), 2.40 (m, 1H), 2.60-2.80 (m, 2H), 2.90 (t, 2H), 3.20-3.40 (m, 1H), 4.10 (t, 2H), 6.60 (dd, 1H), 6.70 (d, 1H), 7.00 (d, 1H), 7.20 (m, 3H), 7.80 (m, 2H).

Example 15

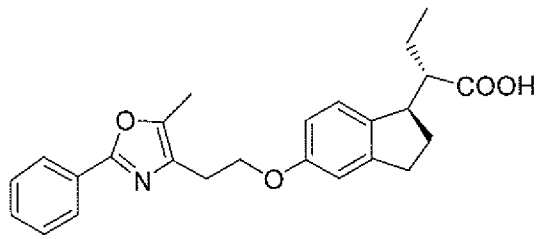
(2S)-2-{(1S)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}butanoic acid



The enantiomer was isolated by chiral HPLC. LC-MS, RT 3.57 min., M+1 406; ^{1}H NMR (CD_2Cl_2): δ 0.93 (t, 3H), 1.48 (ddq, 1H), 1.68 (ddq, 1H), 1.93 (dddd, 1H), 2.18 (dddd, 1H), 2.34 (s, 3H), 2.50 (ddd, 1H), 2.77 (ddd, 1H), 2.87 (ddd, 1H), 2.96 (t, 2H), 3.42 (ddd, 1H), 4.19 (t, 2H), 6.68 (dd, 1H) 6.77 (d, 1H). 7.08 (d, 1H), 7.42 (m, 2H), 7.44 (m, 1H), 7.97 (dd, 2H). ^{13}C NMR: δ 10.4, 12.4, 22.4, 26.6, 29.5, 31.8, 46.5, 51.8, 67.2, 110.9, 113.0, 124.7, 126.2, 128.1, 129.1, 130.2, 133.2, 137.1, 145.6, 146.3, 158.7, 159.7, 180.4.

Example 16

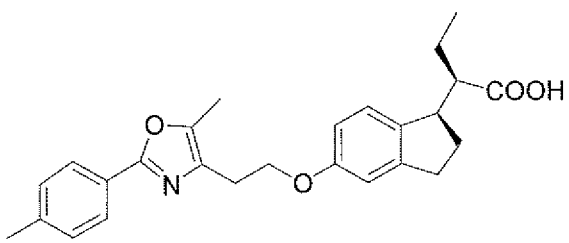
(2S)-2-{(1R)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}butanoic acid



The enantiomer was isolated by chiral HPLC. LC-MS, RT 3.57 min., M+1 406; ^{1}H NMR (CD_2Cl_2): δ 0.93 (t, 3H), 1.61 (ddq, 1H), 1.69 (ddq, 1H), 1.99 (dddd, 1H), 2.19 (dddd, 1H), 2.47 (s, 3H), 2.52 (ddd, 1H), 2.73 (ddd, 1H), 2.89 (ddd, 1H), 3.11 (t, 2H), 3.31 (ddd, 1H), 4.21 (t, 2H), 6.66 (dd, 1H) 6.74 (d, 1H). 7.13 (d, 1H), 7.55 (m, 2H), 7.61 (m, 1H), 8.05 (dd, 2H). ^{13}C NMR: δ 10.5, 12.2, 23.8, 24.8, 30.3, 31.5, 46.4, 50.9, 66.1, 110.8, 112.6, 125.9, 127.4, 123.6, 129.8, 133.3, 129.7, 137.0, 148.4, 146.5, 158.2, 160.5, 181.0.

Example 17

(2R)-2-{(1R)-5-[2-(5-methyl-2-[4-methylphenyl]-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}butanoic acid

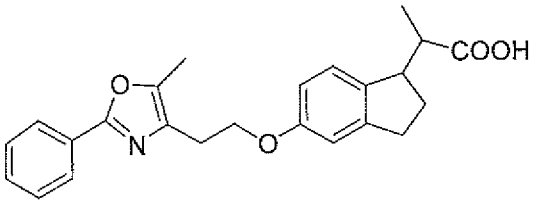


The enantiomer was isolated by chiral HPLC. LC-MS, RT 3.70 min., M+1 420; ^{1}H NMR (CD_2Cl_2): δ 0.95 (t, 3H), 1.40(m, 1H), 1.70 (m, 1H), 1.90 (m, 1H), 2.20 (m, 1H), 2.30 (s, 3H),2.35 (s, 3H), 2.50 (m,

1H), 2.60-2.80 (m, 2H), 2.90 (t, 2H), 3.40 (dd, 1H), 4.20 (t, 2H), 6.60 (dd, 1H), 6.70 (d, 1H), 7.10 (d, 1H), 7.20 (m, 3H), 7.80 (m, 2H).

Example 18

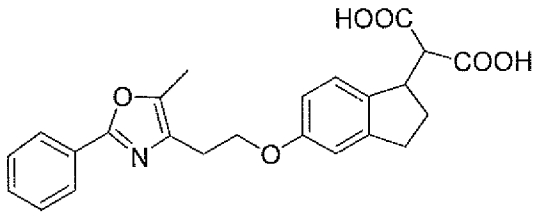
2-(5-{2-[5-methyl-2-phenyl-1,3-oxazol-4-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)propanoic acid



LC-MS, RT 3.41 min., M+1 392; ^{1}H NMR (CD_2Cl_2): δ 1.10 (d, 3H), 1.90 (m, 2H), 2.20 (m, 1H), 2.40 (s, 3H), 2.70-3.00 (m, 2H), 2.95 (t, 2H), 3.45 (m, 1H), 4.20 (t, 2H), 6.70 (dd, 1H), 6.80 (d, 1H), 7.10 (d, 1H), 7.45 (m, 3H), 8.00 (m, 2H).

Example 19

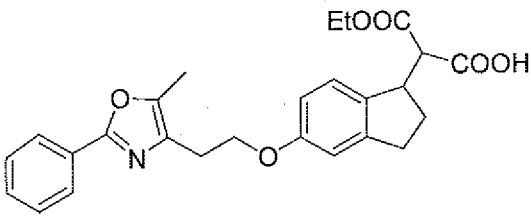
2-{5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}malonic acid



LC-MS, RT 3.00 min., M+1 422; ^{1}H NMR (CD_2Cl_2): δ 1.90 (m, 2H), 2.40 (t, 3H), 2.60-3.00 (m, 3H), 3.40(t, 2H), 3.70 (m, 1H), 4.20 (t, 2H), 6.60 (dd, 1H), 6.80 (d, 1H), 7.10 (d, 1H), 7.50 (m, 3H), 7.95 (m, 2H).

Example 20

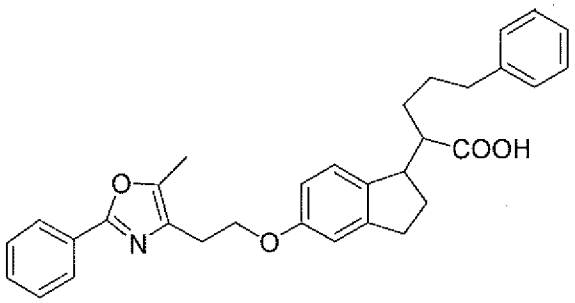
3-ethoxy-2-{5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}-3-oxopropanoic acid



LC-MS, RT 3.39 min., M+1 450; ^{1}H NMR (CD_2Cl_2): δ 1.20 (t, 3H), 2.00(m, 1H), 2.30 (m, 1H), 2.40 (s, 3H), 2.90 (m, 2H), 3.10 (t, 2H), 3.80 (m, 1H), 4.20 (t & q, 4H), 6.70 (dd, 1H), 6.80 (d,1H), 7.10(d, 1H), 7.50 (m, 3H), 8.00 (m, 2H).

Example 21

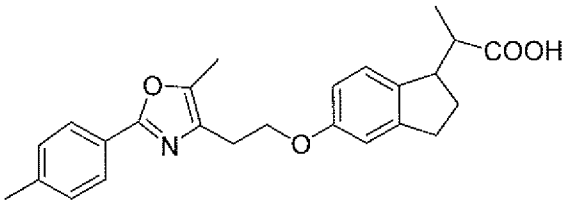
2-{5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}-5-phenylpentanoic acid



LC-MS, RT 3.98 min., M+1 396; ^{1}H NMR (CD_2Cl_2): δ 1.40-1.80 (m, 4H), 1.90-2.20 (m, 2H), 2.35 (s, 3H), 2.40-3.00 (m, 5H), 2.90 (t, 2H), 3.35 (m, 1H), 4.10 (t, 2H), 6.60 (dd,1H), 6.70 (d, 1H), 6.907.20 (m, 6H), 7.30 (m, 3H), 7.95 (m, 2H).

Example 22

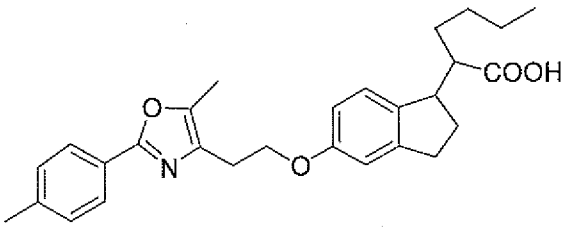
2-(5-{2-[5-methyl-2-(4-methylphenyl)-1,3-oxazol-4-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)propanoic acid



LC-MS, RT 3.52 min., M+1 406; ^{1}H NMR (CD_2Cl_2): δ 1.10 (d, 3H), 1.90 (m, 2H), 2.20 (m, 1H), 2.30 (s, 3H), 2.31(s, 3H), 2.70-3.00 (m, 2H), 2.95 (t, 2H), 3.40 (m, 1H), 4.10 (t, 2H), 6.60 (dd, 1H), 6.70 (d, 1H), 7.00 (d, 1H), 7.20 (d, 2H), 7.80 (d, 2H).

Example 23

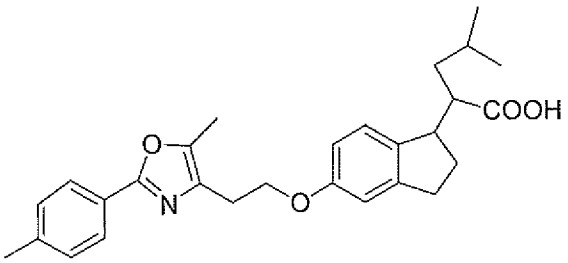
2-(5-{2-[5-methyl-2-(4-methylphenyl)-1,3-oxazol-4-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)hexanoic acid



LC-MS, RT 3.92 min., M+1 448; ^{1}H NMR (CD_2Cl_2): δ 0.93 (t, 3H), 1.10-1.30 (m, 4H), 1.40-1.70 (m, 2H), 1.80-2.20 (m, 2H), 2.30 (s, 3H), 2.31 (s, 3H), 2.40 (m, 1H), 2.60-2.80 (m, 2H), 2.90 (t, 2H), 3.20-3.40 (m, 1H), 4.10 (t, 2H), 6.60 (dd, 1H), 6.70 (d, 1H), 7.00 (d, 1H), 7.20 (d, 2H), 7.80 (d, 2H).

Example 24

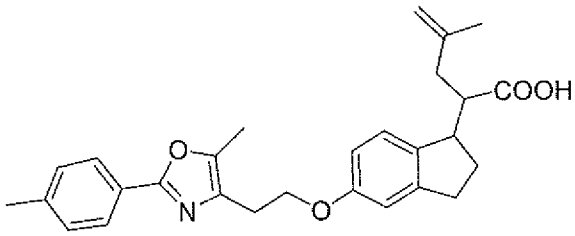
4-methyl-2-(5-{2-[5-methyl-2-(4-methylphenyl)-1,3-oxazol-4-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)pentanoic acid



LC-MS, RT 4.00 min., M+1 448; ^{1}H NMR (CD_2Cl_2): δ 0.93 (m, 6H), 1.20 (m, 1H), 1.40-1.70 (m, 2H), 1.80-2.20 (m, 2H), 2.30 (s, 3H), 2.31 (s, 3H), 2.40 (m, 1H), 2.60-2.80 (m, 2H), 2.90 (t, 2H), 3.20-3.40 (m, 1H), 4.10 (t, 2H), 6.60 (dd, 1H), 6.70 (d, 1H), 7.00 (d, 1H), 7.40 (d, 2H), 8.40 (d, 2H).

Example 25

4-methyl-2-(5-{2-[5-methyl-2-(4-methylphenyl)-1,3-oxazol-4-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)-4-pentenoic acid

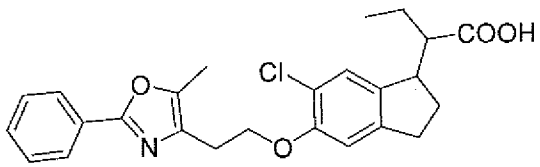


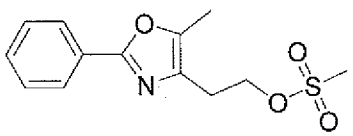
LC-MS, RT 3.74 min., M+1 446; ^{1}H NMR (CD_2Cl_2): δ 1.60 (s, 3H), 1.70 (m, 2H), 1.80-2.20 (m, 2H), 2.30 (s, 3H), 2.31 (s, 3H), 2.40 (m, 1H), 2.60-2.80 (m, 2H), 2.90 (t, 2H), 3.20-3.40 (m, 1H), 4.10 (t, 2H), 5.60 (m, 2H), 6.60 (dd, 1H), 6.70 (d,1H), 7.00 (d, 1H), 7.20 (d, 2H), 7.80 (d, 2H).

Example 26

Preparation of 2-{6-chloro-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}butanoic acid via

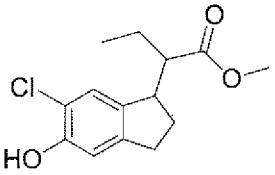
2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethyl methanesulfonate and methyl 2-(6-chloro-5-hydroxy-2,3-dihydro-1H-inden-1-yl)butanoate



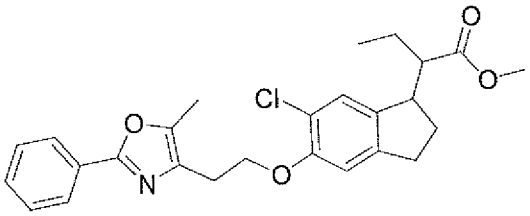


Step 1. To a solution of 2-phenyl-4-methyl-5-hydroxyethyloxazole (500 mg, 2.5 mmol) in 12.5 mL THF, was added methanesulfonyl chloride (0.21 mL, 2.75 mmol) and triethylamine (0.42 mL, 3 mmol). The reaction solution was stirred at rt under argon for two hours then concentrated *in vacuo*. The resulting residue was taken up in ethyl acetate, washed with 1% aqueous hydrochloric acid (three times) and brine. It

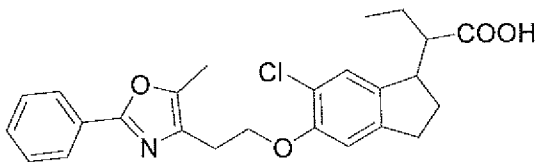
was then dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide (617 mg, 88%): ES-MS *m/z* 282 ($(M+H)^+$); HPLC RT 2.67; ^{1}H NMR (d_6-DMSO) δ 2.33 (s, 3H), 2.89 (t, 2H), 3.13 (s, 3H), 4.41 (t, 2H), 7.47-7.51 (m, 3H), 7.88-7.91 (m, 2H).



Step 2. Sulfuryl chloride (0.035 mL, 0.43 mmol) was added to a solution of methyl-5-hydroxy-2,3-dihydro-1-(2-butanoate) (100 mg, 0.43 mmol) in 2.15 mL acetic acid. The reaction solution was stirred at rt for 30 minutes, then concentrated *in vacuo*. The resulting residue was taken up in ethyl acetate and washed with water, saturated aqueous sodium bicarbonate, and brine. It was then dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide 63 mg of the desired intermediate as a crude yellow oil which was carried on without further purification: GC-MS 269, ($(M+H)^+$); GC RT (min.) 8.71; ^{1}H NMR (d_6-DMSO) δ 0.81 (t, 3H), 1.40-1.63 (m, 2H), 1.77-1.88 (m, 1H), 2.00-2.15 (m, 1H), 2.40-2.80 (m, 3H), 3.15-3.22 (m, 1H), 3.50 (s, 3H), 6.76 (s, 1H), 7.13 (s, 1H), 9.84 (s, 1H),



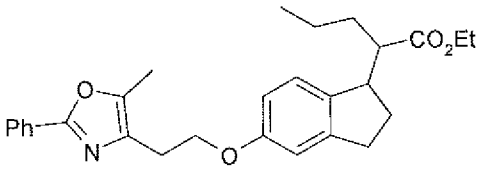
Step 3. A solution of the product obtained in step 2 (30.5 mg, 0.12 mmol) in 0.6 mL DMF was cooled to 0°C in an ice bath. A 60% dispersion of sodium hydride in oil (5.2 mg, 0.13 mmol) was then added and the ice bath was removed. After stirring the reaction mixture for 1 hour at rt, the mesylate from step 1 (34 mg, 0.12 mmol) was added. The reaction mixture was heated at 50°C for 24 hours, then cooled to 0°C. An additional 9.6 mg NaH (60% dispersion in oil) was added and heating was resumed for two hours, after which the reaction mixture was cooled to rt and stirred for 48 hours. At this time, ethyl acetate was added and the organic solution was washed with water and brine (three times), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified through silica gel flash chromatography by using 5:1 hexane:ethyl acetate as the eluant to provide product (19 mg, 35%) as a mixture of diastereomers (3:1): ES-MS *m/z* 454 ($(M+H)^+$); HPLC RT (min.) 4.21; ^{1}H NMR (d_6-DMSO) δ 0.80 (t, 3H), 1.38-1.63 (m, 2H), 1.79-1.90 (m, 1H), 2.02-2.14 (m, 1H), 2.34 (s, 3H), 2.51-2.57 (m, 1H), 2.63-2.84 (m, 2H), 2.91 (t, 2H), 3.19-3.25 (m, 1H), 3.49 (s, 2.3H), 3.58 (s, 0.7H), 4.22 (t, 2H), 7.00 (s, 1H), 7.21 (s, 1H), 7.43-7.51 (m, 3H), 7.85-7.90 (m, 2H).



Step 4. Under the standard hydrolysis conditions, the ester from step 3 was converted to the acid (a mixture of diastereomers 3:2): ES-MS *m/z* 440 ($(M+H)^+$); HPLC RT (min.) 3.69; ^{1}H NMR (d_6-DMSO) δ 0.83 (t, 3H), 2.34 (s, 3H), 2.92 (t, 2H), 4.21 (t, 2H), 7.00-7.02 (d, 1H), 7.12 (s, 0.24H), 7.21 (s, 0.37H), 7.47-7.48 (m, 3H), 7.87-7.90 (m, 2H).

Example 27

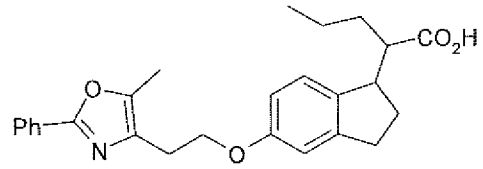
Preparation of ethyl 2-{5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}pentanoate



An oven dried 15 mL round-bottom flask and stir bar, cooled under a stream of Ar(g), was charged with ethyl 2-{5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl} acetate (0.070 g, 0.17 mmol) followed by addition of 0.2 mL THF. The stirred solution was then cooled to –78 °C followed by dropwise addition of lithium bis(trimethylsilyl)amide (1.0 M hexane solution, 0.86 mL, 0.86 mmol). Upon complete addition of base, the solution was allowed to stir at –78°C for 1 hour, then iodopropane (0.142 g, 0.86 mmol) was added via syringe. The contents were then slowly warmed to rt and maintained for 1 hour. The contents of the flask were poured into 5 mL NH_4Cl(aq), then extracted with ethyl acetate (3 x 10 mL). The organic layers were combined and dried over Na_2SO_4 and concentrated *in vacuo* yielding 3.0 mg (4.0% yield) of a colorless film. The product had: ^{1}H NMR (300 MHz, d6-acetone) δ 7.96 (dd, 8.1, 1.5 Hz, 2H), 7.48 (m, 3H), 6.99 (d, 8.4 Hz, 1H), 6.79 (d, 2.7 Hz, 1H), 6.70 (dd, 8.1, 2.7 Hz, 1H), 4.22 (t, 6.9 Hz, 2H), 4.11 (q, 7.2 Hz, 2H), 3.33 (q, 6.6 Hz, 1H), 2.94 (t, 6.9 Hz, 2H), 2.78 (m, 3H), 2.54 (m, 1H), 2.39 (s, 3H), 2.14 (m, 2 H), 1.91 (m, 1H), 1.63 (qt, 10.2, 3.9Hz, 2H), 1.21 (t, 7.2 Hz, 3 H), 0.852 (t, 7.5 Hz, 3 H); mass spectroscopy gave MH^+ of 448.2 (calc'd molecular weight for $C_{28}H_{33}NO_4$ = 447.57).

Example 28

Preparation of 2-{5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}pentanoic acid

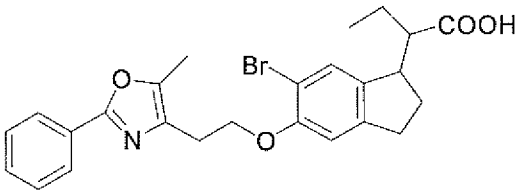


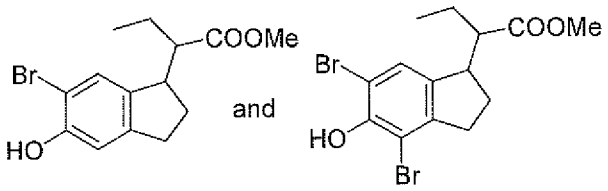
Hydrolysis of the product of Example **27** by the method described above for Example **2** gave a product with the following ^{1}H NMR (300 MHz, d6-acetone); δ 7.96 (dd, 8.1, 1.5 Hz, 2H), 7.48 (m, 3H), 7.10 (d, 8.4 Hz, 1H), 6.79 (d, 2.7 Hz, 1H), 6.71 (dd, 8.1, 2.7 Hz, 1H), 4.22 (t, 6.9 Hz, 2H), 3.40 (m, 1H), 2.91 (t, 6.9 Hz, 2H), 2.74 (m, 1H), 2.58 (m, 1H), 2.39 (s, 3H), 2.26 (m, 1H), 2.11 (m, 1H), 1.95 (m, 2H), 1.84 (m, 1H), 1.62 (m, 2H), 0.859 (td, 6.9, 1.5 Hz, 3H); mass spectroscopy gave MH^+ of 420.1 (calc'd molecular weight for $C_{26}H_{29}NO_4$ = 419.51).

Example 29

Preparation of 2-{6-bromo-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}butanoic acid

via methyl 2-(6-bromo-5-hydroxy-2,3-dihydro-1H-inden-1-yl)butanoate



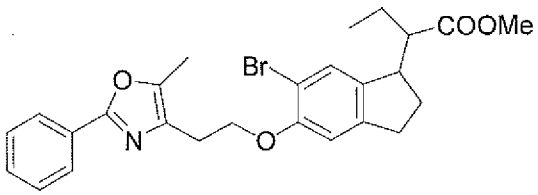


A B

Step 1. A solution of bromine (0.032 mL, 0.60 mmol) in dioxane (3 mL) was cooled to 0°C for 15 minutes after which a solution of 2-(5-hydroxy-indan-1-yl)-butyric acid methyl ester (141 mg, 0.60 mmol) in dioxane (3 mL) was added. After 5 minutes, the ice bath was removed and the reaction was stirred at rt for 4 hours. Solvent was removed by rotary evaporation. The residue was purified by column chromatography (8% EtOAc in hexane) to obtain a colorless oil of mono-bromo intermediate (**A**) (145 mg, 77%) and dibromo intermediate (**B**) (20 mg).

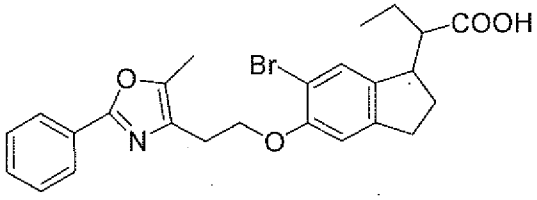
A: R_f = 0.46 (4 : 1 hexane : EtOAc); GC-MS (+Cl): *m/z* = 313 (M^+); ^{1}H NMR (DMSO – d_6): δ 0.840 (m, 3H), 1.511 (m, 2H), 1.905 (m, 1H), 2.091 (m, 1H), 2.410 – 2.793 (m, 3H), 3.212 (m, 1H), 3.505 and 3.512 (s, 3H), 6.713 and 6.753 (s, 1H), 7.034 and 7.274 (s, 1H), 9.932 and 9.934 (s, OH).

B: R_f = 0.30 (4 : 1 hexane : EtOAc); GC-MS(+Cl): *m/z* = 393 (M^+); ^{1}H NMR (DMSO – d_6): δ 0.817 (m, 3H), 1.459 – 1.596 (m, 2H), 1.910 (m, 1H), 2.101 (m, 1H), 2.433 – 2.768 (m, 3H), 3.371 (m, 1H), 3.400 and 3.596 (s, 3H), 7.168 and 7.357 (s, 1H), 9.535 and 9.542 (s, OH).



