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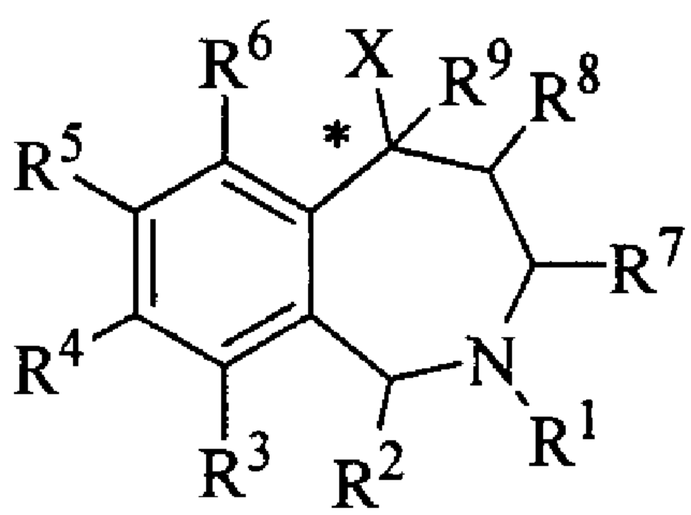
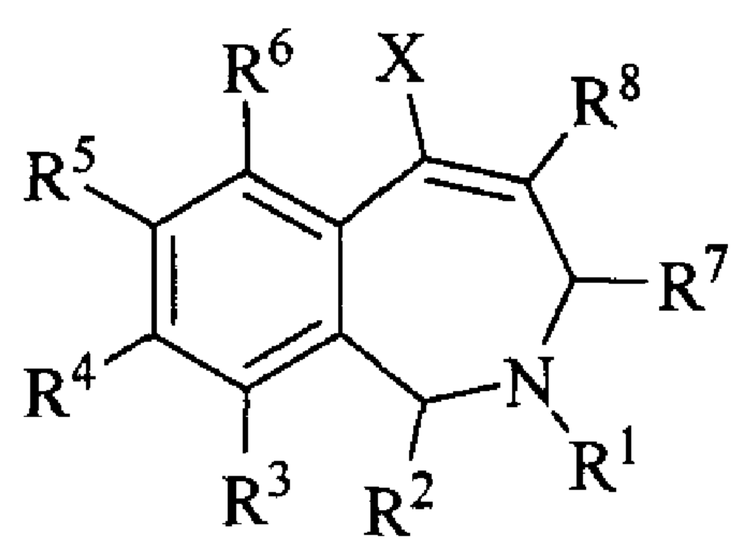
(54) Titre : TETRAHYDROBENZAZEPINES SUBSTITUEES PAR ARYLE ET HETEROARYLE, ET LEUR UTILISATION POUR BLOQUER LA REABSORPTION DE LA NORADRENALINE, DE LA DOPAMINE, ET DE LA SEROTONINE

(54) Title: ARYL- AND HETEROARYL-SUBSTITUTED TETRAHYDROBENZAZEPINES AND USE THEREOF TO BLOCK REUPTAKE OF NOREPINEPHRINE, DOPAMINE, AND SEROTONIN



I(A-E)



II

(57) Abrégé/Abstract:
The compounds of the present invention are represented by the following aryl- and heteroaryl-substituted tetrahydrobenzazepine and dihydrobenzazapine derivatives having formulae I(A-E) and formula (II) where the carbon atom designated * is in the R or S configuration, and the substituents X and R^1-R^9 are as defined herein.

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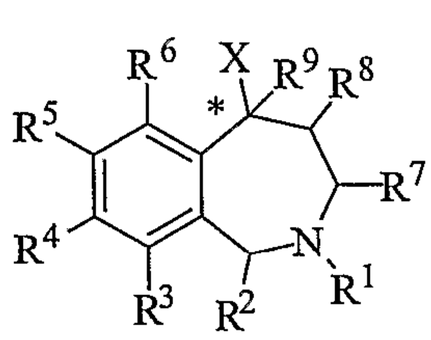
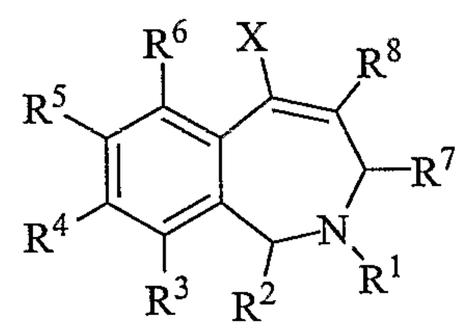
(54) Title: ARYL-AND HETEROARYL-SUBSTITUTED TETRAHYDROBENZAZEPINES AND USE THEREOF TO BLOCK REUPTAKE OF NOREPINEPHRINE, DOPAMINE, AND SEROTONIN

I(A-E)



(II)



(57) Abstract: The compounds of the present invention are represented by the following aryl- and heteroaryl-substituted tetrahydrobenzazepine and dihydrobenzazapine derivatives having formulae I(A-E) and formula (II) where the carbon atom designated * is in the R or S configuration, and the substituents X and R^1-R^9 are as defined herein.

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DEMANDES OU BREVETS VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS COMPREND PLUS D'UN TOME.

CECI EST LE TOME __1___ DE __2 __

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JUMBO APPLICATIONS / PATENTS

THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.

THIS IS VOLUME __1___ OF __2___

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ARYL- AND HETEROARYL-SUBSTITUTED TETRAHYDROBENZAZEPINES AND USE THEREOF TO BLOCK REUPTAKE OF NOREPINEPHRINE, DOPAMINE, AND SEROTONIN

FIELD OF THE INVENTION

[0002] The present invention relates to compounds, compositions, methods for the treatment of various neurological and psychological disorders, and the use of the compounds in combination therapy. In particular, the present invention relates to such compounds, compositions, and methods, where the compounds are novel aryl- and heteroaryl-substituted tetrahydrobenzazepine derivatives.

BACKGROUND OF THE INVENTION

[0003] It is well known that the neurotransmitters, dopamine (DA), norepinephrine (NE), and serotonin (5-HT), regulate a number of biological processes and that decreased levels of DA, NE, and 5-HT are associated with a number of neurological disorders and their physical manifestations. Significant effort has been expended on devising methods for adjusting the levels of these neurotransmitters in order to produce a desired pharmacological effect. Preventing the reuptake of these neurotransmitters in any combination of one, two, or all three of them is likely to be effective in treating these disorders. Targeting the dopamine transporter (DAT), norepinephrine transporter (NET), and the serotonin transporter (SERT) proteins has proven to be an effective way of increasing the levels of the respective monoamines.

[0004] Methylphenidate, currently used for the treatment of attention deficit-hyperactivity disorder, is known to be selective for inhibition of the DAT. Also, U.S. Patent No. 5,444,070 discloses selective inhibitors of the dopamine reuptake as treatments for Parkinson's disease, drug addiction or abuse including cocaine and amphetamines.

[0005] Selective norepinephrine reuptake inhibitors (NARI) have also been disclosed. U.S. Patent No. 6,352,986 describes methods of treating attention deficit-hyperactivity disorder (ADHD), addictive disorders, and psychoactive substance use disorders with Reboxetine. Also, Atomoxetine (Strattera®) is currently marketed as a selective NET reuptake inhibitor for ADHD.

[0006] The use of selective serotonin reuptake inhibitors (SSRI) has been shown to be effective in treating depressive disorders. Sertraline, Citalopram, and Paroxetine are well known examples of SSRIs used to treat disorders, such as depression, obsessive compulsive disorder, and panic attacks. There are several known difficulties with the SSRI class of therapeutics, including the slow onset of action, unwanted side effects, and the existence of a significant subset of the population that is not responsive to SSRI therapy.

[0007] Selective inhibitors of DAT, NET, and SERT reuptake may also be co-administered with each other or with other drugs. U.S. Patent No. 5,532,244 discloses the use of serotonin reuptake inhibitors in combination with a serotonin 1A antagonist for the treatment of obsessive-compulsive disorder, depression, and obesity. The use of a serotonin or norepinephrine reuptake inhibitor in combination with a neurokinin-1 receptor antagonist has been disclosed in U.S. Patent No. 6,121,261 for the treatment of ADHD. U.S. Patent No. 4,843,071 discloses the use of a norepinephrine reuptake inhibitor in combination with a norepinephrine precursor in the treatment of obesity, drug abuse, or narcolepsy. U.S. Patent No. 6,596,741 discloses the use of a NE, DA, or 5-HT inhibitor with either a neurokinin-1 receptor antagonist or a serotonin-1A antagonist for the treatment of a wide variety of conditions.

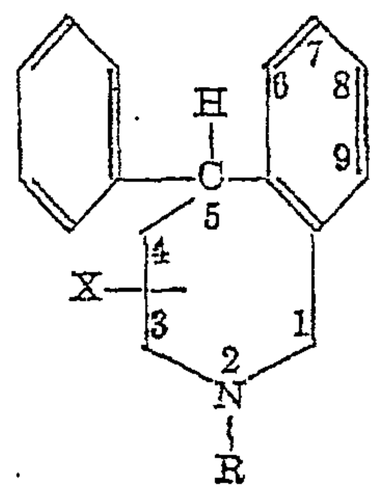
[0008] Also advantageous is the use of compounds that inhibit one or more of the neurotransmitters at the same time. The antidepressant qualities of the dual NET and SERT reuptake inhibitor duloxetine is disclosed in European Patent No. EP 273658. Venlafaxine is disclosed in U.S. Patent No. 4,535,186 as a reuptake inhibitor of both NE and 5-HT for the treatment of depressive disorders. U.S. Patent No. 6,635,675 discloses the use of the dual NE and 5-HT reuptake inhibitor milnacipran for the treatment of chronic fatigue syndrome and fibromyalgia syndrome. In addition, dual NE and 5-HT reuptake inhibitors are also disclosed in U.S. Patent No. 6,136,083 for the treatment of depression. It is also recognized that

compounds which inhibit the reuptake of NE, DA, and 5-HT in varying ratios not specifically mentioned here would also be advantageous.

[0009] Treating illnesses by inhibiting the reuptake of all three of the monoamines either through combination therapy or "triple inhibitors" may have clinical benefit as well. Rationale for inclusion of a dopamine enhancing component in anti-depressant therapy includes observed deficits in dopaminergic function, the success of combination therapy with dopamine agonists and traditional anti-depressants, and an increased sensitivity in dopamine receptors due to chronic anti-depressant administration (Skolnick et al., *Life Sciences*, 73:3175-3179 (2003)). Combination therapy with an SSRI and a noradrenaline and dopamine reuptake inhibitor was shown to be more efficacious in patients with treatment-resistant depression (Lam et al, *J. Clin. Psychiatry*, 65(3):337-340 (2004)). Another study using a combination of a serotonin and norepinephrine reuptake inhibitor with a norepinephrine and dopamine reuptake inhibitor reported a significant decrease in depressive symptoms in patients with refractory major depressive disorder who had failed to respond previously to either agent alone (Papkostas, G. I., *Depression and Anxiety*, 23:178-181 (2006)). In addition, the combination of bupropion-SR with either SSRIs or norepinephrine and dopamine reuptake inhibitors was found to induce less sexual dysfunction than monotherapy (Kennedy et al, *J. Clin. Psychiatry*, 63(3):181-186 (2002)). As such, inhibitory activity against DA reuptake, in addition to NE and 5-HT reuptake, is expected to provide a more rapid onset of anti-depressant effect than other mixed inhibitors which are selective for NET and SERT over DAT. PCT International Publication Nos. WO 03/101453 and WO 97/30997 disclose a class of compounds which are active against all three monoamine transporters. Also, PCT International Patent Publication No. WO 03/049736 discloses a series of 4-substituted piperidines, each of which displays similar activity against DA, NE, and 5-HT transporters. Bicyclo[2.2.1]heptanes (Axford et al., *Bioorg. Med. Chem. Lett.*, 13:3277-3280 (2003)) and azabicyclo[3.1.0]hexanes (Skolnick et al., *Eur. J. Pharm.*, 461:99-104 (2003)) are also described as triple inhibitors of the three monoamine transporters.

[0010] U.S. Patent No. 3,225,031 discloses phenyl tetrahydrobenzazepines of formula 1 (where R is a member of the group consisting of H, lower alkyl and phenyl-lower alkyl, and X is a member of the group consisting of H and methyl), which are

said to be useful in elevating mood or establishing wakefulness. At higher doses, these compounds are said to elicit analgesic response, while their non-toxic quaternary salts are said to be useful as anticholinergic or parasympathetic blocking agents.



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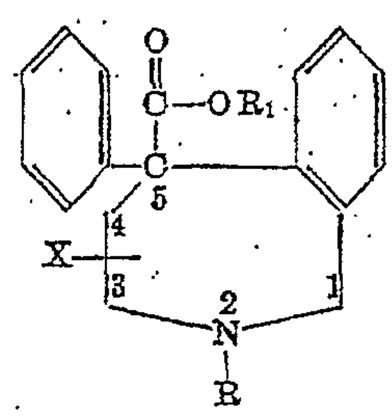
[0011] Phenyl tetrahydrobenzazepines of formula **2**, (where R is a member of the group consisting of H, lower alkyl, lower alkenyl, and isocyclic-lower alkyl having 3-6 cyclic carbon atoms, R_1 is lower alkyl, and X is a member of the group consisting of hydrogen and lower alkyl) described in U.S. Patent No. 3,242,164 are said to possess analgesic activity. The compound of formula **2** possesses an ester functionality at the 5- position of the 2,3,4,5-tetrahydro-1H-benzo[c]azepine core.



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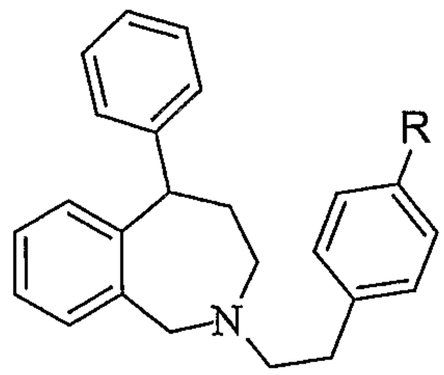
[0012] Japanese Patent Application No. 59013761 discloses the use of phenyl tetrahydrobenzazepines of formula **3** (where R represents a halogen, a hydroxy group, a nitro group, or an amino group) as analgesics.



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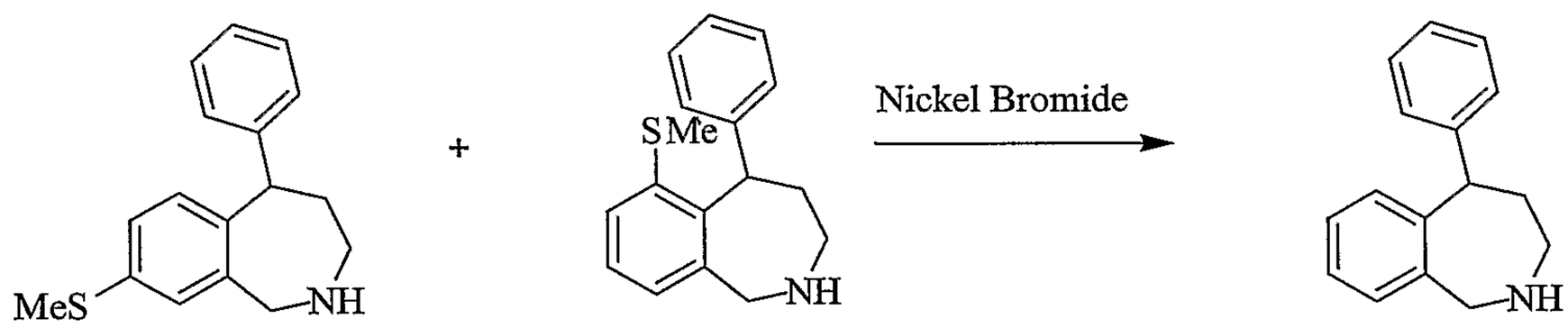
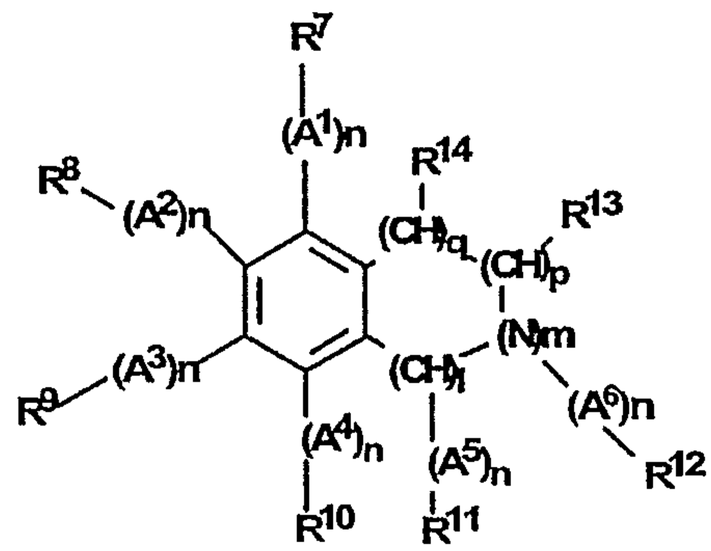
[0013] Compounds, 8-(methylthio)-5-phenyl-2,3,4,5-tetrahydro-1H-benzo[c]azepine (**4**), 6-(methylthio)-5-phenyl-2,3,4,5-tetrahydro-1H-benzo[c]azepine (**5**), and 2,3,4,5-tetrahydro-1H-benzo[c]azepine (**6**), are described in Euerby et al., *Synth. Commun.,* 16:779-784 (1986) and in Euerby et al., *J. Chem. Research (S),* pp. 40-41 (1987) as substrates (**4** and **5**) and product (**6**) in reductive desulphurization of thioethers with nickel bromide. No usage or activity was reported in those references.



4 **5** **6**

[0014] PCT International Patent Publication No. WO 2001/003680 discloses compounds of formula **7** (where C is a carbon; N is a nitrogen; H is a hydrogen; A^1, A^2, A^3, A^4, A^5, and A^6 are independently alkyl, O, S, or -NH; m and n (for each individual A group) are independently 0 or 1; p, q, and 1 are independently 0, 1, or 2; R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and each R^{14} are independently hydrogen, alkyl, alicyclyl, heterocyclyl, or aryl, each R^{13} is independently hydrogen, alkyl, alicyclyl, heterocycyl, aryl, or an anionic group, and adjacent R groups (e.g., R^7 and R^8) may form an unsubstituted or substituted cyclic or heterocyclic ring) as inhibitors of islet amyloid polypeptide (IAPP) associated amyloidosis. These compounds are suggested for use in disorders in which such amyloid deposition occurs, such as diabetes.



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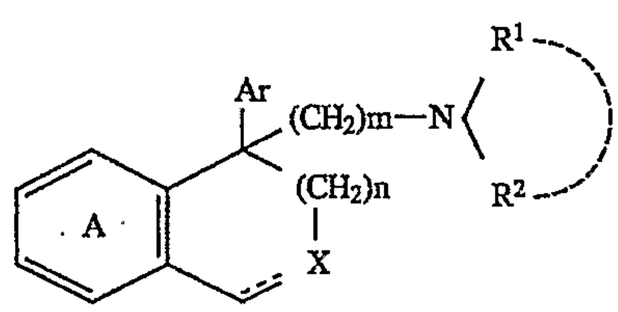
[0015] U.S. Patent No. 5,607,939 discloses compounds of formula **8** (where ring A represents a benzene ring; Ar represents an aromatic group; R^1 and R^2 independently represent hydrogen, acyl, or hydrocarbon group, or R^1 and R^2 taken together with the adjacent nitrogen atom represent a nitrogen-containing heterocyclic group; m represents an integer of 1 to 6; n represents an integer of 2 to 3; ----- represents a single bond or a double bond; X stands for —O— or —NR^3— in which R^3 represents hydrogen, acyl, or hydrocarbon group where ----- is a single bond or ═N— where ----- is a double bond) as gonadotropin-releasing hormone (GnRH) receptor antagonists and suggests their use in acute and chronic CNS disorders, such as dysmnesia. This reference discloses 5-aryl 2,3,4,5-tetrahydro-1H-benzo[c]azepines with particular cyclic aminoalkyl groups at the 5-position of the 2,3,4,5-tetrahydro-1H-benzo[c]azepines.



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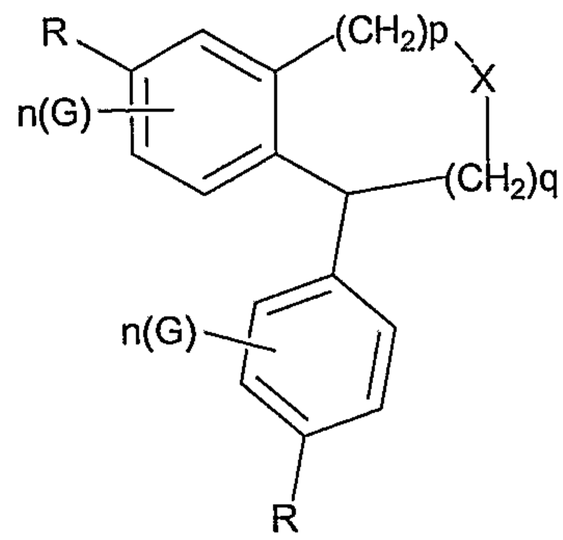
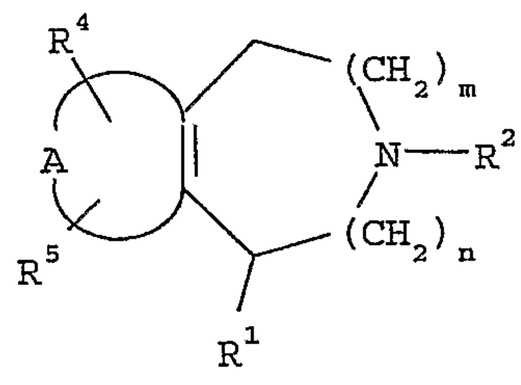
[0016] Great Britain Patent No. GB 2271566 discloses compounds of formula **9** (where n is 0-3; p is 1-2; q is 1-2; X is CH_2, O, or N-R^1, and R^1 is H, C_{1-4} alkyl or C_{3-5} cycloalkyl; R is (a) C_{1-6} alkyl, (b) C_{1-6} alkoxy, (c) hydroxyl, (d) halogen, (e) CN, (f) NO_2, (g) $NHSO_2CH_3$, or (h) COOH; G is H or R) as HIV integrase inhibitors.



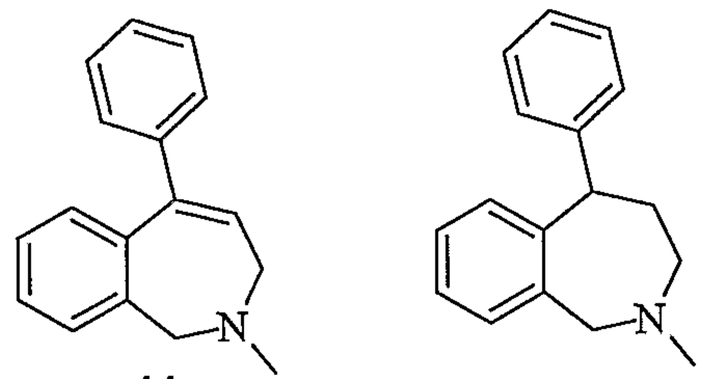
9

[0017] PCT International Patent Publication No. WO 99/045013 discloses compounds of formula **10** (where A together with the double bond of formula **10** forms a cyclic system selected from the group consisting of benzene, thiophene, furan, pyridine, pyrimidine, pyrazine, pyridazine, pyrrole, indole, pyrazole, imidazole, oxazole, isoxazole, and thiazole; R^2 is an optionally substituted C_{1-6}-alkyl, optionally substituted heterocyclyl; R^1 is heteroaryl, optionally substituted; R^4 and R^5 are independently hydrogen, halogen, perhalomethyl, optionally substituted C_{1-6}-alkyl, hydroxy, optionally substituted C_{1-6}-alkoxy, nitro, cyano, amino, optionally substituted mono- or optionally substituted di-C_{1-6}-alkylamino, acylamino, C_{1-6}-alkoxycarbonyl, carboxy, or carbamoyl; m is 0, 1, or 2; n is 0, 1, or 2) for the treatment or prevention of diseases of the endocrinological system.



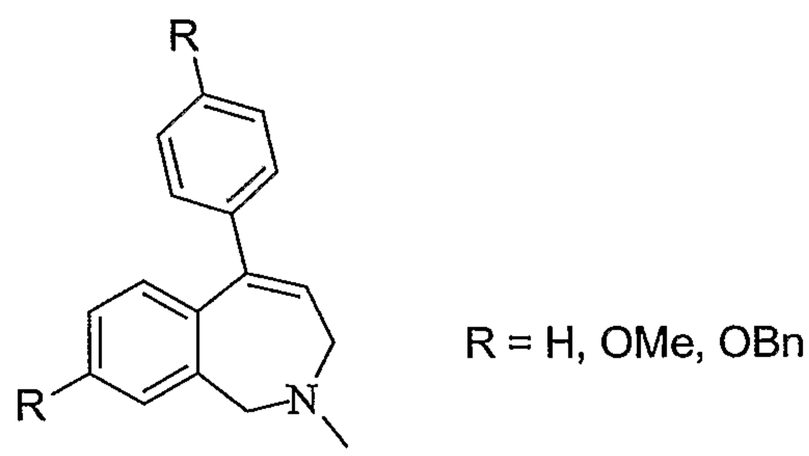
10

[0018] Brooks et al., *Journal of Chemical Society [Section] C: Organic*, pp. 625-627 (1969) describes the synthesis of compound of formula **11** and formula **12** via acid catalyzed ring-closure method. No biological activity of these compounds is reported in the above-mentioned reference. U.S. Patent Nos. 3,655,651 and 3,642,993 disclose a single compound of formula **11** and suggest its sedative-hypnotic effect.



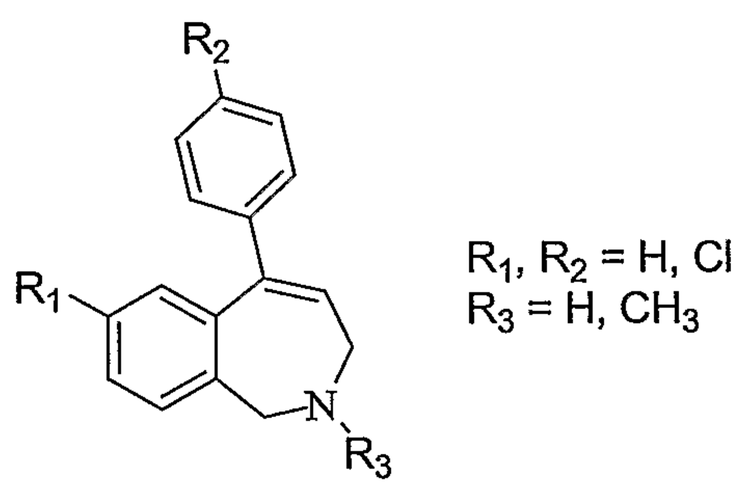
11 **12**

[0019] Arany et al., *J. Chem. Soc, Perkin Trans.* I: 2605-2608 (1999) and Arany et al., *Tetrahedron Letters* 39:3267-3268 (1998) describe compounds of formula **13** as products of electrocyclisation of azomethine ylides. No biological activity of these compounds is reported in the above mentioned references.



13

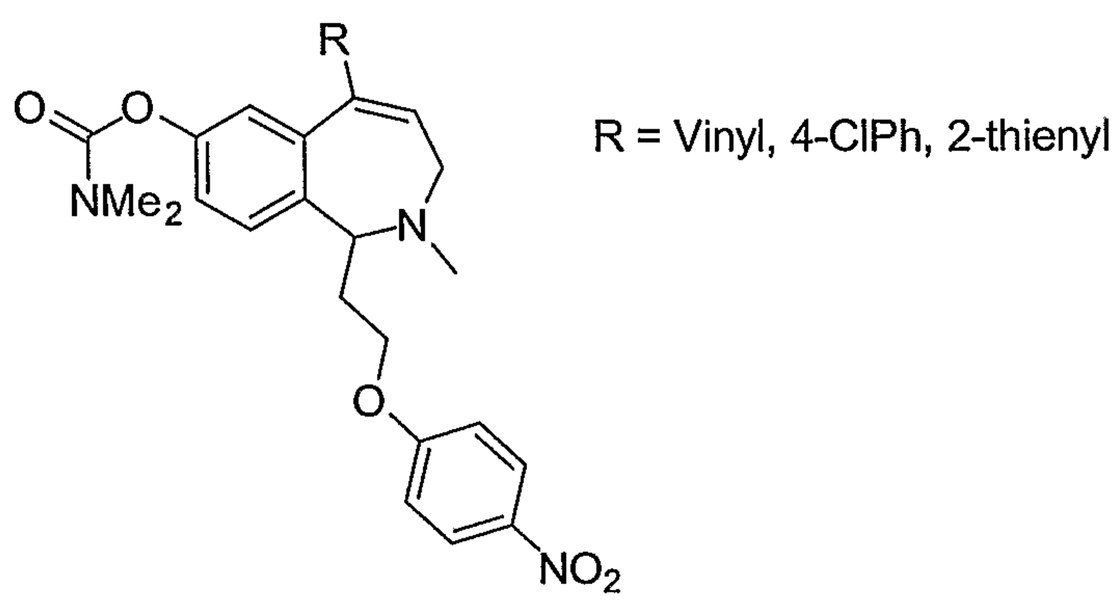
[0020] Gast et al., *Helvetica Chimica Acta*, 60(5):1644-1649 (1977) describes compounds of formula **14** as products of the cyclization of 2-(β-styryl)benzylamine derivatives. No biological activity is disclosed in the above mentioned reference.



14

[0021] Toda et al., *Bioorganic and Medicinal Chemistry*, 11(20):4389-4415 (2003) describes compounds of formula **15** as dual inhibitors of acetylcholinesterase and serotonin transporter and potential agents for Alzheimer's disease. The IC_{50}s for

the serotonin transporter for the three compounds of formula **15** are reported to be > 1000 nM in the above mentioned reference.



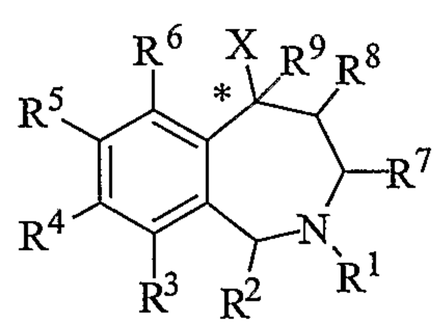
15

[0022] There is still a large need for compounds that block the reuptake of norepinephrine, dopamine, and serotonin and treat various neurological and psychological disorders.

[0023] The present invention is directed to achieving this objective.

SUMMARY OF THE INVENTION

[0024] The present invention relates to compounds represented by the formulae I(A-E) having the following structure:



I(A-E)

where:

the carbon atom designated * is in the R or S configuration; and

X represents a 5- or 6-membered aromatic or nonaromatic monocyclic carbocycle or heterocycle selected from the group consisting of phenyl, pyridyl, 2-oxo-pyridin-1-yl,

pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyranyl, pyrrolyl, furanyl, thiophenyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, and tetrazolyl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}, or other 5- or 6-membered aromatic or non-aromatic monocyclic carbocycles or heterocycles containing 1-4 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

X is a [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycle or heterocycle selected from the group consisting of indenyl, indanyl, benzofuranyl, benzothiophenyl, dihydrobenzothiophenyl, dihydrobenzofuranyl, indolyl, isoindolyl, indolinyl, benzo[1,3]dioxolyl, benzooxazolyl, benzothiazolyl, benzoisothiazolyl, benzoisoxazolyl, indazolyl, benzoimidazolyl, benzotriazolyl, naphthyl, tetrahydronaphthyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, phthalazinyl, quinoxalinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, 2,3-dihydro-benzo[1,4]dioxinyl, 4*H*-chromenyl, dihydrobenzocycloheptenyl, tetrahydrobenzocycloheptenyl, indolizinyl, quinolizinyl, 6*aH*-thieno[2,3-d]imidazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, thieno[2,3-*b*]furanyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[2,3-*b*]pyrazinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, 3,4-dihydro-2H-benzo[*b*][1,4]oxazinyl, imidazo[1,2-*a*]pyrazinyl, 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazinyl, 2-oxo-2,3-dihydrobenzo[*d*]oxazolyl, 3,3-dimethyl-2-oxoindolinyl, 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, and 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}, or other [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycles or heterocycles containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}; or

X is an alkene or alkyne, optionally substituted from 1 to 4 times with substitutents as defined below in R^{15};

R^1 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, each of which is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, each of which is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or
R^2 is gem-dimethyl;

R^3, R^5, and R^6 are each independently selected from the group consisting of H, halogen, $-OR^{12}$, $-S(O)_nR^{13}$, –CN, $-C(O)R^{13}$, $-NR^{10}R^{11}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of the C_1–C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or
R^3, R^5, and R^6 are each independently a 5- or 6-membered monocyclic carbocycle or heterocycle or a [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycle or heterocycle containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

R^4 is H, halogen, $-OR^{12}$, $-S(O)_nR^{13}$, –CN, $-C(O)R^{13}$, $-NR^{10}R^{11}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, where each of the C_1–C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};
R^4 is a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, where the bridged bicyclic ring is optionally substituted from 1 to 3 times with substitutents selected from the group consisting of C_1-C_3 alkyl, $-C(O)R^{13}$, and $-S(O)_nR^{13}$; or
R^4 is phenyl, pyridyl, 2-oxo-pyridin-1-yl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyranyl, furanyl, pyrrolyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl,

indanyl, indenyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, indolinyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, indazolyl, benzimidazolyl, benzooxazolyl, benzothiazolyl, benzoisoxazolyl, benzoisothiazolyl, benzotriazolyl, benzo[1,3]dioxolyl, naphthyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, pthalazinyl, quinoxalinyl, 2,3-dihydro-benzo[1,4]dioxinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, 4*H*-chromenyl, indolizinyl, quinolizinyl, 6*aH*-thieno[2,3-d]imidazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, [1,2,4]triazolo[1,5-*a*]pyridinyl, thieno[2,3-*b*]furanyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[2,3-*b*]pyrazinyl, imidazo[1,2-*a*]pyrazinyl, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazinyl, 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazinyl, 2-oxo-2,3-dihydrobenzo[*d*]oxazolyl, 3,3-dimethyl-2-oxoindolinyl, 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, 3,4-dihydro-2H-benzo[*b*][1,4]oxazinyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazinyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, or other 5- or 6-membered aromatic or non-aromatic monocyclic carbocycles or heterocycles, or [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycles or heterocycles containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

provided that for compounds of formula IA, X is substituted phenyl and R^4 is substituted monocyclic or bicyclic aryl or heteroaryl;
provided that for compounds of formula IB, X is substituted bicyclic aryl or heteroaryl and R^4 is substituted monocyclic or bicyclic aryl or heteroaryl;
provided that for compounds of formula IC, X is substituted phenyl and R^4 is H, $-OR^{12}$, $-S(O)_nR^{13}$, $C(O)R^{13}$, $-NR^{10}R^{11}$, -CN, halogen, or C_1-C_6 alkyl, where each of the C_1-C_6 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};
provided that for compounds of formula ID, X is substituted bicyclic aryl or heteroaryl and R^4 is H, $-OR^{12}$, $-S(O)_nR^{13}$, $C(O)R^{13}$, $-NR^{10}R^{11}$, -CN, halogen, or C_1-C_6 alkyl, where each of the C_1-C_6 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; and

provided that for compounds of formula IE, X is substituted monocyclic heteroaryl and R^4 is substituted monocyclic or bicyclic aryl or heteroaryl;

R^7 is selected from the group consisting of H,–$S(O)_nR^{13}$, –$C(O)R^{13}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of C_1 –C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^8 is selected from the group consisting of H, halogen, –OR^{12}, –$S(O)_nR^{13}$, –CN, -$C(O)R^{13}$, -$NR^{10}R^{11}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of C_1 –C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or

R^7 and R^8 are gem-dimethyl, with the proviso that only one of R^7 and R^8 is gem-dimethyl;

R^9 is H, halogen,-OR^{12}, -SR^{10}, C_1-C_6 alkyl, -CN, or –$NR^{10}R^{11}$, where each of C_1 –C_6 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{10} and R^{11} are each independently selected from the group consisting of H, -$C(O)R^{13}$, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of C_1 –C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};
R^{10} and R^{11} are each independently selected from the group consisting of phenyl, benzyl, and other 5- or 6-membered monocyclic heterocycles, where each of the phenyl, benzyl, and 5- or 6-membered monocyclic heterocycle is optionally substituted from 1 to 3 times with substituents as defined below in R^{14};
R^{10} and R^{11} are taken together with the nitrogen to which they are attached to form a saturated or partially saturated monocyclic or fused bicyclic heterocycle selected from the group consisting of piperidine, pyrrolidine, morpholine, thiomorpholine,

[1,2]oxazinane, isoxazolidine, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 3-oxomorpholino, 3-oxothiomorpholino, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazine, and other monocyclic or fused bicyclic heterocycles containing 1-4 heteroatoms selected from oxygen, nitrogen and sulfur, wherein the heterocycle is attached to the benzazepine core via the nitrogen atom, and is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, $-OR^{12}$, $-NR^{12}R^{13}$, $-S(O)_nR^{13}$, $-C(O)R^{13}$, and C_1-C_4 alkyl, where each of C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{10} and R^{11} are taken together with the nitrogen to which they are attached to form a heterocycle selected from the group consisting of piperazine, 2-oxopiperazinyl, 2-oxo-1,4-diazepanyl, 5-oxo-1,4-diazepanyl, 1,4-diazepane, and other heterocycles containing one additional nitrogen atom in the ring, where the heterocycle is optionally substituted on a ring carbon with from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, $-OR^{12}$, $-NR^{12}R^{13}$, $-S(O)_nR^{13}$, $-C(O)R^{13}$, and C_1-C_4 alkyl, or on the additional nitrogen atom from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of $S(O)_nR^{13}$, $-C(O)R^{13}$, and C_1-C_4 alkyl, wherein each of C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{10} and R^{11} are taken together with the nitrogen to which they are attached to form a heterocycle selected from the group consisting of piperazine, 2-oxopiperazinyl, 2-oxo-1,4-diazepanyl, 5-oxo-1,4-diazepanyl, 1,4-diazepane, and other heterocycles containing one additional nitrogen atom in the ring, where the heterocycle is optionally substituted on the additional nitrogen atom with a substituent selected independently at each occurrence thereof from the group consisting of phenyl, benzyl, and 5- or 6-membered aromatic heterocycles containing 1-3 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, where each of the phenyl, benzyl, and 5- and 6-membered heterocycle is optionally substituted from 1 to 3 times with substituents as defined below in R^{14}; or

when R^4 is $-NR^{10}R^{11}$ or $-C(O)NR^{10}R^{11}$, either R^{10} or R^{11} is a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, where the bridged

bicyclic ring is optionally substituted from 1 to 3 times with substituents selected from the group consisting of C_1-C_3 alkyl, –C(O)R^{13}, and –S(O)$_n$$R^{13}$, or either R^{10} or R^{11} is a C_1-C_3 alkyl substituted with a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, where the bridged bicyclic ring is optionally substituted from 1 to 3 times with substitutents selected from the group consisting of C_1-C_3 alkyl, –C(O)R^{13}, and -S(O)$_n$$R^{13}$;

R^{12} is selected from the group consisting of H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, and –C(O)R^{13}, where each of C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{13} is selected from the group consisting of H, -N$R^{10}$$R^{11}$, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or

R^{12} and R^{13} are each independently selected from the group consisting of phenyl, benzyl, pyridazinyl, pyrimidinyl, pyrazinyl, 5- or 6-membered aromatic monocyclic heterocycles, and [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycles or heterocycles containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}; or

R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a heterocycle selected from the group consisting of piperidine, pyrrolidine, piperazine, 1,4-diazepane, morpholine, thiomorpholine, and other heterocycles containing 1-4 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, where the heterocycle is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, -OR^{10}, –S(O)$_n$$R^{10}$, –C(O)$R^{10}$, -C(O)N$R^{10}$$R^{11}$ and C_1-C_4 alkyl, where each of C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

n is 0, 1, or 2;

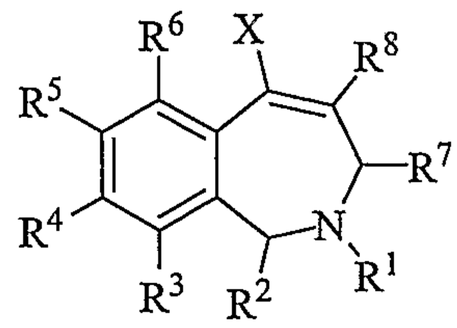
R^{14} is independently selected at each occurrence from a substituent in the group consisting of halogen, $-NO_2$, $-OR^{12}$, $-NR^{10}R^{11}$, $-NR^{12}C(O)_2R^{13}$, $-NR^{12}C(O)NR^{12}R^{13}$, $-S(O)_n R^{13}$, –CN, $-C(O)R^{13}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; and

R^{15} is independently selected at each occurrence from a substituent in the group consisting of –CN, halogen, $C(O)R^{13}$, C_1-C_3 alkyl, $-OR^{12}$, $-NR^{10}R^{11}$, $-S(O)_nR^{13}$, aryl, and heteroaryl, where each of the aryl or heteroaryl groups is optionally substituted from 1 to 4 times with substituents as defined above in R^{14};

with the following provisos that (1) when R^4 is H, X cannot be phenyl; (2) when R^4 is (a) C_{1-6} alkyl, (b) C_1-C_4alkoxy, (c) hydroxyl, (d) halogen, (e) CN, (f) NO_2, (g) $NHSO_2CH_3$, or (h) COOH, X cannot be a phenyl substituted at the *para*-position with the same R^4; (3) when any one of R^3, R^4, R^5, and $R^6$is hydrogen, halogen, perhalomethyl, optionally substituted C_{1-6}-alkyl, hydroxy, optionally substituted C_{1-4}-alkoxy, nitro, cyano, amino, optionally substituted mono- or optionally substituted di-C_{1-4}-alkylamino, acylamino, C_{1-6}-alkoxycarbonyl, carboxy, or carbamoyl, X cannot be furanyl, thienyl, pyrazolyl, tetrazolyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-oxadiazolyl, 1,2,5-thiadiazolyl, benzo[d]isoxazolyl, or benzo[d]isothiazolyl; (4) when R^4 is $-S(O)_nR^{13}$, n cannot be 0; and (5) when R^9 is a substituted alkyl, R^{15} cannot be $-NR^{10}R^{11}$;

or an oxide thereof, or a pharmaceutically acceptable salt thereof.

[0025] Another aspect of the present invention relates to a compound represented by the formula (II) having the following structure:



II

where:

X represents a 5- or 6-membered aromatic or nonaromatic monocyclic carbocycle or heterocycle selected from the group consisting of phenyl, pyridyl, 2-oxo-pyridin-1-yl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyranyl, pyrrolyl, furanyl, thiophenyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, and tetrazolyl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}, or other 5- or 6-membered aromatic or non-aromatic monocyclic carbocycles or heterocycles containing 1-4 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

X is a [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycle or heterocycle selected from the group consisting of indenyl, indanyl, benzofuranyl, benzothiophenyl, dihydrobenzothiophenyl, dihydrobenzofuranyl, indolyl, isoindolyl, indolinyl, benzo[1,3]dioxolyl, benzooxazolyl, benzothiazolyl, benzoisothiazolyl, benzoisoxazolyl, indazolyl, benzoimidazolyl, benzotriazolyl, naphthyl, tetrahydronaphthyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, phthalazinyl, quinoxalinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, 2,3-dihydro-benzo[1,4]dioxinyl, 4*H*-chromenyl, dihydrobenzocycloheptenyl, tetrahydrobenzocycloheptenyl, indolizinyl, quinolizinyl, 6*aH*-thieno[2,3-d]imidazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, thieno[2,3-*b*]furanyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[2,3-*b*]pyrazinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, 3,4-dihydro-2H-benzo[*b*][1,4]oxazinyl, imidazo[1,2-*a*]pyrazinyl, 6,7-dihydro-4*H*-pyrazolo[5,1-

c][1,4]oxazinyl, 2-oxo-2,3-dihydrobenzo[*d*]oxazolyl, 3,3-dimethyl-2-oxoindolinyl, 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, and 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}, or other [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycles or heterocycles containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}; or

X is an alkene or alkyne, optionally substituted from 1 to 4 times with substitutents as defined below in R^{15};

R^1 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, each of which is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, each of which is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or

R^2 is gem-dimethyl;

R^3, R^5, and R^6 are each independently selected from the group consisting of H, halogen, $-OR^{12}$, $-S(O)_nR^{13}$, –CN, $-C(O)R^{13}$, $-NR^{10}R^{11}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of the C_1–C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or

R^3, R^5, and R^6 are each independently a 5- or 6-membered monocyclic carbocycle or heterocycle or a [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycle or heterocycle containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

R^4 is H, halogen, $-OR^{12}$, $-S(O)_nR^{13}$, –CN, $-C(O)R^{13}$, $-NR^{10}R^{11}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, where each of the

C_1–C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^4 is a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, where the bridged bicyclic ring is optionally substituted from 1 to 3 times with substitutents selected from the group consisting of C_1-C_3 alkyl, –C(O)R^{13}, and -S(O)$_n$$R^{13}$; or

R^4 is phenyl, pyridyl, 2-oxo-pyridin-1-yl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyranyl, furanyl, pyrrolyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, indanyl, indenyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, indolinyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, indazolyl, benzimidazolyl, benzooxazolyl, benzothiazolyl, benzoisoxazolyl, benzoisothiazolyl, benzotriazolyl, benzo[1,3]dioxolyl, naphthyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, pthalazinyl, quinoxalinyl, 2,3-dihydro-benzo[1,4]dioxinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, 4*H*-chromenyl, indolizinyl, quinolizinyl, 6*aH*-thieno[2,3-d]imidazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, [1,2,4]triazolo[1,5-*a*]pyridinyl, thieno[2,3-*b*]furanyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[2,3-*b*]pyrazinyl, imidazo[1,2-*a*]pyrazinyl, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazinyl, 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazinyl, 2-oxo-2,3-dihydrobenzo[*d*]oxazolyl, 3,3-dimethyl-2-oxoindolinyl, 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, 3,4-dihydro-2H-benzo[*b*][1,4]oxazinyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazinyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, or other 5- or 6-membered aromatic or non-aromatic monocyclic carbocycles or heterocycles or [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycles or heterocycles containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

R^7 is selected from the group consisting of H,–$S(O)_nR^{13}$, –$C(O)R^{13}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of C_1 –C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or

R^7 is gem-dimethyl;

R^8 is H or C_1-C_6 alkyl, where each of C_1 –C_6 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{10} and R^{11} are each independently selected from the group consisting of H, -$C(O)R^{13}$, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of C_1 -C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{10} and R^{11} are each independently selected from the group consisting of phenyl, benzyl, and other 5- or 6-membered monocyclic heterocycles, where each of the phenyl, benzyl, and 5- or 6-membered monocyclic heterocycle is optionally substituted from 1 to 3 times with substituents as defined below in R^{14};

R^{10} and R^{11} are taken together with the nitrogen to which they are attached to form a saturated or partially saturated monocyclic or fused bicyclic heterocycle selected from the group consisting of piperidine, pyrrolidine, morpholine, thiomorpholine, [1,2]oxazinane, isoxazolidine, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 3-oxomorpholino, 3-oxothiomorpholino, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazine, and other monocyclic or fused bicyclic heterocycles containing 1-4 heteroatoms selected from oxygen, nitrogen and sulfur, wherein the heterocycle is attached to the benzazepine core via the nitrogen atom, and is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, -OR^{12}, -$NR^{12}R^{13}$, –$S(O)_nR^{13}$, –$C(O)R^{13}$, and C_1-C_4 alkyl, where each of C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{10} and R^{11} are taken together with the nitrogen to which they are attached to form a heterocycle selected from the group consisting of piperazine, 2-oxopiperazinyl, 2-oxo-1,4-diazepanyl, 5-oxo-1,4-diazepanyl, 1,4-diazepane, and other heterocycles

containing one additional nitrogen atom in the ring, where the heterocycle is optionally substituted on a ring carbon with from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, $-OR^{12}$, $-NR^{12}R^{13}$, $-S(O)_nR^{13}$, $-C(O)R^{13}$, and C_1-C_4 alkyl, or on the additional nitrogen atom from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of $S(O)_nR^{13}$, $-C(O)R^{13}$, and C_1-C_4 alkyl, wherein each of C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{10} and R^{11} are taken together with the nitrogen to which they are attached to form a heterocycle selected from the group consisting of piperazine, 2-oxopiperazinyl, 2-oxo-1,4-diazepanyl, 5-oxo-1,4-diazepanyl, 1,4-diazepane, and other heterocycles containing one additional nitrogen atom in the ring, where the heterocycle is optionally substituted on the additional nitrogen atom with a substituent selected independently at each occurrence thereof from the group consisting of phenyl, benzyl, and 5- or 6-membered aromatic heterocycles containing 1-3 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, where each of the phenyl, benzyl, and 5- and 6-membered heterocycle is optionally substituted from 1 to 3 times with substituents as defined below in R^{14}; or

when R^4 is $-NR^{10}R^{11}$ or $-C(O)NR^{10}R^{11}$, either R^{10} or R^{11} is a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, where the bridged bicyclic ring is optionally substituted from 1 to 3 times with substituents selected from the group consisting of C_1-C_3 alkyl, $-C(O)R^{13}$, and $-S(O)_nR^{13}$, or either R^{10} or R^{11} is a C_1-C_3 alkyl substituted with a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, where the bridged bicyclic ring is optionally substituted from 1 to 3 times with substitutents selected from the group consisting of C_1-C_3 alkyl, $-C(O)R^{13}$, and $-S(O)_nR^{13}$;

R^{12} is selected from the group consisting of H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, and $-C(O)R^{13}$, where each of C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{13} is selected from the group consisting of H, $-NR^{10}R^{11}$, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or

R^{12} and R^{13} are each independently selected from the group consisting of phenyl, benzyl, pyridazinyl, pyrimidinyl, pyrazinyl, 5- or 6-membered aromatic monocyclic heterocycles, and [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycles or heterocycles containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}; or

R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a heterocycle selected from the group consisting of piperidine, pyrrolidine, piperazine, 1,4-diazepane, morpholine, thiomorpholine, and other heterocycles containing 1-4 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, where the heterocycle is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, $-OR^{10}$, $-S(O)_nR^{10}$, $-C(O)R^{10}$, $-C(O)NR^{10}R^{11}$ and C_1-C_4 alkyl, where each of C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

n is 0, 1, or 2;

R^{14} is independently selected at each occurrence from a substituent in the group consisting of halogen, $-NO_2$, $-OR^{12}$, $-NR^{10}R^{11}$, $-NR^{12}C(O)_2R^{13}$, $-NR^{12}C(O)NR^{12}R^{13}$, $-S(O)_n R^{13}$, –CN, $-C(O)R^{13}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; and

R^{15} is independently selected at each occurrence from a substituent in the group consisting of –CN, halogen, $C(O)R^{13}$, C_1-C_3 alkyl, $-OR^{12}$, $-NR^{10}R^{11}$, $-S(O)_nR^{13}$, aryl,

and heteroaryl, where each of the aryl or heteroaryl groups is optionally substituted from 1 to 4 times with substituents as defined above in R^{14};

with the following provisos that (1) when R^4 is H, X cannot be phenyl or a phenyl substituted at the *para*-position with Cl; (2) when R^4 is H, OMe, or O-benzyl, X cannot be a phenyl substituted at the *para*-position with the same R^4; and (3) when R^2 is a 2-(4-nitrophenoxy)ethyl, R^5 cannot be $OC(O)NMe_2$;

or an oxide thereof, or a pharmaceutically acceptable salt thereof.

[0026] Results of recent clinical investigations with drugs, such as duloxetine, venlafaxine, atomoxetine, and others that work mechanistically through transporter reuptake inhibition, provide evidence that potency and selectivity are important factors in leading to drugs with an improved efficacy, improved therapeutic index, and utility for treatment of new clinical indications. Duloxetine, a dual action transporter reuptake inhibitor, is a selective inhibitor for serotonin transporter protein and norepinephrine transporter protein reuptake (Sorbera et al., *Drugs of the Future,* 25(9):907-916 (2000), and is in clinical development for the treatment of depression and stress urinary incontinence. In clinical studies, researchers attribute the effect of the medication on a broad spectrum of depression symptoms, which include emotional and painful physical symptoms as well as anxiety, to its dual reuptake inhibition of both serotonin and norepinephrine. Venlafaxine, which is also reported to be a selective serotonin and norepinephrine reuptake inhibitor (SNRI class), has been reported to exhibit a more rapid onset of action. The late onset of action has been a drawback with the first generation antidepressants, i.e., the single action serotonin selective reuptake inhibitors (SSRI class). For example, Prozac®, the prototype drug in this class, can take four weeks or longer for full anti-depressive activity to take effect.

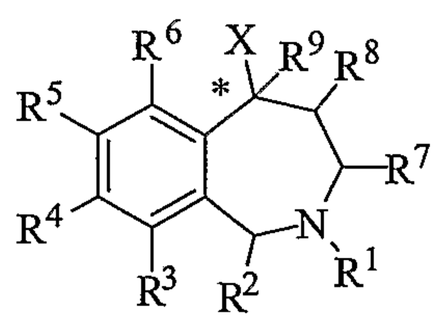
[0027] Atomoxetine (Strattera®) was recently approved for the treatment of ADHD. Atomoxetine is a norepinephrine selective transporter reuptake inhibitor. Unlike Ritalin®, one of the most frequently used drugs for treatment of ADHD, atomoxetine has little or no activity at the dopamine transporter. As a result,

atomoxetine has the advantage that it is not scheduled as a controlled substance because it has minimal potential for substance abuse.

[0028] In a manner similar to the newer clinical agents like atomoxetine, duloxetine, and venlafaxine, the compounds of the present invention may exhibit improved efficacy towards broader symptoms of depression. The compounds of the present invention may also exhibit more rapid onset of action in the treatment of central nervous system (CNS) diseases, such as depression. In addition to providing improved efficacy, the compounds of the present invention may also exhibit fewer undesirable side effects. Finally, because the compounds of the present invention possess a diverse transporter reuptake inhibition profile, they are expected to be useful for a wider variety of CNS disorders.

DETAILED DESCRIPTION OF THE INVENTION

[0029] The present invention relates to compounds represented by the formulae I(A-E) having the following structure:



I(A-E)

where:

the carbon atom designated * is in the R or S configuration; and

X represents a 5- or 6-membered aromatic or nonaromatic monocyclic carbocycle or heterocycle selected from the group consisting of phenyl, pyridyl, 2-oxo-pyridin-1-yl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyranyl, pyrrolyl, furanyl, thiophenyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, and tetrazolyl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}, or other 5- or 6-membered aromatic or non-

aromatic monocyclic carbocycles or heterocycles containing 1-4 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

X is a [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycle or heterocycle selected from the group consisting of indenyl, indanyl, benzofuranyl, benzothiophenyl, dihydrobenzothiophenyl, dihydrobenzofuranyl, indolyl, isoindolyl, indolinyl, benzo[1,3]dioxolyl, benzooxazolyl, benzothiazolyl, benzoisothiazolyl, benzoisoxazolyl, indazolyl, benzoimidazolyl, benzotriazolyl, naphthyl, tetrahydronaphthyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, phthalazinyl, quinoxalinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, 2,3-dihydro-benzo[1,4]dioxinyl, 4*H*-chromenyl, dihydrobenzocycloheptenyl, tetrahydrobenzocycloheptenyl, indolizinyl, quinolizinyl, 6*aH*-thieno[2,3-d]imidazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, thieno[2,3-*b*]furanyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[2,3-*b*]pyrazinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, 3,4-dihydro-2H-benzo[*b*][1,4]oxazinyl, imidazo[1,2-*a*]pyrazinyl, 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazinyl, 2-oxo-2,3-dihydrobenzo[*d*]oxazolyl, 3,3-dimethyl-2-oxoindolinyl, 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, and 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}, or other [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycles or heterocycles containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}; or

X is an alkene or alkyne, optionally substituted from 1 to 4 times with substitutents as defined below in R^{15};

R^1 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, each of which is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, each of which is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or

R^2 is gem-dimethyl;

R^3, R^5, and R^6 are each independently selected from the group consisting of H, halogen, $-OR^{12}$, $-S(O)_nR^{13}$, –CN, $-C(O)R^{13}$, $-NR^{10}R^{11}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of the C_1–C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or

R^3, R^5, and R^6 are each independently a 5- or 6-membered monocyclic carbocycle or heterocycle or a [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycle or heterocycle containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

R^4 is H, halogen, $-OR^{12}$, $-S(O)_nR^{13}$, –CN, $-C(O)R^{13}$, $-NR^{10}R^{11}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, where each of the C_1–C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^4 is a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, where the bridged bicyclic ring is optionally substituted from 1 to 3 times with substitutents selected from the group consisting of C_1-C_3 alkyl, $-C(O)R^{13}$, and $-S(O)_nR^{13}$; or

R^4 is phenyl, pyridyl, 2-oxo-pyridin-1-yl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyranyl, furanyl, pyrrolyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, indanyl, indenyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, indolinyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, indazolyl, benzimidazolyl, benzooxazolyl, benzothiazolyl, benzoisoxazolyl, benzoisothiazolyl, benzotriazolyl, benzo[1,3]dioxolyl, naphthyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl,

pthalazinyl, quinoxalinyl, 2,3-dihydro-benzo[1,4]dioxinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, 4*H*-chromenyl, indolizinyl, quinolizinyl, 6*aH*-thieno[2,3-d]imidazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, [1,2,4]triazolo[1,5-*a*]pyridinyl, thieno[2,3-*b*]furanyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[2,3-*b*]pyrazinyl, imidazo[1,2-*a*]pyrazinyl, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazinyl, 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazinyl, 2-oxo-2,3-dihydrobenzo[*d*]oxazolyl, 3,3-dimethyl-2-oxoindolinyl, 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, 3,4-dihydro-2H-benzo[*b*][1,4]oxazinyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazinyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, or other 5- or 6-membered aromatic or non-aromatic monocyclic carbocycles or heterocycles, or [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycles or heterocycles containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

provided that for compounds of formula IA, X is substituted phenyl and R^4 is substituted monocyclic or bicyclic aryl or heteroaryl;
provided that for compounds of formula IB, X is substituted bicyclic aryl or heteroaryl and R^4 is substituted monocyclic or bicyclic aryl or heteroaryl;
provided that for compounds of formula IC, X is substituted phenyl and R^4 is H, $-OR^{12}$, $-S(O)_nR^{13}$, $C(O)R^{13}$, $-NR^{10}R^{11}$, -CN, halogen, or C_1-C_6 alkyl, where each of the C_1-C_6 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};
provided that for compounds of formula ID, X is substituted bicyclic aryl or heteroaryl and R^4 is H, $-OR^{12}$, $-S(O)_nR^{13}$, $C(O)R^{13}$, $-NR^{10}R^{11}$, -CN, halogen, or C_1-C_6 alkyl, where each of the C_1-C_6 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; and
provided that for compounds of formula IE, X is substituted monocyclic heteroaryl and R^4 is substituted monocyclic or bicyclic aryl or heteroaryl;

R^7 is selected from the group consisting of H,–$S(O)_nR^{13}$, –$C(O)R^{13}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of C_1 –C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^8 is selected from the group consisting of H, halogen, –OR^{12}, –$S(O)_nR^{13}$, –CN, -$C(O)R^{13}$, -$NR^{10}R^{11}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of C_1 –C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or

R^7 and R^8 are gem-dimethyl, with the proviso that only one of R^7 and R^8 is gem-dimethyl;

R^9 is H, halogen,-OR^{12}, -SR^{10}, C_1-C_6 alkyl, -CN, or –$NR^{10}R^{11}$, where each of C_1 –C_6 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{10} and R^{11} are each independently selected from the group consisting of H, -$C(O)R^{13}$, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of C_1 -C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{10} and R^{11} are each independently selected from the group consisting of phenyl, benzyl, and other 5- or 6-membered monocyclic heterocycles, where each of the phenyl, benzyl, and 5- or 6-membered monocyclic heterocycle is optionally substituted from 1 to 3 times with substituents as defined below in R^{14};

R^{10} and R^{11} are taken together with the nitrogen to which they are attached to form a saturated or partially saturated monocyclic or fused bicyclic heterocycle selected from the group consisting of piperidine, pyrrolidine, morpholine, thiomorpholine, [1,2]oxazinane, isoxazolidine, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 3-oxomorpholino, 3-oxothiomorpholino, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazine, and other monocyclic or fused bicyclic heterocycles

containing 1-4 heteroatoms selected from oxygen, nitrogen and sulfur, wherein the heterocycle is attached to the benzazepine core via the nitrogen atom, and is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, $-OR^{12}$, $-NR^{12}R^{13}$, $-S(O)_nR^{13}$, $-C(O)R^{13}$, and C_1-C_4 alkyl, where each of C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};
R^{10} and R^{11} are taken together with the nitrogen to which they are attached to form a heterocycle selected from the group consisting of piperazine, 2-oxopiperazinyl, 2-oxo-1,4-diazepanyl, 5-oxo-1,4-diazepanyl, 1,4-diazepane, and other heterocycles containing one additional nitrogen atom in the ring, where the heterocycle is optionally substituted on a ring carbon with from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, $-OR^{12}$, $-NR^{12}R^{13}$, $-S(O)_nR^{13}$, $-C(O)R^{13}$, and C_1-C_4 alkyl, or on the additional nitrogen atom from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of $S(O)_nR^{13}$, $-C(O)R^{13}$, and C_1-C_4 alkyl, wherein each of C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};
R^{10} and R^{11} are taken together with the nitrogen to which they are attached to form a heterocycle selected from the group consisting of piperazine, 2-oxopiperazinyl, 2-oxo-1,4-diazepanyl, 5-oxo-1,4-diazepanyl, 1,4-diazepane, and other heterocycles containing one additional nitrogen atom in the ring, where the heterocycle is optionally substituted on the additional nitrogen atom with a substituent selected independently at each occurrence thereof from the group consisting of phenyl, benzyl, and 5- or 6-membered aromatic heterocycles containing 1-3 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, where each of the phenyl, benzyl, and 5- and 6-membered heterocycle is optionally substituted from 1 to 3 times with substituents as defined below in R^{14}; or
when R^4 is $-NR^{10}R^{11}$ or $-C(O)NR^{10}R^{11}$, either R^{10} or R^{11} is a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, where the bridged bicyclic ring is optionally substituted from 1 to 3 times with substituents selected from the group consisting of C_1-C_3 alkyl, $-C(O)R^{13}$, and $-S(O)_nR^{13}$, or either R^{10} or R^{11} is a C_1-C_3 alkyl substituted with a bridged bicyclic ring containing 6-12 carbon

atoms and optionally containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, where the bridged bicyclic ring is optionally substituted from 1 to 3 times with substitutents selected from the group consisting of C_1-C_3 alkyl, $-C(O)R^{13}$, and $-S(O)_nR^{13}$;

R^{12} is selected from the group consisting of H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, and $-C(O)R^{13}$, where each of C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{13} is selected from the group consisting of H, $-NR^{10}R^{11}$, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or

R^{12} and R^{13} are each independently selected from the group consisting of phenyl, benzyl, pyridazinyl, pyrimidinyl, pyrazinyl, 5- or 6-membered aromatic monocyclic heterocycles, and [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycles or heterocycles containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}; or

R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a heterocycle selected from the group consisting of piperidine, pyrrolidine, piperazine, 1,4-diazepane, morpholine, thiomorpholine, and other heterocycles containing 1-4 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, where the heterocycle is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, $-OR^{10}$, $-S(O)_nR^{10}$, $-C(O)R^{10}$, $-C(O)NR^{10}R^{11}$ and C_1-C_4 alkyl, where each of C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

n is 0, 1, or 2;

R^{14} is independently selected at each occurrence from a substituent in the group consisting of halogen, $-NO_2$, $-OR^{12}$, $-NR^{10}R^{11}$, $-NR^{12}C(O)_2R^{13}$, $-NR^{12}C(O)NR^{12}R^{13}$, $-S(O)_n R^{13}$, –CN, $-C(O)R^{13}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; and

R^{15} is independently selected at each occurrence from a substituent in the group consisting of –CN, halogen, $C(O)R^{13}$, C_1-C_3 alkyl, $-OR^{12}$, $-NR^{10}R^{11}$, $-S(O)_nR^{13}$, aryl, and heteroaryl, where each of the aryl or heteroaryl groups is optionally substituted from 1 to 4 times with substituents as defined above in R^{14};

with the following provisos that (1) when R^4 is H, X cannot be phenyl; (2) when R^4 is (a) C_{1-6} alkyl, (b) C_{1-4} alkoxy, (c) hydroxyl, (d) halogen, (e) CN, (f) NO_2, (g) $NHSO_2CH_3$, or (h) COOH, X cannot be a phenyl substituted at the *para*-position with the same R^4; (3) when any one of R^3, R^4, R^5, and $R^6$is hydrogen, halogen, perhalomethyl, optionally substituted C_{1-6}-alkyl, hydroxy, optionally substituted C_{1-6}-alkoxy, nitro, cyano, amino, optionally substituted mono- or optionally substituted di-C_{1-6}-alkylamino, acylamino, C_{1-6}-alkoxycarbonyl, carboxy, or carbamoyl, X cannot be furanyl, thienyl, pyrazolyl, tetrazolyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-oxadiazolyl, 1,2,5-thiadiazolyl, benzo[d]isoxazolyl, or benzo[d]isothiazolyl; (4) when R^4 is $-S(O)_nR^{13}$, n cannot be 0; and (5) when R^9 is a substituted alkyl, R^{15} cannot be $-NR^{10}R^{11}$;

or an oxide thereof, or a pharmaceutically acceptable salt thereof.

[0030] As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

[0031] The term "monocyclic carbocycle" means a monocyclic ring system of 5 to about 8 ring carbon atoms, preferably 5 or 6. The ring is nonaromatic, but may contain one or more carbon-carbon double bonds. Representative monocyclic

carbocycles include cyclopentyl, cyclohexyl, cyclopentenyl, cyclohexenyl, and the like.

[0032] The term "monocyclic heterocycle" means a monocyclic ring system consisting of about 5 to 8 ring atoms, preferably 5 or 6, in which one or more of the atoms in the ring system is/are element(s) other than carbon, for example, nitrogen, oxygen, or sulfur. The prefix aza, oxa, or thio before heterocycle means that at least a nitrogen, oxygen, or sulfur atom, respectively, is present as a ring atom. A nitrogen atom of a heteroaryl is optionally oxidized to the corresponding N-oxide. The ring is nonaromatic, but may be fused to an aromatic ring. Representative monocyclic heterocycles include pyrrolidine, piperidine, piperazine, and the like.

[0033] The term "aromatic monocyclic heterocycle" means a monocyclic ring system consisting of about 5 to 8 ring atoms, preferably 5 or 6, in which one or more of the atoms in the ring system is/are element(s) other than carbon, for example, nitrogen, oxygen, or sulfur. The prefix aza, oxa, or thio before heterocycle means that at least a nitrogen, oxygen, or sulfur atom, respectively, is present as a ring atom. A nitrogen atom of a heteroaryl is optionally oxidized to the corresponding N-oxide. The ring is aromatic. Representative aromatic monocyclic heterocycles include pyrrole, pyridine, oxazole, thiazole, and the like.

[0034] The term "fused bicyclic carbocycle" means a bicyclic ring system consisting of about 8 to 11 ring carbon atoms, preferably 9 or 10. One or both of the rings is/are aromatic. Representative fused bicyclic carbocycles include indenyl, indanyl, naphthyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptenyl, dihydrobenzocycloheptenyl, tetrahydrobenzocycloheptenyl, and the like.

[0035] The term "fused bicyclic heterocycle" means a bicyclic ring system consisting of about 8 to 13 ring atoms, preferably 9 or 10, in which one or more of the atoms in the ring system is/are element(s) other than carbon, for example, nitrogen, oxygen, or sulfur. The prefix aza, oxa, or thio before heterocycle means that at least a nitrogen, oxygen, or sulfur atom, respectively, is present as a ring atom. A nitrogen atom of a heteroaryl is optionally oxidized to the corresponding N-oxide. Representative fused bicyclic heterocycles include benzofuranyl, benzothiophenyl, benzoisothiazolyl, benzoisoxazolyl, indazolyl, indolyl, isoindolyl, indolizinyl, benzoimidazolyl, benzooxazolyl, benzothiazolyl, benzotriazolyl, imidazo[1,2-a]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, 5,6,7,8-

tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazinyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, 1H-pyrrolo[2,3-*b*]pyridinyl, chromenyl, dihydrobenzothiophenyl, dihydrobenzofuranyl, indolinyl, quinolinyl, isoquinolinyl, 4H-quinolizinyl, 9*aH*-quinolizinyl, quinazolinyl, cinnolinyl, quinoxalinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, and the like.

[0036] The term "bridged bicyclic ring" means a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur. Representative bridged bicyclic rings include quinuclidine, 9-azabicyclo[3.3.1]nonane, 7-azabicyclo[2.2.1]heptane, 2,5-diazabicyclo[2.2.2]octane, and the like.

[0037] The term "alkyl" means an aliphatic hydrocarbon group which may be straight or branched having about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkyl chain. Representative alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, n-pentyl, and 3-pentyl.

[0038] The term "alkenyl" means an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be straight or branched having 2 to about 6 carbon atoms in the chain. Preferred alkenyl groups have 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkenyl chain. Representative alkenyl groups include ethenyl, propenyl, n-butenyl, and i-butenyl.

[0039] The term "alkynyl" means an aliphatic hydrocarbon group containing a carbon-carbon triple bond and which may be straight or branched having 2 to about 6 carbon atoms in the chain. Preferred alkynyl groups have 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkynyl chain. Representative alkynyl groups include ethynyl, propynyl, n-butynyl, 2-butynyl, 3-methylbutynyl, and n-pentynyl.

[0040] The term "cycloalkyl" means a non-aromatic mono- or multicyclic ring system of about 3 to about 7 carbon atoms, preferably of about 5 to about 7 carbon atoms. Representative monocyclic cycloalkyl include cyclopentyl, cyclohexyl, cycloheptyl, and the like.

[0041] The term "cycloalkylalkyl" means a cycloalkyl-alkyl-group in which the cycloalkyl and alkyl are as defined herein. Representative cycloalkylalkyl groups include cyclopropylmethyl and cyclopentylmethyl.

[0042] The term "aryl" means an aromatic monocyclic or multicyclic ring system of 6 to about 14 carbon atoms, preferably of 6 to about 10 carbon atoms. Representative aryl groups include phenyl and naphthyl.

[0043] The term "heteroaryl" means an aromatic monocyclic or multicyclic ring system of 6 to about 14 ring atoms, preferably of 6 to about 10 ring atoms, in which one or more of the atoms in the ring system is/are element(s) other than carbon, for example, nitrogen, oxygen or sulfur. Representative heteroaryl groups include pyridinyl, pyridazinyl and quinolinyl.

[0044] The term "alkoxy" means an alkyl–O–group where the alkyl group is as herein described. Representative alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy and heptoxy.

[0045] The term "halo" or "halogen" means fluoro, chloro, bromo, or iodo.

[0046] The term "haloalkyl" means both branched and straight-chain alkyl substituted with 1 or more halogen, where the alkyl group is as herein described.

[0047] The term "haloalkoxy" means a C_{1-4} alkoxy group substituted by at least one halogen atom, where the alkoxy group is as herein described.

[0048] The term "substituted" or "substitution" of an atom means that one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded. "Unsubstituted" atoms bear all of the hydrogen atoms dictated by their valency. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds; by "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

[0049] The term "compounds of the invention", and equivalent expressions, are meant to embrace compounds of general formulae I(A-E), as well as formula (II), as hereinbefore described, which expression includes the prodrugs, the pharmaceutically acceptable salts, and the solvates, e.g. hydrates, where the context so

permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits. For the sake of clarity, particular instances when the context so permits are sometimes indicated in the text, but these instances are purely illustrative and it is not intended to exclude other instances when the context so permits.

[0050] The term "pharmaceutically acceptable salts" means the relatively non-toxic, inorganic and organic acid addition salts, and base addition salts, of compounds of the present invention. These salts can be prepared in situ during the final isolation and purification of the compounds. In particular, acid addition salts can be prepared by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative acid addition salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactiobionate, sulphamates, malonates, salicylates, propionates, methylene-bis-b-hydroxynaphthoates, gentisates, isethionates, di-p-toluoyltartrates, methane-sulphonates, ethanesulphonates, benzenesulphonates, p-toluenesulphonates, cyclohexylsulphamates and quinateslaurylsulphonate salts, and the like. (See, for example Berge et al., *J Pharm Sci*, 66:1-sup.19 (1977) and *Remington's Pharmaceutical Sciences*, 17th ed, p. 1418, Mack Publishing Company, Easton, PA (1985).

Base addition salts can also be prepared by separately reacting the purified compound in its acid form with a suitable organic or inorganic base and isolating the salt thus formed. Base addition salts include pharmaceutically acceptable metal and amine salts. Suitable metal salts include the sodium, potassium, calcium, barium, zinc, magnesium, and aluminum salts. The sodium and potassium salts are preferred. Suitable inorganic base addition salts are prepared from metal bases which include sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminum hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide. Suitable amine base addition salts are prepared from amines which have sufficient basicity to form a stable salt, and preferably include the following amines which are frequently used in medicinal chemistry because of their low toxicity and acceptability for medical use: ammonia, ethylenediamine, N-methyl-glucamine, lysine, arginine,

ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, triethylamine, dibenzylamine, ephenamine, dehydroabietylamine, N-ethylpiperidine, benzylamine, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, ethylamine, basic amino acids, e.g., lysine and arginine, and dicyclohexylamine, and the like.

[0051] The term "pharmaceutically acceptable prodrugs" as used herein means those prodrugs of the compounds useful according to the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "prodrug" means compounds that are rapidly transformed *in vivo* to yield the parent compound of the above formula, for example by hydrolysis in blood. Functional groups which may be rapidly transformed, by metabolic cleavage, *in vivo* form a class of groups reactive with the carboxyl group of the compounds of this invention. They include, but are not limited to such groups as alkanoyl (such as acetyl, propionyl, butyryl, and the like), unsubstituted and substituted aroyl (such as benzoyl and substituted benzoyl), alkoxycarbonyl (such as ethoxycarbonyl), trialkylsilyl (such as trimethyl- and triethysilyl), monoesters formed with dicarboxylic acids (such as succinyl), and the like. Because of the ease with which the metabolically cleavable groups of the compounds useful according to this invention are cleaved *in vivo*, the compounds bearing such groups act as pro-drugs. The compounds bearing the metabolically cleavable groups have the advantage that they may exhibit improved bioavailability as a result of enhanced solubility and/or rate of absorption conferred upon the parent compound by virtue of the presence of the metabolically cleavable group. A thorough discussion of prodrugs is provided in the following: Bundgaard, ed., *Design of Prodrugs*, Elsevier (1985); Widder et al., *Methods in Enzymology*, ed., Academic Press, 42:309-396 (1985); "Design and Applications of Prodrugs," Krogsgaard-Larsen, ed., *A Textbook of Drug Design and Development*, Chapter 5:113-191 (1991); Bundgaard, "*Advanced Drug Delivery Reviews*," 8:1-38 (1992); Bundgaard et al., *Journal of Pharmaceutical Sciences*,

77:285 (1988); Nakeya et al., *Chem Pharm Bull*, 32:692 (1984); Higuchi, "Pro-drugs as Novel Delivery Systems" Roche, ed., A.C.S. Symposium Series, Vol. 14, and "Bioreversible Carriers in Drug Design" American Pharmaceutical Association and Pergamon Press (1987).

Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the invention.

[0052] The term "therapeutically effective amounts" is meant to describe an amount of compound of the present invention effective in increasing the levels of serotonin, norepinephrine or dopamine at the synapse and thus producing the desired therapeutic effect. Such amounts generally vary according to a number of factors well within the purview of ordinarily skilled artisans given the description provided herein to determine and account for. These include, without limitation: the particular subject, as well as its age, weight, height, general physical condition and medical history, the particular compound used, as well as the carrier in which it is formulated and the route of administration selected for it; and, the nature and severity of the condition being treated.

[0053] The term "pharmaceutical composition" means a composition comprising compounds of formulae I(A-E) and formula II and at least one component selected from the group comprising pharmaceutically acceptable carriers, diluents, adjuvants, excipients, or vehicles, such as preserving agents, fillers, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents, perfuming agents, antibacterial agents, antifungal agents, lubricating agents and dispensing agents, depending on the nature of the mode of administration and dosage forms. Examples of suspending agents include ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin. Examples of suitable carriers, diluents, solvents or vehicles include water, ethanol, polyols, suitable mixtures

thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Examples of excipients include lactose, milk sugar, sodium citrate, calcium carbonate, and dicalcium phosphate. Examples of disintegrating agents include starch, alginic acids, and certain complex silicates. Examples of lubricants include magnesium stearate, sodium lauryl sulphate, talc, as well as high molecular weight polyethylene glycols.

[0054] The term "pharmaceutically acceptable" means it is, within the scope of sound medical judgment, suitable for use in contact with the cells of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio.

[0055] The term "pharmaceutically acceptable dosage forms" means dosage forms of the compound of the invention, and includes, for example, tablets, dragees, powders, elixirs, syrups, liquid preparations, including suspensions, sprays, inhalants tablets, lozenges, emulsions, solutions, granules, capsules and suppositories, as well as liquid preparations for injections, including liposome preparations. Techniques and formulations generally may be found in Remington's Pharmaceutical Sciences, 17th ed, Easton, Pa., Mack Publishing Company (1985).

[0056] One embodiment of the present invention relates to the compound of formula (IA), where X is substituted phenyl and R^4 is substituted monocyclic or bicyclic aryl or heteroaryl.

[0057] Another embodiment of the present invention relates to the compound of formula (IB), where X is substituted bicyclic aryl or heteroaryl and R^4 is substituted monocyclic or bicyclic aryl or heteroaryl.

[0058] Another embodiment of the present invention relates to the compound of formula (IC), where X is substituted phenyl and R^4 is H, $-OR^{12}$, $-S(O)_nR^{13}$, $C(O)R^{13}$, $-NR^{10}R^{11}$, -CN, halogen, and C_1-C_6 alkyl, where each of the C_1-C_6 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}.

[0059] Another embodiment of the present invention relates to the compound of formula (ID), where X is substituted bicyclic aryl or heteroaryl and R^4 is H, $-OR^{12}$, $-S(O)_nR^{13}$, $C(O)R^{13}$, $-NR^{10}R^{11}$, -CN, halogen, or C_1-C_6 alkyl, where each of the C_1-C_6 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}.

[0060] Another embodiment of the present invention relates to the compound of formula (IE), where X is substituted monocyclic heteroaryl and R^4 is substituted monocyclic or bicyclic aryl or heteroaryl.

