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(56) Related Art
WELCH, W. M. et al. J. Med. Chem. (1984), 27(11), 1508-1515
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BERTOLINI, G. et al. Eur. J. Med. Chem. 1992, 27(7), 663-672
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(54) Title: TETRALONE-BASED MONOAMINE REUPTAKE INHIBITORS

(57) Abstract: The invention relates to novel tetralone based amines and their use in the treatment of central nervous system (CNS) disorders, such as depression, attention deficit hyperactivity disorder (ADHD) and Parkinson's disease. The invention further relates to pharmaceutical compositions containing the compounds and compositions of the invention as well as methods of inhibiting reuptake of one or more monoamine, such as such as dopamine and norepinephrine, from the synaptic cleft, and methods of modulating one or more monoamine transporter.

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TETRALONE-BASED MONOAMINE REUPTAKE INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. §119(e) to U.S. Provisional Patent Application No. 60/756,555, filed January 5, 2005, which application is incorporated herein by reference in its entirety for all purposes.

FIELD OF THE INVENTION

[0002] The invention relates to compounds and compositions for the treatment of central nervous system (CNS) disorders.

BACKGROUND OF THE INVENTION

[0003] Psychiatric disorders are pathological conditions of the brain characterized by identifiable symptoms that result in abnormalities in cognition, emotion, mood, or affect. These disorders may vary in severity of symptoms, duration, and functional impairment. Psychiatric disorders afflict millions of people worldwide resulting in tremendous human suffering and economic burden due to lost productivity and dependent care.

[0004] Over the past several decades, the use of pharmacological agents to treat psychiatric disorders has greatly increased, largely due to research advances in both neuroscience and molecular biology. In addition, chemists have become increasingly sophisticated at creating chemical compounds that are more effective therapeutic agents with fewer side effects, targeted to correct the biochemical alterations that accompany mental disorders.

[0005] Yet, despite the many advances that have occurred, many psychiatric diseases remain untreated or inadequately treated with current pharmaceutical agents. In addition, many of the current agents interact with molecular targets not involved with the psychiatric disease. This indiscriminate binding can result in side effects that can greatly influence the overall outcome of therapy. In some cases the side effects are so severe that discontinuation of therapy is required.

[0006] Depression is an affective disorder, the pathogenesis of which cannot be explained by any single cause or theory. It is characterized by a persistently low mood or diminished interests in one's surroundings, accompanied by at least several of the following symptoms: reduced energy and motivation, difficulty concentrating, altered sleep and appetite, and at times, suicidal ideation (American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, ed. 4. Washington, American Psychiatric Association, 1994). Major depression is associated with high rates of morbidity and mortality, with suicide rates of 10-25% (Kaplan H I, Sadock B J (eds): *Synopsis of Psychiatry*. Baltimore, Williams & Wilkins, 1998, p. 866).

[0007] Depression is believed to result from dysfunction in the noradrenergic or serotonergic systems, more specifically, from a deficiency of certain neurotransmitters (NTs) at functionally important adrenergic or serotonergic receptors.

[0008] Neurotransmitters produce their effects as a consequence of interactions with specific receptors. Neurotransmitters, including norepinephrine (NE) and/or serotonin (5-hydroxytryptamine, or 5-HT), are synthesized in brain neurons and stored in vesicles. Upon a nerve impulse, NTs are released into the synaptic cleft, where they interact with various postsynaptic receptors. Regional deficiencies in the synaptic levels of 5-HT and/or NE are believed to be involved in the etiology of depression, wakefulness, and attention.

[0009] Norepinephrine is involved in regulating arousal, dreaming, and moods. Norepinephrine can also contribute to the regulation of blood pressure, by constricting blood vessels and increasing heart rate.

[0010] Serotonin (5-HT) is implicated in the etiology or treatment of various disorders. The most widely studied effects of 5-HT are those on the CNS. The functions of 5-HT are numerous and include control of appetite, sleep, memory and learning, temperature regulation, mood, behavior (including sexual and hallucinogenic behavior), cardiovascular function, smooth muscle contraction, and

endocrine regulation. Peripherally, 5-HT appears to play a major role in platelet homeostasis and motility of the GI tract. The actions of 5-HT are terminated by three major mechanisms: diffusion; metabolism; and reuptake. The major mechanism by which the action of 5-HT is terminated is by reuptake through presynaptic membranes. After 5-HT acts on its various postsynaptic receptors, it is removed from the synaptic cleft back into the nerve terminal through an uptake mechanism involving a specific membrane transporter in a manner similar to that of other biogenic amines. Agents that selectively inhibit this uptake increase the concentration of 5-HT at the postsynaptic receptors and have been found to be useful in treating various psychiatric disorders, particularly depression.

[0011] Approaches to the treatment of depression over the years have involved the use of agents that increase the levels of NE and 5-HT, either by inhibiting their metabolism (*e.g.*, monoamine oxidase inhibitors) or reuptake (*e.g.*, tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs)).

[0012] There are more than twenty (20) approved antidepressant drugs available in the United States. The classical tricyclic antidepressants (TCAs) currently available block primarily the uptake of NE and also, to varying degrees, the uptake of 5-HT, depending on whether they are secondary or tertiary amines. Tertiary amines such as imipramine and amitriptyline are more selective inhibitors of the uptake of 5-HT than of catecholamines, compared with secondary amines such as desipramine.

[0013] Selective serotonin reuptake inhibitors have been investigated as potential antidepressants. Fluoxetine (PROZAC®), sertraline (ZOLOFT®), and paroxetine (PAXIL®) are three examples of SSRIs currently on the U.S. market. These agents do not appear to possess greater efficacy than the TCAs, nor do they generally possess a faster onset of action; however, they do have the advantage of causing less side-effects. Of these three SSRIs, paroxetine is the most potent inhibitor of 5-HT uptake, fluoxetine the least. Sertraline is the most selective for 5-HT versus NE uptake, fluoxetine the least selective. Fluoxetine and sertraline produce active metabolites, while paroxetine is metabolized to inactive

metabolites. The SSRIs, in general, affect only the uptake of serotonin and display little or no affinity for various receptor systems including muscarinic, adrenergic, dopamine, and histamine receptors.

[0014] In addition to treating depression, several other potential therapeutic applications for SSRIs have been investigated. They include treatment of Alzheimer's disease, aggressive behavior, premenstrual syndrome, diabetic neuropathy, chronic pain, fibromyalgia, and alcohol abuse. For example, fluoxetine is approved for the treatment of obsessive-compulsive disorder (OCD). Of particular significance is the observation that 5-HT reduces food consumption by increasing meal-induced satiety and reducing hunger, without producing the behavioral effects of abuse liability associated with amphetamine-like drugs. Thus, there is interest in the use of SSRIs in the treatment of obesity.

[0015] Venlafaxine (EFFEXOR[®]) is a dual-reuptake antidepressant that differs from the classical TCAs and the SSRIs chemically and pharmacologically in that it acts as a potent inhibitor of both 5-HT and NE uptake. Neither venlafaxine nor its major metabolite have a significant affinity for adrenergic alpha-1 receptors. Venlafaxine possesses an efficacy equivalent to that of the TCAs, and a benign side effect profile similar to those of the SSRIs.

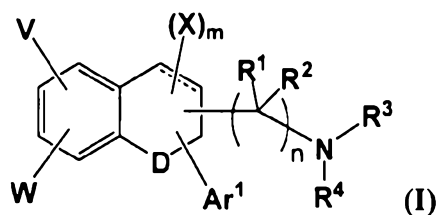
[0016] Dopamine is hypothesized to play a major role in psychosis and certain neurodegenerative diseases, such as Parkinson's disease, where a deficiency in dopaminergic neurons is believed to be the underlying pathology. Dopamine affects brain processes that control movement, emotional response, and ability to experience pleasure and pain. Regulation of DA plays a crucial role in our mental and physical health. Certain drugs increase DA concentrations by preventing DA reuptake, leaving more DA in the synapse. An example is methylphenidate (RITALIN[®]), used therapeutically to treat childhood hyperkinesias and symptoms of schizophrenia. Dopamine abnormalities are believed to underlie some of the core attentional abnormalities seen in acute schizophrenics.

[0017] A therapeutic lag is associated with the use of these drugs. Patients must take a drug for at least three (3) weeks before achieving clinically meaningful symptom relief. Furthermore, a significant number of patients do not respond to current therapies at all. For example, it is currently estimated that up to thirty percent (30%) of clinically diagnosed cases of depression are resistant to all forms of drug therapy.

SUMMARY OF THE INVENTION

[0018] The present invention relates to novel tetralone-based amines and salts thereof. It further relates to novel pharmaceutical compositions, and their use in the treatment of CNS disorders such as depression (e.g., major depressive disorder, bipolar disorder), fibromyalgia, pain (e.g., neuropathic pain), sleep apnea, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), restless leg syndrome, schizophrenia, anxiety, obsessive compulsive disorder, posttraumatic stress disorder, seasonal affective disorder (SAD), premenstrual dysphoria as well as neurodegenerative disease (e.g., Parkinson's disease, Alzheimer's disease).

[0019] The present invention broadly relates to compounds having a structure according to Formula (I):



[0020] In Formula (I), n is an integer selected from 0 to 2. D is a member selected from the group consisting of CX₂, CX-Ar¹, CX-(CR¹R²)_nNR³R⁴, N-Ar¹ and N-(CR¹R²)_nNR³R⁴. The integer m is selected from 0 to 6, with the proviso that when D is N-Ar¹ or N-(CR¹R²)_nNR³R⁴, then m is not greater than 5. Each X is a member independently selected from the group consisting of H, halogen, CN, CF₃, OR⁵, SR⁵, S(O)₂R⁵, NR⁶R⁷, NR⁶S(O)₂R⁵, NR⁶C(O)R⁵, acyl, =X¹, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heterocycloalkyl. X¹ is a member selected from the group consisting of O, S, and NOR^{5'} wherein R^{5'} is a member selected from the group consisting of H, substituted or unsubstituted alkyl and substituted

or unsubstituted heteroalkyl. Each R^5 , R^6 and R^7 is a member independently selected from the group consisting of H, acyl, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl, wherein R^6 and R^7 , together with the atoms to which they are attached, are optionally joined to form a 3- to 7-membered ring.

[0021] Ar^1 in Formula (I) is a member selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and a fused ring system. V and W are members independently selected from the group consisting of H, halogen, CF_3 , CN, OR^9 , SR^9 , $S(O)_2R^9$, $NR^{10}R^{11}$, $NR^{10}S(O)_2R^9$, $NR^{10}C(O)R^9$, acyl, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heterocycloalkyl, wherein V and W, together with the atoms to which they are attached, are optionally joined to form a 5- to 7-membered ring. Each R^9 , R^{10} and R^{11} is a member independently selected from the group consisting of H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, wherein R^{10} and R^{11} , together with the atoms to which they are attached, are optionally joined to form a 3- to 7-membered ring.

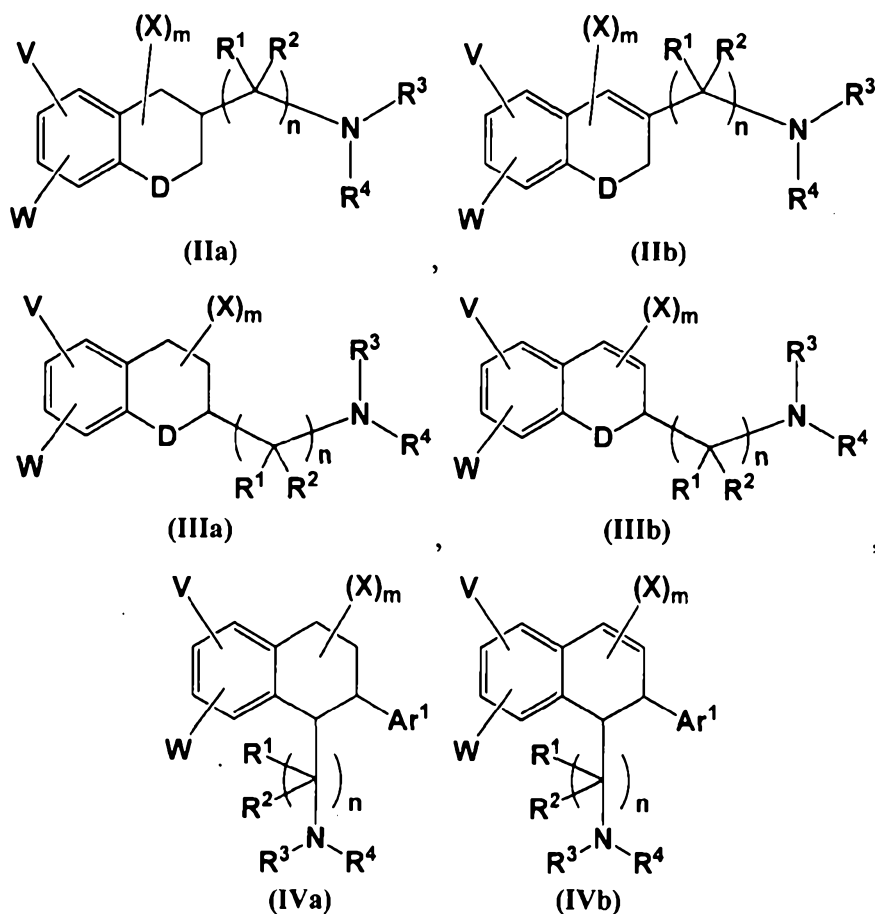
[0022] In Formula (I), each R^1 and R^2 is a member independently selected from the group consisting of H, halogen, CN, CF_3 , OR^{12} , substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted heterocycloalkyl, wherein R^{12} is a member selected from the group consisting of H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted heterocycloalkyl.

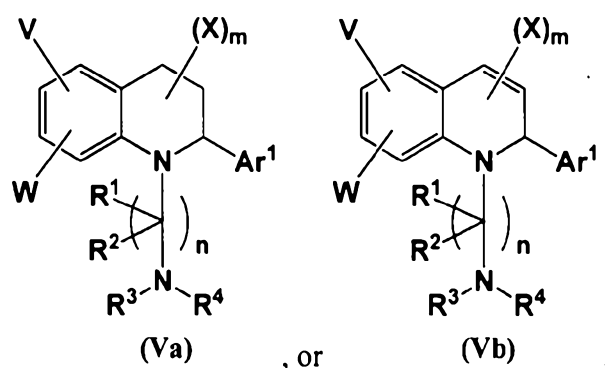
[0023] In Formula (I) R^3 and R^4 are members independently selected from the group consisting of H, OR^{13} , acyl, $S(O)_2R^{14}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted heterocycloalkyl, wherein R^{13} is a member selected from the group consisting of H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted heterocycloalkyl. R^{14} is a member selected

from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted heterocycloalkyl.

[0024] In Formula (I) at least two of R^1 , R^2 , R^3 and R^4 , together with the atoms to which they are attached, are optionally joined to form a 3- to 7-membered ring.

[0024a] In a first aspect the present invention provides a compound having a structure of Formula (IIa), Formula (IIb), Formula (IIIa), Formula (IIIb), Formula (IVa), Formula (IVb), Formula (Va), or Formula (Vb), or a pharmaceutically acceptable salt or solvate thereof:





wherein

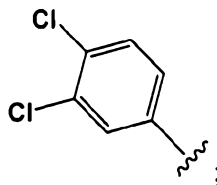
n is an integer selected from 0 to 2;

D is $CX-Ar^1$ or $N-Ar^1$;

m is 1;

each X is independently H or OH;

Ar^1 is



V and W are each independently H or OR^9 ; wherein R^9 is H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl;

R^1 and R^2 are each independently H, halogen, CN, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl; and

R^3 and R^4 are each independently H, substituted or unsubstituted C_1-C_4 alkyl, or substituted or unsubstituted C_1-C_4 heteroalkyl;

wherein at least two of R^1 , R^2 , R^3 , and R^4 , together with the atoms to which they are attached, are optionally joined to form a 3- to 7-membered ring;

and any enantiomer, diastereoisomer, racemic mixture, enantiomerically enriched mixture, and enantiomerically pure form thereof.

[0024b] In one or more preferred embodiments R^1 and R^2 are H. In one or more preferred embodiments, R^3 and R^4 are each independently H or substituted or unsubstituted C_1 - C_4 alkyl. In one or more preferred embodiments n is 0, 1 or 2. In one or more preferred embodiments D is $CX-Ar^1$. In one or more preferred embodiments D is $N-Ar^1$.

[0025] The compounds of the invention can be chiral, racemic or be present in a composition including one or more stereoisomer, such as an enantiomerically or diastereomerically enriched mixture.

[0025a] In a second aspect, the invention provides a composition comprising a first stereoisomer and at least one additional stereoisomer of a compound according to the invention, wherein said first stereoisomer is present in a diastereomeric excess of at least 80% relative to said at least one additional stereoisomer.

[0026] In a third aspect, the invention provides a pharmaceutical composition comprising a compound of the invention or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier, vehicle, diluent or combination thereof.

[0027] In another aspect, the invention provides a method for treating a central nervous system disorder. The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of the invention or a pharmaceutically acceptable salt or solvate thereof, or a composition according to the second or third aspects of the invention.

[0028] In a further aspect, the invention relates to a method of inhibiting reuptake of one or more monoamine from the synaptic cleft. The method comprises administering to a mammalian subject a compound of the invention or a pharmaceutically acceptable salt or solvate thereof, or a composition according to the second or third aspects of the invention.

[0029] In yet another aspect, the invention provides a method of modulating one or more monoamine transporter. The method comprises administering to a mammalian subject a compound of the invention, or a pharmaceutically acceptable salt or solvate thereof, or a composition according to the second or third aspects of the invention.

[0029a] In a further aspect the invention provides the use of a compound of the invention, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a central nervous system disorder.

[0029b] In another aspect the invention provides the use of a compound of the invention, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for inhibiting reuptake of one or more monoamine(s) from the synaptic cleft in a mammalian subject.

[0029c] In another aspect the invention provides the use of a compound of the invention, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for modulating one or more monoamine transporter(s) in a mammalian subject.

[0029d] Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

[0029e] Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this specification.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

[0030] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (*i.e.* C₁-C₁₀ means one to ten carbons). Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. The term "alkyl," unless otherwise noted, is also meant to include those derivatives of alkyl defined in more detail below, such as "heteroalkyl." Alkyl groups that are limited to hydrocarbon groups are termed "homoalkyl".

[0031] The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified, but not limited, by $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$, and further includes those groups described below as "heteroalkylene." Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred

in the present invention. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

[0032] The terms "alkoxy," "alkylamino" and "alkylthio" (or thioalkoxy) are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom, an amino group, or a sulfur atom, respectively.

[0033] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and at least one heteroatom selected from the group consisting of O, N, Si and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S and Si may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Examples include, but are not limited to, $-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)-\text{CH}_3$, $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})_2-\text{CH}_3$, $-\text{CH}=\text{CH}-\text{O}-\text{CH}_3$, $-\text{Si}(\text{CH}_3)_3$, $-\text{CH}_2-\text{CH}=\text{N}-\text{OCH}_3$, and $-\text{CH}=\text{CH}-\text{N}(\text{CH}_3)-\text{CH}_3$. Up to two heteroatoms may be consecutive, such as, for example, $-\text{CH}_2-\text{NH}-\text{OCH}_3$ and $-\text{CH}_2-\text{O}-\text{Si}(\text{CH}_3)_3$. Similarly, the term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-\text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-$ and $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (*e.g.*, alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-\text{CO}_2\text{R}'$ represents both $-\text{C}(\text{O})\text{OR}'$ and $-\text{OC}(\text{O})\text{R}'$.

[0034] The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions

of “alkyl” and “heteroalkyl”, respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like.

[0035] The terms “halo” or “halogen,” by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as “haloalkyl,” are meant to include monohaloalkyl and polyhaloalkyl. For example, the term “halo(C₁-C₄)alkyl” is meant to include, but not be limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0036] The term “aryl” means, unless otherwise stated, a polyunsaturated, aromatic, substituent that can be a single ring or multiple rings (preferably from 1 to 3 rings), which are fused together or linked covalently. The term “heteroaryl” refers to aryl groups (or rings) that contain from one to four heteroatoms selected from N, O, S, Si and B, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxaliny, 5-quinoxaliny, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below.

[0037] For brevity, the term "aryl" when used in combination with other terms (*e.g.*, aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the term "arylalkyl" is meant to include those radicals in which an aryl group is attached to an alkyl group (*e.g.*, benzyl, phenethyl, pyridylmethyl and the like) including those alkyl groups in which a carbon atom (*e.g.*, a methylene group) has been replaced by, for example, an oxygen atom (*e.g.*, phenoxymethyl, 2-pyridyloxymethyl, 3-(1-naphthyloxy)propyl, and the like).

[0038] Each of the above terms (*e.g.*, "alkyl," "heteroalkyl," "aryl" and "heteroaryl") are meant to include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0039] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) are generically referred to as "alkyl group substituents," and they can be one or more of a variety of groups selected from, but not limited to: substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR'C(O)R', -NR'-C(O)NR'R''', -NR'C(O)₂R', -NR-C(NR'R''R''')=NR''', -NR-C(NR'R'')=NR''', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NRSO₂R', -CN and -NO₂ in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R', R'', R''' and R'''' each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, *e.g.*, aryl substituted with 1-3 halogens, substituted or unsubstituted alkyl, alkoxy or thioalkoxy groups, or arylalkyl groups. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''' and R'''' groups

when more than one of these groups is present. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6-, or 7-membered ring. For example, -NR'R'' is meant to include, but not be limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (*e.g.*, -CF₃ and -CH₂CF₃) and acyl (*e.g.*, -C(O)CH₃, -C(O)CF₃, -C(O)CH₂OCH₃, and the like).

[0040] Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are generically referred to as "aryl group substituents." The substituents are selected from, for example: substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-C(O)NR''R''', -NR''C(O)₂R', -NR-C(NR'R''R''')=NR''', -NR-C(NR'R'')=NR'', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NRSO₂R', -CN and -NO₂, -R', -N₃, -CH(Ph)₂, fluoro(C₁-C₄)alkoxy, and fluoro(C₁-C₄)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R'', R''' and R'''' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''' and R'''' groups when more than one of these groups is present.

[0041] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -T-C(O)-(CRR')_q-U-, wherein T and U are independently -NR-, -O-, -CRR'- or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the

formula $-A-(CH_2)_r-D-$, wherein A and D are independently $-CRR'-$, $-O-$, $-NR-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2NR'-$ or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-(CRR')_s-X''-(CR''R''')_d-$, where s and d are independently integers of from 0 to 3, and X'' is $-O-$, $-NR'-$, $-S-$, $-S(O)-$, $-S(O)_2-$, or $-S(O)_2NR'-$. The substituents R, R', R'' and R''' are preferably independently selected from hydrogen or substituted or unsubstituted (C_1-C_6)alkyl.

[0042] As used herein, the term "acyl" describes a substituent containing a carbonyl residue, $C(O)R$. Exemplary species for R include H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heterocycloalkyl.

[0043] As used herein, the term "fused ring system" means at least two rings, wherein each ring has at least 2 atoms in common with another ring. "Fused ring systems may include aromatic as well as non aromatic rings. Examples of "fused ring systems" are naphthalenes, indoles, quinolines, chromenes and the like.

[0044] As used herein, the term "heteroatom" includes oxygen (O), nitrogen (N), sulfur (S) and silicon (Si) and boron (B).

[0045] The symbol "R" is a general abbreviation that represents a substituent group that is selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heterocycloalkyl groups.

[0046] The phrase "therapeutically effective amount" as used herein means that amount of a compound, or composition comprising a compound of the present invention which is effective for producing some desired therapeutic effect (e.g., by inhibiting reuptake of a monoamine from the synaptic cleft of a mammal, thereby modulating the biological consequences of that pathway in the treated organism) at a reasonable benefit/risk ratio applicable to any medical treatment.

[0047] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0048] The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) pH buffered solutions; (21) polyesters, polycarbonates and/or polyanhydrides; and (22) other non-toxic compatible substances employed in pharmaceutical formulations.

[0049] As set out above, certain embodiments of the present compounds may contain a basic functional group, such as amino or alkylamino, and are, thus, capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable acids. The term "pharmaceutically acceptable salts" in this respect, refers to the relatively non-toxic, inorganic and organic acid addition salts of

compounds of the present invention. These salts can be prepared *in situ* in the administration vehicle or the dosage form manufacturing process, or by separately reacting a purified compound of the invention in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed during subsequent purification. Representative salts include the hydrobromide, hydrochloride, sulfate, sulfamate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, tosylate, citrate, maleate, ascorbate, palmitate, fumarate, succinate, tartrate, naphylate, mesylate, hydroxymaleate, phenylacetate, glutamate, glucoheptonate, salicylate, sulfanilate, 2-acetoxybenzoate, methanesulfonate, ethane disulfonate, oxalate, isothionate, lactobionate, and laurylsulphonate salts and the like. See, for example, Berge et al. (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19.

[0050] The term "pharmaceutically acceptable salts" includes salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-

tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge *et al.*, *Journal of Pharmaceutical Science*, 66: 1-19 (1977)). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0051] The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

[0052] In addition to salt forms, the present invention provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

[0053] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention. "Compound or a pharmaceutically acceptable salt or solvate of a compound" intends the inclusive meaning of "or", in that a material that is both a salt and a solvate is encompassed.

[0054] Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers are encompassed within the scope of the present invention. Optically active (R)- and (S)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

[0055] The graphic representations of racemic, ambiscalemic and scalemic or enantiomerically pure compounds used herein are taken from Maehr, *J. Chem. Ed.*, 62: 114-120 (1985): solid and broken wedges are used to denote the absolute configuration of a chiral element; wavy lines indicate disavowal of any stereochemical implication which the bond it represents could generate; solid and broken bold lines are geometric descriptors indicating the relative configuration shown but not implying any absolute stereochemistry; and wedge outlines and dotted or broken lines denote enantiomerically pure compounds of indeterminate absolute configuration.

[0056] The terms “enantiomeric excess” and “diastereomeric excess” are used interchangeably herein. Compounds with a single stereocenter are referred to as being present in “enantiomeric excess,” those with at least two stereocenters are referred to as being present in “diastereomeric excess.”

[0057] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

[0058] The term “central nervous system disorder” refers to any abnormal condition of the central nervous system of a mammal. Central nervous system disorder includes neurodegenerative diseases such Alzheimer’s disease and Parkinson’s disease, neuropsychiatric diseases (e.g. schizophrenia), anxieties, sleep disorders, depression, dementias, movement disorders, psychoses, alcoholism, post-traumatic stress disorder and the like. “Central nervous system disorder” also includes any condition associated with the disorder, such as loss of memory and/or loss of cognition. For instance, a method of treating a neurodegenerative disease would also include treating or preventing loss of neuronal function characteristic of such disease. “Central nervous system disorder” also includes any disease or condition that is implicated, at least in part, in monoamine (e.g., norepinephrine) signaling pathways (e.g., cardiovascular disease).

[0059] The term “pain” refers to all categories of pain, including pain that is described in terms of stimulus or nerve response, e.g., somatic pain (normal nerve response to a noxious stimulus) and neuropathic pain (abnormal response of a injured or altered sensory pathway, often without clear noxious input); pain that is categorized temporally, e.g., chronic pain and acute pain; pain that is categorized in terms of its severity, e.g., mild, moderate, or severe; and pain that is a symptom or a result of a disease state or syndrome, e.g., inflammatory pain, cancer pain, AIDS pain, arthropathy, migraine, trigeminal neuralgia, cardiac ischaemia, and diabetic neuropathy (see, e.g., Harrison’s Principles of Internal Medicine, pp. 93-98 (Wilson *et al.*, eds., 12th ed. 1991); Williams *et al.*, *J. of Med. Chem.* 42: 1481-1485 (1999), herein each incorporated by reference in their entirety). “Pain” is also meant to include mixed etiology pain, dual mechanism pain, allodynia, causalgia, central pain, hyperesthesia, hyperpathia, dysesthesia, and hyperalgesia.

II. Introduction

[0060] One strategy to develop effective therapies is the use of broad spectrum antidepressants that simultaneously inhibit the reuptake of more than one biogenic

amine, such as serotonin (5-HT), norepinephrine (NE) and dopamine (DA). The rationale for this approach is based upon clinical and preclinical evidence showing that deficiencies in dopaminergic function can be correlated with anhedonia, which is a core symptom of depression. Baldessarini, R.J., "Drugs and the Treatment of Psychiatric Disorders: Depression and Mania, in Goodman and Gilman's The Pharmacological Basis of Therapeutics 431-459 (9th ed 1996) Hardman et. al. eds.

[0061] An advantage of the compounds and compositions of the present invention is their ability to increase synaptic availability of three neurotransmitters, NE, 5-HT and DA by inhibiting their reuptake from the synaptic cleft. Skolnick and coworkers report on a body of preclinical evidence suggesting that the therapeutic profile of an antidepressant concurrently increasing the synaptic availability of DA, NE and 5-HT will differ from a compound inhibiting only NE and/or 5-HT. Skolnick, P.; Popik, P.; Janowsky, A.; Beer, B.; Lippa, A. S. "Antidepressant-like actions of DOV-21,947: a "triple" reuptake inhibitor," *Eur. J. Pharm.* 2003, 461, 103.

[0062] For example, Skolnick and coworkers have reported that a compound, DOV 21,947 ((+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane), inhibits the reuptake of serotonin, norepinephrine, and dopamine in human embryonic kidney (HEK293) cells expressing the corresponding human recombinant transporters (IC₅₀ values of 12, 23 and 96 nM, respectively). Skolnick, P.; Popik, P.; Janowsky, A.; Beer, B.; Lippa, A. S. "Antidepressant-like actions of DOV-21,947: a "triple" reuptake inhibitor," *Eur. J. Pharm.* 2003, 461, 99. In addition, DOV 21,947 reduces the duration of immobility in the forced swim test (in rats) and also produces a dose-dependent reduction in immobility in the tail suspension test. Skolnick, P.; Popik, P.; Janowsky, A.; Beer, B.; Lippa, A. S., *Eur. J. Pharm.* 2003, 461, 99. Additional evidence can be found in preclinical data for new triple reuptake inhibitors such as DOV 21,947 in, e.g., U.S. Patent No. 6,372,919, wherein DOV 21,947 was disclosed as having a significantly greater affinity for

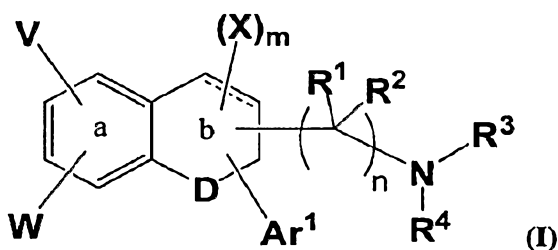
the norepinephrine and serotonin uptake sites than the racemic compound, (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane.

[0063] Taken together, the preclinical data for compounds such as DOV 21,947 indicate that dual or triple reuptake inhibitors may hold potential as novel treatments for depression in the clinic.

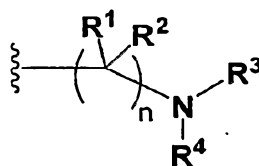
III. Compositions

A. Tetralone Based Amines

[0064] In a first aspect, the invention provides a compound having a structure according to Formula (I):



[0065] Each compound of Formula (I) includes at least one substituent $-Ar^1$ and at least one nitrogen-containing substituent:



attached to ring b.

[0066] In Formula (I), n is an integer selected from 0 to 2. D is a member selected from the group consisting of CX_2 , $CX-Ar^1$, $CX-(CR^1R^2)_nNR^3R^4$, $N-Ar^1$ and $N-(CR^1R^2)_nNR^3R^4$. The 6-membered, non-aromatic ring b of Formula (I) can be mono- or disubstituted at each of the positions of the ring, which is not part of ring a. In an exemplary embodiment, ring b includes up to 6 substituents X, preferably up to 4 substituents X, and more preferably up to 2 substituents X, wherein each X is independently selected. Thus, m is an integer selected from 0

to 6, with the proviso that when D is N-Ar¹ or N-(CR¹R²)_nNR³R⁴, then m is not greater than 5.