Step 2. To a solution of (**A**) from step 1 above (118 mg, 0.38 mmol) in DMF (3.8 mL) at 0°C, was added NaH (60% in mineral oil, 30 mg). After 1 hour, the mesylate as prepared in step 1, Example **26** was added. The mixture was heated to 50°C for 30 hours. The solution was diluted with water, and then extracted with ethyl acetate three times. The combined organic layer was washed with water and brine, then dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (10% ethyl acetate in hexane) to give product (63 mg, 34%); R_f = 0.46 (2 : 1 hexane : EtOAc); ESLC-MS: *m/z* = 498 (MH^+);

^{1}H NMR (DMSO – d_6): δ 0.847 (m, 3H), 1.468 (m, 2H), 1.812 (m, 1H), 2.146 (m, 1H), 2.340 (s, 3H), 2.525 – 2.788 (m, 3H), 2.902 (m, 2H), 3.236 (m, 1H), 3.481 and 3.586 (s, 3H), 4.211 (m, 2H), 6.969 (s, 1H), 7.347 and 7.386 (s, 1H), 7.452 (m, 3H), 7.833 (m, 2H).

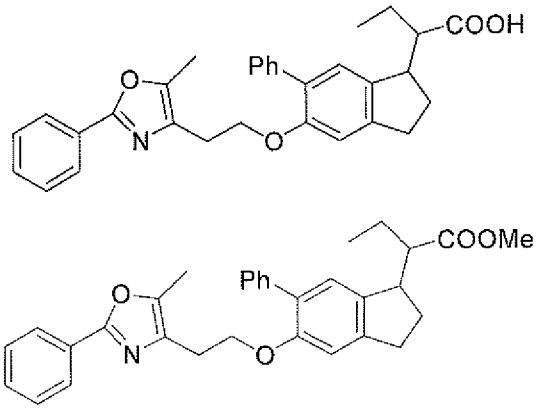


Step 3. To a solution of product from step 2 (5.6 mg) in methanol, was added 3 N KOH (1 mL) followed by addition of THF until the cloudy solution became clear. The mixture was refluxed overnight. Conc. HCl was added to adjust the pH to 2, then extracted three times with ethyl acetate. The organic layers were combined, dried, and concentrated to give white solid (4 mg). R_f = 0.18 (2:1 hexane:EtOAc); ESLC-MS: m/z = 484 (MH^+); ^{1}H NMR (DMSO – d_6): δ 0.832 (m, 3H), 1.468 (m, 2H), 1.812 (m, 1H), 2.146 (m, 1H), 2.405 (m, 1H), 2.788 (m, 2H), 2.904 (m, 2H), 3.015 (m, 1H), 3.136 and 3.138 (s, 3H), 4.209 (m, 2H), 6.987 and 7.344 (s, 1H), 6.972 and 7.251 (s, 1H), 7.487 (m, 3H), 7.882 (m, 2H).

Example 30

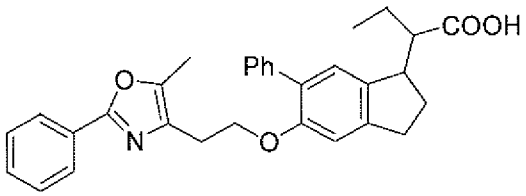
Preparation of 2-{5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-6-phenyl-2,3-dihydro-1H-inden-1-yl}butanoic acid

via methyl 2-{5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-6-phenyl-2,3-dihydro-1H-inden-1-yl}butanoate



Step 1. A mixture of the product of step 2, Example **29** and $Pd(PPh_3)_4$ in THF (1.5 mL) was stirred at rt for 30 minutes. Phenylboronic acid (13.2 mg, 0.108 mmol) and 2 N NaOH were then added into the solution. The mixture was heated to reflux for 14 hours. The solution was allowed to cool down, diluted with water, and extracted with ethyl acetate three times. The combined organic layers were washed with brine and dried over sodium sulfate. The crude product was purified by column chromatography eluting with 5% ethyl acetate in hexane to obtain the desired product (8.6 mg). R_f = 0.48 (2:1 hexane:EtOAc); ESLC-MS: m/z = 496 (MH^+); ^{1}H NMR (DMSO – d_6): δ 0.804 (m, 3H), 1.541 (m, 2H), 1.880 (m, 1H), 1.987

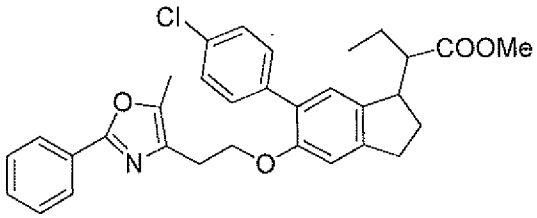
(m, 1H), 2.090 (s, 3H), 2.247 – 2.698 (m, 3H), 2.791 (m, 2H), 3.199 (m, 1H), 3.524 and 3.537 (s, 3H), 4.190 (m, 2H), 6.970 (s, 1H), 7.062 (s, 1H), 7.275 (m, 5H), 7.472 (m, 3H), 7.868 (m, 2H).



Step 2. The ester was hydrolyzed by methods described above to give product: R_f = 0.16 (2 : 1 hexane : EtOAc); ESLC-MS: *m/z* = 482 (MH^+); ^{1}H NMR (DMSO – d_6): δ 0.923 (m, 3H), 1.504 (m, 2H), 1.812 (m, 1H), 2.146 (m, 1H), 2.188 (s, 3H), 2.334 (m, 2H), 2.432 (m, 2H), 2.539 (m, 1H), 2.625 (m, 1H), 4.287 (m, 2H), 7.059 (s, 1H), 7.160 (s, 1H), 7.351 (m, 5H), 7.544 (m, 3H), 7.971 (m, 2H).

Example 31

Preparation of methyl 2-{6-(4-chlorophenyl)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}butanoate

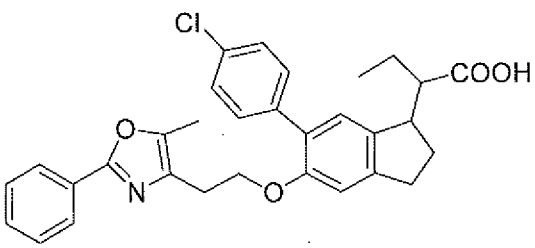


A mixture of the product prepared in step 2, Example **29** (71.4 mg, 0.14 mmol), $NaHCO_3$ (14.3 mg, 0.17 mmol), 4-chlorophenylboronic acid (26.8 mg, 0.17 mmol) in ethylene glycol dimethyl ether (1.5 mL) and water (0.4 mL) was degassed for 20 minutes. $Pd(dppf)Cl_2$ was then added to the solution. The mixture was heated to reflux for 2 days. The mixture was then concentrated and purified with column chromatography (10% EtOAc in hexane) to obtain desired product (25 mg). R_f = 0.51 (2:1 hexane:EtOAc); ESLC-MS: *m/z* = 530 (MH^+); ^{1}H NMR (DMSO – d_6): δ 0.841 (m, 3H), 1.557 (m, 2H), 1.888 (m, 1H), 1.987 (m, 1H), 2.146 (s, 3H), 2.247 – 2.698 (m, 3H), 2.791 (m, 2H), 3.214 (m, 1H), 3.487 and 3.5538 (s, 3H), 4.189 (m, 2H), 6.993 (s, 1H), 7.080 (s, 1H), 7.308 (s, 4H), 7.493 (m, 3H), 7.868 (m, 2H).

By using the above described methods for Examples **26-31** and substituting the appropriate starting materials, the following were made and characterized:

Example 32

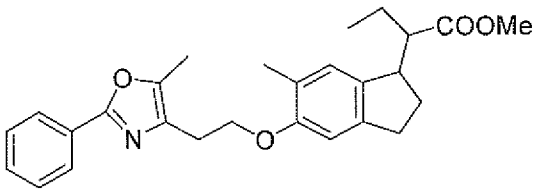
2-{6-chloro-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}butanoic acid



ESLC-MS: m/z = 516 (MH^+); ^{1}H NMR (DMSO – d_6): δ 0.847 (m, 3H), 1.557 (m, 2H), 1.888 (m, 1H), 1.987 (m, 1H), 2.137 (s, 3H), 2.247 – 2.687 (m, 3H), 2.819 (m, 2H), 3.234 (m, 1H), 4.187 (m, 2H), 6.994 (s, 1H), 7.089 (s, 1H), 7.298 and 7.308 (m, 4H), 7.484 (m, 3H), 7.869 (m, 2H).

Example 33

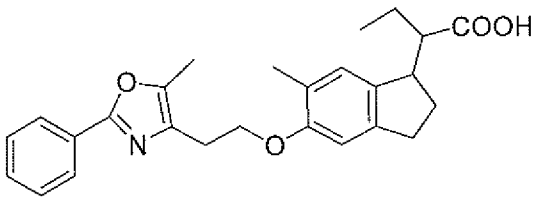
Methyl 2-{6-methyl-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}butanoate



R_f = 0.23 (2:1 hexane:EtOAc); ESLC-MS: m/z = 434 (MH^+); ^{1}H NMR (DMSO – d_6): δ 0.804 (m, 3H), 1.522 (m, 2H), 1.830 (m, 1H), 1.987 (m, 1H), 2.037 (s, 3H), 2.335 (s, 3H), 2.410 – 2.550 (m, 3H), 2.901 (m, 2H), 3.146 (m, 1H), 3.507 (s, 3H), 4.163 (m, 2H), 6.777 (s, 1H), 6.939 (s, 1H), 7.483 (m, 3H), 7.875 (m, 2H).

Example 34

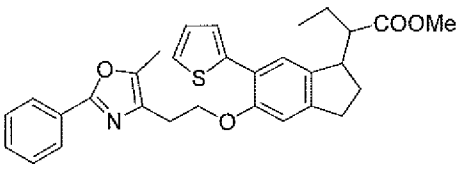
2-{6-methyl-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}butanoic acid



R_f = 0.31 (2:1 hexane:EtOAc); ESLC-MS: m/z = 420 (MH^+); ^{1}H NMR (DMSO – d_6): δ 0.827 (m, 3H), 1.508 (m, 2H), 1.828 (m, 1H), 1.987 (m, 1H), 2.017 (s, 3H), 2.333 (s, 3H), 2.410 – 2.550 (m, 3H), 2.894 (m, 2H), 3.146 (m, 1H), 4.116 (m, 2H), 6.773 (s, 1H), 6.942 (s, 1H), 7.467 (m, 3H), 7.880 (m, 2H).

Example 35

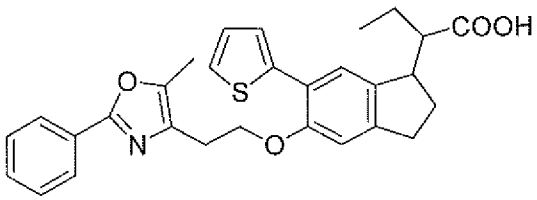
Methyl 2-[5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-6-(2-thienyl)-2,3-dihydro-1H-inden-1-yl]butanoate



R_f = 0.60 (2:1 hexane:EtOAc); ESLC-MS: m/z = 502 (MH^+); ^{1}H NMR (DMSO – d_6): δ 0.801 (m, 3H), 1.535 (m, 2H), 1.891 (m, 1H), 1.987 (m, 1H), 2.299 (s, 3H), 2.410 – 2.550 (m, 3H), 2.988 (m, 2H), 3.146 (m, 1H), 3.506 (s, 3H), 4.337 (m, 2H), 7.011 – 7.041 (m, 2H), 7.405 – 7.493 (m, 5H), 7.884 (m, 2H).

Example 36

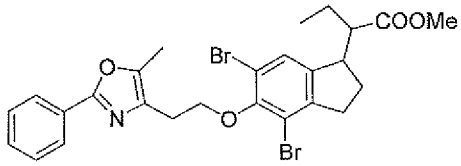
2-[5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-6-(2-thienyl)-2,3-dihydro-1H-inden-1-yl]butanoic acid



R_f = 0.18 (2:1 hexane:EtOAc); ESLC-MS: *m/z* = 488 (MH^+); ^{1}H NMR (DMSO – d_6): δ 0.801 (m, 3H), 1.535 (m, 2H), 1.891 (m, 1H), 1.987 (m, 1H), 2.299 (s, 3H), 2.410 – 2.550 (m, 3H), 2.988 (m, 2H), 3.146 (m, 1H), 4.337 (m, 2H), 7.078 (m, 2H), 7.472 (m, 5H), 7.896 (m, 2H).

Example 37

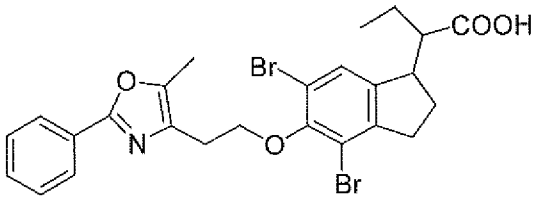
Methyl 2-{4,6-dibromo-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}butanoate



R_f = 0.35 (4:1 hexane:EtOAc); ESLC-MS: *m/z* = 578 (MH^+); ^{1}H NMR (DMSO – d_6): δ 0.847 (m, 3H), 1.468 (m, 2H), 1.812 (m, 1H), 2.146 (m, 1H), 2.350 (s, 3H), 2.407 – 2.788 (m, 3H), 2.982 (m, 2H), 3.225 (m, 1H), 3.480 and 3.588 (s, 3H), 4.145 (m, 2H), 7.276 (s, 1H), 7.458 (m, 3H), 7.866 (m, 2H).

Example 38

2-{4,6-dibromo-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}butanoic acid

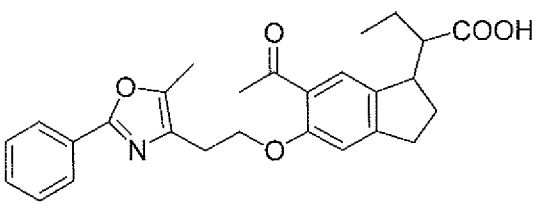


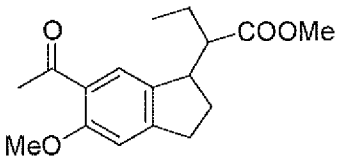
R_f = 0.17 (2:1 hexane:EtOAc); ESLC-MS: *m/z* = 564 (MH^+); ^{1}H NMR (DMSO – d_6): δ 0.847 (m, 3H), 1.468 (m, 2H), 1.812 (m, 1H), 2.146 (m, 1H), 2.361 (s, 3H), 2.414 – 2.781 (m, 3H), 2.995 (m, 2H), 3.123 (m, 1H), 4.125 (m, 2H), 7.345 (s, 1H), 7.437 (m, 3H), 7.886 (m, 2H).

Example 39

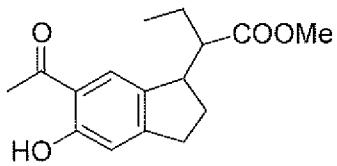
Preparation of 2-{6-acetyl-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}butanoic acid via

methyl 2-(6-acetyl-5-methoxy-2,3-dihydro-1H-inden-1-yl)butanoate

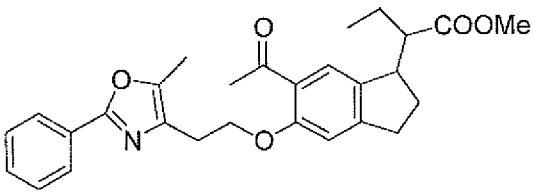




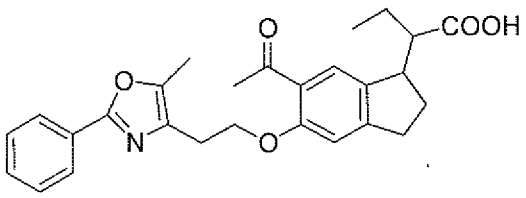
Step 1. To a solution of $AlCl_3$ (103 mg, 0.78 mmol) in methylene chloride (2.5 mL) at 0°C, was added acetyl chloride (0.044 mL, 0.63 mmol), followed by the addition of a solution of methyl 5-methoxy-2,3-dihydro-1H-indene-1-yl-butanoate (130 mg, 0.52 mmol) in methylene chloride (2.7 mL) dropwise. The mixture was stirred at 0°C for 15 minutes. The ice bath was removed and the mixture stirred at rt for 16 hours. The mixture was poured over ice and 4 drops of conc. HCl were added. This mixture was extracted with methylene chloride twice. The combined organic layers were washed with water, 0.05 N NaOH and water. The organic layer was dried, concentrated, and purified by chromatography with 10% EtOAc:hexane to give desired product (103 mg, 68%). R_f = 0.28 (4:1 hexane:EtOAc); GC-MS (+Cl): *m/z* = 291 (M^+); ^1H NMR (DMSO – d_6): δ 0.840 (m, 3H), 1.536 (m, 2H), 1.876 (m, 1H), 2.108 (m, 1H), 2.505 (s, 3H), 2.521 (m, 1H), 2.760 – 2.889 (m, 2H), 3.236 (m, 1H), 3.511 and 3.589 (s, 3H), 3.836 (s, 3H), 7.012 and 7.253 (s, 1H), 7.440 (s, 1H).



Step 2. To a solution of $AlCl_3$ (238 mg, 1.77 mmol) in CH_2Cl_2 (1 mL), was added the product of step 1 (103 mg, 0.35 mmol) in CH_2Cl_2 (2 mL). The mixture was cooled to 0°C for 5 minutes, then EtSH (0.13 mL, 1.77 mmol) was added slowly. The mixture was stirred at this temperature for 4.5 hours. The mixture was then poured over ice water, stirred for 10 minutes, and extracted with CH_2Cl_2 twice. The combined organic layers were washed with water, dried over sodium sulfate, and concentrated to give product (86 mg, 89%). R_f = 0.51 (4:1 hexane:EtOAc); GC-MS (+Cl): *m/z* = 276 (M^+); ^1H NMR (DMSO – d_6): δ 0.841 (m, 3H), 1.574 (m, 2H), 1.888 (m, 1H), 2.094 (m, 1H), 2.585 (s, 3H), 2.639 (m, 1H), 2.729 – 2.847 (m, 2H), 3.244 (m, 1H), 3.513 and 3.628 (s, 3H), 6.774 and 7.503 (s, 1H), 6.792 and 7.715 (s, 1H), 12.117 and 12.143 (s, 1H).



Step 3. The coupling of the hydroxy indene acetic acid ester of step 2 with the mesylate of step 2, Example **26**. ESLC-MS: *m/z* = 462 (MH^+);

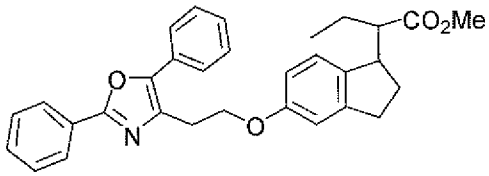


Step 4. The hydrolysis of the product from step 3 was carried out in similar fashion as described above to give product: $R_f = 0.08$ (2:1 hexane:EtOAc); ESLC-MS: $m/z = 448$ (MH^+); ^1H NMR (DMSO – d_6): δ 0.848 (m, 3H), 1.468 (m, 2H), 1.812 (m, 1H), 2.146 (m, 1H), 2.305 (s, 3H), 2.368 (s, 3H), 2.405 (m, 1H), 2.788 (m, 2H), 2.971 (m, 2H), 3.015 (m, 1H), 4.332 (m, 2H), 7.039 and 7.441 (s, 1H), 7.446 (s, 1H), 7.465 (m, 3H), 7.875 (m, 2H).

Using a combination of the above described procedures and substituting the appropriate starting materials, a variety of compounds were prepared and are described below.

Example 40

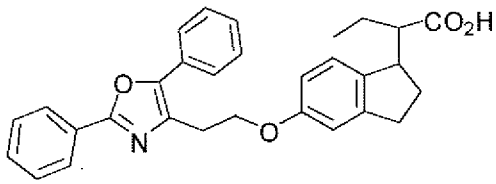
Methyl 2-{5-[2-(2,5-diphenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}butanoate



Yield: 0.09 g, 46%; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.83-0.93 (t, 3 H), 1.55-1.78 (m, 2 H), 1.87-1.97 (m, 1 H), 2.10-2.22 (m, 1 H), 2.44-2.52 (m, 1 H), 2.67-2.80 (m, 1 H), 2.81-2.93 (m, 1 H), 3.21-3.29 (m, 1 H), 3.23-3.33 (t, 2 H), 3.62 (s, 3 H), 4.34-4.43 (t, 2 H), 6.66-6.72 (m, 1 H), 6.76 (s, 1 H), 7.05-7.14 (d, 1 H), 7.33-7.39 (t, 1 H), 7.43-7.51 (m, 5 H), 7.78-7.84 (d, 2 H), 8.06-8.12 (m, 2 H).

Example 41

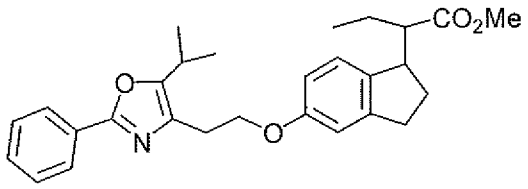
2-{5-[2-(2,5-diphenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}butanoic acid



Yield: 0.07 g, 70%; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85-0.98 (m, 3 H), 1.23-1.47 (m, 1 H), 1.57-1.78 (m, 1 H), 1.88-2.07 (m, 1 H), 2.12-2.27 (m, 1 H), 2.43-2.56 (m, 1 H), 2.68-2.97 (m, 2 H), 3.27-3.35 (t, 2 H), 3.42-3.50 (m, 1 H), 4.34-4.41 (t, 2 H), 6.66-6.73 (d, 1 H), 6.77 (s, 1 H), 7.02-7.16 (d, 1 H), 7.34-7.40 (t, 1 H), 7.43-7.52 (m, 5 H), 7.78-7.83 (d, 2 H), 8.05-8.12 (m, 2 H).

Example 42

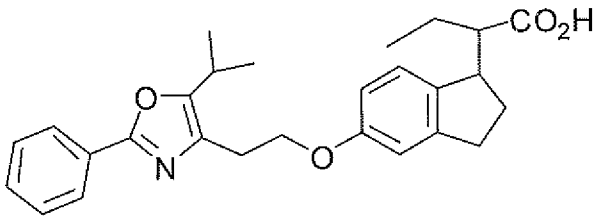
Methyl 2-{5-[2-(5-isopropyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}butanoate



Yield: 0.09 g, 45%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.78-0.96 (t, 3 H), 1.26-1.32 (d, 6 H), 1.51-1.62 (m, 1 H), 1.64-1.75 (m, 1 H), 1.81-1.93 (m, 1 H), 2.07-2.21 (m, 1 H), 2.40-2.51 (m, 1 H), 2.65-2.75 (m, 1 H), 2.77-2.98 (m, 1 H), 2.91-2.98 (t, 2 H), 3.09-3.16 (m, 1 H), 3.21-3.28 (m, 1 H), 3.62 (s, 3 H), 4.10-4.17 (t, 2 H), 6.60-6.68 (d, 1 H), 6.72 (s, 1 H), 7.01-7.13 (d, 1 H), 7.33-7.45 (m, 3 H), 7.94-8.00 (d, 2 H).

Example 43

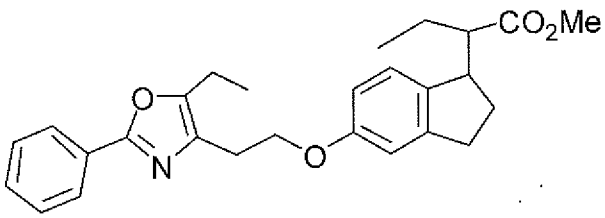
2-{5-[2-(5-isopropyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl} butanoic acid



Yield: 0.08 g, 97%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91-0.98 (t, 3 H), 1.30-1.36 (d, 6 H), 1.58-1.79 (m, 2 H), 1.89-2.05 (m, 1 H), 2.12-2.27 (m, 1 H), 2.44-2.57 (m, 1 H), 2.69-2.80 (m, 1 H), 2.83-2.96 (m, 1 H), 2.97-3.02 (t, 2 H), 3.10-3.21 (m, 1 H), 3.24-3.32 (m, 1 H), 4.14-4.21 (t, 2 H), 6.63-6.71 (d, 1 H), 6.75 (s, 1 H), 7.04-7.16 (d, 1 H), 7.36-7.45 (m, 3 H), 7.94-8.00 (d, 2 H).

Example 44

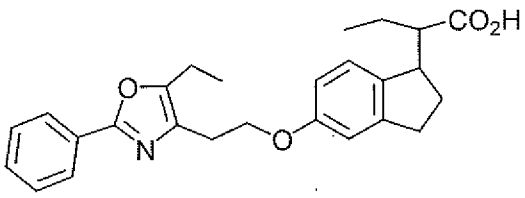
Methyl 2-{5-[2-(5-ethyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-indenyl}butanoate



Yield: 0.14 g, 60%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85-0.91 (t, 3 H), 1.25-1.35 (t, 3 H), 1.58-1.77 (m, 2 H), 1.85-1.97 (m, 1 H), 2.10-2.22 (m, 1 H), 2.44-2.64 (m, 2 H), 2.68-2.80 (q, 2 H), 2.82-2.93 (m, 1 H), 2.95-3.01 (t, 2 H), 3.25-3.34 (m, 1 H), 3.62 (s, 3 H), 4.16-4.25 (t, 2 H), 6.66-6.71 (d, 1 H), 6.75 (s, 1 H), 7.08-7.14 (d, 1 H), 7.38-7.46 (m, 3 H), 7.95-8.01 (m, 2 H).