[0061] Another embodiment of the present invention relates to the compound of formulae (IA-E) where:

X is phenyl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

R^1 is H, methyl, ethyl, or isopropyl;

R^2 is H, methyl, or gem-dimethyl;

R^3 is H, methyl, hydroxy, methoxy, fluoro, chloro, cyano, trifluoromethyl, or trifluoromethoxy;

R^4 is H, halogen, $-OR^{12}$, $-S(O)_nR^{13}$, –CN, $-C(O)R^{13}$, $-NR^{10}R^{11}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, where each of the C_1–C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or

R^4 is a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, where the bridged bicyclic ring is optionally substituted from 1 to 3 times with substitutents selected from the group consisting of C_1-C_3 alkyl, $-C(O)R^{13}$, and $-S(O)_nR^{13}$;

R^5 is H, fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxy or methoxy;

R^6 is H, fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxy or methoxy;

R^7 is H, gem-dimethyl, or C_1–C_4 alkyl, where each of the C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^8 is H, hydroxy, fluoro, chloro, methyl, C_1–C_3 alkyl optionally substituted with hydroxyl or amino, or amino optionally substituted with C_1–C_3 alkyl;

R^9 is H, fluoro, chloro, methyl, hydroxyl, or cyano;

R^{14} is independently selected at each occurrence from a substituent in the group consisting of halogen, $-NO_2$, $-OR^{12}$, $-NR^{10}R^{11}$, $-NR^{12}C(O)_2R^{13}$, $-NR^{12}C(O)NR^{12}R^{13}$, $-S(O)_n R^{13}$, –CN, $-C(O)R^{13}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; and

R^{15} is independently selected at each occurrence from a substituent in the group consisting of halogen, $-C(O)R^{13}$, –CN, C_1-C_3 alkyl, $-OR^{12}$, $-NR^{10}R^{11}$, $-S(O)_nR^{13}$, aryl, and heteroaryl, where each of the aryl or heteroaryl groups is optionally substituted from 1 to 4 times with substituents as defined above in R^{14}.

[0062] Another embodiment of the present invention relates to the compound of formulae (IA-E) where:

X is phenyl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

R^1 is H, methyl, ethyl, or isopropyl;

R^2 is H, methyl, or gem-dimethyl;

R^3 is H, methyl, hydroxy, methoxy, fluoro, chloro, cyano, trifluoromethyl, or trifluoromethoxy;

R^4 is phenyl, pyridyl, 2-oxo-pyridin-1-yl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyranyl, furanyl, pyrrolyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, indanyl, indenyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, indolinyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, indazolyl, benzimidazolyl, benzooxazolyl, benzothiazolyl, benzoisoxazolyl, benzoisothiazolyl, benzotriazolyl, benzo[1,3]dioxolyl, naphthyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, pthalazinyl, quinoxalinyl, 2,3-dihydro-benzo[1,4]dioxinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, 4*H*-chromenyl, indolizinyl, quinolizinyl, 6*aH*-thieno[2,3-d]imidazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, [1,2,4]triazolo[1,5-*a*]pyridinyl, thieno[2,3-*b*]furanyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[2,3-*b*]pyrazinyl, imidazo[1,2-*a*]pyrazinyl, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazinyl, 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazinyl, 2-oxo-2,3-dihydrobenzo[*d*]oxazolyl, 3,3-dimethyl-2-oxoindolinyl, 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, 3,4-dihydro-2H-benzo[*b*][1,4]oxazinyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazinyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, or other 5- or 6-membered aromatic or non-aromatic monocyclic carbocycles or heterocycles or [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycles or heterocycles containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

R^5 is H, fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, or methoxy;

R^6 is H, fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, or methoxy;

R^7 is H, gem-dimethyl, or C_1–C_4 alkyl, where each of the C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^8 is H, hydroxy, fluoro, chloro, methyl, C_1–C_3 alkyl optionally substituted with hydroxyl or amino, or amino optionally substituted with C_1–C_3 alkyl;

R^9 is H, fluoro, chloro, methyl, hydroxyl, or cyano;

R^{14} is independently selected at each occurrence from a substituent in the group consisting of halogen, $-NO_2$, $-OR^{12}$, $-NR^{10}R^{11}$, $-NR^{12}C(O)_2R^{13}$, $-NR^{12}C(O)NR^{12}R^{13}$, $-S(O)_n R^{13}$, –CN, $-C(O)R^{13}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; and

R^{15} is independently selected at each occurrence from a substituent in the group consisting of halogen, $-C(O)R^{13}$, –CN, C_1-C_3 alkyl, $-OR^{12}$, $-NR^{10}R^{11}$, $-S(O)_nR^{13}$, aryl, and heteroaryl, where each of the aryl or heteroaryl groups is optionally substituted from 1 to 4 times with substituents as defined above in R^{14}.

[0063] Another embodiment of the present invention relates to the compound of formulae (IA-E) where:

X represents a 5- or 6-membered monocyclic heterocycle selected from the group consisting of pyridyl, 2-oxo-pyridin-1-yl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyranyl, pyrrolyl, furanyl, thiophenyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, and tetrazolyl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}, or other 5- or 6-membered aromatic or non-aromatic monocyclic carbocycles or heterocycles containing 1-4 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}; or

X, in compounds represented by formula (I), is an alkene or alkyne, optionally substituted from 1 to 4 times with substitutents as defined below in R^{15};

R^1 is H, methyl, ethyl, or isopropyl;

R^2 is H, methyl, or gem-dimethyl;

R^3 is H, methyl, hydroxy, methoxy, fluoro, chloro, cyano, trifluoromethyl, or trifluoromethoxy;

R^4 is H, halogen, $-OR^{12}$, $-S(O)_nR^{13}$, –CN, $-C(O)R^{13}$, $-NR^{10}R^{11}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, where each of the C_1–C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or
R^4 is a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, where the bridged bicyclic ring is optionally substituted from 1 to 3 times with substitutents selected from the group consisting of C_1-C_3 alkyl, $-C(O)R^{13}$, and $-S(O)_nR^{13}$;

R^5 is H, fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, or methoxy;

R^6 is H, fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, or methoxy;

R^7 is H, gem-dimethyl, or C_1–C_4 alkyl, where each of the C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^8 is H, hydroxy, fluoro, chloro, C_1–C_3 alkyl optionally substituted with hydroxyl or amino, or amino optionally substituted with C_1–C_3 alkyl;

R^9 is H, fluoro, chloro, methyl, hydroxyl, or cyano;

R^{14} is independently selected at each occurrence from a substituent in the group consisting of halogen, $-NO_2$, $-OR^{12}$, $-NR^{10}R^{11}$, $-NR^{12}C(O)_2R^{13}$, $-NR^{12}C(O)NR^{12}R^{13}$, $-S(O)_n R^{13}$, –CN, $-C(O)R^{13}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; and

R^{15} is independently selected at each occurrence from a substituent in the group consisting of halogen, $-C(O)R^{13}$, –CN, C_1-C_3 alkyl, $-OR^{12}$, $-NR^{10}R^{11}$, $-S(O)_nR^{13}$, aryl, and heteroaryl, where each of the aryl or heteroaryl groups is optionally substituted from 1 to 4 times with substituents as defined above in R^{14}.

[0064] Another embodiment of the present invention relates to the compound of formulae (IA-E) where:

X represents a 5- or 6-membered monocyclic heterocycle selected from the group consisting of pyridyl, 2-oxo-pyridin-1-yl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyranyl, pyrrolyl, furanyl, thiophenyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, and tetrazolyl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}, or other 5- or 6-membered aromatic or non-aromatic monocyclic carbocycles or heterocycles containing 1-4 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}; or

X, in compounds represented by formula (I), is an alkene or alkyne, optionally substituted from 1 to 4 times with substitutents as defined below in R^{15};

R^1 is H, methyl, ethyl, or isopropyl;

R^2 is H, methyl, or gem-dimethyl;

R^3 is H, methyl, hydroxy, methoxy, fluoro, chloro, cyano, trifluoromethyl, or trifluoromethoxy;

R^4 is phenyl, pyridyl, 2-oxo-pyridin-1-yl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyranyl, furanyl, pyrrolyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, indanyl, indenyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, indolinyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, indazolyl, benzimidazolyl, benzooxazolyl, benzothiazolyl, benzoisoxazolyl, benzoisothiazolyl, benzotriazolyl, benzo[1,3]dioxolyl, naphthyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, pthalazinyl, quinoxalinyl, 2,3-dihydro-benzo[1,4]dioxinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, 4*H*-chromenyl, indolizinyl, quinolizinyl, 6*aH*-thieno[2,3-d]imidazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, [1,2,4]triazolo[1,5-*a*]pyridinyl, thieno[2,3-*b*]furanyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[2,3-*b*]pyrazinyl, imidazo[1,2-*a*]pyrazinyl, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazinyl, 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazinyl, 2-oxo-2,3-dihydrobenzo[*d*]oxazolyl, 3,3-dimethyl-2-oxoindolinyl, 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, 3,4-dihydro-2H-benzo[*b*][1,4]oxazinyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazinyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, or other 5- or 6-membered aromatic or non-aromatic monocyclic carbocycles or heterocycles or [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycles or heterocycles containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

R^5 is H, fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, or methoxy;

R^6 is H, fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, or methoxy;

R^7 is H, gem-dimethyl, or C_1–C_4 alkyl, where each of the C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^8 is H, hydroxy, fluoro, chloro, C_1–C_3 alkyl optionally substituted with hydroxyl or amino, or amino optionally substituted with C_1–C_3 alkyl;

R^9 is H, fluoro, chloro, methyl, hydroxyl or cyano;

R^{14} is independently selected at each occurrence from a substituent in the group consisting of halogen, $-NO_2$, $-OR^{12}$, $-NR^{10}R^{11}$, $-NR^{12}C(O)_2R^{13}$, $-NR^{12}C(O)NR^{12}R^{13}$, $-S(O)_n R^{13}$, –CN, $-C(O)R^{13}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; and

R^{15} is independently selected at each occurrence from a substituent in the group consisting of halogen, $-C(O)R^{13}$, –CN, C_1-C_3 alkyl, $-OR^{12}$, $-NR^{10}R^{11}$, $-S(O)_nR^{13}$, aryl, and heteroaryl, where each of the aryl or heteroaryl groups is optionally substituted from 1 to 4 times with substituents as defined above in R^{14}.

[0065] Another embodiment of the present invention relates to the compound of formulae (IA-E) where:

X is a [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycle or heterocycle selected from the group consisting of indenyl, indanyl, benzofuranyl, benzothiophenyl, dihydrobenzothiophenyl, dihydrobenzofuranyl, indolyl, isoindolyl, indolinyl, benzo[1,3]dioxolyl, benzooxazolyl, benzothiazolyl, benzoisothiazolyl, benzoisoxazolyl, indazolyl, benzoimidazolyl, benzotriazolyl, naphthyl, tetrahydronaphthyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, phthalazinyl, quinoxalinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, 2,3-dihydro-benzo[1,4]dioxinyl, 4*H*-chromenyl, dihydrobenzocycloheptenyl, tetrahydrobenzocycloheptenyl, indolizinyl, quinolizinyl, 6*aH*-thieno[2,3-d]imidazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl,

[1,2,4]triazolo[4,3-*a*]pyridinyl, thieno[2,3-*b*]furanyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[2,3-*b*]pyrazinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, 3,4-dihydro-2H-benzo[*b*][1,4]oxazinyl, imidazo[1,2-*a*]pyrazinyl, 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazinyl, 2-oxo-2,3-dihydrobenzo[*d*]oxazolyl, 3,3-dimethyl-2-oxoindolinyl, 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, and 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}, or other [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycles or heterocycles containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

R^1 is H, methyl, ethyl, or isopropyl;

R^2 is H, methyl, or gem-dimethyl;

R^3 is H, methyl, hydroxy, methoxy, fluoro, chloro, cyano, trifluoromethyl, or trifluoromethoxy;

R^4 is H, halogen, $-OR^{12}$, $-S(O)_nR^{13}$, –CN, $-C(O)R^{13}$, $-NR^{10}R^{11}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, where each of the C_1–C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or

R^4 is a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, where the bridged bicyclic ring is optionally substituted from 1 to 3 times with substitutents selected from the group consisting of C_1-C_3 alkyl, $-C(O)R^{13}$, and $-S(O)_nR^{13}$;

R^5 is H, fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, or methoxy;

R^6 is H, fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, or methoxy;

R^7 is H, gem-dimethyl, or C_1–C_4 alkyl, where each of the C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^8 is H, hydroxy, fluoro, chloro, C_1–C_3 alkyl optionally substituted with hydroxyl or amino, or amino optionally substituted with C_1–C_3 alkyl;

R^9 is H, fluoro, chloro, methyl, hydroxyl, or cyano;

R^{14} is independently selected at each occurrence from a substituent in the group consisting of halogen, $-NO_2$, $-OR^{12}$, $-NR^{10}R^{11}$, $-NR^{12}C(O)_2R^{13}$, $-NR^{12}C(O)NR^{12}R^{13}$, $-S(O)_n R^{13}$, –CN, $-C(O)R^{13}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; and

R^{15} is independently selected at each occurrence from a substituent in the group consisting of halogen, $-C(O)R^{13}$, –CN, C_1-C_3 alkyl, $-OR^{12}$, $-NR^{10}R^{11}$, $-S(O)_nR^{13}$, aryl, and heteroaryl, where each of the aryl or heteroaryl groups is optionally substituted from 1 to 4 times with substituents as defined above in R^{14}.

[0066] Another embodiment of the present invention relates to the compound of formulae (IA-E) where:

X is a [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycle or heterocycle selected from the group consisting of indenyl, indanyl, benzofuranyl, benzothiophenyl, dihydrobenzothiophenyl, dihydrobenzofuranyl, indolyl, isoindolyl, indolinyl, benzo[1,3]dioxolyl, benzooxazolyl, benzothiazolyl, benzoisothiazolyl,

benzoisoxazolyl, indazolyl, benzoimidazolyl, benzotriazolyl, naphthyl, tetrahydronaphthyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, phthalazinyl, quinoxalinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, 2,3-dihydro-benzo[1,4]dioxinyl, 4*H*-chromenyl, dihydrobenzocycloheptenyl, tetrahydrobenzocycloheptenyl, indolizinyl, quinolizinyl, 6*aH*-thieno[2,3-d]imidazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, thieno[2,3-*b*]furanyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[2,3-*b*]pyrazinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, 3,4-dihydro-2H-benzo[*b*][1,4]oxazinyl, imidazo[1,2-*a*]pyrazinyl, 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazinyl, 2-oxo-2,3-dihydrobenzo[*d*]oxazolyl, 3,3-dimethyl-2-oxoindolinyl, 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, and 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}, or other [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycles or heterocycles containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

R^1 is H, methyl, ethyl, or isopropyl;

R^2 is H, methyl, or gem-dimethyl;

R^3 is H, methyl, hydroxy, methoxy, fluoro, chloro, cyano, trifluoromethyl, or trifluoromethoxy;

R^4 is phenyl, pyridyl, 2-oxo-pyridin-1-yl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyranyl, furanyl, pyrrolyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, indanyl, indenyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, indolinyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, indazolyl, benzimidazolyl, benzooxazolyl, benzothiazolyl, benzoisoxazolyl, benzoisothiazolyl, benzotriazolyl,

benzo[1,3]dioxolyl, naphthyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, pthalazinyl, quinoxalinyl, 2,3-dihydro-benzo[1,4]dioxinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, 4*H*-chromenyl, indolizinyl, quinolizinyl, 6*aH*-thieno[2,3-d]imidazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, [1,2,4]triazolo[1,5-*a*]pyridinyl, thieno[2,3-*b*]furanyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[2,3-*b*]pyrazinyl, imidazo[1,2-*a*]pyrazinyl, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazinyl, 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazinyl, 2-oxo-2,3-dihydrobenzo[*d*]oxazolyl, 3,3-dimethyl-2-oxoindolinyl, 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, 3,4-dihydro-2H-benzo[*b*][1,4]oxazinyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazinyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, or other 5- or 6-membered aromatic or non-aromatic monocyclic carbocycles or heterocycles or [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycles or heterocycles containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

R^5 is H, fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, or methoxy;

R^6 is H, fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, or methoxy;

R^7 is H, gem-dimethyl, or C_1–C_4 alkyl, where each of the C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^8 is H, hydroxy, fluoro, chloro, C_1–C_3 alkyl optionally substituted with hydroxyl or amino, or amino optionally substituted with C_1–C_3 alkyl;

R^9 is H, fluoro, chloro, methyl, hydroxyl, or cyano;

R^{14} is independently selected at each occurrence from a substituent in the group consisting of halogen, $-NO_2$, $-OR^{12}$, $-NR^{10}R^{11}$, $-NR^{12}C(O)_2R^{13}$, $-NR^{12}C(O)NR^{12}R^{13}$, $-S(O)_n R^{13}$, –CN, $-C(O)R^{13}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; and

R^{15} is independently selected at each occurrence from a substituent in the group consisting of halogen, $-C(O)R^{13}$, –CN, C_1-C_3 alkyl, $-OR^{12}$, $-NR^{10}R^{11}$, $-S(O)_nR^{13}$, aryl, and heteroaryl, where each of the aryl or heteroaryl groups is optionally substituted from 1 to 4 times with substituents as defined above in R^{14}.

[0067] Another embodiment of the present invention relates to the compound of formulae (IA-E) where:

X is thiophenyl, thiazolyl, pyridinyl, phenyl, naphthyl, benzo[*b*]thiophenyl, benzofuranyl, benzo[*d*][1,3]dioxolyl, 2,3-dihydrobenzo[*b*][1,4]dioxinyl, 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazinyl, or 4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazinyl, optionally substituted with from 1 to 3 substituents selected independently from the group consisting of halogen, methoxy, cyano, trifluoromethyl, trifluoromethoxy, difluoromethoxy, substituted C_1-C_3 alkyl, methanesulfonyl, carbamoyl, C_1-C_3 alkyl-substituted carbamoyl, and acetamido;

R^1 is H, methyl, ethyl, isopropyl, 2-hydroxyethyl, 2,2,2-trifluoroethyl, 2-fluoroethyl, or benzyl;

R^2 is H or gem-dimethyl;

R^3 is H or fluoro;

R^4 is H, methoxy, hydroxyl, methyl, fluoro, bromo, cyano, trifluoromethyl, trifluoromethoxy, acetyl, aminomethyl, 1-aminocyclopropyl, morpholinomethyl, 2-hydroxypropan-2-yl, morpholine-4-carbonyl, 2-morpholinoethoxy, 2-

(dimethylamino)ethyl(methyl)amino, 2-hydroxyethylamino, piperidin-1-yl, piperidin-2-yl, pyrrolidin-1-yl, piperidin-4-ol, morpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-(ethylsulfonyl)piperazin-1-yl, 4-(2-(isopropylamino)-2-oxoethyl)piperazin-1-yl, 4-(pyridin-2-yl)piperazin-1-yl, 4-(pyrimidin-2-yl)piperazin-1-yl, 2-oxopyrrolidin-1-yl, 2-oxopiperidin-1-yl, 6-methylpyridazin-3-yloxy, 6-pyridazin-3-yloxy,1,2,4-oxadiazol-3-yl, 3,5-dimethylisoxazol-4-yl, 1*H*-pyrazol-4-yl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, (methanesulfonyl)phenyl, pyridinyl, aminopyridinyl, pyridazin-3-yl, 6-methylpyridazin-3-yl, 6-(trifluoromethyl)pyridazin-3-yl, 6-aminopyridazin-3-yl, 6-(methylamino)pyridazin-3-yl, 6-(dimethylamino)pyridazin-3-yl, 6-morpholinopyridazin-3-yl, 6-(4-hydroxypiperidin-1-yl)pyridazin-3-yl, 6-(4-methylpiperazin-1-yl)pyridazin-3-yl, (6-(hydroxymethyl)pyridazin-3-yl, 6-(methoxycarbonyl)pyridazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrazin-2-yl, 2-oxopyridin-1(2*H*)-yl, 6-oxo-1,6-dihydropyridazin-3-yl, imidazo[1,2-*a*]pyridin-6-yl, imidazo[1,2-*a*]pyrazin-3-yl, 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, 5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl, 3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl, [1,2,4]triazolo[1,5-*a*]pyridin-6-yl, [1,2,4]triazolo[4,3-*a*]pyridin-6-yl, 3,3-dimethyl-2-oxoindolin-5-yl, 5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl, 3-methyl-[1,2,4]triazolo[4,3-*b*]-pyridazinyl, or [1,2,4]triazolo[4,3-*b*]-pyridazinyl;

R^5 is H or fluoro;

R^6 is H or fluoro;

R^7 is H;

R^8 is H, fluoro, methyl, or hydroxy;

R^9 is H or hydroxy;

R^{14} is independently selected at each occurrence from a substituent in the group consisting of halogen, $-NO_2$, $-OR^{12}$, $-NR^{10}R^{11}$, $-NR^{12}C(O)_2R^{13}$, $-NR^{12}C(O)NR^{12}R^{13}$, $-S(O)_n R^{13}$, –CN, $-C(O)R^{13}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6

cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; and

R^{15} is independently selected at each occurrence from a substituent in the group consisting of halogen, -C(O)R^{13}, –CN, C_1-C_3 alkyl, -OR^{12}, -N$R^{10}R^{11}$, –S(O)$_n R^{13}$, aryl, and heteroaryl, where each of the aryl or heteroaryl groups is optionally substituted from 1 to 4 times with substituents as defined above in R^{14}.

[0068] Other specific compounds of formulae I(A-E) of the present invention are the following 5-carbocyclic/5-heterocyclic-8-heteroaryl tetrahydrobenzazepine compounds:

4-(8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl)morpholine;

4-(2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl)morpholine;

8-methoxy-2-methyl-5-(4-methylpiperazin-1-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

2-methyl-5-(4-methylpiperazin-1-yl)-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-cyclohexyl-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine; and

5-cyclohexyl-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine.

[0069] Other specific compounds of formulae I(A-E) of the present invention are the following tetrahydrobenzazepine compounds with mono- or bicyclic carbocycles or heterocycles at the X substituent and simple (noncyclic) substituents at R^4 (or R^6):

5-(3,4-difluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(3,5-difluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-4-ol;

2,4-dimethyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

4-fluoro-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

8-methoxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

8-methoxy-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

2-ethyl-8-methoxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
2-isopropyl-8-methoxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-methoxy-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-fluoro-8-methoxy-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
7-fluoro-8-methoxy-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-8-methoxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-8-methoxy-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-8-methoxy-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-ol;
5-(4-fluorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-bromophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-chlorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2-chlorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3-chlorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
8-methoxy-2-methyl-5-(4-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
8-methoxy-2-methyl-5-(4-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-ol;
5-(3,4-difluorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3,4-difluorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-ol;
5-(3-chloro-4-fluorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
2-fluoro-4-(8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl)phenol;
2,6-difluoro-4-(8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl)phenol;
2,6-difluoro-4-(8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl)benzonitrile;
5-(4-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-ol;
5-(4-fluorophenyl)-2,8-dimethyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
8-ethynyl-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
8-ethynyl-5-(2-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2-fluorophenyl)-2-methyl-8-(pyridin-2-ylethynyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine;

5-(2-fluorophenyl)-2-methyl-8-((6-methylpyridazin-3-yl)ethynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
1-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)ethanone;
2-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)propan-2-ol;
N-methyl-2-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)ethanesulfonamide;
N,N-dimethyl-2-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)ethanesulfonamide;
8-(2-(1*H*-1,2,4-triazol-1-yl)ethyl)-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
8-(2-(1*H*-1,2,3-triazol-1-yl)ethyl)-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
8-(2-(1*H*-1,2,4-triazol-1-yl)ethyl)-5-(2-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
8-(2-(1*H*-1,2,3-triazol-1-yl)ethyl)-5-(2-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine-8-carbonitrile;
5-(4-chlorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine-8-carbonitrile;
(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)methanamine;
1-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)cyclopropanamine;
4-((2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)methyl)morpholine;
5-(2-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine-8-carboxamide;
5-(2-fluorophenyl)-*N*,2-dimethyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine-8-carboxamide;
5-(2-fluorophenyl)-*N,N*,2-trimethyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine-8-carboxamide;
(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)(morpholino)methanone;
N-(5-(2-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)acetamide;
N-(5-(2-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)isobutyramide;

N-(5-(2-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)picolinamide;
N-(5-(2-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine-3-carboxamide;
N-(5-(2-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)methanesulfonamide;
8-fluoro-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
2-methyl-5-phenyl-8-(trifluoromethyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-chlorophenyl)-8-(trifluoromethoxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
2-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[c]azepin-8-ylamino)ethanol;
2-methyl-2-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-ylamino)propan-1-ol;
N1,N2-dimethyl-*N*1-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[c]azepin-8-yl)ethane-1,2-diamine;
8-methoxy-2-methyl-5-(thiophen-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3-chlorothiophen-2-yl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
2-(8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl)thiazole;
8-methoxy-2-methyl-5-(pyridin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
8-methoxy-2-methyl-5-(pyridin-4-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
4-(2-(5-(4-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yloxy)ethyl)morpholine;
5-(benzo[*b*]thiophen-2-yl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
8-methoxy-2-methyl-5-(naphthalen-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(benzo[*b*]thiophen-5-yl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3-fluoro-1*H*-indol-5-yl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine; and
5-(3-chloro-1*H*-indol-5-yl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine.

[0070] Other specific compounds of formulae I(A-E) of the present invention are the following 5-substituted phenyl-8-hetero (aryl/cyclic) tetrahydrobenzazepine compounds:

4-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)benzonitrile;
3-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)benzonitrile;
2-methyl-8-(4-(methylsulfonyl)phenyl)-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
2-methyl-5-phenyl-8-(1H-pyrazol-4-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-methyl-3-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)-1,2,4-oxadiazole;
2-methyl-5-phenyl-8-(pyridin-4-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridin-2-amine;
2-methyl-5-phenyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
2-methyl-8-(6-methylpyridazin-3-yl)-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-fluoro-8-(6-methylpyridazin-3-yl)-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-fluoro-2-methyl-8-(6-methylpyridazin-3-yl)-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
7-fluoro-2-methyl-8-(6-methylpyridazin-3-yl)-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-2-methyl-5-phenyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-phenyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-2-methyl-5-phenyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-8-(6-methylpyridazin-3-yl)-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(9-fluoro-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(9-fluoro-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
9-fluoro-2-methyl-5-phenyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-phenyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-2-methyl-8-(6-methylpyridazin-3-yl)-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

4-(6-(5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-yl)morpholine;
4-(6-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-yl)morpholine;
N,N-dimethyl-6-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
N-methyl-6-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(6-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-yl)methanol;
6-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-ol;
2-methyl-8-(6-methylpyridazin-3-yloxy)-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
2-methyl-5-phenyl-8-(pyridazin-3-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
1-(methyl(6-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-yl)amino)propan-2-ol;
2-(6-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-ylamino)butan-1-ol;
2-methyl-5-phenyl-8-(pyrimidin-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
2-methyl-5-phenyl-8-(pyrimidin-5-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
2-methyl-5-phenyl-8-(pyrazin-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
2-methyl-5-phenyl-8-(1,2,4-triazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
2-methyl-5-phenyl-8-(1,3,5-triazin-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
8-(imidazo[1,2-a]pyridin-6-yl)-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
2-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)-[1,2,4]triazolo[4,3-*a*]pyridin-3(2*H*)-one;
2-methyl-5-phenyl-8-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
8-(5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl)-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
1-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridin-2(1*H*)-one;

1-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyrrolidin-2-one;
1-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)piperidin-2-one;
2-methyl-5-phenyl-8-(piperidin-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
4-(5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine;
4-(1,1-dimethyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine;
2-methyl-8-(4-methylpiperazin-1-yl)-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
8-(4-(ethylsulfonyl)piperazin-1-yl)-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
N-isopropyl-2-(4-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)piperazin-1-yl)acetamide;
5-phenyl-8-(4-(pyridin-2-yl)piperazin-1-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
2-methyl-5-phenyl-8-(4-(pyridin-2-yl)piperazin-1-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
2-methyl-5-phenyl-8-(4-(pyrimidin-2-yl)piperazin-1-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
4-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine;
4-(2-ethyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine;
4-(2-isopropyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine;
2-(8-morpholino-5-phenyl-4,5-dihydro-1*H*-benzo[*c*]azepin-2(3H)-yl)ethanol;
4-(2-(2-fluoroethyl)-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine;
4-(2-benzyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine;
4-(5-phenyl-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine;
5-(4-chlorophenyl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-chlorophenyl)-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-chlorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-chlorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-4-ol;
5-(4-chlorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(4-chlorophenyl)-2-methyl-8-(pyrazin-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
4-(5-(4-chlorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)-3,5-dimethylisoxazole;
5-(4-chlorophenyl)-2-methyl-8-(pyrimidin-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(5-(4-chlorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)-*N,N*-dimethylpyridazin-3-amine;
6-(5-(4-chlorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)-*N*-methylpyridazin-3-amine;
6-(5-(4-chlorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
4-(5-(4-chlorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine;
5-(4-chlorophenyl)-9-fluoro-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-chlorophenyl)-9-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(5-(4-chlorophenyl)-9-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(5-(4-chlorophenyl)-9-fluoro-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(5-(4-chlorophenyl)-9-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
5-(3,4-dichlorophenyl)-9-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1H-benzo[*c*]azepine;
6-(5-(3,4-dichlorophenyl)-9-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(5-(3,4-dichlorophenyl)-9-fluoro-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
5-(3,4-dichlorophenyl)-9-fluoro-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3,4-dichlorophenyl)-9-fluoro-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(2-chlorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
2-(5-(2-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)benzonitrile;
3-(5-(2-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)benzonitrile;
4-(5-(2-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)benzonitrile;
1-(5-(2-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridin-2(1*H*)-one;
5-(2-fluorophenyl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2-fluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2-fluorophenyl)-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2-fluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
2-ethyl-5-(2-fluorophenyl)-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(5-(2-fluorophenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(5-(2-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(6-(5-(2-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-yl)methanol;
6-fluoro-5-(2-fluorophenyl)-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-fluoro-5-(2-fluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
7-fluoro-5-(2-fluorophenyl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
7-fluoro-5-(2-fluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

7-fluoro-5-(2-fluorophenyl)-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

7-fluoro-5-(2-fluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

6-(7-fluoro-5-(2-fluorophenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;

6-(7-fluoro-5-(2-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;

9-fluoro-5-(2-fluorophenyl)-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

9-fluoro-5-(2-fluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

6-(9-fluoro-5-(2-fluorophenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;

6-(9-fluoro-5-(2-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;

5-(2-fluorophenyl)-2-methyl-8-(pyridin-2-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(2-fluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(2-fluorophenyl)-2-methyl-8-(pyridazin-3-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(2-fluorophenyl)-2-methyl-8-(pyrimidin-2-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(2-fluorophenyl)-2-methyl-8-(4-(pyrimidin-2-yl)piperazin-1-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(2-fluorophenyl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(2-fluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(2-fluorophenyl)-2-methyl-8-(2-(trifluoromethyl)pyrimidin-5-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

2-(5-(2-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyrimidine-5-carbonitrile;
5-(2-fluorophenyl)-2-methyl-8-(5-(trifluoromethyl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2-fluorophenyl)-2-methyl-8-(1,2,4-triazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2-fluorophenyl)-2-methyl-8-(1,3,5-triazin-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2-fluorophenyl)-2-methyl-8-(4-methylpiperazin-1-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-(2-fluorophenyl)-8-(4-methylpiperazin-1-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-(2-fluorophenyl)-8-(piperazin-1-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-(2-fluorophenyl)-2-methyl-8-(4-methylpiperazin-1-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2-fluorophenyl)-2-methyl-8-(4-(pyrimidin-2-yl)piperazin-1-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2-fluorophenyl)-8-(imidazo[1,2-a]pyridin-6-yl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
8-([1,2,4]triazolo[1,5-a]pyridin-6-yl)-5-(2-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
8-([1,2,4]triazolo[4,3-a]pyridin-6-yl)-5-(2-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(5-(2-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)benzo[d]oxazol-2(3*H*)-one;
5-(5-(2-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)benzo[*c*][1,2,5]thiadiazole;
5-(3-fluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3-fluorophenyl)-2-methyl-8-(piperazin-1-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(3-fluorophenyl)-2-methyl-8-(4-methylpiperazin-1-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-(3-fluorophenyl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-(3-fluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(9-fluoro-5-(3-fluorophenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(9-fluoro-5-(3-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
5-(4-fluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-fluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-4-ol;
9-fluoro-5-(4-fluorophenyl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-(4-fluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-(4-fluorophenyl)-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-(4-fluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(9-fluoro-5-(4-fluorophenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(9-fluoro-5-(4-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
9-fluoro-5-(4-fluorophenyl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-(4-fluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-fluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(4-fluorophenyl)-2-methyl-8-(6-(4-methylpiperazin-1-yl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
1-(6-(5-(4-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-yl)piperidin-4-ol;
5-(4-fluorophenyl)-2-methyl-8-(pyrimidin-5-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-fluorophenyl)-2-methyl-8-(1,2,4-triazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-fluorophenyl)-2-methyl-8-(1,3,5-triazin-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
4-(5-(4-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine;
9-fluoro-5-(4-fluorophenyl)-8-(piperazin-1-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-(4-fluorophenyl)-8-(4-methylpiperazin-1-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-(4-fluorophenyl)-2-methyl-8-(4-methylpiperazin-1-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(5-(4-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)-3,3-dimethylindolin-2-one;
5-(4-fluorophenyl)-8-(imidazo[1,2-a]pyrazin-3-yl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-fluorophenyl)-2-methyl-8-(2-(trifluoromethyl)pyrimidin-5-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-fluorophenyl)-2-methyl-8-(5-(trifluoromethyl)pyrimidin-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
8-(6-methylpyridazin-3-yl)-5-p-tolyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
2-methyl-8-(4-(pyrimidin-2-yl)piperazin-1-yl)-5-p-tolyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
2-methyl-8-(6-methylpyridazin-3-yl)-5-p-tolyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
2-methyl-8-(6-methylpyridazin-3-yl)-5-o-tolyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(2-methoxyphenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-methoxyphenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
4-(2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl)phenol;
2-(2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl)phenol;
2-methyl-8-(6-methylpyridazin-3-yl)-5-(4-(trifluoromethoxy)phenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
4-(2-methyl-5-(4-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine;
2-methyl-8-(6-methylpyridazin-3-yl)-5-(3-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
2-(2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl)benzonitrile;
4-(2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl)benzonitrile;
N,N-dimethyl-4-(2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl)benzamide;
2-methyl-8-(6-methylpyridazin-3-yl)-5-(4-(methylsulfonyl)phenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
4-(2-methyl-5-(4-(methylsulfonyl)phenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine;
5-(2,3-difluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,3-difluorophenyl)-9-fluoro-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,3-difluorophenyl)-9-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(5-(2,3-difluorophenyl)-9-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;

6-(5-(2,3-difluorophenyl)-9-fluoro-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
5-(2,4-difluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,4-difluorophenyl)-9-fluoro-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,4-difluorophenyl)-2-methyl-8-(4-methylpiperazin-1-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,4-difluorophenyl)-9-fluoro-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,4-difluorophenyl)-9-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(5-(2,4-difluorophenyl)-9-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(5-(2,4-difluorophenyl)-9-fluoro-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
5-(2,5-difluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,6-difluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,5-difluorophenyl)-9-fluoro-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,5-difluorophenyl)-9-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(5-(2,5-difluorophenyl)-9-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(5-(2,5-difluorophenyl)-9-fluoro-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
5-(3,4-difluorophenyl)-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3,4-difluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(3,4-difluorophenyl)-9-fluoro-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3,4-difluorophenyl)-9-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(5-(3,4-difluorophenyl)-9-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(5-(3,4-difluorophenyl)-9-fluoro-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
5-(3,5-difluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3,5-difluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3,5-difluorophenyl)-9-fluoro-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
4-(5-(3,5-difluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine;
5-(3,5-difluorophenyl)-2-methyl-8-(piperazin-1-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3,5-difluorophenyl)-2-methyl-8-(4-methylpiperazin-1-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3,5-difluorophenyl)-9-fluoro-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3,5-difluorophenyl)-9-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(5-(3,5-difluorophenyl)-9-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(5-(3,5-difluorophenyl)-9-fluoro-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
5-(3,5-difluorophenyl)-6-fluoro-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3,5-difluorophenyl)-6-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

6-(5-(3,5-difluorophenyl)-6-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(5-(3,5-difluorophenyl)-6-fluoro-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
5-(3-chloro-2-fluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-chloro-2-fluorophenyl)-9-fluoro-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-chloro-2-fluorophenyl)-9-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-chloro-2-fluorophenyl)-9-fluoro-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-chloro-2-fluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(5-(4-chloro-2-fluorophenyl)-9-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(5-(4-chloro-2-fluorophenyl)-9-fluoro-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
9-fluoro-5-(2-fluoro-4-methylphenyl)-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2-fluoro-4-methylphenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(9-fluoro-5-(2-fluoro-4-methylphenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(9-fluoro-5-(2-fluoro-4-methylphenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
9-fluoro-5-(2-fluoro-4-methylphenyl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-(2-fluoro-4-methylphenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2-fluoro-3-methylphenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(2-fluoro-4-methoxyphenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2-fluoro-3-methoxyphenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine; and
2-fluoro-4-(2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl)benzonitrile.

[0071] Other specific compounds of formulae I(A-E) of the present invention are the following 5-bicyclic aryl-8-hetero (aryl/cyclic) tetrahydrobenzazepine compounds:
5-(naphthalen-2-yl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
2-methyl-5-(naphthalen-2-yl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(1-fluoronaphthalen-2-yl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3-fluoronaphthalen-2-yl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(5-(naphthalen-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(2-methyl-5-(naphthalen-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
4-(2-methyl-5-(naphthalen-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine;
5-(1-fluoronaphthalen-2-yl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(1-fluoronaphthalen-2-yl)-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-(naphthalen-2-yl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-2-methyl-5-(naphthalen-2-yl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-(1-fluoronaphthalen-2-yl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-(1-fluoronaphthalen-2-yl)-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

6-(9-fluoro-5-(1-fluoronaphthalen-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine; and
6-(9-fluoro-5-(1-fluoronaphthalen-2-yl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine.

[0072] Other specific compounds of formulae I(A-E) of the present invention are the following 5-bicyclic heteroaryl-8-hetero (aryl/cyclic) tetrahydrobenzazepine compounds:
4-(5-(benzo[*b*]thiophen-5-yl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine;
5-(benzo[*b*]thiophen-5-yl)-2-methyl-8-(pyrimidin-5-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(benzo[*b*]thiophen-5-yl)-2-methyl-8-(pyrazin-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(benzo[*b*]thiophen-5-yl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(benzo[*b*]thiophen-5-yl)-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
4-methyl-7-(2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine;
4-methyl-7-(2-methyl-8-morpholino-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine;
4-(5-(benzo[*d*][1,3]dioxol-5-yl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine;
5-(benzo[*d*][1,3]dioxol-5-yl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
4-(5-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine;
5-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3-chloro-1*H*-indol-5-yl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine; and
5-(3-fluoro-1*H*-indol-5-yl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine.

[0073] Other specific compounds of formulae I(A-E) of the present invention are the following aryl- or heteroaryl-substituted tetrahydrobenzazepine compounds:
5-phenyl-8-(pyrimidin-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-phenyl-8-(pyrimidin-5-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-phenyl-8-(pyrazin-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-fluoro-5-(2-fluorophenyl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-fluoro-5-(2-fluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(6-fluoro-5-(2-fluorophenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(6-fluoro-5-(2-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
7-fluoro-5-(2-fluorophenyl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-(2-fluorophenyl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-(2-fluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-(2-fluorophenyl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-(2-fluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2-fluorophenyl)-8-(pyridin-2-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2-fluorophenyl)-8-(6-methylpyridazin-3-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2-fluorophenyl)-8-(pyridazin-3-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-(2-fluorophenyl)-8-(pyridazin-3-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-(2-fluorophenyl)-2-methyl-8-(pyridazin-3-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(9-fluoro-5-(2-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yloxy)pyridazin-3-amine;

6-(9-fluoro-5-(2-fluorophenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yloxy)pyridazin-3-amine;
9-fluoro-5-(2-fluorophenyl)-8-(6-methylpyridazin-3-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-(2-fluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-(2-fluorophenyl)-8-(6-(trifluoromethyl)pyridazin-3-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-(2-fluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
7-fluoro-5-(2-fluorophenyl)-8-(pyridazin-3-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
7-fluoro-5-(2-fluorophenyl)-2-methyl-8-(pyridazin-3-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-fluoro-5-(2-fluorophenyl)-8-(pyridazin-3-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-fluoro-5-(2-fluorophenyl)-2-methyl-8-(pyridazin-3-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2-fluorophenyl)-8-(pyrimidin-2-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-fluorophenyl)-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-fluorophenyl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-fluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(5-(4-fluorophenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(5-(4-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
7-fluoro-5-(4-fluorophenyl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
7-fluoro-5-(4-fluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
7-fluoro-5-(4-fluorophenyl)-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

7-fluoro-5-(4-fluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(7-fluoro-5-(4-fluorophenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(7-fluoro-5-(4-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
7-fluoro-5-(4-fluorophenyl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
7-fluoro-5-(4-fluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-fluoro-5-(4-fluorophenyl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-fluoro-5-(4-fluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-fluoro-5-(4-fluorophenyl)-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-fluoro-5-(4-fluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(6-fluoro-5-(4-fluorophenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(6-fluoro-5-(4-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-fluoro-5-(4-fluorophenyl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-fluoro-5-(4-fluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-fluorophenyl)-8-(pyridin-2-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-fluorophenyl)-2-methyl-8-(pyridin-2-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-fluorophenyl)-8-(6-methylpyridazin-3-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-fluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(4-fluorophenyl)-8-(pyridazin-3-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-fluorophenyl)-2-methyl-8-(pyridazin-3-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-(4-fluorophenyl)-8-(pyridazin-3-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
9-fluoro-5-(4-fluorophenyl)-2-methyl-8-(pyridazin-3-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-fluorophenyl)-8-(pyrimidin-2-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-fluorophenyl)-2-methyl-8-(pyrimidin-2-yloxy)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(4-fluorophenyl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,4-difluorophenyl)-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,4-difluorophenyl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,4-difluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(5-(2,4-difluorophenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(5-(2,4-difluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
5-(2,4-difluorophenyl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,4-difluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,4-difluorophenyl)-7-fluoro-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,4-difluorophenyl)-7-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(5-(2,4-difluorophenyl)-7-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(5-(2,4-difluorophenyl)-7-fluoro-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;

5-(2,4-difluorophenyl)-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,4-difluorophenyl)-9-fluoro-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,4-difluorophenyl)-9-fluoro-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,3-difluorophenyl)-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,3-difluorophenyl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,3-difluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(5-(2,3-difluorophenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(5-(2,3-difluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
5-(2,3-difluorophenyl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,3-difluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,3-difluorophenyl)-7-fluoro-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,3-difluorophenyl)-7-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(5-(2,3-difluorophenyl)-7-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(5-(2,3-difluorophenyl)-7-fluoro-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
5-(2,3-difluorophenyl)-7-fluoro-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,3-difluorophenyl)-7-fluoro-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,3-difluorophenyl)-9-fluoro-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(2,3-difluorophenyl)-9-fluoro-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,3-difluorophenyl)-9-fluoro-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,3-difluorophenyl)-9-fluoro-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3,4-difluorophenyl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3,4-difluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(5-(3,4-difluorophenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(5-(3,4-difluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
5-(3,4-difluorophenyl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3,4-difluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3,4-difluorophenyl)-7-fluoro-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3,4-difluorophenyl)-7-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3,4-difluorophenyl)-7-fluoro-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3,4-difluorophenyl)-7-fluoro-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(5-(3,4-difluorophenyl)-7-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(5-(3,4-difluorophenyl)-7-fluoro-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
5-(3,4-difluorophenyl)-9-fluoro-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3,4-difluorophenyl)-9-fluoro-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(3,4-difluorophenyl)-9-fluoro-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3,4-difluorophenyl)-9-fluoro-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,5-difluorophenyl)-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,5-difluorophenyl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,5-difluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(5-(2,5-difluorophenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(5-(2,5-difluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
5-(2,5-difluorophenyl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,5-difluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,5-difluorophenyl)-7-fluoro-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,5-difluorophenyl)-7-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(5-(2,5-difluorophenyl)-7-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(5-(2,5-difluorophenyl)-7-fluoro-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
5-(2,5-difluorophenyl)-9-fluoro-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,5-difluorophenyl)-9-fluoro-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,6-difluorophenyl)-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,6-difluorophenyl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(2,6-difluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(5-(2,6-difluorophenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(5-(2,6-difluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
5-(2,6-difluorophenyl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,6-difluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,6-difluorophenyl)-7-fluoro-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,6-difluorophenyl)-7-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(5-(2,6-difluorophenyl)-7-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(5-(2,6-difluorophenyl)-7-fluoro-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
5-(2,6-difluorophenyl)-9-fluoro-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2,6-difluorophenyl)-9-fluoro-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3,5-difluorophenyl)-9-fluoro-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3,5-difluorophenyl)-9-fluoro-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3,5-difluorophenyl)-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3,5-difluorophenyl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(5-(3,5-difluorophenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(5-(3,5-difluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;

5-(3,5-difluorophenyl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3,5-difluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3,5-difluorophenyl)-9-fluoro-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3,5-difluorophenyl)-9-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(5-(3,5-difluorophenyl)-9-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(5-(3,5-difluorophenyl)-9-fluoro-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
5-(3,5-difluorophenyl)-9-fluoro-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3,5-difluorophenyl)-9-fluoro-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
2-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)benzonitrile;
2-methyl-8-(4-(methylsulfonyl)phenyl)-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
2-methyl-8-(3-(methylsulfonyl)phenyl)-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
2-methyl-8-(2-(methylsulfonyl)phenyl)-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
4-(5-(2-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)benzonitrile;
3-(5-(2-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)benzonitrile;
2-(5-(2-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)benzonitrile;
5-(2-fluorophenyl)-2-methyl-8-(4-(methylsulfonyl)phenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(2-fluorophenyl)-2-methyl-8-(3-(methylsulfonyl)phenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(2-fluorophenyl)-2-methyl-8-(2-(methylsulfonyl)phenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(5-fluoronaphthalen-2-yl)-2-methyl-8-(6-pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(6-fluoronaphthalen-2-yl)-2-methyl-8-(6-pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(7-fluoronaphthalen-2-yl)-2-methyl-8-(6-pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(8-fluoronaphthalen-2-yl)-2-methyl-8-(6-pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(5-fluoronaphthalen-2-yl)-8-(6-pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(6-fluoronaphthalen-2-yl)-8-(6-pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(7-fluoronaphthalen-2-yl)-8-(6-pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(8-fluoronaphthalen-2-yl)-8-(6-pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(1-fluoronaphthalen-2-yl)-8-(6-pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(2-fluoronaphthalen-2-yl)-8-(6-pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(1-fluoronaphthalen-2-yl)-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(2-fluoronaphthalen-2-yl)-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

9-fluoro-5-(naphthalen-2-yl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

9-fluoro-2-methyl-5-(naphthalen-2-yl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(1-fluoronaphthalen-2-yl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(1-fluoronaphthalen-2-yl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3-fluoronaphthalen-2-yl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(3-fluoronaphthalen-2-yl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(5-(1-fluoronaphthalen-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(5-(1-fluoronaphthalen-2-yl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(5-(3-fluoronaphthalen-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(5-(3-fluoronaphthalen-2-yl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
7-fluoro-5-(naphthalen-2-yl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
7-fluoro-2-methyl-5-(naphthalen-2-yl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
7-fluoro-5-(1-fluoronaphthalen-2-yl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
7-fluoro-5-(1-fluoronaphthalen-2-yl)-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
4-(5-(benzo[*b*]thiophen-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine;
5-(benzo[*b*]thiophen-5-yl)-8-(pyrimidin-5-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(benzo[*b*]thiophen-5-yl)-8-(pyrazin-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(benzo[*b*]thiophen-5-yl)-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(benzo[*b*]thiophen-2-yl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
4-(5-(benzo[*b*]thiophen-2-yl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine;
5-(benzo[*b*]thiophen-2-yl)-2-methyl-8-(pyrimidin-5-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(benzo[*b*]thiophen-2-yl)-2-methyl-8-(pyrazin-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(benzo[*b*]thiophen-2-yl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(benzo[*b*]thiophen-2-yl)-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

6-(5-(benzo[*b*]thiophen-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;

5-(benzo[*b*]thiophen-2-yl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

6-(5-(benzo[*b*]thiophen-2-yl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;

5-(benzo[*b*]thiophen-2-yl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(benzo[*b*]thiophen-2-yl)-9-fluoro-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1H-benzo[*c*]azepine;

5-(benzo[*b*]thiophen-2-yl)-9-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1H-benzo[*c*]azepine;

5-(benzo[*b*]thiophen-2-yl)-9-fluoro-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(benzo[*b*]thiophen-2-yl)-9-fluoro-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

6-(5-(benzo[*b*]thiophen-2-yl)-9-fluoro-2,3,4,5-tetrahydro-1H-benzo[*c*]azepin-8-yl)pyridazin-3-amine;

6-(5-(benzo[*b*]thiophen-2-yl)-9-fluoro-2-methyl-2,3,4,5-tetrahydro-1H-benzo[*c*]azepin-8-yl)pyridazin-3-amine;

5-(benzo[*b*]thiophen-2-yl)-9-fluoro-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(benzo[*b*]thiophen-2-yl)-9-fluoro-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;

5-(benzo[*b*]thiophen-2-yl)-7-fluoro-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1H-benzo[*c*]azepine;

5-(benzo[*b*]thiophen-2-yl)-7-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1H-benzo[*c*]azepine;
5-(benzo[*b*]thiophen-2-yl)-7-fluoro-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(benzo[*b*]thiophen-2-yl)-7-fluoro-2-methyl-8-(6-methylpyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
6-(5-(benzo[*b*]thiophen-2-yl)-7-fluoro-2,3,4,5-tetrahydro-1H-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
6-(5-(benzo[*b*]thiophen-2-yl)-7-fluoro-2-methyl-2,3,4,5-tetrahydro-1H-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
5-(benzo[*b*]thiophen-2-yl)-7-fluoro-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(benzo[*b*]thiophen-2-yl)-7-fluoro-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(benzo[*b*]thiophen-2-yl)-6-fluoro-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1H-benzo[*c*]azepine;
5-(benzo[*b*]thiophen-2-yl)-6-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1H-benzo[*c*]azepine;
5-(benzo[*b*]thiophen-6-yl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(benzo[*b*]thiophen-6-yl)-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine;
5-(benzo[*b*]thiophen-7-yl)-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine; and
5-(benzo[*b*]thiophen-7-yl)-2-methyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine.

[0074] Other embodiments of the present invention are compounds of formulae I(A-E) where the carbon atom designated * is in the R configuration.

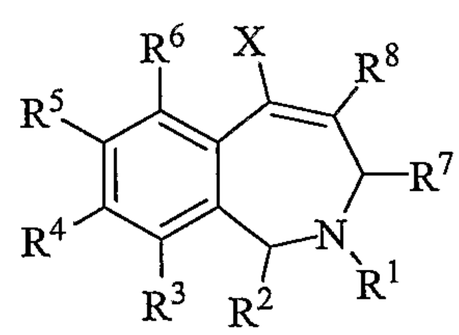
[0075] Other embodiments of the present invention are compounds of formulae I(A-E) where the carbon atom designated * is in the S configuration.

[0076] Another embodiment of the present invention is a mixture of stereoisomeric compounds of formulae I(A-E) where * is in the S or R configuration.

[0077] Within these embodiments, the selection of a particular preferred substituent at any one of R^1–R^9 does not affect the selection of a substituent at any of

the others of R^1-R^8. That is, preferred compounds provided herein have any of the preferred substituents at any of the positions. For example, as described hereinabove, R^1 is preferably C_1-C_6 alkyl; the selection of R^1 as any one of C_1, C_2, C_3, C_4, C_5, or C_6 alkyl, does not limit the choice of R^2 in particular to any one of H, C_1-C_6 alkyl, or C_1-C_6 haloalkyl. Rather, for R^1 as any of C_1, C_2, C_3, C_4, C_5, or C_6 alkyl, R^2 is any of H, C_1, C_2, C_3, C_4, C_5, or C_6 alkyl or C_1, C_2, C_3, C_4, C_5, or C_6 haloalkyl. Similarly, the selection of R^2 as any of H, C_1, C_2, C_3, C_4, C_5, or C_6 alkyl or C_1, C_2, C_3, C_4, C_5, or C_6 haloalkyl does not limit the selection of R^3 in particular to any one of H, halogen, $-OR^{11}$, $-S(O)_n R^{12}$, -CN, $-C(O)R^{12}$, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, or substituted C_4 -C_7 cycloalkylalkyl.

[0078] Another aspect of the present invention relates to a compound represented by the formula (II) having the following structure:



II

where:

X represents a 5- or 6-membered aromatic or nonaromatic monocyclic carbocycle or heterocycle selected from the group consisting of phenyl, pyridyl, 2-oxo-pyridin-1-yl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyranyl, pyrrolyl, furanyl, thiophenyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, and tetrazolyl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}, or other 5- or 6-membered aromatic or non-aromatic monocyclic carbocycles or heterocycles containing 1-4 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

X is a [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycle or heterocycle selected from the group consisting of indenyl, indanyl, benzofuranyl, benzothiophenyl,

dihydrobenzothiophenyl, dihydrobenzofuranyl, indolyl, isoindolyl, indolinyl, benzo[1,3]dioxolyl, benzooxazolyl, benzothiazolyl, benzoisothiazolyl, benzoisoxazolyl, indazolyl, benzoimidazolyl, benzotriazolyl, naphthyl, tetrahydronaphthyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, phthalazinyl, quinoxalinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, 2,3-dihydro-benzo[1,4]dioxinyl, 4*H*-chromenyl, dihydrobenzocycloheptenyl, tetrahydrobenzocycloheptenyl, indolizinyl, quinolizinyl, 6*aH*-thieno[2,3-d]imidazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, thieno[2,3-*b*]furanyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[2,3-*b*]pyrazinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, 3,4-dihydro-2H-benzo[*b*][1,4]oxazinyl, imidazo[1,2-*a*]pyrazinyl, 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazinyl, 2-oxo-2,3-dihydrobenzo[*d*]oxazolyl, 3,3-dimethyl-2-oxoindolinyl, 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, and 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}, or other [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycles or heterocycles containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}; or

X is an alkene or alkyne, optionally substituted from 1 to 4 times with substitutents as defined below in R^{15};

R^1 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, each of which is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, each of which is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or

R^2 is gem-dimethyl;

R^3, R^5, and R^6 are each independently selected from the group consisting of H, halogen, $-OR^{12}$, $-S(O)_nR^{13}$, –CN, $-C(O)R^{13}$, $-NR^{10}R^{11}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of the C_1–C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or

R^3, R^5, and R^6 are each independently a 5- or 6-membered monocyclic carbocycle or heterocycle or a [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycle or heterocycle containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

R^4 is H, halogen, $-OR^{12}$, $-S(O)_nR^{13}$, –CN, $-C(O)R^{13}$, $-NR^{10}R^{11}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, where each of the C_1–C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^4 is a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, where the bridged bicyclic ring is optionally substituted from 1 to 3 times with substitutents selected from the group consisting of C_1-C_3 alkyl, $-C(O)R^{13}$, and $-S(O)_nR^{13}$; or

R^4 is phenyl, pyridyl, 2-oxo-pyridin-1-yl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyranyl, furanyl, pyrrolyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, indanyl, indenyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, indolinyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, indazolyl, benzimidazolyl, benzooxazolyl, benzothiazolyl, benzoisoxazolyl, benzoisothiazolyl, benzotriazolyl, benzo[1,3]dioxolyl, naphthyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, pthalazinyl, quinoxalinyl, 2,3-dihydro-benzo[1,4]dioxinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, 4*H*-chromenyl, indolizinyl, quinolizinyl, 6*aH*-thieno[2,3-d]imidazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, [1,2,4]triazolo[1,5-*a*]pyridinyl, thieno[2,3-*b*]furanyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, furo[2,3-

b]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[2,3-*b*]pyrazinyl, imidazo[1,2-*a*]pyrazinyl, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazinyl, 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazinyl, 2-oxo-2,3-dihydrobenzo[*d*]oxazolyl, 3,3-dimethyl-2-oxoindolinyl, 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, 3,4-dihydro-2H-benzo[*b*][1,4]oxazinyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazinyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, or other 5- or 6-membered aromatic or non-aromatic monocyclic carbocycles or heterocycles or [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycles or heterocycles containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

R^7 is selected from the group consisting of H,–$S(O)_nR^{13}$, –$C(O)R^{13}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of C_1 –C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or

R^7 is gem-dimethyl;

R^8 is H or C_1-C_6 alkyl, where each of C_1 –C_6 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{10} and R^{11} are each independently selected from the group consisting of H, -$C(O)R^{13}$, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of C_1 -C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{10} and R^{11} are each independently selected from the group consisting of phenyl, benzyl, and other 5- or 6-membered monocyclic heterocycles, where each of the phenyl, benzyl, and 5- or 6-membered monocyclic heterocycle is optionally substituted from 1 to 3 times with substituents as defined below in R^{14};

R^{10} and R^{11} are taken together with the nitrogen to which they are attached to form a saturated or partially saturated monocyclic or fused bicyclic heterocycle selected from the group consisting of piperidine, pyrrolidine, morpholine, thiomorpholine,

[1,2]oxazinane, isoxazolidine, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 3-oxomorpholino, 3-oxothiomorpholino, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazine, and other monocyclic or fused bicyclic heterocycles containing 1-4 heteroatoms selected from oxygen, nitrogen and sulfur, wherein the heterocycle is attached to the benzazepine core via the nitrogen atom, and is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, $-OR^{12}$, $-NR^{12}R^{13}$, $-S(O)_nR^{13}$, $-C(O)R^{13}$, and C_1-C_4 alkyl, where each of C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{10} and R^{11} are taken together with the nitrogen to which they are attached to form a heterocycle selected from the group consisting of piperazine, 2-oxopiperazinyl, 2-oxo-1,4-diazepanyl, 5-oxo-1,4-diazepanyl, 1,4-diazepane, and other heterocycles containing one additional nitrogen atom in the ring, where the heterocycle is optionally substituted on a ring carbon with from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, $-OR^{12}$, $-NR^{12}R^{13}$, $-S(O)_nR^{13}$, $-C(O)R^{13}$, and C_1-C_4 alkyl, or on the additional nitrogen atom from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of $S(O)_nR^{13}$, $-C(O)R^{13}$, and C_1-C_4 alkyl, wherein each of C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{10} and R^{11} are taken together with the nitrogen to which they are attached to form a heterocycle selected from the group consisting of piperazine, 2-oxopiperazinyl, 2-oxo-1,4-diazepanyl, 5-oxo-1,4-diazepanyl, 1,4-diazepane, and other heterocycles containing one additional nitrogen atom in the ring, where the heterocycle is optionally substituted on the additional nitrogen atom with a substituent selected independently at each occurrence thereof from the group consisting of phenyl, benzyl, and 5- or 6-membered aromatic heterocycles containing 1-3 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, where each of the phenyl, benzyl, and 5- and 6-membered heterocycle is optionally substituted from 1 to 3 times with substituents as defined below in R^{14}; or

when R^4 is $-NR^{10}R^{11}$ or $-C(O)NR^{10}R^{11}$, either R^{10} or R^{11} is a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, where the bridged

bicyclic ring is optionally substituted from 1 to 3 times with substituents selected from the group consisting of C_1-C_3 alkyl, $-C(O)R^{13}$, and $-S(O)_nR^{13}$, or either R^{10} or R^{11} is a C_1-C_3 alkyl substituted with a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, where the bridged bicyclic ring is optionally substituted from 1 to 3 times with substitutents selected from the group consisting of C_1-C_3 alkyl, $-C(O)R^{13}$, and $-S(O)_nR^{13}$;

R^{12} is selected from the group consisting of H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, and $-C(O)R^{13}$, where each of C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{13} is selected from the group consisting of H, $-NR^{10}R^{11}$, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or

R^{12} and R^{13} are each independently selected from the group consisting of phenyl, benzyl, pyridazinyl, pyrimidinyl, pyrazinyl, 5- or 6-membered aromatic monocyclic heterocycles, and [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycles or heterocycles containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}; or

R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a heterocycle selected from the group consisting of piperidine, pyrrolidine, piperazine, 1,4-diazepane, morpholine, thiomorpholine, and other heterocycles containing 1-4 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, where the heterocycle is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, $-OR^{10}$, $-S(O)_nR^{10}$, $-C(O)R^{10}$, $-C(O)NR^{10}R^{11}$ and C_1-C_4 alkyl, where each of C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

n is 0, 1, or 2;

R^{14} is independently selected at each occurrence from a substituent in the group consisting of halogen, $-NO_2$, $-OR^{12}$, $-NR^{10}R^{11}$, $-NR^{12}C(O)_2R^{13}$, $-NR^{12}C(O)NR^{12}R^{13}$, $-S(O)_n R^{13}$, –CN, $-C(O)R^{13}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; and

R^{15} is independently selected at each occurrence from a substituent in the group consisting of –CN, halogen, $C(O)R^{13}$, C_1-C_3 alkyl, $-OR^{12}$, $-NR^{10}R^{11}$, $-S(O)_nR^{13}$, aryl, and heteroaryl, where each of the aryl or heteroaryl groups is optionally substituted from 1 to 4 times with substituents as defined above in R^{14};

with the following provisos that (1) when R^4 is H, X cannot be phenyl or a phenyl substituted at the *para*-position with Cl; (2) when R^4 is H, OMe, or O-benzyl, X cannot be a phenyl substituted at the *para*-position with the same R^4; and (3) when R^2 is a 2-(4-nitrophenoxy)ethyl, R^5 cannot be $OC(O)NMe_2$;

or an oxide thereof, or a pharmaceutically acceptable salt thereof.

[0079] One embodiment of the present invention relates to the compound of formula (II) where:

X represents a 5- or 6-membered aromatic or nonaromatic monocyclic carbocycle or heterocycle selected from the group consisting of phenyl, pyridyl, 2-oxo-pyridin-1-yl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyranyl, pyrrolyl, furanyl, thiophenyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, and tetrazolyl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}, or other 5- or 6-membered aromatic or non-aromatic monocyclic carbocycles or heterocycles containing 1-4 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

X is a [5,5]-, [6,5]-, [6,6]-, or [6;7]-fused bicyclic carbocycle or heterocycle selected from the group consisting of indenyl, indanyl, benzofuranyl, benzothiophenyl, dihydrobenzothiophenyl, dihydrobenzofuranyl, indolyl, isoindolyl, indolinyl, benzo[1,3]dioxolyl, benzooxazolyl, benzothiazolyl, benzoisothiazolyl, benzoisoxazolyl, indazolyl, benzoimidazolyl, benzotriazolyl, naphthyl, tetrahydronaphthyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, phthalazinyl, quinoxalinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, 2,3-dihydro-benzo[1,4]dioxinyl, 4*H*-chromenyl, dihydrobenzocycloheptenyl, tetrahydrobenzocycloheptenyl, indolizinyl, quinolizinyl, 6*aH*-thieno[2,3-d]imidazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, thieno[2,3-*b*]furanyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[2,3-*b*]pyrazinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, 3,4-dihydro-2H-benzo[*b*][1,4]oxazinyl, imidazo[1,2-*a*]pyrazinyl, 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazinyl, 2-oxo-2,3-dihydrobenzo[*d*]oxazolyl, 3,3-dimethyl-2-oxoindolinyl, 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, and 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}, or other [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycles or heterocycles containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}; or

X is an alkene or alkyne, optionally substituted from 1 to 4 times with substitutents as defined below in R^{15};

R^1 is H, methyl, ethyl, or isopropyl;

R^2 is H, methyl, or gem-dimethyl;

R^3 is H, methyl, hydroxy, methoxy, fluoro, chloro, cyano, trifluoromethyl, or trifluoromethoxy;

R^4 is H, halogen, $-OR^{12}$, $-S(O)_nR^{13}$, –CN, $-C(O)R^{13}$, $-NR^{10}R^{11}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, where each of the C_1–C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^4 is a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, where the bridged bicyclic ring is optionally substituted from 1 to 3 times with substitutents selected from the group consisting of C_1-C_3 alkyl, $-C(O)R^{13}$, and $-S(O)_nR^{13}$; or

R^4 is phenyl, pyridyl, 2-oxo-pyridin-1-yl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyranyl, furanyl, pyrrolyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, indanyl, indenyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, indolinyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, indazolyl, benzimidazolyl, benzooxazolyl, benzothiazolyl, benzoisoxazolyl, benzoisothiazolyl, benzotriazolyl, benzo[1,3]dioxolyl, naphthyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, pthalazinyl, quinoxalinyl, 2,3-dihydro-benzo[1,4]dioxinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, 4*H*-chromenyl, indolizinyl, quinolizinyl, 6*aH*-thieno[2,3-d]imidazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, [1,2,4]triazolo[1,5-*a*]pyridinyl, thieno[2,3-*b*]furanyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[2,3-*b*]pyrazinyl, imidazo[1,2-*a*]pyrazinyl, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazinyl, 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazinyl, 2-oxo-2,3-dihydrobenzo[*d*]oxazolyl, 3,3-dimethyl-2-oxoindolinyl, 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, 3,4-dihydro-2H-benzo[*b*][1,4]oxazinyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazinyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, or other 5- or 6-membered aromatic or non-aromatic monocyclic carbocycles or heterocycles or [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycles or heterocycles containing 1-5 heteroatoms selected from the group consisting of

oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

R^5 is H, fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, or methoxy;

R^6 is H, fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, or methoxy;

R^7 is H, gem-dimethyl, or C_1–C_4 alkyl, where each of the C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^8 is H or C_1–C_3 alkyl;

R^{14} is independently selected at each occurrence from a substituent in the group consisting of halogen, $–NO_2$, $–OR^{12}$, $–NR^{10}R^{11}$, $-NR^{12}C(O)_2R^{13}$, $-NR^{12}C(O)NR^{12}R^{13}$, $–S(O)_n R^{13}$, –CN, $–C(O)R^{13}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; and

R^{15} is independently selected at each occurrence from a substituent in the group consisting of –CN, halogen, $C(O)R^{13}$, C_1-C_3 alkyl, $-OR^{12}$, $-NR^{10}R^{11}$, $–S(O)_nR^{13}$, aryl, and heteroaryl, where each of the aryl or heteroaryl groups is optionally substituted from 1 to 4 times with substituents as defined above in R^{14}.

[0080] Another embodiment of the present invention relates to the compound of formula (II) where:

X is thiophenyl, thiazolyl, pyridinyl, phenyl, naphthyl, benzo[*b*]thiophenyl, benzofuranyl, benzo[*d*][1,3]dioxolyl, 2,3-dihydrobenzo[*b*][1,4]dioxinyl, 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazinyl or 4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazinyl, optionally substituted with from 1 to 3 substituents selected independently from the

group consisting of halogen, methoxy, cyano, trifluoromethyl, trifluoromethoxy, difluoromethoxy, substituted C_1-C_3 alkyl, methanesulfonyl, carbamoyl, C_1-C_3 alkyl-substituted carbamoyl, and acetamido;

R^1 is H, methyl, ethyl, isopropyl, 2-hydroxyethyl, 2,2,2-trifluoroethyl, 2-fluoroethyl, or benzyl;

R^2 is H or gem-dimethyl;

R^3 is H or fluoro;

R^4 is H, methoxy, hydroxyl, methyl, fluoro, bromo, cyano, trifluoromethyl, trifluoromethoxy, acetyl, aminomethyl, 1-aminocyclopropyl, morpholinomethyl, 2-hydroxypropan-2-yl, morpholine-4-carbonyl, 2-morpholinoethoxy, 2-(dimethylamino)ethyl(methyl)amino, 2-hydroxyethylamino, piperidin-1-yl, piperidin-2-yl, pyrrolidin-1-yl, piperidin-4-ol, morpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-(ethylsulfonyl)piperazin-1-yl, 4-(2-(isopropylamino)-2-oxoethyl)piperazin-1-yl, 4-(pyridin-2-yl)piperazin-1-yl, 4-(pyrimidin-2-yl)piperazin-1-yl, 2-oxopyrrolidin-1-yl, 2-oxopiperidin-1-yl, 6-methylpyridazin-3-yloxy, 6-pyridazin-3-yloxy,1,2,4-oxadiazol-3-yl, 3,5-dimethylisoxazol-4-yl, 1*H*-pyrazol-4-yl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, (methanesulfonyl)phenyl, pyridinyl, aminopyridinyl, pyridazin-3-yl, 6-methylpyridazin-3-yl, 6-(trifluoromethyl)pyridazin-3-yl, 6-aminopyridazin-3-yl, 6-(methylamino)pyridazin-3-yl, 6-(dimethylamino)pyridazin-3-yl, 6-morpholinopyridazin-3-yl, 6-(4-hydroxypiperidin-1-yl)pyridazin-3-yl, 6-(4-methylpiperazin-1-yl)pyridazin-3-yl, (6-(hydroxymethyl)pyridazin-3-yl, 6-(methoxycarbonyl)pyridazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrazin-2-yl, 2-oxopyridin-1(2*H*)-yl, 6-oxo-1,6-dihydropyridazin-3-yl, imidazo[1,2-*a*]pyridin-6-yl, imidazo[1,2-*a*]pyrazin-3-yl, 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, 5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl, 3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl, [1,2,4]triazolo[1,5-*a*]pyridin-6-yl, [1,2,4]triazolo[4,3-*a*]pyridin-6-yl, 3,3-dimethyl-2-oxoindolin-5-yl, 5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl, 3-methyl-[1,2,4]triazolo[4,3-*b*]-pyridazinyl, or [1,2,4]triazolo[4,3-*b*]-pyridazinyl;

R^5 is H or fluoro;

R^6 is H or fluoro;

R^7 is H;

R^8 is H, or C_1-C_3 alkyl;

R^{14} is independently selected at each occurrence from a substituent in the group consisting of halogen, $-NO_2$, $-OR^{12}$, $-NR^{10}R^{11}$, $-NR^{12}C(O)_2R^{13}$, $-NR^{12}C(O)NR^{12}R^{13}$, $-S(O)_n R^{13}$, –CN, $-C(O)R^{13}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, where each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; and

R^{15} is independently selected at each occurrence from a substituent in the group consisting of –CN, halogen, $C(O)R^{13}$, C_1-C_3 alkyl, $-OR^{12}$, $-NR^{10}R^{11}$, $-S(O)_nR^{13}$, aryl, and heteroaryl, where each of the aryl or heteroaryl groups is optionally substituted from 1 to 4 times with substituents as defined above in R^{14}.

[0081] Other specific compounds of formula (II) of the present invention are the following compounds:

(*Z*)-8-methoxy-5-phenyl-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(4-chlorophenyl)-8-methoxy-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(4-fluorophenyl)-8-methoxy-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(3-fluorophenyl)-8-methoxy-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(2-fluorophenyl)-8-methoxy-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,4-difluorophenyl)-8-methoxy-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,3-difluorophenyl)-8-methoxy-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,5-difluorophenyl)-8-methoxy-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,6-difluorophenyl)-8-methoxy-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,4-difluorophenyl)-8-methoxy-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-5-(3,5-difluorophenyl)-8-methoxy-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-8-methoxy-2-methyl-5-phenyl-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(4-chlorophenyl)-8-methoxy-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(4-fluorophenyl)-8-methoxy-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(3-fluorophenyl)-8-methoxy-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(2-fluorophenyl)-8-methoxy-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,4-difluorophenyl)-8-methoxy-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,3-difluorophenyl)-8-methoxy-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,5-difluorophenyl)-8-methoxy-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,6-difluorophenyl)-8-methoxy-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,4-difluorophenyl)-8-methoxy-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,5-difluorophenyl)-8-methoxy-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-phenyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(4-chlorophenyl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(4-fluorophenyl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(3-fluorophenyl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(2-fluorophenyl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,4-difluorophenyl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,3-difluorophenyl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine
(*E*)-5-(2,5-difluorophenyl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,6-difluorophenyl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,4-difluorophenyl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,5-difluorophenyl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-2-methyl-5-phenyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(4-chlorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(4-fluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(3-fluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(2-fluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,4-difluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,3-difluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-5-(2,5-difluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,6-difluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,4-difluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,5-difluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-8-(6-methylpyridazin-3-yl)-5-phenyl-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(4-chlorophenyl)-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(4-fluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(3-fluorophenyl)-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(2-fluorophenyl)-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,4-difluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,3-difluorophenyl)-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,5-difluorophenyl)-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,6-difluorophenyl)-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,4-difluorophenyl)-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,5-difluorophenyl)-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-2-methyl-8-(6-methylpyridazin-3-yl)-5-phenyl-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(4-chlorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(4-fluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(3-fluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*Z*)-5-(2-fluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,4-difluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,3-difluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,5-difluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,6-difluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,4-difluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,5-difluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-6-(5-phenyl-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*Z*)-6-(5-(4-chlorophenyl)-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*Z*)-6-(5-(4-fluorophenyl)-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*Z*)-6-(5-(3-fluorophenyl)-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*Z*)-6-(5-(2-fluorophenyl)-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*E*)-6-(5-(2,4-difluorophenyl)-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*E*)-6-(5-(2,3-difluorophenyl)-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*E*)-6-(5-(2,5-difluorophenyl)-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*E*)-6-(5-(2,6-difluorophenyl)-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*E*)-6-(5-(3,4-difluorophenyl)-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*E*)-6-(5-(2,5-difluorophenyl)-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*Z*)-6-(2-methyl-5-phenyl-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;

(*Z*)-6-(5-(4-chlorophenyl)-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*Z*)-6-(5-(4-fluorophenyl)-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*Z*)-6-(5-(3-fluorophenyl)-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*Z*)-6-(5-(2-fluorophenyl)-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*E*)-6-(5-(2,4-difluorophenyl)-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*E*)-6-(5-(2,3-difluorophenyl)-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*E*)-6-(5-(2,5-difluorophenyl)-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*E*)-6-(5-(2,6-difluorophenyl)-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*E*)-6-(5-(3,4-difluorophenyl)-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*E*)-6-(5-(2,5-difluorophenyl)-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*Z*)-2-methyl-5-phenyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(4-chlorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(4-fluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(3-fluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(2-fluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,4-difluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-5-(2,3-difluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,5-difluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,6-difluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,4-difluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,5-difluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-phenyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(4-chlorophenyl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(4-fluorophenyl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(3-fluorophenyl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(2-fluorophenyl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,4-difluorophenyl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,3-difluorophenyl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,5-difluorophenyl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,6-difluorophenyl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,4-difluorophenyl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,5-difluorophenyl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-2-methyl-5-phenyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*Z*)-5-(4-chlorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(4-fluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(3-fluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(2-fluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,4-difluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,3-difluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,5-difluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,6-difluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,4-difluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,5-difluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-9-fluoro-5-(2-fluorophenyl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-9-fluoro-5-(2-fluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-6-(9-fluoro-5-(2-fluorophenyl)-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*E*)-9-fluoro-5-(2-fluorophenyl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-6-(9-fluoro-5-(2-fluorophenyl)-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*E*)-9-fluoro-5-(2-fluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-9-fluoro-5-(2-fluorophenyl)-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-9-fluoro-5-(2-fluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-9-fluoro-5-(4-fluorophenyl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-9-fluoro-5-(4-fluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-6-(9-fluoro-5-(4-fluorophenyl)-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*E*)-9-fluoro-5-(4-fluorophenyl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-6-(9-fluoro-5-(4-fluorophenyl)-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*E*)-9-fluoro-5-(4-fluorophenyl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-9-fluoro-5-(4-fluorophenyl)-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-9-fluoro-5-(4-fluorophenyl)-2-methyl-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,4-difluorophenyl)-9-fluoro-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-6-(5-(2,4-difluorophenyl)-9-fluoro-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*E*)-5-(2,4-difluorophenyl)-9-fluoro-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,4-difluorophenyl)-9-fluoro-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,4-difluorophenyl)-9-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-6-(5-(2,4-difluorophenyl)-9-fluoro-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*E*)-5-(2,4-difluorophenyl)-9-fluoro-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,4-difluorophenyl)-9-fluoro-2-methyl-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-5-(3,4-difluorophenyl)-9-fluoro-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-6-(5-(3,4-difluorophenyl)-9-fluoro-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*E*)-5-(3,4-difluorophenyl)-9-fluoro-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,4-difluorophenyl)-9-fluoro-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,4-difluorophenyl)-9-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-6-(5-(3,4-difluorophenyl)-9-fluoro-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*E*)-5-(3,4-difluorophenyl)-9-fluoro-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,4-difluorophenyl)-9-fluoro-2-methyl-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,5-difluorophenyl)-9-fluoro-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-6-(5-(3,5-difluorophenyl)-9-fluoro-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*E*)-5-(3,5-difluorophenyl)-9-fluoro-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,5-difluorophenyl)-9-fluoro-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,5-difluorophenyl)-9-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-6-(5-(3,5-difluorophenyl)-9-fluoro-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*E*)-5-(3,5-difluorophenyl)-9-fluoro-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,5-difluorophenyl)-9-fluoro-2-methyl-8-(6-methylpyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-5-(2,3-difluorophenyl)-9-fluoro-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,3-difluorophenyl)-9-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,6-difluorophenyl)-9-fluoro-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,6-difluorophenyl)-9-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,5-difluorophenyl)-9-fluoro-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,5-difluorophenyl)-9-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-7-fluoro-5-(2-fluorophenyl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-7-fluoro-5-(2-fluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-7-fluoro-5-(4-fluorophenyl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-7-fluoro-5-(4-fluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,3-difluorophenyl)-7-fluoro-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,3-difluorophenyl)-7-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,4-difluorophenyl)-7-fluoro-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,4-difluorophenyl)-7-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,5-difluorophenyl)-7-fluoro-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,5-difluorophenyl)-7-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(2,6-difluorophenyl)-7-fluoro-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-5-(2,6-difluorophenyl)-7-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,4-difluorophenyl)-7-fluoro-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,4-difluorophenyl)-7-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,5-difluorophenyl)-7-fluoro-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine
(*E*)-5-(3,5-difluorophenyl)-7-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-6-fluoro-5-(2-fluorophenyl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-6-fluoro-5-(2-fluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-6-fluoro-5-(4-fluorophenyl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-6-fluoro-5-(4-fluorophenyl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,5-difluorophenyl)-6-fluoro-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3,5-difluorophenyl)-6-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(naphthalen-2-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-2-methyl-5-(naphthalen-2-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-8-(6-methylpyridazin-3-yl)-5-(naphthalen-2-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-2-methyl-8-(6-methylpyridazin-3-yl)-5-(naphthalen-2-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-6-(5-(naphthalen-2-yl)-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*Z*)-6-(2-methyl-5-(naphthalen-2-yl)-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*Z*)-2-methyl-5-(naphthalen-2-yl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(naphthalen-5-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*Z*)-2-methyl-5-(naphthalen-5-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(naphthalen-6-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-2-methyl-5-(naphthalen-6-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-5-(naphthalen-7-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-2-methyl-5-(naphthalen-7-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(1-fluoronaphthalen-2-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(1-fluoronaphthalen-2-yl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-6-(5-(1-fluoronaphthalen-2-yl)-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*E*)-6-(5-(1-fluoronaphthalen-2-yl)-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(E)-5-(1-fluoronaphthalen-2-yl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1H-benzo[c]azepine;
(*E*)-5-(1-fluoronaphthalen-2-yl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3-fluoronaphthalen-2-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(3-fluoronaphthalen-2-yl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-6-(5-(3-fluoronaphthalen-2-yl)-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*E*)-6-(5-(3-fluoronaphthalen-2-yl)-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(E)-5-(3-fluoronaphthalen-2-yl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1H-benzo[c]azepine;
(*E*)-5-(3-fluoronaphthalen-2-yl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(5-fluoronaphthalen-2-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(5-fluoronaphthalen-2-yl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-5-(6-fluoronaphthalen-2-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(6-fluoronaphthalen-2-yl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(7-fluoronaphthalen-2-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-5-(7-fluoronaphthalen-2-yl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-9-fluoro-5-(naphthalen-2-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-9-fluoro-2-methyl-5-(naphthalen-2-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-6-(9-fluoro-5-(naphthalen-2-yl)-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*Z*)-6-(9-fluoro-2-methyl-5-(naphthalen-2-yl)-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;
(*Z*)-9-fluoro-5-(naphthalen-2-yl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-9-fluoro-2-methyl-5-(naphthalen-2-yl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-9-fluoro-8-(6-methylpyridazin-3-yl)-5-(naphthalen-2-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*Z*)-9-fluoro-2-methyl-8-(6-methylpyridazin-3-yl)-5-(naphthalen-2-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-9-fluoro-5-(1-fluoronaphthalen-2-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-9-fluoro-5-(1-fluoronaphthalen-2-yl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-9-fluoro-5-(3-fluoronaphthalen-2-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-9-fluoro-5-(3-fluoronaphthalen-2-yl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-9-fluoro-5-(5-fluoronaphthalen-2-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;
(*E*)-9-fluoro-5-(5-fluoronaphthalen-2-yl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-9-fluoro-5-(6-fluoronaphthalen-2-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-9-fluoro-5-(6-fluoronaphthalen-2-yl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-9-fluoro-5-(7-fluoronaphthalen-2-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-9-fluoro-5-(7-fluoronaphthalen-2-yl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-7-fluoro-5-(1-fluoronaphthalen-2-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-7-fluoro-5-(1-fluoronaphthalen-2-yl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-7-fluoro-5-(3-fluoronaphthalen-2-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-7-fluoro-5-(3-fluoronaphthalen-2-yl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-7-fluoro-5-(5-fluoronaphthalen-2-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-7-fluoro-5-(5-fluoronaphthalen-2-yl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-7-fluoro-5-(6-fluoronaphthalen-2-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-7-fluoro-5-(6-fluoronaphthalen-2-yl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-7-fluoro-5-(7-fluoronaphthalen-2-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-7-fluoro-5-(7-fluoronaphthalen-2-yl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-6-fluoro-5-(5-fluoronaphthalen-2-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-6-fluoro-5-(5-fluoronaphthalen-2-yl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-6-fluoro-5-(6-fluoronaphthalen-2-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-6-fluoro-5-(6-fluoronaphthalen-2-yl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-6-fluoro-5-(7-fluoronaphthalen-2-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-6-fluoro-5-(7-fluoronaphthalen-2-yl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-5-(benzo[*b*]thiophen-2-yl)-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-5-(benzo[*b*]thiophen-2-yl)-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-6-(5-(benzo[*b*]thiophen-2-yl)-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;

(*E*)-6-(5-(benzo[*b*]thiophen-2-yl)-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine;

(*E*)-5-(benzo[*b*]thiophen-2-yl)-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-5-(benzo[*b*]thiophen-2-yl)-2-methyl-8-(6-(trifluoromethyl)pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-5-(benzo[*b*]thiophen-2-yl)-9-fluoro-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-5-(benzo[*b*]thiophen-2-yl)-9-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-5-(benzo[*b*]thiophen-2-yl)-7-fluoro-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-5-(benzo[*b*]thiophen-2-yl)-7-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine;

(*E*)-5-(benzo[*b*]thiophen-2-yl)-6-fluoro-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine; and

(*E*)-5-(benzo[*b*]thiophen-2-yl)-6-fluoro-2-methyl-8-(pyridazin-3-yl)-2,3-dihydro-1*H*-benzo[*c*]azepine.