[0067] Each X is a member independently selected from the group consisting of H, halogen, CN, CF₃, OR⁵, SR⁵, S(O)₂R⁵, NR⁶R⁷, NR⁶S(O)₂R⁵, NR⁶C(O)R⁵, acyl, =X¹, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heterocycloalkyl. X¹ is a member selected from the group consisting of O, S, and NOR^{5'} wherein R^{5'} is a member selected from the group consisting of H, substituted or unsubstituted alkyl and substituted or unsubstituted heteroalkyl. Each R⁵, R⁶ and R⁷ is a member independently selected from the group consisting of H, acyl, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl, wherein R⁶ and R⁷, together with the atoms to which they are attached, are optionally joined to form a 3- to 7-membered ring.

[0068] Ar¹ in Formula (I) is a member selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and a fused ring system. V and W are aryl group substituents. In an exemplary embodiment V and W are members independently selected from the group consisting of H, halogen, CF₃, CN, OR⁹, SR⁹, S(O)₂R⁹, NR¹⁰R¹¹, NR¹⁰S(O)₂R⁹, NR¹⁰C(O)R⁹, acyl, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heterocycloalkyl, wherein V and W, together with the atoms to which they are attached, are optionally joined to form a 5- to 7-membered ring. Each R⁹, R¹⁰ and R¹¹ is a member independently selected from the group consisting of H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, wherein R¹⁰ and R¹¹, together with the atoms to which they are attached, are optionally joined to form a 3- to 7-membered ring.

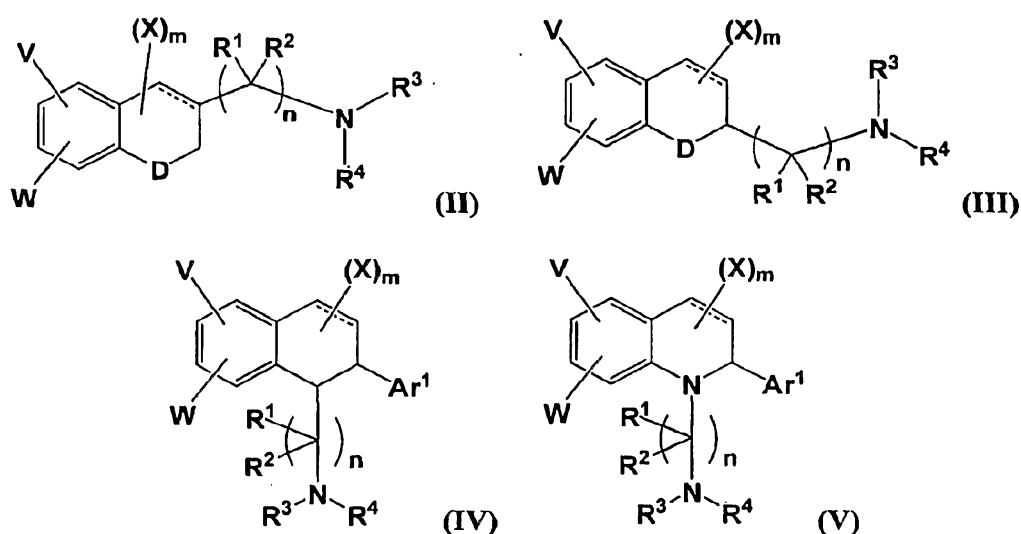
[0069] In Formula (I), each R^1 and R^2 is a member independently selected from the group consisting of H, halogen, CN, CF_3 , OR^{12} , substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted heterocycloalkyl, wherein R^{12} is a member selected from the group consisting of H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted heterocycloalkyl.

[0070] R^3 and R^4 are members independently selected from the group consisting of H, OR^{13} , acyl, $S(O)_2R^{14}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted heterocycloalkyl, wherein R^{13} is a member selected from the group consisting of H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted heterocycloalkyl. R^{14} is a member selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted heterocycloalkyl.

[0071] At least two of R^1 , R^2 , R^3 and R^4 , together with the atoms to which they are attached, are optionally joined to form a 3- to 7-membered ring.

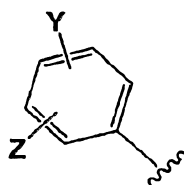
[0072] The compound of the invention can be chiral, racemic or be present in a composition including one or more stereoisomer.

[0073] In an exemplary embodiment, the compound of the invention has a structure, which is a member selected from Formula (II), Formula (III), Formula (IV) and Formula (V):



wherein D is CX-Ar¹ or N-Ar¹. In Formulae (II) to (V), Ar¹, X, V, W, D, R¹, R², R³, R⁴ and the integers m and n are as defined above.

[0074] In a preferred embodiment, Ar¹ in Formulae (I) to (V) is a member selected from substituted or unsubstituted phenyl and substituted or unsubstituted naphthyl. Particularly preferred are those compounds of the invention in which Ar¹ has the structure:

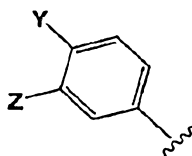


wherein Y and Z are aryl group substituents. In one embodiment, Y and Z are members independently selected from the group consisting of H, halogen, CF₃, CN, OR¹⁶, NR¹⁷R¹⁸, NR¹⁷S(O)₂R¹⁶, NR¹⁷C(O)R¹⁶, acyl, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heterocycloalkyl, wherein Y and Z, together with the atoms to which they are attached, are optionally joined to form a 5- to 7-membered ring.

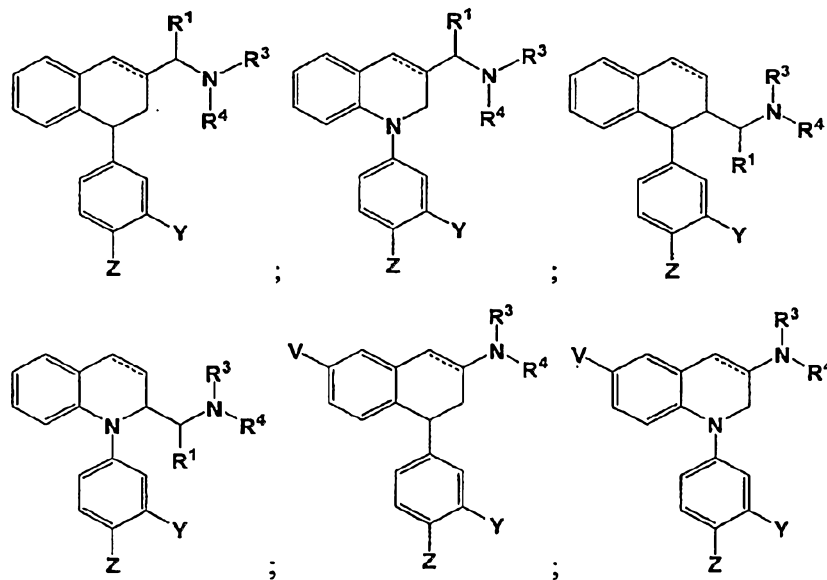
[0075] Each R¹⁶, R¹⁷ and R¹⁸ is a member independently selected from the group consisting of H, substituted or unsubstituted alkyl, substituted or unsubstituted

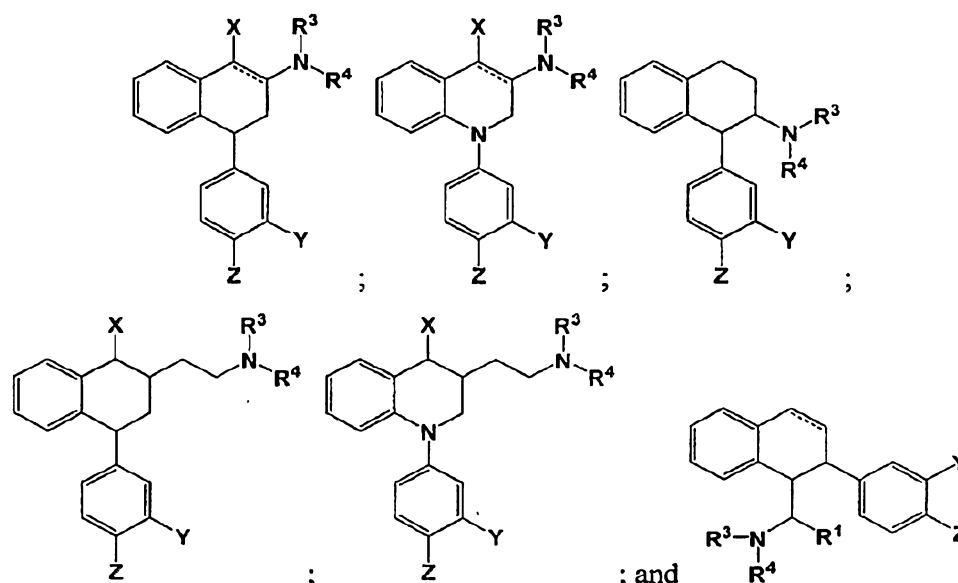
heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heterocycloalkyl. R^{17} and R^{18} , together with the atoms to which they are attached, are optionally joined to form a 3- to 7-membered ring. In an exemplary embodiment, Y and Z are members independently selected from the group consisting of H, halogen, CN and CF_3 .

[0076] In another exemplary embodiment, Ar^1 is a 4,3-substituted phenyl moiety having the structure:



[0077] Exemplary compounds according to this embodiment are provided below:





wherein at least two of R¹, R² and R³, together with the atoms to which they are attached, are optionally joined to form a 5- to 7-membered ring, such as a morpholine, piperidine, pyrrolidine or N-alkyl-piperazine moiety.

[0078] In a preferred embodiment, Y and Z are members independently selected from H, halogen, CN, CF₃ and OR¹⁶. In a particular preferred embodiment, Y and Z are both halogen. In an exemplary embodiment, Ar¹ in Formulae (I) to (V) is 3,4-dichlorophenyl.

[0079] In another preferred embodiment, m in Formulae (I) to (V) is 1; X is H or OR⁵ (e.g., OH). In an exemplary embodiment, R³ and R⁴ are independently H or substituted or unsubstituted C₁-C₄ alkyl or C₁-C₄ heteroalkyl.

B. Compositions Including Stereoisomers

[0080] Compounds of the invention may exist in particular geometric or stereoisomeric forms. The invention contemplates all such compounds, including *cis*- and *trans*-isomers, (-)- and (+)-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, such as enantiomerically or diastereomerically enriched mixtures, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a

substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

[0081] If, for instance, a particular enantiomer of a compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivatization with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as an amino group, or an acidic functional group, such as a carboxyl group, diastereomeric salts may be formed with an appropriate optically active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means known in the art, and subsequent recovery of the pure enantiomers. In addition, separation of enantiomers and diastereomers is frequently accomplished using chromatography employing chiral, stationary phases, optionally in combination with chemical derivatization (e.g., formation of carbamates from amines).

[0082] As used herein, the term “enantiomerically enriched” or “diastereomerically enriched” refers to a compound having an enantiomeric excess (ee) or a diastereomeric excess (de) greater than about 50%, preferably greater than about 70% and more preferably greater than about 90%. In general, higher than about 90% enantiomeric or diastereomeric purity is particularly preferred, e.g., those compositions with greater than about 95%, greater than about 97% and greater than about 99% ee or de.

[0083] The terms “enantiomeric excess” and “diastereomeric excess” are used interchangeably herein. Compounds with a single stereocenter are referred to as being present in “enantiomeric excess”, those with at least two stereocenters are referred to as being present in “diastereomeric excess”.

[0084] For example, the term "enantiomeric excess" is well known in the art and is defined as:

$$ee_a = \left(\frac{\text{conc. of } a - \text{conc. of } b}{\text{conc. of } a + \text{conc. of } b} \right) \times 100$$

The term "enantiomeric excess" is related to the older term "optical purity" in that both are measures of the same phenomenon. The value of ee will be a number from 0 to 100, zero being racemic and 100 being enantiomerically pure. A compound which in the past might have been called 98% optically pure is now more precisely characterized by 96% ee. A 90% ee reflects the presence of 95% of one enantiomer and 5% of the other(s) in the material in question.

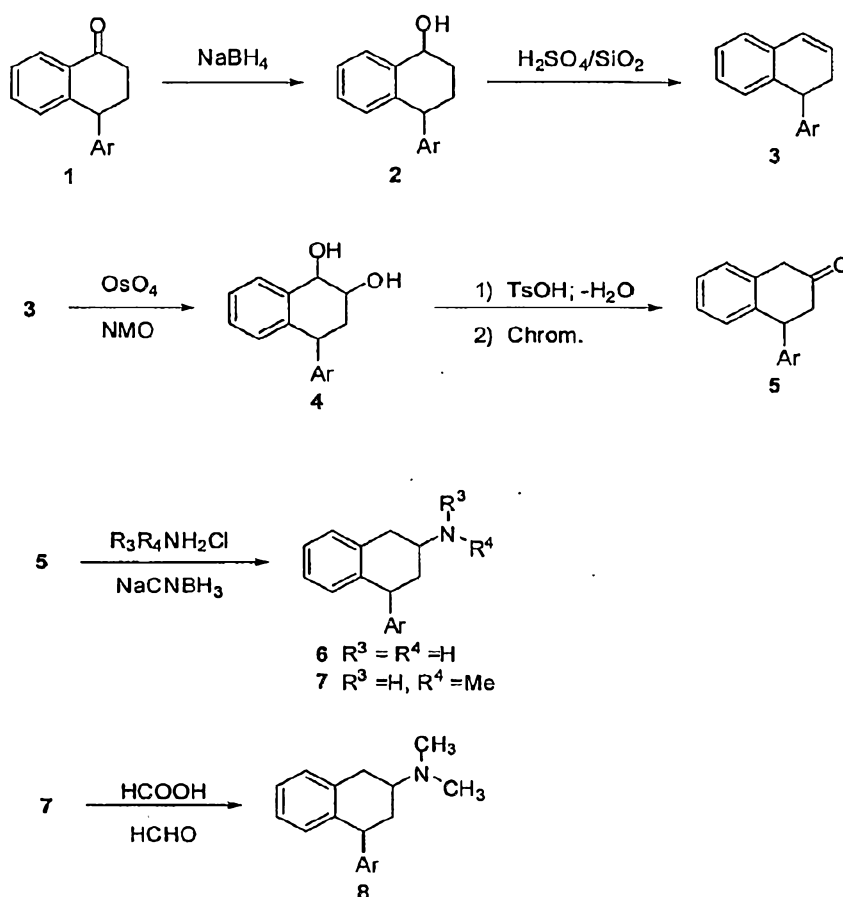
[0085] Hence, in one embodiment, the invention provides a composition including a first stereoisomer and at least one additional stereoisomer of a compound of the invention. The first stereoisomer may be present in a diastereomeric or enantiomeric excess of at least about 80%, preferably at least about 90% and more preferably at least about 95%. In a particularly preferred embodiment, the first stereoisomer is present in a diastereomeric or enantiomeric excess of at least about 96%, at least about 97%, at least about 98%, at least about 99% or at least about 99.5%. Enantiomeric or diastereomeric excess may be determined relative to exactly one other stereoisomer, or may be determined relative to the sum of at least two other stereoisomers. In an exemplary embodiment, enantiomeric or diastereomeric excess is determined relative to all other detectable stereoisomers, which are present in the mixture. Stereoisomers are detectable if a concentration of such stereoisomer in the analyzed mixture can be determined using common analytical methods, such as chiral HPLC.

C. Synthesis of the Compounds

[0086] Compounds of the invention may be synthesized according to Schemes 1 to 11, below. It is within the abilities of a person skilled in the art to select appropriate alternative reagents replacing the exemplary reagents shown in Schemes 1-11 in order to synthesize a desired compound of the invention. It is also within the abilities of a skilled artisan to omit or add synthetic steps when

necessary. As a non-limiting example, Ar in Schemes 1 to 11 is 3,4-dichlorophenyl. Exemplary compound numbers are based on Ar being 3,4-dichlorophenyl.

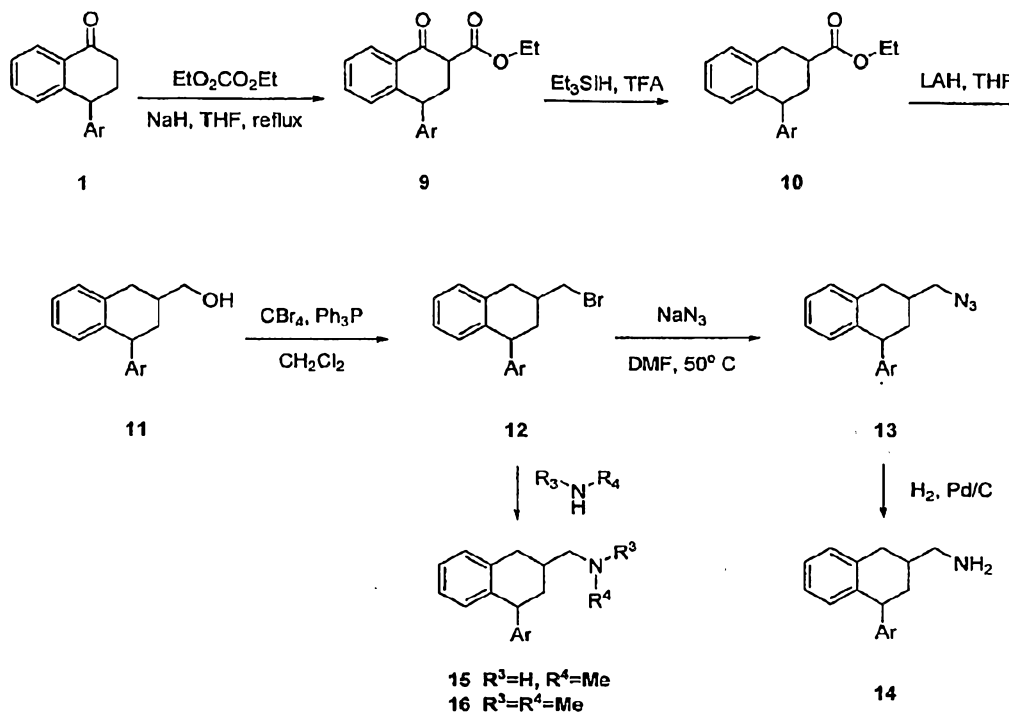
Scheme 1: Exemplary synthetic routes useful for the preparation of compounds of the invention



[0087] Referring to Scheme 1, the beta-tetralone analog 5 is derived from the alpha-tetralone 1 in four steps. The reduced ketone (Compound 2) is dehydrated and the resultant alkene (Compound 3) is converted to the diol (Compound 4). Elimination of water from the diol gives the beta-tetralone (Compound 5). Compound 5 is then condensed with ammonium chloride under reductive amination conditions to give Compound 6, a compound of the invention (e.g., using the preferred 3,4-dichlorophenyl as an example, to give [4-(3,4-

dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-amine). Alternatively, compound 5 is condensed with methylamine hydrochloride under the same conditions to give a compound of the invention, [4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-methyl-amine (Compound 7). Additionally, the monomethyl amine (Compound 7) can be further elaborated under Eschweiler-Clark conditions (using formic acid (HCO₂H) and formaldehyde (HCHO)) to give a compound of the invention, [4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-dimethyl-amine (Compound 8). Compounds 6, 7, or 8 may be synthesized as a mixture of racemic *cis* and *trans*, or may be separated to give an enantiomerically enriched or an enantiomerically pure form of one of its four isomers. *Cis* and *trans* assignments may be made using methods known in the art (e.g., on the basis of NMR coupling patterns). The absolute configuration can, for instance, be determined by synthesis from a precursor of known configuration, or by X-ray crystallographic determination using a suitable crystal of the compound.

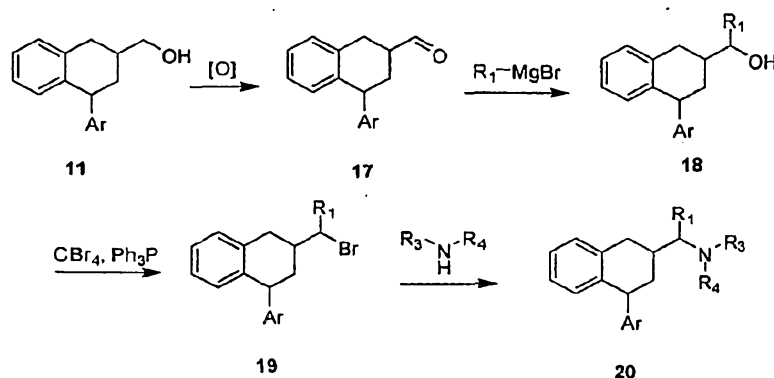
[0088] In another exemplary embodiment, compounds of the invention may be synthesized according to Scheme 2 below:

Scheme 2: Exemplary synthetic routes useful for the preparation of compounds of the invention

[0089] Referring to Scheme 2, acylation of the α -tetralone 4-(3,4-dichlorophenyl)-3,4-dihydro-2H-naphthalen-1-one (Compound 1) with diethylcarbonate was followed by reduction with triethylsilane to give 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid ethyl ester (Compound 10). Reduction and conversion to 3-bromomethyl-1-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalene (Compound 12) is followed by alkylation with sodium azide in DMF to give 3-azidomethyl-1-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalene (Compound 13). Chiral separation of Compound 13 is followed by hydrogenation to give a compound of the invention, C-[4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-methylamine (Compound 14). Alternatively, reduction and conversion to 3-bromomethyl-1-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalene (Compound 12) is followed by alkylation with substituted amines to give 1-phenyl-3-aminoalkyl-1,2,3,4-tetrahydronaphthalenes (Compound 15).

[0090] In yet another exemplary embodiment, compounds of the invention may be synthesized according to Scheme 3 below:

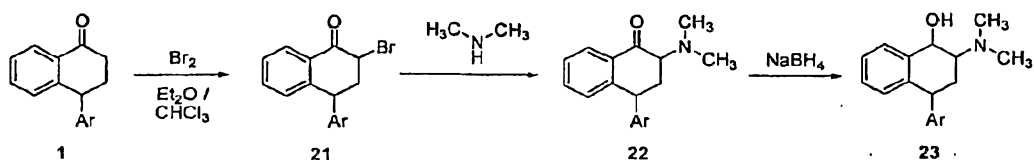
Scheme 3: Exemplary synthetic route useful for the preparation of compounds of the invention



[0091] Referring to Scheme 3, oxidation of [4-(3,4-dichloro-phenyl)-1,2,3,4-tetrahydro-naphthalen-2-yl]-methanol (Compound 11 in Scheme 2) is followed by addition of alkyl Grignard agents and bromination to give substituted 3-bromomethyl-1-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalenes (Compound 19). Displacement with substituted amines gives the desired alpha-substituted amines (Compound 20).

[0092] Alternatively, the compounds of the invention may be synthesized according to Scheme 4 below:

Scheme 4: Exemplary synthetic route useful for the preparation of compounds of the invention

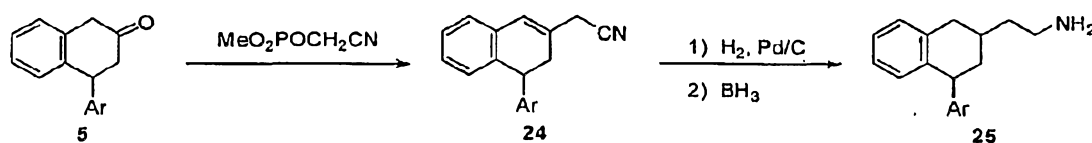


[0093] Referring to Scheme 4, synthesis of the amino alcohol starts from Compound 1. Exposure of the ketone to bromine gives the bromoketone (Compound 21) in quantitative yield. The bromoketone is reacted with dimethylamine to afford Compound 22; which is reduced with sodium

borohydride to give a mixture of diastereomers of the amino alcohol (Compound 23). In one embodiment, separation of the diastereomers is accomplished using a combination of silicagel and chiral column chromatography.

[0094] Alternatively, the compounds of the invention may be synthesized according to Scheme 5 below:

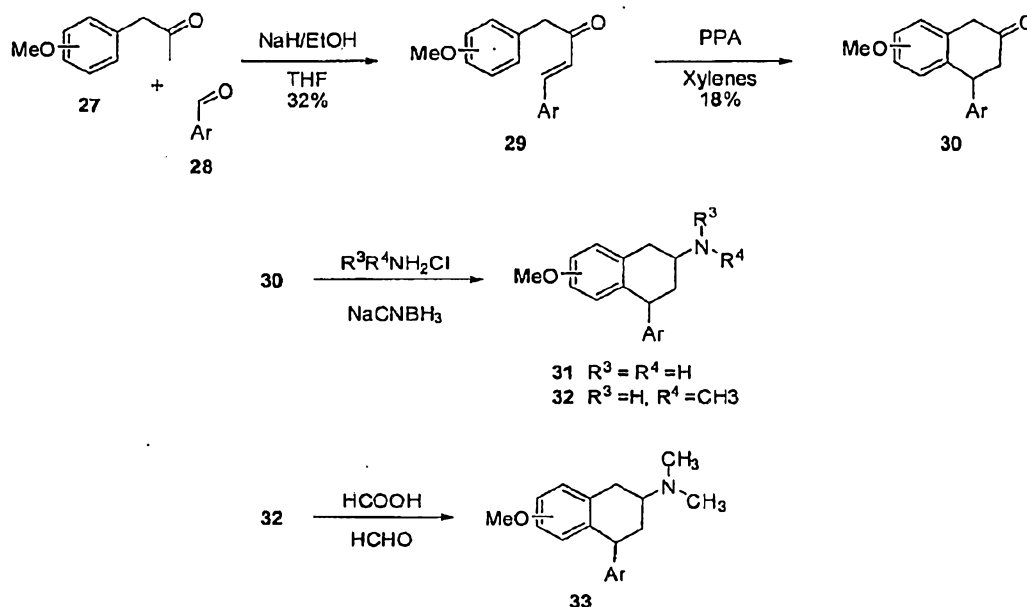
Scheme 5: Exemplary synthetic route useful for the preparation of compounds of the invention



[0095] Referring to Scheme 5, the beta-tetralone 5 is alkylated and reduced to give 2-(1,3-*cis*)-1-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-3-yl)ethanamine (Compound 25). The two diastereomers of Compound 25 can be separated, for instance, as their BOC derivatives using a chiral column.

[0096] In yet another example, the compounds of the invention may be synthesized according to Scheme 6 below:

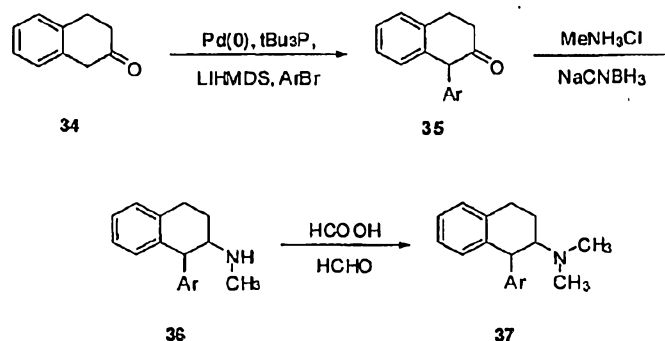
Scheme 6: Exemplary synthetic routes useful for the preparation of compounds of the invention



[0097] Referring to Scheme 6, the methoxyacetophenone is condensed with the aryl aldehyde and the resultant enone is cyclized by the action of PPA. The substituted beta-tetralone 30 may be treated with ammonium chloride or methylamine hydrochloride under reductive-amination conditions to give the amines 31 and 32. The dimethylamine 33 can be prepared by methylation of the methylamine using Eschweiler-Clark conditions.

[0098] Alternatively, the compounds of the invention may be synthesized according to Scheme 7 below:

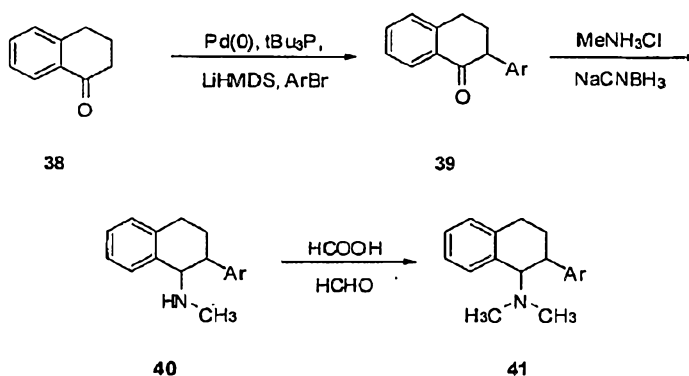
Scheme 7: Exemplary synthetic route useful for the preparation of compounds of the invention



[0099] Referring to Scheme 7, beta-tetralone 34 is condensed with the aryl bromide. The substituted beta-tetralone so produced may be treated with ammonium chloride or methylamine hydrochloride under reductive-amination conditions to give the amine 36. The dimethylamine 37 is prepared by methylation of the methylamine using Eschweiler-Clark conditions.

[0100] Alternatively, the compounds of the invention may be synthesized according to Scheme 8 below:

Scheme 8: Exemplary synthetic procedures useful for the preparation of compounds of the invention

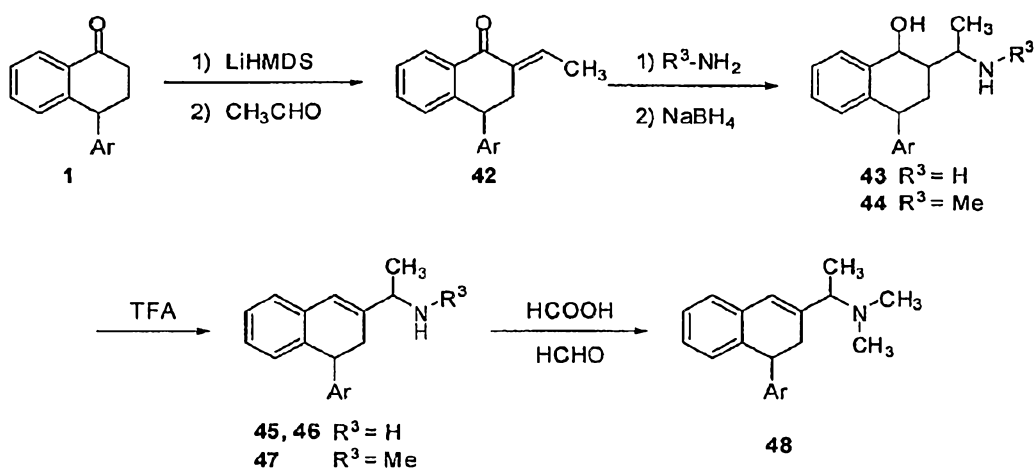


[0101] Referring to Scheme 8, alpha-tetralone 38 is condensed with the aryl bromide. The substituted alpha-tetralone so produced may be treated with ammonium chloride or methylamine hydrochloride under reductive-amination

conditions to give the amine **40**. The dimethylamine **41** is prepared by methylation of the methylamine using Eschweiler-Clark conditions.

[0102] In another embodiment, the compounds of the invention may be synthesized according to Scheme 9 below:

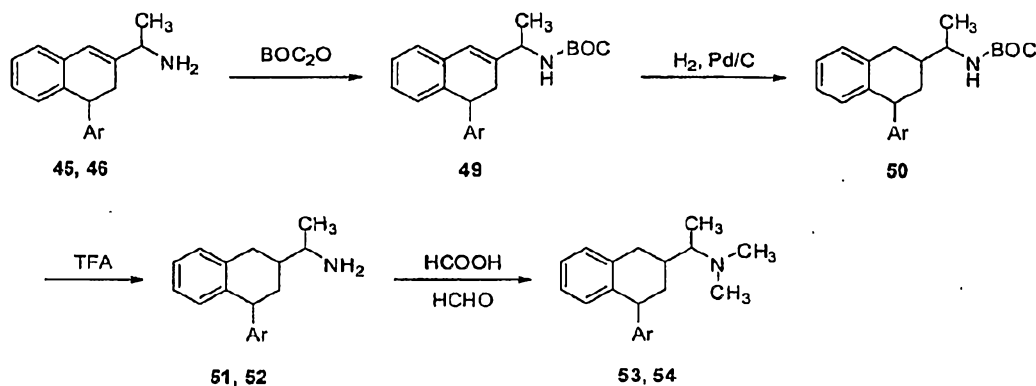
Scheme 9: Exemplary synthetic route useful for the preparation of compounds of the invention



[0103] Referring to Scheme 9, the alpha-tetralone analog **1** is condensed with acetaldehyde to produce the substituted alpha-tetralone **42**, which may be treated with ammonium chloride or methylamine hydrochloride and subsequently reduced to give the amino-alcohols **43** and **44**. The benzylic alcohol can be eliminated to form the unsaturated amines **45/46** and **47**. The dimethylamine **48** is prepared by methylation of the methylamine using Eschweiler-Clark conditions.