Example 45

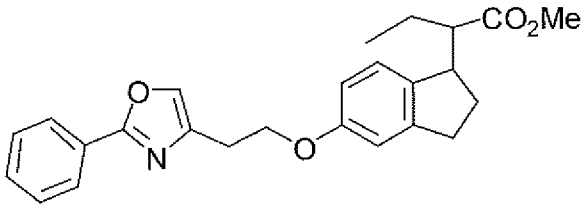
2-{5-[2-(5-ethyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl} butanoic acid



Yield: 0.05 g, 60%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85-0.98 (m, 3 H), 1.21-1.33 (m, 3 H), 1.37-1.54 (m, 1 H), 1.56-1.78 (m, 2 H), 1.87-2.29 (m, 2 H), 2.45-2.60 (m, 1 H), 2.69-2.79 (q, 2 H), 2.85-2.95 (m, 1 H), 2.96-3.01 (t, 2 H), 3.27-3.49 (m, 1 H), 4.14-4.23 (t, 2 H), 6.65-6.71 (d, 1 H), 6.75 (s, 1 H), 7.03-7.17 (d, 1 H), 7.38-7.46 (m, 3 H), 7.95-8.01 (d, 2 H).

Example 46

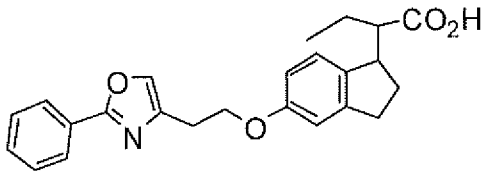
Methyl 2-{5-[2-(2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-indenyl}butanoate



Yield: 0.18 g, 80%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.82-0.92 (t, 3 H), 1.56-1.66 (m, 1 H), 1.67-1.77 (m, 1 H), 1.88-1.99 (m, 1 H), 2.12-2.23 (m, 1 H), 2.43-2.52 (m, 1 H), 2.68-2.81 (m, 1 H), 2.84-2.97 (m, 1 H), 3.02-3.11 (t, 2 H), 3.25-3.33 (m, 1 H), 3.63 (s, 3 H), 4.21-4.30 (t, 2 H), 6.69-6.74 (d, 1 H), 6.79 (s, 1 H), 7.11-7.16 (d, 1 H), 7.41-7.47 (m, 3 H), 7.55-7.58 (m, 1 H), 7.99-8.05 (m, 2 H).

Example 47

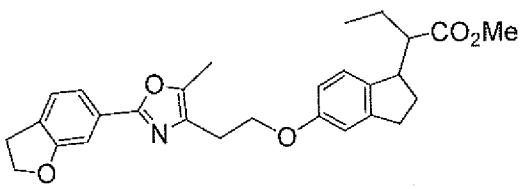
2-{5-[2-(2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}butanoic acid



Yield: 0.07 g, 46%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.84-1.01 (m, 3 H), 1.36-1.51 (m, 1 H), 1.59-1.81 (m, 1 H), 1.88-2.00 (m, 1 H), 2.11-2.29 (m, 1 H), 2 43-2.64 (m, 1 H), 2.68-2.81 (m, 1 H), 2.82-3.00 (m, 2 H), 3.02-3.11 (t, 2 H), 3.23-3.37 (m, 1 H), 4.17-4.28 (t, 2 H), 6.66-6.74 (d, 1 H), 6.78 (s, 1 H), 7.04-7.19 (m, 1 H), 7.39-7.47 (m, 2 H), 7.55 (s, 1 H), 7.98-8.05 (m, 2 H).

Example 48

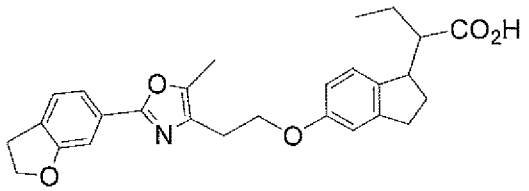
Methyl 2-(5-{2-[2-(2,3-dihydro-1-benzofuran-6-yl)-5-methyl-1,3-oxazol-4-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)butanoate



Yield: 0.17 g, 58%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86-0.97 (t, 3 H), 1.41-1.53 (m, 1 H), 1.61-1.77 (m, 1 H), 1.92-2.01 (m, 1 H), 2.04-2.20 (m, 1 H), 2.40 (s, 3 H), 2.49-2.56 (m, 1 H), 2.71-2.92 (m, 2 H), 3.93-3.00 (t, 2 H), 3.21-3.32 (t, 2 H), 3.34-3.49 (m, 1 H), 3.75 (s, 3 H), 4.18-4.24 (t, 2 H), 4.54-4.70 (t, 2 H), 6.70-6.76 (d, 1 H), 6.79 (s, 1 H), 6.82-6.89 (d, 1 H), 6.92-7.01 (d, 1 H), 7.75-7.80 (d, 1 H), 7.87 (s, 1 H).

Example 49

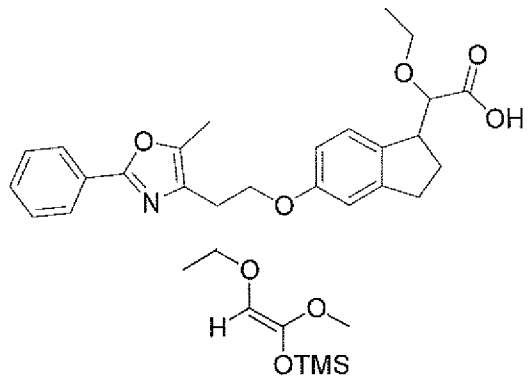
2-(5-{2-[2-(2,3-dihydro-1-benzofuran-6-yl)-5-methyl-1,3-oxazol-4-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)butanoic acid



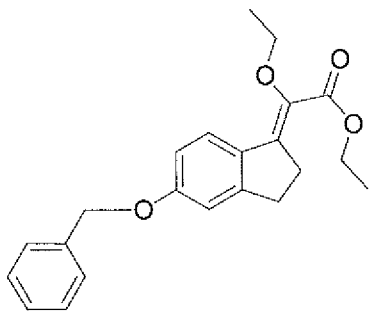
Yield: 0.10 g, 99%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90-1.04 (t, 3 H), 1.41-1.54 (m, 1 H), 1.60-1.76 (m, 1 H), 1.83-1.97 (m, 1 H), 2.12-2.23 (m, 1 H), 2.35 (s, 3 H), 2.48-2.60 (m, 1 H), 2.69-2.90 (m, 2 H), 2.92-3.01 (t, 2 H), 3.18-3.28 (t, 2 H), 3.39-3.50 (m, 1 H), 4.08-4.12 (t, 2 H), 4.46-4.64 (t, 2 H), 6.76-6.71 (d, 1 H), 6.73 (s, 1 H), 6.77-6.84 (d, 1 H), 7.01-7.09 (d, 1 H), 7.71-7.78 (d, 1 H), 7.83 (s, 1 H).

Example 50

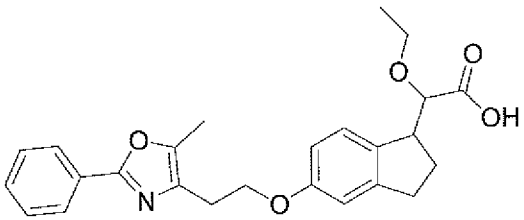
Preparation of ethoxy{5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}acetic acid via ethyl [5-(benzyloxy)-2,3-dihydro-1H-inden-1-ylidene](ethoxy)ethanoate



Step 1. LDA (prepared from 11 mmol DIA and 11 mmole BuLi) was added to methyl 2-ethoxyacetate (10 mmol) in 50 mL THF at -78°C, stirred for 1 hour, then TMSCl (30 mmol) was added. The mixture was concentrated *in vacuo*, and was carried to the next step directly without purification.



Step 2. 5-Benzyloxy-1-indanone in CH_2Cl_2 (5 mL) was slowly added to $TiCl_4$ in CH_2Cl_2 (10 mL) at -78°C, stirred at -60°C for 10 minutes, and cooled to -78°C. The product of step 1 in CH_2Cl_2 (5 mL) was slowly added and stirred for 10 minutes. The reaction was quenched with saturated K_2CO_3, filtered, extracted with ethyl acetate, and dried over sodium sulfate. Column chromatography yielded a colorless oil as product. LC-MSMH^+=353.1, RT = 4.00 min.; NMR ($CDCl_3$, 400 MHz) δ 7.9 (1H, d), 7.25 (5H, m), 6.78 (2 H, m), 4.93 (2H, s), 4.15 (2H, q), 3.75 (2H, q), 3.05 (2H, m), 2.85 (2H, m), 1.22 (6H, m)

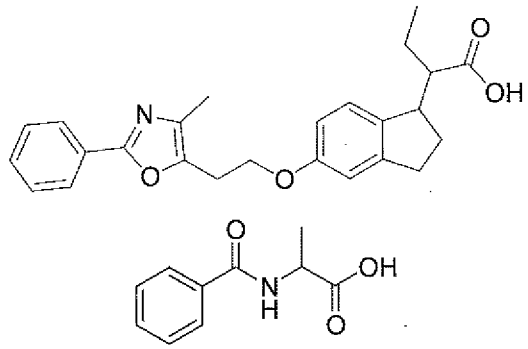


Step 3. Using the product of step 2 as starting material and procedures similar to that described for Example **13**, steps 4-8, the desired final product was prepared and characterized: LC-MS [MH^+] = 422.2, RT = 3.25 min.; NMR ($CDCl_3$, 400 MHz) δ 8.26 (1H, d), 7.55 (2H, m), 7.16 (2H,d), 6.70 (3H, m), 4.16 (2H,q), 3.63 (2H, t) 3.5 (2H, m), 3.30 (1H, m), 3.20 (1H, m), 2.50 (3H, s), 1.10 (3H, m).

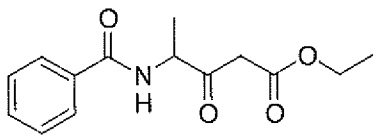
Example 51

Preparation of 2-{5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}butanoic acid

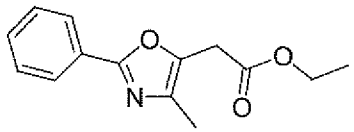
via 2-(4-methyl-2-phenyl-1,3-oxazol-5-yl)ethanol



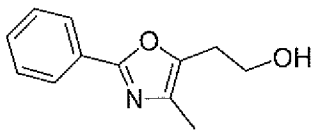
Step 1. To a solution of sodium hydroxide (8.98 g, 224.49 mmol) in water (112.25 mL), was added at rt DL-Alanine (10 g, 112.25 mmol). The resulting solution was heated at 75°C and the benzoyl chloride (15.77 g, 112.25 mmol) was slowly added. The reaction was heated for 30 minutes, and cooled down to 0°C with an ice bath. Conc. HCl was added to adjust the pH to 1, then the white solid was filtrated through a fritted glass funnel and vacuum dried with P_2O_5 overnight. No purification was needed. This gave N-benzoylalanine (19.6 g, 90.4% yield) as white solid. ^{1}H NMR (DMSO-d_6) δ 12.61 (s br, 1H), 8.64 (d, 1H), 7.87-7.85 (m, 2H), 7.52-7.43 (m, 3H), 4.40 (q, 1H), 1.39 (d, 3H).



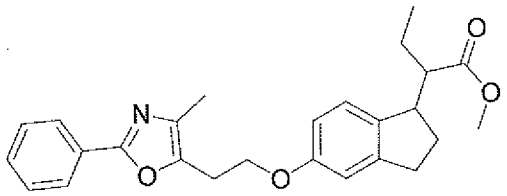
Step 2. In the first flask, N-benzoylalanine (2 g, 10.35 mmol) was dissolved in THF (20 mL), and carbonyl diimidazole (CDI) (1.84 g, 11.39 mmol) was added. The resulting mixture was stirred 1 hour at rt and cooled down to –78°C. Into a second flask, ethyl acetate (3.83 g, 43.48 mmol) in THF (40 mL) was cooled down to –78°C and LDA (24.3 mL, 48.51 mmol, 2 M in THF) pre-cooled to –78°C was added. The resulting solution was stirred 30 minutes at –78°C, and the lithium enolate generated was cannulated into the first flask. The resulting white slurry was stirred 30 minutes at –78°C and warmed up to –10°C. The reaction was quenched with a saturated aqueous solution of NH_4Cl. Phases were separated and the organics were dried over $MgSO_4$ and solvents removed under reduced pressure. The crude product was carried to the next step without purification. This gave ethyl 4-(benzoylamino)-3-oxopentanoate (2.6 g, 95.5% yield) as a white solid. ES-MS *m/z* 263.4 ($(MH)^+$); HPLC RT (min.) 1.53; ^{1}H NMR (Acetone-d_6) δ 8.13 (s br, 1H), 7.93-7.91 (m, 2H), 7.58-7.43 (m, 3H), 4.72 (m, 1H), 4.19-4.01 (q, 2H), 3.67 (s, 2H), 1.47 (d, 3H), 1.15 (t, 3H).



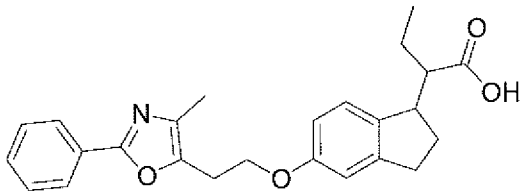
Step 3. To a crude mixture of ethyl 4-(benzoylamino)-3-oxopentanoate (0.6 g, 2.28 mmol) in DMF (4 mL) at rt, was added $POCl_3$ (1.04 g, 6.84 mmol). The resulting solution was heated at 90°C for 1 hour, then cooled down to rt, and poured into ice for 30 minutes. The aqueous solution was carefully added to a saturated aqueous solution of $NaHCO_3$. Phases were separated with EtOAc and the combined organic extracts were dried over MgSO4 and solvent removed under reduced pressure. The crude material was purified on Biotage small column using a solvent gradient of 0 to 50% EtOAc/Hexane. This gave ethyl (4-methyl-2-phenyl-1,3-oxazol-5-yl)acetate (0.269 g 48% yield) as yellowish oil. ES-MS *m/z* 246.2 ($(MH)^+$); HPLC RT (min.) 2.77; ^{1}H NMR ($CDCl_3$) δ 8.01-7.98 (m, 2H), 7.45-7.41 (m, 3H), 4.20 (q, 2H), 3.71 (s, 2H), 2.21 (s, 3H), 1.28 (t, 3H).



Step 4. Ethyl (4-methyl-2-phenyl-1,3-oxazol-5-yl)acetate (0.922 g, 3.76 mmol) in THF (6 mL) at rt, was added $LiBH_4$ 2M/THF (9.41 mL, 4.70 mmol). The reaction was stirred overnight at rt, then treated with 2 N HCl until pH 7. The solvent THF was removed under reduced pressure, EtOAc was added, and phases separated. The combined organic extracts were dried over $MgSO_4$ and solvent concentrated *in vacuo*. The crude material was purified by Biotage using a gradient of 10 to 100% EtOAc/Hexane as solvent mixture. This gave 2-(4-methyl-2-phenyl-1,3-oxazol-5-yl)ethanol (0.193 g, 25% yield) as colorless oil. ES-MS *m/z* 204.2 ($(MH)^+$); HPLC RT (min.) 2.02; ^{1}H NMR (Acetone-d_6) δ 7.98-7.95 (m, 2H), 7.52-7.42 (m, 3H), 3.95 (s br, 1H), 3.82 (t, 2H)m, 2.90 (t, 2H), 2.13 (s, 3H).



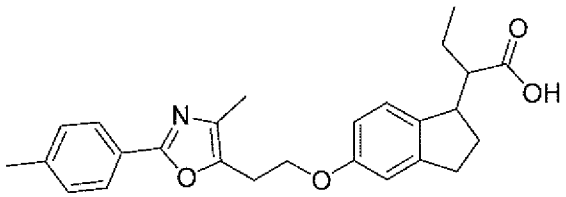
Step 5. DEAD (0.84 mL, 5.28 mmol) in THF (1.5 mL) was slowly added to a solution of the product of step 3 (4.95 mmol), methyl 5-hydroxy-2,3-dihydro-inden-1yl-2-butanoate (0.78 g, 3.3 mmol), PPh_3 (1.4 g, 5.28 mmol) in THF (13 mL). The mixture was stirred at rt overnight. The mixture was filtered, washed with water, brine, dried over sodium sulfate, and concentrated. Column chromatography yielded a colorless oil as product. LC-MS $[C_{26}H_{29}NO_4H]^+ = 420.4$, RT = 4.00 min.; ^1H NMR ($CDCl_3$): δ 7.9 (2H, d), 7.45 (2H, dd), 7.1(d), 6.6-6.8 (3H, m), 4.2 (2H, t), 3.62 (3H, s), 3.3 (1H, m), 3.15 (2H,t), 2.6-3.0 (2H, m, br), 2.5 (1H, m),2.21 (3H, s), 1.95 (1H, m), 1.56-1.6 (3H, br, m), 0.88 (3H, t).



Step 6. KOH (0.5 mL, 3 N) was added to a solution of the product of step 4 (42 mg, 0.1 mmol) in THF/MeOH (1 mL, THF:MeOH 8:2). The mixture was stirred at 70°C for 6 hours, then cooled down. The pH was adjusted to 4 with 1 N HCl. The mixture was extracted with ethyl acetate (3 x 2 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. Column chromatography (2:8/hexane:ethyl acetate) gave a white solid as the product (33 mg, 81%). LC-MS $[C_{25}H_{27}NO_4H]^+ = 406.3$, RT = 3.37 min.; ^1H NMR ($CDCl_3$): δ 8.0 (2H, d), 7.45 (2H, dd), 7.15 (1H, d), 6.7-6.8 (3H, m), 4.2 (2H, t), 3.3 (1H, m), 3.15 (2H,t), 2.6-3.0 (2H, m, br), 2.5 (1H, m), 2.21 (3H, s), 1.95 (1H, m), 1.56-1.6 (3H, br, m), 0.88 (3H, t)

By using the procedure described above for Example **51** and substituting the appropriate starting materials, the following were similarly prepared and characterized.

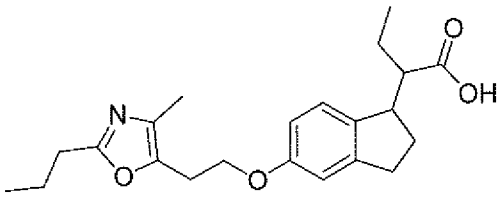
Example 52



LC-MS $[C_{26}H_{29}NO_4H]^+ = 420.3$, RT = 3.52 min.; ^1H NMR ($CDCl_3$): δ 7.87 (2H,d), 7.25 (2H,dd), 7.1(1H,d), 6.6-6.8 (3H, m), 4.2 (2H, t), 3.45 (1H,m), 3.30 (1H, m), 3.15 (2H,t), 2.7-3.0 (2H, m, br), 2.5 (1H, m), 2.4 (3H, s) 1.95 (1H, m), 1.56-1.60 (3H, br ,m), 0.88 (3H,t)

Example 53

2-{5-[2-(4-methyl-2-propyl-1,3-oxazol-5-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}butanoic acid

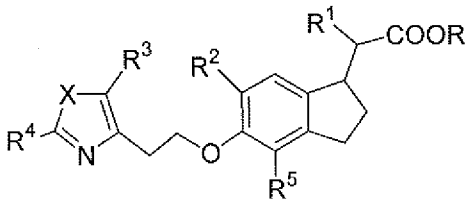


LC-MS $[C_{22}H_{29}NO_4H]^+ = 372.3$, RT = 3.16 min.; ^1H NMR ($CDCl_3$): δ 7.1 (1H,d), 6.6 (2H,d), 4.2 (2H, t), 3.3 (1H,m), 3.3 (1H, m), 2.8 (2H,t), 2.7 (1H, m), 2.6 (2H, t), 2.4 (2H,m), 2.2 (3H, s), 2.0-1.8 (2H,br,m), 0.88 (3H,t)

By using the methods described above for Examples **1-53** and by substituting the appropriate starting materials, compounds of Formula **Ia,** listed in Table 3 below, were similarly prepared.

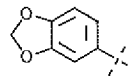
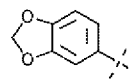
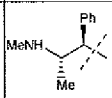
Table 3

Preparative Examples of Compounds of Formula (Ia)



(Ia)

Ex. No.	R	R^1	R^2	R^3	R^4	R^5	X	LC-MS $[M+H]^+$ or NMR
54	H	Et	H	Me	$PhOCH_2$-	H	O	436.2
55	H	Et	H	Me	$PhCH_2$ -	H	O	420
56	H	H	H	Me	Ph	H	O	378.2
57	Me	$Ph(CH_2)_3$-	H	Me	Ph	H	O	3.45/3.52 (t, 3H), 4.10 (t, 2H), 7.3 (m, 3H), 7.83 (d, 2H)
58	Et	EtO_2C-	H	Me	Ph	H	O	478.2
59	Et	Et	H	Me	Ph	H	O	434.3
60	H	MeO	H	Me	Ph	H	O	3.30 (s, 3H), 4.04 (d, 1H), 7.98 (m, 2H)
61	Et	EtO	H	Me	Ph	H	O	450.3

Ex. No.	R	R^1	R^2	R^3	R^4	R^5	X	LC-MS $[M+H]^+$ or NMR
62	H	CF_3CH_2-	H	Me	Ph	H	O	2.51 (s, 3H), 4.36 (m, 2H), 8.32 (m, 2H)
63	Et	CF_3CH_2-	H	Me	Ph	H	O	1.18 (t, 3H), 4.21 (t, 2H), 7.98 (d, 2H)
64	Me	*cyc*-Pr	H	Me	Ph	H	O	432.3
65	H	*cyc*-Pr	H	Me	Ph	H	O	0.02 (m, 1H), 0.12 (m, 1H), 4.18 (m, 2H), 7.94 (m, 2H)
66	H		H	Me	Ph	H	O	512.3
67	H	Et	H	Me	Ph	H	S	422.3
68	H		H	Me	Ph	H	O	526.4
69	H	Et	H	Me	Ph	H	S	422.3
70		Et	H	Me	Ph	H	S	
71	Me	Et	H	Me	Ph	H	O	0.82 (t, 3H), 3.54 (s, 3H), 4.16 (t, 2H), 7.90 (m, 2H)
72	H	Et	H	*i*-Pr	Ph	H	O	434.3
73	H	Et	H	Ph	Ph	H	O	468.3
74	H	Me	H	Me	Ph	H	S	422.3
75	Me	Me	H	Me	Ph	H	S	
76	Me	Et	MeC(O)-	Me	Ph	H	O	462.4

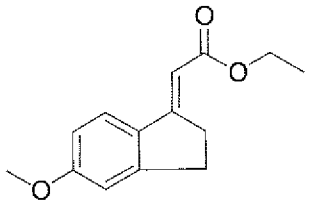
Ex. No.	R	R^1	R^2	R^3	R^4	R^5	X	LC-MS $[M+H]^+$ or NMR
77	Me	Et	4-MeO-Ph	Me	Ph	H	O	526.4
78	H	Et	4-MeO-Ph	Me	Ph	H	O	512.3
79	Me	Et	4-pyridyl	Me	Ph	H	O	497.3
80	H	Et	H	Me	*cyc*-Pentyl	H	O	398
81	H	Et	H	Me	*cyc*-Hexyl	H	O	412
82	H	Et	H	Me	4-Ph-Ph-	H	O	482
83	Et	EtO_2C-	H	Me	4-Me-Ph-	H	O	492.3
84	H	$PhCH_2$-	H	Me	4-Me-Ph-	H	O	482.4
85	Et	*n*-Bu	H	Me	4-Me-Ph-	H	O	476.3
86	Et	Me	H	Me	4-Me-Ph-	H	O	434.3
87	Et	$PhCH_2$-	H	Me	4-Me-Ph-	H	O	510.4
88	H	Et	H	Me	4-MeO-Ph	H	O	436.1
89	H	Et	H	Me	4-*i*-Pr-Ph	H	O	448.2
90	H	Et	H	Me	4-F-$PhCH_2$-	H	O	438.3
91	H	Et	H	Me	4-F-Ph	H	O	424.3
92	H	Et	H	Me	4-Et-Ph	H	O	434.3
93	H	Et	H	Me	4-Cl-$PhOCH_2$-	H	O	470.2
94	H	Et	H	Me	4-Cl-Ph	H	O	440
95	Me	Et	H	Me	4-Cl-Ph	H	S	470.3
96	Me	Et	H	Me	4-Cl-Ph	H	S	470.3
97	H	Et	H	Me	4-CF_3-Ph	H	S	490.3
98	Me	Et	H	Me	4-CF_3-Ph	H	S	504.3
99	H	Et	H	Me	4-CF_3-Ph	H	O	474.3