[0082] Single enantiomers, any mixture of enantiomers, including racemic mixtures, or diastereomers (both separated and as any mixtures) of the compounds of the present invention are also included within the scope of the invention.

[0083] The scope of the present invention also encompasses active metabolites of the present compounds.

[0084] Another embodiment of the present invention is a mixture of compounds of formulae I(A-E), or formula (II), where the compound of formulae I(A-E), or formula (II), is radiolabeled, i.e., where one or more of the atoms described are replaced by a radioactive isotope of that atom (e.g., C replaced by ^{14}C and H replaced by ^{3}H). Such compounds have a variety of potential uses, e.g., as standards and reagents in determining the ability of a potential pharmaceutical to bind to neurotransmitter proteins.

[0085] Another embodiment of the present invention is a pharmaceutical composition containing a therapeutically effective amount of the compound of formulae I(A-E), or formula (II), and a pharmaceutically acceptable carrier.

[0086] Another aspect of the present invention relates to a method of treating a disorder which is created by or is dependent upon decreased availability of serotonin, norepinephrine, or dopamine. The method involves administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I(A-E), or formula (II), or a pharmaceutically acceptable salt thereof. The method of the present invention is capable of treating subjects afflicted with various neurological and psychiatric disorders including, without limitation: lower back pain, attention deficit hyperactivity disorder (ADHD), cognition impairment, anxiety disorders especially generalized anxiety disorder (GAD), panic disorder, bipolar disorder, also known as manic depression or manic-depressive disorder, obsessive compulsive disorder (OCD), posttraumatic stress disorder (PTSD), acute stress disorder, social phobia, simple phobias, pre-menstrual dysphoric disorder (PMDD), social anxiety disorder (SAD), major depressive disorder (MDD), postnatal depression, dysthymia, depression associated with Alzheimer's disease, Parkinson's disease, or psychosis, supranuclear palsy, eating disorders, especially obesity, anorexia nervosa, bulimia nervosa, and binge eating disorder, analgesia, substance abuse disorders (including chemical dependencies) such as nicotine addiction, cocaine addiction, alcohol and amphetamine addiction, Lesch-Nyhan syndrome,

neurodegenerative diseases such as Parkinson's disease, late luteal phase syndrome or narcolepsy, psychiatric symptoms such as anger, rejection sensitivity, movement disorders such as extrapyramidal syndrome, Tic disorders and restless leg syndrome (RLS), tardive dyskinesia, supranuclear palsy, sleep related eating disorder (SRED), night eating syndrome (NES), stress urinary incontinence (SUI), migraine, neuropathic pain, especially diabetic neuropathy, fibromyalgia syndrome (FS), chronic fatigue syndrome (CFS), sexual dysfunction, especially premature ejaculation and male impotence, and thermoregulatory disorders (e.g., hot flashes associated with menopause).

[0087] The compounds provided herein are particularly useful in the treatment of these and other disorders due, at least in part, to their ability to selectively bind to the transporter proteins for certain neurochemicals with a greater affinity than to the transporter proteins for other neurochemicals.

[0088] In another embodiment of the present invention, the above method further involves administering a therapeutically effective amount of a serotonin 1A receptor antagonist or a pharmaceutically acceptable salt thereof. Suitable serotonin 1A receptor antagonists include WAY 100135 and spiperone. WAY 100135 (N-(t-butyl)-3-[a-(2-methoxyphenyl)piperazin-1-yl]-2 phenylpropanamide) is disclosed as having an affinity for the serotonin 1A receptor in U.S. Patent No. 4,988,814, to Abou-Charbia et al. Also, Cliffe et al., *J Med Chem* 36:1509-10 (1993), showed that the compound is a serotonin 1A antagonist. Spiperone (8-[4-(4-fluorophenyl)-4-oxobutyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one) is a well-known compound and is disclosed in U.S. Patent Nos. 3,155,669 and 3,155,670. The activity of spiperone as a serotonin 1A antagonist is described in Middlemiss et al., *Neurosc and Biobehav Rev.* 16:75-82 (1992).

[0089] In another embodiment of the present invention, the above method further involves administering a therapeutically effective amount of a selective neurokinin-1 receptor antagonist or pharmaceutically acceptable salt thereof. Neurokinin-1 receptor antagonists that can be used in combination with the compound of formulae I(A-E), or formula (II), in the present invention are fully described, for example, in U.S. Patent Nos. 5,373,003, 5,387,595, 5,459,270, 5,494,926, 5,162,339,

5,232,929, 5,242,930, 5,496,833, and 5,637,699; PCT International Patent Publication Nos. WO 90/05525, 90/05729, 94/02461, 94/02595, 94/03429,94/03445, 94/04494, 94/04496, 94/05625, 94/07843, 94/08997, 94/10165, 94/10167, 94/10168, 94/10170, 94/11368, 94/13639, 94/13663, 94/14767,94/15903, 94/19320, 94/19323, 94/20500, 91/09844, 91/18899, 92/01688, 92/06079, 92/12151,92/15585, 92/17449, 92/20661, 92/20676, 92/21677, 92/22569, 93/00330, 93/00331, 93/01159, 93/01165, 93/01169, 93/01170, 93/06099, 93/09116, 93/10073, 93/14084, 93/14113, 93/18023, 93/19064, 93/21155, 93/21181, 93/23380, 93/24465, 94/00440, 94/01402, 94/26735, 94/26740, 94/29309, 95/02595, 95/04040, 95/04042, 95/06645, 95/07886, 95/07908, 95/08549, 95/11880, 95/14017, 95/15311, 95/16679, 95/17382, 95/18124, 95/18129, 95/19344, 95/20575, 95/21819, 95/22525, 95/23798, 95/26338, 95/28418, 95/30674, 95/30687, 95/33744, 96/05181, 96/05193, 96/05203, 96/06094, 96/07649, 96/10562, 96/16939, 96/18643, 96/20197, 96/21661, 96/29304,96/29317, 96/29326, 96/29328, 96/31214, 96/32385, 96/37489, 97/01553, 97/01554, 97/03066, 97/08144, 97/14671, 97/17362, 97/18206, 97/19084, 97/19942, 97/21702, and 97/49710; and in U.K. Patent Application Nos. 2 266 529, 2 268 931, 2 269 170, 2 269 590, 2 271 774, 2 292 144, 2 293168, 2 293 169, and 2 302 689; European Patent Publication Nos. EP 0 360 390, 0 517 589, 0 520 555, 0 522 808, 0 528 495, 0 532 456, 0 533 280, 0 536 817, 0 545 478, 0 558 156, 0 577 394, 0 585 913, 0 590 152, 0 599 538, 0 610 793, 0 634 402, 0 686 629, 0 693 489, 0 694 535, 0 699 655, 0 394 989, 0 428 434, 0 429 366, 0 430 771, 0 436 334, 0 443 132, 0 482 539, 0 498 069, 0 499 313, 0 512 901, 0 512 902, 0 514 273, 0 514 274, 0 514 275, 0 514 276, 0 515 681, 0 699 674, 0 707 006, 0 708 101, 0 709 375, 0 709 376, 0 714 891, 0 723 959, 0 733 632 and 0 776 893.

The preparations of such compounds are fully described in the aforementioned patents and publications.

[0090] In another embodiment of the present invention, the above method further involves administering a therapeutically effective amount of a norepinephrine precursor or a pharmaceutically acceptable salt thereof. Suitable norepinephrine precursors include L-tyrosine and L-phenylalanine.

[0091] Another aspect of the present invention is a method of inhibiting synaptic norepinephrine uptake in a patient in need thereof. The method involves

administering a therapeutically effective inhibitory amount of a compound of formulae I(A-E), or formula (II).

[0092] Another aspect of the present invention is a method of inhibiting synaptic serotonin uptake in a patient in need thereof. The method involves administering a therapeutically effective inhibitory amount of a compound of formulae I(A-E), or formula (II).

[0093] Another aspect of the present invention is a method of inhibiting synaptic dopamine uptake in a patient in need thereof. The method involves administering a therapeutically effective inhibitory amount of a compound of formulae I(A-E), or formula (II).

[0094] Another aspect of the present invention is a therapeutic method described herein, where the (+)-stereoisomer of the compound of formulae I(A-E) is employed.

[0095] Another aspect of the present invention is a therapeutic method described herein, where the (-)-stereoisomer of the compound of formulae I(A-E) is employed.

[0096] Another aspect of the present invention is a kit comprising a compound of formulae I(A-E), or formula (II), and at least one compound selected from the group consisting of: a serotonin 1A receptor antagonist compound, a selective neurokinin-1 receptor antagonist compound, and a norepinephrine precursor compound.

[0097] Another aspect of the present invention relates to a method of treating a disorder referred to in the above-mentioned embodiments in a patient in need thereof. The method involves inhibiting synaptic serotonin and norepinephrine uptake by administering a therapeutically effective inhibitory amount of the compound of formulae I(A-E), or formula (II), which functions as both a dual acting serotonin and norepinephrine uptake inhibitor.

[0098] Another aspect of the present invention relates to a method of treating a disorder referred to in the above-mentioned embodiments in a patient in need thereof. The method involves inhibiting synaptic serotonin and dopamine uptake by administering a therapeutically effective inhibitory amount of the compound of formulae I(A-E), or formula (II), which functions as both a dual acting serotonin and dopamine uptake inhibitor.

[0099] Another aspect of the present invention relates to a method of treating a disorder referred to in the above-mentioned embodiments in a patient in need thereof. The method involves inhibiting synaptic dopamine and norepinephrine uptake by administering a therapeutically effective inhibitory amount of the compound of formulae I(A-E), or formula (II), which functions as both a dual acting dopamine and norepinephrine uptake inhibitor.

[0100] Another aspect of the present invention relates to a method of treating a disorder referred to in the above-mentioned embodiments in a patient in need thereof. The method involves inhibiting synaptic norepinephrine, dopamine and serotonin uptake by administering a therapeutically effective inhibitory amount of the compound of formulae I(A-E), or formula (II), which functions as a triple acting norepinephrine, dopamine, and serotonin uptake inhibitor.

[0101] Another aspect of the present invention relates to a method for inhibiting serotonin uptake in mammals. The method involves administering to a mammal requiring increased neurotransmission of serotonin a pharmaceutically effective amount of the compound of formulae I(A-E), or formula (II).

[0102] Another aspect of the present invention relates to a method for inhibiting dopamine uptake in humans. The method involves administering to a human requiring increased neurotransmission of dopamine a pharmaceutically effective amount of the compound of formulae I(A-E), or formula (II).

[0103] Another aspect of the present invention relates to a method for inhibiting norepinephrine uptake in humans. The method involves administering to a human requiring increased neurotransmission of norepinephrine a pharmaceutically effective amount of the compound of formulae I(A-E), or formula (II).

[0104] Another aspect of the present invention relates to a method of suppressing the desire of humans to smoke. The method involves administering to a human in need of such suppression an effective dose, to relieve the desire to smoke, of the compound of formulae I(A-E), or formula (II).

[0105] Another aspect of the present invention relates to a method of suppressing the desire of humans to consume alcohol. The method involves administering to a human in need of such suppression an effective dose, to relieve the desire to consume alcohol, of the compound of formulae I(A-E), or formula (II).

[0106] It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

[0107] Compounds according to the invention, for example, starting materials, intermediates or products, are prepared as described herein or by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature.

[0108] Compounds useful according to the invention may be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, for example those described by Larock, R.C., *Comprehensive Organic Transformations*, VCH publishers, (1989), which is hereby incorporated by reference in its entirety.

[0109] A compound of formulae I(A-E), or formula (II), including a group containing one or more nitrogen ring atoms, may be converted to the corresponding compound where one or more nitrogen ring atom of the group is oxidized to an N-oxide, preferably by reacting with a peracid, for example, peracetic acid in acetic acid or m-chloroperoxybenzoic acid in an inert solvent such as dichloromethane, at a temperature from about room temperature to reflux, preferably at elevated temperature.

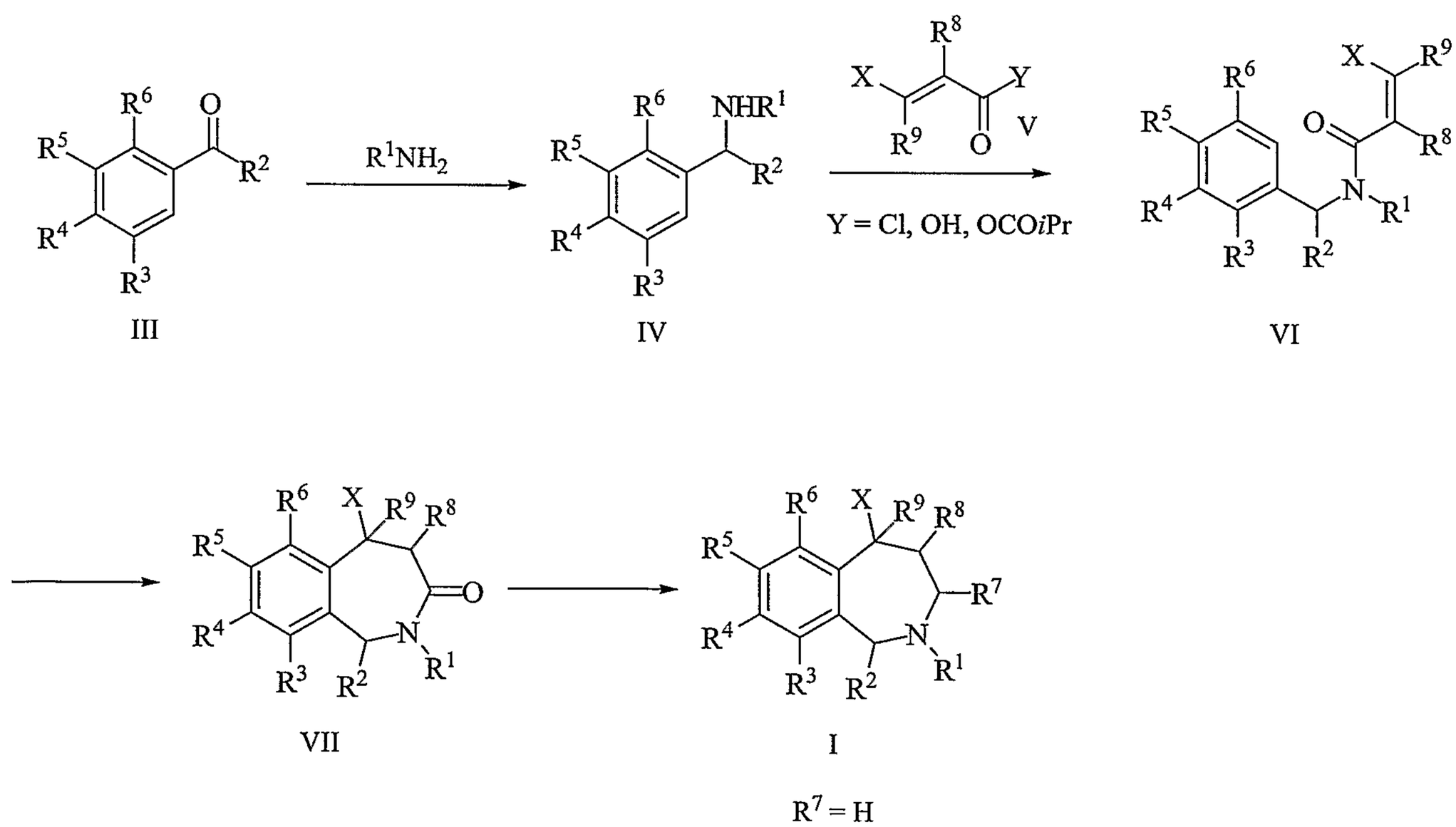
[0110] In the reactions described hereinafter, it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio, or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice; for examples, see Green, *Protective Groups in Organic Chemistry*, John Wiley and Sons (1991) and McOmie, *Protective Groups in Organic Chemistry*, Plenum Press (1973).

[0111] In the reaction schemes described hereinafter, the synthesis of tetrahydrobenzazepines of the formulae I(A-E) functionalized at R^4 with aryl, heteroaryl, or heterocylic groups is described. The synthesis of tetrahydrobenzazepines of the formulae I(A-E) functionalized at R^3, R^5 or R^6 with

aryl, heteroaryl, or heterocyclic groups may be achieved via similar routes, apparent to one skilled in the art of organic synthesis.

[0112] The novel tetrahydrobenzazepine reuptake inhibitors of formula (I; R^4 = aryl, heteroaryl, or heterocyclic) of the present invention can be prepared by the general scheme outlined below (Scheme 1). The R^1-substituted *N*-benzyl amines of formula (IV) may be purchased from commercial sources, or alternatively, obtained from a simple reductive amination protocol. Thus, carbonyl containing compounds of formula (III) may be treated with H_2N-R^1 in lower alkyl alcoholic solvents (preferably methanol or ethanol) at temperatures at or below room temperature. The resulting imine may be reduced most commonly with alkali earth borohydrides (preferably sodium borohydride) to provide the desired amine intermediates of formula (IV).

Scheme 1



[0113] Treatment of intermediates of formula (IV) with cinnamyl chloride, cinnamic acid or cinnamic acid anhydride intermediates of formula (V; Y = Cl, OH, or OCO*i*Pr respectively) cleanly generates the amide products of formula (VI).

Amide formation reactions may be run under a wide variety of conditions familiar to one skilled in the art of organic synthesis. Typical solvents include dimethylformamide and methylene chloride. The reactions may be successfully run at temperatures ranging from 0°C up to room temperature. Reaction progress is conventionally monitored by standard chromatographic and spectroscopic methods.

[0114] Several of the aforementioned intermediates of formula (V; Y = OH) are commercially available. Cinnamic acid anhydrides of the formula (V; Y = OCO*i*Pr) are readily prepared from the corresponding cinnamic acid on treatment with an aliphatic chloroformate such as, but not limited to, isopropyl chloroformate, while cinnamyl chloride intermediates of the formula (V; Y = Cl) are obtained on treatment of an appropriate cinnamic acid with oxalyl chloride or thionyl chloride.

[0115] Compounds of formula (VI) may be cyclized to the dihydrobenzazepinone compounds of formula (VII) by treatment with a strong acid. Suitable acids include, but are not limited to, concentrated sulfuric acid, polyphosphoric acid, methanesulfonic acid, and trifluoroacetic acid. The reactions are run neat or in the optional presence of a co-solvent such as, for example, methylene chloride or 1,2-dichloroethane. The cyclizations may be conducted at temperatures ranging from 0°C up to the reflux point of the solvent employed. One skilled in the art of heterocyclic chemistry will readily understand these conditions or may consult the teachings of Euerby et al., *J. Chem. Research* (S), 40-41 (1987). Cyclizations may also be effected by treatment of compounds of formula (VI) with strong Lewis acids, such as for example, aluminum trichloride, typically in halogenated solvents, such as methylene chloride.

[0116] Reductions of compounds of formula (VII) to the tetrahydrobenzazepines of formula I of the present invention proceed with reducing agents including, for example, borane and lithium aluminum hydride. The reductions are carried out for a period of time between 1 hour to 3 hours at room temperature or elevated temperature up to the reflux point of the solvent employed. If borane is used, it may be employed as a complex for example, but not limited to, borane-methyl sulfide complex, borane-piperidine complex, or borane-tetrahydrofuran complex. One skilled in the art will understand the optimal combination of reducing agents and reaction conditions needed or may seek guidance from Larock, R.C., *Comprehensive*

Organic Transformations, VCH publishers, (1989).

[0117] The compounds of formula (I; R^4 = aryl, heteroaryl) of the present invention may be prepared from the corresponding 8-methoxy, 8-Cl, 8-Br, or 8-I tetrahydrobenzazepine of formula (I; $R^4 = OCH_3$, Cl, Br, I). The 8-methoxy tetrahydrobenzazepine (I; $R^4 = OCH_3$) may be converted to the corresponding phenol of formula (I; R^4 = OH) on treatment with a strong acid or a Lewis acid, such as, but not limited to, hydrobromic acid or boron tribromide. Alternatively, the phenol of formula I (R^4 = OH) may be obtained from the corresponding 8-methoxy tetrahydrobenzazepine of formula I ($R^4 = OCH_3$) on treatment with the sodium salt of an alkyl thiol, preferably ethane thiol. The phenol intermediate of formula (I; R^4 = OH) may be converted into the corresponding triflate of formula (I; $R^4 = OSO_2CF_3$) on treatment with a triflating reagent such as, but not limited to, trifluromethanesulfonic anhydride, in the presence of a base, such as, but not limited to, triethylamine or pyridine. The reaction is carried out in an inert solvent, such as, but not limited to dichloromethane, at temperatures ranging from 0°C to room temperature. Treatment of compounds of formula (I; R^4 = Br, I, OSO_2CF_3) with aryl or heteroaryl boronic acids or aryl or heteroaryl boronic acid esters, of formula R^4-Z where Z is equivalent to $B(OH)_2$ or $B(OR^a)(OR^b)$ (where R^a and R^b are lower alkyl, i.e., C_1-C_6, or taken together, R^a and R^b are lower alkylene, i.e., C_2-C_{12}) and R^4 is the corresponding aryl or heteroaryl group in the presence of a metal catalyst with or without a base in an inert solvent gives benzazepine compounds of formula (I; R^4 = aryl, heteroaryl). Metal catalysts include, but are not limited to, salts or phosphine complexes of Cu, Pd, or Ni (e.g., $Cu(OAc)_2$, $PdCl_2$ $(PPh_3)_2$, $NiCl_2$ $(PPh_3)_2$, $Pd(PPh_3)_4$). Bases may include, but are not limited to, alkaline earth metal carbonates, alkaline earth metal bicarbonates, alkaline earth metal hydroxides, alkali metal carbonates, alkali metal bicarbonates, alkali metal hydroxides, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium diisopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably diisopropylethylamine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to acetonitrile, dialkyl ethers (preferably diethyl ether), cyclic

ethers (preferably tetrahydrofuran or 1,4-dioxane), *N,N*-dialkylacetamides (preferably dimethylacetamide), *N,N*-dialkylformamides (preferably dimethylformamide), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes (preferably methylene chloride). Preferred reaction temperatures range from room temperature up to the boiling point of the solvent employed. The reactions may be run in conventional glassware or in one of many commercially available parallel synthesizer units. Non-commercially available boronic acids or boronic acid esters may be obtained from the corresponding optionally substituted aryl halide as described by Gao et al., *Tetrahedron*, 50:979-988 (1994).

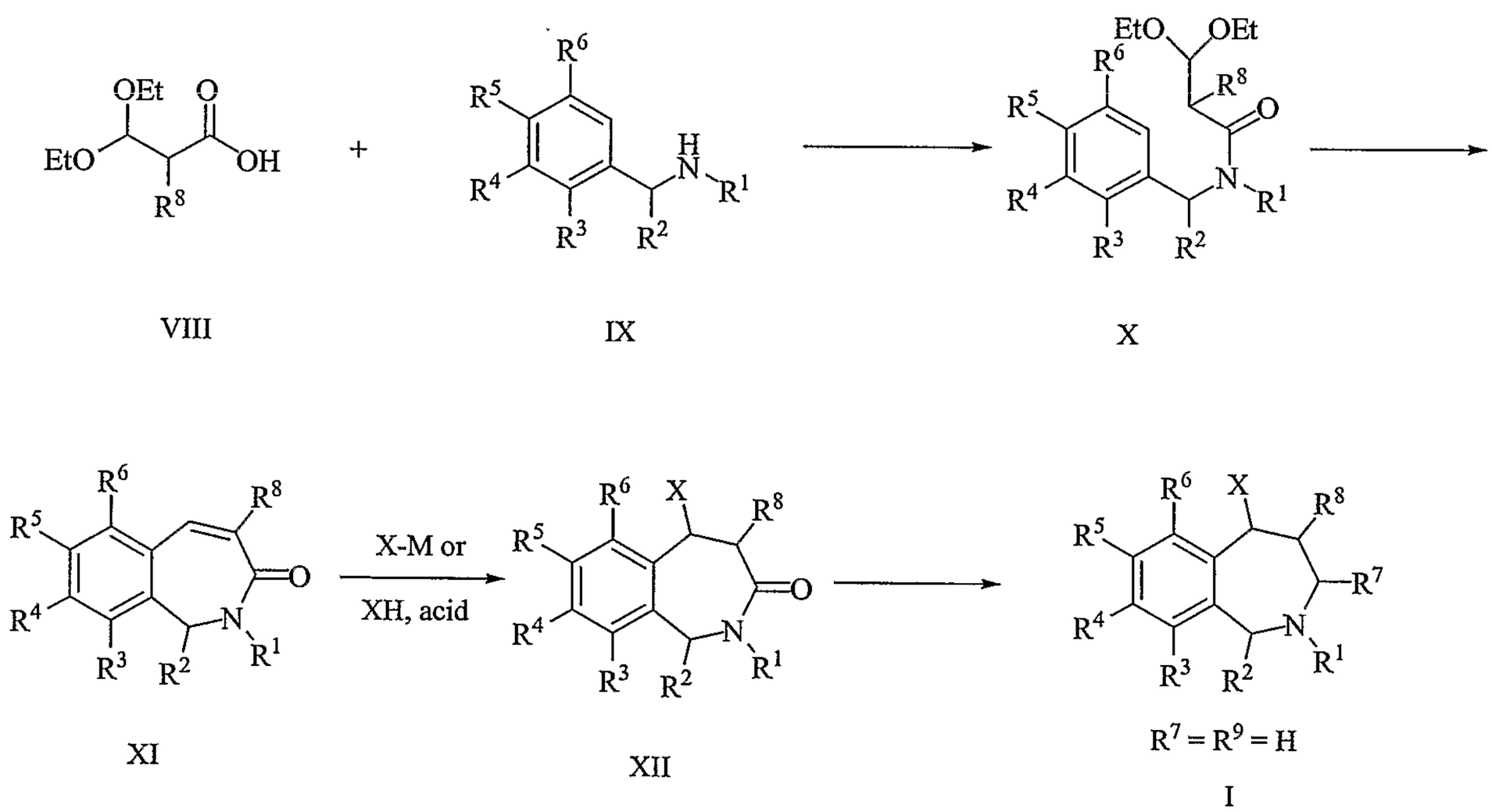
[0118] It will also be appreciated by one skilled in the art that compounds of formula (I; R^4 = Cl, Br, I, OSO_2CF_3) may be converted to the boronic acid or boronate ester and subsequently treated with the desired optionally substituted aryl or heteroaryl halide in discrete steps or in tandem as described by Baudoin et al., *J. Org. Chem.* 67:1199-1207 (2002).

[0119] The compounds of formula (I; R^4 = $-NR^{10}R^{11}$, $-NR^{12}C(O)R^{13}$) of the present invention may be prepared from the compounds of formula (I; R^4 = Cl, Br, I, OSO_2CF_3) on reaction with an appropriate amine, amide or lactam, in the presence of a metal catalyst, with or without a base in an inert solvent. Metal catalysts include, but are not limited to, salts or complexes of Cu, Pd, or Ni (e.g., CuI, $Cu(OAc)_2$, $PdCl_2$(dppf), $NiCl(OAc)_2$, $Ni(COD)_2$). Bases may include, but are not limited to, alkali metal carbonates, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (preferably, sodium *tert*-butoxide), and alkali metal bis(trialkylsilyl)amides (preferably, lithium bis(trimethylsilyl)amide). A supporting ligand, such as, but not limited to L-proline or dimethylethylenediamine is often used. Inert solvents may include, but are not limited to, cyclic ethers (preferably, tetrahydrofuran or 1,4-dioxane), *N,N*-dialkylformamides (preferably, dimethylformamide), dialkylsulfoxides (preferably, dimethylsulfoxide), or aromatic hydrocarbons (preferably, benzene or toluene). Preferred reaction temperatures range from room temperature up to the boiling point of the solvent employed. The reactions may be run in conventional glassware or in a sealed reaction vessel.

[0120] Compounds of formula (I) where R^4 is aryl, heteroaryl, or heterocyclic, R^7 = H, R^8 = H, and R^9 = H may be obtained by using the route outlined in Scheme 2.

Amide intermediate (X) may be prepared by the coupling of an appropriately substituted benzylamine of formula (IX; R^4 = Br, I, OCH_3) with 3,3-diethoxypropanoic acid (VIII; R^8 = H). Amide formation reactions may be run under a wide variety of conditions familiar to one skilled in the art of organic synthesis. Typical solvents include dimethylformamide and methylene chloride. Typical reagents include, but are not limited to, dicyclohexylcarbodiimide, and 1-ethyl-(3-(3-(dimethylamino)propyl)carbodiimide. The reactions may be successfully run at temperatures ranging from 0°C up to room temperature. Reaction progress is conventionally monitored by standard chromatographic and spectroscopic methods.

Scheme 2



[0121] Compounds of formula (X) may be cyclized to give intermediates with the formula (XI) on treatment with a strong acid. Suitable acids include, but are not limited to, concentrated sulfuric acid, polyphosphoric acid, methanesulfonic acid and trifluoroacetic acid. Alternatively, cyclization may be effected by the use of a suitable Lewis acid such as, but not limited to, aluminum trichloride and boron trifluoride etherate. The reactions are run neat or in the optional presence of a co-solvent such as, for example, methylene chloride or 1,2-dichloroethane. The cyclizations may be

conducted at temperatures ranging from 0°C up to the reflux point of the solvent employed.

[0122] Treatment of intermediates with the formula (XI) with an aryl or heteroaryl Grignard or an aryl or heteroaryl lithium reagent X-M generates intermediates with the formula (XII), where X is the corresponding aryl or heteroaryl group. This reaction may be catalyzed by a Lewis acid, such as, but not limited to, trimethylsilyl iodide. Alternatively, intermediates with the formula (XI) may be treated with an arene or heterarene X-H in the presence of a strong acid to generate compounds with the formula (XII), where X is the aryl or heteroaryl group. Suitable acids include, but are not limited to, trifluoromethanesulfonic acid, concentrated sulfuric acid and polyphosphoric acid. Alternatively, a suitable Lewis acid such as, but not limited to, aluminum trichloride and boron trifluoride etherate may be used for the preparation of compounds with the formula (XII) from intermediates with the formula (XI). The reactions are run neat or in the optional presence of a co-solvent such as, for example, methylene chloride or 1,2-dichloroethane, at temperatures ranging from 0°C up to the reflux point of the solvent employed.

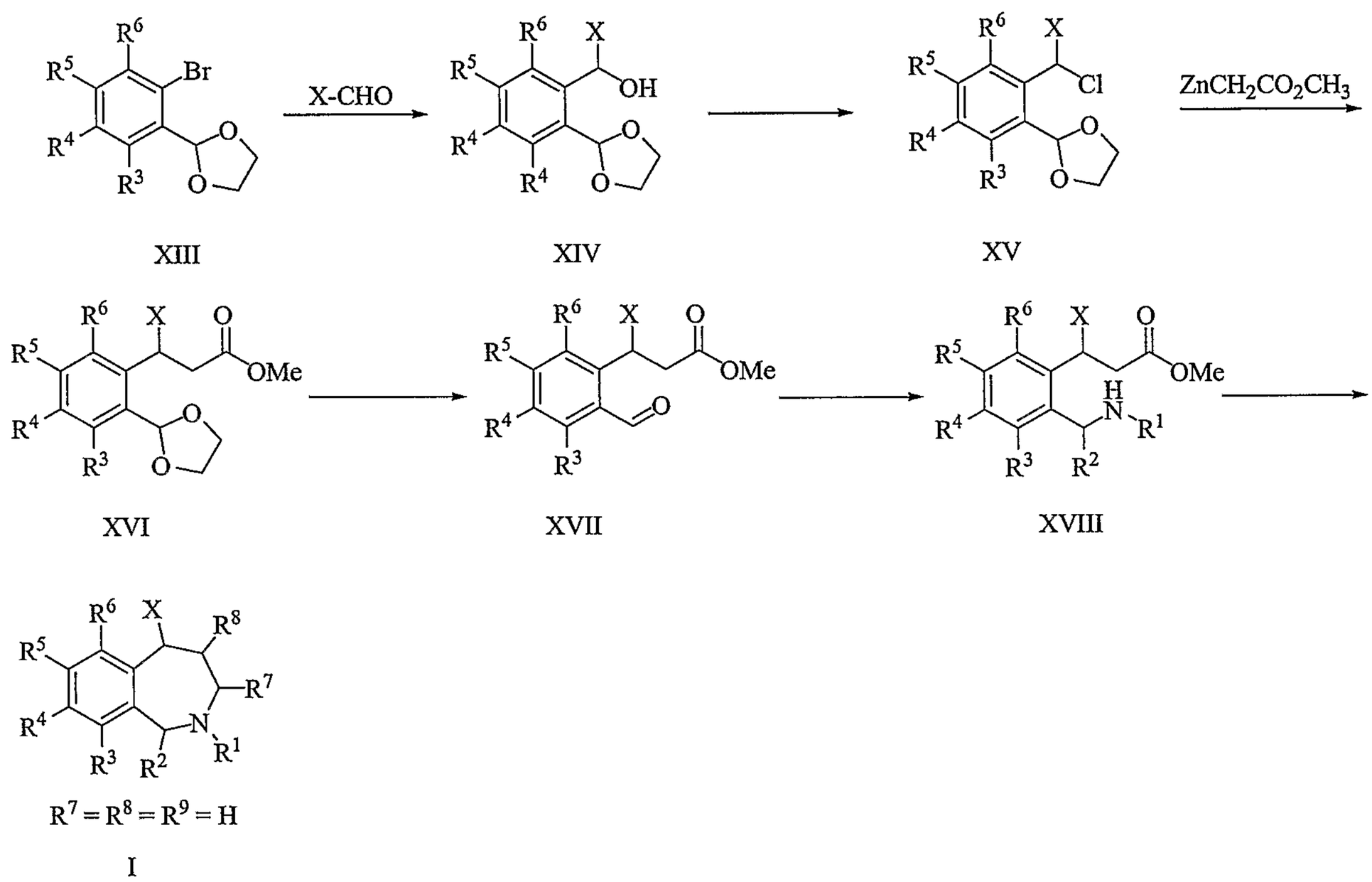
[0123] Reduction of compounds of formula (XII) to the tetrahydrobenzazepines of formula (I) of the present invention proceeds with reducing agents including, for example, borane and lithium aluminum hydride. The reductions are carried out for a period of time between 1 hour to 3 hours at room temperature or elevated temperature up to the reflux point of the solvent employed. If borane is used, it may be employed as a complex for example, but not limited to, borane-methyl sulfide complex, borane-piperidine complex, or borane-tetrahydrofuran complex. One skilled in the art will understand the optimal combination of reducing agents and reaction conditions needed or may seek guidance from Larock, R.C., *Comprehensive Organic Transformations*, VCH publishers, (1989).

[0124] Finally, the compounds of formula (I; R^4 = aryl, heteroaryl or heterocyclic) of the present invention may be prepared from intermediates of formula (I; R^4 = Br, I, OCH_3) as described above for Scheme 1.

[0125] Compounds of formula (I) of the present invention may be prepared by the general scheme outlined in Scheme 3. The acetal-bearing bromoarene intermediate of formula (XIII) may be converted to the intermediate of formula (XIV)

on treatment with an alkyl lithium reagent, followed by reaction of the aryl lithium generated thus with an appropriate aryl or heteroaryl aldehyde X-CHO, where X is the aryl or heteroaryl group. The secondary alcohol of the formula (XIV) may be converted to the corresponding chloride of the formula (XV) on treatment with, for example, methanesulfonyl chloride.

Scheme 3



[0126] Alternatively, the secondary alcohol of the formula (XIV) may also be converted into the corresponding mesylate, tosylate, bromide, or iodide using various methods familiar to one skilled in the art of organic synthesis. Treatment of the intermediate with the formula (XV) with an organozinc reagent such as (2-methoxy-2-oxoethyl)zinc gives the ester of the formula (XVI). One skilled in the art will be familiar with synthetic routes toward the preparation of the aforementioned organozinc reagent. Removal of the acetal protecting group from the intermediate of formula (XVI) may be effected on treatment with, but not limited to, hydrochloric acid, to give the aldehyde with the formula (XVII).

[0127] Reductive amination of the aldehyde intermediate (XVII) with primary amines of the formula R^1NH_2 generates the benzylamine intermediate (XVIII). Reductive amination may involve the use of various reducing agents including, but not limited to, sodium triacetoxyborohydride, and sodium borohydride, and may be catalyzed by various reagents including, but not limited to, magnesium sulfate and titanium isopropoxide.

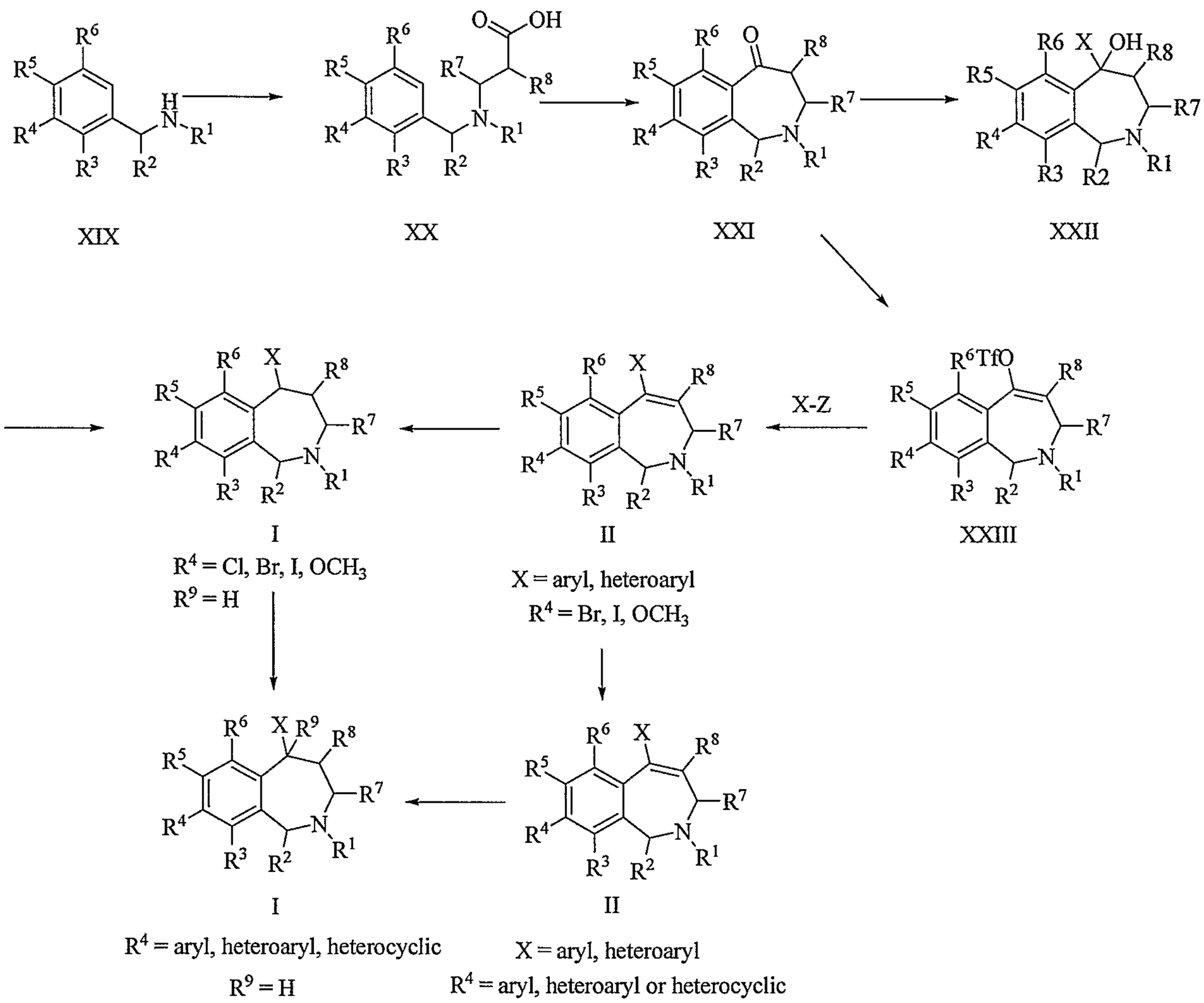
[0128] Compounds of formula (XVIII) may be converted to the corresponding tetrahydrobenzazepine (I) via hydrolysis of the ester, followed by intramolecular condensation with the benzylamine moiety and reduction of the benzazepinone obtained thus using aforementioned methods. Alternatively, compounds of the formula (XVIII), on heating in an appropriate solvent, can be converted into the corresponding dihydrobenzazepinone, which, on reduction using aforementioned methods, gives the tetrahydrobenzazepine of the formula (I). Direct conversion of the intermediate of formula (XVIII) to the tetrahydrobenzazepine of formula (I) may be effected by a one-pot procedure using diisobutylaluminum hydride, followed by sodium borohydride, according to the teachings of Kato et al , *J. Heterocyclic Chemistry*, 32:637-642 (1995),which is hereby incorporated by reference in its entirety.

[0129] Finally, the target compounds of formula (I; R^4 = aryl, heteroaryl, or heterocyclic) of the present invention may be prepared from compounds of formula I (R^4 = Cl, OCH_3) as described above for Scheme 1.

[0130] Compounds of formula (I) where R^4 is aryl, heteroaryl or heterocyclic and R^9 = H may be obtained by using the route outlined in Scheme 4. An appropriately functionalized benzyl amine of the formula (XIX) may be converted to intermediate (XX) on reaction with acrylic acid using methods familiar to one skilled in the art of organic synthesis. The acid with the formula (XX) may be cyclized to give the corresponding 5-benzazepinone of the formula (XXI) on treatment with a strong acid such as, but not limited to, polyphosphoric acid or Eaton's reagent. The 5-benzazepinone of the formula (XXI) may be converted to the secondary alcohol intermediate (XXII) on reaction with an aryl or heteroaryl Grignard reagent or an aryl or heteroaryl lithium reagent. Dehydration and reduction of the intermediate of formula (XXII) using a metal-catalyzed reduction in an acidic medium results in the benzazepine of formula (I). Metal catalysts include, but are not limited to, palladium

on carbon, palladium hydroxide, and Raney nickel. Acids used in the reduction include, but are not limited to, acetic acid, formic acid, and trifluoroacetic acid. Finally, the compounds of formula (I; R^4 = aryl, heteroaryl or heterocyclic) of the present invention may be prepared from intermediates of formula I (R^4 = Cl, Br, I, OCH_3) as described above for Scheme 1.

Scheme 4



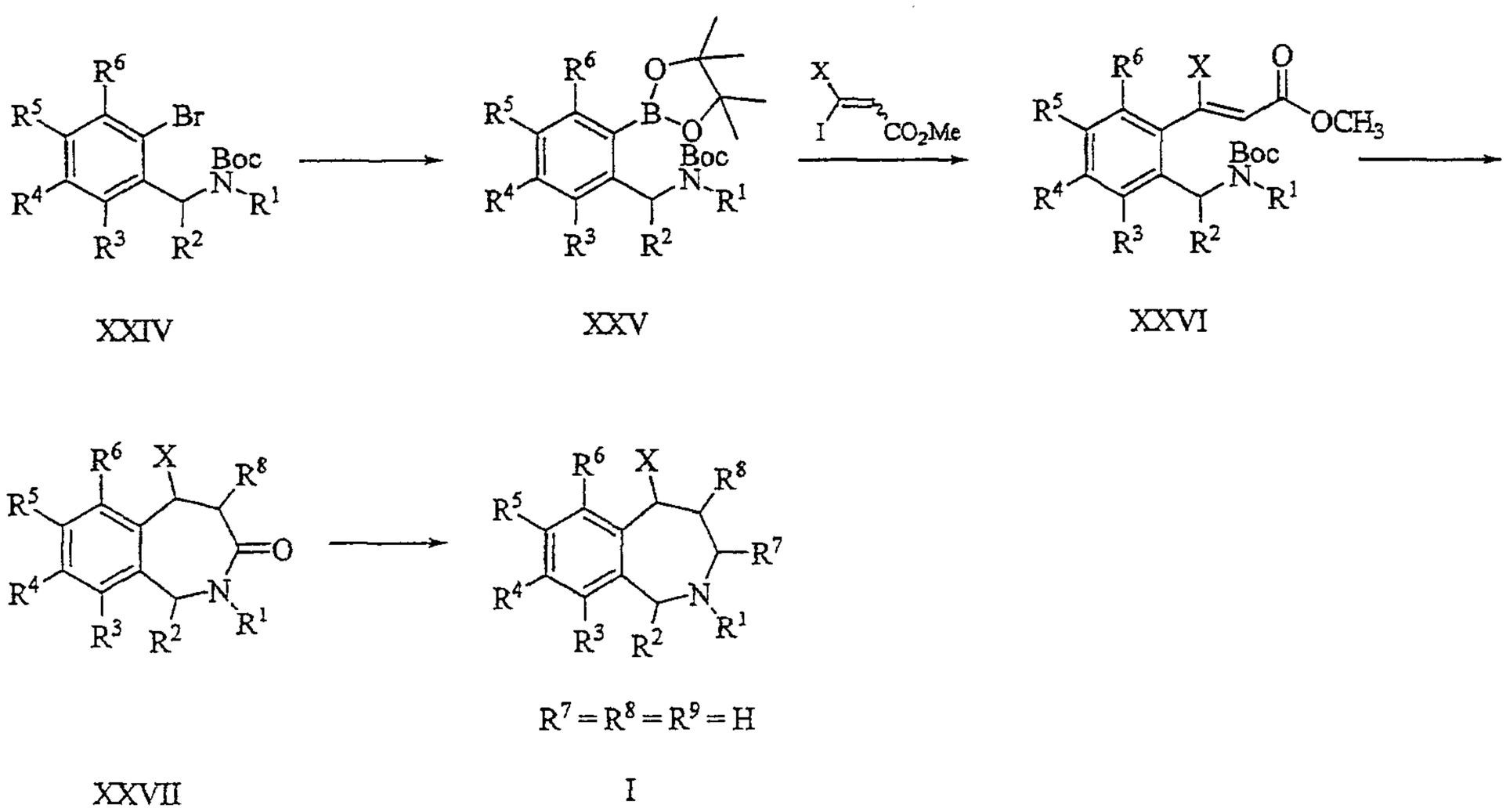
[0131] Alternatively, the 5-benzazepinone of formula (XXI) may be converted into the corresponding vinyl triflate of formula (XXIII) on treatment with a strong base and a triflating reagent, such as, but not limited to, trifluoromethanesulfonic anhydride and *N*-phenyltrifluoromethanesulfonimide. Bases may include, but are not limited to, sodium hydride, lithium hexamethyldisilazide, pyridine, and lithium

diisopropylamide. Dihydrobenzazepine intermediates of the formula (II; X = aryl or heteroaryl) may be obtained by the coupling of the vinyl triflate intermediate of formula (XXIII) with aryl or heteroaryl boronic acids or aryl or heteroaryl boronic acid esters of the formula X-Z, where X is the aryl or heteroaryl group, and where Z is equivalent to $B(OH)_2$ or $B(OR^a)(OR^b)$ (where R^a and R^b are lower alkyl, i.e., C_1-C_6, or taken together, R^a and R^b are lower alkylene, i.e., C_2-C_{12}) in the presence of a metal catalyst, with or without a base in an inert solvent, using the aforementioned methods. Reduction of the dihydrobenzazepine intermediates of the formula (II; X = aryl or heteroaryl) using metal-catalyzed reduction or transfer hydrogenation gives the benzazepines of formula (I). Finally, the compounds of formula (I; R^4 = aryl, heteroaryl or heterocyclic) of the present invention may be prepared from intermediates of formula (I; R^4 = Cl, Br, I, OCH_3) as described above for Scheme 1. The reductions may be run under a wide variety of conditions familiar to one skilled in the art of organic synthesis. The reductions may be carried out using chiral catalysts, which may afford the benzazepine enantiomer of choice based on catalyst selection. Alternatively, the sequence of steps may be reversed, with conversion of the intermediates of formula (II; X = aryl or heteroaryl, R^4 = Br, I, OCH_3) to compounds with formula (II; X = aryl or heteroaryl, R^4 = aryl, heteroaryl, or heterocyclic) using methods described in Scheme 1, followed by reduction to give the target compounds of formula (I; R^4 = aryl, heteroaryl or heterocyclic), also using aforementioned methods.

[0132] Compounds of formula (I) where R^4 is aryl, heteroaryl or heterocyclic, R^7 = H, R^8 = H and R^9 = H may be obtained by using the route outlined in Scheme 5. An appropriately functionalized benzyl amine of the formula (XXIV) may be converted to intermediate (XXV) on reaction with a boron reagent, such as, but not limited to, bis(pinacolato)diboron, in the presence of a metal catalyst and a base in an inert solvent. Catalysts include, but are not limited to, dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane complex, while the base used includes, but is not limited to, potassium acetate in solvents such as, but not limited to, dimethylsulfoxide and dimethylformamide. Reaction of intermediates with the formula (XXV) with methyl 3-iodo aryl (or heteroaryl) acrylates, where X is the aryl or heteroaryl group, gives intermediates of the formula (XXVI). The synthesis of the iodo aryl (or heteroaryl) acrylates may be accomplished by a variety of methods

familiar to one skilled in the art of organic synthesis. Reduction and cyclization of intermediates with the formula (XXVI) may be accomplished by catalytic hydrogenation, followed by heating in an appropriate solvent, such as, but not limited to, toluene, to give the dihydrobenzazepinone intermediate of formula (XXVII). Dihydrobenzazepinones of formula (XXVII) may be reduced using aforementioned methods to give the intermediates of formula (I). Finally, the compounds of formula (I; R^4 = aryl, heteroaryl or heterocyclic) of the present invention may be prepared from intermediates of formula (I; R^4 = Cl, Br, I, OCH_3) as described above for Scheme 1.

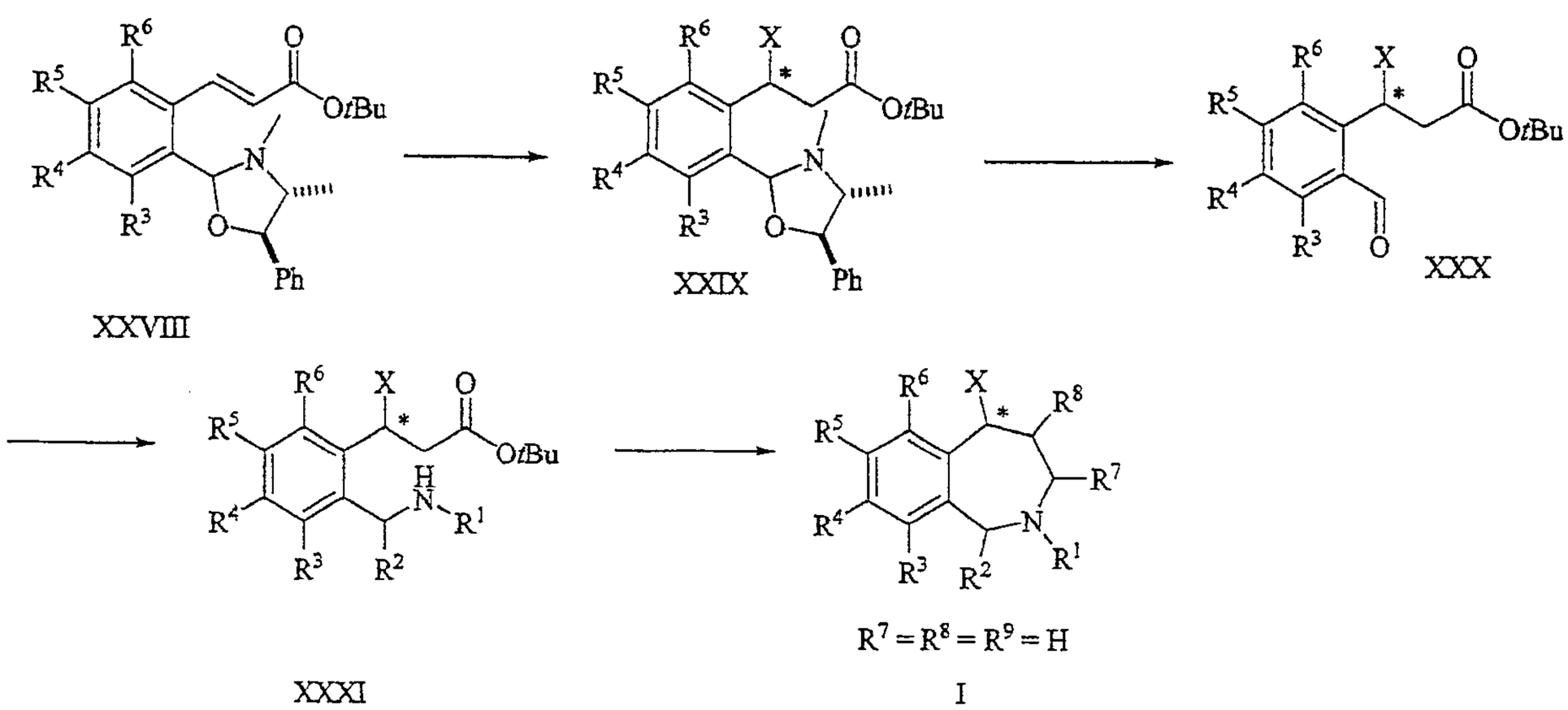
Scheme 5



[0133] Compounds of formula (I) where R^4 is aryl, heteroaryl, or heterocyclic, R^7 = H, R^8 = H, and R^9 = H may be obtained by using the route outlined in Scheme 6. Appropriately functionalized intermediates of formula (XXVIII) bearing a chiral auxiliary may be prepared by following the teachings of Frey et al, *J. Org. Chem.* 63:3120-3124 (1998) and Song et al, *J. Org. Chem.* 64:9658-9667 (1999). The choice of the chiral auxiliary is dictated by the enantiomer of the benzazepine of the formula (I) that is desired, and

includes, but is not limited to, (1*R*, 2*R*)-(-)-psuedoephedrine, and (1*S*, 2*S*)-(-)-psuedoephedrine. One skilled in the art of organic synthesis will be capable of making the optimal choice of the chiral auxiliary to be incorporated into the intermediate of the formula (XXVIII). The intermediate of formula (XXVIII), on treatment with an aryl or heteroaryl Grignard or aryl or heteroaryl lithium reagent, gives the enantiomerically enriched or enantiopure compound of formula (XXIX), depending upon the appropriate choice of the chiral auxiliary and the aryl or heteraryl Grignard or lithium reagent used in the reaction; one may also seek guidance from the teachings of Frey et al, *J. Org. Chem.* 63:3120-3124 (1998) and Song et al, *J. Org. Chem.* 64:9658-9667 (1999). Removal of the chiral auxiliary from the intermediate of formula (XXIX) gives the aldehyde (XXX). The removal of the auxiliary is effected by the use of acids such as, but not limited to, acetic acid and citric acid.

Scheme 6

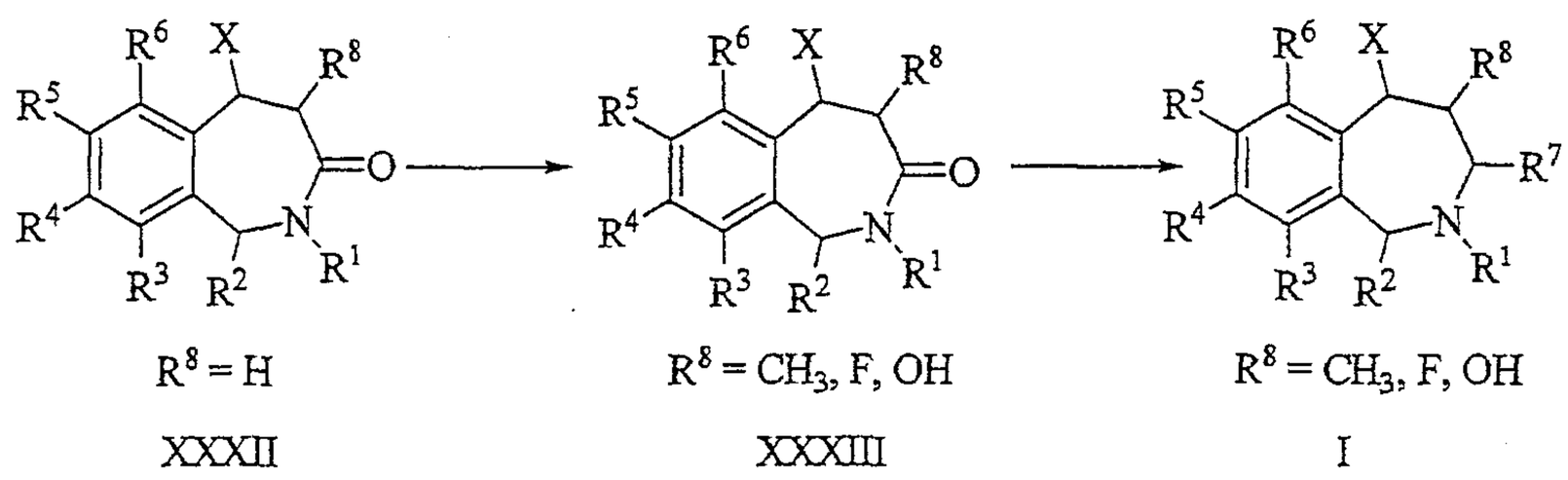


[0134] Reductive amination of the aldehyde intermediate (XXX) with primary amines of the formula R^1NH_2 generates the benzylamine intermediate (XXXI). Reductive amination may involve the use of various reducing agents, including, but not limited to, sodium triacetoxyborohydride and sodium borohydride, and may be catalyzed by various reagents including, but not limited to, magnesium sulfate and titanium isopropoxide.

[0135] Conversion of the intermediate of formula (XXXI) to the tetrahydrobenzazepine of formula (I) may be effected by a one-pot procedure according to the aforementioned teachings of Kato et al , *J. Heterocyclic Chemistry*, 32:637-642 (1995). Finally, the target compounds of formula (I; R^4=aryl, heteroaryl or heterocyclic) of the present invention may be prepared from intermediates of formula I (R^4 = Cl, Br, I, OCH_3) as described above for Scheme 1.

[0136] Compounds of formula (XXXII; R^8 = H) may be conveniently converted into compounds of formula (XXXIII, R^8 = CH_3, F or OH) as shown in Scheme 7 on treatment with a base such as, but not limited to, lithium diisopropylamide, lithium hexamethyldisilazide, and potassium hexamethyldisilazide, followed by trapping with an electrophile such as, but not limited to, iodomethane, oxidodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide) and *N*-fluorobenzenesulfonimide. Finally, the target compounds of formula (I; R^4 = aryl, heteroaryl or heterocyclic) of the present invention may be prepared from intermediates of formula (I; R^4 = Cl, Br, I, OCH_3) as described above for Scheme 1.

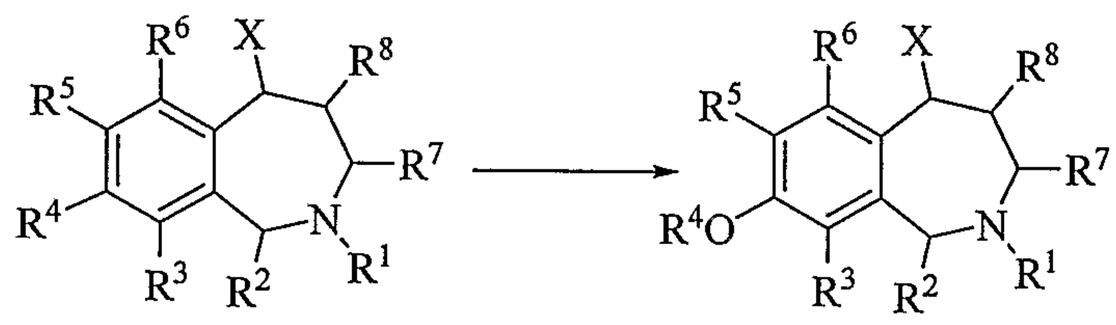
Scheme 7



[0137] Target compounds (I; R^4 = aryl or heteroaryl) of the present invention may be obtained from intermediates of formula (XXXIV; R^4 = OH) on treatment with a base such as, but not limited to, cesium carbonate, sodium hydride, potassium carbonate, and sodium *tert*-butoxide, followed by reaction with an aryl or heteroaryl halide, where X is the aryl or heteroaryl group (Scheme 8). The reactions are run in solvents such as, but not limited to, DMF, 1,4-dioxane and acetonitrile, at temperatures ranging from room temperature up to the reflux point of the solvent employed. Alternatively, the target compounds of formula (I) of the present invention

may be prepared from compounds of formula (XXXIV, R^4 = Br, I, OSO_2CF_3) by coupling with phenols or heteroaryl alcohols in the presence of a metal catalyst, with or without a base in an inert solvent, using literature methods familiar to one skilled in the art of organic synthesis.

Scheme 8

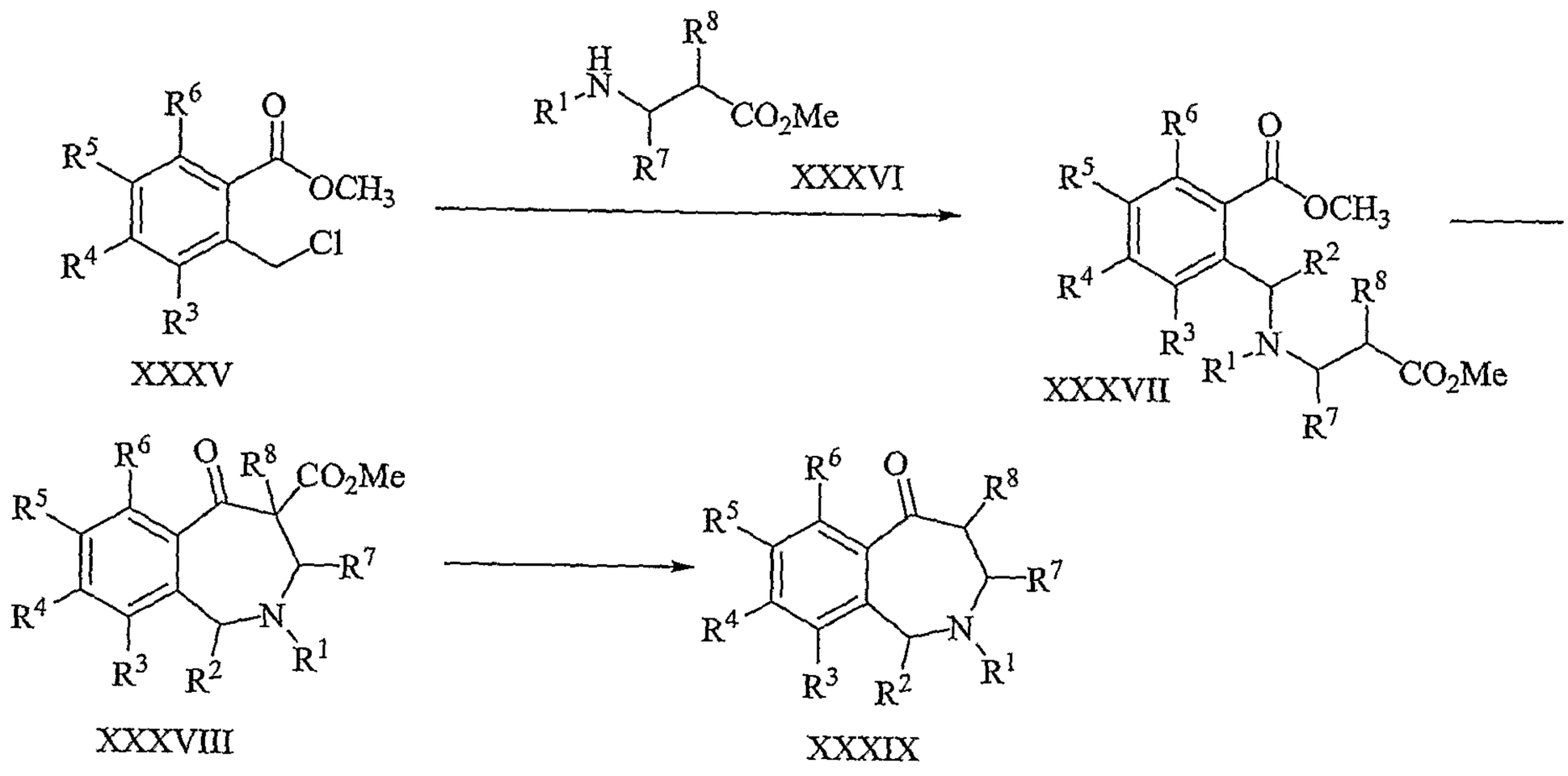


R^4 = OH, OTf, Br, I — XXXIV

R^4 = aryl or heteroaryl — I

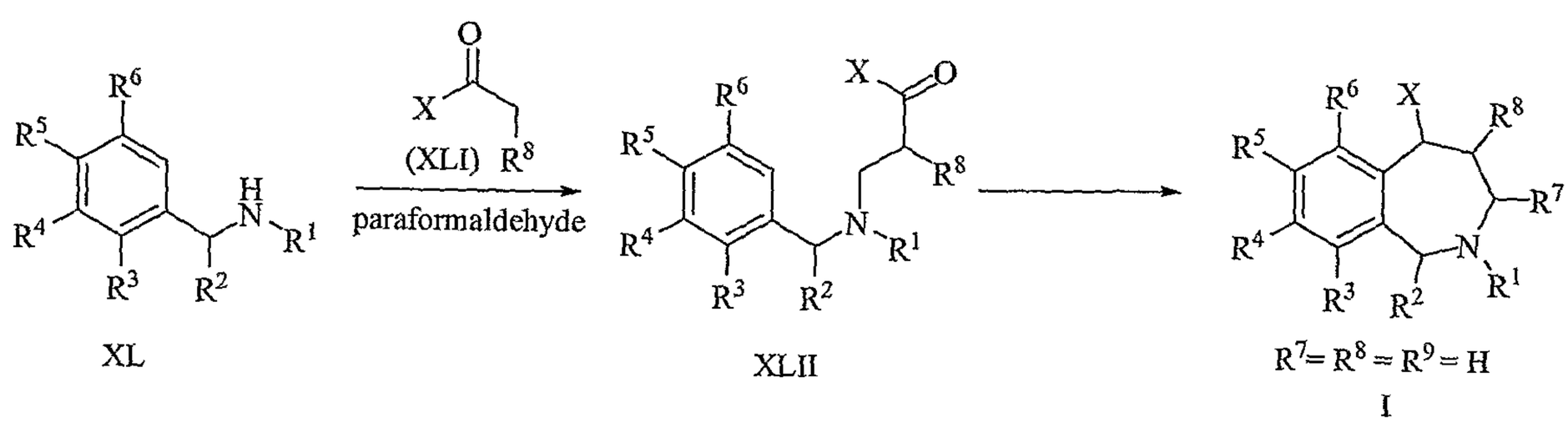
[0138] Compounds of formula (I) where R^4 is aryl, heteroaryl, or heterocyclic, R^7 = H, R^8 = H, and R^9 = H may be obtained by using the route outlined in Scheme 9. As shown in Scheme 9, appropriately functionalized benzyl chlorides of formula (XXXV) may be reacted with amines of the formula (XXXVI) to give tertiary amines of the formula (XXXVII). The aforementioned benzyl chlorides of formula (XXXV) may be obtained from the corresponding lactones via methods familiar to one skilled in the art of organic synthesis. Cyclization of intermediates of formula (XXXVII) to give compounds of formula (XXVIII) may be carried out using a variety of bases, such as, but not limited to, potassium *tert*-butoxide. Hydrolysis and decarboxylation of compounds of the formula (XXXVIII) may be carried out using acids such as, but not limited to, hydrochloric acid and hydrobromic acid, to give the benzazepinones of formula (XXXIX). Finally, the target compounds of formula (I; R^4 = aryl, heteroaryl, or heterocyclic) of the present invention may be prepared from intermediates of formula (I; R^4 = Cl, Br, I, OCH_3) as described above for Scheme 4.

Scheme 9



[0139] Compounds of formula (I) where R^4 is aryl, heteroaryl, or heterocyclic and $R^7 = R^8 = R^9 = H$ may be obtained by using the route outlined in Scheme 10. Appropriately functionalized benzyl amines of the formula (XL) may be reacted with ketones of the formula (XLI) and paraformaldehyde in the presence of an acid such as, but not limited to hydrochloric acid, to give ketones of the formula (XLII). Reduction of the ketone of formula (XLII), followed by cyclization of the resulting alcohol in the presence of acids such as, but not limited to aluminum trichloride results in the formation of benzazepines of fomula (I). Finally, the target compounds of formula (I; R^4 = aryl, heteroaryl, or heterocyclic) of the present invention may be prepared from intermediates of formula (I; R^4 = Cl, Br, I, OCH_3) as described above for Scheme 1.

Scheme 10



[0140] Compounds of formulae I(A-E) may be obtained in enantiomerically pure (R) and (S) form by crystallization with chiral salts as well known to one skilled in the art, or alternatively, may be isolated through chiral HPLC employing commercially available chiral columns.

[0141] It will be appreciated that compounds according to the present invention may contain asymmetric centers. These asymmetric centers may independently be in either the R or S configuration and such compounds are able to rotate a plane of polarized light in a polarimeter. If said plane of polarized light is caused by the compound to rotate in a counterclockwise direction, the compound is said to be the (-) stereoisomer of the compound. If said plane of polarized light is caused by the compound to rotate in a clockwise direction, the compound is said to be the (+) stereoisomer of the compound. It will be apparent to those skilled in the art that certain compounds useful according to the invention may also exhibit geometrical isomerism. It is to be understood that the present invention includes individual geometrical isomers and stereoisomers and mixtures thereof, including racemic mixtures, of compounds of formulae I(A-E), or formula (II), hereinabove. Such isomers can be separated from their mixtures, by the application or adaptation of known methods, for example chromatographic techniques and recrystallization techniques, or they are separately prepared from the appropriate isomers of their intermediates.

[0142] Radiolabelled compounds of the invention are synthesized by a number of means well known to those of ordinary skill in the art, e.g., by using starting materials incorporating therein one or more radioisotopes. Compounds of the present invention where a stable radioisotope, such as carbon-14, tritium, iodine-121, or another radioisotope, has been introduced synthetically are useful diagnostic agents for identifying areas of the brain or central nervous system that may be affected by disorders where norepinephrine, dopamine, or serotonin transporters and their uptake mechanism are implicated.

[0143] The present invention provides compositions containing the compounds described herein, including, in particular, pharmaceutical compositions comprising therapeutically effective amounts of the compounds and pharmaceutically acceptable carriers.

[0144] It is a further object of the present invention to provide kits having a plurality of active ingredients (with or without carrier) which, together, may be effectively utilized for carrying out the novel combination therapies of the invention.

[0145] It is another object of the invention to provide a novel pharmaceutical composition which is effective, in and of itself, for utilization in a beneficial combination therapy because it includes a plurality of active ingredients which may be utilized in accordance with the invention.

[0146] The present invention also provides kits or single packages combining two or more active ingredients useful in treating the disease. A kit may provide (alone or in combination with a pharmaceutically acceptable diluent or carrier) the compounds of formulae I(A-E), or formula (II), and the additional active ingredient (alone or in combination with diluent or carrier) selected from a serotonin 1A receptor antagonist, a selective neurokinin-1 receptor antagonist, and a norepinephrine precursor.

[0147] In practice, the compounds of the present invention may generally be administered parenterally, intravenously, subcutaneously, intramuscularly, colonically, nasally, intraperitoneally, rectally, or orally.

[0148] The products according to the invention may be presented in forms permitting administration by the most suitable route and the invention also relates to pharmaceutical compositions containing at least one product according to the invention which are suitable for use in human or veterinary medicine. These compositions may be prepared according to the customary methods, using one or more pharmaceutically acceptable adjuvants or excipients. The adjuvants comprise, *inter alia*, diluents, sterile aqueous media, and the various non-toxic organic solvents. The compositions may be presented in the form of tablets, pills, granules, powders, aqueous solutions or suspensions, injectable solutions, elixirs or syrups, and can contain one or more agents chosen from the group comprising sweeteners, flavorings, colorings, or stabilizers in order to obtain pharmaceutically acceptable preparations.

[0149] The choice of vehicle and the content of active substance in the vehicle are generally determined in accordance with the solubility and chemical properties of the product, the particular mode of administration and the provisions to be observed in pharmaceutical practice. For example, excipients such as lactose, sodium citrate, calcium carbonate, dicalcium phosphate and disintegrating agents such as starch,

alginic acids and certain complex silicates combined with lubricants such as magnesium stearate, sodium lauryl sulfate and talc may be used for preparing tablets. To prepare a capsule, it is advantageous to use lactose and high molecular weight polyethylene glycols. When aqueous suspensions are used they can contain emulsifying agents or agents which facilitate suspension. Diluents such as sucrose, ethanol, polyethylene glycol, propylene glycol, glycerol, and chloroform or mixtures thereof may also be used.

[0150] For parenteral administration, emulsions, suspensions or solutions of the products according to the invention in vegetable oil, for example sesame oil, groundnut oil, or olive oil, or aqueous-organic solutions such as water and propylene glycol, injectable organic esters such as ethyl oleate, as well as sterile aqueous solutions of the pharmaceutically acceptable salts, are used. The solutions of the salts of the products according to the invention are especially useful for administration by intramuscular or subcutaneous injection. The aqueous solutions, also comprising solutions of the salts in pure distilled water, may be used for intravenous administration with the proviso that their pH is suitably adjusted, that they are judiciously buffered and rendered isotonic with a sufficient quantity of glucose or sodium chloride and that they are sterilized by heating, irradiation or microfiltration.

[0151] Suitable compositions containing the compounds of the present invention may be prepared by conventional means. For example, compounds of the present invention may be dissolved or suspended in a suitable carrier for use in a nebulizer or a suspension or solution aerosol, or may be absorbed or adsorbed onto a suitable solid carrier for use in a dry powder inhaler.

[0152] Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing at least one compound of formulae I(A-E), or formula II.

[0153] The percentage of active ingredient in the compositions of the present invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously, several unit dosage forms may be administered at about the same time. The dose employed will be determined by the physician, and depends upon the desired therapeutic effect, the route of administration and the duration of the treatment, and the condition of the patient. In the adult, the doses are generally from about 0.01 to about 100 mg/kg body weight, preferably

about 0.01 to about 10 mg/kg body weight per day by inhalation, from about 0.01 to about 100 mg/kg body weight, preferably 0.1 to 70 mg/kg body weight, more especially 0.5 to 10 mg/kg body weight per day by oral administration, and from about 0.01 to about 50 mg/kg body weight, preferably 0.01 to 10 mg/kg body weight per day by intravenous administration. In each particular case, the doses will be determined in accordance with the factors distinctive to the subject to be treated, such as age, weight, general state of health and other characteristics which can influence the efficacy of the medicinal product.

[0154] The products according to the present invention may be administered as frequently as necessary in order to obtain the desired therapeutic effect. Some patients may respond rapidly to a higher or lower dose and may find much weaker maintenance doses adequate. For other patients, it may be necessary to have long-term treatments at the rate of 1 to 4 doses per day, in accordance with the physiological requirements of each particular patient. Generally, the active product may be administered orally 1 to 4 times per day. It goes without saying that, for other patients, it will be necessary to prescribe not more than one or two doses per day.

[0155] The present invention provides compounds which inhibit synaptic norepinephrine, dopamine, and serotonin uptake and are, therefore, believed to be useful in treating a disorder which is created by or is dependent upon decreased availability of serotonin, norepinephrine or dopamine. Although the compounds of formulae I(A-E), or formula II, inhibit synaptic norepinephrine, dopamine, and serotonin uptake, in any individual compound, these inhibitory effects may be manifested at the same or vastly different concentrations or doses. As a result, some compounds of formulae I(A-E), or formula II, are useful in treating such a disorder at doses at which synaptic norepinephrine uptake may be substantially inhibited but at which synaptic serotonin uptake or dopamine uptake is not substantially inhibited, or vice versa. Also, some compounds of formulae I(A-E), or formula II, are useful in treating such a disorder at doses at which synaptic dopamine uptake may be substantially inhibited but at which synaptic norepinephrine or serotonin uptake is not substantially inhibited, or vice versa. And, conversely, some compounds of formulae I(A-E), or formula II, are useful in treating such a disorder at doses at which synaptic serotonin uptake may be substantially inhibited but at which synaptic norepinephrine or dopamine uptake is not substantially inhibited, or vice versa. Other

compounds of formulae I(A-E), or formula II, are useful in treating such a disorder at doses at which synaptic norepinephrine, dopamine, and serotonin uptake are substantially inhibited.