[0104] Alternatively, the compounds of the invention may be synthesized according to Scheme 10 below:

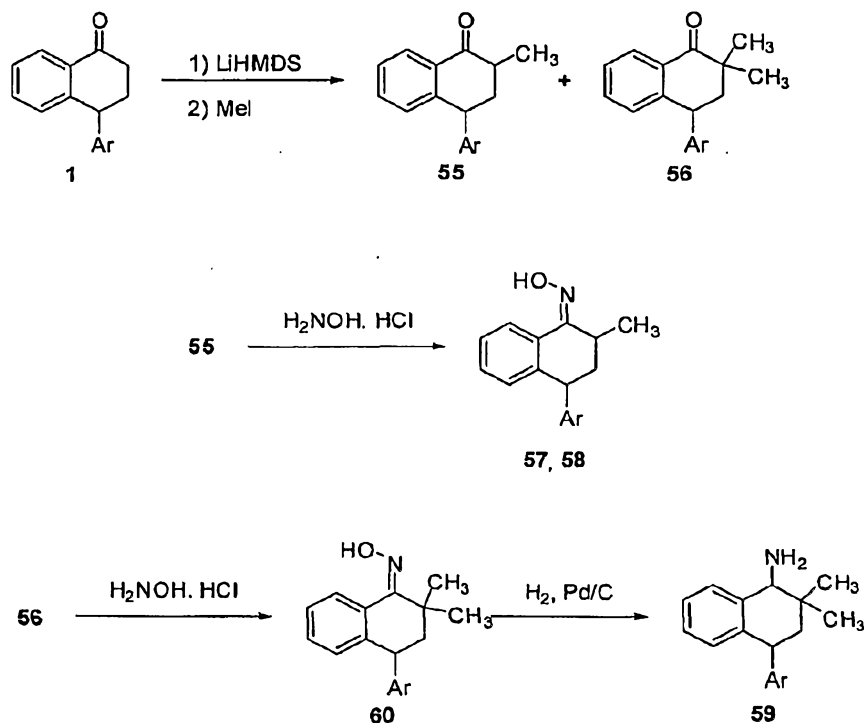
Scheme 10: Exemplary synthetic route useful for the preparation of compounds of the invention



[0105] Referring to Scheme 10, the primary amines **45** and **46** are condensed with Boc-anhydride. The double bond is then hydrogenated and the Boc group is removed with TFA to give the saturated amines **51** and **52**. The dimethylamines **53** and **54** are prepared by methylation of the methylamine using Eschweiler-Clark conditions.

[0106] Alternatively, the compounds of the invention may be synthesized according to Scheme 11 below:

Scheme 11: Exemplary synthetic routes useful for the preparation of compounds of the invention



[0107] Referring to Scheme 11, the alpha-tetralone **1** is deprotonated and reacted with methyl iodide to give both the mono- and di-methylated ketones **55** and **56**, which can be separated. The mono-methylated ketone **55** is condensed with hydroxylamine to give the oxime. Diastereomeric separation gave the oximes **57** (*cis*-diastereomer) and **58** (*trans*-diastereomer). The di-methylated ketone **56** is treated in a similar manner to give the oxime **60**. The oxime can be further reduced with hydrogen to give the amine **59**.

D. Pharmaceutical Compositions

[0108] In another aspect, the present invention provides pharmaceutical compositions including a compound of the invention (e.g., a compound of Formulae (I) to (IV)) or a pharmaceutically acceptable salt or solvate thereof and one or more pharmaceutically acceptable carrier, additive, vehicle, diluent or combinations thereof.

[0109] As described in detail below, the pharmaceutical compositions of the present invention may be specially formulated for administration in solid or liquid form, including those adapted for oral administration, e.g., tablets, drenches (aqueous or non-aqueous solutions or suspensions), parenteral administration (including intravenous and intramuscular), or epidural injection as, for example, a sterile solution or suspension, or sustained release formulation. The pharmaceutical compositions of the present invention may also be specifically formulated for administration transdermally.

[0110] The pharmaceutical compositions of the invention may be administered orally, parenterally, subcutaneously, transdermally, nasally, or by anal suppository. The pharmaceutical compositions of the invention may also be administered using controlled delivery devices.

[0111] Formulations of the present invention include those suitable for oral and parenteral administration, particularly intramuscular, intravenous and subcutaneous administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated and the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect, without being toxic to the patient. Generally, out of one hundred percent, this amount will range from about 1 percent to about ninety-nine percent of active ingredient.

[0112] In certain embodiments, a formulation of the present invention comprises an excipient selected from the group consisting of cyclodextrins, liposomes, micelle forming agents, e.g., bile acids, and polymeric carriers, e.g., polyesters and polyanhydrides; and a compound of the present invention. In certain embodiments, an aforementioned formulation renders orally bioavailable a compound of the present invention.

[0113] Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[0114] Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, caplets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia), each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

[0115] In solid dosage forms of the invention for oral administration (capsules, tablets, caplets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol, glycerol monostearate, and non-ionic surfactants; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the

pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-shelled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[0116] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[0117] The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be formulated for rapid release, e.g., freeze-dried. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

[0118] Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

[0119] Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

[0120] Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[0121] Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain sugars, alcohols, antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[0122] Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable

organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0123] These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms upon the subject compounds may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[0124] In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[0125] Injectable depot forms are made by forming microencapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue. Pharmaceutical compositions or unit dosage forms of the present invention in the form of prolonged-action tablets may comprise compressed tablets formulated to release the drug substance in a manner to provide medication over a

period of time. There are a number of tablet types that include delayed-action tablets in which the release of the drug substance is prevented for an interval of time after administration or until certain physiological conditions exist. Repeat action tablets may be formed that periodically release a complete dose of the drug substance to the gastrointestinal fluids. Also, extended release tablets that continuously release increments of the contained drug substance to the gastrointestinal fluids may be formed.

[0126] Compounds of the invention can be also administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the compounds of this invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled-release.

[0127] All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include extended activity of the drug, reduced dosage frequency, and increased patient compliance. In addition, controlled-release formulations can be used to affect the time of onset of action or other

characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (*e.g.*, adverse) effects.

[0128] Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

[0129] Compounds of the present invention may also be formulated as transdermal, topical, and mucosal dosage forms, which forms include, but are not limited to, ophthalmic solutions, sprays, aerosols, creams, lotions, ointments, gels, solutions, emulsions, suspensions, or other forms known to one of skill in the art. *See, e.g., Remington's Pharmaceutical Sciences*, 16th and 18th eds., Mack Publishing, Easton PA (1980 & 1990); and *Introduction to Pharmaceutical Dosage Forms*, 4th ed., Lea & Febiger, Philadelphia (1985). Transdermal dosage forms include "reservoir type" or "matrix type" patches, which can be applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of active ingredients.

[0130] Suitable excipients (*e.g.*, carriers and diluents) and other materials that can be used to provide transdermal, topical, and mucosal dosage forms encompassed by this invention are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied.

[0131] Depending on the specific tissue to be treated, additional components may be used prior to, in conjunction with, or subsequent to treatment with active

ingredients of the invention. For example, penetration enhancers can be used to assist in delivering the active ingredients to the tissue.

[0132] The pH of a pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or dosage form is applied, may also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. Different salts, hydrates or solvates of the active ingredients can be used to further adjust the properties of the resulting composition.

[0133] When the compounds of the present invention are administered as pharmaceuticals, to humans and animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% of active ingredient in combination with a pharmaceutically acceptable carrier.

[0134] The preparations of the present invention may be given orally and parenterally. They are of course given in forms suitable for each administration route. For example, they are administered in tablets or capsule form, by injection, and by intravenous administration. In one embodiment, oral administrations are preferred.

[0135] The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

[0136] The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

[0137] A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

[0138] In general, a suitable daily dose of a compound of the invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Generally, intravenous, intracerebroventricular and subcutaneous doses of the compounds of this invention for a patient will range from about 0.005 mg per kilogram to about 5 mg per kilogram of body weight per day.

[0139] The terms "treatment" or "treating" is intended to encompass therapy, preventing (prophylaxis), preventing relapse, and amelioration of acute symptoms. Note that "treating" refers to either or both of the amelioration of symptoms and the resolution of the underlying condition. In many of the conditions of the invention, the administration of a compound or composition of the invention may act not directly on the disease state, but rather on some pernicious symptom, and the improvement of that symptom leads to a general and desirable amelioration of the disease state

[0140] The patient receiving this treatment is any animal in need, including primates, in particular humans, and other mammals such as equines, cattle, swine and sheep; and poultry and pets in general.

[0141] The compounds and pharmaceutical compositions of the invention can be administered in conjunction with other pharmaceutical agents, for instance antimicrobial agents, such as penicillins, cephalosporins, aminoglycosides and glycopeptides. Conjunctive therapy thus includes sequential, simultaneous and separate administration of the active compound in a way that the therapeutic effects of the first administered agent have not entirely disappeared when the subsequent agent is administered.

IV. Methods

A. Treatment of CNS Disorders

[0142] In another aspect, the present invention provides a method of treating a central nervous system disorder. The method includes administering to a subject in need thereof a therapeutically effective amount of a compound or composition of the invention, e.g., a compound according to Formulae (I) to (IV), or a pharmaceutically acceptable salt or solvate thereof. This method of treatment is particularly suitable for humans and other mammals.

[0143] In an exemplary embodiment, the central nervous system disorder is a member selected from the group consisting of depression (e.g., major depressive disorder, bipolar disorder), fibromyalgia, pain (e.g., neuropathic pain), sleep related disorders (e.g., sleep apnea, insomnia, narcolepsy, cataplexy) including those sleep disorders, which are produced by psychiatric conditions, chronic fatigue syndrome, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), restless leg syndrome, schizophrenia, anxieties (e.g. general anxiety disorder, social anxiety disorder, panic), obsessive compulsive disorder, posttraumatic stress disorder, seasonal affective disorder (SAD), premenstrual dysphoria, post-menopausal vasomotor symptoms (e.g., hot flashes, night sweats), and neurodegenerative disease (e.g., Parkinson's disease, Alzheimer's disease and

amyotrophic lateral sclerosis), manic conditions, dysthymic disorder, and cyclothymic disorder.

[0144] Central nervous system disorder includes cerebral function disorders, including without limitation, senile dementia, Alzheimer's type dementia, cognition, memory loss, amnesia/amnestic syndrome, epilepsy, disturbances of consciousness, coma, lowering of attention, speech disorders, Lennox syndrome, autism, and hyperkinetic syndrome.

[0145] Neuropathic pain includes without limitation post herpetic (or post-shingles) neuralgia, reflex sympathetic dystrophy/causalgia or nerve trauma, phantom limb pain, carpal tunnel syndrome, and peripheral neuropathy (such as diabetic neuropathy or neuropathy arising from chronic alcohol use).

[0146] Other exemplary diseases and conditions that may be treated using the methods of the invention include obesity; migraine or migraine headache; urinary incontinence, including without limitation involuntary voiding of urine, dribbling or leakage of urine, stress urinary incontinence (SUI), urge incontinence, urinary exertional incontinence, reflex incontinence, passive incontinence, and overflow incontinence; as well as sexual dysfunction, in men or women, including without limitation sexual dysfunction caused by psychological and/or physiological factors, erectile dysfunction, premature ejaculation, vaginal dryness, lack of sexual excitement, inability to obtain orgasm, and psycho-sexual dysfunction, including without limitation, inhibited sexual desire, inhibited sexual excitement, inhibited female orgasm, inhibited male orgasm, functional dyspareunia, functional vaginismus, and atypical psychosexual dysfunction.

B. Inhibition of Monoamine Reuptake

[0147] In another aspect, the invention provides a method of inhibiting reuptake of one or more monoamine from the synaptic cleft. The method includes administering to a subject in need thereof a therapeutically effective amount of a compound or composition of the invention, e.g., a compound according to Formulae (I) to (IV), or a pharmaceutically acceptable salt or solvate thereof. This

method of treatment is particularly suitable for humans and other mammals. In an exemplary embodiment, the monoamine is dopamine, serotonin, norepinephrine or combinations thereof.

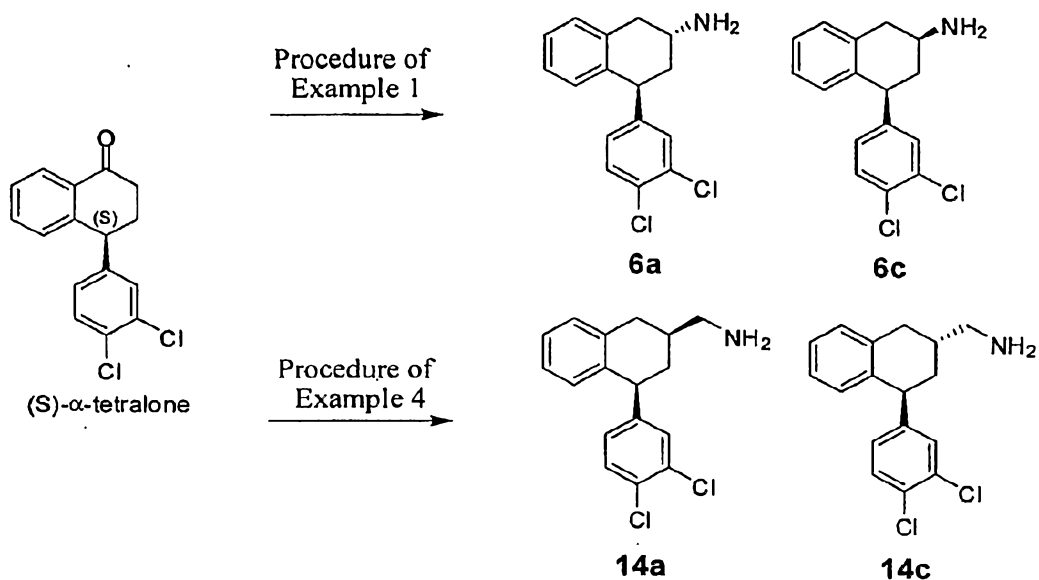
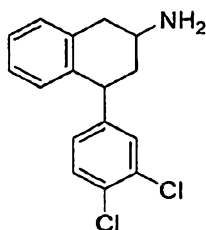
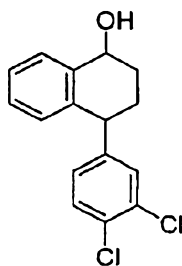
C. Modulation of Monoamine Transporters

[0148] In yet another aspect, the invention provides a method of modulating one or more monoamine transporter. The method includes administering to a subject in need thereof a therapeutically effective amount of a compound or composition of the invention, e.g., a compound according to Formulae (I) to (V), or a pharmaceutically acceptable salt or solvate thereof. This method of treatment is particularly suitable for humans and other mammals. In an exemplary embodiment, the monoamine transporter is dopamine transporter (DAT), serotonin transporter (SERT) or norepinephrine transporter (NET).

EXAMPLES

General: Determination of Absolute Stereochemistry

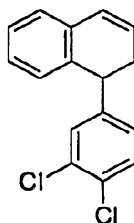
[0149] In this application, relative stereochemistries are used unless otherwise indicated. Assignments of relative stereochemistries were made using NMR techniques (determination of *cis*- and *trans*-configurations, optionally using literature reports for similar compounds). Absolute stereochemistries of selected compounds were determined by synthesis of key intermediates from commercially-available (S)- α -tetralone as outlined in Scheme 12, below. Correlations were made using chiral HPLC analyses. For example, spiking authentic samples into enantiomeric and/or diastereomeric mixtures allowed for a correlation of retention times and structures.

Scheme 12: Synthesis of authentic samples from commercial (S)- α -tetralone**Example 1: Synthesis of [4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-amine (6a-d)****1.1. Synthesis of 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-ol (2)**

[0150] To a stirring mixture of α -tetralone 4-(3,4-dichlorophenyl)-3,4-dihydro-2H-naphthalen-1-one 1 (53 g, 182 mmol) in methanol (400 mL) was added sodium borohydride (12 g) in portions. The mixture was stirred at ambient

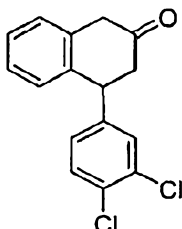
temperature for three hours. Water was added and the volatile components were removed *in vacuo*. The aqueous remainder was extracted with ethyl acetate. The organic phase was separated, washed with water, dried (Na_2SO_4), and evaporated to dryness to yield the crude alcohol (53 g). TLC R_f (25 EA/hex) = 0.25, 0.18. ^1H NMR (CDCl_3 , δ): 7.39 (d, $J = 8.0\text{Hz}$, 1H), 7.3-7.2 (m, 4H), 7.0-6.9 (m, 2H), 4.42 (t, $J = 6.4\text{Hz}$, 1 H), 3.62 (q, $J = 20\text{Hz}$, 2H), 2.9 (m, 2H). ^{13}C NMR (CDCl_3 , δ , mult): 146.9(0), 146.8(0), 139.6(0), 138.9(0), 138.3(0), 137.7(0), 132.3(0), 132.2(1), 130.6(1), 130.5(1), 130.3(1), 130.2(1), 129.8(1), 129.7(1), 129.0(1), 128.2(1), 128.1(1), 128.1(1), 128.0(1), 127.9(1), 127.1(1), 127.0(1), 68.1(1), 67.7(1), 45.0(1), 44.4(1), 30.0(2), 29.9(2), 28.9(2), 28.1(2).

1.2. Synthesis of 1-(3,4-dichlorophenyl)-1,2-dihydronaphthalene (3)



[0151] To a solution of the crude alcohol **2** (53 g) in toluene (500 mL) was added silica gel coated with sulfuric acid (3%, 14 g). The mixture was heated to 100°C and monitored by TLC (prod R_f (25 EA/hex) = 0.58). After three hours, the mixture was filtered. The organic phase was washed with water and sodium bicarbonate solution, dried (Na_2SO_4), and evaporated to give the alkene **3** (42 g, 84%) as a pale-brown solid. TLC R_f (25 EA/hex) = 0.58. GC-MS R_t = 13.55 min, m/z = 274 (M^+). ^1H NMR (CDCl_3 , δ): 7.4-6.7 (m, 7H), 6.54 (d, $J = 9.6\text{ Hz}$, 1H), 6.0 (m, 1H), 4.08 (t, $J=8.0\text{ Hz}$, 1H), 2.7 (m, 1H), 2.5 (m, 1H). ^{13}C NMR (CDCl_3 , δ , mult): 143.6, 136.3, 133.8, 132.2, 130.2, 130.2, 128.1, 127.7, 127.2, 126.4, 129.7, 127.4, 42.8(1), 31.6(2).

1.3. Synthesis of 4-(3,4-dichlorophenyl)-3,4-dihydro-1H-naphthalen-2-one (5)



[0152] To a stirring solution of the alkene **3** (3 g, 10.8 mmol) in acetone (40 mL) was added NMO (2 g, 1.6 eq) and water (10 mL). After the NMO dissolved, osmium tetroxide (1.3 mL, 0.1 M in toluene, 5 mol%) was added and the solution was stirred at ambient temperature for 40 minutes. Sodium bisulfate (10 mL, 10% solution in water) was added and the mixture was stirred for an additional 30 minutes. After this time, the solvent was removed *in vacuo* and the resultant oily solid was partitioned between MTBE and, sequentially, water and brine. The organic solvent was evaporated to yield the crude diol (**4**) as a brown glass. TLC R_f (50 EA/hex) = 0.14. The crude diol (**4**) was sufficiently pure for the next step, and could be confirmed by the three diagnostic peaks that are discernable in the ^1H NMR (4.8, 4.4, 4.2 ppm).

[0153] The diol **4** was dissolved in toluene (200 mL). Tosic acid (600 mg, 30 mol%) was added and the solution was heated to reflux in a Dean-Stark water separator until the diol was consumed. After three hours, the reaction mixture was cooled and most of the toluene was removed. The remaining liquid was partitioned between MTBE and, sequentially, 10% aqueous KOH, water, and brine. The organic layer was evaporated and the crude green oil was separated on silica gel to give the beta-tetralone **5** (1.46 g, 46%) as a pale-yellow oil. TLC R_f (50 EA/hex) = 0.39. GC-MS R_t = 13.54 min, m/z = 290 (M⁺). ^1H NMR (CDCl_3 , δ): 7.39 (d, J = 8.0 Hz, 1H), 7.3-7.2 (m, 4H), 7.0-6.9 (m, 2H), 4.42 (t, J = 6.4 Hz, 1H), 3.62 (q, J = 20 Hz, 2H), 2.9 (m, 2H). ^{13}C NMR (CDCl_3 , δ , mult): 208.2(0), 141.7(0), 137.7(0), 133.0(0), 132.8(0), 131.0(0), 130.6(1), 129.8(1), 128.7(1), 127.8(1), 127.5(1), 127.1(1), 45.4(2), 44.5(2), 43.8(1).

1.4. Synthesis of [4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-naphthalen-2-yl]-amine (6a-d)

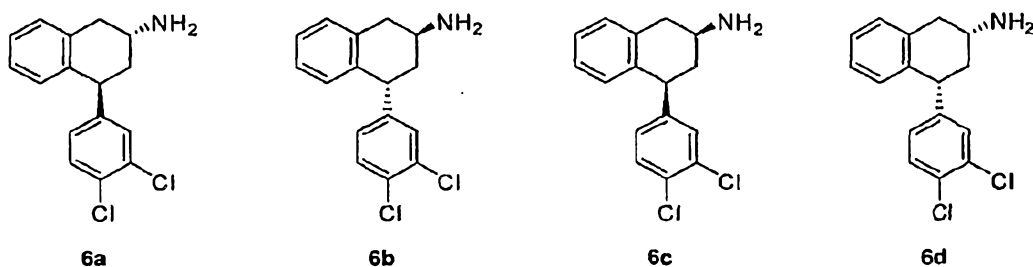
[0154] Ammonium chloride (643 mg, 10 eq) was dissolved in methanol (24 mL) by heating to 50°C. After it cooled, a solution of ketone **5** (350 mg, 1.202 mmol) in THF (18 mL) was added followed by sodium cyanoborohydride 6.0 mL, 5 eq). The mixture was heated in a 50°C oil bath overnight. The reaction was then cooled, quenched with aqueous sodium bicarbonate, and extracted with MTBE. The combined organic layer was washed with brine and evaporated to give a brown-green oil. The oil was separated on silica gel to give the primary amine **6** (145 mg, 41%) as a pale-green oil.

[0155] As isolated, the amine was a mixture of four stereoisomers which were separable using chiral columns. First, the mixture was separated on a Chiracel OD column (90:10:0.1 Hex/IPA/DEA) to give three fractions. Symchiral *trans* (Compound **6a** at 11.9 min, racemic *cis* at 14.7 min, and symchiral *trans* (Compound **6b**) at 22.3 min. The racemic *cis* was then resubmitted to the Chiracel AD column 95:2:3:0.1 Hex/MeOH/EtOH/DEA) to give the symchiral *cis* (Compound **6c**) at 11.1 min and symchiral *cis* (Compound **6d**) at 13.9 min. Retention times are summarized in Table 1, below.

Table 1: Retention times for each diastereomer [min]

	6a	6c	6d	6b
	<i>Trans</i>	<i>Cis</i>	<i>Cis</i>	<i>Trans</i>
HPLC R _t (Chiracel OD, 90:10:0.1 Hex/IPA/DEA)	11.9	14.7	14.7	22.3
HPLC R _t (Chiracel AD, 95:2:3:0.1 Hex/MeOH/EtOH/DEA)		11.1	13.9	

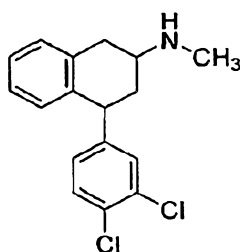
[0156] Absolute stereochemistries for compounds **6a-d** were determined using a combination of NMR techniques (determination of *cis*- and *trans*-configurations) and chiral HPLC analyses using authentic samples, which were prepared from commercial (S)-alpha-tetralone as described above (also compare "General Procedures"). The resulting structures indicating absolute stereochemistries are shown below:



[0157] *Trans*-isomers 6a and 6b: GC-MS $R_t = 13.52$ min, $m/z = 291$ (M⁺). ¹H NMR (CDCl₃, δ): 7.4-6.8 (m, 7H), 4.32 (t, $J = 5.4$ Hz, 1H), 3.3 (m, 1H), 3.17 (dd, $J = 4.9, 16.3$ Hz, 1H), 2.7 (m, 3H), 2.1 (m, 2H). ¹³C NMR (CDCl₃, δ , mult): 160.3(0), 147.2(0), 136.0(0), 135.2(0), 132.3(0), 130.5(1), 130.1(1), 130.0(1), 129.5(1), 128.0(1), 126.9(1), 126.5(1), 43.2(1), 42.9(1), 40.2(2), 38.2(2).

[0158] *Cis*-isomers 6c and 6d: GC-MS $R_t = 13.61$ min, $m/z = 291$ (M⁺). ¹H NMR (CDCl₃, δ): 7.4-6.7 (m, 7H), 4.11 (dd, $J = 5.5, 12.1$ Hz, 1H), 3.26 (ddt, $J = 3.1, 4.9, 11.3$ Hz, 1H), 3.07 (ddd, 2.2, 4.8, 15.9 Hz, 1H), 2.2 (m, 1H), 1.6 (m, 3H). ¹³C NMR (CDCl₃, δ , mult): 146.7(0), 137.8(0), 135.9(0), 132.4(0), 130.6(1), 130.5(1), 129.1(0), 129.1(1), 128.1 (1), 126.5(1), 126.2(1), 130.2(1), 47.6(1), 46.0(1), 44.4(2), 40.2(2).

Example 2: Synthesis of 4-(3,4-dichlorophenyl)-N-methyl-1,2,3,4-tetrahydronaphthalen-2-amine (7a-d)



[0159] To a solution of ketone 5 (350 mg, 1.202 mmol) in THF (18 mL) and methanol (24 mL) was added methylamine hydrochloride (980 mg, 10 eq). After the solid dissolved, sodium cyanoborohydride (6.0 mL, 1 M in THF, 5 eq) was added in one portion. The mixture was heated in a 50°C oil bath overnight before being quenched with aqueous sodium bicarbonate and extracted with MTBE. The

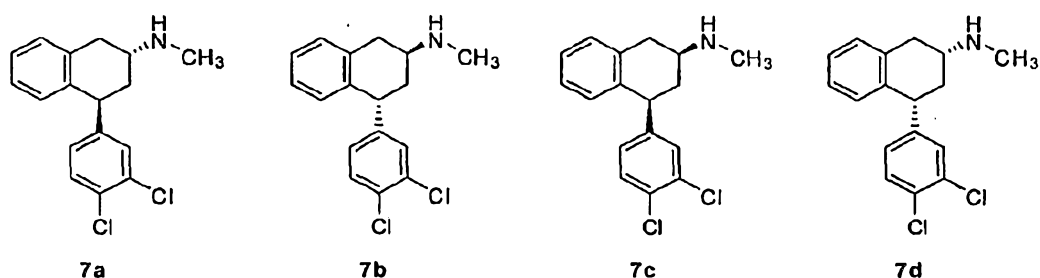
combined organic layer was washed with brine and evaporated to give a brown-green oil. The oil was dissolved in MTBE and extracted into 10% aqueous hydrochloric acid. The aqueous layer was basicified with KOH and extracted with MTBE. The volatile components were removed *in vacuo* and the crude green oil was separated on silica gel to give the methylamine (0.20 g, 54%) as a pale-green oil.

[0160] As isolated, the amine was a mixture of four stereoisomers which were separable on chiral columns. First, the mixture was separated on a Chiracel OD column (98:2:0.1 Hex/IPA/DEA) to give three fractions. Symchiral *trans* (Compound 7a) at 12.4 min, racemic *cis* at 15.8 and 17.6 min, and symchiral *trans* (Compound 7b) at 29.7 min. The racemic *cis* was then resubmitted to a Chiracel AD column (98:2:0.1 Hex/IPA/DEA) to give the symchiral *cis* (Compound 7c) at 20.2 min and symchiral *cis* (SME Compound 7d) at 27.7 min. Retention times are summarized in Table 2, below.

Table 2: Retention times for each diastereomer [min]

	7a	7c	7d	7b
	<i>Trans</i>	<i>Cis</i>	<i>Cis</i>	<i>Trans</i>
HPLC R _t (Chiracel OD, 98:2:0.1 Hex/IPA/DEA)	12.4	15.8	17.6	29.7
HPLC R _t (Chiracel AD, 98:2:0.1 Hex/IPA/DEA)		20.2	27.7	

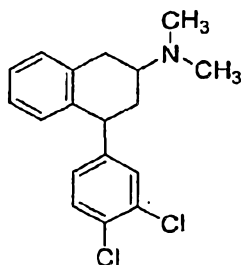
[0161] Absolute stereochemistries of compounds 7a-d were determined using a combination of NMR techniques (determination of *cis*- and *trans*-configurations) and chiral HPLC analyses using authentic samples, which were prepared from commercial (S)-alpha-tetralone as described above (also compare "General Procedures"). The resulting structures indicating absolute stereochemistries are shown below:



[0162] *Trans*-isomers 7a and 7b: LC-MS $R_t = 8.3$ min, $m/z = 306$ (M+1). GC-MS $R_t = 13.64$ min, $m/z = 305$ (M+). ^1H NMR (CDCl_3 , δ): 7.4-6.8 (m, 7H), 4.26 (t, $J=5.8$ Hz, 1H), 3.15 (dd, $J = 4.6, 16.2$ Hz, 1H), 2.9 (m, 1H), 2.66 (dd, $J = 7.8, 16.2$ Hz, 1H), 2.43 (s, 3H), 2.0 (m, 2H), 1.3 (bs, 1 H). ^{13}C NMR (CDCl_3 , δ , mult): 147.5(0), 136.8(0), 135.6(0), 132.2(0), 130.6(1), 130.1(1), 129.9(0), 129.8(1), 129.5(1), 128.1(1), 126.7(1), 126.2(1), 51.1(1), 42.5(1), 37.8(2), 36.0(2), 33.7(3).

[0163] *Cis*-isomers 7c and 7d: LC-MS $R_t = 8.5$ min, $m/z = 306$ (M+1). GC-MS $R_t = 13.82$ min, $m/z = 305$ (M+). ^1H NMR (CDCl_3 , δ): 7.4-6.7 (m, 7H), 4.08 (dd, $J = 5.4, 12.2$ Hz), 3.12 (ddd, $J = 2.2, 4.7, 15.7$ Hz, 1 H), 2.93 (ddt, $J = 2.9, 4.8, 11.2$ Hz, 1H), 2.70 (dd, $J = 11.1, 15.7$ Hz, 1H), 2.52 (s, 3H), 2.3 (m, 1H). ^{13}C NMR (CDCl_3 , δ , mult): 146.8(0), 138.2(0), 135.8(0), 132.4(0), 130.6(1), 130.5(1), 130.2(0), 129.2(1), 129.0(1), 128.1(1), 126.4(1), 126.1(1), 55.5(1), 45.8(1), 40.5(2), 37.4(2), 33.6(3).