Ex. No.	R	R^1	R^2	R^3	R^4	R^5	X	LC-MS $[M+H]^+$ or NMR
100	H	Et	H	Me	4-(*n*-Bu)-Ph	H	O	462.3
101	H	Et	H	Me	4-(*t*-Bu)-Ph	H	O	462.3
102	H	Et	H	Me	3-Me-Ph	H	O	420.4
103	H	Et	H	Me	3-MeO-Ph	H	O	436.3
104	H	Et	H	Me	3-Me-5-isoxazolyl	H	O	411.3
105	H	Et	H	Me	3-F-Ph	H	O	424.2
106	H	Et	H	Me	3-F-4-Me-Ph	H	O	438.2
107	H	Et	H	Me	4-F-3-Me-Ph	H	O	438.3
108	Me	Et	H	Me	3-Cl-Ph	H	S	470.3
109	H	Et	H	Me	3-Cl-Ph	H	O	440.3
110	H	Et	H	Me	3-Cl-Ph	H	S	456.3
111	H	Et	H	Me	3-CF_3-Ph	H	O	474.2
112	H	Et	H	Me	3,5-$(CF_3)_2$-Ph	H	O	542.1
113	H	Et	H	Me	3,4-Me_2-Ph	H	O	434.3
114	H	Et	H	Me	3,4-Cl_2-Ph	H	O	474.2
115	H	Et	H	Me	2,3-Cl_2-Ph	H	O	474.1
116	H	Et	H	Me	3,4-$(MeO)_2$-Ph	H	O	466.3
117	H	Et	H	Me	3,4-methylenedioxy-Ph	H	O	466.3
118	H	Et	H	Me	2-thienyl	H	O	412
119	H	Et	H	Me	2-naphthyl	H	O	456.3
120	H	Et	H	Me	2-Me-Ph	H	O	420.3

Ex. No.	R	R^1	R^2	R^3	R^4	R^5	X	LC-MS $[M+H]^+$ or NMR
121	H	Et	H	Me	2-furyl	H	O	396
122	H	Et	H	Me	2-F-Ph	H	O	424.1
123	H	Et	H	Me	2-benzothienyl	H	O	462.2
124	H	Et	H	Me	2,6-F_2-Ph	H	O	442.2
125	H	Et	H	Me	3,4-F_2-Ph	H	O	442.2
126	H	Et	H	Me	2,4-Cl_2–Ph	H	O	473
127	H	Et	H	Me	1-naphthyl	H	O	456.3
128	Me	Et	H	Me		H	O	0.90 (t, 3H), 3.45 (bs, 4H), 3.74 (s, 3H)

Example 129

Preparation of ethyl (5-methoxy-2,3-dihydro-1*H*-inden-1-ylidene)ethanoate

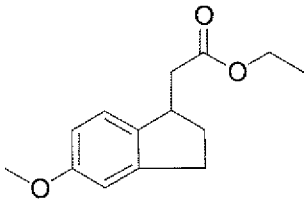


To a solution of 5-methoxyindanone (150 g, 0.91 mol) in anhydrous tetrahydrofuran (4.5 L), was added zinc (30 mesh, 103.64 g, 1.59 mol) and copper(I) chloride (4.53 g, 0.045 mol). The suspension was stirred under Ar atmosphere and refluxed for 15 minutes; approximately a 25% portion of ethyl bromoacetate (133 mL, 1.18 mol) was added to the refluxing mixture in a slow dropwise fashion. After allowing to cool and stirring overnight at rt, TLC showed the presence of desired product, indicating the formation of reactive zinc species. The remainder of ethyl bromoacetate was added dropwise; an exotherm was observed (internal temperature increased to 35°C). After 4 hours, TLC showed complete reaction. After the solids settled to the bottom of the flask, the liquid was siphoned off leaving a small amount behind to cover the solids. The flask was re-charged with 5-methoxyindanone (157.6 g, 1.86 mol total), anhydrous tetrahydrofuran (4.5 L), and zinc (80.92 g, 2.73 mol total). Ethyl bromoacetate (140 mL, 2.36 mol total) was added dropwise. An exotherm was observed (internal temperature increased to 35°C). When the stirred mixture cooled to rt, TLC showed the reaction to be complete. The solids were allowed to settle and the liquid was siphoned off. The combined reaction solutions were concentrated *in vacuo* to a volume of ~ 2L.

The liquid was then poured into sufficient 1N aqueous hydrochloric acid (cooled in ice water) to bring the pH to 1. The product was extracted with ethyl acetate (2 x 1 L, 1 x 500 mL). The combined extracts were washed with water, brine (1 L each), dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a dark red oil which solidified gradually (438.3 g; theoretical yield = 432 g). ^{1}H NMR ($CDCl_3$): δ 7.5 (d, 1H), 6.8 (m, 2H), 6.2 (t, 1 H), 4.2 (q, 2H), 3.8 (s, 3H), 3.3 (m, 2H), 3.0 (t, 2H), 1.3 (t, 3H). MS (CI) *m/z* 233 $[M+H]^+$.

Example 130

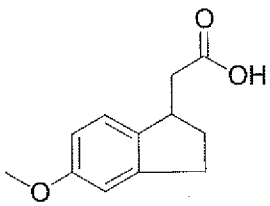
Preparation of ethyl (5-methoxy-2,3-dihydro-1*H*-inden-1-yl)acetate



The crude product of Example 129 was dissolved in absolute ethanol (2.6 L) and hydrogenated at 40 psi of hydrogen over 10% palladium on carbon (21.6 g). Filtration through Celite and concentration of the filtrate afforded 433.3 g of brown oil (99% yield for 2 steps). ^{1}H NMR ($CDCl_3$): δ 7.1 (dd, 1H), 6.8 (d, 1H), 6.7 (dd, 1H), 4.2 (q, 2H), 3.8 (s, 3H), 3.5 (m, 1H), 2.9 (m, 2H), 2.7 (dd, 1H), 2.4 (m, 2H), 1.7 (m, 1H), 1.3 (t, 3H). MS (CI) *m/z* 235 $[M+H]^+$.

Example 131

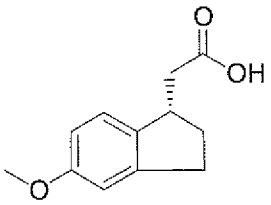
Preparation of (5-methoxy-2,3-dihydro-1*H*-inden-1-yl)acetic acid



To a solution of the crude ester (416 g, 1.77 mol) prepared in Example **130** in 1 L EtOH, was added a solution of NaOH (142 g, 3.54 mol) in 1.5 L water. The cloudy reaction mixture was heated to reflux, during which time the color changed to dark red, and the reaction became homogeneous. After 1 hour, the reaction was cooled to rt, and the EtOH was removed under reduced pressure. The basic aqueous layer was washed with Et_2O (3 x 500 mL), then acidified with conc. HCl to pH ~4 upon which an oil residue formed. The mixture was extracted with Et_2O (4 x 500 mL). The combined extracts were washed with water (2 x 300 mL), brine, then dried over Na_2SO_4. Filtration and evaporation of solvent under reduced pressure gave the title compound (305 g, 83%) as a yellow solid after overnight drying under vacuum. ^{1}H NMR ($CDCl_3$) δ 7.34(d, 1H), 6.71(s, 1H), 6.65(dd, 1H), 3.71(s, 3H), 3.47(m, 1H), 2.80(m, 3H), 2.35(m, 2H), 1.71(m, 1H). MS (CI) *m/z* 207 $[M+H]^+$.

Example 132

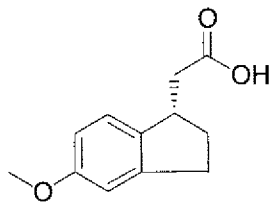
Preparation of [(1*S*)-5-methoxy-2,3-dihydro-1*H*-inden-1-yl]acetic acid



To a solution of the acid (341.0 g, 1.65 mol) prepared in Example **131** in 8.2 L reagent grade acetone, was added *(S)*-(-)-α-methylbenzylamine (223.8 mL, 1.74 mol) dropwise at rt with stirring. A thick white precipitate formed during the addition. An additional 500 mL acetone was added and stirring continued for 1 hour. The solids were collected by filtration, washed with 300 mL acetone, and dried under suction. The solids were then suspended in acetone (8.2 L) and warmed to reflux until all solids dissolved. The solution was cooled slowly overnight, during which time a white precipitate formed. The suspension was cooled to 0°C, then filtered, and the solids were washed with 500 mL acetone. After drying under suction, a sample analyzed by HPLC showed 95% ee. The recrystallization process was repeated as above using 6.7 L acetone. HPLC analysis showed 99% ee. After drying under suction, 192 g salt were obtained. The salt was suspended in 2 L EtOAc and 1 L of 1 N HCl solution, and shaken in a separatory funnel, whereupon the salt dissolved. The organic layer was separated, washed with 1 N HCl (500 mL), water (2 x 300 mL), and brine, then dried over Na_2SO_4. The solvent was evaporated under reduced pressure, giving an oil which soon solidified. The title product (120.5 g, 35%) was obtained as an off-white solid after vacuum drying. ^{1}H NMR ($CDCl_3$) δ 7.10(d, 1H), 6.79(d, 1H), 6.73(dd, 1H), 3.79(s, 3H), 3.55(m, 1H), 2.89(m, 2H), 2.79(dd, 1H), 2.46(dd, 1H), 2.43(m, 1H), 1.80(m, 1H). MS (ESI) *m/z* 207 $[M+H]^+$.

Example 133

Preparation of [(1*S*)-5-methoxy-2,3-dihydro-1*H*-inden-1-yl]acetic acid

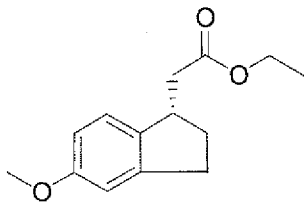


As an alternative to Example **132**, the title compound may also be prepared via an enzymatic process. Thus, a cloudy mixture of the crude ester (500.0 g, 2.13 mol; 87% pure as determined by HPLC) prepared in Example **130**, in 1 L reagent grade acetone, 2.5 L Phosphate Buffer (pH 7.0, 0.05 M) and 2.5 L deionized water was treated in one portion with Amano Lipase PS (150 g), and the mixture stirred efficiently at rt overnight. HPLC analysis of an aliquot (homogeneous aliquot prepared by dissolving aliquot in IPA followed by filtration) showed one peak corresponding to unreacted R-ester and another peak corresponding to desired S-acid. Trace amounts of S-ester and R-acid were noted. 2 N HCl (500 mL, ensure a pH ~2) was added in one portion to the reaction and stirred for 20 minutes. The mixture was filtered and the solids were washed with EtOAc (2 x 500 mL), then water (500 mL). The combined filtrates were further diluted with 1 L EtOAc, and the layers stirred together vigorously. Stirring was stopped and the layers allowed to separate. Emulsions were noted, but could be broken with the addition of solid NaCl and stirring. The aqueous layer

was removed, then extracted with EtOAc (3 x 1 L) in the same fashion. The combined organic extractions were washed with water (4 x 500 mL), then with brine. The resulting organic layer was extracted with a 5% Na_2CO_3 solution (8 x 500 mL). HPLC analysis of the organic layer showed that it contained none of the S-enantiomer acid. The combined Na_2CO_3 extracts were washed with EtOAc (2 x 1 L), then acidified to pH ~2 by the addition of 2N HCl. A white solid precipitated, accompanied by CO_2 evolution. The mixture was extracted with EtOAc (3 x 1 L). The combined extracts were washed with water (2 x 1 L) and brine, then dried over Na_2SO_4. HPLC analysis of this solution showed the material was 98% ee. The solvent was evaporated under reduced pressure, giving an oil which soon solidified. The title product (172.9 g) was obtained as an off-white solid after vacuum drying. This material was recrystallized from boiling hexanes (8.8 L). After overnight cooling, light yellow needles were collected via filtration, washed with hexanes (200 mL), and dried under suction. The title product (146.9 g, 38% from crude starting ester) was obtained as light yellow needles after vacuum drying. ^{1}H NMR results as above.

Example 134

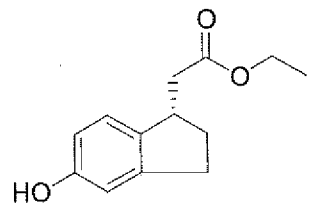
Preparation of ethyl [(1*S*)-5-methoxy-2,3-dihydro-1*H*-inden-1-yl]acetate



To a solution of the acid (305 g, 1.48 mol) prepared in either Example **132** or **133** in 4.8 L absolute EtOH at rt under argon, was added chlorotrimethylsilane (413 mL, 3.25 mol) dropwise. An approximate 5°C rise in temperature was noted during the addition. The reaction was stirred overnight. EtOH was evaporated under reduced pressure, giving a bi-phasic liquid mixture. This was diluted in 500 mL ice-water, then extracted with EtOAc (2 x 750 mL). The combined extracts were washed with water (3 x 300 mL), then with saturated $NaHCO_3$ (200 mL). The organic was washed once more with water (300 mL), then brine, and dried over Na_2SO_4. The title compound (354 g, 102%) was obtained as a light yellow oil after solvent removal and vacuum drying. ^{1}H NMR ($CDCl_3$) δ 7.07(d, 1H), 6.78(d, 1H), 6.71(dd, 1H), 4.18(q, 2H), 3.78(s, 3H), 3.52(m, 1H), 2.89(m, 2H), 2.72(dd, 1H), 2.37(o, 2H), 1.74(m, 1H), 1.28(t, 3H). MS (CI) *m/z* 235 $[M+H]^+$.

Example 135

Preparation of ethyl [(1*S*)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl]acetate

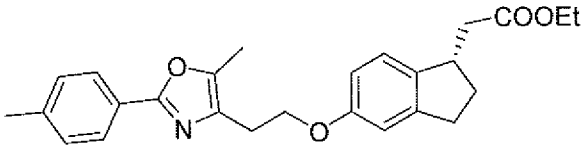


To a cold solution (ice water bath) of the compound (346 g, 1.48 mol) prepared in Example **134** in 4.2 L CH_2Cl_2, was added $AlCl_3$ (984.6 g, 7.38 mol) portionwise under Ar such that the reaction temperature

was maintained below 10°C. The light brown suspension was stirred 10 minutes, then EtSH (546 mL, 7.38 mol) was added dropwise at such a rate that the reaction temperature was maintained below 5°C. After 2.5 hours of stirring below 10°C, the reaction mixture was slowly poured into 6 L ice water with strong agitation. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 1 L). The combined CH_2Cl_2 layers were washed with water (2 x 1 L), then dried over Na_2SO_4. The solvent was removed under reduced pressure, giving a brown oil, which was filtered through a pad of silica gel (eluted with 0-10% EtOAc/Hexanes). Fractions were collected and the title compound (314 g, 96%) was obtained as a thick yellow oil after solvent removal and vacuum drying. ^{1}H NMR ($CDCl_3$) δ 6.92(d, 1H), 6.62(d, 1H), 6.55(dd, 1H), 4.10(q, 2H), 3.43(q, 1H), 2.75(m, 2H), 2.64(dd, 1H), 2.31(dd, 1H), 2.29(m, 1H), 1.67(m, 1H), 1.20 (t, 3H). MS (CI) *m/z* 221 $[M+H]^+$.

Example 136

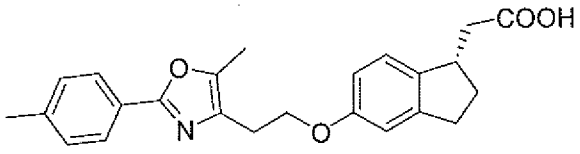
Preparation of ethyl 2-((1*S*)-5-{2-[5-methyl-2-(4-methylphenyl)(1,3-oxazol-4-yl)]ethoxy}indanyl)acetate



A suspension of the ethyl [(1*S*)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl]acetate prepared in Example **135** (507.5 mg, 2.30 mmol), and 2-[5-methyl-2-(4-methylphenyl)-1,3-oxazol-4-yl]ethanol prepared in Example **10** (500 mg, 2.30 mmol), TMAD (792.6 mg, 4.60 mmol), and Ph_3P (1.21 g, 4.60 mmol) in 15 mL anhydrous DCM was stirred at rt under Ar for 12 hours. DCM was removed under reduced pressure. Flash chromatograph of the residue over silica gel using 1% CH_3CN/CH_2Cl_2 gave ethyl 2-((1*S*)-5-{2-[5-methyl-2-(4-methylphenyl)(1,3-oxazol-4-yl)]ethoxy}indanyl)acetate (776.3 mg, 1.85 mmol, 80.5%). HPLC/MS $(M+H)^+$ m/z 420.5.

Example 137

Preparation of 2-((1*S*)-5-{2-[5-methyl-2-(4-methylphenyl)(1,3-oxazol-4-yl)]ethoxy}indanyl)acetic acid



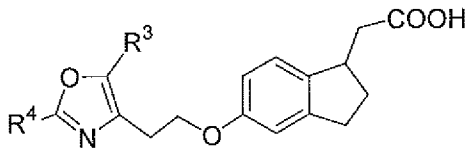
Ethyl 2-((1*S*)-5-{2-[5-methyl-2-(4-methylphenyl)(1,3-oxazol-4-yl)]ethoxy}indanyl)acetate (Example **136,** 776.3 mg, 1.85 mmol) in THF (4.0 ml) was added to a mixture of aqueous LiOH (2 M, 3.7 ml, 7.4 mmol), water (2.0 ml), and EtOH (4.0 ml) at rt. The resulting mixture turned cloudy. This mixture was heated at 40°C (oil-bath temperature). The reaction was completed after 1.5 hours. After cooling to rt, 1 N HCl solution was slowly added to the mixture until pH 4.0. The compound was extracted with EtOAc (3 x 20 ml). The combined EtOAc layers were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue gave 2-((1*S*)-5-{2-[5-methyl-2-(4-methylphenyl)(1,3-oxazol-4-yl)]ethoxy}indanyl)acetic acid (616.8 mg, 1.57 mmol, 85%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.83(d, 2H), 7.21(d, 2H), 7.03(d, 1H),

6.74(d, 1H), 6.69(dd, 1H), 4.19(t, 2H), 3.45(q, 1H), 2.93(t, 2H), 2.78(m, 2H), 2.51(m, 2H), 2.30(s, 3H), 2.25(s, 3H), 1.53(m, 2H).

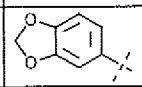
By using the methods described above for Examples **129-137** and by substituting the appropriate starting materials, compounds of Formula **Ia,** listed in Table 4 below, were similarly prepared.

Table 4

Preparative Examples of Compounds of Formula (Ia)



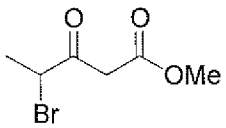
(Ia)

Ex. No.	R^3	R^4	LC/MS [M+H]
138	Me	4-MeO-Ph	408.5
139	Me	3-MeO-Ph	408.5
140	Me	4-Et-Ph	406.5
141	Me	4-CF3-Ph	446.5
142	Me	2-naphthyl	428.5
143	Me	4-(*t*-Bu)-Ph	434.6
144	Me	4-(*n*-Bu)-Ph	434.6
145	Me		422.5
146	Me	3,4-$(Me)_2$-Ph	406.5
147	Me	4-Me-Ph	392.5
148	Me	3-F-Ph	396.5
149	Me	2-benzothienyl	434.5
150	Me	4-*i*-Pr-Ph	420.6
151	Me	*cyc*-Pentyl	370.5

Ex. No.	R^3	R^4	LC/MS [M+H]
152	Me	*cyc*-hexyl	384.5
153	Me	$PhCH_2$	392.5
154	Me	4-F-3-Me-Ph	410.5
155	Me	3-F-4-Me-Ph	410.5
156	Me	4-F-Ph	396.5
157	Et	Ph	392.5
158	Me	$3,4\text{-}(Cl)_2\text{-}Ph$	447.4
159	*n*-Pr	Ph	406.5
160	Me	4-Ph-Ph	454.5
161	Me	3-Cl-Ph	412.4
162	Me	3-Me-Ph	392.5
163	Me	4-CN-Ph	403.4
164	Me	3-CN-Ph	403.4
165	Me	4-Cl-Ph	412.4
166	Me	3-CF3-Ph	446.4
167	Et	4-Et-Ph	420.5
168	Et	4-Me-Ph	406.5
169	Et	4-MeO-Ph	422.4

Example 170

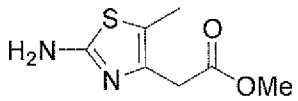
Preparation of methyl 4-bromo-3-oxopentanoate



A dry three-neck flask under an Ar atmosphere was charged with a solution of methyl propionylacetate (20 g, 154 mmol) in $CHCl_3$ (100 mL). Using an addition funnel, bromine (7.9 mL, 24.6 g, 154 mmol) was added dropwise over a period of 2 hours at 0°C. The reaction was then allowed to warm slowly to rt, and the reaction mixture was stirred overnight. A saturated solution of Na_2CO_3 (40 mL) was slowly added, and after stirring the reaction mixture for an additional 15 minutes, the solvents layers were separated and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was then purified by silica gel flash chromatography (10:1 hexanes/EtOAc) to give the desired bromide as a light yellow oil (25 g, 78%). ^{1}H NMR ($CDCl_3$): δ 1.80 (d, 3H), 3.64-3.92 (m, 2H), 3.78 (s, 3H), 4.61 (q, 1H).

Example 171

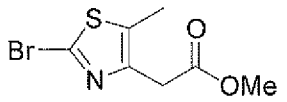
Preparation of methyl (2-amino-5-methyl-1,3-thiazol-4-yl)acetate



To a solution of bromide of Example **170** (18 g, 86 mmol) in toluene (100 mL) was added thiourea (10.5 g, 138 mmol). The reaction mixture was heated to 100°C for 1 hour, cooled to rt, and the solvent removed under reduced pressure. The residue was dissolved with CH_2Cl_2 (100 mL), a saturated solution $NaHCO_3$ (75 mL) added, and the mixture was vigorously stirred for 10 minutes. The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was then recrystallized from CH_2Cl_2/hexanes to provide the product (10 g, 63%) as a white solid. ($C_7H_{10}N_2O_2S$): LC-MS, RT 0.76 min, M+H 187.0; ^{1}H NMR ($CDCl_3$): δ 2.23 (s, 3H), 3.70 (s, 2H), 3.75 (s, 3H), 4.83-4.95 (broad s, 2H).

Example 172

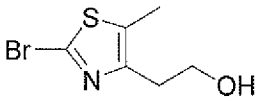
Preparation of methyl (2-bromo-5-methyl-1,3-thiazol-4-yl)acetate



To a solution of $CuBr_2$ (4.03 g, 18.1 mmol) and *t*-butyl nitrite (2.82 mL, 23.8 mmol) in MeCN (210 mL) was added the compound of Example **170** (2.95 g, 15.9 mmol) at -20°C. The reaction mixture was slowly warmed to 15°C, at which point the evolution of N_2 was observed. After stirring for an additional 2 hours at 15°C, the reaction mixture was diluted with Et_2O (400 mL) and washed with a 10% solution of HCl (200 mL). The solvent layers were separated, the aqueous re-extracted with Et_2O (2 x 300 mL), and the combined organic layers dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was then purified by silica gel flash chromatography (98:2, hexanes/EtOAc) to afford bromide Example **172** (1.6 g, 40%) as a colorless oil that solidifies upon standing. ($C_7H_8BrNO_2S$): LC-MS, RT 2.56 min., M+H 250.3; ^{1}H NMR ($CDCl_3$): δ 2.26 (s, 3H), 3.60 (s, 2H), 3.61 (s, 3H).

Example 173

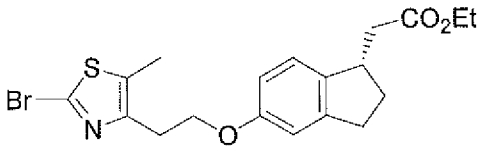
Preparation of 2-(2-bromo-5-methyl-1,3-thiazol-4-yl)ethanol



To a solution of ester prepared in Example **172** (3.80 g, 15.2 mmol) in CH_2Cl_2 (100 mL) was added DIBAL-H (33.4 mL, 33.4 mmol of a 1.0 M solution in toluene) at –78°C. After 15 minutes, the solution was warmed to 0°C and stirred for an additional 90 minutes. An aqueous solution of 2 N HCl (50 mL) was then added dropwise to quench the excess DIBAL-H. The solvent layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 200 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (5:2 hexanes/EtOAc) to yield the product (2.5 g, 74%) as a yellowish oil that solidifies upon standing. (C_6H_8BrNOS) LC-MS, RT 1.38 min., M+H 221.0; ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H), 2.82 (t, 2H), 2.90-3.00 (broad s, 1H), 3.89 (t, 2H).