[0156] The present invention provides compounds where the inhibitory effects on serotonin and norepinephrine uptake occurs at similar or even the same concentrations of these compounds, while the effects on inhibition of dopamine uptake occurs at vastly different concentrations or doses. As a result, some compounds of formulae I(A-E), or formula II, are useful in treating such a disorder at doses at which synaptic serotonin and norepinephrine uptake may be substantially inhibited but at which synaptic dopamine uptake is not substantially inhibited, or vice versa.

[0157] The present invention provides compounds where the inhibitory effects on serotonin and dopamine uptake occurs at similar or even the same concentrations of these compounds while the effects on inhibition of norepinephrine uptake occurs at vastly different concentrations or doses. As a result, some compounds of formulae I(A-E), or formula II, are useful in treating such a disorder at doses at which synaptic serotonin and dopamine uptake may be substantially inhibited but at which synaptic norepinephrine uptake is not substantially inhibited, or vice versa.

[0158] The present invention provides compounds where the inhibitory effects on norepinephrine and dopamine uptake occurs at similar or even the same concentrations of these compounds while the effects on inhibition of dopamine uptake occurs at vastly different concentrations or doses. As a result, some compounds of formulae I(A-E), or formula II, are useful in treating such a disorder at doses at which synaptic norepinephrine and dopamine uptake may be substantially inhibited but at which synaptic serotonin uptake is not substantially inhibited, or vice versa.

[0159] The present invention provides compounds where the inhibitory effects on norepinephrine, dopamine and serotonin uptake occur at similar or even the same concentration. As a result, some compounds of formulae I(A-E), or formula II, are useful in treating such a disorder at doses at which synaptic norepinephrine, dopamine, and serotonin uptake may all be substantially inhibited.

[0160] The concentrations or doses at which a test compound inhibits synaptic norepinephrine, dopamine, and serotonin uptake is readily determined by the use of standard assay and techniques well known and appreciated by one of ordinary skill in

the art. For example, the degree of inhibition at a particular dose in rats can be determined by the method of Dudley, *J Pharmacol Exp Ther* 217:834-840 (1981).

[0161] The therapeutically effective inhibitory dose is one that is effective in substantially inhibiting synaptic norepinephrine uptake, synaptic dopamine uptake, or synaptic serotonin uptake or inhibiting the synaptic uptake of two or more of norepinephrine, dopamine and serotonin uptake. The therapeutically effective inhibitory dose can be readily determined by those skilled in the art by using conventional range finding techniques and analogous results obtained in the test systems described above.

[0162] Compounds of this invention provide a particularly beneficial therapeutic index relative to other compounds available for the treatment of similar disorders. Without intending to be limited by theory, it is believed that this is due, at least in part, to some of the compounds having higher binding affinities for one or two of the neurotransmitter transporters, e.g., selectivity towards the norepinephrine transporter protein ("NET") over the transporters for other neurochemicals, e.g., the dopamine transporter protein ("DAT") and the serotonin transporter protein ("SERT").

[0163] Other compounds of the present invention may demonstrate selectivity towards the SERT over the transporters for other neurochemicals, e.g., the DAT and the NET.

[0164] Still other compounds of the present invention may demonstrate selectivity towards the DAT over the transporters for other neurochemicals, e.g., the SERT and the NET.

[0165] Other compounds of the present invention may demonstrate selectivity towards the SERT and the NET over the transporter for other neurochemical, e.g., the DAT.

[0166] Still other compounds of the present invention may demonstrate selectivity towards the SERT and the DAT over the transporter for other neurochemical, e.g., the NET.

[0167] Still other compounds of the present invention may demonstrate selectivity towards the NET and the DAT over the transporter for other neurochemical, e.g., the SERT.

[0168] Finally other compounds possess nearly identical affinity towards the NET, the DAT, and the SERT.

[0169] Binding affinities are demonstrated by a number of means well known to ordinarily skilled artisans, including, without limitation, those described in the Examples section hereinbelow. Briefly, for example, protein-containing extracts from cells, e.g., HEK293E cells, expressing the transporter proteins are incubated with radiolabelled ligands for the proteins. The binding of the radioligands to the proteins is reversible in the presence of other protein ligands, e.g., the compounds of the present invention; said reversibility, as described below, provides a means of measuring the compounds' binding affinities for the proteins (Ki). A higher Ki value for a compound is indicative that the compound has less binding affinity for a protein than is so for a compound with a lower Ki; conversely, lower Ki values are indicative of greater binding affinities.

[0170] Accordingly, the difference in compound selectivity for proteins is indicated by a lower Ki for the protein for which the compound is more selective, and a higher Ki for the protein for which the compound is less selective. Thus, the higher the ratio in Ki values of a compound for protein A over protein B, the greater is the compounds' selectivity for the latter over the former (the former having a higher Ki and the latter a lower Ki for that compound). Compounds provided herein possess a wide range of selectivity profiles for the norepinephrine, dopamine, and serotonin transporters as reflected by the ratios of the experimentally determined Ki values.

[0171] Selected compounds ("mono action transporter reuptake inhibitors") of the present invention have potent binding affinity for each of the biogenic amine transporters NET, DAT or SERT. For example, selected compounds of the present invention possess potent (NET Ki < 100 nM) and selective binding affinity for NET, where the Ki ratio of DAT/NET and SERT/NET is greater than 10:1. Other selected compounds of the present invention possess potent (SERT Ki < 100 nM) and selective binding affinity for SERT, where the Ki ratio of NET/SERT and DAT/SERT is greater than 10:1. Other selected compounds of the present invention possess potent (DAT Ki < 100 nM) and selective binding affinity for DAT, where the Ki ratio of NET/DAT and SERT/DAT is greater than 10:1.

[0172] Selected compounds ("dual action transporter reuptake inhibitors") of the present invention have potent binding affinity for two of the biogenic amine

transporters, NET, DAT or SERT. For example, selected compounds of the present invention possess potent (NET & SERT Ki values < 100 nM) and selective binding affinity for NET and SERT, where the Ki ratio of DAT/NET and DAT/SERT is greater than 10:1 while the Ki ratio of SERT/NET or NET/SERT is less than 10:1. Other selected compounds of the present invention possess potent (NET & DAT Ki values < 100 nM) and selective binding affinity for NET and DAT, where the Ki ratio of SERT/NET and SERT/DAT is greater than 10:1 while the Ki ratio of DAT/NET or NET/DAT is less than 10:1. Other selected compounds of this invention possess potent (DAT & SERT Ki values < 100 nM) and selective binding affinity for DAT and SERT, where the Ki ratio of NET/DAT and SERT/DAT is greater than 10:1 while the Ki ratio of SERT/NET or NET/SERT is less than 10:1.

[0173] Selected compounds ("triple action transporter reuptake inhibitors") of the present invention have potent binding affinity simultaneously for all three of the biogenic amine transporters, NET, DAT or SERT. For example, selected compounds of this invention possess potent (NET, DAT & SERT Ki values < 100 nM) where the Ki ratios of NET/DAT, NET/SERT, DAT/NET, DAT/SERT, SERT/NET and SERT/DAT are all less than 10:1.

[0174] Selected compounds of the present invention have potent binding affinity (Ki values < 100 nM) for one, two, or three of the biogenic amine transporters, NET, DAT and SERT where the Ki ratios for any of NET/SERT, NET/DAT, DAT/NET, DAT/SERT, SERT/NET, and SERT/DAT fall outside of the bounds defined for the "Mono-, Dual or Triple action transporter reuptake inhibitors" defined above.

[0175] Selected compounds of the present invention have less potent binding affinity (Ki values between 100 nM and 1000 nM) for one, two, or three of the biogenic amine transporters, NET, DAT and SERT, where the Ki ratios for any of NET/SERT, NET/DAT, DAT/NET, DAT/SERT, SERT/NET, and SERT/DAT fall within the bounds defined for the "Mono-, Dual or Triple action transporter reuptake inhibitors" defined above.

[0176] Finally, selected compounds of the present invention have less potent binding affinity (Ki values between 100 nM and 1000 nM) for one, two, or three of the biogenic amine transporters, NET, DAT, and SERT, where the Ki ratios for any of NET/SERT, NET/DAT, DAT/NET, DAT/SERT, SERT/NET, and SERT/DAT fall

outside of the bounds defined for the "mono-, dual or triple action transporter reuptake inhibitors" defined above.

EXAMPLES

[0177] The following examples are provided to illustrate embodiments of the present invention but are by no means intended to limit its scope.

Example 1 – Preparation of (+/-)-8-methoxy-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, fumarate salt

[0178] Step A: To a mixture of (3-methoxybenzyl) methylamine (3.02 g, 20 mmol) and cesium carbonate (7.82 g, 24 mmol) in DMF (50 mL) was added cinnamyl bromide (4.47 g, 22 mmol). The reaction mixture was stirred at room temperature for 15 hours. The reaction mixture was diluted with water and extracted with 1:1 hexanes/ethyl acetate (3×). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated to provide the desired product (3.1 g, 58%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 – 7.37 (m, 2H), 7.32 – 7.29 (m, 2H), 7.23 – 7.20 (m, 2H), 6.93 – 6.91 (m, 2H), 6.81 – 6.78 (m, 1H), 6.54 (d, J = 15.9 Hz, 1H), 6.31 (dt, J = 15.9, 6.6 Hz, 1H), 3.81 (s, 3H), 3.52 (s, 2H), 3.19 (dd, J = 6.6, 1.2 Hz, 2H), 2.25 (s, 3H); ESI MS m/z = 268 $[M + H]^+$. This crude product was used in the next step without further purification.

[0179] Step B: A mixture of the product from step A (1.0 g, 3.74 mmol) and pyrophosphoric acid (25 g) in 1,2-dichloroethane (5 mL) was heated at 100°C for 1 hour. The reaction mixture was cooled, mixed with ice and adjusted to pH 9 with ammonium hydroxide. The reaction mixture was extracted with ethyl acetate (3×). The combined extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated. Purification via MPLC (30% to 50% ethyl acetate/hexanes) provided 6-methoxy-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine (350 mg, 35%) and 8-methoxy-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine (280 mg, 28%); 6-methoxy-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 – 7.21 (m, 2H), 7.19 – 7.13 (m, 2H), 7.06 (d, J = 8.0 Hz, 2H), 6.85 (d, J = 8.1 Hz, 1H), 6.80 (d, J = 7.5 Hz, 1H), 5.12 (t, J = 4.9 Hz, 1H), 3.82 (d, J = 14.3 Hz, 1H), 3.72 (s, 3H), 3.45 (d, J = 13.6 Hz,

1H), 2.92 – 2.85 (m, 1H), 2.75 – 2.70 (m, 1H), 2.34 – 2.29 (m, 2H), 2.27 (s, 3H); ESI MS m/z = 268 $[M + H]^+$; 8-methoxy-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (t, *J* = 7.5 Hz, 2H), 7.26 – 7.23 (m, 1H), 7.17 (d, *J* = 7.5 Hz, 2H), 6.74 (d, *J* = 2.7 Hz, 1H), 6.61 – 6.59 (m, 2H), 4.26 (d, *J* = 8.6 Hz, 1H), 3.91 – 3.90 (m, 1H), 3.76 (s, 3H), 3.70 (d, *J* = 14.1 Hz, 1H), 3.12 – 3.09 (m, 1H), 2.98 – 2.93 (m, 1H), 2.35 (s, 3H), 2.32 – 2.27 (m, 1H), 2.11 – 2.10 (m, 1H). ESI MS m/z = 268 $[M + H]^+$.

[0180] Step C: To a solution of 8-methoxy-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine from step B (260 mg, 0.97 mmol) in ethanol (4 mL) was added fumaric acid (123 mg, 0.97 mmol) in methanol (2 mL). The solvent was removed under reduced pressure. The residue was triturated with ethyl acetate and diethyl ether. The resulting precipitate was collected by filtration, washed with diethyl ether, and dried at 50°C under vacuum to provide (+/-)-8-methoxy-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, fumarate salt (250 mg, 67%, >99% AUC HPLC) as an off-white solid: mp 171–173°C; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.38 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 2H), 7.02 (d, *J* = 2.7 Hz, 1H), 6.86 – 6.78 (m, 2H), 6.67 (s, 2H), 4.50 (dd, *J* = 8.9, 1.9 Hz, 2H), 4.25 (d, *J* = 13.9 Hz, 1H), 3.80 (s, 3H), 3.52 – 3.51 (m, 2H), 2.85 (s, 3H), 2.57 – 2.56 (m, 1H), 2.40 – 2.36 (m, 1H); ESI MS m/z = 268 $[C_{18}H_{21}NO + H]^+$.

<u>Example 2</u> – Preparation of (+/-)-6-methoxy-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, fumarate salt

[0181] Step A: To a mixture of (3-methoxybenzyl)methylamine (3.02 g, 20 mmol) and cesium carbonate (7.82 g, 24 mmol) in DMF (50 mL) was added cinnamyl bromide (4.47 g, 22 mmol). The reaction mixture was stirred at room temperature for 15 hours. The reaction mixture was diluted with water and extracted with 1:1 hexanes/ethyl acetate (3×). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated to provide the desired product (3.1 g, 58%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 – 7.37 (m, 2H), 7.32 – 7.29 (m, 2H), 7.23 – 7.20 (m, 2H), 6.93 – 6.91 (m, 2H), 6.81 – 6.78 (m, 1H), 6.54 (d, *J* = 15.9 Hz, 1H), 6.31 (dt, *J* = 15.9, 6.6 Hz, 1H), 3.81 (s, 3H), 3.52 (s, 2H),

3.19 (dd, J = 6.6, 1.2 Hz, 2H), 2.25 (s, 3H); ESI MS m/z = 268 $[M + H]^+$. This crude product was used in the next step without further purification.

[0182] Step B: A mixture of the product from step A (1.0 g, 3.74 mmol) and pyrophosphoric acid (25 g) in 1,2-dichloroethane (5 mL) was heated at 100°C for 1 hour. The reaction mixture was cooled, mixed with ice and adjusted to pH 9 with ammonium hydroxide. The reaction mixture was extracted with ethyl acetate (3×). The combined extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated. Purification via MPLC (30% to 50% ethyl acetate/hexanes) provided 6-methoxy-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine (350 mg, 35%) and 8-methoxy-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine (280 mg, 28%): 6-methoxy-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 – 7.21 (m, 2H), 7.19 – 7.13 (m, 2H), 7.06 (d, J = 8.0 Hz, 2H), 6.85 (d, J = 8.1 Hz, 1H), 6.80 (d, J = 7.5 Hz, 1H), 5.12 (t, J = 4.9 Hz, 1H), 3.82 (d, J = 14.3 Hz, 1H), 3.72 (s, 3H), 3.45 (d, J = 13.6 Hz, 1H), 2.92 – 2.85 (m, 1H), 2.75 – 2.70 (m, 1H), 2.34 – 2.29 (m, 2H), 2.27 (s, 3H); ESI MS m/z = 268 $[M + H]^+$; 8-methoxy-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (t, J = 7.5 Hz, 2H), 7.26 – 7.23 (m, 1H), 7.17 (d, J = 7.5 Hz, 2H), 6.74 (d, J = 2.7 Hz, 1H), 6.61 – 6.59 (m, 2H), 4.26 (d, J = 8.6 Hz, 1H), 3.91 – 3.90 (m, 1H), 3.76 (s, 3H), 3.70 (d, J = 14.1 Hz, 1H), 3.12 – 3.09 (m, 1H), 2.98 – 2.93 (m, 1H), 2.35 (s, 3H), 2.32 – 2.27 (m, 1H), 2.11 – 2.10 (m, 1H); ESI MS m/z = 268 $[M + H]^+$.

[0183] Step C: To a solution of 6-methoxy-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine from step B (334 mg, 1.25 mmol) in ethanol (5 mL) was added fumaric acid (145 mg, 1.25 mmol) in methanol (3 mL). The solvent was removed under reduced pressure. The residue was triturated with ethyl acetate and diethyl ether. The resulting precipitate was collected by filtration, washed with diethyl ether, and dried at 50°C under vacuum to provide (+/-)-6-methoxy-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, fumarate salt (250 mg, 67%, 96.6% AUC HPLC) as an off-white solid: mp 154–156°C; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.41 – 7.37 (m, 1H), 7.30 (t, J = 7.6 Hz, 2H), 7.23 – 7.17 (m, 2H), 7.05 – 7.03 (m, 3H), 6.68 (s, 2H), 5.25 – 5.24 (m, 1H), 4.29 – 4.27 (m, 1H), 4.11 (d, J = 13.9 Hz,

1H), 3.79 (s, 3H), 3.44 – 3.39 (m, 1H), 3.33 – 3.32 (m, 1H), 2.81 (s, 3H), 2.68 – 2.67 (m, 1H), 2.46 – 2.41 (m, 1H). ESI MS m/z = 268 $[C_{18}H_{21}NO + H]^+$.

Example 3 – Preparation of (+/-)-5-(4-fluorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt

[0184] Step A: A solution of 4-fluorocinnamic acid (2.0 g, 12.0 mmol) and *N*-methylmorpholine (1.9 mL, 16.9 mmol) in anhydrous methylene chloride (100 mL) was cooled to –20°C. Isobutyl chloroformate (1.7 mL, 12.8 mmol) was added dropwise. After 15 minutes, a solution of (3-methoxybenzyl)methylamine (1.8 g, 12.0 mmol) in anhydrous methylene chloride (20 mL) was added dropwise. The reaction was allowed to warm to room temperature and stir under N_2 for 3 hours. The reaction mixture was then washed with 1 M $NaH_2PO_4 \cdot 2H_2O$ (2×), H_2O (2×), and brine, then dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (1:1 ethyl acetate/hexanes) yielded the desired amide (2.7 g, 79%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 15.3, 4.5 Hz, 1H), 7.56–7.42 (m, 2H), 7.33–7.23 (m, 1H), 7.10–7.00 (m, 2H), 6.88–6.80 (m, 2H), 6.83 (s, 1H), 6.78 (d, *J* = 15.3 Hz, 1H), 4.70-4.66 (m,2H), 3.80 (s, 3H), 3.09-3.07 (m, 3H); ESI MS *m/z* = 300 $[C_{18}H_{18}FNO_2 + H]^+$.

[0185] Step B: An excess of polyphosphoric acid (1.5 g) in 1,2-dichloroethane (10 mL) was heated to 100°C. A solution of the product from Step A (614 mg, 2.1 mmol) in 1,2-dichloroethane (5 mL) was added dropwise. The reaction was then allowed to stir at 100°C overnight under N_2. After cooling to room temperature, the reaction was mixed with ice and the pH adjusted to 10 using 6 N NaOH. The reaction mixture was then extracted with ethyl acetate (3×) and the combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Partial purification via flash column chromatography (30–100% ethyl acetate/hexanes) yielded the desired product (289 mg) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09–6.94 (m, 2H), 7.03–6.93 (m, 2H), 6.85 (d, *J* = 8.4 Hz, 1H) 6.72 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.67 (d, *J* = 2.7 Hz, 1H), 4.92 (d, *J* = 16.2 Hz, 1H), 4.46 (dd, *J* = 10.8, 5.1 Hz, 1H), 4.19 (d, *J* = 16.5 Hz, 1H), 3.79 (s, 3H), 3.17 (dd, *J* = 13.8, 10.8 Hz, 1H), 3.05 (s, 3H), 2.98 (dd, *J* = 13.8, 5.1 Hz, 1H).

[0186] Step C: To a stirred solution of lithium aluminum hydride (1 M solution in THF, 0.61 mL, 0.61 mmol) at 0°C under N_2 was added a solution of the

product of Step B (167 mg, 0.56 mmol) in anhydrous THF (5 mL) dropwise via an addition funnel. The reaction mixture was heated to reflux and allowed to stir for 2 hours. The reaction was then cooled back down to 0°C and quenched slowly with 1 N NaOH (2 mL). After diluting with H_2O, the aqueous phase was extracted with ethyl acetate (3×) and the combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (1:1 ethyl acetate/hexanes) yielded the desired benzazepine (110 mg, 32% two steps) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15–7.11 (m, 2H), 7.06–7.00 (m, 2H), 6.75 (d, J = 2.7 Hz, 1H), 6.61 (dd, J = 8.4, 2.7 Hz, 1H), 6.57–6.50 (m, 1H), 4.24 (d, J = 9.3 Hz, 1H), 3.92–3.82 (m, 1 H), 3.77 (s, 3H), 3.67 (d, J = 14.1 Hz, 1H), 3.14–3.06 (m, 1H), 2.95 (ddd, J = 12.6, 9.6, 2.7 Hz, 1H), 2.35 (s, 3H), 2.29–2.20 (m, 1H), 2.12–2.02 (m, 1H).

[0187] Step D: The product of Step C (110 mg, 0.39 mmol) was converted to its hydrochloride salt by dissolving the oil in a minimum amount of ether, adding one equivalent of HCl (1 M solution in ether), and sonicating the solution for a few minutes until salt precipitation occurred. Filtration yielded (+/-)-5-(4-fluorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt (91 mg, 73%, >99% AUC HPLC) as a white solid: mp 149-150°C 149-150°C; ESI MS m/z = 286 $[C_{18}H_{20}FNO + H]^+$.

<u>Example 4</u> – Preparation of (+)-5-(4-fluorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt, and (-)-5-(4-fluorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt

[0188] Pursuant to the general method described above in Example 3, the following products were prepared: (+)-5-(4-fluorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt: mp 246–248°C; ESI MS m/z = 286 $[C_{18}H_{20}FNO + H]^+$; (-)-5-(4-fluorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt: mp 246–248°C; ESI MS m/z = 286 $[C_{18}H_{20}FNO + H]^+$.

Example 5 – Preparation of (+/-)-5-(4-methoxyphenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt

[0189] Pursuant to the general method described above in Example 3, the following product was prepared: (+/-)-5-(4-methoxyphenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt: mp 165-166°C; ESI MS *m/z* = 298 $[C_{19}H_{23}NO_2 + H]^+$.

Example 6 – Preparation of (+)-5-(4-methoxyphenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt and (-)-5-(4-methoxyphenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt

[0190] Pursuant to the general method described above in Example 3, the following products were prepared: (+)-5-(4-methoxyphenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt: mp 193–194°C; ESI MS *m/z* = 298 $[C_{19}H_{23}NO_2 + H]^+$; (-)-5-(4-methoxyphenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt: mp 193–194°C; ESI MS *m/z* = 298 $[C_{19}H_{23}NO_2 + H]^+$.

Example 7 – Preparation of (+/-)-5-(4-chlorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt

[0191] Pursuant to the general method described above in Example 3, the following product was prepared: (+/-)-5-(4-chlorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt: mp = 152-153°C; ESI MS *m/z* 302 $[C_{18}H_{20}ClNO + H]^+$.

Example 8 – Preparation of (+)-5-(4-chlorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt, and (-)-5-(4-chlorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt

[0192] Pursuant to the general method described above in Example 3, the following products were prepared: (+)-5-(4-chlorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt: mp 210–211°C; ESI MS *m/z* = 302 $[C_{18}H_{20}ClNO + H]^+$; (-)-5-(4-chlorophenyl)-8-methoxy-2-methyl-2,3,4,5-

tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt: mp 210–211°C; ESI MS *m/z* = 302 $[C_{18}H_{20}ClNO + H]^+$.

Example 9 – (+/-)-5-(3,4-difluorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt

[0193] Pursuant to the general method described above in Example 3, the following product was prepared: (+/-)-5-(3,4-difluorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt: mp 139-141°C; ESI MS *m/z* = 304 $[C_{18}H_{19}F_2NO + H]^+$.

Example 10 – Preparation of (+/-)-5-(2-chlorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt

[0194] Pursuant to the general method described above in Example 3, the following product was prepared: (+/-)-5-(2-chlorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt: mp 129-132°C; ESI MS *m/z* = 302 $[C_{18}H_{20}ClNO + H]^+$.

Example 11 – Preparation of (+/-)-5-(3-chloro-4-fluorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1H-benzo[c]azepine, hydrochloride salt

[0195] Pursuant to the general method described above in Example 3, the following product was prepared: (+/-)-5-(3-chloro-4-fluorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1H-benzo[c]azepine, hydrochloride salt: mp 167-169°C; ESI MS *m/z* = 320 $[C_{18}H_{19}ClFNO + H]^+$.

Example 12 – Preparation of (+)-8-methoxy-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt, and (-)-8-methoxy-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt

[0196] Pursuant to the general method described above in Example 3, the following products were prepared: (+)-8-methoxy-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt: ESI MS *m/z* 268 $[M+H]^+$; (-)-8-methoxy-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt: ESI MS *m/z* 268 $[M+H]^+$.

Example 13 – Preparation of (+)-5-(4-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-ol, hydrochloride salt

[0197] Step A: A mixture of (+)-5-(4-fluorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine (367 mg, 1.3 mmol) and HBr (48% solution in H_2O, 10 mL) was heated to reflux and allowed to stir for two hours. The solvent and excess HBr were removed under reduced pressure and the resulting solid was partitioned between ethyl acetate and saturated $NaHCO_3$ (aq). After separating the two layers, the aqueous phase was extracted with ethyl acetate (3×). The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide the desired phenol (347 mg, 99%) as a tan solid: $[\alpha]^{25}_D$ -9.1° (*c* 0.3, methanol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13–7.10 (m, 2H), 7.04-7.01 (m, 2H), 6.60 (d, J = 2.5 Hz, 1H), 6.50–6.49 (m, 1H), 6.43 (br s, 1 H), 4.21 (d, J = 9.5 Hz, 1H), 3.86–3.78 (m, 1H), 3.63 (d, J = 14.0 Hz, 1H), 3.13–3.06 (m, 1H), 2.91 (ddd, J = 12.8, 10.0, 2.5 Hz, 1H), 2.40 (s, 3H), 2.32–2.25 (m, 1H), 2.13–2.06 (m, 1H); ESI MS m/z = 272 $[C_{17}H_{18}FNO + H]^+$.

[0198] Step B: The product of Step A (25 mg, 0.09 mmol) was converted to its hydrochloride salt by dissolving the oil in a minimum amount of ether, adding one equivalent of HCl (1 M solution in ether), and sonicating the solution for a few minutes until salt precipitation occurred. Filtration yielded (+)-5-(4-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-ol, hydrochloride salt (21 mg, 74%, 96.6% AUC HPLC) as an off-white solid: mp 159–161°C; ESI MS m/z = 272 $[C_{17}H_{18}FNO + H]^+$.

Example 14 – Preparation of (-)-5-(4-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-ol, hydrochloride salt

[0199] Pursuant to the general method described above in Example 13, the following product was prepared: (-)-5-(4-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-ol, hydrochloride salt: mp 159–161°C; ESI MS m/z = 272 $[C_{17}H_{18}FNO + H]^+$.

Example 15 – Preparation of (-)-5-(4-fluorophenyl)-2,8-dimethyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt

[0200] Step A: To a stirred mixture of (-)-5-(4-fluorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-ol (252 mg, 0.93 mmol) and pyridine (90 μL, 1.1 mmol) in anhydrous CH_2Cl_2 (9.3 mL) at 0°C under N_2 was added triflic anhydride (0.19 mL, 1.1 mmol). Stirring was continued at 0°C for one hour at which time TLC analysis indicated that the reaction had gone to completion. The mixture was then diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ (aq) and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (1:1 ethyl acetate/hexanes) provided the desired triflate (259 mg, 69%) as a yellow oil: ESI MS *m/z* = 404 $[C_{18}H_{17}F_4NO_3S + H]^+$.

[0201] Step B: To a stirred mixture of the product of Step A (125 mg, 0.31 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (2.5 mg, 0.0031 mmol) in anhydrous dioxane (1.8 mL) was added $Zn(CH_3)_2$ (2 M solution in toluene, 0.3 mL, 0.62 mmol) dropwise under N_2. The reaction was heated to reflux and allowed to stir for two hours. The reaction was then quenched methanol (a few drops), diluted with ethyl acetate, and washed with H_2O and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (1:1 ethyl acetate/hexanes) yielded the desired product (85 mg, quantitative yield) as a yellow solid: $[\alpha]^{25}_D$ -6.1° (*c* 0.3, methanol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (dd, *J* = 8.0, 5.5 Hz, 2H), 7.05-7.01 (m, 2H), 6.99 (d, *J* = 1.5 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.51 (br s, 1H), 4.26 (d, *J* = 9.5 Hz, 1H), 3.91–3.83 (m, 1H), 3.68 (d, *J* = 14.5 Hz, 1H), 3.13–3.06 (m, 1H), 2.93 (ddd, *J* = 12.8, 9.5, 2.5 Hz, 1H), 2.34 (s, 3H), 2.28 (s, 3H), 2.24 (dd, *J* = 9.5, 3.0 Hz, 1H), 2.10–2.06 (m, 1H); ESI MS *m/z* = 270 $[C_{18}H_{20}FN + H]^+$.

[0202] Step C: The product of Step B (85 mg, 0.32 mmol) was converted to its hydrochloride salt by dissolving the oil in a minimum amount of ether, adding one equivalent of HCl (1 M solution in ether), and sonicating the solution for a few minutes until salt precipitation occurred. Filtration yielded (-)-5-(4-fluorophenyl)-2,8-dimethyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt (79 mg, 82%, 95.3% AUC HPLC) as an off-white solid: mp 243–244°C; ESI MS *m/z* = 270 $[C_{18}H_{20}FN + H]^+$.

Example 16 – Preparation of (+)-5-(4-fluorophenyl)-2,8-dimethyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt

[0203] Pursuant to the general method described above in Example 15, the following product was prepared: (+)-5-(4-fluorophenyl)-2,8-dimethyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt: mp 243–244°C; ESI MS *m/z* = 270 $[C_{18}H_{20}FN + H]^+$.

Example 17 - Preparation of (+)-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine-8-carbonitrile, maleate salt

[0204] Step A: To a stirred solution of methylamine (40% in H_2O) (28.2 mL, 327.6 mmol) in methanol (100 mL) at room temperature was added *m*-anisaldehyde (20.6 mL, 163.8 mmol) as a solution in methanol (50 mL) dropwise over 20 minutes. The reaction was stirred at room temperature under N_2 for 15 h, then cooled to 0°C and sodium borohydride (6.19 g, 163.8 mmol) was added in portions. After warming to room temperature, the reaction was stirred for 3 hours. The mixture was then concentrated under reduced pressure, dissolved in water, and extracted with methylene chloride (3×). The combined methylene chloride extracts were extracted with 1N HCl (3×) and the combined HCl extracts adjusted to pH 10 by addition of 6N NaOH. The aqueous mixture was then extracted with methylene chloride (3×). The combined methylene chloride extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the desired amine (25.0 g, quantitative yield) as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.22 (m, 1H), 6.91–6.89 (m, 1H), 6.89 (s, 1 H), 6.82–6.79 (m, 1H), 3.81 (s, 3H), 3.74 (s, 2H), 2.46 (s, 3H).

[0205] Step B: A solution of *trans*-cinnamic acid (5.0 g, 33.8 mmol) and *N*-methylmorpholine (5.2 mL, 47.3 mmol) in anhydrous methylene chloride (120 mL) was cooled to –20°C, and then isobutyl chloroformate (4.8 mL, 35.8 mmol) was added dropwise. After 15 minutes, a solution of the amine from Step A above (5.1 g, 33.8 mmol) in anhydrous methylene chloride (30 mL) was added dropwise, then the reaction was allowed to warm to room temperature and stir under N_2 for 3 h. The mixture was washed with 1M sodium dihydrogen phosphate dihydrate (2×), H_2O (2×), and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1:1 ethyl acetate/hexanes) yielded the desired amide (8.3 g, 87%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd,

J = 15.5, 7.5 Hz, 1H), 7.56–7.54 (m, 1H), 7.47–7.46 (m, 1H), 7.36 (dd, J = 14.5, 7.5 Hz, 2H), 7.39–7.33 (m, 1H), 7.31–7.24 (m, 1H), 6.95–6.76 (m, 4H), 4.70–4.66 (m, 2H), 3.80 (s, 3H), 3.09–3.07 (m, 3H); ESI MS *m/z* 282 $[M+H]^+$.

[0206] Step C: An excess of polyphosphoric acid (11 g) in 1,2-dichloroethane (10 mL) was heated to 100°C. A solution of the amide from Step B above (3.8 g, 13.5 mmol) in 1,2-dichloroethane (15 mL) was added dropwise and the reaction was stirred at 100°C for 15 hours under N_2. After cooling to room temperature, the reaction was mixed with ice and the pH adjusted to 9 using concentrated ammonium hydroxide. The reaction mixture was then extracted with ethyl acetate (3×) and the combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Partial purification by flash column chromatography (30–100% ethyl acetate/hexanes) yielded the desired product (1.77 g) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.49 (m, 1H), 7.37–7.35 (m, 1H), 7.29–7.28 (m, 1H), 7.09–7.06 (m, 2H), 6.87 (d, J = 9.0 Hz, 1H) 6.71 (dd, J = 8.5, 2.5 Hz, 1H), 6.66 (d, J = 3.0 Hz, 1H), 5.03 (d, J = 16.5 Hz, 1H), 4.48–4.44 (m, 1H), 4.09 (d, J = 16.5 Hz, 1H), 3.79 (s, 3H), 3.28–3.22 (m, 1H), 3.05 (s, 3H), 2.97–2.93 (m, 1H).

[0207] Step D: To a stirred solution of lithium aluminum hydride (1M solution in THF, 14.7 mL, 14.7 mmol) at 0°C under N_2 was added a solution of the product of Step C above (3.8 g, 13.4 mmol) in anhydrous THF (100 mL) dropwise. The reaction mixture was heated to reflux and stirred for 2 hours. The reaction was then cooled back down to 0°C and quenched slowly with 1N NaOH (30 mL). After diluting with water, the aqueous phase was extracted with ethyl acetate (3×) and the combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1:1 ethyl acetate/hexanes) yielded the desired benzazepine (2.93 g, 38% two steps) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (t, J = 7.5 Hz, 2H), 7.27–7.24 (m, 1H), 7.17 (d, J = 7.5 Hz, 2H), 6.75–6.74 (m, 1H), 6.61–6.60 (m, 1H), 6.61–6.53 (br, 1H), 4.27–4.26 (m, 1H), 3.91–3.86 (m, 1H), 3.77 (s, 3H), 3.73–3.70 (m, 1H), 3.16–3.09 (m, 1H), 2.99–2.94 (m, 1H), 2.35 (s, 3H), 2.33–2.28 (m, 1H), 2.13–2.07 (m, 1H); ESI MS *m/z* 268 $[M+H]^+$. This compound was resolved by preparative chiral HPLC (CHIRALCEL OJ column, using 9:1:0.01 heptane/ethanol/diethylamine as the eluent)

to give the (+)-enantiomer [$[\alpha]^{25}_D$ +3.66° (*c* 0.41, methanol)] and the (–)-enantiomer [$[\alpha]^{25}_D$ –1.16° (*c* 0.43, methanol)].

[0208] Step E: A mixture of the (+)-enantiomer from Step D above (1.19 g, 4.5 mmol) and hydrobromic acid (48% solution in water, 34 mL) was heated to reflux and stirred for 2 hours. The solvent and excess hydrobromic acid were removed under reduced pressure and the resulting solid was partitioned between ethyl acetate and saturated sodium bicarbonate (aq). After separating the two layers, the aqueous phase was extracted with ethyl acetate (3×). The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide the desired phenol (1.10 g, 86%) as a tan solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.5 Hz, 2H), 7.28–7.23 (m, 1H), 7.16 (d, *J* = 7.5 Hz, 2H), 6.54 (s, 1H), 6.48–6.35 (m, 2H), 4.24–4.22 (m, 1H), 3.87–3.77 (m, 1H), 3.66–3.63 (m, 1H), 3.17–3.08 (m, 1H), 2.94–2.89 (m, 1H), 2.42 (s, 3H), 2.35–2.31 (m, 1H), 2.18–2.09 (m, 1H); ESI MS *m/z* 254 $[M+H]^+$.

[0209] Step F: To a stirred mixture of the phenol from Step E above (581 mg, 2.3 mmol) and pyridine (0.22 mL, 2.8 mmol) in anhydrous methylene chloride (23 mL) at 0°C under N_2 was added triflic anhydride (0.46 mL, 2.8 mmol). The reaction was stirred at 0°C for 1 h, at which time TLC analysis indicated the reaction went to completion. The mixture was then diluted with methylene chloride, washed with saturated sodium bicarbonate (aq) and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1:1 ethyl acetate/hexanes) provided the desired triflate (650 mg, 74%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, *J* = 7.5 Hz, 2H), 7.31–7.28 (m, 1H), 7.17 (d, *J* = 7.0 Hz, 2H), 7.09–7.08 (m, 1H), 6.97–6.93 (m, 1H), 6.70–6.64 (br, 1H), 4.33–4.31 (m, 1H), 4.03–3.94 (m, 1H), 3.75–3.72 (m, 1H), 3.18–3.13 (m, 1H), 3.03–2.98 (m, 1H), 2.36 (s, 3H), 2.34–2.29 (m, 1H), 2.12–2.06 (m, 1H); ESI MS *m/z* 386 $[M+H]^+$.

[0210] Step G: To a stirred solution of the triflate from Step F above (249 mg, 0.65 mmol) in DMF (3 mL) at room temperature was added zinc cyanide (152 mg, 1.3 mmol). The reaction mixture was degassed with argon for 2 minutes, then tris(dibenzylideneacetone)-dipalladium(0) (24 mg, 0.026 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (57 mg, 0.10 mmol) were added under argon. The reaction was heated to 130°C and stirred for 4 hours. After cooling to room

temperature, the mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate. The aqueous phase was extracted with additional ethyl acetate (2×), then the combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (2%-10% methanol/methylene chloride) followed by charcoal treatment yielded the desired nitrile (75 mg, 44%) as a light yellow oil: $[\alpha]^{23}_{D}$ -4.00° (*c* 0.08, methanol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.46 (m, 1H), 7.40–7.34 (m, 1H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.32–7.29 (m, 1H), 7.15 (d, *J* = 7.5 Hz, 2H), 6.77–6.67 (br, 1H), 4.37–4.35 (m, 1H), 3.99–3.97 (m, 1H), 3.77–3.74 (m, 1H), 3.19–3.12 (m, 1H), 3.02–2.98 (m, 1H), 2.37 (s, 3H), 2.37–2.29 (m, 1H), 2.16–2.10 (m, 1H); ESI MS *m/z* 263 $[M+H]^+$.

[0211] Step H: To a stirred solution of the nitrile from Step G above (72 mg, 0.27 mmol) in methanol (2.5 mL) at room temperature was added maleic acid (32 mg, 0.27 mmol). The mixture was stirred at room temperature for 1 h and then the solvent was concentrated to approximately 0.5 mL. After diluting with H_2O (2 mL), the mixture was lyophilized for 15 h to provide (+)-2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine-8-carbonitrile, maleate salt (110 mg, 99%, 99.0% AUC HPLC) as an off-white solid: mp 67-69°C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.86 (m, 1H), 7.70–7.69 (m, 1H), 7.45–7.42 (m, 2H), 7.36–7.34 (m, 1H), 7.23–7.21 (m, 2H), 7.06–6.88 (br, 1H), 6.25 (s, 2H), 4.71–4.69 (m, 2H), 4.44–4.42 (m, 1H), 3.66–3.62 (m, 2H), 3.00–2.92 (br, 3H), 2.64–2.53 (br, 1H), 2.46–2.43 (m, 1H); ESI MS *m/z* 263 $[M+H]^+$.

<u>Example 18</u> - Preparation of (+)-2-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)propan-2-ol, L-tartrate salt

[0212] Step A: To a solution of aqueous 2N sodium hydroxide (100 mL) was added methyl 3,3-dimethoxy propionate (25.0 g, 0.17 mol). The reaction solution was stirred at 50°C for 1 hour and then cooled to room temperature. The resultant reaction mixture was acidified with 6N hydrochloric acid to pH 1 and extracted with dichloromethane three times. The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to give the desired acid (22.5 g, quantitative) as a clear colorless oil, which was used in the next step without further purification: ^{1}H

NMR ($CDCl_3$, 300 MHz) δ 4.83 (t, J = 5.7 Hz, 1H), 3.39 (s, 6H), 2.71 (d, J = 5.7 Hz, 2H).

[0213] Step B: To a solution of *m*-anisaldehyde (205 g, 1.5 mol) in methanol (800 mL) at room temperature was added a solution of methylamine in water (130 mL, 1.5 mol, 40 wt. % solution). The resultant solution was cooled to 0°C and sodium borohydride (83 g, 2.3 mol) was added to it in portions. The reaction solution was stirred at 0°C for 2 hours and then warmed to room temperature. The resultant reaction mixture was concentrated *in vacuo* and diluted with water. The organic phase was separated, diluted with ethyl acetate, washed with 1:1 water/brine, dried over sodium sulfate and concentrated *in vacuo* to give the desired benzylamine (158.5 g, 70%) as a clear oil. The combined aqueous extracts were extracted with dichloromethane (3×). The combined dichloromethane extracts were washed with 1:1 water/brine, dried over sodium sulfate and concentrated *in vacuo* to give the desired benzylamine (66.7 g, 29%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (t, J = 8.4 Hz, 1H), 6.91–6.78 (m, 3H), 3.81 (s, 3H), 3.73 (s, 2H), 2.46 (s, 3H).

[0214] Step C: To a mixture of benzylamine (26.3 g, 174 mmol) from Step B above, 3,3-dimethoxypropanoic acid (23.4 g, 174 mmol) from Step A above and dichloromethane (182 mL) at 0°C was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (36.8 g, 192 mmol). The mixture was stirred at room temperature overnight, and then washed with water and saturated sodium bicarbonate. The resulting solution was dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the acetal (42 g, 90%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.20 (m, 1H), 6.84–6.70 (m, 3H), 4.93–4.89 (m, 1H), 4.58, 4.53 (s, 2H, rotamers), 3.79 (s, 3H), 3.44, 3.39 (s, 6H, rotamers), 2.94 (s, 3H), 2.73, 2.70 (d, J = 5.5 Hz, 2H, rotamers). The crude product was used without further purification in the next reaction.

[0215] Step D: To the acetal (42.0 g, 157 mmol) from step C above was added pre-cooled concentrated hydrochloric acid (200 mL) at 0°C. The mixture was gradually warmed to 10°C over 2 hours and 30 minutes. The cold reaction mixture was diluted with ice-cold water, and the white precipitate formed was filtered, washed with cold water and dried. The solid obtained was taken up in dichloromethane and washed with saturated sodium bicarbonate. The resultant solution was dried over

magnesium sulfate, filtered and concentrated *in vacuo* to yield the lactam (20.3 g, 63%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 12.1 Hz, 1H), 6.90 (dd, J = 8.4, 2.7 Hz, 1H), 6.82 (d, J = 2.6 Hz, 1H), 6.29 (d, J = 12.1 Hz, 1H), 4.19 (s, 2H), 3.86 (s, 3H), 3.09 (s, 3H).

[0216] Step E: To an ice-cold mixture of the lactam (20.3 g, 100 mmol) from step D above and benzene (80 mL) was added trifluoromethanesulfonic acid (100 mL). The reaction mixture was warmed to room temperature and stirred for 3 hours. The reddish-brown mixture was then poured into ice-water mixture, and stirred until the ice melted. The product was extracted into dichloromethane (4×), and the combined organic extracts were washed with saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was dissolved in ethyl acetate and filtered through a plug of silica gel. The silica gel was washed with ethyl acetate to give the aryl lactam (26.8 g, 95%) as a white foam: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28–7.25 (m, 2H), 7.22–7.18 (m, 1H), 7.08–7.06 (m, 2H), 6.86 (d, J = 8.6 Hz, 1H), 6.71 (dd, J = 8.5, 2.7 Hz, 1H), 6.66 (d, J = 2.7 Hz, 1H), 5.02 (d, J = 16.1 Hz, 1H), 4.46 (dd, J = 11.3, 5.2 Hz, 1H), 4.10 (d, J = 16.1 Hz, 1H), 3.79 (s, 3H), 3.25 (dd, J = 13.4, 11.5 Hz, 1H), 3.04 (s, 3H), 2.95 (dd, J = 13.4, 5.2 Hz, 1H).

[0217] Step F: To an ice-cold mixture of the lactam (26.8 g, 95.4 mmol) from step E and THF (980 mL) was added borane-dimethylsulfide complex (19.0 mL, 200 mmol). The mixture was warmed to room temperature, and then heated in an oil bath at 50°C for 75 minutes. The reaction mixture was then cooled to 0°C, quenched with methanol (100 mL), and concentrated under reduced pressure. To the residue was added 1,4-dioxane (200 mL) followed by 6N HCl (100 mL) and the mixture was heated under reflux for 2 hours. Additional volumes of 1,4-dioxane (60 mL) and 6N HCl (30 mL) were added to the reaction mixture, which was heated under reflux for 1 hour. The mixture was cooled to room temperature and then in an ice-bath, and a solution of 2N NaOH (20 mL) followed by a solution of 32% sodium hydroxide was added until pH 10. The crude product was extracted into dichloromethane (4×), and the combined organic extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the crude product by flash column chromatography (dichloromethane, then 99:0.9:0.1 to 90:9:1 dichloromethane/methanol/concentrated ammonium hydroxide) gave the amine

(19.4 g, 76%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37–7.32 (m, 2H), 7.26–7.23 (m, 1H), 7.17 (d, J = 7.5 Hz, 2H), 6.74 (d, J = 2.7 Hz, 1H), 6.65–6.55 (m, 2H), 4.26 (d, J = 8.6 Hz, 1H), 3.95–3.84 (m, 1H), 3.76 (s, 3H), 3.69 (d, J = 14.1 Hz, 1H), 3.16–3.05 (m, 1H), 2.98–2.90 (m, 1H), 2.35 (s, 3H), 2.35–2.27 (m, 1H), 2.13–2.00 (m, 1H).

[0218] Step G: The free base of the benzazepine from step F (19.4 g) was resolved by preparative chiral HPLC (CHIRALCEL OJ column, using 80:20:0.1 heptanes/ethanol/diethylamine as the eluent) to give the (+)-enantiomer [$[\alpha]^{25}_D$ +3.66° (c 0.41, methanol)] and (-)-enantiomer [$[\alpha]^{25}_D$ -1.16° (c 0.43, methanol)].

[0219] Step H: A mixture of the (+)-enantiomer from Step G above (1.19 g, 4.5 mmol) and hydrobromic acid (48% solution in water, 34 mL) was heated to reflux and stirred for 2 h. The solvent and excess hydrobromic acid were removed under reduced pressure and the resulting solid was partitioned between ethyl acetate and saturated sodium bicarbonate. After separating the two layers, the aqueous phase was extracted with ethyl acetate (3×). The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide the desired phenol (1.10 g, 86%) as a tan solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, J = 7.5 Hz, 2H), 7.28–7.23 (m, 1H), 7.16 (d, J = 7.5 Hz, 2H), 6.54 (s, 1H), 6.48–6.35 (m, 2H), 4.24–4.22 (m, 1H), 3.87–3.77 (m, 1H), 3.66–3.63 (m, 1H), 3.17–3.08 (m, 1H), 2.94–2.89 (m, 1H), 2.42 (s, 3H), 2.35–2.31 (m, 1H), 2.18–2.09 (m, 1H); ESI MS m/z 254 $[M+H]^+$.

[0220] Step I: To a stirred mixture of the phenol from Step H above (581 mg, 2.3 mmol) and pyridine (0.22 mL, 2.8 mmol) in anhydrous methylene chloride (23 mL) at 0°C under N_2 was added triflic anhydride (0.46 mL, 2.8 mmol). The reaction was stirred at 0°C for 1 h, at which time TLC analysis indicated the reaction went to completion. The mixture was then diluted with methylene chloride, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1:1 ethyl acetate/hexanes) provided the desired triflate (650 mg, 74%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, J = 7.5 Hz, 2H), 7.31–7.28 (m, 1H), 7.17 (d, J = 7.0 Hz, 2H), 7.09–7.08 (m, 1H), 6.97–6.93 (m, 1H), 6.70–6.64 (br, 1H), 4.33–4.31 (m, 1H), 4.03–3.94 (m, 1H), 3.75–3.72 (m, 1H), 3.18–3.13 (m, 1H), 3.03–2.98 (m, 1H), 2.36 (s, 3H), 2.34–2.29 (m, 1H), 2.12–2.06 (m, 1H); ESI MS m/z 386 $[M+H]^+$.

[0221] Step J: To a stirred solution of the triflate from Step I above (516 mg, 1.3 mmol) in anhydrous DMF (6.5 mL) was added lithium chloride (170 mg, 4.0 mmol). The mixture was degassed with argon for 2 minutes, then dichlorobis(triphenylphosphine)palladium(II) (47 mg, 0.067 mmol) was added. After degassing briefly with argon again, tributyl(1-ethoxyvinyl)tin (0.54 mL, 1.6 mmol) was added and the mixture was degassed briefly with argon one more time. The reaction was heated to 90°C and stirred for 3.5 hours, at which time TLC and ESI MS analyses both indicated complete consumption of the starting material and formation of the desired intermediate. The solvent was removed *in vacuo* and the crude material was purified by flash column chromatography (50%-100% ethyl acetate/hexanes) to provide the desired intermediate as a yellow oil. The oil was stirred in 1N HCl (20 mL) at room temperature for 1 hour, solid potassium carbonate was added to adjust the pH to 9, and then the solution was extracted with ethyl acetate (3×). The combined extracts were washed with water and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide the desired methyl ketone (354 mg, 95%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.67–7.65 (m, 1H), 7.37 (t, J = 7.5 Hz, 2H), 7.30–7.29 (m, 1H), 7.17 (d, J = 7.5 Hz, 2H), 6.78–6.70 (br, 1H), 4.38–4.36 (m, 1H), 4.01–3.95 (m, 1H), 3.82–3.79 (m, 1H), 3.17–3.11 (m, 1H), 3.00–2.95 (m, 1H), 2.56 (s, 3H), 2.37 (s, 3H), 2.37–2.30 (m, 1H), 2.17–2.11 (m, 1H).

[0222] Step K: To a stirred solution of the methyl ketone from Step J above (121 mg, 0.43 mmol) in anhydrous THF (4 mL) at -78°C under N_2 was added methylmagnesium iodide (3M solution in diethyl ether, 0.17 mL, 0.52 mmol) dropwise. The reaction was stirred at -78°C for 15 minutes, then warmed to 0°C and stirred for 3 hours. ESI MS indicated the presence of remaining starting material so additional methylmagnesium iodide solution (0.05 mL) was added and the reaction was stirred at 0°C for an additional 2 hours. The reaction was quenched with aqueous saturated ammonium chloride solution, then extracted with methylene chloride (3×). The combined extracts were washed with water and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (9.4:0.5:0.1 methylene chloride/methanol/concentrated ammonium hydroxide) yielded the desired alcohol (40 mg, 31%) as a colorless oil: $[\alpha]^{23}_D$ -3.16° (c 0.10, methanol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, J = 7.5 Hz, 2H), 7.32–7.31 (m, 1H), 7.28–7.25

(m, 1H), 7.18 (d, J = 7.5 Hz, 2H), 7.17–7.15 (m, 1H), 6.62–6.55 (br, 1H), 4.31–4.29 (m, 1H), 3.93–3.88 (m, 1H), 3.74–3.71 (m, 1H), 3.15–3.09 (m, 1H), 2.95–2.89 (m, 1H), 2.38 (s, 3H), 2.36–2.29 (m, 1H), 2.14–2.09 (m, 1H), 1.55 (s, 6H); ESI MS *m/z* 296 $[M+H]^+$.

[0223] Step L: To a stirred solution of the alcohol from Step K above (33 mg, 0.11 mmol) in methanol (3 mL) at room temperature was added L-tartaric acid (17 mg, 0.11 mmol). The mixture was stirred at room temperature for 1 hour and then the solvent was concentrated to approximately 0.5 mL. After diluting with water (2 mL), the mixture was lyophilized for 15 hours to provide (+)-2-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)propan-2-ol, L-tartrate salt (53 mg, 99%, 98.9% AUC HPLC) as a white powder: mp 103–105°C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.56 (s, 1H), 7.42–7.37 (m, 1H), 7.39 (t, J = 7.5 Hz, 2H), 7.30 (t, J = 7.5 Hz, 1H), 7.19 (d, J = 7.5 Hz, 2H), 6.88–6.76 (br, 1H), 4.63–4.52 (m, 1H), 4.56–4.55 (m, 1H), 4.39 (s, 2H), 4.32–4.30 (m, 1H), 3.57–3.51 (m, 2H), 2.85 (s, 3H), 2.62–2.53 (m, 1H), 2.42–2.37 (m, 1H), 1.53 (s, 6H); ESI MS *m/z* 296 $[M+H]^+$.

<u>Example 19</u> - Preparation of (+)-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)(morpholino)methanone, L-tartrate salt

[0224] Step A: To a stirred solution of methylamine (40% in water) (28.2 mL, 327.6 mmol) in methanol (100 mL) at room temperature was added *m*-anisaldehyde (20.6 mL, 163.8 mmol) as a solution in methanol (50 mL) dropwise over 20 minutes. The reaction was stirred at room temperature under N_2 for 15 h, then cooled to 0°C and sodium borohydride (6.19 g, 163.8 mmol) was added in portions. After warming to room temperature, the reaction was stirred for 3 hours. The mixture was then concentrated under reduced pressure, dissolved in water, and extracted with methylene chloride (3×). The combined methylene chloride extracts were extracted with 1N HCl (3×) and the combined HCl extracts adjusted to pH 10 by addition of 6N NaOH. The aqueous mixture was then extracted with methylene chloride (3×). The combined methylene chloride extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the desired amine (25.0 g, quantitative yield) as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.22 (m, 1H), 6.91–6.89 (m, 1H), 6.89 (s, 1 H), 6.82–6.79 (m, 1H), 3.81 (s, 3H), 3.74 (s, 2H), 2.46 (s, 3H).

[0225] Step B: A solution of *trans*-cinnamic acid (5.0 g, 33.8 mmol) and *N*-methylmorpholine (5.2 mL, 47.3 mmol) in anhydrous methylene chloride (120 mL) was cooled to –20°C, and then isobutyl chloroformate (4.8 mL, 35.8 mmol) was added dropwise. After 15 minutes, a solution of the amine from Step A above (5.1 g, 33.8 mmol) in anhydrous methylene chloride (30 mL) was added dropwise, then the reaction was allowed to warm to room temperature and stir under N_2 for 3 hours. The mixture was washed with 1M sodium dihydrogen phosphate dihydrate (2×), H_2O (2×), and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1:1 ethyl acetate/hexanes) yielded the desired amide (8.3 g, 87%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, J = 15.5, 7.5 Hz, 1H), 7.56–7.54 (m, 1H), 7.47–7.46 (m, 1H), 7.36 (dd, J = 14.5, 7.5 Hz, 2H), 7.39–7.33 (m, 1H), 7.31–7.24 (m, 1H), 6.95–6.76 (m, 4H), 4.70–4.66 (m, 2H), 3.80 (s, 3H), 3.09–3.07 (m, 3H); ESI MS *m/z* 282 $[M+H]^+$.

[0226] Step C: An excess of polyphosphoric acid (11 g) in 1,2-dichloroethane (10 mL) was heated to 100°C. A solution of the amide from Step B above (3.8 g, 13.5 mmol) in 1,2-dichloroethane (15 mL) was added dropwise and the reaction was stirred at 100°C for 15 hours under N_2. After cooling to room temperature, the reaction was mixed with ice and the pH adjusted to 9 using concentrated ammonium hydroxide. The reaction mixture was then extracted with ethyl acetate (3×) and the combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Partial purification by flash column chromatography (30–100% ethyl acetate/hexanes) yielded the desired product (1.77 g) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.49 (m, 1H), 7.37–7.35 (m, 1H), 7.29–7.28 (m, 1H), 7.09–7.06 (m, 2H), 6.87 (d, J = 9.0 Hz, 1H) 6.71 (dd, J = 8.5, 2.5 Hz, 1H), 6.66 (d, J = 3.0 Hz, 1H), 5.03 (d, J = 16.5 Hz, 1H), 4.48–4.44 (m, 1H), 4.09 (d, J = 16.5 Hz, 1H), 3.79 (s, 3H), 3.28–3.22 (m, 1H), 3.05 (s, 3H), 2.97–2.93 (m, 1H).

[0227] Step D: To a stirred solution of lithium aluminum hydride (1M solution in THF, 14.7 mL, 14.7 mmol) at 0°C under N_2 was added a solution of the product of Step C above (3.8 g, 13.4 mmol) in anhydrous THF (100 mL) dropwise. The reaction mixture was heated to reflux and stirred for 2 hours. The reaction was then cooled back down to 0°C and quenched slowly with 1N NaOH (30 mL). After diluting with water, the aqueous phase was extracted with ethyl acetate (3×) and the combined extracts were washed with brine, dried over sodium sulfate, filtered, and

concentrated *in vacuo*. Purification by flash column chromatography (1:1 ethyl acetate/hexanes) yielded the desired benzazepine (2.93 g, 38% two steps) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (t, J = 7.5 Hz, 2H), 7.27–7.24 (m, 1H), 7.17 (d, J = 7.5 Hz, 2H), 6.75–6.74 (m, 1H), 6.61–6.60 (m, 1H), 6.61–6.53 (br, 1H), 4.27–4.26 (m, 1H), 3.91–3.86 (m, 1H), 3.77 (s, 3H), 3.73–3.70 (m, 1H), 3.16–3.09 (m, 1H), 2.99–2.94 (m, 1H), 2.35 (s, 3H), 2.33–2.28 (m, 1H), 2.13–2.07 (m, 1H); ESI MS *m/z* 268 $[M+H]^+$. This compound was resolved by preparative chiral HPLC (CHIRALCEL OJ column, using 9:1:0.01 heptane/ethanol/diethylamine as the eluent) to give the (+)-enantiomer $[[\alpha]^{25}_D$ +3.66° (*c* 0.41, methanol)] and the (–)-enantiomer $[[\alpha]^{25}_D$ –1.16° (*c* 0.43, methanol)].

[0228] Step E: A mixture of the (+)-enantiomer from Step D above (1.19 g, 4.5 mmol) and hydrobromic acid (48% solution in water, 34 mL) was heated to reflux and stirred for 2 hours. The solvent and excess hydrobromic acid were removed under reduced pressure and the resulting solid was partitioned between ethyl acetate and saturated sodium bicarbonate. After separating the two layers, the aqueous phase was extracted with ethyl acetate (3×). The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide the desired phenol (1.10 g, 86%) as a tan solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, J = 7.5 Hz, 2H), 7.28–7.23 (m, 1H), 7.16 (d, J = 7.5 Hz, 2H), 6.54 (s, 1H), 6.48–6.35 (m, 2H), 4.24–4.22 (m, 1H), 3.87–3.77 (m, 1H), 3.66–3.63 (m, 1H), 3.17–3.08 (m, 1H), 2.94–2.89 (m, 1H), 2.42 (s, 3H), 2.35–2.31 (m, 1H), 2.18–2.09 (m, 1H); ESI MS *m/z* 254 $[M+H]^+$.

[0229] Step F: To a stirred mixture of the phenol from Step E above (581 mg, 2.3 mmol) and pyridine (0.22 mL, 2.8 mmol) in anhydrous methylene chloride (23 mL) at 0°C under N_2 was added triflic anhydride (0.46 mL, 2.8 mmol). The reaction was stirred at 0°C for 1 hour, at which time TLC analysis indicated the reaction went to completion. The mixture was then diluted with methylene chloride, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1:1 ethyl acetate/hexanes) provided the desired triflate (650 mg, 74%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, J = 7.5 Hz, 2H), 7.31–7.28 (m, 1H), 7.17 (d, J = 7.0 Hz, 2H), 7.09–7.08 (m, 1H), 6.97–6.93 (m, 1H), 6.70–6.64 (br, 1H), 4.33–

4.31 (m, 1H), 4.03–3.94 (m, 1H), 3.75–3.72 (m, 1H), 3.18–3.13 (m, 1H), 3.03–2.98 (m, 1H), 2.36 (s, 3H), 2.34–2.29 (m, 1H), 2.12–2.06 (m, 1H); ESI MS *m/z* 386 $[M+H]^+$.

[0230] Step G: To a stirred solution of the triflate from Step F above (2.60 g, 6.8 mmol) in anhydrous DMF (30 mL) at room temperature was added zinc cyanide (1.58 g, 13.5 mmol). The reaction mixture was degassed with argon for 5 minutes, then 1,1'-bis(diphenylphosphino)ferrocene (599 mg, 1.1 mmol) and tris(dibenzylideneacetone)dipalladium(0) (247 mg, 0.27 mmol) were added under argon. The reaction was heated to 130°C and stirred for 4 hours, at which time ESI MS indicated the reaction went to completion. After cooling to room temperature, the mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate. The aqueous phase was extracted with additional ethyl acetate (3×), then the combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (2.5%-10% methanol/methylene chloride) yielded the desired nitrile (1.1 g, 60%) as a dark brown oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.46 (m, 1H), 7.40–7.34 (m, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.32–7.29 (m, 1H), 7.15 (d, J = 7.5 Hz, 2H), 6.77–6.67 (br, 1H), 4.37–4.35 (m, 1H), 3.99–3.97 (m, 1H), 3.77–3.74 (m, 1H), 3.19–3.12 (m, 1H), 3.02–2.98 (m, 1H), 2.37 (s, 3H), 2.37–2.29 (m, 1H), 2.16–2.10 (m, 1H); ESI MS *m/z* 263 $[M+H]^+$.

[0231] Step H: A mixture of the nitrile from Step G above (290 mg, 1.1 mmol) and an excess of concentrated hydrochloric acid (3.5 mL) was stirred at 100°C for 15 hours, at which time ESI MS indicated the reaction went to completion. The water and excess hydrochloric acid were removed *in vacuo* to provide the desired carboxylic acid as a dark brown solid which was used in the next step without further purification: ESI MS *m/z* 282 $[M+H]^+$.

[0232] Step I: To a stirred solution of the carboxylic acid from Step H above (353 mg, 1.1 mmol, theoretical) in methylene chloride (10 mL) at 0°C were added triethylamine (0.19 mL, 1.3 mmol), morpholine (0.11 mL, 1.2 mmol), and 4-dimethylaminopyridine (14 mg, 0.11 mmol). After stirring at 0°C for 10 minutes, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (234 mg, 1.2 mmol) was added, then the reaction was warmed to room temperature and stirred for approximately 2 days. The reaction mixture was partitioned between ethyl acetate

and saturated sodium bicarbonate. After separating the layers, the aqueous phase was extracted with additional ethyl acetate (3×) and the combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (2.5%-10% methanol/methylene chloride) yielded the desired amide (171 mg, 44% for two steps) as a yellow oil: $[\alpha]^{23}_{D}$ -4.62° (*c* 0.065, methanol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (t, *J* = 7.5 Hz, 2H), 7.29 (d, *J* = 7.0 Hz, 1H), 7.26–7.25 (m, 1H), 7.16 (d, *J* = 7.5 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 1H), 6.73–6.65 (br, 1H), 4.35–4.33 (m, 1H), 3.96–3.88 (m, 1H), 3.82–3.39 (br, 8H), 3.75–3.72 (m, 1H), 3.16–3.10 (m, 1H), 2.98–2.94 (m, 1H), 2.38 (s, 3H), 2.38–2.31 (m, 1H), 2.18–2.11 (m, 1H); ESI MS *m/z* 351 $[M+H]^+$.

[0233] Step J: To a stirred solution of the amide from Step I above (164 mg, 0.47 mmol) in methanol (4 mL) at room temperature was added L-tartaric acid (70 mg, 0.47 mmol). The mixture was stirred at room temperature for 1 hour and then the solvent was concentrated to approximately 0.5 mL. After diluting with water (2 mL), the mixture was lyophilized for 15 hours to provide (+)-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)(morpholino)methanone, L-tartrate salt (220 mg, 94%, 97.4% AUC HPLC) as a light brown powder: ^{1}H NMR (500 MHz, CD_3OD) δ 7.51–7.50 (m, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 7.5 Hz, 2H), 6.95–6.86 (br, 1H), 4.63–4.62 (m, 2H), 4.39 (s, 2H), 4.36–4.33 (m, 1H), 3.79–3.67 (br, 4H), 3.75–3.54 (br, 2H), 3.59–3.52 (m, 2H), 3.52–3.38 (m, 2H), 2.85 (s, 3 H), 2.63–2.54 (m, 1H), 2.43–2.38 (m, 1H); ESI MS *m/z* 351 $[M+H]^+$.

<u>Example 20</u> - Preparation of (+)-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)methanamine, maleate salt

[0234] Step A: To a stirred solution of methylamine (40% in H_2O) (28.2 mL, 327.6 mmol) in methanol (100 mL) at room temperature was added *m*-anisaldehyde (20.6 mL, 163.8 mmol) as a solution in methanol (50 mL) dropwise over 20 minutes. The reaction was stirred at room temperature under N_2 for 15 h, then cooled to 0°C and sodium borohydride (6.19 g, 163.8 mmol) was added in portions. After warming to room temperature, the reaction was stirred for 3 hours. The mixture was then concentrated under reduced pressure, dissolved in water, and extracted with methylene chloride (3×). The combined methylene chloride extracts were extracted

with 1N HCl (3×) and the combined HCl extracts adjusted to pH 10 by addition of 6N NaOH. The aqueous mixture was then extracted with methylene chloride (3×). The combined methylene chloride extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the desired amine (25.0 g, quantitative yield) as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.22 (m, 1H), 6.91–6.89 (m, 1H), 6.89 (s, 1 H), 6.82–6.79 (m, 1H), 3.81 (s, 3H), 3.74 (s, 2H), 2.46 (s, 3H).

[0235] Step B: A solution of *trans*-cinnamic acid (5.0 g, 33.8 mmol) and *N*-methylmorpholine (5.2 mL, 47.3 mmol) in anhydrous methylene chloride (120 mL) was cooled to –20°C, and then isobutyl chloroformate (4.8 mL, 35.8 mmol) was added dropwise. After 15 minutes, a solution of the amine from Step A above (5.1 g, 33.8 mmol) in anhydrous methylene chloride (30 mL) was added dropwise, then the reaction was allowed to warm to room temperature and stir under N_2 for 3 hours. The mixture was washed with 1M sodium dihydrogen phosphate dihydrate (2×), H_2O (2×), and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1:1 ethyl acetate/hexanes) yielded the desired amide (8.3 g, 87%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, J = 15.5, 7.5 Hz, 1H), 7.56–7.54 (m, 1H), 7.47–7.46 (m, 1H), 7.36 (dd, J = 14.5, 7.5 Hz, 2H), 7.39–7.33 (m, 1H), 7.31–7.24 (m, 1H), 6.95–6.76 (m, 4H), 4.70–4.66 (m, 2H), 3.80 (s, 3H), 3.09–3.07 (m, 3H); ESI MS *m/z* 282 $[M+H]^+$.

[0236] Step C: An excess of polyphosphoric acid (11 g) in 1,2-dichloroethane (10 mL) was heated to 100°C. A solution of the amide from Step B above (3.8 g, 13.5 mmol) in 1,2-dichloroethane (15 mL) was added dropwise and the reaction was stirred at 100°C for 15 h under N_2. After cooling to room temperature, the reaction was mixed with ice and the pH adjusted to 9 using concentrated ammonium hydroxide. The reaction mixture was then extracted with ethyl acetate (3×) and the combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Partial purification by flash column chromatography (30–100% ethyl acetate/hexanes) yielded the desired product (1.77 g) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.49 (m, 1H), 7.37–7.35 (m, 1H), 7.29–7.28 (m, 1H), 7.09–7.06 (m, 2H), 6.87 (d, J = 9.0 Hz, 1H) 6.71 (dd, J = 8.5, 2.5 Hz, 1H), 6.66 (d, J = 3.0 Hz, 1H), 5.03 (d, J = 16.5 Hz, 1H), 4.48–4.44 (m, 1H), 4.09 (d, J = 16.5 Hz, 1H), 3.79 (s, 3H), 3.28–3.22 (m, 1H), 3.05 (s, 3H), 2.97–2.93 (m, 1H).

[0237] Step D: To a stirred solution of lithium aluminum hydride (1M solution in THF, 14.7 mL, 14.7 mmol) at 0°C under N_2 was added a solution of the product of Step C above (3.8 g, 13.4 mmol) in anhydrous THF (100 mL) dropwise. The reaction mixture was heated to reflux and stirred for 2 hours. The reaction was then cooled back down to 0°C and quenched slowly with 1N NaOH (30 mL). After diluting with water, the aqueous phase was extracted with ethyl acetate (3×) and the combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1:1 ethyl acetate/hexanes) yielded the desired benzazepine (2.93 g, 38% two steps) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (t, J = 7.5 Hz, 2H), 7.27–7.24 (m, 1H), 7.17 (d, J = 7.5 Hz, 2H), 6.75–6.74 (m, 1H), 6.61–6.60 (m, 1H), 6.61–6.53 (br, 1H), 4.27–4.26 (m, 1H), 3.91–3.86 (m, 1H), 3.77 (s, 3H), 3.73–3.70 (m, 1H), 3.16–3.09 (m, 1H), 2.99–2.94 (m, 1H), 2.35 (s, 3H), 2.33–2.28 (m, 1H), 2.13–2.07 (m, 1H); ESI MS *m/z* 268 $[M+H]^+$. This compound was resolved by preparative chiral HPLC (CHIRALCEL OJ column, using 9:1:0.01 heptane/ethanol/diethylamine as the eluent) to give the (+)-enantiomer $[[\alpha]^{25}_D$ +3.66° (c 0.41, methanol)] and the (–)-enantiomer $[[\alpha]^{25}_D$ –1.16° (c 0.43, methanol)].

[0238] Step E: A mixture of the (+)-enantiomer from Step D above (1.19 g, 4.5 mmol) and hydrobromic acid (48% solution in water, 34 mL) was heated to reflux and stirred for 2 hours. The solvent and excess hydrobromic acid were removed under reduced pressure and the resulting solid was partitioned between ethyl acetate and saturated sodium bicarbonate. After separating the two layers, the aqueous phase was extracted with ethyl acetate (3×). The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide the desired phenol (1.10 g, 86%) as a tan solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, J = 7.5 Hz, 2H), 7.28–7.23 (m, 1H), 7.16 (d, J = 7.5 Hz, 2H), 6.54 (s, 1H), 6.48–6.35 (m, 2H), 4.24–4.22 (m, 1H), 3.87–3.77 (m, 1H), 3.66–3.63 (m, 1H), 3.17–3.08 (m, 1H), 2.94–2.89 (m, 1H), 2.42 (s, 3H), 2.35–2.31 (m, 1H), 2.18–2.09 (m, 1H); ESI MS *m/z* 254 $[M+H]^+$.

[0239] Step F: To a stirred mixture of the phenol from Step E above (581 mg, 2.3 mmol) and pyridine (0.22 mL, 2.8 mmol) in anhydrous methylene chloride (23 mL) at 0°C under N_2 was added triflic anhydride (0.46 mL, 2.8 mmol). The reaction was stirred at 0°C for 1 hour, at which time TLC analysis indicated the

reaction went to completion. The mixture was then diluted with methylene chloride, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1:1 ethyl acetate/hexanes) provided the desired triflate (650 mg, 74%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, J = 7.5 Hz, 2H), 7.31–7.28 (m, 1H), 7.17 (d, J = 7.0 Hz, 2H), 7.09–7.08 (m, 1H), 6.97–6.93 (m, 1H), 6.70–6.64 (br, 1H), 4.33–4.31 (m, 1H), 4.03–3.94 (m, 1H), 3.75–3.72 (m, 1H), 3.18–3.13 (m, 1H), 3.03–2.98 (m, 1H), 2.36 (s, 3H), 2.34–2.29 (m, 1H), 2.12–2.06 (m, 1H); ESI MS *m/z* 386 $[M+H]^+$.

[0240] Step G: To a stirred solution of the triflate from Step F above (2.60 g, 6.8 mmol) in anhydrous DMF (30 mL) at room temperature was added zinc cyanide (1.58 g, 13.5 mmol). The reaction mixture was degassed with argon for 5 minutes, then 1,1'-bis(diphenylphosphino)ferrocene (599 mg, 1.1 mmol) and tris(dibenzylideneacetone)dipalladium(0) (247 mg, 0.27 mmol) were added under argon. The reaction was heated to 130°C and stirred for 4 hours, at which time ESI MS indicated the reaction went to completion. After cooling to room temperature, the mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate. The aqueous phase was extracted with additional ethyl acetate (3×), then the combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (2.5%-10% methanol/methylene chloride) yielded the desired nitrile (1.1 g, 60%) as a dark brown oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.46 (m, 1H), 7.40–7.34 (m, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.32–7.29 (m, 1H), 7.15 (d, J = 7.5 Hz, 2H), 6.77–6.67 (br, 1H), 4.37–4.35 (m, 1H), 3.99–3.97 (m, 1H), 3.77–3.74 (m, 1H), 3.19–3.12 (m, 1H), 3.02–2.98 (m, 1H), 2.37 (s, 3H), 2.37–2.29 (m, 1H), 2.16–2.10 (m, 1H); ESI MS *m/z* 263 $[M+H]^+$.

[0241] Step H: To a stirred solution of the nitrile from Step G above (154 mg, 0.59 mmol) in anhydrous THF (7 mL) was added lithium aluminum hydride (1M in THF, 1.8 mL) at 0°C under N_2. The reaction was allowed to warm to room temperature and stirred for approximately 2 days. ESI MS indicated the reaction went to completion, so the mixture was poured slowly over ice water, then extracted with methylene chloride (3×). The combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column

chromatography (9.5:0.45:0.05 methylene chloride/methanol/concentrated ammonium hydroxide) yielded the desired amine (99 mg, 63%) as a light brown oil: $[\alpha]^{23}_{D}$ +2.22° (*c* 0.050, methanol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.34 (m, 2H), 7.28–7.25 (m, 1H), 7.18 (d, *J* = 7.5 Hz, 2H), 7.14–7.13 (m, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 6.65–6.57 (br, 1H), 4.32–4.30 (m, 1H), 3.95–3.89 (m, 1H), 3.81 (s, 2H), 3.75–3.72 (m, 1H), 3.15–3.09 (m, 1H), 2.97–2.92 (m, 1H), 2.36 (s, 3H), 2.36–2.29 (m, 1H), 2.16–2.10 (m, 1H); ESI MS *m/z* 267 $[M+H]^+$.

[0242] Step I: To a stirred solution of the amine from Step H above (28 mg, 0.11 mmol) in methanol (3 mL) at room temperature was added maleic acid (12 mg, 0.11 mmol). The mixture was stirred at room temperature for 1 hour and then the solvent was concentrated to approximately 0.5 mL. After diluting with water (2 mL), the mixture was lyophilized for 15 h to provide (+)-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)methanamine, maleate salt (39 mg, 97%, 97.6% AUC HPLC) as a light brown powder: ^{1}H NMR (500 MHz, CD_3OD) δ 7.36 (t, *J* = 7.5 Hz, 2H), 7.35–7.34 (m, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 2H), 6.84–6.73 (br, 1H), 6.24 (s, 2H), 4.47–4.46 (m, 1H), 4.18–4.06 (m, 1H), 4.07 (s, 2H), 3.91–3.88 (m, 1H), 3.26–3.19 (m, 1H), 3.17–3.11 (m, 1H), 2.49 (s, 3H), 2.46–2.39 (m, 1H), 2.26–2.19 (m, 1H); ESI MS *m/z* 267 $[M+H]^+$.

<u>Example 21</u> - Preparation of (+)-1-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)cyclopropanamine, maleate salt

[0243] Step A: To a stirred solution of methylamine (40% in water) (28.2 mL, 327.6 mmol) in methanol (100 mL) at room temperature was added *m*-anisaldehyde (20.6 mL, 163.8 mmol) as a solution in methanol (50 mL) dropwise over 20 minutes. The reaction was stirred at room temperature under N_2 for 15 hours, then cooled to 0°C and sodium borohydride (6.19 g, 163.8 mmol) was added in portions. After warming to room temperature, the reaction was stirred for 3 hours. The mixture was then concentrated under reduced pressure, dissolved in water, and extracted with methylene chloride (3×). The combined methylene chloride extracts were extracted with 1N HCl (3×) and the combined HCl extracts adjusted to pH 10 by addition of 6N NaOH. The aqueous mixture was then extracted with methylene chloride (3×). The combined methylene chloride extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the desired amine (25.0 g, quantitative yield) as a light

yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.22 (m, 1H), 6.91–6.89 (m, 1H), 6.89 (s, 1 H), 6.82–6.79 (m, 1H), 3.81 (s, 3H), 3.74 (s, 2H), 2.46 (s, 3H).

[0244] Step B: A solution of *trans*-cinnamic acid (5.0 g, 33.8 mmol) and *N*-methylmorpholine (5.2 mL, 47.3 mmol) in anhydrous methylene chloride (120 mL) was cooled to –20°C, and then isobutyl chloroformate (4.8 mL, 35.8 mmol) was added dropwise. After 15 minutes, a solution of the amine from Step A above (5.1 g, 33.8 mmol) in anhydrous methylene chloride (30 mL) was added dropwise, then the reaction was allowed to warm to room temperature and stir under N_2 for 3 hours. The mixture was washed with 1M sodium dihydrogen phosphate dihydrate (2×), H_2O (2×), and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1:1 ethyl acetate/hexanes) yielded the desired amide (8.3 g, 87%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, J = 15.5, 7.5 Hz, 1H), 7.56–7.54 (m, 1H), 7.47–7.46 (m, 1H), 7.36 (dd, J = 14.5, 7.5 Hz, 2H), 7.39–7.33 (m, 1H), 7.31–7.24 (m, 1H), 6.95–6.76 (m, 4H), 4.70–4.66 (m, 2H), 3.80 (s, 3H), 3.09–3.07 (m, 3H); ESI MS *m/z* 282 $[M+H]^+$.

[0245] Step C: An excess of polyphosphoric acid (11 g) in 1,2-dichloroethane (10 mL) was heated to 100°C. A solution of the amide from Step B above (3.8 g, 13.5 mmol) in 1,2-dichloroethane (15 mL) was added dropwise and the reaction was stirred at 100°C for 15 h under N_2. After cooling to room temperature, the reaction was mixed with ice and the pH adjusted to 9 using concentrated ammonium hydroxide. The reaction mixture was then extracted with ethyl acetate (3×) and the combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Partial purification by flash column chromatography (30–100% ethyl acetate/hexanes) yielded the desired product (1.77 g) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.49 (m, 1H), 7.37–7.35 (m, 1H), 7.29–7.28 (m, 1H), 7.09–7.06 (m, 2H), 6.87 (d, J = 9.0 Hz, 1H) 6.71 (dd, J = 8.5, 2.5 Hz, 1H), 6.66 (d, J = 3.0 Hz, 1H), 5.03 (d, J = 16.5 Hz, 1H), 4.48–4.44 (m, 1H), 4.09 (d, J = 16.5 Hz, 1H), 3.79 (s, 3H), 3.28–3.22 (m, 1H), 3.05 (s, 3H), 2.97–2.93 (m, 1H).

[0246] Step D: To a stirred solution of lithium aluminum hydride (1M solution in THF, 14.7 mL, 14.7 mmol) at 0°C under N_2 was added a solution of the product of Step C above (3.8 g, 13.4 mmol) in anhydrous THF (100 mL) dropwise. The reaction mixture was heated to reflux and stirred for 2 hours. The reaction was

then cooled back down to 0°C and quenched slowly with 1N NaOH (30 mL). After diluting with water, the aqueous phase was extracted with ethyl acetate (3×) and the combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1:1 ethyl acetate/hexanes) yielded the desired benzazepine (2.93 g, 38% two steps) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (t, J = 7.5 Hz, 2H), 7.27–7.24 (m, 1H), 7.17 (d, J = 7.5 Hz, 2H), 6.75–6.74 (m, 1H), 6.61–6.60 (m, 1H), 6.61–6.53 (br, 1H), 4.27–4.26 (m, 1H), 3.91–3.86 (m, 1H), 3.77 (s, 3H), 3.73–3.70 (m, 1H), 3.16–3.09 (m, 1H), 2.99–2.94 (m, 1H), 2.35 (s, 3H), 2.33–2.28 (m, 1H), 2.13–2.07 (m, 1H); ESI MS *m/z* 268 $[M+H]^+$. This compound was resolved by preparative chiral HPLC (CHIRALCEL OJ column, using 9:1:0.01 heptane/ethanol/diethylamine as the eluent) to give the (+)-enantiomer $[[\alpha]^{25}_D$ +3.66° (c 0.41, methanol)] and the (–)-enantiomer $[[\alpha]^{25}_D$ –1.16° (c 0.43, methanol)].