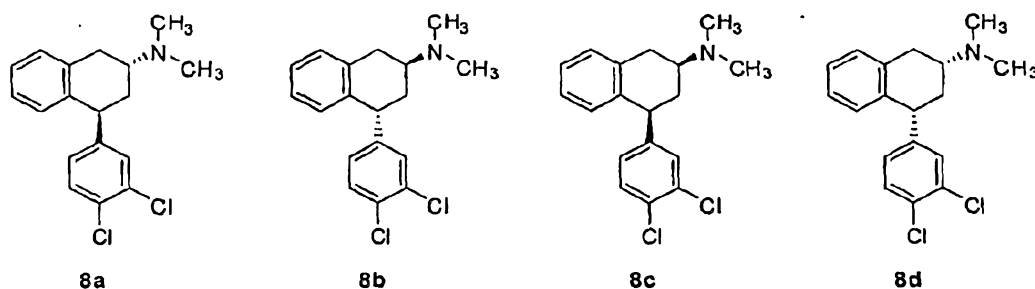
Example 3: Synthesis of [4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-dimethylamine (8a-d)



[0164] The respective methylamine 7 (e.g., 28.4 mg, 0.0927 mmol) was dissolved in 96% formic acid (0.5 mL) and 37% aqueous formaldehyde (0.5 mL) and heated at 100°C for two hours. After cooling, the solution was basicified (aq KOH) and

extracted with MTBE. The organic phase was dried with sodium sulfate, filtered, and evaporated to give the dimethylamine (e.g., 27.1 mg, 93%) as a clear oil.

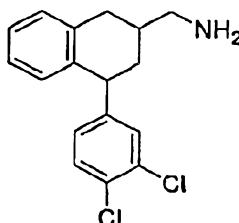
[0165] Absolute stereochemistries for compounds 8a-d were determined and are shown below:



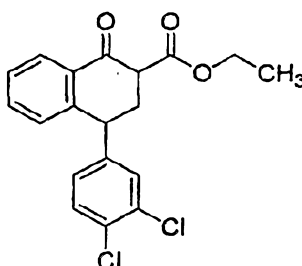
[0166] *Trans*-isomers 8a and 8b: LC-MS $R_t = 9.0$ min, $m/z = 320$ ($M+1$). ^1H NMR (CDCl_3 , δ): 7.4-6.8 (m, 7H), 4.32 (t, $J = 5.4$ Hz, 1 H), 3.02 (dd, $J = 4.8, 16.3$ Hz, 1H), 2.84 (dd, $J = 9.3, 16.3$ Hz, 1H), 2.6 (m, 1H), 2.27 (s, 6H), 2.1 (m, 2H). ^{13}C NMR (CDCl_3 , δ , mult): 147.3(0), 136.6(0), 136.3(0), 132.1(0), 130.5(1), 130.0(1), 129.8(0), 129.5(1), 128.1 (1), 126.7(1), 126.2(1), 129.9(1), 56.0(1), 43.3(1), 41.9(3), 34.9(2), 32.1(2).

[0167] *Cis*-isomers 8c and 8d: LC-MS $R_t = 9.1$ min, $m/z = 320$ ($M+1$). ^1H NMR (CDCl_3 , δ): 7.4-6.7 (m, 7H), 4.07 (dd, $J = 5.3, 12.2$ Hz, 1H), 3.1-2.9 (m, 2H), 2.80 (ddt, $J = 2.5, 4.9, 11.4$ Hz, 1H), 2.37 (s, 6H), 2.3 (m, 1H), 1.65 (q, $J = 12.2$ Hz, 1H). ^{13}C NMR (CDCl_3 , δ , mult): 146.9(0), 138.0(0), 136.3(0), 132.4(0), 130.6(1), 130.5(1), 130.3(0), 129.5(1), 129.0(1), 128.1(1), 126.4(1), 126.1(1), 60.3(1), 46.4(1), 41.4(3), 36.8(2), 32.8(2).

Example 4: Synthesis of (4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)methanamine (14a-d)

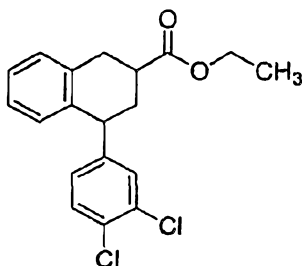


4.1. Synthesis of 4-(3,4-dichlorophenyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid ethyl ester (9)



[0168] To a stirred suspension of NaH (60% dispersion in mineral oil, 1.69 g, 42 mmol) in THF (80 ml) under N₂ was added dropwise diethylcarbonate (4.85 ml, 40 mmol) at room temperature, followed by 4-(3',4'-dichlorophenyl)-3,4-dihydro-1-(2H)-naphthalone 1 (5.82 g, 20 mmol) in THF (20 ml). The mixture was refluxed for 48 hours, then cooled to 0°C. Acetic acid (10 ml) was added dropwise, and the mixture was extracted with Et₂O. The Et₂O extracts were washed with saturated NaHCO₃ solution, brine, dried over MgSO₄, and evaporated. The residue was purified by chromatography, CombiFlash silica gel column (hexane:CH₂Cl₂ = 50:50) to give Compound 9 as a clear oil (5.81 g, 80%). ¹H NMR (CDCl₃) δ 1.30 (t, *J*=7.2 Hz, 3H), 2.77 (dd, *J*= 16 Hz, 9.6 Hz, 1H), 2.91 (dd, *J*= 15.6 Hz, 6.4 Hz, 1H), 4.10 (dd, *J*= 12 Hz, 6.4 Hz, 1H), 4.19-4.30 (m, 2H), 6.87 (d, *J*= 6.8 Hz, 1H), 7.00 (dd, *J*= 8.4 Hz, 2.0 Hz, 1H), 7.27-7.36 (m, 5H), 7.89 (dd, *J*= 8.4 Hz, 2.0 Hz, 1H), 12.50 (s, 1H). ¹³C NMR (CDCl₃) δ 14.5, 29.1, 43.4, 61.0, 95.6, 125.0, 127.6, 127.9, 128.1, 130.2, 130.6, 130.7, 131.0, 131.3, 132.8, 140.4, 143.9, 164.8, 172.6.

4.2. Synthesis of 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid ethyl ester (10)



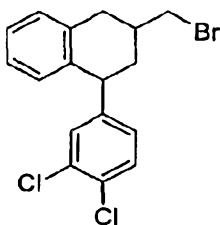
[0169] To a solution of **9** (2.81 g, 7.74 mmol) in TFA (30 ml) was added dropwise Et_3SiH (7.42 ml, 46.44 mmol) at 0°C . Stirring was continued at 0°C for 2 hours. Then, the solvent was evaporated, and the residue was purified by chromatography, CombiFlash silica gel column, hexane / CH_2Cl_2 , CH_2Cl_2 from 0% to 50%, to give compound **10** as a clear oil (mixture of *cis* and *trans* diastereomers, 2.63 g, 97%). ^1H NMR (CDCl_3) δ 1.18-1.34 (m, 3H), 1.88 (dd, $J=25.2$ Hz, 12.4 Hz) and 2.14-2.19 (m, total 1H), 2.25-2.33 (m) and 2.43-2.55 (m, total 1H), 2.67-2.74 (m) and 2.82-2.92 (m, total 1H), 3.00-3.18 (m, 2H), 4.08-4.29 (m, 3H), 6.72-7.42 (m, 7H).

4.3. Synthesis of [4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-naphthalen-2-yl]-methanol (11)

[0170] A solution of **10** (2.55 g, 7.3 mmol) in THF (40 ml) was added dropwise to a stirring mixture of LiAlH_4 (0.304 g, 8.0 mmol) in THF (20 ml) at 0°C . The resulting suspension was stirred at room temperature for 3 hours, then, the mixture was cooled to 0°C , and water (0.15 ml) was added dropwise to destroy the excess hydride. The mixture was filtered, and the solvent was evaporated *in vacuo* to give colorless oil. The residue was purified by chromatography, CombiFlash silica gel column, MeOH / CH_2Cl_2 , MeOH from 0% to 3%, to give **11** as a clear oil (mixture of *cis* and *trans* diastereomers, 1.80 g, 80%). ^1H NMR (CDCl_3) δ 1.31-1.54 (m, 1H), 1.92-1.98 (m, 2H), 2.10-2.26 (m, 1H), 2.54-2.71 (m, 1H), 2.92-3.03 (m, 1H), 3.53-3.75 (m, 2H), 4.07 (dd, $J=12$ Hz, 5.2 Hz) and 4.25 (t, $J=3.6$ Hz, total 1 H), 6.72-7.38 (m, 7H). ^{13}C NMR (CDCl_3) δ 32.0, 32.5, 33.4, 34.6,

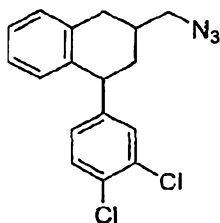
37.5, 37.6, 43.3, 46.3, 67.5, 67.9, 126.3, 126.4, 126.6, 127.0, 128.4, 128.5, 129.5, 129.7, 130.2, 130.5, 130.7, 130.9, 132.4, 132.7, 136.7, 136.9, 138.8, 147.5, 147.9.

4.4. Synthesis of 3-bromomethyl-1-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalene (12)



[0171] To a solution of compound 11 (1.25 g, 4.07 mmol) and CBr_4 (2.33 g, 7.04 mmol) in CH_2Cl_2 (15 ml) was added Ph_3P (1.82 g, 6.92 mmol) in CH_2Cl_2 (15 ml) at 0°C . The reaction was allowed to warm to room temperature overnight, was then poured into water ((40 ml), extracted with CH_2Cl_2 (75 ml), dried over Na_2SO_4 , and the solvent was evaporated. The residue was purified by chromatography, CombiFlash silica gel column, EtOAc hexanes, EtOAc from 0% to 15%, to give compound 12 as a clear oil (mixture of *cis* and *trans* diastereomers, 1.50 g, 99%). ^1H NMR. (CDCl_3) δ 1.52-1.62 (m) and 1.97-2.15 (m, total 2H), 2.25-2.30 (m, 1H), 2.64-2.77 (m, 1H), 3.02-3.12 (m, 1H), 3.34-3.47 (m, 2H), 4.08 (dd, $J=12$ Hz, 5.2 Hz) and 4.26 (t, $J=3.6$ Hz, total 1H), 6.72-7.39 (m, 7H). ^{13}C NMR (CDCl_3) δ 31.8, 34.6, 35.6, 36.8, 37.2, 39.2, 39.3, 39.4, 43.3, 46.4, 126.5, 126.8, 126.9, 127.2, 128.3, 128.4, 128.6, 129.0, 129.4, 129.5, 129.7, 130.2, 130.5, 130.7, 130.9, 132.5, 132.8, 136.1, 136.3, 138.3, 147.0, 147.5.

4.5. Synthesis of 3-azidomethyl-1-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalene (13)



[0172] A mixture of compound **12** (0.293 g, 0.79 mmol) and sodium azide (0.154 g, 2.38 mmol) in DMF (5 ml) was stirred at 60°C for 24 hours. The reaction mixture was filtered and evaporated *in vacuo*. The residue was partitioned between water and EtOAc. The organic layer was separated, washed with water, dried over Na₂SO₄, and evaporated to give compound **13** as a pale yellow oil (mixture of *cis* and *trans* diastereomers, ratio = 1:1.1, 0.18 g, 68%). The diastereomers were separated using a preparative chiral HPLC procedure (ChiralPak OD column; hexanes:MeOH = 98:2; μ = 8 ml/min; and λ = 225 nm) to give compounds **13a-13d** (retention times: 9.8 min, 12.0 min, 14.5 min and 20.1 min, respectively).

[0173] *Cis*-isomers **13a** and **13b**: ¹H NMR (CDCl₃) δ 1.92-2.09 (m, 3H), 2.61 (dd, *J* = 16.4 Hz, 9.8 Hz, 1H), 3.00 (dd, *J* = 16.8 Hz, 4.8 Hz, 1H), 3.29 (d, *J* = 6.0 Hz, 2H), 4.25 (t, *J* = 4.8 Hz, 1H), 6.81-6.92 (m, 2H), 7.08-7.15 (m, 2H), 7.18-7.21 (m, 2H), 7.32 (d, *J* = 6.0 Hz, 1H). ¹³C NMR (CDCl₃) δ 30.2, 33.4, 35.5, 43.2, 56.8, 126.6, 127.2, 128.3, 128.9, 129.6, 130.4, 130.5, 130.8, 132.5, 136.2, 136.6, 147.5.

[0174] *Trans*-isomers **13c** and **13d**: ¹H NMR (CDCl₃) δ 1.53 (dd, *J* = 24.8 Hz, 12.4 Hz, 1H), 2.13-2.25 (m, 2H), 2.67-2.74 (m, 1H), 2.94-3.00 (m, 1H), 3.32-3.41 (m, 2H), 4.08 (dd, *J* = 12 Hz, 5.2 Hz, 1H), 6.74 (d, *J* = 12.4 Hz, 1H), 7.00-7.08 (m, 2H), 7.14-7.18 (m, 2H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 12.4 Hz, 1H). ¹³C NMR (CDCl₃) δ 34.3, 35.4, 38.3, 46.2, 57.3, 126.5, 126.8, 128.4, 129.4, 129.6, 130.6, 130.7, 130.8, 132.7, 136.0, 138.4, 147.1.

4.6. Synthesis of (4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)methanamine (**14a-d**)

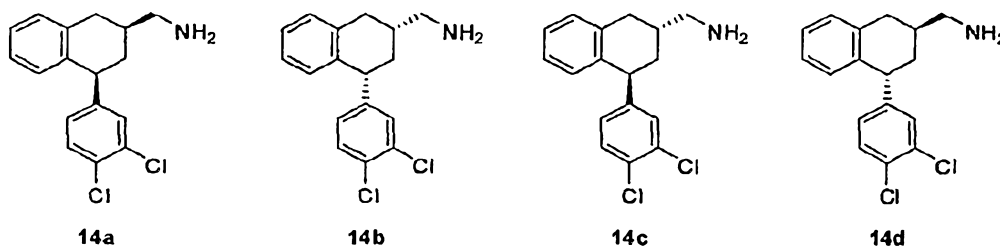
[0175] To a solution of compound **13a** (36 mg, 0.108 mmol), in EtOH (5 ml) was added Pd/C (10%, 13 mg). A hydrogen balloon was attached and the reaction mixture was stirred at room temperature for 15 min. The mixture was filtered and concentrated *in vacuo*. The residue was purified by HPLC, AD column, hexanes:IPA:DEA = 90:10:0.05. Compound **14a** was obtained as a clear oil (23 mg, 70%).

[0176] Compound **14b** was prepared from compound **13b** (32 mg, 0.096 mmol) according to the procedure outlined above and was obtained as a clear oil (19 mg, 63%). LRMS m/z 306.2.

[0177] Compound **14c** was prepared from compound **13c** (33 mg, 0.099 mmol) following the procedure outlined above and was obtained as a clear oil (26 mg, 86%).

[0178] Compound **14d** was prepared from **13d** (32 mg, 0.096 mmol) following the procedure outlined above and was obtained as a clear oil (20 mg, 70%). LRMS m/z 306.2.

[0179] Absolute stereochemistries for compounds **14a-d** were determined using a combination of NMR techniques (determination of *cis*- and *trans*-configurations) and chiral HPLC analyses using authentic samples, which were prepared from commercial (*S*)- α -tetralone as described above (also compare "General Procedures"). The resulting structures indicating absolute stereochemistries are shown below:

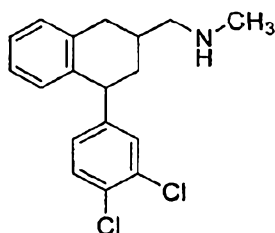


[0180] *Cis*-isomers **14a** and **14b**: ^1H NMR (CDCl_3) δ 1.33 (brs, 2H), 1.75-1.97 (m, 3H), 2.51 (dd, J = 16.8 Hz, 9.8 Hz, 1H), 2.61-2.70 (m, 2H), 3.02 (dd, J = 16.8 Hz, 5.2 Hz, 1H), 4.24 (t, J =3.6 Hz, 1H), 6.81- 6.91 (m, 2H), 7.07-7.12 (m, 2H), 7.16-7.20 (m, 2H), 7.29 (d, J = 6.0 Hz, 1H). ^{13}C NMR (CDCl_3) δ 32.5, 33.8, 35.8, 43.5, 47.8, 126.4, 127.0, 128.4, 129.6, 130.1, 130.2, 130.5, 130.9, 132.4, 137.1, 148.1. LRMS m/z 306.2.

[0181] *Trans*-isomers **14c** and **14d**: ^1H NMR (CDCl_3) δ 1.45 (dd, J = 24.9 Hz, 12.3 Hz, 1H), 1.75 (brs, 2H), 1.92-2.00 (m, 1H), 2.18-2.24 (m, 1H), 2.69-2.80 (m,

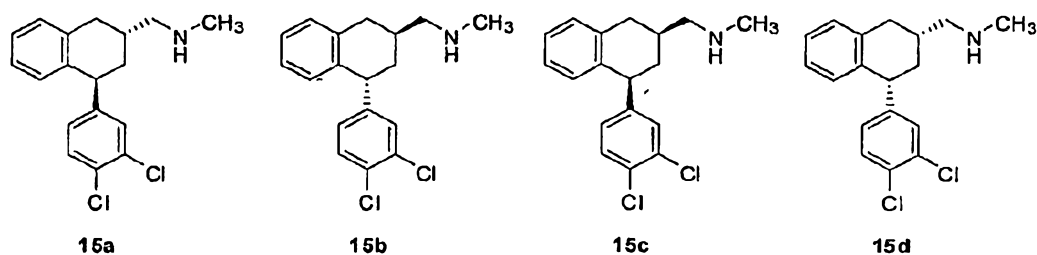
2H), 2.94-3.01 (m, 1H), 4.06 (dd, $J = 12$ Hz, 5.2 Hz, 1H), 6.72 (d, $J = 12.4$ Hz, 1H), 6.99-7.05 (m, 2H), 7.13-7.18 (m, 2H), 7.27 (d, $J = 7.8$ Hz, 1H), 7.36 (d, $J = 12.4$ Hz, 1H). ^{13}C NMR (CDCl_3) δ 34.7, 38.2, 38.7, 46.5, 48.2, 126.3, 126.6, 128.4, 129.4, 129.5, 130.4, 130.7, 130.8, 132.7, 136.9, 138.9, 147.6. LRMS m/z 306.2.

Example 5: Synthesis of [4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-ylmethyl]-methylamine (15a-d)



[0182] A mixture of compound **12** (0.342 g, 0.92 mmol) and methylamine (2.0 M in THF, 4.6 ml, 9.24 mmol) in a sealed tube was heated to 100°C for 5 hours. The reaction mixture was evaporated *in vacuo*. The residue was purified by chromatography, CombiFlash silica gel column, MeOH / CH_2Cl_2 , MeOH from 0% to 5%, to give Compound **15** as a clear oil (mixture of *cis* and *trans* diastereomers, ratio = 1:1.2, 0.201 g, 68%). The enantiomers Compounds **15(a)**, **15(b)**, **15(c)**, and **15(d)** were separated using a preparative chiral HPLC procedure (ChiralPak OD column; hexanes:IPA:DEA = 96:10:0.05; $\mu = 8$ ml/min; and $\lambda = 225$ nm) to give **15a-15d** (retention times: 11.2 min, 14.7 min, 16.3 min, and 21.2 min, respectively).

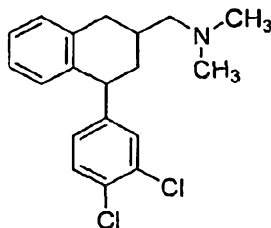
[0183] [0184] Absolute stereochemistries of compounds **15a-d** were determined using a combination of NMR techniques (determination of *cis*- and *trans*-configurations) and chiral HPLC analyses using authentic samples, which were prepared from commercial (S)- α -tetralone as described above (also compare "General Procedures"). The resulting structures indicating absolute stereochemistries are shown below:



[0185] *Trans*-diastereomers **15a and **15b**:** ^1H NMR (CDCl_3) δ 1.04 (brs, 1H), 1.88-1.97 (m, 3H), 2.39 (s, 3H), 2.47-2.56 (m, 3H), 3.21 (dd, $J=12.6$ Hz, 2.7 Hz, 1H), 4.23 (t, $J=3.6$ Hz, 1H), 6.81-6.91 (m, 2H), 7.07-7.12 (m, 2H), 7.16-7.20 (m, 2H), 7.29 (d, $J=6.0$ Hz, 1H). ^{13}C NMR (CDCl_3) δ 29.6, 34.5, 36.4, 37.1, 43.5, 58.0, 126.4, 126.9, 127.3, 128.4, 129.6, 130.0, 130.2, 130.5, 132.4, 137.1, 137.2, 148.0. LRMS m/z 320.3.

[0186] *Cis*-diastereomers **15c and **15d**:** ^1H NMR (CDCl_3) δ 1.35 (brs, 1H), 1.47 (dd, $J=24.9$ Hz, 12.3 Hz, 1H), 2.03-2.13 (m, 1H), 2.17-2.24 (m, 3H), 2.48 (s, 3H), 2.58-2.67 (m, 1H), 2.94-3.11 (m, 1H), 4.06 (dd, $J=12$ Hz, 5.2 Hz, 1H), 6.73 (d, $J=12.4$ Hz, 1H), 6.97-7.05 (m, 2H), 7.09-7.18 (m, 2H), 7.26 (d, $J=7.8$ Hz, 1H), 7.35 (d, $J=12.4$ Hz, 1H). ^{13}C NMR (CDCl_3) δ 35.2, 35.3, 37.1, 39.3, 46.5, 58.5, 126.3, 126.6, 128.5, 129.5, 129.6, 130.3, 130.7, 130.9, 132.6, 137.2, 139.0, 147.6. LRMS m/z 320.3.

Example 6: Synthesis of [4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-ylmethyl]-dimethylamine (16a**, **16b**)**



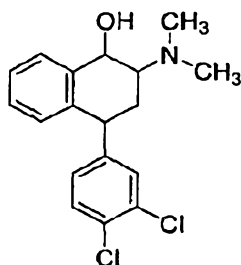
[0187] A mixture of compound **12** (0.40 g, 1.08 mmol) and dimethylamine (2.0 M in THF, 5.4 ml, 10.8 mmol) in a sealed tube was heated to 100°C for 5 hours. The reaction mixture was evaporated *in vacuo*. The residue was purified by chromatography, CombiFlash silica gel column, MeOH / CH_2Cl_2 , MeOH from

0% to 5%, to give **16** as a clear oil (mixture of *cis* and *trans* diastereomers, ratio = 1:1.2, 0.253 g, 70%). *Cis*- and *trans*-diastereomers were separated using a preparative HPLC procedure (ChiralPak OD column; hexanes: EtOH:MeOH:DEA = 96:2:2:0.05; μ = 8 ml/min; and λ = 225 nm) to give a mixture of *cis*-enantiomers (**16a**) and a mixture of *trans*-enantiomers (**16b**).

[0188] *Cis*-diastereomers **16a**: ^1H NMR (CDCl_3) δ 1.42 (dd, J = 24.9 Hz, 12.3 Hz, 1H), 2.03-2.13 (m, 1H), 2.15-2.22 (m, 3H), 2.23 (s, 6H), 2.51-2.61 (m, 1H), 2.94-3.10 (m, 1H), 4.06 (dd, J = 12 Hz, 5.2 Hz, 1H), 6.73 (d, J = 12.4 Hz, 1H), 6.97-7.05 (m, 2H), 7.09-7.18 (m, 2H), 7.26 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 12.4 Hz, 1H). ^{13}C NMR (CDCl_3) δ 33.3, 35.6, 39.7, 46.3, 46.6, 66.6, 126.3, 126.6, 128.5, 129.5, 129.6, 130.3, 130.7, 130.9, 132.6, 137.2, 139.0, 147.7. LRMS m/z 334.3.

[0189] *Trans*-diastereomers **16b**: ^1H NMR (CDCl_3) δ 1.82-2.05 (m, 3H), 2.13 (s, 6H), 2.20-2.25 (m, 2H), 2.50 (dd, J = 12 Hz, 5.2 Hz, 1H), 2.95-3.04 (m, 1H), 4.22 (t, J = 3.6 Hz, 1H), 6.8-1- 6.91 (m, 2H), 7.07-7.12 (m, 2H), 7.16-7.20 (m, 1H), 7.3 (d, J = 6.0 Hz, 1H). ^{13}C NMR (CDCl_3) δ 27.3, 34.6, 36.2, 43.3, 46.0, 65.4, 126.4, 126.9, 127.3, 128.4, 129.6, 130.0, 130.2, 130.5, 132.4, 137.1, 137.2, 148.1. LRMS m/z 334.3.

Example 7: Synthesis of 4-(3,4-dichlorophenyl)-2-(dimethylamino)-1,2,3,4-tetrahydronaphthalen-1-ol (23a-d)



[0190] To a solution of 4-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-1(2H)-one (2g, 6.8mmol) in ether (30mL) and chloroform (10mL) was added bromine (0.4mL, 1.1 eq) dropwise at 0°C. After one hour, the reaction was quenched with aqueous sodium bisulfate and potassium carbonate. The organic layer was

separated and washed with brine before being evaporated to give the crude bromoketone **21** (2.5g, 100%) as a light brown oil. The NMR indicated the presence of a 4:1 mixture of *trans* and *cis* isomers. The *trans*-isomer could be purified from the mixture by repeated crystallization from ether. The bromoketone (150mg, 0.305 mmol) was then combined with dimethylamine (800uL, 2M in THF, 4 eq) in a sealed tube and stirred at ambient temperature for 16 hours. The volatiles were removed *in vacuo* and the residue was dissolved in ethanol (1mL). To this solution was added potassium carbonate (110 mg) and the mixture was stirred for ten minutes. After this time, more ethanol and 100mg of sodium borohydride was added. After one hour of stirring, the reaction was quenched with aqueous sodium bicarbonate and extracted with MTBE. The solvent was evaporated and the residual oil was separated on silica to provide two fractions. The first fraction contained one pair of enantiomers and was separated on a Chiracel OD column to provide compounds **23a** and **23b**. The other fraction was partially separated on a Chiracel OD to give **23c** and **23d**. Stereochemistries were not assigned.

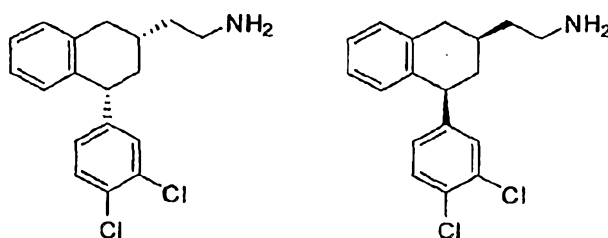
[0191] Enantiomers **23a** and **23b**: GCMS Rt = 14.26 min, m/z = 335 (M+). ¹H NMR (CDCl₃, δ): 7.70 (d, J = 7.8Hz, 1H), 7.3 (m, 2H), 7.19 (t, J = 7.5Hz, 1H), 7.13 (d, J = 2.1Hz, 1H), 6.88 (d, J = 7.7Hz, 1H), 6.81 (dd, J = 2.1, 8.3Hz, 1H), 4.64 (d, J = 9.7Hz, 1H), 4.36 (dd, J = 2.8, 6.2Hz, 1H), 2.6 (m, 1H), 2.21 (s, 6H), 2.08 (td, J = 6.3, 12.4Hz, 1H), 1.96 (dt, J = 3.0, 13.0Hz, 1H).

[0192] **23c**: GCMS Rt = 14.55 min, m/z = 335 (M+). ¹H NMR (CDCl₃, δ): 7.68 (d, J = 7.8Hz, 1H), 7.38 (d, J = 8.2Hz, 1H), 7.2 (m, 2H), 7.11 (t, J = 7.5Hz, 1H), 6.99 (dd, J = 2.0, 8.2Hz, 1H), 6.72 (d, J = 7.8Hz, 1H), 4.74 (d, J = 10.1Hz, 1H), 4.12 (dd, J = 5.7, 11.9Hz, 1H), 2.8 (m, 1H), 2.36 (s, 6H), 2.23 (ddd, J = 2.4, 5.8, 12.8Hz, 1H), 1.59 (q, J = 12.4Hz, 1H).

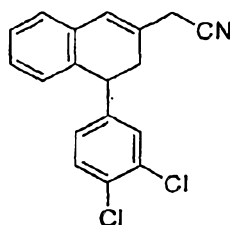
[0193] **23d**: GCMS Rt = 14.31 min, m/z = 335 (M+). ¹H NMR (CDCl₃, δ): 7.51 (d, J = 7.6Hz, 1H), 7.4-7.2 (m, 3H), 7.00 (d, J = 2.0Hz, 1H), 6.97 (d, J = 7.6Hz,

1H), 6.75 (dd, $J = 2.0, 8.3\text{Hz}$, 1H), 4.83 (s, 1H), 4.4 (m, 1H), 2.34 (s, 6H), 2.3 (m, 2H), 2.0 (m, 1H).

Example 8: Synthesis of 2-(1,3-cis)-1-(3,4-dichlorophenyl)-(1,2,3,4-tetrahydronaphthalen-3-yl)ethanamine (25a, 25b)

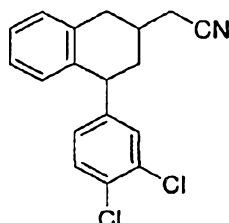


8.1 Synthesis of 2-(1-(3,4-dichlorophenyl)-1,2-dihydronaphthalen-3-yl)acetonitrile (24)



[0194] To a stirred solution of diethyl cyanomethyl phosphonate $\text{EtO}_2\text{POCH}_2\text{CN}$ (0.324mL, 2eq) in THF (2mL) was added sodium hydride (60mg, 60% in oil) in portions. After 30 minutes, 4-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-2(1H)-one (beta-tetralone) (291mg, 1 mmol) was added as a solution in THF (3mL). After the mixture was stirred for two hours at 0°C , the reaction was quenched with ammonium chloride solution, extracted with MTBE, dried over sodium sulfate and evaporated. The residue was separated on silica to give the unsaturated nitrile (0.24g, 77%) as a pale-green oil. GC-MS $R_t = 14.59\text{ min}$, $m/z = 313\text{ (M}^+)$. ^1H NMR (CDCl_3 , δ): 7.37 (d, $J = 8.3\text{Hz}$, 1H), 7.3 (m, 2H), 7.2 (m, 2H), 7.00 (dd, $J = 2.1, 8.3\text{Hz}$, 1H), 6.84 (d, $J = 7.4\text{Hz}$, 1H), 6.64 (bs, 1H), 4.17 (t, $J = 8.1\text{Hz}$, 1H), 3.21 (bs, 2H), 2.69 (dd, $J = 6.9, 17.3\text{Hz}$, 1H), 2.52 (dd, $J = 8.4, 17.2\text{Hz}$, 1H). ^{13}C NMR (CDCl_3 , δ , mult): 143.9(0), 135.2(0), 132.9(0), 132.5(0), 130.7(1), 130.5(1), 130.0(1), 128.2(1), 127.7(1), 127.5(1), 126.8(1), 126.4(1), 116.5(0), 43.1(1), 35.1(2), 25.1(2).