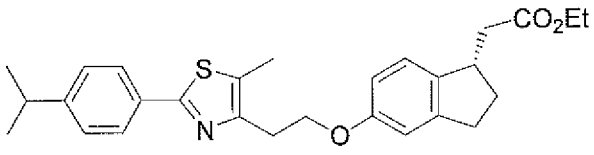
Example 174

Preparation of ethyl {(1*S*)-5-[2-(2-bromo-5-methyl-1,3-thiazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate



Step 1. To a solution of Example **173** (975 mg, 4.39 mmol) and ethyl [(1*S*)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl]acetate (1.06 g, 4.83 mmol) in THF (20 mL) were added Ph_3P (1.88 g, 7.46 mmol) and ADDP (1.96 g, 7.46 mmol). The mixture was vigorously stirred at rt for 72 hours, the solvent removed under reduced pressure, and the residue purified by silica gel flash chromatography (6:1 hexanes/EtOAc) to yield the product (1.4 g, 76%) as a colorless oil that solidifies upon standing. ($C_{19}H_{22}BrNO_3S$) LC-MS, RT 3.92 min., M+H 424.5; ^{1}H NMR ($CDCl_3$): δ 1.26 (t, 3H), 1.65-1.81 (m, 1H), 2.28-2.45 (m, 2H), 2.37 (s, 3H), 2.69 (dd, 1H), 2.75-2.93 (m, 2H), 3.07 (t, 2H), 3.44-3.56 (m, 1H), 4.15 (t, 2H), 4.18 (q, 2H), 6.67 (dd, 1H), 6.73 (d, 1H), 7.03 (d, 1H).

Preparation of ethyl ((1*S*)-5-{2-[2-(4-isopropylphenyl)-5-methyl-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate

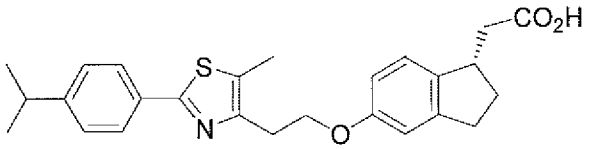


Step 2. To a mixture of toluene (15 mL) and 1,4-dioxane (3 mL), were added the compound of step 1 (300 mg, 0.708 mmol), 4-isopropylbenzene boronic acid (464 mg, 2.83 mmol), and $PdCl_2(dppf).CH_2Cl_2$ (52 mg, 0.071 mmol). A flow of Ar was passed through the mixture for 30 minutes, then a 2 N solution of Na_2CO_3 (3.7 mL, 7.08 mmol) was added and the reaction was heated to 75°C for 18 hours. The reaction mixture was then cooled to rt, diluted with EtOAc (200 mL), and washed with a saturated solution of $NaHCO_3$ (50 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure.

The residue was purified by silica gel flash chromatography (8:1 hexanes/EtOAc), to provide the product (305 mg, 93%) as a colorless oil. ($C_{28}H_{33}NO_3S$): LC-MS, RT 5.17 min., M+H 464.5; ^{1}H NMR ($CDCl_3$): δ 1.17-1.31 (m, 3H), 1.26 (s, 3H), 1.27 (s, 3H), 1.65-1.82 (m, 1H), 2.30-2.43 (m, 2H), 2.46 (s, 3H), 2.72 (dd, 1H), 2.78-3.00 (m, 3H), 3.17 (t, 2H), 3.46-3.57 (m, 1H), 4.17 (q, 2H), 4.27 (t, 2H), 6.71 (d, 1H), 6.78 (s, 1H), 7.04 (d, 1H), 7.55 (AB quartet, 4H).

Example 175

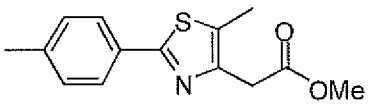
Preparation of ((1*S*)-5-{2-[2-(4-isopropylphenyl)-5-methyl-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



To a solution of Example **174** (305 mg, 0.657 mmol) in a mixture of THF (8 mL), water (8 mL), and EtOH (4 mL), was added LiOH (63 mg, 2.63 mmol). The reaction mixture was vigorously stirred for 24 hours, diluted with water (20 mL), and washed with Et_2O (10 mL). The aqueous phase was then acidified to pH ~1 using 1 N HCl, and then extracted with CH_2Cl_2 (4 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was then purified by silica gel flash chromatography (95:5 CH_2Cl_2/MeOH) to afford product (189 mg, 66%) as a white solid. ($C_{26}H_{29}NO_3S$): LC-MS, RT 3.95 min., M+H 436.4; ^{1}H NMR ($CDCl_3$): δ 1.25 (s, 3H), 1.28 (s, 3H), 1.70-1.82 (m, 1H), 2.32-2.43 (m, 2H), 2.45 (s, 3H), 2.74-2.98 (m, 4H), 3.18 (t, 2H), 3.47-3.54 (m, 1H), 4.28 (t, 2H), 6.72 (dd, 1H), 6.78 (s, 1H), 7.08 (d, 1H), 7.51 (AB quartet, 4H).

Example 176

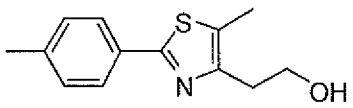
Preparation of methyl [5-methyl-2-(4-methylphenyl)-1,3-thiazol-4-yl]acetate



To a solution of bromide of Example **170** (1.15 g, 5.52 mmol) in toluene (20 mL) was added 4-methyl thiobenzamide (1.0 g, 6.6 mmol). The reaction mixture was heated to reflux for 15 hours, cooled to rt, diluted with EtOAc (150 mL), and washed with a saturated solution of $NaHCO_3$ (50 mL), then with a saturated solution of NH_4Cl (50 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was then purified by silica gel flash chromatography (9:1 hexanes/EtOAc) to afford the product as a pinkish oil that solidified upon standing (1.14 g, 62%). ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 3H), 3.45 (s, 3H), 3.74 (s, 3H), 3.80 (s, 2H), 7.49 (AB quartet, 4H); R_f (0.4, eluant 9:1 hexanes/EtOAc).

Example 177

Preparation of 2-[5-methyl-2-(4-methylphenyl)-1,3-thiazol-4-yl]ethanol

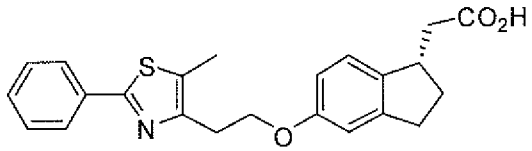


To a solution of the thiazole of Example **176** (1.14 g, 4.37 mmol) in THF (60 mL) at 0°C, was added portion-wise $LiAlH_4$ (663 mg, 17.5 mmol). After 30 minutes, the reaction mixture was warmed to rt and stirred for an additional 60 minutes. The reaction mixture was then cooled to 0°C, and the excess $LiAlH_4$ was quenched by dropwise addition of water (5 mL), 1N NaOH (10 mL), and water (5 mL) sequentially. The mixture was then diluted with a saturated solution of Rochelle salt and extracted with EtOAc (4 x 75 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (3:2 hexanes/EtOAc) to afford the product as a white solid (830 mg, 82%). ($C_{13}H_{15}NOS$): LC-MS, RT 2.50 min., M+H 234.2; ^1H NMR ($CDCl_3$): δ 2.34 (s, 3H), 2.37 (s, 3H), 2.83 (t, 2H), 3.92-4.01 (broad t, 2H), 4.04-4.15 (broad s, 1H), 7.45 (AB quartet, 4H).

The following compounds below were synthesized using one of the two procedures of Examples **170-177** described above.

Example 178

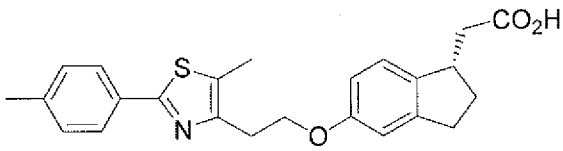
{(1*S*)-5-[2-(5-Methyl-2-phenyl-1,3-thiazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid



($C_{23}H_{23}NO_3S$): LC-MS RT 3.56 min., M + H 394.2; ^1H NMR ($CDCl_3$): δ 1.61-1.78 (m, 1H), 2.19-2.50 (m, 2H), 2.30 (s, 3H), 2.62-2.91 (m, 3H), 3.12 (t, 2H), 3.17-3.26 (m, 1H), 4.12 (t, 2H), 6.70 (d, 1H), 6.79 (s, 1H), 6.98 (d, 1H), 7.21-7.40 (m, 3H), 7.74-7.83 (m, 2H).

Example 179

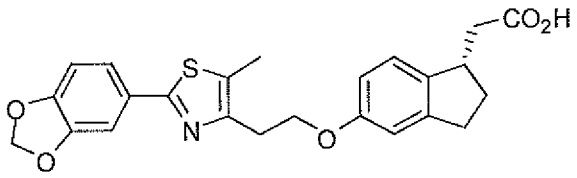
((1*S*)-5-{2-[5-Methyl-2-(4-methylphenyl)-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



($C_{24}H_{25}NO_3S$): LC-MS, RT 3.57 min., M+H 408.5; ^1H NMR ($CDCl_3$): δ 1.61-1.68 (m, 1H), 2.29 (s, 3H), 2.36 (s, 3H), 2.25-2.37[hidden] (m, 2H), 2.63-2.79 (m, 3H), 3.09 (t, 2H), 3.35-3.47 (m, 1H), 4.18 (t, 2H), 6.60 (dd, 1H), 6.68 (s, 1H), 6.97 (d, 1H), 7.42 (AB quartet, 4H), 7.81-8.30 (br, 1H).

Example 180

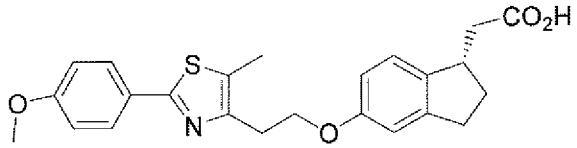
((1*S*)-5-{2-[2-(1,3-Benzodioxol-5-yl)-5-methyl-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



($C_{24}H_{23}NO_5S$): LC-MS, RT 4.04 min., M+H 438.5; ^{1}H NMR ($CDCl_3$): δ 1.71-1.83 (m, 1H), 2.36-2.51 (m, 2H), 2.45 (s, 3H), 2.76-2.96 (m, 3H), 3.15 (t, 2H), 3.48-3.58 (m, 1H), 4.29 (t, 2H), 6.00 (s, 2H), 6.72 (dd, 1H), 6.78 (s, 1H), 6.82 (d, 1H), 7.07 (d, 1H), 7.32-7.40 (m, 2H).

Example 181

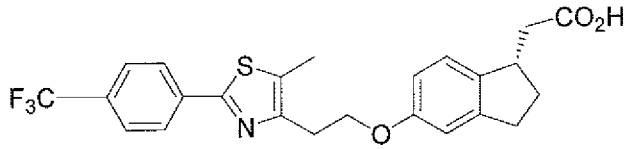
((1*S*)-5-{2-[2-(4-Methoxyphenyl)-5-methyl-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



($C_{24}H_{25}NO_4S$): LC-MS, RT 4.01 min., M+H 424.5; ^{1}H NMR ($CDCl_3$): δ 1.67-1.82 (m, 1H), 2.43 (s, 3H), 2.34-2.47 (m, 2H), 2.72-2.95 (m, 3H), 3.09 (t, 2H), 3.42-3.57 (m, 1H), 3.84 (s, 3H), 4.13 (t, 2H), 6.72 (d, 1H), 6.79 (s, 1H), 7.12 (d, 1H), 7.37 (AB quartet, 4H).

Example 182

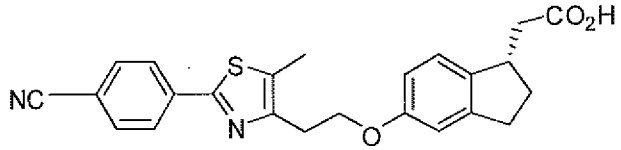
[(1*S*)-5-(2-{5-Methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid



($C_{24}H_{22}F_3NO_3S$):LC-MS, RT 4.47 min., M+H 462.4; ^{1}H NMR ($DMSO_{d6}$): δ 1.63-1.81 (m, 1H), 2.28-2.43 (m, 2H), 2.50 (s, 3H), 2.69 (dd, 1H), 2.74-2.95 (m, 2H), 3.19 (t, 2H), 3.31-3.36 (m, 1H), 4.31 (t, 2H), 6.71 (dd, 1H), 6.78 (s, 1H), 7.08 (d, 1H), 7.87 (AB quartet, 4H).

Example 183

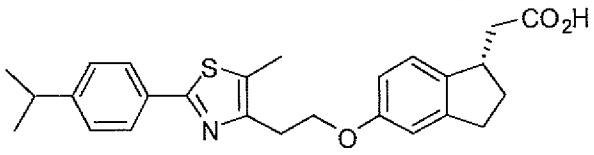
((1*S*)-5-{2-[2-(4-Cyanophenyl)-5-methyl-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



($C_{24}H_{22}N_2O_3S$):LC-MS, RT 3.43 min., M+H 419.6; ^{1}H NMR ($CDCl_3$): δ 1.68-1.85 (m, 1H), 2.31-2.49 (m, 2H), 2.51 (s, 3H), 2.77 (dd, 1H), 2.83-2.94 (m, 2H), 3.18 (t, 2H), 3.43-3.56 (m, 1H), 4.31 (t, 2H), 6.71 (dd, 1H), 6.79 (s, 1H), 7.10 (d, 1H), 7.86 (AB quartet, 4H).

Example 184

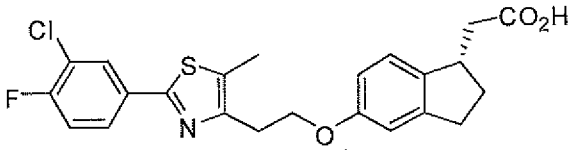
((1*S*)-5-{2-[2-(4-Isopropylphenyl)-5-methyl-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



($C_{26}H_{29}NO_3S$): LC-MS, RT 3.95 min., M+H 436.4; ^{1}H NMR ($CDCl_3$): δ 1.25 (s, 3H), 1.28 (s, 3H), 1.70-1.82 (m, 1H), 2.32-2.43 (m, 2H), 2.45 (s, 3H), 2.74-2.98 (m, 4H), 3.18 (t, 2H), 3.47-3.54 (m, 1H), 4.28 (t, 2H), 6.72 (dd, 1H), 6.78 (s, 1H), 7.08 (d, 1H), 7.51 (AB quartet, 4H).

Example 185

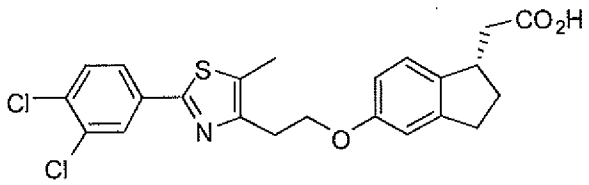
((1*S*)-5-{2-[2-(3-Chloro-4-fluorophenyl)-5-methyl-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



($C_{23}H_{21}ClFNO_3S$): LC-MS, RT 3.89 min., M+H 446.4; ^{1}H NMR ($CDCl_3$): δ 1.68-1.86 (m, 1H), 2.32-2.46 (m, 2H), 2.50 (s, 3H), 2.80 (dd, 1H), 2.84-2.96 (m, 2H), 3.18 (t, 2H), 3.47-3.59 (m, 1H), 4.32 (t, 2H), 6.72 (d, 1H), 6.82 (s, 1H), 7.12 (d, 1H), 7.23 (t, 1H), 7.72-7.82 (m, 1H), 7.97-8.04 (m, 1H).

Example 186

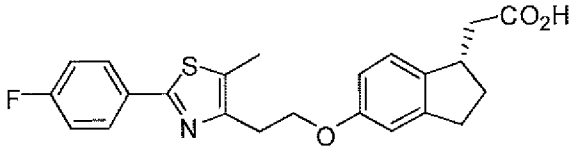
((1*S*)-5-{2-[2-(3,4-Dichlorophenyl)-5-methyl-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



($C_{23}H_{21}Cl_2NO_3S$): LC-MS, RT 4.12 min., M+H 462.0; ^{1}H NMR ($CDCl_3$): δ 1.74-1.88 (m, 1H), 2.36-2.48 (m, 2H), 2.50 (s, 3H), 2.73-2.93 (m, 3H), 3.19 (t, 2H), 3.48-3.55 (m, 1H), 4.30 (t, 2H), 6.71 (d, 1H), 6.79 (s, 1H), 7.09 (d, 1H), 7.52 (d, 1H), 7.61 (dd, 1H), 8.02 (d, 1H).

Example 187

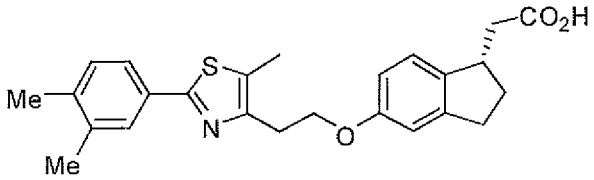
((1*S*)-5-{2-[2-(4-Fluorophenyl)-5-methyl-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



($C_{23}H_{22}FNO_3S$): LC-MS, RT 3.58 min., M+H 412.4; ^{1}H NMR ($CDCl_3$): δ 1.70-1.77 (m, 1H), 2.37-2.45 (m, 1H), 2.44 (s, 3H), 2.70-2.90 (m, 4H), 3.16 (t, 2H), 3.47-3.52 (m, 1H), 4.27 (t, 2H), 6.70 (d, 1H), 6.76 (s, 1H), 7.00-7.10 (m, 3H), 7.82-7.87 (m, 2H).

Example 188

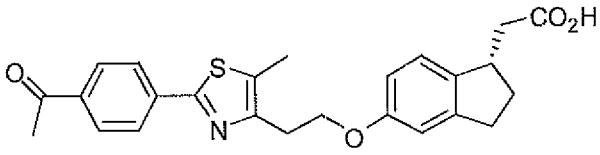
((1*S*)-5-{2-[2-(3,4-Dimethylphenyl)-5-methyl-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



($C_{25}H_{27}NO_3S$): LC-MS, RT 4.39 min., M+H 422.3; ^{1}H NMR ($CDCl_3$): δ 1.70-1.83 (m, 1H), 2.29 (s, 3H), 2.32 (s, 3H), 2.37-2.50 [hidden] (m, 2H), 2.46 (s, 3H), 2.70.-2.90 (m, 3H), 3.32 (t, 2H), 3.45-3.60 (m, 1H), 4.30 (t, 2H), 6.73 (d, 1H), 6.79 (s, 1H), 7.07 (d, 1H), 7.17 (d, 1H), 7.59 (d, 1H), 7.68 (s, 1H).

Example 189

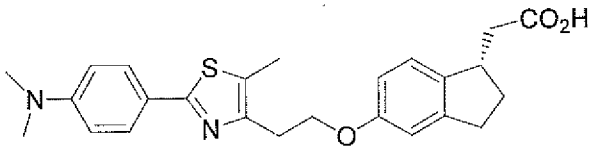
((1*S*)-5-{2-[2-(4-Acetylphenyl)-5-methyl-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



($C_{25}H_{25}NO_4S$): LC-MS, RT 4.01 min., M+H 436.3; ^{1}H NMR ($CDCl_3$): δ 1.70-1.82 (m, 1H), 2.37-2.49 (m, 2H), 2.50 (s, 3H), 2.63 (s, 3H), 2.70-2.90 (m, 3H), 3.20 (t, 2H), 3.45-3.60 (m, 1H), 4.30 (t, 2H), 6.72 (d, 1H), 6.78 (s, 1H), 7.08 (d, 1H), 7.95-8.03 (m, 4H).

Example 190

[(1*S*)-5-(2-{2-[4-(Dimethylamino)phenyl]-5-methyl-1,3-thiazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid

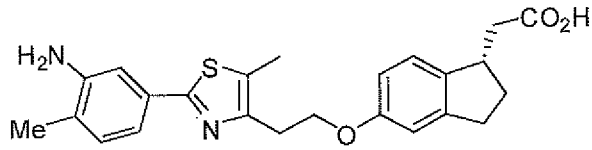


($C_{25}H_{28}N_2O_3S$): LC-MS, RT 2.95 min., M+H 437.2; ^{1}H NMR ($DMSO_{d6}$): δ 1.53-1.65 (m, 1H), 2.12-2.24 (m, 2H), 2.36 (s, 3H), 2.63-2.84 (m, 3H), 2.94 (s, 6H), 3.03 (t, 2H), 3.27-3.38 (m, 1H), 4.18 (t, 2H), 6.65 (d, 1H), 6.75 (s, 1H), 7.08 (d, 1H), 7.17 (AB quartet, 4H).

Example 191

((1*S*)-5-{2-[2-(3-Amino-4-methylphenyl)-5-methyl-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid

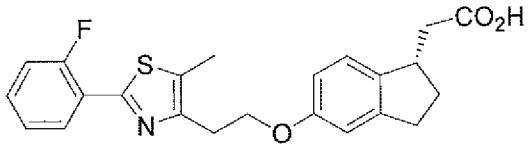
TFA



$C_{24}H_{26}N_2O_3S.C_2F_3O_2$): LC-MS, RT 3.5 min., M+H 423.3; ^{1}H NMR (CD_3OD): δ 1.67-1.82 (m, 1H), 2.25-2.37 (m, 2H), 2.38 (s, 3H), 2.50 (s, 3H), 2.67-2.90 (m, 3H), 3.20 (t, 2H), 3.41-3.56 (m, 1H), 4.32 (t, 2H), 6.71 (d, 1H), 6.79 (s, 1H), 7.09 (d, 1H), 7.42 (d, 1H), 7.69 (dd, 1H), 7.77 (d, 1H).

Example 192

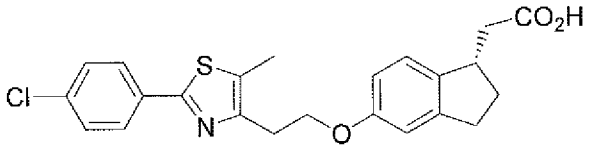
((1*S*)-5-{2-[2-(2-Fluorophenyl)-5-methyl-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



($C_{23}H_{22}FNO_3S$): LC-MS, RT 4.25 min., M+H 412.2; ^{1}H NMR ($CDCl_3$): δ 1.70-1.82 (m, 1H), 2.37-2.48 (m, 2H), 2.49 (s, 3H), 2.74-2.94 (m, 3H), 3.21(t, 2H), 3.42-3.60 (m, 1H), 4.31 (t, 2H), 6.72 (d, 1H), 6.79 (s, 1H), 7.06-7.35 (m, 4H), 8.21(t, 1H).

Example 193

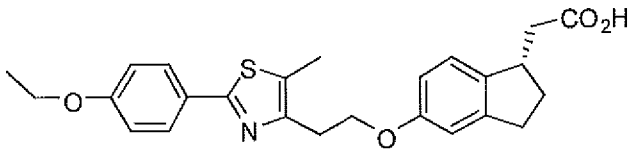
((1*S*)-5-{2-[2-(4-Chlorophenyl)-5-methyl-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



($C_{23}H_{22}ClNO_3S$): LC-MS, RT 4.44 min., M+H 428.2; ^{1}H NMR ($CDCl_3$): δ 1.70-1.81 (m, 1H), 2.35-2.45 (m, 2H), 2.46 (s, 3H), 2.74-2.89 (m, 3H), 3.17 (t, 2H), 3.42-3.60 (m, 1H), 4.28 (t, 2H), 6.71 (d, 1H), 6.77 (s, 1H), 7.07 (d, 1H), 7.36 (d, 2H), 7.79 (d, 2H).

Example 194

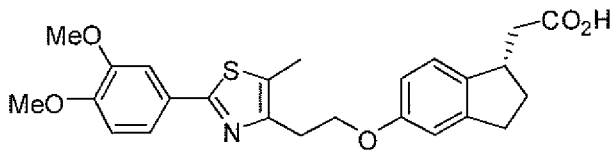
((1*S*)-5-{2-[2-(4-Ethoxyphenyl)-5-methyl-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



($C_{25}H_{27}NO_4S$): LC-MS, RT 3.55 min., M+H 438.5; ^{1}H NMR ($CDCl_3$): δ 1.40 (t, 3H), 1.70-1.82 (m, 1H), 2.35-2.47 (m, 2H), 2.45 (s, 3H), 2.74-2.89 (m, 3H), 3.20 (t, 2H), 3.42-3.59 (m, 1H), 4.07 (q, 2H), 4.29 (t, 2H), 6.71 (d, 1H), 6.76 (s, 1H), 6.91 (d, 1H), 7.06 (d, 2H), 7.82 (d, 2H).

Example 195

((1*S*)-5-{2-[2-(3,4-Dimethoxyphenyl)-5-methyl-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid

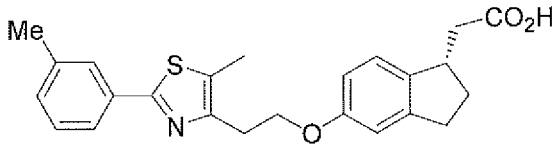


($C_{25}H_{27}NO_5S$): LC-MS, RT 3.86 min., M+H 454.2; ^{1}H NMR ($CDCl_3$): δ 1.67-1.82 (m, 1H), 2.37-2.48 (m, 2H), 2.49 (s, 3H), 2.71-2.87 (m, 3H), 3.27 (t, 2H), 3.42-3.57 (m, 1H), 3.93 (s, 3H), 3.96 (s, 3H),

4.29 (t, 2H), 6.35-6.64 (broad s, 1H), 6.67 (d, 1H), 6.75 (s, 1H), 6.89 (d, 1H), 7.05 (d, 1H), 7.39 (d, 1H), 7.56 (s, 1H).