[0247] Step E: A mixture of the (+)-enantiomer from Step D above (1.19 g, 4.5 mmol) and hydrobromic acid (48% solution in water, 34 mL) was heated to reflux and stirred for 2 hours. The solvent and excess hydrobromic acid were removed under reduced pressure and the resulting solid was partitioned between ethyl acetate and saturated sodium bicarbonate. After separating the two layers, the aqueous phase was extracted with ethyl acetate (3×). The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide the desired phenol (1.10 g, 86%) as a tan solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, J = 7.5 Hz, 2H), 7.28–7.23 (m, 1H), 7.16 (d, J = 7.5 Hz, 2H), 6.54 (s, 1H), 6.48–6.35 (m, 2H), 4.24–4.22 (m, 1H), 3.87–3.77 (m, 1H), 3.66–3.63 (m, 1H), 3.17–3.08 (m, 1H), 2.94–2.89 (m, 1H), 2.42 (s, 3H), 2.35–2.31 (m, 1H), 2.18–2.09 (m, 1H); ESI MS *m/z* 254 $[M+H]^+$.

[0248] Step F: To a stirred mixture of the phenol from Step E above (581 mg, 2.3 mmol) and pyridine (0.22 mL, 2.8 mmol) in anhydrous methylene chloride (23 mL) at 0°C under N_2 was added triflic anhydride (0.46 mL, 2.8 mmol). The reaction was stirred at 0°C for 1 h, at which time TLC analysis indicated the reaction went to completion. The mixture was then diluted with methylene chloride, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1:1 ethyl

acetate/hexanes) provided the desired triflate (650 mg, 74%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, J = 7.5 Hz, 2H), 7.31–7.28 (m, 1H), 7.17 (d, J = 7.0 Hz, 2H), 7.09–7.08 (m, 1H), 6.97–6.93 (m, 1H), 6.70–6.64 (br, 1H), 4.33–4.31 (m, 1H), 4.03–3.94 (m, 1H), 3.75–3.72 (m, 1H), 3.18–3.13 (m, 1H), 3.03–2.98 (m, 1H), 2.36 (s, 3H), 2.34–2.29 (m, 1H), 2.12–2.06 (m, 1H); ESI MS *m/z* 386 $[M+H]^+$.

[0249] Step G: To a stirred solution of the triflate from Step F above (2.60 g, 6.8 mmol) in anhydrous DMF (30 mL) at room temperature was added zinc cyanide (1.58 g, 13.5 mmol). The reaction mixture was degassed with argon for 5 minutes, then 1,1'-bis(diphenylphosphino)ferrocene (599 mg, 1.1 mmol) and tris(dibenzylideneacetone)dipalladium(0) (247 mg, 0.27 mmol) were added under argon. The reaction was heated to 130°C and stirred for 4 hours, at which time ESI MS indicated the reaction went to completion. After cooling to room temperature, the mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate. The aqueous phase was extracted with additional ethyl acetate (3×), then the combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (2.5%-10% methanol/methylene chloride) yielded the desired nitrile (1.1 g, 60%) as a dark brown oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.46 (m, 1H), 7.40–7.34 (m, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.32–7.29 (m, 1H), 7.15 (d, J = 7.5 Hz, 2H), 6.77–6.67 (br, 1H), 4.37–4.35 (m, 1H), 3.99–3.97 (m, 1H), 3.77–3.74 (m, 1H), 3.19–3.12 (m, 1H), 3.02–2.98 (m, 1H), 2.37 (s, 3H), 2.37–2.29 (m, 1H), 2.16–2.10 (m, 1H); ESI MS *m/z* 263 $[M+H]^+$.

[0250] Step H: To a stirred solution of the nitrile from Step G above (143 mg, 0.55 mmol) in anhydrous THF (3 mL) were added titanium(IV) isopropoxide (0.18 mL, 0.60 mmol) and ethylmagnesium bromide (3M in diethyl ether, 0.40 mL, 1.2 mmol) at -78°C. The reaction was stirred for 10 minutes at -78°C and then warmed to room temperature over 1 hour. Boron trifluoride-diethyl etherate (0.14 mL, 1.1 mmol) was added slowly and the reaction was stirred at room temperature for 1 hour. 1N HCl (1.5 mL) and THF (8 mL) were added, then the mixture was basified using 1N NaOH (6 mL). After extracting the mixture with ethyl acetate (3×), the combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (9.5:0.45:0.05 methylene chloride/methanol/concentrated ammonium hydroxide) yielded the desired

cyclopropylamine (22 mg, 14%) as a light brown oil: $[\alpha]^{23}_{D}$ +6.67° (*c* 0.030, methanol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (t, *J* = 7.5 Hz, 2H), 7.27–7.25 (m, 1H), 7.18 (d, *J* = 7.5 Hz, 2H), 7.12–7.11 (m, 1H), 7.00–6.98 (m, 1H), 6.59–6.53 (br, 1H), 4.30–4.28 (m, 1H), 3.92–3.85 (m, 1H), 3.72–3.69 (m, 1H), 3.14–3.08 (m, 1H), 2.95–2.90 (m, 1H), 2.37 (s, 3H), 2.35–2.28 (m, 1H), 2.15–2.08 (m, 1H), 1.03–1.01 (m, 2H), 0.94–0.92 (m, 2H); ESI MS *m/z* 293 $[M+H]^+$.

[0251] Step I: To a stirred solution of the cyclopropylamine from Step H above (19 mg, 0.065 mmol) in methanol (3 mL) at room temperature was added maleic acid (7.5 mg, 0.065 mmol). The mixture was stirred at room temperature for 1 hour and then the solvent was concentrated to approximately 0.5 mL. After diluting with water (2 mL), the mixture was lyophilized for 15 hours to provide (+)-1-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)cyclopropanamine, maleate salt (25 mg, 94%, 93.0% AUC HPLC) as a light brown powder: ^{1}H NMR (500 MHz, CD_3OD) δ 7.39–7.36 (m, 3H), 7.30–7.28 (m, 2H), 7.18–7.17 (m, 2H), 6.86–6.75 (br, 1H), 6.24 (s, 2H), 4.52–4.50 (m, 1H), 4.37–4.29 (m, 1H), 4.09–4.07 (m, 1H), 3.45–3.38 (m, 2H), 2.67 (s, 3H), 2.53–2.43 (m, 1H), 2.33–2.26 (m, 1H), 1.28–1.25 (m, 2H), 1.21–1.18 (m, 2H); ESI MS *m/z* 293 $[M+H]^+$.

<u>Example 22</u> - Preparation of (+)-4-((2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)methyl)morpholine, L-tartrate salt

[0252] Step A: To a stirred solution of methylamine (40% in water) (28.2 mL, 327.6 mmol) in methanol (100 mL) at room temperature was added *m*-anisaldehyde (20.6 mL, 163.8 mmol) as a solution in methanol (50 mL) dropwise over 20 minutes. The reaction was stirred at room temperature under N_2 for 15 hours, then cooled to 0°C and sodium borohydride (6.19 g, 163.8 mmol) was added in portions. After warming to room temperature, the reaction was stirred for 3 hours. The mixture was then concentrated under reduced pressure, dissolved in water, and extracted with methylene chloride (3×). The combined methylene chloride extracts were extracted with 1 N HCl (3×) and the combined HCl extracts adjusted to pH 10 by addition of 6 N NaOH. The aqueous mixture was then extracted with methylene chloride (3×). The combined methylene chloride extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the desired amine (25.0 g, quantitative yield) as a

light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.22 (m, 1H), 6.91–6.89 (m, 1H), 6.89 (s, 1 H), 6.82–6.79 (m, 1H), 3.81 (s, 3H), 3.74 (s, 2H), 2.46 (s, 3H).

[0253] Step B: A solution of *trans*-cinnamic acid (5.0 g, 33.8 mmol) and *N*-methylmorpholine (5.2 mL, 47.3 mmol) in anhydrous methylene chloride (120 mL) was cooled to –20°C, and then isobutyl chloroformate (4.8 mL, 35.8 mmol) was added dropwise. After 15 minutes, a solution of the amine from Step A (5.1 g, 33.8 mmol) in anhydrous methylene chloride (30 mL) was added dropwise, then the reaction was allowed to warm to room temperature and stir under N_2 for 3 hours. The mixture was washed with 1 M sodium dihydrogen phosphate dihydrate (2×), H_2O (2×), and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (1:1 ethyl acetate/hexanes) yielded the desired amide (8.3 g, 87%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, J = 15.5, 7.5 Hz, 1H), 7.56–7.54 (m, 1H), 7.47–7.46 (m, 1H), 7.36 (dd, J = 14.5, 7.5 Hz, 2H), 7.39–7.33 (m, 1H), 7.31–7.24 (m, 1H), 6.95–6.76 (m, 4H), 4.70–4.66 (m, 2H), 3.80 (s, 3H), 3.09–3.07 (m, 3H); ESI MS *m/z* 282 $[M+H]^+$.

[0254] Step C: An excess of polyphosphoric acid (11 g) in 1,2-dichloroethane (10 mL) was heated to 100°C. A solution of the amide from Step B (3.8 g, 13.5 mmol) in 1,2-dichloroethane (15 mL) was added dropwise and the reaction was stirred at 100°C for 15 hours under N_2. After cooling to room temperature, the reaction was mixed with ice and the pH adjusted to 9 using concentrated ammonium hydroxide. The reaction mixture was then extracted with ethyl acetate (3×) and the combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Partial purification via flash column chromatography (30–100% ethyl acetate/hexanes) yielded the desired product (1.77 g) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.49 (m, 1H), 7.37–7.35 (m, 1H), 7.29–7.28 (m, 1H), 7.09–7.06 (m, 2H), 6.87 (d, J = 9.0 Hz, 1H) 6.71 (dd, J = 8.5, 2.5 Hz, 1H), 6.66 (d, J = 3.0 Hz, 1H), 5.03 (d, J = 16.5 Hz, 1H), 4.48–4.44 (m, 1H), 4.09 (d, J = 16.5 Hz, 1H), 3.79 (s, 3H), 3.28–3.22 (m, 1H), 3.05 (s, 3H), 2.97–2.93 (m, 1H).

[0255] Step D: To a stirred solution of lithium aluminum hydride (1 M solution in THF, 14.7 mL, 14.7 mmol) at 0°C under N_2 was added a solution of the product of Step C (3.8 g, 13.4 mmol) in anhydrous THF (100 mL) dropwise. The reaction mixture was heated to reflux and stirred for 2 hours. The reaction was then

cooled back down to 0°C and quenched slowly with 1 N NaOH (30 mL). After diluting with water, the aqueous phase was extracted with ethyl acetate (3×) and the combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (1:1 ethyl acetate/hexanes) yielded the desired benzazepine (2.93 g, 38% two steps) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (t, J = 7.5 Hz, 2H), 7.27–7.24 (m, 1H), 7.17 (d, J = 7.5 Hz, 2H), 6.75–6.74 (m, 1H), 6.61–6.60 (m, 1H), 6.61–6.53 (br, 1H), 4.27–4.26 (m, 1H), 3.91–3.86 (m, 1H), 3.77 (s, 3H), 3.73–3.70 (m, 1H), 3.16–3.09 (m, 1H), 2.99–2.94 (m, 1H), 2.35 (s, 3H), 2.33–2.28 (m, 1H), 2.13–2.07 (m, 1H); ESI MS *m/z* 268 $[M+H]^+$. This compound was resolved by preparative chiral HPLC (CHIRALCEL OJ column, using 9:1:0.01 heptane/ethanol/triethylamine as the eluent) to give the (+)-enantiomer $[[\alpha]^{25}_D$ +3.66° (*c* 0.41, methanol)] and the (–)-enantiomer $[[\alpha]^{25}_D$ –1.16° (*c* 0.43, methanol)].

[0256] Step E: A mixture of the (+)-enantiomer from Step D (1.19 g, 4.5 mmol) and hydrobromic acid (48% solution in H_2O, 34 mL) was heated to reflux and stirred for 2 hours. The solvent and excess hydrobromic acid were removed under reduced pressure and the resulting solid was partitioned between ethyl acetate and saturated sodium bicarbonate. After separating the two layers, the aqueous phase was extracted with ethyl acetate (3×). The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide the desired phenol (1.10 g, 86%) as a tan solid.: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, J = 7.5 Hz, 2H), 7.28–7.23 (m, 1H), 7.16 (d, J = 7.5 Hz, 2H), 6.54 (s, 1H), 6.48–6.35 (m, 2H), 4.24–4.22 (m, 1H), 3.87–3.77 (m, 1H), 3.66–3.63 (m, 1H), 3.17–3.08 (m, 1H), 2.94–2.89 (m, 1H), 2.42 (s, 3H), 2.35–2.31 (m, 1H), 2.18–2.09 (m, 1H); ESI MS *m/z* 254 $[M+H]^+$.

[0257] Step F: To a stirred mixture of the phenol from Step E (581 mg, 2.3 mmol) and pyridine (0.22 mL, 2.8 mmol) in anhydrous methylene chloride (23 mL) at 0°C under N_2 was added triflic anhydride (0.46 mL, 2.8 mmol). The reaction was stirred at 0°C for 1 hour, at which time TLC analysis indicated the reaction went to completion. The mixture was then diluted with methylene chloride, washed with saturated sodium bicarbonate (aq) and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (1:1 ethyl acetate/hexanes) provided the desired triflate (650 mg, 74%) as a yellow

oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, J = 7.5 Hz, 2H), 7.31–7.28 (m, 1H), 7.17 (d, J = 7.0 Hz, 2H), 7.09–7.08 (m, 1H), 6.97–6.93 (m, 1H), 6.70–6.64 (br, 1H), 4.33–4.31 (m, 1H), 4.03–3.94 (m, 1H), 3.75–3.72 (m, 1H), 3.18–3.13 (m, 1H), 3.03–2.98 (m, 1H), 2.36 (s, 3H), 2.34–2.29 (m, 1H), 2.12–2.06 (m, 1H); ESI MS *m/z* 386 $[M+H]^+$.

[0258] Step G: To a stirred solution of the triflate from Step F (2.60 g, 6.8 mmol) in anhydrous DMF (30 mL) at room temperature was added zinc cyanide (1.58 g, 13.5 mmol). The reaction mixture was degassed with argon for 5 minutes, then 1,1'-bis(diphenylphosphino)-ferrocene (599 mg, 1.1 mmol) and tris(dibenzylideneacetone)dipalladium(0) (247 mg, 0.27 mmol) were added under argon. The reaction was heated to 130°C and stirred for 4 hours, at which time ESI MS indicated the reaction went to completion. After cooling to room temperature, the mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate. The aqueous phase was extracted with additional ethyl acetate (3×), then the combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (2.5%-10% methanol/methylene chloride) yielded the desired nitrile (1.1 g, 60%) as a dark brown oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.46 (m, 1H), 7.40–7.34 (m, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.32–7.29 (m, 1H), 7.15 (d, J = 7.5 Hz, 2H), 6.77–6.67 (br, 1H), 4.37–4.35 (m, 1H), 3.99–3.97 (m, 1H), 3.77–3.74 (m, 1H), 3.19–3.12 (m, 1H), 3.02–2.98 (m, 1H), 2.37 (s, 3H), 2.37–2.29 (m, 1H), 2.16–2.10 (m, 1H); ESI MS *m/z* 263 $[M+H]^+$.

[0259] Step H: To a stirred solution of the nitrile from Step G (154 mg, 0.59 mmol) in anhydrous THF (7 mL) was added lithium aluminum hydride (1 M in THF, 1.8 mL) at 0°C under N_2. The reaction was allowed to warm to room temperature and stirred for approximately 2 days. ESI MS indicated the reaction went to completion, so the mixture was poured slowly over ice water, then extracted with methylene chloride (3×). The combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (9.5:0.45:0.05 methylene chloride/methanol/concentrated ammonium hydroxide) yielded the desired amine (99 mg, 63%) as a light brown oil: $[\alpha]^{23}_D$ +2.22° (c 0.050, methanol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.34 (m, 2H), 7.28–

7.25 (m, 1H), 7.18 (d, J = 7.5 Hz, 2H), 7.14–7.13 (m, 1H), 7.01 (d, J = 7.5 Hz, 1H), 6.65–6.57 (br, 1H), 4.32–4.30 (m, 1H), 3.95–3.89 (m, 1H), 3.81 (s, 2H), 3.75–3.72 (m, 1H), 3.15–3.09 (m, 1H), 2.97–2.92 (m, 1H), 2.36 (s, 3H), 2.36–2.29 (m, 1H), 2.16–2.10 (m, 1H); ESI MS *m/z* 267 $[M+H]^+$.

[0260] Step I: To a stirred solution of the amine from Step H (115 mg, 0.43 mmol) in acetonitrile (30 mL) at room temperature were added di(ethylene glycol)di-*p*-tosylate (179 mg, 0.43 mmol) and sodium carbonate (137 mg, 1.3 mmol). The reaction mixture was heated to reflux and stirred for 15 h, then cooled to room temperature and filtered to remove the precipitate. The filtrate was then diluted with methylene chloride, washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash column chromatography (18.8:1:0.2 methylene chloride/methanol/concentrated ammonium hydroxide) yielded the desired product (16 mg, 11%) as a colorless oil, plus some unreacted starting material (9 mg): $[\alpha]^{23}_{D}$ -8.00° (*c* 0.025, methanol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (t, J = 7.5 Hz, 2H), 7.27–7.25 (m, 1H), 7.18–7.17 (m, 2H), 7.14–7.13 (m, 1H), 7.01 (d, J = 7.5 Hz, 1H), 6.61–6.54 (br, 1H), 4.31–4.29 (m, 1H), 3.93–3.86 (m, 1H), 3.70–3.68 (m, 5H), 3.43–3.42 (m, 2H), 3.14–3.09 (m, 1H), 2.96–2.91 (m, 1H), 2.44–2.41 (m, 4H), 2.36 (s, 3H), 2.36–2.29 (m, 1H), 2.14–2.09 (m, 1H); ESI MS *m/z* 337 $[M+H]^+$.

[0261] Step J: To a stirred solution of the morpholine product from Step I (20 mg, 0.059 mmol) in methanol (3 mL) at room temperature was added maleic acid (9 mg, 0.059 mmol). The mixture was stirred at room temperature for 1 hour and then the solvent was concentrated to approximately 0.5 mL. After diluting with water (1.5 mL), the mixture was lyophilized for 2 days to provide (+)-4-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)methyl)morpholine, L-tartrate salt (31 mg, 99%, 96.3% AUC HPLC) as an off-white solid: mp 124-127°C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.49 (s, 1H), 7.39 (t, J = 7.5 Hz, 2H), 7.32–7.29 (m, 2H), 7.19 (d, J = 7.0 Hz, 2H), 6.89–6.77 (br, 1H), 4.58–4.57 (m, 2H), 4.40 (s, 2H), 4.33–4.30 (m, 1H), 3.74–3.72 (m, 4H), 3.70 (s, 2H), 3.57–3.51 (m, 2H), 2.88 (s, 3H), 2.65–2.60 (m, 3H), 2.63–2.54 (m, 2H), 2.43–2.37 (m, 1H); ESI MS *m/z* 337 $[M+H]^+$.

Example 23 - Preparation of (+)-5-(4-chlorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine-8-carbonitrile, maleate salt and (-)-5-(4-chlorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine-8-carbonitrile, maleate salt

[0262] Step A: To a stirred solution of methylamine (40% in H_2O) (28.2 mL, 327.6 mmol) in methanol (100 mL) at room temperature was added *m*-anisaldehyde (20.6 mL, 163.8 mmol) as a solution in methanol (50 mL) dropwise over 20 minutes. The reaction was stirred at room temperature under N_2 for 15 h, then cooled to 0°C and sodium borohydride (6.19 g, 163.8 mmol) was added in portions. After warming to room temperature, the reaction was stirred for 3 hours. The mixture was then concentrated under reduced pressure, dissolved in H_2O, and extracted with methylene chloride (3×). The combined methylene chloride extracts were extracted with 1N HCl (3×) and the combined HCl extracts adjusted to pH 10 by addition of 6N NaOH. The aqueous mixture was then extracted with methylene chloride (3×) and the combined methylene chloride extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the desired amine (25.0 g, quantitative yield) as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.22 (m, 1H), 6.91–6.89 (m, 1H), 6.89 (s, 1 H), 6.82–6.79 (m, 1H), 3.81 (s, 3H), 3.74 (s, 2H), 2.46 (s, 3H).

[0263] Step B: A solution of 4-chlorocinnamic acid (2.0 g, 10.9 mmol) and *N*-methylmorpholine (1.7 mL, 15.3 mmol) in anhydrous methylene chloride (80 mL) was cooled to –20°C and isobutyl chloroformate (1.5 mL, 11.6 mmol) was added dropwise. After 15 minutes, a solution of the amine from Step A above (1.66 g, 10.9 mmol) in anhydrous methylene chloride (20 mL) was added dropwise, then the reaction was allowed to warm to room temperature and stir under N_2 for 3 hours. The mixture was washed with 1M sodium dihydrogen phosphate dihydrate (2×), H_2O (2×), and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (1:1 ethyl acetate/hexanes) yielded the desired amide (2.82 g, 82%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (dd, J = 15.3, 4.8 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.40–7.26 (m, 1H), 6.91 (d, J = 15.3 Hz, 1H), 6.83 (s, 1H), 6.83 (d, J = 12.3 Hz, 1H), 6.77 (d, J = 15.3 Hz, 1H), 4.67 (d, J = 12.3 Hz, 2H), 3.80 (s, 3H), 3.08 (d, J = 4.2 Hz, 3H); ESI MS *m/z* 316 $[M+H]^+$.

[0264] Step C: An excess of polyphosphoric acid (2 g) in 1,2-dichloroethane (10 mL) was heated to 100°C. A solution of the amide from Step B above (527 mg, 1.7 mmol) in 1,2-dichloroethane (5 mL) was added dropwise and the reaction was stirred at 100°C for 15 hours under N_2. After cooling to room temperature, the reaction was mixed with ice and the pH adjusted to 10 using 6N NaOH. The reaction mixture was then extracted with ethyl acetate (3×) and the combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Partial purification via flash column chromatography (30–100% ethyl acetate/hexanes) yielded the desired product (199 mg) as a yellow foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, J = 8.5 Hz, 2H), 7.00 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.5 Hz, 1H) 6.72 (dd, J = 8.5, 2.5 Hz, 1H), 6.67 (d, J = 3.0 Hz, 1H), 4.91 (d, J = 16.5 Hz, 1H), 4.44 (dd, J = 10.5, 5.0 Hz, 1H), 4.19 (d, J = 16.5 Hz, 1H), 3.79 (s, 3H), 3.16 (dd, J = 13.5, 11.0 Hz, 1H), 3.05 (s, 3H), 2.98 (dd, J = 13.5, 5.0 Hz, 1H).

[0265] Step D: To a stirred solution of lithium aluminum hydride (1M solution in THF, 0.48 mL, 0.48 mmol) at 0°C under N_2 was added a solution of the product of Step C above (139 mg, 0.44 mmol) in anhydrous THF (4 mL) dropwise. The reaction mixture was heated to reflux and allowed to stir for 2 hours. The reaction was then cooled back down to 0°C and quenched slowly with 1N NaOH (1 mL). After diluting with H_2O, the aqueous phase was extracted with ethyl acetate (3×) and the combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (1:1 ethyl acetate/hexanes) yielded the desired benzazepine (67 mg, 19% two steps) as a light yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 8.5 Hz, 2H), 6.74 (d, J = 3.0 Hz, 1H), 6.61 (dd, J = 8.5, 2.5 Hz, 1H), 6.55 (br, 1H), 4.24–4.22 (m, 1H), 3.86–3.84 (m, 1H), 3.77 (s, 3H), 3.68–3.65 (m, 1H), 3.10–3.07 (m, 1H), 2.96–2.91 (m, 1H), 2.34 (s, 3H), 2.30–2.23 (m, 1H), 2.10–2.03 (m, 1H); ESI MS *m/z* 302 $[M+H]^+$. This compound was resolved by preparative chiral HPLC (CHIRALPAK AD column, using 9:1:0.01 heptane/ethanol/diethylamine as the eluent) to give the (+)-enantiomer [$[\alpha]^{25}_D$ +5.0° (*c* 0.1, methanol)] and the (–)-enantiomer [$[\alpha]^{25}_D$ –20.0° (*c* 0.1, methanol)].

[0266] Step E: A mixture of the benzazepine from Step D above (1.40 g, 4.6 mmol) and hydrobromic acid (48% solution in water, 30 mL) was heated to reflux

and stirred for 2 hours. The solvent and excess hydrobromic acid were removed under reduced pressure and the resulting solid was partitioned between ethyl acetate and saturated sodium bicarbonate (aq). After separating the two layers, the aqueous phase was extracted with ethyl acetate (3×). The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide the desired phenol (1.09 g, 82%) as a tan solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.5 Hz, 2H), 6.57–6.56 (m, 1H), 6.48–6.47 (m, 1H), 6.48–6.39 (m, 1H), 4.20 (d, J = 8.5 Hz, 1H), 3.84–3.74 (m, 1H), 3.64–3.61 (m, 1H), 3.12–3.05 (m, 1H), 2.93–2.88 (m, 1H), 2.41 (s, 3H), 2.34–2.26 (m, 1H), 2.14–2.06 (m, 1H); ESI MS *m/z* 288 $[M+H]^+$.

[0267] Step F: To a stirred mixture of the phenol from Step E above (552 mg, 1.9 mmol) and pyridine (0.2 mL, 2.3 mmol) in anhydrous methylene chloride (19 mL) at 0°C under N_2 was added triflic anhydride (0.4 mL, 2.3 mmol). The reaction was stirred at 0°C for 1 hour, at which time TLC analysis indicated the reaction went to completion. The mixture was then diluted with methylene chloride, washed with saturated sodium bicarbonate (aq) and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (1:1 ethyl acetate/hexanes) provided the desired triflate (457 mg, 57%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 10.0 Hz, 2H), 7.09 (s, 1H), 6.97 (dd, J = 8.5, 2.5 Hz, 1H), 6.70–6.63 (m, 1H), 4.30 (d, J = 9.5 Hz, 1H), 3.96 (d, J = 14.0 Hz, 1H), 3.72 (d, J = 14.5 Hz, 1H), 3.14–3.11 (m, 1H), 2.99 (ddd, J = 13.3, 10.0, 3.0 Hz, 1H), 2.35 (s, 3H), 2.28 (m, 1H), 2.09–2.03 (m, 1H); ESI MS *m/z* 420 $[M+H]^+$.

[0268] Step G: To a mixture of the triflate (0.55 g, 1.31 mmol) from step F, zinc cyanide (0.31 g, 2.62 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (87 mg, 0.16 mmol) was added DMF (8.7 mL). The solution was purged with argon for 7 minutes, and tris(dibenzylideneacetone)dipalladium (0) (36 mg, 0.04 mmol) was added to it. The reaction mixture was heated at 130°C for 2 hours, then cooled to room temperature, and partitioned between saturated sodium bicarbonate and ethyl acetate. The aqueous layer was separated and washed with ethyl acetate (3×). The combined organic extract was dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography (ethyl acetate, then 99:1 to 95:5 ethyl acetate/methanol) gave the nitrile (0.15 g, 38%): ^{1}H NMR

(500 MHz, $CDCl_3$) δ 7.47 (d, J = 1.4 Hz, 1H), 7.39–7.35 (m, 3H), 7.09–7.05 (m, 2H), 6.73 (br, 1H), 4.33 (d, J = 9.1 Hz, 1H), 4.00–3.94 (m, 1H), 3.74 (d, J = 14.1 Hz, 1H), 3.20-3.05 (m, 1H), 3.00–2.90 (m, 1H), 2.36 (s, 3H), 2.55–2.36 (m, 1H), 2.15–2.05 (m, 1H).

[0269] Step H: The free base of the benzazepine from step G (0.15 g) was resolved by preparative chiral HPLC (CHIRALCEL OD column, using 97:3:0.1 heptanes/isopropanol/diethylamine as the eluent) to give the (-)-enantiomer [$[\alpha]^{25}_D$ -7.11° (c 0.23, methanol)] and the (+)-enantiomer [$[\alpha]^{25}_D$ +5.95° (c 0.22, methanol)]. Both enantiomers were washed with water to remove residual diethylamine. To a solution of the (-)-enantiomer (54 mg, 0.18 mmol) in methanol (10 mL) was added maleic acid (21 mg, 0.18 mmol). The solution was concentrated to dryness and the residue was re-dissolved in methanol (1 mL) and water (5 mL). The resultant solution was lyophilized overnight to give (-)-5-(4-chlorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine-8-carbonitrile, maleate salt (74 mg, 97%, AUC HPLC >99%) as an off-white solid: ^{1}H NMR (500 MHz, CD_3OD) δ 7.86 (d, J = 1.6 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.44 (d, J = 6.3 Hz, 2H), 7.24–7.19 (m, 2H), 6.92 (br, 1H), 6.25 (s, 2H), 4.83–4.41 (m, 2H), 4.40 (d, J = 12.8 Hz, 1H), 3.68–3.47 (m, 2H), 2.94 (s, 3H), 2.63–2.47 (m, 1H), 2.43–2.38 (m, 1H); ESI MS m/z 297 $[M+H]^+$.

[0270] To a solution of the (+)-enantiomer (53 mg, 0.18 mmol) in methanol (10 mL) was added maleic acid (21 mg, 0.18 mmol). The solution was concentrated to dryness, and the residue was re-dissolved in methanol (1 mL) and water (5 mL). The resultant solution was lyophilized overnight to give (+)-5-(4-chlorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine-8-carbonitrile, maleate salt (71 mg, 97%, AUC HPLC 98.9%) as an off-white solid: ^{1}H NMR (500 MHz, CD_3OD) δ 7.86 (d, J = 1.6 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.44 (d, J = 6.3 Hz, 2H), 7.24–7.19 (m, 2H), 6.92 (br, 1H), 6.25 (s, 2H), 4.83–4.41 (m, 2H), 4.40 (d, J = 12.8 Hz, 1H), 3.68–3.47 (m, 2H), 2.94 (s, 3H), 2.63–2.47 (m, 1H), 2.43–2.38 (m, 1H); ESI MS m/z 297 $[M+H]^+$.

Example 24 – Preparation of (+)-2-methyl-8-(6-methyl-pyridazin-3-yl)-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt

[0271] Step A: A solution of *trans*-cinnamic acid (5.0 g, 33.8 mmol) and *N*-methylmorpholine (5.2 mL, 47.3 mmol) in anhydrous methylene chloride (120 mL) was cooled to –20°C. Isobutyl chloroformate (4.8 mL, 35.8 mmol) was added dropwise. After 15 minutes, a solution of (3-methoxybenzyl)methylamine (5.1 g, 33.8 mmol) in anhydrous methylene chloride (30 mL) was added dropwise. The reaction was allowed to warm to room temperature and stir under N_2 for 3 hours. The reaction mixture was then washed with 1 M $NaH_2PO_4 \cdot 2H_2O$ (2×), H_2O (2×), and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (1:1 ethyl acetate/hexanes) yielded the desired amide (8.3 g, 87%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, J = 15.5, 7.5 Hz, 1H), 7.55 (d, J = 6.5 Hz, 1H), 7.47–7.46 (m, 1H), 7.36 (dd, J = 14.5, 7.5 Hz, 2H), 7.39–7.33 (m, 1H), 7.31–7.24 (m, 1H), 6.95–6.76 (m, 4H), 4.70-4.66 (m, 2H), 3.80 (s, 3H), 3.09-3.07 (m, 3H); ESI MS m/z = 282 $[C_{18}H_{19}NO_2 + H]^+$.

[0272] Step B: An excess of polyphosphoric acid (11 g) in 1,2-dichloroethane (10 mL) was heated to 100°C. A solution of the product from Step A (3.8 g, 13.5 mmol) in 1,2-dichloroethane (15 mL) was added dropwise. The reaction was then allowed to stir at 100°C overnight under N_2. After cooling to room temperature, the reaction was mixed with ice and the pH was adjusted to 9 using concentrated NH_4OH. The reaction mixture was then extracted with ethyl acetate (3×) and the combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Partial purification via flash column chromatography (30–100% ethyl acetate/hexanes) yielded the desired product (1.77 g) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (dd, J = 7.5, 2.0 Hz, 1H), 7.37–7.35 (m, 1H), 7.29–7.28 (m, 1H), 7.09–7.06 (m, 2H), 6.87 (d, J = 9.0 Hz, 1H), 6.71 (dd, J = 8.5, 2.5 Hz, 1H), 6.66 (d, J = 3.0 Hz, 1H), 5.03 (d, J = 16.5 Hz, 1H), 4.46 (dd, J = 11.0, 5.0 Hz, 1H), 4.09 (d, J = 16.5 Hz, 1H), 3.79 (s, 3H), 3.25 (dd, J = 14.0, 12.0 Hz, 1H), 3.05 (s, 3H), 2.97–2.93 (m, 1H).

[0273] Step C: To a stirred solution of lithium aluminum hydride (1 M solution in THF, 14.7 mL, 14.7 mmol) at 0°C under N_2 was added a solution of the product of Step B (3.8 g, 13.4 mmol) in anhydrous THF (100 mL) dropwise. The reaction mixture was heated to reflux and allowed to stir for 2 hours. The reaction

was then cooled back down to 0°C and quenched slowly with 1 N NaOH (30 mL). After diluting with H_2O, the aqueous phase was extracted with ethyl acetate (3×) and the combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (1:1 ethyl acetate/hexanes) yielded the desired benzazepine (2.93 g, 38% over two steps) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.33 (m, 2H), 7.29–7.23 (m, 1H), 7.17 (d, J = 7.0 Hz, 2H), 6.74 (d, J = 2.5 Hz, 1H), 6.60 (dd, J = 8.0, 2.5 Hz, 1H), 6.59–6.52 (br, 1H), 4.26 (d, J = 9.0 Hz, 1H), 3.91–3.86 (m, 1H), 3.77 (s, 3H), 3.72 (d, J = 10.0 Hz, 1H), 3.13–3.09 (m, 1H), 2.95 (ddd, J = 12.8, 10.0, 2.5 Hz, 1H), 2.35 (s, 3H), 2.33–2.28 (m, 1H), 2.12–2.06 (m, 1H); ESI MS m/z = 268 $[C_{18}H_{21}NO + H]^+$. This compound was resolved by preparative chiral HPLC (CHIRALCEL OJ column, using 9:1:0.01 heptane/ethanol/triethylamine as the eluent) to give the (+)-enantiomer $[[\alpha]^{25}_D$ +3.66° (c 0.41, methanol)] and the (–)-enantiomer $[[\alpha]^{25}_D$ –1.16° (c 0.43, methanol)].

[0274] Step D: A mixture of the (+)-enantiomer of Step C (1.19 g, 4.5 mmol) and HBr (48% solution in H_2O, 34 mL) was heated to reflux and allowed to stir for 2 hours. The solvent and excess HBr were removed under reduced pressure and the resulting solid was partitioned between ethyl acetate and saturated $NaHCO_3$ (aq). After separating the two layers, the aqueous phase was extracted with ethyl acetate (3×). The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide the desired phenol (1.10 g, 86%) as a tan solid.: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.33 (m, 2H), 7.28–7.23 (m, 1H), 7.16 (d, J = 7.5 Hz, 2H), 6.54 (s, 1H), 6.48–6.35 (m, 2H), 4.23 (d, J = 9.0 Hz, 1H), 3.87–3.77 (m, 1H), 3.64 (d, J = 13.5 Hz, 1H), 3.17–3.08 (m, 1H), 2.91 (ddd, J = 12.8, 10.0, 2.5 Hz, 1H), 2.42 (s, 3H), 2.35–2.31 (m, 1H), 2.18–2.09 (m, 1H); ESI MS m/z = 254 $[C_{17}H_{19}NO + H]^+$.

[0275] Step E: To a stirred mixture of the product of Step D (581 mg, 2.3 mmol) and pyridine (0.22 mL, 2.8 mmol) in anhydrous CH_2Cl_2 (23 mL) at 0°C under N_2 was added triflic anhydride (0.46 mL, 2.8 mmol). Stirring was continued at 0°C for one hour at which time TLC analysis indicated that the reaction had gone to completion. The mixture was then diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ (aq) and brine, dried over sodium sulfate, filtered, and concentrated *in*

vacuo. Purification via flash column chromatography (1:1 ethyl acetate/hexanes) provided the desired triflate (650 mg, 74%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.37 (m, 2H), 7.31-7.28 (m, 1H), 7.17 (d, J = 7.0 Hz, 2H), 7.09 (d, J = 2.5 Hz, 1H), 6.97–6.93 (m, 1H), 6.70–6.64 (br, 1H), 4.32 (d, J = 9.5 Hz, 1H), 4.03–3.94 (m, 1H), 3.73 (d, J = 14.0 Hz, 1H), 3.18–3.13 (m, 1H), 3.03–3.27 (m, 1H), 2.36 (s, 3H), 2.34–2.29 (m, 1H), 2.12–2.06 (m, 1H); ESI MS m/z = 386 $[C_{18}H_{18}F_3NO_3S + H]^+$.

[0276] Step F: To a disposable sealed tube were added bis(pinacolato)diboron (471 mg, 1.7 mmol), potassium acetate (498 mg, 5.1 mmol), and the product of Step E (650 mg, 1.7 mmol) as a solution in anhydrous DMSO (8 mL). The reaction mixture was degassed by a subsurface purge with Ar for one minute. $PdCl_2(dppf)\bullet CH_2Cl_2$ (41 mg, 0.051 mmol) was then added under Ar. The reaction was heated to 80°C and allowed to stir for 3 hours, at which time ESI MS showed that the reaction had gone to completion. After cooling to room temperature, the reaction mixture was diluted with H_2O, then extracted with ethyl acetate (3×). The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide the desired boronate ester (crude) as a dark brown oil, which was taken on to the next step without further purification: ESI MS m/z = 364 $[C_{23}H_{30}BNO_2 + H]^+$.

[0277] Step G: To a disposable sealed tube were added the product of Step F (200 mg, 0.55 mmol, theoretical) as a solution in anhydrous DMF (4.5 mL), sodium carbonate (175 mg, 1.7 mmol) as a solution in H_2O (1 mL), and 3-chloro-6-methylpyridazine (85 mg, 0.66 mmol). The reaction mixture was degassed by a subsurface purge with Ar for one minute. $PdCl_2(dppf)\bullet CH_2Cl_2$ (27 mg, 0.033 mmol) was then added under Ar. The reaction was heated to 100°C and allowed to stir overnight. TLC analysis showed that the reaction went to completion. After cooling to room temperature, the reaction mixture was diluted with H_2O, then extracted with ethyl acetate (3×). The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (95:5 CH_2Cl_2/MeOH) yielded the desired pyridazine (74 mg, 41% over two steps) as a brown oil: $[\alpha]^{25}_D$ -2.0° (c 0.05, methanol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 2.0 Hz, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.72 (d, J = 9.0 Hz, 1H), 7.40–7.33 (m, 3H), 7.30-7.27 (m, 1H), 7.21 (d, J = 7.5 Hz, 2H), 6.85–6.78 (br, 1H), 4.40 (d, J = 8.5 Hz, 1H), 4.06–4.04 (m, 1H), 3.89 (d, J = 14.5 Hz, 1H), 3.20–3.16 (m, 1H), 3.03 (ddd, J =

12.5, 9.8, 2.5 Hz, 1H), 2.75 (s, 3H), 2.41 (s, 3H), 2.40–2.35 (m, 1H), 2.21–2.15 (m, 1H); ESI MS *m/z* = 330 $[C_{22}H_{23}N_3 + H]^+$.

[0278] Step H: The product of Step G (70 mg, 0.21 mmol) was converted to its hydrochloride salt by dissolving the oil in a minimum amount of ether, adding one equivalent of HCl (1 M solution in ether), and sonicating the solution for a few minutes until salt precipitation occurred. Filtration yielded (+)-2-methyl-8-(6-methyl-pyridazin-3-yl)-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt (69 mg, 89%, >99% AUC HPLC) as a light brown solid: mp 168–170°C; ESI MS *m/z* = 330 $[C_{22}H_{23}N_3 + H]^+$.

<u>Example 25</u> – Preparation of (+)-2-methyl-5-phenyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt

[0279] Pursuant to the general method described above in Example 24, the following product was prepared: (+)-2-methyl-5-phenyl-8-(pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt: mp 154–156°C; ESI MS *m/z* = 316 $[C_{21}H_{21}N_3 + H]^+$.

<u>Example 26</u> – Preparation of (+)-dimethyl-[6-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine-8-yl)-pyridazin-3-yl]-amine, maleate salt

[0280] Pursuant to the general method described above in Example 24, the following product was prepared: (+)-dimethyl-[6-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine-8-yl)-pyridazin-3-yl]-amine, maleate salt: mp 99–102°C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.08 (d, *J* = 1.5 Hz, 1H), 7.93 (d, *J* = 10.0 Hz, 1H), 7.88–7.83 (m, 1H), 7.44-7.41 (m, 2H), 7.35–7.31 (m, 2H), 7.25 (d, *J* = 6.0 Hz, 2H), 7.08–6.85 (br, 1H), 6.25 (s, 2H), 4.80–4.70 (br, 1H), 4.67 (d, *J* = 10.5 Hz, 1H), 4.50–4.42 (m, 1H), 3.70–3.60 (m, 2H), 3.25 (s, 6H), 3.01–2.94 (br, 3H), 2.70–2.50 (m, 1H), 2.49–2.46 (m, 1H); ESI MS *m/z* = 359 $[C_{23}H_{26}N_4 + H]^+$.

<u>Example 27</u> – Preparation of (+)-2-methyl-5-phenyl-8-(pyrimidin-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt

[0281] Pursuant to the general method described above in Example 24, the following product was prepared: (+)-2-methyl-5-phenyl-8-(pyrimidin-2-yl)-2,3,4,5-

tetrahydro-1*H*-benzo[*c*]azepine, maleate salt: mp 76-78°C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.85 (d, *J* = 4.5 Hz, 2H), 8.53 (s, 1H), 8.40–8.30 (br, 1H), 7.45–7.42 (m, 2H), 7.39 (t, *J* = 5.0 Hz, 1H), 7.36–7.33 (m, 1H), 7.28–7.21 (br, 2H), 7.04–6.71 (br, 1H), 6.26 (s, 2H), 4.70–4.68 (m, 2H), 4.59–4.38 (br, 1H), 3.77–3.62 (m, 2H), 3.11–2.84 (m, 3H), 2.54–2.41 (m, 2H); ESI MS *m/z* 316 $[M+H]^+$.

Example 28 – Preparation of (+)-2-methyl-5-phenyl-8-(pyrimidin-5-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt

[0282] Pursuant to the general method described above in Example 24, the following product was prepared: (+)-2-methyl-5-phenyl-8-(pyrimidin-5-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt: mp 93-96°C; ^{1}H NMR (500 MHz, CD_3OD) δ 9.16 (s, 1H), 9.10 (s, 2H), 7.86 (m, 1H), 7.73–7.71 (m, 1H), 7.45–7.42 (m, 2H), 7.36–7.33 (m, 1H), 7.26–7.24 (m, 2H), 7.14–6.93 (br, 1H), 6.24 (s, 2H), 4.70–4.68 (m, 2H), 4.48–4.46 (m, 1H), 3.71–3.64 (m, 2H), 3.03–2.92 (br, 3H), 2.73–2.55 (m, 1H), 2.51–2.43 (m, 1H); ESI MS *m/z* 316 $[M+H]^+$.

Example 29 – Preparation of (+)-2-methyl-5-phenyl-8-(pyrazin-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt

[0283] Pursuant to the general method described above in Example 24, the following product was prepared: (+)-2-methyl-5-phenyl-8-(pyrazin-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt: mp 67-69°C; ^{1}H NMR (500 MHz, CD_3OD) δ 9.14 (s, 1H), 8.69 (d, *J* = 1.5 Hz, 1H), 8.56 (m, 1H), 8.24 (d, *J* = 1.5 Hz, 1H), 8.09–8.03 (m, 1H), 7.45–7.42 (m, 2H), 7.36–7.33 (m, 1H), 7.30–7.23 (m, 2H), 7.18–6.82 (br, 1H), 6.26 (s, 2H), 4.71–4.69 (m, 2H), 4.55–4.45 (m, 1H), 3.71–3.63 (m, 2H), 3.05–2.92 (m, 3H), 2.78–2.55 (br, 1H), 2.50–2.43 (m, 1H); ESI MS *m/z* 316 $[M+H]^+$.

Example 30 – Preparation of (+)-6-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine, maleate salt and (-)-6-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine, L-tartrate salt

[0284] Pursuant to the general method described above in Example 24, the following products were prepared: (+)-6-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-

benzo[*c*]azepin-8-yl)pyridazin-3-amine, maleate salt: mp 120-122°C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.06 (s, 1H), 7.89 (d, *J* = 9.5 Hz, 1H), 7.84–7.82 (m, 1H), 7.44–7.41 (m, 2H), 7.35–7.32 (m, 1H), 7.25–7.24 (m, 2H), 7.11 (d, *J* = 9.5 Hz, 1H), 7.05–6.91 (br, 1H), 6.24 (s, 2H), 4.82–4.65 (m, 1H), 4.68–4.66 (m, 1H), 4.47–4.44 (m, 1H), 3.69–3.60 (m, 2H), 3.00–2.92 (br, 3H), 2.70–2.53 (br, 1H), 2.48–2.45 (m, 1H); ESI MS *m/z* 331 $[M+H]^+$; (-)-6-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridazin-3-amine, L-tartrate salt: ^{1}H NMR (500 MHz, CD_3OD) δ 8.03–8.02 (m, 1H), 7.83 (d, *J* = 9.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 2H), 7.04 (d, *J* = 9.0 Hz, 1H), 6.99–6.92 (br, 1H), 4.71–4.64 (m, 1H), 4.64 (d, *J* = 7.5 Hz, 1H), 4.42–4.40 (m, 1H), 4.40 (s, 2H), 3.61–3.58 (m, 2H), 2.89 (s, 3H), 2.65–2.58 (m, 1H), 2.46–2.42 (m, 1H); ESI MS *m/z* 331 $[M+H]^+$.

Example 31 - Preparation of (+)-2-methyl-5-phenyl-8-(pyridin-4-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt

[0285] Pursuant to the general method described above in Example 24, the following product was prepared: (+)-2-methyl-5-phenyl-8-(pyridin-4-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt: mp 91-93°C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.62 (d, *J* = 6.0 Hz, 2H), 7.92–7.91 (m, 1H), 7.77 (d, *J* = 6.0 Hz, 3H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.26–7.25 (m, 2H), 7.16–6.85 (br, 1H), 6.25 (s, 2H), 4.70–4.68 (m, 2H), 4.53–4.43 (m, 1H), 3.72–3.57 (m, 2H), 3.04–2.90 (m, 3H), 2.74–2.52 (br, 1H), 2.51–2.44 (m, 1H); ESI MS *m/z* 315 $[M+H]^+$.

Example 32 - Preparation of (+)-6-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridine-2-amine, maleate salt

[0286] Pursuant to the general method described above in Example 24, the following product was prepared: (+)-6-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyridine-2-amine, maleate salt: mp 112-114°C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.98–7.97 (m, 1H), 7.80 (d, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 7.0 Hz, 2H), 7.06 (d, *J* = 7.0 Hz, 1H), 7.00–6.89 (br, 1H), 6.60 (d, *J* = 8.5 Hz, 1H), 6.24 (s, 2H), 4.76–4.67 (m, 1H), 4.65 (d, *J* = 8.5 Hz, 1H), 4.44–4.41 (m, 1H), 3.66–3.62 (m,

2H), 2.95 (br s, 3H), 2.69–2.57 (m, 1H), 2.47–2.43 (m, 1H); ESI MS *m/z* 330 $[M+H]^+$.

Example 33 - Preparation of (+)-5-methyl-3-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)-1,2,4-oxadiazole, L-tartrate salt

[0287] Step A: To a stirred solution of methylamine (40% in H_2O) (28.2 mL, 327.6 mmol) in methanol (100 mL) at room temperature was added *m*-anisaldehyde (20.6 mL, 163.8 mmol) as a solution in methanol (50 mL) dropwise over 20 minutes. The reaction was stirred at room temperature under N_2 for 15 hours, then cooled to 0°C and sodium borohydride (6.19 g, 163.8 mmol) was added in portions. After warming to room temperature, the reaction was stirred for 3 hours. The mixture was then concentrated under reduced pressure, dissolved in water, and extracted with methylene chloride (3×). The combined methylene chloride extracts were extracted with 1N HCl (3×) and the combined HCl extracts adjusted to pH 10 by addition of 6N NaOH. The aqueous mixture was then extracted with methylene chloride (3×). The combined methylene chloride extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the desired amine (25.0 g, quantitative yield) as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.22 (m, 1H), 6.91–6.89 (m, 1H), 6.89 (s, 1 H), 6.82–6.79 (m, 1H), 3.81 (s, 3H), 3.74 (s, 2H), 2.46 (s, 3H).

[0288] Step B: A solution of *trans*-cinnamic acid (5.0 g, 33.8 mmol) and *N*-methylmorpholine (5.2 mL, 47.3 mmol) in anhydrous methylene chloride (120 mL) was cooled to –20°C, and then isobutyl chloroformate (4.8 mL, 35.8 mmol) was added dropwise. After 15 minutes, a solution of the amine from Step A above (5.1 g, 33.8 mmol) in anhydrous methylene chloride (30 mL) was added dropwise, then the reaction was allowed to warm to room temperature and stir under N_2 for 3 hours. The mixture was washed with 1M sodium dihydrogen phosphate dihydrate (2×), H_2O (2×), and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1:1 ethyl acetate/hexanes) yielded the desired amide (8.3 g, 87%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, J = 15.5, 7.5 Hz, 1H), 7.56–7.54 (m, 1H), 7.47–7.46 (m, 1H), 7.36 (dd, J = 14.5, 7.5 Hz, 2H), 7.39–7.33 (m, 1H), 7.31–7.24 (m, 1H), 6.95–6.76 (m, 4H), 4.70–4.66 (m, 2H), 3.80 (s, 3H), 3.09–3.07 (m, 3H); ESI MS *m/z* 282 $[M+H]^+$.

[0289] Step C: An excess of polyphosphoric acid (11 g) in 1,2-dichloroethane (10 mL) was heated to 100°C. A solution of the amide from Step B above (3.8 g, 13.5 mmol) in 1,2-dichloroethane (15 mL) was added dropwise and the reaction was stirred at 100°C for 15 hours under N_2. After cooling to room temperature, the reaction was mixed with ice and the pH adjusted to 9 using concentrated ammonium hydroxide. The reaction mixture was then extracted with ethyl acetate (3×) and the combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Partial purification by flash column chromatography (30–100% ethyl acetate/hexanes) yielded the desired product (1.77 g) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.49 (m, 1H), 7.37–7.35 (m, 1H), 7.29–7.28 (m, 1H), 7.09–7.06 (m, 2H), 6.87 (d, J = 9.0 Hz, 1H) 6.71 (dd, J = 8.5, 2.5 Hz, 1H), 6.66 (d, J = 3.0 Hz, 1H), 5.03 (d, J = 16.5 Hz, 1H), 4.48–4.44 (m, 1H), 4.09 (d, J = 16.5 Hz, 1H), 3.79 (s, 3H), 3.28–3.22 (m, 1H), 3.05 (s, 3H), 2.97–2.93 (m, 1H).

[0290] Step D: To a stirred solution of lithium aluminum hydride (1M solution in THF, 14.7 mL, 14.7 mmol) at 0°C under N_2 was added a solution of the product of Step C above (3.8 g, 13.4 mmol) in anhydrous THF (100 mL) dropwise. The reaction mixture was heated to reflux and stirred for 2 hours. The reaction was then cooled back down to 0°C and quenched slowly with 1N NaOH (30 mL). After diluting with water, the aqueous phase was extracted with ethyl acetate (3×) and the combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1:1 ethyl acetate/hexanes) yielded the desired benzazepine (2.93 g, 38% two steps) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (t, J = 7.5 Hz, 2H), 7.27–7.24 (m, 1H), 7.17 (d, J = 7.5 Hz, 2H), 6.75–6.74 (m, 1H), 6.61–6.60 (m, 1H), 6.61–6.53 (br, 1H), 4.27–4.26 (m, 1H), 3.91–3.86 (m, 1H), 3.77 (s, 3H), 3.73–3.70 (m, 1H), 3.16–3.09 (m, 1H), 2.99–2.94 (m, 1H), 2.35 (s, 3H), 2.33–2.28 (m, 1H), 2.13–2.07 (m, 1H); ESI MS *m/z* 268 $[M+H]^+$. This compound was resolved by preparative chiral HPLC (CHIRALCEL OJ column, using 9:1:0.01 heptane/ethanol/diethylamine as the eluent) to give the (+)-enantiomer [$[\alpha]^{25}_D$ +3.66° (*c* 0.41, methanol)] and the (–)-enantiomer [$[\alpha]^{25}_D$ –1.16° (*c* 0.43, methanol)].

[0291] Step E: A mixture of the (+)-enantiomer from Step D above (1.19 g, 4.5 mmol) and hydrobromic acid (48% solution in water, 34 mL) was heated to

reflux and stirred for 2 hours. The solvent and excess hydrobromic acid were removed under reduced pressure and the resulting solid was partitioned between ethyl acetate and saturated sodium bicarbonate (aq). After separating the two layers, the aqueous phase was extracted with ethyl acetate (3×). The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide the desired phenol (1.10 g, 86%) as a tan solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, J = 7.5 Hz, 2H), 7.28–7.23 (m, 1H), 7.16 (d, J = 7.5 Hz, 2H), 6.54 (s, 1H), 6.48–6.35 (m, 2H), 4.24–4.22 (m, 1H), 3.87–3.77 (m, 1H), 3.66–3.63 (m, 1H), 3.17–3.08 (m, 1H), 2.94–2.89 (m, 1H), 2.42 (s, 3H), 2.35–2.31 (m, 1H), 2.18–2.09 (m, 1H); ESI MS *m/z* 254 $[M+H]^+$.

[0292] Step F: To a stirred mixture of the phenol from Step E above (581 mg, 2.3 mmol) and pyridine (0.22 mL, 2.8 mmol) in anhydrous methylene chloride (23 mL) at 0°C under N_2 was added triflic anhydride (0.46 mL, 2.8 mmol). The reaction was stirred at 0°C for 1 hour, at which time TLC analysis indicated the reaction went to completion. The mixture was then diluted with methylene chloride, washed with saturated sodium bicarbonate (aq) and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1:1 ethyl acetate/hexanes) provided the desired triflate (650 mg, 74%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, J = 7.5 Hz, 2H), 7.31–7.28 (m, 1H), 7.17 (d, J = 7.0 Hz, 2H), 7.09–7.08 (m, 1H), 6.97–6.93 (m, 1H), 6.70–6.64 (br, 1H), 4.33–4.31 (m, 1H), 4.03–3.94 (m, 1H), 3.75–3.72 (m, 1H), 3.18–3.13 (m, 1H), 3.03–2.98 (m, 1H), 2.36 (s, 3H), 2.34–2.29 (m, 1H), 2.12–2.06 (m, 1H); ESI MS *m/z* 386 $[M+H]^+$.

[0293] Step G: To a stirred solution of the triflate from Step F above (2.60 g, 6.8 mmol) in DMF (30 mL) at room temperature was added zinc cyanide (1.58 g, 13.5 mmol). The reaction mixture was degassed with argon for 2 minutes, then tris(dibenzylideneacetone)-dipalladium(0) (247 mg, 0.27 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (599 mg, 1.1 mmol) were added under argon. The reaction was heated to 130°C and stirred for 4 hours. After cooling to room temperature, the mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate. The aqueous phase was extracted with additional ethyl acetate (3×), and then the combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column

chromatography (2.5%-10% methanol/methylene chloride) yielded the desired nitrile (1.07 g, 60%) as a dark brown oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.46 (m, 1H), 7.40–7.34 (m, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.32–7.29 (m, 1H), 7.15 (d, J = 7.5 Hz, 2H), 6.77–6.67 (br, 1H), 4.37–4.35 (m, 1H), 3.99–3.97 (m, 1H), 3.77–3.74 (m, 1H), 3.19–3.12 (m, 1H), 3.02–2.98 (m, 1H), 2.37 (s, 3H), 2.37–2.29 (m, 1H), 2.16–2.10 (m, 1H); ESI MS *m/z* 263 $[M+H]^+$.

[0294] Step H: To a stirred solution of hydroxylamine hydrochloride (467 mg, 6.7 mmol) in water (8.5 mL) was added sodium carbonate (712 mg, 6.7 mmol) and the nitrile from Step G above (235 mg, 0.90 mmol). The reaction was stirred at reflux for 16 hours, at which time ESI MS indicated the reaction went to completion. After cooling to room temperature, the reaction mixture was partitioned between methylene chloride and water. After separating the layers, the aqueous phase was extracted with additional methylene chloride (2×) and the combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide the desired amidoxime (231 mg, 87%) as a brown solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.47 (m, 1H), 7.36 (t, J = 7.5 Hz, 2H), 7.31–7.26 (m, 2H), 7.17 (d, J = 7.5 Hz, 2H), 6.74–6.66 (m, 1H), 4.79 (br, 2H), 4.35–4.33 (m, 1H), 3.97–3.93 (m, 1H), 3.80–3.77 (m, 1H), 3.15–3.11 (m, 1H), 3.00–2.95 (m, 1H), 2.36–2.30 (m, 1H), 2.35 (s, 3H), 2.15–2.11 (m, 1H); ESI MS *m/z* 296 $[M+H]^+$.

[0295] Step I: The amidoxime from Step H above (230 mg, 0.78 mmol) and *N*, -dimethylacetamide dimethylacetal (1.4 mL, 9.4 mmol) were heated at reflux for 4 hours, at which time ESI MS indicated the reaction went to completion. The reaction mixture was concentrated *in vacuo* and then purified by flash column chromatography (3×) using 9:0.9:0.1 methylene chloride/methanol/concentrated ammonium hydroxide as eluent) and then by preparative HPLC to provide the desired oxadiazole (27 mg, 11%) as a colorless oil: $[\alpha]^{23}_D$ -7.50° (*c* 0.040, methanol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89–7.88 (m, 1H), 7.78–7.76 (m, 1H), 7.37 (t, J = 7.5 Hz, 2H), 7.29 (d, J = 7.5 Hz, 1H), 7.19 (d, J = 7.0 Hz, 2H), 6.81–6.74 (br, 1H), 4.39–4.37 (m, 1H), 4.00 (d, J = 14.0 Hz, 1H), 3.83 (d, J = 14.0 Hz, 1H), 3.18–3.13 (m, 1H), 3.02–2.97 (m, 1H), 2.64 (s, 3H), 2.39–2.32 (m, 1H), 2.36 (s, 3H), 2.17–2.11 (m, 1H); ESI MS *m/z* 320 $[M+H]^+$.

[0296] Step J: To a stirred solution of the oxadiazole from Step I above (25 mg, 0.078 mmol) in methanol (2 mL) at room temperature was added L-tartaric acid (12 mg, 0.078 mmol). The mixture was stirred at room temperature for 1 hour and then the solvent was concentrated to approximately 0.5 mL. After diluting with H_2O (1.5 mL), the mixture was lyophilized for 15 hours to provide (+)-5-methyl-3-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)-1,2,4-oxadiazole, L-tartrate salt (37 mg, 99%, 97.8% AUC HPLC) as an off-white solid: mp 102–104°C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.14–8.13 (m, 1H), 7.97–7.95 (m, 1H), 7.42 (t, J = 7.5 Hz, 2H), 7.33 (t, J = 7.5 Hz, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.03–6.94 (br, 1H), 4.66 (d, J = 7.5 Hz, 2H), 4.43 (s, 2H), 4.43–4.37 (m, 1H), 3.60–3.56 (m, 2H), 2.86 (br s, 3H), 2.65 (s, 3H), 2.65–2.55 (m, 1H), 2.45–2.41 (m, 1H); ESI MS *m/z* 320 $[M+H]^+$.

<u>Example 34</u> - Preparation of (+)-4-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine, maleate salt

[0297] Step A: To a stirred solution of methylamine (40% in H_2O) (28.2 mL, 327.6 mmol) in methanol (100 mL) at room temperature was added *m*-anisaldehyde (20.6 mL, 163.8 mmol) as a solution in methanol (50 mL) dropwise over 20 minutes. The reaction was stirred at room temperature under N_2 for 15 hours, then cooled to 0°C and sodium borohydride (6.19 g, 163.8 mmol) was added in portions. After warming to room temperature, the reaction was stirred for 3 hours. The mixture was then concentrated under reduced pressure, dissolved in water, and extracted with methylene chloride (3×). The combined methylene chloride extracts were extracted with 1N HCl (3×) and the combined HCl extracts adjusted to pH 10 by addition of 6N NaOH. The aqueous mixture was then extracted with methylene chloride (3×). The combined methylene chloride extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the desired amine (25.0 g, quantitative yield) as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.22 (m, 1H), 6.91–6.89 (m, 1H), 6.89 (s, 1 H), 6.82–6.79 (m, 1H), 3.81 (s, 3H), 3.74 (s, 2H), 2.46 (s, 3H).

[0298] Step B: A solution of *trans*-cinnamic acid (5.0 g, 33.8 mmol) and *N*-methylmorpholine (5.2 mL, 47.3 mmol) in anhydrous methylene chloride (120 mL) was cooled to –20°C, and then isobutyl chloroformate (4.8 mL, 35.8 mmol) was added dropwise. After 15 minutes, a solution of the amine from Step A above (5.1 g,

33.8 mmol) in anhydrous methylene chloride (30 mL) was added dropwise, then the reaction was allowed to warm to room temperature and stir under N_2 for 3 hours. The mixture was washed with 1M sodium dihydrogen phosphate dihydrate (2×), H_2O (2×), and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1:1 ethyl acetate/hexanes) yielded the desired amide (8.3 g, 87%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, J = 15.5, 7.5 Hz, 1H), 7.56–7.54 (m, 1H), 7.47–7.46 (m, 1H), 7.36 (dd, J = 14.5, 7.5 Hz, 2H), 7.39–7.33 (m, 1H), 7.31–7.24 (m, 1H), 6.95–6.76 (m, 4H), 4.70–4.66 (m, 2H), 3.80 (s, 3H), 3.09–3.07 (m, 3H); ESI MS *m/z* 282 $[M+H]^+$.

[0299] Step C: An excess of polyphosphoric acid (11 g) in 1,2-dichloroethane (10 mL) was heated to 100°C. A solution of the amide from Step B above (3.8 g, 13.5 mmol) in 1,2-dichloroethane (15 mL) was added dropwise and the reaction was stirred at 100°C for 15 hours under N_2. After cooling to room temperature, the reaction was mixed with ice and the pH adjusted to 9 using concentrated ammonium hydroxide. The reaction mixture was then extracted with ethyl acetate (3×) and the combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Partial purification via flash column chromatography (30–100% ethyl acetate/hexanes) yielded the desired product (1.77 g) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.49 (m, 1H), 7.37–7.35 (m, 1H), 7.29–7.28 (m, 1H), 7.09–7.06 (m, 2H), 6.87 (d, J = 9.0 Hz, 1H) 6.71 (dd, J = 8.5, 2.5 Hz, 1H), 6.66 (d, J = 3.0 Hz, 1H), 5.03 (d, J = 16.5 Hz, 1H), 4.48–4.44 (m, 1H), 4.09 (d, J = 16.5 Hz, 1H), 3.79 (s, 3H), 3.28–3.22 (m, 1H), 3.05 (s, 3H), 2.97–2.93 (m, 1H).

[0300] Step D: To a stirred solution of lithium aluminum hydride (1M solution in THF, 14.7 mL, 14.7 mmol) at 0°C under N_2 was added a solution of the product of Step C above (3.8 g, 13.4 mmol) in anhydrous THF (100 mL) dropwise. The reaction mixture was heated to reflux and stirred for 2 hours. The reaction was then cooled back down to 0°C and quenched slowly with 1N NaOH (30 mL). After diluting with water, the aqueous phase was extracted with ethyl acetate (3×) and the combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1:1 ethyl acetate/hexanes) yielded the desired benzazepine (2.93 g, 38% two steps) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (t, J = 7.5 Hz, 2H), 7.27–7.24 (m, 1H), 7.17

(d, J = 7.5 Hz, 2H), 6.75–6.74 (m, 1H), 6.61–6.60 (m, 1H), 6.61–6.53 (br, 1H), 4.27–4.26 (m, 1H), 3.91–3.86 (m, 1H), 3.77 (s, 3H), 3.73–3.70 (m, 1H), 3.16–3.09 (m, 1H), 2.99–2.94 (m, 1H), 2.35 (s, 3H), 2.33–2.28 (m, 1H), 2.13–2.07 (m, 1H); ESI MS *m/z* 268 $[M+H]^+$. This compound was resolved by preparative chiral HPLC (CHIRALCEL OJ column, using 9:1:0.01 heptane/ethanol/diethylamine as the eluent) to give the (+)-enantiomer $[[\alpha]^{25}_D$ +3.66° (*c* 0.41, methanol)] and the (–)-enantiomer $[[\alpha]^{25}_D$ –1.16° (*c* 0.43, methanol)].

[0301] Step E: A mixture of the (+)-enantiomer from Step D above (1.19 g, 4.5 mmol) and hydrobromic acid (48% solution in water, 34 mL) was heated to reflux and stirred for 2 hours. The solvent and excess hydrobromic acid were removed under reduced pressure and the resulting solid was partitioned between ethyl acetate and saturated sodium bicarbonate (aq). After separating the two layers, the aqueous phase was extracted with ethyl acetate (3×). The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide the desired phenol (1.10 g, 86%) as a tan solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, J = 7.5 Hz, 2H), 7.28–7.23 (m, 1H), 7.16 (d, J = 7.5 Hz, 2H), 6.54 (s, 1H), 6.48–6.35 (m, 2H), 4.24–4.22 (m, 1H), 3.87–3.77 (m, 1H), 3.66–3.63 (m, 1H), 3.17–3.08 (m, 1H), 2.94–2.89 (m, 1H), 2.42 (s, 3H), 2.35–2.31 (m, 1H), 2.18–2.09 (m, 1H); ESI MS *m/z* 254 $[M+H]^+$.

[0302] Step F: To a stirred mixture of the phenol from Step E above (581 mg, 2.3 mmol) and pyridine (0.22 mL, 2.8 mmol) in anhydrous methylene chloride (23 mL) at 0°C under N_2 was added triflic anhydride (0.46 mL, 2.8 mmol). The reaction was stirred at 0°C for 1 hour, at which time TLC analysis indicated the reaction went to completion. The mixture was then diluted with methylene chloride, washed with saturated sodium bicarbonate (aq) and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1:1 ethyl acetate/hexanes) provided the desired triflate (650 mg, 74%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, J = 7.5 Hz, 2H), 7.31–7.28 (m, 1H), 7.17 (d, J = 7.0 Hz, 2H), 7.09–7.08 (m, 1H), 6.97–6.93 (m, 1H), 6.70–6.64 (br, 1H), 4.33–4.31 (m, 1H), 4.03–3.94 (m, 1H), 3.75–3.72 (m, 1H), 3.18–3.13 (m, 1H), 3.03–2.98 (m, 1H), 2.36 (s, 3H), 2.34–2.29 (m, 1H), 2.12–2.06 (m, 1H); ESI MS *m/z* 386 $[M+H]^+$.

[0303] Step G: To a stirred solution of the triflate from Step F above (260 mg, 0.68 mmol) in anhydrous toluene (6 mL) at room temperature were added morpholine (0.12 mL, 1.4 mmol), cesium carbonate (660 mg, 2.0 mmol), and 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (97 mg, 0.20 mmol). The reaction mixture was degassed with argon for 2 minutes, then palladium(II) acetate (23 mg, 0.10 mmol) was added under argon. The reaction was heated to reflux and stirred for 15 hours, at which time ESI MS indicated the reaction went to completion. After cooling to room temperature, the mixture was diluted with methylene chloride and filtered through Celite.* The filtrate was washed with saturated ammonium chloride and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (2%-10% methanol/methylene chloride) yielded the desired morpholine (168 mg, 77%) as a light yellow solid: $[\alpha]^{23}_{D}$ +3.00° (*c* 0.10, methanol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.35 (m, 1H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.16 (d, *J* = 7.5 Hz, 2H), 6.76–6.75 (m, 1H), 6.64–6.53 (m, 2H), 4.27–4.25 (m, 1H), 3.96–3.85 (m, 1H), 3.85 (t, *J* = 5.0 Hz, 4H), 3.75–3.73 (m, 1H), 3.30–3.18 (m, 1H), 3.12 (t, *J* = 5.0 Hz, 4H), 3.01–2.96 (m, 1H), 2.38 (s, 3H), 2.36–2.29 (m, 1H), 2.16–2.09 (m, 1H); ESI MS *m/z* 323 $[M+H]^+$.

[0304] Step H: To a stirred solution of the morpholine from Step G above (160 mg, 0.50 mmol) in methanol (4 mL) at room temperature was added maleic acid (57 mg, 0.50 mmol). The mixture was stirred for 1 hour and then the solvent was concentrated to approximately 0.5 mL. After diluting with water (2 mL), the mixture was lyophilized for 15 hours to provide (+)-4-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine, maleate salt (208 mg, 96%, 98.1% AUC HPLC) as an off-white solid: mp 88-89°C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.40–7.37 (m, 2H), 7.30–7.28 (m, 1H), 7.20–7.15 (br, 2H), 7.06–7.05 (m, 1H), 6.93–6.85 (br, 2H), 6.25 (s, 2H), 4.50–4.48 (m, 2H), 4.34–4.23 (br, 1H), 3.83–3.81 (m, 4H), 3.63–3.52 (m, 2H), 3.16–3.14 (m, 4H), 2.97–2.82 (m, 3H), 2.43–2.35 (m, 2H); ESI MS *m/z* 323 $[M+H]^+$.

<u>Example 35</u> - Preparation of (+)-2-methyl-8-(4-methylpiperazin-1-yl)-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, L-tartrate salt

[0305] Pursuant to the general method described above in Example 34, the following product was prepared: (+)-2-methyl-8-(4-methylpiperazin-1-yl)-5-phenyl-

*Trademark

2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, L-tartrate salt: ^{1}H NMR (500 MHz, CD_3OD) δ 7.37 (t, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 2H), 7.07–7.06 (m, 1H), 6.89 (d, *J* = 7.0 Hz, 1H), 6.79–6.67 (br, 1H), 4.46–4.45 (m, 2H), 4.33 (s, 2H), 4.24–4.21 (m, 1H), 3.51–3.47 (m, 2H), 3.38–3.34 (m, 4H), 3.05–3.02 (m, 4H), 2.81 (s, 3H), 2.66 (s, 3H), 2.59–2.50 (m, 1H), 2.39–2.33 (m, 1H); ESI MS *m/z* 336 $[M+H]^+$.

Example 36 - Preparation of (+)-1-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyrrolidin-2-one, maleate salt

[0306] Step A: To a stirred solution of methylamine (40% in H_2O) (28.2 mL, 327.6 mmol) in methanol (100 mL) at room temperature was added *m*-anisaldehyde (20.6 mL, 163.8 mmol) as a solution in methanol (50 mL) dropwise over 20 minutes. The reaction was stirred at room temperature under N_2 for 15 hours, then cooled to 0°C and sodium borohydride (6.19 g, 163.8 mmol) was added in portions. After warming to room temperature, the reaction was stirred for 3 hours. The mixture was then concentrated under reduced pressure, dissolved in water, and extracted with methylene chloride (3×). The combined methylene chloride extracts were extracted with 1N HCl (3×) and the combined HCl extracts adjusted to pH 10 by addition of 6N NaOH. The aqueous mixture was then extracted with methylene chloride (3×). The combined methylene chloride extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the desired amine (25.0 g, quantitative yield) as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.22 (m, 1H), 6.91–6.89 (m, 1H), 6.89 (s, 1 H), 6.82–6.79 (m, 1H), 3.81 (s, 3H), 3.74 (s, 2H), 2.46 (s, 3H).

[0307] Step B: A solution of *trans*-cinnamic acid (5.0 g, 33.8 mmol) and *N*-methylmorpholine (5.2 mL, 47.3 mmol) in anhydrous methylene chloride (120 mL) was cooled to –20°C, and then isobutyl chloroformate (4.8 mL, 35.8 mmol) was added dropwise. After 15 minutes, a solution of the amine from Step A above (5.1 g, 33.8 mmol) in anhydrous methylene chloride (30 mL) was added dropwise, then the reaction was allowed to warm to room temperature and stir under N_2 for 3 h. The mixture was washed with 1M sodium dihydrogen phosphate dihydrate (2×), H_2O (2×), and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1:1 ethyl acetate/hexanes) yielded the desired amide (8.3 g, 87%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd,

J = 15.5, 7.5 Hz, 1H), 7.56–7.54 (m, 1H), 7.47–7.46 (m, 1H), 7.36 (dd, J = 14.5, 7.5 Hz, 2H), 7.39–7.33 (m, 1H), 7.31–7.24 (m, 1H), 6.95–6.76 (m, 4H), 4.70–4.66 (m, 2H), 3.80 (s, 3H), 3.09–3.07 (m, 3H); ESI MS *m/z* 282 $[M+H]^+$.

[0308] Step C: An excess of polyphosphoric acid (11 g) in 1,2-dichloroethane (10 mL) was heated to 100°C. A solution of the amide from Step B above (3.8 g, 13.5 mmol) in 1,2-dichloroethane (15 mL) was added dropwise and the reaction was stirred at 100°C for 15 hours under N_2. After cooling to room temperature, the reaction was mixed with ice and the pH adjusted to 9 using concentrated ammonium hydroxide. The reaction mixture was then extracted with ethyl acetate (3×) and the combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Partial purification by flash column chromatography (30–100% ethyl acetate/hexanes) yielded the desired product (1.77 g) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.49 (m, 1H), 7.37–7.35 (m, 1H), 7.29–7.28 (m, 1H), 7.09–7.06 (m, 2H), 6.87 (d, J = 9.0 Hz, 1H) 6.71 (dd, J = 8.5, 2.5 Hz, 1H), 6.66 (d, J = 3.0 Hz, 1H), 5.03 (d, J = 16.5 Hz, 1H), 4.48–4.44 (m, 1H), 4.09 (d, J = 16.5 Hz, 1H), 3.79 (s, 3H), 3.28–3.22 (m, 1H), 3.05 (s, 3H), 2.97–2.93 (m, 1H).

[0309] Step D: To a stirred solution of lithium aluminum hydride (1M solution in THF, 14.7 mL, 14.7 mmol) at 0°C under N_2 was added a solution of the product of Step C above (3.8 g, 13.4 mmol) in anhydrous THF (100 mL) dropwise. The reaction mixture was heated to reflux and stirred for 2 hours. The reaction was then cooled back down to 0°C and quenched slowly with 1N NaOH (30 mL). After diluting with water, the aqueous phase was extracted with ethyl acetate (3×) and the combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1:1 ethyl acetate/hexanes) yielded the desired benzazepine (2.93 g, 38% two steps) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (t, J = 7.5 Hz, 2H), 7.27–7.24 (m, 1H), 7.17 (d, J = 7.5 Hz, 2H), 6.75–6.74 (m, 1H), 6.61–6.60 (m, 1H), 6.61–6.53 (br, 1H), 4.27–4.26 (m, 1H), 3.91–3.86 (m, 1H), 3.77 (s, 3H), 3.73–3.70 (m, 1H), 3.16–3.09 (m, 1H), 2.99–2.94 (m, 1H), 2.35 (s, 3H), 2.33–2.28 (m, 1H), 2.13–2.07 (m, 1H); ESI MS *m/z* 268 $[M+H]^+$. This compound was resolved by preparative chiral HPLC (CHIRALCEL OJ column, using 9:1:0.01 heptane/ethanol/diethylamine as the eluent)

to give the (+)-enantiomer [$[\alpha]^{25}_D$ +3.66° (*c* 0.41, methanol)] and the (–)-enantiomer [$[\alpha]^{25}_D$ –1.16° (*c* 0.43, methanol)].

[0310] Step E: A mixture of the (+)-enantiomer from Step D above (1.19 g, 4.5 mmol) and hydrobromic acid (48% solution in water, 34 mL) was heated to reflux and stirred for 2 hours. The solvent and excess hydrobromic acid were removed under reduced pressure and the resulting solid was partitioned between ethyl acetate and saturated sodium bicarbonate. After separating the two layers, the aqueous phase was extracted with ethyl acetate (3×). The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide the desired phenol (1.10 g, 86%) as a tan solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.5 Hz, 2H), 7.28–7.23 (m, 1H), 7.16 (d, *J* = 7.5 Hz, 2H), 6.54 (s, 1H), 6.48–6.35 (m, 2H), 4.24–4.22 (m, 1H), 3.87–3.77 (m, 1H), 3.66–3.63 (m, 1H), 3.17–3.08 (m, 1H), 2.94–2.89 (m, 1H), 2.42 (s, 3H), 2.35–2.31 (m, 1H), 2.18–2.09 (m, 1H); ESI MS *m/z* 254 $[M+H]^+$.

[0311] Step F: To a stirred mixture of the phenol from Step E above (581 mg, 2.3 mmol) and pyridine (0.22 mL, 2.8 mmol) in anhydrous methylene chloride (23 mL) at 0°C under N_2 was added triflic anhydride (0.46 mL, 2.8 mmol). The reaction was stirred at 0°C for 1 hour, at which time TLC analysis indicated the reaction went to completion. The mixture was then diluted with methylene chloride, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1:1 ethyl acetate/hexanes) provided the desired triflate (650 mg, 74%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, *J* = 7.5 Hz, 2H), 7.31–7.28 (m, 1H), 7.17 (d, *J* = 7.0 Hz, 2H), 7.09–7.08 (m, 1H), 6.97–6.93 (m, 1H), 6.70–6.64 (br, 1H), 4.33–4.31 (m, 1H), 4.03–3.94 (m, 1H), 3.75–3.72 (m, 1H), 3.18–3.13 (m, 1H), 3.03–2.98 (m, 1H), 2.36 (s, 3H), 2.34–2.29 (m, 1H), 2.12–2.06 (m, 1H); ESI MS *m/z* 386 $[M+H]^+$.

[0312] Step G: To a sealed tube were added 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (21 mg, 0.036 mmol), cesium carbonate (275 mg, 0.84 mmol) and the triflate from Step F above (232 mg, 0.60 mmol) in 1,4-dioxane (2.5 mL), and 2-pyrrolidinone (55 μL, 0.72 mmol). The reaction mixture was degassed with argon for 2 minutes, then tris(dibenzylideneacetone)dipalladium(0)

(11 mg, 0.012 mmol) was added under argon. The reaction was heated to 100°C and stirred for 15 hours, at which time TLC analysis indicated the reaction went to completion. After cooling to room temperature, the mixture was diluted with methylene chloride, filtered through Celite,* and concentrated *in vacuo*. Purification by flash column chromatography (2%-10% methanol/methylene chloride) yielded the desired pyrrolidinone (155 mg, 80%) as a light yellow oil: $[\alpha]^{23}_{D}$ -2.08° (*c* 0.24, methanol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50–7.49 (m, 1H), 7.35 (t, *J* = 7.0 Hz, 2H), 7.27–7.24 (m, 2H), 7.16 (t, *J* = 7.0 Hz, 2H), 6.71–6.63 (br, 1H), 4.31–4.30 (m, 1H), 3.98–3.89 (m, 1H), 3.85–3.81 (m, 2H), 3.79–3.76 (m, 1H), 3.17–3.11 (m, 1H), 3.01–2.96 (m, 1H), 2.59 (t, *J* = 8.0 Hz, 2H), 2.36 (s, 3H), 2.35–2.29 (m, 1H), 2.18–2.13 (m, 1H), 2.14 (t, *J* = 8.0 Hz, 2H); ESI MS *m/z* 321 $[M+H]^+$.