8.2. Synthesis of 2-(4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetonitrile



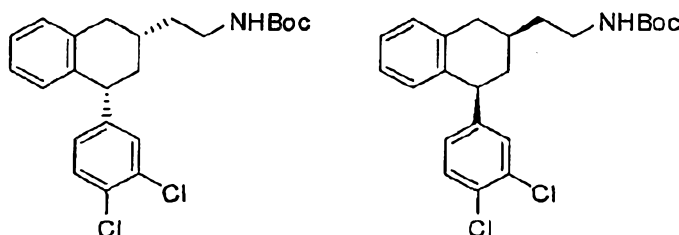
[0195] To a solution of the unsaturated nitrile (210mg, 0.6683mmol) in 1% wet methanol (28mL) was added 5% Pd/C (21mg). The atmosphere was evacuated under vacuum and refilled with hydrogen from a balloon. The reaction was monitored by HPLC and was stopped after 220 minutes. The catalyst was removed by filtration (celite) and the solvent removed *in vacuo*. The residue was diluted with DCM and filtered through an aminopropyl cartridge. The solvent was stripped to give the intermediate (201mg, 95%) as a pale-yellow oil. TLC R_f (50% EA/hex) = 0.56. HPLC R_t (5-100-8) = 11.1 min. ^1H NMR (CDCl_3 , δ): 7.40 (d, J = 8.3Hz, 1H), 7.3 (, 1H), 7.2 (m, 2H), 7.1 (m, 1H), 7.02 (dd, J = 2.1, 8.2Hz, 1H), 6.76 (d, J = 7.7Hz, 1H), 4.12 (dd, J = 5.4, 12.1Hz, 1H), 3.06 (ddd, J = 2.4, 4.3, 16.2Hz, 1H), 2.80 (dd, J = 12.4, 15.6Hz, 1H), 2.48 (dd, J = 2.6, 6.5Hz, 2H), 2.3 (m, 2H), 1.66 (q, J = 12.6Hz, 1H). ^{13}C NMR (CDCl_3 , δ , mult): 146.3(0), 137.6(0), 135.1(0), 132.6(0), 130.6(1), 130.6(1), 129.3(1), 129.0(1), 128.1(1), 126.7(1), 126.6(1), 118.1(0), 45.9(1), 39.6(2), 35.8(2), 31.9(1), 24.2(2).

8.3. Synthesis of 2-(4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)ethanamine (25)

[0196] To a stirring solution of the nitrile (200mg, 0.6324mmol) and THF (8mL) at ambient temperature was added borane-THF (4mL, 6eq) dropwise. After heating in the microwave (maximum temperature 130°C) for five minutes, the reaction was cooled, quenched with 6N HCl, and washed with MTBE. The aqueous layer was chilled, basicified with KOH, and extracted with MTBE. The organic layer was evaporated, diluted with DCM, dried over sodium sulfate, filtered through an aminopropyl cartridge and evaporated to give the pure amine (101mg, 50%) as a pale-yellow oil. LCMS R_t = 9.41 min, m/z = 320 ($M+1$). ^1H

NMR (CDCl₃, δ): 7.36 (d, J = 8.2Hz, 1H), 7.26 (s, 1H), 7.1 (m, 2H), 7.0 (m, 2H), 6.72 (d, J = 7.7Hz, 1H), 4.05 (dd, J = 5.3, 12.0Hz, 1H), 2.92 (dd, J = 2.4, 16.4Hz, 1H), 2.83 (t, J = 7.3Hz, 2H), 2.60 (m, 1H), 2.1 (m, 1H), 2.0 (M, 1H), 1.6-1.4 (m, 3H). ¹³C NMR (CDCl₃, δ , mult): 147.4(0), 138.5(0), 137.0(0), 132.3(0), 130.6(1), 130.4(1), 130.1(0), 129.3(1), 129.0(1), 128.1(1), 126.2(1), 125.9(1), 46.5(1), 41.0(2), 40.8(2), 39.6(2), 36.9(2), 32.3(1).

8.4. Enantiomeric separation of 25; synthesis of tert-butyl 2-(4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)ethylcarbamate (26a, 26b)



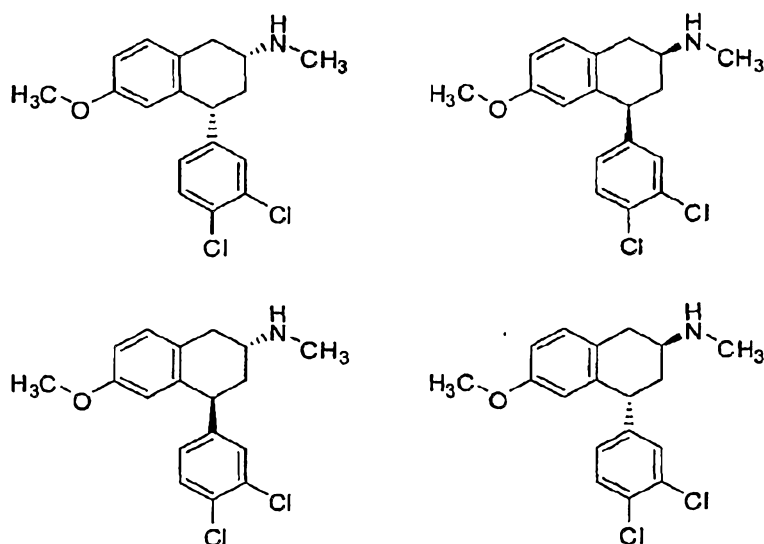
[0197] To a solution of the primary amine (100mg, 0.3122mmol) in ether (3mL) was added 10% KOH (1mL) and BOC anhydride (136mg, 2eq). After two hours at ambient temperature, the solution was extracted with MTBE. The organic phase was separated and the volatiles removed *in vacuo* to give the crude carbamate (208mg) as a 1:1 mixture with excess BOC anhydride. Most of the anhydride was removed by washing an MBTE solution of the crude product with 1M HCl. This material was separated on a Chiracel OD semiprep column (90:10:0.1 Hex/IPA/DEA) to give the fast moving enantiomer **26a** (56.2mg, 50%) and the slow-moving enantiomer **26b** (55.7mg, 50%). NMR analysis suggested that the formed enantiomers have *cis*-configuration. TLC R_f (50% EA/hex) = 0.48. LCMS R_t = 11.16 min. ¹H NMR (CDCl₃, δ): 7.36 (d, J = 8.2Hz, 1H), 7.3 (m, 1H), 7.1 (m, 2H), 7.0 (m, 2H), 6.72 (d, J = 7.7Hz, 1H), 4.56 (bs, 1H), 4.04 (dd, J = 5.4, 12.0Hz, 1H), 3.2 (m, 2H), 2.93 (dd, J = 2.6, 16.3Hz, 1H), 2.60 (dd, J = 12.0, 16.1Hz, 1H), 2.2 (m, 1H), 1.9 (m, 1H), 1.57 (q, J = 7.1Hz, 2H), 1.44 (s, 9H). ¹³C NMR (CDCl₃, δ , mult): 155.9(0), 147.3(0), 138.4(0), 136.7(0), 132.4(0), 130.6(1), 130.4(1), 130.1(0), 129.3(1), 129.0(1), 128.1(1), 126.3(1), 126.0(1), 46.4(1), 40.8(2), 38.1(2), 37.0(2), 36.7(2), 32.3(1), 28.4(3).

8.5. Synthesis of *cis* and *trans*-2-(1-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-3-yl)acetonitrile (25a and 25b)

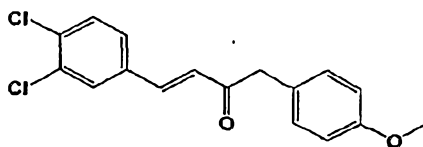
[0198] To a solution of carbamate **26a** (20mg, 0.05585mmol) in CDCl₃ was added HCl (1mL, 4M in dioxane). After 1 hour, the mixture was chilled, quenched with KOH (1mL, 5M in H₂O), extracted with MTBE and evaporated. The crude oil was diluted in DCM, filtered through an aminopropylcartridge and evaporated to give the pure primary amine **25a** (11.5mg, 64%) as a clear oil.

[0199] The second enantiomer was prepared from **26b** using the procedure described above to give the enantiomeric amine **25b** (11.1 mg, 62%) as a clear oil.

Example 9: 4-(3,4-dichlorophenyl)-6-methoxy-N-methyl-1,2,3,4-tetrahydronaphthalen-2-amine (32a.1, 32a.2, 32a.3, 32a.4)



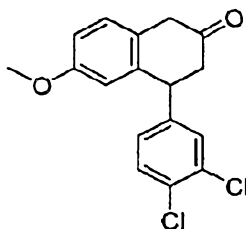
9.1. Synthesis of (E)-4-(3,4-dichlorophenyl)-1-(4-methoxyphenyl)but-3-en-2-one (29a)



[0200] To a cold solution of NaH (40% in mineral oil, 1.0g, 25mmol) in THF (30mL) was added ethanol (0.3mL). After 5 minutes, 1-(4-

methoxyphenyl)propan-2-one (2.0g, 12.2mmol) was added rapidly dropwise as a solution in 12 mL THF. After 30 minutes, 3,4-dichlorobenzaldehyde (2.4g, 13.7mmol) was added as a solution in 24mL THF in one portion. After 2h, the reaction mixture was quenched with aqueous ammonium chloride and the volatile portion was evaporated. The aqueous residue was extracted with MTBE, which was evaporated onto silica gel. The solid material was loaded onto a redisepp cartridge and separated on silica gel to give the enone as a pale-yellow oil (32% yield). TLC R_f (25% EA/Hex) = 0.35. GCMS R_t = 14.42 min m/z = 320 (M^+). TLC R_f (25% EA/Hex) = 0.26. GCMS R_t = 14.5 min m/z = 320 (M^+). 1H NMR ($CDCl_3$, δ): 7.58 (d, J = 1.9Hz, 1H), 7.49 (d, J = 16.0Hz, 1H), 7.44 (d, J = 8.3Hz, 1H), 7.32 (dd, J = 1.9, 8.3Hz, 1H), 7.17 (d, J = 8.5Hz, 2H), 6.89 (d, J = 8.6Hz, 2H), 6.73 (d, J = 16.0Hz, 1H), 3.86 (s, 2H), 3.80 (s, 3H). ^{13}C NMR ($CDCl_3$, δ): 196.9, 158.7, 140.3, 140.3, 140.2, 134.4, 134.3, 133.1, 130.8, 130.4, 129.7, 127.3, 126.3, 125.8, 114.2, 55.2, 47.8.

9.2. Synthesis of 4-(3,4-dichlorophenyl)-6-methoxy-3,4-dihydronaphthalen-2(1H)-one (30a)



[0201] The ketone **29a** (2.0g, 6.23mmol) was dissolved in xylenes (50mL) and stirred with a mechanical stirrer in a three-necked round bottom flask. The flask was fitted with a condenser and heated to 165°C. When the reaction had warmed up, PPA (40g) was added via syringe as rapidly as possible. The reaction mixture was then stirred rapidly and monitored by HPLC. After three hours, the reaction was cooled and the xylene layer was decanted. Evaporation and separation of the crude residue on a redisepp cartridge provided some recovered starting enone (0.34g, 17%) and the desired tetralone (0.36g, 18%) as a clear oil. TLC R_f (25% EA/Hex) = 0.25. GCMS R_t = 14.26 min m/z = 320 (M^+). 1H NMR ($CDCl_3$, δ):

7.40 (d, $J = 8.3\text{Hz}$, 1H), 7.21 (d, $J = 2.0\text{Hz}$, 1H), 7.12 (d, $J = 8.4\text{Hz}$, 1H), 6.96 (dd, $J = 2.1$, 8.3Hz , 1H), 6.84 (dd, $J = 2.6$, 8.4Hz , 1H), 6.53 (d, $J = 2.4\text{Hz}$, 1H), 4.38 (t, $J = 6.3\text{Hz}$, 1H), 3.76 (s, 3H), 3.56 (dd, $J = 20.3$, 42.4Hz , 2H), 2.89 (m, 2H). ^{13}C NMR (CDCl₃, δ): 208.6, 158.6, 141.7, 138.9, 132.8, 131.1, 130.7, 129.8, 129.7, 127.2, 125.0, 113.8, 112.8, 55.2, 45.5, 44.0, 43.8.

9.3. 4-(3,4-dichlorophenyl)-6-methoxy-N-methyl-1,2,3,4-tetrahydronaphthalen-2-amine (32a)

[0202] To a solution of the tetralone **30a** in THF in methanol was added methylamine hydrochloride. After dissolution (10 min), sodium cyanoborohydride was added in a single portion. The resultant mixture was stirred at 50°C for three hours. After cooling, the mixture was diluted with sodium bicarbonate solution and extracted with MTBE. The organic layer was evaporated to give the crude amine **32a** (160mg) as a mixture of four configurational isomers.

[0203] These amines were separated using a combination of Chiracel OD (98:2:0.1 Hex/IPA/DEA) and AD (95:5:0.1 Hex/IPA/DEA) columns. The order of elution changes between the two columns and was defined based on the OD column as peaks E1, E2, E3, and E4. Retention times are summarized in Table 3, below.

Table 3: Retention times for each diastereomer [min]

	32a.1	32a.2	32a.3	32a.4
	E1	E2	E3	E4
	<i>Trans</i>	<i>Cis</i>	<i>Trans</i>	<i>Cis</i>
HPLC R _t (Chiracel OD, 98:2:0.1 Hex/IPA/DEA)	14.1	15.4	17.2	18.6
HPLC R _t (Chiracel AD, 95:5:0.1 Hex/IPA/DEA)	11.0	11.9	9.2	10.2

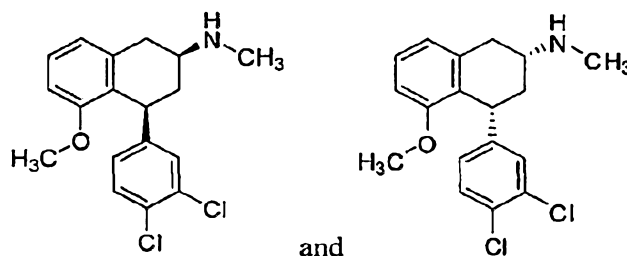
[0204] *Cis*-isomers **32a.2** and **32a.4**: LCMS R_t = 7.00 min $m/z = 336$ (M+1). ^1H NMR (CDCl₃, δ): 7.37 (d, $J = 8.3\text{Hz}$, 1H), 7.29 (d, $J = 2.1\text{Hz}$, 1H), 7.06 (d, $J = 8.4\text{Hz}$, 1H), 7.01 (dd, $J = 2.1$, 8.2Hz , 1H), 6.72 (dd, $J = 2.6$, 8.4Hz , 1H), 6.24 (d, $J = 2.4\text{Hz}$, 1H), 4.04 (dd, $J = 5.4$, 12.3Hz , 1H), 3.64 (s, 3H), 3.06 (ddd, $J = 2.0$, 4.6,

15.4Hz, 1H), 2.89 (tdd, $J = 2.9, 4.7, 11.2\text{Hz}$, 1H), 2.62 (dd, $J = 11.1, 15.3\text{Hz}$, 1H), 2.52 (s, 3H), 2.32 (m, 1H), 1.55 (dd, $J = 12.3, 24.0\text{Hz}$, 1H). ^{13}C NMR (CDCl_3 , δ): 158.0, 146.9, 139.3, 132.6, 130.8, 130.7, 130.6, 130.5, 128.7, 128.3, 114.3, 112.7, 60.7, 55.4, 46.8, 41.7, 37.0, 32.2.

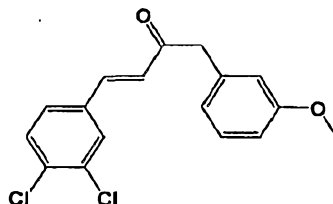
[0205] *Trans*-isomers **32a.1** and **32a.3**: LCMS $R_t = 7.17$ min $m/z = 336$ ($M+1$).

^1H NMR (CDCl_3 , δ): 7.32 (d, $J = 8.3\text{Hz}$, 1H), 7.14 (d, $J = 2.1\text{Hz}$, 1H), 7.08 (d, $J = 8.5\text{Hz}$, 1H), 6.88 (dd, $J = 2.1, 8.3\text{Hz}$, 1H), 6.77 (dd, $J = 2.7, 8.4\text{Hz}$, 1H), 6.38 (d, $J = 2.6\text{Hz}$, 1H), 4.23 (t, $J = 5.8\text{Hz}$, 1H), 3.68 (s, 3H), 3.10 (dd, $J = 4.8, 16.0\text{Hz}$, 1H), 2.9 (m, 1H), 2.61 (dd, $J = 7.9, 16.0\text{Hz}$, 1H), 2.42 (s, 3H), 2.0 (m, 2H), 1.9 (bs, 1H). ^{13}C NMR (CDCl_3 , δ): 158.1, 147.4, 137.9, 132.4, 130.7, 130.6, 130.4, 130.2, 128.3, 127.8, 114.6, 113.5, 55.4, 51.5, 43.1, 37.8, 35.2, 33.7.

Example 10: Synthesis of 4-(3,4-dichlorophenyl)-5-methoxy-N-methyl-1,2,3,4-tetrahydronaphthalen-2-amine (32b.1, 32b.2)



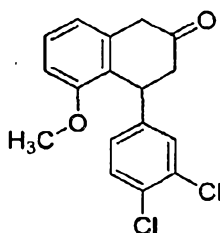
10.1. Synthesis of (E)-4-(3,4-dichlorophenyl)-1-(3-methoxyphenyl)but-3-en-2-one (29b)



[0206] The title compound was prepared in 36% yield from 1-(3-methoxyphenyl)propan-2-one and 3,4-dichlorobenzaldehyde following the procedure outlined in Example 9.1 above. ^1H NMR (CDCl_3 , δ): 7.56 (d, $J = 2.0\text{Hz}$, 1H), 7.48 (d, $J = 16.0\text{Hz}$, 1H), 7.42 (d, $J = 8.3\text{Hz}$, 1H), 7.3 (m, 2H), 6.8 (m,

3H), 6.73 (d, $J = 16.0\text{Hz}$, 1H), 3.88 (s, 2H), 3.79 (s, 3H). ^{13}C NMR (CDCl_3 , δ): 196.5, 159.8, 140.4, 135.3, 134.4, 134.3, 133.1, 130.8, 129.8, 129.7, 127.3, 126.2, 121.7, 115.1, 112.5, 55.1, 48.7.

10.2. 4-(3,4-dichlorophenyl)-5-methoxy-3,4-dihydronaphthalen-2(1H)-one (30c)



[0207] The cyclization of the 2-methoxy aryl enone **29b** following the procedure outlined in Example 9.2 gave a mixture of tetralones. The products were separated by silica gel column chromatography to give the 5-methoxytetralone **30c** (24%) followed by the 7-methoxytetralone **30b** (32%).

[0208] The isolated 5-methoxy tetralone **30c** appeared to be a mixture of rotational isomers that were slow to interconvert on the NMR time-scale. For example, the characteristic bisbenzylic proton coupling pattern appeared at both 4.9 (dd) and 4.4 (t) ppm. The ratio of the two peaks was 85:15. ^1H NMR (CDCl_3 , δ): 7.4-6.5 (m, 6H), 4.95 (dd, $J = 1.9, 6.1\text{Hz}$, 0.85H), 4.37 (t, $J = 6.2\text{Hz}$, 0.15H), 3.80 (s, 3H), 3.6 (m, 0.30H) 3.53 (dd, $J = 21.0, 59.6\text{Hz}$, 1.7H), 2.9 (m, 1.7H), 2.2 (m, 0.30H).

10.3. Synthesis of 4-(3,4-dichlorophenyl)-5-methoxy-N-methyl-1,2,3,4-tetrahydronaphthalen-2-amine (32b.1, 32b.2)

[0209] The title compound was prepared from **30c** following the procedure outlined in Example 9.3. The reaction yielded the *cis* diastereomers selectively (*cis:trans* >10:1). The amine components were isolated from the crude mixture by reverse-phase HPLC and the *cis* enantiomers were then separated using the Chiracel OD (90:10:0.1 Hex/IPA/DEA) column first, followed by the Chiracel AD (2:3:95:0.1 MeOH/EtOH/Hex/IPA) to give the enantiomers **32b.1** and **32b.2**. The retention times for both enantiomers are summarized in Table 4, below.

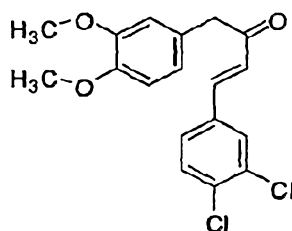
Table 4: Retention times for each *cis*-enantiomer [min]

	32b.1	32b.2
	E1	E2
	<i>Cis</i>	<i>Cis</i>
HPLC R _t (Chiracel OD, 95:5:0.1 Hex/IPA/DEA)	9.3	11.8
HPLC R _t (Chiracel AD, 2:3:95:0.1 MeOH/EtOH/Hex/DEA)	7.60	8.3

[0210] *Cis*-enantiomers (**32b.1** and **32b.2**): LCMS R_t = 7.5min m/z = 336 (M+1).

¹H NMR (CDCl₃, δ): 7.26 (d, J = 8.3Hz, 1H), 7.16 (m, 2H), 6.88 (dd, J = 2.1, 8.3Hz, 1H), 6.79 (d, J = 7.6Hz, 1H), 6.64 (d, J = 8.1Hz, 1H), 4.17 (dd, J = 7.9, 10.2Hz, 1H), 3.44 (s, 3H), 3.02 (dt, J = 3.2, 15.2Hz, 1H), 2.79 (tt, J = 3.5, 11.0Hz, 1H), 2.64 (dd, J = 11.0, 14.8Hz, 1H), 2.48 (s, 3H), 2.44 (m, 1H), 1.4 (m, 2H). ¹³C NMR (CDCl₃, δ): 157.6, 149.3, 138.2, 131.6, 129.9, 128.8, 128.7, 127.6, 126.3, 126.3, 121.6, 108.9, 55.3, 55.0, 41.3, 41.2, 37.6, 33.6.

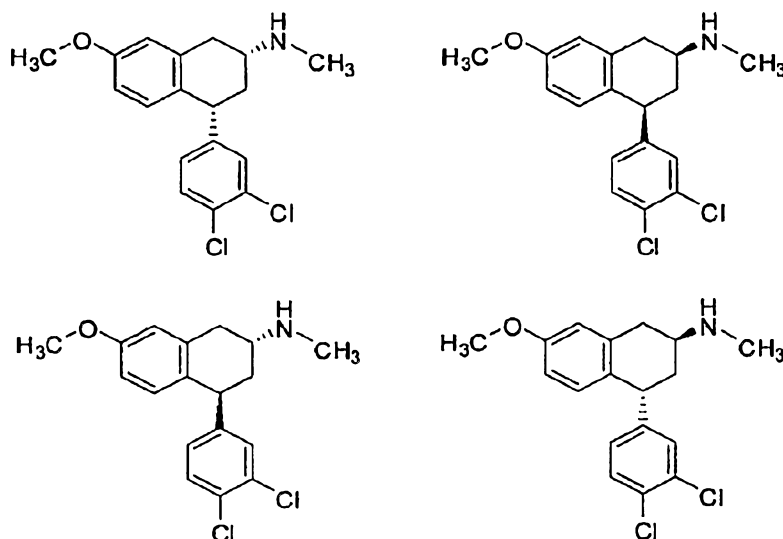
Example 11: Synthesis of (E)-4-(3,4-dichlorophenyl)-1-(3,4-dimethoxyphenyl)but-3-en-2-one (29c)



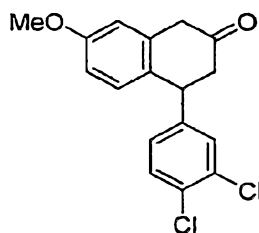
[0211] The title compound was prepared in (37% yield) from following the procedure outlined in Example 9.1, above. TLC R_f (10% EA/Hex) = 0.19.

GCMS R_t = 15.06 min m/z = 350 (M+). ¹H NMR (CDCl₃, δ): 7.57 (d, J = 2.0Hz, 1H), 7.49 (d, J = 16.0Hz, 1H), 7.43 (d, J = 8.3Hz, 1H), 7.31 (dd, J = 2.0, 8.3Hz, 1H), 6.85 (d, J = 8.2Hz, 1H), 6.80 (dd, J = 1.9, 8.2Hz, 1H), 6.75 (d, J = 1.8Hz, 1H), 6.74 (d, J = 16.0Hz, 1H) 3.86 (s, 6H), 3.85 (s, 2H). ¹³C NMR (CDCl₃, δ): 197.0, 149.1, 148.1, 140.4, 134.4, 134.3, 133.2, 130.8, 129.7, 127.3, 126.2, 126.1, 121.6, 112.3, 111.4, 55.8, 48.4.

Example 12: Synthesis of 4-(3,4-dichlorophenyl)-7-methoxy-N-methyl-1,2,3,4-tetrahydronaphthalen-2-amine (32c.1, 32c.2, 32c.3, 32c.4)



12.1. 4-(3,4-dichlorophenyl)-7-methoxy-3,4-dihydronaphthalen-2(1H)-one (30b)



[0212] The cyclization of the 2-methoxy aryl enone **29b** following the procedure outlined in Example 9.1, above, gave a mixture of tetralones. The products were separated by silica gel column chromatography to give the 5-methoxytetralone **30c** (24%) followed by the 7-methoxytetralone **30b** (32%). ¹H NMR (CDCl₃, δ): 7.36 (d, *J* = 8.3 Hz, 1H), 7.19 (d, *J* = 2.1 Hz, 1H), 6.94 (dd, *J* = 2.1, 8.3 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.74 (m, 2H), 4.36 (t, *J* = 6.3 Hz, 1H), 3.79 (s, 3H), 3.57 (dd, *J* = 20.4, 37.5 Hz, 2H), 2.85 (m, 2H).

12.2. Synthesis of 4-(3,4-dichlorophenyl)-7-methoxy-N-methyl-1,2,3,4-tetrahydronaphthalen-2-amine (32c.1, 32c.2, 32c.3, 32c.4)

[0213] The title compound was prepared from **30b** following the procedure outlined in Example 9.3. The amine components were isolated from the crude mixture by reverse-phase HPLC and all four isomers were then separated using a combination of Chiracel OD (90:10:0.1 Hex/IPA/DEA) and AD (95:5:0.1 Hex/IPA/DEA) columns. These isomers were designated E1, E2, E3, and E4 based on the order of elution from the OD column. The order of elution differs on the AD column. Retention times for the isomers are summarized in Table 5, below.

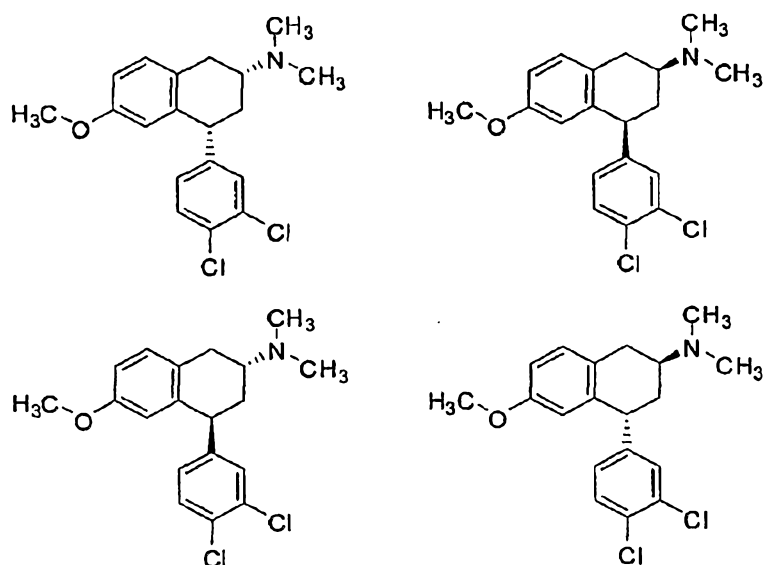
Table 5: Retention times for each isomer [min]

	32c.1	32c.2	32c.3	32c.4
	E1	E2	E3	E4
	<i>Cis</i>	<i>Trans</i>	<i>Trans</i>	<i>Cis</i>
HPLC R _t (Chiracel OD, 90:10:0.1 Hex/IPA/DEA)	7.1	8.2	8.8	12.2
HPLC R _t (Chiracel AD, 95:5:0.1 Hex/IPA/DEA)	15.0	15.0	18.3	13.6

[0214] *Cis*-isomers **32c.1** (E1) and **32c.4** (E4): LCMS R_t = 7.1min m/z = 336 (M+1). ¹H NMR (CDCl₃, δ): 7.32 (d, J = 8.2Hz, 1H), 7.12 (d, J = 2.0Hz, 1H), 6.88 (dd, J = 2.0, 8.3Hz, 1H), 6.78 (d, J = 8.1Hz, 1H), 6.7 (m, 2H), 4.21 (t, J = 5.8Hz, 1H), 3.79 (s, 3H), 3.13 (dd, J = 4.8, 16.3Hz, 1H), 2.90 (m, 1H), 2.67 (dd, J = 7.9, 16.3Hz, 1H), 2.43 (s, 3H), 2.0 (m, 2H), 1.8 (bs, 1H). ¹³C NMR (CDCl₃, δ): 158.2, 147.7, 136.7, 132.1, 130.9, 130.5, 130.1, 129.9, 128.8, 128.0, 113.7, 112.8, 55.2, 51.1, 41.8, 37.8, 36.1, 33.5.

[0215] *Trans*-isomers **32c.2** (E2) and **32c.3** (E3): LCMS R_t = 7.1min m/z = 336 (M+1). ¹H NMR (CDCl₃, δ): 7.37 (d, J = 8.3Hz, 1H), 7.28 (d, J = 2.0Hz, 1H), 7.01 (dd, J = 2.0, 8.2Hz, 1H), 6.6 (m, 3H), 4.02 (dd, J = 5.3, 12.1Hz, 1H), 3.78 (s, 3H), 3.08 (ddd, J = 2.0, 4.6, 15.8Hz, 1H), 2.92 (tdd, J = 2.9, 4.7, 11.2Hz, 1H), 2.69 (dd, J = 11.1, 15.6Hz, 1H), 2.53 (s, 3H), 2.32 (m, 1H), 1.54 (dd, J = 12.2, 24.0Hz, 1H), 1.4 (bs, 1H). ¹³C NMR (CDCl₃, δ): 158.0, 147.0, 137.1, 132.3, 130.5, 130.4, 130.1, 130.1, 128.0, 113.5, 112.5, 55.5, 55.2, 45.1, 40.6, 37.6, 33.6.

Example 13: 4-(3,4-dichlorophenyl)-6-methoxy-N,N-dimethyl-1,2,3,4-tetrahydronaphthalen-2-amine (33a.1, 33a.2, 33a.3, 33a.4)



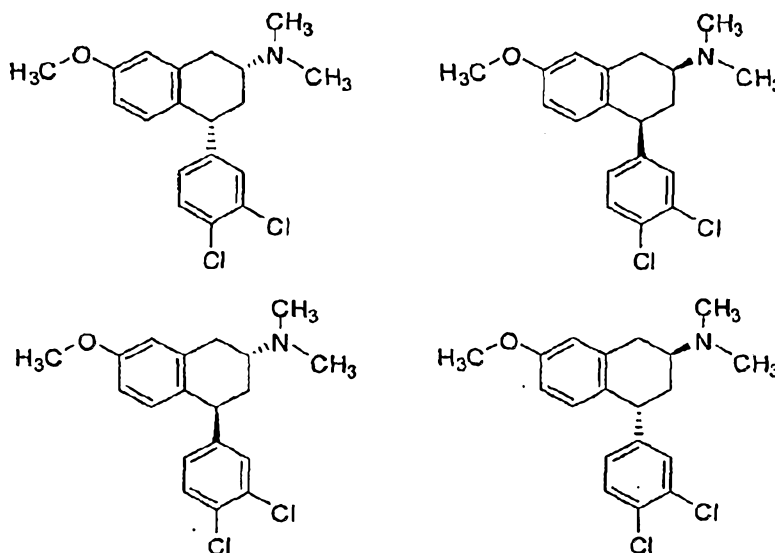
[0216] A solution of the respective methylamine 32a (Example 9) (e.g., 16mg) in formic acid (e.g., 1mL) and formaldehyde (e.g., 1mL) was stirred at 100°C for two hours. After chilling on ice, the solution was quenched with aqueous sodium hydroxide and extracted with MTBE. The solvent was removed and the residue was filtered through an aminopropyl cartridge to give the desired dimethylamine as a clear oil (e.g., 11.5mg).