Example 196

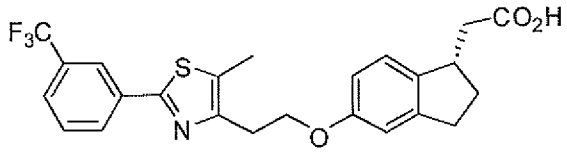
((1*S*)-5-{2-[5- Methyl-2-(3-methylphenyl)-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



($C_{24}H_{25}NO_3S$): LC-MS, RT 3.71 min., M+H 408.2; ^{1}H NMR ($CDCl_3$): δ 1.70-1.82 (m, 1H), 2.38-2.52 (m, 2H), 2.40 (s, 3H), 2.47 (s, 3H), 2.75-2.87 (m, 3H), 3.19 (t, 2H), 3.45-3.60 (m, 1H), 4.29 (t, 2H), 6.72 (d, 1H), 6.78 (s, 1H), 7.07 (d, 1H), 7.19 (d, 1H), 7.30 (t, 1H), 7.64 (d, 1H), 7.75 (s, 1H).

Example 197

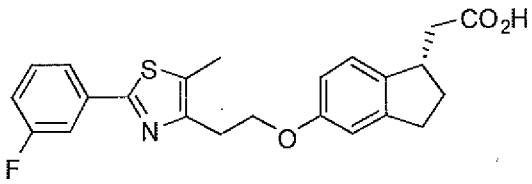
[(1*S*)-5-(2-{5-Methyl-2-[3-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid



($C_{24}H_{22}F_3NO_3S$): LC-MS, RT 3.90 min., M+H 462.1; ^{1}H NMR ($CDCl_3$): δ 1.70-1.82 (m, 1H), 2.38-2.48 (m, 2H), 2.49 (s, 3H), 2.75-2.87 (m, 3H), 3.19 (t, 2H), 3.44-3.59 (m, 1H), 4.30 (t, 2H), 6.72 (d, 1H), 6.79 (s, 1H), 7.07 (d, 1H), 7.52 (t, 1H), 7.61 (d, 1H), 8.01 (d, 1H), 8.13 (s, 1H).

Example 198

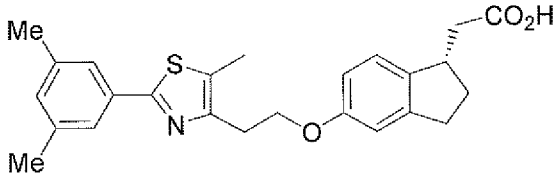
((1*S*)-5-{2-[2-(3-Fluorophenyl)-5-methyl-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



($C_{23}H_{22}FNO_3S$): LC-MS, RT 3.66 min., M+H 412.1; ^{1}H NMR ($CDCl_3$): δ 1.70-1.82 (m, 1H), 2.39-2.47 (m, 2H), 2.48 (s, 3H), 2.76-2.87 (m, 3H), 3.18 (t, 2H), 3.45-3.60 (m, 1H), 4.30 (t, 2H), 6.72 (d, 1H), 6.78 (s, 1H), 7.04-7.09 (m, 2H), 7.36-7.42 (m, 1H), 7.58-7.62 (m, 2H).

Example 199

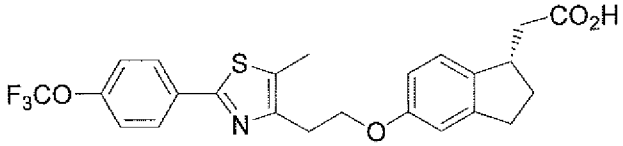
((1*S*)-5-{2-[2-(3,5-Dimethylphenyl)-5-methyl-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



($C_{25}H_{27}NO_3S$): LC-MS, RT 3.88 min., M+H 422.2; ^1H NMR ($CDCl_3$): δ 1.72-1.84 (m, 1H), 2.36 (s, 6H), 2.37-2.45 (m, 2H), 2.46 (s, 3H), 2.75-2.87 (m, 3H), 3.19 (t, 2H), 3.45-3.60 (m, 1H), 4.28 (t, 2H), 6.72 (d, 1H), 6.79 (s, 1H), 7.01 (s, 1H), 7.07 (d, 1H), 7.48 (s, 2H).

Example 200

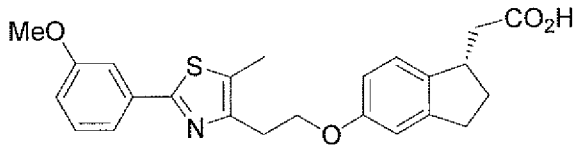
[(1*S*)-5-(2-{5-Methyl-2-[4-(trifluoromethoxy)phenyl]-1,3-thiazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid



($C_{24}H_{22}F_3NO_4S$): LC-MS, RT 3.95 min., M+H 478.1; ^1H NMR ($CDCl_3$): δ 1.72-1.84 (m, 1H), 2.38-2.46 (m, 2H), 2.47 (s, 3H), 2.75-2.87 (m, 3H), 3.18 (t, 2H), 3.45-3.60 (m, 1H), 4.29 (t, 2H), 6.72 (d, 1H), 6.77 (s, 1H), 7.07 (d, 1H), 7.24 (d, 2H), 7.88 (d, 2H).

Example 201

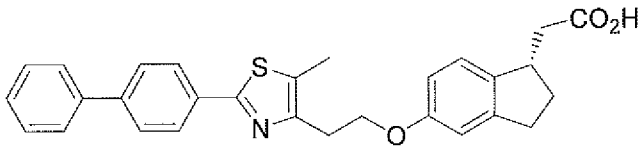
((1*S*)-5-{2-[2-(3-Methoxyphenyl)-5-methyl-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



($C_{24}H_{25}NO_4S$): LC-MS, RT 3.56 min., M+H 424.2; ^1H NMR ($CDCl_3$): δ 1.70-1.82 (m, 1H), 2.37-2.52 (m, 2H), 2.49 (s, 3H), 2.75-2.87 (m, 3H), 3.19 (t, 2H), 3.45-3.57 (m, 1H), 3.87 (s, 3H), 4.30 (t, 2H), 6.72 (d, 1H), 6.79 (s, 1H), 6.95 (d, 1H), 7.10 (d, 1H), 7.32 (t, 1H), 7.40-7.45 (m, 2H).

Example 202

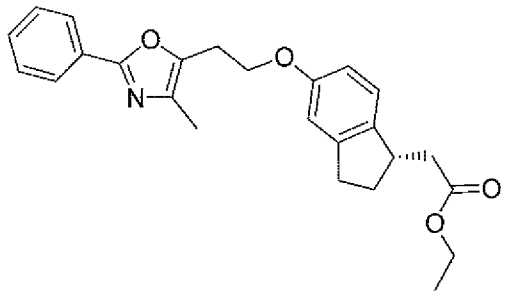
((1*S*)-5-{2-[2-(1,1'-Biphenyl-4-yl)-5-methyl-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



($C_{29}H_{27}NO_3S$): LC-MS, RT 3.96 min., M+H 470.3; ^1H NMR ($CDCl_3$): δ 1.70-1.81 (m, 1H), 2.38-2.48 (m, 2H), 2.49 (s, 3H), 2.75-2.87 (m, 3H), 3.20(t, 2H), 3.43-3.59 (m, 1H), 4.31 (t, 2H), 6.72 (d, 1H), 6.79 (s, 1H), 7.08 (d, 1H), 7.36 (t, 1H), 7.45 (t, 2H), 7.61-7.65 (m, 4H), 7.93 (d, 2H).

Example 203

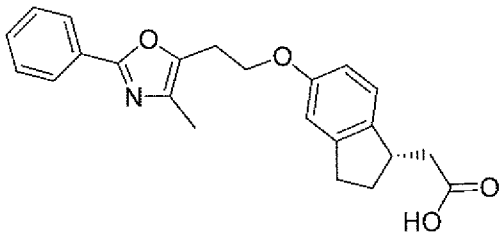
Preparation of ethyl {(1*S*)-5-[2-(4-methyl-2-phenyl-1,3-oxazol-5-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate



ADDP (0.205 g, 0.81 mmol) was added to a mixture of PPh_3 (0.212 g, 0.81 mmol), ethyl [(1*S*)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl]acetate (0.107 g, 0.49 mmol), and 2-(4-methyl-2-phenyl-1,3-oxazol-5-yl)ethanol (step 4, Example **51,** 0.110 g, 0.54 mmol) in THF (5 mL). The reaction was stirred overnight at rt, and additional ADDP (0.136 g, 0.54 mmol) and PPh_3 (0.141g, 0.54 mmol) were added with CH_2Cl_2 (5 mL). The solution was stirred for 24 hours at rt and filtered. The filtrate was evaporated and the resulting mixture was purified by Biotage using a gradient 0 to 50% EtOAc/hexane. Gave ethyl {(1*S*)-5-[2-(4-methyl-2-phenyl-1,3-oxazol-5-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate (0.145 g, 66% yield) as yellowish oil. ES-MS *m/z* 406.2 $((MH)^+)$; HPLC RT (min.) 3.89; ^{1}H NMR (Acetone-d_6) δ 7.85-7.82 (m, 2H), 7.36-7.30 (m, 3H), 6.94 (d, 1H), 6.65 (s, 1H), 6.60-6.55 (m, 1H), 4.10 (t, 2H), 3.98 (q, 2H), 3.31-3.27 (m, 1H), 3.03 (t, 2H), 3.27-2.51 (m, 3H), 2.24-2.14 (m, 2H), 2.18 (s, 3H), 1.58-1.53 (m, 1H), 1.08 (t, 3H).

Example 204

Preparation of {(1*S*)-5-[2-(4-methyl-2-phenyl-1,3-oxazol-5-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid

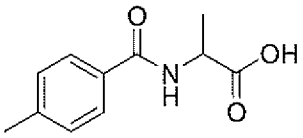


Ethyl {(1*S*)-5-[2-(4-methyl-2-phenyl-1,3-oxazol-5-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate (0.135 g, 0.33 mmol) was dissolved in EtOH (6 mL) and LiOH (0.024 g, 1.0 mmol) was added. Water (3 mL) was added and THF was added until the cloudy solution became clear. The resulting mixture was stirred overnight at rt. HCl (2 N) was added to adjust the pH to 2, then extracted three times with ethyl acetate. The organic layers were combined, dried, and concentrated to give {(1*S*)-5-[2-(4-methyl-2-phenyl-1,3-oxazol-5-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid (0.039 g, 30.6% yield) as colorless oil. ES-MS *m/z* 378.2 $((MH)^+)$; HPLC RT (min.) 3.22; ^{1}H NMR (Acetone-d_6) δ 8.1 (s br 1H) 8.0-7.95 (m, 2H), 7.52-7.43 (m, 3H), 7.15(d, 1H), 6.81 (s, 1H), 6.73 (d, 1H), 4.27 (t, 2H) 3.47-3.40 (m, 1H), 3.18 (t, 2H), 2.90-2.68 (m, 3H), 2.41-2.29 (m, 2H), 2.18 (s, 3H), 1.77-1.68 (m, 1H).

By using the procedure described above for Examples **51, 203**, and **204** and substituting the appropriate starting materials, the following compounds were similarly prepared and characterized.

Example 205

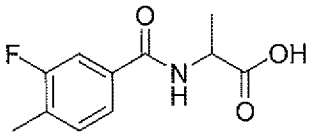
Preparation of *N*-(4-methylbenzoyl)alanine



^{1}H NMR (DMSO-d_6) δ 12.60 (s br, 1H), 8.57 (d, 1H), 7.81 (d, 2H), 7.28 (d, 2H), 4.38 (q, 1H), 2.35 (s, 3H), 1.38 (d, 3H).

Example 206

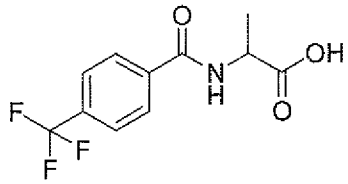
Preparation of *N*-(3-fluoro-4-methylbenzoyl)alanine



^{1}H NMR (DMSO-d_6) δ 12.54 (s br, 1H), 8.67 (d, 1H), 7.65-7.62 (m, 2H), 7.39 (t, 1H), 4.38 (q, 1H), 2.27 (s, 3H), 1.38 (d, 3H).

Example 207

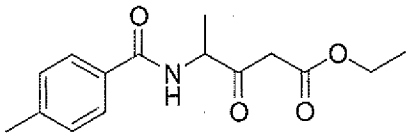
Preparation of *N*-[4-(trifluoromethyl)benzoyl]alanine



^{1}H NMR (DMSO-d_6) δ 12.64 (s br, 1H), 8.91 (d, 1H), 8.08 (d, 2H), 7.85 (d, 2H), 4.42 (q, 1H), 1.40 (d, 3H).

Example 208

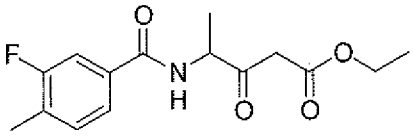
Preparation of ethyl 4-[(4-methylbenzoyl)amino]-3-oxopentanoate



ES-MS *m/z* 278.38 ($(MH)^+$); HPLC RT (min.) 2.04. ^{1}H NMR (Acetone-d_6) δ 8.08 (s br, 1H), 7.90 (d, 2H), 7.28 (d, 2H), 4.72-4.67 (m, 1H), 4.13 (q, 2H), 3.66 (s, 2H), 2.40 (s, 3H), 1.41 (d, 3H), 1.12 (t, 3H).

Example 209

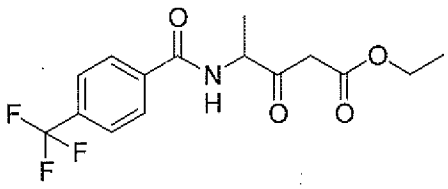
Preparation of ethyl 4-[(3-fluoro-4-methylbenzoyl)amino]-3-oxopentanoate



ES-MS *m/z* 296.4 ($(MH)^+$); HPLC RT (min.) 2.26. ^{1}H NMR (Acetone-d_6) δ 7.75-7.60 (m, 2H), 7.38 (t, 1H), 4.20 (q, 2H), 3.65 (s, 2H), 2.23 (s, 3H), 1.45 (d, 3H), 1.20 (t, 3H).

Example 210

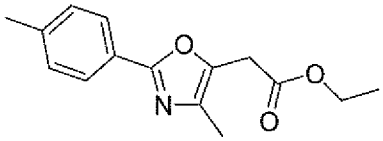
Preparation of ethyl 3-oxo-4-{[4-(trifluoromethyl)benzoyl]amino}pentanoate



ES-MS *m/z* 332.4 ($(MH)^+$); HPLC RT (min.) 2.45. ^{1}H NMR (Acetone-d_6) δ 8.14 (d, 2H), 7.84 (d, 2H), 4.80-4.74 (m, 2H), 4.20 (q, 2H), 3.70 (s, 2H), 1.48 (d, 3H), 1.21 (t, 3H).

Example 211

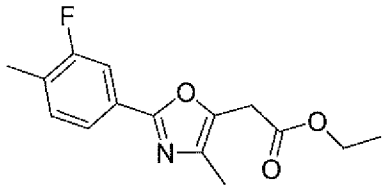
Preparation of ethyl [4-methyl-2-(4-methylphenyl)-1,3-oxazol-5-yl]acetate



ES-MS *m/z* 260.2 ($(MH)^+$); HPLC RT (min.) 2.96. ^{1}H NMR (Acetone-d_6) δ 7.86 (d, 2H), 7.30 (d, 2H), 4.15 (q, 2H), 3.81 (s, 2H), 2.37 (s, 3H), 2.14 (s, 3H), 1.24 (t, 3H).

Example 212

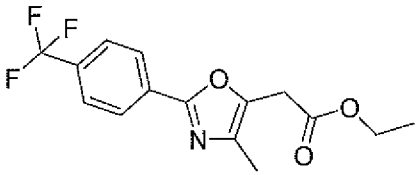
Preparation of ethyl [2-(3-fluoro-4-methylphenyl)-4-methyl-1,3-oxazol-5-yl]acetate



ES-MS *m/z* 278.3 ($(MH)^+$); HPLC RT (min.) 2.89. ^{1}H NMR (Acetone-d_6) δ 7.69 (d, 1H), 7.60 (d, 1H), 7.37 (t, 1H), 4.15 (q, 2H), 3.83 (s, 2H), 2.31 (s, 3H), 2.15 (s, 3H), 1.23 (t, 3H).

Example 213

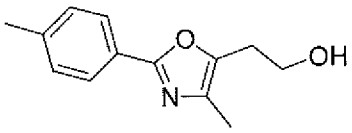
Preparation of ethyl {4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-oxazol-5-yl}acetate



ES-MS *m/z* 314.3 ($(MH)^+$); HPLC RT (min.) 3.27. ^{1}H NMR (Acetone-d_6) δ 8.18 (d, 2H), 7.84 (d, 2H), 4.17 (q, 2H), 3.88 (s, 2H), 2.20 (s, 3H), 1.23 (t, 3H).

Example 214

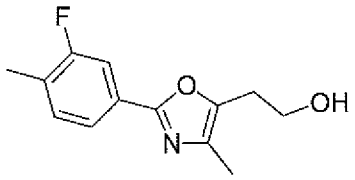
Preparation of 2-[4-methyl-2-(4-methylphenyl)-1,3-oxazol-5-yl]ethanol



ES-MS *m/z* 218.2 ($(MH)^+$); HPLC RT (min.) 2.35. ^{1}H NMR (Acetone d_6) δ 7.85 (d, 2H), 7.27 (d, 2H), 3.99 (s br, 1H), 3.83 (t, 2H), 2.90 (t, 2H), 2.37 (s, 3H), 2.12 (s, 3H).

Example 215

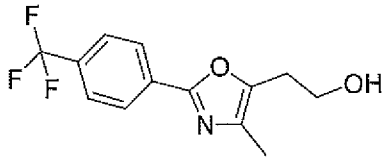
Preparation of 2-[2-(3-fluoro-4-methylphenyl)-4-methyl-1,3-oxazol-5-yl]ethanol



ES-MS *m/z* 236.2 ($(MH)^+$); HPLC RT (min.) 2.46. ^{1}H NMR ($CDCl_3$) δ 7.54 (d, 1H), 7.43 (d, 1H), 7.17 (t, 1H), 3.91 (d, 2H), 3.09 (s br, 1H), 2.88 (t, 2H), 2.29 (s, 3H), 2.13 (s, 3H).

Example 216

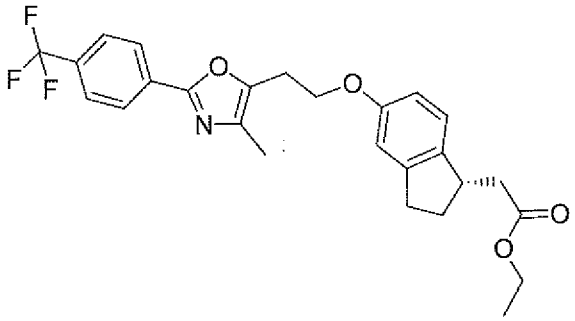
Preparation of 2-{4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-oxazol-5-yl}ethanol



ES-MS *m/z* 272.2 ($(MH)^+$); HPLC RT (min.) 2.71. ^{1}H NMR ($CDCl_3$) δ 8.03 (2, 2H), 7.66 (d, 2H), 3.95 (t, 2H), 2.96 (t, 2H), 2.21 (s, 3H), 1.97 (s br, 1H).

Example 217

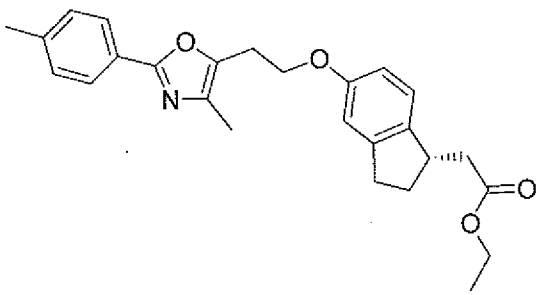
Preparation of ethyl {(1*S*)-5-(2-{4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-oxazol-5-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetate



ES-MS *m/z* 474.5 ($(MH)^+$); HPLC RT (min.) 4.10. ^{1}H NMR (Acetone-d_6) δ 8.16 (d, 2H), 7.83 (d, 2H), 7.09 (d, 1H), 6.80 (s, 1H), 6.72 (dd, 1H), 4.28 (t, 2H), 4.12 (q, 2H), 3.46-3.41 (m, 1H), 3.21 (t, 2H), 2.86-2.65 (m, 3H), 2.39-2.26 (m, 2H), 2.20 (s, 3H), 1.75-1.63 (m, 1H), 1.22 (t, 3H).

Example 218

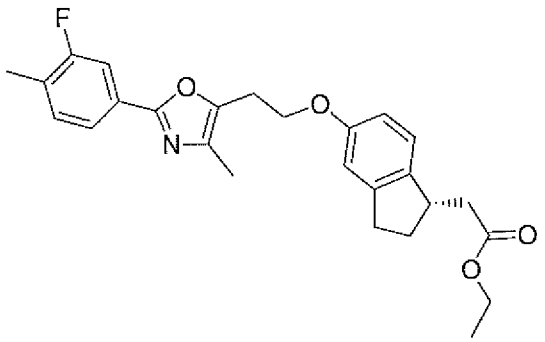
Preparation of ethyl ((1*S*)-5-{2-[4-methyl-2-(4-methylphenyl)-1,3-oxazol-5-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate



TCL Rf = 0.22 Hexane/EtOAc 4:1

Example 219

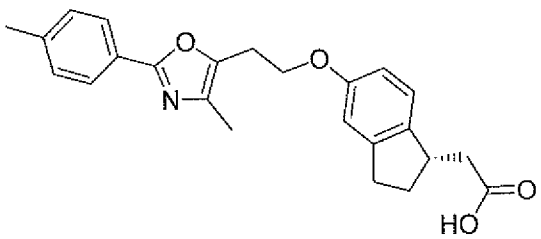
Preparation of ethyl ((1*S*)-5-{2-[2-(3-fluoro-4-methylphenyl)-4-methyl-1,3-oxazol-5-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate



ES-MS *m/z* 438.2 ($(MH)^+$); HPLC RT (min.) 4.18. ^{1}H NMR (Acetone-d_6) δ 6.67 (dd, 1H), 7.59 (dd, 1H), 7.37 (t, 1H), 7.08 (d, 1H), 6.80 (s, 1H), 6.72 (dd, 1H), 4.26 (t, 2H), 4.12 (q, 2H), 3.46-3.38 (m, 1H), 3.17 (t, 2H), 2.89-2.65 (m, 3H), 2.39-2.23 (m, 5H), 2.17 (s, 3H), 1.75-1.63 (m, 1H), 1.23 (t, 3H).

Example 220

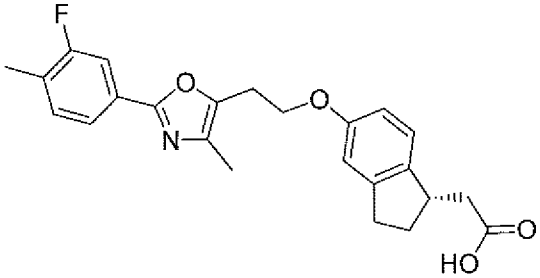
Preparation of ((1*S*)-5-{2-[4-methyl-2-(4-methylphenyl)-1,3-oxazol-5-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



ES-MS *m/z* 392.2 ($(MH)^+$); HPLC RT (min.) 3.36. ^{1}H NMR (Acetone-d_6) δ 7.72 (d, 2H), 7.15 (d, 2H), 6.99 (d, 1H), 6.67 (s, 1H), 6.59 (dd, 1H), 4.12 (t, 2H), 3.33-3.28 (m, 1H), 3.03 (t, 2H), 2.73-2.54 (m, 3H), 2.27-2.21 (m, 5H), 2.02 (s, 3H), 1.64-1.54 (m, 1H).

Example 221

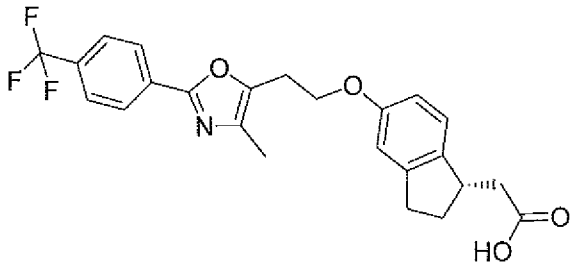
Preparation of ((1*S*)-5-{2-[2-(3-fluoro-4-methylphenyl)-4-methyl-1,3-oxazol-5-yl]ethoxy}-2,3-dihydro-11-inden-1-yl)acetic acid



ES-MS *m/z* 410.2 ($(MH)^+$); HPLC RT (min.) 3.49. ^{1}H NMR (Acetone-d_6) δ 7.68 (dd, 1H), 7.59 (dd, 1H), 7.36 (t, 1H), 7.12 (d, 1H), 6.80 (s, 1H), 6.72 (dd, 1H), 4.26 (t, 2H), 3.47-3.41 (m, 1H, 3.18 (t, 2H), 2.86-2.67 (m, 3H), 2.40-2.28 (m, 5H), 2.17 (s, 3H), 1.18-1.65 (m, 1H).