[0313] Step H: To a stirred solution of the pyrrolidinone from Step G above (142 mg, 0.44 mmol) in methanol (4 mL) at room temperature was added maleic acid (51 mg, 0.44 mmol). The mixture was stirred at room temperature for 1 h and then the solvent was concentrated to approximately 0.5 mL. After diluting with water (2 mL), the mixture was lyophilized for 15 h to provide (+)-1-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyrrolidin-2-one, maleate salt (189 mg, 98%, 98.3% AUC HPLC) as a light yellow powder: ^{1}H NMR (500 MHz, CD_3OD) δ 7.86–7.85 (m, 1H), 7.51–7.41 (m, 1H), 7.42–7.39 (m, 2H), 7.33–7.29 (m, 1H), 7.24–7.15 (br, 2H), 7.05–6.55 (br, 1H), 6.25 (s, 2H), 4.73–4.58 (m, 2H), 4.40–4.29 (m, 1H), 3.93–3.90 (m, 2H), 3.66–3.57 (m, 2H), 3.02–2.84 (m, 3H), 2.60 (t, *J* = 8.0 Hz, 2H), 2.48–2.39 (m, 2H), 2.19 (t, *J* = 7.5 Hz, 2H); ESI MS *m/z* 321 $[M+H]^+$.

<u>Example 37</u> - Preparation of (-)-1-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyrrolidin-2-one, maleate salt

[0314] Pursuant to the general method described above in Example 36, the following product was prepared: (-)-1-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)pyrrolidin-2-one, maleate salt: ^{1}H NMR (500 MHz, CD_3OD) δ 7.86–7.85 (m, 1H), 7.51–7.41 (m, 1H), 7.42–7.39 (m, 2H), 7.33–7.29 (m, 1H), 7.24–7.15 (br, 2H), 7.05–6.55 (br, 1H), 6.25 (s, 2H), 4.73–4.58 (m, 2H), 4.40–4.29 (m, 1H), 3.94–3.90 (m, 2H), 3.66–3.57 (m, 2H), 3.02–2.84 (m, 3H), 2.60 (t, *J* = 8.0 Hz, 2H), 2.48–2.39 (m, 2H), 2.19 (t, *J* = 7.5 Hz, 2H); ESI MS *m/z* 321 $[M+H]^+$.

*Trademark

Example 38 - Preparation of (+)-1-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)piperidin-2-one, maleate salt

[0315] Pursuant to the general method described above in Example 36, the following product was prepared: (+)-1-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)piperidin-2-one, maleate salt: ^{1}H NMR (500 MHz, CD_3OD) δ 7.42–7.39 (m, 3H), 7.33–7.31 (m, 1H), 7.27–7.19 (m, 3H), 7.06–6.69 (br, 1H), 6.25 (s, 2H), 4.69–4.61 (m, 2H), 4.39–4.30 (m, 1H), 3.69–3.63 (m, 2H), 3.70–3.48 (m, 2H), 3.01–2.88 (m, 3H), 2.54–2.51 (m, 2H), 2.48–2.40 (m, 2H), 2.01–1.92 (m, 4H); ESI MS *m/z* 335 $[M+H]^+$.

Example 39 – Preparation of (+)-5-(4-chlorophenyl)-2-methyl-8-(6-methyl-pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt

[0316] Step A: To a stirred solution of methylamine (40% in H_2O) (28.2 mL, 327.6 mmol) in methanol (100 mL) at room temperature was added *m*-anisaldehyde (20.6 mL, 163.8 mmol) as a solution in methanol (50 mL) dropwise over 20 minutes. The reaction mixture was allowed to stir at room temperature under N_2 overnight. The reaction was then cooled to 0°C and sodium borohydride (6.19 g, 163.8 mmol) was added in portions. After warming to room temperature, the reaction was allowed to stir for 3 hours. The mixture was then concentrated under reduced pressure, dissolved in H_2O, and extracted with methylene chloride (3×). The combined methylene chloride extracts were then extracted with 1 N HCl (3×) and the pH of the combined HCl extracts was adjusted to 10 by addition of 6 N NaOH. The aqueous mixture was then extracted with methylene chloride (3×). The combined methylene chloride extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the desired amine (25.0 g, quantitative yield) as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.22 (m, 1H), 6.91–6.89 (m, 1H), 6.89 (s, 1 H), 6.82–6.79 (m, 1H), 3.81 (s, 3H), 3.74 (s, 2H), 2.46 (s, 3H).

[0317] Step B: A solution of 4-chlorocinnamic acid (2.0 g, 10.9 mmol) and *N*-methylmorpholine (1.7 mL, 15.3 mmol) in anhydrous methylene chloride (80 mL) was cooled to –20°C. Isobutyl chloroformate (1.5 mL, 11.6 mmol) was added dropwise. After 15 minutes, a solution of the product from Step A (1.66 g, 10.9

mmol) in anhydrous methylene chloride (20 mL) was added dropwise. The reaction was allowed to warm to room temperature and stir under N_2 for 3 hours. The reaction mixture was then washed with 1 M $NaH_2PO_4 \cdot 2H_2O$ (2×), H_2O (2×), and brine, then dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (1:1 ethyl acetate/hexanes) yielded the desired amide (2.82 g, 82%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (dd, J = 15.3, 4.8 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.29 (m, 1H), 6.91 (d, J = 15.3 Hz, 1H), 6.83 (s, 1H), 6.80 (m, 1H), 6.77 (d, J = 15.3 Hz, 1H), 4.69-4.65 (m, 2H), 3.80 (s, 3H), 3.09-3.07 (m, 3H); ESI MS m/z = 316 $[C_{18}H_{18}ClNO_2 + H]^+$.

[0318] Step C: An excess of polyphosphoric acid (10 g) in 1,2-dichloroethane (40 mL) was heated to 100°C. A solution of the product from Step B (6.1 g, 19.3 mmol) in 1,2-dichloroethane (35 mL) was added dropwise. The reaction was then allowed to stir at 100°C overnight under N_2. After cooling to room temperature, the reaction was mixed with ice and the pH adjusted to 10 using 6 N NaOH. The reaction mixture was then extracted with ethyl acetate (3×) and the combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Partial purification via flash column chromatography (30–100% ethyl acetate/hexanes) yielded the desired product (1.9 g) as a yellow foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, J = 8.5 Hz, 2H), 7.00 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.5 Hz, 1H) 6.72 (dd, J = 8.5, 2.5 Hz, 1H), 6.67 (d, J = 3.0 Hz, 1H), 4.91 (d, J = 16.5 Hz, 1H), 4.44 (dd, J = 10.5, 5.0 Hz, 1H), 4.19 (d, J = 16.5 Hz, 1H), 3.79 (s, 3H), 3.16 (dd, J = 13.5, 11.0 Hz, 1H), 3.05 (s, 3H), 2.98 (dd, J = 13.5, 5.0 Hz, 1H).

[0319] Step D: To a stirred solution of lithium aluminum hydride (1 M solution in THF, 6.6 mL, 6.6 mmol) at 0°C under N_2 was added a solution of the product of Step C (1.89 g, 6.0 mmol) in anhydrous THF (40 mL) dropwise. The reaction mixture was heated to reflux and allowed to stir for 2 hours. The reaction was then cooled back down to 0°C and quenched slowly with 1 N NaOH (15 mL). After diluting with H_2O, the aqueous phase was extracted with ethyl acetate (3×) and the combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (1:1 ethyl acetate/hexanes) yielded the desired benzazepine (829 mg, 14% over two steps) as a

light yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 8.5 Hz, 2H), 6.74 (d, J = 3.0 Hz, 1H), 6.61 (dd, J = 8.5, 2.5 Hz, 1H), 6.55 (br s, 1H), 4.23 (d, J = 8.0 Hz, 1H), 3.86–3.84 (m, 1H), 3.77 (s, 3H), 3.67 (d, J = 14.0 Hz, 1H), 3.10–3.07 (m, 1H), 2.94 (ddd, J = 12.8, 9.5, 2.5 Hz, 1H), 2.34 (s, 3H), 2.30–2.23 (m, 1H), 2.10–2.03 (m, 1H); ESI MS m/z = 302 $[C_{18}H_{20}ClNO + H]^+$. This compound was resolved by preparative chiral HPLC (CHIRALPAK AD column, using 9:1:0.01 heptane/ethanol/triethylamine as the eluent) to give the (+)-enantiomer $[[\alpha]^{25}_D$ +5.0° (c 0.1, methanol)] and the (–)-enantiomer $[[\alpha]^{25}_D$ –20.0° (c 0.1, methanol)].

[0320] Step E: A mixture of (+)-5-(4-chlorophenyl)-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine (252 mg, 0.84 mmol) and HBr (48% solution in H_2O, 6.5 mL) was heated to reflux and allowed to stir for 2 hours. The solvent and excess HBr were removed under reduced pressure and the resulting solid was partitioned between ethyl acetate and saturated $NaHCO_3$ (aq). After separating the two layers, the aqueous phase was extracted with ethyl acetate (3×). The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide the desired phenol (228 mg, 95%) as a tan solid.: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.5 Hz, 2H), 6.57 (d, J = 2.5 Hz, 1H), 6.48–6.47 (m, 1H), 6.48–6.39 (m, 1H), 4.20 (d, J = 8.5 Hz, 1H), 3.84–3.74 (m, 1H), 3.62 (d, J = 14.0 Hz, 1H), 3.12–3.05 (m, 1H), 2.90 (ddd, J = 12.8, 9.5, 2.5 Hz, 1H), 2.41 (s, 3H), 2.30 (m, 1H), 2.14–2.06 (m, 1H); ESI MS m/z = 288 $[C_{17}H_{18}ClNO + H]^+$.

[0321] Step F: To a stirred mixture of the product of Step E (226 mg, 0.78 mmol) and pyridine (76 μL, 0.94 mmol) in anhydrous CH_2Cl_2 (8 mL) at 0°C under N_2 was added triflic anhydride (0.16 mL, 0.94 mmol). Stirring was continued at 0°C for one hour at which time TLC analysis indicated that the reaction had gone to completion. The mixture was then diluted with CH_2Cl_2, washed with sat. $NaHCO_3$ (aq) and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (1:1 ethyl acetate/hexanes) provided the desired triflate (265 mg, 80%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 10.0 Hz, 2H), 7.09 (s, 1H), 6.97 (dd, J = 8.5, 2.5 Hz, 1H), 6.70–6.63 (m, 1H), 4.30 (d, J = 9.5 Hz, 1H), 3.96 (d, J = 14.0 Hz, 1H), 3.72 (d, J = 14.5 Hz, 1H), 3.14–3.11 (m, 1H), 2.99 (ddd, J = 13.3, 10.0, 3.0 Hz, 1H), 2.35 (s, 3H), 2.28 (m, 1H), 2.09–2.03 (m, 1H); ESI MS m/z = 420 $[C_{18}H_{17}ClF_3NO_3S + H]^+$.

[0322] Step G: To a disposable sealed tube were added bis(pinacolato)diboron (173 mg, 0.68 mmol), potassium acetate (182 mg, 1.86 mmol), and the product of Step F (260 mg, 0.62 mmol) as a solution in anhydrous DMSO (5 mL). The reaction mixture was degassed by a subsurface purge with Ar for one minute. $PdCl_2(dppf)\cdot CH_2Cl_2$ (15 mg, 0.019 mmol) was then added under Ar. The reaction was heated to 80°C and allowed to stir for 2 hours, at which time ESI MS showed that the reaction had gone to completion. After cooling to room temperature, the reaction mixture was diluted with H_2O, δ then extracted with ethyl acetate (3×). The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Partial purification via flash column chromatography (95:5 CH_2Cl_2/MeOH) provided the desired boronate ester (246 mg) as a dark brown oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.68–7.64 (m, 1H), 7.32 (d, J = 8.5 Hz, 2H), 7.04 (d, J = 7.0 Hz, 2H), 6.85–6.77 (m, 1H), 4.36 (d, J = 8.5 Hz, 1H), 4.13–4.07 (m, 1H), 3.99 (d, J = 14.5 Hz, 1H), 3.29–3.23 (m, 1H), 3.20–3.13 (m, 1H), 2.49 (s, 3H), 2.42–2.34 (m, 1H), 2.31–2.24 (m, 1H), 1.34 (s, 6H), 1.24 (s, 6H); ESI MS m/z = 398 $[C_{23}H_{29}BClNO_2 + H]^+$.

[0323] Step H: To a disposable sealed tube were added the product of Step G (123 mg, 0.31 mmol) as a solution in anhydrous DMF (2.6 mL), sodium carbonate (98 mg, 0.93 mmol) as a solution in H_2O (0.6 mL), and 3-chloro-6-methylpyridazine (48 mg, 0.37 mmol). The reaction mixture was degassed by a subsurface purge with Ar for one minute. $PdCl_2(dppf)\cdot CH_2Cl_2$ (15 mg, 0.019 mmol) was then added under Ar. The reaction was heated to 100°C and allowed to stir overnight. TLC analysis showed that the reaction had gone to completion. After cooling to room temperature, the reaction mixture was diluted with H_2O, and then extracted with ethyl acetate (3×). The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (95:5 CH_2Cl_2/MeOH) yielded the desired pyridazine (58 mg, 52% for two steps) as a brown oil: $[\alpha]^{25}_D$ -7.14° (*c* 0.14, methanol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 2.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.36 (d, J = 8.5 , 1H), 7.34 (d, J = 8.5 Hz, 2H), 7.14 (d, J = 8.5 Hz, 2H), 6.80 (br s, 1H), 4.37 (d, J = 8.5 Hz, 1H), 4.03–3.98 (m, 1H), 3.85 (d, J = 14.0 Hz, 1H), 3.16–3.11 (m, 1H), 3.00 (ddd, J = 12.5, 9.5, 2.0 Hz, 1H),

2.75 (s, 3H), 2.38 (s, 3H), 2.37–2.30 (m, 1H), 2.17–2.11 (m, 1H); ESI MS *m/z* = 364 $[C_{22}H_{22}ClN_3 + H]^+$.

[0324] Step I: The product of Step H (43 mg, 0.12 mmol) was converted to its hydrochloride salt by dissolving the oil in a minimum amount of ether, adding one equivalent of HCl (1 M solution in ether), and sonicating the solution for a few minutes until salt precipitation occurred. Filtration yielded (+)-5-(4-chlorophenyl)-2-methyl-8-(6-methyl-pyridazin-3-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt (34 mg, 72%, 98.8% AUC HPLC) as a light brown solid: mp 179–181°C (dec); ESI MS *m/z* = 364 $[C_{22}H_{22}ClN_3 + H]^+$.

<u>Example 40</u> – Preparation of (+)-5-(4-chlorophenyl)-2-methyl-8-pyridazin-3-yl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt

[0325] Pursuant to the general method described above in Example 39, the following product was prepared: (+)-5-(4-chlorophenyl)-2-methyl-8-pyridazin-3-yl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, hydrochloride salt: mp 187–189°C (dec); ESI MS *m/z* = 350 $[C_{21}H_{20}ClN_3 + H]^+$.

<u>Example 41</u> – Preparation of (+)-5-(4-chlorophenyl)-2-methyl-8-(pyrazin-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt and (-)-5-(4-chlorophenyl)-2-methyl-8-(pyrazin-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt

[0326] Pursuant to the general method described above in Example 39, the following products were prepared: (+)-5-(4-chlorophenyl)-2-methyl-8-(pyrazin-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt: mp = 87–89°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.69 (s, 1H), 8.56 (s, 1H), 8.25 (s, 1H), 8.11–8.05 (m, 1H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.29–7.22 (m, 2H), 7.15–6.85 (br, 1H), 6.25 (s, 2H), 4.85–4.74 (br, 1H), 4.72–4.68 (m, 1H), 4.53–4.44 (br, 1H), 3.70–3.63 (m, 2H), 3.02–2.93 (br, 3H), 2.70–2.50 (br, 1H), 2.49–2.42 (m, 1H); ESI MS *m/z* = 350 $[C_{21}H_{20}ClN_3 + H]^+$; (-)-5-(4-chlorophenyl)-2-methyl-8-(pyrazin-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt: mp 82-84°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.69 (s, 1H), 8.56 (s, 1H), 8.25 (s, 1H), 8.11–8.05 (m, 1H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.29–7.22 (m, 2H), 7.15–6.85 (br, 1H), 6.25 (s, 2H), 4.85–4.74 (br, 1H), 4.72–

4.68 (m, 1H), 4.53–4.44 (br, 1H), 3.70–3.63 (m, 2H), 3.02–2.93 (br, 3H), 2.70–2.50 (br, 1H), 2.49–2.42 (m, 1H); ESI MS *m/z* = 350 $[C_{21}H_{20}ClN_3 + H]^+$.

Example 42 – Preparation of (-)-5-(4-chlorophenyl)-8-(3,5-dimethylisoxazol-4-yl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt

[0327] Pursuant to the general method described above in Example 39, the following product was prepared: (-)-5-(4-chlorophenyl)-8-(3,5-dimethylisoxazol-4-yl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt: mp 66-68°C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.47 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.36–7.30 (m, 1H), 7.29–7.21 (m, 2H), 7.04–6.78 (br, 1H), 6.25 (s, 2H), 4.77–4.70 (br, 1H), 4.66 (d, *J* = 9.0 Hz, 1H), 4.46–4.39 (br, 1H), 3.69–3.58 (m, 2H), 3.02–2.89 (br, 3H), 2.70–2.50 (br, 1H), 2.48–2.42 (m, 1H), 2.41 (s, 3H), 2.25 (s, 3H); ESI MS *m/z* = 367 $[C_{22}H_{23}ClN_2O + H]^+$.

Example 43 – Preparation of (+)-5-(4-chlorophenyl)-8-(3,5-dimethylisoxazol-4-yl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt

[0328] Pursuant to the general method described above in Example 39, the following product was prepared: (+)-5-(4-chlorophenyl)-8-(3,5-dimethylisoxazol-4-yl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt: mp 196–198°C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.47 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.36–7.30 (m, 1H), 7.29–7.21 (m, 2H), 7.04–6.78 (br, 1H), 6.25 (s, 2H), 4.77–4.70 (br, 1H), 4.66 (d, *J* = 9.0 Hz, 1H), 4.46–4.39 (br, 1H), 3.69–3.58 (m, 2H), 3.02–2.89 (br, 3H), 2.70–2.50 (br, 1H), 2.48–2.42 (m, 1H), 2.41 (s, 3H), 2.25 (s, 3H); ESI MS *m/z* = 367 $[C_{22}H_{23}ClN_2O + H]^+$.

Example 44 – Preparation of (+)-5-(4-chlorophenyl)-2-methyl-8-pyrimidin-2-yl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt

[0329] Pursuant to the general method described above in Example 39, the following product was prepared: (+)-5-(4-chlorophenyl)-2-methyl-8-pyrimidin-2-yl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt: mp 84–85°C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.85 (d, *J* = 5.0 Hz, 2H), 8.53 (d, *J* = 1.5 Hz, 1H), 8.41–8.35 (m, 1H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 5.0 Hz, 1H), 7.27–7.21 (m, 2H), 7.15–6.78 (br, 1H), 6.26 (s, 2H), 4.71–4.69 (m, 1H), 4.53–4.41 (br, 2H), 3.69–3.59 (m, 2H),

3.02–2.91 (br, 3H), 2.71–2.50 (br, 1H), 2.49–2.42 (m, 1H); ESI MS *m/z* = 350 $[C_{21}H_{20}ClN_3 + H]^+$.

Example 45 – Preparation of {6-[5-(4-chlorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine-8-yl]-pyridazin-3-yl}-dimethylamine, maleate salt, single enantiomer

[0330] Pursuant to the general method described above in Example 39, the following product was prepared: {6-[5-(4-chlorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine-8-yl]-pyridazin-3-yl}-dimethylamine, maleate salt, single enantiomer: mp 96–98°C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.09 (s, 1H), 7.99 (d, *J* = 9.0 Hz, 1H), 7.91–7.86 (m, 1H), 7.44–7.39 (m, 3H), 7.27–7.22 (m, 2H), 7.05–6.85 (br, 1H), 6.23 (s, 2H), 4.03–4.69 (br, 1H), 4.68 (d, *J* = 7.0 Hz, 1H), 4.50–4.43 (m, 1H), 3.67–3.58 (m, 2H), 3.26 (s, 6H), 3.01–2.95 (br, 3H), 2.68–2.53 (br, 1H), 2.47–2.42 (m, 1H); ESI MS *m/z* = 393 $[C_{23}H_{25}ClN_4 + H]^+$.

Example 46 – Preparation of (-)-{6-[5-(4-chlorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine-8-yl]-pyridazin-3-yl}-dimethylamine, maleate salt

[0331] Pursuant to the general method described above in Example 39, the following product was prepared: (-)-{6-[5-(4-chlorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine-8-yl]-pyridazin-3-yl}-dimethylamine, maleate salt: mp 109-110°C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.08 (m, 1H), 7.86 (d, *J* = 9.5 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.27–7.20 (br, 1H), 7.22 (d, *J* = 9.5 Hz, 2H), 7.14–6.78 (br, 1H), 6.24 (s, 2H), 4.82–4.62 (br, 1H), 4.67 (d, *J* = 10.0 Hz, 1H), 4.46–4.43 (m, 1H), 3.68–3.54 (m, 2H), 3.22 (s, 6H), 2.99–2.94 (m, 3H), 2.70–2.52 (br, 1H), 2.46–2.41 (m, 1H); ESI MS *m/z* 393 $[M+H]^+$.

Example 47 - Preparation of (-)-4-(5-(4-chlorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine, maleate salt

[0332] Step A: To a stirred solution of methylamine (40% in H_2O) (28.2 mL, 327.6 mmol) in methanol (100 mL) at room temperature was added *m*-anisaldehyde (20.6 mL, 163.8 mmol) as a solution in methanol (50 mL) dropwise over 20 minutes. The reaction was stirred at room temperature under N_2 for 15 hours, then cooled to

0°C and sodium borohydride (6.19 g, 163.8 mmol) was added in portions. After warming to room temperature, the reaction was stirred for 3 hours, then the mixture was concentrated under reduced pressure, dissolved in H_2O, and extracted with methylene chloride (3×). The combined methylene chloride extracts were extracted with 1N HCl (3×) and the combined HCl extracts adjusted to pH 10 by addition of 6N NaOH. The aqueous mixture was then extracted with methylene chloride (3×). The combined methylene chloride extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the desired amine (25.0 g, quantitative yield) as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.22 (m, 1H), 6.91–6.89 (m, 1H), 6.89 (s, 1 H), 6.82–6.79 (m, 1H), 3.81 (s, 3H), 3.74 (s, 2H), 2.46 (s, 3H).

[0333] Step B: A solution of 4-chlorocinnamic acid (2.0 g, 10.9 mmol) and *N*-methylmorpholine (1.7 mL, 15.3 mmol) in anhydrous methylene chloride (80 mL) was cooled to –20°C and isobutyl chloroformate (1.5 mL, 11.6 mmol) was added dropwise. After 15 minutes, a solution of the amine from Step A above (1.66 g, 10.9 mmol) in anhydrous methylene chloride (20 mL) was added dropwise, then the reaction was allowed to warm to room temperature and stir under N_2 for 3 hours. The mixture was washed with 1M sodium dihydrogen phosphate dihydrate (2×), H_2O (2×), and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (1:1 ethyl acetate/hexanes) yielded the desired amide (2.82 g, 82%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (dd, J = 15.3, 4.8 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.40–7.26 (m, 1H), 6.91 (d, J = 15.3 Hz, 1H), 6.83 (s, 1H), 6.83 (d, J = 12.3 Hz, 1H), 6.77 (d, J = 15.3 Hz, 1H), 4.67 (d, J = 12.3 Hz, 2H), 3.80 (s, 3H), 3.08 (d, J = 4.2 Hz, 3H); ESI MS *m/z* 316 $[M+H]^+$.

[0334] Step C: An excess of polyphosphoric acid (2 g) in 1,2-dichloroethane (10 mL) was heated to 100°C. A solution of the amide from Step B above (527 mg, 1.7 mmol) in 1,2-dichloroethane (5 mL) was added dropwise. The reaction was stirred at 100°C for 15 hours under N_2. After cooling to room temperature, the reaction was mixed with ice and the pH adjusted to 10 using 6N NaOH. The reaction mixture was then extracted with ethyl acetate (3×) and the combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Partial purification via flash column chromatography (30–100% ethyl acetate/hexanes) yielded the desired

product (199 mg) as a yellow foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.5 Hz, 2H), 7.00 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 1H) 6.72 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.67 (d, *J* = 3.0 Hz, 1H), 4.91 (d, *J* = 16.5 Hz, 1H), 4.44 (dd, *J* = 10.5, 5.0 Hz, 1H), 4.19 (d, *J* = 16.5 Hz, 1H), 3.79 (s, 3H), 3.16 (dd, *J* = 13.5, 11.0 Hz, 1H), 3.05 (s, 3H), 2.98 (dd, *J* = 13.5, 5.0 Hz, 1H).

[0335] Step D: To a stirred solution of lithium aluminum hydride (1M solution in THF, 0.48 mL, 0.48 mmol) at 0°C under N_2 was added a solution of the product from Step C above (139 mg, 0.44 mmol) in anhydrous THF (4 mL) dropwise. The reaction mixture was heated to reflux and allowed to stir for 2 hours. The reaction was then cooled back down to 0°C and quenched slowly with 1N NaOH (1 mL). After diluting with H_2O, the aqueous phase was extracted with ethyl acetate (3×) and the combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (1:1 ethyl acetate/hexanes) yielded the desired benzazepine (67 mg, 19% two steps) as a light yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 3.0 Hz, 1H), 6.61 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.55 (br, 1H), 4.24–4.22 (m, 1H), 3.86–3.84 (m, 1H), 3.77 (s, 3H), 3.68–3.65 (m, 1H), 3.10–3.07 (m, 1H), 2.96–2.91 (m, 1H), 2.34 (s, 3H), 2.30–2.23 (m, 1H), 2.10–2.03 (m, 1H); ESI MS *m/z* 302 $[M+H]^+$. This compound was resolved by preparative chiral HPLC (CHIRALPAK AD column, using 9:1:0.01 heptane/ethanol/diethylamine as the eluent) to give the (+)-enantiomer $[[\alpha]^{25}_D$ +5.0° (*c* 0.1, methanol)] and the (–)-enantiomer $[[\alpha]^{25}_D$ –20.0° (*c* 0.1, methanol)].

[0336] Step E: A mixture of the benzazepine from Step D above (1.40 g, 4.6 mmol) and hydrobromic acid (48% solution in H_2O, 30 mL) was heated to reflux and stirred for 2 hours. The solvent and excess hydrobromic acid were removed under reduced pressure and the resulting solid was partitioned between ethyl acetate and saturated sodium bicarbonate (aq). After separating the two layers, the aqueous phase was extracted with ethyl acetate (3×). The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide the desired phenol (1.09 g, 82%) as a tan solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 2H), 6.57–6.56 (m, 1H), 6.48–6.47 (m, 1H), 6.48–6.39 (m, 1H), 4.20 (d, *J* = 8.5 Hz, 1H), 3.84–3.74 (m, 1H), 3.64–3.61 (m, 1H), 3.12–3.05 (m, 1H),

2.93–2.88 (m, 1H), 2.41 (s, 3H), 2.34–2.26 (m, 1H), 2.14–2.06 (m, 1H); ESI MS *m/z* 288 $[M+H]^+$.

[0337] Step F: To a stirred mixture of the phenol from Step E above (552 mg, 1.9 mmol) and pyridine (0.2 mL, 2.3 mmol) in anhydrous methylene chloride (19 mL) at 0°C under N_2 was added triflic anhydride (0.4 mL, 2.3 mmol). The reaction was stirred at 0°C for 1 hour, at which time TLC analysis indicated the reaction went to completion. The mixture was then diluted with methylene chloride, washed with saturated sodium bicarbonate (aq) and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (1:1 ethyl acetate/hexanes) provided the desired triflate (457 mg, 57%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 10.0 Hz, 2H), 7.09 (s, 1H), 6.97 (dd, J = 8.5, 2.5 Hz, 1H), 6.70–6.63 (m, 1H), 4.30 (d, J = 9.5 Hz, 1H), 3.96 (d, J = 14.0 Hz, 1H), 3.72 (d, J = 14.5 Hz, 1H), 3.14–3.11 (m, 1H), 2.99 (ddd, J = 13.3, 10.0, 3.0 Hz, 1H), 2.35 (s, 3H), 2.28 (m, 1H), 2.09–2.03 (m, 1H); ESI MS *m/z* 420 $[M+H]^+$.

[0338] Step G: To a stirred solution of the triflate from Step F above (252 mg, 0.60 mmol) in anhydrous toluene (6 mL) at room temperature were added morpholine (0.10 mL, 1.2 mmol), cesium carbonate (586 mg, 1.8 mmol), and 2-(dicyclohexylphosphino)-2',4',6'-tri-*i*-isopropyl-1,1'-biphenyl (86 mg, 0.18 mmol). The reaction mixture was degassed with argon for 2 minutes, then palladium(II) acetate (20 mg, 0.09 mmol) was added under argon. The reaction was heated to reflux and stirred for 24 hours, at which time ESI MS indicated the reaction went to completion. After cooling to room temperature, the mixture was diluted with methylene chloride and filtered through Celite.* The filtrate was washed with saturated ammonium chloride (aq) and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (2%-10% methanol/methylene chloride) yielded the desired morpholine (73 mg, 34%) as a light yellow oil: $[\alpha]^{23}_D$ -2.80° (*c* 0.18, methanol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 6.76–6.75 (m, 1H), 6.63–6.60 (m, 1H), 6.58–6.49 (br, 1H), 4.22 (d, J = 9.0 Hz, 1H), 3.90–3.84 (m, 1H), 3.85 (t, J = 5.0 Hz, 4H), 3.69–3.66 (m, 1H), 3.12 (t, J = 5.0 Hz, 4H), 3.11–3.05 (br, 1H), 2.96–2.92 (m, 1H), 2.35 (s, 3H), 2.30–2.23 (m, 1H), 2.09–2.04 (m, 1H); ESI MS *m/z* 357 $[M+H]^+$.

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[0339] Step H: To a stirred solution of the morpholine from Step G above (125 mg, 0.35 mmol) in methanol (3 mL) at room temperature was added maleic acid (41 mg, 0.35 mmol). The mixture was stirred for 1 hour and then the solvent was concentrated to approximately 0.5 mL. After diluting with H_2O (2 mL), the mixture was lyophilized for 15 hours to provide (-)-4-(5-(4-chlorophenyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine, maleate salt (163 mg, 98%, 96.0% AUC HPLC) as a light purple solid: mp 99-100°C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.40–7.38 (m, 2H), 7.20–7.14 (br, 2H), 7.06 (s, 1H), 6.94–6.88 (br, 2H), 6.25 (s, 2H), 4.66–4.48 (m, 2H), 4.35–4.20 (br, 1H), 3.83–3.81 (m, 4H), 3.69–3.51 (m, 2H), 3.16–3.14 (m, 4H), 3.02–2.82 (m, 3H), 2.41–2.32 (m, 2H); ESI MS *m/z* 357 $[M+H]^+$.

<u>Example 48</u> – Preparation of (+)-5-(4-chlorophenyl)-2-methyl-8-morpholin-4-yl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt

[0340] Pursuant to the general method described above in Example 47, the following product was prepared: (+)-5-(4-chlorophenyl)-2-methyl-8-morpholin-4-yl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt: mp 94-96°C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.39 (d, J = 8.5 Hz, 2H), 7.20–7.15 (m, 2H), 7.06 (d, J = 2.5 Hz, 1H), 6.93–6.88 (br, 1H), 6.80–6.50 (br, 1H), 6.25 (s, 2H), 4.63–4.45 (br, 1H), 4.49 (d, J = 11.0 Hz, 1H), 4.31–4.25 (br, 1H), 3.82 (t, J = 5.0 Hz, 4H), 3.61–3.55 (br, 2H), 3.16 (t, J = 4.5 Hz, 4H), 2.95–2.85 (br, 3H), 2.41–2.36 (m, 2H); ESI MS *m/z* = 357 $[C_{21}H_{25}ClN_2O + H]^+$.

<u>Example 49</u> – Preparation of (+)-8-methoxy-2-methyl-5-naphthalen-2-yl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt and (-)-8-methoxy-2-methyl-5-naphthalen-2-yl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt

[0341] Step A: A solution of 2-naphthylacrylic acid (10.0 g, 50.4 mmol) and *N*-methylmorpholine (7.8 mL, 70.6 mmol) in anhydrous methylene chloride (307 mL) was cooled to –20°C. Isobutyl chloroformate (7.0 mL, 53.5 mmol) was added dropwise. After 90 minutes, a solution of (3-methoxybenzyl)methylamine (7.63 g, 50.45 mmol) in anhydrous methylene chloride (50 mL) was added dropwise. The reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was then washed with 1 M $NaH_2PO_4 \cdot 2H_2O$ (2×), H_2O (2×), and

brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (40:60 to 70:30 ethyl acetate/hexanes) yielded the desired amide (8.60 g, 51%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95–7.55 (m, 6H), 7.52–7.45 (m, 2H), 7.35–7.20 (m, 1H), 7.10–6.75 (m, 4H), 4.73–4.69 (m, 2H), 3.81 (s, 3H), 3.14–3.08 (m, 3H).

[0342] Step B: An excess of polyphosphoric acid (4 g) was heated to 80°C. A solution of the product from step A (2 g, 6.0 mmol) in 1,2-dichloroethane (10.5 mL) was added dropwise to the hot acid. The reaction mixture was maintained at this temperature for 1 hour, and then chlorobenzene (7 mL) was added to it. The reaction mixture was then heated gradually to 120°C over the next one hour and 15 minutes, and then allowed to stir at 120°C overnight. After cooling to room temperature, the reaction was diluted with ethyl acetate and concentrated ammonium hydroxide and stirred for 2 hours. The reaction mixture was then diluted further with water and extracted with dichloromethane (4×). The combined extract was dried over sodium sulfate, filtered, and concentrated *in vacuo*. Partial purification by flash column chromatography (dichloromethane, then 99:1 to 97:3 methylene chloride/methanol) yielded the desired product (1.20 g) as an inseparable mixture with the undesired regioisomer. The mixture was used in the next step without further purification or characterization.

[0343] To a solution of the lactam from above (1.20 g, 3.62 mmol) in tetrahydrofuran (20 mL) at 0°C was added lithium aluminum hydride (4 mL, 4 mmol, 1 M solution in THF) dropwise. The reaction mixture was warmed to room temperature, and stirred for 45 minutes. The reaction was then cooled back down to 0°C and quenched carefully with water (3 mL), followed by sodium hydroxide (3 mL, 15% solution in water) and finally, water (9 mL). The mixture was stirred for 20 minutes, and the precipitate formed was removed by filtration. The filtrate was dried over sodium sulfate, filtered, and concentrated *in vacuo*.

[0344] The above steps were repeated once more, using the amide from step A (6.6 g, 19.9 mmol). The two batches of the crude amine were then combined. Partial purification of the crude product via flash column chromatography (90:10 methylene chloride/hexanes, then methylene chloride, and finally, 99:0.9:0.1 to 95:4.5:0.5 methylene chloride/methanol/concentrated ammonium hydroxide) yielded the desired benzazepine as an inseparable mixture with the undesired regioisomer (1.97 g). The

regioisomers were separated and resolved by preparative chiral HPLC (CHIRALCEL OJ column, using 90:9:1 heptane/IPA/triethylamine as the eluent) to give the (+)-enantiomer [$[\alpha]^{25}_D$ +10° (*c* 0.12, methanol)] and the (–)-enantiomer [$[\alpha]^{25}_D$ –13° (*c* 0.18, methanol)]: (+)-Enantiomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84–7.68 (m, 3H), 7.58 (br s, 1H), 7.47–7.45 (m, 2H), 7.35 (dd, *J* = 5.1, 1.6 Hz, 1H), 6.77 (s, 1H), 6.57 (br s, 2H), 4.43 (d, *J* = 8.3 Hz, 1H), 4.00–3.84 (m, 1H), 3.77 (s, 3H), 3.77-3.75 (m, 1H), 3.21–3.05 (m, 1H), 3.03-2.89 (m, 1H), 2.47–2.31 (m, 1H), 2.41 (s, 3H), 2.21–2.10 (m, 1H); (-)-Enantiomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85–7.68 (m, 3H), 7.58 (br s, 1H), 7.48–7.45 (m, 2H), 7.35 (d, *J* = 8.5 Hz, 1H), 6.78 (s, 1H), 6.58 (br s, 2H), 4.43 (d, *J* = 8.3 Hz, 1H), 4.00–3.84 (m, 1H), 3.77 (s, 3H), 3.77-3.75 (m, 1H), 3.21–3.05 (m, 1H), 3.03-2.89 (m, 1H), 2.47–2.31 (m, 1H), 2.40 (s, 3H), 2.21–2.10 (m, 1H). (The two enantiomers of the undesired regioisomer were also isolated.)

[0345] Step D: To a solution of the (+)- enantiomer (39 mg, 0.12 mmol) in methanol (2 mL), was added maleic acid (14 mg, 0.12 mmol), and the mixture was stirred for 3 hours. Water (10 mL) was added to the mixture, which was then lyophilized to give (+)-8-methoxy-2-methyl-5-naphthalen-2-yl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt as a pale yellow solid (52 mg, 99%, 96.0% AUC HPLC): ^{1}H NMR (500 MHz, CD_3OD) δ 7.95–7.84 (m, 2H), 7.78 (br s, 1H), 7.65–7.49 (br m, 1H), 7.49–7.47 (m, 2H), 7.37 (d, *J* = 8.5 Hz, 1H), 7.08 (s, 1H), 7.05–6.85 (m, 2H), 6.25 (s, 2H), 4.79–4.47 (m, 2H), 4.46–4.21 (m, 1H), 3.81 (s, 3H), 3.68–3.42 (br m, 2H), 3.05–2.26 (br m, 5H).

[0346] Step E (SAM-I-174): To a solution of the (-)-enantiomer (38 mg, 0.12 mmol) in methanol (2 mL), was added maleic acid (14 mg, 0.12 mmol), and the mixture was stirred for 3 hours. Water (10 mL) was added to the mixture, which was then lyophilized to give (-)-8-methoxy-2-methyl-5-naphthalen-2-yl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate sal as a pale yellow solid (50 mg, 95%, 95.8% AUC HPLC): ^{1}H NMR (500 MHz, CD_3OD) δ 7.95–7.84 (m, 2H), 7.78 (br s, 1H), 7.65–7.49 (br m, 1H), 7.49–7.47 (m, 2H), 7.37 (d, *J* = 8.5 Hz, 1H), 7.08 (s, 1H), 7.05–6.85 (m, 2H), 6.25 (s, 2H), 4.79–4.47 (m, 2H), 4.46–4.21 (m, 1H), 3.81 (s, 3H), 3.68–3.42 (br m, 2H), 3.05–2.26 (br m, 5H).

Example 50 – Preparation of (+)-2-methyl-5-naphthalen-2-yl-8-pyridazin-3-yl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt

[0347] Step A: A mixture of (+)-8-methoxy-2-methyl-5-naphthalen-2-yl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine (592 mg, 1.9 mmol) and HBr (48% solution in H_2O, 15 mL) was heated to reflux and allowed to stir for 3 hours. The solvent and excess HBr were removed under reduced pressure and the resulting solid was partitioned between ethyl acetate and saturated $NaHCO_3$ (aq). After separating the two layers, the aqueous phase was extracted with ethyl acetate (3×). The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide the desired phenol (540 mg, 95%) as a tan solid.: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85–7.83 (m, 1H), 7.82 (s, 1H), 7.77–7.75 (m, 1H), 7.59–7.56 (br, 1H), 7.48–7.45 (m, 2H), 7.34 (dd, J = 8.5, 1.5 Hz, 1H), 6.61 (s, 1H), 6.47–6.43 (m, 2H), 4.40 (d, J = 9.0 Hz, 1H), 3.91–3.83 (br, 1H), 3.69 (d, J = 13.5 Hz, 1H), 3.17–3.10 (m, 1H), 2.96 (ddd, J = 12.8, 10.0, 2.5 Hz, 1H), 2.49–2.41 (m, 1H), 2.44 (s, 3H), 2.26–2.19 (m, 1H); ESI MS m/z = 304 $[C_{21}H_{21}NO + H]^+$.

[0348] Step B: To a stirred mixture of the product of Step A (539 mg, 1.8 mmol) and pyridine (0.17 mL, 2.1 mmol) in anhydrous CH_2Cl_2 (18 mL) at 0°C under N_2 was added triflic anhydride (0.36 mL, 2.1 mmol). Stirring was continued at 0°C for one hour at which time TLC analysis indicated the reaction had gone to completion. The mixture was then diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ (aq) and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (1:1 ethyl acetate/hexanes) provided the desired triflate (640 mg, 83%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88–7.85 (m, 2H), 7.80–7.78 (m, 1H), 7.62–7.58 (br, 1H), 7.50–7.47 (m, 2H), 7.33 (dd, J = 8.5, 1.5 Hz, 1H), 7.11 (d, J = 2.5 Hz, 1H), 6.93–6.91 (m, 1H), 6.71–6.66 (br, 1H), 4.49 (d, J = 10.0 Hz, 1H), 4.05–4.03 (m, 1H), 3.77 (d, J = 14.0 Hz, 1H), 3.20–3.17 (m, 1H), 3.06 (ddd, J = 13.0, 10.5, 2.5 Hz, 1H), 2.48–2.40 (m, 1H), 2.38 (s, 3H), 2.21–2.15 (m, 1H); ESI MS m/z = 436 $[C_{22}H_{20}F_3NO_3S + H]^+$.

[0349] Step C: To a disposable sealed tube were added bis(pinacolato)diboron (200 mg, 0.72 mmol), potassium acetate (211 mg, 2.2 mmol), and the product of Step B (312 mg, 0.72 mmol) as a solution in anhydrous DMSO (3 mL). The reaction mixture was degassed by a subsurface sparge with Ar for 2 minutes. $PdCl_2(dppf)\cdot CH_2Cl_2$ (18 mg, 0.022 mmol) was then added under Ar. The

reaction was heated to 80°C and allowed to stir for 3 hours, at which time ESI MS showed that the reaction had gone to completion. After cooling to room temperature, the reaction mixture was diluted with H_2O, and then extracted with ethyl acetate (3×). The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Partial purification via flash column chromatography (95:5 CH_2Cl_2/MeOH) provided the desired boronate ester as a dark brown oil: ESI MS *m/z* = 414 $[C_{27}H_{32}BNO_2 + H]^+$.

[0350] Step D: To a disposable sealed tube were added the product of Step C (296 mg, 0.72 mmol) as a solution in anhydrous DMF (3 mL), sodium carbonate (228 mg, 2.2 mmol) as a solution in H_2O (1.4 mL), and 3-chloropyridazine (188 mg, 1.6 mmol). The reaction mixture was degassed by a subsurface sparge with Ar for 2 minutes. $PdCl_2(dppf)\bullet CH_2Cl_2$ (35 mg, 0.043 mmol) was then added under Ar. The reaction was heated to 100°C and allowed to stir overnight. TLC analysis showed that the reaction had gone to completion. After cooling to room temperature, the reaction mixture was diluted with H_2O, then extracted with ethyl acetate (3×). The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (95:5 CH_2Cl_2/MeOH) yielded the desired pyridazine (128 mg, 49% over two steps) as a light brown oil: $[\alpha]^{25}_D$ -2.9° (*c* 0.07, methanol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.14 (dd, *J* = 5.0, 2.0 Hz, 1H), 8.03 (d, *J* = 2.0 Hz, 1H), 7.88–7.86 (m, 2H), 7.82 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.80–7.79 (m, 1H), 7.72–7.70 (m, 1H), 7.64–7.61 (m, 1H), 7.52–7.50 (m, 1H), 7.50–7.48 (m, 2H), 7.40 (dd, *J* = 8.5, 1.5 Hz, 1H), 6.87–6.80 (br, 1H), 4.57 (d, *J* = 9.5 Hz, 1H), 4.11–4.05 (m, 1H), 3.92 (d, *J* = 14.5 Hz, 1H), 3.21–3.16 (m, 1H), 3.09–3.03 (m, 1H), 2.53–2.46 (m, 1H), 2.41 (s, 3H), 2.28–2.22 (m, 1H); ESI MS *m/z* = 366 $[C_{25}H_{23}N_3 + H]^+$.

[0351] Step E: To a stirred solution of the product of Step D (126 mg, 0.35 mmol) in absolute ethanol (3 mL) at room temperature was added maleic acid (40 mg, 0.35 mmol). Stirring was continued for one hour, and the solvents were then removed under reduced pressure. After dissolving in methanol (1 mL) and diluting with H_2O (3 mL), the mixture was lyophilized overnight to provide (+)-2-methyl-5-naphthalen-2-yl-8-pyridazin-3-yl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt (162 mg, 98%, >99% AUC HPLC) as a light purple solid: mp 99-102°C; ^{1}H NMR (500 MHz, CD_3OD) δ 9.18 (dd, *J* = 4.5, 1.0 Hz, 1H), 8.30 (s, 1H), 8.20 (d, *J* = 8.0 Hz,

1H), 8.03–7.98 (br, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.91–7.89 (m, 1H), 7.83–7.80 (m, 2H), 7.72–7.65 (br, 1H), 7.52–7.50 (m, 2H), 7.44 (d, J = 8.5 Hz, 1H), 7.24–6.93 (br, 1H), 6.24 (s, 2H), 4.90–4.80 (m, 1H), 4.57–4.55 (m, 1H), 3.75–3.65 (m, 2H), 3.35–3.25 (m, 1H), 3.03–2.97 (br, 3H), 2.85–2.70 (br, 1H), 2.62–2.56 (m, 1H); ESI MS m/z = 366 $[C_{25}H_{23}N_3 + H]^+$;

Example 51 – Preparation of (+)-2-methyl-8-morpholin-4-yl-5-naphthalen-2-yl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt

[0352] Step A: To a stirred solution of trifluoromethanesulfonic acid 2-methyl-5-naphthalen-2-yl-2,3-4,5-tetrahydro-1*H*-benzo[*c*]azepine-8-yl ester (325 mg, 0.75 mmol) in anhydrous toluene (4.5 mL) were added morpholine (0.13 mL, 1.5 mmol), cesium carbonate (729 mg, 2.2 mmol), and (2-biphenyl)di-*tert*-butylphosphine (67 mg, 0.22 mmol). The reaction mixture was degassed with argon, then palladium(II)acetate (25 mg, 0.11 mmol) was added and the reaction mixture was degassed again. The reaction was heated to reflux and stirred for 24 hours. After cooling to room temperature, the reaction mixture was diluted with methylene chloride and filtered through Celite*. The filtrate was then washed with saturated NH_4Cl (aq) and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification via MPLC (95:5 methylene chloride/methanol) yielded the desired morpholine distinctive (121 mg, 44%) as a yellow foam: $[\alpha]^{25}_D$ +2.0° (c 0.4, methanol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85–7.83 (m, 2H), 7.78–7.76 (m, 1H), 7.60–7.56 (br, 1H), 7.47–7.45 (m, 2H), 7.36 (d, J = 8.5 Hz, 1H), 6.79 (s, 1H), 6.61–6.56 (br, 2H), 4.42 (d, J = 9.0 Hz, 1H), 3.99–3.90 (m, 1H), 3.84 (t, J = 4.5 Hz, 4H), 3.75 (d, J = 13.5 Hz, 1H), 3.18–3.11 (m, 1H), 3.12 (t, J = 4.5 Hz, 4H), 3.03–2.99 (m, 1H), 2.46–2.39 (m, 1H), 2.39 (s, 3H), 2.22–2.15 (m, 1H); ESI MS m/z = 373 $[C_{25}H_{28}N_2O + H]^+$.

[0353] Step B: To a stirred solution of the product of Step A (72 mg, 0.19 mmol) in absolute ethanol (2 mL) at room temperature was added maleic acid (22 mg, 0.19 mmol). Stirring was continued for one hour, and the solvents were then removed under reduced pressure. After dissolving in methanol (1 mL) and diluting with H_2O (3 mL), the mixture was lyophilized overnight to provide (+)-2-methyl-8-morpholin-4-yl-5-naphthalen-2-yl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt (92 mg, 98%, 99.0% AUC HPLC) as an off-white solid: mp = 110–112°C; ^{1}H

*Trademark

NMR (500 MHz, CD_3OD) δ 7.90 (d, *J* = 8.5 Hz, 1H), 7.88–7.86 (m, 1H), 7.82–7.76 (m, 1H), 7.68–7.50 (br, 1H), 7.49–7.47 (m, 2H), 7.37 (d, *J* = 8.5 Hz, 1H), 7.09 (s, 1H), 7.00–6.82 (br, 1H), 6.75–6.55 (br, 1H), 6.25 (s, 2H), 4.68–4.65 (m, 2H), 4.39–4.26 (br, 1H), 3.83 (m, 4H), 3.66–3.57 (br, 2H), 3.17 (m, 4H), 3.02–2.79 (m, 4H), 2.57–2.45 (br, 1H); ESI MS *m/z* = 373 $[C_{25}H_{28}N_2O + H]^+$;

Example 52 – Preparation of (+)-5-benzo[*b*]thiophen-5-yl-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1H-benzo[*c*]azepine, maleate salt and (–)-5-benzo[*b*]thiophen-5-yl-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt

[0354] Step A: To a solution of 5-bromobenzo [*b*] thiophene (5.0 g, 23.5 mmol) in *N,N*-dimethylformamide (50 mL) at room temperature were added tri-*o*-tolylphosphine (0.64 g, 2.1 mmol) and triethylamine (9.9 mL, 70.4 mmol). The reaction mixture was degreased with argon and then ethyl acrylate (7.7 mL, 70.4 mmol) and tris(dibenzylideneacetone)dipalladium(0) (0.65 g, 0.7 mmol) were added to it. The resultant solution was degreased with argon and then heated at 100°C overnight. The reaction solution was then cooled to room temperature, diluted with ethyl acetate, washed with water (2×), saturated ammonium chloride and brine, dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained was purified by flash column chromatography (95:5 to 93:7 hexanes/ethyl acetate) to give the desired product (2.5 g, 46%) as a light yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.94 (d, *J* = 1.5 Hz, 1H), 7.87 (d, *J* = 8.5 Hz, 1H), 7.81 (d, *J* = 16.0 Hz, 1H), 7.54 (dd, *J* = 8.4 and 1.6 Hz, 1H), 7.49 (d, *J* = 5.4 Hz, 1H), 7.36 (d, *J* = 5.4 Hz, 1H), 6.50 (d, *J* = 15.9 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 1.35 (t, *J* = 7.2 Hz, 3H).

[0355] Step B: To a solution of the ethyl ester (1.76 g, 7.6 mmol) from step A above in a mixture of tetrahydrofuran (30 mL) and methanol (15 mL) was added aqueous sodium hydroxide (15 mL, 1 M). The reaction solution was stirred at room temperature overnight and then acidified with aqueous hydrochloric acid (3 mL, 6 M). The resultant solution was concentrated under reduced pressure and the residue obtained was diluted with water, and then extracted with a 3:1 mixture of chloroform and 2-propanol (3×). The combined organic extract was dried over sodium sulfate and concentrated under reduced pressure to give the crude acid (1.85 g), which was

used in the next step without any purification: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.37 (br s, 1H), 8.17 (s, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 5.4 Hz, 1H), 7.73–7.69 (m, 2H), 7.48 (d, J = 5.3 Hz, 1H), 6.59 (d, J = 16.0 Hz, 1H).

[0356] Step C: To a solution of the acid (1.85 g, 7.6 mmol) from step B above and *N*-methyl morpholine (1.5 mL, 13.7 mmol) in dichloromethane (50 mL) at –20°C was added isobutyl chloroformate (1.2 mL, 9.1 mmol) dropwise. The reaction solution was stirred at –20°C for 45 minutes and then a solution of 3-(methoxybenzyl) methylamine (1.3 g, 8.4 mmol) in dichloromethane (10 mL) was added to it dropwise. The resultant solution was warmed to room temperature and stirred overnight. The reaction solution was then washed with water, saturated sodium bicarbonate and brine, dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained was purified by flash column chromatography (95:5 to 50:50 hexanes/ethyl acetate) to give the desired product (2.0 g, 78%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.96–7.86 (m, 3H), 7.59–7.37 (m, 2H), 7.34–7.26 (m, 2H), 7.04–6.78 (m, 4H), 4.70 (d, J = 13.5 Hz, 2H), 3.80 (s, 3H), 3.10 (d, J = 17.9 Hz, 3H).

[0357] Step D: To a solution of the amide (2.8 g, 8.3 mmol) from step C above in dichloroethane (200 mL) was added Eaton's reagent (20 mL, 126 mmol) and the resultant solution was heated at 90°C for 16 hours. The reaction solution was then cooled to room temperature and diluted with dichloromethane (100 mL) and water (300 mL). To this solution was then added sodium hydroxide (110 mL, 2 M) dropwise. After the addition, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3×). The combined organic extract was washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained was purified by flash column chromatography (60:40:2 hexanes/ethyl acetate/methanol) to give the desired product (1.08 g, 38%) as a light yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.78 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 1.5 Hz, 1H), 7.43 (d, J = 5.5 Hz, 1H), 7.26–7.24 (m, 1H), 7.06 (dd, J = 8.4, 1.7 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 6.71–6.69 (m, 2H), 5.08 (d, J = 16.1 Hz, 1H), 4.59 (dd, J = 11.5, 5.2 Hz, 1H), 4.12 (dd, J = 11.4, 4.2 Hz, 1H), 3.79 (s, 3H), 3.32 (dd, J = 13.7, 11.6 Hz, 1H), 3.07 (s, 3H), 2.99 (dd, J = 13.8, 5.4 Hz, 1H); ESI-MS m/z 338 $[M+H]^+$.

[0358] Step E: To a solution of the lactam (0.90 g, 2.7 mmol) from step D above in tetrahydrofuran (40 mL) was added borane-tetrahydrofuran complex (5.4 mL, 5.4 mmol, 1M in tetrahydrofuran) at room temperature. The resultant solution was heated under reflux for 1 hour and then cooled to room temperature. To this solution was then added an aqueous solution of hydrochloric acid (17 mL, 6 M). The resultant solution was heated under reflux for 1 hour, and then was cooled to room temperature and concentrated under reduced pressure. The residue obtained was basified with an aqueous solution of sodium hydroxide (2 M) to pH ~ 9 and then extracted with ethyl acetate (3×). The combined organic extract was washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained was purified by flash column chromatography (96:3.6:0.4 dichloromethane/methanol/concentrated ammonium hydroxide) to give the desired product (0.55 g, 64%) as a white foam: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85 (d, J = 8.3 Hz, 1H), 7.60 (s, 1H), 7.44 (d, J = 5.4 Hz, 1H), 7.29–7.26 (m, 1H), 7.20 (d, J = 8.3 Hz, 1H), 6.77 (s, 1H), 6.58 (br s, 2H), 4.39 (d, J = 9.0 Hz, 1H), 3.92 (d, J = 13.8 Hz, 1H), 3.77-3.70 (m, 1H), 3.77 (s, 3H), 3.17–3.12 (m, 1H), 2.99 (t, J = 10.4 Hz, 1H), 2.44–2.33 (m, 1H), 2.40 (s, 3H), 2.18–2.14 (m, 1H).

[0359] Step F: The 8-methoxy benzoazepine (0.55 g) from step E above was resolved by preparative chiral HPLC (CHIRALCEL OJ column, using 80:20:0.1 heptane/ethanol/diethylamine as the eluent) to give the (+)-enantiomer [$[\alpha]^{25}_D$ +22.3° (c 0.13, methanol)] and the (–)-enantiomer [$[\alpha]^{25}_D$ –21.4° (c 0.14, methanol)].

[0360] Step G: The (+)-enantiomer (40 mg, 0.12 mmol) was dissolved in methanol (3 mL) and maleic acid (14 mg, 0.12 mmol) was added to it. To this solution was then added water (15 mL) and the resultant solution was lyophilized overnight to provide (+)-5-benzo[b]thiophen-5-yl-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1H-benzo[c]azepine, maleate salt (49 mg, 91%, >99% AUC HPLC) as a white solid: mp 92–96°C; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.93 (d, J = 8.4 Hz, 1H), 7.62–7.58 (m, 2H), 7.33 (d, J = 5.3 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 2.5 Hz, 1H), 6.87 (br s, 2H), 6.24 (s, 2H), 4.66–4.54 (m, 2H), 4.30 (d, J = 14.0 Hz, 1H), 3.81 (s, 3H), 3.56 (br s, 2H), 2.89 (br s, 3H), 2.68–2.44 (m, 2H); ESI-MS m/z 324 $[M+H]^+$.

[0361] Step H : The (–)-enantiomer (38 mg, 0.12 mmol) was dissolved in methanol (3 mL) and maleic acid (14 mg, 0.12 mmol) was added to it. To this solution was then added water (15 mL) and the resultant solution was lyophilized overnight to provide (-)-5-benzo[*b*]thiophen-5-yl-8-methoxy-2-methyl-2,3,4,5-tetrahydro-1H-benzo[*c*]azepine, maleate salt (48 mg, 92%, >99% AUC HPLC) as a white solid: mp 92–95°C; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.93 (d, J = 8.4 Hz, 1H), 7.62–7.58 (m, 2H), 7.33 (d, J = 5.3 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 2.5 Hz, 1H), 6.87 (br s, 2H), 6.24 (s, 2H), 4.66–4.54 (m, 2H), 4.30 (d, J = 14.0 Hz, 1H), 3.81 (s, 3H), 3.56 (br s, 2H), 2.91 (br s, 3H), 2.90–2.44 (m, 2H); ESI-MS m/z 324 $[M+H]^+$.

<u>Example 53</u> – Preparation of (+/-)-8-methoxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt

[0362] Step A: To a solution of aqueous 2N sodium hydroxide (100 mL) was added methyl 3,3-dimethoxy propionate (25.0 g, 0.17 mol). The reaction solution was stirred at 50°C for 1 h and then cooled to room temperature. The resultant reaction mixture was acidified with 6 N hydrochloric acid to pH 1 and extracted with dichloromethane (3×). The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to give the desired acid (18.0 g, 80%) as a clear colorless oil, which was used in the next step without further purification: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.83 (t, J = 5.7 Hz, 1H), 3.39 (s, 6H), 2.71 (d, J = 5.7 Hz, 2H).

[0363] Step B: To a solution of 3-methoxybenzylamine (7.8 g, 57 mmol) and the acid (7.6 g, 57 mmol) from step A above in dichloromethane (400 mL) at room temperature was added 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (12.0 g, 62.7 mmol). The reaction solution was stirred at room temperature for 16 hours. The resultant reaction mixture was washed with water, aqueous 1 N hydrochloric acid, water and aqueous saturated sodium bicarbonate, dried over sodium sulfate and concentrated *in vacuo*. The crude acetal (13.3 g, 92%) as a light yellow was used in the next step without further purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.24 (d, J = 8.0 Hz, 1H), 6.86 (dd, J = 7.5, 0.5 Hz, 1H), 6.83–6.80 (m, 2H), 6.40 (br, 1H), 4.73 (t, J = 5.5 Hz, 1H), 4.44 (d, J = 5.5 Hz, 2H), 3.80 (s, 3H), 3.39 (s, 6H), 2.59 (d, J = 5.5 Hz, 2H).

[0364] Step C: A solution of the acetal (12.2 g, 48.2 mmol) from step B above in concentrated hydrochloric acid (120 mL) was stirred at room temperature for 2 hours. The resultant reaction mixture was diluted with water, saturated with sodium chloride and extracted with chloroform. The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to give the crude product, which was purified by crystallization from dichloromethane to give the desired lactam (5.9 g, 59%) as a light yellow solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29 (d, J = 8.5 Hz, 1H), 7.08 (d, J = 12.0 Hz, 1H), 6.89 (dd, J = 8.0, 2.5 Hz, 1H), 6.78 (d, J = 2.5 Hz, 1H), 6.29 (br, 1H), 6.17 (dd, J = 12.0, 2.0 Hz, 1H), 4.13 (d, J = 5.5 Hz, 2H), 3.84 (s, 3H).

[0365] Step D: To a mixture of the lactam (3.0 g, 16 mmol) from step C above and benzene (9.0 mL, 0.10 mol) was added triflic acid (24.0 mL, 0.27 mol). The reaction solution was stirred at room temperature for 5 hours and then it was diluted with water and extracted with dichloromethane (3×). The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to give the desired 5-phenyllactam (4.4 g, quantitative) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 (t, J = 7.0 Hz, 2H), 7.22 (t, J = 7.0 Hz, 1H), 7.12 (d, J = 7.0 Hz, 2H), 6.86 (d, J = 8.5 Hz, 1H), 6.72 (d, J = 8.5, 2.5 Hz, 1H), 6.64 (d, J = 2.5 Hz, 1H), 6.30 (br, 1H), 4.56 (dd, J = 16.0, 6.0 Hz, 1H), 4.49 (dd, J = 10.5, 4.5 Hz, 1H), 4.27 (dd, J = 16.0, 5.0 Hz, 1H), 3.78 (s, 3H), 3.15 (dd, J = 14.5, 10.5 Hz, 1H), 3.00 (dd, J = 14.5, 4.5 Hz, 1H).

[0366] Step E: To a solution of the 5-phenyllactam (4.2 g, 19.5 mmol) from step D above in THF (120 mL) was added borane•dimethylsulfide (24.5 mL of 2M in tetrahydrofuran, 49 mmol) in batches. The reaction solution was stirred at room temperature for 16 h and then additional borane•dimethylsulfide (5.0 mL of 2M in tetrahydrofuran, 10 mmol) was added to it. The reaction solution was stirred at room temperature for 5 hours and then quenched with methanol. The resultant mixture was concentrated *in vacuo* and the residue obtained was dissolved in dioxane (80 mL) and 6 N hydrochloric acid (40 mL) and heated under reflux for 1 hour. The resultant solution was cooled to room temperature, neutralized with aqueous sodium hydroxide and extracted with dichloromethane (3×). The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The crude product obtained was purified by flash column chromatography (99:0.9:0.1 to 90:9:1 dichloromethane/methanol/concentrated ammonium hydroxide) to give the desired

benzazepine (2.7 g, 54%) as a light yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (t, *J* = 7.5 Hz, 2H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 2H), 6.74 (d, *J* = 2.5 Hz, 1H), 6.66–6.54 (m, 2H), 4.36 (d, *J* = 9.5 Hz, 1H), 4.00 (d, *J* = 15.0 Hz, 1H), 3.87 (d, *J* = 14.5 Hz, 1H), 3.77 (s, 3H), 3.29–3.22 (m, 1H), 3.19–3.14 (m, 1H), 2.27–2.13 (m, 2H), 1.69 (br, 1H).

[0367] Step F: To a solution of the newly obtained benzazepine (0.60 g, 2.4 mmol) from step E above in methanol (10 mL) were added maleic acid (0.28 g, 2.4 mmol). The resultant solution was sonicated for 5 minutes and concentrated *in vacuo*. The residue obtained was dissolved in ethyl acetate and sonicated. The precipitation formed was collected by filtration to give (+/-)-8-methoxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt (0.59 g, 67%, >99% AUC HPLC) as a white solid: mp 154–156°C; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.38 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 2H), 7.01 (d, *J* = 2.5 Hz, 1H), 6.85 (dd, *J* = 8.5, 2.5 Hz, 1H); 6.82–6.79 (m, 1H), 6.24 (s, 2H), 4.53 (d, *J* = 8.5 Hz, 1H), 4.42 (d, *J* = 14.0 Hz, 1H), 4.17 (d, *J* = 14.0 Hz, 1H), 3.80 (s, 3H), 3.52–3.41 (m, 2H), 2.59–2.50 (m, 1H), 2.40–2.35 (m, 1H); ESI MS *m/z* 254 $[M+H]^+$.

<u>Example 54</u> – Preparation of (+/-)-2-ethyl-8-methoxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt

[0368] Step A: To a solution of aqueous 2N sodium hydroxide (100 mL) was added methyl 3,3-dimethoxy propionate (25.0 g, 0.17 mol). The reaction solution was stirred at 50°C for 1 hour and then cooled to room temperature. The resultant reaction mixture was acidified with 6 N hydrochloric acid to pH 1 and extracted with dichloromethane (3×). The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to give the desired acid (18.0 g, 80%) as a clear colorless oil, which was used in the next step without further purification: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.83 (t, *J* = 5.7 Hz, 1H), 3.39 (s, 6H), 2.71 (d, *J* = 5.7 Hz, 2H).

[0369] Step B: To a solution of 3-methoxybenzylamine (7.8 g, 57 mmol) and the acid (7.6 g, 57 mmol) from step A above in dichloromethane (400 mL) at room temperature was added 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (12.0 g, 62.7 mmol). The reaction solution was stirred at room temperature for 16 hours. The resultant reaction mixture was washed with water, aqueous 1 N hydrochloric acid, water and aqueous saturated sodium bicarbonate,

dried over sodium sulfate and concentrated *in vacuo*. The crude acetal (13.3 g, 92%) as a light yellow was used in the next step without further purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.24 (d, J = 8.0 Hz, 1H), 6.86 (dd, J = 7.5, 0.5 Hz, 1H), 6.83–6.80 (m, 2H), 6.40 (br, 1H), 4.73 (t, J = 5.5 Hz, 1H), 4.44 (d, J = 5.5 Hz, 2H), 3.80 (s, 3H), 3.39 (s, 6H), 2.59 (d, J = 5.5 Hz, 2H).

[0370] Step C: A solution of the acetal (12.2 g, 48.2 mmol) from step B above in concentrated hydrochloric acid (120 mL) was stirred at room temperature for 2 hours. The resultant reaction mixture was diluted with water, saturated with sodium chloride and extracted with chloroform. The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to give the crude product, which was purified by crystallization from dichloromethane to give the desired lactam (5.9 g, 59%) as a light yellow solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29 (d, J = 8.5 Hz, 1H), 7.08 (d, J = 12.0 Hz, 1H), 6.89 (dd, J = 8.0, 2.5 Hz, 1H), 6.78 (d, J = 2.5 Hz, 1H), 6.29 (br, 1H), 6.17 (dd, J = 12.0, 2.0 Hz, 1H), 4.13 (d, J = 5.5 Hz, 2H), 3.84 (s, 3H).

[0371] Step D : To a mixture of the lactam (3.0 g, 16 mmol) from step C above and benzene (9.0 mL, 0.10 mol) was added triflic acid (24.0 mL, 0.27 mol). The reaction solution was stirred at room temperature for 5 hours and then it was diluted with water and extracted with dichloromethane (3×). The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to give the desired 5-phenyllactam (4.4 g, quantitative) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 (t, J = 7.0 Hz, 2H), 7.22 (t, J = 7.0 Hz, 1H), 7.12 (d, J = 7.0 Hz, 2H), 6.86 (d, J = 8.5 Hz, 1H), 6.72 (d, J = 8.5, 2.5 Hz, 1H), 6.64 (d, J = 2.5 Hz, 1H), 6.30 (br, 1H), 4.56 (dd, J = 16.0, 6.0 Hz, 1H), 4.49 (dd, J = 10.5, 4.5 Hz, 1H), 4.27 (dd, J = 16.0, 5.0 Hz, 1H), 3.78 (s, 3H), 3.15 (dd, J = 14.5, 10.5 Hz, 1H), 3.00 (dd, J = 14.5, 4.5 Hz, 1H).

[0372] Step E: To a solution of the 5-phenyllactam (4.2 g, 19.5 mmol) from step D above in THF (120 mL) was added borane•dimethylsulfide (24.5 mL of 2M in tetrahydrofuran, 49 mmol) in batches. The reaction solution was stirred at room temperature for 16 hours and then additional borane•dimethylsulfide (5.0 mL of 2M in tetrahydrofuran, 10 mmol) was added to it. The reaction solution was stirred at room temperature for 5 hours and then quenched with methanol. The resultant mixture was concentrated *in vacuo* and the residue obtained was dissolved in dioxane (80 mL) and 6N hydrochloric acid (40 mL) and heated under reflux for 1 hour. The

resultant solution was cooled to room temperature, neutralized with aqueous sodium hydroxide and extracted with dichloromethane (3×). The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The crude product obtained was purified by flash column chromatography (99:0.9:0.1 to 90:9:1 dichloromethane/methanol/concentrated ammonium hydroxide) to give the desired benzazepine (2.7 g, 54%) as a light yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (t, J = 7.5 Hz, 2H), 7.25 (t, J = 7.5 Hz, 1H), 7.16 (d, J = 7.5 Hz, 2H), 6.74 (d, J = 2.5 Hz, 1H), 6.66–6.54 (m, 2H), 4.36 (d, J = 9.5 Hz, 1H), 4.00 (d, J = 15.0 Hz, 1H), 3.87 (d, J = 14.5 Hz, 1H), 3.77 (s, 3H), 3.29–3.22 (m, 1H), 3.19–3.14 (m, 1H), 2.27–2.13 (m, 2H), 1.69 (br, 1H).

[0373] Step F: To a solution of the secondary benzazepine (0.98 g, 3.9 mmol) from step E above in dichloromethane (50 mL) were added acetaldehyde (0.44 mL, 7.7 mmol), sodium triacetoxyborohydride (1.8 g, 8.3 mmol), acetic acid (0.2 mL), and 3Å molecular sieves (1.0 g). The reaction solution was stirred at room temperature for 24 h and then it was diluted with dichloromethane, washed with aqueous 1 N sodium carbonate, dried over sodium sulfate and concentrated *in vacuo*. The crude product obtained was purified by flash column chromatography (dichloromethane to 95:4.5:0.5 dichloromethane/methanol/concentrated ammonium hydroxide) to give the desired *N*-ethyl benzazepine (0.53 g, 48%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (t, J = 7.5 Hz, 2H), 7.25 (t, J = 7.5 Hz, 1H), 7.17 (d, J = 7.5 Hz, 2H), 6.75 (d, J = 2.5 Hz, 1H), 6.68–6.40 (br, 2H), 4.27 (d, J = 8.5 Hz, 1H), 3.94 (d, J = 13.5 Hz, 1H), 3.81 (d, J = 14.5 Hz, 1H), 3.77 (s, 3H), 3.27–3.16 (br, 1H), 3.06–3.01 (m, 1H), 2.55–2.45 (m, 2H), 2.32–2.24 (m, 1H), 2.13–2.04 (br, 1H), 1.11 (t, J = 7.0 Hz, 3H); ESI MS *m/z* 282 $[M+H]^+$.

[0374] Step G: To a solution of the newly obtained *N*-ethyl benzazepine (61 mg, 0.22 mmol) from step F above in methanol (2 mL) were added maleic acid (25 mg, 0.22 mmol) and water (10 mL). The resultant solution was lypholized overnight to give (+/-)-2-ethyl-8-methoxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt (86 mg, 97.4% AUC HPLC) as a white solid: ^{1}H NMR (CD_3OD, 500 MHz) δ 7.42–7.11 (br, 5H), 7.06 (s, 1H), 6.98–6.50 (br, 2H), 6.25 (s, 2H), 4.67–4.16 (br, 5H), 3.81 (s, 3H), 3.70–3.42 (br, 2H), 3.20–2.95 (br, 1H), 2.51–2.21 (br, 1H), 1.43–1.38 (br, 3H); ESI MS *m/z* 282 $[M+H]^+$.

Example 55 – Preparation of (+/-)-2-isopropyl-8-methoxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt

[0375] Pursuant to the general method described above in Example 54, the following product was prepared: (+/-)-2-isopropyl-8-methoxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, maleate salt: mp 172–175°C; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.40–6.32 (br, 8H), 6.24 (s, 2H), 4.63–4.02 (br, 3H), 3.80 (s, 3H), 3.75–3.44 (br, 3H), 2.94–2.23 (br, 2H), 1.29 (br, 6H); ESI MS *m/z* 296 $[M+H]^+$.

Example 56 – Preparation of 4-(5-phenyl-2-(2,2,2-trifluoroethyl)-2,3,4,5,-tetrahydro-1*H*-benzo[*c*]-azepin-8-yl)morpholine, maleate salt

[0376] Step A: To a solution of aqueous 2N sodium hydroxide (100 mL) was added methyl 3,3-dimethoxy propionate (25.0 g, 0.17 mol). The reaction solution was stirred at 50°C for 1 hour and then cooled to room temperature. The resultant reaction mixture was acidified with 6 N hydrochloric acid to pH 1 and extracted with dichloromethane (3×). The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to give the desired acid (18.0 g, 80%) as a clear colorless oil, which was used in the next step without further purification: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.83 (t, J = 5.7 Hz, 1H), 3.39 (s, 6H), 2.71 (d, J = 5.7 Hz, 2H).

[0377] Step B: To a solution of 3-methoxybenzylamine (7.8 g, 57 mmol) and the acid (7.6 g, 57 mmol) from step A above in dichloromethane (400 mL) at room temperature was added 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (12.0 g, 62.7 mmol). The reaction solution was stirred at room temperature for 16 hours. The resultant reaction mixture was washed with water, aqueous 1N hydrochloric acid, water and aqueous saturated sodium bicarbonate, dried over sodium sulfate and concentrated *in vacuo*. The crude acetal (13.3 g, 92%) as a light yellow was used in the next step without further purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.24 (d, J = 8.0 Hz, 1H), 6.86 (dd, J = 7.5, 0.5 Hz, 1H), 6.83–6.80 (m, 2H), 6.40 (br, 1H), 4.73 (t, J = 5.5 Hz, 1H), 4.44 (d, J = 5.5 Hz, 2H), 3.80 (s, 3H), 3.39 (s, 6H), 2.59 (d, J = 5.5 Hz, 2H).

[0378] Step C: A solution of the acetal (12.2 g, 48.2 mmol) from step B above in concentrated hydrochloric acid (120 mL) was stirred at room temperature for 2 hours. The resultant reaction mixture was diluted with water, saturated with sodium

chloride and extracted with chloroform. The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to give the crude product, which was purified by crystallization from dichloromethane to give the desired lactam (5.9 g, 59%) as a light yellow solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29 (d, J = 8.5 Hz, 1H), 7.08 (d, J = 12.0 Hz, 1H), 6.89 (dd, J = 8.0, 2.5 Hz, 1H), 6.78 (d, J = 2.5 Hz, 1H), 6.29 (br, 1H), 6.17 (dd, J = 12.0, 2.0 Hz, 1H), 4.13 (d, J = 5.5 Hz, 2H), 3.84 (s, 3H).

[0379] Step D: To a mixture of the lactam (3.0 g, 16 mmol) from step C above and benzene (9.0 mL, 0.10 mol) was added triflic acid (24.0 mL, 0.27 mol). The reaction solution was stirred at room temperature for 5 hours and then it was diluted with water and extracted with dichloromethane (3×). The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to give the desired 5-phenyllactam (4.4 g, quantitative) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 (t, J = 7.0 Hz, 2H), 7.22 (t, J = 7.0 Hz, 1H), 7.12 (d, J = 7.0 Hz, 2H), 6.86 (d, J = 8.5 Hz, 1H), 6.72 (d, J = 8.5, 2.5 Hz, 1H), 6.64 (d, J = 2.5 Hz, 1H), 6.30 (br, 1H), 4.56 (dd, J = 16.0, 6.0 Hz, 1H), 4.49 (dd, J = 10.5, 4.5 Hz, 1H), 4.27 (dd, J = 16.0, 5.0 Hz, 1H), 3.78 (s, 3H), 3.15 (dd, J = 14.5, 10.5 Hz, 1H), 3.00 (dd, J = 14.5, 4.5 Hz, 1H).

[0380] Step E: To a solution of the 5-phenyllactam (4.2 g, 19.5 mmol) from step D above in THF (120 mL) was added borane-dimethyl sulfide (24.5 mL of 2M in tetrahydrofuran, 49 mmol) in batches. The reaction solution was stirred at room temperature for 16 hours and then additional borane-dimethyl sulfide (5.0 mL of 2M in tetrahydrofuran, 10 mmol) was added to it. The reaction solution was stirred at room temperature for 5 hours and then quenched with methanol. The resultant mixture was concentrated *in vacuo* and the residue obtained was dissolved in dioxane (80 mL) and 6N hydrochloric acid (40 mL) and heated under reflux for 1 hour. The resultant solution was cooled to room temperature, neutralized with aqueous sodium hydroxide and extracted with dichloromethane (3×). The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The crude product obtained was purified by flash column chromatography (99:0.9:0.1 to 90:9:1 dichloromethane/methanol/concentrated ammonium hydroxide) to give the desired benzazepine (2.7 g, 54%) as a light yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (t, J = 7.5 Hz, 2H), 7.25 (t, J = 7.5 Hz, 1H), 7.16 (d, J = 7.5 Hz, 2H), 6.74 (d, J = 2.5 Hz, 1H), 6.66–6.54 (m, 2H), 4.36 (d, J = 9.5 Hz, 1H), 4.00 (d, J = 15.0 Hz, 1H),

3.87 (d, J = 14.5 Hz, 1H), 3.77 (s, 3H), 3.29–3.22 (m, 1H), 3.19–3.14 (m, 1H), 2.27–2.13 (m, 2H), 1.69 (br, 1H).

[0381] Step F: To a solution of the 2*H*-benzazepine (2.9 g, 11.4 mmol) from step E above in dichloromethane (120 mL) were added pyridine (1.8 mL, 23 mmol), 4-dimethylaminopyridine (0.14 g, 1.1 mmol) and acetic anhydride (1.3 mL, 14.2 mmol) at 0°C. The reaction solution was let to warm to room temperature and stirred for 15 hours. The resultant reaction mixture was quenched with aqueous ammonium chloride, washed with 1 N hydrochloric acid and aqueous saturated sodium bicarbonate, dried over sodium sulfate and concentrated *in vacuo*. The crude product obtained (3.2 g, 95%) as a light yellow oil, was used in the next step without further purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (t, J = 7.5 Hz, 2H), 7.24 (t, J = 7.5 Hz, 1H), 7.09 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 2.5 Hz, 1H), 6.82–6.63 (m, 2H), 4.69–4.30 (m, 3H), 3.83–3.47 (m, 5H), 2.41–1.92 (m, 5H).

[0382] Step G: To a solution of the 8-methoxybenzazepine (3.2 g, 10.8 mmol) from step F above in dichloromethane (90 mL) at –78°C was added boron tribromide (10 mL, 0.11 mol) slowly. After the addition, the reaction solution was stirred at -78°C for 4 hours and at room temperature for 1 hour. The resultant reaction mixture was cooled to 0°C, quenched by slow addition of methanol and concentrated *in vacuo*. The residue obtained (3.2 g, quantitative) as an off-white solid, was used in the next step without further purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.99–7.56 (br, 1H), 7.32 (t, J= 7.5 Hz, 2H), 7.23 (t, J = 7.5 Hz, 1H), 7.12 (d, J = 2.5 Hz, 1H), 7.09 (d, J = 7.5 Hz, 2H), 6.73–6.06 (m, 2H), 4.68–4.31 (m, 3H), 3.83–3.54 (m, 2H), 2.47–2.12 (m, 2H), 2.12–1.93 (m, 3H); ESI MS *m/z* 282 $[M+H]^+$.