[0217] *Cis*-enantiomers 33a.2 and 33a.4: LCMS $R_t = 7.87\text{min}$ $m/z = 350$ (M+1). ^1H NMR (CDCl_3 , δ): 7.38 (d, $J = 8.2\text{Hz}$, 1H), 7.28 (d, $J = 2.1\text{Hz}$, 1H), 7.08 (d, $J = 8.4\text{Hz}$, 1H), 7.01 (dd, $J = 2.0, 8.2\text{Hz}$, 1H), 6.73 (dd, $J = 2.6, 8.4\text{Hz}$, 1H), 6.23 (d, $J = 2.4\text{Hz}$, 1H), 4.03 (dd, $J = 5.3, 12.2\text{Hz}$, 1H), 3.64 (s, 3H), 2.96 (m, 1H), 2.83 (m, 1H), 2.75 (tdd, $J = 2.4, 4.3, 11.3\text{Hz}$, 1H), 2.36 (s, 6H), 2.29 (m, 1H), 1.62 (dd, $J = 12.2, 23.8\text{Hz}$, 1H). ^{13}C NMR (CDCl_3 , δ): 158.0, 146.9, 139.3, 132.6, 130.8, 130.7, 130.6, 130.5, 128.7, 128.3, 114.3, 112.7, 60.7, 55.4, 46.8, 41.7, 37.0, 32.2.

[0218] *Trans*-enantiomers 33a.1 and 33a.3: LCMS $R_t = 7.85\text{min}$ $m/z = 350$ (M+1). ^1H NMR (CDCl_3 , δ): 7.32 (d, $J = 8.3\text{Hz}$, 1H), 7.1 (m, 2H), 6.86 (dd, $J = 1.9, 8.3\text{Hz}$, 1H), 6.77 (dd, $J = 2.6, 8.4\text{Hz}$, 1H), 6.41 (d, $J = 2.5\text{Hz}$, 1H), 4.28 (t, $J = 5.2\text{Hz}$, 1H), 3.69 (s, 3H), 2.96 (dd, $J = 4.8, 16.0\text{Hz}$, 1H), 2.77 (dd, $J = 9.3, 15.9\text{Hz}$,

1H), 2.54 (sep, $J = 4.5\text{Hz}$, 1H), 2.26 (s, 6H), 2.1 (m, 2H). ^{13}C NMR (CDCl_3 , δ): 158.1, 147.3, 137.8, 132.4, 130.7, 130.6, 130.3, 128.6, 128.3, 114.4, 114.4, 113.5, 56.4, 55.4, 55.4, 43.8, 42.1, 35.1, 31.5.

Example 14: 4-(3,4-dichlorophenyl)-7-methoxy-N,N-dimethyl-1,2,3,4-tetrahydronaphthalen-2-amine (33c.1, 33c.2, 33c.3, 33c.4)

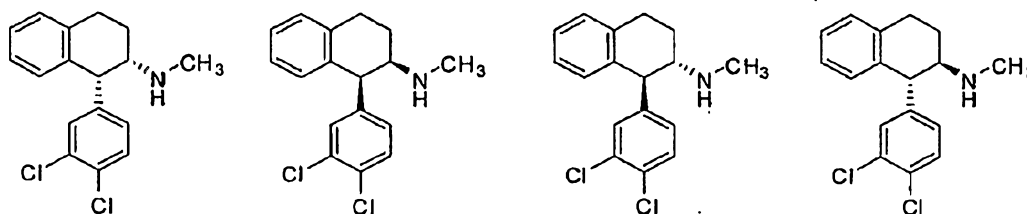


[0219] The title compounds were prepared from 32c.1, 32c.2, 32c.3 and 32c.4, respectively, following the procedure outlined in Example 13. All four enantiomers were obtained.

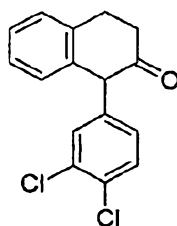
[0220] *Cis*-enantiomers 33c.1 and 33c.4: LCMS $R_t = 8.65\text{min}$ $m/z = 350$ ($M+1$). ^1H NMR (CDCl_3 , δ): 7.31 (d, $J = 8.3\text{Hz}$, 1H), 7.09 (d, $J = 2.1\text{Hz}$, 1H), 6.86 (dd, $J = 2.1, 8.3\text{Hz}$, 1H), 6.80 (d, $J = 8.1\text{Hz}$, 1H), 6.7 (m, 2H), 4.27 (t, $J = 5.2\text{Hz}$, 1H), 3.80 (s, 3H), 2.98 (dd, $J = 4.9, 16.4\text{Hz}$, 1H), 2.82 (dd, $J = 9.3, 16.4\text{Hz}$, 1H), 2.55 (m, 1H), 2.27 (s, 6H), 2.1 (m, 2H).

[0221] *Trans*-enantiomers 33c.2 and 33c.3: LCMS $R_t = 8.72\text{min}$ $m/z = 350$ ($M+1$). ^1H NMR (CDCl_3 , δ): 7.38 (d, $J = 8.3\text{Hz}$, 1H), 7.27 (d, $J = 2.1\text{Hz}$, 1H), 7.01 (dd, $J = 2.0, 8.2\text{Hz}$, 1H), 6.68 (s, 1H), 6.62 (bs, 2H), 4.00 (dd, $J = 4.9, 12.4\text{Hz}$, 1H), 3.78 (s, 3H), 2.9 (m, 2H), 2.78 (tdd, $J = 2.3, 5.2, 11.3\text{Hz}$, 1H), 2.37 (s, 6H), 2.28 (m, 1H), 1.61 (dd, $J = 12.1, 24.0\text{Hz}$, 1H).

Example 15: Synthesis of 1-(3,4-dichlorophenyl)-N-methyl-1,2,3,4-tetrahydronaphthalen-2-amine (36a-d)



15.1. Synthesis of 1-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-2(1H)-one (35)



[0222] To a stirring solution of β -tetralone (34) (1.00g, 6.84mmol) and $\text{Pd}(\text{dba})_2$ (39mg, 1mol%) in toluene was added $t\text{-Bu}_3\text{P}$ (228uL, 10 wt% in hexanes, 1.1%). The solution was chilled (dry-ice bath) before adding LiHMDS (7.5mL, 1M in hexanes, 1.1 eq) followed by 1-bromo-3,4-dichlorobenzene (1 mL, 1.1eq). The solution was then allowed to warm to ambient temperature and heated under microwave radiation for 5 minutes (maximum temperature 140°C). After cooling, the reaction was quenched with aqueous ammonium chloride and extracted with MTBE. The organic layer was dried with sodium sulfate, filtered through celite, and evaporated. The crude oil was separated on silic gel to give the title compound (1.45g, 73%) as a slight brown oil. This material was assayed as 90% pure. TLC R_f (25% EA/Hex) = 0.42. GCMS R_t = 13.21min m/z = 290 (M⁺). ¹H NMR (CDCl₃, δ): 7.37 (d, J = 8.3Hz, 1H), 7.3-7.2 (m, 3H), 7.17 (d, J = 2.1Hz, 1H), 6.9 (m, 2H), 4.68 (s, 1H), 3.1 (m, 2H), 2.7 (m, 2H). ¹³C NMR (CDCl₃, δ): 208.4, 137.7, 136.7, 135.3, 132.7, 131.5, 130.7, 130.5, 129.2, 128.2, 128.1, 127.7, 127.3, 58.6, 37.1, 28.0.

15.2. Synthesis of 1-(3,4-dichlorophenyl)-N-methyl-1,2,3,4-tetrahydronaphthalen-2-amine (36a-d)

[0223] To a solution of tetralone **35** (400mg, 1.374mmol) in THF (10mL) and methanol (15mL) was added methylamine hydrochloride (1.12g, 10eq). The resultant mixture was stirred at 50°C. After dissolution (10 min), sodium cyanoborohydride (6.9mL, 1M in THF, 5eq) was added in a single portion. After 20 hours, the organic layer was evaporated, filtered through silica and an aminopropyl cartridge. The crude oil was then diluted with sodium bicarbonate solution and extracted with MTBE to give the amine (280mg, 66%) as a mixture of four stereoisomers (1:1:1:1).

[0224] These amines were separated using a Chiracel OD (98:2:0.1 Hex/IPA/DEA) column to give three fractions. The first was pure E1; the second was a mixture of E2 and E3; and the third was pure E4. The mixture was further separated using a Chiracel OD (2:3:95:0.1 MeOH/EtOH/Hex/DEA) column. The order of elution of the middle fractions changes between these columns and was defined based on the OD 98:2:0.1 conditions. Retention times are summarized in Table 6, below.

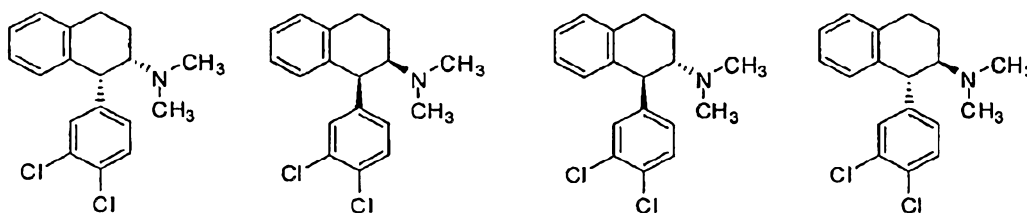
Table 6: Retention times for each isomer [min]

	36c	36a	36d	36b
	E1	E2	E3	E4
	<i>Trans</i>	<i>Cis</i>	<i>Trans</i>	<i>Cis</i>
HPLC R _t (Chiracel OD, 98:2:0.1 Hex/IPA/DEA)	6.0	6.7	7.9	13.7
HPLC R _t (Chiracel OD, 2:3:95:0.1 MeOH/EtOH/Hex/DEA)	5.5	6.2	7.0	10.5

[0225] *Cis*-enantiomers **36a** (E2) and **36b** (E4): LCMS R_t = 8.83 min m/z = 306 (M+1). ¹H NMR (CDCl₃, δ): 7.31 (d, J = 8.3Hz, 1H), 7.2-7.1 (m, 3H), 7.1-7.0 (m, 1H), 6.9 (m, 2H), 4.32 (d, J = 5.1Hz, 1H), 3.1-2.8 (m, 3H), 2.50 (s, 3H), 1.9 (m, 1H), 1.6 (m, 1H). ¹³C NMR (CDCl₃, δ): 142.5, 137.4, 136.4, 132.0, 131.9, 130.5, 129.7, 129.6, 128.8, 126.7, 126.0, 58.5, 48.3, 33.9, 28.1, 23.7.

[0226] *Trans*-enantiomers **36c** (E1) and **36d** (E3): LCMS $R_t = 9.12$ min $m/z = 306$ (M+1). ^1H NMR (CDCl_3 , δ): 7.37 (d, $J = 8.2\text{Hz}$, 1H), 7.2 (m, 1H), 7.1 (m, 1H), 7.0 (m, 1H), 6.97 (dd, $J = 2.0, 8.2\text{Hz}$, 1H), 6.69 (d, $J = 7.8\text{Hz}$, 1H), 3.91 (d, $J = 7.7\text{Hz}$, 1H), 2.94 (t, $J = 6.5\text{Hz}$, 2H), 7.51 (td, $J = 1.4, 7.5\text{Hz}$, 1H), 2.42 (s, 3H), 2.2 (m, 1H), 1/7 (m, 1H). ^{13}C NMR (CDCl_3 , δ): 145.1, 137.0, 136.4, 132.5, 131.4, 131.4, 130.8, 130.0, 129.9, 128.4, 126.7, 126.0, 62.3, 51.4, 33.7, 27.1, 25.5.

Example 16: Synthesis of 1-(3,4-dichlorophenyl)-N,N-dimethyl-1,2,3,4-tetrahydronaphthalen-2-amine (37a-d)



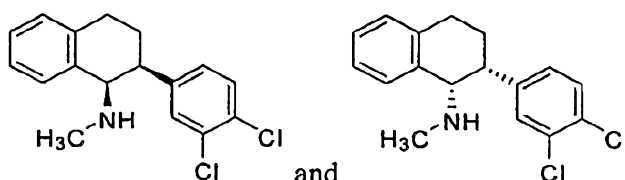
[0227] A stirring solution of the respective methylamine **36** (e.g., 20-25mg) in formic acid (e.g., 1mL) and formaldehyde (e.g., 1mL) was stirred at 100°C for three hours. After chilling on ice, the solution was quenched with saturated aqueous sodium hydroxide (2mL) and extracted with MTBE. The solvent was removed and the residue was filtered through an aminopropyl cartridge to give the desired dimethylamine as a clear oil.

[0228] *Cis*-enantiomers **37a** and **37b**: LCMS $R_t = 11.3$ min $m/z = 320$ (M+1). ^1H NMR (CDCl_3 , δ): 7.26 (d, $J = 8.3\text{Hz}$, 1H), 7.2-7.1 (m, 3H), 7.1-7.0 (m, 1H), 6.9 (m, 2H), 4.34 (d, $J = 4.9\text{Hz}$, 1H), 3.08 (dd, $J = 6.4, 17.4\text{Hz}$, 1H), 2.9 (m, 1H), 2.78 (ddd, $J = 3.0, 5.0, 12.8\text{Hz}$, 1H), 2.19 (s, 3H), 1.95 (m, 1H), 1.71 (ddd, $J = 6.5, 12.9, 24.7\text{Hz}$, 1H). ^{13}C NMR (CDCl_3 , δ): 143.7, 138.4, 135.9, 132.3, 131.4, 130.5, 130.0, 129.9, 129.2, 128.7, 126.6, 126.0, 64.8, 47.7, 43.1, 29.2, 19.6.

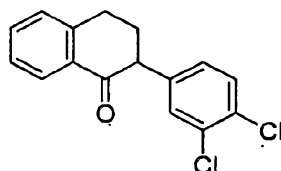
[0229] *Trans*-enantiomers **37c** and **37d**: LCMS $R_t = 11.3$ min $m/z = 320$ (M+1). ^1H NMR (CDCl_3 , δ): 7.32 (d, $J = 8.2\text{Hz}$, 1H), 7.17 (d, $J = 2.0\text{Hz}$, 1H), 7.1 (m, 2H), 7.0 (m, 1H), 6.91 (dd, $J = 2.1, 8.3\text{Hz}$, 1H), 6.72 (d, $J = 7.8\text{Hz}$, 1H), 4.12 (d, $J = 8.3\text{Hz}$, 1H), 2.97 (dt, $J = 5.4, 16.7\text{Hz}$, 1H), 2.9 (m, 1H), 2.75 (td, $J = 2.3, 9.0\text{Hz}$, 1H), 2.29 (s, 3H), 2.0 (m, 1H), 1.7 (m, 1H). ^{13}C NMR (CDCl_3 , δ): 146.6, 137.9,

136.9, 132.0, 131.0, 130.4, 130.0, 129.9, 128.6, 126.2, 126.0, 67.3, 48.2, 41.4, 28.4, 20.5.

Example 17: Synthesis of 2-(3,4-dichlorophenyl)-N-methyl-1,2,3,4-tetrahydronaphthalen-1-amine (40a, 40b)



17.1. Synthesis of 2-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-1(2H)-one (39)



[0230] To a stirring solution of α -tetralone **38** (1.00g, 6.84mmol) and $\text{Pd}(\text{dba})_2$ (39mg, 1mol%) in toluene was added $t\text{-Bu}_3\text{P}$ (228 μL , 10 wt% in hexanes, 1.1%). The solution was chilled (dry-ice bath) before adding LiHMDS (7.5mL, 1M in hexanes, 1.1 eq) followed by 1-bromo-3,4-dichlorobenzene (1 mL, 1.1eq). The solution was then allowed to warm to ambient temperature and heated under microwave radiation for 5 minutes (maximum temperature 140°C). After cooling, the reaction was quenched with aqueous ammonium chloride and extracted with MTBE. The organic layer was dried with sodium sulfate, filtered through celite, and evaporated. The crude oil was separated on silic gel to give the title compound (1.46g, 73%) as a white solid. TLC R_f (25% EA/Hex) = 0.26. GCMS R_t = 13.82 min m/z = 290 (M+). ^1H NMR (CDCl_3 , δ): 8.06 (dd, J = 1.1, 7.8Hz, 1H), 7.51 (td, J = 1.4, 7.5Hz, 1H), 7.40 (d, J = 8.3Hz, 1H), 7.33 (m, 2H), 7.29 (d, J = 1.8Hz, 1H), 7.03 (dd, J = 2.1, 8.3Hz, 1H), 3.7 (m, 1H), 3.2-3.0 (m, 2H), 2.4 (m, 2H). ^{13}C NMR (CDCl_3 , δ): 196.9, 143.7, 139.8, 133.7, 132.4, 132.3, 130.9, 130.5, 130.3, 128.8, 128.0, 127.8, 126.9, 53.6, 30.9, 28.9.

17.2. Synthesis of 2-(3,4-dichlorophenyl)-N-methyl-1,2,3,4-tetrahydronaphthalen-1-amine (40a, 40b)

[0231] To a solution of tetralone **39** (1.00g, 3.43mmol) in THF (25mL) and methanol (40mL) was added methylamine hydrochloride (2.4g, 10eq). The resultant mixture was stirred at 50°C. After dissolution (10 min), sodium borohydride (2.0g, 15eq) was added in 4 portions over 2 days. After cooling, the mixture was diluted with 5% NaOH and stirred for 1 hour. After evaporation, the crude residue was partitioned between MTBE and water and brine. The organic layer was evaporated to give the crude amine as a mixture of starting material, alcohol, and amine. The amine was purified by reverse-phase HPLC to give the title compound (0.33g, 31%).

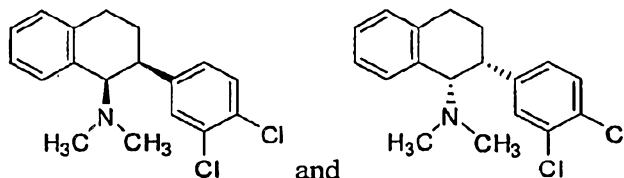
[0232] The enantiomers were separated using a Chiracel OD (98:2:0.1 Hex/IPA/DEA) column. Retention times for each isomer are summarized in Table 7, below.

Table 7: Retention times for both *cis*-enantiomers [min]

	40a	40b
	E1	E2
	<i>Cis</i>	<i>Cis</i>
HPLC R _t (Chiracel OD, 98:2:0.1 Hex/IPA/DEA)	4.3	5.6

[0233] *Cis*-enantiomers **40a** (E1) and **40b** (E2): LCMS R_t = min m/z = 306 (M+1). ¹H NMR (CDCl₃, δ): 7.4 (m, 2H), 7.2 (m, 5H), 3.65 (d, J = 3.5Hz, 1H), 3.11 (dt, J = 3.3, 12.2Hz, 1H), 3.03 (ddd, J = 2.3, 6.4, 17.3Hz, 1H), 2.40 (ddd, J = 6.5, 12.4, 23.8Hz, 1H), 2.18 (s, 3H), 1.95 (sep, J = 3.2Hz, 1H), 0.92 (bs, 1H). ¹³C NMR (CDCl₃, δ): 144.2, 138.5, 135.9, 132.2, 130.2, 130.0, 129.4, 129.2, 127.5, 127.3, 125.4, 114.8, 62.7, 44.0, 36.0, 28.7, 22.6.

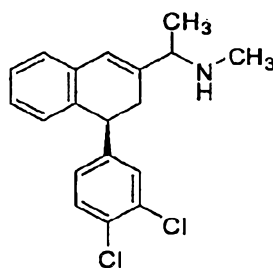
Example 18: Synthesis of *cis*-2-(3,4-dichlorophenyl)-N,N-dimethyl-1,2,3,4-tetrahydronaphthalen-1-amine (41)



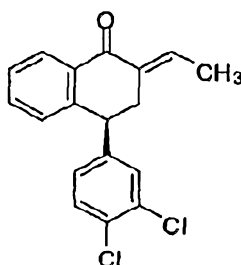
[0234] A solution of the respective methylamine 40 (e.g., 20-25mg) in formic acid (e.g., 1mL) and formaldehyde (e.g., 1mL) was stirred at 100°C for three hours. After chilling on ice, the solution was quenched with saturated aqueous sodium hydroxide (2mL) and extracted with MTBE. The solvent was removed and the residue was filtered through an aminopropyl cartridge to give the desired dimethylamine as a clear oil.

[0235] *Cis*-enantiomers 41a and 41b: LCMS $R_t = 10.33$ min $m/z = 320$ (M+1). ^1H NMR (CDCl_3 , δ): 7.4 (m, 2H), 7.2 (m, 5H), 3.8 (m, 1H), 3.0 (m, 3H), 2.4 (m, 1H), 1.97 (s, 6H), 1.9 (m, 1H). ^{13}C NMR (CDCl_3 , δ): 145.1, 136.4, 136.3, 131.5, 130.5, 130.4, 129.6, 129.5, 129.1, 128.0, 127.1, 125.0, 66.5, 45.9, 45.8, 29.0, 22.6.

Example 19: Synthesis of 1-((S)-4-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-2-yl)-N-methylethanamine (47)

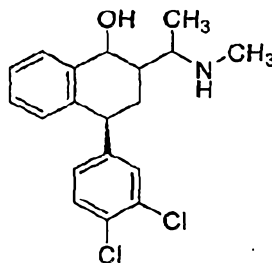


19.1. Synthesis of (S,E)-4-(3,4-dichlorophenyl)-2-ethylidene-3,4-dihydronaphthalen-1(2H)-one (42)



[0236] To a solution of (S)-4-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-1(2H)-one **1** (3.0 g, 10.3 mmol) in THF (50 mL) at -78°C was added LiHMDS (1.0 M, 12.4 mL, 12.4 mmol). The reaction mixture was stirred for 20 min before acetaldehyde (0.55 g, 0.70 mL, 12.41 mmol) was added. The reaction mixture was stirred and warmed to 0°C over 2 h before being quenched with a saturated solution of NH_4Cl (10 mL). The product was extracted with ethyl acetate, dried and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/hexane=1:7 to 1:5) to give (S,E)-4-(3,4-dichlorophenyl)-2-ethylidene-3,4-dihydronaphthalen-1(2H)-one **42** (2.9 g, 88%).

19.2. Synthesis of (4S)-4-(3,4-dichlorophenyl)-2-(1-(methylamino)ethyl)-1,2,3,4-tetrahydronaphthalen-1-ol (44)



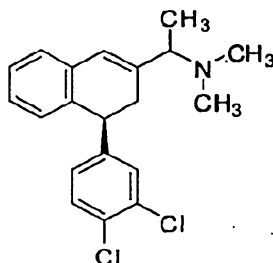
[0237] To a solution of **42** (0.80 g, 2.52 mmol) in THF (10 mL) at ambient temperature was added methylamine solution (2.0 M in THF, 3.78 mL, 7.56 mmol). The reaction mixture was stirred for 4 h before NaBH_4 (0.44 g, 11.49) was added. The reaction mixture was stirred for 3 h before being quenched by a saturated solution of NH_4Cl (10 mL). The product was extracted with diethyl ether, dried and concentrated. The residue was purified by silica gel column

chromatography (ethyl acetate/hexane/0.1% DEA=1:7 to 1:5) to give (4S)-4-(3,4-dichlorophenyl)-2-(1-(methylamino)ethyl)-1,2,3,4-tetrahydronaphthalen-1-ol (**44**) (493 mg, 56%).

19.3. Synthesis of 1-((S)-4-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-2-yl)-N-methylethanamine (47**)**

[0238] To a solution of **44** (480 mg, 1.37 mmol) in CH_2Cl_2 (5 mL) was added TFA (5 mL). The reaction mixture was stirred for 2 h before being concentrated. The residue was subjected to chiral AD column chromatography (ethanol/MeOH/hexane/DEA=3:2:93:0.1) to give **47** as a single diastereomer. The absolute stereochemistry for the stereocenter in the side chain of **47** was not determined. A second stereoisomer was formed, but could not be isolated in pure form. ^1H NMR (400 MHz, CDCl_3) δ 7.32 (d, $J=8.0$ Hz, 1 H), 7.25 (d, $J=2.4$ Hz, 1 H), 7.19 (d, $J=7.2$ Hz, 1 H), 7.15-7.07 (m, 2 H), 6.94 (dd, $J=2.4, 8.4$ Hz, 1H), 6.82 (d, $J=7.2$ Hz, 1 H), 6.47 (s, 1 H), 4.01 (t, $J=8.4$ Hz, 1 H), 3.64 (q, $J=6.4$ Hz, 1 H), 2.71 (dd, $J=7.6, 16.8$ Hz, 1 H), 2.48 (dd, $J=8.0, 16.8$ Hz, 1 H), 2.09 (broad, 2 H), 1.16 (d, $J=8.0$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.95, 143.12, 136.21, 134.01, 132.87, 130.42, 130.21, 128.02, 127.60, 127.62, 127.44, 126.78, 121.12, 52.47, 43.21, 32.58, 20.98; ESI MS m/z 318.0.

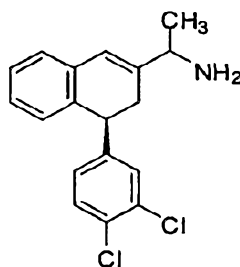
Example 20: Synthesis of 1-((S)-4-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-2-yl)-N,N-dimethylethanamine (48**)**



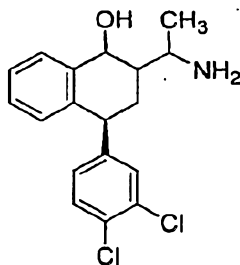
[0239] To a solution of **47** (200 mg, 0.60 mmol) in MeOH (5 mL) was added HCHO (35 mg, 37%, 1.20 ml), HCO_2H (0.3 mL) and $\text{NaB}(\text{CN})\text{H}_3$ (75 mg, 1.20 mmol). The reaction mixture was stirred for 20 min before being concentrated. The residue was dissolved in MeOH (2 mL) and subjected to reverse phase column chromatography ($\text{CH}_3\text{CN}/\text{H}_2\text{O}/0.1\%$ formic acid=5% to 100%) to give **48**

(188 mg, 91%). ^1H NMR (400 MHz, CDCl_3) δ 7.34 (d, $J=8.4$ Hz, 1 H), 7.25 (m, 2 H), 7.20 (m, 2 H) 7.12 (m, 2 H), 7.0 (dd, $J=2.0$, 8.4 Hz, 1 H), 6.83 (d, $J=7.6$ Hz, 1 H), 6.40 (s, 1 H), 4.10 (t, $J=8.4$ Hz, 1 H), 2.65 (d, t, $J=6.4$, 13.2 Hz, 1 H), 2.65 (dd, $J=6.8$, 16.4 Hz, 1 H), 2.54 (dd, $J=9.2$, 16.4 Hz, 1 H), 2.21 (s, 6 H), 1.01 (d, $J=6.8$ Hz, 1 H); ^{13}C NMR (100m Hz, CDCl_3) δ 144.87, 142.04, 136.44, 134.67, 132.42, 130.61, 130.45, 128.16, 127.78, 127.53, 177.43, 126.61, 124.19, 124.12, 67.03, 43.72, 43.83, 43.50, 32.36, 16.45; ESI MS m/z 346.1

Example 21: Synthesis of 1-((S)-4-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-2-yl)ethanamine (45)



21.1. Synthesis of (4S)-2-(1-aminoethyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-ol (43)



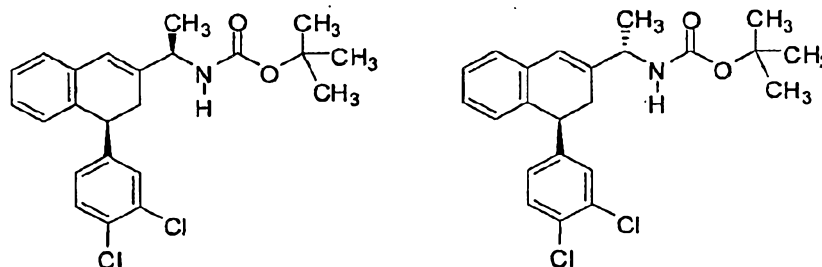
[0240] To a solution of (*S,E*)-4-(3,4-dichlorophenyl)-2-ethylidene-3,4-dihydronaphthalen-1(2H)-one (**42**) (0.60 g, 1.89 mmol) in THF (8 mL) at ambient temperature was added ammonia solution (2.0 M in MeOH, 2.83 mL, 5.67 mmol). The reaction mixture was stirred for 4 h before NaBH_4 (0.14 g, 3.78 mmol) was added. The reaction mixture was stirred for 2 h before being quenched by a saturated solution of NH_4Cl (8 mL). The product was extracted with diethyl ether (30 mL \times 2), dried and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/hexane/0.1% DEA=1:7 to 1:5) to give

(4*S*)-2-(1-aminoethyl)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-ol (**43**) (0.50 g, 50%).

21.2. Synthesis of 1-((*S*)-4-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-2-yl)ethanamine (45**) as a diastereomeric mixture of **45** and **46****

[0241] To a solution of **43** (400 mg, 1.19 mmol) in CH₂Cl₂ (5 mL) was added TFA (5 mL). The reaction mixture was stirred for 2 h before being concentrated. The residue was subjected to reverse phase column chromatography (CH₃CN/H₂O/0.1% Formic acid=5% to 100%) to give 1-((*S*)-4-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-2-yl)ethanamine (0.31 g, 77.5%) as a mixture of two diastereomers (**45** and **46**).

21.3. Synthesis of *tert*-butyl 1-((*S*)-4-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-2-yl)ethylcarbamate (49a**, **49b**)**



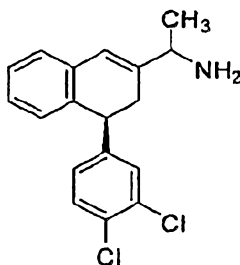
[0242] To a solution of the above mixture of (*R*)- and (*S*)-1-((*S*)-4-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-2-yl)ethanamine (**45**, **46**) (0.3 g, 0.94 mmol) in CH₂Cl₂ (10 mL) was added Et₃N (140 mg, 0.20 mL, 1.42 mmol) and (BOC)₂O (250 mg, 1.13 mmol). The reaction mixture was stirred for 2 h at ambient temperature before being quenched by a saturated NH₄Cl solution (10.0 mL). The product was extracted with CH₂Cl₂ (2 x 15 mL). The combined extracts were washed with saturated brine, dried and concentrated. The resultant residue was purified by silica gel column chromatography (ethyl acetate/hexane=1:5) to give a mixture of *tert*-butyl 1-((*S*)-4-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-2-yl)ethylcarbamate (339 mg, 86%). Diastereomers were separated using a chiral AD column (ethanol/methanol/hexane/DEA=3:2:95:0.1) to give **49a** (fast moving

diastereomer, 160 mg) and **49b** (slow moving diastereomer, 120 mg) of *tert*-butyl-1-((*S*)-4-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-2-yl)ethylcarbamate.

21.4. Synthesis of 1-((*S*)-4-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-2-yl)ethanamine (45**)**

[0243] To a solution of *tert*-butyl-1-((*S*)-4-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-2-yl)ethylcarbamate **49b** (100 mg, 0.24 mmol) in CH₂Cl₂ (5 mL) was added TFA (5 mL). The reaction mixture was stirred for 2 h before being concentrated. The residue was subjected reverse phase column chromatography (CH₃CN/H₂O/0.1% Formic acid=5% to 100%) to give 1-((*S*)-4-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-2-yl)ethanamine **45** (65 mg, 85%). ¹H NMR (400 MHz, CDCl₃) δ 7.33 (d, *J*=8.0 Hz, 1 H), 7.23 (d, *J*=2.4 Hz, 1 H), 7.19 (d, *J*=7.2 Hz, 1 H), 7.14-7.08 (m, 2 H), 6.98 (dd, *J*=2.4, 8.4 Hz, 1 H), 6.82 (d, *J*=7.2 Hz, 1 H), 6.46 (s, 1 H), 4.08 (t, *J*=8.4 Hz, 1 H), 3.61 (q, *J*=6.4 Hz, 1 H), 2.69 (dd, *J*=7.6, 16.8 Hz, 1 H), 2.46 (dd, *J*=8.8, 16.8 Hz, 1 H), 2.10 (broad, 2 H), 1.14 (d, *J*=8.0 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 144.75, 143.04, 136.16, 134.41, 132.52, 130.53, 130.41, 127.96, 127.80, 127.62, 127.52, 126.80, 121.07, 52.17, 43.68, 32.41, 21.53; ESI MS *m/z* 318.0.