Example 222

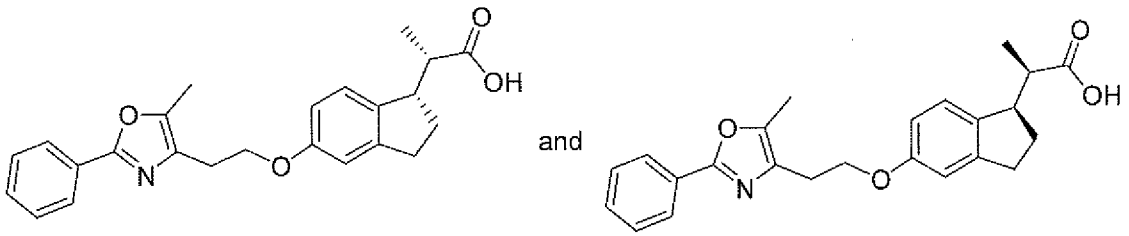
Preparation of [(1*S*)-5-(2-{4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-oxazol-5-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid



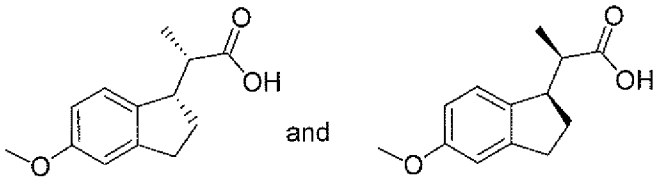
ES-MS *m/z* 446.5 ($(MH)^+$); HPLC RT (min.) 3.47. ^{1}H NMR (Acetone-d_6) δ 8.17 (d, 2H), 7.84 (d, 2H), 7.13 (s, 1H), 6.80 (s, 1H), 6.72 (dd, 1H), 4.28 (t, 2H), 3.46-3.41 (m, 1H), 3.21 (t, 2H), 2.86-2.67 (m, 3H), 2.40-2.28 (m, 2H), 2.20 (s, 3H), 1.77-1.67 (m, 1H).

Example 223

Preparation of (2*S*)-2-{(1*S*)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}propanoic acid and (2*R*)-2-{(1*R*)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}propanoic acid

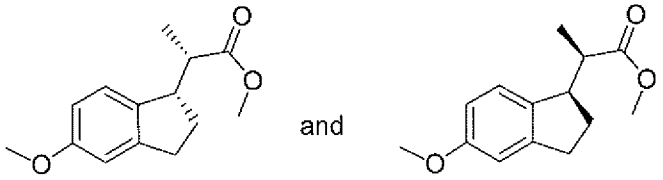


Step 1. Preparation of (2S)-2-[(1S)-5-methoxy-2,3-dihydro-1H-inden-1-yl]propanoic acid and (2R)-2-[(1R)-5-methoxy-2,3-dihydro-1H-inden-1-yl]propanoic acid



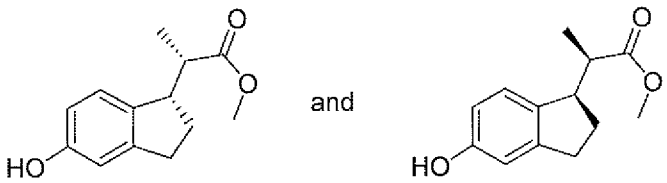
The starting acid (Example **2b**) was reacted using a similar procedure as described in Example **4**, under 60 psi H_2, and using 4.5 g starting material, 1.04 g catalyst, and 4.5 mL triethylamine in 45 mL ethanol and 5 mL THF. The standard extractive workup gave 3.22 g product. LC/MS retention time 2.41 min., NMR (d6-DMSO): 0.87 (d, 3H, α-methyl), 1.75 (m, 1H), 2.04 (m, 1H), 3.66 (s, 3H, methoxy), 6.65 (m, 1H, aryl), 6.76 (s, 1H, aryl), 7.04 (d, 1H, aryl,) 12.18 (bs, 1H, acid.)

Step 2: Preparation of methyl (2S)-2-[(1S)-5-methoxy-2,3-dihydro-1H-inden-1-yl]propanoate and methyl (2R)-2-[(1R)-5-methoxy-2,3-dihydro-1H-inden-1-yl]propanoate



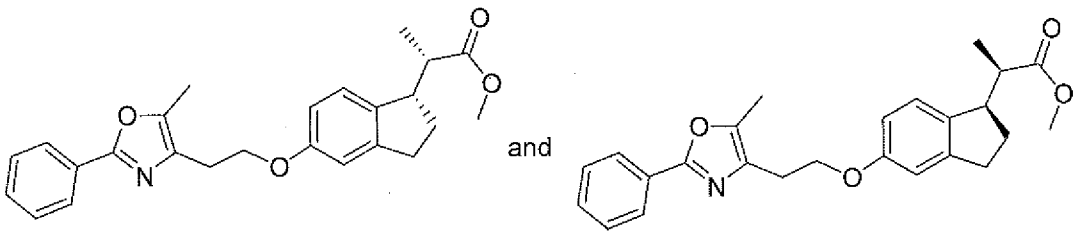
The compound was prepared by the reaction of 1.5 g starting acid, 0.93 mL iodomethane, and 1.75 g sodium bicarbonate in 10 mL methanol under standard esterification conditions as described in Example **6**. Workup gave 1.53 g, 96%. (NMR (CD_2Cl_2): 1.05 (d, 3H, α-methyl), 1.88 (m, 1H), 2.19 (m, 1H), 3.44 (m, 1H), 3.68 (s, 3H, methoxy), 3.77 (s, 3H, ester).

Step 3. Preparation of: methyl (2S)-2-[(1S)-5-hydroxy-2,3-dihydro-1H-inden-1-yl]propanoate and methyl (2R)-2-[(1R)-5-hydrxy-2,3-dihydro-1H-inden-1-yl]propanoate



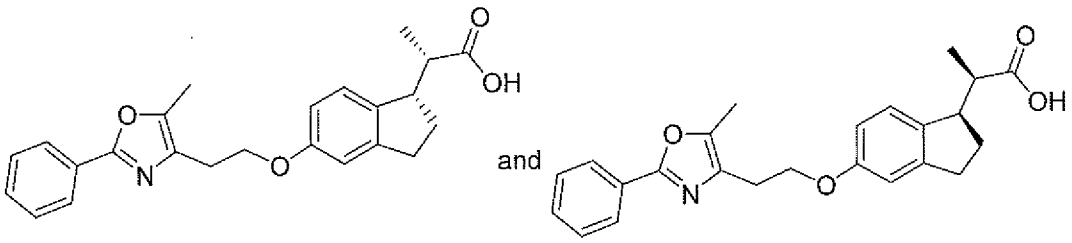
Using the demethylation conditions as described in Example **7** (1.53 g starting material, 4.35 g $AlCl_3$, and 2.4 mL ethanethiol in 20 mL dichloromethane), 1.21 g of product (84%) was obtained. (NMR (CD_2Cl_2): 1.05 (d, 3H, α -methyl), 1.88 (m, 1H), 2.18 (m, 1H), 3.45 (m, 1H), 3.67 (s, 3H, ester), 6.60 (m, 1H, aryl), 6.69 (s, 1H, aryl), 6.93 (d, 1H, aryl.)

Step 4: Preparation of methyl (2S)-2-{(1S)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}propanoate and methyl (2R)-2-{(1R)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}propanoate



Using the standard Mitsunobu coupling procedure as described in Example **11** (0.100 g starting phenol, 0.110 g oxazolylethanol, 0.143 g triphenylphosphine, and 0.137 g ADDP in 2 mL dichloromethane), 0.107 g (58%) of product was obtained after chromatography in 15% EtOAc/hexane. NMR (CD_2Cl_2): 1.62-1.87 (m, 4H), 2.40 (s, 3H, oxazole methyl), 2.98 (t, 2H, methylene), 3.23 (m, 1H), 3.63 (s, 3H, ester), 6.60 (s, 1H, aryl), 6.64 (m, 1H, aryl), 7.42 (m, 3H, aryl), 8.00 (m, 2H, aryl).

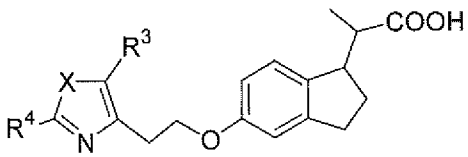
Step 5. (2S)-2-{(1S)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}propanoic acid and (2R)-2-{(1R)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}propanoic acid



The LiOH hydrolysis conditions were applied to 0.090 g of starting ester, yielding 0.082 g (95%) product. NMR (CD_3OD): 0.4-0.75 (m, 4H), 1.18 (s, 3H), 1.75 (t, 2H, methylene), 2.00 (m, 1H), 2.99 (t, 2H, methylene), 5.39 (s, 1H, aryl), 5.48 (m, 1H, aryl), 5.83 (d, 1H, aryl), 6.27 (m, 3H, aryl), 6.76 (m, 2H, aryl).

Using the methods described above and the appropriate starting materials, additional (2*S*, 1*S*) and (2*R*, 1*R*) were similarly prepared, either as diastereomeric (i.e., syn, {(2*S*, 1*S*)/ (2*R*, 1*R*)} and or anti {(2*R*, 1*S*)/ (2*S*, 1*R*)}) mixtures, or as individual enantiomers. These compounds are summarized in Table 5.

Table 5

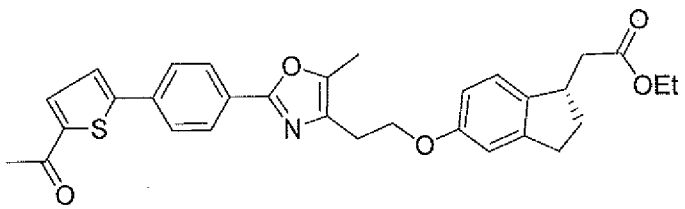


Ex. No.	R^3	R^4	X	Isomer	HPLC RT (min)	LC-MS $[M+H]^+$
224	Me	3,4-$(Cl)_2$-Ph	O	2*S*,1*S*	4.10	460.0
225	Me	3,4-$(Cl)_2$-Ph	O	syn racemate	4.10	460.0
226	Me	3,4-$(Me)_2$-Ph	O	syn racemate	4.32	420.4
227	Me	3,4-$(Me)_2$-Ph	O	2*S*,1*S*	4.32	420.4
228	Me	3-Me-Ph	O	syn racemate	4.19	406.3
229	Me	4-CF_3-Ph	O	syn racemate	3.73	460.2
230	Me	4-CF_3-Ph	O	2*S*,1*S*	3.73	460.2
231	Me	4-CF_3-Ph	O	2*R*,1*R*	3.73	460.2
232	Me	4-Cl-Ph	O	syn racemate	3.61	426.2
233	Me	4-Et-Ph	O	syn racemate	3.70	420.3
234	Me	4-Et-Ph	O	2*S*,1*S*	3.70	420.3
235	Me	4-Et-Ph	O	2*R*,1*R*	3.70	420.3

236	Me	4-Et-Ph	O	syn/anti mixture	3.70	420.3
237	Me	4-Et-Ph	O	2*R*,1*S*	3.70	420.3
238	Me	4-Et-Ph	O	2*S*,1*R*	3.70	420.3
239	Me	4-MeO-Ph	O	syn racemate	3.37	422.3
240	Me	4-MeO-Ph	O	2*R*,1*R*	3.37	422.3
241	Me	4-MeO-Ph	O	2*S*,1*S*	3.37	422.3
242	Me	4-n-Bu-Ph	O	syn racemate	4.08	448.4
243	Me	4-t-Bu-Ph	O	2*S*,1*S*	4.59	448.4
244	Et	4-t-Bu-Ph	O	syn racemate	4.59	448.4
245	Me	4-MeO-Ph	O	2*S*,1*S*	3.58	-
246	Me	4-Cl-Ph	S	syn racemate	3.84	442.2
247	Me	4-Me-Ph	S	syn racemate	4.34	422.3

Example 248

Preparation of ethyl [(1*S*)-5-(2-{2-[4'-(5-acetyl-2-thienyl)-1,1'-biphenyl-4-yl]-5-methyl-1,3-oxazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetate

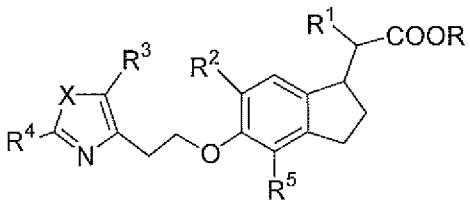


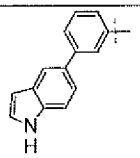
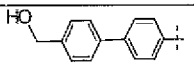
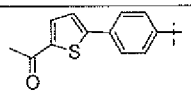
To a solution containing ethyl ((1*S*)-5-{2-[2-(4-bromophenyl)-5-methyl-1,3-oxazol-4-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)acetate (0.100 g, 0.21 mmol) [prepared from 2-[5-methyl-2-(4-bromophenyl)-1,3-oxazol-4-yl]ethanol and ethyl [(1*S*)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl]acetate (Example **135**)], 1,1'-bis(diphenylphosphino)-ferrocene]dichloro palladium(II) (16.9 mg, 0.02 mmol), and 5-acetyl-2-thienylboronic acid (0.062 g, 0.41 mmol) in degassed toluene and dioxane (4:1, 2 mL) was added aqueous 2 M sodium carbonate (0.5 mL). The mixture was heated at 85°C for 16 hours. Solvents were evaporated under vacuum and the residue was dissolved in methanol and acetonitrile and filtered through a C8 reverse phase extraction cartridge. Solvents were evaporated and the residue was dissolved in acetonitrile and purified by HPLC to obtain ethyl [(1S)-5-(2-{2-[4'-(5-acetyl-2-thienyl)-1,1'-biphenyl-4-yl]-5-methyl-1,3-oxazol-4-yl}ethoxy)-2,3-dihydro-1H-inden-1-yl]acetate in 46% yield. (50 mg, 0.09 mmol) MS (electro spray) 530.4 $(M+H)^+$, ^1H NMR ($CDCl_3$) δ 1.24 (t, 3H), 1.71 (m, 1H), 2.37 (m, 5H), 2.57 (s, 3H), 2.68 (m,

1H), 2.83 (m, 2H), 3.03 (m, 2H), 3.48 (m, 1H), 4.17(m, 4H), 6.67 (m, 2H), 7.02 (d, 1H), 7.39 (d, 1H), 7.67 (d, 1H), 7.73 (d, 2H), 8.01 (d, 2H).

Other compounds, prepared by using analogous starting materials and the method described in Example **248** together with the hydrolysis described in Example **11**, are described below in Table 6.

Table 6.

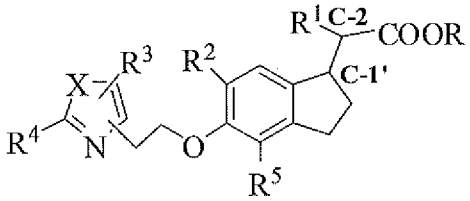


Ex. No.	R	R^1	R^2	R^3	R^4	R^5	X	LC-MS $[M+H]^+$
249	H	H	H	Me		H	O	493.3
250	H	H	H	Me		H	O	484.2
251	H	H	H	Me		H	O	502.2

The foregoing is illustrative of the present invention and is not to be construed as limiting thereof. Although a few exemplary embodiments of this invention have been described, those skilled in the art will readily appreciate that many modifications are possible in the exemplary embodiments without materially departing from the novel teachings and advantages of this invention. Accordingly, all such modifications are intended to be included within the scope of this invention as defined in the claims. Therefore, it is to be understood that the foregoing is illustrative of the present invention and is not to be construed as limited to the specific embodiments disclosed, and that modifications to the disclosed embodiments, as well as other embodiments, are intended to be included within the scope of the appended claims. The invention is defined by the following claims, with equivalents of the claims to be included therein.

THAT WHICH IS CLAIMED IS:

1. A method of treating or preventing psoriasis comprising administering to a subject in need thereof an effective amount of a compound of Formula I:



Formula I

wherein in Formula I

R is H or C_1 - C_6 alkyl;

R^1 is H, COOR, C_3-C_8 cycloalkyl, or

C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_1-C_6 alkoxy, each of which may be unsubstituted or substituted with fluoro, methylenedioxyphenyl, or phenyl which may be unsubstituted or substituted with R^6;

R^2 is H, halo, or C_1-C_6 alkyl which may be unsubstituted or substituted with C_1-C_6 alkoxy, oxo, fluoro, or

R^2 is phenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl,isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrrolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, or morpholinyl, each of which may be unsubstituted or substituted with R^6;

R^3 is H, C_1-C_6 alkyl, or phenyl which may be unsubstituted or substituted with R^6;

X is O or S;

R^4 is C_1-C_6 alkyl or C_3-C_8 cycloalkyl, either of which may be unsubstituted or substituted with fluoro, oxo, or C_1-C_6 alkoxy which may be unsubstituted or substituted with C_1-C_6 alkoxy, or phenyl optionally substituted with R^6, or

each of which may be substituted with phenyl, naphthyl, furyl, thienyl, pyrrolyl, tetrahydrofuryl, pyrrolidinyl, pyrrolinyl, tetrahydrothienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperazinyl, morpholinyl, benzofuryl, dihydrobenzofuryl, benzothienyl, dihydrobenzothienyl, indolyl, indolinyl, indazolyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzisoxazolyl, benzisothiazolyl, benzodioxolyl, quinolyl, isoquinolyl, quinazolinyl, quinoxazolinyl, dihydrobenzopyranyl, dihydrobenzothiopyranyl, or 1,4-benzodioxanyl,

each of which may be unsubstituted or further substituted with R^6, or

C_1-C_6 alkyl may also be substituted with C_3-C_8 cycloalkyl or with phenoxy which may be unsubstituted or substituted with R^6 or with phenyl, naphthyl, furyl, thienyl, pyrrolyl, tetrahydrofuryl, pyrrolidinyl, pyrrolinyl, tetrahydrothienyl, oxazolyl, thiazolyl, imidazolyl,

pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperazinyl, morpholinyl, benzofuryl, dihydrobenzofuryl, benzothienyl, dihydrobenzothienyl, indolyl, indolinyl, indazolyl, benzoxazolyl, benxothiazolyl, benzimidazolyl, benzisoxazolyl,benzisothiazolyl, benzodioxolyl, quinolyl, isoquinolyl, quinazolinyl, quinoxazolinyl, dihydrobenzopyranyl, dihydrobenzothiopyranyl, or 1,4-benzodioxanyl,

each of which may be unsubstituted or substituted with R^6, or

R^4 is phenyl, naphthyl, furyl, thienyl, pyrrolyl, tetrahydrofuryl, pyrrolidinyl, pyrrolinyl, tetrahydrothienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperazinyl, morpholinyl, benzofuryl, dihydrobenzofuryl, benzothienyl, dihydrobenzothienyl, indolyl, indolinyl, indazolyl, benzoxazolyl, benxothiazolyl, benzimidazolyl, benzisoxazolyl, benzisothiazolyl, benzodioxolyl, quinolyl, isoquinolyl, quinazolinyl, quinoxazolinyl, dihydrobenzopyranyl, dihydrobenzothiopyranyl, or 1,4-benzodioxanyl,

each of which may be unsubstituted or substituted with R^6, or with phenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrrolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, morpholinyl, benzodioxolyl, dihydrobenzofuranyl, indolyl, pyrimidinyl or phenoxy,

each of which may be unsubstituted or substituted with R^6;

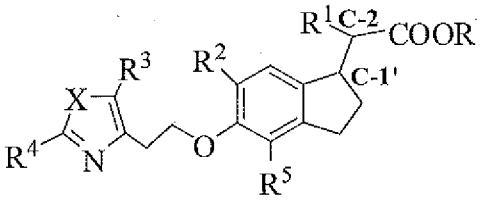
R^5 is H, halo or C_1-C_6 alkyl optionally substituted with oxo; and

R^6 is halo, CF_3, C_1-C_6 alkyl optionally substituted with oxo or hydroxy, or

C_1-C_6 alkoxy optionally substituted with fluoro;

or a pharmaceutically acceptable salt, ester prodrug, stereoisomer, diastereomer, enantiomer, racemate or a combination thereof.

2. The method of Claim 1, wherein the compound has the following structure:



3. The method of Claim 1 or 2, wherein

R is H;

R^1 is H;

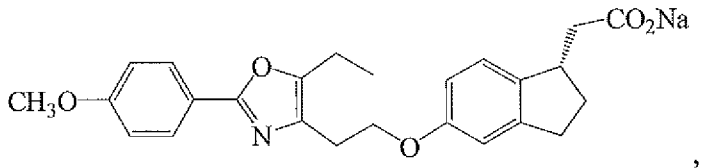
R^2 is H;

R^3 is C_1-C_6 alkyl;

X is O; and

R^4 is a phenyl substituted with R^6, wherein R^6 is C_1-C_6 alkoxyl or C_1-C_6 alkyl.

4. The method of any of Claims 1 to 3, wherein the compound has the following structure:



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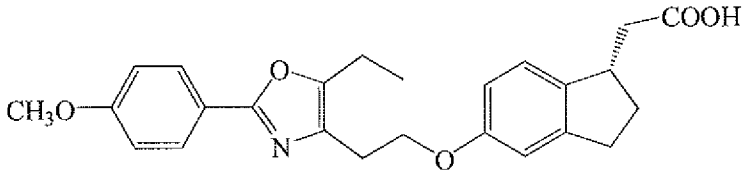

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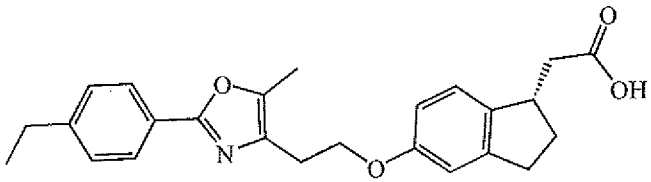

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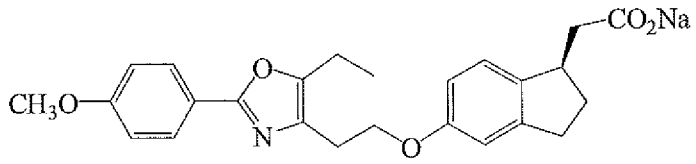

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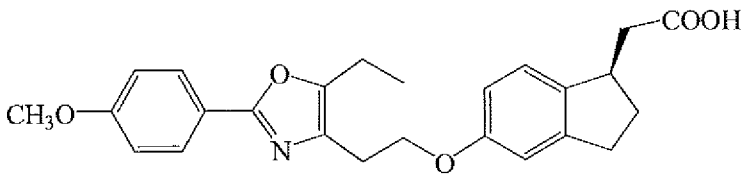
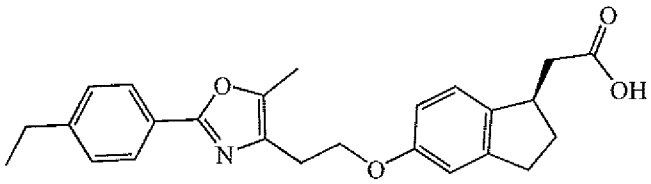


, or

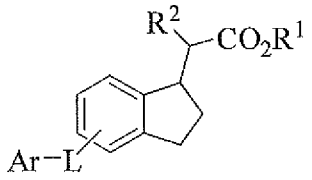


.

5. The method of any of Claims 1-4, wherein the compound is a pharmaceutically acceptable salt thereof, wherein the pharmaceutically acceptable salt is selected from the group consisting of an alkali metal salt, an alkaline earth metal salt, an ammonium salt with organic bases, and a basic nitrogen containing group in the conjugate base that is quaternized with agents selected from the group consisting of alkyl halides and aralkyl.