[0383] Step H: To a solution of the phenol (0.85 g, 3.0 mmol) from step G above in chloroform (30 mL) at 0°C was added triethylamine (5.1 mL, 36 mmol) followed by triflic anhydride (1.0 mL, 6.0 mmol) dropwise. The resultant reaction solution was stirred at room temperature for 12 h and then additional triethylamine (1.0 mL, 7.0 mmol) and triflic anhydride (1.0 mL, 6.0 mmol) were added. The reaction solution was stirred at room temperature for 1 h and then quenched with aqueous saturated sodium bicarbonate. The resultant mixture was extracted with dichlormethane (2×), washed with aqueous saturated ammonium chloride, dried over sodium sulfate and concentrated *in vacuo*. The residue obtained was purified by flash

column chromatography (66:33 to 33:66 hexanes/ethyl acetate) to give the desired triflate (0.52 g, 42%) as an orange solid: ESI MS *m/z* 414 $[M+H]^+$.

[0384] Step I: To a solution of the triflate (0.20 g, 0.48 mmol) from step H above in toluene (5 mL) were added cesium carbonate (0.49 g, 1.5 mmol), 2-(dicyclohexylphosphino)-2',4',6'-tri-*i*-propyl-1,1'-biphenyl (24 g, 0.05 mmol) and morpholine (0.042 mL, 1.0 mmol). The resultant mixture was flushed with argon for 10 minutes, and then palladium(II) acetate (11 mg, 0.05 mmol) was added to it. The reaction solution was heated at 100°C under argon for 13 hours and then cooled to room temperature. The resultant mixture was diluted with dichloromethane, washed with water and brine, dried over sodium sulfate and concentrated *in vacuo*. The crude product obtained was purified by flash column chromatography (99:0.9:0.1to 97:2.7:0.3 dichloromethane/methanol/concentrated ammonium hydroxide) to give the desired 8-morpholinyl benzazepine (0.13 g, 83%) as a white foam: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32 (t, J = 8.0 Hz, 2H), 7.23 (t, J = 7.5 Hz, 1H), 7.09 (d, J = 7.5 Hz, 2H), 6.95–6.65 (m, 3H), 4.78–4.30 (m, 3H), 3.90–3.41 (m, 6H), 3.20–3.13 (m, 4H), 2.43–2.17 (m, 2H), 2.20–1.74 (m, 3H); ESI MS *m/z* 351 $[M+H]^+$.

[0385] Step J: To a solution of the *N*-acetyl benzazepine (0.14 g, 0.40 mmol) from step I above in methanol (10 mL) was added an aqueous 2N solution of sodium hydroxide (10 mL). The reaction solution was heated under reflux for 72 hours and then cooled to room temperature. The resultant reaction mixture was extracted with dichloromethane, washed with water and aqueous saturated sodium bicarbonate, dried over sodium sulfate and concentrated *in vacuo*. The residue obtained was purified by flash column chromatography (dichloromethane to 90:9:1 dichloromethane/methanol/concentrated ammonium hydroxide) to give the desired 2*H*-benzazepine (0.11 g, 89%) as a white foam: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.35 (t, J = 7.5 Hz, 2H), 7.24 (t, J = 7.5 Hz, 1H), 7.14 (d, J = 7.5 Hz, 2H), 6.84 (d, J = 2.5 Hz, 1H), 6.65–6.60 (m, 1H), 6.49–6.38 (br, 1H), 4.33 (d, J = 8.5 Hz, 1H), 3.95 (d, J = 14.5 Hz, 1H), 3.77 (d, J = 14.5 Hz, 1H), 3.71 (t, J = 5.0 Hz, 4H), 3.10–2.87 (m, 6H), 2.21–2.12 (m, 1H), 2.03–1.85 (m, 1H).

[0386] Step K: To a solution of the 2*H*-benzazepine (80 mg, 0.26 mmol) from step J above in acetone (5 mL) were added triethylamine (0.06 mL, 0.43 mmol), *N*,*N*-diisopropylethylamine (0.025 mL, 0.26 mmol) and 2,2,2-trifluoroethyl methanesulfonate (60 mg, 0.26 mmol). The reaction solution was heated under reflux

for 1 hour and then cooled to room temperature and concentrated *in vacuo*. The residue obtained was purified by flash column chromatography (90:10 to 80:20 hexanes/ethyl acetate) to give the *N*-trifluoroethyl benzazepine (70 mg, 69%) as a white foam: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (t, J = 7.5 Hz, 2H), 7.25 (t, J = 7.5 Hz, 1H), 7.15 (d, J = 7.5 Hz, 2H), 6.72 (s, 1H), 6.67–6.50 (br, 2H), 4.29 (d, J = 8.0 Hz, 1H), 4.19–4.07 (br, 1H), 3.90 (d, J = 15.0 Hz, 1H), 3.87–3.84 (m, 4H), 3.32–3.26 (br, 2H), 3.16–3.12 (m, 4H), 3.03–2.89 (m, 2H), 2.26–2.19 (m, 1H), 2.09–2.00 (m, 1H). To a solution of the *N*-trifluoroethyl benzazepine (65 mg, 0.17 mmol) in methanol (2 mL) were added maleic acid (19 mg, 0.17 mmol) and water (10 mL). The resultant solution was lypholized overnight to give 4-(5-phenyl-2-(2,2,2-trifluoroethyl)-2,3,4,5,-tetrahydro-1*H*-benzo[*c*]-azepin-8-yl)morpholine, maleate salt (84 mg, >99.0% AUC HPLC) as a light pink solid: ^{1}H NMR (CD_3OD, 500 MHz) δ 7.32 (t, J = 7.5 Hz, 2H), 7.23 (t, J = 7.5 Hz, 1H), 7.15 (d, J = 7.5 Hz, 2H), 6.84 (d, J = 2.5 Hz, 1H), 6.75 (d, J = 6.5 Hz, 1H), 6.71–6.54 (br, 1H), 6.30 (s, 2H), 4.35 (d, J = 7.5 Hz, 1H), 4.21–4.04 (br, 1H), 3.92 (d, J = 15.0 Hz, 1H), 3.84 (t, J = 5.0 Hz, 4H), 3.29–3.25 (m, 2H), 3.22–3.07 (m, 6H), 2.34–2.27 (m, 1H), 2.06 (d, J = 13.5 Hz, 1H); ESI MS *m/z* 391 $[M+H]^+$.

<u>Example 57</u> - Preparation of (–)-4-(2-ethyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine, maleate salt and (+)-4-(2-ethyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine, maleate salt

[0387] Step A: To a solution of aqueous 2N sodium hydroxide (100 mL) was added methyl 3,3-dimethoxy propionate (25.0 g, 0.17 mol). The reaction solution was stirred at 50°C for 1 hour and then cooled to room temperature. The resultant reaction mixture was acidified with 6 N hydrochloric acid to pH 1 and extracted with dichloromethane (3×). The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to give the desired acid (18.0 g, 80%) as a clear colorless oil, which was used in the next step without further purification: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.83 (t, J = 5.7 Hz, 1H), 3.39 (s, 6H), 2.71 (d, J = 5.7 Hz, 2H).

[0388] Step B: To a solution of 3-methoxybenzylamine (7.8 g, 57 mmol) and the acid (7.6 g, 57 mmol) from step A above in dichloromethane (400 mL) at room temperature was added 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide

hydrochloride (12.0 g, 62.7 mmol). The reaction solution was stirred at room temperature for 16 hours. The resultant reaction mixture was washed with water, aqueous 1 N hydrochloric acid, water and aqueous saturated sodium bicarbonate, dried over sodium sulfate and concentrated *in vacuo*. The crude acetal (13.3 g, 92%) as a light yellow was used in the next step without further purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.24 (d, J = 8.0 Hz, 1H), 6.86 (dd, J = 7.5, 0.5 Hz, 1H), 6.83–6.80 (m, 2H), 6.40 (br, 1H), 4.73 (t, J = 5.5 Hz, 1H), 4.44 (d, J = 5.5 Hz, 2H), 3.80 (s, 3H), 3.39 (s, 6H), 2.59 (d, J = 5.5 Hz, 2H).

[0389] Step C: A solution of the acetal (12.2 g, 48.2 mmol) from step B above in concentrated hydrochloric acid (120 mL) was stirred at room temperature for 2 hours. The resultant reaction mixture was diluted with water, saturated with sodium chloride and extracted with chloroform. The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to give the crude product, which was purified by crystallization from dichloromethane to give the desired lactam (5.9 g, 59%) as a light yellow solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29 (d, J = 8.5 Hz, 1H), 7.08 (d, J = 12.0 Hz, 1H), 6.89 (dd, J = 8.0, 2.5 Hz, 1H), 6.78 (d, J = 2.5 Hz, 1H), 6.29 (br, 1H), 6.17 (dd, J = 12.0, 2.0 Hz, 1H), 4.13 (d, J = 5.5 Hz, 2H), 3.84 (s, 3H).

[0390] Step D: To a mixture of the lactam (3.0 g, 16 mmol) from step C above and benzene (9.0 mL, 0.10 mol) was added triflic acid (24.0 mL, 0.27 mol). The reaction solution was stirred at room temperature for 5 hours and then it was diluted with water and extracted with dichloromethane (3×). The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to give the desired 5-phenyllactam (4.4 g, quantitative) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 (t, J = 7.0 Hz, 2H), 7.22 (t, J = 7.0 Hz, 1H), 7.12 (d, J = 7.0 Hz, 2H), 6.86 (d, J = 8.5 Hz, 1H), 6.72 (d, J = 8.5, 2.5 Hz, 1H), 6.64 (d, J = 2.5 Hz, 1H), 6.30 (br, 1H), 4.56 (dd, J = 16.0, 6.0 Hz, 1H), 4.49 (dd, J = 10.5, 4.5 Hz, 1H), 4.27 (dd, J = 16.0, 5.0 Hz, 1H), 3.78 (s, 3H), 3.15 (dd, J = 14.5, 10.5 Hz, 1H), 3.00 (dd, J = 14.5, 4.5 Hz, 1H).

[0391] Step E: To a solution of the 5-phenyllactam (4.2 g, 19.5 mmol) from step D above in THF (120 mL) was added boran-dimethyl sulfide (24.5 mL of 2M in tetrahydrofuran, 49 mmol) in batches. The reaction solution was stirred at room temperature for 16 hours and then additional borane-dimethyl sulfide (5.0 mL of 2M in tetrahydrofuran, 10 mmol) was added to it. The reaction solution was stirred at

room temperature for 5 hours and then quenched with methanol. The resultant mixture was concentrated *in vacuo* and the residue obtained was dissolved in dioxane (80 mL) and 6N hydrochloric acid (40 mL) and heated under reflux for 1 hour. The resultant solution was cooled to room temperature, neutralized with aqueous sodium hydroxide and extracted with dichloromethane (3×). The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The crude product obtained was purified by flash column chromatography (99:0.9:0.1 to 90:9:1 dichloromethane/methanol/concentrated ammonium hydroxide) to give the desired benzazepine (2.7 g, 54%) as a light yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (t, J = 7.5 Hz, 2H), 7.25 (t, J = 7.5 Hz, 1H), 7.16 (d, J = 7.5 Hz, 2H), 6.74 (d, J = 2.5 Hz, 1H), 6.66–6.54 (m, 2H), 4.36 (d, J = 9.5 Hz, 1H), 4.00 (d, J = 15.0 Hz, 1H), 3.87 (d, J = 14.5 Hz, 1H), 3.77 (s, 3H), 3.29–3.22 (m, 1H), 3.19–3.14 (m, 1H), 2.27–2.13 (m, 2H), 1.69 (br, 1H).

[0392] Step F: To a solution of the benzazepine (0.98 g, 3.9 mmol) from step E above in dichloromethane (50 mL) were added acetaldehyde (0.44 mL, 7.7 mmol), sodium triacetoxyborohydride (1.8 g, 8.3 mmol), acetic acid (0.2 mL), and 3Å molecular sieves (1.0 g). The reaction solution was stirred at room temperature for 24 hours and then it was diluted with dichloromethane, washed with aqueous 1N sodium carbonate, dried over sodium sulfate and concentrated *in vacuo*. The crude product obtained was purified by flash column chromatography (dichloromethane to 95:4.5:0.5 dichloromethane/methanol/concentrated ammonium hydroxide) to give the desired *N*-ethyl benzazepine (0.53 g, 48%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (t, J = 7.5 Hz, 2H), 7.25 (t, J = 7.5 Hz, 1H), 7.17 (d, J = 7.5 Hz, 2H), 6.75 (d, J = 2.5 Hz, 1H), 6.68–6.40 (br, 2H), 4.27 (d, J = 8.5 Hz, 1H), 3.94 (d, J = 13.5 Hz, 1H), 3.81 (d, J = 14.5 Hz, 1H), 3.77 (s, 3H), 3.27–3.16 (br, 1H), 3.06–3.01 (m, 1H), 2.55–2.45 (m, 2H), 2.32–2.24 (m, 1H), 2.13–2.04 (br, 1H), 1.11 (t, J = 7.0 Hz, 3H); ESI MS *m/z* 282 $[M+H]^+$.

[0393] Step G: To a solution of the N-ethyl benzazepine (0.47 g, 1.7 mmol) from step F above in acetic acid (25 mL) was added hydrobromic acid (48% solution in water, 25 mL). The reaction solution was heated at 100°C for 20 hours, and then cooled to room temperature and concentrated *in vacuo*. The residue obtained was dissolved in methylene chloride and water, and then carefully neutralized with aqueous saturated sodium bicarbonate to pH > 8. The organic extract was separated,

washed with water and brine, dried over sodium sulfate and concentrated *in vacuo* to give the desired phenol, which was used in the next step without purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (t, J = 7.5 Hz, 2H), 7.25 (t, J = 7.5 Hz, 1H), 7.16 (d, J = 7.5 Hz, 2H), 6.63 (s, 1H), 6.58–6.38 (br, 2H), 4.25 (d, J = 8.0 Hz, 1H), 3.88 (d, J = 13.0 Hz, 1H), 3.76 (d, J = 14.5 Hz, 1H), 3.24–3.13 (br, 1H), 3.03–2.98 (m, 1H), 2.57–2.50 (m, 2H), 2.34–2.27 (m, 1H), 2.14–2.07 (m, 1H), 1.13 (t, J = 7.0 Hz, 3H); ESI MS *m/z* 268 $[M+H]^+$.

[0394] Step H: To a solution of the phenol (1.7 mmol) from step G above in dichloromethane (20 mL) at 0°C were added pyridine (0.24 mL, 3.0 mmol) and triflic anhydride (0.34 mL, 2.0 mmol). The resultant reaction solution was stirred at 0°C for 2 hours, and then it was diluted with dichloromethane, washed with aqueous saturated sodium bicarbonate, dried over sodium sulfate and concentrated *in vacuo*. The desired triflate obtained as a reddish oil was used in the next step without purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 (t, J = 7.5 Hz, 2H), 7.29 (t, J = 7.5 Hz, 1H), 7.17 (d, J = 7.5 Hz, 2H), 7.08 (d, J = 2.5 Hz, 1H), 6.95 (dd, J = 8.5, 2.0 Hz, 1H), 6.77–6.45 (br, 1H), 4.34 (d, J = 10.0 Hz, 1H), 4.02 (d, J= 15.0 Hz, 1H), 3.85 (d, J = 14.5 Hz, 1H), 3.25 (d, J = 10.5 Hz, 1H), 3.10–3.05 (m, 1H), 2.54–2.46 (m, 2H), 2.34–2.26 (m, 1H), 2.07 (d, J = 11.5 Hz, 1H), 1.11 (t, J = 7.0 Hz, 3H); ESI MS *m/z* 400 $[M+H]^+$.

[0395] Step I: To a solution of the triflate (1.7 mmol) from step H above in toluene (14 mL) were added cesium carbonate (1.6 g, 5.0 mmol), 2-(dicyclohexylphosphino)-2',4',6'-tri-*i*-propyl-1,1'-biphenyl (0.16 g, 0.34 mmol) and morpholine (0.29 mL, 3.3 mmol). The resultant mixture was flushed with argon for 5 minutes, and then palladium(II) acetate (38 mg, 0.17 mmol) was added to it. The reaction solution was capped and heated at 100°C under argon for 4 hours, and then cooled to room temperature. The resultant mixture was diluted with dichloromethane, washed with water and brine, dried over sodium sulfate and concentrated *in vacuo*. The crude product obtained was purified by flash column chromatography (dichloromethane to 95:4.5:0.5 dichloromethane/methanol/concentrated ammonium hydroxide) to give the desired 8-morpholinyl benzazepine (0.25 g, 45%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (t, J = 7.5 Hz, 2H), 7.25 (t, J = 7.5 Hz, 1H), 7.17 (d, J = 7.5 Hz, 2H), 6.76 (d, J = 2.5 Hz, 1H), 6.61 (d, J = 6.0 Hz, 1H), 6.58–6.38 (br, 1H), 4.26 (d, J = 9.0 Hz, 1H), 3.95 (d, J = 14.0 Hz, 1H), 3.85 (t, J = 4.5 Hz, 4H),

3.81 (d, J = 14.5 Hz, 1H), 3.27–3.18 (br, 1H), 3.12 (t, J = 4.5 Hz, 4H), 3.06–3.00 (m, 1H), 2.56–2.47 (m, 2H), 2.32–2.25 (m, 1H), 2.12–2.03 (br, 1H), 1.12 (t, J = 7.0 Hz, 3H); ESI MS *m/z* 337 $[M+H]^+$.

[0396] Step J: The 8-morpholinyl benzazepine (0.31 g) from step I above was resolved by preparative chiral HPLC (CHIRALPAK AD column, using 85:15:0.1 heptane/ethanol/trifluoroacetic acid as the eluent) to give the (+)-enantiomer $[[\alpha]^{25}{}_D$ +2.7° (*c* 0.15, methanol)] (0.14 g) and the (–)-enantiomer $[[\alpha]^{25}{}_D$ –2.9° (*c* 0.21, methanol)] (0.15 g). To a solution of the (+)-enantiomer (0.14 g, 0.42 mmol) in methanol (3 mL) were added maleic acid (49 mg, 0.42 mmol) and water (15 mL). The resultant solution was lyophilized overnight to provide the maleate salt (+)-4-(2-ethyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine, maleate salt (0.19 g, 98.6% AUC HPLC) as a light yellow solid: mp 64–66°C; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.38 (t, J = 7.5 Hz, 2H), 7.29 (t, J = 7.5 Hz, 1H), 7.19 (br, 2H), 7.07 (d, J = 2.5 Hz, 1H), 6.98–6.53 (br, 2H), 6.25 (s, 2.1H), 4.52–4.09 (br, 3H), 3.82 (t, J = 4.5 Hz, 4H), 3.70–3.47 (m, 2H), 3.29–3.00 (m, 6H), 2.80–2.21 (br, 2H), 1.48–1.31 (br, 3H); ESI MS *m/z* 337 $[M+H]^+$.

[0397] To a solution of the (–)-enantiomer (0.14 g, 0.42 mmol) in methanol (3 mL) were added maleic acid (49 mg, 0.42 mmol) and water (15 mL). The resultant solution was lyophilized overnight to provide (-)-4-(2-ethyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine, maleate salt (0.19 g, 98.9% AUC HPLC) as a yellow solid: mp 68–72°C; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.38 (t, J = 7.5 Hz, 2H), 7.29 (t, J = 7.5 Hz, 1H), 7.19 (br, 2H), 7.07 (d, J = 2.5 Hz, 1H), 6.98–6.53 (br, 2H), 6.25 (s, 2H), 4.52–4.09 (br, 3H), 3.82 (t, J = 4.5 Hz, 4H), 3.70–3.47 (m, 2H), 3.29–3.00 (m, 6H), 2.80–2.21 (br, 2H), 1.48–1.31 (br, 3H); ESI MS *m/z* 337 $[M+H]^+$.

Example 58: Preparation of (+)-4-(2-isopropyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine, maleate salt

[0398] Pursuant to the general method described above in Example 57, the following products were prepared: (+)-4-(2-isopropyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine, maleate salt: mp 96–99°C; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.49–6.32 (br, 8H), 6.24 (s, 2H), 4.72–4.10 (br, 3H), 3.82 (t, J

= 4.5 Hz, 4H), 3.71–3.40 (br, 3H), 3.15 (app s, 4H), 2.92–2.20 (br, 2H), 1.72–1.20 (br, 6H); ESI MS *m/z* 352 $[M+H]^+$; (–)-4-(2-isopropyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine, maleate salt: mp 195–197°C; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.49–6.32 (br, 8H), 6.24 (s, 2H), 4.72–4.10 (br, 3H), 3.82 (t, *J* = 4.5 Hz, 4H), 3.71–3.40 (br, 3H), 3.15 (app s, 4H), 2.92–2.20 (br, 2H), 1.72–1.20 (br, 6H); ESI MS *m/z* 352 $[M+H]^+$.

<u>Example 59</u> - Preparation of (+)-2-(8-morpholino-5-phenyl-4,5-dihydro-1*H*-benzo[*c*]azepin-2(3*H*)-yl)ethanol, L-tartrate salt

[0399] Step A: To a solution of aqueous 2N sodium hydroxide (100 mL) was added methyl 3,3-dimethoxy propionate (25.0 g, 0.17 mol). The reaction solution was stirred at 50°C for 1 hour and then cooled to room temperature. The resultant reaction mixture was acidified with 6 N hydrochloric acid to pH 1 and extracted with dichloromethane (3×). The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to give the desired acid (18.0 g, 80%) as a clear colorless oil, which was used in the next step without further purification: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.83 (t, *J* = 5.7 Hz, 1H), 3.39 (s, 6H), 2.71 (d, *J* = 5.7 Hz, 2H).

[0400] Step B: To a solution of 3-methoxybenzylamine (7.8 g, 57 mmol) and the acid (7.6 g, 57 mmol) from step A above in dichloromethane (400 mL) at room temperature was added 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (12.0 g, 62.7 mmol). The reaction solution was stirred at room temperature for 16 hours. The resultant reaction mixture was washed with water, aqueous 1 N hydrochloric acid, water and aqueous saturated sodium bicarbonate, dried over sodium sulfate and concentrated *in vacuo*. The crude acetal (13.3 g, 92%) as a light yellow was used in the next step without further purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.24 (d, *J* = 8.0 Hz, 1H), 6.86 (dd, *J* = 7.5, 0.5 Hz, 1H), 6.83–6.80 (m, 2H), 6.40 (br, 1H), 4.73 (t, *J* = 5.5 Hz, 1H), 4.44 (d, *J* = 5.5 Hz, 2H), 3.80 (s, 3H), 3.39 (s, 6H), 2.59 (d, *J* = 5.5 Hz, 2H).

[0401] Step C: A solution of the acetal (12.2 g, 48.2 mmol) from step B above in concentrated hydrochloric acid (120 mL) was stirred at room temperature for 2 hours. The resultant reaction mixture was diluted with water, saturated with sodium chloride and extracted with chloroform. The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to give the crude product, which was

purified by crystallization from dichloromethane to give the desired lactam (5.9 g, 59%) as a light yellow solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29 (d, J = 8.5 Hz, 1H), 7.08 (d, J = 12.0 Hz, 1H), 6.89 (dd, J = 8.0, 2.5 Hz, 1H), 6.78 (d, J = 2.5 Hz, 1H), 6.29 (br, 1H), 6.17 (dd, J = 12.0, 2.0 Hz, 1H), 4.13 (d, J = 5.5 Hz, 2H), 3.84 (s, 3H).

[0402] Step D: To a mixture of the lactam (3.0 g, 16 mmol) from step C above and benzene (9.0 mL, 0.10 mol) was added triflic acid (24.0 mL, 0.27 mol). The reaction solution was stirred at room temperature for 5 hours and then it was diluted with water and extracted with dichloromethane (3×). The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to give the desired 5-phenyllactam (4.4 g, quantitative) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 (t, J = 7.0 Hz, 2H), 7.22 (t, J = 7.0 Hz, 1H), 7.12 (d, J = 7.0 Hz, 2H), 6.86 (d, J = 8.5 Hz, 1H), 6.72 (d, J = 8.5, 2.5 Hz, 1H), 6.64 (d, J = 2.5 Hz, 1H), 6.30 (br, 1H), 4.56 (dd, J = 16.0, 6.0 Hz, 1H), 4.49 (dd, J = 10.5, 4.5 Hz, 1H), 4.27 (dd, J = 16.0, 5.0 Hz, 1H), 3.78 (s, 3H), 3.15 (dd, J = 14.5, 10.5 Hz, 1H), 3.00 (dd, J = 14.5, 4.5 Hz, 1H).

[0403] Step E: To a solution of the 5-phenyllactam (4.2 g, 19.5 mmol) from step D above in THF (120 mL) was added borane-dimethyl sulfide (24.5 mL of 2M in tetrahydrofuran, 49 mmol) in batches. The reaction solution was stirred at room temperature for 16 hours and then additional borane-dimethyl sulfide (5.0 mL of 2M in tetrahydrofuran, 10 mmol) was added to it. The reaction solution was stirred at room temperature for 5 hours and then quenched with methanol. The resultant mixture was concentrated *in vacuo* and the residue obtained was dissolved in dioxane (80 mL) and 6N hydrochloric acid (40 mL) and heated under reflux for 1 hour. The resultant solution was cooled to room temperature, neutralized with aqueous sodium hydroxide and extracted with dichloromethane (3×). The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The crude product obtained was purified by flash column chromatography (99:0.9:0.1 to 90:9:1 dichloromethane/methanol/concentrated ammonium hydroxide) to give the desired benzazepine (2.7 g, 54%) as a light yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (t, J = 7.5 Hz, 2H), 7.25 (t, J = 7.5 Hz, 1H), 7.16 (d, J = 7.5 Hz, 2H), 6.74 (d, J = 2.5 Hz, 1H), 6.66–6.54 (m, 2H), 4.36 (d, J = 9.5 Hz, 1H), 4.00 (d, J = 15.0 Hz, 1H), 3.87 (d, J = 14.5 Hz, 1H), 3.77 (s, 3H), 3.29–3.22 (m, 1H), 3.19–3.14 (m, 1H), 2.27–2.13 (m, 2H), 1.69 (br, 1H).

[0404] Step F: To a solution of the 2*H*-benzazepine (2.9 g, 11.4 mmol) from step E above in dichloromethane (120 mL) were added pyridine (1.8 mL, 23 mmol), 4-dimethylaminopyridine (0.14 g, 1.1 mmol) and acetic anhydride (1.3 mL, 14.2 mmol) at 0°C. The reaction solution was let to warm to room temperature and stirred for 15 hours. The resultant reaction mixture was quenched with aqueous ammonium chloride, washed with 1 N hydrochloric acid and aqueous saturated sodium bicarbonate, dried over sodium sulfate and concentrated *in vacuo*. The crude product obtained (3.2 g, 95%) as a light yellow oil, was used in the next step without further purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (t, J = 7.5 Hz, 2H), 7.24 (t, J = 7.5 Hz, 1H), 7.09 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 2.5 Hz, 1H), 6.82–6.63 (m, 2H), 4.69–4.30 (m, 3H), 3.83–3.47 (m, 5H), 2.41–1.92 (m, 5H).

[0405] Step G: To a solution of the 8-methoxybenzazepine (3.2 g, 10.8 mmol) from step F above in dichloromethane (90 mL) at –78°C was added boron tribromide (10 mL, 0.11 mol) slowly. After the addition, the reaction solution was stirred at –78°C for 4 h and at room temperature for 1 hour. The resultant reaction mixture was cooled to 0°C, quenched by slow addition of methanol and concentrated *in vacuo*. The residue obtained (3.2 g, quantitative) as an off-white solid, was used in the next step without further purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.99–7.56 (br, 1H), 7.32 (t, J= 7.5 Hz, 2H), 7.23 (t, J = 7.5 Hz, 1H), 7.12 (d, J = 2.5 Hz, 1H), 7.09 (d, J = 7.5 Hz, 2H), 6.73–6.06 (m, 2H), 4.68–4.31 (m, 3H), 3.83–3.54 (m, 2H), 2.47–2.12 (m, 2H), 2.12–1.93 (m, 3H); ESI MS *m/z* 282 $[M+H]^+$.

[0406] Step H: To a solution of the phenol (0.85 g, 3.0 mmol) from step G above in chloroform (30 mL) at 0°C was added triethylamine (5.1 mL, 36 mmol) followed by triflic anhydride (1.0 mL, 6.0 mmol) dropwise. The resultant reaction solution was stirred at room temperature for 12 hours and then additional triethylamine (1.0 mL, 7.0 mmol) and triflic anhydride (1.0 mL, 6.0 mmol) were added. The reaction solution was stirred at room temperature for 1 hour and then quenched with aqueous saturated sodium bicarbonate. The resultant mixture was extracted with dichlormethane (2×), washed with aqueous saturated ammonium chloride, dried over sodium sulfate and concentrated *in vacuo*. The residue obtained was purified by flash column chromatography (66:33 to 33:66 hexanes/ethyl acetate) to give the desired triflate (0.52 g, 42%) as an orange solid: ESI MS *m/z* 414 $[M+H]^+$.

[0407] Step I: To a solution of the triflate (0.20 g, 0.48 mmol) from step H above in toluene (5 mL) were added cesium carbonate (0.49 g, 1.5 mmol), 2-(dicyclohexylphosphino)-2',4',6'-tri-*i*-propyl-1,1'-biphenyl (24 g, 0.05 mmol) and morpholine (0.042 mL, 1.0 mmol). The resultant mixture was flushed with argon for 10 minutes, and then palladium(II) acetate (11 mg, 0.05 mmol) was added to it. The reaction solution was heated at 100°C under argon for 13 hours and then cooled to room temperature. The resultant mixture was diluted with dichloromethane, washed with water and brine, dried over sodium sulfate and concentrated *in vacuo*. The crude product obtained was purified by flash column chromatography (99:0.9:0.1to 97:2.7:0.3 dichloromethane/methanol/concentrated ammonium hydroxide) to give the desired 8-morpholinyl benzazepine (0.13 g, 83%) as a white foam: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32 (t, J = 8.0 Hz, 2H), 7.23 (t, J = 7.5 Hz, 1H), 7.09 (d, J = 7.5 Hz, 2H), 6.95–6.65 (m, 3H), 4.78–4.30 (m, 3H), 3.90–3.41 (m, 6H), 3.20–3.13 (m, 4H), 2.43–2.17 (m, 2H), 2.20–1.74 (m, 3H); ESI MS *m/z* 351 $[M+H]^+$.

[0408] Step J: To a solution of the *N*-acetyl benzazepine (0.14 g, 0.40 mmol) from step I above in methanol (10 mL) was added an aqueous 2 N solution of sodium hydroxide (10 mL). The reaction solution was heated under reflux for 72 hours and then cooled to room temperature. The resultant reaction mixture was extracted with dichloromethane, washed with water and aqueous saturated sodium bicarbonate, dried over sodium sulfate and concentrated *in vacuo*. The residue obtained was purified by flash column chromatography (dichloromethane to 90:9:1 dichloromethane/methanol/concentrated ammonium hydroxide) to give the desired 2*H*-benzazepine (0.11 g, 89%) as a white foam: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.35 (t, J = 7.5 Hz, 2H), 7.24 (t, J = 7.5 Hz, 1H), 7.14 (d, J = 7.5 Hz, 2H), 6.84 (d, J = 2.5 Hz, 1H), 6.65–6.60 (m, 1H), 6.49–6.38 (br, 1H), 4.33 (d, J = 8.5 Hz, 1H), 3.95 (d, J = 14.5 Hz, 1H), 3.77 (d, J = 14.5 Hz, 1H), 3.71 (t, J = 5.0 Hz, 4H), 3.10–2.87 (m, 6H), 2.21–2.12 (m, 1H), 2.03–1.85 (m, 1H).

[0409] Step K: The free base of the benzazepine from step J (800 mg) was resolved by preparative chiral HPLC (CHIRALPAK AD column, using 85:15:0.1 heptane/isopropanol/diethylamine as the eluent) to give the (+)-enantiomer $[[\alpha]^{25}_D$ +4.98° (*c* 0.18, methanol)] and the (-)-enantiomer $[[\alpha]^{25}_D$ -6.83° (*c* 0.18, methanol)].

[0410] Step L: To a solution of the (+)-enantiomer of the benzazepine (72 mg, 0.23 mmol) from step K above in acetonitrile (5 mL) were added potassium carbonate (0.13 g, 0.92 mmol) and 2-bromoethanol (0.032 mL, 0.46 mmol). The reaction solution was stirred under reflux for 3 hours and then cooled to room temperature and concentrated *in vacuo*. The residue obtained was purified by preparative thin layer chromatography (92:7.2:0.8 dichloromethane/methanol/concentrated ammonium hydroxide) to give the *N*-hydroxyethanol benzazepine [$[\alpha]^{25}_{D}$ +0.71° (*c* 0.14, methanol)] (64 mg, 79%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (t, *J* = 7.5 Hz, 2H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 2H), 6.72 (s, 1H), 6.68–6.47 (br, 2H), 4.29 (d, *J* = 8.0 Hz, 1H), 4.03–3.95 (br, 1H), 3.85 (t, *J* = 4.5 Hz, 4H), 3.80 (d, *J* = 14.5 Hz, 1H), 3.58 (t, *J* = 5.0 Hz, 2H), 3.20–3.05 (m, 2H), 3.12 (t, *J* = 4.5 Hz, 4H), 2.63–2.57 (m, 2H), 2.32–2.25 (m, 1H), 2.09 (d, *J* = 14.0 Hz, 1H).

[0411] To a solution of the *N*-hydroxyethanol benzazepine (58 mg, 0.16 mmol) in methanol (2 mL) were added L-tartaric acid (24 mg, 0.16 mmol) and water (10 mL). The resultant solution was lypholized overnight to give (+)-2-(8-morpholino-5-phenyl-4,5-dihydro-1*H*-benzo[*c*]azepin-2(3*H*)-yl)ethanol, L-tartrate salt (80 mg, 97.1% AUC HPLC) as a white solid: mp 93–96°C; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.37 (t, *J* = 7.5 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 2H), 7.03 (d, *J* = 1.5 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 6.85–6.49 (br, 1H), 4.60–4.49 (br, 1H), 4.48 (d, *J* = 8.5 Hz, 1H), 4.40 (s, 2.3H), 4.34 (d, *J* = 13.0 Hz, 1H), 3.87 (t, *J* = 5.0 Hz, 2H), 3,82 (t, *J* = 4.5 Hz, 4H), 3.57 (app s,2H), 3.16–3.14 (m, 6H), 2.62–2.36 (br, 2H); ESI MS *m/z* 353 $[M+H]^+$.

<u>Example 60</u> - Preparation of (+)-4-(2-(2-fluoroethyl)-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine, L-tartrate salt

[0412] Pursuant to the general method described above in Example 59, the following products were prepared: (+)-4-(2-(2-fluoroethyl)-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine, L-tartrate salt: mp 102–105°C; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.36 (t, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 2H), 7.00 (d, *J* = 2.5 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 1H), 6.82–6.54 (br, 1H), 4.77 (dt, *J* = 47.5, 4.5 Hz, 2H), 4.46–4.38 (m, 2H), 4.43 (s, 2H), 4.23 (d, *J* = 14.0 Hz,

1H), 3.82 (t, J = 5.0 Hz, 4H), 3.50 (app s, 2H), 3.34–3.20 (m, 2H), 3.18–3.13 (m, 4H), 2.57–2.24 (br, 2H); ESI MS *m/z* 355 $[M+H]^+$.

Example 61 - Preparation of (+)-4-(2-benzyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine, maleate salt

[0413] Pursuant to the general method described above in Example 59, the following product was prepared: (+)-4-(2-benzyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)morpholine, maleate salt: mp 108–110°C; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.51 (app s, 5H), 7.37 (t, J = 7.5 Hz, 2H), 7.28 (t, J = 7.5 Hz, 1H), 7.18 (d, J = 7.0 Hz, 2H), 7.06–7.54 (br, 2H), 6.87 (d, J = 2.5 Hz, 1H), 6.25 (s, 2H), 4.67–4.07 (br, 5H), 3.82 (t, J = 4.5 Hz, 4H), 3.54–3.43 (br, 2H), 3.13 (t, J = 4.5 Hz, 4H), 2.79–2.12 (br, 2H); ESI MS *m/z* 399 $[M+H]^+$.

Example 62 - Preparation of 2,6-difluoro-4-(8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl)phenol, citrate salt

[0414] Step A: To a solution of aqueous 2 N sodium hydroxide (100 mL) was added methyl 3,3-dimethoxy propionate (25.0 g, 0.17 mol). The reaction solution was stirred at 50°C for 1 hour and then cooled to room temperature. The resultant reaction mixture was acidified with 6 N hydrochloric acid to pH 1 and extracted with dichloromethane three times. The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to give the desired acid (22.5 g, quantitative) as a clear colorless oil, which was used in the next step without further purification: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.83 (t, J = 5.7 Hz, 1H), 3.39 (s, 6H), 2.71 (d, J = 5.7 Hz, 2H).

[0415] Step B: To a solution of *m*-anisaldehyde (205 g, 1.5 mol) in methanol (800 mL) at room temperature was added a solution of methylamine in water (130 mL, 1.5 mol, 40 wt. % solution). The resultant solution was cooled to 0°C and sodium borohydride (83 g, 2.3 mol) was added to it in portions. The reaction solution was stirred at 0°C for 2 hours and then warmed to room temperature. The resultant reaction mixture was concentrated *in vacuo* and diluted with water. The organic phase was separated, diluted with ethyl acetate, washed with 1:1 water/brine, dried over sodium sulfate and concentrated *in vacuo* to give the desired benzylamine (158.5 g, 70%) as a clear oil. The combined aqueous extracts were extracted with

dichloromethane (3×). The combined dichloromethane extracts were washed with 1:1 water/brine, dried over sodium sulfate and concentrated *in vacuo* to give the desired benzylamine (66.7 g, 29%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (t, J = 8.4 Hz, 1H), 6.91–6.78 (m, 3H), 3.81 (s, 3H), 3.73 (s, 2H), 2.46 (s, 3H).

[0416] Step C: To a mixture of benzylamine (26.3 g, 174 mmol) from Step B above, 3,3-dimethoxypropanoic acid (23.4 g, 174 mmol) and dichloromethane (182 mL) at 0 °C was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (36.8 g, 192 mmol). The mixture was stirred at room temperature overnight, and then washed with water and saturated sodium bicarbonate. The resulting solution was dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the acetal (42 g, 90%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.20 (m, 1H), 6.84–6.70 (m, 3H), 4.93–4.89 (m, 1H), 4.58, 4.53 (s, 2H, rotamers), 3.79 (s, 3H), 3.44, 3.39 (s, 6H, rotamers), 2.94 (s, 3H), 2.73, 2.70 (d, J = 5.5 Hz, 2H, rotamers). The crude product was used without further purification in the next reaction.

[0417] Step D: To the acetal (42.0 g, 157 mmol) from step C above was added pre-cooled concentrated hydrochloric acid (200 mL) at 0°C. The mixture was gradually warmed to 10°C over 2 h and 30 minutes. The cold reaction mixture was diluted with ice-cold water, and the white precipitate formed was filtered, washed with cold water and dried. The solid obtained was taken up in dichloromethane and washed with saturated sodium bicarbonate. The resultant solution was dried over magnesium sulfate, filtered and concentrated *in vacuo* to yield the lactam (20.3 g, 63%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 12.1 Hz, 1H), 6.90 (dd, J = 8.4, 2.7 Hz, 1H), 6.82 (d, J = 2.6 Hz, 1H), 6.29 (d, J = 12.1 Hz, 1H), 4.19 (s, 2H), 3.86 (s, 3H), 3.09 (s, 3H).

[0418] Step E: To a solution of the lactam (2.0 g, 9.84 mmol) from step D in trifluoromethanesulfonic acid (20 mL) was added 2,6-difluorophenol (3.84 g, 29.5 mmol). The reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was diluted with cold water, basified with sodium hydroxide until pH 8-9 and extracted with dichloromethane (3 × 300 mL). The extracts were dried other sodium sulfate, filtered and concentrated under reduced pressure. The residue was triturated with ethanol to afford the 5-aryllactam (2.04 g, 62%) as a white solid:

^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.93 (s, 1H), 6.87 (d, J = 2.6 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 6.78–6.73 (m, 3H), 4.87 (d, J = 16.4 Hz, 1H), 4.42 (d, J = 16.4 Hz, 1H), 4.34 (dd, J = 9.8, 4.9 Hz, 1H), 3.73 (s, 3H), 3.09 (dd, J = 13.4, 9.9 Hz, 1H), 2.92–2.86 (m, 1H), 2.87 (s, 3H).

[0419] Step F: To a solution of the 5-aryllactam (2.0 g, 6.0 mmol) from step E in tetrahydrofuran (18 mL) was added borane-dimethylsulfide complex in THF (6 mL, 12.0 mmol, 2M solution). The reaction mixture was heated to reflux for one hour then was concentrated to dryness under reduced pressure. The residue was dissolved in 1,4-dioxane (40 mL) and treated with an aqueous solution of hydrochloric acid (6N, 20 mL) and the mixture was heated to reflux for 3 hours, then concentrated under reduced pressure. The residue was diluted with water (20 mL) and basified until pH 8-9 with a saturated sodium bicarbonate. The solution was extracted with dichloromethane (3×), the combined extracts was dried other sodium sulfate, filtered and concentrated to dryness under reduced pressure to afford the 5-arylbenzazepine (2.04 g, quantitative) as an off-white solid.

[0420] Step G: An analytical sample of the 5-arylbenzazepine (0.32 g) was triturated with a mixture of methanol and ethyl acetate to afford a white solid (0.19 g). To a solution of the 5-arylbenzazepine (0.19 g, 0.59 mmol) in a mixture of water and methanol was added citric acid (0.112 g, 0.59 mmol). The solution was lyophilized overnight to afford 2,6-difluoro-4-(8-methoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl)phenol, citrate salt (0.25 g, 85%, AUC HPLC >99%) as a white solid: mp 88–90°C; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.02 (d, J = 2.6 Hz, 1H), 6.90–6.87 (m, 1H), 6.85–6.78 (m, 1H), 6.72 (d, J = 8.9 Hz, 2H), 4.50-4.43 (m, 1H), 4.41 (dd, J = 8.6, 2.2 Hz, 1H), 4.24 (d, J = 14.0 Hz, 1H), 3.81 (s, 3H), 3.53–3.47 (m, 2H), 3.34 (s, 1H), 2.81 (s, 2H), 2.80 (d, J = 15.4 Hz, 2H), 2.72 (d, J = 15.4 Hz, 2H), 2.58–2.47 (m, 1H), 2.35–2.32 (m, 1H); ESI MS *m/z* 320 $[M+H]^+$.

<u>Example 63</u> - Preparation of 2-fluoro-4-(8-methoxy-2-methyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-5-yl)phenol, maleate salt

[0421] Pursuant to the general method described above in Example 62, the following product was prepared: 2-fluoro-4-(8-methoxy-2-methyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-5-yl)phenol, maleate salt: mp 50–54°C; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.05–7.01 (m, 1H), 6.95–6.82 (m, 3H), 6.79–6.73 (m, 2H), 6.25 (s, 2H),

4.70–4.48 (m, 1H) 4.46–4.39 (m, 1H), 4.35–4.22 (m, 1H), 3.80 (s, 3H), 3.60–3.51 (m, 2H), 2.99–2.81 (m, 3H), 2.43–2.29 (m, 1H); ESI MS *m/z* 302 $[M+H]^+$.

Example 64 - Preparation of (+)-3-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)benzonitrile, L-tartrate salt

[0422] Step A: To a solution of aqueous 2N sodium hydroxide (100 mL) was added methyl 3,3-dimethoxy propionate (25.0 g, 0.17 mol). The reaction solution was stirred at 50°C for 1 hour and then cooled to room temperature. The resultant reaction mixture was acidified with 6 N hydrochloric acid to pH 1 and extracted with dichloromethane three times. The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to give the desired acid (22.5 g, quantitative) as a clear colorless oil, which was used in the next step without further purification: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.83 (t, J = 5.7 Hz, 1H), 3.39 (s, 6H), 2.71 (d, J = 5.7 Hz, 2H).

[0423] Step B: To a solution of *m*-anisaldehyde (205 g, 1.5 mol) in methanol (800 mL) at room temperature was added a solution of methylamine in water (130 mL, 1.5 mol, 40 wt. % solution). The resultant solution was cooled to 0°C and sodium borohydride (83 g, 2.3 mol) was added to it in portions. The reaction solution was stirred at 0°C for 2 hours and then warmed to room temperature. The resultant reaction mixture was concentrated *in vacuo* and diluted with water. The organic phase was separated, diluted with ethyl acetate, washed with 1:1 water/brine, dried over sodium sulfate and concentrated *in vacuo* to give the desired benzylamine (158.5 g, 70%) as a clear oil. The combined aqueous extracts were extracted with dichloromethane (3×). The combined dichloromethane extracts were washed with 1:1 water/brine, dried over sodium sulfate and concentrated *in vacuo* to give the desired benzylamine (66.7 g, 29%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (t, J = 8.4 Hz, 1H), 6.91–6.78 (m, 3H), 3.81 (s, 3H), 3.73 (s, 2H), 2.46 (s, 3H).

[0424] Step C: To a mixture of benzylamine (26.3 g, 174 mmol) from Step B above, 3,3-dimethoxypropanoic acid (23.4 g, 174 mmol) from Step A above and dichloromethane (182 mL) at 0°C was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (36.8 g, 192 mmol). The mixture was stirred at room temperature overnight, and then washed with water and saturated sodium bicarbonate. The resulting solution was dried over magnesium sulfate, filtered and

concentrated *in vacuo* to give the acetal (42 g, 90%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.20 (m, 1H), 6.84–6.70 (m, 3H), 4.93–4.89 (m, 1H), 4.58, 4.53 (s, 2H, rotamers), 3.79 (s, 3H), 3.44, 3.39 (s, 6H, rotamers), 2.94 (s, 3H), 2.73, 2.70 (d, J = 5.5 Hz, 2H, rotamers). The crude product was used without further purification in the next reaction.

[0425] Step D: To the acetal (42.0 g, 157 mmol) from step C above was added pre-cooled concentrated hydrochloric acid (200 mL) at 0°C. The mixture was gradually warmed to 10°C over 2 hours and 30 minutes. The cold reaction mixture was diluted with ice-cold water, and the white precipitate formed was filtered, washed with cold water and dried. The solid obtained was taken up in dichloromethane and washed with saturated sodium bicarbonate. The resultant solution was dried over magnesium sulfate, filtered and concentrated *in vacuo* to yield the lactam (20.3 g, 63%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 12.1 Hz, 1H), 6.90 (dd, J = 8.4, 2.7 Hz, 1H), 6.82 (d, J = 2.6 Hz, 1H), 6.29 (d, J = 12.1 Hz, 1H), 4.19 (s, 2H), 3.86 (s, 3H), 3.09 (s, 3H).

[0426] Step E: To an ice-cold mixture of the lactam (20.3 g, 100 mmol) from step D above and benzene (80 mL) was added trifluoromethanesulfonic acid (100 mL). The reaction mixture was warmed to room temperature and stirred for 3 hours. The reddish-brown mixture was then poured into ice-water mixture, and stirred until the ice melted. The product was extracted into dichloromethane (4×), and the combined organic extracts were washed with saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was dissolved in ethyl acetate and filtered through a plug of silica gel. The silica gel was washed with ethyl acetate to give the aryl lactam (26.8 g, 95%) as a white foam: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28–7.25 (m, 2H), 7.22–7.18 (m, 1H), 7.08–7.06 (m, 2H), 6.86 (d, J = 8.6 Hz, 1H), 6.71 (dd, J = 8.5, 2.7 Hz, 1H), 6.66 (d, J = 2.7 Hz, 1H), 5.02 (d, J = 16.1 Hz, 1H), 4.46 (dd, J = 11.3, 5.2 Hz, 1H), 4.10 (d, J = 16.1 Hz, 1H), 3.79 (s, 3H), 3.25 (dd, J = 13.4, 11.5 Hz, 1H), 3.04 (s, 3H), 2.95 (dd, J = 13.4, 5.2 Hz, 1H).

[0427] Step F: To an ice-cold mixture of the lactam (26.8 g, 95.4 mmol) from step E and THF (980 mL) was added borane-dimethylsulfide complex (19.0 mL, 200 mmol). The mixture was warmed to room temperature, and then heated in an oil

bath at 50°C for 75 minutes. The reaction mixture was then cooled to 0°C, quenched with methanol (100 mL), and concentrated under reduced pressure. To the residue was added 1,4-dioxane (200 mL) followed by 6 N HCl (100 mL) and the mixture was heated under reflux for 2 hours. Additional volumes of 1,4-dioxane (60 mL) and 6 N HCl (30 mL) were added ot the rection mixture, which was heated under reflux for 1 hour. The mixture was cooled to room temperature and then in an ice-bath, and a solution of 2 N NaOH (20 mL) followed by a solution of 32% sodium hydroxide was added until pH 10. The crude product was extracted into dichloromethane (4×), and the combined organic extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the crude product by flash column chromatography (dichloromethane, then 99:0.9:0.1 to 90:9:1 dichloromethane/methanol/concentrated ammonium hydroxide) gave the amine (19.4 g, 76%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37–7.32 (m, 2H), 7.26–7.23 (m, 1H), 7.17 (d, J = 7.5 Hz, 2H), 6.74 (d, J = 2.7 Hz, 1H), 6.65–6.55 (m, 2H), 4.26 (d, J = 8.6 Hz, 1H), 3.95–3.84 (m, 1H), 3.76 (s, 3H), 3.69 (d, J = 14.1 Hz, 1H), 3.16–3.05 (m, 1H), 2.98–2.90 (m, 1H), 2.35 (s, 3H), 2.35–2.27 (m, 1H), 2.13–2.00 (m, 1H).

[0428] Step G: The free base of the benzazepine from step F (19.4 g) was resolved by preparative chiral HPLC (CHIRALCEL OJ column, using 80:20:0.1 heptanes/ethanol/diethylamine as the eluent) to give the (+)-enantiomer [$[\alpha]^{25}_D$ +3.66° (c 0.41, methanol)] and (-)-enantiomer [$[\alpha]^{25}_D$ -1.16° (c 0.43, methanol)].

[0429] Step H: A mixture of the (+)-enantiomer from Step G above (1.19 g, 4.5 mmol) and hydrobromic acid (48% solution in water, 34 mL) was heated to reflux and stirred for 2 hours. The solvent and excess hydrobromic acid were removed under reduced pressure and the resulting solid was partitioned between ethyl acetate and saturated sodium bicarbonate. After separating the two layers, the aqueous phase was extracted with ethyl acetate (3×). The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide the desired phenol (1.10 g, 86%) as a tan solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, J = 7.5 Hz, 2H), 7.28–7.23 (m, 1H), 7.16 (d, J = 7.5 Hz, 2H), 6.54 (s, 1H), 6.48–6.35 (m, 2H), 4.24–4.22 (m, 1H), 3.87–3.77 (m, 1H), 3.66–3.63 (m, 1H), 3.17–3.08 (m, 1H), 2.94–2.89 (m, 1H), 2.42 (s, 3H), 2.35–2.31 (m, 1H), 2.18–2.09 (m, 1H); ESI MS *m/z* 254 $[M+H]^+$.

[0430] Step I: To a stirred mixture of the phenol from Step H above (581 mg, 2.3 mmol) and pyridine (0.22 mL, 2.8 mmol) in anhydrous methylene chloride (23 mL) at 0°C under N_2 was added triflic anhydride (0.46 mL, 2.8 mmol). The reaction was stirred at 0°C for 1 hour, at which time TLC analysis indicated the reaction went to completion. The mixture was then diluted with methylene chloride, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1:1 ethyl acetate/hexanes) provided the desired triflate (650 mg, 74%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, J = 7.5 Hz, 2H), 7.31–7.28 (m, 1H), 7.17 (d, J = 7.0 Hz, 2H), 7.09–7.08 (m, 1H), 6.97–6.93 (m, 1H), 6.70–6.64 (br, 1H), 4.33–4.31 (m, 1H), 4.03–3.94 (m, 1H), 3.75–3.72 (m, 1H), 3.18–3.13 (m, 1H), 3.03–2.98 (m, 1H), 2.36 (s, 3H), 2.34–2.29 (m, 1H), 2.12–2.06 (m, 1H); ESI MS *m/z* 386 $[M+H]^+$.

[0431] Step J: To a sealed tube were added 3-cyanophenylboronic acid (79 mg, 0.54 mmol), potassium bromide (149 mg, 1.3 mmol), potassium hydroxide (70 mg, 1.3 mmol), and a solution of the triflate from Step I above (160 mg, 0.42 mmol) in toluene (4 mL). The reaction mixture was degassed with argon for 1 minute, then tetrakis(triphenylphosphine)palladium(0) (24 mg, 0.021 mmol) was added. After degassing briefly with argon again, the reaction was heated to 80°C and stirred for 5 hours. Additional 3-cyanophenylboronic acid (79 mg, 0.54 mmol) and tetrakis(triphenylphosphine)palladium(0) (24 mg, 0.021 mmol) were then added and the reaction was stirred for 2 hours, at which time ESI MS indicated the reaction went to completion. After cooling to room temperature, the mixture was diluted with 90:10 methylene chloride/methanol and filtered through silica gel, then concentrated *in vacuo*. Purification by flash column chromatography (1%–10% methanol/methylene chloride) yielded the desired benzazepine (41 mg, 29%) as a yellow oil: $[\alpha]^{23}_D$ -10.0° (*c* 0.04, methanol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.40–7.38 (m, 3H), 7.31–7.29 (m, 2H), 7.22–7.21 (m, 2H), 6.79–6.72 (br, 1H), 4.39–4.37 (m, 1H), 4.01–3.99 (m, 1H), 3.83–3.80 (m, 1H), 3.19–3.14 (m, 1H), 3.01–2.97 (m, 1H), 2.41 (s, 3H), 2.44–2.34 (m, 1H), 2.20–2.15 (m, 1H); ESI MS *m/z* 339 $[M+H]^+$.

[0432] Step K: To a stirred solution of the benzazepine from Step J above (40 mg, 0.12 mmol) in methanol (2 mL) at room temperature was added L-tartaric acid (18 mg, 0.12 mmol). The mixture was stirred at room temperature for 1 hour and then the solvent was concentrated to approximately 0.5 mL. After diluting with water (2 mL), the mixture was lyophilized for 15 hours to provide (+)-3-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)benzonitrile, L-tartrate salt (60 mg, 99%, 97.4% AUC HPLC) as a light yellow powder: ^{1}H NMR (500 MHz, CD_3OD) δ 8.03 (s, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.79–7.78 (m, 1H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.64 (t, *J* = 8.0 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.25 (d, *J* = 7.5 Hz, 2H), 7.00–6.94 (br, 1H), 4.73–4.67 (m, 1H), 4.65 (d, *J* = 8.5 Hz, 1H), 4.44–4.41 (m, 1H), 4.41 (s, 2H), 3.65–3.57 (m, 2H), 2.89 (s, 3H), 2.65–2.59 (m, 1H), 2.46–2.43 (m, 1H); ESI MS *m/z* 339 $[M+H]^+$.

<u>Example 65</u> - Preparation of (+)-4-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)benzonitrile, L-tartrate salt

[0433] Pursuant to the general method described above in Example 64, the following product was prepared: (+)-4-(2-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-yl)benzonitrile, L-tartrate salt: ^{1}H NMR (500 MHz, CD_3OD) δ 7.84 (d, *J* = 8.5 Hz, 2H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.80–7.79 (m, 1H), 7.64 (d, *J* = 7.0 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 2H), 7.00–6.93 (br, 1H), 4.69–4.63 (m, 1H), 4.64 (d, *J* = 8.0 Hz, 1H), 4.40 (s, 2H), 4.40–4.38 (m, 1H), 3.59–3.54 (m, 2H), 2.87 (s, 3H), 2.64–2.58 (m, 1H), 2.45–2.41 (m, 1H); ESI MS *m/z* 339 $[M+H]^+$.

<u>Example 66</u> - Preparation of (+)-2-methyl-8-(4-(methylsulfonyl)phenyl)-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, L-tartrate salt

[0434] Pursuant to the general method described above in Example 64, the following product was prepared: (+)-2-methyl-8-(4-(methylsulfonyl)phenyl)-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, L-tartrate salt: ^{1}H NMR (500 MHz, CD_3OD) δ 8.03 (d, *J* = 8.0 Hz, 2H), 7.92 (d, *J* = 8.5 Hz, 2H), 7.84 (s, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.0 Hz, 1H), 7.25 (d, *J* = 7.5 Hz, 2H), 7.02–6.95 (br, 1H), 4.74–4.68 (m, 1H), 4.66 (d, *J* = 9.0 Hz, 1H), 4.45–4.41 (m,

1H), 4.41 (s, 2H), 3.64–3.58 (m, 2H), 3.15 (s, 3H), 2.91 (s, 3H), 2.67–2.59 (m, 1H), 2.47–2.44 (m, 1H); ESI MS *m/z* 392 $[M+H]^+$.

Example 67 - Preparation of (+)-2-methyl-8-(4-methylpiperazin-1-yl)-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine and (-)-2-methyl-8-(4-methylpiperazin-1-yl)-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, L-tartrate salts

[0435] Step A: To a solution of aqueous 2 N sodium hydroxide (100 mL) was added methyl 3,3-dimethoxy propionate (25.0 g, 0.17 mol). The reaction solution was stirred at 50°C for 1 hour and then cooled to room temperature. The resultant reaction mixture was acidified with 6 N hydrochloric acid to pH 1 and extracted with dichloromethane three times. The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to give the desired acid (22.5 g, quantitative) as a clear colorless oil, which was used in the next step without further purification: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.83 (t, J = 5.7 Hz, 1H), 3.39 (s, 6H), 2.71 (d, J = 5.7 Hz, 2H).

[0436] Step B: To a solution of *m*-anisaldehyde (205 g, 1.5 mol) in methanol (800 mL) at room temperature was added a solution of methylamine in water (130 mL, 1.5 mol, 40 wt. % solution). The resultant solution was cooled to 0°C and sodium borohydride (83 g, 2.3 mol) was added to it in portions. The reaction solution was stirred at 0°C for 2 hours and then warmed to room temperature. The resultant reaction mixture was concentrated *in vacuo* and diluted with water. The organic phase was separated, diluted with ethyl acetate, washed with 1:1 water/brine, dried over sodium sulfate and concentrated *in vacuo* to give the desired benzylamine (158.5 g, 70%) as a clear oil. The combined aqueous extracts were extracted with dichloromethane (3×). The combined dichloromethane extracts were washed with 1:1 water/brine, dried over sodium sulfate and concentrated *in vacuo* to give the desired benzylamine (66.7 g, 29%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (t, J = 8.4 Hz, 1H), 6.91–6.78 (m, 3H), 3.81 (s, 3H), 3.73 (s, 2H), 2.46 (s, 3H).

[0437] Step C: To a mixture of benzylamine (26.3 g, 174 mmol) from Step B above, 3,3-dimethoxypropanoic acid (23.4 g, 174 mmol) from Step A above and dichloromethane (182 mL) at 0°C was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (36.8 g, 192 mmol). The mixture was stirred at

room temperature overnight, and then washed with water and saturated sodium bicarbonate. The resulting solution was dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the acetal (42 g, 90%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.20 (m, 1H), 6.84–6.70 (m, 3H), 4.93–4.89 (m, 1H), 4.58, 4.53 (s, 2H, rotamers), 3.79 (s, 3H), 3.44, 3.39 (s, 6H, rotamers), 2.94 (s, 3H), 2.73, 2.70 (d, J = 5.5 Hz, 2H, rotamers). The crude product was used without further purification in the next reaction.

[0438] Step D: To the acetal (42.0 g, 157 mmol) from step C above was added pre-cooled concentrated hydrochloric acid (200 mL) at 0°C. The mixture was gradually warmed to 10°C over 2 hours and 30 minutes. The cold reaction mixture was diluted with ice-cold water, and the white precipitate formed was filtered, washed with cold water and dried. The solid obtained was taken up in dichloromethane and washed with saturated sodium bicarbonate. The resultant solution was dried over magnesium sulfate, filtered and concentrated *in vacuo* to yield the lactam (20.3 g, 63%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 12.1 Hz, 1H), 6.90 (dd, J = 8.4, 2.7 Hz, 1H), 6.82 (d, J = 2.6 Hz, 1H), 6.29 (d, J = 12.1 Hz, 1H), 4.19 (s, 2H), 3.86 (s, 3H), 3.09 (s, 3H).

[0439] Step E: To an ice-cold mixture of the lactam (20.3 g, 100 mmol) from step D above and benzene (80 mL) was added trifluoromethanesulfonic acid (100 mL). The reaction mixture was warmed to room temperature and stirred for 3 hours. The reddish-brown mixture was then poured into ice-water mixture, and stirred until the ice melted. The product was extracted into dichloromethane (4×), and the combined organic extracts were washed with saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was dissolved in ethyl acetate and filtered through a plug of silica gel. The silica gel was washed with ethyl acetate to give the aryl lactam (26.8 g, 95%) as a white foam: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28–7.25 (m, 2H), 7.22–7.18 (m, 1H), 7.08–7.06 (m, 2H), 6.86 (d, J = 8.6 Hz, 1H), 6.71 (dd, J = 8.5, 2.7 Hz, 1H), 6.66 (d, J = 2.7 Hz, 1H), 5.02 (d, J = 16.1 Hz, 1H), 4.46 (dd, J = 11.3, 5.2 Hz, 1H), 4.10 (d, J = 16.1 Hz, 1H), 3.79 (s, 3H), 3.25 (dd, J = 13.4, 11.5 Hz, 1H), 3.04 (s, 3H), 2.95 (dd, J = 13.4, 5.2 Hz, 1H).

[0440] Step F: To an ice-cold mixture of the lactam (26.8 g, 95.4 mmol) from step E and THF (980 mL) was added borane-dimethylsulfide complex (19.0 mL, 200 mmol). The mixture was warmed to room temperature, and then heated in an oil bath at 50°C for 75 minutes. The reaction mixture was then cooled to 0°C, quenched with methanol (100 mL), and concentrated under reduced pressure. To the residue was added 1,4-dioxane (200 mL) followed by 6N HCl (100 mL) and the mixture was heated under reflux for 2 hours. Additional volumes of 1,4-dioxane (60 mL) and 6 N HCl (30 mL) were added ot the rection mixture, which was heated under reflux for 1 hour. The mixture was cooled to room temperature and then in an ice-bath, and a solution of 2 N NaOH (20 mL) followed by a solution of 32% sodium hydroxide was added until pH 10. The crude product was extracted into dichloromethane (4×), and the combined organic extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the crude product by flash column chromatography (dichloromethane, then 99:0.9:0.1 to 90:9:1 dichloromethane/methanol/concentrated ammonium hydroxide) gave the amine (19.4 g, 76%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37–7.32 (m, 2H), 7.26–7.23 (m, 1H), 7.17 (d, J = 7.5 Hz, 2H), 6.74 (d, J = 2.7 Hz, 1H), 6.65–6.55 (m, 2H), 4.26 (d, J = 8.6 Hz, 1H), 3.95–3.84 (m, 1H), 3.76 (s, 3H), 3.69 (d, J = 14.1 Hz, 1H), 3.16–3.05 (m, 1H), 2.98–2.90 (m, 1H), 2.35 (s, 3H), 2.35–2.27 (m, 1H), 2.13–2.00 (m, 1H).

[0441] Step G: The free base of the benzazepine from step F (19.4 g) was resolved by preparative chiral HPLC (CHIRALCEL OJ column, using 80:20:0.1 heptanes/ethanol/diethylamine as the eluent) to give the (+)-enantiomer [$[\alpha]^{25}_D$ +3.66° (c 0.41, methanol)] and (-)-enantiomer [$[\alpha]^{25}_D$ -1.16° (c 0.43, methanol)].

[0442] Step H: A mixture of the (+)-enantiomer from Step G above (1.19 g, 4.5 mmol) and hydrobromic acid (48% solution in water, 34 mL) was heated to reflux and stirred for 2 hours. The solvent and excess hydrobromic acid were removed under reduced pressure and the resulting solid was partitioned between ethyl acetate and saturated sodium bicarbonate. After separating the two layers, the aqueous phase was extracted with ethyl acetate (3×). The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide the desired phenol (1.10 g, 86%) as a tan solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, J = 7.5 Hz, 2H), 7.28–7.23 (m, 1H), 7.16 (d, J = 7.5 Hz, 2H), 6.54 (s, 1H), 6.48–6.35 (m,

2H), 4.24–4.22 (m, 1H), 3.87–3.77 (m, 1H), 3.66–3.63 (m, 1H), 3.17–3.08 (m, 1H), 2.94–2.89 (m, 1H), 2.42 (s, 3H), 2.35–2.31 (m, 1H), 2.18–2.09 (m, 1H); ESI MS *m/z* 254 $[M+H]^+$.

[0443] Step I: To a stirred mixture of the phenol from Step H above (581 mg, 2.3 mmol) and pyridine (0.22 mL, 2.8 mmol) in anhydrous methylene chloride (23 mL) at 0°C under N_2 was added triflic anhydride (0.46 mL, 2.8 mmol). The reaction was stirred at 0°C for 1 hour, at which time TLC analysis indicated the reaction went to completion. The mixture was then diluted with methylene chloride, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1:1 ethyl acetate/hexanes) provided the desired triflate (650 mg, 74%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, J = 7.5 Hz, 2H), 7.31–7.28 (m, 1H), 7.17 (d, J = 7.0 Hz, 2H), 7.09–7.08 (m, 1H), 6.97–6.93 (m, 1H), 6.70–6.64 (br, 1H), 4.33–4.31 (m, 1H), 4.03–3.94 (m, 1H), 3.75–3.72 (m, 1H), 3.18–3.13 (m, 1H), 3.03–2.98 (m, 1H), 2.36 (s, 3H), 2.34–2.29 (m, 1H), 2.12–2.06 (m, 1H); ESI MS *m/z* 386 $[M+H]^+$.

[0444] Step J: To a stirred solution of the triflate from Step I above (298 mg, 0.77 mmol) in anhydrous toluene (7 mL) at room temperature under N_2 were added 1-methylpiperazine (0.17 mL, 1.6 mmol), sodium *tert*-butoxide (223 mg, 2.3 mmol), and 2-(dicyclohexylphosphino)-2',4',6'-tri-*i*-isopropyl-1,1'-biphenyl (111 mg, 0.23 mmol). The reaction mixture was degassed with argon for 2 minutes, then palladium(II) acetate (26 mg, 0.12 mmol) was added under argon. A reflux condenser was attached and the reaction was heated to 100°C and stirred for 4 hours, at which time ESI MS indicated the reaction went to completion. After cooling to room temperature, the reaction mixture was diluted with methylene chloride and filtered through Celite.* The filtrate was then washed with saturated ammonium chloride and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (9.4:0.5:0.1 methylene chloride/methanol/concentrated ammonium hydroxide) yielded the desired piperazine (137 mg, 53%) as a light yellow oil: $[\alpha]^{23}_D$ -4.44° (*c* 0.045, methanol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, J = 7.5 Hz, 2H), 7.26–7.23 (m, 1H), 7.17 (d, J = 7.5 Hz, 2H), 6.77–6.76 (m, 1H), 6.63–6.61 (m, 1H), 6.56–6.49 (br, 1H), 4.24–4.23 (m, 1H), 3.93–3.85 (m, 1H), 3.70–3.67 (m, 1H), 3.17 (t, J = 5.0 Hz, 4H), 3.13–3.08 (m, 1H), 2.96–2.92 (m, 1H), 2.55 (t, J =

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5.0 Hz, 4H), 2.35 (s, 3H), 2.34 (s, 3H), 2.34–2.26 (m, 1H), 2.11–2.05 (m, 1H); ESI MS *m/z* 336 $[M+H]^+$.

[0445] Step K: To a stirred solution of the piperazine from Step J above (132 mg, 0.39 mmol) in methanol (4 mL) at room temperature was added L-tartaric acid (59 mg, 0.39 mmol). The mixture was stirred at room temperature for 1 hour and then the solvent was concentrated to approximately 0.5 mL. After diluting with water (2 mL), the mixture was lyophilized for 15 h to provide (+)-2-methyl-8-(4-methylpiperazin-1-yl)-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, L-tartrate salt (190 mg, 99%, 95.2% AUC HPLC) as a light yellow powder: ^{1}H NMR (500 MHz, CD_3OD) δ 7.37 (t, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 2H), 7.07–7.06 (m, 1H), 6.89 (d, *J* = 7.0 Hz, 1H), 6.79–6.67 (br, 1H), 4.46–4.45 (m, 2H), 4.33 (s, 2H), 4.24–4.21 (m, 1H), 3.51–3.47 (m, 2H), 3.38–3.34 (m, 4H), 3.05–3.02 (m, 4H), 2.81 (s, 3H), 2.66 (s, 3H), 2.59–2.50 (m, 1H), 2.39–2.33 (m, 1H); ESI MS *m/z* 336 $[M+H]^+$.

[0446] Step L: A mixture of the (-)-enantiomer from Step G above (2.76 g, 10.3 mmol) and hydrobromic acid (48% solution in H_2O, 70 mL) was heated to reflux and stirred for 2 hours. The solvent and excess hydrobromic acid were removed under reduced pressure and the resulting solid was partitioned between ethyl acetate and saturated sodium bicarbonate. After separating the two layers, the aqueous phase was extracted with ethyl acetate (3×). The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide the desired phenol (2.23 g, 85%) as a light brown solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.5 Hz, 2H), 7.28–7.23 (m, 1H), 7.16 (d, *J* = 7.5 Hz, 2H), 6.54 (s, 1H), 6.48–6.35 (m, 2H), 4.24–4.22 (m, 1H), 3.87–3.77 (m, 1H), 3.66–3.63 (m, 1H), 3.17–3.08 (m, 1H), 2.94–2.89 (m, 1H), 2.42 (s, 3H), 2.35–2.31 (m, 1H), 2.18–2.09 (m, 1H); ESI MS *m/z* 254 $[M+H]^+$.

[0447] Step M: To a stirred mixture of the phenol from Step L above (2.21 g, 8.7 mmol) and pyridine (0.85 mL, 10.5 mmol) in anhydrous methylene chloride (50 mL) at 0°C under N_2 was added triflic anhydride (1.8 mL, 10.5 mmol). The reaction was stirred at 0°C for 1 hour, at which time TLC analysis indicated the reaction went to completion. The mixture was then diluted with methylene chloride, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography

(1:1 ethyl acetate/hexanes) provided the desired triflate (1.67 g, 50%) as an orange oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, J = 7.5 Hz, 2H), 7.31–7.28 (m, 1H), 7.17 (d, J = 7.0 Hz, 2H), 7.09–7.08 (m, 1H), 6.97–6.93 (m, 1H), 6.70–6.64 (br, 1H), 4.33–4.31 (m, 1H), 4.03–3.94 (m, 1H), 3.75–3.72 (m, 1H), 3.18–3.13 (m, 1H), 3.03–2.98 (m, 1H), 2.36 (s, 3H), 2.34–2.29 (m, 1H), 2.12–2.06 (m, 1H); ESI MS *m/z* 386 $[M+H]^+$.

[0448] Step N: To a stirred solution of the triflate from Step M above (300 mg, 0.78 mmol) in anhydrous toluene (8 mL) at room temperature under N_2 were added 1-methylpiperazine (0.17 mL, 1.6 mmol), sodium *tert*-butoxide (224 mg, 2.3 mmol), and 2-(dicyclohexylphosphino)-2',4',6'-tri-*i*-isopropyl-1,1'-biphenyl (111 mg, 0.23 mmol). The reaction mixture was degassed with argon for 2 minutes, then palladium(II) acetate (26 mg, 0.12 mmol) was added under argon. A reflux condenser was attached and the reaction was heated to 100°C and stirred for 4 hours, at which time ESI MS indicated the reaction went to completion. After cooling to room temperature, the reaction mixture was diluted with methylene chloride and filtered through Celite.* The filtrate was then washed with saturated ammonium chloride and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (9.4:0.5:0.1 methylene chloride/methanol/concentrated ammonium hydroxide) yielded the desired piperazine (124 mg, 48%) as a light brown oil: $[\alpha]^{23}_D$ +3.08° (*c* 0.065, methanol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, J = 7.5 Hz, 2H), 7.26–7.23 (m, 1H), 7.17 (d, J = 7.5 Hz, 2H), 6.77–6.76 (m, 1H), 6.63–6.61 (m, 1H), 6.56–6.49 (br, 1H), 4.24–4.23 (m, 1H), 3.93–3.85 (m, 1H), 3.70–3.67 (m, 1H), 3.17 (t, J = 5.0 Hz, 4H), 3.13–3.08 (m, 1H), 2.96–2.92 (m, 1H), 2.55 (t, J = 5.0 Hz, 4H), 2.35 (s, 3H), 2.34 (s, 3H), 2.34–2.26 (m, 1H), 2.11–2.05 (m, 1H); ESI MS *m/z* 336 $[M+H]^+$.

[0449] Step O: To a stirred solution of the piperazine from Step N above (124 mg, 0.37 mmol) in methanol (4 mL) at room temperature was added L-tartaric acid (55 mg, 0.37 mmol). The mixture was stirred at room temperature for 1 hour and then the solvent was concentrated to approximately 0.5 mL. After diluting with water (2 mL), the mixture was lyophilized for 15 h to provide (-)-2-methyl-8-(4-methylpiperazin-1-yl)-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, L-tartrate salt (180 mg, 99%, 98.6% AUC HPLC) as a light brown powder: ^{1}H NMR (500 MHz,

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CD_3OD) δ 7.37 (t, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 2H), 7.07–7.06 (m, 1H), 6.89 (d, *J* = 7.0 Hz, 1H), 6.79–6.67 (br, 1H), 4.46–4.45 (m, 2H), 4.33 (s, 2H), 4.24–4.21 (m, 1H), 3.51–3.47 (m, 2H), 3.38–3.34 (m, 4H), 3.05–3.02 (m, 4H), 2.81 (s, 3H), 2.66 (s, 3H), 2.59–2.50 (m, 1H), 2.39–2.33 (m, 1H); ESI MS *m/z* 336 $[M+H]^+$.

Example 68 - Preparation of (+)-2-methyl-5-phenyl-8-(4-(pyridin-2-yl)piperazin-1-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, L-tartrate salt

[0450] Pursuant to the general method described above in Example 67, the following product was prepared: (+)-2-methyl-5-phenyl-8-(4-(pyridin-2-yl)piperazin-1-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, L-tartrate salt: mp 117-119°C; ^1H NMR (500 MHz, CD_3OD) δ 8.12–8.10 (m, 1H), 7.61–7.57 (m, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 2H), 7.12–7.11 (m, 1H), 6.95–6.94 (m, 1H), 6.88 (d, *J* = 8.5 Hz, 1H), 6.80–6.72 (br, 1H), 6.72–6.70 (m, 1H), 4.59–4.49 (m, 1H), 4.49 (d, *J* = 8.0 Hz, 1H), 4.41 (s, 2H), 4.30–4.27 (m, 1H), 3.67–3.65 (m, 4H), 3.59–3.49 (m, 2H), 3.31–3.29 (m, 4H), 2.87 (s, 3H), 2.61–2.52 (m, 1H), 2.42–2.36 (m, 1H); ESI MS *m/z* 399 $[M+H]^+$; (-)-2-methyl-5-phenyl-8-(4-(pyridine-2-yl)piperazin-1-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, L-tartrate salt: mp 112-115°C; ^1H NMR (500 MHz, CD_3OD) δ 8.12–8.10 (m, 1H), 7.61–7.57 (m, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 2H), 7.12–7.11 (m, 1H), 6.95–6.94 (m, 1H), 6.88 (d, *J* = 8.5 Hz, 1H), 6.80–6.72 (br, 1H), 6.72–6.70 (m, 1H), 4.59–4.49 (m, 1H), 4.49 (d, *J* = 8.0 Hz, 1H), 4.41 (s, 2H), 4.30–4.27 (m, 1H), 3.67–3.65 (m, 4H), 3.59–3.49 (m, 2H), 3.31–3.29 (m, 4H), 2.87 (s, 3H), 2.61–2.52 (m, 1H), 2.42–2.36 (m, 1H); ESI MS *m/z* 399 $[M+H]^+$.

Example 69 - Preparation of (+)-2-methyl-5-phenyl-8-(4-(pyrimidin-2-yl)piperazin-1-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, L-tartrate salt

[0451] Pursuant to the general method described above in Example 67, the following product was prepared: (+)-2-methyl-5-phenyl-8-(4-(pyrimidin-2-yl)piperazin-1-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, L-tartrate salt: mp 119-121°C; ^1H NMR (500 MHz, CD_3OD) δ 8.34 (d, *J* = 4.5 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 7.0 Hz, 2H), 7.11–7.10 (m, 1H), 6.94 (d, *J* =

DEMANDES OU BREVETS VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS COMPREND PLUS D'UN TOME.

CECI EST LE TOME __1___ DE __2___

NOTE: Pour les tomes additionels, veillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

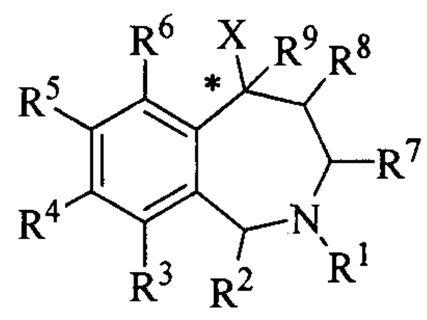
THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.

THIS IS VOLUME __1___ OF __2___

NOTE: For additional volumes please contact the Canadian Patent Office.