Example 22: Synthesis of 1-((*S*)-4-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-2-yl)ethanamine (46**)**

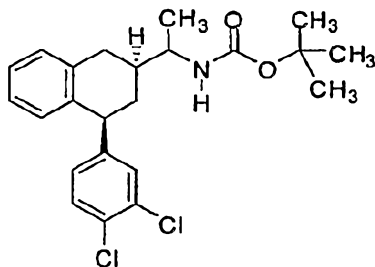


[0244] To a solution of *tert*-butyl-1-((*S*)-4-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-2-yl)ethylcarbamate **49a** (Example 21.3) (100 mg, 0.24 mmol) in CH₂Cl₂ (2 mL) was added TFA (2 mL). The reaction mixture was stirred for 1 h before being concentrated. The residue was subjected to reverse phase column chromatography (CH₃CN/H₂O/0.1% formic acid=5% to 100%) to give **46** (66 mg, 86%). ¹H NMR (400 MHz, CDCl₃) δ 7.34 (d, *J*=8.4 Hz, 1 H), 7.26 (d, *J*=2.0 Hz, 1

H), 7.20 (m, 1 H), 7.16-7.08 (m, 2 H), 7.01 (dd, $J=1.6, 8.0$ Hz, 1 H), 6.80 (d, $J=7.2$ Hz, 1 H), 6.46 (s, 1 H), 4.09 (t, $J=7.6$ Hz, 1 H), 3.59 (q, $J=6.0$ Hz, 1 H), 2.60 (dd, $J=6.8, 16.4$ Hz, 1 H), 2.53 (dd, $J=8.4, 16.4$ Hz, 1 H), 1.38 (broad, 2 H), 1.14 (d, $J=6.8$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.81, 144.36, 136.15, 134.67, 132.51, 130.52, 130.41, 127.98, 127.77, 127.60, 127.34, 126.70, 120.93, 120.90, 51.91, 43.77, 32.86, 22.11; ESI MS m/z 318.0.

Example 23: Synthesis of 1-((2S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)ethanamine (51)

23.1. Synthesis of tert-butyl 1-((2S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)ethylcarbamate (50b)



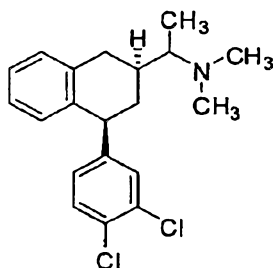
[0245] To a solution of *tert*-butyl 1-((*S*)-4-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-2-yl)ethylcarbamate **49b** (Example 21.3) (60 mg, 0.14 mmol) in ethyl acetate (6 mL) was added palladium on charcoal (30 mg, 5%). The mixture was then stirred under hydrogen (1 atm) for 1 h. The catalyst was removed through a pad of Celite. The filtrate was concentrated. Chiral AD column separation (ethanol/methanol/hexane/DEA=3:2:95:0.1) afforded *tert*-butyl 1-((2*S*,4*S*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)ethylcarbamate (36 mg, 60%).

23.2. Synthesis of 1-((2S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)ethanamine (51)

[0246] To a solution of the above *tert*-butyl 1-((2*S*,4*S*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)ethylcarbamate **50b** (50 mg, 0.12 mmol) in CH_2Cl_2 (3 mL) was added TFA (2 mL). The reaction mixture was stirred for 1 h before being concentrated. The residue was subjected to reverse phase column

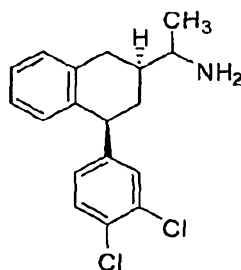
chromatography (CH₃CN/H₂O/0.1% formic acid=5% to 100%) to give **51** (34 mg, 90%). ¹H NMR (400 MHz, CDCl₃) δ 7.36 (d, *J*= 8.0 Hz, 1 H), 7.26 (d, *J*=2.0 Hz, 1 H), 7.12 (m, 2 H), 7.03 (m, 1 H), 7.00 (dd, *J*= 1.6, 8.0 Hz, 1 H), 6.71 (d, *J*=8.0 Hz, 1 H), 4.04 (dd, *J*=5.2, 12.0 Hz, 1 H), 2.92 (m, 2 H), 2.72 (dd, *J*=12.4, 16.0 Hz, 1 H), 2.22 (m, 2 H), 1.85 (m, 1 H), 1.48 (q, *J*=12.0 Hz, 1 H), 1.20 (d, *J*= 6.0 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 147.45, 138.65, 136.88, 132.65, 130.87, 130.69, 130.46, 129.54, 129.43, 128.43, 126.02, 126.26, 77.45, 51.35, 40.70, 41.77, 37.10, 32.94, 20.25; ESI MS *m/z* 320.0.

Example 24: Synthesis of 1-((2*S*,4*S*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)-*N,N*-dimethylethanamine (**53**)

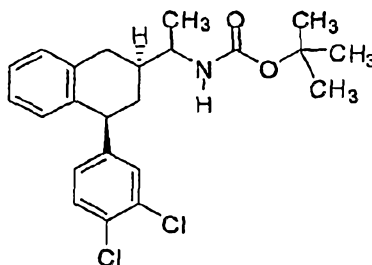


[0247] To a solution of **51** (20 mg, 0.063 mmol) in MeOH (4 mL) was added HCHO (7.5 mg, 37%, 0.25 mmol), HCO₂H (0.10 mL) and NaB(CN)H₃ (19.6 mg, 0.31 mmol). The reaction mixture was stirred for 20 min before being concentrated. The residue was dissolved in MeOH (1 mL) and subjected to reverse phase column chromatography (CH₃CN/H₂O/0.1% formic acid=5% to 100%) to give **53** (18 mg, 85%). ¹H NMR (400 MHz, CDCl₃) δ 7.34 (d, *J*= 8.4 Hz, 1 H), 7.26 (d, *J*=2.0 Hz, 1 H), 7.12 (m, 2 H), 7.04 (m, 1 H), 7.00 (dd, *J*= 2.0, 8.4 Hz, 1 H), 6.73 (d, *J*=7.6 Hz, 1 H), 4.02 (dd, *J*=5.6, 12.4 Hz, 1 H), 2.90 (m, 1 H), 2.45 (m, 1 H), 2.35 (m, 1 H), 2.56 (s, 6 H), 2.0 (m, 1 H), 1.42 (q, *J*=12.0 Hz, 1 H), 1.01 (d, *J*= 6.8 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 147.77, 139.09, 137.36, 132.50, 130.96, 130.55, 130.23, 129.56, 129.49, 128.49, 126.47, 126.18, 64.10, 46.94, 41.30, 38.71, 38.16, 37.74, 9.19; ESI MS *m/z* 348.2.

Example 25: Synthesis of 1-((2S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)ethanamine (52)



25.1. Synthesis of tert-butyl 1-((2S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)ethylcarbamate (50a)



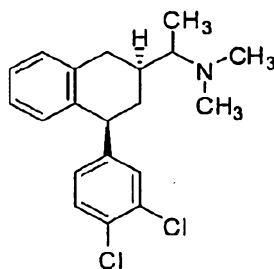
[0248] To a solution of *tert*-butyl (*S*)-1-((*S*)-4-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-2-yl)ethylcarbamate **49a** (Example 21.3) (60 mg, 0.14 mmol) in ethyl acetate (8 mL) was added palladium on charcoal (30 mg, 5%). The mixture was then stirred under hydrogen (1 atm) for 1 h. The catalyst was filtered off through a pad of Celite. The filtrate was concentrated. Chiral AD column separation (ethanol/methanol/hexane/DEA=3:2:95:0.1) afforded *tert*-butyl 1-((2*S*,4*S*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)ethylcarbamate (isomer 2) (40 mg, 67%).

25.2. Synthesis of (*S*)-1-((2*S*,4*S*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)ethanamine (52)

[0249] To a solution of the above *tert*-butyl 1-((2*S*,4*S*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)ethylcarbamate **50a** (40 mg, 0.096 mmol) in CH₂Cl₂ (2 mL) was added TFA (2 mL). The reaction mixture was stirred for 1 h before being concentrated. The residue was subjected reverse phase column chromatography (CH₃CN/H₂O/0.1% Formic acid=5% to 100%) to give **52** (32.7

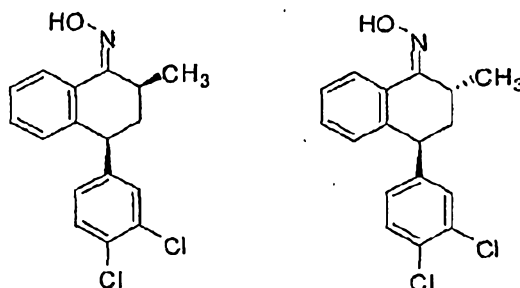
mg, 86%). ^1H NMR (400 MHz, CDCl_3) δ 7.36 (d, $J=8.0$ Hz, 1 H), 7.27 (d, $J=2.0$ Hz, 1 H), 7.15 (m, 2 H), 7.02 (m, 2 H), 6.72 (d, $J=7.6$ Hz, 1 H), 4.04 (dd, $J=5.2$, 12.0 Hz, 1 H), 2.95 (m, 2 H), 2.78 (dd, $J=12.0$, 15.6 Hz, 1 H), 2.13 (m, 1 H), 1.80 (m, 1 H), 1.51 (q, $J=12.4$ Hz, 1 H), 1.35 (broad, 1 H), 1.14 (d, $J=6.4$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.67, 138.79, 137.29, 132.64, 130.88, 130.68, 130.41, 129.57, 129.43, 128.43, 126.58, 126.15, 51.16, 46.91, 42.31, 37.48, 32.60, 21.20; ESI MS m/z 320.1.

Example 26: Synthesis of 1-((2S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)-N,N-dimethylethanamine (54)

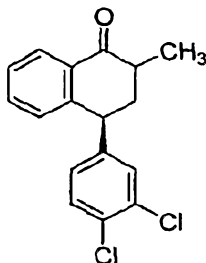


[0250] To a solution of **52** (20 mg, 0.063 mmol) in MeOH (3 mL) was added HCHO (7.5 mg, 37%, 0.25 mmol), HCO_2H (0.20 mL) and $\text{NaB}(\text{CN})\text{H}_3$ (19.6 mg, 0.31 mmol). The reaction mixture was stirred for 10 min before being concentrated. The residue was dissolved in MeOH (1.5 mL) and subjected to reverse phase column chromatography ($\text{CH}_3\text{CN}/\text{H}_2\text{O}/0.1\%$ Formic acid=5% to 100%) to give **54** (17 mg, 86%). ^1H NMR (400 MHz, CDCl_3) δ 7.37 (d, $J=8.4$ Hz, 1 H), 7.27 (d, $J=6.0$ Hz, 1 H), 7.19 (d, $J=7.6$ Hz, 1 H), 7.13 (d, $J=1.2$ Hz, 1 H), 7.02 (m, 2 H), 6.72 (d, $J=7.6$ Hz, 1 H), 4.05 (dd, $J=5.2$, 12.0 Hz, 1 H), 3.12 (m, 1 H), 2.65 (dd, $J=11.6$, 16.4 Hz, 1 H), 2.36 (m, 1 H), 2.18 (m, 1 H), 1.92 (m, 1 H), 1.42 (q, $J=12.4$ Hz, 1 H), 0.97 (d, $J=6.4$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.79, 138.80, 137.82, 132.61, 130.91, 130.67, 129.57, 129.31, 128.43, 127.03, 126.54, 126.06, 63.90, 47.00, 40.96, 38.74, 38.24, 35.11, 8.90; ESI MS m/z 348.2.

Example 27: Synthesis of (4*S,Z*)-4-(3,4-dichlorophenyl)-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one oxime (57 and 58)



27.1. Synthesis of (4*S*)-4-(3,4-dichlorophenyl)-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (55)



[0251] To a solution of (*S*)-4-(3,4-dichlorophenyl)-3,4-dihydronaphthalen-1(2*H*)-one (**1**) (2.0 g, 6.89 mmol) in THF (50 mL) at -78°C was added LiHMDS (1.0 M in THF, 8.27 mL, 8.27 mmol). The reaction mixture was stirred for 20 min at -78°C before MeI (1.17 g, 0.52 mL, 8.27 mmol) was added. The reaction mixture was stirred and warmed to 0°C over 2 h before being quenched by a saturated solution of NH_4Cl (20 mL). The product was extracted with ethyl acetate (100 mL x 2), dried and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/hexane=1:7 to 1:5) to give (*S*)-4-(3,4-dichlorophenyl)-2,2-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (**56**) (0.33 g, 15%) and (4*S*)-4-(3,4-dichlorophenyl)-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (**55**) (1.25 g, 60%).

27.2. Synthesis of (4*S,Z*)-4-(3,4-dichlorophenyl)-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one oxime (57 and 58)

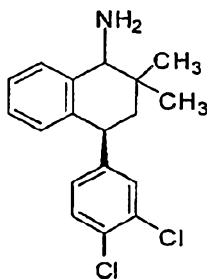
[0252] To a solution of (4*S*)-4-(3,4-dichlorophenyl)-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (**55**) (1.2 g, 3.92 mmol) in CH_2Cl_2 (30 mL) and

MeOH (20 mL) was added $\text{NH}_2\text{OH}\cdot\text{HCl}$ (0.41 g, 5.92 mmol) and Et_3N (1.19 g, 11.84 mmol). The reaction mixture was heated at reflux. After 1 h, H_2O (10 mL) was added and the resultant mixture was heated at reflux for 5 h before being concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/hexane=1:7 to 1:5). Oxime **57**, eluted from the column first (0.51 g, 41%) followed by the oxime **58** (0.49, 39%).

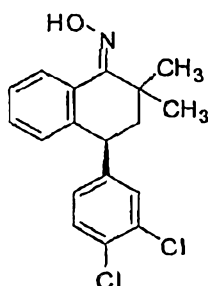
[0253] Isomer **57**: ^1H NMR (400 MHz, CDCl_3) δ 7.75 (dd, $J=1.2, 7.6$ Hz, 1 H), 7.44 (d, $J=8.4$ Hz, 1 H), 7.32 (d, $J=2.0$ Hz, 1 H), 7.26 (m, 2 H), 7.06 (dd, $J=1.6, 8.0$ Hz, 1 H), 6.40 (d, $J=7.6$ Hz, 1 H), 4.10 (dd, $J=7.2, 14.0$ Hz, 1 H), 3.45 (m, 1 H), 2.30 (m, 1 H), 1.75 (m, 1 H), 1.30 (d, $J=6.8$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.59, 143.46, 142.69, 132.96, 131.56, 130.83, 129.61, 128.43, 127.44, 126.81, 125.78, 99.29, 44.01, 38.69, 30.51, 18.43; ESI MS m/z 320.2.

[0254] Isomer **58**: ^1H NMR (400 MHz, CDCl_3) δ 8.49 (s, 1 H), 7.97 (dd, $J=2.0, 6.8$ Hz, 1 H), 7.38 (d, $J=8.0$ Hz, 1 H), 7.30-7.20 (m, 3 H), 6.99 (dd, $J=2.0, 8.4$ Hz, 1 H), 6.80 (d, $J=8.0$ Hz, 1 H), 4.18 (dd, $J=4.4, 11.6$ Hz, 1 H), 3.74 (m, 1 H), 2.13 (d, t, $J=4.8, 13.6$ Hz, 1 H), 1.97 (d, t, $J=4.4, 13.6$ Hz, 1 H), 1.64 (s, 1 H), 1.30 (d, $J=7.2$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.72, 145.87, 140.35, 132.83, 130.99, 130.85, 130.16, 129.74, 129.43, 128.40, 127.31, 124.87, 41.09, 38.51, 26.74, 15.85; ESI MS m/z 320.2.

Example 28: Synthesis of (4S)-4-(3,4-dichlorophenyl)-2,2-dimethyl-1,2,3,4-tetrahydronaphthalen-1-amine (59)



28.1. Synthesis of (*S,Z*)-4-(3,4-dichlorophenyl)-2,2-dimethyl-3,4-dihydronaphthalen-1(2H)-one oxime (60)



[0255] To a solution of (*S*)-4-(3,4-dichlorophenyl)-2,2-dimethyl-3,4-dihydronaphthalen-1(2H)-one (**56**) (0.8 g, 2.51 mmol) in CH₂Cl₂ (20 mL) and MeOH (15 mL)-H₂O (5 mL) was added NH₂OH·HCl (0.35 g, 5.04 mmol) and Et₃N (1.01 g, 10.1 mmol). The resultant mixture was heated at reflux for 5 h before being concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/hexane=1:7 to 1:5) to give (*S,Z*)-4-(3,4-dichlorophenyl)-2,2-dimethyl-3,4-dihydronaphthalen-1(2H)-one oxime (**60**) (0.72 g, 84%).

28.2. Synthesis of (1*R*,4*S*)-4-(3,4-dichlorophenyl)-2,2-dimethyl-1,2,3,4-tetrahydronaphthalen-1-amine (59)

[0256] To a solution of **60** (30 mg, 0.089 mmol) in acetic acid (3 mL) was added palladium on charcoal (30 mg, 5%). The mixture was then stirred under hydrogen (1 atm) for 1 h. The catalyst was filtrated away through a pad of Celite. The filtrate was concentrated. The resultant residue was purified by chiral OJ column (ethanol/methanol/hexane/DEA=3:2:95:0.1) to give **59** (12.5 mg, 44%). ¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, *J*=8.0 Hz, 1 H), 7.44-7.38 (m, 2 H), 7.38-7.24 (m, 2 H), 6.81 (d, *J*=7.6 Hz, 1 H), 7.03 (dd, *J*=1.6, 8.0 Hz, 1 H), 4.28 (dd, *J*=4.4, 12.4 Hz, 1 H), 2.19 (dd, *J*=13.6, 12.4 Hz, 1 H), 2.06 (dd, *J*=13.6, 4.4 Hz, 1 H), 1.58 (s, 1 H), 1.27 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 145.39, 144.92, 133.53, 133.01, 133.68, 131.19, 131.09, 131.01, 129.24, 128.51, 128.31

Example 29: Experimental Conditions for Monoamine Uptake Assays

[0257] The compounds of the invention were tested for their inhibition of functional uptake of 5-HT, NE, or DA, in synaptosomes prepared from rat whole brain, hypothalamus, or corpus striatum, respectively. Compounds were tested initially at 10 μ M in duplicate, and if $\geq 50\%$ inhibition of uptake was observed, they were tested further at 10 different concentrations in duplicate in order to obtain full inhibition curves. IC₅₀ values (concentration inhibiting control activity by 50%) were then determined by nonlinear regression analysis of the inhibition curves and tabulated below.

29.1. Serotonin Functional Uptake Assay for Rat Reuptake Transporter

[0258] Quantification of 5-HT uptake was performed using synaptosomes isolated in a 0.32M sucrose buffer from a male Wistar rat cortex. The uptake of radiolabelled 5-HT by synaptosomes (100 μ g of proteins/point) was allowed by incubating them in a well for 15 min at 37 °C in presence of test compounds and [³H]5-hydroxytryptamine (serotonin; 0.1 μ Ci/point).

[0259] Synaptosomes and [³H]serotonin were prepared in a Krebs buffer pH 7.4 containing 25 mM NaHCO₃, 11 mM glucose and 50 μ M ascorbic acid. This incubation buffer was oxygenated during 5 minutes before incubation. Basal control was incubated for 15 minutes at 4 °C in order to avoid any uptake. Following this incubation the uptake was stopped by filtration through a unifilter 96-wells GFB Packard plate washed with Krebs buffer containing 25 mM NaHCO₃ in order to eliminate the free [³H]serotonin. The radioactivity associated to the synaptosomes retained on the unifilter corresponding to the uptake was then measured with a microplate scintillation counter (Topcount, Packard) using a scintillation fluid. Nonspecific binding was measured in the presence of an excess of cold, unlabeled ligand. Specific binding was obtained by subtracting nonspecific binding from total binding.

[0260] The reference compound was imipramine tested at 10 concentrations ranging from 10⁻¹¹ M to 10⁻⁵ M in order to obtain an IC₅₀ value. See, Perovics and

Müller, "Pharmacological profile of hypericum extract: effect on serotonin uptake by postsynaptic receptors," *Arzeim. Forsch./Drug Res.*, 45:1145-1148 (1995).

29.2. Serotonin Functional Uptake Assay for Human Reuptake Transporter

[0261] Inhibition of human serotonin reuptake transporter was assayed using the recombinant human serotonin transporter expressed in HEK-293 cells using a published method (Gu H, Wall S, Rudnick G. Stable expression of biogenic amine transporters reveals differences in inhibitor sensitivity, kinetics, and ion dependence. *J Biol Chem.* 269 (10): 7124–7130, 1994)). HEK-293 cells expressing human serotonin transporter were plated before the assay. Test compound and/or vehicle was preincubated with cells in modified HEPES buffer pH 7.1 or pH 7.4 for 20 minutes at 18 to 25°C and 65 nM [³H]serotonin was then added for an additional timed incubation period (ten to thirty minutes). Cells with internalized [³H]serotonin were washed and the amount of tritium taken into cells is counted using a liquid scintillation counter to determine [³H]serotonin uptake. Non-specific binding of tritium was measured in a control reaction containing 10 µM fluoxetine, and was subtracted from the counts for assays to correct for non-specific binding of tritium. Reduction of [³H]serotonin uptake by 50 percent or more (≥50%) relative to an uninhibited control reaction indicates significant inhibitory activity. Compounds were screened at 10, 1, 0.1, 0.01 and 0.001 µM. The reference compound for the assay was fluoxetine, for which the IC₅₀ value of 7.1 nM was obtained in a typical experiment.

29.3. Dopamine Functional Uptake Assay for Rat Reuptake Transporter

[0262] Quantification of dopamine uptake was performed using synaptosomes isolated in a 0.32 M sucrose buffer from a male Wistar rat striatum. The uptake of radiolabelled dopamine by synaptosomes (20 µg of proteins/point) was allowed by incubating them for 15 minutes at 37 °C in the presence of test compounds and [³H]-dopamine (0.1 µCi/point). The experiment was performed in a deep well.

[0263] Synaptosomes and [³H]-dopamine were prepared in a Krebs buffer pH 7.4 containing 25 mM NaHCO₃, 11 mM glucose and 50 µM ascorbic acid. This

incubation buffer was oxygenated for 5 minutes before incubation. Basal control was incubated for 15 minutes at 4 °C in order to avoid any uptake. Following this incubation, the uptake was stopped by filtration through a unifilter 96-wells GFB Packard plate washed with Krebs buffer containing 25 mM NaHCO₃ in order to eliminate free [³H]-dopamine. The radioactivity associated to the synaptosomes retained onto the unifilter corresponding to the uptake was then measured with a microplate scintillation counter (Topcount, Packard) using a scintillation fluid.

[0264] The reference compound was GRB12909 tested at 8 concentrations ranging from 10⁻¹¹ M to 10⁻⁶ M in order to obtain an IC₅₀ value. See, Jankowsky et al., "Characterization of sodium-dependent [³H]GBR-12935 binding in brain: a radioligand for selective labeling of the dopamine transport complex," *J. Neurochem*, 46:1272-1276 (1986).

29.4. Dopamine Functional Uptake Assay for Human Reuptake Transporter

[0265] Inhibition of human dopamine reuptake transporter was assayed using the recombinant human dopamine transporter expressed in CHO-K1 or HEK293 cells using a published method (Pristupa, Z.B., Wilson, J.M., Hoffman, B.J., Kish, S.J. and Niznik, H.B. Pharmacological heterogeneity of the cloned and native human dopamine transporter: disassociation of [³H]GBR12,935 binding. *Mol. Pharmacol.* 45: 125-135, 1994). Either CHO-K1 or HEK293 cells expressing human recombinant dopamine transporter were plated before the assay. Test compound and/or vehicle was preincubated with cells in modified HEPES buffer pH 7.1 or pH 7.4 for 20 minutes at 18 to 25°C and 50 nM [³H]dopamine was then added for an additional timed incubation period (10 to 30 minutes). After washing the cells to remove [³H]dopamine not internalized, the cells were lysed, and the amount of tritium in the lysate was measured using a liquid scintillation counter to determine [³H]dopamine uptake. Non-specific binding of tritium was measured in a control reaction containing 10 µM nomifensine, and was subtracted from the counts for assays to correct for non-specific binding of tritium. Reduction of [³H]dopamine uptake by 50 percent or more (≥50%) relative to an uninhibited control reaction indicates significant inhibitory activity. Compounds

were screened at 10, 1, 0.1, 0.01 and 0.001 μ M. The reference compound for the assay was nomifensine, for which the IC_{50} value of 11 nM was obtained in a typical experiment.

29.5. Norepinephrine Functional Uptake Assay For Rat Reuptake Transporter

[0266] Quantification of norepinephrine uptake was performed using synaptosomes isolated in a 0.32 M sucrose buffer from a male Wistar rat hypothalamus. The uptake of radiolabelled norepinephrine by synaptosomes (100 μ g of proteins/point) was allowed by incubating them for 20 minutes at 37 °C in presence of test compounds and [3 H]-norepinephrine (0.1 μ Ci/point). The experiment was performed in a deep well.

[0267] Synaptosomes and [3 H]-norepinephrine were prepared in a Krebs buffer pH 7.4 containing 25 mM $NaHCO_3$, 11 mM glucose and 50 μ M ascorbic acid. This incubation buffer was oxygenated for 5 minutes before incubation. Basal control was incubated for 20 minutes at 4 °C in order to avoid any uptake. Following this incubation, the uptake was stopped by filtration through a unifilter 96-wells GFB Packard plate washed with Krebs buffer containing 25 mM $NaHCO_3$ in order to eliminate the free [3 H]-norepinephrine. The radioactivity associated to the synaptosomes retained onto the unifilter corresponding to the uptake was then measured with a microplate scintillation counter (Topcount, Packard) using a scintillation fluid.

[0268] The reference compound is protriptyline tested at 13 concentrations ranging from 10^{-11} M to 10^{-5} M in order to obtain an IC_{50} value. See, Perovics and Muller, "Pharmacological profile of hypericum extract: effect on serotonin uptake by postsynaptic receptors," *Arzeim. Forsch./Drug Res.*, 45:1145-1148 (1995).

29.6. Norepinephrine Functional Uptake Assay for Human Reuptake Transporter

[0269] Inhibition of human norepinephrine reuptake transporter was assayed using the recombinant human norepinephrine transporter expressed in either HEK293 or MDCK cells using a published method (Galli A, DeFelice LJ, Duke

BJ, Moore KR, Blakely RD. Sodium dependent norepinephrine-induced currents in norepinephrine-transporter-transfected HEK-293 cells blocked by cocaine and antidepressants. *J. Exp. Biol.* 198: 2197-2212, 1995). The cells were plated before the assay. Test compound and/or vehicle was preincubated with cells in modified HEPES buffer pH 7.1 or pH 7.4 for 20 minutes at 18 to 25°C. Following the preincubation, 25 nM [³H]norepinephrine was added for an additional timed incubation period (10 to 20 minutes). After the cells were washed to remove [³H]norepinephrine not internalized, the cells were lysed, and the amount of tritium in the cell lysate was measured using a liquid scintillation counter to determine [³H]norepinephrine uptake. Non-specific binding of tritium was measured in a control reaction containing 10 μM imipramine (or 10 μM nisoxetine), and was subtracted from the counts for assays to correct for non-specific binding of tritium. Reduction of [³H]norepinephrine uptake by 50 percent or more (≥50%) relative to an uninhibited control reaction indicates significant inhibitory activity. Compounds were screened at 10, 1, 0.1, 0.01 and 0.001 μM. The reference compounds for the assay were desipramine and nisoxetine, for which IC₅₀ values of 1.9 nM and 5.3 nM respectively were obtained in typical experiments.

29.7. Results

[0270] The results for the monoamine uptake assays are summarized in Table 6, below:

Table 6: *In vitro* Results for Monoamine Uptake Assays

Compound No.	Human IC ₅₀ (nM)		
	SERT	NET	DAT
6a	46	124	350
6b	1830	731	408
6c	84	855	894
6d	108	174	175
7a	6	27	114
7b	125	117	62
7c	8	45	281
7d	107	73	72
8a	7	167	454
8b	108	174	176
8c	3	164	273
8d	20	98	319
14a	2	28	11
14b	19	257	111
14c	1	92	45
14d	61	371	92
15a	9	72	125
15b	54	126	103
15c	23	210	111
15d	16	372	484

Compound No.	Human IC ₅₀ (nM)		
	SERT	NET	DAT
16a mixture of cis-enantiomers	311	565	332
16b mixture of trans-enantiomers	970	309	339
23a	117	710	371
23b	1300	48	67
23c	2360	36	21
23d	48	65	48
25a	1	26	32
25b	79	158	50
32a.1	162	1210	1080
32a.2	130	467	415
32a.3	4380	1050	1500
32a.4	958	786	1680
32b.1	359	2328	83
32b.2	307	2315	496
32c.1	68	571	18
32c.2	29	112	109
32c.3	105	198	92
32c.4	209	111	78
33a.1	475	2310	781
33a.2	156	2260	396
33a.3	207	1170	2290
33a.4	808	1700	1410
33c.1	24	943	194

Compound No.	Human IC ₅₀ (nM)		
	SERT	NET	DAT
33c.2	8	684	67
33c.3	616	906	83
33c.4	92	1899	224
36a	1090	3454	511
36b	2521	7087	1603
36c	26	745	88
36d	868	1615	204
37a	355	2379	235
37b	742	499	106
37c	70	1186	284
37d	3153	1005	36
40a	2468	>10,000	3407
40b	7725	>10,000	1792
41a	3165	>10,000	2276
41b	9737	>10,000	1124
45	876	53	174
46	50	580	1660
47	44	1180	1140
48	134	2720	2440
51	2	12	30
52	8	122	622
53	58	399	495
54	815	1700	1900

Compound No.	Human IC ₅₀ (nM)		
	SERT	NET	DAT
57	3180	3890	997
58	1700	2840	436
59	5502	>10000	1083

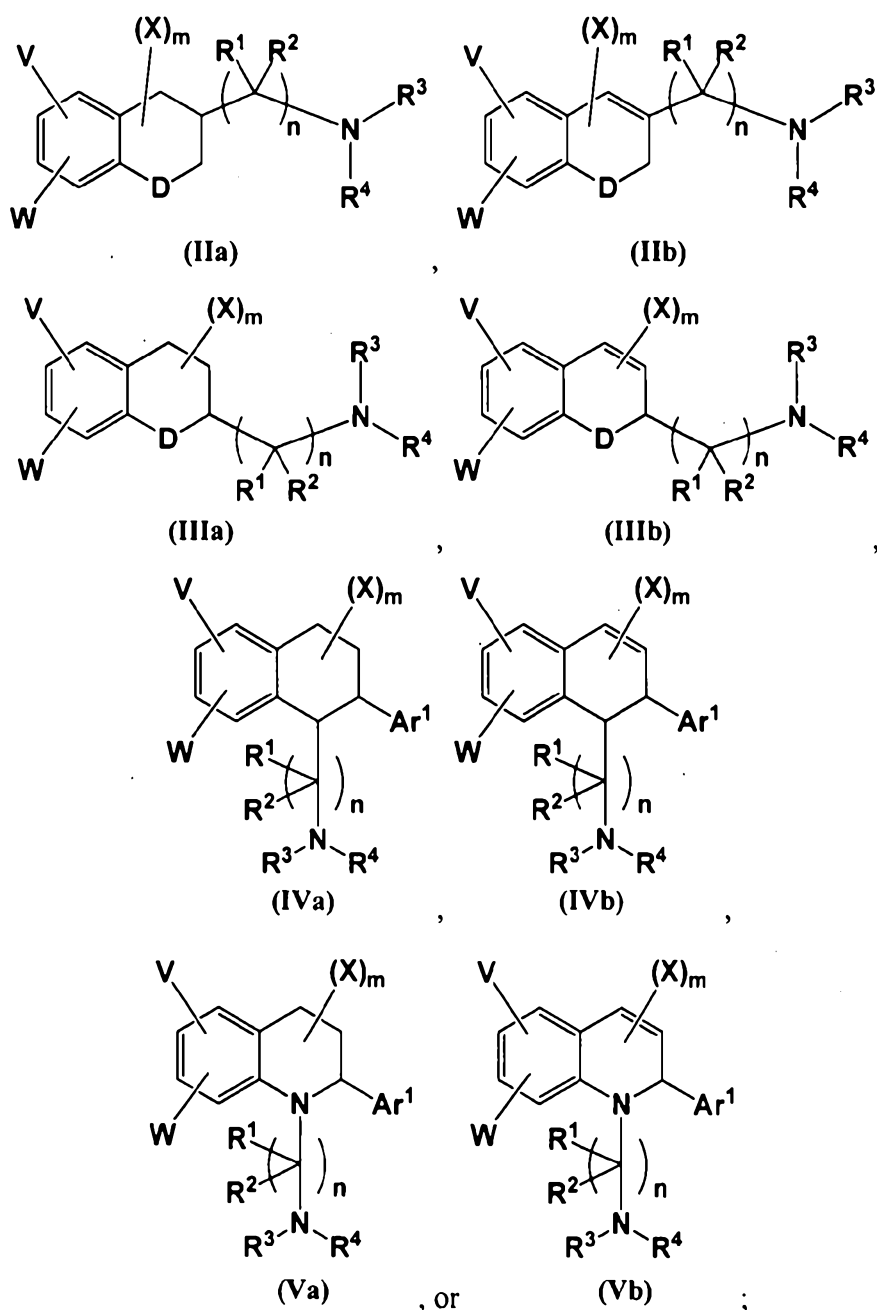
[0271] In Table 6, compound numbers correspond to those used in the Schemes and Examples above. In addition, the following abbreviations have been used in Table I: SERT, serotonin transporter; NET, norepinephrine transporter; and DAT, dopamine transporter.