6. The method of any of Claims 1 to 5, wherein the compound is a meglumine, potassium or sodium salt thereof.

7. A method of treating or preventing psoriasis comprising administering to a subject in need thereof an effective amount of a compound of Formula VI:

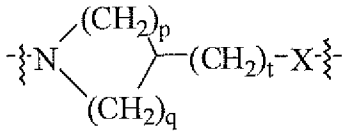


Formula VI

wherein

R^1 and R^2 are independently H, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

L is a linker and selected from the group consisting of $-(CH_2)_m-X-$, $-Y-(CH_2)_n-X-$, and



,

wherein

X is selected from the group O, S, S(=O), and $S(=O)_2$,

Y is selected from the group O, NR^5, S, S(=O), and $S(=O)_2$,

m is 1, 2, or 3,

n is 2, 3, or 4,

t is 0 or 1,

p is 0,1, 2, or 3,

q is 1, 2, 3, or 4,

wherein the sum of p and q is 1, 2, 3, or 4;

Ar is phenyl or a 6-membered heteroaryl containing up to three N atoms,

wherein said Ar is optionally substituted at any available position by 1 to 5 independently selected R^3 groups, and

optionally fused to a 5- or 6-membered saturated carbocyclic ring,

a 5- or 6-membered unsaturated carbocyclic ring, or

a 5- or 6-membered heterocyclic ring containing up to 3 additional heteroatoms selected from N, O, and S,

wherein said fused ring may be optionally substituted at any available position by 1 to 4 independently selected R^4 groups;

R^3 is selected from the group consisting of hydroxy, SH, halo, CN, NO_2, C(=O)OH, C(=O)-OC_1-C_6 alkyl, C(=O)-OC_3-C_6 cycloalkyl, NR^6R^7, C(=O)NR^6R^7, C(=S)NR^6R^7, C_1-C_6 alkyl optionally substituted with halo, OH, NR^6R^7, or C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 thioalkyl, C_2-C_6 alkenyl, C_1-C_6

haloalkoxy, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, phenoxy optionally substituted on the phenyl ring with halo, C_1-C_6 alkyl, or C_1-C_6 alkoxy, and

a mono or bicyclic ring radical selected from the group consisting of

e) phenyl optionally fused to

a 5- or 6-membered saturated or partially unsaturated carbocylic ring, or

a 5- or 6-membered saturated or partially unsaturated heterocyclic ring containing from 1-3 heteroatoms selected from N, O, and S,

f) a 5- or 6-membered heterocyclic ring radical containing up to 4 heteroatoms selected from N, O, or S, optionally fused to

a 5- or 6-membered saturated or partially unsaturated carbocylic ring, or

a 5- or 6-membered saturated or partially unsaturated heterocyclic ring containing from 1-3 heteroatoms selected from N, O, and S,

said mono or bicyclic ring radical being optionally substituted with up to 5 groups independently selected from the group consisting of halo, hydroxy, oxo, CN, C_1-C_6 alkyl optionally substituted with halo, OH, NR^6R^7, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 thioalkyl, C_1-C_6 haloalkoxy, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_6 acyl, C(=O)OH, $CH_2C(=O)OH$, NR^6R^7, $C(=O)NR^6R^7$, $C(=O)OC_1$-C_6 alkyl, and $C(=O)OC_3$-C_6 cycloalkyl;

R^4 is selected from the group consisting of oxo, hydroxy, halo, CN, NR^6R^7, C_1-C_6 alkyl optionally substituted with OH, NR^6R^7, or C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 thioalkyl, C_1-C_6 haloalkoxy, C_3-C_8 cycloalkyl, and C_3-C_8 cycloalkoxy;

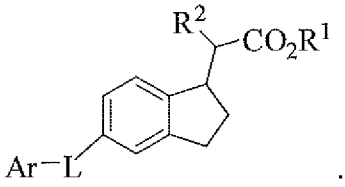
R^5 is selected from the group consisting of H, C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl, C_1-C_6 acyl, benzyl optionally substituted with halo, C_1-C_6 alkoxy, C_1-C_6alkyl, CN, NH_2, $N[(C_1$-$C_3)alkyl]_2$, NO_2, or CF_3, C_3-C_6 cycloalkyl, and $C(=O)OC_1$-C_6 alkyl; and

R^6 and R^7 are independently selected from the group consisting of H, C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl, C_1-C_6 acyl, benzyl optionally substituted with halo, C_1-C_6 alkoxy, $(C_1$-$C_6)alkyl$, CN, NH_2, $N[(C_1$-$C_3)alkyl]_2$, NO_2, or CF_3, C_3-C_6 cycloalkyl, and phenyl optionally substituted with halo, C_1-C_6 alkoxy, $(C_1$-$C_6)alkyl$, CN, $N[(C_1$-$C_3)alkyl]_2$, NO_2, or CF_3, or

R^6 and R^7 may be taken together with the nitrogen atom to which they are attached to form a 5- or 6-membered heterocyclic ring optionally interrupted by NR^5 or O;

or a pharmaceutically acceptable salt, ester prodrug, stereoisomer, diastereomer, enantiomer, racemate or a combination thereof.

8. The method of Claim 7, wherein the compound of Formula VI has the following structure



9. The method of claim 7 or 8, wherein,

R^1 and R^2 are H,

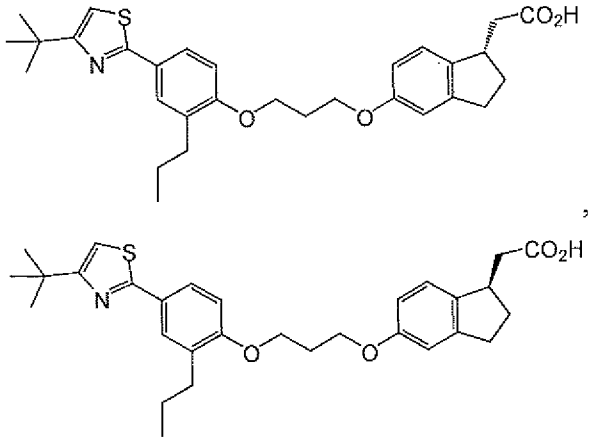
L is $-O-(CH_2)_n-O$, wherein n is 2, 3 or 4,

Ar is a phenyl substituted with one to five R^3,

wherein each occurrence of R^3 is independently C_1-C_6 alkyl or a 5- or 6-member heterocyclic ring containing up to 4 hetero atoms selected from the group consisting of N, O and S,

wherein the heterocyclic ring is substituted with C_1-C_6 alkyl.

10. The method of any of Claims 7-9, wherein the compound has the following structure:



or a pharmaceutically acceptable salt thereof.

11. The method of any of Claims 7-10, wherein the compound is a pharmaceutically acceptable salt thereof, wherein the pharmaceutically acceptable salt is selected from the group consisting of alkali metal salts, alkaline earth metal salts, ammonium salts with organic bases, and basic nitrogen containing groups in the conjugate base that is quaternized with agents selected from the group consisting of alkyl halides and aralkyl.

12. The method of any of Claims 7-11, wherein the compound of Formula VI is a meglumine, potassium or sodium salt thereof.

13. The method according to any of Claims 1-12, wherein said compound is administered topically.

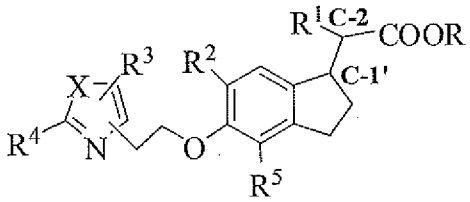
14. The method according to any of Claims 1-13, wherein said compound is administered intracutaneously, subcutaneously, orally, buccally, transdermally, rectally, or otically.

15. The method of any of Claims 1-14, further comprising administration of one or more additional therapeutic agent.

16. The method of Claim 15, wherein the one or more additional therapeutic agent is selected from the group consisting of a corticoid, a vitamin D analog, methrotrexate, ciclosporin, a fumarate, adalimunag, alefecept, afalizumab, etanercept, infliximab, a steroid, a retinoid, an antimicrobial compound, an antioxidant, an anti-inflammatory compound, salicylic acid, an endothelin antagonist, an immunomodulating agent, an angiogenesis inhibitor, a inhibitor of FGF, VEGF, HGF or EGF, an inhibitor of an EGF, FGF, VEGF, or HGF receptor, a tyrosine kinase inhibitor, a protein kinase C inhibitor, and a combination thereof.

17. The method of any of Claims 1-16, further comprising one or more coadjuvant therapy selected from phototherapy or photochemotherapy.

18. A method of treating or preventing Alzheimer's disease comprising administering to a subject in need thereof an effective amount of a compound of Formula I:



Formula I

wherein in Formula I

R is H or C_1 - C_6 alkyl;

R^1 is H, COOR, C_3-C_8 cycloalkyl, or C_1 - C_6 alkyl, C_2-C_6 alkenyl, or C_1-C_6 alkoxy each of which may be unsubstituted or substituted with fluoro, methylenedioxyphenyl, or phenyl which may be unsubstituted or substituted with R^6;

R^2 is H, halo, or C_1-C_6 alkyl which may be unsubstituted or substituted with C_1-C_6 alkoxy, oxo, fluoro, or

R^2 is phenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl,isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrrolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, or morpholinyl,

each of which may be unsubstituted or substituted with R^6;

R^3 is H, C_1-C_6 alkyl, or phenyl, which may be unsubstituted or substituted with R^6;

X is O or S;

R^4 is C_1-C_6 alkyl or C_3-C_8 cycloalkyl, either of which may be unsubstituted or substituted with fluoro, oxo, or C_1-C_6 alkoxy which may be unsubstituted or substituted with C_1-C_6 alkoxy, or phenyl optionally substituted with R^6,

each of which may be substituted with phenyl, naphthyl, furyl, thienyl, pyrrolyl, tetrahydrofuryl, pyrrolidinyl, pyrrolinyl, tetrahydrothienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperazinyl, morpholinyl, benzofuryl, dihydrobenzofuryl, benzothienyl, dihydrobenzothienyl, indolyl, indolinyl, indazolyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzisoxazolyl, benzisothiazolyl, benzodioxolyl, quinolyl, isoquinolyl, quinazolinyl, quinoxazolinyl, dihydrobenzopyranyl, dihydrobenzothiopyranyl, or 1,4-benzodioxanyl,

each of which may be unsubstituted or further substituted with R^6, or

C_1-C_6 alkyl may also be substituted with C_3-C_8 cycloalkyl or with phenoxy which may be unsubstituted or substituted with R^6 or with phenyl, naphthyl, furyl, thienyl, pyrrolyl, tetrahydrofuryl, pyrrolidinyl, pyrrolinyl, tetrahydrothienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperazinyl, morpholinyl, benzofuryl, dihydrobenzofuryl, benzothienyl, dihydrobenzothienyl, indolyl, indolinyl, indazolyl, benzoxazolyl, benxothiazolyl, benzimidazolyl, benzisoxazolyl,benzisothiazolyl, benzodioxolyl, quinolyl, isoquinolyl, quinazolinyl, quinoxazolinyl, dihydrobenzopyranyl, dihydrobenzothiopyranyl, or 1,4-benzodioxanyl,

each of which may be unsubstituted or substituted with R^6, or

R^4 is phenyl, naphthyl, furyl, thienyl, pyrrolyl, tetrahydrofuryl, pyrrolidinyl, pyrrolinyl, tetrahydrothienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperazinyl, morpholinyl, benzofuryl, dihydrobenzofuryl, benzothienyl, dihydrobenzothienyl, indolyl, indolinyl, indazolyl, benzoxazolyl, benxothiazolyl, benzimidazolyl, benzisoxazolyl, benzisothiazolyl, benzodioxolyl, quinolyl, isoquinolyl, quinazolinyl, quinoxazolinyl, dihydrobenzopyranyl, dihydrobenzothiopyranyl, or 1,4-benzodioxanyl,

each of which may be unsubstituted or substituted with R^6, or with phenyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrrolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, morpholinyl, benzodioxolyl, dihydrobenzofuranyl, indolyl, pyrimidinyl or phenoxy,

each of which may be unsubstituted or substituted with R^6;

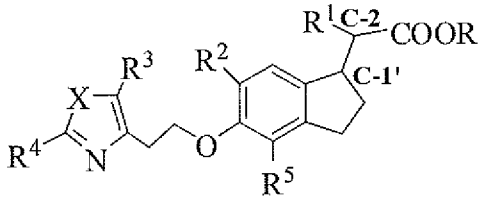
R^5 is H, halo or C_1-C_6 alkyl optionally substituted with oxo; and

R^6 is halo, CF_3, C_1-C_6 alkyl optionally substituted with oxo or hydroxy, or

C_1-C_6 alkoxy optionally substituted with fluoro;

or a pharmaceutically acceptable salt, ester, prodrug, stereoisomer, diastereomer, enantiomer, racemate or a combination thereof.

19. The method of Claims 18, wherein the compound has the following structure:



20. The method of Claim 18 or 19, wherein

R is H,

R^1 is H,

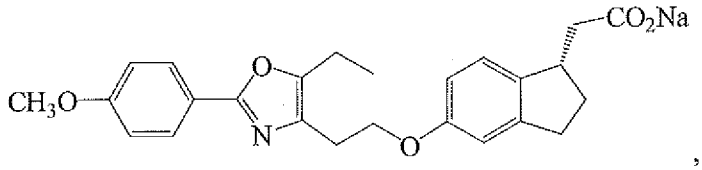
R^2 is H,

R^3 is C_1-C_6 alkyl,

X is O, and

R^4 is a phenyl substituted with R^6, wherein R^6 is C_1-C_6 alkoxyl or C_1-C_6 alkyl.

21. The method of any of Claims 18-20, wherein the compound has the following structure:



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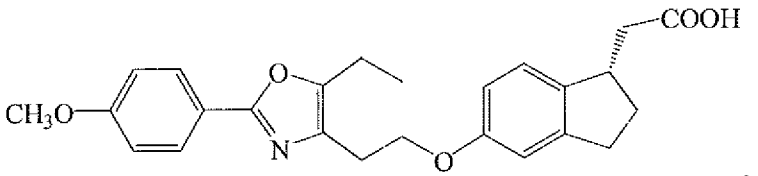

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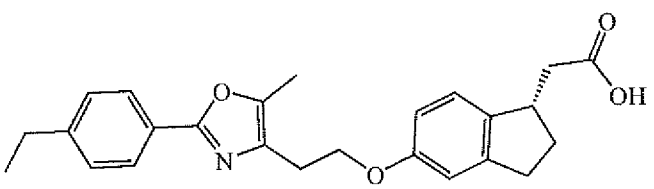

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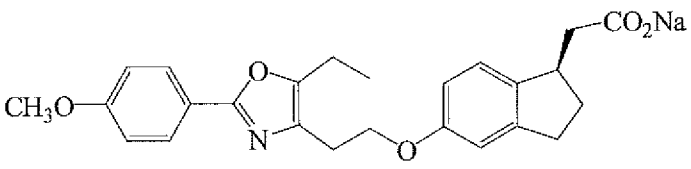

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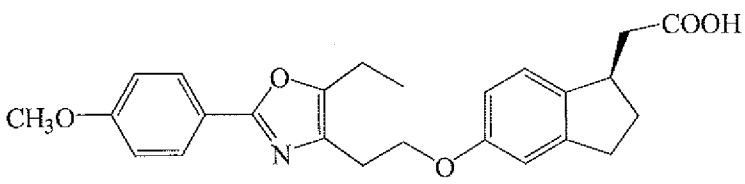
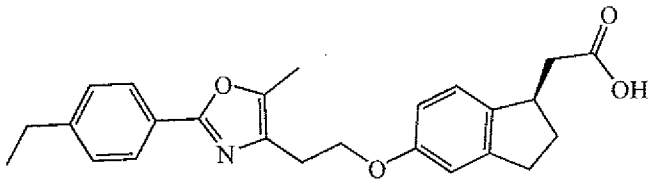


or



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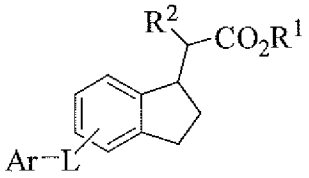
22. The method of any of Claims 18-21, wherein the compound is a pharmaceutically acceptable salt thereof, wherein the pharmaceutically acceptable salt is selected from the group consisting of alkali metal salts, alkaline earth metal salts, ammonium salts with organic bases, and basic nitrogen containing groups in the conjugate base that is quaternized with agents selected from the group consisting of alkyl halides and aralkyl.

23. The method of any of Claims 18-22, wherein the compound is a meglumine, potassium or sodium salt thereof.

24. A method of treating or preventing Alzheimer's disease comprising administering to a subject in need thereof an effective amount of a compound of Formula VI:

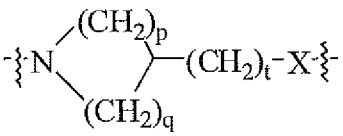


Formula VI

wherein

R^1 and R^2 are independently H, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

L is a linker and selected from the group consisting of $-(CH_2)_m-X-$, $-Y-(CH_2)_n-X-$, and



,

wherein

X is selected from the group O, S, S(=O), and $S(=O)_2$,

Y is selected from the group O, NR^5, S, S(=O), and $S(=O)_2$,

m is 1, 2, or 3,

n is 2, 3, or 4,

t is 0 or 1,

p is 0,1, 2, or 3,

q is 1, 2, 3, or 4,

wherein the sum of p and q is 1, 2, 3, or 4;

Ar is phenyl or a 6-membered heteroaryl containing up to three N atoms,

wherein said Ar is optionally substituted at any available position by 1 to 5 independently selected R^3 groups, and

optionally fused to a 5- or 6-membered saturated carbocyclic ring,

a 5- or 6-membered unsaturated carbocyclic ring, or

a 5- or 6-membered heterocyclic ring containing up to 3 additional

heteroatoms selected from N, O, and S,

wherein said fused ring may be optionally substituted at any available position by 1 to 4 independently selected R^4 groups;

R^3 is selected from the group consisting of hydroxy, SH, halo, CN, NO_2, C(=O)OH, C(=O)-OC_1-C_6 alkyl, C(=O)-OC_3-C_6 cycloalkyl, NR^6R^7, $C(=O)NR^6R^7$, $C(=S)NR^6R^7$, C_1-C_6 alkyl optionally substituted with halo, OH, NR^6R^7, or C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 thioalkyl, C_2-C_6 alkenyl, C_1-C_6 haloalkoxy, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, phenoxy optionally substituted on the phenyl ring with halo, C_1-C_6 alkyl, or C_1-C_6 alkoxy, and

a mono or bicyclic ring radical selected from the group consisting of

g) phenyl optionally fused to

a 5- or 6-membered saturated or partially unsaturated carbocylic ring, or

a 5- or 6-membered saturated or partially unsaturated heterocyclic ring containing from 1-3 heteroatoms selected from N, O, and S,

h) a 5- or 6-membered heterocyclic ring radical containing up to 4 heteroatoms selected from N, O, or S, optionally fused to

a 5- or 6-membered saturated or partially unsaturated carbocylic ring, or

a 5- or 6-membered saturated or partially unsaturated heterocyclic ring containing from 1-3 heteroatoms selected from N, O, and S,

said mono or bicyclic ring radical being optionally substituted with up to 5 groups independently selected from the group consisting of halo, hydroxy, oxo, CN, C_1-C_6 alkyl optionally substituted with halo, OH, NR^6R^7, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 thioalkyl, C_1-C_6 haloalkoxy, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_6 acyl, C(=O)OH, $CH_2C(=O)OH$, NR^6R^7, $C(=O)NR^6R^7$, C(=O)OC_1-C_6 alkyl, and C(=O)OC_3-C_6 cycloalkyl;

R^4 is selected from the group consisting of oxo, hydroxy, halo, CN, NR^6R^7, C_1-C_6 alkyl optionally substituted with OH, NR^6R^7, or C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 thioalkyl, C_1-C_6 haloalkoxy, C_3-C_8 cycloalkyl, and C_3-C_8 cycloalkoxy;

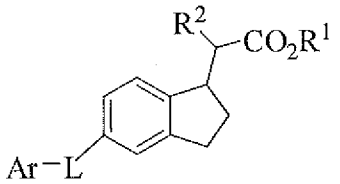
R^5 is selected from the group consisting of H, C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl, C_1-C_6 acyl, benzyl optionally substituted with halo, C_1-C_6 alkoxy, (C_1-C_6)alkyl, CN, NH_2, N[(C_1-C_3)alkyl]$_2$, NO_2, or CF_3, C_3-C_6 cycloalkyl, and C(=O)OC_1-C_6 alkyl; and

R^6 and R^7 are independently selected from the group consisting of H, C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl, C_1-C_6 acyl, benzyl optionally substituted with halo, C_1-C_6 alkoxy, (C_1-C_6)alkyl, CN, NH_2, N[(C_1-C_3)alkyl]$_2$, NO_2, or CF_3, C_3-C_6 cycloalkyl, and phenyl optionally substituted with halo, C_1-C_6 alkoxy, (C_1-C_6)alkyl, CN, N[(C_1-C_3)alkyl]$_2$, NO_2, or CF_3, or

R^6 and R^7 may be taken together with the nitrogen atom to which they are attached to form a 5- or 6-membered heterocyclic ring optionally interrupted by NR^5 or O;

or a pharmaceutically acceptable salt, ester prodrug, stereoisomer, diastereomer, enantiomer, racemate or a combination thereof.

25. The method of Claim 24, wherein the compound has the following structure:



26. The method of Claim 24 or 25, wherein

R^1 and R^2 are H,

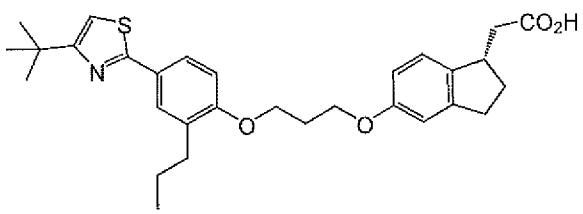
L is –O-(CH_2)$_n$-O, wherein n is 2, 3 or 4,

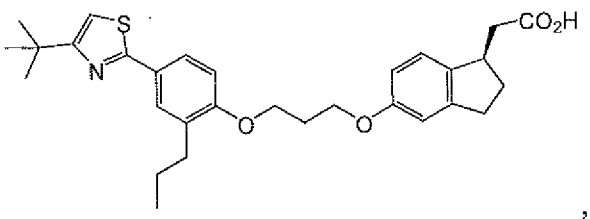
Ar is a phenyl substituted with one to five R^3,

wherein each occurrence of R^3 is independently C_1-C_6 alkyl or a 5- or 6-member heterocyclic ring containing up to 4 heteroatoms selected from N, O or S,

wherein the heterocyclic ring is substituted with C_1-C_6 alkyl.

27. The method of any of Claims 24-26, wherein the compound has the following structure:





or a pharmaceutically acceptable salt thereof.

28. The method of any of Claims 24-27, wherein the compound is a pharmaceutically acceptable salt thereof, wherein the pharmaceutically acceptable salt is selected from the group consisting of alkali metal salts, alkaline earth metal salts, ammonium salts with organic bases, and basic nitrogen containing groups in the conjugate base that is quaternized with agents selected from the group consisting of alkyl halides and aralkyl.

29. The method of any of Claims 24-28, wherein the compound is a meglumine, potassium or sodium salt thereof.

30. The method according to any of Claims 18-29, wherein said compound is administered intravenously, orally, buccally, transdermally, rectally, nasally or otically.

31. The method of any of Claims 18-30, further comprising administration of one or more additional therapeutic agent.

32. The method of Claim 31, wherein said one or more additional therapeutic agent is used to treat or prevent Alzheimer's disease.

33. The method of Claim 32, wherein said one or more additional therapeutic agents is a cholinesterase inhibitor or a NMDA inhibitor.

34. The method of Claim 33, wherein said additional therapeutic agent is selected from the group consisting of tacrine, galantamine, rivastigamine, donepezil and memantine.

35. The method of Claim 31, wherein said one or more additional therapeutic agent is selected from the group consisting of an antioxidant, an anti-inflammatory, a gamma secretase inhibitor, a neurotrophic agent, an acetyl cholinesterase inhibitor, HMG-CoA reductase inhibitors (or statin), an A beta peptide, and an anti-A beta peptide.

36. The method of Claim 31, wherein said one or more additional therapeutic agent is selected from the group consisting of naproxen, ibuprofen, diclofenac, indomethacin, nabumetone, piroxicam, celecoxib, aspirin, simvastatin (Zocor), atovastatin (Lipitor), rosuvastatin (Crestor), and fluvastatin (Lescol).

37. The method of any of Claims 18-36, wherein the subject possesses one or more risk factors for developing Alzheimer's disease selected from the group consisting of a family history of the disease, a genetic predisposition for the disease, elevated serum cholesterol, adult-onset diabetes mellitus, elevated baseline hippocampal volume, elevated cerebrospinal fluid levels of total tau, elevated cerebrospinal fluid levels of phospho-tau, and lowered cerebrospinal fluid levels of A β(1-42).

38. A compound of Formula I or VI for carrying out a method of treatment of any of Claims 1-17.

39. The use of a compound of Formula I or VI for the preparation of a medicament for carrying out a method of any one of Claims 1-17.

40. A compound of Formula I or VI for carrying out a method of treatment of any of Claims 18-37.

41. The use of a compound of Formula I or VI for the preparation of a medicament for carrying out a method of any one of Claims 18-37.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/37227

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 211/06 (2010.01)
USPC - 546/205
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): C07D 211/06 (2010.01)
USPC: 546/205

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8): C07D 211/06; A61K 31/00, 31/67, 31/555 (2010.01)
USPC: 546/205; 514/96,185,210.4

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST; PGPB, USPT, EPAB, JPAB; GoogleScholar; Dialog,indane acetic acid, meglumine, psoriasis, Alzheimer's

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,683,325 A (FRENETTE et al.) 28 July 1987 (28.07.1987) col 2, ln 14-25 col 2, ln 32-40, col 2, ln 60-65, col 3, ln 1-10, col 2, ln 27-28, col 3, ln 21, col 3, ln 25-26, col 4, ln 25-26, col 14, ln 32-40	1-3 and 6-9
Y	US 2003/0216391 A1 (LOWE et al.) 20 November 2003 (20.11.2003) para[0045], para[0150], para[0362]	1-3, 6 and 18-20
Y	US 2006/0084680 A1 (CANTIN et al.) 20 April 2006 (20.04.2006) Abstract, para[0448], para[0736]	7-9 and 24-27
Y	US 2009/0041722 A1 (LIU et al.) 12 February 2009 (12.02.2009) para[0005], para[0038], para[0148], para[0153]	18-20 and 24-27

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 July 2010 (21.07.2010)	04 AUG 2010
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/37227

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: claims 4-5, 10-17, 21-23, 28-41
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.