WHAT IS CLAIMED IS:

1. A compound of formulae I(A-E) having the following structure:



I(A-E)

wherein:

the carbon atom designated * is in the R or S configuration; and

X represents a 5- or 6-membered aromatic or nonaromatic monocyclic carbocycle or heterocycle selected from the group consisting of phenyl, pyridyl, 2-oxo-pyridin-1-yl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyranyl, pyrrolyl, furanyl, thiophenyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, and tetrazolyl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}; or
X is a [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycle or heterocycle selected from the group consisting of indenyl, indanyl, benzofuranyl, benzothiophenyl, dihydrobenzothiophenyl, dihydrobenzofuranyl, indolyl, isoindolyl, indolinyl, benzo[1,3]dioxolyl, benzooxazolyl, benzothiazolyl, benzoisothiazolyl, benzoisoxazolyl, indazolyl, benzoimidazolyl, benzotriazolyl, naphthyl, tetrahydronaphthyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, phthalazinyl, quinoxalinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, 2,3-dihydro-benzo[1,4]dioxinyl, 4*H*-chromenyl, dihydrobenzocycloheptenyl, tetrahydrobenzocycloheptenyl, indolizinyl, quinolizinyl, 6*aH*-thieno[2,3-d]imidazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, thieno[2,3-*b*]furanyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[2,3-*b*]pyrazinyl, benzo[*c*][1,2,5]oxadiazolyl,

benzo[*c*][1,2,5]thiadiazolyl, 3,4-dihydro-2H-benzo[*b*][1,4]oxazinyl, imidazo[1,2-*a*]pyrazinyl, 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazinyl, 2-oxo-2,3-dihydrobenzo[*d*]oxazolyl, 3,3-dimethyl-2-oxoindolinyl, 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, and 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

R^1 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, each of which is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, each of which is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or
R^2 is gem-dimethyl;

R^3, R^5, and R^6 are each independently selected from the group consisting of H, halogen, $-OR^{12}$, $-S(O)_nR^{13}$, –CN, $-C(O)R^{13}$, $-NR^{10}R^{11}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, wherein each of the C_1–C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or
R^3, R^5, and R^6 are each independently a 5- or 6-membered monocyclic carbocycle or heterocycle or a [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycle or heterocycle containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

R^4 is H, halogen, $-OR^{12}$, $-S(O)_nR^{13}$, –CN, $-C(O)R^{13}$, $-NR^{10}R^{11}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, wherein each of the C_1–C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^4 is a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, wherein the bridged bicyclic ring is optionally substituted from 1 to 3 times with substitutents selected from the group consisting of C_1-C_3 alkyl, $-C(O)R^{13}$, and $-S(O)_nR^{13}$; or

R^4 is phenyl, pyridyl, 2-oxo-pyridin-1-yl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyranyl, furanyl, pyrrolyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, indanyl, indenyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, indolinyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, indazolyl, benzimidazolyl, benzooxazolyl, benzothiazolyl, benzoisoxazolyl, benzoisothiazolyl, benzotriazolyl, benzo[1,3]dioxolyl, naphthyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, pthalazinyl, quinoxalinyl, 2,3-dihydro-benzo[1,4]dioxinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, 4*H*-chromenyl, indolizinyl, quinolizinyl, 6*aH*-thieno[2,3-d]imidazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, [1,2,4]triazolo[1,5-*a*]pyridinyl, thieno[2,3-*b*]furanyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[2,3-*b*]pyrazinyl, imidazo[1,2-*a*]pyrazinyl, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazinyl, 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazinyl, 2-oxo-2,3-dihydrobenzo[*d*]oxazolyl, 3,3-dimethyl-2-oxoindolinyl, 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, 3,4-dihydro-2H-benzo[*b*][1,4]oxazinyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazinyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, [1,2,4]triazolo[4,3-*b*]pyridazinyl, or 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

provided that for compounds of formula IA, X is optionally substituted phenyl and R^4 is optionally substituted monocyclic or bicyclic aryl or heteroaryl;

provided that for compounds of formula IB, X is optionally substituted bicyclic aryl or heteroaryl and R^4 is optionally substituted monocyclic or bicyclic aryl or heteroaryl;

provided that for compounds of formula IC, X is optionally substituted phenyl and R^4 is H, $-OR^{12}$, $-S(O)_nR^{13}$, $C(O)R^{13}$, $-NR^{10}R^{11}$, -CN, halogen, or C_1-C_6 alkyl, wherein each of the C_1-C_6 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

provided that for compounds of formula ID, X is optionally substituted bicyclic aryl or heteroaryl and R^4 is H, $-OR^{12}$, $-S(O)_nR^{13}$, $C(O)R^{13}$, $-NR^{10}R^{11}$, -CN, halogen, or C_1-C_6 alkyl, wherein each of the C_1-C_6 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; and

provided that for compounds of formula IE, X is optionally substituted monocyclic heteroaryl and R^4 is optionally substituted monocyclic or bicyclic aryl or heteroaryl;

R^7 is selected from the group consisting of H,$-S(O)_nR^{13}$, $-C(O)R^{13}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, wherein each of C_1 –C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^8 is selected from the group consisting of H, halogen, $-OR^{12}$, $-S(O)_nR^{13}$, –CN, $-C(O)R^{13}$, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, wherein each of C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or

R^7 and R^8 are gem-dimethyl, with the proviso that only one of R^7 and R^8 is gem-dimethyl;

R^9 is H, halogen,$-OR^{12}$, $-SR^{10}$, C_1-C_6 alkyl, -CN, or $-NR^{10}R^{11}$, wherein each of C_1 –C_6 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{10} and R^{11} are each independently selected from the group consisting of H, $-C(O)R^{13}$, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, wherein each of C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{10} and R^{11} are each independently selected from the group consisting of phenyl, benzyl, and other 5- or 6-membered monocyclic heterocycles, wherein each of the phenyl, benzyl, and 5- or 6-membered monocyclic heterocycle is optionally substituted from 1 to 3 times with substituents as defined below in R^{14};

R^{10} and R^{11} are taken together with the nitrogen to which they are attached to form a saturated or partially saturated monocyclic or fused bicyclic heterocycle selected from the group consisting of piperidine, pyrrolidine, morpholine, thiomorpholine, [1,2]oxazinane, isoxazolidine, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 3-oxomorpholino, 3-oxothiomorpholino, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazine, and other monocyclic or fused bicyclic heterocycles containing 1-4 heteroatoms selected from oxygen, nitrogen and sulfur, wherein the heterocycle is attached to the benzazepine core via the nitrogen atom, and is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, $-OR^{12}$, $-NR^{12}R^{13}$, $-S(O)_nR^{13}$, $-C(O)R^{13}$, and C_1-C_4 alkyl, wherein each of C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{10} and R^{11} are taken together with the nitrogen to which they are attached to form a heterocycle selected from the group consisting of piperazine, 2-oxopiperazinyl, 2-oxo-1,4-diazepanyl, 5-oxo-1,4-diazepanyl, 1,4-diazepane, and other heterocycles containing one additional nitrogen atom in the ring, wherein the heterocycle is optionally substituted on a ring carbon with from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, $-OR^{12}$, $-NR^{12}R^{13}$, $-S(O)_nR^{13}$, $-C(O)R^{13}$, and C_1-C_4 alkyl, or on the additional nitrogen atom from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of $S(O)_nR^{13}$, $-C(O)R^{13}$, and C_1-C_4 alkyl, wherein each of C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{10} and R^{11} are taken together with the nitrogen to which they are attached to form a heterocycle selected from the group consisting of piperazine, 2-oxopiperazinyl, 2-oxo-1,4-diazepanyl, 5-oxo-1,4-diazepanyl, 1,4-diazepane, and other heterocycles containing one additional nitrogen atom in the ring, wherein the heterocycle is optionally substituted on the additional nitrogen atom with a substituent selected independently at each occurrence thereof from the group consisting of phenyl, benzyl, and 5- or 6-membered aromatic heterocycles containing 1-3 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, wherein each of the phenyl, benzyl, and 5- and 6-membered heterocycle is optionally substituted from 1 to 3 times with substituents as defined below in R^{14}; or

when R^4 is $-NR^{10}R^{11}$ or $-C(O)NR^{10}R^{11}$, either R^{10} or R^{11} is a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group

consisting of oxygen, nitrogen, and sulfur, wherein the bridged bicyclic ring is optionally substituted from 1 to 3 times with substituents selected from the group consisting of C_1-C_3 alkyl, $-C(O)R^{13}$, and $-S(O)_nR^{13}$, or either R^{10} or R^{11} is a C_1-C_3 alkyl substituted with a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, wherein the bridged bicyclic ring is optionally substituted from 1 to 3 times with substitutents selected from the group consisting of C_1-C_3 alkyl, $-C(O)R^{13}$, and $-S(O)_nR^{13}$;

R^{12} is selected from the group consisting of H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, and $-C(O)R^{13}$, wherein each of C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{13} is selected from the group consisting of H, $-NR^{10}R^{11}$, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, wherein each of C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or

R^{12} and R^{13} are each independently selected from the group consisting of phenyl, benzyl, pyridazinyl, pyrimidinyl, pyrazinyl, 5- or 6-membered aromatic monocyclic heterocycles, and [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycles or heterocycles containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}; or

R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a heterocycle selected from the group consisting of piperidine, pyrrolidine, piperazine, 1,4-diazepane, morpholine, thiomorpholine, and other heterocycles containing 1-4 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, wherein the heterocycle is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, $-OR^{10}$, $-S(O)_nR^{10}$, $-C(O)R^{10}$, $-C(O)NR^{10}R^{11}$ and C_1-C_4 alkyl, wherein each of C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

n is 0, 1, or 2;

R^{14} is independently selected at each occurrence from a substituent in the group consisting of halogen, $-NO_2$, $-OR^{12}$, $-NR^{10}R^{11}$, $-NR^{12}C(O)_2R^{13}$, $-NR^{12}C(O)NR^{12}R^{13}$, $-S(O)_n R^{13}$, –CN, $-C(O)R^{13}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; and

R^{15} is independently selected at each occurrence from a substituent in the group consisting of –CN, halogen, $C(O)R^{13}$, C_1-C_3 alkyl, $-OR^{12}$, $-NR^{10}R^{11}$, $-S(O)_nR^{13}$, aryl, and heteroaryl, wherein each of the aryl or heteroaryl groups is optionally substituted from 1 to 4 times with substituents as defined above in R^{14};

with the following provisos that (1) when R^4 is H or C_{1-4} alkoxy, X cannot be phenyl; (2) when R^4 is (a) C_{1-6} alkyl, (b) C_{1-4}alkoxy, (c) hydroxyl, (d) halogen, or (e) CN, X cannot be a phenyl substituted at the *para*-position with the same R^4; (3) when any one of R^3, R^4, R^5, and R^6 is hydrogen, halogen, perhalomethyl, optionally substituted C_{1-6}-alkyl, hydroxy, optionally substituted C_{1-4} alkoxy, cyano, amino, optionally substituted mono- or optionally substituted di-C_{1-4} alkylamino, acylamino, or carbamoyl, X cannot be furanyl, thienyl, pyrazolyl, tetrazolyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-oxadiazolyl, 1,2,5-thiadiazolyl, benzo[d]isoxazolyl, or benzo[d]isothiazolyl; (4) when R^4 is $-S(O)_nR^{13}$, n cannot be 0; and (5) when R^9 is a substituted alkyl, R^{15} cannot be $-NR^{10}R^{11}$;

or an oxide thereof, or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein X is optionally substituted phenyl and R^4 is substituted monocyclic or bicyclic aryl or heteroaryl.

3. The compound according to claim 1, wherein X is optionally substituted bicyclic aryl or heteroaryl and R^4 is optionally substituted monocyclic or bicyclic aryl or heteroaryl.

4. The compound according to claim 1, wherein X is optionally substituted phenyl and R^4 is H, $-OR^{12}$, $-S(O)_nR^{13}$, $C(O)R^{13}$, $-NR^{10}R^{11}$, -CN, halogen, or C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted from 1 to 3 times with substituents as defined in R^{15}.

5. The compound according to claim 1, wherein X is optionally substituted bicyclic aryl or heteroaryl and R^4 is selected from the group consisting of H, $-OR^{12}$, $-S(O)_nR^{13}$, $C(O)R^{13}$, $-NR^{10}R^{11}$, -CN, halogen, and C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted from 1 to 3 times with substituents as defined in R^{15}.

6. The compound according to claim 1, wherein X is optionally substituted monocyclic heteroaryl and R^4 is optionally substituted monocyclic or bicyclic aryl or heteroaryl.

7. The compound according to claim 1, wherein:

X is phenyl, optionally substituted from 1 to 4 times with substituents as defined in R^{14};

R^1 is H, methyl, ethyl, or isopropyl;

R^2 is H, methyl, or gem-dimethyl;

R^3 is H, methyl, hydroxy, methoxy, fluoro, chloro, cyano, trifluoromethyl, or trifluoromethoxy;

R^5 is H, fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxy or methoxy;

R^6 is H, fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxy or methoxy;

R^7 is H, gem-dimethyl, or C_1–C_4 alkyl, wherein each of the C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined in R^{15};

R^8 is H, hydroxy, fluoro, or chloro; and

R^9 is H, fluoro, chloro, methyl, hydroxyl, or cyano.

8. The compound according to claim 7, wherein:

R^4 is H, halogen, $-OR^{12}$, $-S(O)_nR^{13}$, –CN, $-C(O)R^{13}$, $-NR^{10}R^{11}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, wherein each of the C_1–C_6 alkyl, C_2-C_6 alkenyl,

C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined in R^{15}; or

R^4 is a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, wherein the bridged bicyclic ring is optionally substituted from 1 to 3 times with substitutents selected from the group consisting of C_1-C_3 alkyl, $-C(O)R^{13}$, and $-S(O)_nR^{13}$.

9. The compound according to claim 7, wherein R^4 is phenyl, pyridyl, 2-oxo-pyridin-1-yl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyranyl, furanyl, pyrrolyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, indanyl, indenyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, indolinyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, indazolyl, benzimidazolyl, benzooxazolyl, benzothiazolyl, benzoisoxazolyl, benzoisothiazolyl, benzotriazolyl, benzo[1,3]dioxolyl, naphthyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, pthalazinyl, quinoxalinyl, 2,3-dihydro-benzo[1,4]dioxinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, 4*H*-chromenyl, indolizinyl, quinolizinyl, 6*aH*-thieno[2,3-d]imidazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, [1,2,4]triazolo[1,5-*a*]pyridinyl, thieno[2,3-*b*]furanyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[2,3-*b*]pyrazinyl, imidazo[1,2-*a*]pyrazinyl, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazinyl, 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazinyl, 2-oxo-2,3-dihydrobenzo[*d*]oxazolyl, 3,3-dimethyl-2-oxoindolinyl, 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, 3,4-dihydro-2H-benzo[*b*][1,4]oxazinyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazinyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, optionally substituted from 1 to 4 times with substituents as defined in R^{14}.

10. The compound according to claim 1, wherein:

X represents a 5- or 6-membered monocyclic heterocycle selected from the group consisting of pyridyl, 2-oxo-pyridin-1-yl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyranyl, pyrrolyl, furanyl, thiophenyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl,

thiadiazolyl, triazolyl, and tetrazolyl, optionally substituted from 1 to 4 times with substituents as defined in R^{14};

R^1 is H, methyl, ethyl, or isopropyl;

R^2 is H, methyl, or gem-dimethyl;

R^3 is H, methyl, hydroxy, methoxy, fluoro, chloro, cyano, trifluoromethyl, or trifluoromethoxy;

R^5 is H, fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, or methoxy;

R^6 is H, fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, or methoxy;

R^7 is H, gem-dimethyl, or C_1–C_4 alkyl, wherein each of the C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined in R^{15};

R^8 is H, hydroxy, fluoro, or chloro; and

R^9 is H, fluoro, chloro, methyl, hydroxyl, or cyano.

11. The compound according to claim 10, wherein:

R^4 is H, halogen, $-OR^{12}$, $-S(O)_nR^{13}$, –CN, $-C(O)R^{13}$, $-NR^{10}R^{11}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, wherein each of the C_1–C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined in R^{15}; or
R^4 is a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, wherein the bridged bicyclic ring is optionally substituted from 1 to 3 times with substitutents selected from the group consisting of C_1-C_3 alkyl, $-C(O)R^{13}$, and $-S(O)_nR^{13}$.

12. The compound according to claim 10, wherein R^4 is phenyl, pyridyl, 2-oxo-pyridin-1-yl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyranyl, furanyl, pyrrolyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, indanyl, indenyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, indolinyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, indazolyl, benzimidazolyl, benzooxazolyl,

benzothiazolyl, benzoisoxazolyl, benzoisothiazolyl, benzotriazolyl, benzo[1,3]dioxolyl, naphthyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, pthalazinyl, quinoxalinyl, 2,3-dihydro-benzo[1,4]dioxinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, 4*H*-chromenyl, indolizinyl, quinolizinyl, 6*aH*-thieno[2,3-d]imidazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, [1,2,4]triazolo[1,5-*a*]pyridinyl, thieno[2,3-*b*]furanyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[2,3-*b*]pyrazinyl, imidazo[1,2-*a*]pyrazinyl, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazinyl, 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazinyl, 2-oxo-2,3-dihydrobenzo[*d*]oxazolyl, 3,3-dimethyl-2-oxoindolinyl, 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, 3,4-dihydro-2H-benzo[*b*][1,4]oxazinyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazinyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, [1,2,4]triazolo[4,3-*b*]pyridazinyl, or 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, optionally substituted from 1 to 4 times with substituents as defined in R^{14}.

13. The compound according to claim 1, wherein:

X is a [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycle or heterocycle selected from the group consisting of indenyl, indanyl, benzofuranyl, benzothiophenyl, dihydrobenzothiophenyl, dihydrobenzofuranyl, indolyl, isoindolyl, indolinyl, benzo[1,3]dioxolyl, benzooxazolyl, benzothiazolyl, benzoisothiazolyl, benzoisoxazolyl, indazolyl, benzoimidazolyl, benzotriazolyl, naphthyl, tetrahydronaphthyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, phthalazinyl, quinoxalinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, 2,3-dihydro-benzo[1,4]dioxinyl, 4*H*-chromenyl, dihydrobenzocycloheptenyl, tetrahydrobenzocycloheptenyl, indolizinyl, quinolizinyl, 6*aH*-thieno[2,3-d]imidazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, thieno[2,3-*b*]furanyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[2,3-*b*]pyrazinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, 3,4-dihydro-2H-benzo[*b*][1,4]oxazinyl, imidazo[1,2-*a*]pyrazinyl, 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazinyl, 2-oxo-2,3-dihydrobenzo[*d*]oxazolyl, 3,3-dimethyl-2-oxoindolinyl, 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, and 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, optionally substituted from 1 to 4 times with substituents as defined in R^{14};

R^1 is H, methyl, ethyl, or isopropyl;

R^2 is H, methyl, or gem-dimethyl;

R^3 is H, methyl, hydroxy, methoxy, fluoro, chloro, cyano, trifluoromethyl, or trifluoromethoxy;

R^5 is H, fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, or methoxy;

R^6 is H, fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, or methoxy;

R^7 is H, gem-dimethyl, or C_1–C_4 alkyl, wherein each of the C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined in R^{15};

R^8 is H, hydroxy, fluoro, or chloro; and

R^9 is H, fluoro, chloro, methyl, hydroxyl, or cyano.

14. The compound according to claim 13, wherein:

R^4 is H, halogen, $-OR^{12}$, $-S(O)_nR^{13}$, –CN, $-C(O)R^{13}$, $-NR^{10}R^{11}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, wherein each of the C_1–C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined in R^{15}; or
R^4 is a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, wherein the bridged bicyclic ring is optionally substituted from 1 to 3 times with substitutents selected from the group consisting of C_1-C_3 alkyl, $-C(O)R^{13}$, and $-S(O)_nR^{13}$.

15. The compound according to claim 13, wherein R^4 is phenyl, pyridyl, 2-oxo-pyridin-1-yl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyranyl, furanyl, pyrrolyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, indanyl, indenyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, indolinyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, indazolyl, benzimidazolyl, benzooxazolyl, benzothiazolyl, benzoisoxazolyl, benzoisothiazolyl, benzotriazolyl, benzo[1,3]dioxolyl, naphthyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, pthalazinyl, quinoxalinyl, 2,3-dihydro-

benzo[1,4]dioxinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, 4*H*-chromenyl, indolizinyl, quinolizinyl, 6*aH*-thieno[2,3-d]imidazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, [1,2,4]triazolo[1,5-*a*]pyridinyl, thieno[2,3-*b*]furanyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[2,3-*b*]pyrazinyl, imidazo[1,2-*a*]pyrazinyl, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazinyl, 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazinyl, 2-oxo-2,3-dihydrobenzo[*d*]oxazolyl, 3,3-dimethyl-2-oxoindolinyl, 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, 3,4-dihydro-2H-benzo[*b*][1,4]oxazinyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazinyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, optionally substituted from 1 to 4 times with substituents as defined in R^{14}.

16. The compound according to claim 1, wherein:

X is thiophenyl, thiazolyl, pyridinyl, phenyl, naphthyl, benzo[*b*]thiophenyl, benzofuranyl, benzo[*d*][1,3]dioxolyl, 2,3-dihydrobenzo[*b*][1,4]dioxinyl, 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazinyl, or 4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazinyl, optionally substituted with from 1 to 3 substituents selected independently from the group consisting of halogen, methoxy, cyano, trifluoromethyl, trifluoromethoxy, difluoromethoxy, substituted C_1-C_3 alkyl, methanesulfonyl, carbamoyl, C_1-C_3 alkyl-substituted carbamoyl, and acetamido;

R^1 is H, methyl, ethyl, isopropyl, 2-hydroxyethyl, 2,2,2-trifluoroethyl, 2-fluoroethyl, or benzyl;

R^2 is H or gem-dimethyl;

R^3 is H or fluoro;

R^4 is H, methoxy, hydroxyl, methyl, fluoro, bromo, cyano, trifluoromethyl, trifluoromethoxy, acetyl, aminomethyl, 1-aminocyclopropyl, morpholinomethyl, 2-hydroxypropan-2-yl, morpholine-4-carbonyl, 2-morpholinoethoxy, 2-(dimethylamino)ethyl(methyl)amino, 2-hydroxyethylamino, piperidin-1-yl, pyrrolidin-1-yl, piperidin-4-ol, morpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-(ethylsulfonyl)piperazin-1-yl, 4-(2-(isopropylamino)-2-oxoethyl)piperazin-1-yl, 4-(pyridin-2-yl)piperazin-1-yl, 4-(pyrimidin-2-yl)piperazin-1-yl, 2-oxopyrrolidin-1-yl, 2-oxopiperidin-1-yl, 6-methylpyridazin-3-yloxy, 6-pyridazin-3-yloxy,1,2,4-oxadiazol-3-yl, 3,5-dimethylisoxazol-4-yl, 1*H*-

pyrazol-4-yl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, (methanesulfonyl)phenyl, pyridinyl, aminopyridinyl, pyridazin-3-yl, 6-methylpyridazin-3-yl, 6-(trifluoromethyl)pyridazin-3-yl, 6-aminopyridazin-3-yl, 6-(methylamino)pyridazin-3-yl, 6-(dimethylamino)pyridazin-3-yl, 6-morpholinopyridazin-3-yl, 6-(4-hydroxypiperidin-1-yl)pyridazin-3-yl, 6-(4-methylpiperazin-1-yl)pyridazin-3-yl, (6-(hydroxymethyl)pyridazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrazin-2-yl, 2-oxopyridin-1(2*H*)-yl, 6-oxo-1,6-dihydropyridazin-3-yl, imidazo[1,2-*a*]pyridin-6-yl, imidazo[1,2-*a*]pyrazin-3-yl, 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, 5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl, 3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl, [1,2,4]triazolo[1,5-*a*]pyridin-6-yl, [1,2;4]triazolo[4,3-*a*]pyridin-6-yl, 3,3-dimethyl-2-oxoindolin-5-yl, 3-methyl-[1,2,4]triazolo[4,3-*b*]-pyridazinyl, or [1,2,4]triazolo[4,3-*b*]-pyridazinyl;

R^5 is H or fluoro;

R^6 is H or fluoro;

R^7 is H;

R^8 is H, fluoro, or hydroxy; and

R^9 is H or hydroxy.

17. The compound according to claim 1, wherein the carbon atom designated * is in the *R* configuration.

18. The compound according to claim 1, wherein the carbon atom designated * is in the *S* configuration.

19. The compound according to claim 1, wherein the compound is a (+) stereoisomer.

20. The compound according to claim 1, wherein the compound is a (-) stereoisomer.

21. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the compound according to claim 1.

22. A use of a therapeutically effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof, for treating a disorder which is created by or is dependent upon decreased availability of norepinephrine, dopamine, or serotonin, in a patient in need of such treatment.

23. A use of therapeutically effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for treating a disorder which is created by or is dependent upon decreased availability of norepinephrine, dopamine, or serotonin, in a patient in need of such treatment.

24. The use according to claim 22 or 23, further comprising:

a use of a therapeutically effective amount of a serotonin 1A receptor antagonist or a pharmaceutically acceptable salt thereof.

25. The use according to claim 24, wherein the serotonin 1A receptor antagonist is N-(t-butyl)-3-[a-(2-methoxyphenyl)piperazin-1-yl]-2-phenylpropanamide or spiperone.

26. The use according to claim 22 or 24, further comprising:

a use of a therapeutically effective amount of a selective neurokinin-1 receptor antagonist or a pharmaceutically acceptable salt thereof.

27. The use according to claim 22 or 23, further comprising:

a use of a therapeutically effective amount of a norepinephrine precursor or a pharmaceutically acceptable salt thereof.

28. The use according to claim 27, wherein the norepinephrine precursor is L-tyrosine or L-phenylalanine.

29. The use according to claim 22 or 23, wherein the disorder is selected from the group consisting of: lower back pain, attention deficit hyperactivity disorder (ADHD),

cognition impairment, anxiety disorders, generalized anxiety disorder (GAD), panic disorder, bipolar disorder or manic depression or manic-depressive disorder, obsessive compulsive disorder (OCD), posttraumatic stress disorder (PTSD), acute stress disorder, social phobia, simple phobias, pre-menstrual dysphoric disorder (PMDD), social anxiety disorder (SAD), major depressive disorder (MDD), postnatal depression, dysthymia, depression associated with Alzheimer's disease, Parkinson's disease, or psychosis, supranuclear palsy, eating disorders, obesity, anorexia nervosa, bulimia nervosa, binge eating disorder, analgesia, substance abuse disorders, chemical dependencies, nicotine addiction, cocaine addiction, alcohol and amphetamine addiction, Lesch-Nyhan syndrome, neurodegenerative diseases, Parkinson's disease, late luteal phase syndrome or narcolepsy, psychiatric symptoms, anger, rejection sensitivity, movement disorders, extrapyramidal syndrome, Tic disorders, restless leg syndrome (RLS), tardive dyskinesia, supranuclear palsy, sleep related eating disorder (SRED), night eating syndrome (NES), stress urinary incontinence (SUI), migraine, neuropathic pain, diabetic neuropathy, fibromyalgia syndrome (FS), chronic fatigue syndrome (CFS), sexual dysfunction, premature ejaculation, male impotence, and thermoregulatory disorders.

30. The use according to claim 29, wherein the disorder is lower back pain.

31. The use according to claim 29, wherein the disorder is attention deficit hyperactivity disorder.

32. The use according to claim 29, wherein the disorder is anxiety disorder.

33. The use according to claim 29, wherein the disorder is bipolar disorder or manic depressive disorder.

34. The use according to claim 29, wherein the disorder is major depressive disorder.

35. The use according to claim 29, wherein the disorder is postnatal depression.

36. The use according to claim 29, wherein the disorder is dysthymia.

37. The use according to claim 29, wherein the disorder is depression associated with Alzheimer's disease, Parkinson's disease, or psychosis.

38. The use according to claim 29, wherein the disorder is eating disorder.

39. The use according to claim 29, wherein the disorder is obesity.

40. The use according to claim 29, wherein the disorder is substance abuse disorder.

41. The use according to claim 29, wherein the disorder is neurodegenerative disease.

42. The use according to claim 29, wherein the disorder is Parkinson's disease.

43. The use according to claim 29, wherein the disorder is neuropathic pain.

44. The use according to claim 29, wherein the disorder is diabetic neuropathy.

45. The use according to claim 29, wherein the disorder is fibromyalgia syndrome.

46. The use according to claim 29, wherein the disorder is sexual dysfunction.

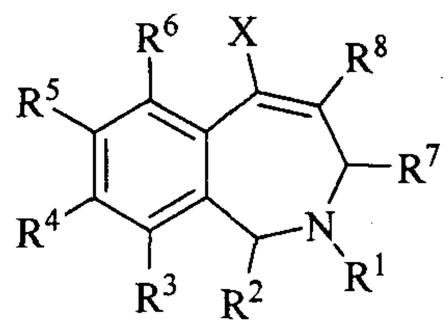
47. The use according to claim 29, wherein the disorder is premature ejaculation.

48. The use according to claim 29, wherein the disorder is stress urinary incontinence.

49. The use according to claim 29, wherein the disorder is thermoregulatory disorder.

50. The use according to claim 49, wherein the thermoregulatory disorder is hot flashes.

51. A compound of formula (II) having the following structure:



II

wherein:

X represents a 5- or 6-membered aromatic or nonaromatic monocyclic carbocycle or heterocycle selected from the group consisting of phenyl, pyridyl, 2-oxo-pyridin-1-yl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyranyl, pyrrolyl, furanyl, thiophenyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, and tetrazolyl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}; or
X is a [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycle or heterocycle selected from the group consisting of `indenyl, indanyl, benzofuranyl, benzothiophenyl, dihydrobenzothiophenyl, dihydrobenzofuranyl, indolyl, isoindolyl, indolinyl, benzo[1,3]dioxolyl, benzooxazolyl, benzothiazolyl, benzoisothiazolyl, benzoisoxazolyl, indazolyl, benzoimidazolyl, benzotriazolyl, naphthyl, tetrahydronaphthyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, phthalazinyl,

quinoxalinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, 2,3-dihydro-benzo[1,4]dioxinyl, 4*H*-chromenyl, dihydrobenzocycloheptenyl, tetrahydrobenzocycloheptenyl, indolizinyl, quinolizinyl, 6*aH*-thieno[2,3-d]imidazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, thieno[2,3-*b*]furanyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[2,3-*b*]pyrazinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, 3,4-dihydro-2H-benzo[*b*][1,4]oxazinyl, imidazo[1,2-*a*]pyrazinyl, 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazinyl, 2-oxo-2,3-dihydrobenzo[*d*]oxazolyl, 3,3-dimethyl-2-oxoindolinyl, 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, and 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

R^1 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, each of which is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, each of which is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or
R^2 is gem-dimethyl;

R^3, R^5, and R^6 are each independently selected from the group consisting of H, halogen, $-OR^{12}$, $-S(O)_nR^{13}$, –CN, $-C(O)R^{13}$, $-NR^{10}R^{11}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, wherein each of the C_1–C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or
R^3, R^5, and R^6 are each independently a 5- or 6-membered monocyclic carbocycle or heterocycle or a [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycle or heterocycle containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

R^4 is H, halogen, $-OR^{12}$, $-S(O)_nR^{13}$, –CN, $-C(O)R^{13}$, $-NR^{10}R^{11}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, wherein each of the C_1–C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^4 is a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, wherein the bridged bicyclic ring is optionally substituted from 1 to 3 times with substitutents selected from the group consisting of C_1-C_3 alkyl, $-C(O)R^{13}$, and $-S(O)_nR^{13}$; or

R^4 is phenyl, pyridyl, 2-oxo-pyridin-1-yl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyranyl, furanyl, pyrrolyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, indanyl, indenyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, indolinyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, indazolyl, benzimidazolyl, benzooxazolyl, benzothiazolyl, benzoisoxazolyl, benzoisothiazolyl, benzotriazolyl, benzo[1,3]dioxolyl, naphthyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, pthalazinyl, quinoxalinyl, 2,3-dihydro-benzo[1,4]dioxinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, 4*H*-chromenyl, indolizinyl, quinolizinyl, 6*aH*-thieno[2,3-d]imidazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, [1,2,4]triazolo[1,5-*a*]pyridinyl, thieno[2,3-*b*]furanyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[2,3-*b*]pyrazinyl, imidazo[1,2-*a*]pyrazinyl, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazinyl, 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazinyl, 2-oxo-2,3-dihydrobenzo[*d*]oxazolyl, 3,3-dimethyl-2-oxoindolinyl, 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, 3,4-dihydro-2H-benzo[*b*][1,4]oxazinyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazinyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, [1,2,4]triazolo[4,3-*b*]pyridazinyl, or 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

R^7 is selected from the group consisting of H,$-S(O)_nR^{13}$, $-C(O)R^{13}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, wherein each of C_1 –C_6 alkyl, C_2-C_6

alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or

R^7 is gem-dimethyl;

R^8 is H or C_1-C_6 alkyl, wherein each of C_1 –C_6 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{10} and R^{11} are each independently selected from the group consisting of H, -C(O)R^{13}, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, wherein each of C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{10} and R^{11} are each independently selected from the group consisting of phenyl, benzyl, and other 5- or 6-membered monocyclic heterocycles, wherein each of the phenyl, benzyl, and 5- or 6-membered monocyclic heterocycle is optionally substituted from 1 to 3 times with substituents as defined below in R^{14};

R^{10} and R^{11} are taken together with the nitrogen to which they are attached to form a saturated or partially saturated monocyclic or fused bicyclic heterocycle selected from the group consisting of piperidine, pyrrolidine, morpholine, thiomorpholine, [1,2]oxazinane, isoxazolidine, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 3-oxomorpholino, 3-oxothiomorpholino, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazine, and other monocyclic or fused bicyclic heterocycles containing 1-4 heteroatoms selected from oxygen, nitrogen and sulfur, wherein the heterocycle is attached to the benzazepine core via the nitrogen atom, and is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, -OR^{12}, -N$R^{12}R^{13}$, –S(O)$_n$$R^{13}$, –C(O)$R^{13}$, and C_1-C_4 alkyl, wherein each of C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{10} and R^{11} are taken together with the nitrogen to which they are attached to form a heterocycle selected from the group consisting of piperazine, 2-oxopiperazinyl, 2-oxo-1,4-diazepanyl, 5-oxo-1,4-diazepanyl, 1,4-diazepane, and other heterocycles containing one additional nitrogen atom in the ring, wherein the heterocycle is optionally substituted on a ring carbon with from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of

halogen, cyano, $-OR^{12}$, $-NR^{12}R^{13}$, $-S(O)_nR^{13}$, $-C(O)R^{13}$, and C_1-C_4 alkyl, or on the additional nitrogen atom from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of $S(O)_nR^{13}$, $-C(O)R^{13}$, and C_1-C_4 alkyl, wherein each of C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};
R^{10} and R^{11} are taken together with the nitrogen to which they are attached to form a heterocycle selected from the group consisting of piperazine, 2-oxopiperazinyl, 2-oxo-1,4-diazepanyl, 5-oxo-1,4-diazepanyl, 1,4-diazepane, and other heterocycles containing one additional nitrogen atom in the ring, wherein the heterocycle is optionally substituted on the additional nitrogen atom with a substituent selected independently at each occurrence thereof from the group consisting of phenyl, benzyl, and 5- or 6-membered aromatic heterocycles containing 1-3 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, wherein each of the phenyl, benzyl, and 5- and 6-membered heterocycle is optionally substituted from 1 to 3 times with substituents as defined below in R^{14}; or
when R^4 is $-NR^{10}R^{11}$ or $-C(O)NR^{10}R^{11}$, either R^{10} or R^{11} is a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, wherein the bridged bicyclic ring is optionally substituted from 1 to 3 times with substituents selected from the group consisting of C_1-C_3 alkyl, $-C(O)R^{13}$, and $-S(O)_nR^{13}$, or either R^{10} or R^{11} is a C_1-C_3 alkyl substituted with a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, wherein the bridged bicyclic ring is optionally substituted from 1 to 3 times with substitutents selected from the group consisting of C_1-C_3 alkyl, $-C(O)R^{13}$, and $-S(O)_nR^{13}$;

R^{12} is selected from the group consisting of H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, and $-C(O)R^{13}$, wherein each of C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{13} is selected from the group consisting of H, $-NR^{10}R^{11}$, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, wherein each of C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or

R^{12} and R^{13} are each independently selected from the group consisting of phenyl, benzyl, pyridazinyl, pyrimidinyl, pyrazinyl, 5- or 6-membered aromatic monocyclic heterocycles, and [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycles or heterocycles containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}; or

R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a heterocycle selected from the group consisting of piperidine, pyrrolidine, piperazine, 1,4-diazepane, morpholine, thiomorpholine, and other heterocycles containing 1-4 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, wherein the heterocycle is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, $-OR^{10}$, $-S(O)_nR^{10}$, $-C(O)R^{10}$, $-C(O)NR^{10}R^{11}$ and C_1-C_4 alkyl, wherein each of C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

n is 0, 1, or 2;

R^{14} is independently selected at each occurrence from a substituent in the group consisting of halogen, $-NO_2$, $-OR^{12}$, $-NR^{10}R^{11}$, $-NR^{12}C(O)_2R^{13}$, $-NR^{12}C(O)NR^{12}R^{13}$, $-S(O)_n R^{13}$, –CN, –$C(O)R^{13}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; and

R^{15} is independently selected at each occurrence from a substituent in the group consisting of –CN, halogen, $C(O)R^{13}$, C_1-C_3 alkyl, $-OR^{12}$, $-NR^{10}R^{11}$, $-S(O)_nR^{13}$, aryl, and heteroaryl, wherein each of the aryl or heteroaryl groups is optionally substituted from 1 to 4 times with substituents as defined above in R^{14};

with the following provisos that (1) when R^4 is H, X cannot be phenyl or a phenyl substituted at the *para*-position with Cl; (2) when R^4 is H, OMe, or O-benzyl, X cannot be a phenyl substituted

at the *para*-position with the same R^4; and (3) when R^2 is a 2-(4-nitrophenoxy)ethyl, R^5 cannot be $OC(O)NMe_2$;

or an oxide thereof, or a pharmaceutically acceptable salt thereof.

52. The compound according to claim 51, wherein:

R^1 is H, methyl, ethyl, or isopropyl;

R^2 is H, methyl, or gem-dimethyl;

R^3 is H, methyl, hydroxy, methoxy, fluoro, chloro, cyano, trifluoromethyl, or trifluoromethoxy;

R^5 is H, fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, or methoxy;

R^6 is H, fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, or methoxy;

R^7 is H, gem-dimethyl, or C_1–C_4 alkyl, wherein each of the C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined in R^{15}; and

R^8 is H or C_1–C_3 alkyl.

53. The compound according to claim 51, wherein:

X is thiophenyl, thiazolyl, pyridinyl, phenyl, naphthyl, benzo[*b*]thiophenyl, benzofuranyl, benzo[*d*][1,3]dioxolyl, 2,3-dihydrobenzo[*b*][1,4]dioxinyl, 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazinyl or 4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazinyl, optionally substituted with from 1 to 3 substituents selected independently from the group consisting of halogen, methoxy, cyano, trifluoromethyl, trifluoromethoxy, difluoromethoxy, substituted C_1-C_3 alkyl, methanesulfonyl, carbamoyl, C_1-C_3 alkyl-substituted carbamoyl, and acetamido;

R^1 is H, methyl, ethyl, isopropyl, 2-hydroxyethyl, 2,2,2-trifluoroethyl, 2-fluoroethyl, or benzyl;

R^2 is H or gem-dimethyl;

R^3 is H or fluoro;

R^4 is H, methoxy, hydroxyl, methyl, fluoro, bromo, cyano, trifluoromethyl, trifluoromethoxy, acetyl, aminomethyl, 1-aminocyclopropyl, morpholinomethyl, 2-hydroxypropan-2-yl, morpholine-4-carbonyl, 2-morpholinoethoxy, 2-(dimethylamino)ethyl(methyl)amino, 2-hydroxyethylamino, piperidin-1-yl, pyrrolidin-1-yl, piperidin-4-ol, morpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-(ethylsulfonyl)piperazin-1-yl, 4-(2-(isopropylamino)-2-oxoethyl)piperazin-1-yl, 4-(pyridin-2-yl)piperazin-1-yl, 4-(pyrimidin-2-yl)piperazin-1-yl, 2-oxopyrrolidin-1-yl, 2-oxopiperidin-1-yl, 6-methylpyridazin-3-yloxy, 6-pyridazin-3-yloxy,1,2,4-oxadiazol-3-yl, 3,5-dimethylisoxazol-4-yl, 1*H*-pyrazol-4-yl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, (methanesulfonyl)phenyl, pyridinyl, aminopyridinyl, pyridazin-3-yl, 6-methylpyridazin-3-yl, 6-(trifluoromethyl)pyridazin-3-yl, 6-aminopyridazin-3-yl, 6-(methylamino)pyridazin-3-yl, 6-(dimethylamino)pyridazin-3-yl, 6-morpholinopyridazin-3-yl, 6-(4-hydroxypiperidin-1-yl)pyridazin-3-yl, 6-(4-methylpiperazin-1-yl)pyridazin-3-yl, (6-(hydroxymethyl)pyridazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrazin-2-yl, 2-oxopyridin-1(2*H*)-yl, 6-oxo-1,6-dihydropyridazin-3-yl, imidazo[1,2-*a*]pyridin-6-yl, imidazo[1,2-*a*]pyrazin-3-yl, 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, 5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl, 3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl, [1,2,4]triazolo[1,5-*a*]pyridin-6-yl, [1,2,4]triazolo[4,3-*a*]pyridin-6-yl, 3,3-dimethyl-2-oxoindolin-5-yl, 3-methyl-[1,2,4]triazolo[4,3-*b*]-pyridazinyl, or [1,2,4]triazolo[4,3-*b*]-pyridazinyl;

R^5 is H or fluoro;

R^6 is H or fluoro;

R^7 is H; and

R^8 is H or C_1-C_3 alkyl.

54. The compound according to claim 51, wherein the compound is a (+) stereoisomer.

55. The compound according to claim 51, wherein the compound is a (-) stereoisomer.

56. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the compound according to claim 51.

57. A use of a therapeutically effective amount of a compound according to claim 50, for treating a disorder which is created by or is dependent upon decreased availability of norepinephrine, dopamine, or serotonin, in a patient in need of such treatment.

58. A use of a therapeutically effective amount of a compound according to claim 50, for the preparation of a medicament for treating a disorder which is created by or is dependent upon decreased availability of norepinephrine, dopamine, or serotonin, in a patient in need of such treatment.

59. The use according to claim 57 or 58, further comprising:

a use of a therapeutically effective amount of a serotonin 1A receptor antagonist or a pharmaceutically acceptable salt thereof.

60. The use according to claim 59, wherein the serotonin 1A receptor antagonist is N-(t-butyl)-3-[a-(2-methoxyphenyl)piperazin-1-yl]-2-phenylpropanamide or spiperone.

61. The use according to claim 57 or 58, further comprising:

a use of a therapeutically effective amount of a selective neurokinin-1 receptor antagonist or a pharmaceutically acceptable salt thereof.

62. The use according to claim 57 or 58, further comprising:

a use of a therapeutically effective amount of a norepinephrine precursor or a pharmaceutically acceptable salt thereof.

63. The use according to claim 62, wherein the norepinephrine precursor is L-tyrosine or L-phenylalanine.

64. The use according to claim 57 or 58, wherein the disorder is selected from the group consisting of: lower back pain, attention deficit hyperactivity disorder (ADHD), cognition impairment, anxiety disorders, generalized anxiety disorder (GAD), panic disorder, bipolar disorder or manic depression or manic-depressive disorder, obsessive compulsive disorder (OCD), posttraumatic stress disorder (PTSD), acute stress disorder, social phobia, simple phobias, pre-menstrual dysphoric disorder (PMDD), social anxiety disorder (SAD), major depressive disorder (MDD), postnatal depression, dysthymia, depression associated with Alzheimer's disease, Parkinson's disease, or psychosis, supranuclear palsy, eating disorders, obesity, anorexia nervosa, bulimia nervosa, binge eating disorder, analgesia, substance abuse disorders, chemical dependencies, nicotine addiction, cocaine addiction, alcohol and amphetamine addiction, Lesch-Nyhan syndrome, neurodegenerative diseases, Parkinson's disease, late luteal phase syndrome or narcolepsy, psychiatric symptoms, anger, rejection sensitivity, movement disorders, extrapyramidal syndrome, Tic disorders, restless leg syndrome (RLS), tardive dyskinesia, supranuclear palsy, sleep related eating disorder (SRED), night eating syndrome (NES), stress urinary incontinence (SUI), migraine, neuropathic pain, diabetic neuropathy, fibromyalgia syndrome (FS), chronic fatigue syndrome (CFS), sexual dysfunction, premature ejaculation, male impotence, and thermoregulatory disorders.

65. The use according to claim 64, wherein the disorder is lower back pain.

66. The use according to claim 64, wherein the disorder is attention deficit hyperactivity disorder.

67. The use according to claim 64, wherein the disorder is anxiety disorder.

68. The use according to claim 64, wherein the disorder is bipolar disorder or manic depressive disorder.

69. The use according to claim 64, wherein the disorder is major depressive disorder.

70. The use according to claim 64, wherein the disorder is postnatal depression.

71. The use according to claim 64, wherein the disorder is dysthymia.

72. The use according to claim 64, wherein the disorder is depression associated with Alzheimer's disease, Parkinson's disease, or psychosis.

73. The use according to claim 64, wherein the disorder is eating disorder.

74. The use according to claim 64, wherein the disorder is obesity.

75. The use according to claim 64, wherein the disorder is substance abuse disorder.

76. The use according to claim 64, wherein the disorder is neurodegenerative disease.

77. The use according to claim 64, wherein the disorder is Parkinson's disease.

78. The use according to claim 64, wherein the disorder is neuropathic pain.

79. The use according to claim 64, wherein the disorder is diabetic neuropathy.

80. The use according to claim 64, wherein the disorder is fibromyalgia syndrome.

81. The use according to claim 64, wherein the disorder is sexual dysfunction.

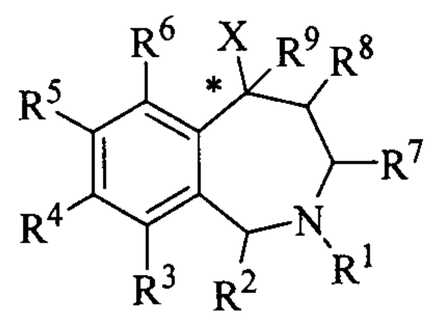
82. The use according to claim 64, wherein the disorder is premature ejaculation.

83. The use according to claim 64, wherein the disorder is stress urinary incontinence.

84. The use according to claim 64, wherein the disorder is thermoregulatory disorder.

85. The use according to claim 84, wherein the thermoregulatory disorder is hot flashes.

86. A process for preparation of a product compound of formulae I(A-E) having the following structure:



I(A-E)

wherein:

the carbon atom designated * is in the R or S configuration; and

X represents a 5- or 6-membered aromatic or nonaromatic monocyclic carbocycle or heterocycle selected from the group consisting of phenyl, pyridyl, 2-oxo-pyridin-1-yl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyranyl, pyrrolyl, furanyl, thiophenyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, and tetrazolyl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}; or

X is a [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycle or heterocycle selected from the group consisting of indenyl, indanyl, benzofuranyl, benzothiophenyl, dihydrobenzothiophenyl,

dihydrobenzofuranyl, indolyl, isoindolyl, indolinyl, benzo[1,3]dioxolyl, benzooxazolyl, benzothiazolyl, benzoisothiazolyl, benzoisoxazolyl, indazolyl, benzoimidazolyl, benzotriazolyl, naphthyl, tetrahydronaphthyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, phthalazinyl, quinoxalinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, 2,3-dihydro-benzo[1,4]dioxinyl, 4*H*-chromenyl, dihydrobenzocycloheptenyl, tetrahydrobenzocycloheptenyl, indolizinyl, quinolizinyl, 6*aH*-thieno[2,3-d]imidazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, thieno[2,3-*b*]furanyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[2,3-*b*]pyrazinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, 3,4-dihydro-2H-benzo[*b*][1,4]oxazinyl, imidazo[1,2-*a*]pyrazinyl, 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazinyl, 2-oxo-2,3-dihydrobenzo[*d*]oxazolyl, 3,3-dimethyl-2-oxoindolinyl, 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, and 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

R^1 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, each of which is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, each of which is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or
R^2 is gem-dimethyl;

R^3, R^5, and R^6 are each independently selected from the group consisting of H, halogen, $-OR^{12}$, $-S(O)_nR^{13}$, –CN, $-C(O)R^{13}$, $-NR^{10}R^{11}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, wherein each of the C_1–C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or
R^3, R^5, and R^6 are each independently a 5- or 6-membered monocyclic carbocycle or heterocycle or a [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycle or heterocycle containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

R^4 is H, halogen, $-OR^{12}$, $-S(O)_nR^{13}$, –CN, $-C(O)R^{13}$, $-NR^{10}R^{11}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, wherein each of the C_1–C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^4 is a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, wherein the bridged bicyclic ring is optionally substituted from 1 to 3 times with substitutents selected from the group consisting of C_1-C_3 alkyl, $-C(O)R^{13}$, and $-S(O)_nR^{13}$; or

R^4 is a monocyclic or bicyclic aryl or heteroaryl selected from the group consisting of phenyl, pyridyl, 2-oxo-pyridin-1-yl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyranyl, furanyl, pyrrolyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, indanyl, indenyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, indolinyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, indazolyl, benzimidazolyl, benzooxazolyl, benzothiazolyl, benzoisoxazolyl, benzoisothiazolyl, benzotriazolyl, benzo[1,3]dioxolyl, naphthyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, pthalazinyl, quinoxalinyl, 2,3-dihydro-benzo[1,4]dioxinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, 4*H*-chromenyl, indolizinyl, quinolizinyl, 6*aH*-thieno[2,3-d]imidazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, [1,2,4]triazolo[1,5-*a*]pyridinyl, thieno[2,3-*b*]furanyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[2,3-*b*]pyrazinyl, imidazo[1,2-*a*]pyrazinyl, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazinyl, 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazinyl, 2-oxo-2,3-dihydrobenzo[*d*]oxazolyl, 3,3-dimethyl-2-oxoindolinyl, 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, 3,4-dihydro-2H-benzo[*b*][1,4]oxazinyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazinyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, [1,2,4]triazolo[4,3-*b*]pyridazinyl, and 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

provided that for compounds of formula IA, X is optionally substituted phenyl and R^4 is optionally substituted monocyclic or bicyclic aryl or heteroaryl;

provided that for compounds of formula IB, X is optionally substituted bicyclic carbocycle or heterocycle and R^4 is optionally substituted monocyclic or bicyclic aryl or heteroaryl;

provided that for compounds of formula IC, X is optionally substituted phenyl and R^4 is H, $-OR^{12}$, $-S(O)_nR^{13}$, $C(O)R^{13}$, $-NR^{10}R^{11}$, -CN, halogen, or C_1-C_6 alkyl, wherein each of the C_1-C_6 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};
provided that for compounds of formula ID, X is optionally substituted bicyclic carbocycle or heterocycle and R^4 is H, $-OR^{12}$, $-S(O)_nR^{13}$, $C(O)R^{13}$, $-NR^{10}R^{11}$, -CN, halogen, or C_1-C_6 alkyl, wherein each of the C_1-C_6 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; and
provided that for compounds of formula IE, X is optionally substituted aromatic monocyclic heterocycle and R^4 is optionally substituted monocyclic or bicyclic aryl or heteroaryl;

R^7 is selected from the group consisting of H,$-S(O)_nR^{13}$, $-C(O)R^{13}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, wherein each of C_1 –C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^8 is selected from the group consisting of H, halogen, $-OR^{12}$, $-S(O)_nR^{13}$, –CN, $-C(O)R^{13}$, $-NR^{10}R^{11}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, wherein each of C_1 –C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or

R^7 and R^8 are gem-dimethyl, with the proviso that only one of R^7 and R^8 is gem-dimethyl;

R^9 is H, halogen,$-OR^{12}$, $-SR^{10}$, C_1-C_6 alkyl, -CN, or $-NR^{10}R^{11}$, wherein each of C_1 –C_6 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{10} and R^{11} are each independently selected from the group consisting of H, $-C(O)R^{13}$, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, wherein each of C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};
R^{10} and R^{11} are each independently selected from the group consisting of phenyl, benzyl, and other 5- or 6-membered monocyclic heterocycles, wherein each of the phenyl, benzyl, and 5- or 6-membered monocyclic heterocycle is optionally substituted from 1 to 3 times with substituents as defined below in R^{14};

R^{10} and R^{11} are taken together with the nitrogen to which they are attached to form a saturated or partially saturated monocyclic or fused bicyclic heterocycle selected from the group consisting of piperidine, pyrrolidine, morpholine, thiomorpholine, [1,2]oxazinane, isoxazolidine, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 3-oxomorpholino, 3-oxothiomorpholino, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazine, and other monocyclic or fused bicyclic heterocycles containing 1-4 heteroatoms selected from oxygen, nitrogen and sulfur, wherein the heterocycle is attached to the benzazepine core via the nitrogen atom, and is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, $-OR^{12}$, $-NR^{12}R^{13}$, $-S(O)_nR^{13}$, $-C(O)R^{13}$, and C_1-C_4 alkyl, wherein each of C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{10} and R^{11} are taken together with the nitrogen to which they are attached to form a heterocycle selected from the group consisting of piperazine, 2-oxopiperazinyl, 2-oxo-1,4-diazepanyl, 5-oxo-1,4-diazepanyl, 1,4-diazepane, and other heterocycles containing one additional nitrogen atom in the ring, wherein the heterocycle is optionally substituted on a ring carbon with from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, $-OR^{12}$, $-NR^{12}R^{13}$, $-S(O)_nR^{13}$, $-C(O)R^{13}$, and C_1-C_4 alkyl, or on the additional nitrogen atom from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of $S(O)_nR^{13}$, $-C(O)R^{13}$, and C_1-C_4 alkyl, wherein each of C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{10} and R^{11} are taken together with the nitrogen to which they are attached to form a heterocycle selected from the group consisting of piperazine, 2-oxopiperazinyl, 2-oxo-1,4-diazepanyl, 5-oxo-1,4-diazepanyl, 1,4-diazepane, and other heterocycles containing one additional nitrogen atom in the ring, wherein the heterocycle is optionally substituted on the additional nitrogen atom with a substituent selected independently at each occurrence thereof from the group consisting of phenyl, benzyl, and 5- or 6-membered aromatic heterocycles containing 1-3 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, wherein each of the phenyl, benzyl, and 5- and 6-membered heterocycle is optionally substituted from 1 to 3 times with substituents as defined below in R^{14}; or

when R^4 is $-NR^{10}R^{11}$ or $-C(O)NR^{10}R^{11}$, either R^{10} or R^{11} is a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group consisting

of oxygen, nitrogen, and sulfur, wherein the bridged bicyclic ring is optionally substituted from 1 to 3 times with substituents selected from the group consisting of C_1-C_3 alkyl, –C(O)R^{13}, and –S(O)$_n$$R^{13}$, or either R^{10} or R^{11} is a C_1-C_3 alkyl substituted with a bridged bicyclic ring containing 6-12 carbon atoms and optionally containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, wherein the bridged bicyclic ring is optionally substituted from 1 to 3 times with substitutents selected from the group consisting of C_1-C_3 alkyl, –C(O)R^{13}, and -S(O)$_n$$R^{13}$;

R^{12} is selected from the group consisting of H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, and –C(O)R^{13}, wherein each of C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{13} is selected from the group consisting of H, -N$R^{10}$$R^{11}$, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, wherein each of C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; or

R^{12} and R^{13} are each independently selected from the group consisting of phenyl, benzyl, pyridazinyl, pyrimidinyl, pyrazinyl, 5- or 6-membered aromatic monocyclic heterocycles, and [5,5]-, [6,5]-, [6,6]-, or [6,7]-fused bicyclic carbocycles or heterocycles containing 1-5 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally substituted from 1 to 4 times with substituents as defined below in R^{14}; or

R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a heterocycle selected from the group consisting of piperidine, pyrrolidine, piperazine, 1,4-diazepane, morpholine, thiomorpholine, and other heterocycles containing 1-4 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, wherein the heterocycle is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, -OR^{10}, –S(O)$_n$$R^{10}$, –C(O)$R^{10}$, -C(O)N$R^{10}$$R^{11}$ and C_1-C_4 alkyl, wherein each of C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

n is 0, 1, or 2;

R^{14} is independently selected at each occurrence from a substituent in the group consisting of halogen, $-NO_2$, $-OR^{12}$, $-NR^{10}R^{11}$, $-NR^{12}C(O)_2R^{13}$, $-NR^{12}C(O)NR^{12}R^{13}$, $-S(O)_n R^{13}$, –CN, $-C(O)R^{13}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; and

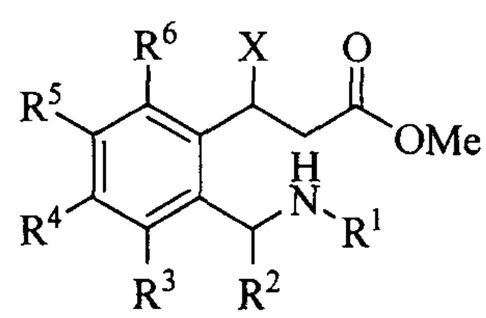
R^{15} is independently selected at each occurrence from a substituent in the group consisting of –CN, halogen, $C(O)R^{13}$, C_1-C_3 alkyl, $-OR^{12}$, $-NR^{10}R^{11}$, $-S(O)_nR^{13}$, aryl, and heteroaryl, wherein each of the aryl or heteroaryl groups is optionally substituted from 1 to 4 times with substituents as defined above in R^{14};

with the following provisos that (1) when R^4 is H or C_{1-4} alkoxy, X cannot be phenyl; (2) when R^4 is (a) C_{1-6} alkyl, (b) C_{1-4} alkoxy, (c) hydroxyl, (d) halogen, or (e) CN, X cannot be a phenyl substituted at the *para*-position with the same R^4; (3) when any one of R^3, R^4, R^5, and R^6 is hydrogen, halogen, perhalomethyl, optionally substituted C_{1-6}-alkyl, hydroxy, optionally substituted C_{1-4} alkoxy, cyano, amino, optionally substituted mono- or optionally substituted di-C_{1-4} alkylamino, acylamino, or carbamoyl, X cannot be furanyl, thienyl, pyrazolyl, tetrazolyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-oxadiazolyl, 1,2,5-thiadiazolyl, benzo[d]isoxazolyl, or benzo[d]isothiazolyl; (4) when R^4 is $-S(O)_nR^{13}$, n cannot be 0; and (5) when R^9 is a substituted alkyl, R^{15} cannot be $-NR^{10}R^{11}$;

or an oxide thereof, or a pharmaceutically acceptable salt thereof,

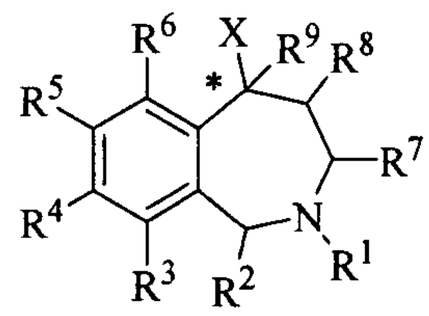
said process comprising:

treating an intermediate compound of the formula:



under conditions effective to produce the product compound.

87. A compound of formulae I(A-E) having the following structure:



I(A-E)

wherein:

the carbon atom designated * is in the R or S configuration; and

X is phenyl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

R^1 is H or C_1-C_6 alkyl;

R^2 is H;

R^3 is H;

R^4 is pyridazinyl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

R^5 is H;

R^6 is H;

R^7 is H;

R^8 is H;

R^9 is H; and

R^{14} is independently selected at each occurrence from halogen or C_1-C_6 alkyl, wherein C_1-C_6 alkyl is optionally substituted from 1 to 3 times with halogen,

or an oxide thereof, or a pharmaceutically acceptable salt thereof.

88. The compound according to claim 87, wherein R^1 is H.

89. The compound according to claim 87, wherein R^1 is methyl.

90. The compound according to claim 87, wherein R^4 is pyridazin-3-yl, 6-methylpyridazin-3-yl, or 6-(trifluoromethyl)pyridazin-3-yl.

91. The compound according to claim 90, wherein R^4 is 6-(trifluoromethyl)pyridazin-3-yl.

92. The compound according to claim 87, wherein R^{14} is fluorine or chlorine.

93. The compound according to claim 87, wherein X is disubstituted with R^{14} and wherein R^{14} at each occurrence is a halogen.

94. The compound according to claim 87, wherein the carbon atom designated * is in the *R* configuration.

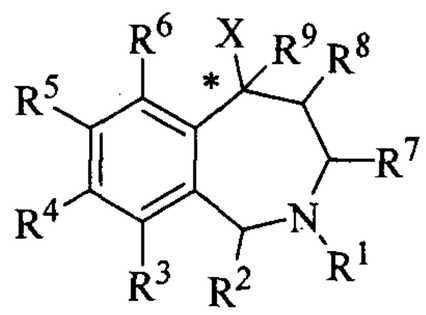
95. The compound according to claim 87, wherein the carbon atom designated * is in the *S* configuration.

96. The compound according to claim 87, wherein the compound is a (+) stereoisomer.

97. The compound according to claim 87, wherein the compound is a (-) stereoisomer.

98. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound as defined in any one of claims 87 to 97.

99. A compound of formulae I(A-E) having the following structure:



I(A-E)

wherein:

the carbon atom designated * is in the R or S configuration;

X is phenyl, optionally substituted from 1 to 4 times with substituents as defined in R^{14};

R^1 is H, methyl, ethyl, or isopropyl;

R^2 is H, methyl, or gem-dimethyl;

R^3 is H, methyl, hydroxy, methoxy, fluoro, chloro, cyano, trifluoromethyl, or trifluoromethoxy;

R^4 is pyridazinyl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

R^5 is H, fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxy or methoxy;

R^6 is H, fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxy or methoxy;

R^7 is H, gem-dimethyl, or C_1-C_4 alkyl, wherein each of the C_1-C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined in R^{15};

R^8 is H;

R^9 is H;

R^{10} and R^{11} are each independently selected from H, -C(O)R^{13}, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, where each of C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};
R^{10} and R^{11} are each independently selected from phenyl, benzyl, or other 5- or 6-membered monocyclic heterocycles, where each of the phenyl, benzyl, and 5- or 6-membered monocyclic heterocycle is optionally substituted from 1 to 3 times with substituents as defined below in R^{14};
R^{10} and R^{11} are taken together with the nitrogen to which they are attached to form a saturated or partially saturated monocyclic or fused bicyclic heterocycle selected from piperidine, pyrrolidine, morpholine, thiomorpholine, [1,2]oxazinane, isoxazolidine, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 3-oxomorpholino, 3-oxothiomorpholino, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazine, or other monocyclic or fused bicyclic heterocycles containing 1-4 heteroatoms selected from oxygen, nitrogen or sulfur, wherein the heterocycle is attached to the benzazepine core via the nitrogen atom, and is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from halogen, cyano, -OR^{12}, -N$R^{12}R^{13}$, –S(O)$_n$$R^{13}$, –C(O)$R^{13}$, or C_1-C_4 alkyl, where each of C_1-C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};
R^{10} and R^{11} are taken together with the nitrogen to which they are attached to form a heterocycle selected from piperazine, 2-oxopiperazinyl, 2-oxo-1,4-diazepanyl, 5-oxo-1,4-diazepanyl, 1,4-diazepane, or other heterocycles containing one additional nitrogen atom in the ring, where the heterocycle is optionally substituted on a ring carbon with from 1 to 3 times with a substituent selected independently at each occurrence thereof from halogen, cyano, -OR^{12}, -N$R^{12}R^{13}$, –S(O)$_n$$R^{13}$, –C(O)$R^{13}$, or C_1-C_4 alkyl, or on the additional nitrogen atom from 1 to 3 times with a substituent selected independently at each occurrence thereof from S(O)$_n$$R^{13}$, –C(O)$R^{13}$, or C_1-C_4 alkyl, wherein each of C_1-C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};
R^{10} and R^{11} are taken together with the nitrogen to which they are attached to form a heterocycle selected from piperazine, 2-oxopiperazinyl, 2-oxo-1,4-diazepanyl, 5-oxo-1,4-diazepanyl, 1,4-

diazepane, or other heterocycles containing one additional nitrogen atom in the ring, where the heterocycle is optionally substituted on the additional nitrogen atom with a substituent selected independently at each occurrence thereof from phenyl, benzyl, or 5- or 6-membered aromatic heterocycles containing 1-3 heteroatoms selected from oxygen, nitrogen, or sulfur, where each of the phenyl, benzyl, and 5- and 6-membered heterocycle is optionally substituted from 1 to 3 times with substituents as defined below in R^{14};

R^{12} is selected from H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, or $-C(O)R^{13}$, where each of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{13} is C_1-C_4 alkyl;

R^{14} is independently selected at each occurrence from halogen, $-NO_2$, $-OR^{12}$, $-NR^{10}R^{11}$, $-NR^{12}C(O)_2R^{13}$, $-NR^{12}C(O)NR^{12}R^{13}$, $-S(O)_n R^{13}$, –CN, $-C(O)R^{13}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; and

R^{15} is independently selected at each occurrence from –CN, halogen, $C(O)R^{13}$, C_1-C_3 alkyl, $-OR^{12}$, $-NR^{10}R^{11}$, $-S(O)_nR^{13}$, aryl, or heteroaryl, wherein each of the aryl or heteroaryl groups is optionally substituted from 1 to 4 times with substituents as defined above in R^{14}; and

n is 0, 1, or 2.

100. The compound according to claim 99, wherein X is phenyl substituted from 1 to 4 times with halogen.

101. The compound according to claim 100, wherein the halogen is F or Cl.

102. The compound according to claim 99, wherein R^1 is H.

103. The compound according to claim 99, wherein R^2 is H.

104. The compound according to claim 99, wherein R^3 is H.

105. The compound according to claim 99, wherein R^4 is pyridazin-3-yl.

106. The compound according to claim 99, R^4 is substituted with $-CF_3$.

107. The compound according to claim 99, wherein R^5 is H.

108. The compound according to claim 99, wherein R^6 is H.

109. The compound according to claim 99, wherein R^7 is H.

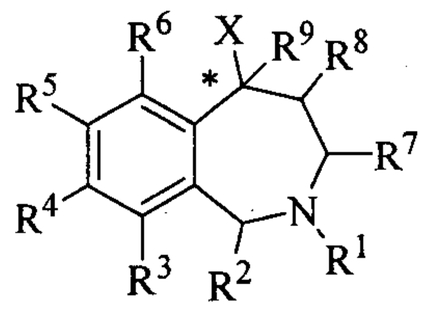
110. The compound according to claim 99, wherein
R^1, R^2, R^3, R^5, R^6, R^7, R^8, and R^9 are H;
R^4 is pyridazin-3-yl; and
X is phenyl substituted from 1 to 4 times with halogen.

111. The compound according to claim 110, wherein R^4 is substituted with $-CF_3$.

112. The compound according to claim 99, wherein
R^1, R^2, R^3, R^5, R^6, R^7, R^8, and R^9 are H;
R^4 is pyridazin-3-yl substituted with $-CF_3$; and
X is phenyl substituted from 1 to 4 times with F or Cl.

113. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound as defined in any one of claims 99 to 112.

114. A compound of formulae I(A-E) having the following structure:



I(A-E)

wherein:

the carbon atom designated * is in the R or S configuration;

X is phenyl, optionally substituted from 1 to 4 times with substituents as defined in R^{14};

R^1 is H, methyl, ethyl, or isopropyl;

R^2 is H, methyl, or gem-dimethyl;

R^3 is H, methyl, hydroxy, methoxy, fluoro, chloro, cyano, trifluoromethyl, or trifluoromethoxy;

R^4 is pyrimidinyl, optionally substituted from 1 to 4 times with substituents as defined below in R^{14};

R^5 is H, fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxy or methoxy;

R^6 is H, fluoro, chloro, methyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxy or methoxy;

R^7 is H, gem-dimethyl, or C_1–C_4 alkyl, wherein each of the C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined in R^{15};

R^8 is H, hydroxy, fluoro, or chloro,

R^9 is H, fluoro, chloro, methyl, hydroxyl, or cyano;

R^{10} and R^{11} are each independently selected from H, -C(O)R^{13}, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, where each of C_1 –C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{10} and R^{11} are each independently selected from phenyl, benzyl, or other 5- or 6-membered monocyclic heterocycles, where each of the phenyl, benzyl, and 5- or 6-membered monocyclic heterocycle is optionally substituted from 1 to 3 times with substituents as defined below in R^{14};
R^{10} and R^{11} are taken together with the nitrogen to which they are attached to form a saturated or partially saturated monocyclic or fused bicyclic heterocycle selected from piperidine, pyrrolidine, morpholine, thiomorpholine, [1,2]oxazinane, isoxazolidine, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 3-oxomorpholino, 3-oxothiomorpholino, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazine, or other monocyclic or fused bicyclic heterocycles containing 1-4 heteroatoms selected from oxygen, nitrogen or sulfur, wherein the heterocycle is attached to the benzazepine core via the nitrogen atom, and is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from halogen, cyano, $-OR^{12}$, $-NR^{12}R^{13}$, $-S(O)_nR^{13}$, $-C(O)R^{13}$, or C_1-C_4 alkyl, where each of C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};
R^{10} and R^{11} are taken together with the nitrogen to which they are attached to form a heterocycle selected from piperazine, 2-oxopiperazinyl, 2-oxo-1,4-diazepanyl, 5-oxo-1,4-diazepanyl, 1,4-diazepane, or other heterocycles containing one additional nitrogen atom in the ring, where the heterocycle is optionally substituted on a ring carbon with from 1 to 3 times with a substituent selected independently at each occurrence thereof from halogen, cyano, $-OR^{12}$, $-NR^{12}R^{13}$, $-S(O)_nR^{13}$, $-C(O)R^{13}$, or C_1-C_4 alkyl, or on the additional nitrogen atom from 1 to 3 times with a substituent selected independently at each occurrence thereof from $S(O)_nR^{13}$, $-C(O)R^{13}$, or C_1-C_4 alkyl, wherein each of C_1–C_4 alkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};
R^{10} and R^{11} are taken together with the nitrogen to which they are attached to form a heterocycle selected from piperazine, 2-oxopiperazinyl, 2-oxo-1,4-diazepanyl, 5-oxo-1,4-diazepanyl, 1,4-diazepane, or other heterocycles containing one additional nitrogen atom in the ring, where the heterocycle is optionally substituted on the additional nitrogen atom with a substituent selected independently at each occurrence thereof from phenyl, benzyl, or 5- or 6-membered aromatic heterocycles containing 1-3 heteroatoms selected from oxygen, nitrogen, or sulfur, where each of the phenyl, benzyl, and 5- and 6-membered heterocycle is optionally substituted from 1 to 3 times with substituents as defined below in R^{14};

R^{12} is selected from H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, or $-C(O)R^{13}$, where each of C_1–C_6 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{13} is selected from H, $-NR^{10}R^{11}$, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, wherein each of C_1-C_4 alkyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15};

R^{14} is independently selected at each occurrence from halogen, $-NO_2$, $-OR^{12}$, $-NR^{10}R^{11}$, $-NR^{12}C(O)_2R^{13}$, $-NR^{12}C(O)NR^{12}R^{13}$, $-S(O)_n R^{13}$, –CN, $-C(O)R^{13}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkylalkyl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and C_4-C_7 cycloalkylalkyl is optionally substituted from 1 to 3 times with substituents as defined below in R^{15}; and

R^{15} is independently selected at each occurrence from –CN, halogen, $C(O)R^{13}$, C_1-C_3 alkyl, $-OR^{12}$, $-NR^{10}R^{11}$, $-S(O)_nR^{13}$, aryl, or heteroaryl, wherein each of the aryl or heteroaryl groups is optionally substituted from 1 to 4 times with substituents as defined above in R^{14}; and

n is 0, 1, or 2.

115. The compound according to claim 114, wherein X is phenyl substituted from 1 to 4 times with halogen.

116. The compound according to claim 115, wherein the halogen is F.

117. The compound according to claim 114, wherein R^1 is H.

118. The compound according to claim 114, wherein R^2 is H.

119. The compound according to claim 114, wherein R^3 is H.

120. The compound according to claim 114, wherein R^4 is pyrimidin-2-yl.

121. The compound according to claim 114, wherein R^4 is substituted with –$S(O)_n R^{13}$, wherein n is 2.

122. The compound according to claim 114, wherein R^5 is H.

123. The compound according to claim 114, wherein R^6 is H.

124. The compound according to claim 114, wherein R^7 is gem-dimethyl.

125. The compound according to claim 114, wherein R^8 is H.

126. The compound according to claim 114, wherein R^9 is H.

127. The compound according to claim 114, wherein R^{13} is C_1-C_4 alkyl.

128. The compound according to claim 114, wherein
R^1, R^2, R^3, R^5, R^6, R^8, and R^9 are H;
R^4 is pyrimidin-2-yl;
R^7 is gem-dimethyl; and
X is phenyl substituted from 1 to 4 times with halogen.

129. The compound according to claim 128, wherein R^4 is substituted with –$S(O)_n R^{13}$, wherein n is 2.

130. The compound according to claim 129, wherein R^{13} is methyl.

131. The compound according to claim 114, wherein
R^1, R^2, R^3, R^5, R^6, R^8, and R^9 are H;
R^4 is pyrimidin-2-yl substituted with –$S(O)_n R^{13}$, wherein n is 2;
R^7 is gem-dimethyl; and

X is phenyl substituted from 1 to 4 times with F.

132. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound as defined in any one of claims 114 to 131.

133. Use of a compound as defined in any one of claims 87 to 97, 99 to 112 and 114 to 131, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disorder which is created by or is dependent upon decreased availability of norepinephrine, dopamine, or serotonin.

134. Use of a compound as defined in any one of claims 87 to 97, 99 to 112 and 114 to 131, or a pharmaceutically acceptable salt thereof, for treating a disorder which is created by or is dependent upon decreased availability of norepinephrine, dopamine, or serotonin.

135. The use according to claim 133 or 134, wherein said compound is for use with a serotonin 1A receptor antagonist or a pharmaceutically acceptable salt thereof.

136. The use according to claim 135, wherein the serotonin 1A receptor antagonist is N-(t-butyl)-3-[a-(2-methoxyphenyl)piperazin-1-yl]-2-phenylpropanamide or spiperone.

137. The use according to claim 133 or 134, wherein said compound is for use with a selective neurokinin-1 receptor antagonist or a pharmaceutically acceptable salt thereof.

138. The use according to claim 133 or 134, wherein said compound is for use with a norepinephrine precursor or a pharmaceutically acceptable salt thereof.

139. The use according to claim 138, wherein the norepinephrine precursor is L-tyrosine or L-phenylalanine.

140. The use according to claim 133 or 134, wherein the disorder is: lower back pain, attention deficit hyperactivity disorder (ADHD), cognition impairment, anxiety disorders, generalized anxiety disorder (GAD), panic disorder, bipolar disorder or manic depression or manic-depressive disorder, obsessive compulsive disorder (OCD), posttraumatic stress disorder (PTSD), acute stress disorder, social phobia, simple phobias, pre-menstrual dysphoric disorder (PMDD), social anxiety disorder (SAD), major depressive disorder (MDD), postnatal depression, dysthymia, depression associated with Alzheimer's disease, Parkinson's disease, or psychosis, supranuclear palsy, eating disorders, obesity, anorexia nervosa, bulimia nervosa, binge eating disorder, analgesia, substance abuse disorders, chemical dependencies, nicotine addiction, cocaine addiction, alcohol and amphetamine addiction, Lesch-Nyhan syndrome, neurodegenerative diseases, Parkinson's disease, late luteal phase syndrome or narcolepsy, psychiatric symptoms, anger, rejection sensitivity, movement disorders, extrapyramidal syndrome, Tic disorders, restless leg syndrome (RLS), tardive dyskinesia, supranuclear palsy, sleep related eating disorder (SRED), night eating syndrome (NES), stress urinary incontinence (SUI), migraine, neuropathic pain, diabetic neuropathy, fibromyalgia syndrome (FS), chronic fatigue syndrome (CFS), sexual dysfunction, premature ejaculation, male impotence, or thermoregulatory disorders.

141. The use according to claim 140, wherein the disorder is lower back pain.

142. The use according to claim 140, wherein the disorder is attention deficit hyperactivity disorder.

143. The use according to claim 140, wherein the disorder is anxiety disorder.

144. The use according to claim 140, wherein the disorder is bipolar disorder or manic depressive disorder.

145. The use according to claim 140, wherein the disorder is major depressive disorder.

146. The use according to claim 140, wherein the disorder is postnatal depression.

147. The use according to claim 140, wherein the disorder is dysthymia.

148. The use according to claim 140, wherein the disorder is depression associated with Alzheimer's disease, Parkinson's disease, or psychosis.

149. The use according to claim 140, wherein the disorder is eating disorder.

150. The use according to claim 140, wherein the disorder is obesity.

151. The use according to claim 140, wherein the disorder is substance abuse disorder.

152. The use according to claim 140, wherein the disorder is neurodegenerative disease.

153. The use according to claim 140, wherein the disorder is Parkinson's disease.

154. The use according to claim 140, wherein the disorder is neuropathic pain.

155. The use according to claim 140, wherein the disorder is diabetic neuropathy.

156. The use according to claim 140, wherein the disorder is fibromyalgia syndrome.

157. The use according to claim 140, wherein the disorder is sexual dysfunction.

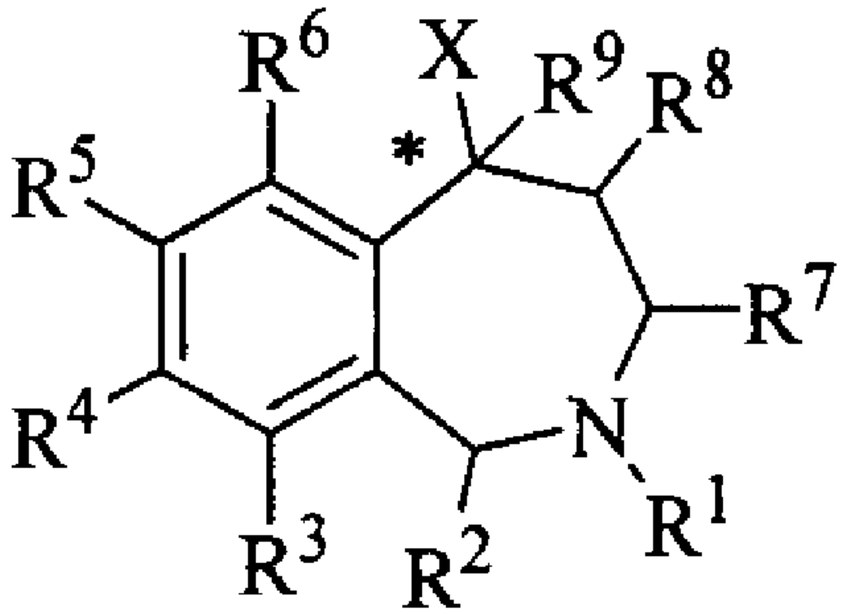
158. The use according to claim 140, wherein the disorder is premature ejaculation.

159. The use according to claim 140, wherein the disorder is stress urinary incontinence.

160. The use according to claim 140, wherein the disorder is thermoregulatory disorder.

161. The use according to claim 140, wherein the thermoregulatory disorder is hot flashes.

162. The compound according to claim 99, wherein R^4 is pyridazin-3-yl, 6-methylpyridazin-3-yl, 6-(trifluoromethyl)pyridazin-3-yl, 6-aminopyridazin-3-yl, 6-(methylamino)pyridazin-3-yl, 6-(dimethylamino)pyridazin-3-yl, 6-morpholinopyridazin-3-yl, 6-(4-hydroxypiperidin-1-yl)pyridazin-3-yl, 6-(4-methylpiperazin-l-yl)pyridazin-3-yl, or (6-(hydroxymethyl)pyridazin-3-yl.



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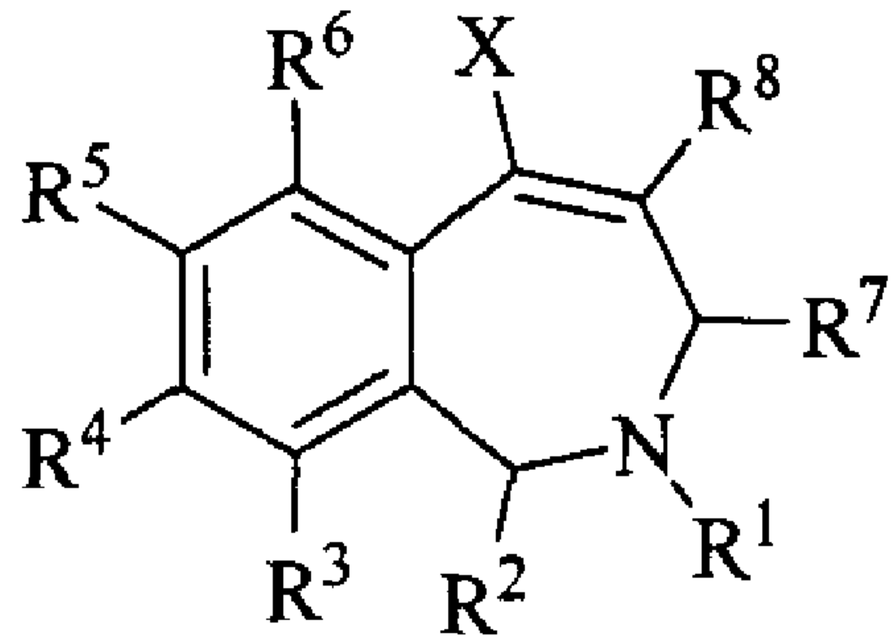

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