[0272] These results indicate that compounds of the invention exhibit potent inhibition on the neuronal uptake of NE, DA, and/or 5-HT, and compare favorably with potencies seen for various existing therapeutic agents. For example, reported potencies (IC₅₀ or K_i values) of approved and launched drugs include: fluoxetine (PROZAC®), 7 nM for inhibition of human 5-HT reuptake transporter; methylphenidate (RITALIN®), 193 nM and 38 nM for inhibition of human dopamine and norepinephrine reuptake transporters respectively; amitriptyline (ELAVIL®), 13 and 3 nM for inhibition of the human norepinephrine and serotonin reuptake transporters respectively, and venlafaxine (EFFEXOR®), a so-called serotonin norepinephrine reuptake inhibitor, or SNRI) 145 and 1420 nM, for inhibition of the human serotonin, and norepinephrine reuptake transporters respectively. The multiple inhibition of the neuronal uptake of NE, DA and/or 5-HT displayed by the compounds of the invention provides the clinician with the ability to more effectively treat CNS disorders, including without limitation affective disorders, cerebral function disorders, anxiety disorders, neuropathic pain, and migraine or migraine headache, by elevating various monoamine levels in the brain simultaneously and over the same dose-range without the need to titrate separate drugs.

[0273] The present invention is not to be limited in scope by the specific embodiments disclosed in the examples which are intended as illustrations of a few aspects of the invention and any embodiments that are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art and are intended to fall within the scope of the appended claims.

The claims defining the invention are as follows:

1. A compound having a structure of Formula (IIa), Formula (IIb), Formula (IIIa), Formula (IIIb), Formula (IVa), Formula (IVb), Formula (Va), or Formula (Vb), or a pharmaceutically acceptable salt or solvate thereof:



wherein

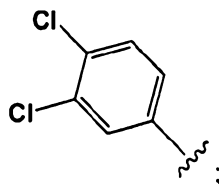
n is an integer selected from 0 to 2;

D is CX-Ar¹ or N-Ar¹;

m is 1;

each X is independently H or OH;

Ar¹ is



V and W are each independently H or OR⁹; wherein R⁹ is H, substituted or
5 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or
unsubstituted heterocycloalkyl;

R¹ and R² are each independently H, halogen, CN, substituted or unsubstituted
alkyl, or substituted or unsubstituted heteroalkyl; and

10 R³ and R⁴ are each independently H, substituted or unsubstituted C₁–C₄ alkyl, or
substituted or unsubstituted C₁–C₄ heteroalkyl;

wherein at least two of R¹, R², R³, and R⁴, together with the atoms to which they
are attached, are optionally joined to form a 3- to 7-membered ring;

15 and any enantiomer, diastereoisomer, racemic mixture, enantiomerically
enriched mixture, and enantiomerically pure form thereof.

2. The compound of claim 1, wherein R¹ and R² are H.

3. The compound of claim 1 or 2, wherein R³ and R⁴ are each independently H
or substituted or unsubstituted C₁–C₄ alkyl.

4. The compound of any one of claims 1 to 3, wherein n is 0.

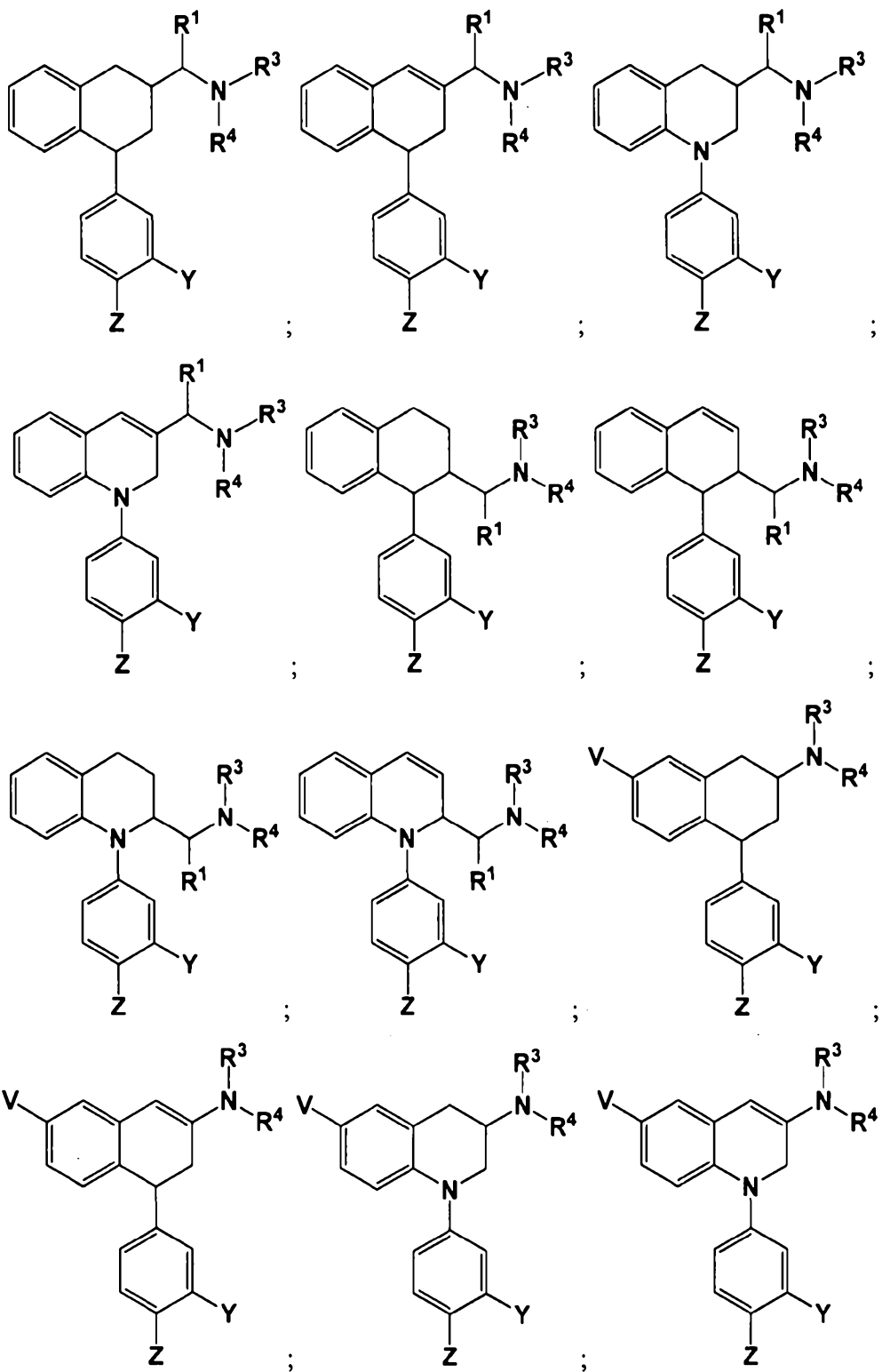
20 5. The compound of any one of claims 1 to 3, wherein n is 1.

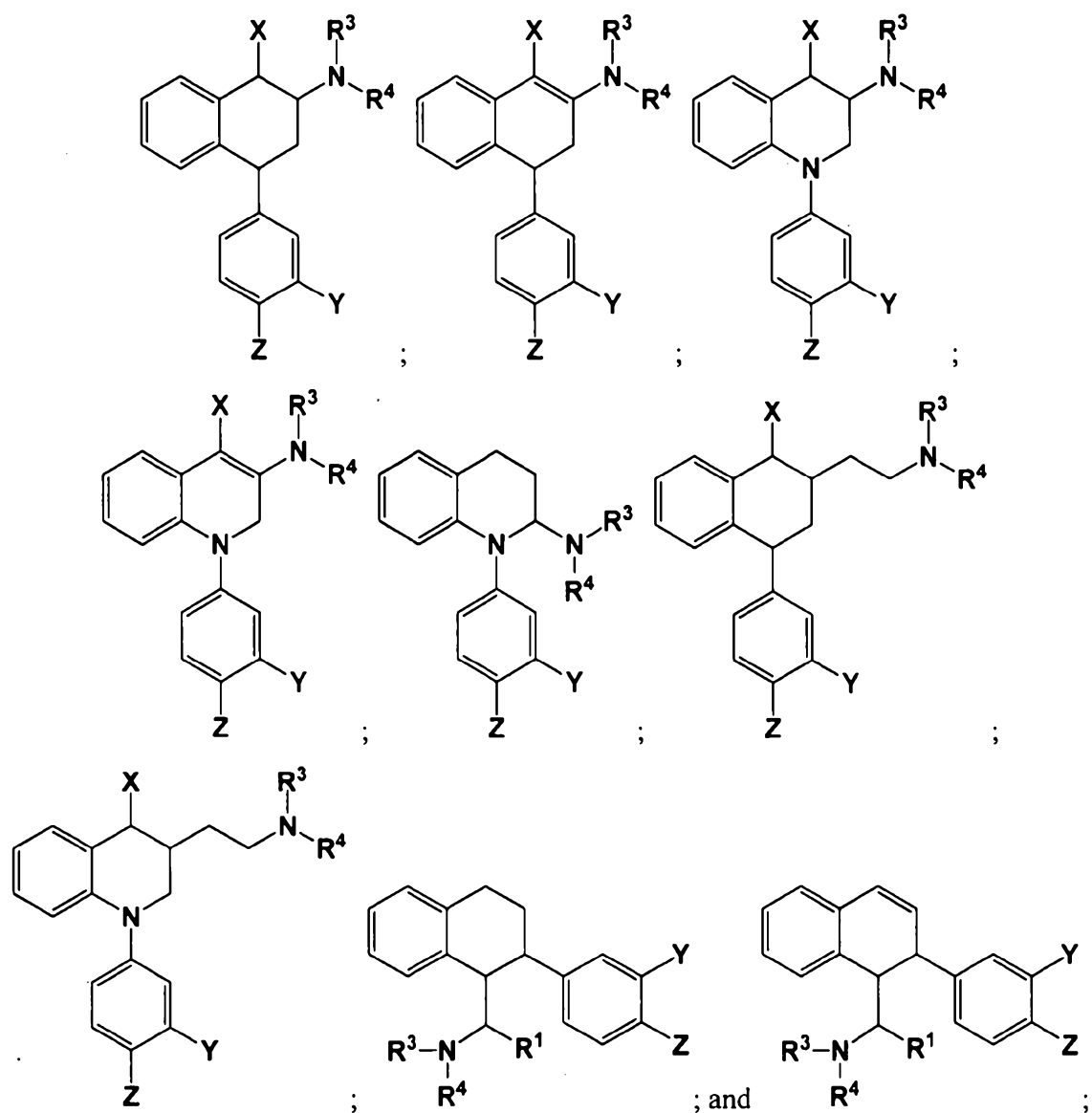
6. The compound of any one of claims 1 to 3, wherein n is 2.

7. The compound of any one of claims 1 to 6, wherein D is CX-Ar¹.

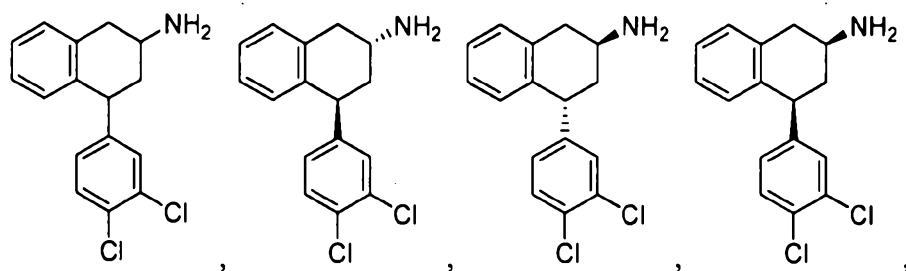
8. The compound of any one of claims 1 to 6, wherein D is N-Ar¹.

9. The compound of any one of claims 1 to 3, having a structure selected from:

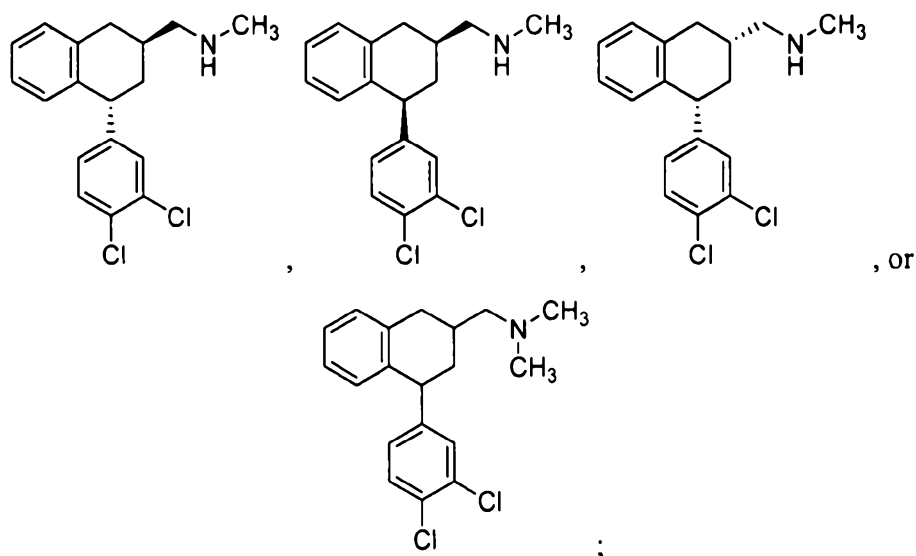




- 5 10. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound is:

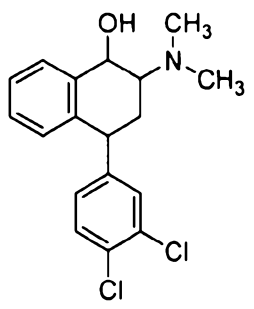


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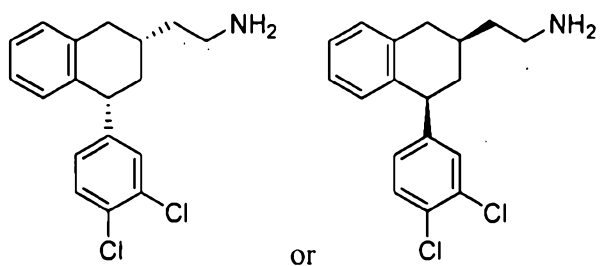
and any enantiomer, diastereoisomer, racemic mixture, enantiomerically enriched mixture, and enantiomerically pure form thereof.

- 5 12. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound is:



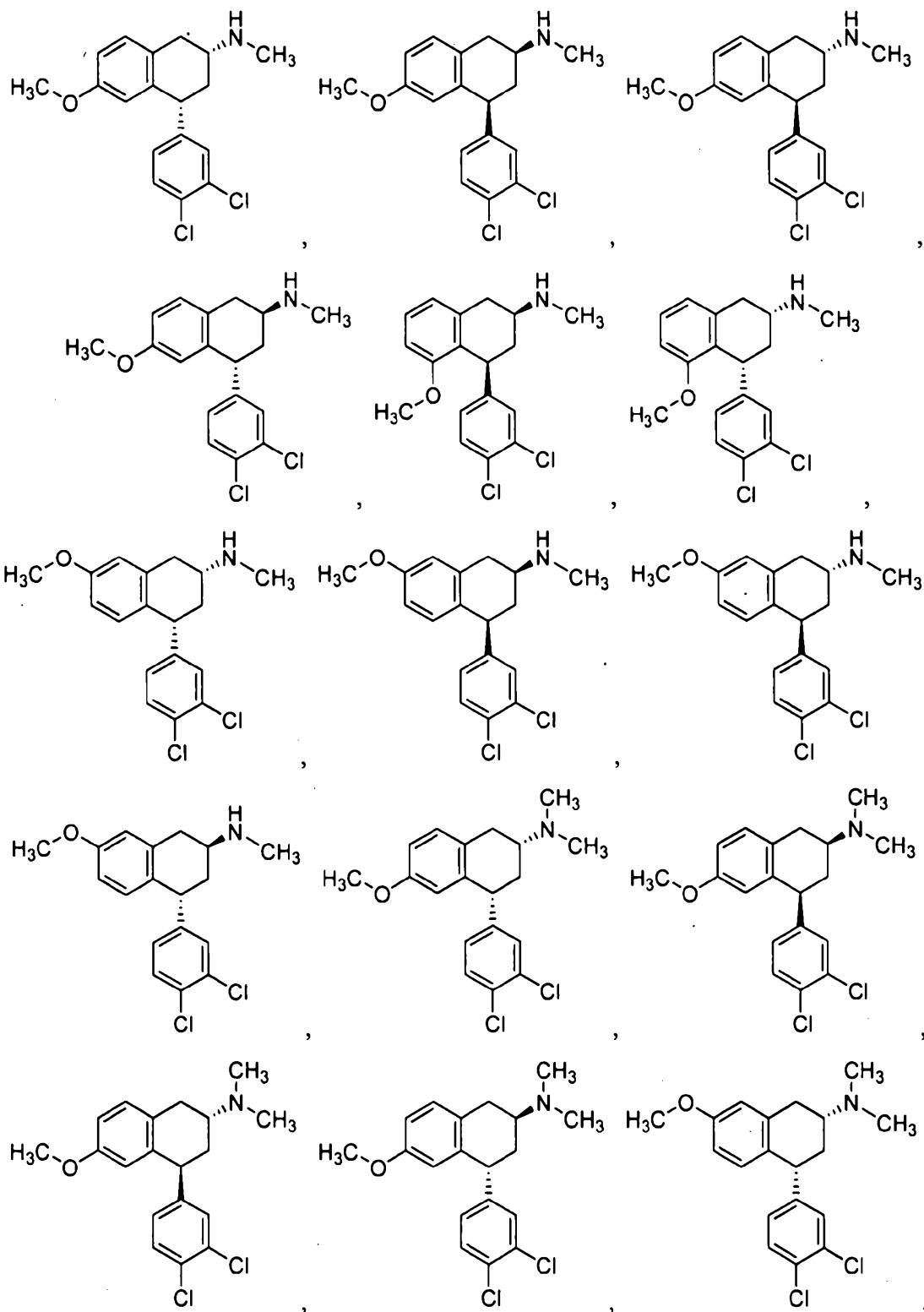
and any enantiomer, diastereoisomer, racemic mixture, enantiomerically enriched mixture, and enantiomerically pure form thereof.

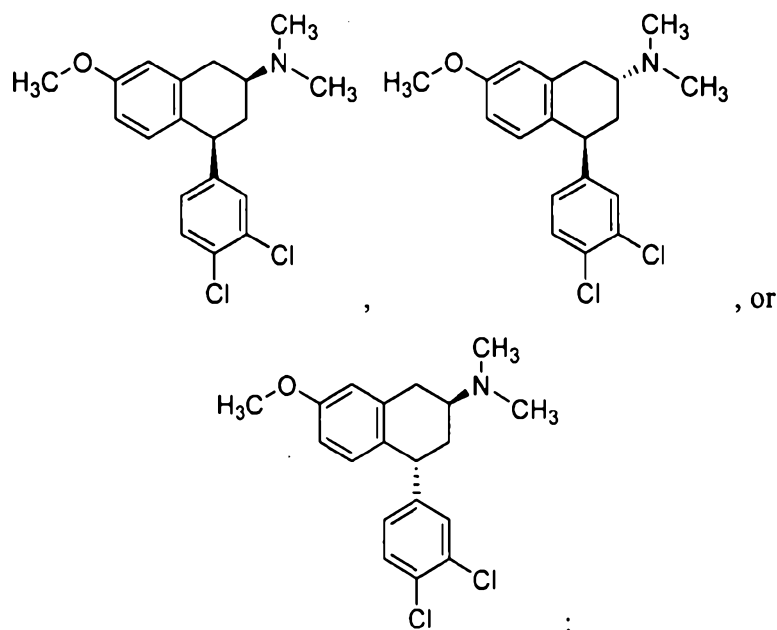
- 10 13. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound is:



and any enantiomer, diastereoisomer, racemic mixture, enantiomerically enriched mixture, and enantiomerically pure form thereof.

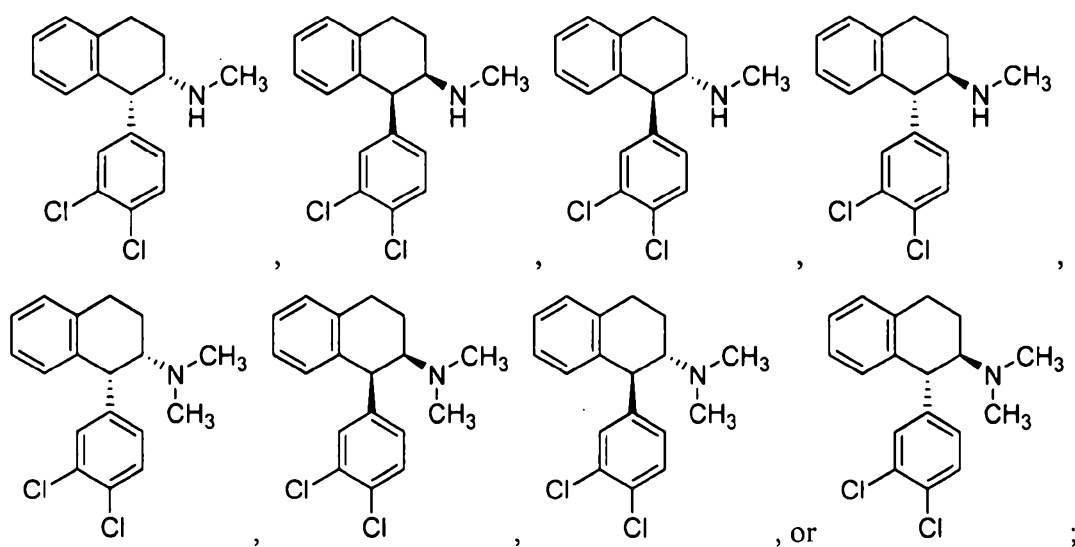
14. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound is:





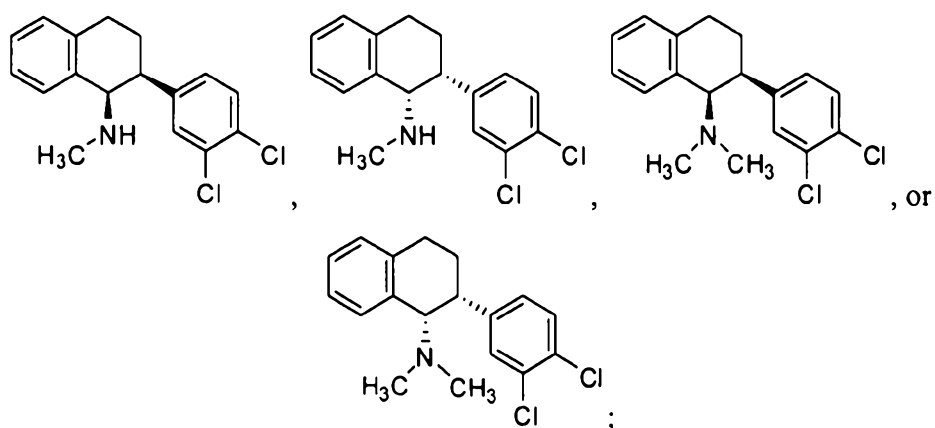
and any enantiomer, diastereoisomer, racemic mixture, enantiomerically enriched mixture, and enantiomerically pure form thereof.

- 5 15. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound is:



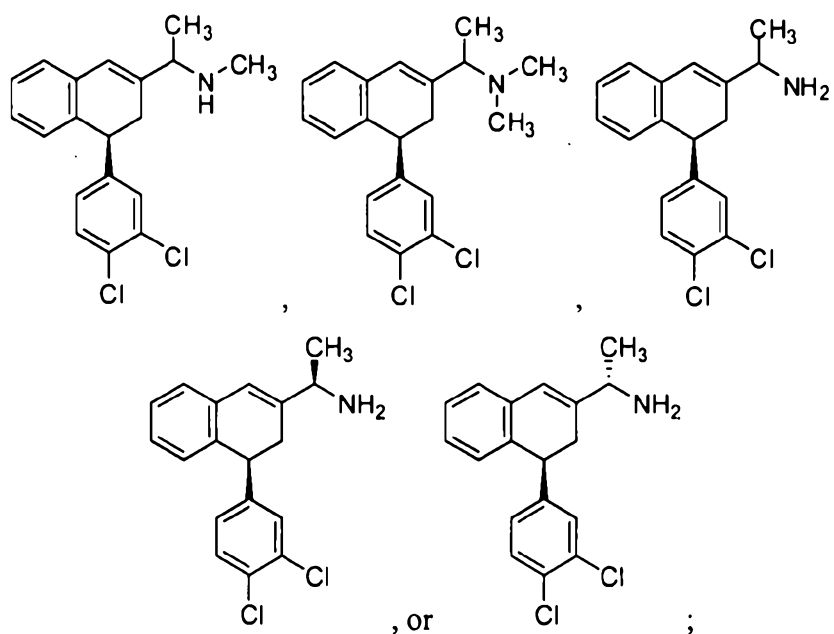
- 10 and any enantiomer, diastereoisomer, racemic mixture, enantiomerically enriched mixture, and enantiomerically pure form thereof.

16. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound is:



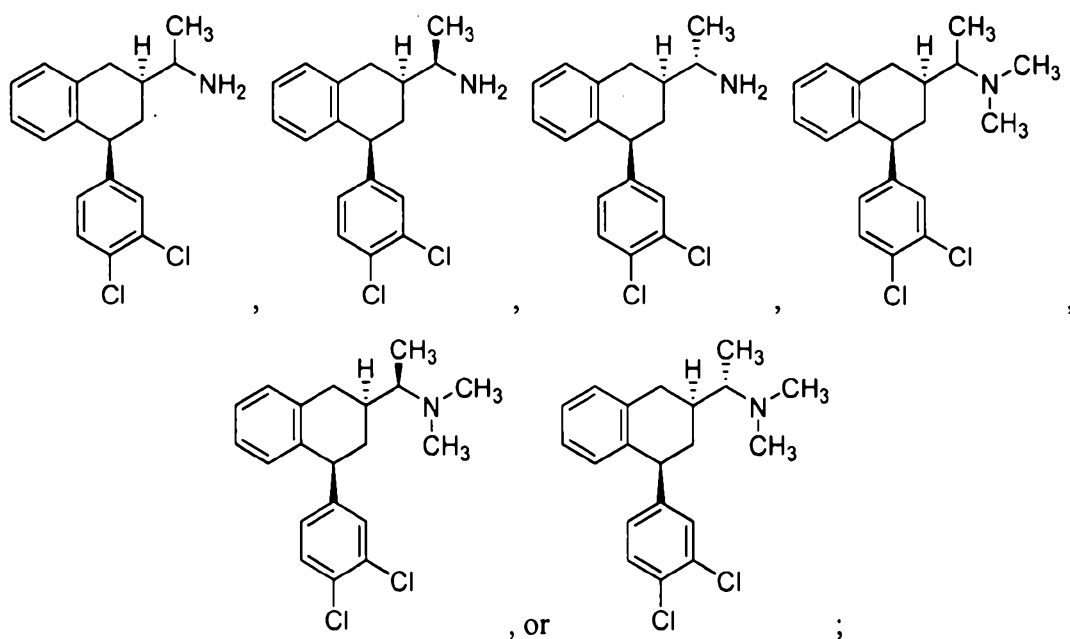
and any enantiomer, diastereoisomer, racemic mixture, enantiomerically enriched mixture, and enantiomerically pure form thereof.

- 5 17. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound is:



- 10 and any enantiomer, diastereoisomer, racemic mixture, enantiomerically enriched mixture, and enantiomerically pure form thereof.

18. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound is:



and any enantiomer, diastereoisomer, racemic mixture, enantiomerically enriched mixture, and enantiomerically pure form thereof.

- 5 19. A composition comprising a first stereoisomer and at least one additional stereoisomer of a compound according to any one of claims 1 to 18, wherein said first stereoisomer is present in a diastereomeric excess of at least 80% relative to said at least one additional stereoisomer.

- 10 20. A pharmaceutical composition comprising a compound according to any one of claims 1 to 18, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier, vehicle or diluent.

- 15 21. A method for treating a central nervous system disorder, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt or solvate thereof, or a composition according to claim 19 or 20.

- 20 22. The method of claim 21, wherein said central nervous system disorder is a member selected from the group consisting of depression, fibromyalgia, pain, sleep apnea, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), restless leg syndrome, schizophrenia, anxiety, obsessive compulsive disorder, posttraumatic stress disorder, seasonal affective disorder (SAD), premenstrual dysphoria and a neurodegenerative disease.

23. The method according to claim 22, wherein said neurodegenerative disease is Parkinson's disease.

24. The method according to claim 22, wherein said pain is neuropathic pain.

25. A method of inhibiting reuptake of one or more monoamine from the synaptic cleft, said method comprising administering to a mammalian subject a compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt or solvate thereof, or a composition of claim 19 or 20.

26. The method of claim 25, wherein said monoamine is serotonin, dopamine, norepinephrine or a combination thereof.

27. A method of modulating one or more monoamine transporter, said method comprising administering to a mammalian subject a compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt or solvate thereof, or a composition of claim 19 or 20.

28. The method of claim 27, wherein said monoamine transporter is serotonin transporter (SERT), dopamine transporter (DAT), norepinephrine transporter (NET) or combinations thereof.

29. Use of a compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a central nervous system disorder.

30. The use according to claim 29, wherein said central nervous system disorder is selected from depression, fibromyalgia, pain, sleep apnea, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), restless leg syndrome, schizophrenia, anxiety, obsessive compulsive disorder, post-traumatic stress disorder, seasonal affective disorder (SAD), premenstrual dysphoria, and a neurodegenerative disease.

31. The use according to claim 29, wherein said central nervous system disorder is Parkinson's disease.

32. The use according to claim 29, wherein said central nervous system disorder is neuropathic pain.

33. Use of a compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for inhibiting reuptake of one or more monoamine(s) from the synaptic cleft in a mammalian subject.

5 34. The use according to claim 33, wherein said monoamine is serotonin, dopamine, or norepinephrine, or a combination of two or more thereof.

35. Use of a compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for modulating one or more monoamine transporter(s) in a mammalian subject.

10 36. The use according to claim 35, wherein said monoamine transporter is serotonin transporter (SERT), dopamine transporter (DAT), or norepinephrine transporter (NET), or a combination of two or more thereof.